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Diarrhea in Children with *Plasmodium falciparum* Malaria: A Case–Control Study on the Prevalence and Response to Antimalarial Treatment

Andrea Lo Vecchio,[1]† Francesca Wanda Basile,[1]† Dario Bruzzese,[2] Fabiola Di Dato,[1] Pamella Aol,[3,4] Venice Omona,[3] Andrea Smarrazzo,[1] and Alfredo Guarino[1]*

[1]*Department of Translational Medical Science – Section of Pediatrics, University of Naples Federico II, Naples, Italy;* [2]*Department of Public Health, University of Naples Federico II, Naples, Italy;* [3]*St. Mary's Hospital, Lacor, Gulu, Uganda;* [4]*Department of Pediatric and Child Health, Makerere College of Health Science, Kampala, Uganda*

Abstract. The role of *Plasmodium* in the etiology of acute diarrhea in developing countries remains controversial, and gastrointestinal (GI) symptoms are inconsistently reported in malaria. In this observational case–control study, we investigated the prevalence and risk factors for GI symptoms in hospitalized malarious children aged 1 month to 5 years in northern Uganda. Children with a diagnosis of *Plasmodium falciparum* malaria were enrolled as cases, and feverish children in whom malaria was excluded were enrolled as controls. Among 451 malarious children, 46.1% had GI symptoms at admission. Compared with controls, the frequency of diarrhea (24.8% versus 11.2%, $P < 0.001$) and vomiting (35.5% versus 17.5%, $P < 0.001$) was significantly higher in children with malaria, who had a higher chance of showing either vomiting (odds ratio [OR]: 3.22; 95% CI: 2.14–4.91) or diarrhea (OR: 3.14; 95% CI: 1.99–5.07) at hospital admission. A subgroup analysis performed in children with severe malaria, severe anemia, or high-grade fever confirmed these results. Diarrhea was more frequent in infants and children younger than 3 years than in older children. The analysis of 71 malarious children with diarrhea who received intravenous artesunate showed that the symptom resolved within the first 24 hours since the beginning of the treatment in 85.9% of cases. The 3-fold higher prevalence of diarrhea and vomiting in malarious children compared with febrile controls may provide rationale for incorporating malaria testing in the symptom-guided diagnostic approach of the young child with diarrhea and vomiting in malaria-endemic settings.

INTRODUCTION

Malaria remains a major global health concern and was responsible for about 405,000 deaths globally in 2018, most of which occurred in children younger than 5 years.[1]

In this age-group, diarrhea itself constitutes a common reason for hospital referral, accounting for approximately 9% of all deaths worldwide, although the annual number of deaths has decreased significantly in the last years.[2]

In low-resource settings, most cases of diarrhea present as acute gastroenteritis, most frequently caused by rotavirus or enteric Gram-negative pathogens. However, it is well established that diarrhea can represent an accompanying symptom of several systemic infectious diseases, in which the main target is not the gastrointestinal (GI) tract.[3]

An association between malaria and GI damage has been hypothesized in severe forms of *Plasmodium falciparum* malaria.[4] Gut barrier damage can be regarded as the endpoint of several pathogenetic processes that take place at various stages in *Plasmodium* spp. infection, involving principally—but not only—intestinal microcirculation, consequently affecting the enterocytes.

On a functional level, a study by Wilairatana et al.[5] demonstrated that adults with acute malaria had a pathologic differential sugar absorption test, suggesting that both intestinal absorption and permeability were impaired during the disease.

Moreover, it is well established that the increased cytoadherence of the infected erythrocytes to small-vessel endothelium leads to rosetting and sequestration of red blood cells (RBCs). The process of sequestration in the GI tract has been documented in postmortem histopathological sections of children who died of malaria.[6]

In addition, increased plasma levels of intestinal fatty acid–binding protein, a biomarker of acute intestinal damage, have been demonstrated in children with malaria.[7,8]

Among the clinical counterparts of these processes, children with severe *P. falciparum* malaria are at increased risk of concomitant invasive bacterial infections with enteric Gram-negative organisms, particularly *Escherichia coli* strains and non-typhoidal *Salmonellae*.[9] The hypothesized mechanism is bacterial translocation favored by the impaired gut barrier function and increased permeability.[7,8]

In animal models, *Plasmodium* spp. parasitemia is associated with increased GI permeability probably because of ileal mastocytosis and raised histamine levels. Interestingly, a mast cell–deficient mouse showed not only less intestinal permeability but also reduced bacterial translocation.[10,11]

Despite this premise, whether *Plasmodium* plays an active role in the etiology of acute gastroenteritis in developing countries remains a controversial issue.

