Demographic, Socioeconomic, and Geographic Factors Leading to Severe Malaria and Delayed Care Seeking in Ugandan Children: A Case–Control Study

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Abstract. We studied associations between delayed care seeking, demographic, socioeconomic, and geographic factors and likelihood of severe malaria in Ugandan children. The study was based at Jinja Hospital, Uganda. We enrolled 325 severe malaria cases and 325 uncomplicated malaria controls matched by age and residence. Patient details, an itinerary of events in response to illness, household information, and location of participants' residences were captured. Conditional logistic regression was used to determine risk factors for severe malaria and delayed care seeking. Delayed care seeking (≥ 24 hours after fever onset; odds ratio [OR] 5.50; 95% confidence interval [CI] 2.70, 11.1), seeking care at a drug shop as the initial response to illness (OR 3.62; 95% CI 1.86, 7.03), and increasing distance from place of residence to the nearest health center (OR 1.45; 95% CI 1.17, 1.79) were independent risk factors for severe malaria. On subgroup analysis, delayed care seeking was a significant risk factor in children with severe malaria attributable to severe anemia (OR 15.6; 95% CI 3.02, 80.6), but not unconsciousness (OR 1.13; 95% CI 0.30, 4.28). Seeking care at a drug shop (OR 2.84; 95% CI 1.12, 7.21) and increasing distance to the nearest health center (OR 1.18; 95% CI 1.01, 1.37) were independent risk factors for delayed care seeking. Delayed care seeking and seeking care at a drug shop were risk factors for severe malaria. Seeking care at a drug shop was also a predictor of delayed care seeking. The role of drug shops in contributing to delayed care and risk of severe malaria requires further study.

INTRODUCTION

Despite reported declines in malaria mortality, the burden of infection remains high, particularly in sub-Saharan Africa, where about 90% of worldwide morbidity and mortality occurs.^{1,2} Of five *Plasmodium* species that cause human infection, *Plasmodium falciparum* is the most virulent and is responsible for the large majority of infections in sub-Saharan Africa.³ Infection with *P. falciparum* results in one of three possible outcomes: asymptomatic parasitemia, defined as the presence of asexual parasites in the blood without symptoms; uncomplicated malaria, which entails febrile illness not associated with signs of severe disease; and severe malaria, characterized by various syndromes of organ dysfunction, which if not treated promptly may result in death.⁴ In children, severe malaria most commonly manifests as either severe anemia or cerebral malaria.³

Prompt access to appropriate antimalarial treatment, ideally within the first 24 hours after fever onset, is promoted by the World Health Organization (WHO) for prevention of progression from uncomplicated to severe malaria.⁴ This strategy is logical as progression to severe disease requires extensive parasite multiplication over time.⁵ Support for delayed care seeking as a risk factor for severe malaria is largely based on results from cross-sectional studies demonstrating association between longer duration of symptoms and severe malaria^{6–9} and demonstration of rapid progression of uncomplicated to severe malaria.^{10,11} However, some studies have not shown an association between duration of symptoms and risk of severe malaria.^{12,13}

Demographic, socioeconomic, and behavioral factors and distance from residence to health facilities are known

determinants of delayed seeking of appropriate care among children with malaria.^{14–20} However, their contribution to severe malaria is unclear, with available studies yielding conflicting results.^{6,12,13,21–25} Variations in findings may be attributable to differences in study design and analysis, varied impacts of complex host–parasite interactions that affect disease presentation and small sample sizes.^{26–30}

The association between delayed care seeking as specifically defined by the WHO (delay ≥ 24 hours after fever onset) and progression from uncomplicated to severe malaria remains undetermined. In addition, the predictors of delayed care seeking in children with malaria have not been well elucidated. The primary objective of this study was to determine risk factors of severe malaria, including delayed care seeking from public facilities. In addition, we assessed predictors of delayed care seeking in Ugandan children.

METHODS

Ethics statement. Informed consent was obtained from the parents or guardians of all study participants. The study protocol was approved by the Uganda National Council of Science and Technology and the Institutional Review Boards of the School of Medicine, Makerere University-College of Health Sciences, and the University of California, San Francisco.

Study design. A matched case–control design was used to compare demographic, socioeconomic, family-related, and geographic factors between cases and controls. Incident cases were children with severe malaria, and controls were children with uncomplicated malaria. Each case was matched to a control by age and subcounty of residence. After enrollment, information on events that took place in response to the child's illness, from the onset of illness to the time when the child was enrolled, were systematically obtained and recorded, facilitating quantification of time to event data for two retrospective cohorts; case cohort and control cohort.

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Site. The study was based at the children's ward of Jinja Hospital, Jinja District, Uganda. It is the largest hospital in eastern Uganda, serving as a regional referral hospital with a catchment area encompassing 12 districts located in the east central (ten) and central (two) regions of the country from where controls were enrolled (Figure 1). The catchment area is considered a region of moderate to high malaria transmission intensity.³¹ Nearly half of the population in the east central and central regions is in the lowest wealth bracket of the region and residents are engaged predominantly in subsistence agriculture.³²

Matching. Considering the possible confounding effect of age on associations between risk factors and severe malaria, controls were matched to cases by age. Targeted age groupings for matching were 6 to < 12 months, 1 to < 3 years, 3 to < 5 years, and ≥ 5 years. In addition, controls were

matched to cases by location of residence (within a subcounty level) and calendar time (enrollment within one month of case.) We believe that the latter two matching criteria resulted in selection of controls with an exposure distribution identical to that of the population that gave rise to the cases, as evidenced by the similarity in characteristics of the uncomplicated malaria controls and neighborhood controls selected from within the same village as cases (Supplemental Table 1).

