

Malaria-Related Deaths among U.S. Travelers, 1963–2001

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Nearly 1500 malaria cases occur each year in the United States; approximately 60% are among U.S. travelers. Despite the availability of sophisticated medical care, malaria-related deaths continue to occur. The authors reviewed all 185 fatal cases between 1963 and 2001 that were reported to the National Malaria Surveillance System: 123 (66.5%) occurred among U.S. travelers, and of these, 114 (92.7%) were attributed to *Plasmodium falciparum*. Failure to take or adhere to recommended chemoprophylaxis, to promptly seek medical care for post-travel illness, and to promptly diagnose and treat suspected malaria all contributed to fatal out-

comes. Health care providers need to take a travel history, obtain a blood film for suspected malaria, and use the 24-hour malaria management advice available through the Centers for Disease Control and Prevention (CDC) Malaria Hotline (770-488-7788) or the CDC Malaria Web site (www.cdc.gov/Malaria). Hospitals must maintain intravenous quinidine gluconate on formulary because it is the only drug available to treat severe malaria in the United States.

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Malaria is an enormous global public health problem, responsible for up to 500 million febrile illnesses and approximately 1 million deaths each year (1). The burden of disease is primarily in sub-Saharan Africa, where approximately 90% of all malaria-related deaths occur in children younger than 5 years of age (1).

In contrast, nearly 1500 cases of malaria are reported each year in the United States (2). Almost all infections are acquired outside of the United States since indigenous transmission of malaria was interrupted in the United States in the late 1940s (3). Although some cases occur in refugees and immigrants, U.S. travelers overseas are now the largest group of persons given a diagnosis of malaria. In 2000 (the most recent year for which U.S. Department of Commerce data are available), approximately 27.7 million U.S. travelers visited countries affected by malaria (4), and 825 cases of imported malaria among U.S. civilians were reported to the National Malaria Surveillance System (NMSS) (2). Despite attempts at increasing awareness of malaria among travelers and health care workers, malaria-related deaths among travelers occur nearly every year. A previous review of mortality from *Plasmodium falciparum* malaria in travelers between 1959 and 1987 was published in 1990 (5); no systematic review has been conducted since. We therefore performed a systematic review of malaria deaths in the United States from 1963 (the first year for which complete case reports are still available) through 2001 (the last year for which data are complete) to describe trends, elucidate risk factors, and identify potential public health actions to prevent future malaria-related deaths among U.S. travelers.

METHODS

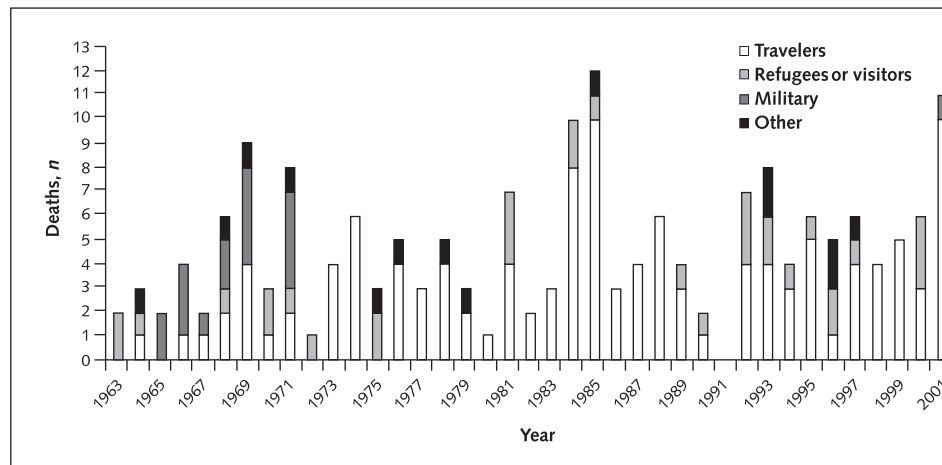
Malaria is a notifiable disease in the United States. Malaria cases (including fatal cases) are reported to the NMSS, which is administered by the Centers for Disease Control and Prevention (CDC) Malaria Branch. The NMSS is a passive case detection system that relies on U.S. state and local health departments and health care provid-

ers to report laboratory-confirmed malaria cases. Cases diagnosed outside the United States or one of its territories are not included. The CDC publishes an annual summary of malaria surveillance in the United States as a supplement to *Morbidity and Mortality Weekly Report*, which includes case summaries of all fatal malaria cases. We reviewed and screened all fatal cases that occurred between 1963 and 2001, and we included only U.S. travelers in our review.