The incidence of diarrhea in children with malaria is highly variable in previous reports from the literature, and the few existing case–control studies report no association between clinical malaria or parasitemia and diarrhea.[12,13] Of 184 Nigerian children with uncomplicated malaria, diarrhea was reported only in less than 10%.[14]

The aim of our study was to investigate the prevalence of acute diarrhea as a presenting symptom of children hospitalized for severe malaria in north Uganda, a perennial transmission setting, and to examine host- and pathogen-dependent risk factors for occurrence of diarrhea.

MATERIALS AND METHODS

Study design and setting. An observational case–control study was conducted at the St. Mary's Lacor Hospital children's ward, the largest medical institution providing pediatric care in northern Uganda (Gulu district). The pediatric department is dedicated to the management and follow-up of

* Address correspondence to Alfredo Guarino, Department of Translational Medical Science, University of Naples Federico II, Via Pansini 5, Naples 80131, Italy. E-mail: alfguari@unina.it
† These authors contributed equally to this work.

children up to 5 years of age, accounting for about 8,000 admissions every year and more than 3,500 diagnoses of malaria in 2016, with a case fatality rate of approximately 1%.

Data of children aged ≤ 5 years who were discharged from the children's ward with a diagnosis of malaria on every Monday between January 1, 2016 and December 31, 2016 were collected. Information about symptom presentation, district of provenance, season (wet or dry season), duration of fever, clinical features during hospitalization, treatment, clinical outcome, and length of stay were recorded.

All data were extracted manually from medical records and loaded into a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA), with the help of three residents in pediatrics who were involved in the international student exchange program between the University of Naples Federico II and the St. Mary's Lacor Hospital.

Study definitions and inclusion/exclusion criteria. Children aged 1 month to 5 years presenting at St. Mary' Hospital with fever (temperature > 37.5°C) and receiving a final diagnosis of malaria were enrolled as cases. A diagnosis of malaria was confirmed with the positivity of rapid diagnostic test (RDT) and/or blood smear (BS). When a BS was not performed, cases were selected according to a positive RDT only if they had not been treated for malaria in the previous 2 weeks. CareStart™ malaria HRP2 (AccessBio, Somerset, NJ) served as the RDT to identify *P. falciparum*. Parasitemia at diagnosis was expressed as a semi-quantitative thick blood film count: "+" (1–10 parasites/100 high power field [hpf]), "++" (10–100 parasites/100 hpf), and "+++" (> 1 parasite/hpf). The severity of anemia was defined according to the WHO classification as hematocrit < 15% or hemoglobin < 5 g/dL.[15] In the subgroup analysis of children with severe malaria, severity was defined by the presence of at least one of the 2015 WHO criteria.[16]

Children aged ≤ 5 years admitted for fever on the same days at the institution, in whom the diagnosis of malaria was excluded, were enrolled as controls with a case:control ratio of 2:1. All cases and controls who were afebrile on admission had at least one episode of fever (body temperature > 37.5°C) recorded in the first 24 hours after admission.

Children with a diagnosis of *Plasmodium* other than *falciparum*, and those with known underlying chronic conditions, including severe acute malnutrition, were excluded. Malaria was treated either with intravenous artesunate or artemisinin-based combination therapy (ACT), according to the 2015 WHO dosage recommendations.[16]

Outcome measures. The prevalence of diarrhea, defined by the passage of three or more stools in the 24 hours before admission, was considered as the primary outcome. End of diarrheal episode was defined by the presence of at least two consecutive normal evacuations.

To assess the course of GI symptoms during the standard treatment of malaria and to investigate the time of response and possible factors affecting an early (< 24 hours) or late resolution (> 24 hours) of symptoms, the characteristics and duration of diarrhea, vomiting, and other clinical symptoms, as well as the degree of dehydration according to the 2013 WHO hospital care for children guidelines, were recorded at admission and during hospitalization.[15]

The need for antimalarial or intravenous rehydration fluids and the length of hospital stay were considered as secondary outcomes.

