AFRICAN CHILDREN WITH MALARIA IN AN AREA OF INTENSE
PLASMODIUM FALCIPARUM TRANSMISSION: FEATURES ON ADMISSION
TO THE HOSPITAL AND RISK FACTORS FOR DEATH

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Abstract. Malaria remains the most important parasitic cause of mortality in humans. Its presentation is thought
to vary according to the intensity of Plasmodium falciparum transmission. However, detailed descriptions of presenting
features and risk factors for death are only available from moderate transmission settings. Such descriptions help to
improve case management and identify priority research areas. Standardized systematic procedures were used to
collect clinical and laboratory data on 6,624 children admitted to hospital over a 1-year period in an intensely
malarious part of Tanzania. Frequencies of signs and symptoms were calculated and their association with a fatal
outcome was assessed using multivariate logistic regression. There were 72 deaths among 2,432 malaria cases (case
fatality rate [CFR] = 3.0%); 44% of the cases and 54% of the deaths were in individuals less than 1 year of age.
There was no association between level of parasitemia and CFR. Increased risk of dying was independently found in
all children with hypoglycemia (odds ratio [OR] = 6.7, 95% confidence interval [CI] = 3.9–11.7), in children 1–7
months of age with tachypnea (OR = 8.8, 95% CI = 2.6–30.5) and dehydration (OR = 5.0, 95% CI = 1.9–14.2),
and in children 8 months to 4 years of age with chest indrawing (OR = 4.7, 95% CI = 2.0–11.2) and inability to
localize a painful stimulus (OR = 6.9, 95% CI = 2.9–16.5). Children in the bottom quartile of weight-for-age were
more likely to die (OR = 2.1, 95% CI = 1.3–3.5). Eight percent of the malaria cases had severe anemia (packed cell
volume < 15%) but 24% received a blood transfusion. The epidemiology of malaria disease may be more complex
than previously thought. Improved case management in a wide variety of health facilities may result from adequate
identification and treatment of dehydration and hypoglycemia. Transfusion-requiring anemia is a major problem and
sustainable, effective preventive measures are urgently needed.

More than half of the world’s population lives in areas endemic for Plasmodium falciparum malaria, resulting in
more than 400 million clinical cases and between one and three million deaths every year.1 Young children living in
sub-Saharan Africa carry the largest part of this burden.2 Although the epidemiology of P. falciparum infection has
been well described in a variety of settings, the description of malaria as a life-threatening disease is less complete. Such
descriptions can improve case management by identifying children at highest risk of dying; focusing scarce resources
on such patients may reduce case fatality rates. Furthermore, these studies provide valuable insights into underlying
pathophysiologic processes.

Common manifestations of severe malaria in children include cerebral malaria and severe anemia. The relative
importance of each presentation is thought to vary according to the intensity of transmission, with severe anemia being
increasingly important as transmission intensity increases and cerebral malaria more common at lower transmission
intensities.3,4 There are a number of reports describing indicators of adverse outcome in children who satisfy criteria for cerebral
malaria5-7 or severe malaria anemia.8 However, the only comprehensive review of children with malaria presenting to
hospital in Africa6 comes from an area of seasonal transmission with estimates of the entomologic inoculation rate
(EIR) of 0–69 infected bites per person per year.9 Independent predictors of a fatal outcome were impaired consciousness,
respiratory distress, hypoglycemia, and jaundice. More than 80% of malaria deaths had impaired consciousness or
respiratory distress on admission. We report from an intense-

METHODS

Study area. The study was based at St. Francis Designated District Hospital in Ifakara, Kilombero district, in
southern Tanzania. This hospital has 375 beds, including 70 in the pediatric ward. The area, described in more detail
elsewhere,11 has intense all-year malaria transmission, with an estimated EIR of more than 300 infectious bites per
person per year.12 Malaria control is based on early diagnosis and treatment with chloroquine, which is readily available.
Sixty percent of the pediatric outpatients with malaria have positive urine test results for chloroquine and estimates of
7-day parasitologic resistance of up to 65% are reported.13 Fifteen percent of malaria admissions less than 2 years old
were involved in either an anemia prevention study14 or an ongoing malaria vaccine trial. Although non-placebo recipients
may have a modified risk of developing malaria, it seems unlikely that once admitted, risk factors for death would be
different from non-study children. The study received ethical clearance from the Tanzanian Commission for Science and Technology.

