Carriage of Chloroquine-Resistant Parasites and Delay of Effective Treatment Increase the Risk of Severe Malaria in Gambian Children

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Two hundred thirty-four Gambian children with severe falciparum malaria who were admitted to the pediatric ward of a rural district hospital each were matched for age with a same-sex control subject presenting as an outpatient with uncomplicated falciparum malaria. Severe malarial anemia (SMA) was the most common presentation (152 cases), followed by cerebral malaria (38 cases) and hyperparasitemia (26 cases). Children presenting with SMA were significantly younger and more likely to carry gametocytes than were children with other severe presentations. Alleles of the genes \textit{pfcrt} and \textit{pfmdr1} associated with chloroquine-resistant parasites occurred together among cases presenting with SMA alone more often than among their matched controls (odds ratio, 2.08 [95% confidence interval, 1.04–4.38]; \(P = .039\)). Costs of travel to the hospital of more than US $0.20, use of mosquito repellents, and carriage of resistant parasites were identified as independent risk factors for severe malaria in the case-control analysis. We conclude that, in this setting, poor access to the hospital and a high prevalence of chloroquine-resistant parasites lead to a delay of adequate treatment for young children with malaria, who may then develop SMA.

Infection with \textit{Plasmodium falciparum} results in severe malaria (SM) in 1%–2% of clinical cases [1]. This represents an enormous burden on African health care systems. Among African children, severe malarial anemia (SMA) is the most common form of SM in areas where malaria is highly endemic. In contrast, in areas of lower endemicity, especially where malaria is seasonal, cerebral malaria (CM) is the most important form of SM [2, 3]. In both settings, the fatality rate among children with SMA is lower than that among children with CM [2, 4]. Factors associated with the apparently sporadic occurrence of SM include the duration of symptomatic infection [5], the species and/or strain of infecting parasite [6], host age, host genotype, state of immunity, nutritional status, and the effectiveness of any antimalarial drugs used before presentation [7]. Socioeconomic factors that have been linked to the risk of developing SM include income, overcrowding [8], antimalarial self-medication, and use of mosquito repellent [5, 9]. Others dispute the importance of social, economic, and behavioral factors [6, 10]; however, since extended duration of symptomatic infection may increase the risk of developing SM, excluding CM [11], it is likely that socioeconomic factors that delay effective treatment will increase the risk of SM.

Delay in effective treatment may also be caused by parasite resistance to widely available antimalarial drugs, and it is therefore likely that a significant proportion of African children develop SM, particularly SMA, as
a result of persistence of drug-resistant parasites after treatment for uncomplicated malaria with ineffective antimalarials. In sub-Saharan Africa, the increasing prevalence of resistance to chloroquine (CQ) during the 1980s and 1990s has been associated with a measurably higher burden of severe disease and mortality [12]. Although there is broad agreement that, if unchecked, the spread of drug resistance may cause a substantial increase in mortality due to malaria across the globe [13], there have been no controlled studies that accurately measure the contribution of resistant parasites to the risk of SM, although 1 study of 36 severe Indian cases, mainly among adults, found an excess of parasites carrying the pfcrT76T allele [14]. Multifactorial studies of socioeconomic, parasitological and clinical parameters in different settings are therefore needed to understand the complex etiology of SM and to provide a rational basis for more-effective public health interventions to reduce malaria-related mortality.

In the present study, we employed a matched case-control design, using patients with mild malaria as controls, to investigate risk factors for developing SM among Gambian children presenting to a provincial health care facility. In particular, we investigated the importance of parasitological parameters, the presence of parasites carrying markers of CQ resistance, and socioeconomic factors in the presentation of malaria as severe disease. Results are compared among the 3 most prevalent clinical categories observed: CM, SMA, and hyperparasitemia (HP).

