GAPS IN THE CHILDHOOD MALARIA BURDEN IN AFRICA: CEREBRAL MALARIA, NEUROLOGICAL SEQUELAE, ANEMIA, RESPIRATORY DISTRESS, HYPOGLYCEMIA, AND COMPLICATIONS OF PREGNANCY

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Abstract. Evaluations of the African childhood malaria burden do not fully quantify the contributions of cerebral malaria (CM), CM-associated neurological sequelae, malarial anemia, respiratory distress, hypoglycemia, and pregnancy-related complications. We estimated the impact of these malaria manifestations on members of the African population < 5 years old. Calculations were based on an extensive literature review that used National Library of Medicine search engines, other bibliographic sources, and demographic data. In sub-Saharan Africa, CM annually affects 575,000 children < 5 years of age and 110,000 (~19% case fatality rate [CFR]) die. Childhood survivors of CM experience developmental and behavioral impairments: each year, 9,000–19,000 children (> 2% of survivors of CM) < 5 years of age in Africa experience neurological complications lasting > 6 months. Severe malarial anemia heavily burdens hospitals with rising admission and CFRs and with treatments that are complicated by limited and sometimes contaminated blood supplies. Severe malarial anemia occurs 1.42–5.66 million times annually and kills 190,000–974,000 (> 13% CFR) children < 5 years of age annually. Respiratory distress, hypoglycemia, and overlapping clinical manifestations cause 1.12–1.99 million cases and > 225,000 (> 18% CFR) additional deaths among African children with malaria. Maternal, placental, or fetal malaria infection during pregnancy adversely affects development and survival of fetuses and newborns through low birth weight (LBW), maternal anemia, and possibly abortion and stillbirth. Between 167,000 and 967,000 cases of malaria-associated LBW occur yearly; malaria-induced LBW kills 62,000–363,000 (> 38% CFR) newborns each year. All the gaps in the burden comprise 0.4–1.7 million malaria deaths annually, > 50% of which are due to severe malarial anemia. These malaria-induced medical problems constitute major clinical, public health, and research challenges in that they may contribute to more than double the mortality than is generally acknowledged.

INTRODUCTION

Severe underreporting by patients and insufficient worldwide surveillance hampers epidemiological studies on the toll of malaria. The World Health Organization (WHO) estimates that malaria caused 300–500 million infections, 100 million clinical cases (Plasmodium falciparum), and 1.5–2.7 million deaths in 1994. More than 40% of the world’s population lives in the more than 100 countries with endemic malaria; populations in Africa, Latin America and the Caribbean, Southeast Asia, the Eastern Mediterranean, the Western Pacific, and parts of Europe experience malaria transmission. Despite gross underreporting, the majority of cases and deaths are estimated to occur in sub-Saharan Africa, especially in children < 5 years of age. The African malaria toll is difficult to quantify, and previous reports convey highly variable morbidity and mortality estimates (Table 1). Variability results from different estimation methods and from presumptive diagnoses that depend on often inaccurate febrile histories and clinical signs and symptoms without laboratory confirmation, and on estimates of transmission risks. With these qualifiers, WHO recognized that its mortality estimates could vary by a factor of 3. Except for one report focusing on Africa, specific manifestations are not detailed in reports on the overall malaria disease burden.

Malaria manifests in a variety of disease forms. Acute infections can lead to cerebral malaria (CM), anemia, respiratory distress, or hypoglycemia; acute CM infections sometimes have long-term neurological consequences. Repeated infections contribute to severe anemia. Malaria during pregnancy reduces birth weights and contributes to maternal, fetal, and infant mortality. Compared with CM, other forms of acute malaria, severe malarial anemia, perinatal manifestations, and long-term consequences of CM receive much less attention.

This analysis focuses on young African patients with malaria with cerebral manifestations and other conditions that require better understanding and clinical care. Yet many people experiencing these severe forms of malaria do not seek medical attention. By analyzing data from carefully defined studies and by accounting for patients that do not seek health care, these estimates help to more accurately represent the malaria burden in Africa.

MATERIALS AND METHODS

Literature in the National Library of Medicine was searched via PubMed and MEDLINE search engines. Research articles, reviews, books, and other reports published 1966–1999 were identified by key word searches. Key phrases included malaria epidemiology, malaria morbidity and mortality (acute, chronic/repeated, and perinatal), CM, postmalaria neurological sequelae, severe malarial anemia, respiratory distress, malaria hyperpneic syndrome, hypoglycemia, pregnancy-related malaria, and other variations. Bibliographies of reviews were browsed to identify additional articles, particularly those from WHO and United Nations sources and those published before 1966, when MEDLINE entries begin. The searches identified over 200 pertinent articles. From the collected reports, original scientific data and reliable demographic data were examined further and used in our calculations.

