Provisional Data Report on Malaria Surveillance and Use of Antimalarial Chemoprophylaxis January – December 2001

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TABLE OF CONTENTS

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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 1990, U.S. travelers visiting areas where chloroquine-resistance has been reported are advised by CDC to use the antimalarial drugs mefloquine or doxycycline for prophylaxis.

In July 2000, the Food and Drug Administration approved Malarone™, a fixed combination of atovaquone and proguanil, for the treatment and prevention of *P. falciparum* malaria.

Based on data that showed the efficacy of Malarone for the prevention of malaria in non-immune persons, CDC revised its malaria prevention guidelines in November 2000 to add Malarone as one of three antimalarial drug options for persons traveling to areas where chloroquine-resistant *P. falciparum* has been reported.

To monitor 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, 2001 to December 31, 2001.

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 chloroquine, doxycycline, Malarone, 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**: comfirmed 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 are 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 1,092 reports of malaria among persons in the United States through NMSS with a date of onset between January 1, 2001 and December 31, 2001.

The infecting species of Plasmodium was identified in 937 (85.8%) of these cases (Table 1).

One thousand and ninety-one (99.9%) of the 1092 cases were imported. Seven hundred and nine (65.0%) of the 1091 cases were in U.S. civilians (including military personnel) who acquired the infection outside the United States. The remainder of this report will focus solely on these civilian cases. Of the 709 cases, 474 (66.9%) were acquired in Africa, 106 (15.0%) in the Americas and 103 (14.5%) in Asia (Table 2).

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

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

Information concerning the use of chemoprophylaxis was known for 640 (90.3%) of the 709 U.S. civilians who had imported malaria. Three hundred fifty (54.7%) of the 640 civilians had not taken any chemoprophylaxis, and 123 of the remaining 290 (42.4%) had not taken a drug recommended by CDC for the area visited, which included thirteen people who took a recommended drug in combination with a nonrecommended drug and were subsequently excluded from this report. Only 150 (23.4%) of the 640 U.S. civilians had taken a medication recommended by CDC (2).

Of the 150 case-patients who took one of the drugs recommended by CDC, 108 (72.0%) took mefloquine weekly, 23 (15.3%) took doxycycline daily, 11 (7.3%) took chloroquine, and 6 (4.0%) took Malarone. Two additional cases took a combination of mefloquine and doxycycline, and were excluded from further analyses.

Of the 123 case-patients who took a nonrecommended antimalarial drug, 56 (45.5%) 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 128 of the 148 case-patients who took a drug recommended by the CDC. Twenty were found to be either of mixed species (n = 2) or the species could not be determined (n = 18) and were excluded from the following analyses.

Cases of P. vivax or P. ovale. Among the 128 U.S. civilians who developed malaria after using recommended chemoprophylaxis, 75 cases (68.6%) were caused by *P. vivax* (n = 63) or *P. ovale* (n = 12). Twenty-nine 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 28 cases were relapsing infections. Fourteen 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 three cases of P.vivax 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 128 malaria-infected U.S. civilians who took recommended prophylaxis, 46 (35.9%) had *P. falciparum* and 7 (5.5%) 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.

Prophylaxis failure rates. In the year 2001, a total of 379,000 and 65,000 prescriptions were sold for mefloquine and malarone, respectively. Thus, prophylaxis failure rates for the two drugs among cases who reported being adherent were 1.85 and 1.54 per 100,000 prescriptions, respectively. This number was 8.44 per 100,000 for mefloquine failures among all cases, regardless of adherence to prophylaxis.

DISCUSSION

One thousand and ninety-one cases of imported malaria between January and December 2001, including 709 in U.S. civilians, 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, 473 (73.9%) of the 640 imported malaria cases among U.S. civilians 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 150 (23.4%) persons who reported taking recommended prophylaxis, 29 (19.3%) 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, sixty-nine (9.7%) of the 709 malaria case surveillance reports of imported malaria in U.S. civilians had missing information on whether or not chemoprophylaxis was used.

