

# HIV Infection, Malnutrition, and Invasive Bacterial Infection among Children with Severe Malaria

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(See the editorial commentary by Breman on pages 344–5)

**Background.** Human immunodeficiency virus (HIV) infection, malnutrition, and invasive bacterial infection (IBI) are reported among children with severe malaria. However, it is unclear whether their cooccurrence with falciparum parasitization and severe disease happens by chance or by association among children in areas where malaria is endemic.

**Methods.** We examined 3068 consecutive children admitted to a Kenyan district hospital with clinical features of severe malaria and 592 control subjects from the community. We performed multivariable regression analysis, with each case weighted for its probability of being due to falciparum malaria, using estimates of the fraction of severe disease attributable to malaria at different parasite densities derived from cross-sectional parasitological surveys of healthy children from the same community.

**Results.** HIV infection was present in 133 (12%) of 1071 consecutive parasitemic admitted children (95% confidence interval [CI], 11%–15%). Parasite densities were higher in HIV-infected children. The odds ratio for admission associated with HIV infection for admission with true severe falciparum malaria was 9.6 (95% CI, 4.9–19); however, this effect was restricted to children aged  $\geq 1$  year. Malnutrition was present in 507 (25%) of 2048 consecutive parasitemic admitted children (95% CI, 23%–27%). The odd ratio associated with malnutrition for admission with true severe falciparum malaria was 4.0 (95% CI, 2.9–5.5). IBI was detected in 127 (6%) of 2048 consecutive parasitemic admitted children (95% CI, 5.2%–7.3%). All 3 comorbidities were associated with increased case fatality.

**Conclusions.** HIV, malnutrition and IBI are biologically associated with severe disease due to falciparum malaria rather than being simply alternative diagnoses in co-incidentally parasitized children in an endemic area.

Falciparum malaria is a common cause of severe illness among children in sub-Saharan Africa [1]. Human immunodeficiency virus (HIV) infection, malnutrition, and invasive bacterial infection (IBI) are reported among children with severe malaria [2–16]. However, it is unclear whether these conditions are actually as-

sociated with severe malaria among children living in areas where malaria is endemic.

The clinical signs of severe malaria have been carefully defined, but even when they are supported by *Plasmodium falciparum* parasitemia, not all severe disease is due to malaria. For example, in Malawi, another cause of death was found during postmortem examinations of 23% of children who fulfilled the World Health Organization (WHO) criteria for cerebral malaria prior to death [16]. In Kenya, 9% of children whose cases fulfill the same definition had encephalopathic viruses detected in cerebrospinal fluid (CSF) specimens [17], and among all parasitemic children who were admitted to the hospital, 26% of inpatient deaths were accompanied by bacteremia [3]. One ex-

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planation is that, in areas of endemicity, asymptomatic malaria parasites are observed among children who present with non-malarial conditions. The alternative explanation is that severe malaria is associated with other conditions, either biologically or through shared risk factors.

Direct comparison of comorbidities between malaria slide-positive and -negative, hospitalized patients is inappropriate for 2 reasons: (1) among slide-positive cases, not all disease is due to malaria; and (2) among slide-negative cases, HIV infection, malnutrition, and IBI themselves may be causes of (or be strongly associated with) severe disease. Rather, longitudinal studies or comparisons with children in the community must be undertaken.

Studies of severe malaria usually exclude parasitemic children with clinical evidence of other illnesses, such as malnutrition, meningitis, or pneumonia. However, this approach assumes a priori that parasitemia is coincidental and excludes the possibility of the actual coexistence of severe malaria with other diseases.

There is no “gold standard” to determine, in an individual child, that severe disease is or is not due to malaria in an area where malaria is endemic. Therefore, malarial parasitemia should always be treated in severely ill children. However, the likelihood of illness being due to malaria is related to parasite density, a marker of immunity, which develops with age (ie, with exposure). In studies of uncomplicated malaria, a method for determining the fraction of fevers attributable to malaria using cross-sectional parasite density data from healthy children in the community was derived by Smith et al [18]. We recently applied this method to severe malaria for defining the end points of intervention trials [19]. However, this does not address whether comorbidities may be biologically associated with severe malaria.