Clinical surveillance and case definition. Since mid 1994, Ifakara Health Research and Development Centre has
operated a round-the-clock surveillance system of all admissions to the pediatric ward (0–15 years of age). On admission,
specially trained project Clinical Officers (COs) sought

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and severely anemic if the PCV was , according to standard World Health Organization (WHO) criteria.

Dehydration was assessed according to standardized questionnaire on all children. The COs were supervised daily by project physicians who also held regular training sessions. Questionnaires were scrutinized by a project physician and errors or inconsistencies were discussed with the CO concerned. The signs and symptoms recorded are shown in Table 1. A capillary blood sample was collected to measure packed cell volume (PCV) and blood glucose concentration. Thick and thin blood films were prepared for quantification of *P. falciparum* parasitemia. A clinical diagnosis of malaria was made by a project clinician at the time of discharge if, in the light of laboratory investigations and the clinical course of the patient, malaria was considered a main diagnosis. This paper reports findings on children with a clinical diagnosis of malaria confirmed by a blood slide positive for asexual forms of *P. falciparum*. Children with abnormal cerebrospinal fluid were not included as malaria cases.

Children were considered anemic if the PCV was < 25% and severely anemic if the PCV was < 15%. Severe respiratory distress was defined by chest indrawing or deep breathing. A relatively subjective assessment of conscious level (normal/impaired) was made. For those ≥ 6 months old more objective assessments of neurologic status included the child’s ability to sit unsupported and, if 6 months old, the ability to localize a painful stimulus (sternal rub). Ability to localize pain was assessed 30 min after a convolution, 6 hr after sedating medication, and after hypoglycemia had been corrected. Dehydration was assessed according to standard World Health Organization (WHO) criteria. With the exception of information on blood transfusions (collected from May 1996), all data was collected between October 1995 and September 1996.

### Inpatient care of malaria cases

According to Tanzanian national guidelines, uncomplicated malaria was treated with chloroquine or sulfadoxine-pyrimethamine. Children with complicated malaria who failed to respond to chloroquine, were unable to tolerate oral medication, or who had transfusion-requiring anemia received intravenous (IV) quinine. Based on a previous study, only children with a PCV of < 12% or with a PCV of 12–18% and clinical compromise were transfused. Before transfusion, children were given frusemide to reduce the risk of cardiac failure. Hypoglycemia was treated with IV 50% glucose solution, repeated as necessary. Paracetamol was given to children with high fevers. Convulsions were treated with up to two doses of rectal or IV diazepam followed by intramuscular phenobarbitone if seizures continued. Children with persistent altered consciousness or repeated convulsions received presumptive treatment for meningitis until a lumbar puncture excluded this possibility.

### Laboratory procedures

The PCVs were measured using a microcentrifuge and a Hawksley (Lancing, United Kingdom) hemocrit reader. The blood glucose concentration was determined using Glucostix® (Bayer, Inc., Basingstoke, United Kingdom) at the bedside. Blood slides were stained with Giemsa and the number of asexual *P falciparum* per 200 leukocytes was counted. All blood slides were read twice and the results were compared. A third reading was performed if there was disagreement in terms of positivity/negativity or if the ratio of the two readings was < 0.67 or > 1.33. The majority reading was used for positive/negative discrepancies and the geometric mean of the three readings was used for discordant density assessments, assuming a white blood cell count of 8,000/µl. These methods are described in detail elsewhere.