We defined a malaria-related death in a U.S. traveler as 1) a death reported to NMSS and subsequently published in the annual surveillance summary for which malaria was a direct or indirect cause of death, 2) a malaria diagnosis and death that occurred in the United States or one of its territories, 3) death from a malarial infection that was acquired outside of the United States or one of its territories, and 4) death of a U.S. resident who traveled abroad for any nonmilitary purpose for any length of time at any point before onset of malaria.

We abstracted cases that met these inclusion criteria and entered them into a database (Epi-Info 6.01, CDC, Atlanta, Georgia). We used Stata software, version 7 (Stata Corp., College Station, Texas), for all statistical analyses. We also used several definitions. We defined *time to seeking care* as the number of days between symptom onset and first visit to a medical provider (coded as “unknown” if treatment-seeking details were not available in the case summary), *time to diagnosis* as the number of days between the first visit to a medical provider and the diagnosis of malaria (coded as “unknown” if these dates were not specified), *time to treatment* as the number of hours between a diagnosis of malaria and the initiation of antimalarial treatment, *appropriateness of chemoprophylaxis regimen* as the extent to which CDC recommendations published at the time of travel were followed, and *appropriateness of treatment* as the determination based on the most recent recommendation from *The Medical Letter* for that year. We coded adherence to chemoprophylaxis as “adherent” or “nonadherent” if this was specifically mentioned; if not, we coded this as “unknown.” We defined a *preventable death* as one in which the person 1) took no chemoprophylaxis,

Figure 1. Number of malaria deaths among travelers, refugees or visitors, and military in the United States, 1963–2001.



2) took (or was prescribed) inappropriate chemoprophylaxis, 3) took the correct chemoprophylaxis but did not completely adhere to the prescribed regimen, 4) delayed seeking medical care for more than 2 days after the onset of symptoms, 5) sought medical care but did not receive a diagnosis on the day of initial presentation with malaria, 6) was given a diagnosis of malaria but treatment began more than 1 day after diagnosis, or 7) was treated with an antimalarial drug that was inappropriate for the infecting species and region of acquisition.

RESULTS

From 1963 to 2001, 185 malaria-related deaths were reported to the CDC: 123 (66.5%) occurred among U.S. travelers, 31 (16.8%) occurred among refugees and visitors, 17 (9.2%) occurred among military personnel, and 14 (7.6%) occurred among unknown or other groups (percentages add to 100.1% because of rounding) (Figure 1). The number of deaths among U.S. travelers has remained relatively constant over time, varying between 0 and 10 deaths (median, 3). Among the 123 U.S. travelers, 49 (39.8%) were women and the median age was 51 years (mean, 48.7 years [range, 12 to 91 years]). Most deaths (114 [92.7%]) were attributed to *P. falciparum*, 4 (3.3%) were attributed to *P. vivax*, 2 (1.6%) were attributed to *P. malariae*, and 1 (0.8%) was attributed to *P. ovale*. In 2 (1.6%) cases, the species was not determined or not reported. The percentage of erythrocytes infected with *P. falciparum* was reported for 46 cases (mean, 21.4% [range, 1% to 60%]).

Estimated Case-Fatality Rate, Species of Infection, and Origin of Infection

The estimated case-fatality rate for U.S. travelers with reported cases of imported malaria (all species) was 0.9% (range, 0% to 4.4% by year). For 1985 to 2001, the only years for which complete computerized data are available, the case-fatality rate was 1.3% for *P. falciparum*, 0.06% for

P. vivax, 0.3% for *P. malariae*, and 0.3% for *P. ovale*. These case-fatality rates are probably an overestimate (particularly for non-*P. falciparum* malaria) because deaths are more likely to be reported than nonfatal cases. Most fatal cases (93 cases [75.6%]) were acquired in Africa: Kenya (25 cases), Nigeria (15 cases), and Liberia (10 cases) were the most probable frequent origins of infections, accounting for 40.6% of fatal cases. The duration of stay varied widely (<1 day to 23 years), with a median stay of 22 days. Tourism was the most frequently identified motive for travel (17.9%), with business (16.3%), missionary work (13.8%), and visiting friends or relatives (11.4%) as the next most common reasons. During the most recent years reviewed (1989 to 2001), the relative importance of these travel motives shifted: Visiting friends and relatives is now the most frequently reported motive for travel among fatal cases (21.3%), followed by business (19.2%), missionary work (10.6%), and tourism (8.5%).

