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Epidemiologic Features Impacting the Presentation of Malaria in Children in Houston

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Abstract

Background—Malaria is diagnosed in children in the United States despite availability of effective chemoprophylaxis. The features impacting the presentation of malaria diagnosed in a nonendemic setting are not well characterized in children.

Methods—A retrospective chart review was conducted of children with peripheral smear-confirmed malaria diagnosed from 1994 to 2007 at 4 tertiary referral hospitals in Houston, TX.

Results—Among 104 children with malaria, 43 were recent immigrants and 61 were travelers leaving the United States. Severe malaria accounted for 21 (20%) of episodes. Children residing in the United States accounted for 86% of those with severe malaria. Factors relating to malaria severity included vacation-related travel ($P = 0.005$), female gender ($P = 0.02$), birth in the United States ($P = 0.043$), short travel duration ($P = 0.024$), and short duration from return to presentation ($P = 0.023$). Children with severe malaria more often had a history of vomiting ($P = 0.048$) and presented with hepatomegaly ($P = 0.008$), heart murmur ($P = 0.041$), and higher parasitemia ($P < 0.001$) than those with uncomplicated malaria. Vacation-related travel (OR: 19.7; 95% CI: 2.2–174.6) and hepatomegaly (OR: 6.1; 95% CI: 1.1–32.8) remained significant risk factors for severity by multivariate analysis. Prophylaxis appropriate to region of travel was documented in only 8 of 47 children leaving the United States.

Conclusions—Children diagnosed in Houston with severe malaria usually had traveled from the United States to malaria-endemic regions without benefit of appropriate prophylaxis. Malaria-related morbidity in nonendemic countries could potentially be reduced by optimizing adherence to prophylactic regimens.

Keywords

traveler; immigrant; malaria; *Plasmodium falciparum*

Despite the availability of effective preventive strategies, millions of cases of malaria occur annually, contributing to more than 10% of child mortality worldwide.¹ The burden of malaria is primarily borne in malaria-endemic regions, but malaria-related morbidity and

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mortality also occurs in the United States because of travel to malarious regions.² Passive surveillance through the Centers for Disease Control and Prevention (CDC) identified 1445 children diagnosed with malaria in the United States in 2006. When a reason for travel was known, children who traveled to visit friends or relatives constituted a majority of these cases.² Children diagnosed with malaria in North America usually are recent immigrants or have traveled from the continent without benefit of adequate prophylaxis.^{3–7}

Pretravel consultations, which should include options for malaria prophylaxis, are accessed infrequently by travelers at high risk for malaria.^{8–13} Immigrants returning to their country of origin to visit friends or relatives are less likely to receive pretravel advice than those traveling for other purposes and are less likely to adhere to prophylactic regimens than are those born in nonmalaria-endemic regions.¹⁴ A review of pediatric malaria in Houston from 1988 to 1993 found that three-fourths of children had visited the family's country of origin and that a majority did not receive proper prophylaxis, though severity of malaria was not specifically described.⁵

Most imported malaria in the United States is acquired in sub-Saharan and particularly in West Africa.² Malaria caused by *Plasmodium falciparum* is commonly acquired in US travelers to Africa and is of particular concern as it can lead to severe disease.¹⁵ Houston has a substantial West African population who may not appreciate the risk of malaria acquisition associated with travel to visit their family and relatives and the importance of chemoprophylaxis.¹⁶ We examined the contemporary epidemiology of malaria in Houston children to define prophylaxis practices and to delineate features associated with acquisition of severe malaria.