### Data processing and statistical methods

Data were double-entered using a FoxPro database version 2.6 (Microsoft Corporation, Redmond, WA). Statistical analyses were performed using STATA (Stata Corporation, College Station, TX) or Epi-Info version 6 (Centers for Disease Control and Prevention, Atlanta, GA). The association between dichotomous variables was assessed using Pearson’s chi-square test or Fisher’s exact test. Chi-square tests for heterogeneity and trend were used for variables with more than two levels. Children 1–7 months of age and those 8 months to 5 years of age were analyzed separately. This was because the ability to locate a painful stimulus, strongly associated with risk of death, is unreliable in the younger age group.

Variables associated with death at a level of *P < 0.10* in univariate analysis were included in multivariate logistic regression modeling. First, variables were separated into groups of 2–3 clinically related factors, e.g., dyspnea, chest indrawing, nasal flaring, and a logistic model produced with death or survival as the outcome controlling for age. Backward elimination was used to drop variables with no significant effect (*P > 0.05*) on outcome, when added to a model containing the other variables in the group. Remaining variables were regrouped and the process was repeated up to 3 times to avoid problems of collinearity and unstable estimates, and to minimize the effects of missing data. The relatively few variables remaining were included in a logistic model that was refined using backward elimination. Pairwise interactions between variables in the final models were assessed. Throughout this paper, numbers appearing in parentheses after percentages or odds ratios (ORs) are 95% confidence intervals.

### Missing data

Data on transfusion were missing for 48% of the malaria cases. These children had a higher case fatality rate (CFR) (4.5% versus 1.7%, OR 2.7 (1.6–4.4), *P <
0.001), their median age was lower (12.9 months versus 14.4 months; \(P = 0.001\)), and they were less likely to be involved in an intervention study (9.0% versus 11.9%, \(OR = 0.73\) (0.6–0.9), \(P = 0.02\)). Data was also missing on the ability to locate a painful stimulus for 15% of the malaria cases more than 8 months old. These children had a higher CFR than other children (5.0% versus 2.5%, \(OR = 2.0\) (1.0–3.9), \(P = 0.01\)). All other variables were 96% complete.

**RESULTS**

During 1 year of surveillance there were 6,483 admissions with complete age and survival data. Of these, 2,432 (37%) had a confirmed clinical diagnosis of malaria and 72 of them died, giving a CFR of 3.0% (2.3–3.6). Approximately 50% of the malaria deaths occurred within 24 hr of admission. A total of 44% of the malaria cases and 54% of the malaria deaths occurred before 1 year of age (Figure 1). There was a predominance of boys over girls among cases (males = 53%, 1,293 of 2,430; \(P = 0.001\)).

Malaria cases presented with a measured axillary temperature of \(\geq 37.5^\circ C\) 76% (1,834 of 2,427) of the time. Of those who were apyrexial at presentation, 90% (535 of 592) had a history of fever. Fifty-four (3.3%) children between 8 months and 4 years of age had no history of fever and were apyrexial at presentation, 90% (535 of 592) had a higher CFR than other children (5.0% versus 2.5%, \(OR = 2.0\) (1.0–3.9), \(P = 0.01\)). All other variables were 96% complete.

**Figure 1.** Malaria by age: number of cases, deaths, severe anemia, and blood transfusions (BT). PCV = packed cell volume.

Relationship between parasitemia, case fatality rate, and prevalence of blood transfusion

<table>
<thead>
<tr>
<th>Parasitemia ((\mu l))</th>
<th>Case fatality rate*</th>
<th>Transfusion rate†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/N)</td>
<td>% (n/N)</td>
</tr>
<tr>
<td>1–4,999</td>
<td>3.6 (18/507)</td>
<td>26.8 (56/209)</td>
</tr>
<tr>
<td>5,000–19,999</td>
<td>2.5 (13/515)</td>
<td>26.4 (78/296)</td>
</tr>
<tr>
<td>20,000–99,999</td>
<td>3.0 (23/982)</td>
<td>23.9 (130/543)</td>
</tr>
<tr>
<td>(\geq 100,000)</td>
<td>3.1 (14/450)</td>
<td>20.7 (51/246)</td>
</tr>
</tbody>
</table>

* \(x^2 = 0.9, P = 0.8\)  
† \(x^2 = 3.1, P = 0.4\).