Here, we present findings on HIV infection, malnutrition, and IBI among 3068 consecutively admitted children with clinical features compatible with severe malaria and 592 control subjects from the community. We estimated the probability that each case was due to malaria using estimates of the fraction of severe disease attributable to malaria at different parasite densities, which we derived from multiple cross-sectional parasitological surveys of healthy children from the same community [18].

## METHODS

**Location.** Kilifi District Hospital (Kilifi, Kenya) serves ~240,000 people in an area where malaria is endemic (<1 to 120 mosquito bites are infective for *P. falciparum* each year) [20]. The prevalence of HIV infection at the hospital antenatal clinic in 2000 was 9.8% [21]. No dedicated services for HIV treatment were in place during the study. Prophylactic trimethoprim-sulfamethoxazole was not in use. The study was

approved by the Kenyan National Scientific and Ethical Review Committees.

**Clinical and laboratory methods.** Research clinicians provided care and collected standardized clinical and laboratory data on all pediatric admissions for the period August 1998 through July 2002 [3]. We defined clinical features compatible with severe malaria as a history of fever or axillary temperature  $\geq 37.5^{\circ}\text{C}$  plus  $\geq 1$  of the following characteristics: impaired consciousness (ie, inability to localize a painful stimulus for children aged  $>8$  months or lack of directed eye movements for infants aged  $\leq 8$  months), respiratory distress (ie, deep breathing), and severe anemia (hemoglobin concentration,  $<50$  g/L) [22].

Weight-for-age z scores were calculated using National Center for Health Statistics reference data with use of EpiInfo, version 6.04b (Centers for Disease Control and Prevention). Kwashiorkor was defined as the presence of bipedal edema and characteristic skin and hair changes. Malnutrition was defined as being severe underweight (weight-for-age z score, less than  $-3$ ) or having kwashiorkor.

Thick and thin blood smears were stained with Giemsa and examined for asexual forms of *P. falciparum*, which was expressed as individual red and white blood cell counts per microliter (MDII-18 automated cell counter; Beckman/Coulter). Two additional slides were performed at 4–6-h intervals if the first slide yielded negative results.

Blood was aerobically cultured for pathogenic bacteria (Bactec; Becton-Dickinson) [3]. Lumbar punctures were conducted in accordance with a clinical protocol [23]. Bacterial meningitis was defined as a positive CSF culture, positive CSF latex agglutination test, bacteria noted on a Gram stain, or a CSF leukocyte count  $>50$  cells/ $\mu\text{L}$  [23]. The leukocyte count criterion was included because we provided intravenous antibiotics to and delayed lumbar puncture among children with deep coma or focal neurological signs. IBI was defined as bacteremia or bacterial meningitis.

HIV status was determined for all admitted children from October 1999 by anonymized enzyme-linked immunosorbent assay at the end of the study; status was confirmed by polymerase chain reaction for children aged  $<18$  months (Amplior; Roche). Results that include HIV infection are limited to this systematically collected subset.

Diagnostic facilities for other pathologies included radiography; stool, urine, and sputum microscopy and culture; and renal and liver function testing and biopsy.

**Clinical management.** Children with impaired consciousness or deep breathing were normally admitted to the high-dependency unit and treated with intravenous quinine until the results of 3 slides were confirmed to be negative or, if a slide yielded positive results, until clinical and parasitological recovery, when a single dose of oral sulfadoxine-pyrimeth-

amine (recommended first-line treatment at that time) was given. Children in the high-dependency unit were treated with intravenous penicillin and chloramphenicol until CSF and/or blood culture results were known.

