Association of Transmission Intensity and Age With Clinical Manifestations and Case Fatality of Severe *Plasmodium falciparum* Malaria

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Context There are concerns that malaria control measures such as use of insecticide-treated bed nets, by delaying acquisition of immunity, might result in an increase in the more severe manifestations of malaria. An understanding of the relationships among the level of exposure to *Plasmodium falciparum*, age, and severity of malaria can provide evidence of whether this is likely.

Objective To describe the clinical manifestations and case fatality of severe *P falciparum* malaria at varying altitudes resulting in varying levels of transmission.

Design, Setting, and Patients A total of 1984 patients admitted for severe malaria to 10 hospitals serving populations living at levels of transmission varying from very low (altitude >1200 m) to very high (altitude <600 m) in a defined area of northeastern Tanzania, studied prospectively from February 2002 to February 2003. Data were analyzed in a logistic regression model and adjusted for potential clustering within hospitals.

Main Outcome Measures Specific syndromes of severe malaria; mortality.

Results The median age of patients was 1 year in high transmission, 3 years in moderate transmission, and 5 years in low transmission areas. The odds of severe malarial anemia (hemoglobin <5 g/dL) peaked at 1 year of age at high transmission and at 2 years at moderate and low transmission intensities and then decreased with increasing age ($P=.002$). Odds were highest in infants (0-1 year: referent; 2-4 years: odds ratio [OR], 0.83; 95% confidence interval [CI], 0.72-0.96), 5 to <15 years: OR, 0.44; 95% CI, 0.27-0.72; ≥15 years: OR, 0.44; 95% CI, 0.27-0.73; $P<.001$) and high transmission intensity areas (altitude <600 m: referent; 600 m to 1200 m: OR, 0.55; 95% CI, 0.35-0.84; >1200 m: OR, 0.55; 95% CI, 0.26-1.15; P for trend=.03). The odds of cerebral malaria were significantly higher in low transmission intensity areas (altitude of residence <600 m: referent; 600 m to 1200 m: OR, 3.17; 95% CI, 1.32-7.60; >1200 m: OR, 3.76; 95% CI, 1.96-7.18; P for trend=.003) and with age 5 years and older (0-1 year: referent; 2-4 years: OR, 1.57; 95% CI, 0.82-2.99; 5 to <15 years: OR, 6.07; 95% CI, 2.98-12.38; ≥15 years: OR, 6.24; 95% CI, 3.47-11.21; $P<.001$). The overall case-fatality rate of 7% (139 deaths) was similar at high and moderate levels of transmission but increased to 13% in low transmission areas ($P=.03$), an increase explained by the increase in the proportion of cases with cerebral malaria.

Conclusions Age and level of exposure independently influence the clinical presentation of severe malaria. Our study suggests that an increase in the proportion of cases with more fatal manifestations of severe malaria is likely to occur only after transmission has been reduced to low levels where the overall incidence is likely to be low.

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In sub-Saharan Africa, malaria continues to impose an enormous burden, causing between 0.5 and 2 million deaths per year.[1] The Roll Back Malaria initiative aims to halve malaria mortality by 2010,[2] with a strategy relying heavily on the use of insecticide-treated bed nets (ITNs), which have been shown to reduce all-cause mortality among children younger than 5 years by a mean of 17% in the first 2 years after their introduction.[3]

However, there have been concerns that the delay in the acquisition of functional immunity to *Plasmodium falciparum* and the increase in the mean age of susceptibility to severe malaria that result from use of ITNs could increase the more fatal forms of the disease.[4,5] This effect would not be apparent initially, when children benefit from both reduced exposure and the partial im-

See also Patient Page.

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munity gained from previously high levels of exposure. However, the next generation of children growing up under conditions of reduced exposure might be vulnerable to a rebound in mortality as they become older.

These concerns are supported by evidence that hospital admission rates for severe malaria may plateau at moderate levels of transmission,[5-9] that cerebral malaria becomes increasingly prevalent as transmission intensity declines, and that, in any given area, the mean age of children with cerebral malaria is higher than that of children with severe malarial anemia.[5,7,10,11] Because the case-fatality rate associated with cerebral malaria has consistently been observed to be 2 to 5 times higher than that associated with severe anemia,[12,13] ITN use could result in a paradoxical increase in mortality. However, the evidence for this concern is indirect, being based on comparisons of hospital admissions for malaria between distant populations or where the prevalence of syndromes of severe malaria has been used as a proxy for expected mortality.

Recently, Lindblade et al[14] reported that the reduction in all-cause mortality associated with ITN use in the first year of life was sustained for up to 6 years in western Kenya with no evidence of rebound mortality compared with controls, although controls were given ITNs after the second year of the study and subsequent mortality among them was predicted from age-specific mortality in controls in the first 2 years of the trial. These findings are consistent with at least 2 other studies; Binka et al[15] reported no evidence of increased mortality 7 years after the end of a randomized trial of ITNs in Ghana, and Diallo et al[16] found no evidence of a shift of mortality to older ages after 6 years of following a randomized trial of insecticide-treated curtains in Burkina Faso.