Statistical analysis. Because of the specific setting of this study, an unbalanced sample size was a priori selected, with a 2:1 ratio between cases and controls. Assuming a rate of diarrhea in the control group equal to 10% and considering as clinically relevant a 2-fold increase of such rate in cases (corresponding to an odds ratio (OR) of 2.25), a sample size of 203 controls and 406 cases was deemed sufficient to highlight such difference, if truly exists, with a power of 0.9 and a two-sided significance level of 0.05. Sample size was further inflated in view of a propensity score–matching analysis planned to account for the observational nature of the study.

Quantitative variables were reported as mean ± SD, and variables with skewed distributions were presented as median and interquartile range (IQR). Results and data from the two groups of patients (cases and controls) were compared by using *t*-test or the Mann–Whitney nonparametric test, as appropriate. Categorical variables were summarized and reported as frequencies and percentages and compared through Fisher's exact test or chi-square test, as appropriate.

The association between malaria and GI symptoms was further quantified using crude OR with the corresponding 95% CIs. To control for confounding variables, a propensity score was estimated using a logistic regression model with the case/control indicator as the dependent variable and the following covariates as independent variables: age, gender, season of enrollment, and district of provenance. Matched cohorts were then obtained using a nearest-neighbor matching algorithm (1:1 ratio, without replacement) with a caliber of 0.01. All analyses involving the two matched cohorts were based on an unpaired approach. Missing data were not imputed. Two-sided *P*-values < 0.05 were considered statistically significant.

Statistical analysis was performed using the *R* statistical platform version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).[17]

Ethical disclosure. All sensible data were recorded in the spreadsheet by using a single-patient alphanumeric code and managed anonymously. The study protocol was approved by the Lacor Hospital Institutional Research and Ethics Committee and by the Uganda National Council for Science and Technology (study reference number: HS225ES).

RESULTS

Study population. Among the 556 patients who received a diagnosis of malaria in the days of enrollment, three were excluded because of non–falciparum *Plasmodium* infection, 102 were excluded for insufficient data reported in clinical folders, and 451 (209/46.3% females, median age 30 months, IQR: 17–47) were finally enrolled in the study as cases (Table 1). Most patients were enrolled during the wet season (298, 66.1%), and the majority (65.1%) came from Gulu district.

In 410 children (90.9%), the diagnosis was based on positive BS, and in those with negative (25, 5.5%) or not performed BS (16, 3.3%), the diagnosis was confirmed by a positive RDT. Most patients had > 1 parasite/hpf, and 43 (9.5%) presented neurological symptoms. Eighty-seven patients (19.2%) met the WHO criteria for severe malaria, and 56 (12.4%) children had severe anemia, 12 of whom received blood transfusions (Table 1).

Two-hundred ninety-two patients accessing the same institution during the study period with fever served as controls. The diagnosis of malaria was excluded, and most of them

TABLE 1
Characteristics of study population before and after propensity score matching