For increased focus, CM and neurological sequelae following CM, severe malarial anemia, respiratory distress, hy-
pnergency were studied. Morbidity and mortality of each manifestation in sub-Saharan African children were tabulated from incidence reports, prevalence estimates, and demographic findings. Data from articles on these forms of malaria were used to calculate the importance of each manifestation to the childhood malaria burden in Africa. Children aged 0–9 years were considered for CM because the database was collected in an area where this age range was at greatest risk; for all other manifestations, the focus is on children aged 0–4 years, the most susceptible group and the group at highest risk for mortality. Rates were computed by use of demographic data from the United Nations, other international sources, and unpublished data.

**RESULTS**

**Diagnoses and demographics.** Most patients with malaria who present to clinics have fever or history of fever. In regions where malaria is endemic, fever and other symptoms characterize and define acute malaria with or without laboratory confirmation. However, the usefulness of fever as a diagnostic symptom of malaria varies. Outside of clinical health centers, blood samples are not routinely taken; an estimated 30–60% of cases have parasites when actually confirmed. Most clinical cases result from *Plasmodium falciparum,* and parasite density and species are noted infrequently. The clinical condition is characterized frequently by coma, febrile illness with convulsions, and other neurological impairments. This manifestation is misdiagnosed when clinicians do not differentiate between malaria-induced altered consciousness and similar disorders caused by hyperpyrexia, anemia from viral hepatitis, respiratory complications due to pneumonia, psychosis, intoxications or infections such as bacteremia, meningitis, and tetanus. Up to 60% of fatal cases of CM are either misdiagnosed or receive a delayed diagnosis. Cognitive, behavioral, and sensory disorders in CM survivors are labeled collectively as postmalaria neurological sequelae.

The morbidity of CM was calculated by estimating its incidence in children and extrapolating such data to the childhood population in at-risk regions of sub-Saharan Africa. Brewer and others studied 377 probable patients with CM and 980 other pediatric admissions during 4 months in a Gambian hospital with a catchment of 128,000 children <10 years old. The Gambian data come from a region where malaria transmission is becoming unstable. Despite the changing endemicity, the study site received malaria risks projected by the mapping study’s climate suitability model to our mid-1998 population estimates and calculated that 116.6 million children <5 years old and 96.6 million aged 5–9 years live in sub-Saharan Africa. Of these children, 94.3 million aged <5 years and 77.8 million aged 5–9 years old lived in regions with stable malaria transmission in 1998.

**Cerebral malaria and postmalaria neurological sequelae.** Although CM has no fixed pathognomonic signs, the clinical condition is characterized frequently by coma, febrile illness with convulsions, and other neurological impairments. Most clinical cases result from *Plasmodium falciparum,* and parasite density and species are noted infrequently. The clinical condition is characterized frequently by coma, febrile illness with convulsions, and other neurological impairments. This manifestation is misdiagnosed when clinicians do not differentiate between malaria-induced altered consciousness and similar disorders caused by hyperpyrexia, anemia from viral hepatitis, respiratory complications due to pneumonia, psychosis, intoxications or infections such as bacteremia, meningitis, and tetanus. Up to 60% of fatal cases of CM are either misdiagnosed or receive a delayed diagnosis. Cognitive, behavioral, and sensory disorders in CM survivors are labeled collectively as postmalaria neurological sequelae.

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<table>
<thead>
<tr>
<th>Region</th>
<th>Study</th>
<th>Publication year</th>
<th>Clinical cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing world</td>
<td>Murray and Lopez[^2^]</td>
<td>1996</td>
<td>No data</td>
<td>856,000</td>
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<tr>
<td>World</td>
<td>Bruce-Chwatt[^4^]</td>
<td>1952</td>
<td>250 million</td>
<td>2.5 million</td>
</tr>
<tr>
<td>Africa</td>
<td>Breman and Campbell[^5^]</td>
<td>1988 (&lt;5 years)</td>
<td>No data</td>
<td>685,000</td>
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<tr>
<td>Africa</td>
<td>Bruce-Chwatt[^4^]</td>
<td>1952 (&lt;10 years)</td>
<td>No data</td>
<td>1 million</td>
</tr>
<tr>
<td>Africa</td>
<td>Stürchler[^4^]</td>
<td>1989</td>
<td>190.1 million</td>
<td>1.9 million</td>
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<tr>
<td>Africa</td>
<td>Brinkmann and Brinkmann[^7^]</td>
<td>1991</td>
<td>189 million</td>
<td>No data</td>
</tr>
<tr>
<td>Africa</td>
<td>Baudon and others[^8^]</td>
<td>1987</td>
<td>35 million</td>
<td>No data</td>
</tr>
</tbody>
</table>

