Nutritional Modulation of Malaria Morbidity and Mortality

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This review critically examines the relationship between nutritional status and malaria. The data indicate that protein-energy malnutrition is associated with greater malaria morbidity and mortality in humans. In addition, controlled trials of either vitamin A or zinc supplementation show that these nutrients can substantially reduce clinical malaria attacks. Data for iron indicate that supplementation may minimally aggravate certain malarial indices in some settings and also strongly improve hematologic status. Withholding of iron supplements from deficient population is, therefore, not currently indicated. Available evidence for other nutrients describe varied effects, with some deficiencies being exacerbative (e.g., thiamine), protective (e.g., vitamin E), or both exacerbative and protective in different settings (e.g., riboflavin, vitamin C). The roles of folate, other B vitamins, unsaturated fatty acids, amino acids, and selenium are also examined. Study of the interactions between nutrition and malaria may provide insight to protective mechanisms and result in nutrient-based interventions as low-cost and effective adjuncts to current methods of malaria prevention and treatment.

Malaria, the most significant human parasitic disease, remains a major cause of morbidity, anemia, and mortality worldwide. Malaria currently accounts for about 200 million morbidity episodes and 2–3 million deaths each year, estimates that have been increasing over the last three decades [1]. It has long been acknowledged that populations residing in malarious areas generally live under conditions that lead to poor nutritional status. The groups at highest risk for the adverse effects of malaria, children and pregnant women, are also most affected by poor nutrition.

Although it has been suspected that nutrition might influence susceptibility to infection by the malaria parasite or modify the course of disease, there have been relatively few efforts to examine such interactions. Among the studies, some suggest that poor nutritional status or selective nutrient deficiencies may actually be protective; others suggest exacerbative effects of certain deficiencies. Recently, placebo-controlled field trials showed that vitamin A and zinc supplementation may significantly reduce the burden of malarial disease. Although an understanding of the influence of nutrition on malaria is far from complete, it is clear that nutrition strongly influences the disease burden of malaria.

To date, malaria control has focused on reduction of man-mosquito contact, chemoprophylaxis, rapid treatment, and development of a malaria vaccine. Clearly, additional low-cost and effective means to assist in the prevention and treatment of malaria are needed. This review describes the history and current knowledge of malaria and nutrition and suggests nutrient-based interventions that may represent novel low-cost and effective adjuncts to current methods of malaria treatment and prevention.

Early Perceptions of the Impact of Nutrition on Malaria

Before 1950 it was widely accepted that malnutrition led to greater susceptibility to malaria. The Indian Famine Commission in 1898 reported that malaria was more frequent and fatal in persons with poor diets [2], and historical accounts from the late nineteenth and early twentieth centuries indicated that famines in north India and Sri Lanka tended to precipitate malaria epidemics [3, 4]. Reports from 1920 to 1940 in Corsica [5], Algeria [5], Vietnam [6], Turkey [7], and Ghana [8] stated that malaria was more frequent and severe among those who were undernourished. In 1954, Garnham [9], a prominent malariologist of the time, concluded that the clinical effects and mortality from malaria were more severe in malnourished children. There was, however, anecdotal evidence to the contrary, such as the failed 1897 attempt by an Italian industrialist to protect farmers in the malaria-infested Pontine marshes with generous provisions of food and quinine [10]. Other reports found no association between nutritional status and malaria morbidity [11], and some suggested that postfamine increases in food consumption exacerbated malaria [12].
Unfortunately, most of these reports were based on limited clinical and epidemiologic observations or even anecdotal information. Little, if any, quantitative data or methodologic information was published to substantiate the conclusions. By the early 1950s, scientists had begun to improve quantification of interactions between nutrition and malaria. Three studies from Ghana and Nigeria published between 1954 and 1971 [13–15] were particularly influential and strongly promoted the notion that malnutrition was in fact protective for malaria. This idea was reinforced by a series of studies by Murray et al. [16–19] from 1975 to 1980 on refeeding and malaria in famine victims in Niger and Sudan. Animal studies appeared to support these reported malaria suppressive effects of a poor diet, leading to the perception that malnourished children are less susceptible to malaria infection, morbidity, and mortality [20–23].

Careful review of these studies plus more recent epidemiologic data strongly indicate that the relationship between malaria and nutritional status is more complex and that general malnutrition is in fact an important risk factor for increased malaria morbidity and mortality. Additional field studies and results from experimental malaria studies indicate that multiple specific nutrients, such as vitamin A, zinc, iron, thiamine, riboflavin, and vitamin E, strongly affect the course of malaria infection and pathology.

Protein Energy Malnutrition (PEM)

Several studies examined the association between malnutrition, usually PEM, and malaria morbidity and mortality. The early studies generally assessed nutritional status by subjective clinical evaluation, while later studies utilized anthropometric indicators and reference standards to determine poor nutritional status based on low weight-for-age (underweight), low height-for-age (stunting), or low weight-for-height (wasting). Some studies were of clinic outpatients; others were hospital admissions or community-based cross-sectional studies. Most were case-control studies, but some were longitudinal surveillance of cohorts. In most, the malaria-related outcomes persisted to prevalence of infection or frequency of clinical attacks of *Plasmodium falciparum*, although some had data for *Plasmodium vivax*. Multiple experimental animal studies of PEM or protein deficiency were also conducted: These ranged from the initial avian malaria studies with *Plasmodium lophurae* and *Plasmodium gallinaceum* to the primate models of *Plasmodium knowlesi* and *Plasmodium cynomolgi* and rat and murine models using primarily *Plasmodium berghei* but also *Plasmodium yoelii* and *Plasmodium vinckeii*.

The interpretation of this body of data has generally been that PEM or protein deficiency protects the host against malaria morbidity and mortality [20–23]. However, a reappraisal of the data presented herein indicates that the effect of PEM on the host is more complex and in many cases predisposes to excess morbidity and mortality.

Clinic-based studies. Among the first study of PEM and malaria was a large-scale clinic-based study in Uganda [24, 25] (table 1), which concluded there was no association between nutritional status and malaria mortality. This study was less than ideal as nutritional status was based on qualitative and subjective indicators (e.g., thin or pale hair or being “very” thin), malaria diagnosis was based only on spleen enlargement, and mortality risk was estimated by the presence or absence of sibling mortality. Another smaller clinic-based study in India reported progressively increasing parasite density with improved nutritional status [26], suggesting that malnutrition was protective. However, two additional studies, one in Brazil [27] and one in Soviet army personnel [28], reported greater frequency or more severe malaria in those who were malnourished.

