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UNDERNUTRITION AS AN UNDERLYING CAUSE OF MALARIA MORBIDITY
AND MORTALITY

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ABSTRACT

Undernutrition is highly prevalent in many areas in which morbidity and mortality from malaria is unacceptably high. That undernutrition exacerbates diarrhea and respiratory infections is widely demonstrated, however, research suggests that it may exacerbate, palliate, or have little effect on malaria outcomes. This review examines the global burden of malaria associated with various nutrient deficiencies as well as underweight status and determines that, although the association is complex and requires additional research, improved nutritional status lessens the severity of malaria episodes and results in fewer deaths due to malaria. Deficiencies in vitamin A, zinc, iron, folate, as well as other micronutrients, are responsible for a substantial proportion of malaria morbidity and mortality. It is recommended that nutrition programs be integrated into existing malaria intervention programs.

INTRODUCTION

Malaria is a major cause of morbidity and mortality in tropical and subtropical regions. Malaria often afflicts populations that are both impoverished and malnourished, and a large portion of the burden of malaria falls upon the most vulnerable within the population, children and pregnant women.¹ A variety of interventions are utilized to combat malaria, including insecticide-treated bed nets, environmental control, chemoprophylaxis, and prompt, appropriate case management.² There exists no single solution or program to combat malaria, rather a comprehensive approach is required with concurrent interventions on many levels.

Nutrition plays a major role in maintaining health, and malnutrition appears to generate vulnerability to a wide variety of diseases and general ill health.^{3,4} Opinions are mixed regarding how undernutrition, whether it is characterized in terms of growth faltering or micronutrient malnutrition, affects susceptibility to malarial illness and mortality. Historical observational studies provide some evidence of harm resulting from adequate nutrition,⁵⁻¹⁰ whereas more recent studies indicate either no evidence of benefit or some benefits resulting from nutritional adequacy.^{1,11,12} Animal studies suggest that improved nutritional status is protective against malaria, but consensus has yet to be reached regarding its effects in human populations.¹ The purpose of this paper is to review the evidence from recent epidemiologic work on undernutrition as an underlying cause of malaria morbidity and mortality, and to highlight areas in which further research is required. The paper will review published research both on underweight or growth faltering in children, as well as particular micronutrient deficiencies that are considered relevant to the malaria-malnutrition association – iron, zinc and vitamin A.

Underweight

Undernutrition is considered to be the underlying cause of more than 50% of all childhood deaths in the world.¹³ Undernutrition diminishes the ability of all systems of the body to perform properly, with particularly grave consequences in young children. The relationship between underweight status and ill health, however, is complex because ill health often results in undernutrition and undernutrition increases susceptibility to disease, particularly severe disease. Numerous studies have demonstrated associations between undernutrition and growth retardation, impaired mental development, and increased susceptibility to infectious diseases.¹⁴⁻¹⁹

Undernutrition is generally characterized by comparing the weights or lengths of children at a given age to distribution of weights or lengths of generally healthy children, and calculating this relationship in terms of standard deviation scores or z-scores.²⁰ Z-scores can then be categorized in terms nutritional terms as mild (-1.01 to -2.00 SD), moderate (-2.01 to -3.0 SD) or severe (<-3.0 SD) undernutrition. The World Health Organization (WHO) maintains a global database on child growth and malnutrition in order to calculate the prevalence of undernutrition among children under five for each of the 14 WHO mortality regions.^{21,22} They utilize weight-for-age to assess underweight as an indicator of undernutrition because of its availability and its ability to capture both stunting (generally associated with long-term undernutrition) and wasting (manifestation of recent and acute undernutrition). As shown in Table 1, the regions with the highest prevalence of undernutrition in children under five are found in Southeast Asian regions B and D (25.8%, 45.9%) and African regions D and E (32.2%, 31.1%). As shown in Table 1, these are also the regions, especially in Africa, with high malaria burdens.²³

Children who are underweight are thought to have increased susceptibility to malaria for a variety of reasons, most notably through a reduction in the function of the immune system. When a child is undernourished, he or she may be unable to mount an appropriate immune response to the malaria parasite due to reduction in T lymphocytes, impairment of antibody formation, decreased complement formation, and atrophy of thymus and other lymphoid tissues, among others.²⁴

Early observational studies suggested a protective effect of undernutrition against malarial morbidity and mortality.^{5-8,10} Subsequently, a plethora of animal studies were conducted to resolve whether protein-energy malnutrition exerted protective effects against malaria morbidity and mortality. Although a number of studies concluded that protein-deprived animals experience less morbidity and mortality due to malaria, there was also evidence that the protein-deprived animals were also less able to clear the infection and develop less of an antibody response to the parasite.¹ Human studies conducted in resource-poor and famine environments have reported protective effects of undernutrition, assessed through clinical evaluations, autopsy reports, or refeeding programs.⁵⁻⁹ More recent studies, however, have not been unable to demonstrate a significant association between underweight status and malarial illness.^{1,11,25}

Recently, a series of analyses were conducted to obtain pooled estimates of the relationship between underweight and malaria morbidity and mortality across published studies (morbidity) or from extant data obtained from large prospective cohort studies (mortality).²³ This was done for the World Health Organization Comparative Risk Assessment (CRA) project, which sought estimates of the relationships between various risk factors, including undernutrition, and morbidity and mortality by cause. For

morbidity, data from two cohort studies were combined to calculate a pooled relative risk of clinical malaria among children with weight for age z-scores < -2 SD. Children who were moderately to severely underweight were found to have an increased but not statistically significant risk of a clinical malaria attack as compared to those better nourished (1.31, 95% confidence interval (CI): 0.92-1.88). For mortality, the authors examined multiple levels of underweight in studies in which anthropometric status was ascertained and children were followed prospectively for survivorship and cause of death was determined using described verbal autopsy methods.²³ Using analytic procedures pioneered by Pelletier et al.,^{13,17,26} data from three cohort studies with data on malaria attacks were combined to calculate a pooled relative risk of malaria mortality among children with varying levels of undernutrition. Children with z-scores < -3.0 SD were 9.49 (3.25-27.66) times more likely to die, those with z-scores between -2 and -3 SD were 4.48 (2.20-9.15) times more likely to die, and those with z-scores between -1 and -2 SD were 2.12 (1.48-3.02) times more likely to die from malaria than children with z-scores > -1 SD.²³

