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Presentation and Treatment Outcomes of Liberian Children Age 5 Years and Under Diagnosed With Severe Malaria

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Abstract

Malaria is endemic in Liberia with a prevalence rate of up to 60% in some regions, and it has been a major cause of death in children under 5 years of age. Prior to the recent Ebola epidemic, we undertook a prospective, hospital-based pilot study at the National Referral Hospital in Monrovia, to characterize the presentation, accuracy of diagnosis, and treatment outcomes of children presenting for treatment of malaria. From June 2013 to May 2014, we recruited children 5 years and under who presented to the JFK Medical Center with suspected malaria. We collected both clinical and laboratory data on admission and on discharge. We enrolled 477 patients with an average age of 1.6 years. Demographic factors associated with testing negative for malaria included regular bed net use and prior treatment for malaria. The most common presenting symptoms of severe malaria in this population were headache and seizures. Of 246 patients admitted and treated for severe malaria, 33% tested negative by rapid diagnostic test and blood smear for malaria. The case fatality rate was higher for the patients who tested negative for malaria (4.9%) versus those who tested positive (0.6%). Three children who tested negative for malaria showed evidence of undiagnosed *Salmonella typhi* infection. These results suggest that malaria may be overdiagnosed and that the diagnoses of other infectious diseases, which present in a similar fashion, may be neglected. These findings underscore the need to develop rapid diagnostic tests to screen for alternative causes of febrile illness.

Keywords

malaria, fever, children, West Africa

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Introduction

Liberia is a West African country with a high clinical and public health burden of malaria. Recent data from the President's Malaria Initiative show that malaria continues to be a significant problem in Liberia, and it accounts for more than 40% of outpatient visits and 33% of inpatient deaths.¹ Based on the results from the Liberian Malaria Indicator Surveys in 2016,² the prevalence of malaria parasitemia by rapid diagnostic testing (RDT) in children under age 5 years was 66% in 2005, 37% in 2009, and 45% in 2016. Malaria is most prevalent in the north central and southeastern parts of the country, where prevalence is over 60%.

Since the civil war in Liberia, little research has been undertaken to study the clinical presentation of malaria

in children in Liberia. Little is also known about the accuracy of diagnosis and the effectiveness of antimalaria treatment in Liberian children and whether other potentially life-threatening causes of febrile illness, which mimic malaria, may exist in this population.

It has been established in other malaria endemic countries that differentiating malaria from other causes of pediatric febrile illness can be challenging. A striking

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example is the recent Ebola virus outbreak in West Africa, which posed many diagnostic and management challenges, since Ebola virus disease (EVD) shares many of the same symptoms as malaria.³ Other more common etiologies of febrile illness, such as *Salmonella typhi* and viral infections, are also prevalent and can also present in a similar fashion.^{4,5} Severely constrained laboratory resources often make a definitive diagnosis difficult to determine by clinical findings alone, and makes effective treatment challenging.

We undertook a prospective, hospital-based study to characterize severe malaria in Liberian children age 5 years and under. We also evaluated the accuracy of diagnosis and effectiveness of treatment for malaria in this population. Finally, we piloted a study looking at 2 potential alternative causes of febrile illness, *S typhi* and *Dengue virus*, in children who were hospitalized for malaria but tested negative for this parasite.

Methods

Study Overview

We carried out a prospective longitudinal study of the clinical course for children seen for or admitted with suspected malaria over a 12-month period from June 2013 through May 2014 at the JFK Medical Center, Monrovia, Liberia. We recruited both children being admitted for severe malaria and outpatients with uncomplicated presentations, to compare the clinical and demographic characteristics of each presentation. The study was terminated due to the Ebola epidemic, which reached Monrovia in late May 2014.

Study Setting

The study site, JFK Medical Center, is a tertiary care facility situated in Monrovia, the capital city, and is the National Referral Hospital for the country. The under 5 (U5) unit consists of 30 beds with a census of about 250 admissions per month. Children admitted to this unit are 5 years of age and under, and approximately 42% of these admissions are for the treatment of malaria. The outpatient clinic sees approximately 1800 children per month, and it is estimated that 40% are seen for suspected malaria.

Patient Recruitment

Inclusion criteria included the following: (1) presentation to the pediatric "U5" unit at JFK Medical Center; (2) signs and symptoms on admission consistent with severe malaria including prostration, weakness, impaired

consciousness, seizures, respiratory distress, and treatment initiated for severe malaria; (3) parental written consent; and (4) age range birth to 5 years of age. Exclusion criteria included children currently on treatment for HIV or other complicated illnesses, which may affect immune function.