Early studies of hospital admissions for severe malaria. Early hospital-based studies strongly influenced current perceptions of malaria and malnutrition. In 1954 an autopsy report by Edington [13] indicated that 4 Ghanaian children who died of cerebral malaria were well nourished. Other accounts from South Africa in 1960 [35] reported that malaria was rare in malnourished children. This was followed in 1967 by another qualitative report from Edington [36], who noted that children dying of cerebral malaria in Nigeria were usually well nourished and that cerebral malaria was rare in children with kwashiorkor. Case-control studies from Nigeria by Hendrickse and colleagues in 1967 [14] and 1971 [15] concluded that children with malaria were less likely to be malnourished or have convulsions. Hendrickse [14] also reaffirmed the apparent protection due to kwashiorkor. A subsequent autopsy report from Nigeria of 25 malnourished children indicated that only 2 had died of malaria [37].

Although these reports appeared convincing of a protective effect of malnutrition on malaria, several characteristics of the studies weaken the conclusions. Most importantly, the study populations comprised clinic cases or malnourished children and comparisons were of those with or without malaria. In the absence of healthy community controls, one could only conclude that malaria is less exacerbated by malnutrition than other conditions. The overall prevalence of malnutrition among malaria cases in these studies was remarkably high, suggesting possible synergy with malnutrition. A more informative analysis would have included the relationship between the degree of malnutrition among malaria cases and the risk of malaria mortality. Unfortunately, such analyses were not done, partly because malnutrition was categorized by relatively nonstandardized qualitative descriptors rather than by quantitative assessment. In some studies, incomplete analyses of the data were made. For example, Hendrickse reported decreased risk of convulsions in malnourished malaria patients, but the same decline in convulsion risk was also observed for malnourished non-malaria patients. There was also a lack of information on socioeconomic status or residence of the cases. Well-nourished cases may tend to come from urban areas and have less acquired...
Table 1. Interaction between malnutrition and *Plasmodium falciparum* (*Pf*): clinic and hospital-based studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study group/design</th>
<th>No. of subjects</th>
<th>Age group, years&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Index of nutritional status&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Malaria related outcome</th>
<th>Observations</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gongora and colleague (1959) [24, 25]</td>
<td>Uganda</td>
<td>Clinical malaria out-patients</td>
<td>22,000</td>
<td>&lt;6</td>
<td>Malnutrition</td>
<td>Splenomegaly with sibling mortality</td>
<td>Higher reported sibling mortality in patients with spleen enlargement or malnutrition but no stronger association if both were present</td>
<td>Neutral</td>
</tr>
<tr>
<td>Ahmad et al. (1985) [26]</td>
<td>India</td>
<td>Clinical malaria out-patients</td>
<td>75</td>
<td>Birth–12</td>
<td>Weight for age (Indian standard)</td>
<td>Parasite density</td>
<td>Patients with progressively greater malnutrition had lower <em>Pf</em> parasitemia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Antagonistic</td>
</tr>
<tr>
<td>Pereira et al. (1995) [27]</td>
<td>Brazil</td>
<td>Clinical malaria out-patients: <em>Pf</em> patients vs. healthy controls</td>
<td>120</td>
<td>17–72</td>
<td>Weight for height (Quetelet index)</td>
<td>Clinical malaria</td>
<td><em>Pf</em> cases weighed 13% less than healthy controls</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Hendrickse (1967) [14]</td>
<td>Nigeria</td>
<td>Hospital admissions</td>
<td>333</td>
<td>Children</td>
<td>Malnutrition</td>
<td>Parasite density, mortality</td>
<td>Heavy infections more frequent in malnourished children; cause of death rarely malaria in malnourished children</td>
<td>Antagonistic</td>
</tr>
<tr>
<td>Hendrickse et al. (1971) [15]</td>
<td>Nigeria</td>
<td>Hospital admissions: <em>Pf</em> patients vs. febrile cases</td>
<td>295</td>
<td>Birth–10</td>
<td>Malnutrition</td>
<td>Clinical malaria</td>
<td>Malnourished children 0.64 times as likely to have convulsions, malnutrition in patients ~6 times more frequent than in population</td>
<td>Antagonistic, synergistic</td>
</tr>
<tr>
<td>Razanamparany et al. (1995) [29], Randraitsi-harissa et al. (1993) [30]</td>
<td>Madagascar</td>
<td>Hospital admissions: all <em>Pf</em> admissions</td>
<td>1549</td>
<td>Birth–14</td>
<td>Malnutrition (standardized but not described)</td>
<td>Malaria mortality</td>
<td>Malnourished patients 2.5 times more likely to die&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Oulumese et al. (1997) [31]</td>
<td>Nigeria</td>
<td>Hospital admissions: cerebral malaria vs. other causes</td>
<td>376</td>
<td>1–5</td>
<td>Wellcome classification</td>
<td>Malaria mortality</td>
<td>Malnourished patients 3.5 times more likely to die or have neurologic deficits&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Renaudin (1997) [32]</td>
<td>Chad</td>
<td>Hospital admissions: all <em>Pf</em></td>
<td>227</td>
<td>1 month–5</td>
<td>Weight for height (NCHS standard), ≤2 SD</td>
<td>Malaria mortality</td>
<td>Wasted patients 1.5 times more likely to die&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Faye et al. (1998) [33]</td>
<td>Senegal</td>
<td>Hospital admissions: <em>Pf</em> deaths vs. <em>Pf</em> survivors</td>
<td>104</td>
<td>&lt;5</td>
<td>Weight for age (NCHS standard), ≤2 SD</td>
<td>Malaria mortality</td>
<td>Underweight patients 2.8 times more likely to die&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Man et al. (1998) [34]</td>
<td>The Gambia</td>
<td>Hospital admissions: all <em>Pf</em></td>
<td>8385</td>
<td>Birth–5</td>
<td>Weight for age (NCHS standard), ≤2 SD</td>
<td>Malaria mortality</td>
<td>Underweight patients 1.3 times more likely to die&lt;sup&gt;c&lt;/sup&gt; weighed ~0.35 kg less than community control children</td>
<td>Synergistic</td>
</tr>
</tbody>
</table>

<sup>a</sup> Years unless noted otherwise.

<sup>b</sup> Low height-for-age refers to stunting, low weight-for-age to underweight, and low height-for-age to wasting. In most cases, percentiles were determined by comparison with Harvard or National Center for Health Statistics (NCHS) standards for anthropometry. Malnutrition is classification based on subjective indicators rather than on some standard measure.