Use of Chemoprophylaxis

Nearly half of persons ($n = 57$ [46.3%]) took no chemoprophylaxis, and information on the use of chemoprophylaxis was not available for an additional 32 persons (26%). Of the 34 persons who reported taking chemoprophylaxis, 12 (35.3%) took a drug or drug combination that was inappropriate for the region of travel, and 20 (58.8%) took an appropriate chemoprophylactic drug. Information was insufficient in 2 individuals to determine whether the drug regimen was appropriate. Of the 20 persons who took an appropriate drug, 6 (30%) did not adhere to the prescribed regimen. No information on adherence was available for an additional 7 persons (35%). Therefore, 7 of 123 individuals (5.7%) were known to take appropriate chemoprophylaxis and adhere to the regimen. The reasons these individuals became ill with malaria is not known, but the most likely reasons are unreported nonadherence to the recommended regimen and malabsorption of the antima-

Table 1. Drugs Used in the Prophylaxis of Malaria*

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Atovaquone–proguanil (Malarone, GlaxoSmithKline, Research Park Triangle, North Carolina)	Primary prophylaxis in areas with chloroquine-resistant or mefloquine-resistant <i>Plasmodium falciparum</i>	Adult tablets contain 250 mg of atovaquone and 100 mg of proguanil hydrochloride 1 adult tablet orally per d	Pediatric tablets contain 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride Weight-based dosing: 11–20 kg: 1 tablet 21–30 kg: 2 tablets 31–40 kg: 3 tablets ≥40 kg: 1 adult tablet daily	Begin 1–2 d before travel to malarious areas. Take daily at the same time each d while in the malarious area and for 7 d after leaving such areas. Contraindicated in persons with severe renal impairment (creatinine clearance < 30 mL/min). Atovaquone–proguanil should be taken with food or a milky drink. Not recommended for children < 11 kg, pregnant women, and women who are breastfeeding infants weighing < 11 kg.
Chloroquine phosphate (Aralen, Sanofi-Synthelabo, Inc., New York, New York; and generic)	Primary prophylaxis only in areas with chloroquine-sensitive <i>P. falciparum</i>	300-mg base (500 mg of salt) orally, once per wk	5 mg/kg of body weight–base (8.3 mg/kg of salt) orally, once per wk, up to maximum adult dose of 300-mg base	Begin 1–2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas. May exacerbate psoriasis.
Doxycycline (many brand names and generic)	Primary prophylaxis in areas with chloroquine-resistant or mefloquine-resistant <i>P. falciparum</i>	100 mg orally per d	≥8 y of age: 2 mg/kg up to adult dose of 100 mg/d	Begin 1–2 d before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 28 d after leaving such areas. Contraindicated in children < 8 y of age and pregnant women.
Hydroxychloroquine sulfate (Plaquenil, Sanofi-Synthelabo, Inc.)	An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive <i>P. falciparum</i>	310-mg base (400 mg of salt) orally, once per wk	5 mg/kg–base (6.5 mg/kg of salt) orally, once per wk, up to maximum adult dose of 310-mg base	Begin 1–2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas.
Mefloquine (Lariam, Roche Laboratories, Inc., Nutley, New Jersey; and generic)	Primary prophylaxis in areas with chloroquine-resistant <i>P. falciparum</i>	228-mg base (250 mg of salt) orally, once per wk	Weight-based dosing: ≤15 kg: 4.6 mg/kg–base (5 mg/kg of salt) orally, once per wk 15–19 kg: 1/4 tablet once per wk 20–30 kg: 1/2 tablet once per wk 31–45 kg: 3/4 tablet once per wk ≥46 kg: 1 tablet once per wk	Begin 1–2 wk before travel to malarious areas. Take weekly on the same day of the week while in the malarious area and for 4 wk after leaving such areas. Contraindicated in persons allergic to mefloquine and in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Not recommended for persons with cardiac conduction abnormalities.

