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CASE STUDY

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Risk factors for death among children with severe malaria, Ivukula sub-county, Namutumba district, Eastern Uganda, september 2021–february 2022

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Abstract

Background In February 2022, the Ministry of Health received reports of more than 100 child deaths from a 'strange disease' in Namutumba District over a period of 6 months from politicians through the media. Preliminary investigations by the district rapid response team confirmed the strange disease to be severe malaria. The scope of severe malaria deaths was investigated, associated factors identified, and recommendations made for control measures to inform early malaria treatment strategies in Namutumba District.

Methods A retrospective study was conducted in March 2022 in the most affected subcounty (Ivukula Subcounty) involving cases and controls. A case was defined as a death with a positive malaria test, fever and any of the following: convulsions, difficulty breathing, yellowing of eyes or palms, tea-coloured urine, anaemia (evidenced by pale eyes or palms, or clinically-identified in medical records), loss of consciousness, or reduced urine output (very little or no urine in a day) in a child ≤ 12 years from September 2021 to February 2022 in Ivukula Subcounty, Namutumba District. Controls were survivors with the same signs and symptoms, recruited in a 2:1 ratio with cases. Cases and controls were actively searched using a door-to-door approach with the help of community health workers. Caretakers were interviewed to obtain data on signs and symptoms, socio-demographic information, health-seeking behaviours and health system risk factors. Drugs and bloodstock status information was obtained from health workers using an interview guide. Factors associated with death were identified using multivariate logistic regression and thematic analysis for qualitative data.

Results Among 46 cases, 29 (63%) were < 5 years, and 23 (50%) were female. Death among children with severe malaria was significantly associated with treatment non-completion (aOR = 9.7, 95%CI 1.8–53) and inability to receive blood transfusion for anaemic patients (aOR = 7.1, (95%CI 1.4–36). Healthcare workers reported that inability to reach referral sites due to transport costs, stockouts of anti-malarials and blood products at health facilities, and absence

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of integrated community case management of childhood illnesses (iCCM) contributed to deaths among children with severe malaria.

Conclusion Lack of access to anti-malarial treatment and to blood transfusions among anaemic patients due to stockouts were associated with severe malaria deaths among children ≤ 12 years in Ivukula Subcounty. Recommendations made were: accurate quantification of anti-malarials for health facilities, offering transport support to severe patients referred to higher-level facilities, and increasing access to blood products. Activation of iCCM could facilitate public health efforts against severe malaria in the district.

Keywords Malaria, Severe malaria, Malaria death, Risk factors, Uganda

Background

Globally, the scale-up of malaria prevention and control measures has made a significant contribution to the fight against malaria, with notable gains between 2000 and 2020 resulting in a 36% reduction in malaria mortality [1] Despite this decrease, the number of malaria-related deaths remains high, reaching 627,000 in 2020, with the World Health Organization (WHO) African Region bearing the highest burden. Globally, Uganda is the third highest contributor of malaria cases and eighth highest contributor of malaria deaths according to the World Malaria Report (WMR); most of these deaths occur among children < 5 years [1, 2].

In Uganda, malaria is endemic in 95% of the country, with the remaining 5% prone to epidemics. It is one of the leading causes of morbidity and mortality in the country, responsible for 30–50% of outpatient visits and 15–20% of hospital admissions [3]. The primary interventions for malaria control in Uganda have been the distribution of insecticide-treated bed nets (ITNs) and prompt treatment with artemisinin-based combination therapy (ACT)[4]. However, additional measures have been adopted in selected high-burden districts, including integrated community case management of childhood illnesses (iCCM) since 2010 [5, 6], indoor residual spraying since 2014 [7, 8], and seasonal malaria chemoprevention in Karamoja Region since 2021 [9]. Despite these interventions, progress towards malaria elimination has stalled [1]. Uganda now registers more malaria deaths annually (19,600 deaths in 2021) than it did when the interventions just started (12,686 in 2014 and 13,964 in 2015) [1]; 80% of the deaths occur among children below 5 years [4]. According to the Uganda Malaria Indicator Survey 2018–2019, the malaria prevalence among children below 5 years in Uganda is 9%. However, the prevalence of malaria among children below 5 years is highest in Karamoja region (34%), West Nile region (22%) and Busoga region (21%)[10, 11].