Unlike the malaria-case surveillance report used for the report in 2000, the current form also includes information on adherence to prophylactic regimens that was incorporated in the definition of prophylaxis failure. However, data on adherence were only available for 36 (50.7%) of the 71 non-relapsing cases. Prophylaxis failure rates were marginally higher for mefloquine than for malarone: 1.85 versus 1.54 per 100,000 prescriptions, respectively.

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, 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, May 2002

Table 1. Total number of reported malaria cases -- United States, January - December 2001

Plasmodium Species	Number	(%)
P. vivax	333	30.5
P. falciparum	504	46.2
P. malariae	48	4.4
P. ovale	42	3.9
Undetermined	155	14.2
Mixed	10	0.9
Total	1092	100.0

Table 3. Characteristics of imported malaria cases in U.S. civilians who took recommended prophylactic regimens (n=148), January - December 2001

Characteristic*	Mefloquine (n = 108)	Doxycycline (n = 23)	Chloroquine** (n = 11)	Malarone (n = 6)
Age in years; mean (SD)	27.5 (17.8)	32.3 (17.0)	36.2 (14.8)	28.7 (28.9)
Gender (male); no (%)	69 (63.9)	9 (39.1)	11 (100)	1 (16.7)
Species (%)				
P. falciparum	35 (32.4)	11 (47.8)	0 (0)	0 (0)
P. vivax	42 (38.9)	8 (34.8)	8 (72.7)	5 (83.3)
P. ovale	11 (10.2)	1 (4.4)	0 (0)	0 (0)
P. malariae	6 (5.6)	1 (4.4)	0 (0)	0 (0)
Unknown	14 (13.0)	2 (8.7)	1 (9.1)	1 (16.7)
Mixed	0 (0)	0 (0)	2 (18.2)	0 (0)
Top 2 States reporting highest number of malaria cases	California (n=18) New York (n=11)	California (n=7) Four states (n=2)	Four states (n=2)	California, Colorado (n=2) Michigan, Wisconsin (n=1)
Top 2 Countries or regions of acquisition with highest number of cases	Nigeria (n=15) Ghana (n=13)	Indonesia, Ghana (n=5) Guinea, Uganda (n=2)	Honduras (n=6) Guatemala (n=2)	Ethiopia (n=2) India, Indonesia, Kenya, PNG (n=1)
Patients who were hospitalized; no (%)	55 (50.9)	10 (43.5)	5 (45.5)	3 (50.0)
Patients with complicated malaria; no (%)***	1 (0.9)	2 (8.7)	0 (0)	0 (0)
Fatal Cases	2 (1.9)	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. civilians after use of recommended prophylaxis, (n =71)

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	April	Honduras	Chloroquine	Unknown	0
2	August	Indonesia	Doxycycline	No	9
3	December	Cameroon	Doxycycline	Unknown	38
4	February	Indonesia	Doxycycline	Unknown	Ill before return
5	November	Ethiopia	Malarone	No	Ill before return
6	November	Indonesia	Malarone	No	43
7	December	Ethiopia	Malarone	Yes	32
8	December	Liberia	Mefloquine	Yes	3
9	August	Indonesia	Mefloquine	Unknown	10
10	September	Africa	Mefloquine	No	11
11	December	Ethiopia	Mefloquine	No	11
12	September	Africa	Mefloquine	No	11
13	February	Zambia	Mefloquine	Unknown	20
14	November	India	Mefloquine	Unknown	35
15	August	Papua New Guinea	Mefloquine	Unknown	41
16	August	Guinea	Mefloquine	Yes	45
17	February	Mexico	Mefloquine	Unknown	Ill before return
P. falciparum					
1	September	Uganda	Doxycycline	Unknown	0
2	August	Ghana	Doxycycline	Unknown	Unknown
3	January	Zambia	Doxycycline	Unknown	10
4	August	Ivory Coast	Doxycycline	Unknown	13
5	June	Nigeria	Doxycycline	Unknown	3
6	November	Guinea	Doxycycline	No	4
7	May	Indonesia	Doxycycline	Unknown	18
8	April	Malawi	Doxycycline	No	19
9	September	Papua New Guinea	Doxycycline	No	54
10	December	Guinea	Doxycycline	Unknown	Ill before return
11	May	Ghana	Doxycycline	No	Unknown
12	July	Nigeria	Mefloquine	No	0
13	June	Cameroon	Mefloquine	No	2
14	September	Nigeria	Mefloquine	No	Unknown
15	September	Nigeria	Mefloquine	Unknown	4
16	May	Nigeria	Mefloquine	No	4
17	September	Africa	Mefloquine	Unknown	5
18	July	Nigeria	Mefloquine	Unknown	6
19	November	Tanzania	Mefloquine	No	8
20	August	Cameroon	Mefloquine	Unknown	9

