Original Investigation

Effect of Iron Fortification on Malaria Incidence in Infants and Young Children in Ghana
A Randomized Trial

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IMPORTANCE In sub-Saharan Africa, malaria is a leading cause of childhood morbidity and iron deficiency is among the most prevalent nutritional deficiencies. In 2006, the World Health Organization and the United Nations Children's Fund released a joint statement that recommended limiting use of iron supplements (tablets or liquids) among children in malaria-endemic areas because of concern about increased malaria risk. As a result, anemia control programs were either not initiated or stopped in these areas.

OBJECTIVE To determine the effect of providing a micronutrient powder (MNP) with or without iron on the incidence of malaria among children living in a high malaria-burden area.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, cluster randomized trial of children aged 6 to 35 months (n = 1958 living in 1552 clusters) conducted over 6 months in 2010 in a rural community setting in central Ghana, West Africa. A cluster was defined as a compound including 1 or more households. Children were excluded if iron supplement use occurred within the past 6 months, they had severe anemia (hemoglobin level <7 g/dL), or severe wasting (weight-for-length *z* score <−3).

INTERVENTIONS Children were randomized by cluster to receive a MNP with iron (iron group; 12.5 mg/d of iron) or without iron (no iron group). The MNP with and without iron were added to semiliquid home-prepared foods daily for 5 months followed by 1-month of further monitoring. Insecticide-treated bed nets were provided at enrollment, as well as malaria treatment when indicated.

MAIN OUTCOMES AND MEASURES Malaria episodes in the iron group compared with the no iron group during the 5-month intervention period.

RESULTS In intention-to-treat analyses, malaria incidence overall was significantly lower in the iron group compared with the no iron group (76.1 and 86.1 episodes/100 child-years, respectively; risk ratio (RR), 0.87 [95% CI, 0.79-0.97]), and during the intervention period (79.4 and 90.7 episodes/100 child-years, respectively; RR, 0.87 [95% CI, 0.78-0.96]). In secondary analyses, these differences were no longer statistically significant after adjusting for baseline iron deficiency and anemia status overall (adjusted RR, 0.87; 95% CI, 0.75-1.01) and during the intervention period (adjusted RR, 0.86; 95% CI, 0.74-1.00).

CONCLUSION AND RELEVANCE In a malaria-endemic setting in which insecticide-treated bed nets were provided and appropriate malaria treatment was available, daily use of a MNP with iron did not result in an increased incidence of malaria among young children.

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In sub-Saharan Africa, malaria is a leading cause of childhood morbidity and mortality, and iron deficiency is among the most prevalent preventable nutritional deficiencies.[1,2] The provision of iron to children with iron deficiency anemia can enhance motor and cognitive development and reduce the prevalence of severe anemia.[3] However, studies have suggested that iron deficiency anemia may offer protection against malaria infection and that the provision of iron may increase malaria morbidity and mortality.[4,5] In 2003, a large randomized, placebo-controlled trial of iron supplementation in children in Pemba, Zanzibar, Tanzania, was stopped early due to a higher proportion of hospitalizations or deaths in the groups receiving iron.[5] A subgroup analysis of this study revealed that the risk of adverse events was increased in children who were iron replete at baseline.[5]

The results of this trial prompted the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) in 2006 to release a joint statement recommending that in malaria-endemic areas, iron supplementation (drops, syrup, or tablets) be given only to children who have anemia and are at risk of iron deficiency.[6] Because it is not feasible to meet these population-wide screening requirements, great uncertainty was generated around policies for routine iron supplementation in areas in which malaria is highly prevalent. The joint statement by the WHO and UNICEF was ambiguous on the use of fortification, such as iron-containing micronutrient powders (MNPs).

In recent years, the WHO has modified its standard guideline development process, including the formation of a guideline review committee, to ensure that all recommendations are based on internationally accepted best practices and systematic reviews of the evidence.[7] In 2011, using this revised process, the WHO amended the guidelines for the control of iron deficiency among children aged 6 to 23 months to specifically recommend home fortification of foods with iron-containing MNP.[8] The guideline indicated "In malaria-endemic areas, the provision of iron should be implemented in conjunction with measures to prevent, diagnose and treat malaria," but did not address the safety of using MNP in malaria-endemic regions.[9] Considering this persistent gap in the literature, the aim of our study was to determine the effect of providing MNP with or without iron on the incidence of malaria among children living in a high malaria-burden area.

Methods

Participants

We conducted a community-based, cluster randomized trial in the Wenchi and Tain districts of the Brong-Ahafo Region, Ghana. Malaria is holoendemic in Ghana, with an estimated 3.2 million cases in 2008, most caused by *Plasmodium falciparum*.[10] In the area studied, malaria transmission is highest during the rainy season (April-November).[11] Anemia prevalence among preschool-aged children is 76.1% (95% CI, 73.9%-78.2%).[2] These districts were selected based on their proximity to the Kintampo Health Research Centre (KHRC), where our laboratory and data management teams were located. The population of Wenchi and Tain (153 633 in 2010) is representative of the Ghanaian general population, and particularly of rural regions. The number of children younger than 5 years (11 215 in 2010) represents approximately 0.3% of the total preschool-aged child population in Ghana (11 215/3 533 000).

