Am. J. Trop. Med. Hyg., 98(3), 2018, pp. 683–691
doi:10.4269/ajtmh.17-0681

Anemia was an Uncommon Complication of Severe Malaria in a High-Transmission Rural Area of Western Uganda

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Abstract. The clinical epidemiology of severe malaria among patients presenting to peripheral health centers has not been well described. We conducted a prospective, observational cohort study to describe the epidemiology and clinical manifestations of severe malaria in a highland area of declining transmission intensity in Western Uganda. Individuals presenting with a history of fever were screened with a malaria rapid diagnostic test (RDT). We prepared blood smears and conducted clinical and laboratory testing for those with a positive RDT. We defined severe malaria in accordance with World Health Organization guidelines for research and epidemiological studies. A total of 6,641 individuals underwent testing for malaria. Ninety-six of 1,462 (6.6%) participants with confirmed parasitemia satisfied the criteria for severe malaria. The incidence of severe malaria peaked between 2 and 3 years of age (incidence rate ratio = 17.1, 95% confidence interval = 8.4–34.9, $P < 0.001$) and then declined steadily until age 10. However, we also found a second peak among those ≥ 50 years of age. Severe anemia was uncommon, detected in only 5.3% of cases. Instead, shock (22.2%) and lactic acidosis (19.4%) were most frequently encountered. Our results suggest that the clinical characteristics of severe malaria presenting to rural, peripheral health centers may be different than previously observed in referral centers. These findings merit further investigation into the optimal methods for identification and management of severe malaria in rural health centers in the region.

INTRODUCTION

After more than a decade of investments in control programs, significant progress has been made in reducing the global burden of malaria.[1] Yet, severe *Plasmodium falciparum* malaria remains a leading cause of pediatric morbidity and mortality in sub-Saharan Africa, accounting for nearly 300,000 deaths among children less than 5 years of age.[2] Although much of the gains were achieved by reducing malaria transmission, there have been relatively few advances in the diagnosis and clinical management of severe malaria, a situation that some consider to be a neglected strategic priority.[3]

Traditionally, severe malaria has been diagnosed based on the presence of one of three distinct clinical syndromes: severe anemia, cerebral malaria, or respiratory distress. The prevalence of these syndromes among children with severe malaria, however, varies with transmission intensity. Severe anemia is generally more common in areas of high transmission, whereas cerebral malaria is more common in areas with low or seasonal transmission.[4–7] In a high-transmission area of Uganda, for example, a recent study found that 65% of children with severe malaria admitted to a large academic referral center had severe anemia, whereas only 20% had cerebral malaria.[8]

Most of the landmark studies describing these syndromes were conducted at district hospitals and referral centers. Yet in Uganda, nearly one-third of children with acute febrile illness who seek care do so at public health centers.[9] These facilities are not staffed by physicians and typically lack the requisite laboratory infrastructure to establish a diagnosis of severe malaria.[10] Although most guidelines recommend referral for patients with severe malaria, the financial and logistic resources required may limit this practice.[11,12] Therefore, a better understanding of the epidemiology and clinical manifestations of severe malaria in peripheral health centers is of critical importance to developing appropriate diagnostic algorithms and treatment protocols for these resource-limited settings.

We conducted a prospective cohort study in rural Uganda among individuals presenting to a rural health-care facility with undifferentiated fever. The objectives of the study were to describe the demographic, clinical, and laboratory characteristics of severe malaria at a peripheral health center in a high-transmission setting. As a secondary objective, we sought to examine the burden of severe malaria in adults, which is less well studied but could become increasingly important as malaria transmission and acquired immunity decline, and as life expectancy increases in many endemic countries.

MATERIALS AND METHODS

Study setting. The Bugoye Level III Health Center (BHC) in the Kasese District of Western Uganda (0°18′ N, 30°5′ E) functions as the primary health center for the Bugoye subcounty. This rural sub-county comprises 36 villages and covers an area of approximately 55 km^2. The catchment area of the health center includes more than 50,000 residents of the Bugoye sub-county as well as residents of neighboring villages from the Maliba sub-county immediately to the East. The health center maintains general, pediatric, and obstetric wards for inpatient services, along with a busy outpatient department (OPD) that cares for 60–80 patients per day. Clinical officers, nurses, midwives, and laboratory technicians employed by the Ugandan Ministry of Health staff the health center. During

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TABLE 1

Study criteria for severe malaria required *Plasmodium falciparum* parasitemia on microscopy and/or polymerase chain reaction and any one of the following

Impaired consciousness	Blantyre coma score < 3 for children under 5 years of age or Glasgow coma score < 11 for adults
Metabolic acidosis	Plasma bicarbonate of < 15 mmol/L or venous plasma lactate > 5 mmol/L
Hypoglycemia	Blood or plasma glucose < 40 mg/dL (< 2.2 mmol/L)
Severe anemia	A hemoglobin concentration < 5 g/dL in children < 12 years and < 7 g/dL in adults together with a parasite count > 10,000/μL
Kidney injury	Plasma or serum creatinine > 3 mg/dL & blood urea nitrogen ≥ 20 mg/dL
Pulmonary edema	Oxygen saturation < 92% on room air with a respiratory rate > 30/minutes
Shock	Systolic blood pressure < 70 mm Hg
Convulsions	History of seizures during present illness
Hyperparasitemia	*P. falciparum* parasitemia > 250,000/μL

evening hours and on weekends when the OPD is closed, patients are referred directly for review at the inpatient ward. Patients requiring a higher level of care are usually referred to Kilembe Mines Hospital, a district hospital, which is located approximately 25 km from BHC via a mix of dirt and paved roads. Transport, often by motorcycle, typically takes 45 minutes at costs that can represent the weekly income for a typical subsistence farmer.[13]

Like much of Uganda, the climate in Bugoye permits year-round malaria transmission marked by semiannual transmission peaks typically after the end of the rainy seasons.[14] The two most recent malaria indicator surveys undertaken in the region found declining parasitemia prevalence of 48.4% and 17.6% in 2009 and 2014, respectively.[9,15]

Study design. The rapid diagnostic test (RDT) for severe malaria study was a prospective, observational cohort study of patients with a parasitological diagnosis of malaria conducted from May to November 2015. Study staff recorded demographic information, clinical history, and vital signs to include temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation on all individuals presenting to the OPD using a study-specific encounter form. Health facility staff, typically nurses and clinical officers, then performed clinical evaluations of all patients in accordance with local protocols, recording diagnostic and treatment plans on the same encounter form. Individuals with fever (axillary temperature ≥ 38°C) or other symptoms suspicious for malaria as determined by the attendant provider were eligible for inclusion.