**PATIENTS, MATERIALS, AND METHODS**

**Study population.** This study was conducted in Farafenni, The Gambia, an area characterized by moderate- to high-intensity seasonal malaria. Patients were enrolled from September to December 2002, and all consenting patients with SM admitted to Farafenni hospital during this high transmission period were included. Children ≤10 years of age were defined as SM cases if they presented with ≥1 of the following plus confirmed *P. falciparum* parasitemia:

1. Blantyre coma score ≤2
2. Severe anemia (hemoglobin [Hb] level <6 g/dL or packed cell volume [PCV] <17%)
3. Respiratory distress (respiratory rate >40 breaths/min plus 2 of the following: nasal flaring, intercostal indrawing, subcostal recession, or grunting)
4. Repeated generalized convulsions (≥3 convulsions/24 h or 2 witnessed seizures in 24 h)
5. Hypoglycemia (glucose level ≤2.2 mmol/L)
6. Renal failure (urine output <12 mL/kg/day)
7. Hemoglobinuria (dark red/black urine)
8. Jaundice
9. Prostration (inability to sit upright for a child >7 months old or inability to drink for a child too young to sit)
10. HP (≥250,000 parasites/µL)

11. Hyperpyrexia (≥40°C)
12. Circulatory collapse

This case definition was adapted from the World Health Organization classification [15], which has been used for many years in The Gambia [16], with the addition of HP. Patients meeting this definition were excluded if other concomitant diseases were diagnosed.

The matched control for each SM case was identified as the first child with mild malaria presenting at the clinic who was of the same age (within 12 months) and sex. We did not match for place of residence, since we intended to test this variable as a risk factor. Mild malaria in children ≤10 years of age was defined as described elsewhere [17]. SM cases were treated with parenteral quinine or CQ plus sulfadoxine-pyrimethamine, in accordance with Gambian government treatment guidelines.

Children with Hb levels ≤5 g/dL were assessed clinically and transfused when possible. Of the patients with uncomplicated malaria, 194 participated in a trial of chloroquine plus sulfadoxine-pyrimethamine versus coartemether, which is described elsewhere [18]. The remaining 40 controls were not followed after treatment.

All enrolled patients gave fingerprick blood samples for thick blood films and filter-paper blood spots for DNA extraction. For patients with mild malaria, anemia was assessed by measuring PCV in centrifuged EDTA capillaries. Temperature, weight, height, and middle arm circumference were measured. In a clinical examination, spleen size, liver size, jaundice, clinical signs of anemia and dehydration, heart frequency, respiratory rate, and signs of intercostal recessions were noted. Consciousness was assessed, in SM cases only, by use of the Blantyre Coma Scale [19], after hypoglycemia was corrected and 30 min after the last dose of anticonvulsant. For SM cases, blood levels of Hb and glucose were measured using handheld analyzers (HemoCue). A questionnaire evaluating socioeconomic indicators and the use of antimosquito measures by the household was administered to the parent or guardian by a trained, experienced fieldworker. Cases were not actively followed after discharge. The outcome of SM was recorded at the time of discharge as “survived,” “died,” or “absconded.”

Informed consent was obtained from all patients or their parents or guardians. Ethical approval for the study was obtained from the Joint Gambian Government/Medical Research Council Ethics Committee.

**Genotyping drug-resistance markers.** DNA was extracted from filter-paper blood spots by use of established methods [20]. Amplification of *pfcrT* and *pfmdr1* sequences and detection of allelic variants was performed by polymerase chain reaction (PCR)–restriction fragment length polymorphism and PCR–sequence-specific oligonucleotide probe analysis, exactly as described elsewhere [21], except that an additional pair of oligonucleotide probes (5′-AGGTTTATATATTGGTGTC-3′ and
5′-AGGTTTATTTATTTGGTC-3′) was designed for the determination of alleles at the \textit{pfmdr1} 184 locus.

In one genotyping experiment, DNA extracted from filter-paper blood spots from SM cases was stored on three 96-well plates, with DNA from controls on 3 further plates. Genotyping then proceeded following the sample order on these plates. In a second experiment, a new DNA sample was generated for each case and control and was stored on 6 plates, as in the first experiment. A team member who took no part in subsequent sample manipulation then randomized the order of the 72 columns on these 6 plates and produced 6 "scrambled" secondary plates. A team member blinded to the sample order then performed genotyping procedures on these scrambled plates. All results in both experiments were double-scored independently by 2 team members. Discrepancies were decided on by agreement or by a third scorer before decoding. For calculation of the risk associated with each particular presentation genotype, mixed-genotype infections with both wild-type and resistance-associated alleles at 1 locus (i.e., K and T at \textit{pfcr7} 76, N and Y at \textit{pfmdr1} 86, and Y and F at \textit{pfmdr1} 184) were coded as resistant. Mixed genotypes at each locus were uncommon, so only a very small number of individuals were mixed at \textless{}1 locus. Thus, the implied drug sensitivity of an isolate was rarely ambiguous in multiple-locus analyses.

