Asymptomatic malaria in the etiology of iron deficiency anemia: a malariologist’s viewpoint¹–³

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In populations that are frequently exposed to malaria, a large proportion of individuals are in a state of premunition, whereby infection occurs without symptoms or signs other than a reduction in hemoglobin concentration by 10–20 g/L. The immunity resulting from frequent exposure to infectious mosquito bites is sufficient to control but not prevent infection, is slowly acquired, and is rapidly lost in infection-free conditions. Left untreated, such asymptomatic Plasmodium infections may persist for months. When treated, reinfection can occur rapidly, because individuals in many areas receive 3–4 infectious mosquito bites per night. Such reinfections are not necessarily accompanied by symptoms. The prevalence and density of parasitemia, as well as the level of infection-induced inflammation, are dependent on age, pregnancy status, and previous exposure to infection. In highly endemic areas, the prevalence and density of parasitemia reaches a peak at the age of 6–36 mo, and thereafter declines with age; in conditions of low, seasonal transmission, a state of premunition is often not attained.

Malaria-induced inflammation is common even in individuals with asymptomatic infection and may be associated with impaired intestinal absorption of ingested iron, impaired release of storage iron from hepatocytes, and impaired recycling by macrophages of iron that is derived from phagocytosis of senescent or parasitized erythrocytes. Although sequestration of iron may contribute to suppression of erythropoiesis during malaria attacks, such effects are usually transient: the loss of iron from lysed cells through excretion is usually limited, and sequestered iron can be recycled shortly after antimalarial therapy (1). Because asymptomatic infections typically last much longer, however, they may contribute to the burden of iron deficiency anemia and decrease the efficacy of iron interventions.

In a nonrandomized crossover study reported in this issue of the Journal, Cercamondi et al (2) report suppression of iron absorption in young, nonpregnant, nonlactating Beninese women without malaria symptoms but with asexual Plasmodium parasites >500/μL blood. Intestinal iron absorption averaged 10% while infected and 18% after treatment. Systemic iron utilization (83–85%) was not altered. These results are similar to findings in Gambian children recovering from acute episodes of malaria (1).

What is the significance of this reduced iron absorption in asymptomatic malaria to the overall burden of iron deficiency anemia in malaria-endemic areas? It is worth noting that only a small fraction of the women screened by Cercamondi et al (or of the women with positive blood smear tests) had parasite densities within the eligible range to take part in the study. Thus, the effect of infection in the overall population of women may be less than suggested by the data from the women selected (2). On the other hand, asymptomatic children often have much higher parasite densities than the values reported by Cercamondi et al, possibly resulting in an even stronger inhibition of iron absorption. Finally, few of the women studied were anemic at baseline, and effects on iron absorption may be less pronounced in those with anemia.

There is surprisingly little evidence from trials, however, that the efficacy of iron interventions in children depends on malaria. Cercamondi et al (2) assert that iron interventions are less efficacious in malaria-endemic areas than in malaria-free areas; however, these areas may differ in other factors that determine the response to iron. In 2 randomized trials that were conducted in Kenyan preschool children living in varying levels of malaria endemicity, there was neither evidence that intermittent administration of antimalarial drugs resulted in marked improvement in iron status nor that it enhanced the efficacy of concurrent iron supplementation (3, 4). In Kenyan schoolchildren, there was no evidence that asymptomatic infections at baseline, which were left untreated, influenced the magnitude of the effect of fortification with iron as NaFeEDTA (5). These and other trials have conclusively shown, however, that iron interventions alone can improve iron status in iron-deficient pediatric populations exposed to malaria. The notion that screening and treatment of Plasmodium infection should allow for efficacious and safe universal iron supplementation, as suggested by De Mast et al (6), is not supported by epidemiologic evidence.

Further studies are thus required to reconcile the discrepant findings from Cercamondi et al (2) and the trials mentioned in the previous paragraph. Although Plasmodium infection may impair absorption of iron from a single sorghum meal (2), this inhibition may be less pronounced when averaged over many

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² The author is supported by the INSTAPA project, which receives funding from the European Union’s Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 211484.

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First published online November 10, 2010; doi: 10.3945/ajcn.110.006700.
meals in a diet, with different staple foods and varying amounts of phytate and polyphenols. In addition, the effect of *Plasmodium* infection on iron metabolism and erythropoiesis may vary between populations. For example, in the study by Cercamondi et al (2), serum transferrin receptor concentrations were lower at day 1 than at day 15, suggesting that erythropoiesis was suppressed during *Plasmodium* infection despite serum erythropoietin concentrations being higher. Although a malaria-associated decrease in serum transferrin receptor concentration has been reported in several studies, other studies have found that asymptomatic *Plasmodium* infection is associated with elevated serum transferrin receptor concentrations, suggesting increased erythropoiesis (7, 8).

The author is supported by the INSTAPA project, which receives funding from the European Union’s Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 211484. The work of Cercamondi et al was cofunded by the same project.

**REFERENCES**