An explanation for this difference between what might be expected from studies of hospital admissions for severe malaria at differing levels of *P falciparum* transmission and the results of long-term follow-up of populations following widespread introduction of ITNs is unclear. One possibility is that much of the reduction in mortality attributed to ITNs might be due to a reduction in indirect malaria mortality; ie, deaths not directly due to malaria but that would not have occurred without previous episodes of malaria.[17] Another possibility is that studies of how the manifestations of severe malaria vary with different levels of *P falciparum* transmission have been unable to determine the independent effects of different transmission rates, age, and exposure, to study sufficient numbers of patients to analyze mortality as an outcome measure, or to avoid confounding arising from comparisons of distant populations.[18,19]

Comparing the patterns of severe malaria in stable populations living under different levels of exposure can provide an estimate of the likely long-term impact of malaria control on the type and severity of clinical malaria, with the caveat that human (eg, hemoglobin polymorphisms) and parasite (eg, genetic diversity) factors associated with high malaria transmission may persist for many years following reductions in *P falciparum* transmission. We have thus carried out the first large-scale prospective study, within a single area, of the clinical pattern, age, and outcome of admissions to hospital for severe malaria at different intensities of transmission of *P falciparum*.

METHODS

Study Area

The study was conducted in northeastern Tanzania, an area characterized by the Eastern Arc of mountains, where a culturally and ethnically similar population lives at altitudes ranging from sea level to approximately 1800 m and where altitude has been shown to be a valid proxy for the intensity of *P falciparum* transmission.[20] Malaria transmission is seasonally endemic across the region, and the mean number of infected bites per person per year (entomological inoculation rate) varies from 100 to more than 500 at altitudes below 600 m, from 2 to 34 at altitudes from 600 through 1200 m, and from 0.03 to 2 at altitudes above 1200 m.[20,21] These 3 bands of altitude were selected as proxy measures of high, moderate, and low transmission, respectively.

Sulphadoxine-pyrimethamine is the first-line antimalarial treatment in the study area. At low altitude, 7-day parasitological failure rates have been reported to exceed 40%[22] and genetic markers of high-level sulphadoxine-pyrimethamine resistance have been found to be equally prevalent at different altitudes in the study area.[23] Data suggest that nutritional status in children younger than 5 years may vary with altitude in the study area[24]; thus, nutritional data were collected and have been controlled for in the analysis.

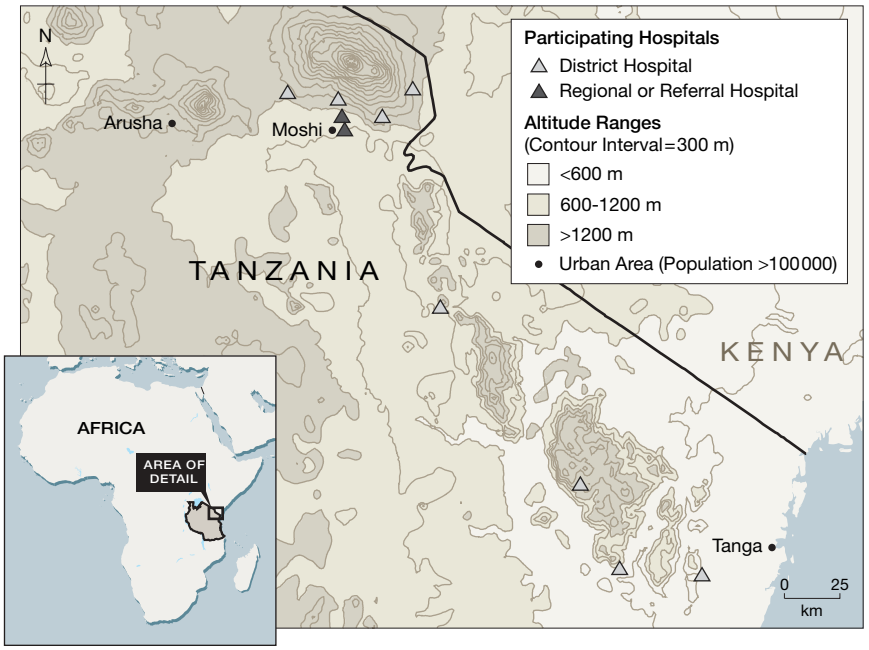
Study Hospitals

Ten of the 13 district, regional, or referral hospitals that served the area were selected on the basis that they routinely provided the standard of care defined in Tanzanian national guidelines for the treatment of severe malaria[25] and were willing to participate in the study. Six were district hospitals situated at altitudes from 940 to 1450 m, 2 were a regional and a referral hospital serving a semiurban area of 141 500 people at an altitude of 900 to 970 m, and 2 were district hospitals situated on the coastal plain at 320 and 198 m, respectively (FIGURE 1).

The study took place at 9 hospital sites for 1 year starting in February 2002 and at 1 hospital for 6 months starting in August 2002. Because of the large number of admissions to the district hospital at lowest altitude, cases under the age of 13 years were recruited on alternate calendar days; alternation was consistent throughout the study to avoid overrepresentation of any day of the week. A 4-month pilot study was conducted during which training sessions were held for hospital staff, with particular attention paid to the consistency of application of clinical definitions and assessments. Consistency checks were made regularly throughout the study. At the 3 busiest

hospitals, a research team was based in the pediatric ward and visited other wards 2 to 3 times per day. In each of the remaining 7 district hospitals, a study clinician and a team of hospital staff collected data in the course of their usual work, supported by twice-weekly supervisory visits by a senior project clinician.