\textbf{Data analysis.} Data were double-entered in EPI-INFO (version 6.0; Centers for Disease Control and Prevention). Analyses were performed in SPSS (version 10.0; SPSS) or Stata (version 8.1; StataCorp). Continuous variables were compared between groups by Student’s \textit{t} test. Differences in proportions were tested by \chi^2 or Fisher’s exact test. Independent risk factors for the outcome “severe malaria” were determined using (conditional) multiple logistic regression models. Comparisons used asymptotic likelihood-ratio tests, which were transformed into odds ratios (ORs). In univariate analyses, the significance of the ORs of matched case-control data was tested using McNemar’s exact test.

\textbf{RESULTS}

\textbf{Patients.} A total of 234 patients were enrolled as SM cases, with a mean age of 2.3 years (range, 1 month to 10 years), of whom 54.7\% (128/234) were male. SMA, defined as malaria parasitemia plus circulating Hb levels <6 g/dL, was the most common presentation of SM, followed by CM, defined as malaria parasitemia plus a Blantyre coma score \textless{}2, and HP, defined as parasitemia at presentation \textless{}250,000 parasites/\mu{}L. There was some overlap among these syndromes (figure 1). The guardians of 4 eligible patients did not give consent for participation.

Outcome was recorded for 220 cases, among whom there were 19 deaths before discharge. There were no recorded deaths among the 194 controls who participated in a trial of antimalarial therapy [18]. Nine patients with SMA, 1 patient with HP, and 3 patients in other categories absconded before discharge and have no recorded outcome. The SM case fatality rate in this study was 8.6\% (19/234). The case fatality rate was highest among children with CM, at 18.4\% (7/38), compared with 7.7\% (11/143) among children with SMA; 3 of these deaths were of children with manifestations of both CM and SMA.

Mean age, gametocyte carriage rate, and mean parasitemia at presentation were compared among the clinical categories of SM (table 1). Patients with SMA, with or without other manifestations of severe disease, were significantly younger, were more likely to carry gametocytes at presentation, and had a significantly lower mean parasitemia at presentation than all other patients. Conversely, those presenting with CM, with or without other manifestations, were significantly older than all others, with few gametocyte carriers.

Gametocyte carriage has also been linked to both lower parasitemia at presentation and lower Hb levels among uncomplicated malaria cases [22]. We therefore looked for further evidence linking anemia and gametocyte carriage among 1359 children with microscopy-confirmed \textit{P. falciparum} asexual parasitemia identified by screening at the Farafenni outpatient clinic in 2002, as described elsewhere [18]. Children carrying
gametocytes \((n = 88)\) presented with a mean PCV of 24.1\% (95\% confidence interval [CI], 22.8\%–25.5\%), whereas those without gametocytes \((n = 1251)\) presented with a mean PCV of 29.7\% (95\% CI, 29.4\%–30.0\%) \((P < .001, 2\text{-sided Student’s } \tau \text{ test})\). Therefore, \(P. \text{falciparum}\) gametocyte carriage is associated with both mild and severe anemia in Gambian children with clinical malaria.

**CQ-resistance genotypes of parasites at presentation.** Parasite genotypes at all 3 loci tested were successfully determined in 131 (56\%) of the 234 cases in the first genotyping experiment (see Patients, Materials, and Methods). In the second experiment, PCR successes at all 3 loci were obtained in 106 cases \((69.2\%)\). Of these, 135 \((83.3\%)\) were matched to controls with SM Risk. The prevalence of the resistance-associated alleles \(pfcrt 76T, pfmdr1 86Y, \) and \(pfmdr1 184F\) were 63.9\%, 45.4\%, and 85.8\%, respectively, among SM cases and 53.7\%, 42.0\%, and 74.1\%, respectively, among the matched controls. We observed significant associations between carriage of \(pfcrt 76T\) and \(pfmdr1 86Y\) \((P = .014 \text{ and } .001, \text{ in cases and controls, respectively})\), which reflects the linkage disequilibrium between these loci in this population \([19]\). There is also a significant association between \(pfmdr1 86Y\) and \(pfmdr1 184F\) \((P < .001 \text{ in both groups})\), as would be expected of loci only 300 bp apart on the chromosome. The risk of presentation with SM associated with each of these alleles, alone and in combination, is shown in table 2.

