
SAFETY OF IRON

SUPPLEMENTATION PROGRAMS

IN MALARIA-ENDEMIC REGIONS

Problem Statement

Iron deficiency affects more than 2 billion people and, on a global basis, is the most common cause of anemia. Programs to control iron deficiency anemia (IDA) may yield numerous benefits to public health, including improved health and development in children, reduced mortality in pregnant women and young children, and increased work productivity in all individuals. A reduction in IDA by the year 2000 was adopted by the World Summit for Children in 1990 and the International Conference of Nutrition in 1992. In anemia control programs, oral iron supplementation is important in almost all contexts.

IDA occurs in areas where malaria transmission is endemic, most notably sub-Saharan Africa. Severe anemia is increasingly recognized as an important manifestation of severe malaria in young children.¹⁻² Laboratory evidence and early evidence from clinical trials had suggested that several interactions may exist between iron status and malaria such that iron supplementation may increase the risk of malaria infection and morbidity. Concern about the safety of iron supplementation given to individuals in malarious areas has sometimes been a barrier to the implementation of iron supplementation programs. In light of the urgent need to control IDA throughout the world, a review of the available evidence on the risks and benefits of iron supplementation in malarious areas was undertaken.

Summary of Evidence

A systematic search identified nine published³⁻¹¹ and four unpublished¹²⁻¹⁵ placebo-controlled, randomized trials of iron supplementation in malarious areas for which malariometric indices had been recorded. The 13 trials ranged in sample size from 80 to 841, totaling 5230 subjects. The 13 trials included two with infants,^{3,4} four in preschool children,^{5,6,12,13} three in school-age children,^{7,8,15} four in adults,^{9-11,14} and two in pregnant women.^{10,11} Outcomes consisted of malaria parasite prevalence and density, clinical malaria attacks, splenomegaly, hemoglobin concentrations, and prevalence of anemia. All but two of the trials, which took place in Papua New Guinea,^{3,8} were carried out in Africa. First, the studies were reviewed to assess their quality and similarity. Then the data were summarized quantitatively to assess the effect of iron on various malaria-related endpoints, and to examine the modification of that effect by location, endemicity, age, pregnancy, and dose.

The trials differed in numerous ways, and no two trials were identical in the majority of design elements. When all trials were considered together for shared outcomes, the following results were obtained. Iron supplementation was associated with a small, non-statistically signifi-

cant increase in the risk of a clinical malaria attack (relative risk [RR] = 1.1, 95% confidence interval [CI] = 0.9–1.3, $n = 8$ trials).^{3,4,6,8,9,13–15} However, in most of the trials this outcome was assessed using case definitions of low specificity, which could lead to underestimation of the relative risk. Iron supplementation did increase the odds of being slide-positive for *Plasmodium falciparum* at the end of the supplementation period (RR = 1.17, 95% CI = 1.08–1.25, $n = 13$).^{3–15} When baseline levels were taken into account, the absolute increase in the prevalence of infection was 5.7% (95% CI = –1.2 to 12.6, $n = 9$),^{3–6,8–10,15} which was nonsignificant. There was also a nonsignificant increase (RR = 1.12, 95% CI = 0.99–1.26, $n = 6$)^{3,6,7,12,14,15} in the risk of an enlarged spleen among those given iron. Of the nine trials reporting some measure of parasite density,^{5,6,8,10–15} seven showed a higher level in the iron group,^{5,6,8,11,13–15} although the clinical importance of this measure is uncertain. Taken as a whole, the magnitude of these changes indicates that the increase in the risk of malaria morbidity is small or nonexistent. The relation of malaria outcomes to iron supplementation across trials was not related to age, anemia, or change in hemoglobin level; however, there was limited power to examine these relationships in the small number of studies available.

There was an improvement in hemoglobin concentration in all trials where this outcome was examined. The degree of increase was highly variable, with eight of the trials showing mean increases of between 0.2 and 1.2 g/dL^{3,4,7,8,10,11,13,14} and three having increases of more than 2.5 g/dL.^{6,9,15} Overall, the effect of iron supplementation on hemoglobin was an increase of 1.25 g/dL (95% CI = 1.20–1.30, $n = 11$).^{3,4,6–11,13–15} In studies that reported an effect on severe anemia, the summary estimate was RR = 0.50 (95% CI = 0.45–0.54, $n = 4$).^{10,13–15} Only one study, in Tanzanian infants, reported the effect of iron supplementation on the incidence of severe anemia (hematocrit < 25%), and this was 28.8% (95% CI = 6.3–45.8)⁴ lower in the iron group. These hematologic changes are large and likely to confer substantial benefits to the health of populations.