Clinical Assessment and Data Collection

A research nurse who speaks local dialects interviewed parents and obtained patient demographics and information about clinical signs and symptoms of malaria. A standardized data collection form was utilized, which included the World Health Organization (WHO) criteria of severe malaria. Parents were also asked about any additional symptoms not listed on the form.

At the time of hospital discharge, or on hospital day 3, whichever was first, the research nurse obtained additional clinical information from inpatient study subjects to assess treatment-related outcomes.

Clinical Laboratory Studies

In Liberia, the U5 clinical lab was utilized to perform malaria diagnostic laboratory studies. The *First Response* malaria rapid diagnostic test (Premier Medical Solutions, Inc, Denver, CO), which tests for the malaria HRP2 antigen, was used to diagnose patients with malaria. Admitted patients also had a malaria thick blood smear and hemoglobin level performed, as per standard protocol. The presence of malaria parasites was determined using Giemsa-stained slides and read by trained microscopists. For the purposes of this study, malaria smears were also obtained on hospital discharge or on hospital day 3, whichever came first, to check for clearance of parasites.

Clinical Management

The majority of patients were seen initially by a trained medical officer in the outpatient department of JFK Medical Center. Patients who were acutely ill and needed urgent medical attention were brought directly to the U5 unit for inpatient admission. Many of these patients were started presumptively on malaria treatment, due to the acuity of their illness. Outpatients who were found to be RDT positive, but judged by the medical officer providing as not having symptoms or signs of severe malaria, were treated at home with oral ACT (artemether 20 mg/lumefantrine 120 mg), 1 pill twice daily for 3 days, according to a standard protocol.

Patients who were judged to have signs and symptoms of severe malaria (RDT positive, symptoms of

severe malaria by WHO criteria) were referred for inpatient admission. These patients received a malaria smear and hemoglobin level prior to the initiation of treatment. Inpatients were treated using either intravenous (IV) quinine (20 mg/kg loading dose, then 10 mg/kg every 8 hours for at least 3 doses) or IV artesunate (2.4 mg/kg IV every 12 hours for at least 3 doses). At the time that this study was performed, Liberian national guidelines had recently changed to require IV artemisinin-based compounds be used as first-line treatment for inpatient treatment of severe malaria. Typically, there is no investigation performed to determine if patients have cleared their parasitemia on discharge.

After completing the specified course of IV treatment, children were discharged home with an additional 3-day course of oral ACT. We performed a repeat malaria blood smear on hospital discharge. Typically, there is no follow-up to check if patients have completely cleared their parasites after completing treatment.

Research Laboratory Methods

Finger prick or venous blood samples for future investigations were obtained from enrolled study participants and collected using sterile technique into BD anti-coagulated Microtainer tubes (~500 μ L). Blood samples obtained on admission for research purposes were centrifuged in the JFK laboratory to separate plasma from blood cell pellet. The samples were then frozen in -20°C freezer until transport. Samples were transferred by air carrier to UMass Medical School for further investigation.

Immunological Studies

Plasma samples from patients admitted with presumed severe malaria, but who proved to be RDT and blood smear negative were analyzed for the presence of other potential pathogens. Commercially available ELISA assays were used to detect IgM (immunoglobulin M) antibodies specific to *S typhi* (My BioSource, sensitivity 95%, positive predictive value 77%) and *Dengue* NS1 antigen (Corgenix, sensitivity 72%, positive predictive value 100%).^{6,7}

Data Analysis

All data were transferred to a database that was created in REDCap. We performed descriptive statistics on all variables of interest. We explored the relationship among the individual covariates with malaria cases (hospitalized patients who were RDT positive and achieved resolution of symptoms and clearance of parasitemia by discharge)

and also between cases and noncases, and patients with severe (patients who were RDT positive and with symptoms of severe malaria) versus mild disease (patients who were RDT positive but with no symptoms of severe disease). As appropriate, between group differences were examined using χ^2 tests of independence (categorical variables), *t* tests (continuous variables), or the equivalent nonparametric tests depending on the distribution of the variables. A 2-sided $P < .05$ was considered to be statistically significant.

We performed logistic regression analysis to determine the demographic and clinical characteristics that were most significantly associated with severe malaria (RDT-positive inpatients). Results were age adjusted, since age was noted to be a significant confounder.

