THE BURDEN OF MALARIA IN PREGNANCY IN MALARIA-ENDEMIC AREAS

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Abstract. Pregnant women in malarious areas may experience a variety of adverse consequences from malaria infection including maternal anemia, placental accumulation of parasites, low birth weight (LBW) from prematurity and intrauterine growth retardation (IUGR), fetal parasite exposure and congenital infection, and infant mortality (IM) linked to preterm-LBW and IUGR-LBW. We reviewed studies between 1985 and 2000 and summarized the malaria population attributable risk (PAR) that accounts for both the prevalence of the risk factors in the population and the magnitude of the associated risk for anemia, LBW, and IM. Consequences from anemia and human immunodeficiency virus infection in these studies were also considered. Population attributable risks were substantial: malaria was associated with anemia (PAR range = 3–15%), LBW (8–14%), preterm-LBW (8–36%), IUGR-LBW (13–70%), and IM (3–8%). Human immunodeficiency virus was associated with anemia (PAR range = 12–14%), LBW (11–38%), and direct transmission in 20–40% of newborns, with direct mortality consequences. Maternal anemia was associated with LBW (PAR range = 7–18%), and fetal anemia was associated with increased IM (PAR not available). We estimate that each year 75,000 to 200,000 infant deaths are associated with malaria infection in pregnancy. The failure to apply known effective antimalarial interventions through antenatal programs continues to contribute substantially to infant deaths globally.

INTRODUCTION

The problem of malaria infection in pregnant women was initially described nearly 65 yr ago.1 Descriptive studies in sub-Saharan Africa from the 1950s through 1984 focused on Plasmodium falciparum infections and described the frequency of placental infection and specific adverse consequences.2–7 Relatively few population-based studies have been reported from Asia or the Americas, and where studies do exist, most have focused on high-transmission areas and infections with P. falciparum.8 Infection rates have been consistently demonstrated to be highest in women in their first and second pregnancies, with lower rates in later pregnancies.9–20 Because of high rates of parasitemia in pregnancy, particularly in many settings in sub-Saharan Africa, the World Health Organization has recommended presumptive malarial treatment followed by additional prevention measures during pregnancy.11 Plasmodium falciparum infection in pregnancy leads to parasite sequestration in the maternal placental vascular space, with consequent maternal anemia12,13,15 and infant low birth weight (LBW)9,10,14–17 due to both prematurity15,17 and intrauterine growth retardation (IUGR).4,14,15,17 LBW is known to be the most important risk factor for infant mortality.18,19 Anemia, undernutrition, and human immunodeficiency virus (HIV) infection are also common events in malarious areas and contribute to LBW. Malaria infection in pregnancy may lead to anemia in pregnancy, and HIV infection in pregnancy confers additional risk for higher frequency and higher density of malaria during pregnancy;20 thus, these conditions are integrally linked, and P. falciparum is not the only cause of LBW in these malaria-endemic settings.21,22 Low birth weight is also associated with newborn gender (more common in girls), maternal stature (more common in shorter and smaller women), and birth order (more common in first or low-birth-order pregnancies); however, these characteristics cannot be changed and are not amenable to interventions once a pregnancy has begun.

In the next year, an estimated more than 50 million pregnancies will occur in malaria-endemic areas, and approximately half of these will be in sub-Saharan Africa, where P. falciparum transmission is most intense.21 To assess the magnitude of the burden of malaria in pregnancy and its contribution to infant mortality, we evaluated data from published and unpublished studies during the last 15 yr (1985–2000) and focused on sub-Saharan Africa, where data are most available. Because of the multiple pathways for the chain of events between maternal malaria infection and infant mortality, we specifically sought studies that evaluated malaria, anemia, and HIV infection and their contribution to low birth weight and potentially to infant mortality. There is a paucity of population-based data on malaria in pregnancy in settings of low malaria endemicity. Because malaria exposure in pregnancy is much less common in these lower-endemicity settings and may be caused by nonfalciparum species, which are thought to have less impact on the pregnancy, the burden of malaria in pregnancy in these other settings is likely to be relatively lower. However, because of our focus on the higher-endemicity settings, the estimates obtained from our review likely underestimate the total global burden of malaria infection in pregnancy.