Based on these pooled relative risks and the estimates of underweight prevalence, the fraction of malaria morbidity and mortality attributable to underweight could be calculated (population attributable risk or PAR) (Tables 2 and 3). The worldwide attributable risk fraction was 8.2% for weight for age < -2 SD, although again because the risk estimate was not statistically significant, the confidence interval around this estimate could include 0%, meaning no contribution of underweight to malarial morbidity. The PAR was 57.3% for malaria mortality due to low weight for age (WA <-1 SD). Combining the prevalence data and the attributable risk fractions, the authors calculated

that 549,200 malaria deaths were attributable to undernutrition in children under five years of age.²³

Since the underlying data for the relative risk estimate is based on cohort studies, this estimate is likely to be confounded by a number of factors, including previous malarial episodes, micronutrient deficiencies, poverty, and poor access to health care. When considered within the spectrum of underweight severities, there appears to be a risk gradient. The most underweight children have the highest risk of malaria mortality and risk decreases with improved underweight status as identified by z-scores. Although the highest risk is associated with the most severely underweight children, the burden of disease or deaths is greater for children with mild to moderate underweight status because of the high prevalence of children with mild to moderate underweight status in many countries. Therefore, one needs to develop interventions that assist not only the severely underweight children, but also tackle the full spectrum of undernutrition within the population.^{16,23}

Iron deficiency anemia

That iron deficiency adversely affects human health is widely recognized.²⁷⁻³⁰ Iron plays a critical role in the transport of oxygen throughout the body and in cellular processes of growth and division. Iron deficiency results in a decrease in the hemoglobin concentration, which when sufficiently low is identified as anemia. In contrast, malaria causes anemia through cytokine-mediated suppression of hematopoiesis, and in addition, when infected with Plasmodium falciparum, the erythrocyte changes and becomes vulnerable to clearance.³¹ Hookworm and other infections which cause blood loss also contribute to iron deficiency and anemia, often severe anemia.³² All types of anemia,

regardless of cause, reduce the oxygen transported throughout the body, and this leads to decreased productivity, and increased risk of cardiovascular events.³³ Other poor health outcomes associated with iron deficiency and anemia include poor neurologic development in children, premature labor, low birth weight, and increased maternal and infant mortality.^{27,28,30,33} Pregnant women are particularly susceptible to iron deficiency because of the increased demands on their iron stores by the developing fetus.³²

Between two and five billion people worldwide are at least mildly iron deficient, making iron deficiency the most common micronutrient deficiency in humans today.^{34,35} Iron deficiency is responsible for the majority of anemia worldwide, but in malaria endemic regions, malaria makes a significant contribution to anemia. Folate and vitamin A deficiencies have also been linked with anemia, although to a lesser degree.³⁶⁻³⁸ The prevalence of anemia is often used to estimate the extent of iron deficiency in a population, even though in certain populations there may be other causes of anemia. As shown in Table 2, in malaria endemic regions, the prevalence of anemia in young children ranges from 50-70%.³² In order to obtain a conservative estimate of how much anemia is due to iron deficiency, one can look at the change in hemoglobin concentration over time with iron supplementation. Estimates range from 21% to 85% with an average of 51%.³⁹ A similar proportion of anemia was found to be alleviated with iron supplementation in clinical trials from malaria-endemic regions,⁴⁰ indicating similar beneficial hematological effects in both malaria endemic and non-malarious regions.

Despite the efficacy of supplementary iron for the prevention and treatment of iron deficiency and anemia, debate over the use of iron supplements in malaria-endemic regions continues because of concerns that they may increase susceptibility to malaria.

The nutritional immunity theory was developed from studies that observed a protective effect of iron deficiency on malaria severity.⁴¹ The theory suggests that depriving the parasite of essential nutrients (iron, in particular) creates an uninhabitable internal environment, thus preventing the parasite from fully proliferating. In 1985, a study in mice found that the entire iron-replete group of mice infected with Plasmodium chabaudi died, whereas the iron-deficient mice were far less likely to die. When the iron-deficient mice were then fed iron-sufficient foods, they fell victim to recrudescence parasitemia.⁴² More recent experimental evidence refutes the earlier nutritional immunity hypothesis and concludes no significant protection of iron deficiency in young rats.⁴³ In fact, iron deficiency impairs immune responses, including T-lymphocyte production and activity, natural killer cell activity, and neutrophil function.⁴⁴

The authors of the WHO CRA report on iron³² did not summarize findings across studies to examine the contribution of iron deficiency anemia to malaria disease burden. However, Shankar et al.⁴⁵ conducted a meta-analysis of 12 published and unpublished placebo-controlled iron supplementation trials^{7,46-56} to examine the effect of iron supplementation on malaria morbidity. Overall, there was a significantly heightened risk of infection as measured at the end of the study associated with malaria and iron supplementation (1.17, 1.08-1.25). Iron supplementation appeared to increase other malariometric indices, including risk of a malaria attack (1.09, 0.92-1.30; 8 studies) and spleen enlargement (1.12, 0.99-1.26; 6 studies), although the increases were not significant. The hematologic improvements in the iron supplementation groups summarized over the studies were significant and included an average increase in hemoglobin levels of 1.2 g/dL (1.2-1.3) and a 50% decrease in the risk of severe anemia

(45%-54%).⁴⁵ Thus, iron supplementation had the unintended consequence of marginally increasing certain malariometric indices in clinical trials. Consensus has not yet been reached on the risks and benefits associated with iron supplementation and malaria morbidity and mortality.⁴⁴ Although more research is indicated, current knowledge suggests that the alleviation of anemia through iron supplementation is likely to benefit all iron-deficient populations, including those in malaria-endemic regions.

Zinc deficiency

Zinc is a required element in basic biological processes such as gene expression, cellular growth and differentiation.⁵⁷ Due to the ubiquity of zinc in these basic processes, zinc deficiency can result in depressed immune function, growth faltering, and morbidity.^{58,59} One of the first clinical signs of inadequate zinc is depressed immunity⁶⁰ which may be reversed with zinc supplementation. A meta-analysis of zinc supplementation trials concluded that zinc deficiency contributes to growth faltering in young children in developing countries.⁶¹ A number of clinical trials have examined the effects of zinc supplementation on the incidence of diarrhea and pneumonia in children, and a pooled analysis of the results of these clinical trials indicated that the control group experienced a significantly higher risk of disease compared with the zinc supplementation group.⁶²⁻⁶⁴

Although the importance of zinc for human health is widely recognized, estimating the burden of disease resulting from zinc deficiency has been difficult due to inadequate tools with which to measure zinc deficiency.^{65,66} Plasma zinc levels are commonly used to assess zinc deficiency, but this method is neither adequately sensitive nor specific due primarily to zinc homeostasis.⁶⁶ In response to this lack of readily

available biomarkers, the International Zinc Nutrition Consultative Group (IZiNCG) developed a method to estimate the prevalence of zinc deficiency in a population by examining the availability of zinc in the local diet.⁶⁷ Using this method, the global prevalence of zinc deficiency has been found to range from 6-73% among WHO subregions, with an average prevalence of 31% worldwide.⁶⁴ As shown in Table 1, inadequate zinc intakes are highly prevalent in areas of the world affected by malaria. Given the high prevalence of zinc deficiency and the known role of zinc in immune function, it is important to consider whether zinc deficiency affects malarial morbidity and mortality.