Ethical Approval

Institutional review board (IRB) approval was obtained from the IRB at JFK Medical Center, Monrovia, Liberia, and from the University of Massachusetts Medical School, Worcester, MA (UMass IRB Docket # H00001063).

Results

Patient Enrollment

During the period from June 2013 to May 2014, a total of 478 children ranging in age from 0 to 5 years who presented to JFK Medical Center in Monrovia with fever and suspected malaria were enrolled in this study (Figure 1). Sixteen patients were excluded due to missing data. Of the 462 remaining, 233 (50.4%) tested positive by RDT for malaria. Of those testing positive, 165 (70.8%) met the WHO criteria for severe malaria and were admitted to the hospital for IV treatment as previously described. The other 68 RDT-positive patients had uncomplicated malaria and were treated as outpatients with oral ACT.

Demographic and Clinical Characteristics of Children With Malaria

Demographic Characteristics. The average age of patients enrolled in the study was 1.6 years. Table 1 shows demographic and clinical characteristics of children evaluated in this study by RDT status. There were a significantly greater proportion of patients less than 1 year of age in the RDT-negative group versus the RDT-positive group, 52% versus 26%, respectively. There were also a significantly greater proportion of patients less than 1 year of age who had uncomplicated versus severe disease, 52% versus 17%, respectively.

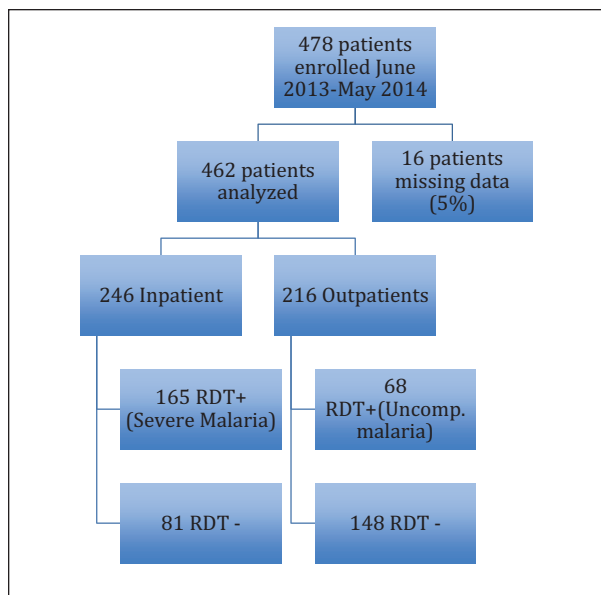


Figure 1. Patients recruited to study. A total of 478 patients presented to the hospital with fever and signs and symptoms consistent with malaria and were enrolled in the study. Patients with missing data were excluded. Of the 462 patients with data, 246 had suspected severe malaria, and were admitted. A total of 216 had milder disease, and were evaluated as outpatients. Eighty-one of the 246 patients admitted with a diagnosis of severe malaria tested negative for malaria. Of the 216 outpatients with symptoms of malaria, only 68 tested positive for malaria.

Only 31% of parents reported regular bed net use; 40% of children had a history of treatment or hospitalization for malaria in the past. Overall, 22% had used an antimalarial medication obtained from a clinic or pharmacy prior to presentation to treat the current febrile illness. Of these, 26% were RDT-negative patients and 19% were RDT-positive patients. Since HRP2 antigen and RDT positivity persists from 2 to 4 weeks after treatment of active infection, it is unlikely that the RDT-negative patients, who typically presented with fever for less than 4 days, were cases of malaria.

Children who tested RDT positive were older and were more likely to be from an urban environment versus those who were RDT negative. This is likely due to the fact that access to hospital care is very challenging in rural environments. Children who tested negative for malaria were more likely to be sleeping under bed nets regularly as compared with their RDT-positive counterparts (Table 1 and Figure 2).

Demographic characteristics associated with severe malaria (WHO criteria, inpatient admission) versus those associated with uncomplicated malaria (outpatient treatment) are shown in Table 2 and Figure 2. Patients

from urban areas were more likely to present with severe malaria. Alternatively, patients with uncomplicated disease were more likely to have been using bed nets regularly, used an antimalarial medication prior to presentation, and were more likely to have been treated for malaria in the past when compared with those who presented with severe disease.

Clinical Characteristics. Clinical signs and symptoms were elicited from all study participants and are shown in Table 1. The clinical symptoms most significantly associated with a diagnosis of malaria were headache and vomiting (Figure 2). Vomiting was not a symptom on the original checklist; rather it was a symptom that was added when patients were asked about “other symptoms.” It was found to be significantly associated with testing RDT positive in this population. The only clinical symptom significantly associated with being RDT negative was diarrhea.