Figure 1. Study Area and Participating Hospitals



Clinical Data Collection

All nonpregnant patients admitted with an intention to treat for malaria were eligible for inclusion and no patient refused participation. Signed (or thumbprint) informed consent to participate was obtained from patients or their relatives in every case. Age, sex, brief clinical history, and village of residence were recorded, followed by an assessment for criteria of potentially severe disease based on World Health Organization criteria and previous studies of severe malaria in African children.[12,13,26] Patients with moderate anemia (defined as hemoglobin 5 to <8 g/dL) were also eligible for inclusion. The criteria for inclusion in the study were therefore (1) severe anemia (hemoglobin <5 g/dL) or moderate anemia (hemoglobin 5 to <8 g/dL) (HaemoCue AB, Ängelholm, Sweden); (2) prostration, defined as inability to sit unsupported (observed) if aged 1 year or older or inability to suck or drink (observed) if younger than 1 year; (3) impaired consciousness, defined as unresponsiveness to pain (sternal rub) if younger than 1 year or inability to localize pain if 1 year or older; (4) confusion, defined as disorientation in time or place for those aged 5 years or older; (5) respiratory distress, defined as the presence of lower chest wall inspiratory recession or abnormally deep respiration; and (6) any degree of jaundice, judged by inspection of the sclera.

If any of these 6 criteria were present, additional data were collected on axillary temperature, skin turgor, height and weight if younger than 5 years, history of convulsion or use of anticonvulsant medication, and, if there was a reduced response to pain, blood glucose level (Accu-Check Active, Roche Diagnostics, Mannheim, Germany). Cerebral malaria was considered synonymous with "malaria with impaired consciousness"[7] and was defined as impaired consciousness with any malaria parasitemia (defined below), blood glucose level greater than 38 mg/dL (2.1 mmol/L), no convulsions within 1 hour of diagnosis, and no anticonvulsants administered within 6 hours of diagnosis. Outcome and treatment given were recorded at discharge or death.

Nutritional status was assessed using *z* scores for weight and age.

Malaria Slide Reading

The number of *P falciparum* asexual parasites per 200 leukocytes was counted on Giemsa-stained thick blood films. A slide was considered negative only after scanning 100 high-power fields. All slides were read twice independently. A third reading was performed if there was discrepancy between positivity and negativity or if there was more than a 33% difference in parasite count and a difference of more than 10 parasites per 200 leukocytes. According to this definition, discrepancies were observed for 706 (15.5%) of 4547 slides, which were then read by a third expert slide reader. The majority result was accepted for positive/negative discrepancies and the geometric mean density of parasites was calculated assuming a white blood cell count of 8000/μL. The findings on cases with negative slide results have been reported elsewhere.[27]

Social and Geographic Data

Using principal components analysis,[28] a socioeconomic score was generated for each individual based on the number of occupants and rooms in households, roof construction, and access to electricity. Altitude of residence was calculated from a global positioning system reading (Trimble Navigation Ltd, Sunnyvale, Calif) taken from the center of each village from which cases had been admitted. Tanzanian National Census data (2002) from districts in the study area suggest that 14.4%, 13.2%, and 14.8% of the population were younger than 5 years in areas below 600 m, between 600 and 1200 m, and above 1200 m, respectively.[29] In the same study area, Drakeley et al (unpublished data) found

that 28% of children younger than 5 years used bed nets, 6% of which had been impregnated with insecticide in the previous 6 months; these prevalences did not vary by altitude.

Sample Size Calculation and Data Analysis

We estimated that 8% of cases at high transmission would be fatal and that 1230 cases would be sufficient to detect a 50% difference in case fatality between high and moderate transmission bands with 80% power and 95% confidence. Data were double-entered in Access 2000 (Microsoft Corp, Redmond, Wash), and statistical analysis was performed using STATA, version 8 (Stata Corp, College Station, Tex). Initial survey tabulations and univariate analysis examined the distribution of cases and case fatality overall and within categories of various factors. A logistic regression model with weighted estimates and robust standard errors was used to assess the effect of various factors on severe cases and mortality allowing for clustering within hospitals. An adjusted Wald test was used to assess the fit of all models and interactions between factors in the model. Collinearity diagnostics were used to assess intercorrelation between predictor variables prior to modeling. Adjusted odds ratios (AORs) quoted in the text have been adjusted for factors specified in the Tables.

The data were weighted to adjust for the sampling of children on alternate days in 1 district hospital and stratified into two 6-month periods to allow for the hospital that was included only for the latter 6 months. Weighted counts are presented in the results. Weight-for-age *z* scores for children were derived from Epi Info (Centers for Disease Control and Prevention, Atlanta, Ga), which uses a reference population of US children.

Ethical Approval

Ethical approval for the study was granted by the ethical committees of the National Institute for Medical Research, Dar es Salaam, Tanzania, and the London School of Hygiene and Tropical Medicine, London, England.

RESULTS

Summary of Cases in the Study

During the year, 16 775 nonpregnant patients were admitted to the study hospitals with an intention to treat for malaria. Of these, 12 327 did not meet the study criteria for severe disease, of whom 5076 had a positive blood slide result for *P falciparum* at any density and 47 (0.9%) died.

Of the 4448 patients (27%) who fulfilled the study criteria for severe disease, blood slide results were available for 4261 (95%); 1984 (47%) were positive for any density of *P falciparum*, among whom 139 (7%) died. The following analyses are based on these 1984 cases using weighted estimates adjusted for the sample design.

Age and Altitude as Risk Factors for Severe Malaria

Most cases (1560 [62%]) lived in an area of high transmission below 600 m; 830 (33%) lived between 600 and 1200 m and 113 (4.5%) lived above 1200 m (TABLE 1). Eighty-six percent of cases were younger than 5 years and only 6.5% were aged 15 years or older. The median age of cases increased with increasing altitude, and the age distribution was highly skewed in the low and middle altitude bands(FIGURE 2A); the median (mean) ages of cases were 1 (1.9), 3 (6.0), and 5 (17.1) years for the altitude bands of lower than 600 m, 600 to 1200 m, and higher than 1200 m, respectively.