There are 99 villages across the 2 districts, consisting of 8548 compounds. A village was eligible for inclusion in the study if the inhabiting families had at least 1 child younger than 35 months. All compounds and households in these districts had been previously enumerated, and this database was used to identify the target study villages and the number and age of children in a compound beginning with compounds nearest to the KHRC, then moving to adjacent villages along the main road network.

Children aged 6 to 35 months eating solid foods and living in the study area for at least the following 6 months were eligible for enrollment. Exclusion criteria included severe anemia (hemoglobin level <7.0 g/dL), severe malnutrition (weight-for-length *z* score<−3.0), receipt of iron supplements within the past 6 months, or chronic illness (eg, congenital abnormalities). Those with a confirmed diagnosis of malaria (defined as a positive rapid diagnostic test) received antimalarial treatment before enrollment. All young children in each target village were screened for eligibility and enrolled (if written consent was obtained) until the desired sample size was met.

This trial was approved by the institutional ethics committee of the KHRC, the Ghana Health Service ethics committee, and the Food and Drugs Board of Ghana, as well as by the Hospital for Sick Children research ethics board, Toronto, Ontario, Canada. Written informed consent for participation in this trial was obtained from parents or caregivers.

Procedures

The study was originally designed to include both the dry and rainy seasons; however, due to budgetary constraints, as well as unforeseen regulatory restrictions, the trial was conducted only during the rainy season. It was anticipated that this change would not affect the integrity of the trial because mosquito bite rates are typically higher during the rainy season, thus maximizing the opportunity for malaria and anemia assessment.

Participants were enrolled between March and April 2010 and randomized by cluster to an iron group or no iron group. A cluster was defined as a compound representing 1 or more households (or family units) living in the same residence with at least 1 eligible child enrolled in the study. Those in the iron group received a MNP (Sprinkles; Ped-Med Limited and Sprinkles Global Health Initiative Inc) containing 12.5 mg of elemental iron (as microencapsulated ferrous fumarate) plus ascorbic acid (30 mg), vitamin A (400 µg), and zinc (5 mg).[12] The no iron group received a similar fortificant that did not contain iron. The dose of micronutrients (including iron) was based on recommendations made by the WHO, the International Nutritional Anemia Consultative Group, and UNICEF and the dose given was the same, independent of the age or weight of the children.[13] Caregivers were instructed to provide MNP daily by mixing the contents of 1 package with a small portion of semi-

liquid food, such as porridge or thin gruel. This dosing regimen was continued for 5 months. Participants were subsequently monitored for 1 additional month after discontinuing the MNP.

At enrollment, each child was provided with a 1-week supply of MNP packages and an insecticide-treated bed net, and their caregivers were educated on their appropriate use. Throughout the study, each household was visited weekly by a field researcher, who conducted a health assessment (including axillary temperature), collected information on intervention adherence, insecticide-treated bed net use, and morbidity, and replenished the supply of MNP. Caregivers saved empty and unused packages, which were counted at time of delivery of a new supply. Adherence was calculated as the actual number of packages used divided by the expected number used (given perfect adherence) multiplied by 100. Participants who were not present during a home visit and who could not be located for 3 consecutive revisit attempts by a field worker were reported as temporarily absent until the next scheduled follow-up. If a child became ill between routine monitoring visits, caregivers were advised to visit the closest health facility.

Randomization and Masking

Simple random allocation was performed at the cluster level using a computer-generated model. Randomization results were recorded on enrollment lists, which were divided by field worker area, thus concealing the allocation sequence and allowing field researchers to efficiently enroll and assign participants to groups. Cluster randomization was used primarily to avoid cross-contamination between intervention groups through food sharing. This randomization scheme also facilitated tracking of participants throughout the study period, especially those who moved within or outside of the study area. Packages containing the fortification with or without iron looked identical with the exception of a subtle A or B mark on the label. The study team, caregivers, and data analysts were blinded to the A and B designations. The randomization code was not revealed to any study-related personnel until the data analysis was completed.

Data Collection

Study identity cards (provided to caregivers at enrollment) were used to track participants who visited a health facility. If a child had a fever (axillary temperature >37.5°C or reported a fever within the past 48 hours) or was admitted to a health facility, a blood sample was taken to determine malaria status (and corresponding treatment) via a rapid diagnostic test (Paracheck Pf Device, Orchid Biomedical Systems), as well as parasite speciation and count via microscopy. Blood smears were prepared at the KHRC laboratory. Thin films were fixed with methanol and both thick and thin films were stained with Giemsa. Each smear was read twice by independent microscopists. Children with confirmed malaria diagnoses (determined by a rapid diagnostic test) were provided with first-line antimalarial treatment (artesunate plus amodiaquine or artemether plus lumefantrine).