Carriage of \(pfcrt 76T\) and \(pfmdr1 184F\), either alone or in combination, was found to be associated with a small increase in the risk of SM \((\text{not significant at the } 5\% \text{ level})\). We then performed matched case-control analysis of the contribution of these resistance-associated alleles to SM after stratification of patients as having CM or SMA \(\text{(table 3)}\). Children with indicators of both CM and SMA were analyzed in both strata. There was not sufficient power to further stratify cases into the subgroups shown in figure 1.

SM cases presenting with SMA were significantly more likely to harbor parasites that carried both the \(pfcrt 76T\) and \(pfmdr1 184F\) alleles than were their matched controls. This association was not seen among SM cases presenting with CM; however, the wide CIs for the OR estimates \((\text{table 3})\) suggest that there was inadequate power to test this for CM. To further investigate the relationship between anemia and chloroquine resistance, the mean Hb levels were examined in children harboring parasites with and without these 2 resistance-associated mutations. Among the 68 children in all SM categories whose parasites did not harbor both mutations, the mean Hb level was 6.14 g/dL \((95\% \text{ CI}, 5.47–6.81 \text{ g/dL})\), whereas, among the 85 children who harbored parasites with both mutations, the mean Hb level was 5.22 g/dL \((95\% \text{ CI}, 4.71–5.73 \text{ g/dL})\) \((P = .027, 2\text{-sided Student’s } \tau \text{ test})\). Therefore, simultaneous carriage of parasites with both of these mutations occurred in children with a mean Hb level below the severe anemia threshold of 6 g/dL. We found no relationship between carriage of these mutations and Blantyre coma score \((\text{data not shown})\).
Table 2. Risk of severe malaria associated with mutations in \textit{pfcrt} and \textit{pfmdr1}, compared with that in matched controls with uncomplicated malaria.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No.</th>
<th>OR (95% CI)</th>
<th>(P^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{pfcrt} 76T</td>
<td>141</td>
<td>1.63 (0.95–2.82)</td>
<td>.077</td>
</tr>
<tr>
<td>\textit{pfmdr1} 86Y</td>
<td>185</td>
<td>1.27 (0.81–2.01)</td>
<td>.28</td>
</tr>
<tr>
<td>\textit{pfmdr1} 184F</td>
<td>183</td>
<td>1.64 (0.97–2.81)</td>
<td>.064</td>
</tr>
<tr>
<td>\textit{pfcrt} 76T + \textit{pfmdr1} 86Y</td>
<td>138</td>
<td>1.31 (0.76–2.27)</td>
<td>.37</td>
</tr>
<tr>
<td>\textit{pfcrt} 76T + \textit{pfmdr1} 184F</td>
<td>135</td>
<td>1.65 (0.99–2.80)</td>
<td>.053</td>
</tr>
<tr>
<td>\textit{pfmdr1} 86Y + \textit{pfmdr1} 184F</td>
<td>183</td>
<td>1.34 (0.89–2.06)</td>
<td>.18</td>
</tr>
<tr>
<td>\textit{pfcrt} 76T + \textit{pfmdr1} 86Y + \textit{pfmdr1} 184F</td>
<td>135</td>
<td>1.38 (0.79–2.43)</td>
<td>.29</td>
</tr>
</tbody>
</table>

\textbf{NOTE.} CI, confidence interval; OR, odds ratio.

\(^a\) No. of paired cases and matched controls with genotype data at the loci tested.

\(^b\) McNemar’s exact test, in univariate matched case-control comparisons.

Socioeconomic risk factors for SM. Univariate analysis of a series of socioeconomic indices identified the following risk factors for SM: lengthy travel time to the hospital, high costs of travel to the hospital, longer duration of illness, use of insect repellent, and parents’ lack of educational or professional attainment. Conditional logistic regression was then used to identify the factors that were independently associated with the risk of SM. These are summarized in table 4. Travel costs and distance from the hospital were strongly correlated, and therefore only travel costs were included in the regression analysis.