MATERIALS AND METHODS

Patients

A review of records for patients from birth to 17 years of age with a discharge diagnosis of malaria was conducted at 4 hospitals with tertiary pediatric care in Houston, Texas (Texas Children's Hospital [TCH], Ben Taub General Hospital, Memorial Hermann Hospital [MHH] and Lyndon Baines Johnson Hospital) from January 1994 to December 2007. The Institutional Review Boards for Baylor College of Medicine and Affiliated Hospitals, Harris County Hospital District and The University of Texas Health Science Center at Houston approved the protocol. Procedures were in accordance with the ethical standards for human subject research for the respective institutional review boards. Informed consent could not practicably be obtained and was not required. Subjects were identified through review of the consultation records for the Pediatric Infectious Diseases Services and by an International Classification of Diseases, ninth revision (ICD-9) code search. Medical records, laboratory, microbiologic, and diagnostic imaging findings of identified patients were reviewed. Malaria cases reported to the Houston Department of Health and Human Services were reviewed for the same interval.

Definitions

Malaria was identified if it was listed as a discharge diagnosis and a positive malaria smear was documented. Children lacking smear-positive evidence of malaria and those with unavailable medical record were excluded. A child was designated as traveling for vacation on the basis of information from the medical record. Most vacationing travelers were visiting the family's country of origin or friends and relatives. Appropriate prophylaxis was defined as the use of malaria prophylaxis appropriate to the region of travel. Treatment of malaria was considered delayed when antimalarial therapy was implemented more than 24 hours after presentation for medical care. A traveler was defined as a child presumed to have

departed from and returned to the United States, whereas an immigrant was any child whose travel originated outside of the United States. Severe malaria was defined as malaria complicated by parasitemia greater than 5%, cerebral malaria, severe anemia (hemoglobin less than 5 g/dL), pulmonary edema, abnormalities in coagulation, circulatory collapse and shock (indicated by the need for inotropic support), acute renal failure, metabolic acidosis, or hypoglycemia, as adapted from the definition used by the Centers for Disease Control and Prevention though without restriction to *P. falciparum* as the infecting species.¹⁵

Statistical Analysis

Factors relating to an outcome of severe malaria versus uncomplicated malaria were compared using a χ^2 or Fisher exact test for categorical variables and a Wilcoxon rank sum test or Kruskal-Wallis test for continuous variables with a nonparametric distribution. A *P* value of less than 0.05 was taken to be significant. Epidemiologic characteristics relating to the failure to receive pretravel prophylaxis, failure to take prophylaxis once prescribed or the occurrence of a delay in diagnosis were compared in a similar manner. Multivariate logistic regression was performed on risk factors that were associated with the development of severe malaria at a *P* $\leq$ 0.15. Data were maintained in a Microsoft Office Access 2003 (Microsoft Corporation, Redmond, WA) database and statistical analyses were performed with STATA 9 (Stata Corporation, College Station, TX, 2005).

RESULTS

Subject Group

The ICD-9 code search and query of infectious disease service databases yielded 149 potential cases of pediatric malaria during the 14-year interval. Fourteen were excluded based upon incorrect coding (8 subjects), diagnosis beyond the study interval (2 subjects), or age beyond that specified (4 subjects), leaving 135 potential subjects. Thirty-one were not further reviewed because a malaria smear was not performed (3 cases), record of a positive malaria smear was not available (22), or the chart could not be located (6 cases), leaving 104 children, each with 1 episode of malaria, to comprise the subject group. The Houston Department of Health and Human Services reported 79 episodes of pediatric malaria over the same interval. A lack of identifiers precluded a direct comparison of subjects from the Health Department with those from the record review.

Demographics

The median age of the 104 children (58 male and 46 female) was 7.2 years (range: 19 days to 17.4 years). Eighty-six children had a documented reason for travel. Of these, 43 were immigrants, and 43 had traveled from the United States. Eighteen children without an identified reason for travel but with explicit trip duration were also considered travelers, increasing the number to 61. Forty-two of 54 vacationing travelers were visiting the family's country of origin. Of travelers, the country of birth was most often the United States (86% for whom country of birth was specified) but for 33 of 61 children it was not specified. The median duration of travel was 30 days.