Children with severe anemia, without impaired consciousness or respiratory distress, were normally treated on the pediatric ward. Blood transfusion, antibiotics, malnutrition management, and other treatments were given in accordance with WHO recommendations [24]. Malaria was treated with sulfadoxine-pyrimethamine.

**Community data.** During the period 1997–2004, we conducted 7 cross-sectional surveys in the wet and dry seasons at 3 locations in the catchment of the hospital representing low, medium, and high malaria transmission [25]. In these surveys, 11,823 parasite density measurements were obtained from 2397 afebrile, healthy children [19]. Data on HIV status and malnutrition in the community were derived from 592 healthy children aged  $\geq 60$  days and were individually matched with hospital admission data for children with proven bacteremia on the basis of age, sex, season, and homestead location for the period 1999–2002.

**Statistical analysis.** We included all children aged  $\geq 60$  days with admission signs compatible with severe malaria, except those cases that were due to accidents. The 2-sided Fisher exact test,  $\chi^2$  test,  $\chi^2$  test for trend, and multivariable logistic regression were used to examine categorical data. Multivariable linear regression was used to examine parasite density. The Kruskal-Wallis test was used to compare distributions of age, because these data were skewed.

To estimate the probability that each case was due to falciparum malaria, we used estimates of the fraction of severe disease attributable to malaria calculated using a logistic method [18] from parasite densities among admitted children with severe disease and the community-based parasite surveys, as previously described [19]. Slide-negative cases were assumed to have zero probability of being due to malaria. We estimated the odds of admission with true, severe malaria, compared with community control data, using multiple logistic regression models in which each case was weighted for the probability of being true, severe malaria and was adjusted for age by specifying “probability weights” in Stata software, version 9.0 (Stata Corporation), which has robust variance estimation for this regression technique.

## RESULTS

Clinical signs compatible with severe malaria were present in 3362 (19%) of 17,301 consecutively admitted children. We excluded 294 admitted children (9%) with contaminated ( $n = 278$ ) or missing ( $n = 16$ ) blood cultures, leaving 3068 patients. Parasitemia was detected in 2048 (67%); it was detected in 1986 on the first slide, 35 on the second, and 27 on the third.

The age of parasitemic admitted children (median age, 22 months; interquartile range [IQR], 11–40 months) was similar to that of nonparasitemic admitted children (median age, 19 months; IQR, 9–41 months) and of 592 community control subjects (median age, 23 months; IQR, 12–41 months).

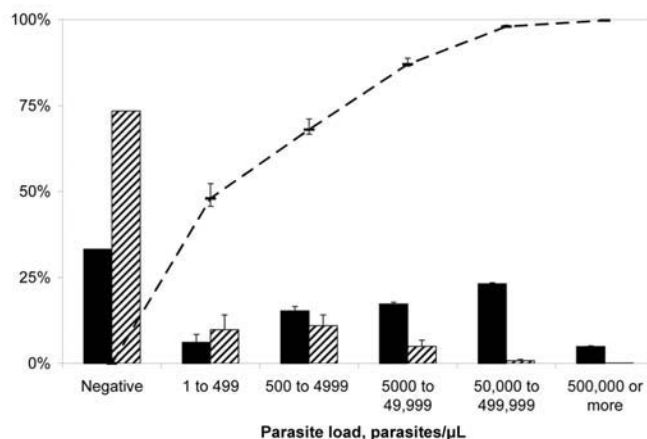
In community surveys, 3142 (26%) of 11,823 malaria slides yielded positive results. A parasite density of  $\geq 50,000$  parasites/ $\mu\text{L}$  occurred in 100 community slides ( $<1\%$ ) and in 711 slides (23%) for admitted children. Among admitted children with a positive malaria slide, the overall fractions of severe disease and death attributable to malaria were 85% (95% confidence interval [CI], 84%–86%) and 76% (95% CI, 71%–80%), respectively. Among children with parasite densities of  $\geq 50,000$  parasites/ $\mu\text{L}$ , 98% (95% CI, 97%–99%) of severe cases of disease and 95% (95% CI, 92%–97%) of deaths were attributable to malaria (figure 1). Parasite densities of  $\geq 500,000$  parasites/ $\mu\text{L}$  did not occur in the community; therefore, all cases of disease were considered to be attributable to malaria.