Despite the slow progress, Uganda has committed to reducing malaria cases by 80% and malaria deaths to near zero (< 1 death per 100,000 population per year) by 2030. The Uganda Malaria Reduction Strategic Plan 2020–2022, along with other strategic documents by the National Malaria Control Division, underscores the adoption of an approach grounded in the High Burden High Impact (HBHI) principles. The approach aims to improve diagnosis and treatment for malaria through private sector engagement and community systems strengthening for improved service delivery at all levels[11–13].

Severe malaria develops in approximately one in six malaria cases among children [14]. Severe malaria is a medical emergency requiring urgent and aggressive treatment with 3 doses of intravenous artesunate in 24 h. This treatment is followed by a complete dose of artemether and lumefantrine (AL) for 3 days [4]. Manifestations of severe malaria include cerebral malaria (impairment of consciousness including convulsions and/or coma), severe anaemia and haemoglobinuria due to haemolysis (indicated by tea coloured urine), acute respiratory distress syndrome, abnormalities in blood coagulation, low blood pressure caused by cardiovascular collapse, hyperparasitaemia, and metabolic acidosis due to acute kidney injury. Without treatment, severe malaria can lead to death within 24 h [15].

On February 17, 2022, an uptick in severe malaria deaths was reported in Namutumba District, primarily among children ≤ 12 years. At the time, the malaria test positivity rate in the district was 90% [16]. An investigation was conducted to determine the scope of severe malaria deaths, identify associated factors, and recommendations for control measures to inform early malaria treatment strategies.

Methods

Outbreak area

Namutumba District is located in the eastern part of Uganda, a region highly endemic for malaria [17, 18]. The district is made up of 2 constituencies and 20 sub-counties, of which Ivukula is one, and has a total population of approximately 320,000 people. The population is served by 2 private hospitals, 1 public health centre (H/C) IV, seven H/C IIIs, and 25 H/C IIs [19].

Severe malaria is managed in Uganda's free healthcare system by health centres at level III and above [4, 20].

These facilities are supplied with severe malaria treatment once every 2 months and these quantities are based on quantifications made by health facilities once every year. Severe malaria management is further supported by private hospitals and high-level private clinics. Additionally, blood transfusion services are offered at the public H/C IV in Namutumba District; however, blood products must be sent from Jinja Regional Referral Hospital on request, located approximately an hour away, and the availability is not consistent. Patients requiring management beyond what the H/C IV can provide are referred to Iganga Hospital, Jinja Regional Referral Hospital, or Mbale Regional Referral Hospital which are 31 km, 71 km, and 79 km away, respectively (Fig.1).

Case definition and case finding

A case was defined as a death occurring during September 2021 to February 2022 in a child ≤ 12 years of age in Ivukula Subcounty, Namutumba District with a positive malaria test (rapid diagnostic tests or microscopy), fever and any of the following: convulsions, difficulty breathing, yellowing of eyes or palms, tea-coloured urine, anaemia (evidenced by pale eyes or palms, or clinically-identified in medical records), loss of consciousness, or reduced urine output (very little or no urine, below 200mls in 24 h). Due to the lack of clinical records for most patients, clinical descriptions from literature were used to provide reference on presentation and caretakers' verbal reports of symptoms to classify cases.

