MAJOR ARTICLE

Malaria, Anemia, and Malnutrition in African Children—Defining Intervention Priorities

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Background. Malaria, anemia, and malnutrition contribute substantially to childhood morbidity in sub-Saharan Africa, but their respective roles and interactions in conferring disease are complex. We aimed to investigate these interactions.

Methods. In 2002, we assessed plasmodial infection, anemia, and nutritional indices in 2 representative surveys comprising >4000 children in northern Ghana.

Results. Infection with *Plasmodium* species was observed in 82% and 75% of children in the rainy and dry season, respectively. The fraction of fever attributable to malaria was 77% in the rainy season and 48% in the dry season and peaked in children of rural residence. Anemia (hemoglobin level, <11 g/dL) was seen in 64% of children and was, in multivariate analysis, associated with young age, season, residence, parasitemia, *P. malariae* coinfection, and malnutrition (odds ratio [OR], 1.68 [95% confidence interval {CI}, 1.38–2.04]). In addition, malnutrition was independently associated with fever (axillary temperature, ⩾37.5°C; OR, 1.59 [95% CI, 1.13–2.23]) and clinical malaria (OR, 1.67 [95% CI, 1.10–2.50]).

Conclusions. Malnutrition is a fundamental factor contributing to malaria-associated morbidity and anemia, even if the latter exhibits multifactorial patterns. Our data demonstrate that malaria-control programs alone may not have the desired impact on childhood morbidity on a large scale without concomitant nutrition programs.

Malaria, anemia, and malnutrition are key public-health challenges in pediatric populations in sub-Saharan Africa [1]. Nutrition may be a factor in modulating malaria morbidity and mortality, in that malnutrition has been suggested to influence susceptibility to and manifestation of malaria [2, 3]. Moreover, it may be an even more important risk factor for anemia than malaria itself [4]. In contrast, some studies have indicated that malaria control alone effectively reduces the prevalence of childhood anemia [5]. Data on these interconnected health determinants in northern Ghana, a typical area of high malaria transmission, are almost entirely lacking. In light of scarce resources and overburdened health systems, these measures should nonetheless lead the way in determining intervention priorities. Therefore, convincing data on the extent of malaria, nonmalarial fever, seasonal *Plasmodium* species distribution, anemia, and malnutrition, as well as their respective effects on childhood morbidity, are indispensable.

In the remote Northern Region of Ghana, we conducted 2 representative cross-sectional surveys, in the rainy season and in the dry season in 2002, of children 6 months to 9 years of age. In each season, >2000 randomly selected children were screened in Tamale, the capital of Ghana's Northern Region, and in the surrounding districts. Our analyses focused on (1) the prevalences of clinical malaria, nonmalarial fever, infection with *Plasmodium* species, anemia, and nutritional deficits and (2) the interactions between these parameters and their clinical implications. On the basis of these analyses, we aimed to detect the factors exhibiting the highest impact on childhood morbidity, to propose priority interventions.

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PATIENTS AND METHODS

Study area and sampling method. Northern Ghana has a savannah-type climate. Malaria transmission is perennial, with seasonal variations [6]. Malaria control relies on rapid diagnosis and treatment. At the time that the present study was conducted, chloroquine was the first-line antimalarial drug; however, chloroquine resistance in this area is high [7, 8]. In periurban Tamale, the incidence of malaria episodes (febrile parasitemia or parasite load >5000 parasites/μL) in children <5 years of age was ~2.8 cases/child/year in the year 2000 (F.P.M., S.E., and U.B., unpublished data). More than half of the children with severe malaria admitted to Tamale hospital show severe anemia (hemoglobin [Hb] level, <5 g/dL) [9]; data on the incidence of severe malaria in this area are lacking. Bed nets are not commonly used [10].