**HIV infection.** HIV status was determined in 1755 (92%) of 1914 consecutively admitted children starting in October 1999. Children who were not tested were more likely to have died (19% vs. 12%;  $P = .01$ ). HIV infection was present in 133 (12%; 95% CI, 10%–15%) of 1071 parasitemic admitted children, 119 (17%; 95% CI, 15%–21%) of 684 nonparasitemic admitted children ( $P = .004$ ), and 10 (1.7%; 95% CI, 0.8%–3.1%) of 592 community control subjects.

Among nonparasitemic admitted children with HIV infection, there was a bimodal age distribution, with peaks at 6 and 24 months. Among parasitemic admitted children, the distribution was unimodal. Children with HIV infection were older (median age, 38 months; IQR, 26–63 months) than HIV-uninfected admitted children (median age, 19 months; IQR, 10–35 months;  $P < .001$ ). The prevalence of HIV infection varied with age among parasitemic admitted children: for children aged  $\leq 1$  year, 1.8% (95% CI, 0.02%–3.2%); for those aged  $> 1$  year, 16% (95% CI, 14%–19%).

Parasite density was higher among HIV-infected admitted children (median, 37,500 parasites/ $\mu\text{L}$ ; IQR, 2680–172,150 parasites/ $\mu\text{L}$ ) than among HIV-uninfected admitted children (median, 22,352 parasites/ $\mu\text{L}$ ; IQR, 2213–142,590 parasites/ $\mu\text{L}$ ;  $P = .02$ , by age-adjusted linear regression). HIV-infected children were more likely to die (figure 2).

The age-adjusted odds ratio for admission with severe disease associated with HIV infection, weighted for the probability of being a true malaria case, was 9.6 (95% CI, 4.9–19). An interaction term for age  $< 1$  year was statistically significant ( $P = .021$ ). The stratified odds ratios were 1.4 (95% CI, 0.3–7.4) for age  $< 1$  year and 12 (95% CI, 5.7–25) for age  $\geq 1$  year. The estimated weighted odds ratio for a fatal, true malaria admission associated with HIV infection was 15 (95% CI, 6.5–33).



**Figure 1.** Distribution of *Plasmodium falciparum* parasite density among 3068 admitted children with signs of severe malaria and 11,823 cross-sectional community samples and the calculated fraction of severe disease attributable to malaria. Solid bars, admitted children; striped bars, community surveys; line, calculated fraction of severe disease attributable to malaria (weighted by age and location) with 95% confidence interval.

**Malnutrition.** Malnutrition occurred in 507 (25%; 95% CI, 23%–27%) of 2048 parasitemic admitted children, 373 (37%; 95% CI, 34%–40%) of 1020 nonparasitemic admitted children ( $P < .001$ ), and 44 (7.4%; 95% CI, 5.4%–9.8%) of 592 community controls. Children with malnutrition were slightly older (median age, 24 months; IQR, 13–38) than were those without malnutrition (median age, 21 months; IQR, 10–40;  $P = .004$ ).

Parasite density was lower in malnourished admitted children (median, 13,619 parasites/μL; IQR, 1603–98,650 parasites/μL) in than nonmalnourished admitted children (median, 27,330 parasites/μL; IQR, 2570–176,685 parasites/μL;  $P < .001$ , by age-adjusted linear regression). However, among admitted children with parasite loads  $\geq 50,000$  parasites/μL, 20% (95% CI, 17%–23%) were malnourished. Malnutrition was associated with an increased case-fatality rate at all parasite densities (figure 2).