Initial testing for malaria was performed using the Standard Diagnostics 05FK60 Malaria Ag *P. falciparum*/Pan RDT assay (Standard Diagnostics, Hagal-Dong, Korea). Study RDTs were obtained directly from the manufacturer, stored in the original packaging at room temperature, and used in accordance with the manufacturer's instructions before the expiry date.

Study staff with training in laboratory medicine prepared thin and thick blood smears for all patients with a positive RDT result. Those with a negative RDT were defined as not having severe malaria and did not undergo further testing, except for the 15% of individuals who underwent microscopy for quality control. Smears were fixed with methanol and stained in 10% Giemsa. Microscopists, who had undergone validation testing (Shoklo Malaria Research Unit) and were blinded to the RDT results, reviewed all slides in accordance with World Health Organization (WHO) guidelines.[16] Two independent microscopists read all slides. A third, senior microscopist reviewed the slides when there were discrepancies between the first two reads. Dried blood spots were obtained from a subset of participants over a 1-month period and real-time polymerase

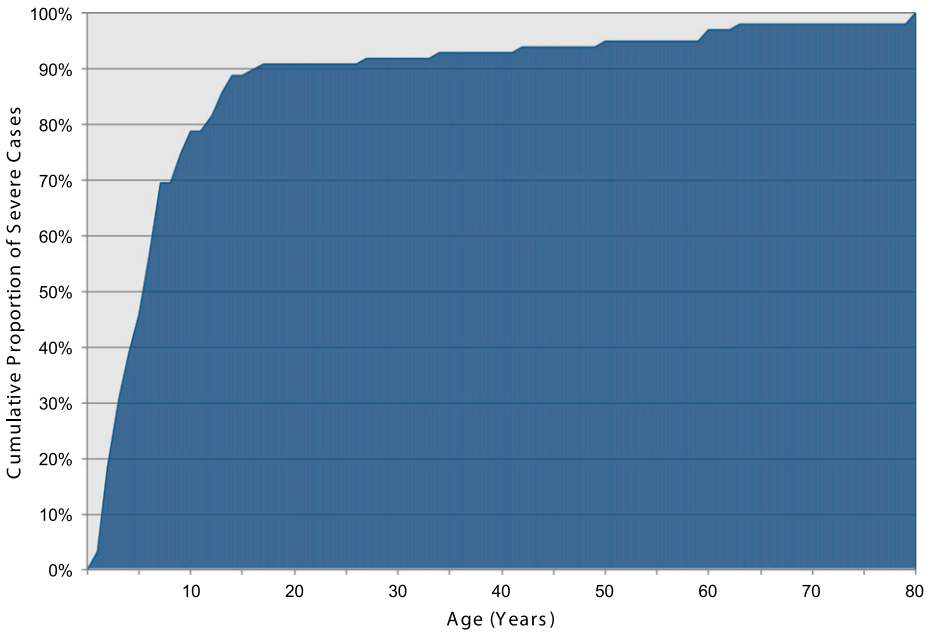


FIGURE 1. Cumulative proportion of severe malaria cases showing that nearly 90% of cases observed before the age of 15 years. This figure appears in color at www.ajtmh.org.

TABLE 2
Laboratory results of patients meeting the criteria for severe *Plasmodium falciparum* malaria stratified by age

