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Malaria Surveillance — United States, 2012

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Malaria Surveillance — United States, 2012

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Abstract

Problem/Condition: Malaria in humans is caused by intraerythrocytic protozoa of the genus *Plasmodium*. These parasites are transmitted by the bite of an infective female *Anopheles* mosquito. The majority of malaria infections in the United States occur among persons who have traveled to regions with ongoing malaria transmission. However, malaria is also occasionally acquired by persons who have not traveled out of the country, through exposure to infected blood products, congenital transmission, laboratory exposure, or local mosquitoborne transmission. Malaria surveillance in the United States is conducted to identify episodes of local transmission and to guide prevention recommendations for travelers.

Period Covered: This report summarizes cases in persons with onset of symptoms in 2012 and summarizes trends during previous years.

Description of System: Malaria cases diagnosed by blood film, polymerase chain reaction, or rapid diagnostic tests are mandated to be reported to local and state health departments by health-care providers or laboratory staff. Case investigations are conducted by local and state health departments, and reports are transmitted to CDC through the National Malaria Surveillance System (NMSS), National Notifiable Diseases Surveillance System (NNDSS), or direct CDC consults. For the first time, CDC conducted antimalarial drug resistance testing on blood samples submitted to CDC by health-care providers or local/state health departments. Data from these reporting systems serve as the basis for this report.

Results: CDC received 1,687 reported cases of malaria with an onset of symptoms in 2012 among persons in the United States, including 1,683 cases classified as imported, one laboratory-acquired case, one nosocomial case, and two cryptic cases. The total number of cases represents a 12% decrease from the 1,925 cases reported for 2011. *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 58%, 17%, 3%, and 3% of cases, respectively. Twenty (1%) patients were infected by two species. The infecting species was unreported or undetermined in 17% of cases, a decrease of 6 percentage points from 2011. Polymerase chain reaction testing determined or corrected the species for 45 (43%) of the 104 samples submitted for drug resistance testing. Of the 909 patients who reported purpose of travel, 604 (66%) were visiting friends or relatives (VFR). Among the 983 cases in U.S. civilians for whom information on chemoprophylaxis use and travel region was known, 63 (6%) patients reported that they had followed and adhered to a chemoprophylaxis drug regimen recommended by CDC for the regions to which they had traveled. Thirty-two cases were reported in pregnant women, among whom only one adhered to chemoprophylaxis. Among all reported cases, 231 (14%) were classified as severe infections in 2012. Of these, six persons with malaria died in 2012. Beginning in 2012, there were 104 blood samples submitted to CDC that were tested for molecular markers associated with antimalarial drug resistance. Of the 65 *P. falciparum*-positive samples, 53 (82%) had genetic polymorphisms associated with pyrimethamine drug resistance, 61 (94%) with sulfadoxine resistance, 29 (45%) with chloroquine resistance, 1 (2%) with mefloquine drug resistance, 2 (3%) with atovaquone resistance, and none with artemisinin resistance.

Interpretation: Despite the 12% decline in the number of cases reported in 2012 compared with 2011, the overall trend in malaria cases has been increasing since 1973. Although progress has been made in reducing the global burden of malaria, the disease remains endemic in many regions, and the use of appropriate prevention measures by travelers is still inadequate.

Public Health Actions: Completion of data elements on the malaria case report form increased slightly in 2012 compared with 2011, but still remains unacceptably low. This incomplete reporting compromises efforts to examine trends in malaria cases and prevent infections. VFRs continue to be a difficult population to reach with effective malaria prevention strategies. Evidence-based prevention strategies that effectively target VFRs need to be developed and implemented to have a substantial impact on the numbers of imported malaria cases in the United States. Although more patients reported taking chemoprophylaxis to prevent malaria, the majority reported not taking it, and adherence was poor among those who did take chemoprophylaxis. Proper use of malaria chemoprophylaxis will prevent the majority of malaria illness and reduce the risk for severe disease (http://www.cdc.gov/malaria/travelers/drugs.html). Malaria infections can be fatal if not diagnosed and treated promptly with antimalarial medications appropriate for the patient's age and medical history, the likely country of malaria acquisition, and previous use of antimalarial chemoprophylaxis. Recent molecular laboratory advances have enabled CDC to identify and conduct molecular surveillance

of antimalarial drug resistance (http://www.cdc.gov/malaria/features/ars.html). These advances will allow CDC to track, guide treatment, and manage drug resistant malaria parasites both domestically and globally. For this to be successful, specimens should be submitted for cases diagnosed in the United States and for ongoing specimen collection and testing globally. Clinicians should consult the CDC Guidelines for Treatment of Malaria and contact the CDC's Malaria Hotline for case management advice when needed. Malaria treatment recommendations can be obtained online (http://www.cdc.gov/malaria/diagnosis_treatment) or by calling the Malaria Hotline (770-488-7788 or toll-free at 855-856-4713).

Introduction

Malaria in humans is caused by infection with one or more of several species of *Plasmodium* (i.e., *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and occasionally other *Plasmodium* species) parasites. The parasite is transmitted by the bite of an infective female *Anopheles* mosquito. *P. falciparum* and *P. vivax* species cause the most infections worldwide. *P. falciparum* is the agent that most commonly causes severe and potentially fatal malaria (see Definitions). According to the most recently available information, an estimated 207 million clinical cases and 627,000 (0.3%) deaths were reported worldwide in 2012, mostly among children aged <5 years living in sub-Saharan Africa (*1*). *P. vivax* and *P. ovale* have dormant liver stages, which can reactivate and cause malaria several months or years after the initial infection. *P. malariae* can result in long-lasting infections and, if untreated or inadequately treated, can persist asymptomatically in the human host for years, even a lifetime (*1*). Approximately half of the world's population live in regions where malaria is transmitted (i.e., approximately 100 countries in parts of Africa, Asia, the Middle East, Eastern Europe, Central and South America, Caribbean, and Oceania) (*1*). Before the 1950s, malaria was endemic throughout the southeastern United States; an estimated 600,000 cases occurred in 1914 (*2*). During the late 1940s, a combination of improved housing and socioeconomic conditions, environmental management, vector-control efforts, and case management was successful at interrupting malaria transmission in the United States* (3). Since then, malaria case surveillance has been maintained to detect locally acquired cases that could indicate instances of local transmission, to monitor patterns of resistance to antimalarial drugs, and to guide malaria prevention recommendations for international travelers. Malaria vector mosquitoes are still present in the United States (*4*).

The majority of reported malaria cases diagnosed each year in the United States are imported from regions where mosquitoborne malaria transmission is known to occur, although congenital infections and infections resulting from exposure to blood or blood products also are reported in the United States (*5*). In addition, rare cases of local mosquitoborne transmission have been reported (*6*). State and local health departments and CDC investigate reported malaria cases in the United States, and CDC analyzes data from imported cases to detect trends in acquisition.

The signs and symptoms of malaria illness are varied, but the majority of patients have fever (*7*). Other common symptoms include headache, back pain, chills, increased sweating, myalgia, nausea, vomiting, diarrhea, and cough. A diagnosis of malaria should always be considered for persons with these symptoms who have traveled to an area with known malaria transmission. Malaria also should be considered in the differential diagnosis of persons who have fever of unknown origin, regardless of their travel history. Untreated infections can rapidly progress to coma, renal failure, respiratory distress, and death. This report summarizes malaria cases reported to CDC among persons with onset of symptoms in 2012.

Methods

Data Sources

Malaria case data were reported to the National Malaria Surveillance System (NMSS) and the National Notifiable Diseases Surveillance System (NNDSS) (*8*). Although both systems rely on passive reporting, the numbers of reported cases might differ because of differences in collection and transmission of data. A substantial difference between the data collected in these two systems is that NMSS receives more detailed clinical and epidemiologic data regarding each case (e.g., information concerning the area to/from which the infected person has traveled). Malaria cases can be reported to CDC through either NMSS or NNDSS or through a direct consultation with CDC malaria staff; therefore, cases reported through these various paths are compared, deduplicated, compiled, and analyzed. The Armed Forces Health Surveillance Center (AFHSC) provided information about additional military cases that were not reported to state health departments, and those were added to the NMSS database. This report presents data on the aggregate of cases reported to CDC through all reporting systems.

Malaria cases are classified as confirmed or suspected using the 2009 Council of State and Territorial Epidemiologists (CSTE)/CDC case definition (*9*). Malaria cases are further

*The term United States includes all states and territories.

categorized by infecting species: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale.* When more than a single species is detected, the case is categorized as a mixed infection. All categories are mutually exclusive. Diagnosis of malaria is made by blood film microscopy or polymerase chain reaction (PCR). A rapid diagnostic test (RDT) can be used to detect malaria antigens; however, the diagnosis must be confirmed by either microscopy or PCR to be counted as a case. Each malaria case is reported by health-care providers or laboratories to local or state health departments and to CDC. CDC staff review all reports when received and request additional information from the provider or the state, if necessary (e.g., when no recent travel is reported to or from a country where malaria is endemic). Reports of other cases are telephoned to CDC directly by health-care providers, usually when they are seeking assistance with diagnosis or treatment. Information regarding cases reported directly to CDC is shared with the relevant state health department. All cases that have been reported as acquired in the United States are investigated further, including all induced, congenital, introduced, and cryptic cases (see Definitions). Information derived from uniform case report forms is entered into a database and analyzed annually (http://www.cdc.gov/malaria/resources/pdf/report/malaria_formpdf).

The chi-square test was used to calculate p values and assess differences between variables reported in 2012 compared with previous years. A p value of <0.05 was considered statistically significant. Linear regression using least-squares methods was used to calculate the average increase in the number of cases since the early 1970s.

Definitions

The following definitions are used in malaria surveillance for the United States:

- **U.S. residents** — Persons residing in the United States, including both civilian and U.S. military personnel, regardless of legal citizenship.
- **U.S. civilians** — Any U.S. residents, excluding U.S. military personnel.
- **Foreign residents** — Persons who hold resident status in a country other than the United States.
- **Travelers visiting friends or relatives** — Immigrants, ethnically and racially distinct from the major population of the country of residence (a country where malaria is not endemic), who return to their homeland (a country where malaria is endemic) to visit friends or relatives. Included in the visiting friends and relatives (VFR) category are family members (e.g., spouse or children) who were born in the country of residence.
- **Laboratory criteria for diagnosis:** Demonstration of malaria parasites on blood film, PCR, or by RDT (followed by blood film confirmation).
- **Confirmed case:** Symptomatic or asymptomatic infection that occurs in a person in the United States or one of its territories who has laboratory-confirmed (by microscopy or PCR) malaria parasitemia, regardless of whether the person had previous episodes of malaria while in other countries. A subsequent episode of malaria is counted as an additional case, regardless of indicated *Plasmodium* species, unless the case is indicated as a treatment failure resulting from drug resistance.
- **Suspect case:** Symptomatic or asymptomatic infection that occurs in a person in the United States or one of its territories who has *Plasmodium* species detected by rapid diagnostic antigen testing without confirmation by microscopy or PCR, regardless of whether the person experiences previous episodes of malaria while in other countries.
- **Partial immunity:** Immunity in persons born in malaria endemic areas who have survived multiple infections with malaria. While these persons remain susceptible to malaria, their subsequent infections, however, are less likely to be severe. This protection from severe malaria wanes if the person is no longer exposed to repeated malaria infections. Several antibodies have been identified that are a part of the immune response to malaria, but there is no test that can classify individuals as immune or not.