To determine treatment success, children were followed up for 14 days and blood samples were collected on days 7 and 14 to determine malaria status (using a rapid diagnostic test and microscopy). At baseline and at the end of the 5-month intervention period, complete blood cell counts were determined using a hematology autoanalyzer (Horiba ABX Micros 60-OT-CT-OS-CS). Plasma C-reactive protein (CRP) was determined using an immunoturbidimetric method (QuickRead CRP, Orion Diagnostica), and serum ferritin was measured using an enzyme immunoassay (Spectro Ferritin S-22, Ramco Laboratories Inc).

Outcomes

The primary outcome of malaria was defined as parasitemia of any density (determined using microscopy) plus reported fever within 48 hours or axillary temperature higher than 37.5°C.[14] Secondary outcomes included malaria with parasite density higher than 5000/μL, anemia (hemoglobin level <10 g/dL),[15] iron deficiency (ferritin level <30 μg/L),[15] hospital admission, and clinical diagnoses of pneumonia (cough, tachypnea, lower chest wall indrawing, consolidation or pleural effusion on a chest film), diarrhea (>3 loose or watery stools in 24 hours), cerebral malaria, or meningitis among children who were admitted to a health facility during the study period. Due to not having the capacity to perform lumbar puncture, cerebral malaria and meningitis were diagnosed based on clinical assessment.

Recognizing that infection and inflammation will confound the interpretation of ferritin, we also conducted our analyses after excluding specimens with elevated CRP levels (>8 mg/L) and used a ferritin cutoff of 12 μg/L to define iron deficiency.[16,17] Anemia status was not a primary outcome because previous studies[18-20] completed by our research group have demonstrated the efficacy of MNP with iron in reducing anemia rates among young Ghanaian children by up to 60% compared with controls. Given that we have already demonstrated efficacy, the primary objective of this study was to determine the safety of a MNP with iron in terms of the risk of malaria among young children living in a high malaria-burden area.

Trial Monitoring

A data and safety monitoring board met 3 times during the course of the trial. Outcome data were compiled and summarized after completion of the enrollment phase and mid-intervention. It was agreed a priori that the trial would be terminated if a clinically significant greater incidence of malaria or surrogate measures of clinical severity (ie, deaths and hospitalizations) occurred in the iron group compared with the no iron group.

Statistical Analysis

We hypothesized that the incidence of malaria among children would be significantly higher in the iron group compared with the no iron group. Using a baseline rate of 3.44 episodes/child/year,[21] 80% power, a .05 type I error rate, and assuming that all children would begin the trial at a similar risk level, we estimated that 351 child-years would be required to

detect a clinically significant (15%) increase in malaria incidence rates. After accounting for a 15% loss to follow-up, as well as testing the hypothesis twice (for the interim safety analysis), the sample size was calculated as 1940 children (970 per group). Estimates of cluster size and within- or between-cluster variation were not included in the sample size calculation because cluster sizes were expected to be small and within-cluster comparisons were not considered to be clinically meaningful.

The database was created and managed using Visual Fox Pro version 9.0 (Microsoft). All data were entered twice and verified for typographical errors, extreme observations, and discrepancies. Data collection errors were verified on a regular basis, and all discrepancies were resolved prior to breaking the randomization code.

Variables were first explored and summarized using descriptive statistics. Malaria incidence was compared between groups using generalized estimating equations (Poisson family) to account for the clustered randomization and small cluster sizes. Risk ratios (RRs) were derived by estimating and comparing the probability of becoming infected with malaria among those exposed vs unexposed to the iron intervention. The control (no iron) group was used as the reference. To verify that overdispersion was not a significant factor in the primary analysis, a negative binomial model was fit using the generalized, linear mixed-modeling framework and these results were similar to the results from the generalized estimating equation model. The number of hospital admissions and other diagnoses were analyzed using similar methods.

Secondary and exploratory analyses included adjustments for baseline iron deficiency and anemia status, as well as comparisons of malaria risk across subgroups, defined according to baseline hemoglobin and ferritin levels (eg, anemia with or without iron deficiency, anemia with iron deficiency only, anemia without iron deficiency only, etc). Risk ratios for iron deficiency and anemia subgroups were obtained by combining coefficients from the full model with group × iron deficiency and group × anemia interaction terms, respectively.

Statistical testing was 2-sided with a significance level of .05. Malaria rates (expressed as the number of episodes divided by person-time) were calculated manually. All other analyses and calculations, including intracluster correlation coefficients, were conducted on an intention-to-treat basis using R software (R Foundation for Statistical Computing) and Stata version 11 (StataCorp).

Results

As depicted in **Figure 1**, 2220 children aged 6 to 35 months from 2561 clusters in 22 villages were screened. More than 80% of these children (n = 1958) met inclusion criteria, representing 1552 clusters. Of the 262 children who were excluded after screening, 62 were absent at the time of enrollment. The main reasons for excluding the remaining 200 children appear in Figure 1. By the end of the study, 3% were lost to follow-up (25 in the iron group and 29 in the no iron group), leaving 942 in the iron group and 962 in the no iron group for a total observation time of 863.8 child-years. The primary reason for loss to follow-up was moving out of the study area (Figure 1).