	Age < 5			Age 5–15			Age ≥ 15				
Characteristic	Uncomplicated	Severe	*P**	Uncomplicated	Severe	*P**	Uncomplicated	Severe	*P**	*P* value†	*P* value‡
Patients (*n*, %)	142 (79.3)	37 (20.7)	–	687 (93.5)	48 (6.5)	–	528 (98.0)	11 (2.0)	–	–	–
Female (*n*, %)	64 (45.1)	17 (46.0)	0.92	337 (49.7)	20 (41.7)	0.28	316 (60.8)	8 (72.7)	0.42	0.074	0.13
Onset (median, IQR)	2 (1–3)	2 (1–3)	0.39	2 (2–3)	3 (2–3)	0.93	3 (2–4)	2 (2–3)	0.67	0.77	0.23
Symptoms (*n*, %)											
Fever	136 (97.2)	38 (97.3)	0.97	636 (92.6)	44 (91.7)	0.82	482 (91.3)	11 (100.0)	0.31	0.30	1.0
Cough	81 (57.0)	19 (51.4)	0.54	255 (37.1)	19 (39.6)	0.73	166 (31.4)	2 (18.2)	0.35	0.20	0.07
Rhinorrhea	41 (28.9)	6 (16.2)	0.12	130 (18.9)	10 (20.8)	0.75	76 (14.4)	1 (9.1)	0.62	0.38	0.56
Diarrhea	27 (19.0)	9 (24.3)	0.47	71 (10.3)	6 (12.5)	0.64	30 (5.7)	4 (36.4)	< 0.001	0.07	0.43
Convulsion	–	8 (21.6)	–	–	3 (6.3)	–	–	0 (0.0)	–	–	0.048§
Vital signs (*n*, %)											
MUAC (cm)	17.1	14.6	0.77	–	–	–	–	–	–	–	–
Coma scale‖	4.96	4.73	0.001	15.0	14.9	0.14	15.0	13.8	< 0.001	0.006	–
Febrile	46 (33.6)	21 (56.8)	0.01	182 (27.4)	17 (37.0)	0.16	71 (14.3)	1 (10.0)	0.70	0.13	0.025
Tachpynea	6 (4.7)	5 (15.2)	0.034	82 (12.5)	6 (13.3)	0.87	86 (17.2)	7 (70.0)	< 0.001	0.001	0.002
Tachycardic	37 (27.6)	13 (40.6)	0.15	248 (36.3)	18 (40.0)	0.62	141 (27.0)	7 (63.6)	0.007	0.17	0.19
Shock	–	6 (18.2)	–	–	12 (26.1)	–	–	2 (18.2)	–	0.59	1.0
Pulmonary edema	–	9 (27.3)	–	–	5 (11.1)	–	–	1 (10.0)	–	0.92	0.28
Microscopy results											
GMPD	7,016/μL	38,139/μL	< 0.001	8,453/μL	31,253/μL	< 0.001	3,292/μL	12,211/μL	0.03	0.14	0.08
> 100,000 (*n*, %)	20 (14.1)	16 (43.2)	< 0.001	45 (6.6)	16 (33.3)	< 0.001	12 (2.3)	2 (18.2)	0.001	0.33	0.15
Hyperparasitemia	–	**9 (24.3)**	–	–	**10 (20.8)**	–	–	**0 (0.0)**	–	–	**0.70**§
Anemia											
Hb (Mean, 95% CI)	10.1 g/dL	9.9 g/dL	0.61	11.7 g/dL	11.5 g/dL	0.43	13.4 g/dL	12.5 g/dL	0.14	0.17	0.003
Hb < 5 g/dL (*n*, %)	**2 (1.6)**	**1 (3.0)**	**0.59**	–	**2 (4.2)**	–	–	**0 (0.0)**	–	–	**0.79**
Hypoglycemia (*n*, %)	–	**0 (0.0)**	–	–	**3 (6.4)**	–	–	**3 (30.0)**	–	**0.04**	–
Kidney injury (*n*, %)	–	**0 (0.0)**	–	–	**0 (0.0)**	–	–	**3 (27.3)**	–	–	–
Acidosis (*n*, %)											
Lactate (mean)	2.08	2.83	0.001	1.93	3.44	< 0.001	1.67	3.36	< 0.001	0.89	0.42
> 5 mmol/L	–	**4 (14.3)**	–	–	**12 (25.5)**	–	–	**3 (27.3)**	–	**0.91**	**0.35**
HCO_3 (,ean)	21.3	19.0	< 0.001	23.7	21.8	< 0.001	25.0	21.6	< 0.001	0.92	0.04
HCO_3 < 15 mmol/L	–	**5 (17.9)**	–	–	**3 (6.4)**	–	–	**1 (9.1)**	–	**0.75**	**0.50**

CI = confidence interval; GMPD = geometric mean parasite density; Hb = hemoglobin; HCO_3 = serum bicarbonate; IQR = interquartile range; MUAC = mid-upper arm circumference. Values in bold represent measures that define the criteria for severe malaria.
* *P* value for comparison of uncomplicated vs. severe malaria within the respective age category.
† *P* value for comparison between age categories 5–15 years and ≥ 15 years of age (reference) with severe malaria.
‡ *P* value for comparison between age categories < 5 years and ≥ 15 years of age (reference) with severe malaria.
§ No observations in the reference group; comparison made between age categories 5–15 years and < 5 years.
‖ Glasgow Coma Score used for patients ≥ 5 years of age; Blantyre Coma Score used for patients < 5 years of age.

chain reaction (PCR) was performed to assess the accuracy of microscopy, details of which are published elsewhere.[17]

Hemoglobin levels were measured using the Hemocue Hb 201+ analyzer (Hemocue, Brea, CA), whereas serum chemistry and venous blood gas values were obtained using the Abbott iStat analyzer (Abbott, Princeton, NJ) with the CHEM8+ and CG4+ cartridges.

After diagnostic testing was complete, point-of-care results were provided to the responsible provider for clinical management purposes. Patients with diagnostic tests positive for malaria were treated at the discretion of the attendant provider which is typically patterned according to national guidelines.[18] Available treatment options usually include oral artemether/lumefantrine for uncomplicated malaria or parenteral quinine or artesunate for severe malaria. We recorded treatment and disposition plans, including admission to the inpatient ward and referral to higher level facilities. Information on mortality was retrospectively abstracted from the inpatient registers.

Statistical analysis. We defined severe malaria in accordance with the WHO guidelines for research and epidemiological studies.[19,20] These criteria are outlined in Table 1. Notably, these criteria are less dependent on clinical assessments, such as the presence of acidotic breathing, the determination of which can vary significantly with the level of health worker training and clinical skill.[10,21,22] For this study, we defined hyperparasitemia as a threshold of ≥ 250,000 parasites/μL.

We first summarized demographic, clinical, and laboratory characteristics of the cohort and compared them between those with uncomplicated and severe malaria using linear regression for continuous variables and Pearson's χ^2 testing and/or logistic regression for categorical variables. We stratified results by age, with three primary categories: age < 5, 5–15, and ≥ 15 years. Parasite densities were log-transformed and reported as geometric means.

We determined the age-specific incidence rate ratio (IRR) of severe malaria among individuals with microscopically confirmed parasitemia using generalized negative binomial regression models with robust standard errors. We first examined differences between the above-described age categories, and then performed an exploratory analysis among children < 15 years by treating age as a continuous variable. We also compared the IRR of severe malaria between those 15–49 years old and older patients, defined as those ≥ 50 years of age. Using similar methods, we determined the village-level IRR for all villages with at least three cases of severe malaria over the study period, defining Bugoye village, where the health center is located as the reference village.