This report also uses terminology derived from the recommendations of the World Health Organization (*10*). Definitions of the following terms are included for reference:

- **Autochthonous malaria:**
  - **Indigenous.** Mosquitoborne transmission of malaria in a geographic area where malaria occurs regularly.
  - **Introduced.** Mosquitoborne transmission of malaria from a person with an imported case in an area where malaria does not occur regularly.
- **Imported malaria:** Malaria acquired outside a specific area. In this report, imported cases are those acquired outside the United States and its territories.
- **Induced malaria:** Malaria acquired through artificial means (e.g., blood transfusion, organ transplantation, or by using shared syringes).
- **Relapsing malaria:** Recurrence of disease after it has been apparently cured. In malaria, true relapses are caused by reactivation of dormant liver-stage parasites (hypnozoites) of *P. vivax* and *P. ovale*.
- **Severe malaria:** A case of malaria with one or more of the following manifestations: neurologic symptoms, renal failure, severe anemia (defined by hemoglobin [Hb] <7g/dL), acute respiratory distress syndrome (ARDS),

jaundice, or ≥5% parasitemia (*11*). To attempt to include severe cases in which clinical criteria were not reported, persons who were treated for severe malaria (i.e., artesunate, quinidine, and/or an exchange blood transfusion) despite having no specific severe manifestations reported also are counted as a severe case in this analysis.

- **Cryptic malaria:** A case of malaria for which epidemiologic investigations fail to identify a plausible mode of acquisition (this term applies primarily to cases found in countries where malaria is not endemic).

Laboratory Diagnosis of Malaria

To diagnose malaria promptly, physicians must obtain a travel history from every febrile patient. Malaria should be included in the differential diagnosis of every febrile patient who has traveled to a malarious area. If malaria is suspected, a Giemsa-stained film of the patient's peripheral blood should be examined for parasites as soon as possible. Thick and thin blood films must be prepared correctly because diagnostic accuracy depends on blood film quality and examination by experienced laboratory personnel (*12*). This simple test can quickly detect the presence of malaria parasites and can also be used to determine the species and percentage of red blood cells that are infected, which are all essential pieces of knowledge to have for the appropriate treatment of persons infected with malaria. Some reference laboratories and health departments can diagnose malaria using PCR, although this is generally reserved for cases for which blood film diagnosis of malaria is inadequate and for confirmation of species. PCR results are also often not available quickly enough to be of use in the initial diagnosis and treatment of a patient with malaria.

In addition, BinaxNOW Malaria, an RDT that detects circulating malaria-specific antigens, is widely available for use by U.S. laboratories. The test is only approved for use by hospital and commercial laboratories, not by individual clinicians or the general public (*13*,*14*). In the United States, use of RDTs can decrease the amount of time required to determine whether a patient is infected with malaria but does not eliminate the need for standard tests (*14*). RDTs are not able to speciate or quantify malaria parasites. Positive and negative RDTs must be confirmed by microscopy (*5*).

Drug Resistance Surveillance

In 2012, CDC's Malaria Branch began molecular surveillance for malaria drug resistance. The goal is to evaluate cases of malaria diagnosed and treated in the United States as a means of detecting and characterizing malaria parasites that carry genetic markers (typically single nucleotide polymorphisms [SNP] in one or more loci) associated with drug resistance. These data will help to understand where foci of resistance to different drugs are present or emerging in specific parts of the world where malaria is endemic. For each sample submitted, species confirmation testing is conducted using a duplex real-time PCR capable of detecting the four human infecting *Plasmodium* species. For mixed infections, samples also will be processed by nested-PCR using species-specific primers that accurately detect the minority population of the co-infecting malaria species. Molecular fingerprinting methods based on microsatellite markers and SNP are used to identify antimalarial drug resistance patterns for *P. falciparum* samples only. Each one is tested for molecular markers associated with resistance to chloroquine, sulfadoxine-pyrimethamine, mefloquine, atovaquone, and artemisinins.

The parasite DNA is subjected to PCR amplification using appropriate primers and sequenced using Sanger method using ABI 3130 capillary sequencer according with described methods (*15*). Fragments of genes encoding molecular targets of chloroquine (chloroquine resistance transporter gene, *pfcrt*), pyrimethamine (dihydrofolate reductase gene, *dhfr*), sulfadoxine (dihydropteroate synthase gene, *dhps*), atovaquone (cytochrome b gene, *cytb*), mefloquine (multidrug resistance 1 protein gene, *pfmdr-1* and *pfmdr-1* copy number), and artemisinin (Mal13-1718319) were analyzed for polymorphisms by comparing each sequence to the reference genome. All reactions were conducted in triplicate on a Stratagene MX3005P (Agilent Technologies) real-time PCR machine. Resistance was assessed for the following drugs: chloroquine, pyrimethamine, sulfadoxine, atovaquone, mefloquine, and artemisinins.

Chloroquine resistance. The *pfcrt* gene sequence was analyzed in order to identify polymorphism at codons C72S, M74I, N75E and K76T.

Pyrimethamine resistance. The *dhfr* gene sequence was analyzed in order to identify polymorphism at codons A16V, C50R, N51I, C59R, S108T/N, and I164L.

Sulfadoxine resistance. The *dhps gene* sequence was analyzed in order to identify polymorphism at codons S436A, A437G, and K540E.

Atovaquone resistance. The *cyto b* gene sequence was analyzed in order to identify polymorphism at codons I258M and Y268S (*16*).

Mefloquine resistance. The *pfmdr-1* gene sequence was analyzed in order to identify polymorphism at codons N86Y, Y184F, S1034C, N1042D, and D1246Y.

***pfmdr-1* copy number**. The a real-time PCR assay was used to determine copy number of *pfmdr-1* relative to that of a single copy gene, seryl-T synthetase, using the comparative cycle threshold ($\Delta\Delta C_T$) method (*17*). The measured copy number of the *pfmdr-1* gene is relative to that of a standard

calibrator parasite, 3D7, which has a single copy of *pfmdr-1*. In addition, DNA from Indochina W2 and Dd2 was used as multiple copy numbers controls.

Artemisinin resistance: Pyrosequencing was used to test for artesmisinin resistance at previously reported (*18*) polymorphisms located on chromosome 10 (MAL10-688956) and chromosome 12 (MAL13-1718319) that are associated with artemisinin resistance in *P. falciparum* parasites. Recently, another artemisinin resistance gene called kelch K13-propeller domain containing gene was reported (*19*). However, samples were not tested for this gene because the protocols to test for this marker at CDC were still under development. When the protocols are complete, all samples will be tested for this mutation.

Resistance was then classified into levels based on the number of accumulated mutations detected. Samples classified as sensitive demonstrated no mutations. For chloroquine, mefloquine, atovaquone, and artemisinin, resistance was defined as having detected any mutations. For pyrimethamine and sulfadoxine, resistance was defined as low if one mutation was detected, moderate if two mutations were detected, and high if three or more mutations were detected.

Results

General Surveillance

In 2012, CDC received 1,687 reports concerning cases of malaria among persons in the United States and its territories, representing a 12% decrease from the 1,925 cases reported with onset of symptoms in 2011. Although the number of cases decreased from 2012, overall there has been an increasing trend in the total number of cases since 1973. On average, 28.6 additional cases are reported in the United States each year since 1973 (Figure 1). In 2012, a total of 1,164 cases occurred among U.S. residents, 328 cases among foreign residents, and 195 cases among patients with unknown or unreported resident status (Table 1). The proportion of cases with unknown resident status decreased 6 percentage points from 2011 to 2012 (18% to 12%).

Plasmodium Species

Among the 1,687 cases reported in 2012, the infecting species of *Plasmodium* was identified and reported in 1,399 (83%) cases. Overall, the proportion of cases with complete reporting of species increased by 7% compared with 2011 (77%) (Table 2) (*5*); approximately half of the increase was a result of species identified by PCR as part of the drug resistance testing conducted at CDC. The identified species was corrected in six of 104 additional specimens submitted for drug resistance testing. *P. falciparum* and *P. vivax* comprised the majority of infections and were identified in 70% and 20% of 1,399 infected persons with species reported, respectively. The percentage of identified cases that were *P. vivax* decreased 8 percentage points from 2011. Among 1,326 cases for whom both the region of acquisition and the infecting species were known, *P. falciparum* accounted for 84% of infections acquired in Africa, 6% in Asia, 66% in Central America and the Caribbean, and 26% in South America (Table 3). In Central America and the Caribbean, the proportion of infections that were caused by *P. falciparum* decreased by 9 percentage points compared with 2011. This was likely a result of a decrease in the total number of cases reported from Haiti. Cases reported from Haiti decreased from 171 in 2010 to 72 in 2011 to 35 in 2012 (*5*,*20*). Infections attributed to *P. vivax* accounted for 6% acquired in Africa, 86% in Asia, 29% in Central America and the Caribbean, 65% in South America, and 71% in Oceania.