			Unmatched			Matched		
			Malaria (451)	Controls (292)	*P*-value	Malaria (262)	Controls (262)	*P*-value
Characteristics		Female (*N*, %)	209 (46.3)	113 (38.7)	0.048	105 (40.1)	102 (38.9)	0.858
		Median age (months) [IQR] (range)	30 [17; 47] (1–75)	27 [12; 41.8] (2–96)	0.009	29.2 ± 18 (1–72)	29.4 ± 18.6 (2–71)	0.875
		Dry season	153 (33.9)	112 (38.4)	0.249	97 (37)	98 (37.4)	1
		Median length of stay (days) [IQR] (range)	2 [2; 4] (1–11)	4 [3; 6] (1–26)	< 0.001	2 [2; 4] (1–10)	4 [3; 6] (1–26)	< 0.001
District of provenience (*N*, %)		Gulu	190 (65.1)	271 (60.1)	< 0.001	181 (69.1)	181 (69.1)	0.986
		Amuru	42 (14.4)	110 (24.4)		39 (14.9)	42 (16)	
		Nwoya	17 (5.8)	37 (8.2)		20 (7.6)	17 (6.5)	
		Oyam	9 (3.1)	16 (3.5)		9 (3.4)	9 (3.4)	
		Others	34 (11.6)	17 (3.8)		13 (5)	13 (5)	
Diagnostic tests (*N*, %)	Rapid diagnostic test	Positive	160 (35.5)	0 (0)	< 0.001	88 (33.6)	0 (0)	< 0.001
		Negative	0 (0)	116 (39.7)		0 (0)	106 (40.5)	
		Not performed	291 (64.5)	175 (59.9)		174 (66.4)	155 (59.2)	
	Blood smear	1–10 parasites/ 100 hpf	31 (6.9)	0 (0)	< 0.001	18 (6.9)	0 (0)	< 0.001
		10–100 parasites/ 100 hpf	88 (19.5)	0 (0)		48 (18.3)	0 (0)	
		> 1 parasite/hpf	291 (64.5)	0 (0)		172 (65.6)	0 (0)	
		Negative	25 (5.5)	190 (65.1)		13 (5)	170 (64.9)	
		Not performed	16 (3.5)	102 (34.9)		11 (4.2)	92 (35.1)	
Symptoms (*N*, %)		Fever at admission	437 (97.5)	244 (83.6)	< 0.001	253 (97.7)	219 (83.6)	< 0.001
		Fever > 38.5°	194 (45)	74 (25.3)	< 0.001	106 (43.1)	70 (26.7)	< 0.001
		Severe anemia	56 (12.4)	17 (5.8)	0.005	36 (13.7)	16 (6.1)	0.006
		Seizures*	28 (6.2)	–	–	12 (4.6)	–	–
		Cerebral malaria	15 (3.3)	–	–	7 (2.7)	–	–
		Blackwater fever	8 (1.8)	–	–	4 (1.5)	–	–
		Any gastrointestinal symptom	208 (46.1)	71 (24.3)	< 0.001	129 (49.2)	61 (23.3)	< 0.001
		Vomiting	160 (35.5)	51 (17.5)	< 0.001	100 (38.2)	42 (16.0)	< 0.001
		Diarrhea	112 (24.8)	33 (11.3)	< 0.001	76 (29.0)	30 (11.5)	< 0.001
		Diarrhea, median duration [IQR] (range)	2 [1; 3] (0.5–7)	2 [1; 2] (1–4)	0.119	2 [1; 3] (0.5–7)	1.5 [1; 2] (1–3)	0.08
Dehydration		No	432 (96)	281 (96.2)	0.381	253 (96.6)	253 (96.6)	0.296
		Some	12 (2.7)	10 (3.4)		5 (1.9)	8 (3.1)	
		Severe	6 (1.3)	1 (0.3)		4 (1.5)	1 (0.4)	

IQR = interquartile range.
* Single episodes not followed by long-lasting alteration of consciousness (not defining criteria for cerebral malaria).

received a final diagnosis of lower respiratory tract infection, bronchiolitis, or sepsis.

Prevalence and characterization of GI symptoms. Among the 451 children with malaria, 208 patients (46.1%) had GI symptoms at hospital admission (Table 1). Diarrhea was reported in 112 (24.8%) children with a mean of 5.1 ± 2.4 evacuations/day. One hundred sixty children (35.5%) had vomiting, and 64 (14.2%) presented both symptoms. Most children had no or mild dehydration, and only 3% of them presented severe dehydration (Table 1).

In comparison with controls, the frequency of diarrhea (24.8% versus 11.2%, $P < 0.001$) and vomiting (35.5% versus 17.5%, $P < 0.001$) was significantly higher in children with malaria (Table 2), and this finding was confirmed in the propensity-matched population ($P < 0.001$). Children accessing to the hospital with malaria had a three-time higher chance to present with GI symptoms than controls (OR: 3.14; 95% CI: 1.99–5.07) (Figure 1).

Similarly, vomiting was reported in 38.2% of children with malaria and in only 16.0% of controls, resulting in a significantly higher risk of malaria in children vomiting at hospital admission (OR: 3.22; 95% CI: 2.14–4.91) (Table 1, Figure 1).

Diarrhea showed an age-related distribution and was more frequently reported in young children with malaria (matched population). By contrast, vomiting was similarly distributed according to age range (Table 3).