Severe malaria cases: definition and selection. Cases were defined as hospitalized children aged 4 months to 10 years with a positive malaria blood smear and one of three severe malaria syndromes: 1) severe anemia ($Hb < 5$ g/dl; measured by HemoCue AB), 2) impaired consciousness (Blantyre coma score < 4),³³ or 3) respiratory distress (intercostal or subcostal recession without crackles or other evidence of pneumonia on auscultation). When possible,

FIGURE 1. Study site. Map demonstrating locations of residence's for both severe malaria cases and uncomplicated malaria cases within the catchment area of Jinja Hospital. This figure appears in color at www.ajtmh.org.

comatose children (Blantyre coma score < 3) had a lumbar puncture performed to exclude children with bacterial or viral meningitis, and children with clinical evidence of a specific nonmalarial febrile illness or chronic disease were excluded. Cases were consecutively sampled as they presented to Jinja Hospital during the study period.

Uncomplicated malaria controls: definition and selection.

Uncomplicated malaria controls were children with fever and a blood smear positive for *P. falciparum* parasites, but without clinical evidence of severe malaria, danger signs,³⁴ or other known causes of febrile illness. Children with history of a blood transfusion in the past 3 months were excluded. Eligible children were consecutively enrolled from a level III or IV health center located in the same geographical area (subcounty) as the matched case.

Data collection. For both cases and controls information was collected using three questionnaires. The first questionnaire detailed patient demographics, history of current illness, physical examination findings, and initial laboratory findings. The second questionnaire detailed events during the course of illness before enrollment. An event consisted of reported symptoms, action taken, and intervention(s) given in response to illness. Date and time of occurrence of new symptoms, action taken, and intervention(s) were documented based on the respondent's approximation. For each action, the decision-maker was documented. If an antimalarial was given, frequency and duration of treatment were recorded. Dosing was categorized as either appropriate or inappropriate, based on the WHO treatment guidelines.⁴ If the action was "sought care at a health center," distance from home, time taken to reach the center, type of center, timing, and type of services offered was recorded in the order of events. Date and time of occurrence of two critical events were determined using probing interview techniques: first, when fever was first noted (onset of illness), and second, when the child arrived at the health center where the child was enrolled (time of seeking appropriate care). The third questionnaire was used to collect information concerning the child's caregiver and head of household (relation to child, age, education level, religion, and employment status). House characteristics (building materials, roofing material, water source, toilet type, lighting, and cooking materials) and possessions were documented and used to construct a wealth index for each child.

Geographical coordinates. Garmin Handheld Global Positioning System (GPS) Navigators (GARMIN eTrex Legend H) were used to record coordinates of participants' homes and health centers where uncomplicated malaria cases were recruited. GPS coordinates of towns and public health facilities in Uganda were retrieved from external data sources.³⁵ The GPS coordinates were measured using the NAVSTAR GPS Satellite Network System, and accuracy was enhanced using the Wide Area Augmentation System (<http://www8.garmin.com/aboutGPS/waas.html>). Waypoint data were imported from the GPS navigators and stored in Garmin Base Camp software as GPX files. Data were exported from Garmin Base Camp to QGIS (QGIS Development Team, 2009 QGIS Geographic Information System; <http://www.qgis.org>) for data viewing, editing, analysis, and projection of maps.

Sample size estimation. Sample size was predetermined based on an existing study of genetic polymorphisms and malaria, powered to detect an association between α -thalassemia and severe malaria.

With the population prevalence of the α -thalassemia trait estimated at 44% and allowing for 5% of patients being excluded from analysis after enrollment because of false positive results, we required a total sample size of 650 children (325 children in each arm) to detect a minimum odds ratio (OR) of 0.5 for risk of severe malaria among children with α -thalassemia, assuming power of 80%, alpha of 0.05, and 35% prevalence of α -thalassemia in controls. With 325 cases and 325 controls, the study had 90% power to detect an OR of two in disease exposure, assuming 46% prevalence of delayed seeking of care among controls, with a 95% level of confidence.

Analysis. All data were entered using Microsoft Access (Microsoft Corporation) and analyzed using STATA (version 14; STATA Corp., College Station, TX). Time taken to seek appropriate care was computed based on the difference between time when fever was first noted and time of arrival at the health center where the child was enrolled. Delayed care seeking was defined as care seeking ≥ 24 hours after fever onset at the health center where the child was enrolled and provided with appropriate antimalarial treatment. Descriptive statistics were reported as proportions and medians with interquartile ranges. Distributions of baseline characteristics in either study group were compared using the chi-squared test and the Wilcoxon signed rank test for categorical and continuous data, respectively. We used conditional logistic regression, a matched analytical approach, as our statistical method for identification of risk factors for severe malaria. Unmatched analysis on matched data (even when incomplete) compromises the validity of effect estimates; even though estimates may be more precise.³⁶ For purposes of comparison, we also ran other models based on restricted conditional logistic regression (limited to successfully age-matched case-control pairs; equivalent to 74% of case-control pairs) and unconditional logistic regression, with adjustment for age. In the unadjusted analysis, univariable conditional logistic regression models and the Mantel-Haenszel matched pairs test were used to measure the association of continuous and categorical variables between cases and controls, respectively. Principal component analysis was used to create a wealth index from nine variables: ownership of mobile telephones, radios, clocks, cupboards, sofas, and tables; number of rooms in the house; number of meals eaten per day; access to an improved toilet; and roofing, wall, and floor materials. The first component accounted for 25.8% of the total variation, a value within the range of other studies.³⁷ Suitability of the nine variables in performing factorial analysis was confirmed using Bartlett's test of sphericity ($P < 0.001$) and the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (0.787).