21	July	Guinea	Mefloquine	Unknown	12
22	October	Africa	Mefloquine	No	14
23	November	Ghana	Mefloquine	Unknown	15
24	July	Sierra Leone	Mefloquine	Yes	21
25	August	Nigeria	Mefloquine	No	24
26	August	Ghana	Mefloquine	No	27
27	August	Guinea	Mefloquine	Yes	43
28	July	Ghana	Mefloquine	No	46
29	August	Mozambique	Mefloquine	Unknown	67
30	May	Mali	Mefloquine	Unknown	105
31	June	Haiti	Mefloquine	Unknown	Ill before return
32	November	Ghana	Mefloquine	No	Ill before return
33	January	Nigeria	Mefloquine	No	Ill before return
34	June	Ghana	Mefloquine	Unknown	Ill before return
35	September	Malawi	Mefloquine	No	Ill before return
36	April	Papua New Guinea	Mefloquine	Unknown	Unknown
37	September	Nigeria	Mefloquine	No	0
38	October	Africa, West	Mefloquine	Unknown	Unknown
39	August	Tanzania	Mefloquine	No	Unknown
40	Unknown	Nigeria	Mefloquine	Unknown	Unknown
41	August	Zambia	Mefloquine	Unknown	Unknown
42	December	Africa, West	Mefloquine	Unknown	Unknown
43	Unknown	Ghana	Mefloquine	No	Unknown
44	May	Ghana	Mefloquine	Unknown	Unknown
45	July	Africa	Mefloquine	Unknown	Unknown
46	November	Nigeria	Mefloquine	No	Unknown
P. malariae					
1	August	Ghana	Doxycycline	No	14
2	September	Ghana	Mefloquine	No	19
3	March	Kenya	Mefloquine	Yes	24
4	November	Tanzania	Mefloquine	Unknown	115
5	May	Guinea	Mefloquine	Unknown	179
6	May	South Africa	Mefloquine	Yes	Unknown
7	September	Cameroon	Mefloquine	Unknown	Unknown
P. ovale					
1	October	Ivory Coast	Mefloquine	Yes	3

* Excludes *P. Vivax or P. ovale* infections occuring 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 2001

Plasmodium Species	Failures by Recommended Drug				Total Failures
	mefloquine	doxycycline	chloroquine	malarone	
P. vivax	2	0	0	1	3
P. falciparum	2	0	0	0	2
P. malariae	2	0	0	0	2
P. ovale	1	0	0	0	1
Total	7	0	0	1	8

*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 2001

Plasmodium Species	Failures by Recommended Drug				Total Failures
	mefloquine	doxycycline	chloroquine	malarone	
P. vivax	5	2	1	0	8
P. falciparum	17	7	0	0	24
P. malariae	3	0	0	0	3
P. ovale	0	0	0	0	0
Total	25	9	1	0	35

Figure 1. Number of imported malaria cases in U.S. civilians, by state in which the disease was diagnosed – United States, January– December 2001 (n=709)