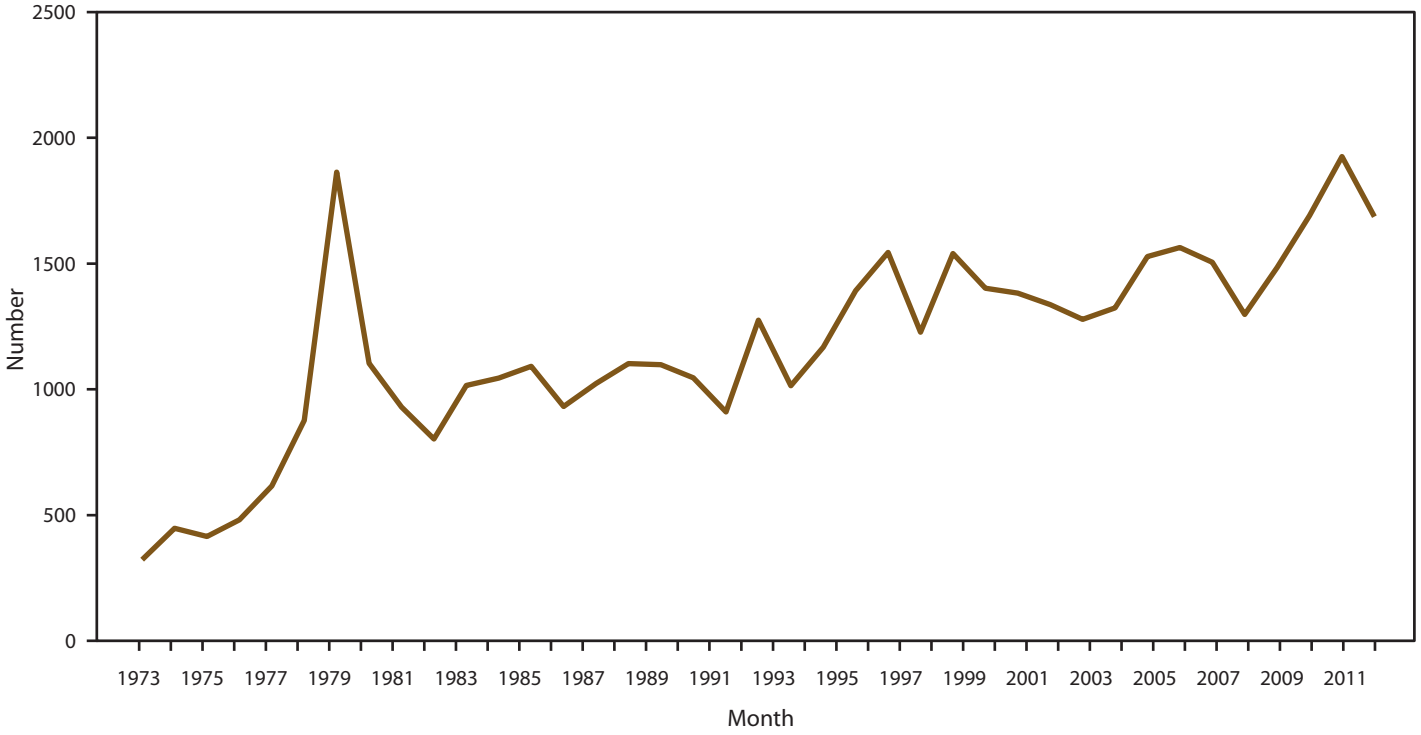
Region of Acquisition and Diagnosis

Among the 1,687 reported cases, one laboratory-acquired case, one nosocomial case, and two cryptic cases were reported. A total of 1,683 reported cases were classified as imported. Information on region of acquisition was missing for 147 (9%) imported cases, an improvement from 2011 (n = 268 [14%]). Of 1,536 imported cases for which the region of acquisition was known, 1,220 (79%) were acquired in Africa, 200 (13%) in Asia, 68 in the Caribbean and Central America (4%), 41 in South America (3%), and seven (0.5%) in Oceania (Table 3). Countries in West Africa[†] accounted for 809 (66%) cases acquired in Africa. Although the overall percent of cases acquired in West Africa remained unchanged from 2011, the distribution of cases within Africa changed; a decrease in the number of cases acquired in Ghana (156 in 2011 and 117 in 2012) was balanced out by increases in the number of cases acquired in Nigeria (213 in 2011 and 244 in 2012) and Cóte d'Ivoire (28 cases in 2011 and 48 in 2012). In Asia, the number of cases that were acquired in South Asia[§] decreased significantly from 330 in 2011 to 183 in 2012. Decreases were observed in all countries, with the largest decrease in India where there was a 42% reduction in the number of cases (223 in 2011 and 130 in 2012). The number of cases acquired in Afghanistan and Pakistan decreased substantially (100 in 2011 and 53 in 2012) for both Afghanistan and Pakistan combined). The 53% decrease in cases acquired in Afghanistan was a result of decreased cases among U.S. military personnel serving in Afghanistan. One

[†] Countries that are considered West Africa include: Benin, Burkina Faso, Cape Verde, Cóte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, Togo.

[§] Countries that are considered South Asia include: Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka (Ceylon).

FIGURE 1. Number of malaria cases among U.S. military personnel and U.S. and foreign civilians — United States, 1973-2012



third fewer cases were acquired from Central American and the Caribbean in 2012, attributed entirely to the 51% decrease in cases from Haiti (72 in 2011 and only 35 in 2012). The number of cases acquired in South America was not notably different from 2011 (35 in 2011 and 41 in 2012) (Table 3).

In the United States, eight reporting areas accounted for 50% of the 1,687 reported malaria cases: New York City (n = 235), California (n = 123), Maryland (n = 123), Texas (n = 110), Georgia (n = 72) Virginia (n = 72), New Jersey (n = 64), and Pennsylvania (n = 63) (Figure 2). The states with the greatest change in reported malaria cases in 2012 were Florida, which decreased by 48% from 2011 (120 in 2011 vs. 62 in 2012), and New Jersey, which decreased by 39% (104 in 2011 vs. 64 in 2012). The reduction in the number of cases in Florida was attributed to the reduction in cases from both India (16 in 2011 vs. two in 2012) and Haiti, which decreased for the second year in a row (25 cases in 2011 and 11 cases in 2012). Similarly, the reduction in cases in New Jersey was a result of the reduction in cases from India (22 in 2011 vs. eight in 2012) and Nigeria (21 in 2011 vs. eight in 2012).

Imported Malaria by Resident Status

Among the 1,489 imported malaria cases of known resident status, 1,161 (78%) occurred among U.S. residents and 328 (22%) among residents of other countries. Among the 1,161 imported malaria cases among U.S. residents, 921 (79%) were acquired in Africa, 111 (10%) in Asia, 50 in Central America and the Caribbean (4%), and 32 in South America (3%) (Table 4). This represents a significant increase in cases among U.S. residents who acquired malaria in Africa compared with 2011 (921 in 2012 vs 818 in 2011) and a trend observed since 2008. The number of cases acquired in Asia decreased significantly from 2011 (111 in 2012 vs. 218 in 2011) because of the reduction in the number of cases acquired in India. Cases acquired in the Americas among U.S. residents decreased significantly compared with 2011 (82 in 2012 vs. 113 in 2011) probably because of a decrease in cases that were acquired in Haiti that were reported in Florida. No significant change was noted in the cases acquired in Oceania between 2011 and 2012. Of the 328 imported cases among foreign residents, 230 (70%) were acquired in Africa, 72 (22%) in Asia, 14 (4%) in Central America and the Caribbean, and five (2%) in South America. The countries of acquisition with the most significant reduction in the reported number of cases of malaria in foreign residents were India, Ethiopia, and Eritrea, whereas cases acquired in Nigeria and Uganda increased among foreign residents. Among 268 foreign residents for whom purpose of visit to the United States was known, 73 (27%) were among VFRs and 141 (53%) occurred in recent immigrants or refugees, among whom 77% (n = 108) were from Africa.

TABLE 1. Number of malaria cases* among U.S. military personnel and U.S. and foreign civilians — United States, 1970-2012

Year	U.S. military personnel	U.S. civilians	Foreign residents	Status not recorded	Total
1970	4,096	90	44	17	**4,247**
1971	2,975	79	69	57	**3,180**
1972	454	106	54	0	**614**
1973	41	103	78	0	**222**
1974	21	158	144	0	**323**
1975	17	199	232	0	**448**
1976	5	178	227	5	**415**
1977	11	233	237	0	**481**
1978	31	270	315	0	**616**
1979	11	229	634	3	**877**
1980	26	303	1,534	1	**1,864**
1981	21	273	809	0	**1,103**
1982	8	348	574	0	**930**
1983	10	325	468	0	**803**
1984	24	360	632	0	**1,016**
1985	31	446	568	0	**1,045**
1986	35	410	646	0	**1,091**
1987	23	421	488	0	**932**
1988	33	550	440	0	**1,023**
1989	35	591	476	0	**1,102**
1990	36	558	504	0	**1,098**
1991	22	585	439	0	**1,046**
1992	29	394	481	6	**910**
1993	278	519	453	25	**1,275**
1994	38	524	370	82	**1,014**
1995	12	599	461	95	**1,167**
1996	32	618	636	106	**1,392**
1997	28	698	592	226	**1,544**
1998	22	636	361	208	**1,227**
1999	55	833	381	271	**1,540**
2000	46	827	354	175	**1,402**
2001	18	891	316	158	**1,383**
2002	33	849	272	183	**1,337**
2003	36	767	306	169	**1,278**
2004	32	775	282	235	**1,324**
2005	36	870	297	325	**1,528**
2006	50	736	217	561	**1,564**
2007	33	701	263	508	**1,505**
2008	19	510	176	593	**1,298**
2009	18	661	201	604	**1,484**
2010	46	1,085	368	192	**1,691**
2011	91	1,098	386	350	**1,925**
2012	43	1,121	328	195	**1,687**

* A case was defined as symptomatic or asymptomatic illness that occurs in the United States or one of its territories in a person who has laboratory-confirmed malaria parasitemia (microscopy or PCR), regardless of whether the person had previous attacks of malaria while in other countries. A subsequent attack of malaria occurring in a person is counted as an additional case if the demonstrated *Plasmodium* species differs from the initially identified species or if it is indicated as a relapsing infection demonstrating the same *Plasmodium* species as identified previously. If a subsequent attack of malaria occurring as a result of a drug resistance failure then the case is not counted as an additional case.

Seasonality of Malaria Diagnosed in the United States

The number of cases of *P. falciparum* reported in the United States peaked in January and August and occurred primarily among persons who indicated travel to Africa (Figure 3). These peaks likely correlated with peak travel times to African destinations related to winter and summer holidays (*21*). The number of *P. vivax* cases reported in the United States peaked in July, but that peak was much smaller than for *P. falciparum*. Most of those cases were among persons who indicated travel to Asia (most of whom had traveled to India).

Interval Between Arrival in the United States and Illness Onset

Among the 1,395 imported malaria cases with an identified *Plasmodium* species, the interval between both the date of arrival in the United States and onset of illness was known for 1,070 (77%) cases (Table 5). Onset of symptoms began before arrival in the United States in 132 (12%) cases; the remaining 938 (88%) patients experienced malaria symptoms on or after arrival to the United States. Onset of malaria symptoms occurred 0–29 days after arrival in 645 (81%) of the 797 *P. falciparum* cases and in 74 (42%) of the 178 *P. vivax* cases.

Imported Malaria Among U.S. Military Personnel

In 2012, a total of 43 cases of imported malaria were reported among U.S. military personnel, a significant decrease from the 92 reported in 2011. Region of travel was known for 29 cases and unspecified for 14 cases. Twenty military personnel reported travel to Afghanistan and seven to various regions in Africa. One each reported travel to Honduras and South Korea. Compared with 2011, fewer patients reported travel to Afghanistan and none reported travel to Haiti, likely as a result of changes in U.S. military presence in those regions (*22*). Information on infecting species was known for 29 cases; 23 cases were identified as *P. vivax* and six as *P. falciparum*. Among those 29 cases, 18 occurred in persons who reported having taken at least 1 dose of an appropriate drug for primary chemoprophylaxis; only four (22%) reported adhering to the regimen. Among the 23 patients infected with *P. vivax*, 15 reported treatment with primaquine to avoid future relapses. Only two of the 43 cases were classified as severe; both cases were caused by *P. vivax* infection.

Chemoprophylaxis Use Among U.S. Civilians

Information about chemoprophylaxis use and travel area was known for 984 (85%) of the 1,161 U.S. civilians who had imported malaria. Of these 984 persons, 336 (34%) had taken chemoprophylaxis. Among the 336 persons who reported taking malaria chemoprophylaxis, 89 (26%) did not

TABLE 2. Number of malaria cases, by *Plasmodium* species and year — United States, 2008-2012

Plasmodium Species	2008		2009		2010		2011		2012	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
P. falciparum	527	(40.6)	687	(46.3)	982	(58.1)	948	(49.3)	985	(58.4)
P. vivax	190	(14.6)	166	(11.2)	325	(19.2)	420	(21.8)	280	(16.6)
P. malariae	19	(1.5)	32	(2.1)	35	(2.1)	50	(2.6)	54	(3.2)
P. ovale	18	(1.4)	29	(2.0)	33	(1.9)	51	(2.6)	59	(3.5)
P. knowlesi	1	(0.1)	0	(0)	0	(0)	0	(0)	0	(0)
Mixed	8	(0.6)	13	(0.9)	13	(0.8)	21	(1.1)	21	(1.2)
Undetermined	535	(41.2)	557	(37.5)	303	(17.9)	435	(22.6)	288	(17.1)
Total	**1,298**	**(100)**	**1,484**	**(100)**	**1,691**	**(100)**	**1,925**	**(100)**	**1,687**	**(100)**