Clinical data were also analyzed to determine if there were clinical symptoms that were associated with severe malaria (RDT-positive inpatients) versus uncomplicated disease (RDT-positive outpatients; Table 2). Headache, prostration, weakness, and seizures were significantly associated with severe disease. The symptoms most significantly associated with uncomplicated disease included diarrhea and cough (Figure 2).

Treatment Outcomes

A total of 246 patients were admitted to the hospital with febrile illness and malaria and were presumptively treated for malaria. These patients were assessed on admission and followed through discharge or hospital day 3 to determine their outcomes (Figure 3).

Among these 246 patients admitted and treated presumptively for malaria, 165 (67%) tested positive for malaria by RDT. The remaining 81 patients tested negative by RDT and malaria smear. There were 5 deaths in this young patient cohort, including 1 in the malaria-positive group and 4 in the malaria-negative group. The hospital case fatality rate for patients with RDT-positive malaria was 0.6%; the case fatality rate for those who tested RDT negative, but who were still treated for malaria, was 4.9%. Due to the lack of diagnostic capacity, the causes of death were not well defined.

Of the 165 patients who were admitted and tested positive for malaria, 142 (86%) responded effectively to treatment (resolved symptoms, parasite cleared on day 3 smear). However, 19 patients (11%) admitted with RDT-positive malaria did not clear their parasites after treatment and harbored parasite levels ranging from 1+ to 4+. Nevertheless, the patients in this group had resolved

Table 1. Demographic and Clinical Characteristics of Children With Severe Malaria.

Characteristics	RDT Positive (n = 232)		RDT Negative (n = 230)		P
Demographic characteristics					
Age in months (mean)	25.0		14.0		<.001
	n	%	n	%	
Sex (female)	107	46.1	105	45.7	.93
Regular bed net use	50	21.6	82	35.7	<.001
Treated for malaria in past	92	40.0	93	40.4	.92
WHO-defined symptoms of severe malaria					
Febrile days (mean)	3.75		3.66		.68
Impaired consciousness	19	8.2	10	4.30	.12
Jaundice	2	0.01	2	0.01	1.00
Prostration/weakness	149	64.2	98	42.6	<.001
Respiratory distress	38	16.4	17	7.39	.013
Seizures	57	24.5	26	11.3	.002
Severe anemia (Hgb < 5.0 mg/dL)	9	7.09	0	0.00	
Hyperparasitemia	69		0	0.00	
Other symptoms reported					
Cough	142	61.2	128	55.7	.26
Diarrhea	50	22.3	51	22.2	.91
Headache	179	77.0	117	50.9	<.001
Vomiting	90	38.8	47	20.4	<.001

Abbreviations: RDT, rapid diagnostic testing; WHO, World Health Organization; Hgb, hemoglobin.

their acute symptoms by day 3 and were discharged home, with malaria-positive blood smears (parasitemia is not routinely retested after symptoms resolve). The average age of this cohort was 28 months, and only 2 were less than 9 months old. The majority of these patients were treated with IV artesunate as a monotherapy.

Patients who were hospitalized, but were RDT negative, were screened retrospectively for 2 alternative causes of febrile illness: *Dengue virus* and *S typhi*. A total of 3 patients (3.7%) who were RDT negative tested positive for *S typhi* IgM by ELISA. All of these children, who were older than 3 years, were treated with antimalarials, but none received antibiotics because this test was done retrospectively as part of this pilot research project. Of the 3 patients, 2 resolved symptoms and were discharged on day 3. Since the patient's symptoms resolved without antibiotic treatment, it is possible that this represented a false positive test result. The third patient did not resolve symptoms immediately and was hospitalized for 7 days. The hospitalized RDT-negative patients were also tested retrospectively for *Dengue virus* by ELISA to NS1 antigen, but none tested positive.

Discussion

We undertook this pilot study prior to the Ebola epidemic to learn about how severe malaria presents in

Liberia and whether we could identify additional risk factors associated with severe disease in young children 5 years and under. We also sought to determine the outcomes of children admitted to the hospital with a diagnosis of severe malaria. Finally, we were interested in learning if patients who were being admitted and treated for severe malaria could be suffering from an undiagnosed, alternative type of febrile illness. To our knowledge, there have been no prior studies that describe the presenting features and clinical outcomes of severe malaria in Liberian children.