A 2-stage cluster-sampling strategy with probability proportional to population size was followed in Tamale (categorized as urban) and the surrounding districts of East Gonja, Savelugu/Nanton, Tolon/Kumbungu, West Gonja, and Yendi (categorized as rural). Given an estimated minimal *P. falciparum* infection prevalence of 0.5, a desired precision around the estimate of 0.01, and a design effect of 2.0, a minimum sample size of 750 children in each season was calculated. The sample was based on the year 2000 population and housing census. Sampling was performed between January and April 2002 (dry season) and between July and October 2002 (rainy season). At the first sampling stage, 30 communities or census units were randomly selected. Then, households or compounds were selected, and all resident children 6 months to 9 years of age were recruited. Written informed consent was obtained from the parents, and the study protocol was reviewed and approved by the Ethics Committee of the University for Development Studies, Tamale, and the Regional Ministry of Health, Tamale, Northern Region, Ghana, and the Ethics Committee, Charité Universitätsmedizin Berlin, Berlin, Germany.

Field and laboratory procedures. The age, sex, and axillary temperature of every child was documented, and a venous blood sample was collected into EDTA. Fever was characterized as an axillary temperature ≥37.5°C. Hb levels were measured using a HemoCue photometer. Anemia was defined as an Hb level <11 g/dL, and severe anemia was defined as an Hb level <7 g/dL [11]. The number of malaria parasites per 200 white blood cells (WBCs) was counted on Giemsa-stained thick blood films, and parasite density was calculated on the basis of a putative mean WBC count of 8000 cells/μL. The term "parasitemia" refers to a positive result on expert microscopy. Malaria was defined as any parasitemia plus fever. Children with mild malaria were treated with sulfadoxine-pyrimethamine, as were children with malaria parasite loads >5000 parasites/μL, irrespective of symptoms. Patients with severe malaria, as defined by current World Health Organization (WHO) criteria [12], were transferred to the next hospital for treatment. Other diseases were treated as appropriate. DNA was extracted using commercial kits (Qiamp blood kit; Qiagen). *Plasmodium* species were identified by nested polymerase chain reaction (PCR) assays [13]. PCR analysis was available for 2108 children in the dry season and 2118 children in the rainy season. A coinfection was defined as infection with *P. falciparum* plus 1 other species.

Assessment of nutritional status. Complete nutritional data (weight and height) were determined in 2905 children (1456 girls and 1449 boys; 1091 of urban residence and 1814 of rural residence; 1577 in the rainy season and 1328 in the dry season; 1501 <5 years of age and 1404 ≥5 years of age). Weight-for-height *z* scores, height-for-age *z* scores, and weight-for-age *z* scores were calculated on the basis of the National Centre for Health Statistics (NCHS/WHO) reference data set, using Epi-Info (version 3.3.2; Centers for Disease Control and Prevention); scores less than −2 are indicative of wasting, stunting, and underweight, respectively. Corresponding scores less than −3 indicate severe nutritional conditions [14]. The terms "malnutrition" and "nutritional deficits" refer to any of the abovementioned more specific nutritional conditions.

Statistical analyses. Data analysis was performed using Stata statistical software (version 9.1; StataCorp). Parasite densities were normalized by $\log_{10}$ transformation, and geometric mean parasite densities (GMPDs) and 95% confidence intervals (CIs) were calculated. The proportion of fever attributable to malaria was defined as the population-attributable fraction and was estimated according to Smith et al. [15]. Continuous variables were compared between groups by Mann-Whitney *U* test, and proportions were compared by χ^2 test. Odds ratios (ORs) and 95% CIs were computed. Evaluation of potential determinants of fever, clinical malaria, and anemia was performed by logistic-regression analysis and by the construction of parsimonious models. Stepwise backward selection was performed, and final models included those factors that retained statistical significance. To adjust for a multiple-comparisons problem and avoid spurious associations, the α level was set at .01.

RESULTS

We examined 2119 children in the rainy season and 2109 children in the dry season. The median age was 48 months (range, 6–108 months), and the median axillary temperature was 36.6°C (range, 36.0°C–41.5°C); 50.6% of the children were girls, and 40.2% resided in urban areas. Clinical and parasitological characteristics of the study population are given in tables 1 and 2. Except for the larger proportion of young children in the rainy season, clinical parameters did not differ by season. Hence, comparisons between seasons were adjusted for age.

Influence of seasonality. Season showed a marked influence on clinical and parasitological parameters. Parasitemia was

Table 1. Characteristics of the study population, by season and age group.