[^2^]: From all species of malaria; other estimates reflect mostly *Plasmodium falciparum.*
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Figure 1. Case fatality rate (CFR) in 35 studies of cerebral malaria in African children. The number of enrolled patients with cerebral malaria (CM) in each study is indicated on the x-axis. The open square (± 1 standard deviation) represents the weighted mean fatality rate of childhood cerebral malaria in African health clinics (pooled n = 3,275).

Figure 2. Prevalence of postmalaria neurological sequelae (PMNS) in survivors of cerebral malaria (CM) < 5 years old. Gray bars represent prevalence of sequelae at hospital discharge and black bars at 1–6 months after discharge. Data from 4 individual studies are plotted; the final entry on the right was calculated from the population-weighted means of these sub-Saharan Africa (SSA) studies. The numbers of patients, examined at hospital discharge and at follow-up, are listed in parentheses, respectively.
hemoglobin < 50 g/L or hematocrit < 15%. Mild or severe anemia accompanied by *P. falciparum* infection is designated uncomplicated and severe malarial anemia, respectively. However, the connection between malaria and anemia is difficult to define because some people experience parasitemia in the absence of malarial disease, whereas others become anemic as parasites are cleared.9 Differential diagnosis of malarial anemia is also difficult because malnutrition, hemoglobinopathies, and other common disorders contribute to anemia in Africa.9,61

We determined the hospital admission rate of severe malarial anemia, estimated the actual incidence of disease, calculated the average case fatality, and extrapolated these figures to describe morbidity and mortality of severe malarial anemia in sub-Saharan African children. In the study by Snow and others, the annual admission rate for severe malarial anemia was 7.6 per 1,000 children within 15 km of hospitals. In a 1990–1992 study of health clinics in rural Malawi, the annual admission rate for this condition was 54.7 per 1,000 children < 5 years old; in urban areas, the rate dropped to 5.3 per 1,000 children.62 Less than one quarter of all people with malaria visit health clinics; however, those with severe malarial anemia are more likely to seek attention.7 We doubled the severe malarial anemia admission rate used by Snow and others to minimally estimate the true incidence in clinics and homes. For children < 5 years old, we propose that the overall incidence of severe malarial anemia in different transmission zones of sub-Saharan Africa. 7-62

We adjusted the incidence of CM (derived previously as 6.1 cases of CM per 1,000 children aged < 5 years) to reflect the proportional incidence of respiratory distress (8.4 respiratory distress cases per 1,000 children aged < 5 years) and hypoglycemia (8.1 cases of hypoglycemia per 1,000 children aged < 5 years). As with CM, one third of these estimates specify people who do not reach health clinics. We did not calculate the incidence for children aged 5–9 years because respiratory distress affects children significantly younger than for CM (mean ages 19 versus 35 months, respectively).66 Case fatality among children with malaria with respiratory distress was 13.9% (n = 251); this mortality was calculated as 1.2 deaths per 1,000 children < 5 years old. Twenty to thirty percent of pediatric malaria admissions with hypoglycemia die (n = 925,26,41,66); the hypoglycemia CFR is estimated to be 1.6–2.8 deaths per 1,000 children < 5 years old.

**Malaria and pregnancy.** During pregnancy, malaria infections of the mother, the placenta, and the fetus adversely affect fetal and newborn survival, especially through low birth weight (LBW; delivery weight < 2,500 g). Maternal malaria is reported during pregnancy if clinical signs and symptoms reflect infection or if parasitemia is demonstrated in peripheral maternal blood.71,72 Fetal infection is detected by placental or umbilical cord-blood parasitemia.72,73 In Africa, many pregnant women are parasitic, particularly *Plasmodium vivax* and *Plasmodium falciparum*. In studies as part of the Africa Child Survival Initiative–Combating Childhood Communicable Diseases (ACSI-CCCD) project that took place in an endemic region of rural Malawi, peripheral parasitemia was detected in 45% of pregnant women before delivery (n = 4,127).74 At delivery, there is a parasite concentration-dependent correlation between maternal peripheral blood parasitemia, placental, and umbilical cord-blood (fetal) parasitemia.72 Parasites were detected at delivery in 16% of ACSI-CCCD maternal peripheral blood samples (n = 1,790), 21% of placental blood samples (n = 1,743), and 7% of umbilical cord-blood samples (n = 1,743).73