The purposeful selection approach recommended by Hosmer and Lemeshow was used to select variables for inclusion in the final logistic regression model.³⁸ In brief, variables that demonstrated a significant ($P < 0.25$) association with severe malaria risk in the unadjusted analysis were included in a preliminary effects model. For the final effects model, variables were removed if they were nonsignificant ($P > 0.15$), did not contribute to collinearity, were not confounders, and did not impact on model fitness (see Supplemental Table 2). Age was included in the final model to account for residual confounding attributed to incomplete matching and possible selection bias introduced by matching on age. Household building materials were not included as

explanatory variables in the final effects model because of “multicollinearity” concerns with the wealth index, which was constructed based on building materials. Potential confounders were assessed using the Chest Command in Stata 14.0 and kept in the model if they changed the OR of predictor variables of interest by 15% or more. Model fitness was assessed using the likelihood ratio test. Considering that risk factors may differ depending on the severe malaria syndrome, we ran subgroup conditional logistic models for case-control pairs limited to cases with only severe anemia or unconsciousness, including variables that were only significant ($P < 0.05$) in the final model and that were clinically relevant confounders. In the subgroup analysis, the variables “danger symptoms on the first day of illness” and “having gametocytes” were associated with small numbers of discordant case-control pairs resulting in unintelligible effect estimates and confidence intervals (CI) and were thus excluded from the final models.

To factor in the contribution of distance to the nearest public health center to severe malaria occurrence, we ran a multivariable conditional logistic model limited to the study population with valid GPS data. The GPS coordinate data were used to compute distances between case and control homes and other locations, including visited health center and nearest public health center. Nearest public health centers were categorized as level II or higher, or level III or higher. Visited health centers represented the center where controls were enrolled and were subsequently listed as the center where cases would have initially sought formal care, even if they did not. In the final multivariable analysis, distance to health

facilities was the distance between a home and the nearest public health center, regardless of whether cases or controls attended that center.

Determination of risk factors for delayed care seeking at the health center where a child was enrolled was based on logistic regression with a dichotomous outcome (care seeking within 24 hours after fever onset or not). To account for the biased representation of cases in our case-control sample, we performed a weighted logistic regression. The population incidence of cases was estimated to be 2,000 cases per 100,000 people per year (0.02) based on the WHO Uganda’s malaria country profile.³⁹ This information was used to calculate sampling weights for cases and controls, as has been described by others.^{40–42}

RESULTS

Study participants. We screened 1009 severe malaria cases and 528 uncomplicated malaria controls between March 2015 and March 2016 (Figure 2). Of the screened cases, lack of evidence of specified severe malaria criteria (427, 42%) was the most common reason for exclusion. Among controls, we excluded 196 (37%) children. Low levels of parasitemia, refusal to consent, clinical evidence of other febrile illness, and evidence of severe malaria were the common reasons for exclusion of controls. Of the 332 case-control pairs, seven were not included in the final analysis: three pairs had cases with negative malaria test results, one had a reenrolled case, and three had at least one missing questionnaire. Therefore, 325 matched case-control pairs were analyzed.

Severe malaria cases

Uncomplicated malaria controls

FIGURE 2. Study profile.

Baseline characteristics. Severe malaria cases and uncomplicated malaria controls had similar characteristics, but cases were younger (median 1.9 versus 2.1 years; $P < 0.001$), more likely to be hyperparasitemic (10.4% versus 4.3%; $P = 0.003$), and more likely to have gametocytes identified (28.1% versus 15.1%; $P < 0.001$) at enrollment (Table 1). Compared with caregivers of controls, caregivers of cases were likely to be older ($P = 0.01$) and employed ($P < 0.001$). Household heads of cases had fewer years of education than those of controls ($P = 0.03$) and the median distance of case participants' homes from the nearest public health center or town was greater than that of control homes (Table 1).

Characteristics of children with severe malaria (cases). Among the total of three severe malaria defining syndromes, the most common complication was severe anemia (Hb < 5 g/dl; 49.4%), followed by impaired consciousness (32.1%), and respiratory distress (18.5%; Figure 3). Approximately two-thirds of children with severe malaria presented with only one of the defining severe malaria syndromes, including severe anemia (64.8% of those with one defining syndrome) and impaired consciousness (26.5%). Respiratory distress was uncommon in isolation or in combination with other severe malaria defining syndromes.