The demographic, anthropometric, and biochemical characteristics of the study population were similar between groups at baseline (**Table 1**). Baseline prevalence of malaria parasitemia was 31.4% (95% CI, 28.5%-34.4%; 304/967) in the iron group and 30.8% (95% CI, 27.9%-33.7%; 305/991) in the no iron group. Moderate anemia (hemoglobin level of 7-10 g/dL) was similar between groups at baseline with 39.9% (95% CI, 36.8%-43.0%; 386/967) in the iron group and 39.6% (95% CI, 36.5%-42.6%; 392/991) in the no iron group. Iron deficiency was also similar between groups (ferritin level <30 μg/L) with 43.6% (95% CI, 40.5%-46.7%; 421/966) in the iron group vs 46.7% (95% CI, 43.6%-49.8%; 462/990) in the no iron group.

After excluding a total of 367 baseline blood samples (188 in the iron group and 179 in the no iron group) due to high CRP, and adjusting the ferritin cutoff to 12 μg/L, the prevalence of iron deficiency was 23.2% (95% CI, 20.3%-26.2%; 181/779) in the iron group vs 23.5% (95% CI, 20.6%-26.4%; 191/812) in the no iron group. The mean number of children younger than 5 years per household was 1.6 (range, 1-7) in the iron group and 1.5 (range, 1-8) in the no iron group. Approximately 55.5% (95% CI, 53.4%-57.8%; 1087/1958) of all participants were receiving breast milk.

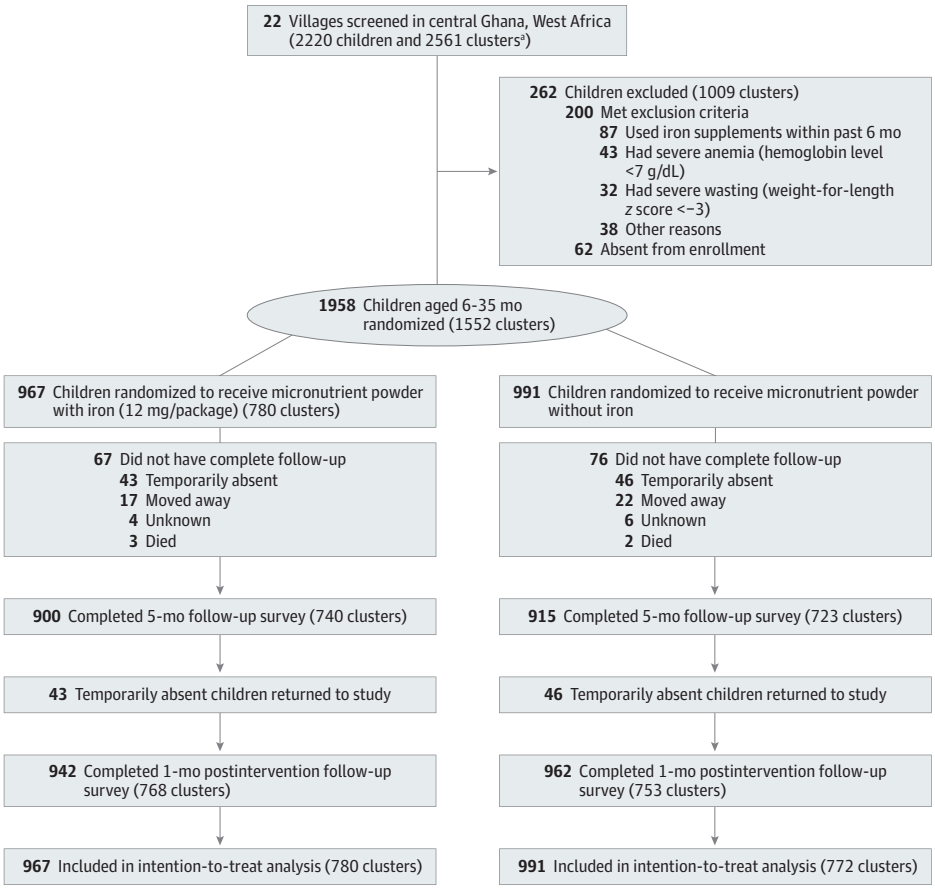
Throughout the intervention period, adherence to the use of MNP and insecticide-treated bed nets were similar between the iron group and the no iron group. For MNP, adherence was 88.1% (95% CI, 86.9%-89.4%) for the iron group and 88.0% (95% CI, 86.7%-89.3%) for the no iron group. For insecticide-treated bed nets, adherence was 92.9% (95% CI, 92.5%-93.2%) for the iron group and 92.8% (95% CI, 92.5%-93.2%) for the no iron group.

Intention-to-treat analyses yielded an overall incidence of malaria of 76.1 episodes/100 child-years in the iron group and 86.1 episodes/100 child-years in the no iron group, which was significantly lower in the iron group (RR, 0.87; 95% CI, 0.79-0.97) (**Table 2**). During the 5-month intervention period, the incidence of malaria was 79.4 episodes/100 child-years in the iron group and 90.7 episodes/100 child-years in the no iron group, which was significantly lower in the iron group (RR, 0.87; 95% CI, 0.78-0.96).