To better investigate the determinants of GI symptoms in malarious children, we conducted a subgroup analysis categorizing children for the level of parasitemia, severity of anemia, the degree of fever, and the severity of malaria according to the WHO criteria.

TABLE 2
Treatment of children with malaria

	Treatment	Number of treated children/total (%)
Antimalarial treatment	Artesunate IV*	447 (99)
451/451 (100)	Artemether/lumefantrine	4 (1)
Antibiotic treatment	Antibiotics IV	3 (0.66)
9/451 (2)	Antibiotics oral	6 (1.3)
Antidiarrheal treatment	IV rehydration	19 (9.1)
83/208 (39.9)	Oral rehydration	70 (33.6)
	Zinc	59 (28.3)

ACT = artemisinin-based combination therapy.
* Three doses (0–12–24 hours), followed either by ACT or prosecution of once daily IV treatment until able to swallow ACT.

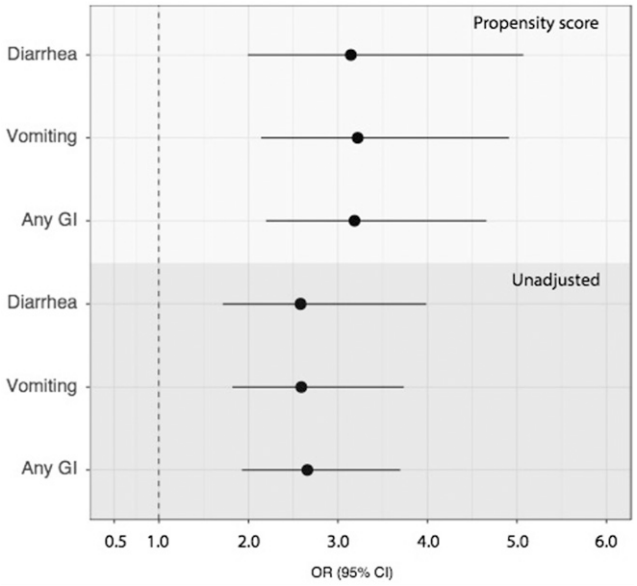

FIGURE 1. Risk of malaria in children presenting with gastrointestinal (GI) symptoms (expressed as odds ratio [OR] with 95% CIs).

Gastrointestinal symptoms, either diarrhea or vomiting, were independent from the level of parasitemia and anemia. Among the 291 children with > 1 parasite/hpf, 130 (44.7%) showed any GI symptoms, with a similar distribution among children with lower parasite densities (54/119 45.4%; P = 0.896). The presence of anemia (P = 0.965), as well as its degree, categorized as no anemia, moderate, or severe anemia (P = 0.375) had no impact on the prevalence of GI symptoms.

To investigate high fever as a factor associated per se with the presence of diarrhea or vomiting, we performed a second propensity score analysis including fever 38.5°C or higher as an additional parameter when selecting the propensity-matched population. We obtained two groups of 240 children each, matched for age, gender, season of enrollment, village, and fever ≥ 38.5°C. The prevalence of diarrhea (28.3% versus 11.4%, OR: 3.45; 95% CI: 2.12–5.6) and vomiting (33.8% versus 17.9%, OR: 2.33; 95% CI: 1.53–3.57) was significantly higher in children with malaria than in those with fever because of other causes (P < 0.001 for both symptoms). Similarly, we found a significantly higher risk of presenting diarrhea (OR: 3.85; 95% CI: 1.45–10.26; P = 0.007) or vomiting (OR: 4.21; 95% CI: 1.93–9.18; P < 0.001) in children satisfying the WHO criteria for severe malaria than a matched control population (propensity score population, n = 79).

Treatment of children with malaria. All children with laboratory-confirmed malaria were treated with antimalarial agents. Four patients received oral treatment with artemether/lumefantrine, and all the other patients received intravenous artesunate at diagnosis (0 hour) and then at 12 and 24 hours, followed by ACT as per WHO guidelines. (Table 2). A total of 24 children with inability to swallow continued once daily intravenous artesunate beyond the third dose, until they could tolerate oral treatment; among those, three had persistent vomiting. Seventy (33.6%) of the 208 children with GI symptoms received oral rehydration therapy during hospital stay, and only 19 (9.1%) received intravenous rehydration (Table 2).