TABLE 3. Number of imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2012

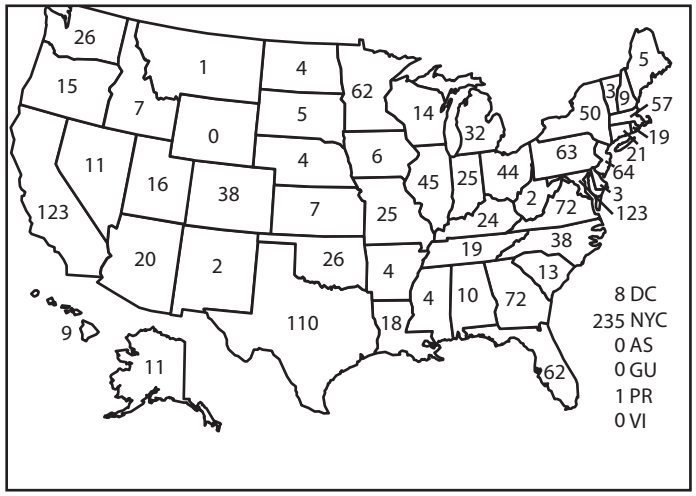
Country of Acquisition	*P. vivax*	*P. falciparum*	*P. malariae*	*P. ovale*	Mixed	Unknown	Total
Africa	**65**	**884**	**44**	**52**	**11**	**164**	**1,220**
Angola	0	4	1	0	0	0	**5**
Benin	0	7	0	0	0	0	**7**
Botswana	0	1	0	0	0	0	**1**
Burkina Faso	0	15	0	0	0	3	**18**
Burundi	0	1	0	1	0	0	**2**
Cameroon	0	21	1	2	0	7	**31**
Central African Republic	0	2	0	0	0	1	**3**
Chad	0	3	0	0	0	0	**3**
Congo, Republic of	1	15	0	2	0	8	**26**
Cóte d'Ivoire	1	41	3	0	0	3	**48**
Democratic Republic of Congo	0	4	0	0	0	3	**7**
Equatorial Guinea	2	7	0	0	0	0	**9**
Eritrea	3	0	0	0	0	1	**4**
Ethipoia	23	9	0	1	3	5	**41**
Gabon	0	0	1	0	0	0	**1**
Gambia	0	9	0	0	0	0	**9**
Ghana	2	95	2	4	2	12	**117**
Guinea	2	42	2	0	0	3	**49**
Kenya	1	29	4	5	1	6	**46**
Liberia	3	70	8	3	0	17	**101**
Madagascar	0	1	0	0	0	0	**1**
Malawi	1	5	0	0	0	0	**6**
Mali	1	15	0	0	0	3	**19**
Mauritania	3	1	0	0	0	2	**6**
Mozambique	0	3	1	0	0	0	**4**
Niger	0	3	0	0	0	1	**4**
Nigeria	8	189	5	9	0	33	**244**
Rwanda	0	2	1	1	0	0	**4**
Senegal	0	11	0	0	0	0	**11**
Sierra Leone	1	85	4	6	0	19	**115**
Somalia	0	1	0	0	0	1	**2**
South Africa	0	1	0	1	0	0	**2**
South Sudan	0	3	0	0	0	0	**3**
Sudan	5	39	0	3	0	15	**62**
Tanzania	0	10	1	2	1	0	**14**
Togo	0	23	0	0	0	0	**23**
Uganda	4	35	4	8	1	9	**61**
Zambia	0	6	0	0	1	0	**7**
Zimbabwe	0	1	0	0	0	0	**1**
Central Africa, unspecified	0	1	0	0	0	0	**1**
East Africa, unspecified	1	14	3	2	0	3	**23**
Southern Africa, unspecified	0	2	0	0	1	0	**3**
West Africa, unspecified	0	30	2	1	0	5	**38**
Africa, unspecified	3	28	1	1	1	4	**38**

Table continued on next page.

TABLE 3. (*Continued*) Number of imported malaria cases, by country of acquisition and *Plasmodium* species — United States, 2012

Country of Acquisition	*P. vivax*	*P. falciparum*	*P. malariae*	*P. ovale*	Mixed	Unknown	Total
Asia	**149**	**11**	**5**	**2**	**6**	**27**	**200**
Afghanistan	27	0	0	0	0	1	**28**
Burma (Myanmar)	2	0	0	0	0	0	**2**
Cambodia	1	0	0	0	0	0	**1**
India	94	9	5	1	4	17	**130**
Indonesia	0	1	0	0	0	1	**2**
Malaysia	3	0	0	0	0	0	**3**
Pakistan	17	0	0	1	1	6	**25**
South Korea	1	0	0	0	0	0	**1**
Thailand	4	1	0	0	1	0	**6**
Southeast Asia, unspecified	0	0	0	0	0	1	**1**
Asia, unspecified	0	0	0	0	0	1	**1**
Central America and the Caribbean	**17**	**39**	**2**	**0**	**1**	**9**	**68**
Bahamas	0	1	0	0	0	0	**1**
Costa Rica	1	0	0	0	0	1	**2**
Dominican Republic	1	5	0	0	0	1	**7**
El Salvador	0	0	0	0	0	1	**1**
Guatemala	6	0	1	0	0	0	**7**
Haiti	0	31	1	0	0	3	**35**
Honduras	5	0	0	0	1	2	**8**
Jamaica	0	2	0	0	0	1	**3**
Nicaragua	2	0	0	0	0	0	**2**
Panama	2	0	0	0	0	0	**2**
South America	**20**	**8**	**1**	**1**	**1**	**10**	**41**
Brazil	2	0	0	0	0	2	**4**
Colombia	2	1	0	0	0	1	**4**
Guyana	11	5	1	1	1	5	**24**
Peru	4	2	0	0	0	1	**7**
Suriname	0	0	0	0	0	1	**1**
South America, unspecified	1	0	0	0	0	0	**1**
Oceania	**5**	**0**	**1**	**0**	**1**	**0**	**7**
Papua New Guinea	5	0	1	0	1	0	**7**
Middle East	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Unknown	**23**	**40**	**1**	**4**	**1**	**78**	**147**
Total	**279**	**982**	**54**	**59**	**21**	**288**	**1,683**

FIGURE 2. Number of malaria cases*, by state in which the disease was diagnosed — United States, 2012



* (N=1,687).

report specific drug type taken. Of the remaining 247 persons, 200 (81%) had taken a CDC-recommended medication and 26 (11%) had taken a medication that is not recommended by CDC for the area visited. Of the 200 who reported taking CDC-recommended chemoprophylaxis, 52 (26%) had taken mefloquine, 99 (50%) had taken doxycycline, 43 (22%) had taken atovaquone/proguanil, and none took chloroquine or primaquine. Six additional patients reported taking more than one CDC-recommended malaria chemoprophylaxis medication for the specific travel region. Information about infecting species was available for 176 (88%) patients who had taken a recommended antimalarial drug and was undetermined for the remaining 24 patients. Moreover, among the 182 who reported taking CDC-recommended chemoprophylaxis and for whom adherence was known, 119 (65%) reported nonadherence (i.e., missed doses).

Cases of P. vivax *or* P. ovale *After Recommended Prophylaxis Use.* Among the 176 patients who took chemoprophylaxis appropriately and had information on infecting species, 33 (19%) cases were

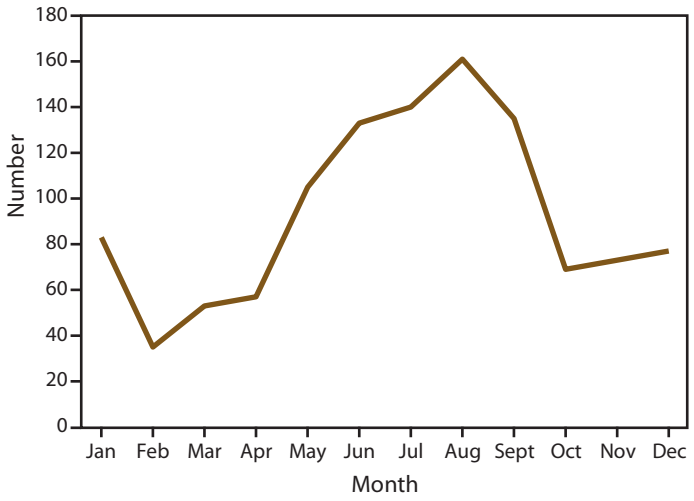
TABLE 4. Number and percentage of imported malaria cases among U.S. and foreign residents, by region of acquisition — United States, 2012

	United States		Foreign		Total	
Area or region	No.	(%)	No.	(%)	No.	(%)
Africa	921	(79.3)	230	(70.1)	**1151**	**(77.3)**
Asia	111	(9.6)	72	(22.0)	**183**	**(12.2)**
Central America/ Caribbean	50	(4.3)	14	(4.3)	**64**	**(4.3)**
South America	32	(2.8)	5	(1.5)	**37**	**(2.5)**
Oceania	6	(0.5)	1	(0.3)	**7**	**(0.5)**
Unknown	41	(3.5)	6	(1.8)	**47**	**(3.2)**
Total	**1,161**	**(100)**	**328**	**(100)**	**1,489**	**(100)**

caused by *P. vivax*, and 11 (6%) cases were caused by *P. ovale*. Of the 44 cases of *P. vivax* or *P. ovale*, information on 15 cases was insufficient (i.e., missing data regarding symptom onset or return date from travel) to assess if this was an acute infection or a relapse infection. Onset of symptoms for 17 reported cases occurred >45 days after the patient arrived in the United States. The clinical features of these cases are consistent with relapsing infections and do not indicate primary prophylaxis failures. Twelve cases occurred ≤45 days after the patient returned to the United States; these cases are consistent with acute infection and could indicate primary prophylaxis failures. Among the 12 cases, six patients were nonadherent with their malaria chemoprophylaxis regimen, and one patient did not provide adherence information. The remaining five patients reported adherence with an antimalarial chemoprophylaxis regimen. Two patients who reported adherence to the chemoprophylaxis regimen had traveled to Afghanistan and had both taken doxycycline for malaria chemoprophylaxis. Two others traveled to Africa; one took doxycycline and the other took mefloquine for malaria chemoprophylaxis. The patient who traveled to Papua New Guinea was a missionary who had taken doxycycline for malaria chemoprophylaxis. Possible explanations for infection in these patients include inappropriate dosing, unreported nonadherence, malabsorption of the drug, an early relapse from hypnozoites established at the start of the trip, or possibly emerging parasite resistance.

Cases of P. falciparum *or* P. malariae *After Recommended Prophylaxis Use.* The 176 cases of malaria reported among persons who had taken a recommended antimalarial drug for chemoprophylaxis included 118 cases of *P. falciparum*, eight cases of *P. malariae,* and six cases with mixed infection. Of the 118 *P. falciparum* cases, 117 (99%) were acquired in Africa and one (1%) in the Asia. Seventy-seven (65%) of the 118 *P. falciparum* patients reported nonadherence to the antimalarial drug regimen, 29 (25%) patients reported adherence, and 12 patients had no adherence information available. Of the 29 cases in which patients reported adherence with antimalarial chemoprophylaxis, one traveled to Indonesia and took doxycycline for malaria chemoprophylaxis and

FIGURE 3. Number of imported malaria cases among U.S. residents, by month of symptom onset, 2012



28 had traveled to Africa. Of those who traveled to Africa, 15 patients took mefloquine, seven took doxycycline, and six took atovaquone/proguanil. Of the eight *P. malariae* cases, three reported adherence to the antimalarial drug regimen, all of whom had traveled to Africa (two took atovaquone/proguanil and one took doxycycline).

Patients with a Recent History of Malaria

Of the 1,683 imported cases, data on history of malaria was known for 1,222 (73%) cases; 262 (21%) patients reported a history of a malaria infection during the preceding 12 months. Among the 262 cases, 112 were *P. falciparum* (43%), 74 (28%) were *P. vivax*, nine (3%) were *P. malariae*, 22 (8%) were *P. ovale*, seven (3%) were mixed infections, and 38 (15%) reported no species. One person had malaria three times in 2012, with a different species each time. A total of 12 probable relapses were identified based on onset date, date of previous infection, and previous infection species type: nine *P. vivax* cases and three *P. ovale* case. Among the 12 relapses, five patients (four were *P. vivax* infections and one was a *P. ovale* infection) subsequently received primaquine as part of treatment to avoid future relapses.