There was no significant variation by altitude in socioeconomic score ($P=.13$), reported travel time to the hospital

Table 1. Ages and Case-Fatality Rates of Patients Admitted to the Hospital With Different Manifestations of Severe Malaria, by Altitude of Residence*

Clinical Syndrome	All Cases	Altitude of Residence		
		<600 m	600-1200 m	>1200 m
Severe anemia†				
No.‡	1064	777	258	29
Age, median (mean), y	1 (2.2)	1 (1.4)	2 (3.9)	2 (8.4)
Case-fatality rate, No. (%)	90 (8.5)	68 (8.8)	18 (7.0)	4 (13.8)
Cerebral malaria§				
No.‡	176	46	105	25
Age, median (mean), y	5 (12.4)	1 (4.5)	6 (11.0)	26 (31.5)
Case-fatality rate, No. (%)	40 (22.7)	22 (47.8)	15 (14.3)	5 (20.0)
Respiratory distress‖				
No.‡	292	197	75	20
Age, median (mean), y	1 (4.8)	1 (1.4)	3 (9.5)	5 (12.1)
Case-fatality rate, No. (%)	87 (29.9)	54 (27.4)	26 (34.7)	7 (35.0)
Other¶				
No.‡	1127	665	416	46
Age, median (mean), y	1 (4.1)	1 (2.4)	2 (5.6)	5 (13.8)
Case-fatality rate, No. (%)	33 (2.9)	25 (3.8)	5 (1.2)	3 (6.5)
All cases				
No.‡	2503	1560	830	113
Age, median (mean), y	1 (4.5)	1 (1.9)	3 (6.0)	5 (17.1)
Case-fatality rate, No. (%)	185 (7.4)	120 (7.7)	50 (6.0)	15 (13.3)

*Data are missing for altitude of residence in 47 cases (including 5 deaths), cerebral malaria in 116 cases, anemia in 18 cases, and respiratory distress in 3 cases. Numbers shown are adjusted for the 50% sample taken of children younger than 13 years admitted to 1 lowland site. The actual number of cases and deaths among those residing lower than 600 m was 1022 (72 deaths [7.0%]), among those residing between 600 m and 1200 m was 803 (47 deaths [6.0%]), and among those residing higher than 1200 m was 112 (15 deaths [13.8%]).
†Hemoglobin level less than 5 g/dL.
‡All numbers are weighted to allow for sampling design. Syndromes are not mutually exclusive.
§No response to pain among children younger than 1 year or inability to localize pain among children aged 1 year or older, both with blood glucose level greater than 38 mg/dL (2.1 mmol/L), no convulsions present within 1 hour, and no anticonvulsant medications used within 6 hours.
‖Presence of lower chest wall inspiratory recession or abnormally deep respiration.
¶Any combination of moderate anemia (hemoglobin level 5 to <8 g/dL), prostration, confusion, or jaundice in the absence of severe anemia, cerebral malaria, or respiratory distress.

(*P*=.92), mean reported number of days of illness prior to admission (*P*=.32), or use of antimalarial agents in the 48 hours prior to admission (41% overall; *P*=.20). Prior use of antimalarial agents was significantly more likely if illness had lasted 3 or more days (*P*<.001) (complete data available from the authors).

Clinical Syndromes of Severe Malaria

Forty-nine percent of cases (and 78.9% of deaths) presented with cerebral malaria, severe anemia, or respiratory distress; 218 cases (16.4%) experienced more than 1 of these syndromes. The combination of respiratory distress and anemia accounted for 64% of all cases with more than 1 syndrome.

The odds of having a particular clinical syndrome among the admissions for severe malaria compared with baseline groups for age (≤1 year) and altitude (<600 m) are shown in TABLE 2. A significant reduction in the odds of severe anemia with increasing age group (*P*<.001) and with increasing band of altitude of residence (*P*=.03) was observed. In addition, the odds of severe anemia adjusted for the factors listed in Table 2 were positively associated with respiratory distress (AOR, 1.65; 95% confidence interval [CI], 1.17 to 2.33; *P*=.004), illness of 3 or more days (AOR, 1.73; 95% CI, 1.45-2.06; *P*=.007), increase in travel time (per hour) to hospital (AOR, 1.2; 95% CI, 1.11-1.30; *P*<.001), and use of an antimalarial agent in the 48 hours prior to admission (AOR, 1.34; 95% CI, 1.16-1.66; *P*=.001) and were negatively associated with reported use of a bed net (AOR, 0.75; 95% CI, 0.64-0.91; *P*=.003).

The odds of having cerebral malaria increased significantly with both increasing age group (*P*<.001) and increasing altitude of residence (*P*=.003). Cerebral malaria was also associated with respiratory distress (AOR, 3.32; 95% CI, 1.89-5.83; *P*<.001).