The incidence of malaria-induced LBW was derived from

![Figure 3](image-url)
demographic data and several independent reports on malaria during pregnancy. On the basis of meta-analysis by Kramer, LBW accompanies 5–20% of African births. In 4 studies of pregnant women in prenatal health clinics, 12% (range, 5–50%) of LBW deliveries in sub-Saharan Africa were related to malaria. From the mean African birth rate (41 per 1,000 total people) and the prevalence of LBW and malaria-associated LBW, we estimate that malaria-associated LBW occurs in 7.8–45.3 of every 1,000 live births.

Mortality risks are high for LBW newborns: infants born with LBW are 40 times more likely to die during the first month than babies with normal birth weight; mortality risks remain 10 times higher than those of normal birth weight infants during months 1–11. On the basis of relative mortality risks, we estimate that the fatality rate of newborns with malaria-related LBW is 37.5%. At this degree of case fatality and with the current birth rate, 3–17 deaths occur per 1,000 live births from malaria-induced LBW annually.

Adjustments for multiple manifestations. In some patients, combined malaria manifestations are present and calculations of the contribution of each manifestation can be arbitrary. Hypoglycemia is present in 10–20% of patients with CM. Among children with severe malaria anemia, 10.4% (n = 508) were also diagnosed with respiratory distress, and 5.5% (n = 508) showed signs and symptoms of CM. Of children with respiratory distress, half (n = 251) were defined as severe (documented chest recession or abnormal deep breathing); half of the patients with severe respiratory distress also had impaired consciousness (n = 133). Some patients with nonevasive respiratory distress are likely to have impaired consciousness, but these data are lacking. Therefore, at least one quarter of children with malaria who have any form of respiratory distress also have impaired consciousness. Because more than half of all patients with impaired consciousness fit the CM definition (n = 330), we assumed that half the patients with combined respiratory distress and impaired consciousness have CM. This implies that > 12% of cases of respiratory distress in children overlap with CM. With these data, we estimated the incidence of each manifestation (annual cases per 1,000 children < 5 years old in at-risk regions) as follows: CM alone, 0.9–3.5; severe malarial anemia alone, 1.2–5.0; respiratory distress alone, 1.4–5.4; and hypoglycemia alone, 6.9–7.5.