The remainder of this paper is confined to data on children 1 month to 5 years of age because this was the age group within which malaria cases and deaths were concentrated. There were no neonatal malaria deaths and only 2 malaria deaths in children more than 5 years old. Table 3 shows by age group the prevalence, mortality rates, and associated odds of dying of signs and symptoms significantly associated with death in both age groups. Where appropriate, these data for other signs and symptoms are presented in the text. Hyperglycemia increased the risk of death at least 6-fold compared with normoglycemic children (Table 3).

**Specific clinical presentations of acute malaria.** Overall, 1 in 6 children with malaria had clinically detectable dehydration and 7% (24 of 363) of them died. Among the dehydrated children, 85% fulfilled the WHO criteria for mild dehydration. Twenty percent of malaria cases 1–7 months of age were reported to breast-feed poorly on presentation and these children were more likely to die than those who were feeding normally (OR = 5.5 (2.4–12.6), \(P < 0.0001\)). Although the frequency of vomiting was similar in the two age groups (40%), it was only associated with death in younger children (OR = 2.4 (1.0–5.4), \(P = 0.04\)). A history of diarrhea, present in 16% of the younger children and 9% of the older children, also increased the risk of younger children dying (OR = 2.6 (1.0–6.3), \(P = 0.07\)), as did a sunken fontanelle (OR = 3.6 (1.4–9.4), \(P = 0.02\)).

Maternal reports of difficulty in breathing, observed nasal flaring, chest indrawing, and severe respiratory distress were all associated with an increased risk of death. Additionally, 52% of the younger children with tachypnea were at increased risk of dying (OR = 4.5 (1.6–12.9), \(P = 0.003\)), although this was not a risk factor in older children (OR = 0.7 (0.4–1.3), \(P = 0.3\)). Older children with deep breathing (\(n = 68\)) were more likely to die (OR = 3.6 (1.5–8.5), \(P = 0.003\)), as were children in this age group with crackles or crepitations on auscultation (\(n = 216\), OR = 3.2 (1.7–6.0), \(P < 0.001\)).

Although 61% of the younger children and 37% of the older children had a PCV < 25%, only 14% and 6%, respectively, fulfilled the criteria for severe anemia (PCV < 15%). The prevalence of severe anemia and frequency of blood transfusion decreased with age (Figure 1). Children less than 1 year of age received 60% (187 of 311) of the blood transfusions and nearly half (26 of 55) of the malaria admissions 1–4 months of age received a blood transfusion. Pallor was a common clinical sign, present in 59% (382 of 652) of the younger children and 31% (501 of 1,624) of the older children, but was significantly associated with death only in younger children (OR = 3.5 (1.2–9.9), \(P = 0.02\)). Similarly, splenomegaly was prevalent in both age groups (56% of younger and 39% of older children) but only associated with an increase in the odds of dying in younger children (OR = 2.9 (1.0–8.9), \(P = 0.03\)). Hepatomegaly, probably related to cardiac failure, was associated with a more than tripled risk of dying in both age groups. Jaundice was present in only 17 (1%) children of whom 3 died (\(P > 0.1\)).