Parameter	Dry season			Rainy season		
	All (n = 2109)	Age <5 years (n = 1267)	Age 5–9 years (n = 842)	All (n = 2119)	Age <5 years (n = 1104)	Age 5–9 years (n = 1015)
Parasitemia	1171 (55.5)[a]	615 (48.5)	556 (66.0)[b]	1307 (61.7)	624 (56.6)	683 (67.3)[b]
GMPD (95% CI), parasites/μL	505 (459–555)[a]	555 (486–633)	455 (398–520)[b]	1429 (1283–1591)	2350 (2008–2749)	908 (789–1044)
Fever	122 (5.8)	88 (7.0)	34 (4.0)[b]	135 (6.4)	95 (8.6)	40 (4.0)[b]
Clinical malaria	58 (2.8)[a]	34 (2.7)	24 (2.9)	104 (4.9)	72 (6.5)	32 (3.2)[b]
PCR-detected malaria[c]	82 (3.9)[a]	52 (4.1)	30 (3.6)	119 (5.6)	82 (7.4)	37 (3.7)[b]
Fever attributable to malaria[d]	58 (47.5)[a]	34 (38.6)	24 (70.6)[b]	104 (77.0)	72 (75.8)	32 (80.0)
Hb level, mean (SD), g/dL	10.5 (2.2)[a]	10.1 (2.6)	11.1 (1.3)[b]	10.0 (1.7)	9.3 (1.7)	10.8 (1.3)[b]

NOTE. Data are no. (%) of subjects, unless otherwise indicated. CI, confidence interval; GMPD, geometric mean parasite density; Hb, hemoglobin; PCR, polymerase chain reaction.

[a] Significant difference between seasons (Mann-Whitney U test or χ^2 test; $P < .001$).

[b] Significant difference between age categories within the season (Mann-Whitney U test or χ^2 test; $P < .001$).

[c] Sample sizes for assessment of this parameter were as follows. Dry season: all, n = 2108; age <5 years, n = 1266; age 5–9 years, n = 842. Rainy season: all, n = 2118; age <5 years, n = 1103; age 5–9 years, n = 1015.

[d] Sample sizes for assessment of this parameter were as follows. Dry season: all, n = 122; age <5 years, n = 88; age 5–9 years, n = 34. Rainy season: all, n = 135; age <5 years, n = 95; age 5–9 years, n = 40.

detected in 1307 children (61.7%) in the rainy season and in 1171 children (55.5%) in the dry season. The positive predictive values for a febrile child having malaria in the respective seasons were 0.77 and 0.48. PCR revealed infection with *Plasmodium* species in 81.6% and 74.5% of children in the respective seasons ($P < .001$) (table 2). Compared with the reference standard of PCR, the positive predictive value of microscopy was 0.80. In the rainy season, the prevalence of clinical malaria was higher, GMPD was higher, and Hb levels were lower, compared with those in the dry season (table 1). Overall, anemia was seen in 2707 children (64.1%), and severe anemia was seen in 168 children (4.0%). Both conditions were more common in the rainy season than in the dry season (OR, 1.52 [95% CI, 1.34–1.73] and OR, 2.66 [95% CI, 1.86–3.80], respectively).

Age-dependent patterns. Overall, children <5 years of age had lower prevalences of infection with *P. falciparum, P. ovale,* and *P. malariae* than did older children. Nevertheless, in these young children, clinical malaria and fever were more common, parasite counts were higher, and Hb levels were lower than in older children (tables 1 and 2).

Plasmodium *species.* Patterns of age and season influencing the distribution of *Plasmodium* species are shown in table 2. *P. falciparum* was detected in 75% of all children in the dry season and in 82% of children in the rainy season. The occurrence of *P. ovale* was influenced not by season but by age. *P. malariae* prevailed in the rainy season and was more commonly found in older children. Triple-species infections were rare. The number of *Plasmodium* species infecting an individual had no influence on Hb levels (data not shown).

