Risk Factors for Imported Fatal *Plasmodium falciparum* Malaria, France, 1996–2003

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Plasmodium falciparum malaria is a serious health hazard for travelers to malaria-endemic areas and is often diagnosed on return to the country of residence. We conducted a retrospective study of imported falciparum malaria among travelers returning to France from malaria-endemic areas from 1996 through 2003. Epidemiologic, clinical, and parasitologic data were collected by a network of 120 laboratories. Factors associated with fatal malaria were identified by logistic regression analysis. During the study period, 21,888 falciparum malaria cases were reported. There were 96 deaths, for a case-fatality rate of 4.4 per 1,000 cases of falciparum malaria. In multivariate analysis, risk factors independently associated with death from imported malaria were older age, European origin, travel to East Africa, and absence of chemoprophylaxis. Fatal imported malaria remains rare and preventable. Pretravel advice and malaria management should take into account these risk factors, particularly for senior travelers.

Imported malaria is increasingly reported in Europe and North America, with an estimated 30,000 cases yearly (*1,2*). In 2000, the countries with the highest rates of imported malaria were France (≈8,000 estimated cases), United Kingdom (2,069 cases), United States (1,402 cases), Italy (986 cases), and Germany (732 cases) (*3,4*). Imported *Plasmodium falciparum* malaria is a serious health hazard for travelers to malaria-endemic areas, owing to the potentially severe illness and high case-fatality rates (case-fatality rate per 1,000: France 4; Italy 6.5; UK 8.5; USA 13; Germany 30.4) (*4,5*). Risk factors associated with fatal imported malaria are poorly known. Limited series have suggested that the fatality rate is significantly lower for migrants from malaria-endemic areas than for patients from areas not endemic for the disease (*6–8*). Antimalarial chemoprophylaxis, even incomplete or inappropriate, may also confer a degree of protection (*9–11*). Better knowledge of the characteristics and risk factors for fatal imported malaria might help to improve prevention and patient management. We retrospectively analyzed the main features of fatal imported falciparum malaria observed in France during 1996–2003 and compared them with those for nonfatal cases.

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Methods

Description of Surveillance System (Data Sources)

Imported malaria is not a mandatory notifiable disease in metropolitan France. The data for this study were collected by a reporting network of 120 selected hospital laboratories and were analyzed by the French National Reference Center for Imported and Autochthonous Malaria Epidemiology (CNREPIA). Participants of the network were asked to report imported malaria cases whenever the laboratory observed asexual forms of *P. falciparum* in a patient's blood film. Data from the national medical informatics systems and from 2 exhaustive studies (National Quality Control Survey) suggested that these cases represented 50%–55%

of the total number of imported falciparum malaria cases in France during the study period (*12,13*). A standard 57-item questionnaire, completed by clinicians and biologists for each reported case, collected basic demographic, epidemiologic, clinical, and parasitologic information (including prophylaxis and treatment). In addition, a detailed clinical description was obtained for each fatal case.