Purpose of Travel

Purpose of travel to regions in which malaria is endemic was reported for 908 (81%) of the 1,118 U.S. civilians with imported malaria (Table 6). Of the 908 who reported purpose of travel, 603 (66%) were VFRs, 80 (5%) were missionaries, and 92 (6%) were traveling for business. The proportions of business travelers increased from 2011 (7% to 10%), and the proportion of military travelers decreased (7% in 2011 vs. 4% in 2012).

TABLE 5. Number and percentage of imported malaria cases, by interval between date of arrival in the United States and onset of illness and *Plasmodium* species[*] — United States, 2012

	P. vivax		*P. falciparum*		*P. malariae*		*P. ovale*		Mixed		Total	
Interval (days)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
<0[†]	11	(6.2)	113	(14.2)	4	(10.0)	2	(5.0)	2	(13.3)	132	(12.3)
0–29	74	(41.6)	645	(80.9)	18	(45.0)	13	(32.5)	6	(40.0)	756	(70.7)
30–89	35	(19.7)	28	(3.5)	12	(30.0)	11	(27.5)	1	(6.7)	87	(8.1)
90–179	24	(13.5)	7	(0.9)	3	(7.5)	9	(22.5)	2	(13.3)	45	(4.2)
180–364	27	(15.2)	3	(0.4)	2	(5.0)	4	(10.0)	4	(26.7)	40	(3.7)
≥365	7	(3.9)	1	(0.1)	1	(2.5)	1	(2.5)	0	(0.0)	10	(0.9)
Total	**178**	**(100)**	**797**	**(100)**	**40**	**(100)**	**40**	**(100)**	**15**	**(100)**	**1,070**	**(100)**

* Persons for whom *Plasmodium* species, date of arrival in the United States, or date of onset of illness is unknown are not included.
† Cases in this row are in patients who had onset of illness before arriving in the United States.

TABLE 6. Number* and percentage of imported malaria cases among U.S. civilians, by purpose of travel at the time of acquisition — United States, 2012

Category	No.	(%)
Visiting friends and relatives	603	(53.9)
Tourist	32	(2.9)
Missionary or dependent	80	(7.2)
Business representative	92	(8.2)
Student or teacher	47	(4.2)
Air crew or sailor	4	(0.4)
Peace Corps	6	(0.5)
Other	44	(3.9)
Unknown	210	(18.8)

* N = 1,118.

Malaria by Age

Among the 1,663 cases among patients for whom age was known, 257 (15%) occurred in persons aged <18 years, 1,334 (80%) in persons aged 18–64 years, and 72 (4%) in persons aged ≥65 years. Although the majority of cases occur in persons aged 18–64 years, pediatric cases are of particular interest because the preventive care of most children is determined by parents or guardians. Among the 257 cases among persons aged <18 years, 130 (51%) occurred among U.S. civilian children, 106 (41%) occurred among children of persons categorized as having a foreign resident status at the time their malaria infection was acquired, and 21 (8%) occurred among children of unknown resident status. Of the 130 cases among U.S. civilian children, eight (6%) were aged <2 years, 17 (13%) were aged 2–4 years, 58 (45%) were aged 5–12 years, and 47 (36%) were aged 13–17 years. A total of 118 (92%) of the cases among U.S. civilian children for whom country of exposure was known were attributable to travel to Africa. Among the 105 U.S. civilian children for whom reason for travel was known, 91 (87%) were VFRs, seven (7%) were traveling for educational purposes, five (5%) were traveling for missionary work, one (1%) was a tourist, and one (1%) accompanied their parent/guardian on a business trip. Of the 117 children for whom chemoprophylaxis information was known, 46 (39%) were reported as having taken chemoprophylaxis, of whom 21 (46%) had taken an appropriate regimen; however, only five (24%) of these 21 patients reported adherence.

Hospitalization

Information on hospitalization was reported for 87% (n = 1,473) of all cases. Among those persons, 69% (n = 1,023) were hospitalized. The majority of those cases were *P. falciparum* (n = 664 [65%]), of which 159 (24%) were considered severe. The second largest proportion of cases were identified as *P. vivax* (n = 168 [16%]) infections. The majority of hospitalized *P. vivax* patients had uncomplicated malaria infections; however, 12% (n = 20) were severe.

Treatment in Uncomplicated Imported Malaria Cases

Of the 1,453 imported cases of uncomplicated malaria in 2012, information on treatment medicines was available for 1,123 (77%). Of these, 680 (61%) were *P. falciparum*, 209 (19%) *P. vivax*, 34 (3%) *P. malariae*, 45 (4%) *P. ovale*, 17 (2%) mixed cases, and 138 (12%) where species type was unknown or not reported. *The CDC Guidelines for Treatment of Malaria in the United States* (*5*), herein referred to as the CDC Guidelines for Treatment, was used to determine whether the medicines listed for treatment were appropriate.

Of the 1,123 patients with uncomplicated malaria with available information on treatment, 925 (82%) were treated appropriately according to the CDC Guidelines for Treatment, and 198 (18%) patients received inappropriate treatment. The percent of patients with uncomplicated disease who were treated appropriately was unchanged from 2011. Among the patients who were treated appropriately, 167 (18%) indicated taking

other antimalarial drugs in addition to those recommended by CDC guidelines. Because the CDC surveillance report form does not record the sequence of treatment events, it is difficult to understand and characterize the intended purpose of additional antimalarial treatment drugs. Therefore, for the purpose of this report, these 167 patients were considered to be treated appropriately. Among the 198 inappropriately treated patients, 13 (7%) had received the recommended chemoprophylaxis but subsequently had inappropriately received the same drug for treatment. Antimalarial drugs used for treatment should differ from the drugs received for chemoprophylaxis because of the potential for toxicity and reduced efficacy.

Adequacy of treatment varied by species. For the 680 *P. falciparum* cases, 576 (85%) patients were treated appropriately according to CDC Guidelines for Treatment, of which 118 (20%) received additional antimalarial drugs. The 104 *P. falciparum* cases that were treated with an inappropriate treatment regimen included seven pregnant patients. Among the 34 *P. malariae* cases, 29 (85%) patients were treated appropriately according to CDC Guidelines for Treatment, of whom two (7%) received other antimalarial drugs in addition to those recommended by CDC. Five (15%) patients infected with *P. malariae* were treated with an inappropriate treatment regimen.

Among the 209 patients with *P. vivax* cases for whom treatment information was reported, 178 (85%) were treated with an appropriate antimalarial drug to address their acute infection, of which 11 (6%) received other antimalarial drugs in addition to those recommended by CDC. Of the 178 *P. vivax* cases who received an appropriate treatment for their acute infection, less than half (n = 79 [44%]) were also treated with primaquine for relapse prevention, which CDC recommends for all cases of mosquito-acquired *P. vivax* infections. Among the 45 patients with *P. ovale* for whom treatment information was reported, 32 (71%) were treated with an appropriate antimalarial drug to address their acute infection, of whom one (3%) received other antimalarial drugs in addition to those recommended by CDC. Of the 32 *P. ovale* patients who received an appropriate treatment for their acute infection, nine (28%) also were treated with primaquine for relapse prevention. Among the 17 mixed cases for whom treatment information was reported, 12 (71%) patients were treated appropriately according to CDC Guidelines for Treatment. Eight of those received other antimalarial drugs in addition to the CDC-recommended regimens. Of the five mixed cases that were not treated appropriately, four included at least one relapsing species, and only one (25%) received primaquine.

According to the CDC Guidelines for Treatment, when species is unknown, a treatment regimen for a *P. falciparum* infection should be used to presumptively treat infection. Among the 138 cases where species was unknown, 98 (71%) patients were treated appropriately according to CDC Guidelines for Treatment, of whom 27 (28%) received other antimalarial drugs in addition to those recommended by CDC. Forty (29%) patients received an inappropriate treatment regimen. Incomplete reporting of species and treatment medications might affect whether the case is classified as having been treated appropriately or not.

Severe Malaria

Among the 1,687 reported cases, 231 (14%) were classified as severe malaria, including six cases in which patients died. Most (78%) severe cases occurred in persons aged ≥18 years, and 22% occurred in children aged <18 years, six (12%) of whom were aged <3 years. Age was not reported for four (2%) patients. No association was found between severe disease and age or resident status. Among the 217 cases in patients with known resident status, 166 (77%) were U.S. residents. The predominant species among the severe cases was *P. falciparum* (n = 173 [75%]), which is not significantly different than 2011 (n = 198 [73%]).

Where information on prophylaxis was known (n = 200), 52 (26%) persons reported taking a recommended chemoprophylaxis; however, only seven reported adherence to the drug regimen, including three who took doxycycline, two who used mefloquine, and two who took atovaquone/proguanil. No significant association was observed between severe disease and use of prophylaxis. Although some patients had multiple clinical complications associated with an infection, the largest proportion of patients experienced severe anemia (22%), followed by renal failure (16%), cerebral malaria (11%), ARDS (7%), and jaundice (2%). Patients with severe disease were more likely to receive inappropriate treatment than those with uncomplicated disease. Among the 231 severe cases, 109 (47%) patients were treated with quinidine and 86 (37%) were treated with an oral antimalarial drug. Twenty-six (11%) patients were treated with intravenous artesunate provided by CDC through an investigational new drug protocol. Patients diagnosed with uncomplicated malaria can be effectively treated with oral antimalarial drugs. However, patients who are considered to have severe disease should be treated aggressively with parenteral antimalarial therapy (*23*).

No significant difference was observed in the number of days from date of return to date of hospitalization between severe and uncomplicated *P. falciparum* cases (15.7 days for severe and 14.7 days for uncomplicated). In addition, no significant difference was observed in the length of time between date of onset and date of hospitalization between severe and uncomplicated *P. falciparum* cases (5.7 days for severe and

5.8 days for uncomplicated), unlike in 2011 when severe cases had significantly longer intervals between date of onset and date of hospitalization than uncomplicated cases (5.7 days for severe and 2.2 days for uncomplicated) (*5*). The dates on which patients first saw a medical provider were not collected, so time from first provider encounter to hospitalization could not be examined.

Among patients for whom reason for travel was known, most (55%) of the severe cases were in VFRs (comparable with 2011), of whom 65% specified acquisition from West Africa; 75% of severe cases were identified as *P. falciparum* infections. None of the severe cases were acquired in Haiti, a significant decrease from 2011 when 5% of the severe cases were acquired in Haiti. In Haiti, virtually all malaria is caused by *P. falciparum*.

A significant association between travel for business and severe malaria was identified, unlike in 2011 when no association was found. Among patients who traveled for business, 22% (26 of 118) developed severe disease, compared with 14% (148 of 1,088) of those traveling for other purposes. No significant association was found between travel for missionary work and severe malaria in 2012, whereas in 2011 there was a significant association.

Malaria During Pregnancy

A total of 32 cases of malaria were reported among pregnant women in 2012, representing 6% of cases among all women (n = 523). The number of pregnant women with malaria did not change significantly from the 37 cases reported in 2011. In addition, no significant differences were noted among pregnant women with malaria compared with nonpregnant women in terms of species type, reason for travel, or region of infection acquisition. Of the 32 cases among pregnant women, five (16%) cases were severe. Among the 30 cases for whom *Plasmodium* species type was known, 24 (80%) were *P. falciparum* infection, including four in patients who presented with severe malaria. Four (13%) were *P. vivax*, none of which had severe malaria; one case was identified as a *P. ovale* infection, and one case was a mixed infection. Two cases did not have a species reported, and one of those was a severe case. Twelve (38%) cases occurred among U.S. civilians, all of whom reported travel to Africa. Among the 10 U.S. civilian pregnant women with known reason for travel, 90% were VFRs. Of the 12 cases of malaria reported among U.S. civilian pregnant women, two reported taking malaria chemoprophylaxis. One reported adherence to mefloquine, and the other did not report which chemoprophylaxis was taken. No information was available on birth outcomes.