Clinical and Demographic Features of Severe Malaria in Liberian Children

In resource-limited settings such as Liberia, it is presumed that the majority of patients do not seek hospital care due to distance, lack of transportation, and expense. Studies performed in other countries with high malaria burdens have been helpful in understanding health care seeking behaviors of parents with children experiencing symptoms of malaria, and how these behaviors differ in rural versus urban environments.⁸⁻¹⁰ Replicating these studies in Liberia will be an important next step in moving forward with malaria control programs. Also, in these remote regions, there are few diagnostic resources available to help distinguish malaria from a myriad of

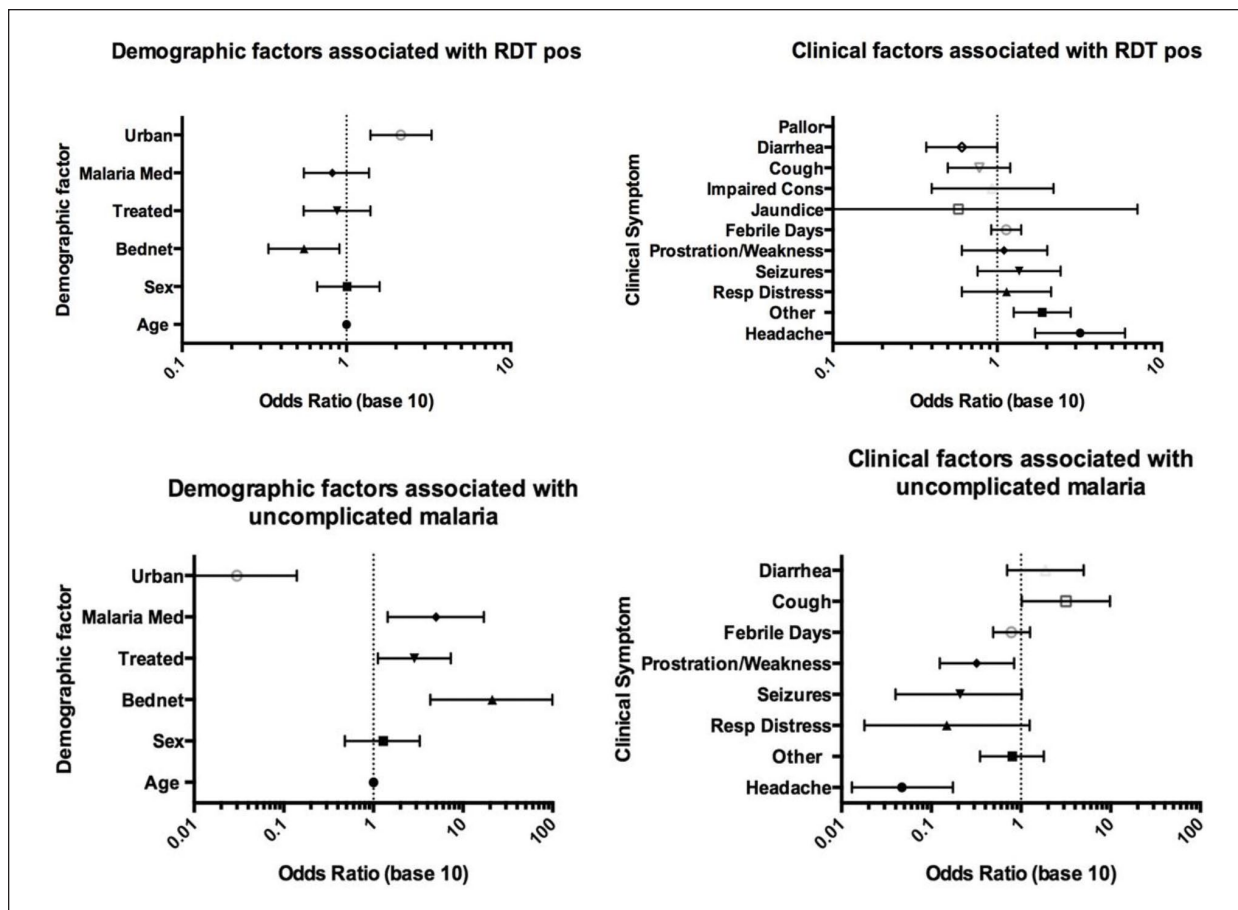


Figure 2. Logistic regression analysis of demographic and clinical features associated with rapid diagnostic testing (RDT)-positive patients versus RDT-negative (top panel) and with RDT-positive outpatients (uncomplicated malaria) versus RDT-positive inpatients (severe malaria; bottom panels).

other febrile illnesses. Distinguishing children at risk for severe malaria can be useful in identifying those children who need prompt referral for hospital management. The use of RDTs in these remote regions has been extremely helpful for this reason.