TABLE 3
Distribution of diarrhea and vomiting in malarial children according to age

	Age range, *N* (%)			
Symptom	≤ 12 months (*N* = 54)	12–36 months (*N* = 128)	> 36 months (*N* = 80)	*P*-value
Diarrhea	27 (50.0)	35 (27.0)	14 (17.5)	< 0.0001
Vomiting	22 (40.7)	48 (37.5)	30 (37.5)	0.909

Clinical course of GI symptoms and response to antimalarial treatment. Data on the clinical course of diarrhea were available for 101/106 (95.2%) children presenting with diarrhea (71 with malaria and 30 controls). In children with malaria, the resolution of diarrhea occurred within the first 12 hours after the start of intravenous artesunate therapy in 65.7% patients, within the first 24 hours in 85.9% of cases, and within 48 hours for the 98.6% of patients (Figure 2). The four patients treated with artemether/lumefantrine were not included in the analysis as none of them had any GI symptom. Resolution of diarrhea was significantly more rapid in cases treated with antimalarial therapy than in controls receiving only rehydration and zinc supplementation (Figure 2).

The mean length of hospital stay was significantly longer in malarial children who presented with GI symptoms than in those who did not (3.13 ± 1.78 versus 2.66 ± 1.38 days, P = 0.007). This difference was not affected by the occurrence of severe complications and was even strengthened when adjusted for the presence of seizures, cerebral malaria, and blackwater fever (P = 0.005).

Zinc supplementation. To investigate a potential effect of zinc therapy on the resolution of diarrhea, micronutrient supplementation during the hospital stay was recorded in all children. About one-third of malarial children (59, 28.3%) received oral zinc supplementation. However, an inverse relationship was observed between zinc administration and duration of diarrhea in children with malaria.

Zinc supplementation was reported in 16 of 56 (28.5%) patients who presented with diarrheal resolution at 12 hours after antimalarial therapy onset and in 31 of 43 (72.0%) children in whom diarrhea persisted (P = 0.001). After 24 hours, a similar distribution was recorded, with 47.3% of children without diarrhea and 73.1% of those with persistence of diarrhea receiving oral zinc supplementation (P = 0.02).

DISCUSSION

The literature provides scarce and inconsistent evidence on the prevalence and characteristics of GI symptoms during malaria in children.[12–14] Data from our study show that in a setting of perennial malaria transmission, there was a higher prevalence of diarrhea and vomiting in feverish children who received a diagnosis of *P. falciparum* malaria than in children with fever of non-malarial origin. This association is confirmed, and even strengthened, following the application of a propensity score–matching model, which created and compared two homogenous populations for variables such as gender, age, season, and geographical origin.

In malarial children, GI symptoms were more frequent than other well-known malaria complications, including severe anemia, hypoglycemia, blackwater fever, and central nervous system involvement.