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Table 1—Continued

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Primaquine (Sanofi-Synthelabo, Inc.)	An option for primary prophylaxis in special circumstances; call the CDC Malaria Hotline (770-488-7788) for additional information	30-mg base (52.6 mg of salt) orally per d	0.6 mg/kg–base (1.0 mg/kg of salt) up to adult dose orally per d	Begin 1–2 d before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 d after leaving such areas. Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level. Use in consultation with malaria experts.
Primaquine (Sanofi-Synthelabo, Inc.)	Used for terminal prophylaxis to decrease the risk for relapses of <i>P. vivax</i> and <i>P. ovale</i> infection	30-mg base (52.6 mg of salt) orally per d for 14 d after departure from the malarious area	0.6 mg/kg–base (1.0 mg/kg of salt) up to adult dose orally per d for 14 d after departure from the malarious area	Indicated for persons who have had prolonged exposure to <i>P. vivax</i> and <i>P. ovale</i> or both. Contraindicated in persons with G6PD deficiency. Also contraindicated during pregnancy and lactation unless the infant being breastfed has a documented normal G6PD level.

* Source: Centers for Disease Control and Prevention. *Health Information for International Travel, 2003–2004*. Atlanta: U.S. Department of Health and Human Services, Public Health Service; 2003. CDC = Centers for Disease Control and Prevention; G6PD = glucose-6-phosphate dehydrogenase.

larial drug. Table 1 summarizes the chemoprophylaxis regimens currently recommended by the CDC (6).

Presenting Symptoms

Fever was the most common presenting symptom, reported for 77.2% of fatal cases, followed by chills (45.9%) (Table 2). Although the classic symptoms of fever and chills or sweats were very common, 23 persons (18.7%) presented with no history of these symptoms. Symptom onset ranged from 18 days before return to 4 years after return (median, 5 days after return; *P. ovale* was the infecting species for the case 4 years after return). One woman, a 91-year-old who died after developing *P. malariae* infection, became symptomatic an unknown number of years after traveling to China.

Time to Seeking Care and Diagnosis

Forty-six persons (37.4%) waited more than 1 day after symptom onset before seeking medical care (median, 4.5 days [range, 2 to 28 days]). We could not determine the timing of care-seeking for 58 persons (47.2%). Of the 90 individuals for whom the case report provides adequate information, 61 (67.8%) did not obtain a diagnosis of malaria on the same day as the medical visit. The time to diagnosis ranged from 1 day to 17 days (median, 4 days). In 4 persons, the species was initially misidentified. Diagnosis of *P. malariae* infection was later changed to *P. fal-*

ciparum infection in 2 cases, *P. vivax* infection was later changed to *P. falciparum* infection in 1 case, and *P. falciparum* infection was later corrected to *P. vivax* infection in 1 case. In 22 of the 123 U.S. travelers (17.9%), malaria was diagnosed only at autopsy.

Delay in Initiating Antimalarial Treatment and Choice of Antimalarial Therapy

Of 109 persons who had the opportunity to receive therapy (that is, they received medical attention before death), 6 (5.5%) had a delay of 12 to 24 hours (median, 24 hours) and 18 (16.5%) never received antimalarial therapy. In 12 of these 18 cases, malaria was diagnosed only at autopsy. Among the other 6 cases, 3 persons were hospitalized, but diagnosis was delayed and the patient died before therapy could be initiated; 2 persons died in the emergency department after malaria had been diagnosed but before therapy was initiated; and 1 person died at home, having been seen at an outpatient clinic where a blood film was obtained but follow-up never occurred. The number of fatal cases of malaria with delays in initiating therapy may be greater, but most case reports are not sufficiently detailed to determine this.

Of 90 persons who received antimalarial therapy and for whom the drug used is known, 9 (10.0%) were given therapy that was inappropriate for the species, region of

acquisition, or existing treatment recommendations. In 7 of these cases, chloroquine therapy (alone or in combination with proguanil) was initially given for treating *P. falciparum* acquired in areas with known chloroquine-resistant *P. falciparum* malaria. In 5 of these 7 cases, therapy was later changed to a quinine- or quinidine-containing regimen. In 1 case, quinine was paired with mefloquine for treatment (increasing the risk for cardiotoxicity). In another case, sulfadoxine–pyrimethamine therapy alone was started for treating severe malaria (an inadequate therapy for severe malaria, even for infections acquired in areas with *P. falciparum* sensitive to sulfadoxine–pyrimethamine, because of the relative slowness of this drug in killing malaria parasites), and quinine was later added. Eleven (8.9%) patients received exchange transfusions as adjunct therapy.

Location of Death, Complications, and Autopsy Findings

Most patients who died (104 patients [84.6%]) were hospitalized or died in the emergency department, and 18 (14.8%) died at home or en route to the hospital. In 1 case, information was insufficient to determine whether the person died at home or in the hospital. Among hospitalized patients, the range of time between admission and death was 0 to 42 days (mean, 6.8 days; median, 4 days). The range of time between onset of symptoms and death was 2 to 43 days (mean, 12.6 days; median, 9.5 days) for the 90 patients for whom this information could be calculated.