Finally, we performed multivariable regression analyses using generalized negative binomial regression models with robust standard errors to explore the demographic, clinical, and laboratory parameters associated with the primary outcome of interest, severe malaria, in each age group. Covariates that would routinely be available at a peripheral health center (e.g., demographics, physical examination findings, and microscopy results) were included in the multivariable model, regardless of the level of significance in the univariable modeling. A resulting P value of < 0.05 was considered statistically significant in the final models. Data were analyzed with Stata 12.1 (Stata Corp., College Station, TX).

Ethics statement. Ethical approval of the study was provided by the institutional review boards of Partners Healthcare, the University of North Carolina at Chapel Hill, the Mbarara University of Science and Technology, and the Uganda National Council for Science and Technology. Written informed consent was obtained from all adult study participants and the caregivers of participating children.

RESULTS

During the 6-month study period, a total of 6,681 individuals presented with a history and/or symptoms suspicious for malaria and underwent testing with an RDT. Characteristics of the study cohort are shown in Supplemental Table 1. RDT results were available for 99.4% (6,641/6,681) of individuals. Nearly 40% (2,562/6,641) of those tested had a positive RDT result and of these, approximately 80% (2,085/2,562) consented to participate in the study protocol. Microscopic examination confirmed the presence of *P. falciparum* parasitemia in 1,462 (70.1%) of individuals with a positive RDT, either as an isolated infection (1,440, 98.5%) or in combination with another *Plasmodium* species (22, 1.5%). Among the subset of samples that underwent parallel real-time PCR ($N = 267$) for quality control, slide reading demonstrated a high degree of agreement ($\kappa = 0.85$).[17] Individuals with microscopically confirmed parasitemia were subsequently included in the subsequent analyses.

Ninety-six of 1,462 (6.6%) participants with confirmed parasitemia satisfied the criteria for severe *P. falciparum* malaria (Supplemental Table 2). Nearly half of severe cases occurred in children < 5 years of age and almost 90% of cases were diagnosed among children < 15 years of age (Figure 1). The proportion of individuals with severe as compared with uncomplicated malaria was highest among children between < 5 years of age (37 of 187 cases, 19.8%) and lowest among adults age ≥ 15 years of age (11 of 562 cases, 2.0%) (Table 2).

The age-related rate of severe malaria was highest in children < 5 years of age (IRR = 10.1, 95% confidence interval

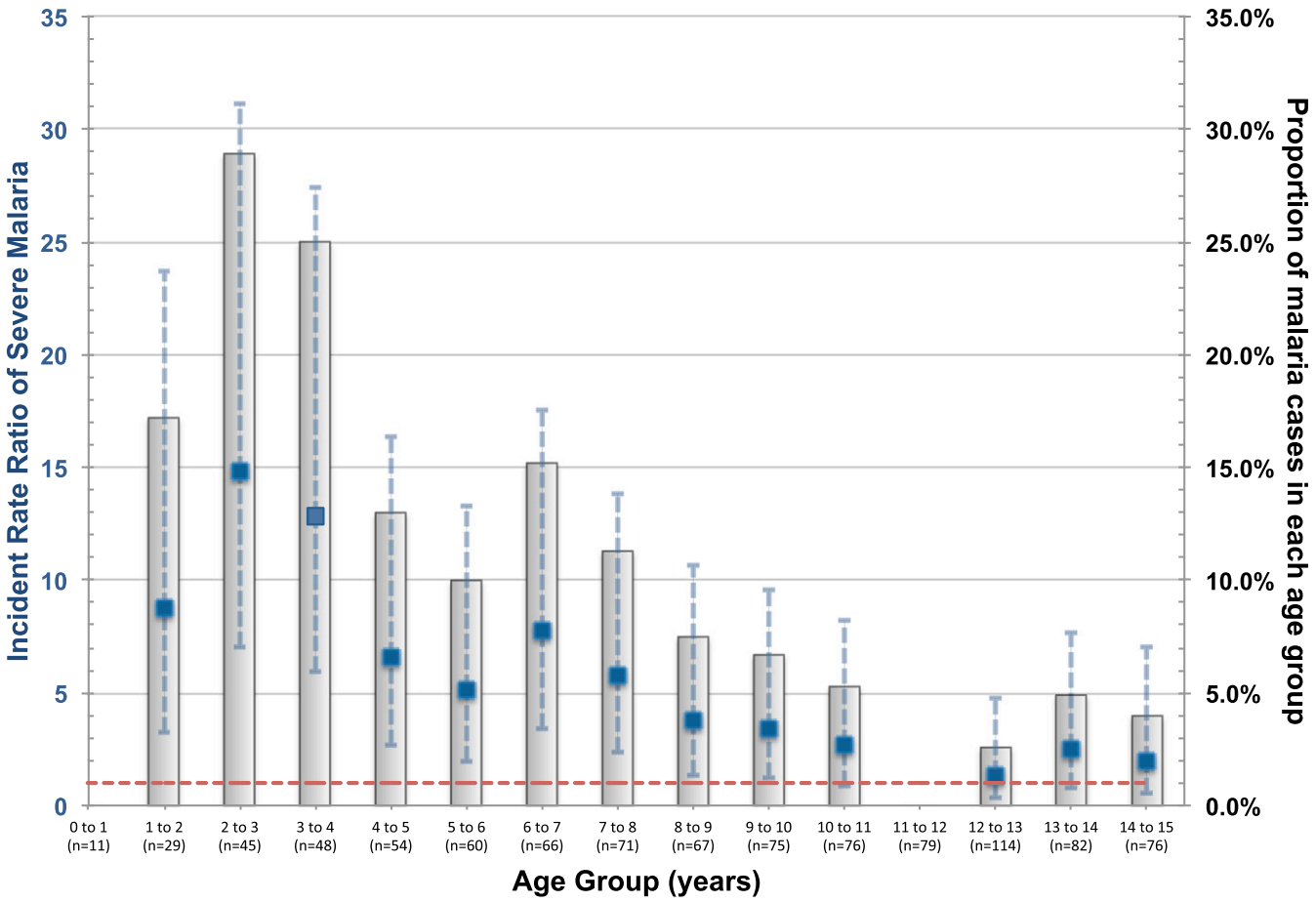


FIGURE 2. The age-related incident rate ratio of severe as compared with uncomplicated malaria (blue squares) in relation to individuals ≥ 15 years of age demonstrates peak incidence rate in children 2–4 years of age. The elevated rate of severe malaria persists until 11 years of age, after which it is similar to individuals ≥ 15 years of age. This figure appears in color at www.ajtmh.org.