Data Analysis

The study population consisted of all *P. falciparum*–infected patients reported to CNREPIA during 1996–2003. Deaths occurring during hospitalization for malaria were considered malaria related. The case-fatality rate per 1,000 patients was calculated for all relevant exposure variables. Various exposure categories were created for the analysis: patients were divided into European travelers (persons born and residing in areas not endemic for malaria), European expatriates (residing in malaria-endemic African countries), African travelers (persons born in Africa who reside mostly in France or another country not endemic for malaria), African residents (persons born and residing in Africa), and others. Use of malaria chemoprophylaxis, as reported by the patients, was categorized as follows: no use; use of ineffective drugs (e.g., chloroquine, proguanil, pyrimethamine, sulfadoxine-pyrimethamine); and use of effective drugs (mefloquine, atovaquone-proguanil, doxycycline, and chloroquine-proguanil). Logistic regression was used to identify factors associated with fatal malaria and to estimate odds ratios and 95% confidence intervals (CIs) for the association between exposure variables and death. Dummy variables were used for variables with >2 categories. Variables with $p<0.25$ were introduced in the multivariate logistic regression model. A manual backward stepwise approach was used to remove nonsignificant variables, and only variables with $p<0.05$ were retained in the final model. Interactions were sought by introducing interaction terms in the logistic regression model and testing for their significance ($p<0.05$). Because data were missing for the variables "region of malaria acquisition" (n = 9), "chemoprophylaxis" (n = 2,366), and "time between onset and diagnosis" (n = 3,845), multiple imputation for missing data was performed for the final model by using the multivariate imputation by chained equations (MICE) method described by Van Buuren et al. (*14*). The MICE method involves imputations of missing values by appropriate regression models and generation of multiple datasets (in our case, 5) to take into account the uncertainty involved in imputing the missing values. Standard complete-data methods are then used on each dataset, and results are combined to produce estimates with CIs and p values. Statistical analysis was performed by using EpiInfo, version 3.3 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and Stata 8 (Stata Corporation, College Station, TX, USA).

Results

During the 1996–2003 period, 27,085 malaria cases were reported to CNREPIA; 21,888 of these patients had *P. falciparum* malaria, which constituted the study population. Included were 20,436 (93.4%) uncomplicated cases, 825 (3.8%) severe cases, 433 (2%) asymptomatic cases, 161 (0.7%) cases of hyper-reactive malarial splenomegaly, and 33 (0.1%) unspecified cases. Cases attributable to species other than *P. falciparum* and cases attributable to species combinations that included *P. falciparum* were not considered in the analysis (no fatal cases of imported malaria due to *Plasmodium* species other than *P. falciparum* were reported during the study period). The annual number of malaria cases reported by the network increased until 1999–2000, then stabilized at ≈3,000 cases per year (Table 1). Most patients were male (sex ratio M:F = 1.7), and the median (range) age was 29.0 (0–96) years. Most patients had acquired malaria in Africa: 59.2% in West Africa, 26.2% in central Africa, 11.2% in Madagascar and the Comoros Islands, and 0.9% in East Africa (Table 2 and online Appendix Table, available from www.cdc.gov/EID/content/13/6/883-appT.htm). Others (2.5%) had returned mainly from French Guiana, Haiti, India, Sri Lanka, Thailand, and Indonesia. African travelers were most numerous (44.6%), followed by European travelers (26.5%), African residents (12.9%), and European expatriates living in Africa (5.4%); "others" represented 10.6%. Few patients (30.4%) reported taking effective chemoprophylaxis, and more than half the patients had not taken any. The median duration of stay was 32 days (interquartile range 21–62). The median time from return to symptom onset was 6 days (interquartile range 1–12), and 10% of patients had their first symptoms before returning to France. The median time from symptom onset to diagnosis was 3 days (interquartile range 1–6). Compared with Europeans, Africans were more likely to seek care at a hospital (73.0% vs. 62.7%, $p<0.001$). Diagnoses were fairly evenly distributed between spring-summer (55.5%) and fall-winter (45.5%). At diagnosis, 7.9% of patients had high-level parasitemia (>5% of parasitized erythrocytes).

Description of Fatal Cases

Ninety-six patients died of malaria; 55 were European travelers; 12, European expatriates; 11, African travelers; 10, African residents; and 8, other. One case was diagnosed postmortem. Repatriations for medical reasons occurred in 13 of 96 fatal cases (1 African resident, 5 European travelers, and 7 European expatriates). Among the patients who died, the sex ratio (M:F) was 3.3, and the median (range) age was 47 (2–92) years. Three study participants who died were <15 years of age, and 5 were >70 years of age. Thirty (31.3%) of the patients who died had taken antimalarial chemoprophylaxis, and 2 were re-

Table 1. Distribution of falciparum malaria cases and deaths by calendar year, 1996–2003, France

Year	No. reported deaths	No. falciparum malaria cases	Case-fatality rate per 1,000
1996	8	1,804	4.4
1997	10	2,057	4.9
1998	9	2,459	3.7
1999	9	3,385	2.7
2000	12	3,355	3.6
2001	13	3,035	4.3
2002	15	2,919	5.1
2003	20	2,874	7.0
Total	96	21,888	4.4

ported to have correctly taken prophylaxis appropriate for the region visited.