METHODS

Data review. We reviewed studies reported between 1985 and 2000 in which information was available on malaria infection in pregnancy; associated conditions (e.g., anemia, HIV infection); and/or adverse outcomes of pregnancy, including low birth weight, prematurity, and infant mortality.10,13–17,20,22–4 We conducted a literature search using MEDLINE, cross-referencing the following terms: 1) malaria or falciparum malaria, 2) pregnancy, pregnancy complications, or pregnancy complications infectious, 3) HIV or HIV-1, and 4) anemia. For the designated years of 1985–2000, this review yielded 789 articles for categories 1+2, 98 articles for categories 1+2+3, and 15 articles for categories 1+2+3+4. Only articles written in English were reviewed. Because the search did
not identify certain articles that were known to us, we used references from selected articles to identify additional published literature for review. We also reviewed unpublished data from large studies for which published information was not yet available (for studies in Mali, Fansi M, unpublished data; for studies in Kenya, ter Kuile F, unpublished data).

To be considered for incorporation in the final review, articles had to provide information on the frequency or prevalence of outcomes and risk factors and information on risk estimates, preferably from multivariate analysis for associations between multiple purported risk factors and outcomes. We focused on outcomes of maternal malaria infection (peripheral or placental infection), maternal anemia, LBW, preterm-LBW, IUGR-LBW, and infant mortality. When possible, we examined the contributions of *Plasmodium falciparum* malaria, anemia, and HIV to these adverse outcomes, both because each condition likely affects the others and because the evaluation allowed for relative comparisons of their impact on infant mortality, either directly (with HIV infection in the newborn) or through the contribution to preterm-LBW or IUGR-LBW. Maternal malaria infection and anemia were considered as risk factors and as outcomes in these analyses, because HIV may contribute to increased risk for malaria and malaria may contribute to increased risk of anemia. Only 2 study settings reported on the full sequence of events (e.g., malaria → LBW → infant mortality); however, because the infant mortality risk associated with LBW is described in a variety of populations around the world, we assumed that contributors to LBW were linked to subsequent infant mortality.

We used reported risk estimates (either risk ratios or odds ratios) and prevalence of the risk factor in the population to determine population attributable risk (PAR), sometimes referred to as the etiologic fraction, or that proportion of all associations were observed. The prevalence of the condition likely affected the others and because the evaluation allowed for relative comparisons of their impact on infant mortality, either directly (with HIV infection in the newborn) or through the contribution to preterm-LBW or IUGR-LBW. Maternal malaria infection and anemia were considered as risk factors and as outcomes in these analyses, because HIV may contribute to increased risk for malaria and malaria may contribute to increased risk of anemia. Only 2 study settings reported on the full sequence of events (e.g., malaria → LBW → infant mortality); however, because the infant mortality risk associated with LBW is described in a variety of populations around the world, we assumed that contributors to LBW were linked to subsequent infant mortality.

We used reported risk estimates (either risk ratios or odds ratios) and prevalence of the risk factor in the population to
determine population attributable risk (PAR), sometimes referred to as the etiologic fraction, or that proportion of all events (e.g., LBW, infant death) that are associated with the factor of interest (e.g., malaria, anemia, or HIV). A standard formula was used to calculate PAR:

\[ PAR = \frac{p(RR - 1)}{1 + p(RR - 1)} \]

where *p* is the prevalence of the risk factor, and *RR* is the risk estimate. The review of the articles suggested that there were sufficient differences in the geographic settings and in the prevalence of malaria, anemia, and HIV that a formal meta-analysis was not appropriate. Instead, we present ranges of the prevalence of the risk factors and ranges of the PAR estimates simply to understand the relative magnitude of the problem of malaria in pregnancy and its associated conditions.

Finally, we evaluated studies of interventions and the estimates of efficacy for interventions, examining the impact of “failing to use existing effective interventions” as a risk factor for the burden of malaria, LBW, and infant mortality. Because malaria prevention in pregnancy is not widely implemented and because few studies report on the actual implementation of interventions, we report an upper limit of this PAR by assuming that the prevalence of the risk factor (i.e., “not receiving the intervention”) was 90% in these populations.