The mean number of malaria cases yearly was 7 (range: 3–13). Fewer children were diagnosed during the second than in the first 7 years of study (44 vs. 60 children). Sixty percent of children were diagnosed at TCH, 18% at Ben Taub General Hospital, 14% at Lyndon Baines Johnson Hospital, and 8% at MHH. Cases peaked in summer months, with 34% of episodes diagnosed in July and August (Fig., Supplemental Digital Content 1, <http://links.lww.com/INF/A263>).

Of the 61 children leaving from the United States, 90% traveled to West Africa, 5% to Central America, and 5% to Asia. Among 55 travelers to West Africa, 51 traveled to Nigeria. A majority (79%) of travelers visited their family's country of origin. Episodes in immigrant children occurred more often in the first than in the second 7 years of study (33 vs. 10 children). Over the entire interval, the proportion of immigrants with malaria decreased an average of 4% per year (P for trend = 0.004). Immigrant children hailed primarily from Honduras (44%) and Nigeria (30%), with the remainder from Cameroon, Congo, El Salvador, India, Liberia, Nicaragua, Pakistan, Vietnam, and the Philippines. Two children of recently immigrated women had congenital malaria. Malaria occurred in 4 sibling pairs.

Severity of Malaria

Twenty-one children had severe and 83 had uncomplicated malaria (Table 1). Those with severe malaria presented primarily to TCH (71%) and MHH (19%). Children evaluated at MHH represented a high proportion of severe as compared with uncomplicated malaria (19% vs. 5%, $P = 0.029$). Children with severe malaria were more likely to have traveled for the purpose of vacation (67% vs. 27%, $P = 0.005$), to be female (67% vs. 39%, $P = 0.02$), to be US-born (64% vs. 35%, $P = 0.048$), to have been present in the United States for a shorter time after return from travel before presentation (median: 13 days vs. 25 days, $P = 0.023$) and to have had a shorter trip duration (median: 23.5 days vs. 35 days, $P = 0.024$) than were children with uncomplicated malaria.

Fifteen children with severe malaria had *P. falciparum* and 6 had *Plasmodium vivax* malaria. Severe *P. vivax* malaria was acquired in Honduras (3 cases), Liberia (2 cases), and Nigeria (1 case). The manifestations of severe *P. vivax* malaria were parasitemia greater than 5% (2 children), severe anemia, (3 child), coagulation abnormalities (1 child), and cardiovascular shock (1 child). One child had more than one manifestation. One child with severe *P. vivax* malaria had sickle cell anemia. There were no other identified risk factors to explain the severity of disease.

Presenting Features

Admission features for children with severe and uncomplicated malaria are shown in Table 2. The common presenting features in all children were fever, lethargy, and chills, with a median maximum temperature of 104°F in each group. Children with severe malaria more often had a history of vomiting (81%) than those with uncomplicated malaria (57%) ($P = 0.048$). Pallor was the most commonly documented physical finding for all children within 24 hours of admission. Hepatomegaly, abdominal distension, and a heart murmur were observed more often in children with severe than with uncomplicated malaria (71% vs. 39%, $P = 0.008$; 42% vs. 15%, $P = 0.008$, and 67% vs. 42%, $P = 0.041$, respectively).

P. falciparum was the most common malaria species documented (52%). Others were *P. vivax* (37%), *P. falciparum* together with *P. vivax* (3%), non-*falciparum* species (2%), and 1% each of *Plasmodium malariae*, *P. ovale*, and *P. vivax* together with *P. malariae*. A species was not designated in 4% of smears. Children with severe malaria had significantly higher admission (median: 10% vs. 0.5%, $P < 0.001$), and peak parasitemia (median: 11.2% vs. 1.5%, $P < 0.001$) than children with uncomplicated malaria (Table 3). The median hemoglobin nadir (6.5 g/dL vs. 9.5 g/dL, $P \leq 0.001$) and platelet count nadir ($36 \times 10^3/\text{mm}^3$ vs. $97 \times 10^3/\text{mm}^3$, $P < 0.001$) were also significantly lower in children with severe than with uncomplicated malaria. Multivariate logistic regression analysis indicated that, when adjusted for species, gender, reason for travel, time since return, presence of murmur, presence of hepatomegaly, admission platelet count, and admission hemoglobin, only vacation-related travel (OR: 19.7; 95% CI: 2.2–174.6) and hepatomegaly (OR: 6.1; 95% CI:

1.1–32.8) remained significant risk factors for severe malaria. In contrast, higher admission hemoglobin was associated with a lower risk for severe malaria (OR: 0.6; 95% CI: 0.4–0.8).