<sup>c</sup> Significance at *P* < .05.
immunity, whereas malnourished cases could come from outlying areas of higher transmission leading to greater immunity. Indeed, Edington [36] reported that the children with cerebral malaria tended to have less hookworm, an observation possibly related to socioeconomic status. Lastly, the conclusions based on patients with kwashiorkor may not be generalizable to overall malnutrition because aflatoxins, a causative agent of kwashiorkor, are toxic to malaria parasites in vitro and in vivo [38, 39].

Recent studies of hospital admissions for severe malaria. In the last 10 years, studies have been completed on the relationship between malnutrition and malaria. These larger studies more carefully documented nutritional status by reference standards (i.e., height, weight, and age) and evaluated malnutrition as a risk factor for malaria mortality among hospital admissions. Five studies conducted in Madagascar [29, 30], Nigeria [31], Chad [32], The Gambia [34], and Senegal [33] indicate that malnourished patients are 1.3–3.5 times more likely to die or have permanent neurologic sequelae than normally nourished malaria patients. In addition, in the study from The Gambia, malaria patients typically weighed 350 g less than healthy control children [34]. In all studies, as seen by Hendrickse, malnourished hospital patients were less likely to have malaria than other infections, suggesting that although malaria may be exacerbated by malnutrition, other diseases may be more adversely affected. Indeed, additional analyses in The Gambia study [34] confirm the greater impact of malnutrition on risk of death for diarrhea and pneumonia. In contrast to these reports, one study of 60 hospital patients in India reported that parasitemia tended to increase with improving nutritional status; however, no data on clinical outcomes were presented [40].

Cross-sectional studies of malarriometric indicators. Several cross-sectional surveys also favor a synergistic relationship between malnutrition and malaria (table 2). Studies in Malawi [41], Zambia [42], Papua New Guinea [43], Sudan [44], Tanzania [45], Chad [46], and Zaire [47] indicate greater risk for infection [41, 42, 45–47], malaria illness [44], or spleen enlargement [43] among malnourished children. A study in Colombia found that malnourished children had lower anti-malaria antibody levels [48]. This could be interpreted as a synergistic effect if malnutrition suppresses antibody response to malaria or possibly antagonistic if malnutrition protects against infection such that antibodies are not produced. In Tanzania, there was no effect of nutritional status on anti-parasite antibody levels [49]. A study in Burkina Faso found no association between parasite prevalence and nutritional status [50].

Longitudinal cohort studies and effects of nutrition on drug-resistant malaria. Longitudinal cohort studies in Tanzania [56], Vanuatu [53] and Congo [55] indicate that malnutrition predisposes children to malaria illness (table 2). Another report from The Gambia [52] indicates little effect of malnutrition on malaria attacks, while one report from Papua New Guinea suggests that stunted children may be more resistant to malaria attacks [54]. However, this protection was not seen in underweight children. Of interest, the stunted children also exhibited increased immune responses to malaria antigens, whereas the wasted children had suppressed responses. One additional semilongitudinal study (multiple cross-sectional cohort surveys) in Zaire [57] found no association between nutritional status and mortality. Because malaria was the primary cause of death in that study, the authors inferred there was no association between nutrition and malaria mortality. However, analysis of the association between nutritional status and malaria deaths, as determined by verbal autopsy, were not presented. Further evidence supporting an exacerbative role of malnutrition on malaria can be seen in several drug-resistance studies. Malnourished Rwandan refugees had slower parasite clearance, higher parasite titers at presentation, and more severe drug resistance [58]. Likewise, in the Solomon Islands, malnourished children were 3.6 times more likely to have drug-resistant malaria [59, 60].

Studies during famine relief. The 1945 report of the Bengal Famine Commission noted that refeeding tended to precipitate malaria disease in persons with low-grade infections [12]. The presence of malaria in famine victims during nutritional rehabilitation was subsequently examined in a series of studies by the Murray family. During the Sahelian famine in Niger when victims were hospitalized for refeeding, many patients developed *P. falciparum* malaria within a few days [17], often resulting in cerebral pathology. Because there was no malaria transmission at the hospital, it was believed that feeding provided essential nutrients for sequestered parasites, leading to recrudescence infection [16, 17]. In another study, famine victims were given either grain or milk for rehabilitation and it was observed that those given grain were more likely to experience recrudescence cerebral malaria [18]. These studies suggest that both quality and quantity of the diet is an important determinant of malaria morbidity. The Murrays concluded that the interaction between poor diet and malaria is part of an ecologic balance between humans and malaria, which they interpreted as a beneficial aspect of malnutrition. Of note, however, the eco-biology of nutritional rehabilitation of famine-stricken persons is likely to be distinct from that of the more common condition of chronic malnutrition.

Studies of PEM in animals. A variety of animal experiments have also contributed to the idea that PEM reduces malaria morbidity. Early work showed that monkeys maintained on a low-protein diet had lower parasitemia [61–63]. However, the animals were either unable to clear the infection, resulting in multiple recrudescences [65], or parasitemia appeared earlier and lasted longer [64]. Immune responses were also suppressed [64]. However, for monkeys with cerebral malaria, protein-deprived animals had fewer parasitized erythrocytes in the cerebral capillaries and did not develop the disrupted endothelium seen in normally fed monkeys. Still,
cerebral and pulmonary edema were present in all animals regardless of dietary regimen [66].

These primate experiments were complemented by a variety of informative data from studies of rodent malaria. A comprehensive series of investigations by Ramakrishnan and colleagues [67–72] in the early 1950s indicated that malaria parasitemia was less severe in protein-deprived rats and that survival was enhanced. They also showed that methionine and p-aminobenzoic acid promoted the infection in starving rats [67]. Of importance, it was clear that protein-deprived animals were unable to clear the infection [72] and that protein restriction in young rats exacerbated malaria parasitemia and mortality [69]. Moreover, parasite densities were higher and more lethal during relapses in protein-deprived animals [72]. Lastly, starved animals experienced strong relapse infections when food was given [69].

Additional studies by Edirisinghe and colleagues [22, 73–76] documented that acute and chronic protein deprivation depressed peak parasitemia more than 75% and prevented death. However, as shown in previous work, the animals were unable to clear the infection [75], and antibodies preventing parasite growth did not adequately develop. Elegant work by Fern et al. [76] then demonstrated that readdition of threonine to a low-protein diet restored susceptibility and that this effect was enhanced by valine, isoleucine, and methionine. However, phenylalanine, tyrosine, lysine, histidine, and tryptophan did not appear to have this promoting effect. Of interest, the amino acids that had the greatest modulatory effect on the infection tended to be those least abundant in hemoglobin, the main amino acid source for the parasite, indicating the potential importance of nonhemoglobin amino acids in parasite survival.

