Iron deficiency and anemia control for infants and young children in malaria-endemic areas: a call to action and consensus among the research community[1–3]

Kimberly B. Harding* and Lynnette M. Neufeld
Micronutrient Initiative, Ottawa, Ontario, Canada

ABSTRACT

WHO recommendations on iron supplementation for infants and young children in malaria-endemic areas changed dramatically from universal to targeted supplementation for iron-deficient children only, after a trial in a high malaria transmission area showed an increased risk of hospital admission and mortality among iron-replete children following iron and folic acid supplementation. Since this time, there has been much debate and little agreement among the nutrition research community on how to move forward, and country policy and program decision makers have been left with incomplete guidance on how to address young child iron deficiency and anemia in their countries. The focus of a recent symposium during the American Society for Nutrition annual meeting, held in Washington, DC, in April 2011, was on exploring options for addressing iron deficiency and anemia among infants and young children in malaria-endemic areas, *now*, with safe, effective, and feasible interventions that provide iron. Papers based on the invited presentations are included in this supplement. The first paper is a review of the relationship between iron and malaria. The second is an analysis of theoretical and practical considerations regarding the targeted approach of providing iron and includes results from field testing noninvasive screening devices. This is followed by a review of the safety of universal provision of iron through home-fortification products in malaria-endemic areas. The final papers provide a call to action by highlighting pending research issues (fourth paper) and feasible strategies to move programs forward (fifth paper). *Adv. Nutr. 3: 551–554, 2012.*

In 2006, WHO and UNICEF issued a joint statement advising that, in settings where malaria and other infectious disease prevalence is high, iron and folic acid supplementation be targeted at young children who are anemic and at risk of iron deficiency (ID), in the presence of effective infectious disease control (1). After an expert consultation that year, similar but more specific recommendations were published in 2007; notably, the target group was specified as children younger than 2 y of age and iron supplementation was recommended for only those with detected ID where a screening system for ID is available and for only those with clinical symptoms of severe anemia where screening is not available (2). This advice against universal iron supplementation was a dramatic departure from the normative guidelines at the time (3,4). The change in recommendations was a result of findings from the now-infamous large-scale trial that took place in Pemba, Zanzibar, a setting with year-round malaria transmission and high mortality from infectious disease, where the iron and folic acid intervention arms were stopped early due to safety concerns (5). Results showed that iron and folic acid supplementation, with or without zinc, among children 1 to 35 mo of age resulted in a greater risk of hospitalization and death compared with placebo (although increased risk of death was not statistically significant). Results from an embedded substudy, which included more intensive illness diagnosis and treatment and collected detailed information on iron status and anemia, were in contrast to the main study findings and showed non-statistically significant trends towards fewer adverse events

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* To whom correspondence should be addressed. E-mail: kharding@micronutrient.org.

among children in the iron and folic acid groups (with or without zinc) compared with placebo. The benefit was highly pronounced and statistically significant among those with ID (indicated by zinc protoporphyrin), anemia, or both. Conversely, there was a trend toward increased risk of adverse events among iron-replete children (with or without anemia), hence the new recommendations for supplementing only those with ID.

Despite the previous WHO guidance for universal iron supplementation to prevent iron deficiency anemia in infants and young children in settings where anemia prevalence is >40% (3,4), many iron supplementation programs in malaria-endemic areas up to this time did not meet the conditions necessary for success and impact [i.e., high coverage (large proportion of children reached) and adequate utilization (consumption of supplements according to program design)]. Therefore, the actual likelihood of adverse effects among a large proportion of children in malaria-endemic settings was probably low. However, programs were stopped in these settings, particularly in sub-Saharan Africa, due to fears of causing harm and the lack of clarity on how to implement safe, effective, and feasible programs that followed the new WHO recommendations.

The WHO meeting participants' recommendations addressed some important aspects of program design and implementation, but several important concerns remained. For example, they recommended using processed complementary foods fortified with iron to control ID in malaria-endemic areas among all children 6 to 24 mo of age (2). Although this may be a viable option is some settings, there are several limitations to this approach, (e.g., food is much more expensive than supplements, and if programs are not carefully designed, the foods may not be well targeted due to intrahousehold sharing). If fortified processed complementary foods are not available, the recommendation was to provide iron supplementation only to children with detected ID or clinical symptoms of severe anemia (where screening systems are not available) and in conjunction with malaria prevention and control measures (2). Using the latter approach, however, children with anemia but without severe clinical symptoms would not be given supplemental iron, leaving them at risk of the negative consequences of anemia and ID. The feasibility of screening also presents a major challenge in low-resource settings where caregivers and their young children do not have regular access to well-equipped health services, as is often the case in settings with high ID, anemia, and malaria burdens. WHO meeting participant recommendations provided no guidance on which, if any, other indicators could be used where the preferred indicator (zinc protoporphyrin-to-heme ratio) is not an option (2). Those in the research community understand that a lack of information impedes further recommendations, but that is little consolation to policymakers and those planning and implementing programs.