Clinical data for patients who died are shown in Table 3. Fever was the most common initial symptom. All patients, except the one whose case was diagnosed postmortem, were hospitalized and received antimalarial therapy within 12 hours of diagnosis. Median parasitemia at admission was high (10%), although 10% of patients had parasitemia <1%. One case of black water fever and 1 case of splenic rupture were observed. Forty-three (44.8%) patients required mechanical ventilation, and 24 (25%) required hemofiltration. Three (3.1%) patients underwent exchange transfusion.

Risk Factors for Death

The case-fatality rate was 4.4 deaths per 1,000 cases during the study period and did not change over time (calendar years) (standard χ^2 for trends test; Table 1). Many factors were associated with an increased risk for death in univariate analysis, including older age, male sex, European origin, travel to East Africa, short stays (≤15 days), time to diagnosis, and initial visit to a general practitioner (online Appendix Table). However, male sex, short stays, visit to a general practitioner, and diagnosis during the fall-winter season were no longer predictive of death after age and ethnic origin were controlled for in multivariate analysis. Table 4 shows the results of multivariate analysis. Low hemoglobin levels (≤8 g/dL), low platelet counts ($\leq 50\times10^9$/L), high leukocyte counts ($>10\times10^9$/L), and high-level parasitemia (>5%) were all associated with increased risk for death among patients with measurements for these variables (online Appendix Table). The risk factors for death identified in this study were not different between Africans and Europeans (test of interaction not significant).

Discussion

To our knowledge, this is the largest retrospective study aimed at identifying risk factors for fatal imported malaria. France has large numbers of migrants of African origin. Those populations are particularly at risk of acquiring malaria when visiting friends and relatives (*15–17*).

Table 2. Distribution of falciparum malaria cases and deaths by country of acquisition, 1996–2003

Country	No. deaths	No. falciparum malaria cases	Case-fatality rate per 1,000
Cape Verde	1	4	250.0
Senegal	12	2,234	5.4
Mauritania	1	96	10.4
Guinea-Bissau	1	50	20.0
Guinea	3	823	3.6
Mali	8	2,124	3.8
Côte d'Ivoire	15	4,623	3.2
Burkina Faso	5	740	6.8
Ghana	1	194	5.2
Togo	3	604	5.0
Benin	3	1,012	3.0
Niger	3	152	19.7
Nigeria	2	123	16.3
Cameroon	12	2,707	4.4
Equatorial Guinea	1	31	32.3
Gabon	4	671	6.0
Congo	4	885	4.5
Central African Republic	1	728	1.4
Tanzania	1	38	26.3
Kenya	4	101	39.6
Djibouti	1	12	83.3
Mozambique	1	29	34.5
Comoros Islands	1	2,017	0.5
Madagascar	4	432	9.3
Others, several countries or unknown	4	1,458	2.7
Total	96	21,888	4.4