Fever attributable to malaria. A total of 6.1% (n = 257) of children were febrile, and 63% (n = 162) of fever cases were attributable to malaria. The fraction of fever cases attributable to malaria, however, was more than three quarters in the rainy season but less than half in the dry season (table 1). In the rainy season, the attributable fraction was basically independent of age, whereas, in the dry season, it was almost twice as high in children ⩾5 years of age than in younger children. In addition, the attributable fraction was higher in children of rural residence than in children of urban residence (68.7% vs. 31.3%).

Nutritional status. Nutritional status was assessed and stratified by age, sex, and residence in 2905 children (table 3). Both underweight and stunting were observed in ~24% of the children, and wasting was observed in 15%. The corresponding severe nutritional conditions (z score less than −3) occurred in 7.7%, 5.8%, and 4.8% of children, respectively. All nutritional deficiencies were more common in younger children than in older children (table 3). Although sex showed no clear influence, urban residence was associated with both underweight and wasting. Season significantly affected only the weight-for-height z score (−0.8 [SD, 1.3] in the rainy season and −0.4 [SD, 1.2] in the dry season). In univariate analysis, underweight, stunting, and wasting had considerable impact on morbidity (table 4). Underweight, for instance, not only predicted clinical malaria and febrile disease per se but also was a more important risk factor for anemia than was *P. falciparum* infection.

Independent predictors for clinical presentation. Associations of clinical findings at presentation are displayed in table 4. In multivariate analysis, fever was independently linked to underweight and young age. Risk factors for clinical malaria were, again, underweight and the rainy season. In contrast, anemia was predicted by several independent factors, including *P. falciparum* infection, the rainy season, underweight, age <5 years, *P. malariae* coinfection, and rural residence (table 4).

Table 2. *Plasmodium* species, as determined by genotyping, and their distribution by season and age group.

Species or species combination	Dry season			Rainy season		
	All (n = 2108)	Age <5 years (n = 1266)	Age 5–9 years (n = 842)	All (n = 2118)	Age <5 years (n = 1103)	Age 5–9 years (n = 1015)
P. falciparum	1570 (74.5)[a]	846 (66.8)	724 (86.0)[b]	1729 (81.6)	848 (76.9)	881 (86.8)[b]
P. ovale	115 (5.5)	46 (3.6)	69 (8.2)[b]	112 (5.3)	35 (3.2)	77 (7.6)[b]
P. malariae	205 (9.7)[a]	75 (5.9)	130 (15.4)[b]	279 (13.2)	98 (8.9)	181 (17.8)[b]
P. falciparum + *P. ovale*	68 (3.2)	31 (2.4)	37 (4.4)	65 (3.1)	25 (2.3)	40 (3.9)
P. falciparum + *P. malariae*	152 (7.2)[a]	55 (4.3)	97 (11.5)[b]	214 (10.1)	78 (7.1)	136 (13.4)[b]
P. falciparum + *P. ovale* + *P. malariae*	37 (1.8)	9 (.7)	28 (3.3)[b]	38 (1.8)	5 (.5)	33 (3.3)[b]
P. malariae + *P. ovale*	1 (.1)	0 (0)	1 (.1)	6 (.3)	2 (.2)	4 (.4)

NOTE. Data are no. (%) of subjects. Results for *P. falciparum, P. ovale,* and *P. malariae* infections include mixed infections. The χ^2 test was used to assess significance in all comparisons.

[a] Significant difference between seasons ($P < .001$).

[b] Significant difference between age categories within the season ($P < .001$).

DISCUSSION

Resistance to infectious diseases and childhood anemia have been closely connected to the nutritional status of children [4, 16]. Malnutrition contributes to malaria-associated mortality [9]. Anemia is a virtually obligatory symptom of malaria, and severe anemia constitutes the most frequent defining symptom of severe malaria [12]. Although the interplay of malaria, anemia, and malnutrition is complex, its comprehension is nevertheless crucial for our understanding of childhood morbidity and for the development of effective intervention strategies.