Seven percent of the children 8 months old who were
TABLE 3
Prevalence of signs and symptoms and risk factors for death in Tanzanian children admitted with malaria*

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Mortality</th>
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<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
<td>N (%) OR  (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Children 1–7 months of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>528/652 (81)</td>
<td>11 (2) 1.0</td>
</tr>
<tr>
<td>Mild</td>
<td>104/652 (16)</td>
<td>10 (10) 5.0 (2.1–11.8)</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>20/652 (3)</td>
<td>2 (10) 5.2† (0–22.8)</td>
</tr>
<tr>
<td>History of dyspnea</td>
<td>113/652 (17)</td>
<td>12 (11) 5.7§ (2.5–13.0)</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>164/653 (25)</td>
<td>14 (9) 5.0§ (2.2–11.5)</td>
</tr>
<tr>
<td>Indrawing</td>
<td>119/653 (18)</td>
<td>10 (8) 3.7§ (1.6–8.4)</td>
</tr>
<tr>
<td>Severe respiratory distress</td>
<td>130/653 (20)</td>
<td>10 (8) 3.3§ (1.4–7.5)</td>
</tr>
<tr>
<td>PCV ≥25%</td>
<td>241/621 (39)</td>
<td>4 (2) 1.0</td>
</tr>
<tr>
<td>15–24%</td>
<td>294/621 (47)</td>
<td>9 (3) 1.9 (0.6–5.8)</td>
</tr>
<tr>
<td>Hepatomegaly &gt;2 cm</td>
<td>86/621 (14)</td>
<td>6 (7) 4.4# (1.3–15.0)</td>
</tr>
<tr>
<td>History of ≥3 seizures</td>
<td>35/653 (5)</td>
<td>4 (11) 4.1†† (1.4–12.2)</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>8/639 (1)</td>
<td>2 (25) 9.7‡‡ (0.0–34.1)</td>
</tr>
<tr>
<td>Unable to locate pain§§</td>
<td>71/653 (11)</td>
<td>10 (14) 7.2§ (3.1–16.7)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>54/636 (8)</td>
<td>8 (15) 7.1¶¶ (2.9–17.3)</td>
</tr>
<tr>
<td>WAZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50th percentile</td>
<td>443/651 (68)</td>
<td>10 (2) 1.0</td>
</tr>
<tr>
<td>25–50th percentile</td>
<td>122/651 (19)</td>
<td>7 (6) 2.6 (1.0–6.9)</td>
</tr>
<tr>
<td>≤25th percentile</td>
<td>86/651 (13)</td>
<td>6 (7) 3.2## (1.2–8.9)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Children 8 months–4 years of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1,379/1,618 (85)</td>
<td>12 (5) 1.0</td>
</tr>
<tr>
<td>Mild</td>
<td>203/1,618 (13)</td>
<td>7 (3) 1.4 (0.6–3.1)</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>36/1,618 (2)</td>
<td>5 (14) 6.2‡ (2.4–16.4)</td>
</tr>
<tr>
<td>History of dyspnea</td>
<td>121/1,624 (7)</td>
<td>9 (7) 3.1¶ (1.5–6.5)</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>260/1,626 (16)</td>
<td>14 (5) 2.3¶ (1.2–4.3)</td>
</tr>
<tr>
<td>Indrawing</td>
<td>157/1,626 (10)</td>
<td>13 (8) 3.8§ (2.0–7.3)</td>
</tr>
<tr>
<td>Severe respiratory distress</td>
<td>176/1,626 (11)</td>
<td>15 (9) 4.1§ (2.2–7.7)</td>
</tr>
<tr>
<td>PCV ≥25%</td>
<td>998/1,582 (63)</td>
<td>24 (2) 1.0</td>
</tr>
<tr>
<td>15–24%</td>
<td>493/1,582 (31)</td>
<td>19 (4) 1.6 (0.9–3.0)</td>
</tr>
<tr>
<td>Hepatomegaly &gt;2 cm</td>
<td>91/1,582 (6)</td>
<td>4 (4) 1.9** (0.7–5.3)</td>
</tr>
<tr>
<td>History of ≥3 seizures</td>
<td>46/1,626 (3)</td>
<td>4 (9) 3.4† (1.2–9.5)</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>54/1,578 (3)</td>
<td>6 (11) 4.6‡‡ (1.9–11.2)</td>
</tr>
<tr>
<td>Unable to locate pain§§</td>
<td>234/1,620 (14)</td>
<td>19 (8) 4.3§ (2.4–7.8)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>108/1,569 (7)</td>
<td>12 (11) 6.4§ (3.2–12.8)</td>
</tr>
</tbody>
</table>