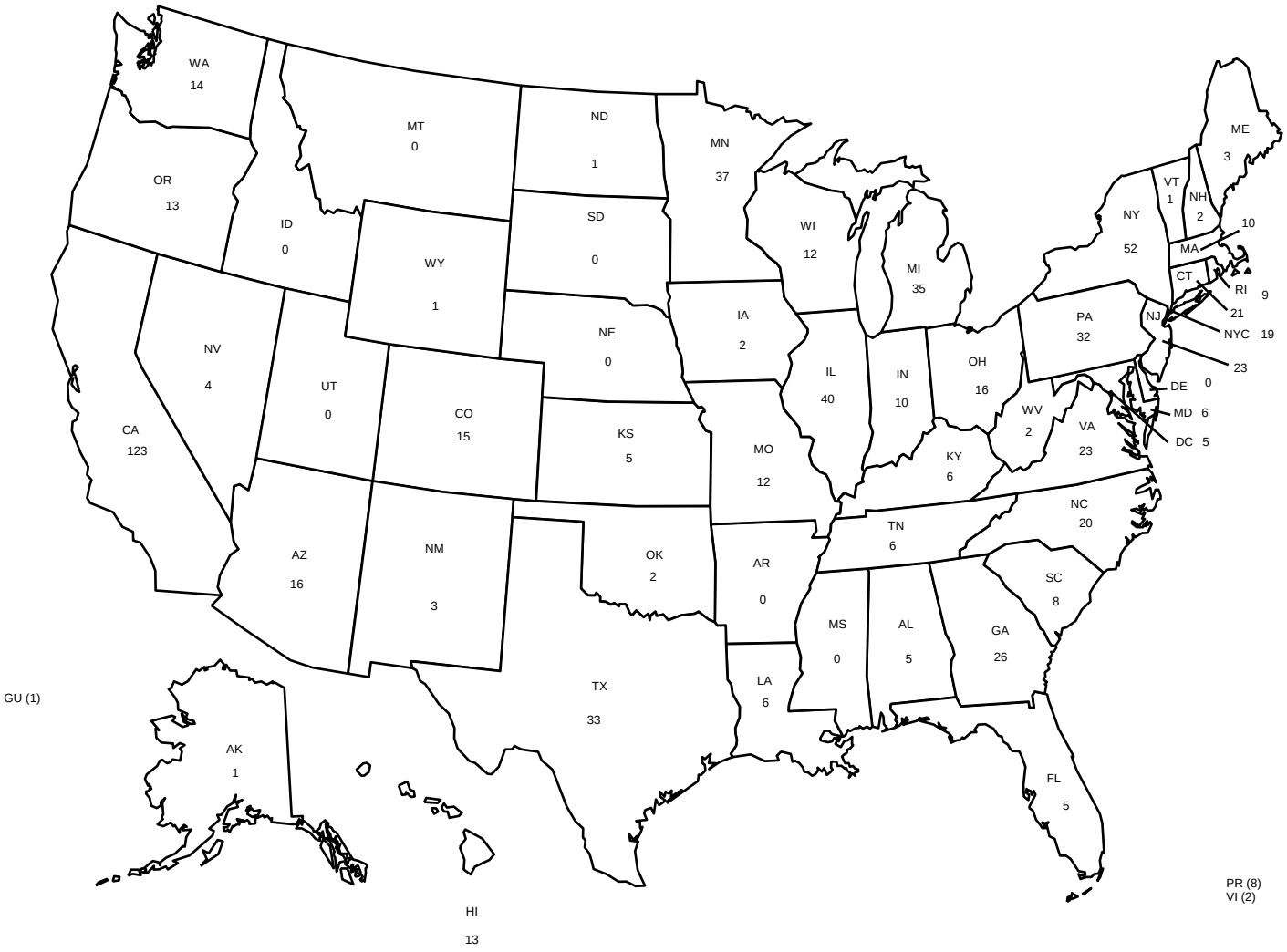

Table 2. Number of imported malaria cases in U.S. civilians, by Plasmodium species and area of acquisition - United States, January - December 2001