Zinc deficiency decreases the ability of the body to respond to infection, affecting both cell-mediated immune responses and humoral responses.⁶⁰ B cell proliferation is less dependent on zinc than is T cell proliferation; however, zinc deficiency does result in fewer naïve B cells available to produce antibodies to new antigens.⁶⁸ However, zinc deficiency has been hypothesized to exacerbate malaria and other diseases (HIV, Tuberculosis) that rely on macrophage killing of infected cells.⁶⁰

As part of the acute phase response to infection, plasma zinc decreases as it is sequestered with metallothionein in the liver. Because zinc is a required nutrient for both the host and the parasite, this may be viewed as an adaptive response to deprive the parasite of required nutrients. However, it is important to bear in mind that despite decreased plasma zinc concentrations, the plasma concentrations remain well above any requirements of a parasite for replication.⁶⁰

Numerous animal studies have demonstrated the role of zinc in the immune response to infectious disease.⁶⁰ The studies that investigated the relationship between

zinc and malaria also showed a protective effect of zinc supplementation. For example, zinc supplementation of mice during infection with Plasmodium berghei resulted in decreased markers of oxidative stress.⁶⁹ In addition, moderate zinc deficiency was found to result in 40% mortality from a traditionally non-lethal form of rodent malaria, Plasmodium yoelii.⁷⁰

To date, three field trials have been performed to investigate the preventive effects of zinc supplementation on malaria morbidity and mortality in children.⁷¹⁻⁷³ In the Gambia (n=110), children who received 70 mg zinc supplementation twice weekly for 15 months had 32% (P=0.09) fewer malaria-related clinic visits than did the placebo group, but this was only marginally significant and the diagnostic criteria for malaria were not stated.⁷² A randomized trial in Papua New Guinea (n=274) found a 38% (3%-60%) reduction in clinic visits for slide-confirmed malaria in the group that received 10 mg elemental zinc supplementation six days a week for 46 weeks compared with a placebo group.⁷³ Finally, a randomized trial took place in Burkina Faso (n=709) that provided either placebo or 12.5 mg zinc sulphate supplementation six days a week for six months.⁷¹ This trial was unable to show a difference in malarial illness between the two groups (0.98, 0.86-1.11). They were, however, able to show a significant decrease in the prevalence of diarrhea in the zinc group (0.87, 0.79-0.95), confirming other evidence that zinc supplementation significantly decreases diarrhea morbidity. The Gambia and Papua New Guinea studies both used health center-based clinically-confirmed malaria episodes as their primary outcome of interest, whereas the Burkina Faso study incorporated household surveillance for fever along with the administration of the zinc supplements, and thus, was far more sensitive for identifying febrile days. But in an area with a high

background prevalence of parasitemia such as Burkina Faso, it is not clear how many were actually clinical malaria attacks. Furthermore, identification of these febrile days resulted in early treatment with anti-malarial drugs, potentially preventing more severe malarial illnesses.

Due to these differences in design, the Burkina Faso study was not considered comparable to the Gambia and Papua New Guinea studies and was dropped from a meta-analysis performed for the WHO CRA Project.⁶⁴ Combining the data from the Gambia and Papua New Guinea trials resulted in a pooled estimate of a 36% (9%-55%) decrease in malaria episodes brought to the health centers in the zinc supplementation group. A relative risk of 1.56 (1.29-1.89) for health center malaria episodes in zinc deficient young children was derived by calculating the inverse of the pooled odds ratio of the protective effect of zinc supplementation. In the absence of direct data, these risk estimates were extended to include deaths due to malaria as well. Based on the prevalences of inadequate zinc intake (Table 1) and the relative risk calculated from the pooled analyses, zinc deficiency in children 0-4 years old may be responsible for approximately 20% of malaria clinic attacks (Table 2) and 193,000 malaria deaths each year (Table 3).

Unlike many causes of death and disability, zinc deficiency is ultimately preventable with adequate support. Current intervention strategies focus on zinc supplementation, fortification of locally acceptable foods, and dietary modification to consume greater amounts of animal products and fewer fiber and phytates. Given the public health importance of zinc deficiency, the development of effective programs to reduce zinc deficiency is of high priority.

Vitamin A

Vitamin A plays an essential role in the immune response and in eye health.⁷⁴ The dominant symptom of severe vitamin A deficiency is xerophthalmia, a major cause of blindness in Africa and Latin America that initially appears as night blindness and results in corneal ulceration and blindness if left untreated.⁷⁵ Severe vitamin A deficiency is rare and most vitamin A associated morbidity results from mild to moderate deficiency. Vitamin A supplementation has been shown to increase general eye health, as well as decrease measles, diarrhea, and all-cause mortality.⁷⁴⁻⁸¹

There are a number of ways to measure prevalence of vitamin A deficiency.^{74,75} Serum retinol concentrations are often used with a cut-off of <0.70 umol/l. The prevalence of xerophthalmia or corneal lesions in a population can also be used to infer the prevalence of deficiency in the population. Ideally, one would like to be able to determine how much vitamin A is stored in the liver, and there are isotope dilution techniques currently being developed for this purpose.^{82,83} Regional prevalences have been calculated using existing country specific data on the prevalence of vitamin A deficiency determined by serum retinol concentration and clinical eye signs (Table 1).⁸⁴ As shown, vitamin A deficiency is common in malaria-endemic regions of the world.

Vitamin A plays an essential role in the proper functioning of the immune system and is believed to be necessary for host resistance to malaria, although early animal studies suggested that deficiency was protective.¹ In 1946, a study of vitamin A deficient chicks indicated severe vitamin A deficiency was associated with slightly milder infection with malaria compared with well nourished chicks, while the same experiment with ducks was unable to demonstrate an association.⁸⁵ Later studies in rats indicated that vitamin A deficient rats were significantly more susceptible to the rat malaria parasite

Plasmodium berghei than were those rats with adequate vitamin A intake.⁸⁶ Follow up studies, however, were less convincing and only able to demonstrate increased susceptibility to malaria in those rats with very severe vitamin A deficiencies that began when the rats were very young.⁸⁷ Overall, animal studies suggest that vitamin A deficient animals are more vulnerable to malaria morbidity and mortality.