The specific areas affected were unclear at the time of the investigation (March 2022). To identify the most affected sub-counties, data on severe and fatal malaria cases was reviewed using the electronic district health information system (DHIS2) [16]. Inpatient registers from all public and private health facilities in Namutumba District were subsequently reviewed. However, these data sources did not support the reported increase in deaths among children; only 8 malaria deaths had been reported in DHIS2 from September 2021 to February 2022 in Namutumba District, with no apparent spatial or temporal pattern. A hypothesis was made that the deaths might be occurring in the community among children who did not reach health facilities. To investigate this further, an attempt to contact one Village Health Team member (VHT, or community health worker) from each of the 640 villages of Namutumba District by phone was made to obtain the number of all deaths among children ≤ 12 years that occurred in the communities from 1st September 2021 to 28th February 2022, regardless of the cause. One hundred eighty (180) VHTs were reached in the one-day calls were made, the rest of the VHTs were not accessible by phone. Of the 180 VHTs, 134 reported one or more child deaths (Range 1–6 per VHT) making a total of 514 child deaths for the period reviewed. Responses were based on VHT registers for deaths among children 5 years and below and on VHT recall for deaths among children above 5 years. Note that VHT registers record child deaths below 5 years and maternal deaths and these are reported quarterly to the Health Information Management System (HMIS); District Health Information System (DHIS2) using HMIS 097b report; however, the cases of children below 5 years were not reported in the DHIS2 system.

Subcounty death rates were calculated and cause-specific death rates among children ≤ 12 years using these data. The VHTs shared details of the manner of death,

Fig. 1 Location of Namutumba District and Ivukula Subcounty on the map of Uganda and the relevant health facilities used in the referral pathway. H/C: Health Centre, RRH: Regional referral hospital

reporting a positive malaria test where this applied; this informed the conclusion of a malaria death. Due to the lack of age-specific population data, total population was used as a denominator for calculation of attack rates.

Among the 20 subcounties evaluated, Ivukula Subcounty had the highest malaria death rate among children during the period of interest (3.9/1,000, compared with 2.6/1,000 in all other subcounties) yet only 12.2% of the reached VHTs were from this subcounty. As a result, our subsequent case-finding focused on Ivukula Subcounty. Cases in Ivukula Subcounty were analysed by age, sex, location, and time.

Hypothesis generation

Beyond the descriptive epidemiology from the cases identified and listed through active case search, key informant interviews (KIIs) were conducted with the VHTs, health facility in-charges, and health facility staff. This was done to identify factors that might have been associated with malaria deaths to support hypothesis generation. Ten KIIs were conducted with 2 health facility in-charges, 4 health facility staff, and 4 VHTs using a semi-structured interview guide to assess for health system factors like: availability of drugs and other required therapeutics and health seeking factors for community members like timeliness to seek care, completion of referrals and hindering factors. The interviews were conducted by the investigators in person, audio-recorded, transcribed and analysed thematically. Furthermore, clinic logs were reviewed to assess stocks of anti-malarial drugs for 2 Health Centre IIs and 1 Health Centre III in Ivukula Subcounty from September 2021 to February 2022.

A retrospective investigation of deaths among children ≤ 12 years

A retrospective investigation was conducted to review severe malaria cases among children ≤ 12 between September 2021 and February 2022 in Ivukula Subcounty to identify factors associated with death. Risk factors assessed included child and caregiver demographics including age, sex, relationship of the care giver to the child, education level of the caregiver; socio-economic status of the caregiver (employment and monthly income); child clinical information (signs and symptoms presented) and history of severe malaria. Additionally, care-seeking practices and care provided at health facilities were assessed: symptom onset, delays to care-seeking from either facility or community, level of health facility visited, completion of referral for referred patients and level of the facility visited, receipt of complete dose of required medication, receipt of blood transfusion for anemic patients. Controls were survivors who otherwise had the same clinical, demographic, and time definition as cases. Controls were matched to cases by parish (one administrative level above a village) of residence in a ratio of 2:1. All children with active signs and symptoms of severe malaria at the time of the investigation were excluded because of uncertainty of their outcomes later on. For homesteads with more than one case or control, only one case was considered to reduce opportunities for collinearity in analysis.

A semi-structured questionnaire was constructed in Epi-info 7.2.5.0 (CDC, Atlanta, USA). Data were then collected from home caregivers of 46 cases and and 77 controls (a total of 123 respondents) using an electronic copy of this form. In the absence of electronic forms due to gadget failures, paper-based forms were used and later entered into the database manually each evening after data collection. Data were cleaned and analysed using Epi-info version 7.2.5.0 software (CDC, Atlanta, USA). Multivariable logistic regression was conducted to determine levels of association; all variables with p-values < 0.05 in bivariate analysis were considered for multivariable analysis except for variables that showed collinearity.