Cerebral malaria was the most commonly reported clinical complication, occurring in 59 cases (48.0%). Renal failure (54 cases [43.9%]), the acute respiratory distress syndrome (39 cases [31.7%]), anemia (26 cases [21.1%]), and disseminated intravascular coagulation (14 cases [11.4%]) were the next most commonly cited complications. Blackwater fever was reported in only 1 case, in 1971.

Splenic rupture was identified as a direct or precipitating cause for 6 deaths (4.9%). In 4 of 6 cases, this diagnosis was made only at autopsy, while in 2 cases the diagnosis was made by imaging or detection of abdominal blood at laparotomy, albeit too late to avoid a fatal outcome. In 4 of 6 cases, *P. falciparum* was the infecting species. The remaining 2 cases included 1 case of *P. vivax* and 1 case of *P. ovale*. The age range among patients with a ruptured spleen was 12 to 51 years (median, 28 years), which is significantly younger than that among fatal cases without splenic rupture (median, 51 years; $P = 0.007$). The spleen ruptured 3 to 15 days after the onset of symptoms (median, 11 days) and 0 to 8 days after the onset of antimalarial treatment (median, 5 days; 1 person died before reaching the hospital).

Autopsy findings were reported for 50 cases (40.7%). *Plasmodium* species in any organ was the most common finding (27 cases [54.0%]), followed by pulmonary edema (19 cases [38.0%]), malarial pigment in any organ (18 cases [36.0%]), cerebral edema (11 cases [22.0%]), and hepatomegaly or splenomegaly (11 cases [22.0%]).

Table 2. Presenting Symptoms of 123 U.S. Travelers Who Died of Malaria, 1963–2001

Symptom	Travelers, n (%)
Fever	95 (77.2)
Chills	56 (45.9)
Mental status changes	24 (19.7)
Myalgia	23 (18.9)
Fatigue or malaise	22 (18.0)
Diarrhea	20 (16.4)
Weakness	20 (16.4)
Vomiting	20 (16.4)
Headache	19 (15.6)
Nausea	19 (15.6)
Nonspecific respiratory symptoms	9 (7.4)
Lethargy	8 (6.6)
Cough	8 (6.6)
Abdominal pain	8 (6.6)
Jaundice	8 (6.6)
Sweats	5 (4.1)
Dizziness	4 (3.3)
Anorexia	3 (2.5)
Seizures	2 (1.6)
Other	22 (17.9)