High travel costs were an independent risk factor for SM, as was a longer duration of illness. Maternal education did not have a statistically significant association with SM in the regression analysis. Use of either commercially produced coils or local mosquito repellents was associated with SM, but this was not significant at the 5% level.

We then included the data for each of the 3 molecular markers simultaneously in the logistic-regression model. Since 2-locus and multilocus genotypes are not independent, they were not included. After the variables shown in table 4 were adjusted for, patients presenting with SM remained significantly more likely to harbor parasites with the \textit{pfmdr1} 184F allele than did patients with uncomplicated malaria. \textit{pfcrt} 76T and \textit{pfmdr1} 86Y were not independently associated with SM in this model (table 5).

DISCUSSION

During a single transmission season between September and December 2002, we examined the presentation profiles of 3 distinct clinical syndromes—SMA, CM, and HP—among 234 children with severe falciparum malaria admitted to the pediatric ward of Farafenni hospital. The most common presentation syndrome, SMA, contributed to more deaths than CM, despite a lower case fatality rate. Children with SMA were, on average, significantly younger than other children with SM and were more likely to present with moderate parasitemia and gametocytemia. These features are consistent with the etiology of SMA involving a long duration of infection, inadequate treatment, and poorly developed acquired immunity.

SMA cases were significantly more likely to carry parasites with CQ resistance–associated mutations in both the \textit{pfcrt} and \textit{pfmdr1} genes than were their matched controls. After adjustment for other loci and for socioeconomic factors, carriage of parasites harboring the \textit{pfmdr1} 184F allele remained independently associated with SM. We conclude that, in this region of West Africa, where CQ is freely available and widely used, CQ resistance is contributing to excess cases of SMA and to a substantial burden of avoidable mortality among very young chil-
Table 4. Socioeconomic risk factors for severe malaria.

<table>
<thead>
<tr>
<th>Potential risk factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel costs&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 Dalasi</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥10 Dalasi</td>
<td>6.03 (2.92–12.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use of mosquito repellent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No repellent</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Repellent used</td>
<td>1.71 (0.98–2.98)</td>
<td>.058</td>
</tr>
<tr>
<td>Education of mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some education</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>1.74 (0.94–3.24)</td>
<td>.079</td>
</tr>
<tr>
<td>Duration of illness&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 days</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>≥4 days</td>
<td>2.32 (1.24–4.32)</td>
<td>.008</td>
</tr>
</tbody>
</table>

NOTE. A total of 180 case-control pairs were included in the regression analysis. Significant values are highlighted in bold. CI, confidence interval; OR, odds ratio.

<sup>a</sup> Conditional fixed-effects logistic regression.

<sup>b</sup> In 2002, 10 Dalasi was equivalent to approximately US $0.20. This corresponds to an important bank note; a 10 Dalasi note is a significant expense. Median travel costs were 0 Dalasi (range, 0–20 Dalasi) and 5 Dalasi (range, 0–75 Dalasi) among controls and cases, respectively.

<sup>c</sup> The median duration of illness among cases was 3 days.

This is most likely due to ineffective treatment of mild malaria cases, as has been suggested elsewhere [12].

We were surprised to find that the Pfmdr1 184F allele, in concert with Pfcr7 76T, was associated with the risk of severe disease in our matched case-control analysis. Previous studies of CQ resistance have focused on the role of Pfmdr1 86Y, and we have found associations between this allele, treatment failure, and mosquito transmission success in the Farafenni area [21, 23]. Since Pfmdr1 86Y and Pfmdr1 184F are closely linked loci (300 bp apart) on the chromosome, it is possible that these associations are due to the role of the Pfmdr1 184F mutation in CQ resistance. Interestingly, whereas the wild-type/resistant Pfmdr1 haplotype 86N/184F was commonly found among cases and controls (95 and 71 patients, respectively), the converse resistant/wild-type Pfmdr1 haplotype 86Y/184Y was less common in both groups than would be expected by chance (5 and 9 patients, respectively), suggesting that the Pfmdr1 184F mutation preceeds Pfcr7 86Y or is under stronger directional selection. We are planning to reevaluate the role of Pfmdr1 in CQ resistance in light of these findings. Functional studies clearly implicate Pfcr7 76T as the key mutation conferring CQ resistance; however, changes in Pfmdr1 are also associated with resistance and may partially compensate for the loss of fitness caused by resistance-conferring mutations in Pfcr7 [21]. Thus, resistant parasites (i.e., those with the genotype Pfcr7 76T) that also carry mutant forms of Pfmdr1 may have a survival advantage that renders them more likely to contribute to prolonged disease after CQ treatment and, thus, may be common among SM cases.