### RESULTS

A total of 34 reports were considered for this review (Table 1). These reports came from 25 investigations in 8 sub-Saharan African countries (Kenya = 6 investigations; Malawi = 5; Tanzania = 3; Gambia = 2; Burkina Faso = 1; Cameroon = 1; Mali = 1; Mozambique = 1; and Uganda = 1) and 2 non-African settings (Papua New Guinea = 2 investigations; Thailand = 2). As seen in Table 1, the study group sizes ranged from 159 to greater than 10,000 persons, and endemicity varied as seen by variations in maternal parasitemia rates between 6% in urban Mozambique and 65% in Tanzania. Additionally, the categorization of variables ranged widely, as demonstrated by the variable criteria for anemia (any, mild or moderate, or severe). Finally, 12 studies were largely observational but may have reported on the effect of interventions, whereas 13 studies involved intervention trials.

### Malaria. *Plasmodium falciparum* malaria in pregnancy appeared to contribute to anemia and LBW through both preterm-LBW and IUGR-LBW in a relatively consistent fashion across different studies and settings (Table 2). The prevalence of malaria infection in pregnancy ranged from approximately 10% to 65% across the settings where these associations were observed. The prevalence of the conditions of severe anemia, LBW, preterm-LBW, and IUGR-LBW; the risk estimates from various studies; and the PAR for malaria’s contribution to these conditions are shown in Table 2. Estimates of malaria’s contribution to LBW were modest and consistent across studies—accounting for approximately 8–14% of LBW and IUGR-LBW and approximately 8–36% of preterm LBW.

From 2 studies, maternal malaria was estimated to contribute to 3–8% of infant mortality. One study provided a much higher PAR estimate (30%) for infant mortality caused by maternal malaria infection, but this was an ecologic comparison between very different communities, and unmeasured contributions to infant mortality may have biased this estimate.

### Anemia. Maternal anemia during pregnancy, associated with maternal malaria or many other causes, ranged in prevalence from 2–30% (based on differing cutoffs for hemoglobin levels; see review by Guyatt and Snow). Table 3 shows risk estimates and PAR estimates for maternal anemia and LBW, IUGR-LBW, and infant mortality. Maternal anemia appears to contribute to a PAR ranging from 7% to 18% for LBW and less than 48% for IUGR-LBW. Published studies did not describe relative contributions to preterm-LBW, and one indirect estimate suggested that maternal anemia may contribute to approximately one-fourth of infant mortality.