Table 2

<table>
<thead>
<tr>
<th>Malaria manifestations*</th>
<th>Incidence per 1,000 child-years</th>
<th>CFR (%)</th>
<th>Mortality (deaths per 1,000 child-years)</th>
<th>Total morbidity (no. cases)</th>
<th>Total mortality (no. deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM total†</td>
<td>6.1</td>
<td>19.2</td>
<td>1.2</td>
<td>575,000</td>
<td>110,000</td>
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<tr>
<td>Neurological sequelae &lt; 6 months</td>
<td>0.5–0.8</td>
<td>No data</td>
<td>No data</td>
<td>47,000–75,000</td>
<td>No data</td>
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<td>Neurological sequelae &gt; 6 months</td>
<td>0.1–0.2</td>
<td>No data</td>
<td>No data</td>
<td>9,000–19,000</td>
<td>No data</td>
</tr>
<tr>
<td>Severe malarial anemia total†</td>
<td>15–60</td>
<td>13.4–17.2</td>
<td>2.0–10.3</td>
<td>1,42,566 million</td>
<td>190,000–974,000</td>
</tr>
<tr>
<td>Respiratory distress total†</td>
<td>8.4</td>
<td>13.9</td>
<td>1.2</td>
<td>792,000</td>
<td>110,000</td>
</tr>
<tr>
<td>Hypoglycemia total†</td>
<td>8.1</td>
<td>20–35</td>
<td>1.6–2.8</td>
<td>764,000</td>
<td>153,000–267,000</td>
</tr>
<tr>
<td>CM alone</td>
<td>0.9–3.5</td>
<td>16–18</td>
<td>0.1–0.6</td>
<td>85,000–330,000</td>
<td>14,000–59,000</td>
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<td>Severe malarial anemia alone</td>
<td>12–50</td>
<td>11.7–16.6</td>
<td>1.4–8.3</td>
<td>132,000–783,000</td>
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<td>Respiratory distress alone</td>
<td>1.4–5.4</td>
<td>10–12</td>
<td>0.1–0.6</td>
<td>132,000–509,000</td>
<td>13,000–61,000</td>
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<td>Hypoglycemia alone</td>
<td>6.9–7.5</td>
<td>20–35</td>
<td>1.4–2.2</td>
<td>651,000–708,000</td>
<td>130,000–208,000</td>
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<tr>
<td>CM and severe malarial anemia</td>
<td>1–3</td>
<td>18–20</td>
<td>0.2–0.6</td>
<td>94,000–283,000</td>
<td>17,000–57,000</td>
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<td>CM and respiratory distress</td>
<td>1.0</td>
<td>20–35</td>
<td>0.2–0.4</td>
<td>94,000</td>
<td>19,000–33,000</td>
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<tr>
<td>CM and hypoglycemia</td>
<td>0.6–1.2</td>
<td>30–50</td>
<td>0.2–0.6</td>
<td>57,000–113,000</td>
<td>11,000–40,000</td>
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<td>Severe malarial anemia and respiratory distress</td>
<td>2–6</td>
<td>17.5–22.5</td>
<td>0.4–1.4</td>
<td>189,000–566,000</td>
<td>33,000–127,000</td>
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<tr>
<td>Malaria-associated LBW</td>
<td>8–45 of 1,000</td>
<td>37.5</td>
<td>3–17</td>
<td>167,000–967,000</td>
<td>62,000–363,000</td>
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<tr>
<td>live births</td>
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<td></td>
<td></td>
<td>live births</td>
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<tr>
<td>Total of listed manifestations</td>
<td>34.2–123.9</td>
<td>No data</td>
<td>6.9–31.7</td>
<td>2.7–8.4 million</td>
<td>0.4–1.7 million</td>
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<tr>
<td>(25.2–78.9)</td>
<td></td>
<td></td>
<td>(4.0–14.7)</td>
<td>(2.5–7.4 million)</td>
<td>(0.4–1.4 million)</td>
</tr>
<tr>
<td>All malarial febrile episodes</td>
<td>1,600–5,400</td>
<td>0.2–1.5</td>
<td>9.4–24.0</td>
<td>150.9–509.4 million</td>
<td>0.9–2.3 million</td>
</tr>
</tbody>
</table>

* CM = cerebral malaria; LBW = low birth weight.
† Estimates listed as “total” include all cases, including those from overlapping conditions.
Data in parentheses do not include malaria-induced LBW.

We acknowledge the contribution of each manifestation can be arbitrary. Hypoglycemia is present in 10–20% of patients with CM. Among children with severe malaria anemia, 10.4% (n = 508) were also diagnosed with respiratory distress, and 5.5% (n = 508) showed signs and symptoms of CM. Of children with respiratory distress, half (n = 251) were defined as severe (documented chest recession or abnormal deep breathing); half of the patients with severe respiratory distress also had impaired consciousness (n = 133). Some patients with nonevasive respiratory distress are likely to have impaired consciousness, but these data are lacking. Therefore, at least one quarter of children with malaria who have any form of respiratory distress also have impaired consciousness. Because more than half of all patients with impaired consciousness fit the CM definition (n = 330), we assumed that half the patients with combined respiratory distress and impaired consciousness have CM. This implies that > 12% of cases of respiratory distress in children overlap with CM. With these data, we estimated the incidence of each manifestation (annual cases per 1,000 children < 5 years old in at-risk regions) as follows: CM alone, 0.9–3.5; severe malarial anemia alone, 1.2–5.0; respiratory distress alone, 1.4–5.4; and hypoglycemia alone, 6.9–7.5; CM and severe malarial anemia, 1–3; CM and respiratory distress, 1.0; CM and hypoglycemia, 0.6–1.2; and severe malarial anemia and respiratory distress, 2–6 (Table 2).