We identified several demographic factors that help distinguish children who are at risk for severe disease. Consistent with studies from other malaria endemic countries, we found that young age is a significant risk factor in this population of children who are exposed to a constant, high level of malaria transmission. In our population, the mean age of all children who tested RDT positive for malaria was 2.1 years. The mean age of children with severe malaria, requiring hospitalization, was slightly higher (2.4 years).

Very young children, from age 0 to 12 months, were less likely to test positive for malaria even when symptomatic. This likely reflects the presence of maternal IgG antibodies in this age group. Maternal antimalaria

immunoglobulin confers protection from malaria and is thought to persist from birth up to 6 to 9 months of age.¹¹ In contrast, slightly older children (1-4 years) were more likely to have severe malaria. Since maternal antibody is waning at this point, children in this age group have little immunity and are constantly exposed to infective mosquitoes.

These results are consistent with prior epidemiologic studies of severe malaria in other countries with high transmission, such as Tanzania and Kenya, which have shown that the median age of children affected is inversely proportional to transmission intensity.¹² In areas of intense malaria transmission such as Liberia, younger children with undeveloped immunity are more likely to be affected and hospitalized, as was seen in our study.

In comparing patients with severe versus uncomplicated malaria, we found that a higher percentage of patients with uncomplicated presentations had reported prior episodes of malaria. This suggests that children

Table 2. Demographic and Clinical Characteristics of Patients With Severe (Inpatient) Versus Uncomplicated (Outpatient) Malaria.

Characteristics	RDT + Inpatients (n = 165)		RDT + Outpatients (n = 68)		P
Age (mean, years)	2.41		1.37		<.001
	n	%	n	%	
Female	68	41.2	39	57.3	<.001
Urban	104	63.0	34	50.0	<.001
Regular bed net use	20	12.1	30	44.1	<.001
Treated for malaria in the past	48	29.0	45	66.1	<.001
Antimalarial use prior to presentation	8	6.99	30	44.8	<.001
Headache	156	94.0	24	35.3	<.001
Prostration/weakness	133	80.1	16	23.5	<.001
Impaired consciousness	18	10.8	1	0.00	.016
Pallor	0	0.00	0	0.00	1.00
Seizure	54	32.5	3	2.94	<.001
Cough	107	64.5	35	48.5	.08
Diarrhea	37	22.3	13	17.6	.73
Jaundice	1	0.01	0	0.00	1.000
Respiratory distress	36	21.7	0	0.01	<.001
Vomiting	81	48.8	9	13.2	<.001
Febrile days (mean)	3.70		3.81		.67

Abbreviation: RDT, rapid diagnostic testing.