### HIV. Maternal HIV infection has been shown to contribute to maternal malaria, maternal anemia, LBW, and direct infection of the newborn infant, which currently is 100% fatal. The prevalence of maternal HIV infection in areas where maternal malaria studies have been reported has ranged from 3% to 27%. Table 4 shows prevalence estimates for the outcomes of malaria, anemia, and LBW; the risk estimates for the HIV association with these conditions; and the PAR estimates. HIV is estimated to contribute to malaria infection in pregnancy (PAR = 10–27%), maternal anemia (PAR = 12–15%), and LBW (PAR = 11–38%). Because HIV infection of the newborn is fatal, the contribution of HIV to infant mortality may reach or exceed 50% in some settings with high rates of maternal HIV infection and high rates of mother-to-infant HIV transmission.
<table>
<thead>
<tr>
<th>Main study author (reference)</th>
<th>Site</th>
<th>Number of subjects</th>
<th>Maternal parasite prevalence</th>
<th>Anemia cutoff</th>
<th>HIV data</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shulman (12)</td>
<td>Kenya</td>
<td>275</td>
<td>23.6%</td>
<td>Hb &lt; 11, Hb &lt; 7</td>
<td>Yes</td>
<td>Observational</td>
</tr>
<tr>
<td>Cot (13, 26)</td>
<td>Cameroon</td>
<td>209</td>
<td>57.8%</td>
<td>Hct &lt; 30%</td>
<td>No</td>
<td>CPx intervention trial with CQ</td>
</tr>
<tr>
<td>Steketee (15, 20, 22)</td>
<td>Malawi</td>
<td>4,220/1,766</td>
<td>39%</td>
<td>Hct &lt; 30%</td>
<td>Yes</td>
<td>CPx intervention with CQ or MQ</td>
</tr>
<tr>
<td>Sullivan (17)</td>
<td>Malawi</td>
<td>178</td>
<td>37%</td>
<td>Hct &lt; 25%</td>
<td>No</td>
<td>Observational</td>
</tr>
<tr>
<td>Verhoeff (27, 28)</td>
<td>Malawi</td>
<td>621</td>
<td>22.0%</td>
<td>Hb &lt; 8</td>
<td>Yes</td>
<td>Observational with women on PIT with SP</td>
</tr>
<tr>
<td>Cot (13, 29)</td>
<td>Burkina Faso</td>
<td>1,148</td>
<td>19%</td>
<td>Hct &lt; 30%</td>
<td>No</td>
<td>CPx intervention with CQ</td>
</tr>
<tr>
<td>Brabin (30)</td>
<td>Papua New Guinea</td>
<td>386</td>
<td>24.7%</td>
<td>Hb &lt; 8</td>
<td>No</td>
<td>Observational</td>
</tr>
<tr>
<td>Greenwood (23)</td>
<td>Gambia</td>
<td>1,468</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>CPx study with birth-weight and mortality outcomes</td>
</tr>
<tr>
<td>Nosten (31)</td>
<td>Thailand</td>
<td>339</td>
<td>75.5% person-weeks</td>
<td>Hct &lt; 30%</td>
<td>No</td>
<td>CPx intervention with MQ</td>
</tr>
<tr>
<td>Parise (32)</td>
<td>Kenya</td>
<td>713</td>
<td>45%</td>
<td>Hb &lt; 11, Hb &lt; 7</td>
<td>Yes</td>
<td>PIT intervention with SP and CQ</td>
</tr>
<tr>
<td>Van Eijk (33)</td>
<td>Kenya</td>
<td>4,608</td>
<td>20.7%</td>
<td>Hb &lt; 11, Hb &lt; 7</td>
<td>Yes</td>
<td>Observational</td>
</tr>
<tr>
<td>Bloland (34)</td>
<td>Malawi</td>
<td>1,347</td>
<td>23.5%</td>
<td>NR</td>
<td>Yes</td>
<td>CPx intervention with CQ and MQ</td>
</tr>
<tr>
<td>Schulte (35, 36)</td>
<td>Malawi</td>
<td>159</td>
<td>65%</td>
<td>Mean Hb</td>
<td>No</td>
<td>PIT intervention with SP</td>
</tr>
<tr>
<td>Rogerson (37)</td>
<td>Malawi</td>
<td>1,044</td>
<td>28.5%</td>
<td>Hb 7–9, Hb &lt; 7</td>
<td>No</td>
<td>Observational, national program using PIT with SP</td>
</tr>
<tr>
<td>Mutabingwa (38)</td>
<td>Tanzania</td>
<td>327</td>
<td>62.4%</td>
<td>Hb 8–9, Hb &lt; 8</td>
<td>No</td>
<td>CPx intervention with CQ and Proguanil</td>
</tr>
<tr>
<td>D’Alessandro (39)</td>
<td>Gambia</td>
<td>537</td>
<td>27%</td>
<td>Hb &lt; 8</td>
<td>No</td>
<td>Observational with bed-net intervention</td>
</tr>
<tr>
<td>ter Kuile (40)</td>
<td>Kenya</td>
<td>2,435</td>
<td>20% person-weeks</td>
<td>Hct &lt; 30%</td>
<td>No</td>
<td>Bed-net intervention trial</td>
</tr>
<tr>
<td>Osman (41)</td>
<td>Mozambique</td>
<td>908</td>
<td>6%</td>
<td>Hb &lt; 10</td>
<td>No</td>
<td>Observational</td>
</tr>
<tr>
<td>Matteelli (42)</td>
<td>Tanzania</td>
<td>389</td>
<td>65.5%</td>
<td>Hb &lt; 8</td>
<td>No</td>
<td>Observational</td>
</tr>
<tr>
<td>Ndyomugenyi (43)</td>
<td>Uganda</td>
<td>853</td>
<td>62.1%</td>
<td>Hb &lt; 10, Hb &lt; 8</td>
<td>No</td>
<td>Observational</td>
</tr>
<tr>
<td>Dolan (44)</td>
<td>Thailand</td>
<td>341</td>
<td>35% incidence</td>
<td>Hct &lt; 30%</td>
<td>No</td>
<td>Bed-net intervention trial</td>
</tr>
<tr>
<td>Menendez (45)</td>
<td>Tanzania</td>
<td>1,177</td>
<td>35.2%</td>
<td>NR</td>
<td>No</td>
<td>Observational</td>
</tr>
<tr>
<td>Shulman (46)</td>
<td>Kenya</td>
<td>1,131</td>
<td>23.7%</td>
<td>Hb &lt; 8</td>
<td>No</td>
<td>PIT intervention with SP</td>
</tr>
<tr>
<td>Brabin (47)</td>
<td>Papua New Guinea</td>
<td>7,106/4,548</td>
<td>NR</td>
<td>Hb &lt; 11, Hb &lt; 7</td>
<td>No</td>
<td>Ecologic comparison coastal and highland areas</td>
</tr>
<tr>
<td>Verhoeff (48, 49, 50)</td>
<td>Malawi</td>
<td>4,104/1,523</td>
<td>19.0%</td>
<td>Hb &lt; 8</td>
<td>No</td>
<td>Observational</td>
</tr>
<tr>
<td>Shulman (51)</td>
<td>Kenya</td>
<td>503</td>
<td>10.2%</td>
<td>Hb &lt; 7</td>
<td>Yes</td>
<td>Bed-net intervention trial</td>
</tr>
</tbody>
</table>