Drug Resistance

In 2012, a total of 104 blood samples were sent to CDC and tested for genetic markers associated with resistance to antimalarial drugs. Thirty-two state and local health departments submitted samples for testing. Species of malaria parasite was confirmed by PCR to be *P. falciparum* in 69 (66%) samples, followed by *P. vivax* (14 [13%]), *P. ovale* (12 [12%]), and *P. malariae* (nine [9%]). PCR determined or corrected the species for 45 (43%) samples submitted (Table 7). Of the *P. falciparum*-positive samples with results, 53 (82%) had genetic polymorphisms associated with pyrimethamine drug resistance, 61 (94%) with sulfadoxine resistance (23 with low and 38 with moderate resistance genotypes), 29 (45%) with chloroquine resistance, one (2%) with mefloquine resistance, two (3%) with atovaquone resistance, and none with artemisinin resistance (Table 8). One case showed the presence of both chloroquine-resistant and chloroquine-sensitive *P. falciparum* parasites. Of the patients that reported location of recent travel, most reported recent travel to Africa. Two of the samples tested were for the two cryptic cases in 2012 who reported no recent travel outside of the United States. In addition, one case of mefloquine prophylaxis failure was documented in a traveler from Ivory Coast infected with mefloquine-resistant *P. falciparum* and two cases involving U.S. workers returning from Nigeria in whom atovaquone/proguanil resistance developed during treatment (*24*).

Selected Malaria Case Reports

Triple infection

Case. In June 2012, a man aged 22 years returned to the U.S. from a 3-week trip to a remote village in Uganda where he reported taking no prophylaxis or use of mosquito netting and reported experiencing numerous mosquito bites. The day

TABLE 7. Comparison of malaria species reported on specimen submission form and polymerase chain reaction (PCR) results — United States, 2012

Species reported on specimen submission form	Species identified by PCR				
	P. falciparum	*P. vivax*	*P. ovale*	*P. malariae*	Total
P. falciparum	46	0	0	2	**48**
P. vivax	0	7	1	1	**9**
P. ovale	1	0	5	1	**7**
P. malariae	0	0	0	1	**1**
Unknown/missing	22	7	6	4	**39**
Total	**69**	**14**	**12**	**9**	**104**

TABLE 8. Antimalarial drug resistance test* results among *Plasmodium falciparum* specimens by drug and region of malaria acquisition — United States, 2012

	Region							
Resistance test	**Africa**	**Asia**	**Central American and the Caribbean**	**South America**	**Oceana**	**Middle East**	**Unknown**	**Total**
Pyrimethamine (No.)	**60**	**0**	**2**	**1**	**0**	**0**	**2**	**65**
Sensitive (%)	(17)	(0)	(100)	(0)	(0)	(0)	(0)	**(18)**
Low level resistance (%)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	**(0)**
Moderate level resistance (%)	(13)	(0)	(0)	100	(0)	(0)	(0)	**(14)**
High level resistance (%)	(70)	(0)	(0)	(0)	(0)	(0)	(100)	**(68)**
Sulfadoxine (No.)	**60**	**0**	**2**	**1**	**0**	**0**	**2**	**65**
Sensitive (%)	(3)	(0)	(100)	(0)	(0)	(0)	(0)	**(6)**
Low level resistance (%)	(37)	(0)	(0)	(0)	(0)	(0)	(50)	**(35)**
Moderate level resistance (%)	(60)	(0)	(0)	(100)	(0)	(0)	(50)	**(59)**
High level resistance (%)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	**(0)**
Chloroquine (No.)	**60**	**0**	**2**	**1**	**0**	**0**	**2**	**65**
Sensitive (%)	(55)	(0)	(100)	(0)	(0)	(0)	(50)	**(55)**
Resistant (%)	(45)	(0)	(0)	(100)	(0)	(0)	(50)	**(45)**
Mefloquine (No.)	**60**	**0**	**2**	**1**	**0**	**0**	**2**	**65**
Sensitive (%)	(98)	(0)	(100)	(100)	(0)	(0)	(100)	**(98)**
Resistant (%)	(2)	(0)	(0)	(0)	(0)	(0)	(0)	**(2)**
Atovaquone (No.)	**60**	**0**	**2**	**1**	**0**	**0**	**2**	**65**
Sensitive (%)	(97)	(0)	(100)	(100)	(0)	(0)	(100)	**(97)**
Resistant (%)	(3)	(0)	(0)	(0)	(0)	(0)	(0)	**(3)**
Artemisinin (No.)	**52**	**0**	**2**	**0**	**0**	**0**	**2**	**56**
Sensitive (%)	(100)	(0)	(100)	(0)	(0)	(0)	(100)	**(100)**
Resistant (%)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	**(0)**

* Sensitive is defined as having no mutations. For chloroquine, mefloquine, atovaquone, and artemisinin testing, resistance is defined as having any mutations. For pyrimethamine and sulfadoxine testing, resistance is defined as low (one mutation), moderate (two mutations), or high (three or more mutations).

after he returned to the United States, he presented to a hospital experiencing headache, myalgia, nausea, weakness, and aches and pains in his muscles and joints. He was hospitalized for 2 days. *P. falciparum* parasites were identified on his thick and thin smears and confirmed by PCR. He was treated with quinine and doxycycline. Approximately 6 weeks later, he again began experiencing symptoms consistent with malaria. He sought care and was hospitalized for 5 days. Doctors at this hospital were concerned about possible treatment failure because the patient had been treated for malaria already and had not left the United States since returning from Uganda 6 weeks earlier. Blood films and blood samples were sent to CDC for identification and drug resistance testing. *P. malariae* was identified on the blood smear and confirmed by PCR. The patient was treated and discharged from the hospital. Three months later, despite not traveling outside of the country since returning from Uganda earlier that year, the patient became sick again. He experienced side pain, fever, chills, and shakes. He was admitted to the hospital for 4 days and was treated with mefloquine and primaquine. CDC was asked to assist with the identification and drug resistance testing. *P. ovale* was identified by blood smear and confirmed by PCR. Because molecular markers associated with drug resistance to *P. ovale* are not known, no further molecular characterization was done. The patient recovered completely.

Laboratory-acquired Malaria

Case. In March 2012, a laboratory employee who worked with malaria-infected mosquitoes began experiencing onset of an illness including malaise and chills. He sought medical consultation for what was suspected as a bacterial urinary tract infection. Five days later, he developed a fever of 103.0°F (39.4°C). In addition to the blood tests being done for the suspected infection, the patient prepared a blood smear and had it examined by a co-worker. A suspect parasite was identified on smear, and the patient sought care at his occupational health clinic. Parasites were not seen on a subsequent blood smear; however, *P. vivax* DNA was detected by PCR. Further molecular genotyping indicated that the source of the infection was the same strain (i.e., had the identical genetic sequence) that was used by the patient in his laboratory during November 2010–January 2011. The laboratory employee reported having traveled to the Bahamas four months before onset of his illness. Although sporadic outbreaks of malaria in the Bahamas as a result of introduction of *P. falciparum* have been reported, there are no reports of *P. vivax* being present. Because there was no report of international travel to areas that are endemic for vivax malaria or no receipt of blood or blood products, and because the strain of the laboratory parasite was identical to the infecting strain, this case was considered a

laboratory-acquired infection. The employee had no recognized laboratory accident and, as a result, it is presumed that the infection was acquired via the bite of an infective mosquito. He was treated with chloroquine and primaquine and recovered completely. An investigation of the laboratory determined that all appropriate procedures for handling infected mosquitoes were in place and seemed to have been followed by laboratory staff. Measures to capture escaped mosquitoes, such as UV light traps, were noted and in good operating condition. To augment safety procedures, higher risk laboratory activities (e.g., mosquito dissections) were restricted to a separate secure laboratory to reduce distractions and the potential for inadvertent exposures.

Nosocomial Malaria

Case. In March 2012, a woman aged 41 years who was resident of a long-term care facility with no recent international travel was admitted to a hospital with chills, nausea, and a fever to 104°F (40°C). She was found to have hemolytic anemia and thrombocytopenia. A blood smear revealed infection with *P. falciparum* and a parasitemia of 7.5%. She was treated successfully with clindamycin and quinidine. An investigation was initiated to evaluate the source of her infection. All conceivable malaria risk factors that involved exposure within the few weeks before she became ill were considered during the investigation (i.e., travel to an area where malaria is endemic, transfusion with contaminated blood or blood products, nonsterile intravenous drug use with another person who was parasitemic, local mosquito transmission, and nosocomial transmission during her hospitalization two weeks earlier for a laparoscopic cholecystectomy).

The patient immigrated to the United States from Guyana in the mid-1990s but had not traveled for many years. During her laparoscopic cholecystectomy, she experienced minimal blood loss, had stable hemoglobin levels during that hospitalization, and did not receive any blood or blood products. Her medical chart confirmed that she did not have a history of intravenous drug use. No evidence of mosquito activity was detected in either her residence or the hospital where she had her surgery. To assess whether the infection was already present at the time of her surgery, retained clinical specimens from that procedure were tested for the presence of malaria antigens by immunohistochemistry and for genetic material by PCR, both of which were negative.

A review of hospital records of patients admitted during the same time as the cholecystectomy identified a female patient aged 42 years with malaria acquired in Nigeria. She was admitted to the same floor only three rooms away from the other patient. A review of hospital records and procedures did not identify evidence of how the nosocomial transmission occurred. However, analysis of selected polymorphic regions of MSP-1 and MSP-2 genes and neutral microsatellite repeat markers indicated that the malaria parasites from both patients were likely identical, with matching genetic backgrounds at well-described locations in the *P. falciparum* genome. Investigators concluded that nosocomial transmission occurred during the time in which both women were hospitalized.

Cryptic Cases

Two cases reported in 2012 were categorized as cryptic malaria because epidemiologic investigations did not identify a plausible mode of acquisition.

Case 1. In September 2012, a woman aged 24 years developed fever, chills, diarrhea, myalgia, splenomegaly, and headaches. She reported no travel outside of the United States since moving from Liberia in 1999. Microscopy demonstrated that she was infected with *P. falciparum* with a 2% parasitemia. She was treated with atovaquone-proguanil and recovered. The state health department reviewed their vector-control data to determine whether the explanation of local transmission could be supported and found no data to support local transmission in the area where the patient lived. Further molecular testing conducted at CDC demonstrated that the parasite's molecular profile was similar to infections known to be circulating in West Africa. Despite this, the origin of the infection remains undetermined.

Case 2. In August 2012, a man aged 63 years who was originally from Haiti developed a febrile illness. After 3 weeks, he sought medical attention and infection with *P. falciparum* was diagnosed. He worked as a farm hand and stated that he had not been out of the country in more than 10 years. CDC confirmed the diagnosis using PCR. The state health department reviewed their vector-control data to determine whether the explanation of local transmission could be supported and found no data to support local transmission in the area where the patient lived. Further molecular testing indicated that the parasite had genetic fingerprints based on microsatellite repeat data that was similar to Haitian parasite population. In addition, the molecular profile of this parasite was genetically identical to two samples from infections known to be recently circulating in Haiti, further suggesting the potential origin of this parasite was from Haiti.

Fatal Cases

Case 1. In early October 2012, a man aged 56 years originally from Mali returned to the United States following a 6 month stay visiting friends and relatives. It is not known if he used one of the recommended malaria chemoprophylaxis regimens. Two weeks after returning he was found by his housemates to have developed confusion and a decreased level of alertness. They were not aware of any additional recent illness, specifically

reporting no recent fever, chills, or vomiting. While in the emergency department, he was noted to be tachycardic, tachypneic, and hypertensive. He progressed into respiratory failure and was intubated. A blood smear revealed infection with *P. falciparum* with an 8% parasitemia. Treatment with doxycycline and quinidine were started. However, the next morning he developed bradycardia and went into cardiac arrest. Resuscitation attempts were unsuccessful, and he died on October 19, 2012.