In our study, more than half of the children were parasitemic, regardless of the season, indicating hyperendemic malaria transmission with only little seasonal variation. PCR revealed infection with *Plasmodium* in more than three quarters of children. The unexpectedly high transmission exceeds by far that seen in the nearby Kassena-Nankana District and in other endemic countries like Mozambique [10, 17]. In our study, half of all febrile children in the dry season and more than three quarters in the rainy season had malaria, which stresses the overwhelming burden of malaria in this area. Although fever per se occurred less often, fever attributable to malaria was more common in older children than in younger children, at least in the dry season. During that period, young children are often febrile because of diseases like acute respiratory tract infections or otitis (authors' unpublished data). Such increased susceptibility of young children to infections has been attributed to low levels of IgA and IgG subclasses, as a result of a slow maturation of immunoglobulin, among other factors [18]. In addition, febrile children—and young children, in particular—are often presumptively treated with chloroquine, a drug of poor antimalarial efficacy in the study area but with antipyretic effects [7, 8].

Malaria control in sub-Saharan Africa relies mostly on early diagnosis and treatment, and, to a lesser extent, on transmission control. New strategies advocate intermittent preventive treatment or chemoprophylaxis with antimalarials for children and pregnant women [19, 20]. Yet, despite indisputable achievements, malaria is still out of control in sub-Saharan Africa. Do we concentrate excessively on the infection and its symptoms and neglect causes that may increase susceptibility to disease and are, thus, even more-important targets for interventions?

Worldwide, ~50% of infant deaths are attributable to malnutrition. The deleterious effect of malnutrition has been shown for measles, pneumonia, diarrhea, and malaria [21]. However, the mechanisms contributing to increased susceptibility to and/or manifestation of malaria are far from being thoroughly understood. Early animal studies suggested that malarial parasitemia in malnourished monkeys appeared earlier and lasted longer than that in nonmalnourished monkeys; in addition, immune responses were suppressed [22]. These results were subsequently confirmed in rodents [23]. Findings in humans point to an impaired ability of malnourished children to mount effective immune responses when exposed to pathogens. Atrophy of lymphoid tissues like the thymus is believed to be part of the underlying pathogenesis [3]. This results in a reduction in T lymphocyte counts, including T cell subsets, and, thus, in decreased numbers of effector cells and decreased formation of cytokines, which are important for parasite clearance. In addition, there is increasing evidence that antibody and complement formation is modulated by nutritional status [24]. In The Gambia, chronically malnourished young children were found to have an increased risk of consecutive malaria episodes (relative risk, 1.35) [25]. Chronic malnutrition, however, was actually long believed to confer protection against malaria morbidity [26], an interpretation that is frequently found in older studies [27] but that has been challenged by recent results [21]. In a study in Burkina Faso, no association between malnutrition and malaria morbidity could be demonstrated, but malnourished children had a >2-fold higher risk of dying than did

Table 3. Nutritional status in Ghanaian children aged 6 months to 9 years

Study-population stratum	Underweight[a]	Stunting[b]	Wasting[c]
All children (n = 2905)			
z score <−2, no. (%)	688 (23.7)	683 (23.5)	423 (14.6)
z score <−3, no. (%)	223 (7.7)	168 (5.8)	141 (4.8)
Overall z score, mean (SD)	−1.2 (1.2)	−1.1 (1.3)	−0.6 (1.3)
Children ⩾5 years (48.3%; n = 1404)			
z score <−2, no. (%)	249 (17.7)	288 (20.5)	157 (11.2)
z score <−3, no. (%)	56 (4.0)	59 (4.2)	55 (3.9)
Overall z score, mean (SD)	−1.1 (1.0)	−1.0 (1.2)	−0.6 (1.2)
Children <5 years (51.7%; n = 1501)			
z score <−2, no. (%)	439 (29.2)[d]	395 (26.3)[e]	266 (17.7)[f]
z score <−3, no. (%)	167 (11.1)[g]	109 (7.3)[h]	86 (5.7)[i]
Overall z score, mean (SD)	−1.2 (1.3)	−1.2 (1.3)	−0.7 (1.4)
Girls (50.1%; n = 1456)			
z score <−2, no. (%)	323 (22.2)	316 (21.7)	208 (14.3)
z score <−3, no. (%)	124 (8.5)	76 (5.2)	75 (5.2)
Overall z score, mean (SD)	−1.2 (1.3)	−1.1 (1.3)	−0.7 (1.3)
Boys (49.9%; n = 1449)			
z score <−2, no. (%)	365 (25.2)[j]	367 (25.3)[j]	215 (14.8)[j]
z score <−3, no. (%)	99 (6.8)[j]	92 (6.3)[j]	66 (4.6)[j]
Overall z score, mean (SD)	−1.3 (1.3)	−1.2 (1.3)	−0.6 (1.4)
Rural residence (62.4%; n = 1814)			
z score <−2, no. (%)	372 (20.5)	424 (23.4)	219 (12.1)
z score <−3, no. (%)	130 (7.2)	111 (6.1)	69 (3.8)
Overall z score, mean (SD)	−1.0 (1.2)	−1.1 (1.2)	−0.5 (1.3)
Urban residence (37.6%; n = 1091)			
z score <−2, no. (%)	316 (29.0)[k]	259 (23.7)[l]	204 (18.7)[m]
z score <−3, no. (%)	93 (8.5)[l]	57 (5.2)[l]	72 (6.6)[n]
Overall z score, mean (SD)	−1.3 (1.2)	−1.2 (1.2)	−0.8 (1.4)