Because malarial illness is most severe in young children, special attention was given to the four trials^{4,5,12,13} conducted in infants or preschool children using oral iron supplementation at recommended doses (i.e., ≤ 2.5 mg iron/kg body weight). Clinical attack rates were not affected (RR = 0.99, 95% CI = 0.75–1.30, $n = 2$),^{4,14} with one trial reporting a nonsignificant decrease (RR = 0.90)⁴ and the other a nonsignificant increase (RR=1.21).¹⁴ The RR of being infected with malaria was 1.05 (95% CI = 0.97–1.14, $n = 4$), with two trials reporting an increase in infected individuals^{5,13} (RRs = 1.10 and 1.27) one statistically significant (1.27)¹³ and two reporting nonsignificant decreases^{4,12} (RRs = 0.76 and 0.96, respectively). The incremental changes in the prevalence of malaria infection were –3.6%,⁴ +1.3%,¹² and +7.5%,⁵ with a combined change of –0.5% (95% CI = –5.9 to 4.8, $n = 3$). The increases in hemoglobin levels for the two trials reporting this outcome were 0.7 and 1.2 g/dL, yielding a combined improvement of 1.1 g/dL (95% CI = 0.95–1.30, $n = 2$).^{4,13} In summary, clinically important risk elevations are not ruled out by these data, but the evidence for them is weak. These data do, however, demonstrate a clinically important effect on anemia, which may have important implications for child health and survival.

**Policy
Considerations
and
Recommendations**

The synthesis of these trials could not resolve the effects of iron supplementation on malaria among children suffering from protein-energy malnutrition, severe anemia, severe malaria, or low birth weight. However, in the trials where these subgroups were represented, adverse effects of iron were not demonstrated. The trials were from a limited number of ethnic groups, and the meta-analysis could not elucidate effects on genetic subgroups of populations. Because of the surveillance techniques used and the limited number of person-years of observation, it was not possible to assess the effects of iron supplementation on the risk of severe malaria. The effects on nonmalaria morbidity and other infectious morbidity secondary to malaria were also not evaluated in most of the trials. Finally, the influence of longer-term supplementation (> 4 months) on various outcomes is unknown. Studies that used higher doses of oral iron and one that administered parenteral iron suggest that these forms of supplementation may be associated with a higher risk of malarial illness.

1. Current international guidelines recommend the routine use of iron supplements for individuals living in communities at significant risk of iron deficiency.¹⁶ The available data from malaria-endemic regions indicate that the known benefits of iron supplementation are likely to outweigh the risk of adverse effects caused by malaria. The implication is, therefore, that oral iron supplementation should continue to be recommended in malarious areas where IDA is prevalent. The subgroups that should be targeted for accelerated implementation of oral iron supplementation are pregnant women and young children, especially infants of low birth weight.
2. Because the number of studies is still limited, INACG, in collaboration with WHO and UNICEF, should review new information as it becomes available from further analyses of existing data, results from trials in progress, and early experience with program implementation. The present evidence does not preclude the possibility of an increased risk of malarial illness or malaria-related secondary infection in some iron-supplemented individuals. However, in view of the clearly demonstrated improvements in hematologic status, implementation of oral iron supplementation programs in malarious areas should be actively promoted.
3. Countries should develop specific national guidelines for implementing and monitoring iron supplementation in coordination with malaria interventions to control anemia. Innovative strategies are needed to ensure the availability and distribution of iron to target populations. Iron supplementation should be carried out within the context of an integrated strategy for anemia prevention and treatment that also addresses the importance of malaria-related anemia, which frequently is unrecognized and untreated in young children and pregnant women.

Recommendations for Program Monitoring and Research

The evidence from these 13 trials cannot preclude an increased risk of malarial illness from iron supplementation in some individuals, and additional research is needed to continue to quantify the risks and benefits of iron supplementation in malarious areas. Additional investigation is needed regarding: age of supplementation (before 6 months of age versus after 6 months of age), duration of supplementation (longer than 4 months), and frequency of supplementation (daily versus weekly). Information is especially needed for outcomes such as risk of severe malarial morbidity, all-cause morbidity, and all-cause mortality. This information may be obtained through further research studies or careful monitoring and evaluation of programs.

Because there is limited experience with iron supplementation programs in young children, programs should be carefully monitored in the initial stages in accord with current guidelines.¹⁶ Consideration should be given to including operational research components, for example, using sentinel site surveillance of key risk indicators. Attention should be given to identifying sites of differing malarial endemicity and ethnic composition, including sites outside of Africa. In the context of operational research, monitoring should include all causes of morbidity, and should use slide confirmation to diagnose malaria illness.

Finally, the following specific questions were recommended as areas where additional evidence would be valuable:

- Are there identifiable subgroups in which risks of adverse effects of iron supplementation are higher or lower than for the general population? Examples include children suffering from protein-energy malnutrition, low-birth-weight infants, individuals with severe anemia, individuals non-immune to malaria, and individuals with hemoglobinopathies or thalassemic syndromes.
- If an increased risk of malarial morbidity is demonstrated in future studies, is it related solely to iron status—suggesting that iron deficiency is protective—or to the physiological events related to the metabolism of supplementary doses of iron? There is a need for additional basic research on *Plasmodium* iron metabolism to identify the nature of the relevant parasite-host interaction.
- What is the effect of iron supplementation on birth weight and growth of children in malarious areas?