These overlapping conditions lead to high mortality. Case fatality of children with combined severe malarial anemia and CM is similar to overall CM fatality rates; for this combination, we use a CFR range of 18–20%. For patients with impaired consciousness and severe respiratory distress, case fatality was 31.7% (n = 63). However, if restricted to CM and respiratory distress (severe and noneverse), we estimate that case fatality ranges 20–35%. Patients with CM and hypoglycemia have an especially poor prognosis: in Malawi, case fatality was as high as 66% (n = 15). We made a conservative estimate that case fatality of combined CM and hypoglycemia varies from 30–50%. In patients with combined respiratory distress and severe malarial anemia, blood transfusions limit fatality rates to levels similar to either condition alone. However, people outside of health centers do not benefit from life-saving transfusions. To account for this difference, we increased the CFR of combined severe malarial anemia and respiratory distress to 17.5–22.5%. The high fatality rates of combined conditions may skew mortality estimates that use unadjusted rates. To make corrections for singular manifestations, fatality rates were reduced as follows: CM alone (CFR 16–18%); severe malarial anemia alone (CFR 11.7–16.6%); and respiratory distress alone (CFR 10–12%). The mortality rates for each con-
The toll of each manifestation on the entire at-risk child population was calculated from the incidence of febrile episodes in children. Four to nine annual febrile episodes occur in children aged <5 years; each year, 377.3–849.0 million febrile episodes occur in children aged <5 years. Malaria is associated with 30–60% of all fevers. We calculated that the annual incidence of malaria febrile episodes is 1.6–5.4 per African child <5 years old; at this level, 150.9–509.4 million febrile malaria episodes occur in at-risk children each year.

Febrile malaria illnesses are a major source of hospital admissions in sub-Saharan Africa. From previous reports, we determined that the annual hospital admission rate for children <5 years presenting with malaria or febrile episodes is 31 per 1,000 children; this rate suggests that 2.9 million children with malaria are admitted to clinics in endemic areas each year. Because only 8–25% of patients with malaria actually visit clinics and 20–90% of febrile episodes are treated with antimalarial therapy, mortality varies. Analysis of data from 2 hospital-based studies of malaria mortality and one malaria mapping report suggests that malaria causes 9.4–24 annual deaths per 1,000 children <5 years old in Africa (overall CFR 0.2–1.5%). On the basis of the incidence of malarial febrile episodes and mortality, 890,000 to 2.26 million annual childhood deaths result from all forms of malaria in sub-Saharan areas with endemic transmission.

The toll of each manifestation on the entire at-risk child population in Africa was measured from the incidence and fatality estimates (Table 2). Each year, CM affects 575,000 children <5 years old. On the basis of the incidence of CM, the CM survival rate (80.8%; n = 3,27522–24,27–48), the prevalence of sequelae among childhood survivors of CM and the percentage of sequelae that persist, 47,000–75,000 patients <5 years old experience some neurological impairment associated with CM during or after their hospital stays; 9,000–19,000 children <5 years old have persistent neurological problems for at least 6 months after hospital discharge. Severe malarial anemia occurs in 1.42–5.66 million children <5 years old annually; most cases occur in East and West Africa (Figure 4). Approximately 792,000 children with malaria <5 years old develop respiratory distress yearly; 764,000 children with malaria are diagnosed with hypoglycemia. Some children <5 years old experience overlapping conditions (Table 2): there are 94,000–283,000 cases of combined CM and severe malarial anemia, 94,000 cases of CM with respiratory distress, 57,000–113,000 cases of CM and hypoglycemia, and 189,000–566,000 cases of combined severe malarial anemia and respiratory distress. The impact of malaria-induced LBW was deduced from the total number of live births. The mean birth rate for sub-Saharan Africa (41 per 1,000 total people48) and total at-risk population (520.9 million) indicate that 21.4 million births occurred in at-risk regions in 1998. On the basis of our incidence estimates for these regions, malaria leads to 167,000–967,000 LBW deliveries annually. Each year, the combination of the malaria manifestations studied herein contributes 2.7–8.4 million serious malaria complications.

The targeted manifestations contribute a large percentage of annual malaria mortality in African children <5 years old (Table 2). Cerebral malaria and respiratory distress cause 110,000 deaths each; severe malarial anemia kills 190,000–974,000 (Figure 4); hypoglycemia claims 153,000–267,000 children. The contributions of each of these severe manifestations to the gaps in the childhood malaria burden are shown in Figures 5 and 6. Of the 8.76 million maximum such events that occur yearly, almost two thirds are due to severe malarial anemia; >50% of the 1.82 million deaths

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**Figure 4.** Extrapolated morbidity and mortality of severe malarial anemia in children <5 years old in different geographic regions of sub-Saharan Africa. Gray bars represent cases; black bars represent deaths. Ranges are indicated with bars.
area also caused by severe malarial anemia. Many fatalities are associated with combined manifestations: 17,000–57,000 annual deaths in children < 5 years old in Africa are caused by CM coupled with severe malarial anemia; 19,000–33,000 deaths are due to combined CM and respiratory distress; 11,000–40,000 deaths are from CM and hypoglycemia; 33,000–127,000 deaths occur from a combination of severe malarial anemia and respiratory distress. Malaria-induced LBW deliveries result in 62,000–363,000 newborn deaths per year. In total, the malaria manifestations described here are responsible for 437,000 to 1.75 million annual deaths in children < 5 years old.