Risk factors for severe malaria. With unadjusted analysis, increasing age was protective against severe malaria (OR 0.56, $P < 0.001$; Table 2). Delayed care seeking at the health

center (OR 3.77, $P < 0.001$) where a child was enrolled and seeking care at a drug shop as the first response to illness (OR 3.20, $P < 0.001$) were significantly associated with severe malaria (Table 2). If the child's mother was the first decision-maker, compared with others being the decision-maker, the odds of severe malaria were reduced (OR 0.46, $P < 0.001$). Employment of the child's caregiver (OR 2.14, $P < 0.001$) or the head of household (OR 2.05, $P = 0.007$) were associated with severe malaria (Table 2). With multivariable analysis, variables contributing to collinearity and of no significance to model fitness or interpretation were excluded (Supplemental Table 2: selection of variables). In the final model, delayed care seeking (OR 5.50, $P < 0.001$) and seeking care at a drug shop as an initial response to illness (OR 3.62, $P < 0.001$) were associated with severe malaria. Other factors associated with severe malaria were employment of the caregiver and the caregiver having more than three children aged less than 5 years. The child's mother being the first decision-maker (OR 0.45, $P = 0.014$) was the only factor significantly protective against severe malaria. Increasing socioeconomic position was associated with increased likelihood of severe malaria. No significant interactions were noted in the final model. Other analytical approaches (restricted conditional logistic regression and unconditional logistic regression, with adjustment for age; Supplemental Table 3) yielded the same results as the overall conditional logistical regression model. Among

TABLE 1
Baseline characteristics of the study population

Variable	Uncomplicated malaria controls	Severe malaria cases	P value
	N = 325	N = 325	
Child characteristics			
Age, median (IQR)	2.16 (1.34–3.15)	1.99 (1.14–2.96)	< 0.001
Female, n (%)	156 (48.1%)	153 (47.0%)	0.785
Breast feed exclusively for 6 months	210 (66.2%)	230 (73.7%)	0.041
Sleeps in net, n (%)	233 (71.6%)	250 (76.9%)	0.497
Danger symptoms on day 1 of illness, n (%)	20 (6.15%)	38 (11.6%)	0.013
Parasite density (geometric mean)	29,198	26,157	0.633
Hyperparasitemia ($> 250,000$ parasites/ μ L)	14 (4.3%)	34 (10.4%)	0.003
Gametocytemia, n (%)	50 (15.5%)	91 (28.1%)	< 0.001
Hemoglobin	9.8 (8.2–10.8)	4.5 (3.5–6.3)	< 0.001
Caregiver characteristics			
Age, median (IQR)	26 (22–32)	28 (23–35)	0.015
Mother care taker, n (%)	284 (87.3%)	261 (80.5%)	0.018
Years of education, median (IQR)	7 (5–10)	7 (5–10)	0.279
Employed, n (%)	170 (52.6%)	225 (70.7%)	< 0.001
Polygamous relationship, n (%)	69 (27.2%)	83 (32.4%)	0.204
Head of household characteristics			
Age, median (IQR)	32 (28–40)	36 (30–45)	0.139
Years of education, median (IQR)	8 (6–12)	7 (5–11)	0.033
Employed, n (%)	213 (79.4%)	228 (84.7%)	0.110
Home characteristics			
≥ 3 children in home, n (%)	44 (13.6%)	72 (22.5%)	0.003
Residence near a water body, n (%)	136 (42.3%)	147 (46.0%)	0.344
Distance in km to nearest HC* (II and higher), median (IQR)	1.37 (0.67–2.33)	1.75 (0.89–2.80)	0.008
Distance in km to nearest HC* (III and higher), median (IQR)	1.88 (0.95–3.38)	3.33 (1.97–4.87)	< 0.001
Distance in km to listed HC† (III and higher), median (IQR)	3.46 (1.26–10.6)	8.24 (4.10–15.9)	< 0.001
Distance in km to nearest town, median (IQR)	2.18 (0.96–4.09)	3.54 (1.78–5.42)	< 0.001
Socioeconomic position			
1 (lowest)	86 (28.9%)	66 (22.7%)	0.159
2	69 (23.2%)	75 (25.8%)	
3	73 (24.5%)	72 (24.8%)	
4 (highest)	69 (23.2%)	77 (26.5%)	

HC = health center; IQR = interquartile range.

* Health center closest to the residence of the patient.

† Health center where the control was enrolled.

FIGURE 3. Venn diagram: Distribution of the three principal severe malaria syndromes among the cases. This figure appears in color at www.ajtmh.org.

patients with available GPS data, increasing distance to the nearest health center at level III or higher was associated with severe malaria (OR 1.45, $P < 0.001$; Table 2). Distance to the nearest health center at level II or higher was not associated with severe malaria. When the final regression model was restricted to a subgroup of cases and controls in which the case had severe malaria solely attributed to unconsciousness ($N = 59$ pairs) or severe anemia ($N = 141$ pairs), delayed seeking of care was a significant risk factor for severe malaria among children presenting with severe anemia (OR 15.6, $P = 0.001$), but not those presenting with unconsciousness (OR 1.13, $P = 0.853$; Table 3).