* OR = odds ratio; CI = confidence interval; PCV = packed cell volume; – = no data available; WAZ = weight for age.
† Chi-square test for trend; P < 0.001.
‡ Pearson’s chi-square test for no dehydration compared to rest. 0.05 > P < 0.01.
§ Pearson’s chi-square test. P < 0.001.
¶ Pearson’s chi-square test. 0.01 > P < 0.001.
# Fisher’s exact test for PCV ≥25% compared to rest (F1b P = 0.9). 0.05 > P < 0.01.
** Fisher’s exact test for PCV ≥25% compared to rest (F1b P = 0.9).
†† Fisher’s exact test. 0.05 > P < 0.01.
‡‡ Fisher’s exact test. 0.01 > P < 0.001.
§§ Only children ≥8 months old.
¶¶ Fisher’s exact test. P < 0.001.
## Fisher’s exact test for > 50th percentile compared to rest. 0.01 > P < 0.001.
### Chi-square test for trend. 0.01 > P < 0.001.
unable to locate a painful stimulus had a 10-fold increase in their risk of dying. Inability to sit was also a major risk factor for death in these children (OR = 4.5 (2.5–8.0), \( P < 0.001 \)) though not in those 6–7 months old (OR = 2.8 (0.6–\( \infty \), \( P = 0.4 \)). Children with impaired consciousness were also at increased risk of dying, as were those with a history of 3 or more convulsions in the 24 hr preceding admission.

Malnutrition was associated with an adverse outcome. Children in the lower quartile of weight-for-age Z-scores were more likely to die than their better-nourished counterparts, as were the 29% of older children in the lower quartile of weight-for-height z-scores (OR = 2.5 (1.2–5.2), \( P = 0.01 \)). Three of the 8 older children with oral candida died (OR = 21.5 (5.5–84.2), \( P = 0.001 \)), and this condition was confined to children in the lowest weight-for-age category. Older children with orange hair, typical of severe malnutrition in African children (\( n = 79 \)), also had a greater risk of death than children with normal hair (OR = 2.4 (1.0–6.1), \( P = 0.07 \)). In these older children, edema (OR = 3.8 (1.3–10.6), \( P = 0.03 \)) was more commonly associated with poor anthropometric indices than with a PCV < 15%. For example, 47% (18 of 38) of the edema cases were in the lowest weight-for-height category, but only 16% (6 of 37) of the edema cases had a PCV < 15%.

**Patterns of clinical presentation.** Figure 2 shows the clinical presentations of malaria with their associated CFR and indicates the extent of overlap between presentations. Almost half (305 of 635) of the younger malaria cases are represented within the circles compared with 36% (523 of 1,445) of the older children. This figure illustrates the importance of dehydration and severe respiratory distress in the presentation of malaria. There was no clear predominance of severe anemia over impaired consciousness in either age group.

**Multivariate analysis.** The results of multivariate logistic regression modeling are presented in Table 4. In younger children, tachypnea, dehydration, hypoglycemia, inability to breast feed normally, and impaired consciousness were all independently associated with a 3–9-fold increase in the risk of a fatal outcome.
In older children, multivariate analysis showed that hypoglycemia, chest indrawing, inability to locate a painful stimulus, the presence of edema, and the absence of a history of fever were independent predictors of death. We were concerned that children who had no available information on their ability to locate a painful stimulus were different from children with this information. To assess the robustness of the model, we repeated the analysis without the ability to locate a painful stimulus. The factors that remained independently associated with death were hypoglycemia (OR = 5.6 (2.6–12.2)), chest indrawing (OR = 3.4 (1.6–7.4)), absence of a history of fever (OR = 4.0 (1.4–11.5), inability to sit (OR = 2.4 (1.2–4.8)), and oral candidiasis (OR = 16.2 (2.8–93.7)).