The Kaplan-Meier curves in **Figure 2** also illustrate the difference in overall cumulative incidence of malaria across groups during the course of the trial (log-rank $P = .04$). Similar associations were seen for malaria with parasite counts greater than 5000/μL, although differences between groups only reached statistical significance during the intervention period (62.7 and 71.4 episodes/100 child-years in the iron group and no iron group, respectively; RR, 0.86 [95% CI, 0.77-0.97]).

In a secondary analysis, after adjusting for baseline iron deficiency (ferritin level <30 μg/L) and moderate anemia (hemoglobin level of 7-10 g/dL), all differences were no longer statistically significant (overall malaria: adjusted RR, 0.87 [95%

Figure 1. Trial Profile



[a]Defined as a compound representing 1 or more households (or family units) living in the same residence with at least 1 eligible child enrolled in the study.

CI, 0.75-1.01]; malaria and malaria with parasite counts >5000/μL during the intervention period: adjusted RR, 0.86 [95% CI, 0.74-1.00] and adjusted RR, 0.86 [95% CI, 0.72-1.02], respectively).

Furthermore, an exploratory analysis of subgroups defined according to baseline levels of hemoglobin and ferritin indicated that the presence of both iron deficiency and moderate anemia at baseline was associated with a lower risk of malaria (68.7 and 100.4 episodes/100 child-years in the iron group and no iron group, respectively; RR, 0.67 [95% CI, 0.50-0.88]) and of malaria with parasitemia greater than 5000/μL (50.8 and 79.6 episodes/100 child-years in the iron group and no iron group, respectively; RR, 0.62 [95% CI, 0.45-0.86]), whereas the association between iron deficiency without anemia and malaria did not demonstrate significance (Table 2). In the iron group, children who were iron replete and had anemia at baseline also had a reduced risk of malaria with parasitemia greater than 5000/μL (64.6 and 90.6 episodes/100 child-years in the iron group and no iron group, respectively; RR, 0.72 [95% CI, 0.54-0.98]). There were no otherwise apparent associations between iron repletion at baseline and the risk of malaria or malaria with parasitemia greater than 5000/μL.

At the end of the intervention period, blood samples were obtained from 1815 children. The primary reason for incomplete blood samples in 143 participants was temporary absence (89/143). Of the children who were present at the end of the intervention period, 57.8% (95% CI, 54.6%-61.0%; 529/915) had moderate anemia in the no iron group vs 53.8% (95% CI, 50.5%-57.0%; 484/900) in the iron group. During this same period, 7.7% (95% CI, 5.9%-9.4%; 70/915) in the no iron group had severe anemia vs 4.2% (95% CI, 2.9%-5.5%; 38/900) in the iron group.

Among participants who had anemia at baseline (n = 778), and for whom additional blood samples were obtained at the end of the intervention period (n = 704; 349 in no iron group vs 355 in iron group), mean hemoglobin level decreased in the no iron group from 9.05 g/dL (SD, 0.78 g/dL) to 8.75 g/dL (1.4 g/dL) (mean change, −0.31 g/dL; 95% CI, −0.46 to −0.16 g/dL) and increased in the iron group from 9.04 g/dL (0.79 g/dL) to 9.12 g/dL (1.44 g/dL) (mean change, 0.08 g/dL; 95% CI, −0.08 to 0.24 g/dL) for a mean pooled difference (no iron group minus iron group) of −0.39 g/dL (95% CI, −0.61 to −0.17 g/dL). The statistical comparison of mean change in hemoglobin level between groups ($P< .001$) was performed using a *t* test (PROC TTEST, SAS version 9.3, SAS Institute Inc). Iron deficiency was more prevalent in the no iron group (35.3% [95% CI, 32% to 39%]; 251/711) compared with the iron group (23.7% [95% CI, 21% to 27%]; 160/675) at the end of the intervention period (χ^2 test

Table 1. Baseline Characteristics of Children

	Iron Group (n = 967)[a]	No Iron Group (n = 991)[a]
No. of clusters	780	772
Cluster size, median (range)	1 (1 to 4)	1 (1 to 5)
Male sex, No. (%)	496 (51.3)	502 (50.7)
Age, mean (SD) [range], mo	19.5 (8.6) [6 to 46]	19.4 (8.6) [6 to 36]
Anthropometric status		
Had wasting, No. (%) [95% CI]	88 (9.1) [7.2 to 10.9]	74 (7.5) [5.8 to 9.2]
Weight-for-length *z* score, mean (SD)[b]	−0.64 (0.99)	−0.62 (0.97)
Had stunted growth, No. (%) [95% CI]	152 (15.7) [13.4 to 18.1]	158 (15.9) [13.6 to 18.2]
Length-for-age *z* score, mean (SD)[b]	−0.90 (1.18)	−0.88 (1.23)
Underweight, No. (%) [95% CI]	132 (13.6) [11.4 to 15.9]	119 (12.0) [9.9 to 14.0]
Weight-for-age *z* score, mean (SD)[b]	−0.93 (0.99)	−0.91 (0.97)
Hemoglobin level, mean (SD), g/dL	10.3 (1.3)	10.3 (1.3)
Serum ferritin level, geometric mean, µg/L[c]	30.7	29.7
Parasite density, geometric mean, count/µL	3189.5	2838.6
Household education, No. (%)	(n = 907)	(n = 929)
None	304 (33.5)	302 (32.5)
Any	604 (66.5)	628 (67.6)
No. of people in household, mean (SD)	6.1 (2.8)	6.0 (2.8)
Wealth index of household, No. (%)	(n = 906)	(n = 931)
High	464 (51.2)	474 (50.9)
Low	442 (48.8)	458 (49.2)
Age of introduction of complementary foods, No. (%)[d]	(n = 894)	(n = 920)
≤6 mo	785 (87.8)	802 (87.2)
>6 mo	109 (12.2)	119 (12.9)
Consumed at least 1 iron-fortified product in previous 7 d prior to enrollment, No. (%)	(n = 894) 17 (1.9)	(n = 928) 26 (2.8)