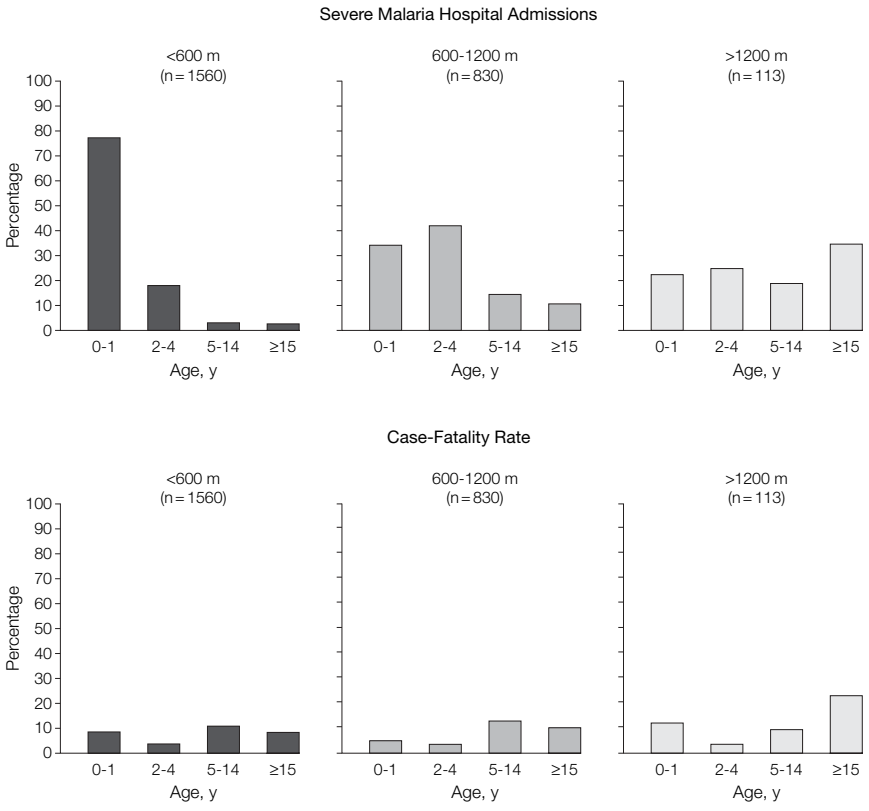
The odds of respiratory distress were higher among infants than those older than 1 year (*P*=.03) but did not vary with age after 1 year (*P*=.70). Cerebral malaria (AOR, 4.0; 95% CI, 2.42-6.60; *P*<.001) and severe anemia (AOR, 1.56; 95% CI, 1.03-2.38; *P*=.04) were associated with an increase in the odds of respiratory distress, as was an increase in travel time (per hour) to hospital (AOR, 1.13; 95% CI, 1.00-1.94; *P*<.001), while use of an antimalarial agent in the 48 hours prior to admission was associated with a reduced risk of respiratory distress (AOR, 0.76; 95% CI, 0.61-0.94; *P*=.01).

Information on malnutrition (weight-for-age *z* score <2 SDs below median of reference population) was available for 96% of patients younger than 5 years and did not vary by altitude (*P*=.20). In the models for children younger than 5 years, malnutrition was not a predictor for any of the 3 severe disease syndromes or case fatality (complete data available from the authors).

Although the odds of the 3 syndromes of severe malaria varied with age and altitude (FIGURE 3), the overall shape of the age distribution curve of odds for each syndrome was similar at each band of altitude. Thus, the odds of admission with severe anemia were highest in children younger than 2 years at all altitude bands and fell most steeply between 2 and 4 years of age. Similarly, the odds of admission with cerebral malaria were consistently low for those younger than age 4 years at all altitude bands and increased in those aged 5 years or older, but with a progressively steep gradient with increasing altitude.

Of the 1227 cases (48.0%) of severe malaria (by our criteria) without severe anemia, cerebral malaria, or respiratory distress, 841 (68.5%) had moderate anemia (hemoglobin level 5 to <8 g/dL) only, 120 (9.8%) had prostration only, and 156 (12.7%) had a combination of prostration and mod-

Figure 2. Age Distribution of Hospital Admissions With Study Criteria of Severe Malaria and Case-Fatality Rate for Each Altitude Band of Residence



Percentages are adjusted for sampling methods.

erate anemia. The remaining 83 cases (6.8%) had combinations of moderate anemia or prostration with confusion or jaundice. Prostration was more likely in the middle and upper bands of altitude compared with the lowest band ($P<.001$) but did not vary by age among those older than 1 year. As with severe anemia, the risk of moderate anemia (hemoglobin 5 to <8 g/dL) decreased with age ($P=.001$) and decreasing altitude ($P=.03$).

Severe Malaria Deaths by Age, Altitude, and Syndrome

Case fatality by altitude is shown in Figure 2B; case-fatality rates were similar in the middle and lowest bands of altitude ($P=.40$) but higher in the highest band of altitude (altitude <600 m: reference; 600 m to 1200 m: AOR, 0.39; 95% CI, 0.18-0.83; >1200 m: AOR, 0.69; 95% CI, 0.42-1.15; $P=.05$). Case fatality by age showed a J-shaped pattern, being higher in those younger than 1 year, declining between ages 2 and 5 years, and then increasing progressively with increasing age (0-1 year: referent; 2-4 years: AOR, 0.28; 95% CI, 0.18-0.41; 5 to <15 years: AOR, 0.71; 95% CI, 0.27-1.88; ≥15 years: AOR, 0.99; 95% CI, 0.37-2.62; $P<.001$). All other predictors from the case-fatality model are shown in TABLE 3. Respiratory distress was most strongly associated with a fatal outcome (AOR, 6.54; 95% CI, 4.59-9.31; $P<.001$), followed by cerebral malaria (AOR, 3.88; 95% CI, 1.67-9.09; $P=.004$). In addition to age, the risk of mortality was also strongly influenced by prostration (AOR, 4.36; 95% CI, 2.30-8.26; $P<.001$), convulsions while in the hospital (AOR, 2.90; 95% CI, 1.21-6.94; $P=.02$), and an increase in travel time (per hour) to the hospital (AOR, 1.13; 95% CI, 1.05-1.21; $P=.003$).