Bibliography

1. Newton CR, Warn PA, Winstanley PA, et al. Severe anaemia in children living in a malaria endemic area of Kenya. *Tropical Medicine and International Health* 1997;2:165–78
2. Snow RW, Bastos de Azevedo I, Lowe BS, et al. Severe childhood malaria in two areas of markedly different falciparum transmission in east Africa. *Acta Tropica* 1994;57:289–300
3. Oppenheimer SJ, Gibson FD, Macfarlane SB, et al. Iron supplementation increases prevalence and effects of malaria: report on clinical studies in Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1986;80:603–12
4. Menendez C, Kahigwa E, Hirt R, et al. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* 1997;350:844–9
5. Chippaux JP, Schneider D, Aplogan A, et al. Effets de la supplementation en fer sur l'infection palustre. *Bulletin de la Societe de Pathologie Exotique* 1991;84:54–62
6. Smith AW, Hendrickse RG, Harrison C, et al. The effects on malaria of treatment of iron-deficiency anaemia with oral iron in Gambian children. *Annals of Tropical Paediatrics* 1989;9:17–23
7. Lawless JW, Latham MC, Stephenson LS, et al. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. *Journal of Nutrition* 1994;124:645–54
8. Harvey PWJ, Heywood PF, Nesheim MC, et al. The effect of iron therapy on malarial infection in Papua New Guinean schoolchildren. *American Journal of Tropical Medicine and Hygiene* 1989;40:12–8
9. Murray MJ, Murray AB, Murray MB, Murray CJ. The adverse effect of iron repletion on the course of certain infections. *British Medical Journal* 1978;2:1113–5
10. Fleming AF, Ghatoura GBS, Harrison KA, et al. The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Annals of Tropical Medicine and Parasitology* 1986;80:211–33
11. Menendez C, Todd J, Alonso PL, et al. The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;88:590–3
12. Stoltzfus RJ, Albonico M, Montresor A, et al. The effect of iron supplementation on morbidity in preschool children in Zanzibar. Unpublished data, 1998
13. Adam Z. Iron supplementation and malaria: a randomized, placebo-controlled field trial in rural Ethiopia **Ph.D. thesis**. London School of Tropical Medicine and Hygiene, London, 1997 [effects in children]

14. Adam Z. Iron supplementation and malaria: a randomized, placebo-controlled field trial in rural Ethiopia **Ph.D. thesis**. London School of Tropical Medicine and Hygiene, London, 1997 [effects in pregnant women]
15. Gebreselassie H. Iron supplementation and malaria infection: results of a randomized controlled field trial [Ph.D. thesis]. McGill University, Montreal, 1996
16. INACG/WHO/UNICEF (Stoltzfus R and Dreyfuss ML). Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. ILSI Press. Washington, DC, 1998

Acknowledgement

This consensus statement was written by an expert panel convened by International Nutritional Anemia Consultative Group (INACG) on September 28-29, 1998 and is based on review and discussion of a meta-analysis carried out by Anuraj Shankar, Steve Goodman, and Rebecca Stoltzfus. The full meta-analysis will be published separately. Correspondence about the meta-analysis may be directed to Dr. Shankar (<ashankar@jhsph.edu>).

INACG is grateful to Rebecca Stoltzfus and Bernard Brabin for their leadership of the expert panel discussions. The members of the expert panel were Dr. Bernard Brabin, Liverpool School of Tropical Medicine, Dr. Frances R. Davidson, Agency for International Development (USAID), Dr. Bruno de Benoist, World Health Organization, Dr. Steve Goodman, The Johns Hopkins University, Dr. Peter Kazembe, Lilongwe Central Hospital, Dr. Sean R. Lynch, Eastern Virginia Medical School, Dr. Clara Menendez, University Hospital-Barcelona, Dr. Stephen Oppenheimer, Oxford University, Dr. Anuraj Shankar, The Johns Hopkins University, Dr. Caroline Shulman, London School of Hygiene & Tropical Medicine, Dr. Rebecca Stoltzfus, The Johns Hopkins University, and Dr. Jane Zucker, UNICEF. Dr. Eunyong Chung, USAID, Dr. Carter Diggs, USAID, Dr. Samuel Kahn, USAID, and Dr. Timothy Quick, USAID, also participated in the meeting. Dr. Ross Coppel, Monash University, and Dr. Jeremy Brock, University of Glasgow served as external reviewers. The contribution of these experts to the development of the final product is greatly appreciated.

INACG is indebted to USAID for its continued support of activities aimed at controlling iron deficiency anemia in developing countries



This publication was made possible by support from the Office of Health and Nutrition, Bureau for Global Programs, Field Support and Research, U.S. Agency for International Development (USAID) under cooperative agreements HRN-5122-A-00-3046-00 and HRN-A-00-98-00027-00 with the International Life Sciences Institute (ILSI) Research Foundation.

This report does not necessarily reflect the scientific recommendations of USAID or ILSI.

Additional copies of this and other INACG publications are available free of charge to developing countries and for US\$3.50 to developed countries. Copies can be ordered from the INACG Secretariat at:

INACG Secretariat
ILSI Human Nutrition Institute
1126 Sixteenth Street, NW
Washington, DC 20036-4810 USA
omni@ilsi.org

Printed December 1999 in the United States of America.