[a] Unit of analysis is individual child unless otherwise indicated.

[b] Estimated using the World Health Organization growth reference charts (≤−2 SD).

[c] Baseline level was calculated after removing observations with high C-reactive protein values. Final sample size was 1591 (n = 779 in the iron group and n = 812 in the no iron group).

[d] Indicates first semisolid food fed to an infant and is used concurrently with breast milk or formula.

P< .001). The denominators in this subanalysis represent all remaining end line ferritin observations after those samples with high CRP levels (>8 mg/L) were removed from the analysis (n = 220 and n = 194, respectively).

Overall, hospital admission rates did not differ significantly between groups (39.1 and 32.9 admissions/100 child-years in the iron group and no iron group, respectively; RR, 1.17 [95% CI, 0.98-1.40]; **Table 3**). However, during the 5-month intervention period, there were more children admitted to the hospital in the iron group vs the no iron group (156 vs 128, respectively; RR, 1.23 [95% CI, 1.02-1.49]). Among children who were ever assessed at an outpatient health facility, which may or may not have resulted in being admitted or having received treatment, the incidence of pneumonia, diarrhea, or other clinical diagnoses (cerebral malaria or meningitis) with or without a concurrent malaria diagnosis also did not differ between groups. There was a total of 5 deaths during the study (3 in the iron group and 2 in the no iron group). According to medical and verbal autopsy reports, 3 deaths were due to septicemia and malaria (1 in the iron group and 2 in the no iron group); additionally, there was 1 death due to severe dehydration (likely partly attributable to diarrhea) with malnutrition and 1 due to a road traffic incident (both deaths were in the iron group).

Discussion

To our knowledge, this was the first study to assess the effect of daily fortification with powdered micronutrients including iron at home on malaria incidence in a malaria-endemic setting. The overall incidence of malaria was lower in the iron group compared with the no iron group, but after adjustment for baseline values for iron deficiency and moderate anemia, these differences were no longer statistically significant. Similar associations were found during the 5-month intervention period only for both malaria and malaria with parasite counts greater than 5000/µL (severe malaria). A secondary analysis demonstrated that malaria risk was reduced among the subgroup of those in the iron group who had iron deficiency and anemia at baseline.

Children in the iron group experienced fewer malaria episodes, but more in this group were admitted to the hospital during the intervention period. However, rates did not differ overall between groups. A similar relationship was found by Sazawal et al[5] in the randomized Zanzibar main trial; however, this relationship was not found in their smaller substudy. In their main trial, there was a higher RR of hospital admission among children in both treatment groups (iron and folic acid with or without zinc) compared with those in the pla-

Table 2. Effect of Providing Micronutrient Powder With Iron on the Incidence of Malaria and Malaria With Parasitemia