* CPx = chemoprophylaxis; PIT = preventive intermittent treatment; CQ = chloroquine; MQ = mefloquine; SP = sulfadoxine-pyrimethamine; Hb = hemoglobin in g/dL; Hct = hematocrit; HIV = human immunodeficiency virus; NR = not reported.

† The number of study subjects included in the different analyses in the report varied depending on missing data.
Failure to use effective interventions. Interventions have been demonstrated to substantially reduce the frequency of malaria, anemia, LBW, and HIV transmission to the newborn and their contribution to infant mortality, either directly or indirectly. We used efficacy data from intervention studies to obtain estimates of the maximum likely impact of the intervention and then assumed that a maximum of 90% of pregnant women were not using the intervention (thus setting the prevalence of “failure to use” at 90%). These upper-limit estimated PARs associated with the failure to apply effective interventions are shown in Table 5. Failure to use intermittent presumptive malaria treatment, malaria chemoprophylaxis, or insecticide-impregnated bed nets may contribute to 26–90% of maternal malaria, 21–84% of maternal anemia, 26–82% of LBW, and 3–8% of infant mortality.

Estimates of the contribution of malaria in pregnancy to infant mortality. Although many studies have investigated 1 or several of the links between maternal malaria infection and its adverse consequences, only 2 studies have attempted to estimate the actual contribution of malaria to infant mortality.22-23 No study has made the direct observation because the required sample size to make the observation is prohibitively large. However, the estimates are modest (3–8% of infant mortality) and likely reflect the range of possible contribution. Because infant mortality varies widely across the malaria-endemic settings (50–160 per 1,000 live births), one can approximate that globally, 75,000 to 200,000 infant deaths might be attributable each year to malaria infection during pregnancy.

Discussion

This review of recent information from published and some unpublished data suggests that in pregnant women in malaria-endemic areas, P. falciparum malaria, anemia, and HIV in pregnancy contribute to each other and to the adverse outcomes of LBW (through prematurity or IUGR) and infant mortality. Overall, although the contribution of malaria in pregnancy to infant mortality may be modest, the wide geographic distribution of infection around the tropics and the high mortality rate in malaria-endemic settings leads to a substantial number of infant deaths linked to malaria in pregnancy—estimated to be 75,000 to 200,000 infant deaths annually.