Patients with combinations of severe anemia, altered consciousness, or respiratory distress had particularly high case-fatality rates; the combinations of cerebral malaria and respiratory distress, severe anemia and respiratory distress, and severe anemia and cerebral malaria were associated with case fatalities of 58%, 24%, and 16% respectively.

Among the 1227 cases without respiratory distress, severe anemia, or cerebral malaria there were 40 deaths (3.3%); in this group, case fatality did not vary between categories of moderate anemia, prostration, confusion, or jaundice ($P=.90$). Although those with hemoglobin levels between 5 and less than 8 g/dL did not meet World Health Organization criteria for severe malaria, they had a significantly greater case-fatality rate (3.1%) than those who did not have severe malaria or moderate anemia (0.9%) ($P<.001$).

Table 2. Logistic Regression Model of Odds of Severe Anemia, Cerebral Malaria, or Respiratory Distress Among Patients Admitted to the Hospital With Severe Malaria by Age Group and Altitude of Residence*

	Unadjusted OR	Adjusted OR (95% CI)	*P* Value†
Severe anemia‡			
Age group, y			
0-1	1.00	1.00	<.001
2-4	0.66	0.83 (0.72-0.96)	
5 to <15	0.35	0.44 (0.27-0.72)	
≥15	0.28	0.44 (0.27-0.73)	
Altitude of residence, m			
<600	1.00	1.00	.03
600-1200	0.45	0.55 (0.35-0.84)	
>1200	0.39	0.55 (0.26-1.15)	
Cerebral malaria‡			
Age group, y			
0-1	1.00	1.00	<.001
2-4	2.45	1.57 (0.82-2.99)	
5 to <15	10.30	6.07 (2.98-12.38)	
≥15	11.59	6.24 (3.47-11.21)	
Altitude of residence, m			
<600	1.00	1.00	.003
600-1200	5.02	3.17 (1.32-7.60)	
>1200	9.57	3.76 (1.96-7.18)	
Respiratory distress‡			
Age group, y			
0-1	1.00	1.00	.03
2-4	0.68	0.72 (0.53-0.98)	
5 to <15	1.14	0.93 (0.51-1.69)	
≥15	1.05	0.79 (0.31-2.05)	
Altitude of residence, m			
<600	1.00	1.00	.06
600-1200	0.69	0.62 (0.32-1.18)	
>1200	1.48	1.16 (0.45-3.04)	

Abbreviations: CI, confidence interval; OR, odds ratio.
*The following variables were assessed during model construction: respiratory distress, severe anemia, cerebral malaria, age group, altitude band of residence, geometric mean parasite density, axillary temperature on admission, reduced skin turgor (judged by delayed return of pinched skin over anterior abdominal wall), increased respiratory rate (>50/min if aged ≤1 year or >40/min if age >1 year), any convulsion while in the hospital, socioeconomic score, reported use of any antimalarial agent within 48 hours prior to admission, reported number of days ill prior to admission, reported hours of travel to the hospital, and weight-for-age nutritional status.
†*P* values by Wald test.
‡For definitions, see "Methods" section and Table 1.

COMMENT

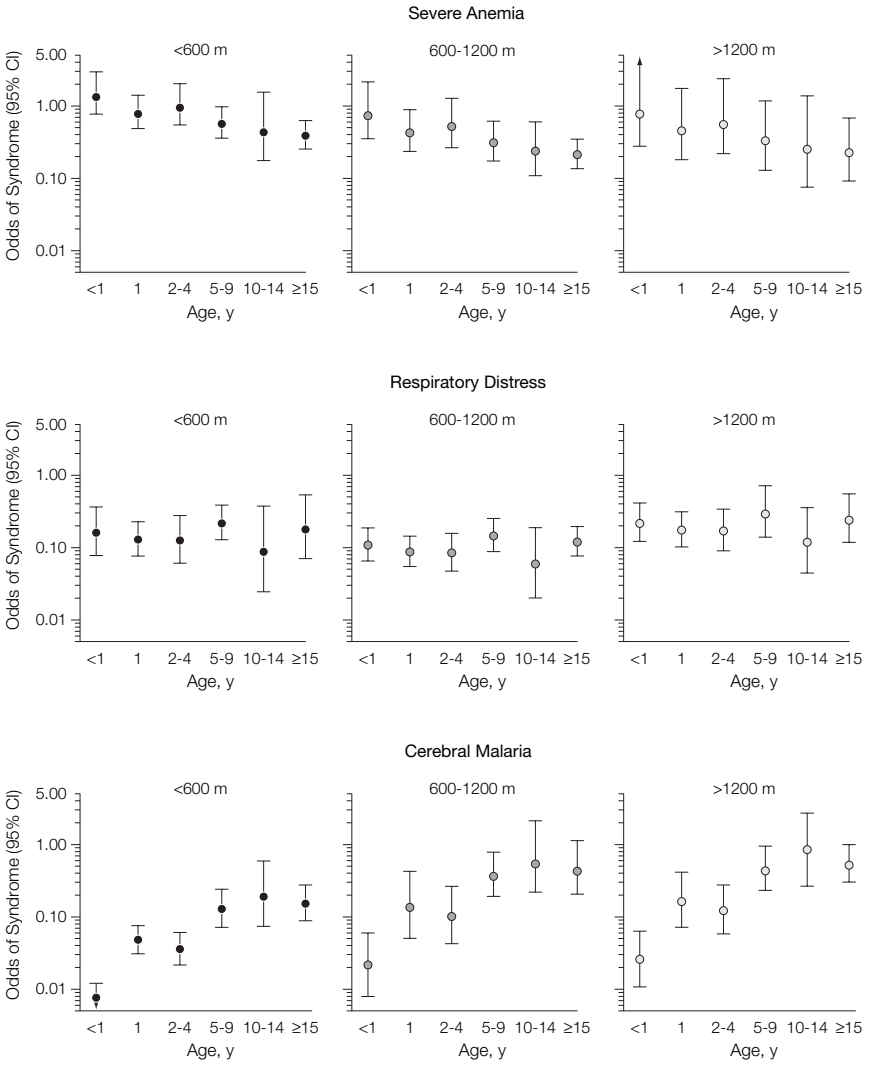
We have prospectively demonstrated differences in the pattern of severe malaria at transmission intensities varying from hyperendemic to hypoendemic. Although some of the findings (for example, the association between increasing median age of severe disease and decreasing transmission intensity) are consistent with several previous studies, our study, to our knowledge, is the first to be able to evaluate separately the effects of age and transmission intensity, with outcomes across the complete range of malaria transmission.