Table 3. Clinical data for 96 patients with fatal malaria, 1996–2003, France

Clinical data	No. travelers (%)
Initial symptoms	
Fever	80 (83.3)
Mental status changes	45 (46.9)
Jaundice	24 (25)
Diarrhea	18 (18.7)
Respiratory symptoms	13 (13.5)
Coma	11 (11.5)
Vomiting	9 (9.4)
Convulsions	6 (6.2)
Lethargy	5 (5.2)
Cough	4 (4.2)
Shock syndrome	4 (4.2)
Severity criteria* during clinical course	
Renal failure	70 (72.9)
Shock syndrome	60 (62.5)
Cerebral malaria	55 (57.3)
Acute respiratory distress syndrome	44 (45.8)
Acidosis	36 (37.5)
Disseminated intravascular coagulation	30 (31.2)
Pulmonary edema	12 (12.5)
Scleral icterus	11 (11.5)
Convulsions	9 (9.4)
Other conditions	
Nosocomial infection	24 (25)
Cardiac failure	49 (51)
Cerebral edema	10 (10.4)

*Severity criteria according to World Health Organization, 2000.

Migrants of African origin travel for longer periods in highly malaria-endemic areas (globally, 75% of malaria infections and 89% of *P. falciparum* infections in travelers are acquired in sub-Saharan Africa [*18*]), are less likely to have pretravel encounters with a healthcare provider, and are therefore unlikely to take antimalarial prophylaxis (*18*). These factors explain why France, in comparison with many other European countries or the United States, has so many malaria cases and why the country appears to receive disproportionally high numbers of malaria-infected returning travelers from Africa (*19*), rather than from Asia or South America. As a result, *P. falciparum* is overrepresented in imported malaria in France in comparison with other industrialized countries. The case-fatality rate (4.4 per 1,000 cases) is among the lowest in the World Health Organization (WHO) 2004 Computerized Information System for Infectious Diseases database, probably because of the large proportion of African migrants in our study population.

The following characteristics were independently associated with death from falciparum malaria, according to multivariate analysis: older age, origin in an area not endemic for malaria, infection in East Africa, and no effective chemoprophylaxis. Increasing age has also been a risk factor for fatal falciparum malaria in smaller studies (*10,11,13,20,21*). As has been reported elsewhere (*21*), we found a gradual increase in risk over the entire age spectrum, resulting in particularly high risk among elderly patients. This factor should be taken into account when offering pretravel health advice, particularly as the age of international travelers increases.

Severe malaria and death were particularly frequent among nonimmigrants, as previously reported in smaller series (*6–8,13,22*). These results are consistent with the hypothesis of persistent acquired immunity, even after several years of nonexposure, which may partially protect African immigrants from fatal malaria, as previously shown for severe forms of malaria (*23*). Genetic factors, selected at the population level over centuries of exposure to the parasite, may also partly explain the relative protection of African immigrants compared with Europeans (*24,25*).

Except for the Comoros Islands (0.5 cases per 1,000 cases of falciparum malaria), countries accounting for large numbers of cases in this study (Senegal, Cameroon, Mali, and Côte d'Ivoire) had similar case-fatality rates (3.2 to 5.4 cases per 1,000 cases of falciparum malaria). Most travelers returning from the Comoros Island were migrants; few were European tourists. East African countries such as Djibouti, Kenya, Mozambique, and Tanzania accounted for fewer cases but a disproportionate number of fatalities (34.1 cases per 1,000). Ben-Ami et al. recently reported a high rate of severe malaria (6 of 29 cases, including 1 death) among patients who visited Mombassa, Kenya (*26*). More generally, Krause et al. reported that falciparum malaria acquired in Africa had a higher case-fatality rate than falciparum malaria acquired elsewhere (*11*). During the period of our study, an increase in malaria deaths, probably related to higher levels of drug resistance, was seen in residents of East Africa but not in those of West Africa (*27*). Those observations are not necessarily linked, but particular attention should be paid to travelers returning from these areas. Further studies are needed to confirm and explain these findings.

The risk for death was higher when prophylaxis was absent or ineffective than when appropriate prophylaxis was taken. On the basis of interview data, only 2 authentic failures of prophylaxis were suspected among our patients, but drug and metabolite concentrations were not assayed. These results are consistent with those of Krause et al., who reported that study participants who had taken chemoprophylaxis with chloroquine-proguanil were less likely to die than those who had not taken chemoprophylaxis (*11*). These results once again underline the importance of recommending antimalarial prophylaxis for travelers to malaria-endemic areas (*28*).