Subsequent studies in rats and mice confirmed that low-protein diets suppressed parasitemia [77–81] and inhibited cell-mediated immunity [77] and that effects were reversible by addition of para-aminobenzoic acid [78]. Effects on mortality were less consistent. In some cases, low-protein diets suppressed parasitemia but mortality was higher, albeit delayed [82]. Addition of threonine and methionine to the low-protein diet decreased mortality [82], although either alone had no effect when added to the deficient diet. Others observed no effect on mortality in moderately malnourished mice but noted increased deaths in severely malnourished animals [83]. Protein-deficient diets were, however, consistently protective for rodent cerebral malaria [80, 81, 84].

Synthesis of data regarding the effect of PEM on malaria. The considerable data from humans and animals, although complex, provide ample evidence to draw some conclusions regarding the interaction between protein-calorie malnutrition and malaria. Although it is frequently mentioned that PEM is protective for malaria [20–23], more recent data and careful reexamination of the results of human and animal studies indicate that malnutrition is associated with increased infection rates, clinical malaria attacks, and considerably higher likelihood of malaria mortality in humans.

The hospital-based studies that suggested a protective effect of malnutrition are inconclusive due to the many methodologic and design issues discussed above. Similarly, the animal-based data that are often cited as supportive evidence that malnutrition is protective are less clear when carefully examined. For instance, although parasitemia tended to be lower in poorly fed animals, they were unable to clear the infection, and immune responses to the parasite were suppressed. This led to more chronic infections and more severe relapses. Also, malnutrition was particularly deleterious in younger animals [69], an observation consistent with some age-related data from human studies [55]. The multiple studies in rodents indicating that certain amino acids and PABA have distinct parasite-promoting effects are important, but not necessarily incompatible with the apparently deleterious effects of general malnutrition on malaria. Additional data concerning the impact of selected human diets richer or poorer in certain amino acids are needed. It is notable that for cerebral malaria in animals, poor diets are consistently protective, whereas data from humans clearly indicate that malnourished children are more likely to die of cerebral malaria. This discrepancy may be rooted in differences in the etiology of cerebral pathology in animals and humans.

It should also be appreciated that certain age-dependent relationships may underlie some inconsistencies linking malnutrition and malaria in humans. Severe clinical malaria is more frequent in young children (i.e., <3 years) and tends toward severe malaria anemia. In contrast, for older children (i.e., >3 years), cerebral malaria is more frequently encountered. Likewise, various indicators of nutritional status have age-dependent distributions. Wasting (low weight for height) is seen more frequently in young children than in older children for whom stunting (low height for age) is generally more prevalent. Thus, if such age-based differences were not taken into account, a clinic-based study of severe malaria cases could erroneously conclude that wasting was protective for cerebral malaria.

Famine or starvation presents a special case. It is consistently observed in humans and animals that refeeding an infected starved host reactivates low-grade infections. This may suggest that increases in parasite replication following refeeding are sufficiently rapid to temporarily outpace development of adequate immunity. Given that famines caused by political and/or meteorologic causes are not unusual, special attention should be given to malaria during nutritional rehabilitation of famine victims. This should include malaria prophylaxis and careful surveillance. In addition, it may be possible to develop refeeding regimens that minimize parasite recrudescence and hasten development of immunity.