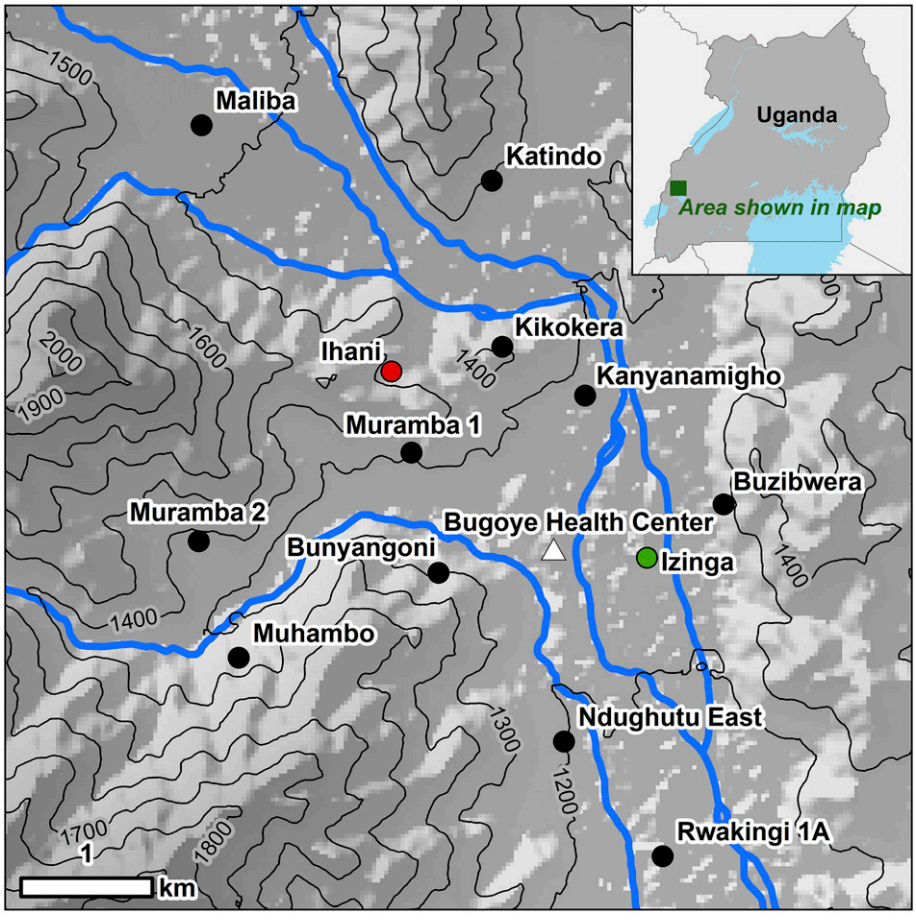
[CI] = 5.26–19.4, $P < 0.001$) but remained elevated in children aged 5–15 years (IRR = 3.20, 95% CI = 1.68–6.11, $P < 0.001$) compared with those ≥ 15 years of age. When we subdivided the age groups further, we found that the rate of severe malaria was highest in children aged 2–3 years (IRR = 14.8, 95% CI = 7.02–31.1, $P < 0.001$) (Figure 2). After age 11, the relative rate of severe malaria was similar to that of those ≥ 15 years of age.

To examine the association between older age and severe malaria, we subdivided those individuals ≥ 15 years of age into two categories: 1) 15–49 years, who served as the reference group and 2) ≥ 50 years of age. The relative rate of severe malaria was significantly higher in the older age group (IRR = 7.56, 95% CI = 2.36–24.2, $P = 0.001$), which was similar to the rate observed in children 5–15 years of age ($P = 0.60$).

Among the 12 villages with at least three cases of severe malaria, we identified two villages with different relative rates of severe malaria when compared with Bugoye village, where the health center is located. In Izinga, a low-lying village immediately to the East, the relative rate of severe malaria was significantly lower (adjusted IRR [aIRR] = 0.42, 95% CI = 0.18–1.00, $P = 0.05$). In contrast, there was a trend toward a higher relative rate in the village of Ihani (aIRR = 2.51, 95% CI = 0.79–7.9, $P = 0.12$), which sits on a hillside approximately 1 km from the health center (Figure 3). The mean age of individuals with confirmed parasitemia in Ihani was 24.6 years (16.8–32.5), whereas in Izinga, it was 12.2 years (95% CI = 10.6–13.8, $P < 0.001$), suggesting more intense transmission intensity in Izinga.

When the villages were stratified into quartiles of elevation, we observed another trend toward a higher relative rate of severe malaria among individuals from the highest elevation villages ($N = 18$, aIRR = 1.82, 95% CI = 0.96–3.44, $P = 0.07$). We could not detect a significant difference in the age of severe malaria cases between villages of high and low elevation (median age 8.5 versus 5.5 years, $P = 0.40$).