High travel costs were found to be an important independent risk factor for SM in the case-control analysis, reflecting the fact that the patients in our control group, on average, lived closer to the hospital than did the patients in the SM case group. Children living ≥5–10 km away from the hospital who contract uncomplicated malaria will seek treatment at village health care posts or private pharmacies, where they are likely to be treated with CQ, or will have their treatment postponed altogether because of travel costs. Thus, these children seldom appear among the control group but may appear as SM cases if their condition worsens as a result of persisting malaria and their parents seek hospital treatment. This is an important potential confounding variable in our analysis: patients more distant from the town are likely to differ significantly from Farafenni dwellers in a number of important socioeconomic parameters and are also more likely to be among the cases rather than the controls. In particular, the impact of urban versus rural domicile has previously been noted in a study of SM in West Africa [4]. Nevertheless, our regression analysis shows that use of insect repellent and carriage of parasites harboring the Pfmdr1 184F allele remained significant risk factors for SM, after adjustment for travel costs.

To account for any potential confounding, we repeated an exploratory analysis restricted to those cases from table 5, and their matched controls, with travel costs of ≤20 Dalasi. This is within the range of costs in the control group as a whole. One hundred eighty-one cases remained in this analysis. Travel costs remained an important risk factor (OR, 3.11; P = .026). After adjustment, both use of insect repellent (OR, 2.73; P = .014) and carriage of the Pfmdr1 184F allele (OR, 3.29; P = .022) remained significant risk factors for being in the SM case group rather than the control group. Future studies could overcome this problem through use of an identical defined catchment area for all enrolled cases and controls. Integration with a demographic surveillance system would facilitate this.

The socioeconomic factors that are associated with the risk of SM in our study are those indicative of economic poverty, poor education, and poor access to health care. The use of insect repellent was important, which may reflect heterogeneity in risk factor for SM in the case-control analysis, reflecting the fact that the patients in our control group, on average, lived closer to the hospital than did the patients in the SM case group. Children living ≥5–10 km away from the hospital who contract uncomplicated malaria will seek treatment at village health care posts or private pharmacies, where they are likely to be treated with CQ, or will have their treatment postponed altogether because of travel costs. Thus, these children seldom appear among the control group but may appear as SM cases if their condition worsens as a result of persisting malaria and their parents seek hospital treatment. This is an important potential confounding variable in our analysis: patients more distant from the town are likely to differ significantly from Farafenni dwellers in a number of important socioeconomic parameters and are also more likely to be among the cases rather than the controls. In particular, the impact of urban versus rural domicile has been previously noted in a study of SM in West Africa [4]. Nevertheless, our regression analysis shows that use of insect repellent and carriage of parasites harboring the Pfmdr1 184F allele remained significant risk factors for SM, after adjustment for travel costs.

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in mosquito density; those families employing repellents probably do so because of high exposure to mosquitoes. Our findings are consistent with the view that the youngest children in the poorest households with poorly educated families and living some distance away from the hospital are more at risk of developing SM, particularly SMA, because of ineffective CQ treatment for uncomplicated malaria or no treatment at all. Only when the child’s illness persists or worsens can parents deem the expensive journey to the district hospital necessary, by which time prolonged infection, characterized by gametocytemia and reduced parasitemia, may have led to SMA. In this scenario, socioeconomic deprivation and drug-resistant parasite populations coincide to exacerbate one of the most significant diseases of poverty in sub-Saharan Africa: SMA in very young children.

This is the first controlled study, to our knowledge, that demonstrates an association between parasites carrying genetic markers of CQ resistance and risk of SM in African children. In our study area, SMA may be the most important cause of malaria-related mortality. Many of these deaths could be prevented by rapid and effective treatment of acute uncomplicated falciparum malaria in children.

Acknowledgments

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References