Results

Descriptive epidemiology

Sixty-one (61) deaths were identified among children ≤ 12 years, of which 51 fit the case definition of severe malaria. Ten were from other causes (neonatal deaths (5), unknown cause (2), anaemia without fever (1), convulsions without fever (1) and severe pneumonia (1)). Among the 51 remaining cases, 32 (63%) were < 5 years. The median age was 4 years (IQR 2–6) and 26 (51%) were male. The highest number of child deaths in Ivukula Subcounty were recorded in January 2022 (14; 27%) followed by October 2021 (10; 20%) and September 2021 (9; 18%) (Fig. 2).

Hypothesis generation findings

Health facility stock assessment

All health facilities assessed reported that they received two cycles of 2-month drug deliveries in the assessed 6 months (September 2021-February 2022) (Table 1), indicating that one drug delivery cycle was missed. For each 2-month cycle, the H/C III received 200 doses of artesunate (sufficient for 66 patients), which was completely used up in 14 days; H/C II facilities did not receive artesunate because they are not mandated to treat severe malaria.

Qualitative interview findings

Caregivers and key informants from the health facilities and VHTs frequently mentioned anti-malarial drug

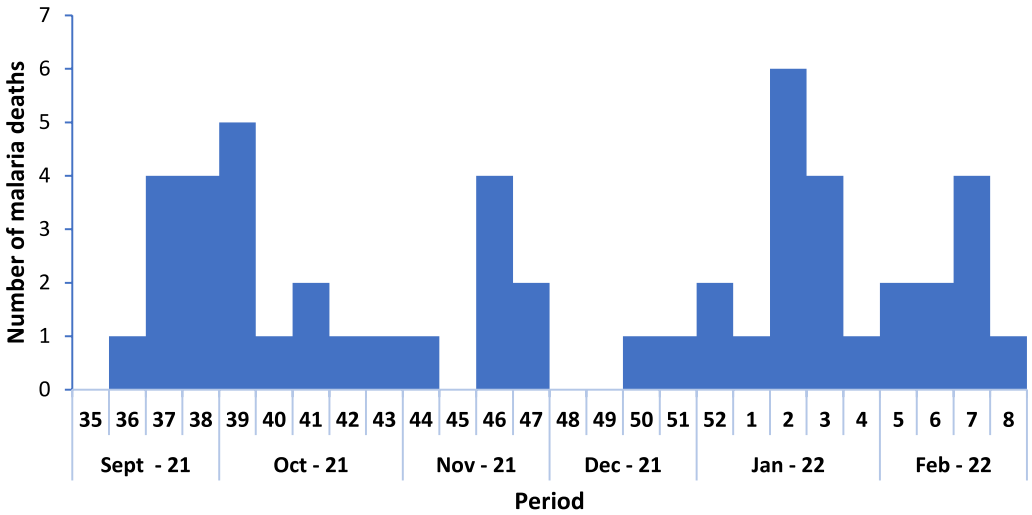

Fig. 2 Distribution of malaria deaths by date of occurrence among children ≤ 12 years in Ivukula Subcounty, September 2021 to February 2022 (n = 51)

Table 1 The quantity of anti-malarial drugs delivered in a single 2-month cycle and their consumption period for facilities in Ivukula Subcounty, Namutumba District, September 2021-February 2022

Facility	Artemether-lumefantrine (AL) packs received per 2 months cycle (30 doses/pack)	Days from receipt to stockout of AL	Artesunate doses received	Days from receipt to stockout of artesunate
Lwatama Health Centre II	34	21	–	–
Namasita Health Centre II	10	45	–	–
Ivukula Health Centre III	60	21	200	14

stockouts as a barrier to patients receiving or completing treatment.

> *"During periods of reduced stock of artesunate, patients are given only the start dose and are advised to buy the rest, but this does not happen due to finance challenges...." - Health worker at a Health Centre III.*

Other findings reported by health workers and VHTs included lack of access to blood products for severely anaemic patients and inability to reach the high-level health facilities when referred due to failure to facilitate transport costs mainly due to economic constraints.