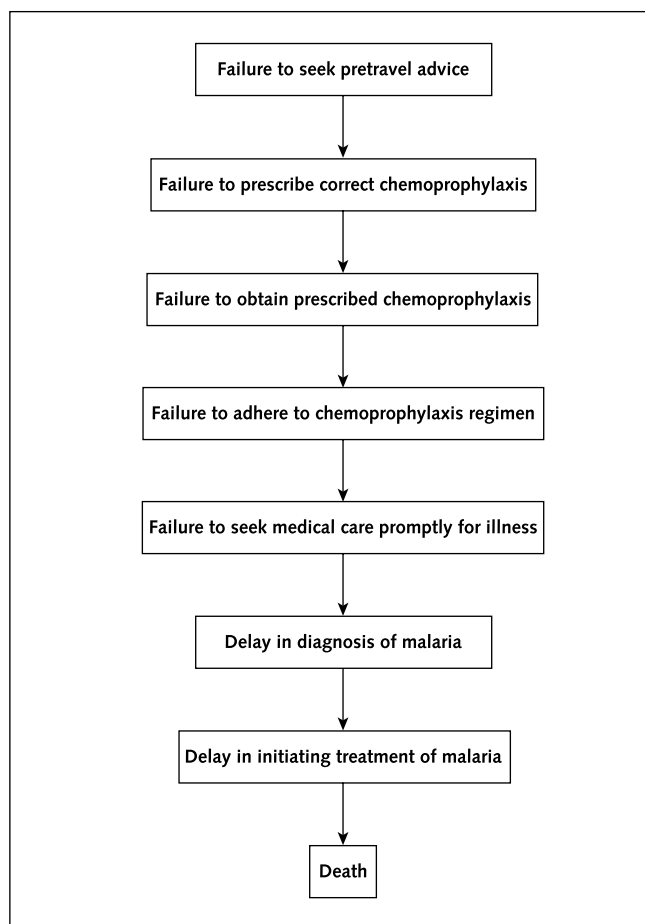
Preventability of Deaths

Most deaths ($n = 105$ deaths [85.4%]) were considered preventable. For 83 (79.0%) of these 105 patients, their own decisions may have contributed to death, including failure to take chemoprophylaxis, to adhere to the prescribed chemoprophylaxis regimen, or to seek medical attention promptly (within 2 days) once symptoms occurred. For 70 of these 105 persons (66.7%), medical errors may have contributed to the fatal outcome; these errors include failure to prescribe the correct chemoprophylaxis regimen, failure to diagnose malaria on initial presentation, failure to initiate treatment promptly on diagnosis, or treatment with an antimalarial drug that was inappropriate for the infecting species or region of acquisition. **Figure 2** summarizes the factors that lead to a malaria-related death.

DISCUSSION

Between 1963 and 2001, nearly 1 of every 100 U.S. travelers with malaria diagnosed and reported to the NMSS on return to the United States died. *Plasmodium falciparum* was responsible for nearly all of these deaths. Although fever was by far the most common primary symptom among those who died, symptoms were frequently protean and nonspecific and often included respiratory and gastrointestinal symptoms. Almost all deaths identified in this review were preventable. Most travelers made decisions that may have contributed to death. Some did not take any chemoprophylaxis, some took the correct chemoprophylactic regimen but did not fully adhere to the prescribed regimen, and others delayed seeking care once they became ill. For more than half of all deaths, errors related to the provision of health care may have contributed to a fatal outcome: prescription of the wrong chemoprophylaxis drug, delay in diagnosing malaria or initiating

Figure 2. Potential contributing factors to malaria-related fatalities among U.S. travelers.



treatment, or use of an inappropriate treatment drug. In some instances, the correct antimalarial treatment drug was not available in the hospital or had expired. Given the speed with which *P. falciparum* malaria can be fatal, particularly in nonimmune travelers, these delays in delivering appropriate treatment may have contributed to death. This current estimated case-fatality rate for *P. falciparum* is lower than what has been previously reported for the United States during earlier time periods (3.8% for 1966 to 1987) (5).

Travelers and health care providers must be educated about the importance of malaria prevention (Table 3): chemoprophylaxis (the correct regimen taken as directed) and personal protection measures (such as insecticide-treated mosquito nets and insect repellents containing DEET [N,N-diethyl-3-methylbenzamide]). These prevention measures are detailed in *Health Information for International Travel*, also known as the “Yellow Book,” published biennially by CDC (6), and are also available on the Internet (www.cdc.gov/travel/yb/index.htm). Despite the availability of these recommendations, several reports (primarily of nonfatal malaria cases) over the past 20 years document travelers’ failing to take any chemoprophylaxis, travelers’

taking inappropriate chemoprophylaxis that is against the region of travel, or travelers’ not completely adhering to the prescribed chemoprophylactic regimen (7–18).

Of particular note, chemoprophylaxis with chloroquine and proguanil (not currently marketed in the United States) is still frequently used in areas with chloroquine-resistant *P. falciparum* malaria (12, 19). Both nonfatal (17, 19) and fatal malaria cases have been reported after chloroquine–proguanil use for malaria chemoprophylaxis (9, 16), and the CDC no longer recommends this combination as a chemoprophylaxis option for travelers to areas with chloroquine-resistant *P. falciparum* (6). This combination was once listed as a third-line option but was removed when atovaquone–proguanil became available. In areas with chloroquine-sensitive *P. falciparum*, proguanil

Table 3. Summary of Key Findings of Review of Malaria Deaths among U.S. Travelers, 1963–2001, and Recommended Action Items To Reduce Mortality