Even though the new WHO recommendations were specific to children younger than 2 y of age, in practice, they affected older children as well because many countries have programs with broader age ranges (e.g., younger than 5 y of age). In addition, and perhaps more importantly, this atmosphere of fear and uncertainty also hampered the discussion and introduction of new programs that provide iron to infants and young children in forms other than the traditional iron supplements. There has been a paradigm shift, most notable since the Pemba trial, from approaches that deliver only 1 or 2 micronutrients (e.g., iron or iron/folic acid supplementation) to those that aim at improving infant and young child nutrition more broadly (6,7). A major focus of the latter approach is improving the quality of complementary foods, including increasing the density of iron and other micronutrients, most commonly through home fortification using multiple micronutrient powders or lipid-based nutrient supplements. Although it was acknowledged that home fortification may be safer than iron supplements due to the food base, the WHO meeting participants advised that the same precautions be adopted when using these products as with iron supplements because their safety had not been demonstrated yet (2). Due to this recommendation and fears of causing harm, the introduction of these new products into programs has also been challenged and many program and policy decision makers working in malaria-endemic areas have been hesitant to act until there is evidence of safety and clear normative guidance recommending this approach.

It has been 5 years since the initial response by WHO to the Pemba trial findings. Although there has been some progress in the understanding of potential underlying biological mechanisms (8), there has also been considerable debate and little agreement among the nutrition research community on options for addressing ID and anemia in malaria-endemic contexts and how to move policies and programs forward (9–13). In 2009, Ojukwu et al. (11) published a Cochrane Review of iron supplementation among children in malaria-endemic areas and concluded that that screening is not necessary because iron supplementation did not increase the risk of malaria or death where malaria control was in place. This did not, however, convince everyone that iron could be provided safely without screening first. Questions remained, for example regarding the degree of malaria control necessary before the risk was adequately decreased (13). The 2009 Cochrane Review was recently updated and included subgroup analysis to assess safety of iron supplementation in different age groups, including those younger than 2 y; the authors came to essentially the same conclusion as in the 2009 review (14).

The debate around provision of iron to young children in malaria-endemic areas has not been without consequences. In Africa alone, the region with the greatest malaria burden (15), it is estimated that tens of millions of young children are at risk of ID, anemia, and their negative effects, especially on child development (16–18). Country policy and program decision makers have been left for 5 years with incomplete guidance on how to address these issues in their countries. As a result, malaria-affected countries have increasingly sought guidance on programming iron interventions from

agencies such as the Micronutrient Initiative as well as researchers. The scientific community has a vital role in helping develop policy guidance, and country program decision makers turn to this group for feasible advice that is based on the best available evidence, even if the evidence is not perfect. The imperfect understanding of the risks and benefits of providing iron to young children in malaria-endemic areas presents an immense and important challenge to this community. According to a recent commentary on this issue, however, the public health community should be as willing to intervene as it is to refrain from intervening on issues of such great public health relevance (10). Unfortunately, the substantial benefit of iron and folic acid supplementation among iron-deficient and/or anemic children seen in the Pemba substudy has been systematically overlooked, which has prevented a truly balanced approach to considering the risks and benefits of intervening and not intervening.

Several randomized, controlled trials using iron-containing home-fortification products have been conducted in malaria-endemic areas (19,20). On a very small scale in proportion to the burden, programs using these products have been implemented in malaria-endemic settings outside the controlled environment of a clinical trial [e.g., in Kenya (21,22)]. WHO very recently issued 2 new relevant guidelines, one on multiple micronutrient powders for children 6 to 23 mo of age (23) and one on intermittent iron supplementation for preschool- and school-age children (24). Both guidelines acknowledged that data on malaria and other illness outcomes are lacking and reiterated that measures to prevent, diagnose, and treat malaria should accompany provision of iron. Both also suggested these interventions for settings where anemia prevalence among the target population is >20%; however, there was no mention of targeting the interventions at anemic or iron-deficient individuals. A WHO guideline specifically on iron supplementation for children in malaria-endemic areas is expected soon [though it will not be specific to children younger than 2 y of age, as the WHO meeting participant recommendations were (2)].

Although several forums on this topic have been organized at recent international meetings, their focus has generally not been on programmatically relevant issues to assist policymakers and program designers in making decisions that maximize the potential benefits and minimize any potential harm of programs that provide iron to infants and young children. The objective of a recent symposium at the American Society for Nutrition annual meeting, held in Washington, DC, in April 2011, was to explore options for addressing ID and anemia among infants and young children in malaria-endemic areas, *now* with safe, effective, and feasible interventions that provide iron. Papers based on the invited presentations are included in this supplement. The first paper is a review of what is known about the relationship between iron and malaria (25). The second paper is an analysis of some key theoretical and practical considerations on screening for anemia and/or ID and targeted provision of iron (26). This paper also reviews the screening technology available and under development and reports on results from field testing noninvasive devices to measure hemoglobin levels. This is followed by a review of the evidence on safety of universal provision of iron in malaria-endemic areas through home-fortification products, which also includes an overview of the current theories on the biological mechanisms responsible for the adverse effects of iron on infectious disease (6). The fourth paper is an overview of the important research needs from basic science to global policy (27). The final paper highlights the dilemma at hand and proposes feasible strategies to move forward with programs that minimize the risk and maximize the benefit of iron interventions while we wait for the results of research that will eventually further inform these strategies (7).