Time to Treatment and Clinical Management

Forty-eight percent of children had a delay in treatment of malaria. Time to treatment (3.1 vs. 2 days) for children with severe and uncomplicated malaria did not differ significantly. Children with a delay in treatment had returned home for longer (23 vs. 14 days; $P = 0.037$) and were more likely to have a history of vomiting at presentation (76% vs. 51%; $P = 0.01$) than those without a delay.

A pediatric infectious disease specialist participated in the care of 76% of the children. Thirteen children received parenteral treatment with quinidine and all children also received oral therapy. Quinine was prescribed most commonly (56%) followed by chloroquine (37%), mefloquine (7%), sulfadoxine-pyrimethamine (6%), and atovaquone-proguanil (1% of children).

Use of Prophylaxis

There was no difference in the use of prophylaxis between children with severe and uncomplicated malaria (68% vs. 64%) or between children who were traveling to their families' country of origin versus traveling for other reasons (67% vs. 50%, $P = \text{NS}$). Of the 61 travelers, 48 traveled to the family's country of origin and 9 of these traveled explicitly to visit friends or relatives. Thirteen children traveled for other reasons.

Forty-seven travelers had documentation that malaria prophylaxis was used. There was no difference in the use of prophylaxis based upon reason for travel. Seventeen travelers had a pretravel medical provider visit. The highest proportion occurred in children traveling to visit family members or friends, as 5 of 9 of them obtained pretravel advice. Adherence with prophylaxis was documented in only 11 of 24 children for whom information was specified. Prophylaxis was documented as appropriate for the region of travel in 8 travelers and mefloquine, alone or in combination, was the most common agent (27% of regimens). Only 4 of these 8 children were documented to have taken prophylaxis by the prescribed regimen. Four were diagnosed with severe malaria, at least one of whom had received appropriate prophylaxis. There was no difference in use of pretravel services, use of prophylaxis or the agent for prophylaxis for children visiting relatives or friends compared with other travelers.

Course

Fifteen children received outpatient treatment and 89 were admitted to hospital for treatment. Eighteen were admitted to an intensive care unit, with duration of stay ranging from 1 to 8 days. A peak parasitemia of greater than 5% occurred primarily in *P. falciparum* malaria, and was observed in 31% of 52 children in whom degree of parasitemia was specified. Five percent of children had severe anemia. Simple transfusions were required in 17% of children and 7% required exchange transfusion. There were no differences in occurrence of these procedures in children with delayed compared with those with prompt treatment. There were no episodes of pulmonary edema or cerebral edema. Two children who had *P. vivax* malaria did not initially receive treatment for the exoerythrocytic phase of disease and had recrudescence of symptoms; each recovered without sequelae after treatment. Two additional children (one each with *P. falciparum* and *P. vivax*) had recrudescence of symptoms despite appropriate therapy as each child had return of parasitemia without additional exposure to a malaria-endemic region. There were no deaths or evident neurologic sequelae.