> *"Caretakers often go home with very sick children due to lack of transport to referral health facilities and wait until transport money is acquired, hence children die from home before transport charges are acquired or during transportation to the health facilities after money for transport charges is acquired..." - VHT*
>
> *"...We often fail to pick blood products from the regional blood bank located 71 kilometers away due to lack of fuel for the ambulance, and at times when we have fuel, the blood bank too has no blood products..." -In-charge of Nsinze Health Centre IV*

A hypothesis was made that age and sex of the child, type of caregiver and education level, the duration from onset of severe malaria symptoms to seeking high-level care, the health facility visited, availability of drugs and blood products, and completion of referral could be contributing to the malaria deaths.

Demographic characteristics

Of the 51 case-patients, five (10%) were excluded because they came from the same household as another case. A total of 46 case-patients and 77 controls were enrolled in the case–control study. Twenty-nine (63%) cases and 40 (52%) controls were aged < 5 years (p = 0.23). Similar proportions of cases (23; 50%) and controls (41; 53%) were females (p = 0.73). Caregivers of cases were older than caregivers of controls (median age 42 vs 35 years, p = 0.01). Twenty-five (54%) case caregivers and 27 (35%) control caregivers had no education or lower primary education only (p = 0.10) (Table 2).

Table 2 Demographic and clinical exposures of children ≤ 12 years evaluated for association with severe malaria deaths in Ivukula subcounty, Namutumba District, September 2021-February 2022

Characteristic	Cases (N = 46) n (%)	Controls (N = 77) n (%)	COR (95% CI)	AOR (95% CI)
Child characteristics				
Age in years				
< 5	29 (63)	40 (52)	Ref	Ref
≥ 5	17 (37)	37 (48)	0.6 (0.3–1.4)	0.5 (0.1–2.8)
Median age (years)	3.5	4.5	NA	
Sex				
Female	23 (50)	41 (53)	Ref	Ref
Male	23 (50)	36 (47)	1.1 (0.5–2.3)	0.8 (0.2–3.9)
Clinical characteristics				
Anaemia				
No	7 (15)	34 (44)	Ref	
Yes	39 (85)	43(56)	4.5 (1.8–11.3) ***	–
Convulsions				
No	30 (65)	36 (47)	Ref	–
Yes	16 (35)	41 (53)	0.5 (0.22–1.0)	
Difficulty in breathing				
No	22 (48)	29 (38)	Ref	–
Yes	24 (52)	48 (62)	0.6 (0.3–1.4)	
Jaundice				
No	9 (20)	32 (42)	Ref	–
Yes	37 (80)	45 (58)	2.9 (1.2–6.9) *	
Loss of consciousness				
No	33 (72)	64 (83)	Ref	–
Yes	13 (28)	13 (17)	1.9 (0.8–4.6)	
Tea coloured Urine				
No	18 (39)	44 (57)	Ref	
Yes	28 (61)	33 (43)	2.1 (0.99–4.4)	
Needed blood transfusion				
No	16 (42)	18 (45)	Ref	–
Yes	22 (58)	22 (55)	2.9 (1.3–6.7) **	
Received blood transfusion				
No	13 (59)	4 (18)	6.5 (1.6–25.8) **	7.1 (1.4–36.2) **
Yes	9 (41)	18 (82)	Ref	Ref

COR Crude Odds Ratio, AOR Adjusted Odds Ratio

*p < 0.05

**p < 0.01

***p < 0.001

Clinical characteristics

Anaemia was more common among cases than controls (85% vs 44%; p = 0.002), as was jaundice (80% vs 58%, p = 0.01). Convulsions were non-significantly more common among controls than cases (53% vs 35%, p = 0.06). Experiencing tea-coloured urine was more common among cases than controls (61% vs 43%, p = 0.05). Cases were more likely to need blood transfusion than controls (58% vs 32%, p < 0.001) and, among those who needed it, were less likely to receive it (41% vs 82%, p < 0.001) (Table 2).