Given that PEM appears to exacerbate malaria and that PEM is frequently accompanied by deficiencies in other nutrients, it is conceivable that multiple specific nutrients may influence malaria infection and pathology. Several studies have
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study design</th>
<th>No. of subjects</th>
<th>Age group&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Index of nutritional status&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Malaria-related outcome</th>
<th>Observations</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burges et al. (1975) [41]</td>
<td>Malawi</td>
<td>Cross-sectional</td>
<td>445</td>
<td>Birth–5</td>
<td>Weight-for-height (Harvard standard), &lt;80 percentile</td>
<td>Infection rate</td>
<td>Underweight children had greater prevalence of malaria&lt;sup&gt;c&lt;/sup&gt; (data not in format that allowed risk estimate)</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Wenlock (1979) [42]</td>
<td>Zambia</td>
<td>Cross-sectional</td>
<td>6938</td>
<td>All ages</td>
<td>Weight-for-age (Harvard standard), &lt;80 percentile</td>
<td>Infection rate</td>
<td>Underweight persons were 1.27 times more likely to be infected&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Sharp and Harvey (1980) [43]</td>
<td>Papua New Guinea</td>
<td>Cross-sectional</td>
<td>166</td>
<td>Birth–5</td>
<td>Height-for-age (Harvard standard), &lt;90 percentile</td>
<td>Spleen enlargement</td>
<td>Stunted children were 1.9 times more likely to have enlarged spleen&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic</td>
</tr>
<tr>
<td>El Samani et al. (1987) [44]</td>
<td>Sudan</td>
<td>Cross-sectional</td>
<td>445</td>
<td>Birth–5</td>
<td>Weight-for-age (NCHS standard), &lt;90 percentile</td>
<td>Signs of malaria illness</td>
<td>Underweight children 1.4 times more likely to have recent malaria illness&lt;sup&gt;c&lt;/sup&gt; (not slide confirmed)</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Mbago and Namfua (1991) [45]</td>
<td>Tanzania</td>
<td>Cross-sectional</td>
<td>949</td>
<td>1–4</td>
<td>Weight-for-height (Dugdale index, kg/cm&lt;sup&gt;0.85&lt;/sup&gt;)</td>
<td>Reported malaria illness</td>
<td>Wasted children more likely to have reported malaria illness in previous 2 weeks (no validation of reliability for malaria illness)</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Renaudin and Lombart (1994) [46]</td>
<td>Chad</td>
<td>Cross-sectional</td>
<td>144</td>
<td>Birth–1</td>
<td>Weight-for-age (NCHS standard), &lt;90 percentile</td>
<td>Infection rate</td>
<td>Underweight children 1.54 times more likely to be infected&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Tshikuka et al. (1997) [47]</td>
<td>Zaire</td>
<td>Cross-sectional</td>
<td>558</td>
<td>4 months–10</td>
<td>Height-for-age, weight-for-height (NCHS standard), &lt;2 SD</td>
<td>Infection rate</td>
<td>Stunted and wasted children 1.2–1.4 times more likely to be infected&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic</td>
</tr>
<tr>
<td>Dominguez-Vasquez and Alzate-Sanchez (1990) [48]</td>
<td>Colombia</td>
<td>Cross-sectional</td>
<td>124</td>
<td>Birth–6</td>
<td>Height-for-age, weight-for-height (Waterlow)</td>
<td>Immune response</td>
<td>Stunted and wasted children had decreased antibody responses to malaria antigens&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Synergistic or antagonistic</td>
</tr>
<tr>
<td>Carswell et al. (1981) [49]</td>
<td>Tanzania</td>
<td>Cross-sectional</td>
<td>244</td>
<td>School-age children</td>
<td>Weight-for-age, weight-for-height, &lt;90 percentile</td>
<td>Immune response to parasite</td>
<td>No association between underweight or wasted children and antibody levels to malaria antigens</td>
<td>Neutral</td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Design</td>
<td>Sample Size</td>
<td>Age</td>
<td>Measurements</td>
<td>Disease Outcome</td>
<td>Impact</td>
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<tr>
<td>Monjour et al. (1982) [50]</td>
<td>Burkina Faso</td>
<td>Cross-sectional survey</td>
<td>165</td>
<td>6 months-3</td>
<td>Weight-for-age (Harvard standard), &lt;70 percentile</td>
<td>Infection rate</td>
<td>Underweight children 0.90 times as likely to be infected</td>
<td></td>
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<tr>
<td>Sturchler et al. (1987) [51]</td>
<td>Tanzania</td>
<td>Longitudinal surveillance (multiple cross-sectional)</td>
<td>170</td>
<td>1 month-15</td>
<td>Low growth</td>
<td>Infection rate</td>
<td>Children with low growth tended to be more frequently infected</td>
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<tr>
<td>Snow et al. (1991) [52]</td>
<td>The Gambia</td>
<td>Longitudinal surveillance of malaria attacks for 4 months</td>
<td>138</td>
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<td>Weight-for-age, height-for-age, weight-for-height (NCHS standard), &lt;2 SD</td>
<td>Clinical malaria, parasite density</td>
<td>No impact of nutritional status on clinical malaria; nonsignificant tendency to higher parasite density in well-nourished children</td>
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<tr>
<td>Williams et al. (1997) [53]</td>
<td>Vanuatu</td>
<td>Longitudinal surveillance of malaria attacks for 1 year</td>
<td>1511</td>
<td>Birth-10</td>
<td>Weight-for-age, weight-for-height (NCHS standard), &lt;2</td>
<td>Clinical malaria</td>
<td>Underweight children more likely to have P. vivax attack and tendency toward more P. falciparum attacks</td>
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<tr>
<td>Genton et al. (1998) [54]</td>
<td>Papua New Guinea</td>
<td>Longitudinal surveillance of malaria attacks for 1 year</td>
<td>136</td>
<td>10 months-5</td>
<td>Height-for-age, weight-for-height (NCHS standard), &lt;2</td>
<td>Clinical malaria</td>
<td>Stunted children had lower risk for malaria attacks;^c multimalaria cell mediated immunity higher in stunted children,^c but antibody responses to malaria lower in wasted children^b ^d Antagonistic with some synergistic</td>
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<tr>
<td>Tonglet et al. (1999) [55]</td>
<td>Congo</td>
<td>Longitudinal surveillance (3-month staggered cohorts for 1 year)</td>
<td>842</td>
<td>Birth-2</td>
<td>Weight-for-age, height-for-age, arm circumference (NCHS standard), &lt;2 SD</td>
<td>Clinical malaria (not slide confirmed)</td>
<td>Malnourished children tend to have more malaria attacks if &lt;9 months old</td>
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^a Years unless noted otherwise.
^b Low height-for-age refers to stunting, low weight-for-age to underweight, and low height-for-age to wasting. In most cases, percentiles were determined by comparison with Harvard or National Center for Health Statistics (NCHS) standards for anthropometry. Malnutrition is classification based on subjective indicators rather than on some standard measure.
^c Significance at P < .05.
examined the effects of deficiencies of multiple minerals and vitamins on malaria in humans and experimental animal models, and many of these studies are discussed below.

**Vitamin A**

Vitamin A is essential for normal immune function [85], and several studies suggest it could play a role in potentiating resistance to malaria. Early work in vitamin A-deficient ducks indicated that vitamin A deficiency exacerbated malaria [86]. Further studies in vitamin A-deficient rats and mice showed an increased susceptibility to malaria that was readily reversed by supplementation [87, 88]. More recently, a genetic locus, which includes cellular retinol binding protein 1, was shown to modulate malaria mortality and parasitemia in mice [89]. In vitro, addition of free retinol to *P. falciparum* cultures reduced parasite replication in one study [90] but not in another [91].

In humans, cross-sectional studies in preschool children and adults have reported inverse associations between plasma vitamin A levels and *P. falciparum* parasitemia [92–97]. In addition, low plasma vitamin A levels were associated with ocular pathology during severe malaria [98]. However, these associations may have been due to an acute-phase response [92, 96, 97]. Still, selective depletion of plasmaborne provitamin A carotenoids during acute malaria attacks has been described [92], suggesting higher utilization of vitamin A during clinical malaria episodes. The vitamin A–malaria link is further strengthened by a study in which low baseline vitamin A status was associated with increased risk of parasitemia, although confounding by age could not be excluded [51]. In contrast, a substudy of a vitamin A trial in preschool children in Ghana found no statistically significant effects of vitamin A on *P. falciparum* morbidity or mortality [99]. However, no longitudinal surveillance of slide-confirmed malaria morbidity was done [100].

The most definitive study to date of the effects of vitamin A on malaria was recently completed in Papua New Guinea [101]. In this double-blind placebo-controlled trial, vitamin A supplementation reduced the frequency of *P. falciparum* episodes by 30% (95% confidence interval [CI], 14–43; *P* = .0013) among preschool children. At the end of the study, geometric mean parasite density was 36% lower in the vitamin A group than in the placebo group, and the proportion of children with spleen enlargement was reduced by 11%, although neither difference was significant. It was clear that children aged 12–36 months benefited most: They had 35% (95% CI, 14–50; *P* = .0023) fewer malaria attacks, 26% fewer enlarged spleens, and a 68% reduction in parasite density. Overall, given the considerable and relatively consistent data in humans and animals, it appears that vitamin A deficiency exacerbates malaria illness.

**Zinc**

Zinc is required for normal immune function [102] and reduces the incidence of diarrhea and pneumonia [103]. Indeed, zinc is essential for a variety of lymphocyte functions implicated in resistance to malaria, including production of IgG, interferon-γ, and tumor necrosis factor-α and microbial activity of macrophages [102, 104].