Risk factors for delayed care seeking. As delayed care seeking from health centers where study participants were enrolled and provided with appropriate care was associated with increased risk of severe malaria, we studied factors associated with this delay. With unadjusted analysis, seeking care at a drug shop as the initial response to illness and caregivers in a polygamous relationship were significantly associated with delayed (≥ 24 hours after fever onset) care seeking (Table 4). With adjusted analysis, seeking care at a drug shop was significantly associated with delayed care seeking (OR 2.84, $P = 0.028$). The caregiver (OR 2.35, $P = 0.018$) being in a polygamous relationship was significantly associated with delayed care seeking. Considering children with valid GPS data, distance to the nearest level III and higher health center was the only factor significantly associated with delay in care seeking (OR 1.18, $P = 0.031$). In the model including distance data, seeking care at a drug shop did not demonstrate a significant association with delay in care seeking.

DISCUSSION

We used a case-control design to assess factors associated with severe malaria in Uganda. Delayed care seeking at the health center where the child was enrolled was a potent risk factor for severe malaria. Seeking care at a drug shop as the initial response to illness and increasing distance from

place of residence to the nearest health center were associated with delayed care seeking and with severe malaria. Associations between distance to a health center and delayed care seeking,⁴³ and between delayed care seeking and severe malaria have been described previously.^{6,8} We add to our understanding of the pathway toward severe malaria the important influence of drug shops; seeking care at a drug shop was strongly associated with both delayed care seeking and likelihood of severe malaria.

Prior studies have shown inconsistent results regarding the impact of delayed care seeking on severe malaria risk.⁶⁻⁹ These studies demonstrated association between longer duration of symptoms or arbitrarily set cut-offs defining duration of symptoms before admission and severe malaria, but they did not consider the standard WHO definition of delay and severe malaria risk. One study conducted in the Gambia showed lack of association between duration of symptoms and severe malaria, a finding attributed to difficulties in recollection of accurate historical information by distressed mothers.¹² Our study design enabled accurate history taking, and we found that delayed care seeking at health centers was a risk factor for severe malaria, even when delay was defined based on a narrow time frame of 24 hours after fever onset. Interestingly, delayed care seeking was associated with severe malaria due to anemia, but not that due to unconsciousness. Lack of association between delayed care seeking within 24 hours and severe malaria attributed to unconsciousness, a surrogate for cerebral malaria, suggests that in these children illness evolution was too rapid to be impacted by improved care seeking. Considering these results, whereas it remains imperative to urge prompt care for all febrile children, only efforts to prevent malaria may have significant impacts on the risk of cerebral malaria.

Drug shops are a popular choice of care in Uganda.^{44,45} Drug shops are more accessible and approachable than health facilities, even in rural settings. This improved accessibility has led some experts to advocate a role of drug shops in improving access to health services by filling in gaps in the health sector.⁴⁶⁻⁴⁹ However, we found a strong association between seeking care at a drug shop as the initial response to illness and delayed care seeking at public health centers. Seeking care at drug shops was also independently associated with an increased risk of severe malaria. Our findings implicate drug shops as barriers to access to appropriate antimalarial treatment, presumably by offering false assurance of adequate care and thereby allowing for progression from uncomplicated to severe malaria. In a survey conducted in Eastern Uganda, only 25% of children with fever seen at a drug shop received an artemisinin-based combination therapy (ACT), the first-line therapy for malaria in Africa. Of those who received an ACT, only 18% completed a full course of therapy.⁵⁰ Similar findings were demonstrated in Tanzania, with prohibitive costs charged for appropriate doses.⁵¹ Among sampled drug shops in western Kenya, non-recommended and cheaper monotherapies were available, potentially encouraging inadequate therapy.⁵² Subtherapeutic dosing has obvious potential bad consequences, including failure to cure infections, prolongation of illness, selection of drug resistance, and progression to severe disease.⁵¹ In our study, initially seeking care at a drug shop more than tripled the likelihood of severe malaria compared with children who did not access drug shops.

TABLE 2

Unadjusted and adjusted analysis of factors associated with severe malaria among 325 children with severe malaria (cases) and 325 children with uncomplicated malaria (controls) in Jinja District, Uganda