Factors associated with deaths among cases and controls with severe malaria in Ivukula subcounty, Namutumba district

Community VHT consultations in Ivukula Subcounty were infrequent; few cases (6%) or controls (13%) sought care from a VHT due to inactive integrated community

case management of childhood illnesses (iCCM) including malaria. After symptom onset, a non-significantly higher proportion of cases than controls sought care in the first 24 h (52% vs 35%, p = 0.09). The highest proportion of cases (43%) and controls (49%) accessed their first level of care from a H/C III, as recommended, while 39% of cases and 24% of controls accessed their first level of care from small private clinics. Completion of treatment given at the first facility was much less frequent among cases than controls (22% vs 61%, p < 0.001) (Table 3). The main reasons for lack of completion were drug stockouts for both cases (47%) and controls (76%).

Among those who went to a second facility following referral to a high-level facility, the most common facilities visited were H/C IIs (38% of cases and 43% of controls) located near their homes. Among those given treatment, completion was again more frequent among controls than cases (89% vs 11%, p = < 0.001) (Table 3).

In bivariate analysis, five variables were significantly associated with death among children with severe malaria (Tables 2, 3). In multivariate analysis, need for blood transfusion, jaundice, and having anaemia were excluded from the final model due to collinearity with receiving blood transfusion. After adjustment for child age, child sex, and time to seek care, inability to complete treatment (aOR = 9.7, 95%CI 1.8–53), and inability to receive transfusion when needed (aOR = 7.1, 95%CI 1.4–36) were significantly associated with death.

Discussion

Forty-six (46) unreported malaria deaths were identified among children through community-based case searches in Ivukula Subcounty, Uganda during late 2021 and early 2022. Lack of access to complete anti-malarial treatment and lack of access to blood transfusions among anaemic patients requiring blood increased risk of death. Drug stockouts and inability to pay for treatment during stockouts of free drugs contributed to the inability to complete anti-malarial treatment.

In contrast to prior studies of severe malaria conducted elsewhere in sub-Saharan Africa, no association was identified between age and mortality [21, 22]. This might be explained by the overall lower median age of the study population (< 5 years) compared to previously-studied populations [23], or perhaps the narrow age range studied (≤ 12 years). In a meta-analysis conducted from a number of African countries, mortality increased steadily from 6% among the patients aged < 10 years to 36.5% among the patients aged > 50 years [24]. Similar findings are seen in a study conducted in Zambia where age was not significant due to low median age of both cases and controls (< 2yrs) [25].

A strong association was identified between lack of access to complete anti-malarial treatment and deaths among children; data suggested that stockouts were the primary reason that children were unable to complete treatment. Other studies in Uganda have shown that the frequent stockouts of artesunate are a major reason why children with severe malaria do not receive appropriate treatment based on severe malaria treatment guidelines [26] and studies in other parts of Africa have similarly noted anti-malarial drug stockouts as a key challenge to completion of malaria treatment [27–30]. According to the WHO, poorly treated severe malaria can lead to high death rates, while effective treatment and supportive care reduces mortality to 10–20% [31]. To effectively reduce malaria death rates, it is critical to ensure sufficient supplies of drugs to treat the number of cases that occur or implement more effective prevention measures. Anecdotally, during the study it was revealed that people often avoid visits to the health centre when their child has malaria if they know the centre is stocked out. Beyond reducing the likelihood that a child will receive appropriate treatment, this also all but guarantees that a case will not be reported, resulting in an underestimation of the burden of the disease, especially during periods with high numbers of malaria cases. The excess cases identified in the district during community searches, compared to the number reported in DHIS2, also suggests that this may be occurring. However, stockouts may not always reflect inaccurate estimations of drug needs in a district.

Studies in Africa have showed that pilfering and resale of drugs is sometimes done by healthcare workers to provide them with an alternate source of income, and this has greatly contributed to drug stockouts [32–34]. Investigations into reasons for missed drug deliveries at higher levels of the supply chain, reassessing the appropriate quantities of drugs needed by health centres in the district, especially during upsurges, and ensuring delivery of required drugs could address the challenge of frequent stockouts, improve treatment completion, and thus reduce death.