Bruneel et al. reported that platelet counts were significantly lower in patients who eventually died of *P. falciparum*–infected patients than in survivors (*8*) and that leukocyte counts also tended to be higher. In our popula-

Table 4. Factors independently associated with deaths among patients treated for falciparum malaria in French hospitals, 1996–2003 (n = 21,888)*

Variable	Odds ratio	95% Confidence interval	p value
Age			
Per increase of 10 y	1.78	(1.56–2.02)	<0.001
Origin and residence			
African travelers	1		
African residents	3.15	(1.32–7.51)	
European travelers	6.79	(3.49–13.2)	<0.001
European expatriates	4.44	(1.91–10.3)	
Others	3.02	(1.21–7.57)	
Region of malaria acquisition			
West Africa	1		
Central Africa	0.86	(0.52–1.41)	
East Africa	3.39	(1.49–7.72)	0.02
Madagascar and Comoros Islands	0.61	(0.24–1.53)	
Others	0.47	(0.11–1.95)	
Chemoprophylaxis			
Effective drugs†	1		
No chemoprophylaxis	2.07	(1.19–3.61)	0.04
Ineffective drugs†	1.90	(0.91–3.95)	

*Multiple imputations were used for missing data for the variables "region of malaria acquisition" (n = 9) and "chemoprophylaxis" (n = 2,366) (see Methods).
†Effective drugs were mefloquine, atovaquone-proguanil, doxycycline, and chloroquine-proguanil; ineffective drugs were chloroquine, proguanil, pyrimethamine, and sulfadoxine-pyrimethamine.

tion, a platelet count $<50\times10^9$/L was associated with increased risk of dying; this effect was particularly marked at counts $<10\times10^9$/L. Disseminated intravascular coagulation, which is associated with marked thrombocytopenia, was frequent in patients who later died (Table 3). Leukocyte counts $>10\times10^9$ cells/L were also associated with increased mortality, and the effect was particularly marked at counts $>15\times10^9$ cells/L. Hyperleukocytosis in this setting may be related to cytokine or cortisol release or to bacterial (especially nosocomial) infections, which were frequent in our patients who eventually died (Table 3). Bruneel et al. found that hyperparasitemia (>5%), a WHO severity criterion, was weakly linked to death. Although the number of circulating parasitized erythrocytes may not accurately reflect the number of adherent red cells in deep organ capillaries, which are the source of most clinical complications (*29*), hyperparasitemia appeared to be an important predictor of death in our series. However, parasitemia and some biologic data (hemoglobin, platelet counts, and leukocyte counts) could not be included in our multivariate analysis because an excessive amount of data were missing. In particular, hemoglobin, platelet count, and leukocyte count data were missing for more than half the patients.

A limitation of our study is that our network for collecting data accounted for only 50%–55% of total malaria cases imported to France. Two annual exhaustive studies (National Quality Control Survey [*30*]; F. Legros, unpub. data) suggest that representativeness of our sites was correct. Thus, risk factors associated with death in imported malaria would not likely differ for cases not seen in our network.

Severe and fatal malaria, even though it is eminently preventable, continues to be seen in areas that are not endemic for malaria (*31,32*). Fatal cases are rare in patients who take appropriate prophylaxis. With the current increases in intercontinental travel, numbers of elderly travelers, risk for transmission in malaria-endemic areas, and drug-resistant strains of *P. falciparum* (*16,33*), the numbers of fatal cases of imported malaria should be carefully monitored in the coming years in France and other industrialized countries. Preventive measures remain necessary for all travelers, including those from Africa, for whom adherence is often poor (*34*). Posttravel care should also be reinforced to reduce the interval between symptom onset and diagnosis (*35,36*).

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