The hypothesized mechanism through which vitamin A mediates susceptibility to malaria is increased phagocytosis of parasitized erythrocytes and reduced pro-inflammatory cytokine responses to infection. Vitamin A may assist in the upregulation of CD36 expression which aids in phagocytosis and may activate substances (peroxisome proliferators-activated receptor - PPAR α) which inhibit the inflammatory responses associated with severe and cerebral malaria.⁸⁸

Cross-sectional studies suggest an inverse relationship between plasma retinol concentrations and increased malaria parasitemia,⁸⁹⁻⁹⁴ but, as with all observational and cross-sectional studies, the causality of the association is uncertain. More clear causal evidence on vitamin A and malaria would come from randomized controlled trials, but to date, only two clinical trials of vitamin A supplementation have been conducted in regions with endemic malaria.⁹⁵⁻⁹⁷ A clinical trial in Papua New Guinea found a significantly lower risk of malaria morbidity in the vitamin A group compared with the placebo group (0.70, 0.57-0.87).⁹⁵ A clinical trial in Ghana found no association between vitamin A supplementation and malaria morbidity or mortality, however, this study did not have the statistical power to detect a difference of less than 70% between the two groups.^{96,98}

For the purposes of the WHO CRA project, the relative risk of malaria attributable to vitamin A deficiency was calculated by taking the inverse of the protective effect seen in the Papua New Guinea study.⁸⁴ Combining the risk estimates with vitamin A prevalence data, the PAR of malaria morbidity and mortality for vitamin A was calculated (Table 2 and 3). The fraction of malaria morbidity attributable to vitamin A deficiency was determined to be 20% worldwide, but was considerably higher in malaria endemic regions. Over 90% of the 187,000 malaria deaths worldwide attributable to vitamin A deficiency occur in Africa.⁸⁴

Current intervention strategies include supplementation, fortification of a variety of foods, and education regarding the importance of vitamin A rich foods in the diet.

Other nutritional factors

There are a number of other micronutrients that play a role in the immune system and have been associated with malaria incidence, including folate, long-chain polyunsaturated fatty acids, antioxidants, riboflavin, and thiamine.¹ Of these, folate has often been studied because of the role folate plays in the mode of action of some types of antimalarial drugs. Sulfadoxine + pyrimethamine (SP) works primarily through the interruption of folate metabolism in the parasite and is commonly used in areas in which chloroquine resistance has spread. Sometimes mutations cause the parasite to become less sensitive to the antifolates like SP, inducing resistance. Another way resistance to SP is thought to occur is because some lines of Plasmodium falciparum are able to access exogenous folate and thus circumnavigate the blocked folate synthesis mechanism.⁹⁹ It is the latter means to resistance that worries nutritionists. Folate supplementation is provided widely in antenatal programs in developing countries to prevent and treat

anemia.³⁵ Folic acid also plays a major role in cell mediated immunity, as well as DNA and protein synthesis in general. Initial studies of folic acid supplementation demonstrated decreased anemia in the folic acid supplementation group, and there was no sign of interference with anti-malarial activity of pyrimethamine.¹⁰⁰ However, a more recent clinical trial looked at the effects of chloroquine and SP treatments in conjunction with iron and folic acid supplementation in the Gambia and found that folic acid supplementation significantly increased SP treatment failure rate, while iron supplementation was not associated with increased prevalence of malaria.¹⁰¹ Improving the folic acid status of women in order to prevent anemia and neural tube defects is undisputedly necessary; yet questions remain regarding the effect folic acid supplementation has on the effectiveness of anti-folates used in malaria treatment.

Fatty acids are thought to be toxic to Plasmodium falciparum and deficiency should be corrected.^{102,103} Deficiencies of antioxidants like vitamins E and C, however, appear to damage the parasite through increased exposure to oxygen radicals and may therefore be protective to the host.¹⁰⁴ Along the same vein, deficiency of riboflavin may also be protective for the host because it encourages oxidative activity which is harmful for the parasite.¹⁰⁵⁻¹⁰⁷ However, recently published studies have put into question the theory that a reduction in antioxidants is protective. A longitudinal study in Uganda found that children with acute malaria have depressed plasma concentrations of antioxidants.¹⁰⁸ In addition, scientists in Gabon used high performance liquid chromatography to determine riboflavin levels in acute malaria cases and were unable to find an association between riboflavin deficiency and parasitemia.¹⁰⁹ Finally, with regard

to thiamine, an observational study concluded that deficiency was associated with more severe infections, cerebral malaria in particular.¹¹⁰

The relationship between malarial illness and nutrition is undeniably complex. Additional effort must be put into elucidating the contributions of each micronutrient, both individually and in combination, with regard to malaria.

DISCUSSION

Existing evidence strongly suggests that micronutrient deficiencies and general undernutrition increase the burden of malaria morbidity and mortality. Attributable fractions calculated by the CRA project^{23,64,84} demonstrate that large numbers of children under five likely suffer and die from malaria due to nutritional inadequacies in terms of protein energy, zinc and vitamin A. These numbers can be interpreted in a very hopeful fashion because these illness episodes and deaths are entirely preventable with appropriate nutritional interventions. Available evidence suggests that iron supplementation programs may result in no or a small increased risk of malarial illness, but this must be verified, and weighed against the known benefits of preventing and treating anemia. Overall, contrary to previously held beliefs regarding the undernourished individual being an unattractive host for the parasite, it seems that a well-nourished individual is better able to mount an immune response and is more capable of withstanding and clearing infection.

Susceptibility to malaria among famine victims that are in a re-feeding program may, however, be a problem. The evidence indicates that re-feeding famine victims enables multiplication of the parasite more quickly than it restores the resistance of the

individual, leading to parasite recrudescence. In famine relief, it is recommended that malaria chemoprophylaxis is provided at the time of re-feeding and that the population is monitored carefully for malaria and provided with appropriate treatment.

The diagnosis of malaria mortality or morbidity is notoriously non-specific, particularly in endemic areas with year-round transmission, indicating a research need for better diagnostic tools. Although the CRA authors reviewed studies with similar definitions, subtle differences may have resulted in biased estimates of the beneficial effects of the nutritional interventions. More concerted effort to reach consensus on definitions of malaria morbidity and to use them in future studies is necessary if we are to refine our estimates of the malaria burden attributable to undernutrition.