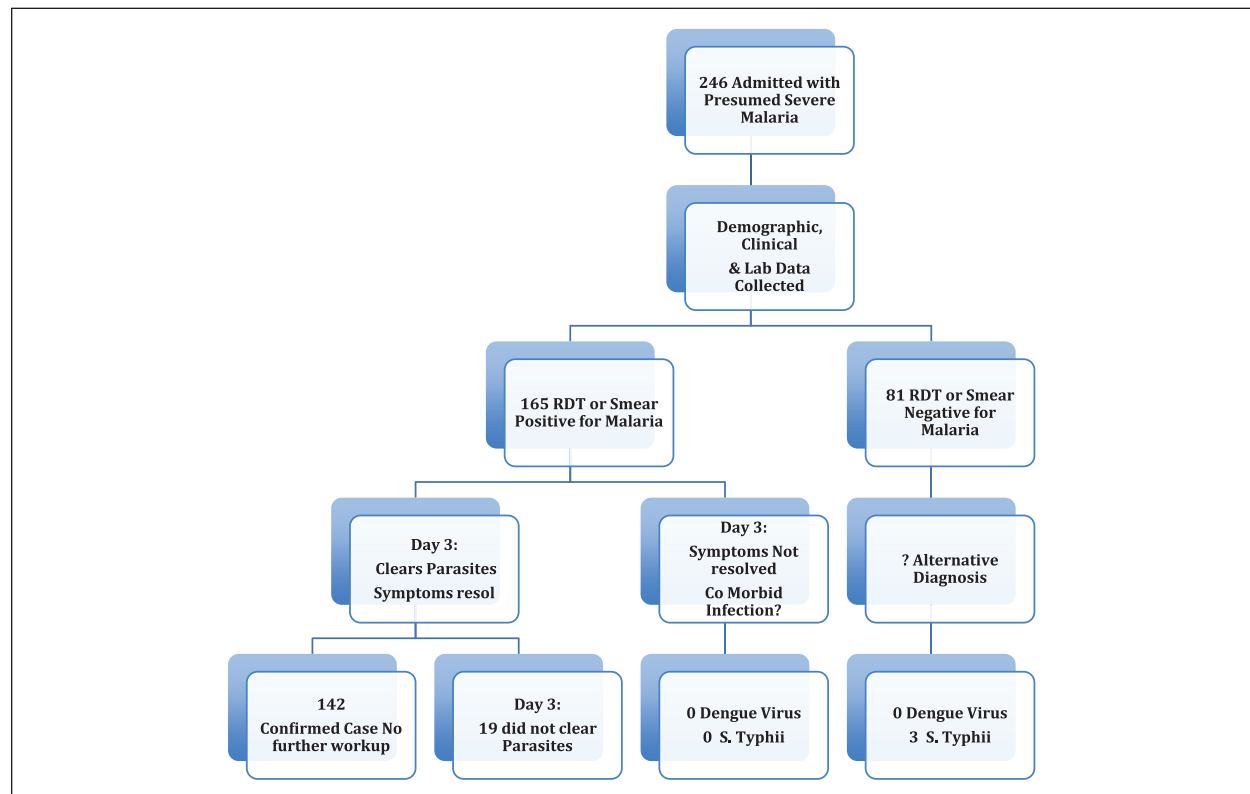


Figure 3. Results of febrile case investigations for admitted patients. Of the 246 patients who were admitted with severe malaria, 165 tested positive for malaria by rapid diagnostic testing (RDT) and malaria blood smear. Patients who tested positive for malaria were then screened for malaria on discharge. Of the admitted patients, 81 tested negative by smear and/or RDT. These patients were tested for *Salmonella typhi* and *Dengue virus* as alternative causes of their fever.

with reported past infections had an opportunity to develop semiprotective antimalarial immunity that would result in uncomplicated infections compared with those with no reported past infections. This finding is consistent with other reports in the literature.¹³

We identified several clinical symptoms that are associated with severe malaria in Liberian children, and which may help identify high-risk patients. In particular, prostration, weakness, seizures, and respiratory distress were significantly associated with being hospitalized and RDT positive. A large number of children in our population also presented with symptoms of headache and vomiting, which were highly associated with severe disease. These findings align with the WHO criteria for severe malaria, which have been described previously.^{14,15} Our findings are consistent with these observations and provide reassurance that clinical signs and symptoms of malaria are informative in this setting. In addition, in this setting, headache and vomiting may also be important clinical indicators of malaria. These symptoms have frequently been described in populations presenting with malaria, although are not listed as WHO criteria.^{16,17}

Treatment Outcomes

Many public health efforts designed to address the management of malaria in Africa have focused on bringing patients with febrile illness to hospital attention, but few studies have examined the accuracy of diagnosis and appropriateness of hospital treatment. Current protocols in use to diagnose severe malaria are based on reducing the risk of mortality and are sensitive, but not specific.¹⁸ Yet the presumptive diagnosis of malaria, and the consequent neglect of alternative diagnoses in hospitalized patients have been demonstrated to affect morbidity and mortality. Therefore, second motivation for this pilot study was to evaluate the accuracy of diagnosis and treatment outcomes for children admitted with and treated for severe malaria in the hospital setting.

With regard to accuracy of diagnosis, 67% of patients admitted with a diagnosis of severe malaria were accurately diagnosed. However, approximately one third of the children in our study who were admitted and treated for severe malaria were RDT negative and malaria smear negative on admission. Consequently, we noted a 4-fold increase in case fatality rates in the RDT negative patients when compared with the RDT positive patients. This suggests that their deaths were caused by an alternative, undiagnosed, and therefore untreated illness.