Currently there is no satisfactory method for characterizing the exposure of large populations to *P falciparum*. Microvariation of malaria transmission occurs for a variety of reasons. In addition, we estimate that less than 3% of the study population may have been misassigned to a band of altitude of residence because the village spanned more than 1 altitude band. However, empirical data[20,21] and the increase in age of cases with increasing altitude in our study, consistent with previous studies[10,11] are good evidence that altitude in the study area is a good proxy measure of transmission intensity. Unlike other measures, altitude data have the advantage of availability at a village level over a wide area.

Our analysis is based on proportions and risks of syndromes among cases of severe malaria without reference to an estimate of incidence. Although not ideal, estimates of incidence of severe malaria from hospital admission rates have produced highly variable results[5,6,30,31] that can distort the true picture of how syndromes of clinical malaria vary with transmission intensity. We have thus reserved estimates of incidence for a separate analysis at a later date. The age distribution of severe malaria cases and known entomological inoculation rate in our low transmission sites suggest epidemic-prone, unstable malaria where hospital admission rates for severe malaria have been found to be consistently low.[5,9] In addition, hospital admissions for severe malaria may not be representative of all severe malaria cases, as an unknown proportion of cases never present to the formal health care system.[32] This inevitable limitation of hospital studies is almost impossible to overcome because early detection through community surveillance itself changes the probability of progression to severe malaria, as suggested by our finding of the association between duration of illness and fatal outcome of severe malaria. It seems likely that failure to present to the hospital is more likely for infants than for older children and adults since the signs of illness can be difficult to detect and infants do not draw attention to their illness as do older children. If this is true, our findings will have tended to underestimate syndromes that are most frequent in infants, the commonest of which was severe anemia. We were unable to determine whether cases occurred because of transfusion or vertical transmission. However, in this highly endemic area, transfusion is unlikely to be a common cause of transmission. Finally, about a quarter of children younger than 5 years used bed nets. However, use of bed nets did not vary by altitude and, therefore, was unlikely to confound our analysis.

Severe malarial anemia, although carrying a lower risk of death than either cerebral malaria or respiratory distress, accounted for more than half of the ad-

Figure 3. Adjusted Odds of Severe Anemia, Cerebral Malaria, or Respiratory Distress Among Patients Admitted to the Hospital With Study Criteria for Severe Malaria by Age Group and Altitude Band of Residence



Odds are adjusted for sampling methods. Odds of syndrome is defined as the probability of having the specified syndrome divided by the probability of not having that syndrome. For definitions of severe anemia, cerebral malaria, and repiratory distress, see "Methods" section of the text and Table 2. CI indicates confidence interval.

missions meeting strictly defined World Health Organization criteria for severe malaria[26] and almost a third of all such deaths. Severe anemia was strongly age-dependent, and this association was similar at all levels of transmission, suggesting that age-related physiological factors, independent of acquired immunity, modify the risk of severe anemia. We also found, with borderline significance, that severe anemia was more common at higher transmission intensities independent of age, probably related to the more perennial pattern of malaria transmission in lowland areas.[33] The duration of reported illness was longer for cases of severe anemia than for other severe malaria syndromes. This finding, in conjunction with evidence that in the community, anemia is much more common in children younger than 2 years than in those 2 years or older,[34] suggests that severe malarial anemia is often an exacerbation of a chronic process that has either gone undetected by caregivers or is the result of treatment failure. Our findings suggest that there is an age-related "window of vulnerability" to severe anemia and that protection of infants and young children from severe malarial anemia is most unlikely to result in an increase in this form of the disease in older age groups. Two-year follow-up of children who were protected from severe anemia in infancy by intermittent presumptive treatment tends to support this conclusion, in that these children did not show any increased risk of severe anemia in the second year of life compared with children who had not received intermittent presumptive treatment.[35]