Referrals to higher-level facilities that could manage severe malaria were frequently not completed. The inability to pay for transport charges led to caretakers only accessing lower-level facilities near them, yet those facilities were not equipped to manage severe malaria cases. This could be due to the high poverty rate in the affected region of Busoga (61%), higher than the national average of 47% [35]. Addressing this issue may require providing additional support for referral systems, such as providing transport support to enable all referred patients to reach the intended referral hospital. Additionally, making pre-referral treatment such as rectal artesunate available at the community level could improve referral outcomes

Table 3 Care giver and health system factors evaluated for association with death among children with severe malaria, Ivukula Subcounty, Namutumba District, September 2021 – February 2022

Characteristic	Cases (n = 46)		Controls (n = 77)		COR (95% CI)	AOR (95% CI)
	n	(%)	n	(%)		
Caregiver characteristics						
Age in years						
18–24	4	(9)	7	(9)	Ref	–
25–44	20	(43)	52	(68)	0.67 (0.17–2.6)	
≥ 45	22	(48)	18	(23)	2.14 (0.54–8.5)	
Median age	42		35		NA	
Type of caregiver						
Father	12	(26)	17	(22)	Ref	–
Mother	21	(46)	52	(68)	0.57 (1.23–1.4)	
Grandparent	13	(28)	8	(10)	2.3 (0.73–2.3)	
Level of education						
Secondary	8	(17)	17	(22)	Ref	–
Upper Primary	13	(28)	33	(43)	0.8 (0.3–2.4)	
None-Lower Primary	25	(54)	27	(35)	1.9 (0.7–5.4)	
Health facility attended first for patients with severe malaria						
Health facility type						
Health centre II	5	(11)	13	(18)		
Health centre III	20	(43)	35	(49)		
Health centre IV	1	(2)	3	(4)		
Hospital	2	(4)	0	(0)		
Private clinic	18	(39)	17	(24)		
Drug shop	0	(0)	3	(4)		
Given antimalarial drugs at first facility						
Yes	32	(69)	50	(70)	Ref	–
No	14	(31)	21	(30)	0.95 (0.4–2.2)	
Completed treatment given at first facility						
Yes	10	(22)	47	(61)	Ref	Ref
No	36	(78)	30	(39)	5.6 (2.4–13.0) ***	9.7 (1.8–52.9) **
Reasons for not completing treatment (among those that could not)						
Death	10	(28)	0	(0)		
Failure to feed	1	(3)	0	(0)	–	–
Drug stock outs	17	(47)	22	(76)		
Blood products stock out	6	(17)	2	(7)		
Referred	0	(0)	1	(3)		
Failure to pay	2	(6)	4	(14)		
Time between illness onset to visiting first facility						
≤ 1 day	24	(52)	25	(35)	Ref	Ref
> 1 day	22	(48)	46	(65)	0.5 (0.2–1.0)	0.8 (0.2–3.7)
Facilities visited after first HF (only for referred patients, n = 66)						
Health facility type	n = 29		n = 37			
Health centre II	11	(38)	16	(43)		
Health centre III	3	(10)	4	(11)		
Health centre IV	9	(31)	11	(30)		
Hospital	5	(17)	4	(11)		
Private clinic	1	(3)	2	(5)		
Given treatment at second facility						

Table 3 (continued)

Characteristic	Cases (n = 46)		Controls (n = 77)		COR (95% CI)	AOR (95% CI)
	n	(%)	n	(%)		
Yes	9	(31)	18	(48)	Ref	–
No	20	(69)	19	(51)	0.5 (0.2–1.3)	
Completed treatment given at second facility						
Yes	1	(11)	16	(89)	Ref	–
No	8	(89)	2	(11)	42.5 (4.1–434.9) ***	

COR Crude Odds Ratio, AOR Adjusted Odds Ratio

*p < 0.05

**p < 0.01

***p < 0.001

[36]. Alternatively, upgrading the available H/C IV to hospital status and some of the H/C II facilities to H/C III level, which are able to manage severe malaria, could improve service access.