To test this hypothesis, we screened the 81 RDT negative hospitalized patients for 2 potential pathogens,

which share clinical features with malaria: *S typhi*, a pathogen known to be endemic in this population,⁴ and *Dengue virus*, a pathogen which has been reported in the West African region.¹⁹ *S typhi* presents in a similar fashion as malaria, with high fever and vomiting. If left untreated, it can lead to intestinal perforation and death. There were 3 children who tested positive for this pathogen, making it the likely cause of their illness. This supports our finding that children who are presumed to have malaria are at high risk of being undiagnosed and the true cause of their illness left untreated. Our pilot study screened for only 2 alternative causes of illnesses. Prior studies have also demonstrated that overdiagnosis of malaria, and the resulting neglect of other diagnoses, results in higher fatality rates for the patients who do not have malaria. A prospective hospital-based study performed in 10 hospitals in Tanzania concluded that patients admitted with a diagnosis of malaria who were slide negative were often not treated with antibiotics and had twice the hospital case-fatality rate of their slide positive counterparts.²⁰

Future studies designed to elucidate the causes of acute febrile illness will be important if undertaken in West Africa, since it is likely that EVD may be endemic in this area.

With regard to treatment outcomes, the majority of the 165 admitted, RDT-positive patients (87%) responded to antimalarial treatment with IV quinine or artesunate, resolved their symptoms, and were discharged home by hospital day 3. However, 11.5% of patients with malaria were noted to have persistent parasitemia on their day 3 blood smear and had not cleared their parasites at the time of discharge. Patients are not usually checked for persistence of parasitemia on discharge, so this was a new finding. The treatment protocol includes an additional 3-day course of artemisinin-based combination therapy (ACT) given to patients to complete postdischarge, so it is possible that these patients did eventually clear their parasites. There is no follow-up data to support this; however, as patients do not typically follow up for repeat blood smear after their treatment is completed.

This group of patients who did not clear their parasitemia will be an important group to follow in future studies for many reasons. It is well known that malaria treatment does not always induce sterilizing immunity, and even though a child may no longer suffer the symptoms of malaria or be at risk of death, they can still harbor parasites. These children who carry malaria asymptotically also serve as a reservoir to infect others. Therefore, determining if they have cleared their infection is of great importance. Furthermore, those children who continue to harbor parasites after treatment is complete could be doing so because they are developing

tolerance to malaria parasites. The mechanisms involved in the development of this tolerance are important in understanding how immunity to malaria develops. This correlate of protection could be useful in strategies used in malaria vaccine development. Finally, it is possible that these patients may have not cleared parasites because of antimalarial drug resistance, as has been described by the WHO.²¹ Polymorphisms in 2 drug resistance genes, *pfprt* and *pfmdr1*, have recently been described in Liberia.²² Surveillance methods should continue to screen such patients for parasites harboring drug resistance mutations.

Strengths of this study include the fact that, to our knowledge, this is the first study investigating the demographic and clinical characteristics of malaria in Liberian children since the second civil war, which began in 1999. Our data are also novel in that they were collected prior to the EVD epidemic and may be helpful in establishing baseline characteristics of this population.

Our pilot study had several limitations that need to be kept in mind in interpreting the study results. We worked with a relatively small sample of patients who were referred to, and treated at, the national referral hospital. This population of patients may not be representative of the Liberian population as a whole, so we do not know if our results are generalizable. Our limited budget prevented full exploration of WHO signs and symptoms of malaria, such as hyperglycemia, acidosis, and hyperparasitemia. These laboratory investigations are not routinely performed on patients at JFK Medical Center; therefore, we were not able to validate symptoms with clinical diagnostics. We were also unable to screen for other types of pathogens known to be prevalent in African children, such as non-typhoid *Salmonella* and *Streptococcus pneumoniae*. Finally, we were unable to follow patients after hospital discharge, to learn if they later cleared their parasites after discharge.

Our pilot study is a first step in characterizing the presentation and treatment of malaria in young children and defining the landscape of acute febrile illness in Liberia. Further investigations are needed to better define the myriad causes of febrile illnesses in this setting, as has been accomplished in other countries.²³ This knowledge will help make decisions about resource allocation and to determine which additional diagnostic testing will need to be implemented. The recent EVD epidemic underscores the crucial need for this information. It is postulated that if an RDT for EVD existed at the time of the outbreak, the number of deaths caused by this outbreak would have been up to one third fewer.²⁴ A better approach to malaria, and a better understanding of alternative causes of acute febrile illness that exist in

this region will help develop relevant point of care diagnostics and broader treatment algorithms and will ultimately translate into improved outcomes for young children.

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Author Contributions

B.C-A implemented and oversaw all aspects of the research study and assisted in writing the manuscript; P.M assisted with study design, securing funding, and in writing the manuscript. K.U contributed with data entry; E.A assisted with all lab studies performed at JFK and preservation of samples; A.M provided supervision and mentorship to the team.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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