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Iron Deficiency and Severe *Plasmodium falciparum* Malaria

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(See the Major Article by Gwamaka et al, on pages 1137–44.)

It is noteworthy that micronutrient malnutrition, including iron (Fe) deficiency (ID), is usually highly prevalent in malaria endemic areas. Since the 1960s, it was believed that micronutrient deficiencies are associated with increased morbidity and mortality from malaria and that malaria, in turn, may contribute to poor nutritional status, thus reflecting the classic vicious cycle of malnutrition and infection [1].

Worldwide, ID (usually defined as a ferritin level <12 µg/L) is the most prevalent nutritional deficiency, affecting over 2 billion people [2]. Infants, women of childbearing age, and preschool-aged children are particularly affected because Fe requirements increase during growth, pregnancy, and lactation.

The treatment of ID, which usually includes Fe supplementation, represents one of the priority areas within the World Health Organization micronutrient initiative program. However, iron

supplementation is still a contentious issue because there is fear that it will lead to detrimental effects on plasmodial infections. This is in line with the nutritional immunity theory, which was developed based on bacterial infection studies that observed a protective effect of ID on disease severity [3]. This theory suggests that depriving the parasite of essential nutrients such as Fe creates an unfavorable internal environment, thus preventing the parasite from full proliferation. However, the mechanism(s) involved is not fully understood and remains to be elucidated.

With regard to Fe deficiency/supplementation in the face of infection with malaria, various conflicting disease outcomes have been reported from different studies. Oppenheimer et al [4] and more recently Sazawal et al [5] demonstrated that Fe supplementation increased the risk of malaria among children in endemic areas. Although malaria risks were not increased in some other Fe supplementation trials, these results have raised concern over routine Fe supplementation programs in malarious areas [6, 7].

In this issue of *Clinical Infectious Diseases*, Gwamaka and colleagues, recognizing that remarkably few studies have examined the relationship between Fe status and malaria in unsupplemented populations, present a study that sought to evaluate the impact of physiologic Fe on the risk of malaria [8]. The study claims that, together with antibody-

mediated immunities against infection and disease acquired with age, ID provides strong protection against parasitemia and malaria-associated morbidity and mortality during childhood.

They used a well-defined cohort of mothers and their children in Tanzania, whom they followed up for up to 3 years. They first identified a high prevalence of ID in their birth cohort, which far exceeds that reported from healthy European children but is consistent with previous results. The proportion of mothers with ID at delivery was similarly high. Why is the prevalence of ID so high in the children and mothers in the study area? The authors speculated that this concordance may reflect a shared Fe-poor diet or inherited mutations in Fe metabolism. In the latter possibility, the genetic polymorphisms related to Fe transport, storage, regulation, or heme synthesis might have been selected by malaria, resulting in a balance between ID anemia and protection against malaria disease in accordance with malaria hypothesis. Concerning an Fe-poor diet, one thing we do not know is if all infants were breastfed, and if they were, for how long. Breastfeeding would help to explain the high prevalence of ID recorded in this group. The income/education of the mothers would also be related to the diet, especially in such a setting. The study considered the effects of confounding factors, such as sickle cell status, but, nevertheless, it failed to look out

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for other hemoglobinopathies and helminthic infections, such as hookworm. It would also have been informative if the study considered the effects of other micronutrients such as vitamin A, which is an essential nutrient for the hematopoietic system and is known to have an effect on Fe uptake. These factors should be included in future studies.

The determination of ID using either hematological or biochemical parameters (including serum Fe, ferritin, transferrin, and soluble transferrin receptor) is often difficult, particularly in malaria-endemic regions, because they are both affected by infections, including malaria itself as well as other infections or inflammation. As such, some inflamed individuals with ID will be misclassified as Fe replete. This study effectively addressed this potential misclassification in several ways, including the establishment of separate threshold levels of ferritin for inflamed and noninflamed ID subjects, by measuring C-reactive protein levels or by the restriction of analyses of concurrent Fe status and parasitemia to samples obtained during nonsick visits.

Overall, the study clearly shows that malaria risk is influenced by physiologic Fe status and that Fe supplementation may have adverse effects, even among children with ID. What do these results mean for the primary healthcare activities targeting children at peripheries in Sub-Saharan Africa, where both ID and malaria are common?

Iron deficiency and malaria both have serious hematological consequences, and ID anemia is associated with growth failure (both physical and intellectual) in children. An understanding of the interaction between the 2 may provide better insight into public health strategies targeted toward their control. As such, intervention against both ID and malaria would require integrated and synergistic approaches. In this context, Fe supplementation together with intensive deployment of effective intervention tools, such as artemisinin-combination

treatment and insecticide-treated bed nets, would be an attractive option. Iron supplementation programs can be more safely conducted if early diagnosis and treatment for malaria cases functions well. Especially, in circumstances where current scaled-up control activities have already decreased malaria morbidity and mortality or where malaria elimination has already been integrated into the healthcare agenda, there should not be any reservation for Fe supplementation because an ID status is no longer required for protection against malaria disease.

Effective control would also require the diagnosis and treatment of other underlying causes of ID and anemia, thus highlighting the importance of treatment programs for other coinfections, including human immunodeficiency virus and helminthic infections, and other micronutrient deficiencies. This should take into account the specific etiology and prevalence of ID in a given setting and population group. And, of course, the sustainability of any control program would be critical.

Studies focused on assessing the effect of both targeted and community-based micronutrient interventions on disease outcome, especially in the groups most at risk, would also be of critical importance. These studies should take into consideration the transmission intensity and prevalence of malaria infection, prevalence of ID (if of public health relevance for community intervention or not), general nutrition, and prevalence of hemoglobinopathies and other infections. Improvements in diagnostic tools to distinguish ID anemia from anemia of inflammation/chronic disease are also necessary.

In conclusion, although the benefits of Fe supplementation have generally been considered to outweigh the potential associated risks, Gwamaka et al highlight the fact that caution is required, because supplementation might carry the risk of increased severity of disease in the presence of malaria. However, the following questions still remain to be addressed:

- How should Fe be delivered—via oral administration, parenteral administration, or food fortification programs?
- What dose of Fe supplementation is both safe and effective?
- What is the optimal duration of Fe supplementation in order to observe an appreciable effect/response?
- Does Fe supplementation affect the course of other infections aside from malaria?
- Is there any interaction between ID and other micronutrient deficiencies, such as vitamin A and zinc, per se?
- In areas where malaria prevalence and mortality is on the decrease, would the same strategy be relevant? What are the changes that would be required?

Whatever the decision, whether to supplement or not, the benefits need to be optimized in order to minimize risk.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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