	Malaria					Malaria With Parasitemia >5000/μL				
	Iron Group (444.8 Child-Years of Follow-up)		No Iron Group (455.8 Child-Years of Follow-up)			Iron Group (444.8 Child-Years of Follow-up)		No Iron Group (455.8 Child-Years of Follow-up)		
	No.	Episodes (Rate/100 Child-Years)	No.	Episodes (Rate/100 Child-Years)	Risk Ratio (95% CI)	No.	Episodes (Rate/100 Child-Years)	No.	Episodes (Rate/100 Child-Years)	Risk Ratio (95% CI)
Overall[a,b]	966	338 (76.1)	989	392 (86.1)	0.87 (0.79-0.97)	966	273 (61.4)	989	308 (67.6)	0.89 (0.80-1.00)
Intervention (wk 1-20)	966	294 (79.4)	989	344 (90.7)	0.87 (0.78-0.96)	966	232 (62.7)	989	271 (71.4)	0.86 (0.77-0.97)
Postintervention (wk 21-24)	942	44 (60.9)	962	48 (65.1)	0.95 (0.71-1.26)	942	41 (56.8)	962	37 (50.2)	1.15 (0.83-1.59)
Serum ferritin, μg/L[c]										
<30	421	108 (67.1)	462	156 (88.1)	0.75 (0.65-0.87)	421	86 (53.4)	462	121 (68.3)	0.76 (0.65-0.90)
≥30	545	186 (89.2)	528	188 (93.1)	0.94 (0.82-1.09)	545	146 (70.0)	528	150 (74.3)	0.94 (0.80-1.10)
<12 (CRP ≤8 mg/L)	181	49 (71.0)	191	64 (87.0)	0.81 (0.63-1.03)	181	43 (62.3)	191	52 (70.7)	0.86 (0.67-1.12)
≥12 (CRP ≤8 mg/L)	598	181 (79.1)	621	203 (85.6)	0.92 (0.81-1.06)	598	144 (62.9)	621	156 (65.8)	0.95 (0.81-1.11)
Hemoglobin, g/dL										
7.0-10.0	386	117 (79.3)	392	158 (105.2)	0.74 (0.65-0.86)	386	85 (57.6)	392	127 (84.7)	0.68 (0.58-0.80)
>10.0	581	177 (79.5)	599	186 (81.1)	0.96 (0.84-1.12)	581	147 (66.0)	599	144 (62.8)	1.03 (0.86-1.22)
Iron replete[d]										
Plus anemia	195	67 (90.1)	191	81 (111.2)	0.83 (0.64-1.08)	195	48 (64.6)	191	66 (90.6)	0.72 (0.54-0.98)
No anemia	350	119 (88.7)	337	107 (82.8)	1.04 (0.82-1.32)	350	98 (73.1)	337	84 (65.0)	1.09 (0.83-1.42)
Iron deficiency[d]										
Plus anemia	190	50 (68.7)	200	77 (100.4)	0.67 (0.50-0.88)	190	37 (50.8)	200	61 (79.6)	0.62 (0.45-0.86)
No anemia	231	58 (65.8)	262	79 (78.7)	0.84 (0.63-1.12)	231	46 (52.2)	262	60 (59.7)	0.93 (0.67-1.28)

Abbreviation: CRP, C-reactive protein.

SI conversion factor: To convert hemoglobin to g/L, multiply by 10.

[a] Three participants (1 in the iron group and 2 in the no iron group) are missing malaria incidence and intervention duration data due to loss to follow-up before the first monitoring visit.

[b] The intracluster correlation coefficient (strength of resemblance among participants in the same cluster) equals 0.0804 for malaria and 0.1033 for malaria with parasitemia.

[c] Two participants (1 per group) are missing baseline data for this variable.

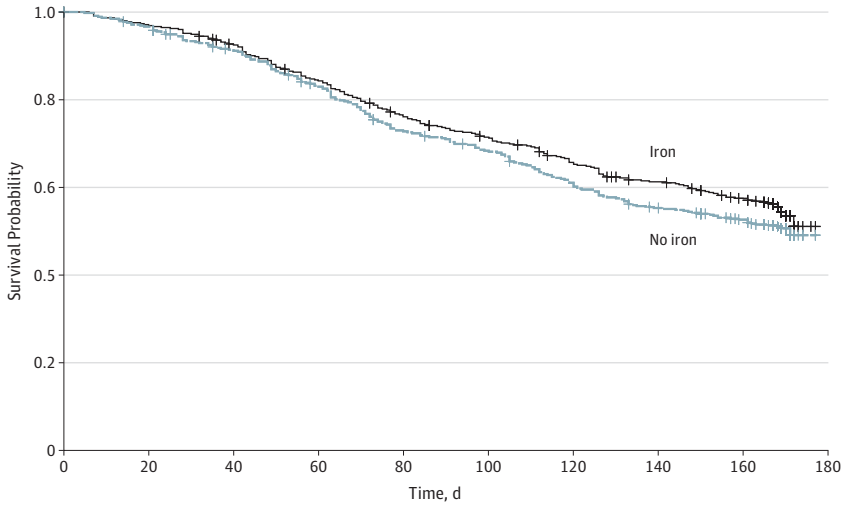
[d] Defined using ferritin cutoff of 30 μg/L. The risk ratios were obtained by combining coefficients from the full model with interaction terms. *P* values for the group × iron deficiency interaction were not statistically significant (*P* > .10). The *P* value for the group × anemia interaction was significant for malaria with parasitemia (*P* = .02) but not for malaria only (*P* = .14).

cebo group (RR, 1.11; 95% CI, 1.01-1.23). Also similar to the main trial in Zanzibar, we did not see a significant association between iron intake and the risk of diarrhea, regardless of concurrent malaria status. This comparison should be interpreted with caution, however, because our analysis included all children who ever visited a health facility during the study period (not just those who were admitted).

Comparing the risk of death between the current study in Ghana and the main trial in Zanzibar is also difficult due to the large difference in sample sizes (32 155 children in Zanzibar vs 1958 in Ghana), and limited statistical power to detect such effects. In Ghana, 2 of 3 deaths (in the iron group) were associated with infection and malaria, whereas in the Zanzibar main trial, the risk of infection-related adverse events was significantly higher among children in the iron, folic acid, and zinc group who also had positive malaria test results (RR, 1.84; 95% CI, 1.31-2.57).[5] In the Zanzibar substudy (n = 2413), there were no differences in deaths (RR, 0.73; 95% CI, 0.31-1.71) or hospital admissions (RR, 0.76; 95% CI, 0.54-1.06) between the combined intervention group (iron and folic acid with or without zinc) and the placebo group. It must be noted that children enrolled in the main trial in Zanzibar were not provided with insecticide-treated bed nets or treatment for sepsis or malaria, whereas in the current trial (and in the Zanzibar substudy), insecticide-treated bed nets and treatment were provided.