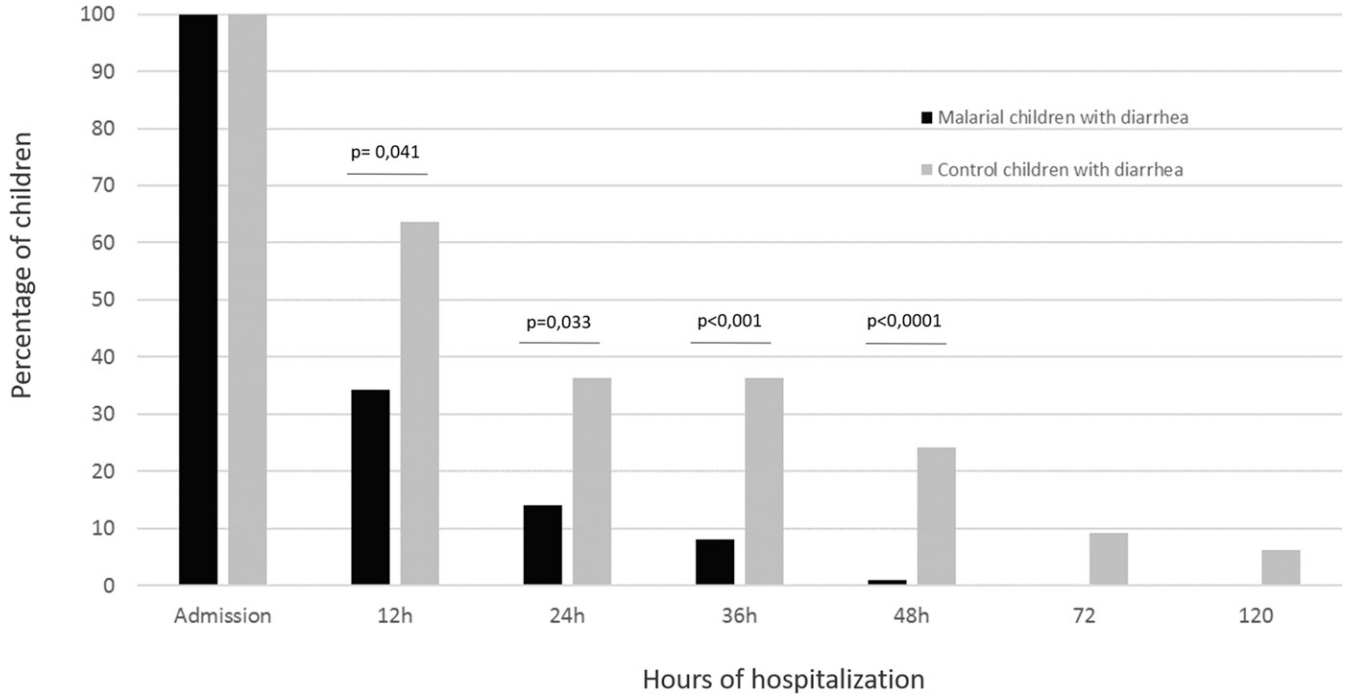

FIGURE 2. Time distribution of children with diarrhea after specific antimalarial treatment.

Our findings shed new light on the relationship between falciparum malaria and GI symptoms in a real-life hospital setting in Uganda. The 3-fold higher prevalence of diarrhea and vomiting in children with malaria than other febrile infections may provide rationale for incorporating malaria testing in the symptom-guided diagnostic approach of the young children with diarrhea and vomiting in malaria-endemic settings.[15]

However, despite their high frequency, vomiting and diarrhea seem to be minor complications not related to severe clinical features. Oral rehydration solution (ORS) was prescribed only in one-third of patients complaining of GI symptoms. The under-prescription of oral rehydration in our population may reflect two phenomena: first, the underestimation of the symptom by physicians, also demonstrated by the low prescription of zinc supplementation. Second, in this circumstance, the low number of prescriptions may be the consequence of a reporting bias; in children with no dehydration, clinicians verbally encourage caregivers to increase the amount of fluids, or to autonomously administer ORS, which can be taken from small, free-access tanks distributed across the ward. Only a small fraction of patients with GI symptoms had moderate-to-severe dehydration with the need for intravenous rehydration therapy. The presence of GI symptoms affected the average length of hospital stay in malarial children.

In line with previous evidence, a different distribution of diarrhea was observed according to child age, with infants being more frequently affected.[14] The prevalence of vomiting did not show significant differences in the various age-groups.

Further investigations will be needed to clarify the pathogenic mechanisms underlying this age correlation and could include the evaluation of gut mucosal immunity, intestinal barrier maturity, and microbiota in response to *Plasmodium* spp. infection.[18–20]

Our results show no correlation between the level of parasitemia and the presence of GI symptoms. This finding could reflect the well-known phenomenon of the sequestration of *P. falciparum*–infected RBCs in the microcirculation of certain intestinal districts.[6,21,22]

However, it should be noted that the semi-quantitative reporting system for BSs in use at St. Mary's Hospital may not be adequate for the purposes of this analysis. In this sense, new techniques like the dosage of HRP2 would be more appropriate to measure the total body parasite biomass.[23]

We observed a time-related effect of antimalarial treatment on the resolution of diarrhea. Already at 24 hours after admission, more than half of the children no longer showed diarrhea. During this time lapse, all children had received three administrations of intravenous artesunate (at diagnosis and after 12 and 24 hours).[16]