It may be noted that we have considered these nutritional deficiencies as distinct entities, although they commonly are found in the same individuals. Much of the data summarized in the CRA come from published and unpublished randomized controlled trials of micronutrient supplements, and thus estimate the risk associated with each individual risk factor. For example, although underweight individuals may also be vitamin A deficient, the converse may not be true, in that one need not be underweight to be vitamin A deficient. Therefore, underweight status and vitamin A deficiency effects are relatively independent. This independence is confirmed in vitamin A supplementation trials that found mortality reductions with Vitamin A in both poorer and better nourished children.^{77,78} Because zinc deficiency contributes to growth faltering, there may be some overlap of the risks from underweight and zinc deficiency,⁶¹ although it is important to point out that zinc supplementation has been effective in reducing infectious disease in

children independent of their overall nutritional status as characterized by weight or height.^{62,63}

In summary, the evidence suggests that improving nutritional status of young children in multiple ways may reduce malaria morbidity and mortality, and should be considered within the packet of interventions to reduce the global burden of disease due to malaria. Careful evaluations of nutrition programs in malaria-endemic areas are needed to confirm this. Although treated separately in terms of estimating disease burden, improving nutritional status should follow an integrated approach, tackling both growth faltering and micronutrient deficiencies at the same time, and considering behavioral approaches as well as supplementation and fortification. The ultimate impact of integrated nutrition programs on malaria morbidity and mortality remains to be tested. However, regardless of their effect on malaria, such programs are important for reducing growth faltering and deaths in young children due to other causes such as diarrhea and pneumonia, and the beneficial externalities of nutrition programs likely extend to human capital formation, adult work capacity, and overall quality of life.

Reference List

1. Shankar AH, 2000. Nutritional modulation of malaria morbidity and mortality. *J Infect Dis* 182 Suppl 1:S37-53.: S37-S53.
2. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS, 2003. How many child deaths can we prevent this year? *The Lancet* 362: (9377) 65-71.
3. Semba RD, Bloem M, eds., 2001. Nutrition and Health in Developing Countries. Humana Press, Totowa, NJ.
4. Martorell R, Haschke F, eds., 2001. Nutrition and Growth. Nestle Nutrition Workshop Series, Pediatric Program, Vol. 47, Lipincott, Williams & Wilkins, Philadelphia, PA.
5. Hendrickse RG, Hasan AH, Olumide LO, Akinkunmi A, 1971. Malaria in early childhood. An investigation of five hundred seriously ill children in whom a "clinical" diagnosis of malaria was made on admission to the children's emergency room at University College Hospital, Ibadan. *Ann Trop Med Parasitol* 65: (1) 1-20.
6. Murray MJ, Murray NJ, Murray AB, Murray MB, 1975. Refeeding-malaria and hyperferraemia. *Lancet* 1: (7908) 653-654.
7. Murray MJ, Murray AB, Murray MB, Murray CJ, 1978. The adverse effect of iron repletion on the course of certain infections. *Br Med J* 2: (6145) 1113-1115.
8. Murray MJ, Murray AB, Murray NJ, Murray MB, 1978. Diet and cerebral malaria: the effect of famine and refeeding. *Am J Clin Nutr* 31: (1) 57-61.

9. Edington G, 1954. Cerebral malaria in the Gold Coast African: four autopsy reports. *Ann Trop Med Parasitol* 48: 300-306.
10. Murray MJ, Murray AB, Murray MB, Murray CJ, 1976. Somali food shelters in the Ogaden famine and their impact on health. *Lancet* 1: (7972) 1283-1285.
11. Man WD, Weber M, Palmer A, Schneider G, Wadda R, Jaffar S, Mulholland EK, Greenwood BM, 1998. Nutritional status of children admitted to hospital with different diseases and its relationship to outcome in The Gambia, West Africa. *Trop Med Int Health* 3: (8) 678-686.
12. Tshikuka JG, Gray-Donald K, Scott M, Olela KN, 1997. Relationship of childhood protein-energy malnutrition and parasite infections in an urban African setting. *Trop Med Int Health* 2: (4) 374-382.
13. Pelletier DL, Frongillo EA, Jr., Schroeder DG, Habicht JP, 1995. The effects of malnutrition on child mortality in developing countries. *Bull World Health Org* 73: 443-448.
14. Tomkins A, Watson F, 2003. Malnutrition and infection: a review. *United Nations Administrative Committee on Coordination/Subcommittee on Nutrition* 5. ACC/SCN State-of-the-Art Series, Nutrition Policy Discussion Paper No. 5.
15. Victora CG, Barros FC, Kirkwood BR, Vaughan JP, 1990. Pneumonia, diarrhea, and growth in the first 4 y of life: a longitudinal study of 5914 urban Brazilian children. *Am J Clin Nutr* 52: (2) 391.

16. Pelletier DL, 1994. The relationship between child anthropometry and mortality in developing countries: implications for policy, programs and future research. *J Nutr* 124: (10 Suppl) 2047S-2081S.
17. Pelletier DL, Frongillo EA, Jr., Habicht JP, 1993. Epidemiologic evidence for a potentiating effect of malnutrition on child mortality. *Am J Public Health* 83: (8) 1130-1133.
18. Pollitt E, Gorman KS, Engle PL, Martorell R, Rivera J, 1993. Early supplementary feeding and cognition: effects over two decades. *Monogr Soc Res Child Dev* 58: (7) 1-99.
19. Rice AL, Sacco L, Hyder A, Black RE, 2000. Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. *Bull World Health Organ* 78: (10) 1207-1221.
20. Lohman T.G., Roche A.F., Martorell R. (1988) Anthropometric standardization reference manual. Human Kinetics Books, Champaign, IL.
21. de Onis M, Monteiro C, Akre J, Glugston G, 1993. The worldwide magnitude of protein-energy malnutrition: an overview from the WHO Global Database on Child Growth. *Bull World Health Org* 71: (6) 703-712.
22. de Onis M, Frongillo EA, Blossner M, 2000. Is malnutrition declining? An analysis of changes in levels of child malnutrition since 1980. *Bull World Health Org* 78: (10) 1222-1233.
23. Fishman S, Caulfield LE, de Onis M, Blossner M, Hyder A, Mullany L, Black

RE, 2003. Malnutrition and the global burden of disease: underweight. In: Comparative Quantification of Health Risks: The Global and Regional Burden of Disease due to 25 Selected Major Risk Factors. World Health Organization/Harvard University Press, Cambridge, (in press).