**DISCUSSION**

We have described the presentation of children admitted with malaria and their risk factors for death in a hospital with good case management set in an area of intense *P. falciparum* transmission. This intense transmission is underlined by the high proportion of malaria cases and deaths in children less than 1 year of age. However, malaria cases reaching a hospital have been likened to the tip of an iceberg. More than 80% of childhood deaths occur in the home,11 and factors such as access to medical care and patterns of health-seeking behavior vary between areas and will alter the pattern of presentation of cases to a hospital. In our study, more boys than girls were admitted with malaria. Although they may actually develop more malaria severe enough to warrant admission, this imbalance may also reflect household level gender-bias in treatment seeking behavior or exposure. Hospital-based studies may be a poor reflection of disease patterns in the community.

Dehydration has not been previously quantified as a presenting feature of life-threatening malaria. One in six children presented with some dehydration, and although the majority of these cases were mild, this was one of the few factors independently related to death in children 1–7 months of age. Our findings should raise awareness of this contributor to malaria mortality, which frequently could be treated at home or at primary health care facilities.

Respiratory features, including severe respiratory distress, were common and associated with increased mortality. In particular, tachypnea and chest indrawing were independently associated with death. These may be due to underlying metabolic acidosis20 caused by a combination of factors such as infection, dehydration, and severe anemia with or without heart failure. Crackles and crepitations on auscultation were associated with death in older children, and although their etiology is not clear, they frequently resolve with malaria treatment (Schellenberg D, unpublished data).

Anemia was a common presentation of malaria since 44% of the admitted malaria cases had a PCV < 25%. However, severe anemia (PCV < 15%) was relatively uncommon, was not an independent risk factor for death, and was associated with a relatively low CFR. This may give the impression that anemia is a frequent but inconsequential presentation of malaria in this area. This is clearly not the case since 24% of the children with malaria had to be transfused during the course of their admission and these transfusions were given according to strict criteria. Why was the transfusion rate so high when the prevalence of severe anemia was relatively low? First, children without severe anemia may be compromised. Indeed, 30% (33 of 111) of the children transfused with a PCV > 18% had signs consistent with heart failure on admission. This questions the adequacy of the current definition of severe anemia in guiding management. Second, after admission, hemolysis of erythrocytes will cause a decrease in the PCV and this may provoke clinical distress. Third, dehydration-induced hemoconcentration could yield an underestimate of the prevalence of severe anemia, although an analysis of the likely impact of rehydration suggested that very few children would fall into the severe anemia category as a result. Whatever the explanation, transfusion of blood is a life-saving intervention and may obscure the role of anemia as a contributor to overall malaria mortality.

Neurologic features were unexpectedly common and inability to locate pain on admission was one of the strongest independent predictors of a fatal outcome. Seven percent of children fulfilled some definitions of coma9 and cerebral malaria.7 The etiology of coma in children with malaria is unclear. The pathophysiologic process behind the impaired consciousness in our children may be different from that described in malaria cases in other areas.21 There is a need...
to standardize the definition and specificity of the term cerebral malaria.

Contrary to classical teaching, our data suggest that children with poor nutritional status were at increased risk of dying once they are admitted with malaria. Edema and oral candidiasis, which are strongly associated with malnutrition, were independent predictors of death in older children. Although dehydration would reduce weight-for-age it would not affect height-for-age, which was associated with an increased risk of death in older children. Malnourished children were also more likely to be hypoglycemic, possibly reflecting a reduced gluconeogenic capacity, and were more likely to experience respiratory distress than their better nourished counterparts. The implications of these findings are considerable in a continent with high levels of both malaria and malnutrition.