Case 2. In May 2012, a woman aged 31 years returned to the United States after a 2-week trip to Ghana for missionary work. She had not used malaria chemoprophylaxis while in Ghana. Approximately 3 days after returning to the United States she was brought into the emergency department by ambulance complaining of a febrile illness. She had no significant past medical history. At that time, she was alert and had a normal neurologic examination. A blood smear was positive for *P. falciparum* parasites at 25% parasitemia and she had thrombocytopenia and a mild lactic acidosis but no additional signs of severe malaria. She was started on oral quinine and doxycycline. The next morning, she still had a normal neurologic examination and repeat parasitemia was 29%. However, that afternoon she was found to be unresponsive. Her medications were switched from oral antimalarials to intravenous quinidine and doxycycline, and then to artesunate. She was also given an exchange transfusion. Her parasitemia dropped to 2%–3%, but she remained unresponsive and a head CT showed evidence of some cerebral edema. She was intubated to protect her airway and had a ventriculostomy. A repeat blood smear was negative on the third day of her hospitalization, but she remained unresponsive. The following day, scans of her head showed severe cerebral edema with brainstem herniation. She was declared brain dead, support was withdrawn, and she died on May 8.

Case 3. In April 2012, a week after returning from a 1-month trip to Ghana to visit friends and relatives, a woman age 37 years from Ghana residing in the United States developed a fever and sought medical attention. She had not taken any malaria chemoprophylaxis while on her trip. She was treated with empiric antibiotics; no tests for malaria were conducted. A few days later, with no resolution of symptoms, she returned to her doctor's office and was found to be hypotensive and dehydrated. She was transported to the emergency department where she was received a diagnosis of *P. falciparum* malaria with a parasitemia >5%. She was started on intravenous quinidine and doxycycline. Approximately 48 hours later, she developed ARDS and was intubated. Her lung injury appeared to have been extensive, and she was unable to be weaned from the ventilator. She suffered complications of a prolonged intensive care unit stay, including a pneumothorax with chest tube placement. Eventually she was unable to maintain adequate oxygenation despite maximum ventilator support and she died 7 weeks after admission on June 22.

Case 4. In May 2012, a woman aged 38 years returned to the United States from a 6-week trip to Nigeria where she was visiting family. She had not used malaria chemoprophylaxis, which is recommended for travelers to Nigeria. She had been diagnosed with breast cancer in 2010, which continued to progress despite several surgical and medical interventions. She went directly to a hospital upon her return with a chief complaint of severe pain in the right breast. A large ulcerating tumor mass was discovered on her chest wall that appeared to be infected. She remained hospitalized for approximately a month until her death on June 4. She experienced numerous complications during her hospitalization including pneumonia, empyema with chest tube placement, *Pseudomonas* urinary tract infection, ARDS, lactic acidosis and shock in addition to her diagnosis of *P. falciparum* malaria with a 2% parasitemia. She was initially treated with oral malarone and then intravenous artesunate because of concerns that she was not able to absorb oral medications appropriately. On the morning of June 4, she developed cardiac arrest, and resuscitation efforts were unsuccessful.

Case 5. In late May 2012, a woman aged 60 years was admitted to the hospital after a major motor vehicle crash. She had been the driver and was found ejected from the vehicle and unconscious. She was intubated by paramedics before arriving at the hospital. She had major head trauma, a pneumothorax, an aortic tear, and a ruptured spleen. She was surgically stabilized, including a splenectomy, and received multiple blood transfusions. Initial laboratory work revealed thrombocytopenia. She became febrile in the evening of her first day of hospitalization. On hospital day 2, malaria parasites were incidentally noted on her CBC and determined to be *P. falciparum* with a parasitemia of 37%. It was subsequently determined that the patient had recently returned from a 2-month trip to Liberia. It was not known if she was taking malaria chemoprophylaxis. She had reported that she had run out of her medicines while in Liberia, but it was unclear if this referred to her chronic medicines or malaria chemoprophylaxis. According to her son, she had been feeling poorly before the car crash. Quinidine and doxycycline were added to her medications and she was also treated with exchange transfusion. Her parasitemia decreased rapidly to <1% by 24 hours after those interventions and her smear was negative after 5 days. Two days later, it was determined that she was not experiencing a neurologic recovery and the decision was made to withdraw support. She died on June 7. Although autopsy results attributed her death to the motor vehicle accident, the crash might have been attributed to cerebral malaria.

Case 6. In June 2012, a 55 year-old male resident of South Africa arrived in the United States on business. He reported visiting Angola en route to the United States, but further details of his travel in Angola were not reported. He began feeling unwell the day after arriving in the United States but did not seek care at that time. Two weeks later, he noticed that his urine was dark and then he stopped producing urine entirely. He did not seek medical care until 2 days later when he was found on the floor of his hotel room and was taken by ambulance to an emergency department. He was arousable and able to provide a brief travel history. He received a diagnosis of severe falciparum malaria (4.6% parasitemia) with anuric renal failure, jaundice, and lactic acidosis. He was given 9 liters of normal saline and a single dose of intravenous doxycycline and transferred to another hospital for exchange transfusion and dialysis. At the second hospital, the patient was intubated and intravenous quinidine was ordered. It is unclear if he ever received any. The patient developed cardiac arrest (pulseless electrical activity and then asystole) during the exchange transfusion. Resuscitation was unsuccessful and he was declared dead that evening.

Discussion

In 2012, a total of 1,687 malaria cases were reported in the United States, representing a 12% decrease from 2011 (*5*) when a 40-year high of 1,925 cases were reported. Despite the decrease in cases from 2011, there has been a stable increasing trend in the number of cases since the early 1970s following the end of the Vietnam War. This pattern appears to be similar to that being reported in other parts of the world. For example, in the United Kingdom, the number of imported cases has risen significantly since the 1970s (*25*). Additionally, 1,378 malaria cases were reported in 2012 in the United Kingdom, an 18% decrease from 2011 (n = 1,677) (*26*). The majority of the U.S. cases were acquired in sub-Saharan Africa, which is also similar to the data reported by the United Kingdom. Despite progress in reducing the number of malaria cases in regions where malaria is endemic (*1*), international travel appears to be growing steadily, and use of appropriate prevention measures by travelers is still inadequate. The World Tourism Organization reported that there were approximately one billion international travelers in 2012, with notable increases in overall travel (4.0%), travel to Asia and the Pacific (7.0%), and travel to Africa (5.9%) (*21*). Although travel to Africa increased 5.9% from 2011 to 2012, differences by region persisted. Travel to North Africa increased 8.7% from 2011, in contrast to the decline of 9.1% from 2010 to 2011 that was a result of the Arab Spring and political transitions in North Africa. Travel to Sub-Saharan Africa increased by 4.4% from 2011 to 2012 (*27*).

International travelers are a heterogeneous group with different motivations, levels of education, and barriers for chemoprophylaxis use. They represent both short-stay (e.g., air crew) and long-term travelers (e.g., Peace Corps volunteers, tourists, missionaries, disaster and relief workers, and military personnel) (*28–31*). In addition, there are a variety of reasons travelers do not use malaria chemoprophylaxis, including lack of awareness of their risks for malaria and the potential severity of the disease (*28–31*) as well as concerns about the side effects of medications (*31*). As a result, interventions to improve chemoprophylaxis require a multifaceted approach. Health-care providers need to tailor interventions to their particular populations to increase awareness, understanding, or acceptance of malaria chemoprophylaxis (*32*).

As international travel increases, prevention messages and health communication strategies become even more important for protecting the traveling community from communicable diseases. Prevention messages directed toward Africa-bound travelers, particularly those whose destination is West Africa, should be emphasized in early spring, accompanied with a reminder in late fall through early winter. Malaria prevention messages directed toward Asia-bound travelers, specifically those bound for India, should be intensified in late spring. Travelers should be informed of the risk for malaria and strongly encouraged to use protective measures, including chemoprophylaxis. Imported malaria can reintroduce malaria into regions, including the United States, where the disease is not endemic and environmental conditions are present that can support the lifecycle of the parasite, including the presence of an appropriate *Anopheles* vector.

Of the 1,683 imported cases, 253 (15%) reports did not provide information regarding U.S. resident status, 147 (9%) did not have information regarding travel history, and 293 (17%) did not have information on species. Although the percentage of cases with incomplete data elements decreased slightly in 2012 compared with 2011, it still remains unacceptably high. For most of the cases with missing residential status, travel history, and species, reporting to CDC was done electronically to NNDSS and not by the NMSS case report form. At this time, NNDSS is unable to receive malaria-specific data elements from state and local health departments. States and local health departments are strongly encouraged to report cases using the NMSS case report form until malaria-specific data can be received electronically by NNDSS. Because incomplete reporting compromises efforts to examine trends in malaria cases in the United States and prevent infections among travelers, all elements on the NMSS case report form should be completed. Local and state health departments, health-care providers, and other health personnel should be vigilant in reporting complete information for malaria cases.

Specifically, if certain variables are not reported (e.g., species, residence, and country of acquisition), efforts should be made to obtain complete information for comprehensive analysis. Beginning in 2014, CSTE released a revised case definition for malaria highlighting the importance of determining the species and parasitemia at the time of diagnosis and strongly encouraging PCR testing for each case (*33*).

In the Caribbean region, endemic transmission of malaria ended in the mid-1960s, except in the island of Hispaniola, which includes the countries of the Dominican Republic and Haiti (*34*). An increase in the numbers of malaria cases acquired in Haiti had already been noted before the January 2010 earthquake (*12*). This increase continued throughout 2010 and was likely the result of both increased transmission in Haiti and increased volume of travel between the United States and Haiti by relief aid workers and Haitians returning to visit friends and relatives (*20*,*35*,*36*). The number of cases reported decreased from 172 in 2010 to 72 in 2011 and to 35 in 2012. Despite this significant decrease from 2010, the number of cases acquired in Haiti in 2012 is similar to the number acquired there before the 2010 earthquake (*35*). Of the 35 cases that were acquired in Haiti, only four (6%) patients reported taking prophylaxis. One of the five reported taking all of the prophylaxis, and one of the patients that did not report taking prophylaxis died. Failure to take chemoprophylaxis is the most common risk factor for acquisition of malaria among travelers to regions where the disease is endemic. Messages must be conveyed to VFR travelers that they are at substantial risk for malaria despite beliefs that partial immunity offers protection from disease (*37*). Recent reports of emerging molecular markers of chloroquine drug resistance in Haiti (*38,39*) indicate a need for increased vigilance for evidence of clinical chloroquine chemoprophylaxis or treatment failure. However, chloroquine remains an effective choice for chemoprophylaxis and treatment of malaria acquired in Haiti. Health-care providers should contact CDC to assist with the evaluation of possible chloroquine failures identified among U.S. travelers or Haitian immigrants to the United States. Efforts are underway to eliminate malaria from Central America and the Caribbean region by 2020, so that the number of cases from Haiti is expected to decrease over the next decade (*40*).

Although laboratory-acquired mosquitoborne infections are rare, cases have been reported in the United States (*5,41,42*). One case of malaria in 2012 occurred after laboratory exposure to mosquitoes carrying malaria parasites. Malaria can be acquired in a laboratory through inadvertent contact with infected blood from humans or animals or through inadvertent contact with an infective mosquito. Containment measures should be followed when working with infected mosquitoes, including continuous use of light traps, air curtains, negative pressure rooms, and minimized distractions (*43*).