The age adjusted odds ratio for malnutrition of admission with severe disease, weighted for the probability of being a true malaria case, was 4.0 (95% CI, 2.9–5.5). There was no evidence of an age effect. There was no interaction ( $P = .77$ ) between the effects of HIV infection and malnutrition on the odds of admission with severe malaria. The estimated weighted odds ratio for fatal true malaria admission associated with malnutrition was 6.5 (95% CI, 4.2–10).

**IBI.** IBI was detected in 127 (6.2%; 95% CI, 5.2%–7.3%) of 2048 parasitemic admitted children and 185 (18%; 95% CI, 16%–21%) of 1020 nonparasitemic admitted children ( $P < .001$ ). Among admitted children with parasite loads of  $\geq 50,000$  and  $\geq 500,000$  parasites/μL, IBI was detected in 4.0% (95% CI, 2.7%–5.3%) and 4.7% (95% CI, 1.2%–8.0%), respectively.

*Streptococcus pneumoniae* and *Haemophilus influenzae* constituted the majority of isolates in nonparasitemic admitted children (figure 3) but constituted a lower proportion of isolates

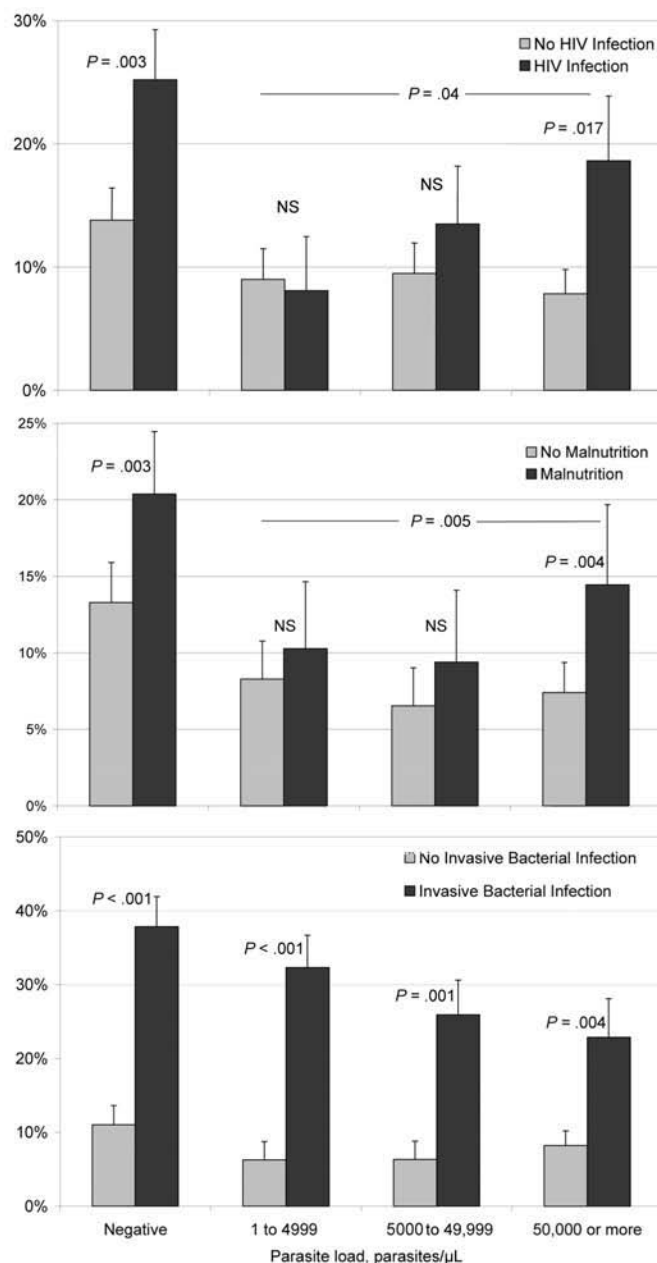
for children with malaria parasitemia ( $P = .02$  for both). Nontyphoidal salmonellae constituted a greater proportion ( $P = .005$ ) of isolates among parasitemic admitted children. For children with parasite loads  $\geq 50,000$  parasites/μL, gram-negative isolates other than nontyphoidal salmonellae and *H. influenzae* (principally, *Acinetobacter* species, *Escherichia coli*, and *Pseudomonas aeruginosa*) were common.