Variables	All children† (N = 325 pairs)				Children with GPS data‡ (N = 240 pairs)			
	Number of severe malaria cases		Unadjusted analysis		Number of severe malaria cases		Adjusted analysis	
	N = 325, n (%)*	Odds ratio	P value		N = 240, n (%)*	Odds ratio	P value	
Health care seeking characteristics								
Delayed to seek appropriate care	287 (88.3%)	3.77 (2.35, 6.03)	< 0.001		213 (88.7%)	5.50 (2.70, 11.1)	< 0.001	
Went to a drug shop as 1st response	104 (32.0%)	3.20 (2.11, 4.86)	< 0.001		78 (32.5%)	3.62 (1.86, 7.03)	< 0.001	
Ant malarial given on day 1 of illness	33 (10.1%)	1.00 (0.60, 1.64)	1.000		30 (12.5%)	\$	–	
Mother took decision on first day	215 (67.4%)	0.46 (0.32, 0.68)	< 0.001		159 (67.9%)	0.45 (0.24, 0.78)	0.010	
Child characteristics								
Age in year	NA	0.56 (0.42, 0.76)	< 0.001		NA	0.49 (0.32, 0.73)	0.001	
Female, n (%)	153 (47.0%)	0.94 (0.68, 1.30)	0.744		117 (48.7%)	\$	–	
Breast feed exclusively for 6 months	230 (73.7%)	1.46 (1.00, 2.14)	0.046		159 (69.1%)	\$	–	
Sleeps in net	250 (76.9%)	1.26 (0.80, 1.98)	0.305		182 (81.6%)	\$	–	
Danger symptoms on day 1 of illness,	38 (11.6%)	2.12 (1.17, 3.84)	0.010		32 (13.3%)	4.58 (1.73, 12.1)	0.002	
Hyperparasitemia (> 250,000 parasites/μL)	34 (10.4%)	2.42 (1.30, 4.52)	0.003		22 (9.1%)	\$	–	
Gametocytemia	91 (28.1%)	2.10 (1.42, 3.11)	< 0.001		66 (27.7%)	1.86 (1.05, 3.28)	0.032	
Caregiver characteristics								
Age in years	NA	1.01 (0.99, 1.02)	0.101		NA	\$	–	
Is the child's mother	261 (80.5%)	0.60 (0.39, 0.92)	0.020		196 (82.0%)	\$	–	
Years of education	NA	0.99 (0.94, 1.03)	0.747		–	\$	–	
Employed	225 (70.7%)	2.14 (1.52, 3.00)	< 0.001		163 (69.6%)	3.10 (1.77, 5.45)	0.015	
In a polygamous relationship	83 (25.5%)	1.25 (0.88, 1.79)	0.205		67 (35.2%)	\$	–	
Head of home characteristics								
Age in years, median (IQR)	NA	1.00 (0.99, 1.01)	0.721		NA	\$	–	
Years of education	NA	0.96 (0.92, 1.00)	0.064		NA	0.94 (0.87, 1.00)	0.078	
Employed	228 (84.7%)	2.05 (1.20, 3.49)	0.007		168 (83.1%)	\$	–	
Home characteristics								
Distance in km to nearest HC (II and higher)	\$	\$	–		NA	\$	0.231	
Distance in km to nearest HC (III and higher)	\$	\$	–		NA	1.15 (0.91, 1.47)	0.231	
Distance in km to nearest town ≥ 3 children in home, n (%)	\$	\$	–		NA	1.45 (1.17, 1.79)	< 0.001	
Residence near a water body	72 (22.5%)	1.85 (1.22, 2.81)	0.003		50 (21.2%)	\$	–	
Cement floor	147 (46.0%)	1.18 (0.85, 1.64)	0.317		105 (44.8%)	2.78 (1.02, 7.60)	0.045	
Dung floor	121 (37.2%)	0.78 (0.55, 1.09)	0.149		91 (38.4%)	\$	–	
Iron roof	107 (32.9%)	2.51 (1.68, 3.76)	< 0.001		77 (32.0%)	\$	–	
Grass roof	283 (87.0%)	0.75 (0.45, 1.23)	0.256		210 (88.6%)	\$	–	
Mud wall	30 (9.2%)	1.04 (0.60, 1.80)	0.888		23 (9.5%)	\$	–	
Cement wall	68 (20.9%)	1.27 (0.85, 1.90)	0.225		50 (20.8%)	\$	–	
Socioeconomic position	211 (65.7%)	1.01 (0.72, 1.43)	0.933		158 (66.6%)	\$	–	
1 (lowest)	66 (22.7%)	Referent	–		46 (21.6%)	Referent	–	
2	75 (25.8%)	1.61 (0.97, 2.69)	0.064		60 (28.1%)	3.26 (1.18, 8.97)	0.022	
3	72 (24.8%)	1.38 (0.82, 2.31)	0.218		52 (24.4%)	1.91 (0.63, 5.82)	0.251	
4 (highest)	77 (26.5%)	1.71 (1.00, 2.92)	0.046		55 (25.8%)	2.80 (1.05, 7.47)	0.039	

GPS = global positioning system; IQR = interquartile range; NA = not applicable.

* Column frequency.

† Analysis applied to all children; distance data not included in the analysis.

‡ Analysis restricted to children with valid GPS data; distance data included in the analysis.

\$ Not included in final model.

TABLE 3
Adjusted analysis of factors associated for specified sub-groups of children with severe malaria in Jinja District, Uganda

Variables	Severe malaria anemia (N = 141 pairs)		Impaired consciousness (N = 59 pairs)	
	Odds ratio	P value	Odds ratio	P value
Health care seeking characteristics				
Delayed to seek appropriate care	15.6 (3.02, 80.6)	0.001	1.13 (0.30, 4.28)	0.853
Went to a drug shop as 1st response	7.55 (1.94, 29.2)	0.003	5.41 (1.25, 23.2)	0.023
Mother took decision on first day	0.40 (0.15, 1.08)	0.071	0.43 (0.09, 2.04)	0.294
Child characteristics				
Age in year	0.38 (0.17, 0.82)	0.015	0.46 (0.21, 0.99)	0.048
Danger symptoms on day 1 of illness	*	*	*	*
Gametocytemia	4.14 (1.53, 11.1)	0.005	*	—
Caregiver characteristics				
Employed	3.81 (1.44, 10.0)	0.007	4.29 (1.13, 16.2)	0.032
Head of home characteristics				
Years of education	0.92 (0.82, 1.05)	0.255	1.08 (0.91, 1.29)	0.359
Home characteristics				
≥ 3 children in home, n (%)	2.14 (0.60, 7.62)	0.240	7.75 (0.96, 62.4)	0.054
Dung floor				
Mud wall				
Socioeconomic position	1 (lowest)	Referent	Referent	—
	2	1.81 (0.53, 6.21)	0.65 (0.08, 5.02)	0.681
	3	0.64 (0.16, 2.60)	0.42 (0.05, 2.97)	0.386
	4 (highest)	2.60 (0.77, 8.70)	0.77 (0.96, 6.20)	0.808

* Not included in final model.