1. Many patients who died did not take any malaria chemoprophylaxis. Educate health care providers about available resources for up-to-date prophylaxis recommendations: *Health Information for International Travel* (the “Yellow Book”) (www.cdc.gov/travel/yb/index.htm) CDC Travelers’ Health Web site (www.cdc.gov/travel) Educate travelers about the need for malaria chemoprophylaxis; especially important for those visiting friends and relatives.
2. Many patients who died did not completely adhere to recommended chemoprophylaxis regimens. Advise travelers about the importance of complete adherence to prescribed malaria chemoprophylaxis regimens.
3. Many patients who died did not seek prompt medical care once symptoms began. Clinicians providing pretravel advice need to stress importance of seeking medical care for illnesses in the 3 mo after return. All travelers should develop a plan for illness (abroad or after return to the United States).
4. Diagnostic delays common among fatal cases. Take basic travel history when relevant. Order malaria blood films for suspected malaria. Read blood films immediately; qualified laboratory personnel should be on call. Repeat negative blood slides from suspected malaria cases (a total of 3 blood film examinations in 24 h).
5. Delays in initiating antimalarial treatment contributed to many fatalities. Promptly initiate appropriate antimalarial treatment. If diagnosis of malaria is suspected and cannot be confirmed or if diagnosis of malaria is confirmed but species cannot be determined, immediately initiate antimalarial treatment that is effective against *Plasmodium falciparum*. Educate health care providers about resources on up-to-date treatment recommendations: CDC Malaria Web site (www.cdc.gov/malaria) CDC Malaria Hotline (24-hour advice line for clinicians: 770-488-7788) Intravenous quinidine should be available on hospital formularies. If quinidine is not available, obtain it from a local source (other pharmacy or regional distributor). If no local source available, contact Eli Lilly and Company, the current U.S. manufacturer of quinidine gluconate (800-821-0538, Monday to Friday, 7:30 a.m. to 6:00 p.m., or 317-276-2000 after hours) to arrange for rapid shipment of the drug.

* CDC = Centers for Disease Control and Prevention.

adds little to the efficacy of chloroquine and is inferior to other more efficacious options, such as atovaquone-proguanil, doxycycline, and mefloquine (and now primaquine as a second-line option in special circumstances). This regimen should not be in the chemoprophylaxis armamentarium, except under extraordinary circumstances.

A Canadian review of malaria cases from 2 hospital-based tropical disease centers found a similar problem with traveler delay in seeking care after the onset of symptoms (mean, 6.7 days), although only 1 death was recorded (20). This same review also noted that although most patients had a history of fever, only half were febrile at presentation, and that other signs and symptoms were nonspecific. Similar findings have also been reported in previous reviews of fatal malaria cases in the United States (5, 21) and nonfatal cases elsewhere (17). Similar to our study finding, other reports have consistently noted the failure of clinicians to prescribe appropriate chemoprophylaxis to travelers who seek pretravel advice (22) and to appropriately diagnose and treat malaria among returning travelers (17, 23–26).

These data suggest that clinicians must help prevent further unnecessary malaria-related deaths (Table 3). First, when relevant, health care providers must take a basic travel history on patients. Obtaining a travel history is not optional in a febrile patient, and relying on the patient to volunteer this information may result in crucial history being overlooked. Second, health care providers must obtain a malaria blood film for all patients with suspected malaria. Treatment with an appropriate antimalarial drug must be initiated once malaria has been diagnosed. If malaria is suspected but prompt laboratory diagnosis is not possible, antimalarial treatment should be initiated pending results of the malaria blood film.

For many years, malaria experts have called for better education of health care providers in managing malaria. This call to action, however, has not eliminated errors in diagnosis and management that sometimes have tragic consequences, as evidenced by these data. Because clinicians see malaria infrequently, they should be informed that public health authorities are available to assist with diagnosis and management. The CDC provides a 24-hour Malaria Hotline (770-488-7788) for this purpose. The U.S. guidelines for malaria treatment are being written by the CDC with input from outside experts. These complete guidelines will be available on the Internet and will provide accurate, up-to-date, evidence-based recommendations to clinicians (Parise M. CDC. Personal communication). A table outlining CDC-recommended treatment regimens is already available on the CDC Malaria Web site (www.cdc.gov/malaria).

The timeliness of malaria diagnostic capacity must be improved. Many, if not most, hospitals have little experience in reading malaria blood films. Health facilities must have established contact with local or state public health laboratories who can provide either the needed laboratory service (often slides may be shipped overnight to these fa-

cilities) or guidance on the availability of local laboratories with the necessary experience to accurately read a malaria blood film. In other cases in which the laboratory personnel with malaria slide reading experience may not be on duty, hospitals and laboratories must develop systems for having such staff on call and available 24 hours. Although much has been written about rapid diagnostic tests for malaria, no product is currently approved for use in the United States, and available data suggest that these tests do not have adequate sensitivity at low parasite densities that can cause disease in nonimmune travelers (27) to avoid potentially fatal, false-negative results. An approved rapid diagnostic test would nonetheless be useful because a positive test result might speed the initiation of antimalarial drug treatment. However, if such an approved test was used in the future, malaria must still be confirmed with a blood film. If no alternative diagnostic means were available (that is, microscopy or polymerase chain reaction), a rapid test would need to be repeated, which is currently done with blood films.