DISCUSSION

These estimates clarify more fully the contribution of CM and associated neurological sequelae, severe malarial anemia, respiratory distress, hypoglycemia, and complications of pregnancy to the toll of malaria. We estimated the baseline level of malaria cases and deaths, compared our findings with previous estimates, and calculated the mortality of specific malaria manifestations. Our baseline estimates of overall malaria mortality in African children < 5 years old compare similarly to previous estimates: 890,000 to 2.26 million malaria-attributable deaths versus the WHO estimate of 1.35–2.43 million deaths. To gauge manifestation-specific mortality, we compared each complication to the estimate of overall malaria mortality (median, 1.58 million; range, 0.89–2.26 million deaths); we used the median of the range for these comparisons. Each manifestation contributes variably to the malaria mortality: CM, 7%; respiratory distress, 7%; hypoglycemia, 13%; malaria-induced LBW, 14%; and severe malarial anemia, 37%. When adjusted for overlapping conditions (e.g., CM with severe malarial anemia), these manifestations of severe malaria lead to 69% of all malaria mortality in African children (range, 49.3–77.2%). Mortality from CM, severe malarial anemia, respiratory distress, hypoglycemia, combinations of manifestations, and malaria-related LBW account for 18–125% of mortality estimated by WHO. Our estimates do not include epidemic cases and deaths, yet the malaria manifestations examined here for children < 5 years old may contribute more than double the mortality than is generally acknowledged for endemic and epidemic deaths combined. When older children and adults are included the combination of endemic and epidemic malaria, deaths may greatly exceed existing estimates.

The major and most ominous manifestations of severe malaria in African children are CM, severe malarial anemia, respiratory distress (malaria hyperpneic syndrome), and hypoglycemia; patients with these conditions represent most of the severely ill malarious child population. Coupled with LBW newborns, these conditions are associated with most of malaria-related fatalities. In addition to mortality, the morbidity of these forms of malaria are significant.

Despite high case fatality, CM is not a major source of childhood deaths; this condition causes < 12.4% of malaria mortality in children aged < 5 years in Africa. However, the disability caused by CM is extremely important. Neurological sequelae stemming from CM were recognized > 40 years ago, yet their importance to the toll of malaria is not discussed in most estimates. Although only a small percentage of patients with CM experience these disorders, the severity and duration of neurological manifestations significantly affect children, their caretakers, and the social and economic fabric of their communities. In this review, there was a time-dependent trend with regard to neurological sequelae: studies conducted during 1990–1994 reported higher levels of sequelae (14.3%; 95% CI, 5.9–22.7;43,44,46–48,50–54,56,57) than studies conducted during 1962–1977 (8.0%; 95% CI, 0.0–16.0);39 and 1980–1989 (10.6%; 95% CI, 4.8–16.3).22,24,37,38,41,42. Are these sequelae increasing? Although not significant at 95% confidence, these analyses of CM and neurological sequelae might reflect a gradually improving diagnostic awareness amongst physicians and investigators, increased follow-up and referral, or more virulent falciparum parasites.

Alternatively, if the trend becomes more pronounced, the increase might reflect rising drug resistance. Certainly, the frequency of chloroquine treatment failures has increased, and fatality rates have risen. The behavioral and cognitive implications of neurological sequelae are poorly understood.
British children who had febrile convulsions during childhood showed no academic or behavioral deficiencies at age 10 years, whereas Finnish children with epileptic seizures had increased risks for social and educational problems as adults. Similar long-term studies have not been performed in Africa, where psychological and psychiatric facilities are less available and standardized evaluations for African populations have not been developed or used. The substantial needs of African children with CM-induced neurological disabilities such as cortical blindness, deafness, cerebral palsy, and hemiplegia may not be fulfilled in the home or local health clinic. Residual impairments including learning disabilities adversely affect educational and work-related achievements, and longitudinal studies are urgently needed to assess these unresolved complications in children.