24. Scrimshaw NS, SanGiovanni JP, 1997. Synergism of nutrition, infection, and immunity: an overview. *Am J Clin Nutr* 66: (2) 464S-477S.

25. Tshikuka JG, Gray-Donald K, Scott M, Olela KN, 1997. Relationship of childhood protein-energy malnutrition and parasite infections in an urban African setting. *Trop Med Int Health* 2: (4) 374-382.

26. Pelletier DL, Frongillo EA, Jr., Schroeder DG, Habicht JP, 1994. A methodology for estimating the contribution of malnutrition to child mortality in developing countries. *J Nutr* 124: (10 Suppl) 2106S-2122S.

27. Beard JL, 2001. Iron biology in immune function, muscle metabolism and neuronal functioning. *J Nutr* 131:568S-580S.

28. Brabin BJ, Premji Z, Verhoeff F, 2001. An analysis of anaemia and child mortality. *J Nutr* 131:636S-645S.

29. Haas JD, Brownlie T, 2001. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr* 131:676S-690S.

30. Grantham-McGregor S, Ani C, 2001. A review of studies on the effect of iron deficiency on cognitive development in children. *J Nutr* 131:649S-666S.

31. Biggs B, Brown G. Malaria. In: Gillespie S, Pearson R, editors. Principles and Practice of Clinical Parasitology. John Wiley & Sons Ltd; 2001. p. 53-98.
32. Stoltzfus RJ, Mullany L, Black RE, 2003. Iron deficiency anemia. In: Comparative Quantification of Health Risks: The Global and Regional Burden of Disease due to 25 Selected Major Risk Factors. World Health Organization/Harvard University Press, Cambridge, (in press).
33. Brabin BJ, Hakimi M, Pelletier D, 2001. An analysis of anaemia and pregnancy-related maternal mortality. *J Nutr* 131:604S–614S.
34. Stoltzfus RJ, 2001. Defining Iron-Deficiency Anemia in Public Health Terms: A Time for Reflection. *J Nutr* 131: (2) 565S.
35. Stoltzfus RJ, Dreyfuss M, 1998. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. ILSI Press, Washington DC.
36. Fleming AF, 1982. Iron deficiency in the tropics. *Clin Haematol* 11: (2) 365-388.
37. Masawe AE, 1981. Nutritional anaemias. Part 1: Tropical Africa. *Clin Haematol* 10: (3) 815-842.
38. Baker SJ, 1981. Nutritional anaemias. Part 2: Tropical Asia. *Clin Haematol* 10: (3) 843-871.
39. Beaton G, 2002. Functional outcomes of iron deficiency and iron deficiency in pregnancy and beyond. Proceedings of the INACG Symposium, February 15-26, 2001, Hanoi, Vietnam.

40. INACG, 2000. Safety of iron supplementation programs in malaria-endemic regions. ILSI, Washington, DC.
41. Kochan I, 1973. The role of iron in bacterial infections, with special consideration of host-tubercle bacillus interaction. *Curr Top Microbiol Immunol* 60: 1-30.
42. Harvey PW, Bell RG, Nesheim MC, 1985. Iron deficiency protects inbred mice against infection with *Plasmodium chabaudi*. *Infect Immun* 50: (3) 932-934.
43. Cardoso MA, Ferreira MU, Ribeiro GS, Penteadó MD, Andrade Junior HF, 1996. Dietary iron supplementation does not aggravate experimental malaria in young rats. *J Nutr* 126: (2) 467-475.
44. Oppenheimer SJ, 2001. Iron and its relation to immunity and infectious disease. *J Nutr* 131: (2S-2) 616S-633S.
45. Shankar AH, Fishman S, Goodman S, Stoltzfus RJ. Iron supplementation and morbidity due to *Plasmodium falciparum*: a meta-analysis of randomized controlled trials, unpublished report.
46. Oppenheimer SJ, Gibson FD, Macfarlane SB, et al, 1986. Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. *Trans Royal Soc Trop Med Hyg* 80: 603-12.
47. Menendez C, Kahigwa E, Hirt R, et al, 1997. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* 350: 844-9.

48. Chippaux JP, Schneider D, Apolgan A, Dyck JL, Berger J, 1991. Effets de la supplementation en fer sur l'infection palustre. *Bull de la Soc Pathol et Exotique* 84; 54-62.
49. Smith AW, Hendrickse RG, Harrison C, Hayes RJ, Greenwood BM, 1989. The effects of malaria of treatment of iron-deficiency anaemia with oral iron in Gambian children. *Ann Trop Paediatr* 9; 17-23.
50. Stoltzfus RJ, Albonico M, Tielsch JM, 1998. The effect of iron supplementation on hematological indicators in preschool children in Zanzibar, unpublished.
51. Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM, 1994. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. *J Nutr* 124: 645-54.
52. Adam Z, 1996. Iron supplementation and malaria: a randomized, placebo-controlled field trial in rural Ethiopia [dissertation]. London: University of London.
53. Gebreselassie H, 1996. Iron supplementation and malaria infection: results of a randomized controlled field trial [dissertation]. Montreal: McGill University.
54. Harvey PWJ, Heywood PF, Nesheim MC, et al., 1989. The effect of iron therapy on malarial infection in Papua New Guinea schoolchildren. *Am J Trop Med* 40; 12-8.
55. Fleming AF, Ghatoura GBS, Harrison KA, Briggs ND, Dunn DT, 1986. The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Ann Trop Med Parasit* 80; 211-33.

56. Menendez C, Todd J, Alonso PL, et al., 1994. The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Trans Royal Soc Trop Med Hyg* 88; 590-3.
57. Macdonald RS, 2000. The role of zinc in growth and cell proliferation. *J Nutr* 130: (5S Suppl) 1500S-1508S.
58. Sandstead HH, 1991. Zinc deficiency. A public health problem? *Am J Dis Child* 145: (8) 853-859.
59. Hambidge M, 2000. Human zinc deficiency. *J Nutr* 130: (5S Suppl) 1344S-1349S.
60. Shankar AH, Prasad AS, 1998. Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr* 68: (2 Suppl) 447S-463S.
61. Brown KH, Peerson JM, Rivera J, Allen LH, 2002. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 75: (6) 1062-1071.
62. Zinc Investigators' Collaborative Group (S. Sazawal and R.E. Black, coordinators), 1999. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: Pooled analysis of randomized controlled trials. *J Pediatr* 135(6): 689-697.
63. Zinc Investigators' Collaborative Group, 2000. Therapeutic effects of zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 72: 1516-1522.