Blood films of patients with suspected malaria should be read immediately. However, if the diagnosis of malaria is suspected and cannot be confirmed, or if a diagnosis of malaria is confirmed but species determination is not possible, antimalarial treatment effective against *P. falciparum* must be initiated immediately. Confirmed, possible, and suspected cases of *P. falciparum* should all be considered medical emergencies. Sending a patient home to await results of a malaria blood film without antimalarial therapy or hospitalizing a patient for whom blood slide results will not be available for more than several hours without initiating immediate treatment with an antimalarial is not an acceptable course of action. Negative blood slides from suspected malaria cases should be repeated (a total of 3 blood film examinations in 24 hours) if symptoms persist and other underlying causes are not found. Resistance of *P. falciparum* to chloroquine is nearly worldwide, except in some geographic regions, such as most of Central America (6). Therefore, therapy for presumed *P. falciparum* malaria from areas with known chloroquine resistance should always include a drug that is effective against such resistant strains.

Hospitals must have intravenous quinidine gluconate on formulary because it is the only drug currently approved and available in the United States for treating severe malaria. In recent years, quinidine has become less widely available because its use as an antiarrhythmic drug has decreased, and many hospitals no longer stock it (28). Deaths related to the poor availability of quinidine have been noted previously in the United States (29), Canada (16), and Israel (24), and our findings re-emphasize this problem. The cost of maintaining quinidine gluconate on formulary would be minimal. The average 70-kg adult would require approximately nine 800-mg vials to complete 72 hours of treatment with quinidine gluconate (10 mg/kg of body weight for the loading dose and 70 hours of contin-

uous infusion at 0.02 mg/kg per minute). The wholesale cost of this therapy is approximately \$154.00 (\$17.11 per vial), and the shelf life at room temperature for injection is 2 years. If a hospital does not have quinidine gluconate on formulary, the hospital should attempt to obtain it from a local source (other pharmacy or regional distributor) that will minimize delays in initiating treatment. If no local or regional drug sources are available, pharmacists should contact Eli Lilly and Company, the current U.S. manufacturer of quinidine gluconate (800-821-0538, Monday to Friday, 7:30 a.m. to 6:00 p.m., or 317-276-2000 after hours), to arrange for rapid shipment of the drug.

The artemisinin derivatives are efficacious and widely used overseas for treating severe malaria. The CDC is investigating how to make a parenteral artemisinin available under a restricted-access protocol for persons who may have quinidine-resistant malaria or severe quinidine intolerance. The availability of an approved parenteral artemisinin product that has met the U.S. Food and Drug Administration's requirements for proof of safety, efficacy, and manufacturing practices would be a much-needed addition to the U.S. armamentarium of drugs for treating severe malaria.

Our study has several limitations. First, not all malaria-related deaths may be reported to CDC. Conversely, however, malaria-related deaths may be over-represented in the NMSS because fatal cases are more likely to have been reported than nonfatal cases; this probably inflated the overall case-fatality rate. Second, NMSS is a passive data collection system that may provide data that are more difficult to interpret than prospectively collected data. Third, case histories in the NMSS malaria surveillance summaries are often brief or incomplete. Because information on deaths has not been collected or presented in a standardized format, omissions, such as whether the person sought medical care before the diagnosis was made, are difficult to interpret. Fourth, key variables, such as delay in seeking treatment and delay in diagnosis, are not available for nonfatal cases; thus, the contribution of these problems to malaria mortality among U.S. travelers cannot be quantitated. Finally, the NMSS collects information about malaria cases diagnosed only in the United States. Malaria cases and malaria-related deaths among U.S. travelers that occur overseas are not included in this study, although other reports have documented their occurrence (30–32).

In summary, nearly 1 of every 100 U.S. travelers with malaria diagnosed and reported to the NMSS on return to the United States died, and *P. falciparum* is responsible for nearly all deaths. Communication with health care providers and travelers about malaria as a life-threatening illness must be improved. Providers must educate travelers about the need for appropriate chemoprophylaxis and personal protection measures if they travel to malarious areas and to develop a plan for illness (abroad or after return to the United States). Health care providers must also be reminded about the importance of taking a travel history,

obtaining a blood film for suspected malaria, and using the 24-hour malaria management advice available through the CDC Malaria Hotline (770-488-7788). Intravenous quinidine gluconate must be maintained on hospital formularies because it is the only drug available to treat severe malaria in the United States.

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