This time-related association is suggestive and could support the hypothesis of a direct correlation between *P. falciparum* infection and the presence of diarrhea. In support of this interpretation, a recent study from Ghana reported a higher percentage of malaria in children younger than 5 years of age with acute diarrhea than in those without diarrhea.[24] In this population, *P. falciparum* was the most frequently identified pathogen after viruses in children with acute diarrhea. However, the study did not include data on coinfections and other clinical symptoms, making it difficult to estimate the proportion of malarious children who were asymptomatic carriers.[24]

In addition to artesunate and rehydrating therapy, about a third of children with diarrhea received zinc supplementation, in keeping with the international guidelines for the management of acute gastroenteritis.[15,25] However, administration of zinc was not associated with a faster resolution of diarrhea in our population, but malarial children receiving zinc showed a lower chance of diarrhea resolution than those who were not

treated with zinc. We hypothesize that zinc therapy may have been prescribed in adjunct to antimalarial treatment in patients with higher severity of diarrhea.

Our study has some limitations mainly related to its retrospective nature and the difficulties to retrieve accurate data from part of the initial study population. A propensity-matched population has been used to minimize the selection bias and to compare prevalence and characteristics of GI symptoms. No microbiological data on the fecal samples of malarial children were available; thus, we cannot exclude the presence of specific pathogens of the GI tract.

In the absence of microbiological data on stools, there is the possibility that among the cases with a discharge diagnosis of malaria and GI symptoms, some may have had instead a febrile gastroenteritis and asymptomatic parasitemia, especially at lower parasite densities.[26] However, when we move from this assumption, the comparison with non-malarious controls still supports the association of *P. falciparum* infection and GI symptoms, regardless of the etiology.

It has to be noted that the population of our study was a homogeneous population consisting of young children discharged from the hospital with a diagnosis of severe malaria, hence treated with intravenous artesunate. For the definition of severity of each case, we relied on the judgment of clinicians who admitted the children for intravenous therapy; however, in our retrospective analysis, we were able to identify only 87 children who met the WHO criteria for severe malaria.

We are aware that the real incidence of clinical (i.e., prostration—common in very sick young children) or laboratory conditions that define severe malaria (i.e., lactic acidosis, radiologically confirmed pulmonary edema, renal impairment not presenting as overt blackwater fever, and hyperparasitemia) cannot be estimated, because of the lack of missing information in patients' charts and limited access to diagnostic resources (blood gas analysis, chest X-rays, routine renal, and liver function tests) in the study setting. For these reasons, we believe that the proportion of children with severe malaria is likely to be underestimated. However, the analysis of a subgroup population unequivocally meeting the WHO criteria for severe malaria further supported our results.

It appears that the resolution of diarrhea in children with malaria receiving intravenous treatment is more rapid than what was previously described with oral treatment in the preartemisinin derivatives era, and it is in line with the hypothesis of intestinal damage and reduced intestinal absorption during malaria.[14] Considering the variety of mechanisms that can alter barrier function during infection, further studies are needed to understand this phenomenon. We do not exclude a direct role of the artesunate, considering its described antioxidant/anti-inflammatory effect.[27,28] For this purpose, in the future, it will be interesting to compare GI symptoms responses in children receiving intravenous treatment versus ACT.

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Authors' addresses: Andrea Lo Vecchio, Fabiola Di Dato, Andrea Smarrazzo, and Alfredo Guarino, Department of Translational Medical Science–Section of Pediatrics, University of Naples Federico II, Naples, Italy, E-mails: andrea.lovecchio@unina.it, fabydd88@gmail.com, and.smarrazzo@gmail.com, and alfguari@unina.it. Francesca Wanda Basile, Baylor College of Medicine Children's Foundation Uganda, Kampala, Uganda, E-mail: francesca.basile@bcm.edu. Dario Bruzzese, Department of Public Health, University of Naples Federico II, Naples, Italy, E-mail: dbruzzes@unina.it. Pamella Aol, Department of Pediatric and Child Health, Makerere College of Health Science, Kampala, Uganda, E-mail: mwapamella@gmail.com. Venice Omona, St. Mary's Hospital, Lacor, Gulu, Uganda, E-mail: veniceomon@gmail.com.

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