Our results suggest that it may be appropriate to rethink policies that use informal drug shops as tools for malaria treatment and control. These shops suffer from lack of medical knowledge, stocking of unregistered poor quality drugs, and the potential for profit-driven suboptimal practices.⁵³ Interventions including subsidizing costs of ACTs sold at drug shops, training of drug vendors, and registration of drug shops have been shown to improve standards of malaria case management.^{54,55} In Tanzania, the National Malaria Control Program adopted the accrediting drug dispensing outlet (ADDO) program as a private sector mechanism to supplement the distribution of subsidized ACTs.⁵⁶ This approach resulted in increased access to affordable ACTs for underserved populations.⁵⁷ However, this success was not without limitations, and sustaining positive changes remains a concern.^{56,58} Furthermore, a recent assessment of the role of ADDOs in the health care system showed dispensing practices for pneumonia deviating from the norm, a practice attributed to patient demand for antibiotics and profit motivated practices.⁵⁹ Similar trends might be seen with ACTs for malaria. In Ghana, the Affordable Medicines Facility–malaria initiative resulted in significant increases in availability of ACTs in drug shops, with less than half of the shops having ACTs soon after the intervention and over two years after initiation, availability of ACTs remained unchanged. Also of concern, the availability of nonstandardized herbal based antimalarials remained high during and after the intervention, sometimes surpassing availability of ACTs.⁶⁰ Considering this background and our results, more study is needed to determine if optimal malaria control strategies should include drug shops as key providers of care or if emphasis should be directed primarily towards improving care at public health centers.

Longer distance from place of residence to public health centers was a notable risk factor for both delayed care seeking and severe malaria, consistent with findings from other studies showing that distance to a health center is a deterrent to prompt use of the more formal health services offered at public health centers.^{15,18,20,43,61} This finding is enlightening, considering that for both cases and controls average

distances from patients' homes to the nearest health center were well within a 5 km radius, the acceptable distance between a population and a health center recommended by the Ministry of Health, Uganda.⁶² Thus, factors beyond geographical access may have deterred caregivers from seeking care at public health centers. Associations between distance to health centers and both delayed seeking of care and severe malaria were only significant when considering centers at level III or higher. These results suggest that lower-level health centers offered less efficacious care, highlighting the need to improve services offered at these centers.

Other risk factors associated with increased likelihood of severe malaria included the following. First, gametocytemia was associated with severe malaria, likely because gametocytemia serves as a marker for prolonged infection, with gametocytogenesis peaking 7–10 days after asexual parasitaemia.³ Second, families with more than three children less than five years of age in the household were associated with severe malaria, suggesting that social dynamics linked to caring for multiple children compromised good family support.⁶³ Third, surprisingly, having an employed caregiver or head of household was associated with severe malaria although there was no association between employment and delayed care seeking. Fourth, higher socioeconomic status of the household was associated with severe malaria, contrasting with findings from other studies.⁶ This finding is unexplained, but an association between higher socioeconomic status and decreased exposure to mosquitoes,⁶⁴ leading to decreased malaria specific immunity and predisposition to severe disease might play a role. The mother being the first decision-maker was the only protective factor against severe malaria, highlighting the importance of women's autonomy in a home, a characteristic associated with appropriate care seeking.^{65–68} Increasing age was protective against severe malaria, a paradoxical finding considering that we matched on age. However, this finding could be explained by incomplete matching, and wide age ranges within matched case-control pairs.

TABLE 4

Weighted unadjusted and adjusted analysis for factors associated with delay in care seeking (≥ 24 hours after fever onset) at health centers where children were enrolled