Despite imperfect knowledge on the risks and benefits of providing iron to infants and young children in malaria-endemic areas, the nutrition and malaria research communities must work together to provide country policy and program decision makers with feasible advice that is based on the best available evidence. Findings from current and future research can help improve this advice, but, as with most topics in health and nutrition, we must be willing to work with incomplete knowledge and not let it impede the progress of programs that save and improve children's lives.

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Literature Cited

1. World Health Organization and United Nations Children's Fund. Iron supplementation of young children in regions where malaria transmission is intense and infectious disease highly prevalent. WHO UNICEF Joint Statement. 2006 Available from: http://www.who.int/child_adolescent_health/documents/iron_statement/en/index.html.
2. World Health Organization. Conclusions and recommendations of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas. Food Nutr Bull. 2007;28:S621–7.
3. International Nutritional Anemia Consultative Group. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Washington, DC: International Life Sciences Institute Press; 1998.
4. World Health Organization. Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers. Geneva: WHO Press; 2001.
5. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, Dhingra U, Kabole I, Deb S, Othman MK, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet. 2006;367:133–43.
6. Dewey KG, Baldiviez LM. Safety of universal provision of iron through home-fortification of complementary foods in malaria-endemic areas. Adv Nutr.2012;3:555–9.
7. Stoltzfus RJ. Iron and malaria interactions: programmatic ways forward. Adv Nutr.2012;3:579–82.
8. Hurrell R. Iron and malaria: absorption, efficacy and safety. Int J Vitam Nutr Res. 2010;80:279–92.
9. Stoltzfus R. Commentary: Cochrane Review on Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. Int J Epidemiol. 2010;39:34–5.
10. Suchdev PS, Leeds IL, McFarland DA, Flores R. Is it time to change guidelines for iron supplementation in malarial areas? J Nutr. 2010; 140:875–6.

11. Ojukwu JU, Okebe JU, Yahav D, Paul M. Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. Cochrane Database Syst Rev. 2009;(3):CD006589.
12. Verhoef H, Veenemans J. Safety of iron-fortified foods in malaria-endemic areas. Am J Clin Nutr. 2009;89:1949–50.
13. Roth DE, Black RE, Ojukwu JU, Okebe JU, Yahav D, Paul M. Commentary on 'Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas' with a response from the review authors. Evid Based Child Health. 2010;5:1186–8.
14. Okebe JU, Yahav D, Shbita R, Paul M. Oral iron supplementations for children in malaria-endemic areas. Cochrane Database Syst Rev. 2011;(10):CD006589.
15. World Health Organization. World Malaria Report 2010 [Internet]. Geneva: WHO Press; 2010. Available from: http://www.who.int/malaria/world_malaria_report_2010/en/index.html.
16. World Health Organization, Centers for Disease Control and Prevention. Worldwide prevalence of anaemia 1993–2005: WHO global database on anaemia. Geneva: WHO Press; 2008.
17. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, Carter JA., International Child Development Steering Group. Child development: risk factors for adverse outcomes in developing countries. Lancet. 2007;369:145–57.
18. Lozoff B. Iron deficiency and child development. Food Nutr Bull. 2007;28:S560–71.
19. Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. Am J Clin Nutr. 2007;86:412–20.
20. Smuts CM, Dhansay MA, Faber M, van Stuijvenberg ME, Swanevelder S, Gross R, Benadé AJ. Efficacy of multiple micronutrient supplementation for improving anemia, micronutrient status, and growth in South African infants. J Nutr. 2005;135:653S–9S.
21. Micronutrient powder (MixMe™) use in Kakuma refugee camp in Kenya. Health, 2009. Available from: http://www.nutritionimprovement.com/pdf/kenya_briefing.pdf.
22. Suchdev PS, Ruth L, Obure A, Were V, Ochieng C, Ogange L, Owuor M, Ngure F, Quick R, Juliao P, et al. Monitoring the marketing, distribution, and use of Sprinkles micronutrient powders in rural western Kenya. Food Nutr Bull. 2010;31:S168–78.
23. World Health Organization Guideline: Use of multiple micronutrient powders for home fortification of foods consumed by infants and children 6–23 months of age. Geneva: WHO Press; 2011. Available from: http://www.who.int/elena/titles/micronutrientpowder_infants/en/index.html.
24. World Health Organization Guideline: Intermittent iron supplementation in preschool and school-age children. Geneva: WHO Press; 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241502009_eng.pdf.
25. Spottiswoode N, Fried M, Drakesmith A, Duffy PE. Implications of malaria on iron-deficiency control strategies. Adv Nutr. 2012;3:570–8.
26. Crowley C, Solomons NW, Schümann K. Targeted provision of oral iron: the evolution of a practical screening option. Adv Nutr. 2012;3:560–9.
27. Prentice AM, Cox SE. Iron and malaria interactions: research needs from basic science to global policy. Adv Nutr. 2012;3:583–91.