Anaemia is one of the major complications of malaria, contributing directly or indirectly to hospitalization and deaths in young children. Blood transfusion can be a life-saving intervention for children with severe malaria-related anaemia [37–39]. However, in Ivukula Subcounty, few of the children who needed blood transfusion received it. This has also been seen in other studies in Uganda and other parts of Africa where failure to access blood transfusion has contributed to deaths among children with severe malaria [25, 40]. While malaria is responsible for anaemia due to haemolysis, anaemia in turn lowers the body's immunity leading to increased exposure to malaria infections and hence repeated cycles of illness [41]. Some researchers have suggested adding measurement of haemoglobin (Hb) levels as an additional parameter in malaria management for timely diagnosis and treatment of anaemia and, when necessary, timely referral [42]. This policy may be useful for stakeholders in Uganda to consider as they evaluate approaches to reduce the burden of severe malaria deaths among children.

Unfortunately, Ivukula Subcounty has no health facility equipped to provide blood transfusion services. Blood transfusion services are sought from the district H/C IV, which is also supplied by the regional blood bank in Jinja (Jinja Regional Referral Hospital). However, respondents in this study reported that blood products are frequently stocked out at the H/C IV due to the inability to collect blood stocks from the regional blood bank. Other researchers have shown an association between early malaria mortality and untreated anaemia among children in Africa and an increased general challenge in access to blood products in Uganda due to limited supply [25]. Addressing this issue requires strengthening blood donation campaigns in communities and extending blood transfusion services closer to the communities by equipping H/C IIIs with blood storage equipment.

Study limitations

A limitation to this study was the absence of medical records for review. Because of this, clinical definitions were used and caretakers' memory was relied on to remember the child's presentation. For case-patients, the majority of the caregivers had discarded the records immediately after the loss of their child or were not provided with the records at the health facilities. Secondly, only a subset of VHTs within the district were reached, the villages where VHTs were not reached might have had different death rates from those whose VHTs were reached.

Conclusion

Factors associated with severe malaria deaths among children ≤ 12 years in Ivukula Subcounty in late 2021 and early 2022 were multifactorial. These included lack of access to appropriate anti-malarial treatment, and to blood transfusions among anaemic patients, stockouts of malaria drugs and blood products, and inability to reach high level referral facilities. These issues represented both health system and individual challenges that need to be addressed. Strengthening accurate quantification of anti-malarial drugs with proper monitoring to ensure availability of drugs for appropriate treatment, increasing the availability of blood products in the district and offering transport support to patients referred to higher-level facilities could reduce malaria mortality among children in the district. Additionally, activation of iCCM in the communities and upgrading of the H/C IV to hospital status could enable improved access to malaria and severe malaria treatment with limited referrals.

Abbreviations

AR	Attack rate
CI	Confidence interval
DHIS2	District Health Information System (DHIS2)
H/C	Health facility
ICCM	Integrated Community Case Management
SD	Standard deviation
OR	Odds ratio
aOR	Adjusted odds ratio
VHT	Village health teams

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Author contributions
GMZ, BS, ZK, PCK, MW, RA, JFZ, SNK, OL, HNN, MN, BA, RZ, PK and TK investigated the outbreak under technical guidance and supervision of JH, AA, DK, RM, BK, JG and JK. GMZ & BS analysed and interpreted the data. GMZ drafted the manuscript. GMZ, LB, AA, critically reviewed the manuscript for intellectual content. All co-authors read and approved the final manuscript. GMZ is the guarantor of the paper.

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Availability of data and materials
The datasets upon which our findings are based belong to the Uganda Public Health Fellowship Program. For confidentiality reasons the datasets are not publicly available. However, the data sets can be availed upon reasonable request from the corresponding author and with permission from the Uganda Public Health Fellowship Programme.

Declarations

Ethics approval and consent to participate
This investigation was in response to a public health emergency and was therefore determined to be non-research. The MoH gave the directive to investigate this outbreak. Written informed consent in English and the local language was sought from respondents or caretakers of diseased children. They were informed that their participation was voluntary and their refusal would not result in any negative consequences. To protect the confidentiality of the respondents, each was assigned a unique identifier which was used instead of their names. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy. § §See e.g., 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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