DISCUSSION

The 2 distinct groups of children in Houston at risk for malaria are travelers from and immigrants to the United States. Compared with recent reports indicating that malaria in North American travelers exceeded cases in foreign nationals immigrating to the United States, the frequency with which malaria occurred in recently arrived immigrant children in our series was high (41%).^{2,5,7,17} This high proportion of malaria in recently immigrated children was last reported in North America in 1995 and has not been observed since the 1980s in Europe.^{6,18}

Episodes of malaria in immigrants, especially those from Honduras or Nigeria, were particularly common in the earlier years of our review. Houston's Hispanic and black populations increased by 62% and 9%, respectively, from 1990 to 2000,¹⁹ although overall legal immigration into Houston declined 15% from 1992 to 2000.²⁰ In the United States as a whole, immigration from Honduras and Nigeria increased from 1990 to 1999,²¹ so national migration patterns can partially explain the trends we observed. It also is possible that malaria in immigrants is declining in association with decreasing immigration in the United States since 2001.

Children traveling from the United States to a family's country of origin, a group known to be at high risk for malaria acquisition, also comprised a large proportion of our subjects.^{2,12,18} Although travelers visiting friends and relatives are reportedly less likely to use prophylaxis or travel services when returning to a country of origin, we did not find this to be the case.^{9,11,13,22,23} Only slightly more than one-half of our child travelers used prophylaxis and only a subset used prophylaxis appropriate to the region of travel. This low uptake of prophylaxis is in accord with data citing use of prophylaxis in no more than one-half of all travelers.^{5-7,17,18,24} Our children explicitly designated as those visiting friends and relatives actually obtained pretravel advice somewhat more often than other travelers (56% vs. 25%), a trend noted in some geographic regions.^{25,26}

Stauffer et al²⁷ noted that the main reasons for progression to severe malaria were delays in diagnosis and inappropriate treatment while McCaslin et al¹⁷ concluded that delays in diagnosis were associated with increased severity of disease. Treatment delay occurred frequently in our children, but we found no difference in time to diagnosis or treatment in children with severe versus uncomplicated malaria, and no increase in the occurrence of complications among children with delayed diagnosis or treatment. Treatment delay did relate to a longer duration spent in the United States after return from travel.

The argument for appropriate prophylaxis is supported by our data that indicate that 86% of all episodes of severe malaria could have been prevented, as they occurred in US residents. Three children who entered the United States as immigrants (7%) had severe malaria as compared with 30% of children leaving the United States as travelers ($P = 0.005$). Immigrant children possibly had partial immunity to malaria through living in malaria-endemic regions.²⁸ The implications of severe *P. falciparum* malaria morbidity are of such import that prophylactic therapy is specifically targeted against this species.⁸ Recent data suggest that *P. vivax* also contributes to the burden of severe malaria in children and our findings support this view.²⁹ When adjusting for other variables, *Plasmodium* species was not an independent risk factor for malaria severity, though this observation may be limited by our sample size.

A multifaceted approach will be necessary to prevent imported malaria. Compared with an earlier report, the number of malaria cases in Houston children has increased.⁵ For children leaving the United States to visit malaria-endemic regions, efforts must raise awareness of the risk of contracting malaria and of the need for appropriate prophylaxis, particularly for

travelers to West Africa. In malaria-endemic countries where prophylaxis is not generally recommended, methods of prevention focus on use of insecticide treated nets and indoor residual spraying.³⁰ A high index of suspicion for malaria for any febrile child arriving or returning to the United States is warranted, especially during the summer months and winter holiday season, as indicated in Figure, Supplemental Digital Content 1, <http://links.lww.com/INF/A263>.

Pediatric malaria continues to occur in Houston. Child travelers from the United States often do not receive adequate prophylaxis and often develop severe malaria. Our study design precluded full characterization of access to pretravel services and identification of specific reasons for inadequate prophylaxis. The tools employed for malaria speciation were also limited by study design. We believe that species misidentification is unlikely as the diagnosing pathologists from these tertiary hospitals were experienced in evaluation of malaria smears. We also were unable to define the incidence of malaria because the precise population of children at risk could not be defined. Despite these limitations, our findings constitute a basis for the design of targeted interventions for child travelers in developed countries to reduce the occurrence of this potentially preventable disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Epidemiologic Features in Children With Severe and Uncomplicated Malaria