64. Caulfield L, Black RE, 2003. Zinc Deficiency. In: Comparative Quantification of Health Risks: The Global and Regional Burden of Disease due to 25 Selected Major Risk Factors. World Health Organization/Harvard University Press, Cambridge, (in press).
65. Hambidge M, 2003. Biomarkers of Trace Mineral Intake and Status. *J Nutr* 133: (3) 948S.
66. Brown KH, 1998. Effect of infections on plasma zinc concentration and implications for zinc status assessment in low-income countries. *Am J Clin Nutr* 68: (2 Suppl) 425S-429S.
67. Brown KH, Wuehler SE, Peerson JM (2001) The importance of zinc in human nutrition and estimation of the global prevalence of zinc deficiency. *Food and Nutrition Bulletin*, **22**:113–125.
68. Ibs KH, Rink L, 2003. Zinc-Altered Immune Function. *J Nutr* 133: (5) 1452S.
69. Arif AJ, Mathur PD, Chandra S, Singh C, Sen AB, 1987. Effect of zinc diet on xanthine oxidase activity of liver of mice infected with Plasmodium berghei. *Indian J Malariol* 24: (1) 59-63.
70. Shankar AH, 1995. Zinc deficiency exacerbates experimental malaria infection in mice. *FASEB J* 9: (A4269).
71. Muller O, Becher H, van Zweeden AB, Ye Y, Diallo DA, Konate AT, Gbangou A, Kouyate B, Garenne M, 2001. Effect of zinc supplementation on malaria and other

causes of morbidity in west African children: randomised double blind placebo controlled trial. *BMJ* 322: (7302) 1567.

72. Bates CJ, Evans PH, Dardenne M, Prentice A, Lunn PG, Northrop-Clewes CA, Hoare S, Cole TJ, Horan SJ, Longman SC, ., 1993. A trial of zinc supplementation in young rural Gambian children. *Br J Nutr* 69: (1) 243-255.

73. Shankar AH, Genton B, Baisor M, Paino J, Tamja S, Adiguma T, Wu L, Rare L, Bannon D, Tielsch JM, West KP, Jr., Alpers MP, 2000. The influence of zinc supplementation on morbidity due to Plasmodium falciparum: a randomized trial in preschool children in Papua New Guinea. *Am J Trop Med Hyg* 62: (6) 663-669.

74. Sommer A, West KJ. Vitamin A Deficiency: health, survival and vision. Oxford University Press, Inc New York; 1996.

75. Sommer A. Nutritional blindness: xerophthalmia and keratomalacia. Oxford University Press, New York; 1982.

76. Beaton G, Martorell R, Aronson K, 1993. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. 13. ACC/SCN Statement-of-the-Art, Nutrition policy discussion paper.

77. West KP, Jr., Pokhrel RP, Katz J, LeClerq SC, Khatri SK, Shrestha SR, Pradhan EK, Tielsch JM, Pandey MR, Sommer A, 1991. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 338: (8759) 67-71.

78. Sommer A, Tarwotjo I, Djunaedi E, et al, 1986. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. *Lancet* 1:1169-73.
79. Markowitz LE, Nzilambi N, Driskell WJ, Sension MG, Rovira EZ, Nieburg P, Ryder RW, 1989. Vitamin A levels and mortality among hospitalized measles patients, Kinshasa, Zaire. *J Trop Pediatr* 35: (3) 109-112.
80. Hussey GD, Klein M, 1990. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 323: (3) 160-164.
81. Fawzi WW, Mbise R, Spiegelman D, Fataki M, Hertzmark E, Ndossi G, 2000. Vitamin A supplements and diarrheal and respiratory tract infections among children in Dar es Salaam, Tanzania. *J Pediatr* 137: (5) 660-667.
82. Haskell MJ, Mazumder RN, Peerson JM, Jones AD, Wahed MA, Mahalanabis D, Brown KH, 1999. Use of the deuterated-retinol-dilution technique to assess total-body vitamin A stores of adult volunteers consuming different amounts of vitamin A. *Am J Clin Nutr* 70: (5) 874-880.
83. Ribaya-Mercado JD, Solon FS, Dallal GE, Solomons NW, Fermin LS, Mazariegos M, Dolnikowski GG, Russell RM, 2003. Quantitative assessment of total body stores of vitamin A in adults with the use of a 3-d deuterated-retinol-dilution procedure. *Am J Clin Nutr* 77: (3) 694-699.

84. Rice AL, West KP, Jr., Black RE, 2003. Vitamin A Deficiency. In: Comparative Quantification of Health Risks: The Global and Regional Burden of Disease due to 25 Selected Major Risk Factors. World Health Organization/Harvard University Press, Cambridge, (in press).
85. Roos A, Hegsted D, Stare F, 1946. Nutritional studies with the duck. IV. The effect of vitamin deficiencies on the course of *P. lophurae* infection in the duck and the chick. *J Nutr* 32: 473-484.
86. Krishnan S, Krishnan AD, Mustafa AS, Talwar GP, Ramalingaswami V, 1976. Effect of vitamin A and undernutrition on the susceptibility of rodents to a malarial parasite *Plasmodium berghei*. *J Nutr* 106: (6) 784-791.
87. Stoltzfus RJ, Jalal F, Harvey PW, Nesheim MC, 1989. Interactions between vitamin A deficiency and *Plasmodium berghei* infection in the rat. *J Nutr* 119: (12) 2030-2037.
88. Serghides L, Kain KC, 2002. Mechanism of protection induced by vitamin A in *falciparum* malaria. *Lancet* 359: (9315) 1404-1406.
89. Filteau SM, Morris SS, Abbott RA, Tomkins AM, Kirkwood BR, Arthur P, Ross DA, Gyapong JO, Raynes JG, 1993. Influence of morbidity on serum retinol of children in a community-based study in northern Ghana. *Am J Clin Nutr* 58: (2) 192-197.
90. Galan P, Samba C, Luzeau R, Amedee-Manesme O, 1990. Vitamin A deficiency in pre-school age Congolese children during malarial attacks. Part 2: Impact of parasitic disease on vitamin A status. *Int J Vitam Nutr Res* 60: (3) 224-228.