There was no evidence of an association between IBI and age. Sixty-two percent of parasitemic admitted children with bacteremia had neither HIV infection nor malnutrition, 22% had malnutrition only, 4% had HIV infection only, and 12% had both HIV infection and malnutrition.

IBI was strongly associated with death (figure 2). However, the case-fatality rate for IBI decreased with increasing parasite density ( $P = .05$ , by  $\chi^2$  test for trend). Among admitted children with parasite loads  $\geq 50,000$  parasites/μL, the case-fatality rate for those infected with gram-negative organisms other than nontyphoidal salmonellae or *H. influenzae* was 29% (4 of 14 children), compared with 8.5% (72 of 847) among those without IBI ( $P = .05$ ), suggesting that these organisms were not simply contaminants.

## DISCUSSION

Among children with severe malaria, the comorbidities we studied were common, were frequently fatal, and appeared to be biologically associated with true severe malaria disease, rather than alternative causes of disease in asymptotically parasitized children. An association between HIV infection and malaria has been established in adults [13, 26] but not in children in malaria-endemic areas. Cohort studies from Zaire during the 1980s found no association between HIV infection and malaria in young children [27, 28]. In South Africa, in an area

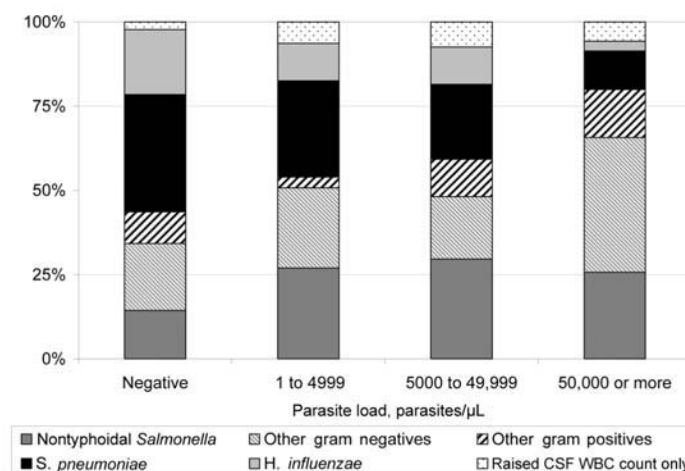


**Figure 2.** Case-fatality ratio with and without human immunodeficiency virus (HIV) infection, malnutrition, and invasive bacterial infection among children admitted to the hospital with signs of severe malaria, by *Plasmodium falciparum* parasite density. *P* values refer to age-adjusted odds ratios for death.

of unstable transmission—and, consequently, a high fraction of parasitemic disease attributable to malaria—HIV infection was associated with severe malaria but not with parasite density [12]; however, that study was too small to identify an association with mortality. More recently, in Malawi, HIV infection was reported in 16% of children who were admitted to the hospital with clinically defined severe malaria, and there was no association with death [5]. This prevalence appears to be

higher than expected among children in the community, but no formal comparison was made.

In a malaria-endemic area, we found that HIV infection was associated with admission to the hospital with true severe malaria among these children. This finding and the higher parasite density suggest a failure of acquired immunity, as is proposed to occur among adults [26]. We found no evidence that HIV infection was associated with an increased risk of malaria in



**Figure 3.** Bacterial isolates among 312 children admitted to the hospital with signs of severe malaria and invasive bacterial infection, by *Plasmodium falciparum* parasite density. CSF, cerebrospinal fluid; WBC, white blood cell.

infants, who have not yet acquired natural immunity to severe malaria. We may have underestimated the effects of HIV infection, because deaths were overrepresented among persons who were not tested. An odds ratio of nearly 10 represents a profound effect of untreated HIV infection on severe malaria. Therefore, diagnosis of HIV infection is important, because trimethoprim-sulfamethoxazole prophylaxis prevents malaria [29].