The most common clinical manifestation of severe malaria was shock (systolic blood pressure < 70 mm Hg), which was present in 22.2% (20 of 90) of cases with similar frequency



Village	Elevation (m)	Screened	TPR	Severe (n, %)	aIRR*	95% CI	*p*-value
Bugoye	1,265	622	38.3%	11 (1.8)	REF	REF	REF
Ihani	1,409	94	42.5%	4 (4.5)	2.51	0.79 – 7.98	0.12
Izinga	1,225	617	50.2%	8 (1.5)	0.42	0.18 – 1.00	0.05

Abbreviations: *TPR = RDT test positive rate; aIRR = adjusted incidence rate ratio;*
*Rate ratios adjusted for age category (<5 years, 5 to 15 years, >15 years)

FIGURE 3. Map of the Bugoye sub-county highlighting the villages with higher (Ihani) and lower (Izinga) relative risk of severe malaria, compared with Bugoye village, where the health center is located. This figure appears in color at www.ajtmh.org.

TABLE 3
Age-stratified multivariable regression analysis of correlates of severe malaria

	Age < 5 years			Age 5–15 years		
	aIRR	95% CI	*P* value	aIRR	95% CI	*P* value
Female sex	1.37	0.61–3.08	0.45	0.71	0.35–1.44	0.34
Dry season	0.85	0.41–1.79	0.67	0.97	0.81–1.17	0.78
Symptoms						
Cough	0.85	0.40–1.79	0.66	1.42	0.71–2.84	0.32
Diarrhea	1.06	0.47–2.40	0.89	0.88	0.27–2.91	0.84
Rhinorrhea	0.31	0.08–1.23	0.10	1.11	0.48–2.60	0.81
Vital signs						
Febrile	1.26	0.62–2.57	0.53	0.74	0.33–1.64	0.45
Tachycardic	1.05	0.46–2.37	0.91	1.19	0.59–2.41	0.63
Hypoxia	**4.36**	**2.26–8.42**	**< 0.001**	**3.39**	**1.52–7.60**	**0.003**
Parasitemia						
1–2,499		REF				
2,500–9,999	1.29	0.34–4.93	0.71	1.04	0.34–3.11	0.95
10,000–99,999	1.75	0.61–5.02	0.30	1.78	0.66–4.78	0.26
100,000–249,999	1.50	0.44–5.11	0.52	2.05	0.47–8.89	0.34

aIRR = adjusted incidence rate ratio; CI = confidence interval. Bold values represent criteria for severe malaria.

between age groups. Seizures were reported in 11.5% (11 of 96) cases, most of who were < 5 years of age (P = 0.051), whereas impaired consciousness defined as a Blantyre Coma Score < 3 or Glascow Coma Score < 11 was only noted in one 5-year-old child and two elderly adults. In the logistic regression analysis, few demographic, seasonal, or clinical factors were predictive of severe malaria (Table 3).

Of the laboratory criteria defining severe malaria, lactic acidosis (19 of 96 cases, 19.8%) and hyperparasitemia (19 of 96 cases, 19.8%) were the most frequently identified. The