In common with previous studies,[8,10,11] we have observed that the proportion of cases with cerebral malaria increases with falling transmission intensity. However, we have also observed a consistent association with age: cerebral malaria tends to be relatively uncommon in children younger than 5 years at all transmission levels and then rises sharply beginning at 5 years at low and moderate levels of transmission but remains low at high transmission. The consistency of the finding suggests that (as for severe anemia) age-dependent physiological factors that operate independent of acquired immunity influence susceptibility to cerebral malarial-like syndromes. That cerebral malaria is relatively less common at higher transmission suggests that frequent exposure to *P falciparum* in infancy and early childhood allows the development of protective immune mechanisms prior to the onset of physiological susceptibility to cerebral complications of malaria. Our findings with regard to both age and altitude are consistent with the theory that cerebral malaria is to at least some extent an immunopathological syndrome mediated by adaptive immune responses primed by prior exposure to malaria or to cross-reacting antigens.[36] However, not all studies have observed such a relationship among risk of cerebral malaria syndromes, age, and exposure to infection,[11,13] and it seems likely that these relationships are complex and multifactorial, consistent with evidence that cerebral malaria is a mixed pathophysiological entity.[7,37]

As in other studies,[12,13] we found that respiratory distress was associated with high case fatality but that the odds for respiratory distress were generally low, and we found no association between respiratory distress and age or transmission intensity.

Age-specific case fatality was J-shaped, reaching its lowest level between the ages of 3 and 4 years; the initial decline is likely to be due to rapid acquisition of immunity to severe disease among those living in areas of high transmission, which may occur after very few infections,[38] and the subsequent increase in case fatality in children older than 5 years was accounted for by the increasing proportion of cases with cerebral malaria. A J- or U-shaped

Table 3. Logistic Regression Model of Predictors of a Fatal Outcome for Cases Admitted to the Hospital With at Least 1 of the Study Criteria for Severe Malaria*

Risk Factor	Unadjusted OR	Adjusted OR (95% CI)	*P* Value†
Age group, y			
0-1	1.00	1.00	<.001
2-4	0.43	0.28 (0.18-1.41)	
5 to <15	1.48	0.71 (0.27-1.88)	
≥15	1.90	0.99 (0.37-2.62)	
Altitude of residence, m			
<600	1.00	1.00	.05
600-1200	0.77	0.39 (0.18-0.83)	
>1200	1.84	0.69 (0.42-1.15)	
Respiratory distress‡			
No	1.00	1.00	<.001
Yes	8.97	6.54 (4.59-9.31)	
Cerebral malaria‡			
No	1.00	1.00	.004
Yes	5.16	3.88 (1.67-9.09)	
Convulsion in hospital			
No	1.00	1.00	.02
Yes	4.73	2.90 (1.21-6.94)	
Prostration§			
No	1.00	1.00	<.001
Yes	4.00	4.36 (2.30-8.26)	
Travel time to hospital, per hour	1.09	1.13 (1.05-1.21)	.003

Abbreviations: CI, confidence interval; OR, odds ratio.
*The following variables were assessed during the model construction: respiratory distress, severe anemia, cerebral malaria, age group, altitude band of residence, geometric mean parasite density, axillary temperature on admission, reduced turgor (judged by delayed return of pinched skin over anterior abdominal wall), increased respiratory rate (>50/min if aged 1 year or younger or >40/min if older than 1 year), any convulsion while in the hospital, socioeconomic score, reported use of any antimalarial agent within 48 hours prior to admission, reported number of days ill prior to admission, reported hours of travel to the hospital, and weight-for-age nutritional status.
†*P* values by Wald test.
‡For definitions, see "Methods" section of text and Table 1.
§Inability to sit unsupported (observed) if aged 1 year or older or inability to suck or drink (observed) if younger than 1 year.

pattern of age-specific case fatality is in general agreement with data amalgamated from multiple sites by Marsh and Snow,[8] although in their series, case fatality reached its lowest level between ages 1 and 2 years. The CIs around both these estimates are wide and there is a need for a larger study to define this, since partial control of malaria, such as can be achieved with use of ITNs, is likely to be associated with a relatively small increase in mean age of severe malaria in children younger than 5 years.

Our data on severe malaria in adults are difficult to interpret because despite the size of the study, the number of cases was small and the pattern and severity of disease may have been confounded by human immunodeficiency virus (HIV) infection, estimated to affect 17% of antenatal clinic patients and 7% of blood donors in this part of Tanzania, but there are currently no data on differential HIV prevalence in different altitude bands in the study area.[39] Nevertheless, case fatality among adults with severe malaria was higher than among children, consistent with studies of malaria among travelers[40] and nonimmune migrants in Asia.[41]

We have found evidence of a complex relationship between intensity of *P falciparum* exposure, age, clinical manifestations, and fatality of malaria, suggesting that age-related factors influence susceptibility to severe malaria independent of acquired immunity, an observation that might provide valuable leads toward an understanding of the pathophysiological basis of severe malaria. Our data are encouraging in that reduction in transmission of *P falciparum* in highly endemic areas is likely to increase the median age of severe malaria from around 1 year to 3 years of age, an age at which severe malarial anemia becomes less likely, the risks of cerebral malaria have not yet increased, and the overall case-fatality rate was at its lowest. However, further reductions in *P falciparum* transmission are likely to result in a higher proportion of cases with cerebral malaria, with a consequent increase in case-fatality rates, but at these levels of transmission our data suggest that the incidence of severe malaria is likely to be low. This would seem to be a price worth paying for the benefits of malaria control.

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Great ability develops and reveals itself increasingly with every new assignment.
—Baltasar Gracian (1601-1658)