Malnutrition is associated with many life-threatening infections. However, early reports suggested that it might be protective for malaria [10, 30, 31], whereas recent studies have suggested otherwise [6, 7]. We found that malnutrition was less common among parasitemic than nonparasitemic admitted children, potentially causing a misleading impression that malnutrition is protective. However, malnutrition was far more common among children with true severe malaria cases than in the community. Some weight loss may occur with acute illness, but we believe that this is unlikely to account for our observations [32]. An odds ratio of 6.5 for fatal admission concurs with estimates modelled from pooled data by Caulfield et al [6]. Our findings strongly support the view that improving nutrition is likely to reduce malaria-related deaths.

There are several reports of IBI—especially IBI due to *Salmonella* species [2, 8, 9, 11, 15, 33]—among children with severe malaria. Some report no association between IBI and mortality among children with severe malaria, suggesting that IBI may be benign in this context [5, 8]. We found no evidence that severe malaria was associated with *S. pneumoniae* or *H. influenzae* infection. However, nontyphoidal salmonellae and other gram-negative organisms were more common than expected and were associated with increased mortality, compared with patients who did not have bacteremia. This finding is in

contrast to the findings relating to mortality from Malawi and Gambia [5, 8] and likely reflects their exclusion of children with evidence of other infections from being classified as having severe malaria. The decreasing case-fatality rate for bacteremia with parasite density probably reflects the changing pattern of bacterial isolates with parasite density (figure 3).

We did not collect data on bacteremia among healthy children in the community. However, among children who attended the outpatient department at our hospital, we previously found a 2% prevalence of bacteremia [34], as well as a <1% prevalence among those without fever (A. Brent; personal communication). Therefore, we expect that the prevalence of bacteremia among healthy children in the community is <1%, which is at least 4 times lower than the prevalence among children with severe malaria and a high parasite density, in whom almost all disease is due to malaria.

Most IBIs among children with severe malaria did not occur in the context of malnutrition or HIV infection. It is conceivable that IBI may result in a loss of immunological control of an asymptomatic parasitemia. However, we believe that IBI is more likely to have occurred as a direct consequence of severe malaria. In addition to immunoparesis [35, 36], sequestration in the microvasculature of the gut [37, 38] and at other barriers may permit bacterial invasion. If so, some IBIs will be prevented by antimalaria interventions.

Could these apparent associations reflect bias toward admission to the hospital for children who have both parasitemia and a comorbidity? At health care centers in our area, microscopy was rarely available. Furthermore, evidence from East Africa suggests that microscopy has limited influence on practice [39, 40]. We believe that parasitemia was unlikely to influence admission after reaching the hospital, because the chil-

dren were severely ill and clearly required admission. There was no HIV testing of children and little voluntary counseling and testing of adults at the time of the study. The presence of IBI would not have been known to parents or health care workers. Therefore, we think that, for HIV infection and IBI, bias is unlikely. Malnutrition is visible to parents and health care workers and, therefore, could have influenced presentation to the hospital in either direction. Our experience is that parents seek care because their child is sick rather than for malnutrition per se. However, it is impossible to exclude significant bias in relation to malnutrition.

It is possible that the age- and location-weighted attributable fraction calculation did not accurately represent admissions. However, associations were strong at parasite densities  $\geq 50,000$  parasites/ $\mu\text{L}$  in which almost all severe disease was attributable to malaria, reflecting the fact that these parasite densities very rarely occurred at any age or location in the community surveys but were common among admitted children.

By considering the fraction of severe disease attributable to malaria, we found that HIV infection (outside infancy), malnutrition, and IBI occur more frequently among hospitalized children with true severe malaria than expected by chance. We conclude that these important comorbidities are true biological associations of severe malaria rather than simply alternative reasons for admission in asymptotically parasitized children.

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