We offer this estimate with caution and with the recognition that no single study has been conducted, or likely ever will be conducted, with sufficient power to observe the full sequence of events from maternal malaria infection to infant mortality. In addition, these estimates are derived from attributable risk estimates that suggest “attribution” but not “full cause.” That is, PAR estimates for multiple conditions (risk factors) leading to a single event (e.g., infant mortality) may sum to more than 100%, suggesting that they contribute to a proportion of the event, but may not be the only cause of that proportion of the event. Despite this, the estimate that maternal malaria infection may contribute to 3% of infant mortality22 did not include any contribution of malaria to maternal anemia and its possible contribution to infant mortality. Indeed, this estimate of 3% may be a low estimate.
The estimate of malaria contributing to 8% of infant mortality is an approximation based on a composite of a PAR of 18% for primigravida and 4% for multigravida and likely includes the combination of malaria and anemia risks. Thus, we believe that the range of our summary estimate covers the spectrum of contribution of maternal malaria to infant mortality. Our review did not consider the effects of maternal malaria on subsequent infant morbidity, including increased risk for infant malaria infection and infant anemia. In addition, although malaria in pregnancy also contributes to maternal deaths and congenital malaria with risk for infant death in areas of lower malaria endemicity, including sub-Saharan Africa, these deaths were not considered, and the estimate offered here likely underestimates the total global mortality contribution from malaria in pregnancy.

Several studies demonstrate that HIV contributes to approximately 25% of maternal malaria infections and contributes importantly to maternal anemia. Thus, although UNAIDS estimates that in 1998, 510,000 children were infected with HIV, most by mother-to-infant transmission, and that these infections will be fatal, HIV is also contributing to infant mortality through maternal malaria and anemia. Additionally, there remains concern that maternal malaria infection of the placenta may contribute to mother-to-child HIV transmission if this is true, then maternal malaria infection may contribute to more infant mortality than is suggested here.

The studies reviewed here also demonstrate that substantial reductions in maternal malaria, anemia, and LBW have been achieved by intervention programs, including the use of preventive intermittent treatment, chemoprophylaxis, and the use of insecticide-treated nets. In fact, the studies suggest that between 25% and 90% of these adverse events might be prevented by full implementation of existing interventions (see Table 5). Interventions also exist for maternal anemia (e.g., good nutrition, iron and folate supplementation, and hookworm treatment) and for reduction of mother-to-infant HIV transmission (e.g., short-course zidovudine or nevirapine), and these can also be provided through antenatal care programs. Better application of these malaria, anemia, and HIV interventions could markedly reduce the infant mortality burden of these diseases. An antenatal care program that includes effective prevention for maternal malaria, anemia, and mother-to-infant HIV transmission, along with other usual services (e.g., monitoring the progress of pregnancy, assessing high-risk pregnancies, providing neonatal tetanus prevention, syphilis testing and treatment, gonocont.
MALARIA IN PREGNANCY

pectral ophthalmia neonatorum prevention, micronutrient supplementation) can be employed in a cost-effective manner, and will save many lives.

We benefited from previous review articles on the topic of malaria in pregnancy, and were able to include some of that work; however, like these other reviews, this review also has limitations. This was not a formal meta-analysis to re-
view risk estimates; rather, it focused on establishing the range and magnitude of risks for adverse outcomes associated with malaria, anemia, and HIV on LBW and infant mortality. The studies that were reviewed come from limited geographic areas (most in sub-Saharan Africa) and were limited to P. falciparum malaria. Different studies present differ-
ent outcomes and different classifications of risk factors and outcomes, and only a few had sufficient power to ex-
amine the spectrum of risk factors that might contribute to the adverse events associated with malaria, anemia, and HIV combined. Some studies that showed substantial contribu-
tions of malaria to LBW and anemia (e.g., Bouvier and colleagues and Meuris and colleagues) were not included because risk estimates were not reported in a manner that could be included in PAR estimates. Some studies did not observe a statistically significant association between certain risks and outcomes; however, in most cases these studies had small sample sizes and had insufficient power. No studies demonstrated any protective benefit from factors that we reviewed as “risk” factors. The relative consistency of find-
ings and estimates across the studies suggests that malaria infection in pregnancy does present a real and quantifiable risk for infant mortality.

In conclusion, maternal malaria infection and the often accompanying anemia and HIV in these pregnant women contribute importantly to the global burden of infant mor-
tality. The real tragedy is that effective interventions have been identified in a number of studies, and today, the failure to provide these interventions continues to contribute sub-
stantially to infant deaths around the world.

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MALARIA IN PREGNANCY

35