[a] Data pertain to weight-for-age z score.
[b] Data pertain to height-for-age z score.
[c] Data pertain to weight-for-height z score.
[d] Comparison with children ⩾5 years: odds ratio (OR), 1.92 (95% confidence interval [CI], 1.60–2.30); P < .0001.
[e] Comparison with children ⩾5 years: OR, 1.38 (95% CI, 1.16–1.65); P = .0002.
[f] Comparison with children ⩾5 years: OR, 1.71 (95% CI, 1.38–2.13); P < .0001.
[g] Comparison with children ⩾5 years: OR, 3.01 (95% CI, 2.18–4.17); P < .0001.
[h] Comparison with children ⩾5 years: OR, 1.79 (95% CI, 1.27–2.50); P = .0004.
[i] Comparison with children ⩾5 years: not significant (P > .01).
[j] Comparison with girls: not significant (P > .01).
[k] Comparison with children of rural residence: OR, 1.58 (95% CI, 1.32–1.89); P < .0001.
[l] Comparison with children of rural residence: not significant (P > .01).
[m] Comparison with children of rural residence: OR, 1.68 (95% CI, 1.35–2.07); P < .0001.
[n] Comparison with children of rural residence: OR, 1.79 (95% CI, 1.26–2.54); P = .0006.

nonmalnourished children [28]. Similarly, in a previous study in Tamale, we have shown that underweight increased the risk of fatal outcome of severe malaria ~3-fold [9]. Here, we provide evidence that underweight not only increases the risk of clinical malaria by ~70% but also is a risk factor for fever and anemia.

Temporal patterns may also have implications for the role of malnutrition in malaria. Stunting and wasting result from chronic and acute nutritional deficits, respectively. The high proportion (15%) of children with wasting in our study population is of particular concern, when we compare our data with, for example, data from the Kenyan coast [29]. In children with wasting in Papua New Guinea, humoral responses to malarial antigens have been found to be low, suggesting that wasting is a risk factor for malaria [26]. Stunting, on the other hand, has been found to be associated with clinical malaria in Kenya [30]. In the present study in northern Ghana, wasting and stunting were also correlated with an increased risk of malaria-associated morbidity. In multivariate models, however, these associations did not hold true.

Socioeconomic factors may influence malaria morbidity, although their respective roles are somewhat controversial [31]. Because of civil conflicts during our study, curfew, and resulting

Table 4. Univariate and multivariate analysis of factors associated with clinical presentation in 2905 Ghanaian children.