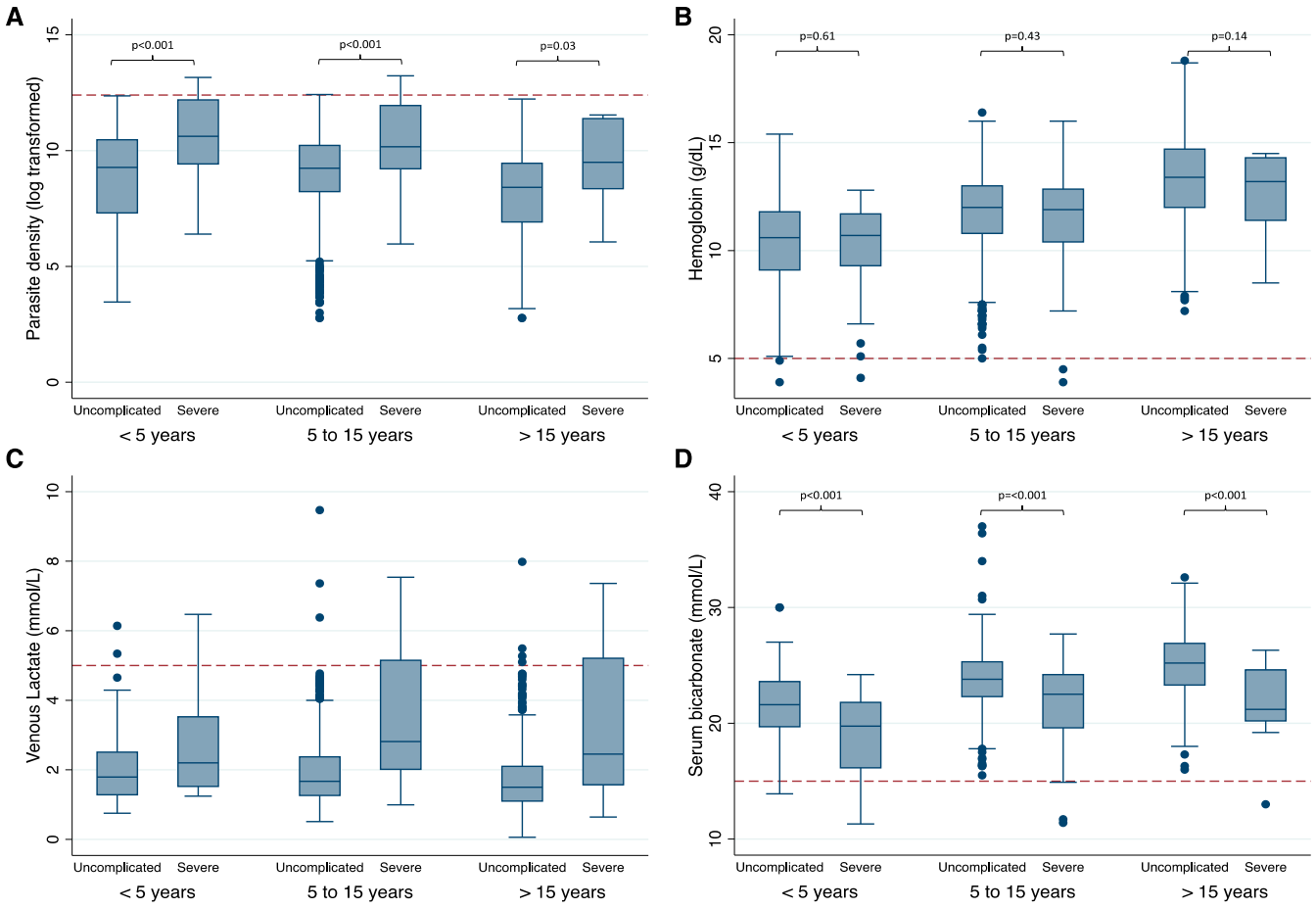


FIGURE 4. Box plots showing log-transformed parasite densities (**A**), hemoglobin levels (**B**), venous lactate (**C**), and serum bicarbonate levels (**D**), among those with uncomplicated and severe malaria stratified by age category. The dashed red line represents the respective threshold for severe malaria for each measure. This figure appears in color at www.ajtmh.org.

prevalence of lactic acidosis was similar across the three age strata. Higher lactate levels were associated with increasing parasite density (β = 0.1 mmol/L per log parasite density, 95% CI = 0.8–0.13, $P < 0.001$), and lactate levels were significantly higher among patients with severe malaria than those with uncomplicated malaria (3.24 versus 1.84 mmol/L, $P < 0.001$) (Figure 4C).

Across all age groups, patients with severe malaria had significantly higher parasite densities than those with uncomplicated malaria, and among those with severe malaria, the level of parasitemia was significantly higher among younger children (Figure 1A). Hyperparasitemia (≥ 250,000 parasites/μL) was observed only in children < 15 years of age. In the logistic regression analysis, higher parasite densities were not associated with higher rates of severe malaria among children, most notably among those < 5 years of age (Table 3).

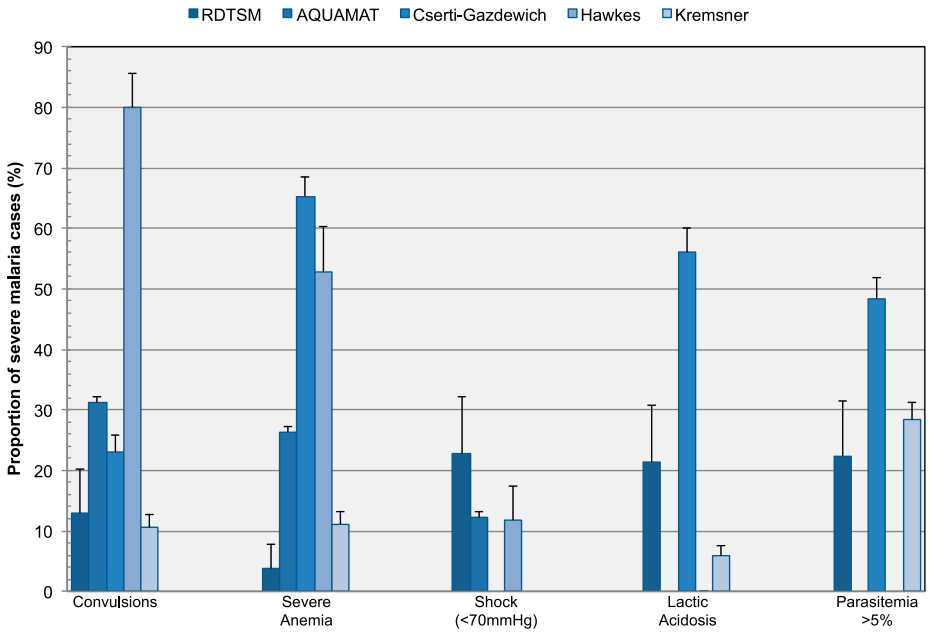
Mean hemoglobin levels were lower among participants with severe malaria compared with uncomplicated malaria, yet when controlling for age, there was no significant difference in the hemoglobin level between those with severe and uncomplicated malaria (Figure 3B). Instead, there was a general trend toward lower hemoglobin levels in younger children. Severe malaria anemia (Hb < 5.0 g/dL), however, was an infrequent complication, being found in only 3.3% of severe cases (Table 3).

Of the individuals meeting the criteria for severe malaria, only one child, who presented with severe anemia, was referred from the outpatient clinic to the district hospital. The overall rate of admission to the health center inpatient ward for patients meeting the criteria for severe malaria was 44.3% (39 of 88), with rates ranging from 63.3% (19 of 30) for children < 5 years of age to 18.2% (2 of 11) for individuals ≥ 15 years of age. In comparison, the rate of admission for patients with uncomplicated malaria was 14.0% (274 of 1,956). Whereas discharge disposition was not recorded in individuals with a negative RDT, the rate of admission was non-significantly higher among those with a positive RDT and positive confirmatory microscopy than those with a positive RDT, but negative microscopy (18.3% versus 9.8%, $P = 0.22$). No inpatient deaths were reported during the study period.

Among the six cases of severe malaria in individuals ≥ 50 years of age, the geometric mean parasite density was 23,389 parasites/μL compared with 1,916 parasites/μL in those of similar age with uncomplicated malaria ($P = 0.008$). The mean lactic acid level was also significantly higher in those who met the criteria for severe malaria (3.77 versus 1.73 mmol/L, $P < 0.001$). Manifestations of severe malaria were three cases of kidney injury including one case with concurrent pulmonary edema and impaired consciousness, one case of impaired consciousness with a parasite density > 100,000 parasites/μL, one case of lactic acidosis with a parasite density of > 40,000 parasites/μL, and one case of shock accompanied by a parasite density of > 40,000 parasites/μL.