Feature	Severe Malaria (n = 21)	Uncomplicated Malaria (n = 83)
Mean [median] age in years (range)	6.6 [5.6] (1.1–17.3)	8.6 [8.1] (0.05–17.4)
Age less than 5 yr	8 (38)**	28 (34)
Female gender	14 (67)	32 (39)*
Ethnicity		
Asian	0 (0)	5 (6)
Black	18 (86)	55 (66)
Hispanic	3 (14)	22 (27)
Unknown	0 (0)	1 (1)
Reason for travel		
Vacation (includes those visiting friends and relatives)	14(67)	22 (27)*
Immigrant	3 (14)	40 (48)*
Other	3 (14)	4 (5)
Unknown	1 (5)	17 (20)
Travel to West Africa	16/18 (89) [†]	39/43 (91) [†]
Child born in the United States	9/14 (64) [†]	19/55 (35) ^{†‡}
Mean [median] days since return (range) [§]	20.7 [13] (0–120)	64.5 [25] (0–730) [‡]
Mean [median] duration of trip in days for travelers (range) [¶]	29.9 [23.5] (7–90)	94.2 [35] (7–730) [‡]

* $P \leq 0.02$ compared to group with severe malaria by χ^2 , Fisher exact test, or Wilcoxon rank-sum tests.

** Number (%) of children.

[†] Denominator is the number of children for whom data were specified.

[‡] $P < 0.05$ compared to group with severe malaria by Wilcoxon rank sum test.

[§] Denominator 21 and 79 for severe and uncomplicated, respectively.

[¶] Denominator 16 and 37 for severe and uncomplicated, respectively.

TABLE 2**Clinical Features in Children With Severe or Uncomplicated Malaria**

Feature	Severe Malaria (n = 21) No. (%) Children	Uncomplicated Malaria (n = 83) No. (%) Children
Signs and symptoms		
Fever	21 (100)	77 (93)
Lethargy	18/18 (100)*	33/38 (87)
Chills	10 /13 (77)	38/47 (81)
Vomiting	17/21 (81)	45/79 (57) [†]
Abdominal pain	15/18 (83)	35/52 (67)
Headache	9/15 (60)	34/47 (72)
Diarrhea	7/19 (37)	22/74 (30)
Physical findings		
Pallor	14/14 (100)	22/25 (88)
Heart murmur	14/21 (67)	32/77 (42) [†]
Splenomegaly	10/21 (48)	33/74 (45)
Hepatomegaly	15/21 (71)	28/72 (39) [†]
Abdominal distention	8/19 (42)	11/75 (15) [†]
Jaundice	7/10 (70)	9/22 (41)
Scleral icterus	7/17 (41)	16/60 (27)

* Denominator is the number of children for whom data were specified.

[†] $P \leq 0.048$ compared to group with severe malaria by χ^2 test.

TABLE 3**Laboratory Results in Severe or Uncomplicated Malaria**

Laboratory Value	Severe Malaria (n = 21)	Uncomplicated Malaria (n = 83)
Percent parasitemia at admission *	11.3 [10.0] (0.1–40) [†]	1.0 [0.5] (0.02–5) [‡]
Peak percent parasitemia	13.7 [11.2] (1–40)	1.8 [1.5] (0.02–5) [‡]
Hemoglobin at admission (g/dL)	7.6 [7.8] (2.9–11.3)	10.2 [10.1] (5.5–16.6) [‡]
Platelet count at admission (×10 ³ /mm ³)	83.0 [51.0] (15–255)	143.4 [133] (17–394) [‡]
Creatinine at admission (mg/dL)	0.8 [0.5] (0.3–5.9)	0.6 [0.6] (0.2–1.4)
Alanine aminotransferase at admission (IU/mL)	72 [54] (13–293)	36 [24] (5–271)

* Data are based upon the number of children for whom information was available.

[†] Data are expressed as mean, median (in square brackets), and range.

[‡] $P < 0.002$ compared to group with severe malaria by Wilcoxon rank sum test.