Cross-sectional studies among school-age children in Papua New Guinea [102] and in pregnant women in Malawi [105] revealed inverse associations between zinc status and *P. falciparum* parasitemia. In addition, a placebo-controlled trial of zinc supplementation in preschool children in The Gambia documented a 30% reduction in health center attendance due to *P. falciparum* [106], although this was not statistically significant. In mice, zinc supplements decreased markers of oxidative stress during infection with *P. berghei* [107]. Additional murine studies indicated that moderate zinc deficiency resulted in 40% mortality from the normally nonlethal rodent malaria *P. yoelii* 17X-NL [108].

A recently completed placebo-controlled trial of zinc supplementation of preschool children in Papua New Guinea provides additional evidence for the role of zinc in malaria [109]. In this study, zinc supplementation reduced the frequency of health center attendance due to *P. falciparum* malaria by 38%. Moreover, a 69% reduction was observed for malaria episodes accompanied by high levels of parasitemia (i.e., ≥100,000 parasites/μL), suggesting that zinc may preferentially protect against more severe malaria episodes. Although these effects are encouraging, additional trials are needed to document the geographic regions and conditions of malaria transmission in which zinc might be effective and to determine the potential effect on severe malaria. As for vitamin A, concordance between animal and human studies strongly suggests a significant exacerbative effect of even mild zinc deficiency on malaria.

**Iron**

Iron deficiency affects nearly 2 billion people worldwide and results in over 500 million cases of anemia [110]. Additional sequelae include poor neurologic development, lower work capacity, low birth weight, and increased maternal and infant mortality [111, 112]. The burden of both iron deficiency and malaria falls primarily on preschool children and pregnant women [113, 114], and iron supplementation of these groups is the primary means of preventing and treating anemia. Multiple studies have attempted to evaluate the benefit of iron supplementation in malaria-endemic areas [19, 115–134]. Some studies reported that iron supplementation increased the risk of developing or reactivating malarial illness [19, 115, 118], while others reported no significant adverse effects [123, 125, 135]. Experiments with rodent malaria have also yielded conflicting results [135–138]. To clarify this issue, a systematic review and meta-analysis of placebo-controlled trials of iron supplemen-
tion in humans was recently completed [139]. Data from 13 trials, 9 published [19, 115–118, 120, 123, 125, 127] and 4 unpublished [119, 121, 122, 124] (5230 subjects) were pooled to obtain composite effects of iron supplements on malaria attack rates, parasite prevalence, parasite density, prevalence of enlarged spleens, hemoglobin levels, and anemia.

Iron supplementation resulted in a nonsignificant 9% (relative risk [RR] = 1.09; 95% CI, 0.92–1.30; n = 8) increase in the risk of a malaria attack. End-of-trial cross-sectional data indicated a 17% (RR = 1.17; 95% CI, 1.08–1.25; n = 13) greater risk of infection in those given iron. For trials providing baseline data, the absolute increase in infection rates was 5.7% (95% CI, −1.2 to 8.5; n = 9), which was not significant. Iron supplements were also associated with a nonsignificant 12% (RR = 1.12; 95% CI, 0.99–1.26; n = 6) increase in risk of spleen enlargement. Qualitative assessment of parasite density suggested a tendency toward higher levels in persons receiving iron. A subanalysis of trials that implemented iron supplementation regimens in accord with international dosing recommendations revealed no evidence for increased infection or morbidity. Overall, hemoglobin levels improved by 1.2 g/dL (95% CI, 1.2–1.3; n = 11) following iron supplementation, and the risk of anemia was reduced by 50% (RR = 0.50; 95% CI, 0.45–0.54; n = 4).

The data indicate that prophylactic iron supplementation was associated with increases in certain malarialmetric indices. However, these tended to be relatively small effects. In contrast, improvements in hematologic status following iron supplementation were substantial and with clear public health benefit. It should be noted that the meta-analysis was unable to address the effects of oral iron supplements on severe malaria. In addition, although some evidence suggested greater adverse effects for persons residing in areas with moderate levels of malaria transmission, the specific effects of iron supplementation in certain settings or populations could not be determined. Overall, the meta-analysis suggests that iron supplementation programs in accord with international dosing guidelines should be advocated for iron-deficient populations residing in malaria-endemic areas. Ideally, malaria surveillance and control activities should be continued in such areas or integrated into those programs.

Folate

Folate is a crucial nutrient for cellular growth and is considered important for erythrocyte production. For these reasons and for its role in preventing neural tube defects, folate supplementation is part of prenatal care programs in most countries. Given that folate metabolism of the parasite is also a target for several antimalarial drugs, the interactions between host folate status and supplementation in malaria-endemic areas is of interest.

Folate deficiency was first seen to enhance susceptibility to avian malaria [140]. In contrast, primate malaria species were unable to survive in severely folate-deficient rhesus monkeys [141]. This protective effect of folate deficiency differs from observations in humans. Low infection rates were reported in pregnant women who were consuming a diet high in folates [142], and greater infection rates were also reported in those suffering from megaloblastic anemia [143]. However, malaria itself may induce folate deficiency [143, 144], and there is some evidence of improper red cell utilization of folates during malaria infection [145]. A trial of prophylactic folate supplementation in preschool children in The Gambia [146] showed no adverse effects for malaria. Also, a trial of folate supplements in pregnant women [147] showed no adverse effect on parasitemia, even though reticulocyte counts increased.

As mentioned, there has been concern over the possible interference of folate supplements with antifolate antimalarial drugs (e.g., pyrimethamine). Several studies have attempted to resolve this issue. Two separate trials reported that development of *P. falciparum* in vivo was not affected by folate supplements given with pyrimethamine [148, 149]. In one study, the folates were even given in doses sufficient to reverse the side-effects of high-dose pyrimethamine [149, 150]. However, a recent trial found greater treatment failure for pyrimethamine when folate supplements were given [151]. Overall, these data suggest that folate deficiency may exacerbate malaria morbidity. Although the routine use of folate supplements in malarious areas has been advocated to prevent or treat anemia [143], additional studies may be warranted despite strong evidence suggesting no adverse effects of folate supplements on drug efficacy.

Riboflavin

Riboflavin (vitamin B2) has an influence on malaria morbidity. The relationship appears to be one of antagonism such that deficiency confers a degree of protection. In Papua New Guinea, riboflavin-deficient infants are less likely to be infected with malaria [152, 153]. Similar observations were made in India [154] and The Gambia [155]. In India, malaria parasitemia was less severe in riboflavin-deficient persons [156], although the course of clinical illness appeared worse. Because riboflavin is an essential factor for glutathione peroxidase, an antioxidant enzyme, it has been proposed that deficiency promotes an oxidative environment that leads to destruction of the parasite. Indeed, lipid peroxidation was increased in riboflavin-deficient children with malaria infection [157], and reduced glutathione peroxidase activity was observed in red cells from riboflavin-deficient infected persons [158]. Reduced glutathione peroxidase activity persists in some populations in malarious areas despite adequate riboflavin intake [159], suggesting that isoforms with reduced activity confer resistance to malaria.