Hundreds of thousands of children experience respiratory distress, hypoglycemia, and combinations of these and other conditions during bouts of malaria. The contributions of these particular disorders to the toll of malaria are poorly understood. In African children, respiratory distress manifests through systemic acidosis; the condition has been termed malaria hyperpneic syndrome. Only 2 reports discuss this form of respiratory distress specifically, although metabolic acidosis is reported in many patients with malaria. Hypoglycemia is observed in many patients with and without malaria. In African children, hypoglycemia manifests before treatment, rather than after quinine therapy, as is the case for adults. Respiratory distress and hypoglycemia cause >100,000 deaths annually. In combination with other malaria manifestations, especially CM and hypoglycemia, these conditions lead to extremely high case fatality. Future studies should carefully examine and follow malaria patients with respiratory distress or hypoglycemia.

We calculated a wide morbidity range for severe malarial anemia in children in endemic regions on the basis of a risk-stratified review of clinical reports. At its minimum, this range likely reflects actual hospital admissions; at the maximum, it may represent the true prevalence of malaria-associated severe anemia in clinics and homes. Falciparum malaria is the primary cause of such anemia, although Plasmodium vivax infections in the Americas and Asia may contribute through repetition and malnutrition. Severe malarial anemia is responsible for a large portion of hospital admissions; however, most cases occur outside health centers. Our estimates are based primarily on clinical studies of anemia where patients with severe conditions could receive blood transfusions. Life-saving transfusions are generally not available to victims treated at home, and, where available in clinics, transfusions pose serious risks from blood-borne pathogens.

Studies on treatments for severe malarial anemia highlight the difficulties of assessing the effect of malaria on non-malarial infections and other conditions. The most important problem of this type in Africa is infection with the human immunodeficiency virus type 1 (HIV-1), which may complicate malaria infection. HIV-1 infection reduces women’s immunological abilities to limit malaria infection during pregnancy. Placental malaria infection may also increase the risk of perinatal HIV-1 transmission. Transfusion risks for severely anemic malaria patients are hampered by HIV-1–contaminated blood and plasma. Transfusions pose serious HIV-1 and other blood-borne infection risks; such risks are not well quantified. The prevalence of HIV-1–contaminated blood varies enormously: 0.5–20.0% of transfused blood in sub-Saharan Africa may contain HIV-1; and up to 70% of hospitalized children with anemia receive blood transfusions in Africa. The high risk of acquiring HIV-1 through blood transfusion must be weighed against the mortality risk of severe anemia for these children. Potential treatment risks such as these need further investigation to better ensure the health of all African patients.

In addition to childhood morbidity and mortality, malaria-associated LBW affects the newborn population. Although LBW is the most important cause of mortality for malign-associated pregnancies, other complications may contribute to morbidity and mortality of mothers, fetuses, and newborns. Maternal malaria contributes to maternal morbidity, especially in primigravidae, through hypoglycemia and anemia. A relationship between malaria during pregnancy and stillbirth or abortion is suspected but has not been definitively proven, particularly in Africa. In any case, mortality from malaria-induced LBW is an important characteristic of the toll of malaria, one that has not been included in previous estimates. Our findings suggest that at least 13% of malaria mortality in African children <5 years old is due to this complication.

The toll of malaria in epidemic risk areas is highly variable; our analysis does not reflect the impact of malaria epidemics. A recent study identified 15 reports that detail epidemic-related morbidity and mortality. Epidemics affect people with partial immunity in the eastern African highlands and the Horn of Africa, and those with virtually no immunity in southern and eastern Africa. We did not examine populations aged >5 years; an exception was made for patients with CM aged 5–9 years because a study in The Gambia found the mean age of patients with CM to be twice that of severe anemia patients. Other manifestations of malaria (e.g., acute renal failure and pulmonary edema) were not investigated because they do not occur in African children with the frequency that they do in adults. Our analysis concentrates on populations in endemic regions (80.9% of the sub-Saharan population), and we identified relatively high morbidity and mortality in moderate- to high-risk areas. Because malaria morbidity in older age groups declines at high levels of transmission intensity, lower transmission regions are likely to account for much disease and death as well.

Because of the important malaria burden in Africa, each manifestation warrants the attention of bench scientists, clinicians, epidemiologists, public health workers, and funding agencies. Rising drug resistance and the burgeoning HIV and acquired immunodeficiency syndrome epidemic compound the complexities of treating malaria patients with antimalarial drugs and blood transfusions. Because early detection and treatment of malaria reduce morbidity and mortality, new and improved diagnostics, surveillance, and disease management practices and interventions are necessary. As data are accrued, there will be more precise estimations of both malaria’s burden and the impact of improved and new methods used to reduce each manifestation, allowing the gap to be closed.
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