DISCUSSION

In this prospective cohort of individuals seeking care at a peripheral health center in rural Western Uganda, we found that



Study	Year(s)	Country	Study Type	Hospital Type	Ages (yrs)	Severe (n)
AQUAMAT	2005-10	Multiple	RCT	Academic/Referral	0 – 15	5,425
Cserti-Gazdewich	2007-09	Uganda	Cohort	Academic/Referral	0.5 – 12	855
Hawkes	2011-13	Uganda	RCT	Regional Referral	1 – 10	180
Kremsner	2011-12	Multiple	RCT	Academic/Referral	0.5 – 10	1,047

Abbreviations: *RCT = randomized controlled trial*

FIGURE 5. Prevalence of clinical findings among patients with severe malaria as reported in recent studies in the sub-Saharan African Region. This figure appears in color at www.ajtmh.org.

severe anemia was an uncommon manifestation of severe malaria. Although young children had lower hemoglobin levels than adolescents and adults, we found no differences within age groups between those who did and did not meet the criteria for severe malaria. These results are in contrast to reports from other regions of intense malaria transmission, which historically are drawn from large referral centers (Figure 5).[8,23–25] Instead, shock and lactic acidosis were the most common complications, each present in approximately 20% of cases. These findings suggest that the clinical characteristics of severe malaria presenting to rural, peripheral health centers may be different than previously observed in referral centers, and therefore merit additional investigation of the optimal methods for identification and management of severe malaria in rural health centers in the region.[26,27]

There are a number of potential explanations for the low prevalence of severe anemia in our cohort. First, given that the general population prevalence of anemia in Uganda has declined precipitously over the last decade,[9] it is possible that this finding reflects wide-scale improvements in childhood nutrition and the management of soil-transmitted helminthiases.[28] Second, as first-line artemisinin combination therapies have become increasingly available, there is more rapid clearing of parasitemia and less treatment failure.[29,30] Lastly, the epidemiology of severe malaria at peripheral facilities may be different than that observed in hospital-based populations, where most of the prior studies about the classification of severe malaria were conducted. This difference could be explained by the referral to higher level facilities and/or bypassing of peripheral health among the most severe cases.

Although no inpatient deaths were recorded during the study period, the primary objective of the study was to assess the accuracy of an RDT, and we did not follow patients beyond the initial disposition decision made in the outpatient clinic. It is possible that we underestimated mortality in the event that 1) deaths were not accurately recorded in inpatient registers or 2) deaths occurred after transfer to a higher level facility or post-discharge from the outpatient clinic or inpatient ward, outcomes of which are typically not provided to the referring center. Similar trends have been demonstrated elsewhere, albeit in referral hospitals, where it was found that a significant proportion of deaths and adverse events occurred after discharge.[31,32]

The incidence rate of severe malaria in our cohort peaked between 2 and 3 years of age, a finding that is consistent with the moderate-to-high intensity of transmission.[33] Yet an elevated risk of severe malaria persisted throughout the first decade of life, with nearly a quarter of cases (21 of 96, 21.9%) occurring in individuals older than 10 years of age. We also identified a second period of risk among adults ≥ 50 years of age, which was similar in magnitude to that seen in children 5–15 years of age ($P = 0.60$). This finding suggests the possibility of an age-related decline in functional immunity similar to other infectious diseases, which could have a significant public health impact as life expectancy increases in malaria endemic countries.

To our knowledge, this study represents the first investigation of severe malaria in sub-Saharan Africa using widely accepted, objective clinical and laboratory criteria conducted outside of district hospitals or academic referral centers. The study also has a number of limitations. First, the study was conducted at a single site over a relatively short time period, and the number of severe cases was relatively small, despite the large number of individuals screened. Second, the rate of study nonparticipation was relatively high, especially among young children. We hypothesize that parents may have declined study-related testing, which entailed another blood draw and a longer wait, once the RDT results were known. However, as previously reported, we found little evidence in differences in clinical status or disposition between those who did and did not participate, partially mitigating this concern.[34] Third, our study design did not incorporate a control group comprised of RDT negative individuals. Therefore, it is possible that we have attributed manifestations of severe malaria to *P. falciparum* parasitemia when in fact individuals had alternative causes of illness in the setting of asymptomatic parasitemia. Lastly, study staff, who were responsible for recording the clinical histories and vital signs used to define severe malaria, were nonprofessional health-care workers. Before study implementation, we conducted 3 days of didactic and practical training with the staff, who were then supervised by the site director, a senior clinical officer. In addition, we attempted to minimize the potential for measurement bias by using automated equipment, including thermometers, blood pressure cuffs, and pulse oximeters.

CONCLUSIONS

At a peripheral health center in rural Uganda, severe anemia was an uncommon complication of severe malaria. Instead, shock and lactic acidosis were the most common findings, each encountered in approximately 20% of cases. These results merit further investigation, with a renewed focus on the optimal identification and triage of severe malaria in rural health centers, particularly because adverse outcomes associated with lactic acidosis is high.

Received August 26, 2017. Accepted for publication November 21, 2017.

Published online December 26, 2017.

Note: Supplemental tables appear at www.ajtmh.org.

Acknowledgments: We thank the clinical staff and patients of the Bugoye Health Centre for their continued support. We also appreciate the efforts of Dr. Jonathan Parr who reviewed an early draft of the manuscript.

Financial support: This work was supported by the Harvard Global Health Initiative and Thrasher Research Fund to R.B. Standard Diagnostics provided the rapid diagnostic tests for the study at no cost. Abbott Point of Care provided the iStat analyzers and the associated cartridges to the study. M.J.S. received support from the National Institutes of Health (K23MH099916). R.B. received support from the National Institutes of Health (T32 AI007151). E.M., M.N., and M.M. received grant support for this work from Abbott Point of Care. Neither Standard Diagnostics nor Abbott Point of Care had any role in the design or conduct of the study or preparation of the manuscript.

Disclosures: All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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