There is evidence for other mechanisms as well. *P. falciparum*-infected erythrocytes have an increased requirement for riboflavin [160]. Moreover, riboflavin analogues inhibit the
growth of parasites in vitro [161] and in vivo in experimental murine malaria [161]. In some cases these activities also correlated with reduced activity of glutathione reductase [161]. Riboflavin-deficient rats are also more resistant to malaria [162]. However, the studies in rats also suggested that the protective effect was not due to increased susceptibility of erythrocytes to oxidative damage, hemolysis, or erythropoiesis [163]. In contrast to the rodent studies, riboflavin-deficient chicks were more susceptible to *P. gallinaceum* [164].

Despite the human and animal-based evidence that riboflavin deficiency is protective, recent in vitro experiments suggest that high doses of riboflavin suppress parasite growth by preventing the oxidation of hemoglobin needed for digestion by the parasite [165]. Thus, although low riboflavin status may be protective, high-dose riboflavin therapy may prove beneficial for malaria patients. Paradoxically, the protective and exacerbative functions would be based on different sites of action for the same antioxidant properties of riboflavin. This again emphasizes the complex pathways through which nutrients influence malaria parasites and host morbidity.

**Thiamine and Pyridoxine**

A recent report from Thailand suggests that deficiency of thiamine (vitamin B1) is associated with greater risk of severe malaria and with simple clinical malaria [166]. This is consistent with early experiments in which thiamine-deficient ducks were more susceptible to avian malaria [167]. There are also reports that acute cerebral ataxia following malaria can be treated with thiamine [168], suggesting that disrupted thiamine metabolism may be a pathologic feature of malaria. The role of pyridoxine (vitamin B6) is less clear. In the sole experimental study of rats infected with *P. berghei*, pyridoxine deficiency attenuated the course of parasitemia [169]. Of interest, erythrocyte pyridoxine metabolism is down-regulated in humans with β-thalassemia [170], possibly indicating a protective effect of B6 deficiency. Additional studies are needed to clarify the role of B vitamins in malaria.

**Vitamin E and Other Antioxidants**

Several reports indicate that deficiencies of vitamin E and other antioxidants tend to protect against malaria infection [171]. As discussed above, the explanation most frequently given is that the absence of antioxidants makes the parasite more vulnerable to damage by oxygen radicals produced by the immune system. In humans, it was initially proposed that the exacerbative effects on cerebral malaria following refeeding of famine victims with grain was due to the vitamin E content of the grain [18]—a notion supported by the absence of cerebral malaria among famine victims given milk, which normally lacks vitamin E [172]. Other reports suggest that persons with lower plasma vitamin E levels recover more quickly from clinical malaria [173, 174].

The exacerbative effect of vitamin E on experimental animal malaria was first described in 1957 by Godfrey [175], who demonstrated that the antimalarial effects of cod liver oil in mice were reversible by giving vitamin E. Multiple studies in rodent systems confirm a protective effect of vitamin E deficiency [176–180] and the ability of vitamin E to abrogate the protective effects of pro-oxidant compounds, such as peroxidizable fatty acids, on malaria [177–180]. Of interest, vitamin E deficiency is also protective against murine cerebral malaria [181] in which oxidative damage plays a significant pathologic role. Studies of avian malaria in the duck also showed a protective effect of vitamin E deficiency [182].

No human studies have addressed the role of selenium in malaria. A few animal studies indicate that selenium has little role in modulating rodent malaria [183, 184]. However, selenium-deficient ducks were more susceptible to avian malaria [182]. Human data are clearly needed to clarify the influence of selenium on malaria.

Vitamin C has also been studied in animals but there have been few human studies. In monkeys, vitamin C deficiency exacerbated malaria [185]; however, in mice, results have been mixed. Godfrey [175] reported that large doses of vitamin C, as with vitamin E, abrogates the protective effect of cod liver oil. This was not the case, however, when lower doses were used in conjunction with vitamin E-deficient mice [171], nor did vitamin C supplements modify the course of parasitemia in normal mice. However, given that mice can synthesize vitamin C from precursors, the conclusions from such experiments are unclear. In contrast, there are also reports that highlight the role that vitamin C can play as a catalyst for generation of malarialcidal free radicals in conjunction with iron or copper [171, 186–189]. It has therefore been suggested that vitamin C supplementation may have a role in case management of malaria [188, 189].

Another antioxidant, β-carotene, has strong free-radical quenching properties and is nontoxic even at high doses. Indeed, β-carotene may have a protective role in murine cerebral malaria [190] in which oxygen radical-mediated damage plays a role, and some human studies have indicated specific modulation of plasma β-carotene levels during infection [92, 191, 192]. There are also anecdotal accounts of protective effects from hypercarotenemia [193] due to high consumption of palm oil, a rich source of β-carotene.

Overall, the data concerning antioxidants indicate that although antioxidant nutrients may have an exacerbative role under some conditions, it is not possible to predict the effect of a nutrient on malaria morbidity or mortality based on its antioxidant properties alone. Clearly, as seen with riboflavin and vitamin C, more detailed knowledge of the site of action of antioxidants on the parasite and host may prove useful. In addition, examination of the broader biologic functions of com-
pounds referred to as antioxidants may provide insight. Perhaps most importantly, there is a need for data from clinical trials in humans concerning the effects of antioxidant nutrients on malaria morbidity and mortality. Given that oxygen and nitrogen radical production is strongly activated during malaria illness and has been implicated in associated pathologies [194], there may be a role for antioxidants as adjunct for management of clinical malaria.

Summary and Conclusion

The studies reviewed indicate that nutrition is a key factor in modulating malaria morbidity and mortality. The effects of PEM, widely prevalent in malarious areas worldwide, substantially increase the public health burden of malaria. Deficiencies in several specific micronutrients (e.g., vitamin A and zinc) also exacerbate malaria. Of importance, nutritional modulation of malaria morbidity and mortality highlights the complex nature of resistance to malaria. Different nutrients such as vitamin A, zinc, and iron selectively modify different aspects of malaria immunity and pathology. For example, although both zinc and vitamin A reduce the incidence of *P. falciparum* episodes, the protective efficacy of zinc is greatest for *P. falciparum* episodes accompanied by hyperparasitemia, with little effect on cross-sectional malariometric indices [109]; however, while vitamin A provided little or no protection against episodes with hyperparasitemia, it tended to reduce splenomegaly and parasite densities [101]. Likewise, iron and riboflavin have distinct effects on malaria morbidity.