		All children (N = 650)†				Children with GPS data (N = 480)‡			
		Children who delayed to seek care	Unadjusted		Adjusted		Children who delayed to seek care	Adjusted	
Variables	N = 513, n (%)*		Odds ratio	P value	N = 383, n (%)*	P value	N = 383, n (%)*	Odds ratio	P value
Health care seeking characteristics									
Went to a drug shop as 1st response	127 (24.7%)	2.72 (1.14, 6.50)	0.024	2.84 (1.12, 7.21)	0.028	96 (25.0%)	1.73 (0.80, 3.70)	0.158	
Ant malarial given on day 1 of illness	55 (10.7%)	1.41 (0.61, 3.22)	0.411	§	–	47 (12.2%)	§	–	
Mother took decision on first day	366 (71.3%)	0.49 (0.25, 0.95)	0.037	0.63 (0.28, 1.41)	0.266	277 (72.3%)	0.81 (0.36, 1.82)	0.614	
Child characteristics									
Age in years	NA	0.94 (0.81, 1.10)	0.483	§	–	NA	§	–	
Female	242 (47.1%)	0.92 (0.58, 1.47)	0.745	§	–	191 (49.8%)	§	–	
Breast feed exclusively for 6 months	337 (65.9%)	0.57 (0.34, 0.97)	0.042	§	–	243 (63.4%)	§	–	
Sleeps in net	373 (72.1%)	0.88 (0.47, 1.64)	0.695	§	–	272 (71.0%)	§	–	
Danger symptoms on day 1 of illness	46 (8.9%)	2.49 (0.76, 8.16)	0.132	§	–	37 (9.6%)	§	–	
Hyperparasitemia (> 250,000 parasites/μL)	41 (7.9%)	2.66 (0.62, 11.3)	0.183	§	–	26 (6.7%)	§	–	
Gametocytemia	119 (23.2%)	1.17 (0.61, 2.27)	0.624	§	–	91 (23.7%)	§	–	
Caregiver characteristics									
Age in years	NA	1.01 (0.99, 1.03)	0.156	§	–	NA	§	–	
Child's mother	421 (82.0%)	0.42 (0.18, 0.99)	0.048	§	–	316 (82.5%)	§	–	
Years of education	NA	0.93 (0.86, 0.99)	0.038	0.96 (0.88, 1.05)	(0.389)	NA	0.91 (0.83, 0.99)	0.035	
Employed	314 (61.2%)	0.87 (0.54, 1.40)	0.591	§	–	224 (58.4%)	–	–	
In a polygamous relationship	128 (24.9%)	1.94 (1.03, 3.65)	0.040	2.35 (1.15, 4.80)	0.018	104 (27.1%)	2.79 (1.18, 6.57)	0.019	
Head of household characteristics									
Age in years	NA	1.00 (0.99, 1.01)	0.441	§	–	NA	§	–	
Years of education	NA	0.96 (0.91, 1.02)	0.253	§	–	NA	§	–	
Employed	341 (80.2%)	0.44 (0.21, 0.93)	0.032	0.45 (0.19, 1.06)	0.071	252 (78.0%)	0.52 (0.22, 1.26)	0.152	
Home characteristics									
Distance in km to nearest HC (> HC II)	NA	§	–	§	–	NA	1.11 (0.89, 1.38)	0.349	
Distance in km to nearest HC III (> HC III)	NA	§	–	§	–	NA	1.18 (1.01, 1.37)	0.031	
Distance in km to nearest town	NA	§	–	§	–	NA	§	–	
≥ 3 children in home, n (%)	97 (18.9%)	1.22 (0.60, 2.46)	0.569	§	–	68 (17.7%)	§	–	
Residence near a water body	222 (43.2%)	1.11 (0.69, 1.80)	0.641	§	–	168 (43.8%)	§	–	
Cement floor	191 (37.2%)	0.55 (0.34, 0.89)	0.015	§	–	138 (36.0%)	§	–	
Dung floor	132 (25.7%)	1.05 (0.57, 1.93)	0.875	§	–	95 (24.8%)	§	–	
Iron roof	451 (87.9%)	0.98 (0.45, 2.12)	0.960	§	–	335 (87.4%)	§	–	
Grass roof	49 (9.5%)	1.17 (0.50, 2.71)	0.714	§	–	40 (10.4%)	§	–	
Mud wall	99 (19.3%)	1.23 (0.65, 2.33)	0.511	§	–	75 (19.5%)	§	–	
Cement wall	331 (64.5%)	0.73 (0.44, 1.21)	0.223	§	–	247 (64.4%)	§	–	
Socioeconomic position	1 (lowest)	124 (26.9%)	Referent	–	Referent	–	96 (27.6%)	Referent	–
	2	119 (25.8%)	1.32 (0.50, 3.47)	0.561	1.05 (0.44, 2.51)	0.905	93 (26.8%)	1.00 (0.45, 2.36)	0.986
	3	106 (22.9%)	1.11 (0.44, 2.77)	0.815	0.48 (0.20, 1.17)	0.107	76 (21.9%)	0.90 (0.19, 1.75)	0.823
	4 (highest)	112 (24.3%)	1.19 (0.42, 3.41)	0.736	0.55 (0.23, 1.33)	0.193	82 (23.6%)	1.02 (0.26, 2.56)	0.954

NA = not applicable.

* Column frequency.

† Analysis applied to all children; distance data not included in the analysis.

‡ Analysis restricted to children with valid GPS data; distance data included in the analysis.

§ Not included in final model.

This study had limitations. First, it was subject to inherent limitations of case-control studies, particularly selection bias attributable to enrollment of nonrepresentative controls although we enrolled geographically and time matched controls to minimize this bias. Second, recall bias may have inadvertently affected the validity of the historical information collected. Caregivers of sicker children may have exaggerated or underrated their responses in anticipation of benefit, and

their responses may have been incomplete as a result of anxiety attributable to their child's state of health. Third, inability to certainly exclude comorbidities in children with parasitemia may have resulted in misclassification of either cases or controls. Lastly, attaining balanced numbers of the three studied manifestations of severe malaria was a challenge, limiting sample size for some syndromes, and thus minimizing our ability to draw comparisons across the different syndromes.

Notwithstanding, our study provides useful insights into important modifiable risk factors for delayed care seeking and for severe malaria. We show that delayed care seeking and seeking care at a drug shop as the first response to illness were significantly associated with risk of severe disease. In addition, we demonstrate that prompt care seeking at public health centers remains a challenge, with distance from residence to health centers a hindrance in accessing these facilities. Considering their potential to cause harm, caution is recommended in incorporating drug shops as service providers. Above all, enhancement of formal public health systems in sub-Saharan Africa should be a high priority.

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