Country	P. vivax	P. falciparum	P. malariae	P. ovale	Unknown	Mixed	Total
Africa	58	304	27	23	58	4	474
Benin	0	2	0	0	1	0	3
Botswana	1	2	0	0	0	0	3
Burkina Faso	0	1	0	0	0	0	1
Burundi	1	0	0	0	0	0	1
Cameroon	3	8	1	0	1	0	13
Central African Republic	0	1	0	0	0	0	1
Congo	0	3	1	1	0	0	5
Equatorial Guinea	0	1	0	0	0	0	1
Ethiopia	7	1	1	1	0	0	10
Gabon	0	1	0	0	0	0	1
Gambia	1	3	0	0	0	0	4
Ghana	4	61	5	6	9	1	86
Guinea	1	6	1	0	0	0	8
Ivory Coast	0	10	1	2	3	0	16
Kenya	8	15	2	1	7	0	33
Liberia	1	15	0	1	1	0	18
Malagasy Republic	2	1	0	0	2	0	5
Malawi	1	3	0	0	2	0	6
Mali	0	4	0	1	1	0	6
Mauritania	0	0	0	0	1	0	1
Mozambique	0	3	0	0	1	0	4
Nigeria	4	109	8	1	21	1	144
Rwanda	2	0	0	0	0	0	2
Senegal	0	1	1	0	0	0	2
Sierra Leone	2	3	0	1	2	0	8
South Africa	0	5	2	0	0	0	7
Sudan	2	1	0	0	0	0	3
Tanzania	1	6	1	1	0	0	9
Togo	0	1	0	0	0	0	1
Uganda	10	9	0	3	2	1	25
Zambia	2	2	0	1	0	0	5
Zimbabwe	0	3	0	0	0	0	3
Africa, Central Unspecified	1	0	0	0	0	0	1
Africa, West Unspecified	0	8	0	1	0	0	9
Africa, South unspecified	0	0	0	1	1	0	2

Africa, Unspecified	4	15	3	1	3	1	27
Asia	69	13	4	4	12	1	103
Bangladesh	1	0	0	0	1	0	2
Burma	3	0	0	0	1	0	4
Cambodia	1	0	0	0	0	0	1
China	0	1	0	0	0	0	1
India	29	4	3	2	4	1	43
Indonesia	23	6	1	1	2	0	33
Iraq	1	0	0	0	0	0	1
South Korea	3	0	0	1	3	0	7
Laos	0	1	0	0	0	0	1
Nepal	1	0	0	0	0	0	1
Pakistan	2	0	0	0	1	0	3
Phillippines	0	1	0	0	0	0	1
Thailand	2	0	0	0	0	0	2
Yemen	2	0	0	0	0	0	2
Southeast Asia, Unspecified	1	0	0	0	0	0	1
Central America and Carribbean	55	13	1	1	6	4	80
Belize	3	0	0	0	0	0	3
Costa Rica	2	0	0	0	0	0	2
Dominican Republic	0	0	0	1	0	0	1
El Salvador	6	0	0	0	0	0	6
Guatemala	16	0	1	0	4	1	22
Haiti	2	12	0	0	1	0	15
Honduras	22	1	0	0	1	3	27
Nicaragua	3	0	0	0	0	0	3
America, Central Unspecified	1	0	0	0	0	0	1
North America	3	0	1	0	1	0	5
Mexico	3	0	1	0	1	0	5
South America	14	5	1	0	1	0	21
Argentina	0	0	0	0	1	0	1
Brazil	2	0	0	0	0	0	2
Ecuador	6	1	1	0	0	0	8

Guyana	1	2	0	0	0	0	3
Peru	2	1	0	0	0	0	3
Venezuela	1	0	0	0	0	0	1
America, South Unspecified	2	1	0	0	0	0	3
Oceania	11	3	0	0	4	0	18
Papua New Guinea	11	3	0	0	3	0	17
Vanuatu	0	0	0	0	1	0	1
Unknown	3	4	0	0	1	0	8
Total	213	342	34	28	83	9	709