Zlotkin S, Newton S, Aimone AM, Azindow I, Amenga-Etego S, Tchum K, Mahama E, Thorpe KE, Owusu-Agyei S. **Effect of iron fortification on malaria incidence in infants and young children in Ghana: a randomized trial.** JAMA 2013;310:938-47.

Prentice AM, Verhoef H, Cerami C. **Iron fortification and malaria risk in children.** JAMA 2013;310(9):914-5.

Introduction

The provision of iron supplements to children living in a malaria-endemic region has been cause for concern since a trial in Pemba, Tanzania found that routine iron–folic acid supplements given with or without zinc resulted in an increased rate of severe adverse events in young children (1). In 2006, a World Health Organization (WHO) consultation on this issue concluded that iron supplements, given in the form of syrup or tablets, should be distributed only in the context of comprehensive and effective health care, including provision of insecticide-treated bed nets and vector control for the prevention of malaria, and prompt recognition and treatment of malaria cases (2). At the time of the WHO consultation, the safety of iron preparations administered as micronutrient powders (MNP), crushable tablets, and lipid-based nutrient supplements for home fortification of complementary foods for infants and young children, was uncertain in highly malaria-endemic regions (2).

This issue of NNA summarizes an article and an accompanying editorial published in the *Journal of the American Medical Association (JAMA),* which described the results of a randomized trial of MNP in young children living in a malaria-endemic region of Ghana.

Methods

The study was conducted as a community-based, cluster-randomized trial during the rainy season in the Brong-Ahafo Region of Ghana. Children were eligible if they were 6 – 35 months of age, ate solid foods at the time of enrollment and had not received iron supplements within the past 6 months. Children with severe anemia (hemoglobin < 70 g/L), severe acute malnutrition (weight-for-length Z-score <-3) or chronic illness were excluded. Children with a positive rapid diagnostic test result confirming malaria received antimalarial treatment before enrollment. The children received either a MNP containing 12.5 mg iron with 30 mg ascorbic acid, 400 µg vitamin A and 5 mg zinc (iron group) or the same MNP without iron (no iron group). Caregivers were instructed to provide the MNP daily for 5 months by mixing the powder with a small portion of porridge or thin gruel. All children received an insecticide-treated bed net at the beginning of the study, were visited weekly for morbidity surveillance and received treatment for malaria in case of a positive rapid diagnostic test.

For data analyses, malaria was defined as parasitemia of any density based on microscopic reading plus reported fever within the previous 48 hours or axillary temperature above 37.5 °C. Moderate anemia was defined as hemoglobin concentration between 70 to 100 g/L and iron deficiency as plasma ferritin < 30 µg/L.

Results and Conclusions

Among 2220 screened children, 1958 were eligible for enrollment. At baseline, 31% of children in both groups showed malaria parasitemia and 40% had moderate anemia. Iron deficiency was similar in both groups (44% in iron group vs 47% in no iron group). Caregivers in both study groups reported high adherence to MNP (88%) and use of bed nets (93%).
Overall, malaria incidence was significantly lower in the iron group compared to the no iron group (76.1 vs. 86.1 episodes/100 child-years, respectively; risk ratio (RR) 0.87 (95% confidence interval (CI), 0.79 – 0.97)). This difference was no longer significant after adjusting for the presence of iron deficiency and anemia at baseline. The adjusted RR for all malaria was 0.87 (95% CI, 0.75 – 1.01) and for malaria with parasite counts >5000/µL was 0.86 (95% CI, 0.72 – 1.02). Hospital admission rates did not differ between the two groups (39.1 and 32.9 admissions/100 child-years in the iron and no iron groups; RR 1.17 (95% CI, 0.98 – 1.40)). However, the number of children who were admitted to hospital was greater in the iron group than in the no iron group during the 5-month intervention period (156 vs. 128 respectively; RR 1.23 (95% CI, 1.02 – 1.49)).

There was a modest impact of the iron-containing MNP on anemia and iron status, although the prevalence of moderate anemia remained high in both groups. In particular, 53.8% (95% CI, 50.5 – 57.0%) of the children in the iron group and 57.8% (95% CI, 54.6 – 61.0%) of children in the no iron group had moderate anemia at the end of the 5-months study period. Iron deficiency was less prevalent in the iron group (23.7% (95% CI, 21 – 27%) than in the no iron group (35.3% (95% CI, 32 – 39%) at the end of the intervention period (χ^2 test $P<0.001$).

The authors concluded that providing daily MNP containing 12.5 mg of iron in a malaria-endemic setting did not result in an increased incidence of malaria among young children when insecticide treated bed nets and appropriate malaria treatment were provided.

Program and Policy Implications

The present study investigated the safety of distributing MNP to young Ghanaian children at high risk of malaria. There was no overall increase in malaria incidence when children received iron-containing MNP. However, the increased number of hospital admissions among children in the iron group compared to the no iron group constitutes a potential adverse effect, and these findings add to the concerns about the safety of iron administration in highly malaria-endemic regions. In the accompanying editorial, Prentice *et al.* (3) conclude that "until a means of safely administering iron in infectious environments has been developed, there remains an imperative to reduce the infectious burden as a prerequisite to moving poor populations from their current state of widespread iron deficiency and anemia".

NNA Editor's Comments *

Carefully weighing the risk and benefits of any intervention is important. While iron deficiency is a public health concern, due to its effect on immune function, cognitive development and physical capacity, the provision of iron supplements with or without food should be considered carefully, especially among individuals at high risk of malaria and other infections. In the large intervention trial in Pemba, mentioned above, the provision of iron supplements led to an increase in adverse events in iron-replete children,

whereas children who had iron deficiency anemia benefited from iron supplements (1). There is new evidence that moderate iron deficiency and anemia is associated with reduced risk of malaria among young children (4), and that malaria risk increases with treatment of anemia, as parasites preferentially infect young red blood cells (5). Moreover, another recent trial of MNP conducted in Pakistan reported an increase in reported diarrhea and chest in-drawing among 6 to 18 months old children who received MNP compared to a non-supplemented control group (6), though there was no difference in persistent diarrhea, fever, or hospitalizations. These sets of findings argue for caution in distributing iron supplements to young children, and the need to monitor children closely for infection during and after the period of supplementation. An integrated approach for treatment and prevention of malaria and other infections should remain a priority along with efforts to improve micronutrient intake and status in young children.

***** These comments have been added by the editorial team and are not part of the cited publication.

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