91. Friis H, Mwaniki D, Omondi B, Muniu E, Magnussen P, Geissler W, Thiong'o F, Michaelsen KF, 1997. Serum retinol concentrations and *Schistosoma mansoni*, intestinal helminths, and malarial parasitemia: a cross-sectional study in Kenyan preschool and primary school children. *Am J Clin Nutr* 66: (3) 665-671.
92. Samba DC, Basco LK, Bleiberg-Daniel F, Lemmonier D, Le Bras J, 1992. Absence of effect of retinol on the in vitro development of *Plasmodium falciparum*. *Int J Vitam Nutr Res* 62: (1) 99-100.
93. Tabone MD, Muanza K, Lyagoubi M, Jardel C, Pied S, Amedee-Manesme O, Grau GE, Mazier D, 1992. The role of interleukin-6 in vitamin A deficiency during *Plasmodium falciparum* malaria and possible consequences for vitamin A supplementation. *Immunology* 75: (3) 553-554.
94. Thurnham DI, Singkamani R, 1991. The acute phase response and vitamin A status in malaria. *Trans R Soc Trop Med Hyg* 85: (2) 194-199.
95. Shankar AH, Genton B, Semba RD, Baisor M, Paino J, Tamja S, Adiguma T, Wu L, Rare L, Tielsch JM, Alpers MP, West KP, Jr., 1999. Effect of vitamin A supplementation on morbidity due to *Plasmodium falciparum* in young children in Papua New Guinea: a randomised trial. *Lancet* 354: (9174) 203-209.
96. Binka FN, Ross DA, Morris SS, Kirkwood BR, Arthur P, Dollimore N, Gyapong JO, Smith PG, 1995. Vitamin A supplementation and childhood malaria in northern Ghana. *Am J Clin Nutr* 61: (4) 853-859.

97. Glasziou PP, Mackerras DE, 1993. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 306: (6874) 366-370.
98. Shankar AH, 1995. Vitamin A and malaria. *Am J Clin Nutr* 62: (4) 842-843.
99. Macreadie I, Ginsburg H, Sirawaraporn W, Tilley L, 2000. Antimalarial drug development and new targets. *Parasitol Today* 16: (10) 438-444.
100. Tong M, Strickland G, Votteri B, Gunning J, 1970. Supplemental folates in the therapy of Plasmodium falciparum malaria. *JAMA* 214: 2330-2333.
101. van Hensbroek MB, Morris-Jones S, Meisner S, Jaffar S, Bayo L, Dackour R, Phillips C, Greenwood BM, 1995. Iron, but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria. *Trans R Soc Trop Med Hyg* 89: (6) 672-676.
102. Krugliak M, Deharo E, Shalmiev G, Sauvain M, Moretti C, Ginsburg H, 1995. Antimalarial effects of C18 fatty acids on Plasmodium falciparum in culture and on Plasmodium vinckei petteri and Plasmodium yoelii nigeriensis in vivo. *Exp Parasitol* 81: (1) 97-105.
103. Arun KC, Das UN, 1999. Lipid peroxides, nitric oxide and essential fatty acids in patients with Plasmodium falciparum malaria. *Prostaglandins Leukot Essent Fatty Acids* 61: (4) 255-258.
104. Levander OA, Ager AL, Jr., 1993. Malarial parasites and antioxidant nutrients. *Parasitology* 107 Suppl.:S95-106.: S95-106.

105. Oppenheimer SJ, Bull R, Thurnham DI, 1983. Riboflavin deficiency in Madang infants. *P N G Med J* 26: (1) 17-20.
106. Thurnham DI, Oppenheimer SJ, Bull R, 1983. Riboflavin status and malaria in infants in Papua New Guinea. *Trans R Soc Trop Med Hyg* 77: (3) 423-424.
107. Dutta P, Pinto J, Rivlin R, 1985. Antimalarial effects of riboflavin deficiency. *Lancet* 2: (8463) 1040-1043.
108. Metzger A, Mukasa G, Shankar AH, Ndeezi G, Melikian G, Semba RD, 2001. Antioxidant status and acute malaria in children in Kampala, Uganda. *Am J Trop Med Hyg* 65: (2) 115-119.
109. Traunmuller F, Ramharter M, Lagler H, Thalhammer F, Kremsner PG, Graninger W, Winkler S, 2003. Normal riboflavin status in malaria patients in Gabon. *Am J Trop Med Hyg* 68: (2) 182-185.
110. Krishna S, Taylor AM, Supanaranond W, Pukrittayakamee S, ter Kuile F, Tawfiq KM, Holloway PA, White NJ, 1999. Thiamine deficiency and malaria in adults from southeast Asia. *Lancet* 353: (9152) 546-549.

Table 1. Prevalence (%) of underweight and micronutrient deficiencies in children 0-4 in regions of the world in which malaria is a public health problem^{23,32,64,84}

Region	Weight-for-age z-score			Anemia	Zinc deficiency	Vitamin A deficiency
	< -3	< -2	< -1			
AFR-D	7	25	38	60	37	28
AFR-E	7	24	38	60	62	35
EMR-D	5	20	38	63	52	23
SEAR-B	5	21	38	49	34	48
SEAR-D	13	33	36	66	73	30
WPR-B	2	14	34	49	9	14

AFR-D: Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea- Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo;

AFR-E: Botswana, Burundi, Central African Republic, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe;

EMR-D: Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen

SEAR-B: Indonesia, Sri Lanka, Thailand;

SEAR-D: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal;

WPR-B: Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam;

Table 2 Fraction of clinical malarial attacks attributable to nutritional deficiencies^{23,64,84}

Region	Population Attributable Fraction (%)		
	Underweight < -2 Z-score	Zinc deficiency	Vitamin A deficiency
AFR-D	8.4	17.1	18
AFR-E	8.1	26.0	22
EMR-D	6.6	18.5	15
SEAR-B	6.8	3.0	27
SEAR-D	11.8	3.9	19
WPR-B	4.1	0.0	10
World	8.2	20.1	20

See Table 1 for countries in each region

Table 3. Malaria mortality and fraction of deaths attributable to nutritional deficiencies^{23,64,84}

Region	Malaria deaths in children 0-4 (000s)	Population Attributable Fraction (%)		
		Underweight	Zinc	Vitamin A
AFR-D	435.2	57.7	17.1	18.2
AFR-E	415.5	56.7	26.0	21.7
EMR-D	45.4	51.3	18.5	15.0
SEAR-B	3.3	52.0	3.0	30.3
SEAR-D	54.1	66.4	3.9	18.5
WPR-B	3.0	39.8	0.0	0.0
World	958.5	57.3	20.1	19.5

See Table 1 for countries in each region