Clinical presentation, risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Fever[a]				
Age <5 years	1.77 (1.26–2.50)	.0006	1.68 (1.20–2.34)	.003
Underweight[b]	1.71 (1.21–2.43)	.002	1.59 (1.13–2.23)	.008
Wasting[c]	1.74 (1.16–2.60)	.004	…	
Clinical malaria[d]				
Rainy season	1.91 (1.23–2.96)	.002	1.82 (1.20–2.78)	.005
Underweight[b]	1.77 (1.15–2.71)	.006	1.67 (1.10–2.50)	.009
Wasting[c]	1.86 (1.14–3.02)	.007	…	
Anemia[e]				
Age <5 years	2.34 (2.00–2.74)	<.0001	2.56 (2.18–3.01)	<.0001
Rainy season	1.98 (1.62–2.21)	<.0001	1.90 (1.62–2.23)	<.0001
Underweight[b]	1.83 (1.51–2.21)	<.0001	1.68 (1.38–2.04)	<.0001
P. malariae coinfection	1.63 (1.22–2.17)	.0005	1.59 (1.18–2.14)	.002
P. falciparum infection[f]	1.34 (1.11–1.62)	.002	1.40 (1.14–1.72)	.001
Rural residence	1.49 (1.28–1.75)	<.0001	1.35 (1.14–1.60)	.0005
Stunting[g]	1.47 (1.22–1.78)	<.0001	…	

NOTE. CI, confidence interval; OR, odds ratio.

[a] Axillary temperature, ⩾37.5ºC.
[b] Weight-for-age *z* score, <−2.
[c] Weight-for-height *z* score, <−2.
[d] Parasitemia plus fever.
[e] Hemoglobin level, <11 g/dL.
[f] As determined by polymerase chain reaction assay.
[g] Height-for-age *z* score, <−2.

limited working hours per day, we were not able to assess these factors reliably. Hence, our results are narrowed in this regard. Nevertheless, we consider nutritional status to be a consequence of socioeconomic status rather than vice versa and, thus, believe that we have assessed the more comprehensive (biometric) parameters. The cross-sectional nature of the present study also has its limitations, particularly with respect to volatile parameters such as fever. Still, considering the large sample size and within the given boundaries of multivariate modeling, we consider our results to be valid and representative of children living in this part of Africa.

Anemia is abundant in this study population, and, beyond (for example) age, season, and underweight, coinfection with *P. malariae* was found to be an independent risk factor. Overall, coinfection with *P. malariae* was observed in no more than 7% of children, but the prevalence can be as high as 13%, depending on season and age. Since *P. malariae* coinfection increased the risk of anemia 1.6-fold, it is of clinical concern. Data from Nigeria have implicated anemia as being associated with an increasing number of species and clones infecting an individual [32], which argues against a specific role of *P. malariae* in the pathogenesis of anemia. Yet, the number of *Plasmodium* species identified in our study group did not influence Hb levels. *P. malariae*–infected subjects in Gabon were more rapidly reinfected with *P. falciparum* after treatment than were those without *P. malariae* infection [33]. Such shorter parasite-free intervals may explain the association between *P. malariae* infection and anemia. In addition, *P. malariae* infection may, like *P. vivax* infection, lead to pronounced splenomegaly and splenic pooling [34].

Effects of mixed infections, cross-species immunity, and species interactions have been discussed for many years, yet data are inconclusive [35, 36]. In contrast to data from Nigeria [35], our data indicate that *P. malariae* infection peaked in the rainy season and in older children. Likewise, increased gametocyte rates of *P. malariae* in the rainy season and shortly thereafter have been reported from Sierra Leone [37]. *P. malariae* infection in northern Ghana seems to be a rainy-season phenomenon. The high prevalence of *P. ovale* is noteworthy but, nevertheless, resembles that found in Guinea-Bissau [38]. Although widespread chloroquine use predominantly in young children may explain the occurrence of *P. ovale* and *P. malariae* infection in older children [8], we believe that the pressure exerted on the parasite by the abundance of chloroquine demands caution in drawing conclusions on the natural history of species interactions in malaria-endemic areas.

On the whole, malaria exerts a heavy burden and a dramatic impact on morbidity in childhood. Yet, is malaria control alone enough to significantly reduce childhood morbidity? We identified malnutrition as a major underlying cause of malaria-

associated morbidity. Therefore, malaria-control programs will have limited effects if we do not recognize and consequently target the underlying causes of the disease. Medical staff on all levels ought to be trained to detect poor nutritional status in children. Nutritional counseling and education of mothers followed by feeding programs have to specifically focus on improving the health of the malnourished. This, alongside malaria-control measures of proven efficacy, may be apt to reduce the burden of malaria-associated morbidity on a large scale.

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