Apart from identification and treatment of dehydration, our study has immediate implications for improved case management of malaria. Hypoglycemia, which was detected by Glucostix, was a common independent predictor of death. Thus, the lack of a well-equipped laboratory need not prevent assessment of this treatable complication. Hyperpyrexia and hyperparasitemia, which are supplementary criteria in the current WHO definition of severe malaria, were not associated with an adverse prognosis. Indeed, the risk of death was inversely related to body temperature and was not related to parasite density on admission. There are a number of possible explanations for this apparent lack of association between parasite density and risk of dying or risk of potentially life-saving transfusion. Prior home treatment with chloroquine may reduce parasite densities without fundamentally modifying the course of the disease, particularly in areas where drug resistance is endemic. Alternatively, severe malaria cases may have sequestered parasites in vital organs, reducing peripheral parasitemias at the same time as increasing the risk of death. Apart from the interest of considering the possible pathophysiologic mechanisms involved, these results call for reconsideration of the importance of parasite densities in guiding treatment and determining prognosis.

The definition of severe malaria in sub-Saharan Africa needs careful consideration. The current WHO criteria, developed in 1990, do not include respiratory distress or dehydration. Some included features are either rare in African children (jaundice, renal failure, pulmonary edema, disseminated intravascular coagulopathy, and macroscopic hemoglobinuria) or of questionable use as prognostic indicators (PCV < 15%, hyperparasitemia, and hyperpyrexia). Progress in understanding the epidemiology of malaria disease, assessing the efficacy of interventions, and improving case management will be facilitated by the development of criteria more applicable to African children, who bear the brunt of the world’s malaria mortality.

The relationship between intensity of transmission, clinical presentation, and malaria mortality has been poorly described to date. Based on few reports, it is widely believed that malaria has distinct presentations in different transmission settings. One comparison included data from the same hospital as our study and reported prevalences of severe anemia and cerebral malaria of 39% and 3%, respectively, compared with 8% and 7% in this study. These contrasting results are likely to be due to the lack of an adequate inpatient surveillance system at the time. The surveillance system for our study was first established in mid 1994 and was modeled closely on the system used in Kilifi (Kenya), which generated data for the only other detailed description of clinical malaria presenting to a hospital. Our study permits a true comparison of the clinical presentation of malaria and risk factors for death between the two sites. In the Kilifi study (seasonal transmission with an EIR of 0–69 bites per person per year), the prevalence of cerebral malaria was 10%, which was only marginally higher than the 7% we report from Ifakara. At the same time, the prevalence of severe anemia in Kilifi was 27%, which was three times higher than the 8% we report from the area of very high transmission. A similar prevalence of severe anemia (8.5%) has been reported from another area of intense perennial transmission in neighboring Malawi. Inherent weakness in the techniques to estimate the EIR, the lack of standardized definitions of intensity of transmission, the role of seasonality, health-seeking behavior, as well as the prevalence of malnutrition may account for the apparent lack of marked differences in the disease pattern between the two sites. On the other hand, it may be that the suggested clear-cut transmission-dependent differences in the clinical presentation of malaria may be considerably more complex than previously thought.

In conclusion, the relationship between clinical presentation of malaria and intensity of P. falciparum transmission needs to be more thoroughly investigated. Improved case management in a wide range of health facilities may result from adequate treatment of dehydration and simple tests to assess hypoglycemia. Clinicians, researchers, and children would all benefit from the development of criteria for the definition of severe malaria that are more relevant to African children. Transfusion-requiring anemia was an important presentation of malaria in our setting, a particularly pertinent finding in a continent where a significant proportion of children live beyond the reach of potentially life-saving blood transfusions. Against a background of a need for further work on the epidemiology of malaria disease, improved case management and the development of sustainable measures for the prevention of anemia are high and achievable priorities.

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REFERENCES