Nosocomial transmission of malaria is uncommon in the United States. This report documents a 2012 case of nosocomial malaria transmitted during the patient's hospitalization. A review of hospital records and procedures did not identify evidence of how the nosocomial transmission occurred. However, previous reports of nosocomial transmission of malaria in the United States have been associated with needlestick exposures and reuse of saline flush syringes (*44,45*). This case highlights the importance of strict adherence to body and fluid precautions in health-care settings.

In 2012, a total of 43 cases were reported among military personnel, a 53% decrease from 2011 (n = 92), and according to the AFHSC, the lowest number of cases in the past nine years (*22*). Approximately half of the 2012 cases among military personnel were acquired in Afghanistan. Although use of prophylaxis is higher in the military population in Afghanistan compared with the civilian population, adherence remains low (adherence was 22% among those who reported taking any chemoprophylaxis). Adherence determined in this report is much lower than results of a recent survey of United States military service members serving in Afghanistan, which found adherence to chemoprophylaxis to be 60% (*46*). Reasons for these differences might include over-reporting of adherence among the survey respondents and missing information on chemoprophylaxis adherence reported to NMSS or AFHSC. Before 2010, cases among patients who were traveling for military duty to regions where malaria is endemic were only reported to CDC by local and state health departments and private health clinicians. However, after CDC partnered with AFHSC, additional cases occurring among the military are being identified that might have not been identified previously by local or state health departments or private health-care providers, thus improving opportunities to monitor and survey trends or changes (e.g., in geographical transmission and prophylaxis or treatment failures among the deployed military population).

Of the 206 uncomplicated cases of *P. vivax* or *P. ovale* in men and in women who were not pregnant at the time of diagnosis (primaquine is contraindicated during pregnancy), only 88 (43%) received primaquine. Primaquine is the only antimalarial active against the dormant parasite liver forms and prevents relapses (*47*). In addition to their treatment for acute malaria, all persons who have mosquito-acquired *P. vivax* and *P. ovale* diagnosed and who are not G6PD deficient should receive a course of primaquine for relapse prevention (*23*). In 2011, the Food and Drug Administration reported that primaquine was back ordered because of manufacturing issues reported by the only pharmaceutical company producing

primaquine in the United States, Sanofi-Aventis (*48*). Providers were urged to keep patients on weekly chloroquine prophylaxis to prevent relapses. Only 35 (30%) of *P. vivax* and *P. ovale* patients who did not receive primaquine received chloroquine. Because the CDC surveillance report form does not record the dates of treatment, understanding and determining the intended purpose of chloroquine treatment in these cases is difficult. Primaquine became available again in late 2012 (*49*).

This report includes the first results of the molecular surveillance data to assess the prevalence of resistance markers associated with antimalarial drug resistance. In total, CDC received 104 specimens from 32 state and local health departments. The prevalence of resistance markers varied for different drugs such as pyrimethamine, sulfadoxine, chloroquine, mefloquine, and atovaquone. No resistance to artemisinin derivatives was identified. In many places around the world, malaria parasites have become resistant to the antimalarial drugs used to treat cases of malaria illness, and it is important to identify and track those resistance patterns. As CDC receives and tests more samples, it will be able to identify evolving changes in resistance patterns in different countries; many countries do not conduct molecular surveillance and report it to publicly available databases. These data will help to formulate prevention and treatment recommendations for those traveling from the United States to areas where malaria is endemic and to determine country of acquisition for cases with no reported travel information. In the instance of these cryptic cases, this drug resistance testing provides additional assurance that malaria transmission is not occurring in the United States. All cases of malaria diagnosed in the United States should be evaluated for drug resistance markers. This testing is available for all cases of malaria diagnosed in the United States and is conducted at CDC without cost. CDC encourages all laboratories in the United States to make use of this service for all of the cases of malaria that they diagnose (http://www.cdc.gov/malaria/features/ars.html).

Six fatal cases were reported in 2012, less than half the number of fatal cases reported in 2010 but equal to that in 2009 (*12*). The fatalities were all from *P. falciparum* infections. One patient delayed seeking treatment after onset of symptoms, one was initially treated with oral antimalarials despite having a hyperparasitemia (≥5%), and one was discharged with empiric antibiotics without a recommended workup for fever in a traveler returning from an area where malaria is endemic. Providers should also include malaria in the differential diagnosis of fever in a person who has returned from travel to a malarious area to facilitate a prompt diagnosis. Signs and symptoms of malaria often are nonspecific but typically include fever. Other symptoms include headache, chills, increased sweating, back pain, myalgia, diarrhea, nausea, vomiting, and cough. Health-care providers should ask all febrile patients for a travel history. Any delay in the diagnosis and treatment of malaria can result in complications, regardless of the effectiveness of the treatment regimen. Patients suspected of having malaria infection should be evaluated through microscopic examination of thick and thin blood smears (*50*). Thick blood smears are more sensitive in detecting malaria parasites because the blood is more concentrated, which allows for a greater volume of blood to be examined. Thin smears aid in parasite species identification and quantification (*50*). Blood films should be read immediately; off-hours, qualified personnel who can perform this function should be on-call. Laboratories unable to provide immediate smear microscopy should maintain a supply of malaria antigen detection kits to assist with the initial diagnosis of malaria, which can subsequently be confirmed by microscopy or PCR.

The choice of a specific antimalarial treatment regimen should be based on several important factors, including the probable geographic origin of the parasite, the *Plasmodium* species, parasite density, and the patient's clinical status (*51*). In a 2010 nationwide survey of laboratories in the United States, most laboratories surveyed offered malaria diagnostic testing services but very few were in complete compliance with all of the Clinical and Laboratory Standards Institute guidelines for analysis and reporting of results. In addition, most laboratories reported very few cases annually (*52*). The case definition used in 2014 for malaria surveillance in the United States has been revised to include identification of malaria parasites, determination of species, and quantification of the parasitemia (*33*). Microscopy is still considered the best method for the immediate diagnosis of malaria; however, PCR testing is particularly valuable for species confirmation and should be used to confirm the results of microscopy and to evaluate for mixed infections. CDC's Parasitology Diagnostic Service team provides no cost diagnostic services to laboratories and health professionals diagnosing cases of malaria, including microscopy, PCR testing, and drug resistance testing performed by experts who test thousands of specimens each year. Of the 1,687 cases, species confirmation was provided by CDC for <10% of cases. Only 104 specimens were submitted to CDC for drug resistance testing in 2012; for approximately half of those specimens, PCR testing identified or corrected the species. The second cryptic case highlighted above illustrates the utility of having a large number of drug resistance profiles by geography and time. Increasing the proportion of cases with diagnosis confirmation and drug resistance testing will improve the understanding of malaria epidemiology as presented in annual malaria surveillance summaries.

This report describes a case of malaria in which the patient presented with hyperparasitemia (≥5%) with no other signs

of severe malaria and was treated with oral medications; she developed additional complications quickly and died. Patients with suspected or confirmed malaria who are severely ill should be treated aggressively with parenteral antimalarial therapy. Quinidine gluconate continues to be recommended for parenteral malaria therapy. However, this medication is no longer available in many hospital formularies. Because parenteral quinidine gluconate is potentially cardiotoxic, it should be administered in an intensive care setting with continuous cardiac and frequent blood pressure monitoring. As an alternative to quinidine gluconate, intravenous artesunate is also highly effective in the treatment of severe malaria and is available as an investigational new drug (IND) through CDC. Artesunate is stocked at nine sites around the United States and can be rapidly shipped at no cost to clinicians. Certain guidelines and eligibility requirements must be met to enroll a patient in the treatment protocol. Physicians who administer the drug to patients must notify CDC of any adverse event after administration and comply with the IND protocol (*53*). To enroll a patient with severe malaria in this treatment protocol, health-care providers should telephone the CDC Malaria Hotline at 770-488-7788 or toll-free at 855-856-4713, Monday–Friday, 9 a.m.–5 p.m., Eastern time. At other times, callers should telephone 770-488-7100 and ask to speak with a CDC Malaria Branch clinician. Travelers and health-care providers are encouraged to use CDC resources on malaria prevention and treatment, and contact the CDC Malaria Branch for assistance with diagnostic or case management needs.

Detailed recommendations for preventing malaria are available to the general public 24 hours a day online at http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria.aspx#990. Additional information on malaria prevention recommendations is also available through the online CDC malaria map application at http://www.cdc.gov/malaria/map. The application is an interactive map that provides information on malaria throughout the world. Users can search or browse countries, cities, and place names and get information about malaria in that particular location and see recommended malaria prophylaxis for that area. Also, CDC biannually publishes recommendations in *Health Information for International Travel* (commonly referred to as *The Yellow Book*), which is available and updated on the CDC Travelers' Health website at http://www.cdc.gov/Features/TravelersHealth.html; the publication is also available for purchase from Oxford University Press, Inc., at http://www.oup.com/us or telephone 1-800-451-7556 (Table 9).

Health-care providers should be familiar with prevention, recognition, and treatment of malaria and are encouraged to consult appropriate sources for malaria prevention and

TABLE 9. Sources for malaria prophylaxis, diagnosis, and treatment recommendations

Type of information	Source	Availability	Telephone number, internet address, or electronic mail address
Prophylaxis	CDC's Traveler's Health Internet site (includes online access to Health Information for International Travel)	24 hours/day	http://wwwnc.cdc.gov/travel
	Health Information for International Travel (The Yellow Book)	Order from Oxford University Press, Inc. Order Fulfillment 198 Madison Avenue, New York, NY 10016-4314	800-451-7556 or http://www.oup.com/us/
	CDC's Malaria Branch Internet site with Malaria Information and Prophylaxis, By Country (Red Pages)	24 hours/day	http://www.cdc.gov/malaria/travelers/country_table/a.html
	CDC Malaria Map Application	24 hours/day	http://www.cdc.gov/malaria/map
Diagnosis	CDC's Division of Parasitic Diseases and Malaria diagnostic internet site (DPDx)	24 hours/day	http://www.dpd.cdc.gov/dpdx
	CDC's Division of Parasitic Diseases and Malaria diagnostic CD-ROM (DPDx)	Order by electronic mail from CDC Division of Parasitic Diseases and Malaria	dpdx@cdc.gov
Treatment	CDC Malaria Branch	9:00 am–5:00 pm Eastern time, Monday–Friday	770-488-7788 or toll-free 855-856-4713*
	CDC Malaria Branch	5:00 pm–9:00 am Eastern time on weekdays and all day weekends and holidays	770-488-7100* (This number is for the CDC's Emergency Operations Center. Ask staff member to page the person on call for the Malaria Branch.) http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html

* These numbers are intended for use by health-care professionals only.

treatment recommendations (Table 9). Health-care providers should be aware of diagnostic and treatment resources available in their facilities, including availability at night or on weekends. A recent evaluation of malaria diagnosis capabilities among U.S. laboratories demonstrated that although malaria diagnostic testing services were available to the majority of U.S. laboratories surveyed, very few were in compliance with all of the current guidelines (*34*). To maintain and improve malaria and other parasitic disease diagnosis capabilities in the United States, CDC's Parasitology Diagnostic Service team conducts training courses several times per year (http://www.cdc.gov/dpdx/index.htm). Physicians seeking assistance with the diagnosis (including telediagnosis) or treatment of patients with suspected or confirmed malaria should call CDC's Malaria Hotline at telephone 770-488-7788 or toll-free 855-856-4713 during regular business hours or CDC's Emergency Operations Center at telephone 770-488-7100 during evenings, weekends, and holidays (ask to page the person on call for the Malaria Branch), or access CDC's Internet site at http://www.cdc.gov/malaria/diagnosis_treatment/index.html. These resources are intended for use by health-care providers only.

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