In general, little is known of the mechanisms whereby nutrients affect the immunity and pathophysiology of malaria infection. Certainly, the immunomodulatory properties of nutrients such as vitamins A and B complex, zinc, and folate are likely to be important. However, other effects of nutrients, including gene regulation in multiple tissues and antioxidant functions, could influence pathologic processes such as hypoglycemia, dyserythropoiesis, free-radical production, parasite sequestration, and apoptosis. The impact of a nutrient on disease outcome is influenced not only by the effect on the host but also by the effect of the nutrient on the biology of the parasite itself. The potentially protective and exacerbative roles played by deficiency and supplementation are illustrated by the ambiguous effects of riboflavin and vitamin C. Additional study of the mechanistic basis for the effects of nutrients may prove useful in elucidating mechanisms of immunity and pathology of malaria, possibly leading to new therapies or vaccines.

Efforts are needed to more carefully assess the role of nutrition and selective nutrients on malaria morbidity and mortality. Although this review was generally limited to nutrients for which there are some human data, animal studies have implicated potentially important effects of other nutrients on malaria, such as biotin [68, 195–197], fatty acids [198, 199], magnesium [200], and pantothenic acid [157, 201, 202].

<table>
<thead>
<tr>
<th>Table 3. Interaction between selected nutrient deficiencies and malaria in humans and animal models.</th>
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<td><strong>Nutrient deficiency</strong></td>
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<td><strong>Thiamine (B1)</strong></td>
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<td><strong>Riboflavin (B2)</strong></td>
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<td><strong>Pantothenic acid</strong></td>
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NOTE. ND, no data available; ↑, outcome increased; ↓, decreased; ←, results inconsistent; morbidity, any reported effect on malaria-related acute illness not including death; antagonistic, nutrient deficiency appeared to be protective for malaria; synergistic, deficiency appeared to exacerbate malaria.
3 presents a general summary of the effects of micronutrient deficiencies on malaria from human and experimental animal studies. Additionally, in vitro studies, beyond the scope of this review, implicate important roles for multiple nutrients and their analogues in parasite growth and survival. However, wide gaps in knowledge remain on the roles of key micronutrients on malaria, such as iodine and vitamin D.

Regarding clinical applications for case management of severe or drug-resistant malaria, this review provides evidence that riboflavin, β-carotene, vitamin C, other antioxidants, and zinc may prove useful. For general potentiating resistance to malaria, additional studies are needed, especially with respect to vitamins A, thiamine, riboflavin, zinc, specific amino acids, iodine, and fatty acids. There may also be important relationships between host nutritional status and malaria transmission. Concerns over exacerbative effects of some nutrients on malaria morbidity (e.g., iron and certain antioxidants) need to be addressed. However, rather than withholding of micronutrient supplementation from clearly malnourished populations, an integrated approach to malaria control and nutritional improvement should be adopted. Association of a deficiency with protection is not necessarily synonymous with supplementation being exacerbative. If certain nutrients are confirmed to be exacerbative for malaria in certain settings, novel methods for improving host nutritional status, perhaps in conjunction with other protective nutrients, would need to be developed. Indeed, the selective effects of specific nutrients on malaria morbidity and pathology suggest that specifically formulated multinutrient supplements may be envisaged to assist in the prevention or treatment of malaria.

The diverse and ubiquitous roles played by nutrients in both human and parasite biology underscore the need for carefully controlled community- and clinic-based field trials to document the effects of nutrients on malaria in humans. There is also a strong need for trials that integrate mechanistic studies to determine how nutrients influence specific and well-defined indicators of malaria immunity and pathology. Additional public health issues include examination of different nutritional requirements for pregnant women, adults, and children with respect to malaria. The unique physiology of malnutrition and malaria in severely malnourished persons, such as those encountered under famine conditions, warrants further attention. It would also be useful to understand how malaria affects dietary intake, dietary patterns, and food beliefs surrounding malaria illness. Much of this future research would include examination of *P. falciparum* in Africa; however, areas of Asia and Latin America should not be neglected. Although, the role of nutrition in *P. vivax* malaria is likely to be important.

From the public health perspective, the future success of malaria control lies in the ability to implement multiple effective interventions that are technologically and economically sustainable. The current focus on early detection and treatment, insecticide-treated bed nets, and vector control through environmental management are useful tools. Moreover, a malaria vaccine with at least partial efficacy may be available within the next decade.

This review underscores the strong role that nutrition plays in modulating malaria morbidity and mortality and illustrates the considerable potential for nutrient-based interventions in combating malaria. The observation that selective micronutrient supplementation with vitamin A or zinc can substantially lower malaria attack rates illustrates the potential of targeted nutrient-based interventions as adjuncts to malaria control programs. At less than $0.10 (US) for a 1-year supply [203], vitamin A supplementation would rank among the more cost-effective interventions for malaria [204]. Although micronutrient supplementation cannot replace other effective means to combat malaria, the concept of micronutrient-assisted control and stimulation of immunity to malaria (MACSIMAL) should be advocated. The MACSIMAL approach offers other advantages as well. For example, micronutrient supplementation may mitigate the delay in acquired immunity associated with bed nets [205] and chemoprophylaxis [116]. In addition, nutrients may substantially reduce morbidity from other infectious diseases [103, 206].

In summary, the deleterious effects of PEM and certain micronutrient deficiencies on malaria morbidity and mortality are substantial. Improvements in dietary intake of both macro- and micronutrients are likely to have considerable impact on reducing the disease burden of malaria. Thus, the study of nutritional modulation of malaria can both broaden basic knowledge of malaria biology and facilitate development of low-cost and effective nutrient-based interventions.

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This review was made possible by contributions from several persons who helped conceptualize the importance of nutrition on malaria. I especially thank Blaise Genton and Michael P. Alpers, Papua New Guinea Institute of Medical Research; Richard D. Semba, Alan L. Scott, Nirbhay Kumar, Robert E. Black, Rebecca J. Stoltzfus, James M. Tielsch, and Johns Hopkins Schools of Medicine and Public Health; Harry Goodall, University of Dundee; Paul Arthur, Kintampo Health Research Center, B. D. Akanmori, Noguchi Memorial Institute of Medical Research; James Kazura, Case Western Reserve University School of Medicine; and Neal Alexander, London School of Tropical Medicine and Hygiene. I also thank Sylvia N. Crone, Jeffrey McGuckin, Patrick Racca, Allisyn Moran, Ingrid Friberg, and Heather Haberle, for research assistance in producing this review.

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