In Ghana, the provision of iron fortification did not increase the risk of malaria, whereas in the Zanzibar trial,[5] investigators found that iron and folic acid supplementation was associated with an increased risk of all-cause and malaria-related mortality and morbidity. These contrasting findings may be explained by design differences between the 2 studies. First, the Zanzibar study was designed to assess mortal-

Figure 2. Product-Limit Survival Estimates for Time to First Malaria Episode in the Iron and No Iron Groups



No. at risk

Iron	966	936	890	810	732	681	623	579	535
No iron	992	957	897	814	712	664	592	536	495

The curves are significantly different (log-rank $P = .04$).

Table 3. Effect of Providing Micronutrient Powder With Iron at the Time of Hospital Admissions and Other Diagnoses

	No. (%) of Children		
	Iron Group (n = 967; 444.8 Child-Years of Follow-up)	No Iron Group (n = 991; 455.8 Child-Years of Follow-up)	Risk Ratio (95% CI)
Hospital admissions			
Overall[a]	174 (18.0)	150 (15.1)	1.17 (0.98-1.40)
Intervention (wk 1-20)	156 (16.1)	128 (12.9)	1.23 (1.02-1.49)
Postintervention (wk 21-24)	18 (2)	22 (2)	0.82 (0.52-1.29)
Other diagnoses[b]			
Malaria	283 (29.3)	287 (29.0)	1.00 (0.81-1.23)
Pneumonia	13 (1)	11 (1)	1.20 (0.67-2.14)
Pneumonia and positive rapid diagnostic test[c]	6 (<1)	6 (<1)	1.02 (0.46-2.25)
Diarrhea	162 (16.8)	147 (14.8)	1.12 (0.86-1.46)
Diarrhea and positive rapid diagnostic test[c]	132 (13.7)	133 (13.4)	1.00 (0.76-1.32)
Cerebral malaria or meningitis	10 (1)	8 (1)	1.28 (0.59-2.78)
Other diagnosis and positive rapid diagnostic test[c]	10 (1)	6 (<1)	1.71 (0.68-4.31)

[a] The intracluster correlation coefficient (strength of resemblance among participants in the same cluster) equals 0.050 for hospital admissions overall and 0.0338 for other diagnoses.

[b] Any diagnosis of malaria (via rapid diagnostic test), pneumonia, diarrhea, or other (cerebral malaria or meningitis) among those children who were ever assessed at an outpatient health facility, which may or may not have resulted in being admitted or having received treatment during the study period.

[c] Positive rapid diagnostic test for *Plasmodium falciparum*.

ity as a primary outcome, whereas the primary outcome in Ghana was malaria incidence. Second, as previously indicated, the provision of insecticide-treated nets and malaria treatment was not included in the Zanzibar study, which may have modified the effect of the intervention. In a recently published systematic review, Ojukwu et al[22] reported that iron supplementation did not increase the risk of malaria (14 trials); however, this effect was reversed in settings in which regular malaria surveillance and treatment services were not provided. Iron fortification interventions were not included in this review.[22] Because MNPs are taken with food, the absorption characteristics may be different from that of supplements, perhaps with reduced and delayed peak plasma iron levels. Although direct evidence of this difference with iron products has not been studied, there is evidence of a difference in drug absorption when the same drugs are taken with and without food.[23,24] This may have led to a reduction in the amount of available free iron in the blood stream and thus potentially reduced the risk of malaria infection among the Ghanaian participants.

An important similarity among the key findings from our trial and those from the Zanzibar trial is the apparent positive association between the provision of iron and reduced risk of malaria among children who had iron deficiency and anemia at baseline, and no association among those with iron deficiency without anemia. In contrast to the Zanzibar study, however, we did not see an increased risk of malaria among those children who were iron replete and had anemia at baseline. This discrepancy may be partly explained by differences in indicators used to define iron deficiency. In Ghana, iron deficiency was defined using serum ferritin, whereas in Zanzibar erythrocyte zinc protoporphyrin was used. Both ferritin and zinc pro-

toporphyrin levels are elevated during an infection or inflammatory response,[25,26] which may lead to under- or overestimation of iron deficiency prevalence. Although we tried to accommodate for this effect by removing ferritin observations from the analysis if CRP was also elevated, these findings should be interpreted with caution. C-reactive protein is an indicator of the early stage (first 24-48 hours) of an inflammatory response.[27] When inflammation-inducing stimuli are applied over short periods of time (eg, acute infections), increases in both CRP and ferritin will correlate strongly over the first 48 hours of infection onset, then CRP levels decline and ferritin levels remain elevated.[25,28] In these cases, additional information on the later stages of inflammation (eg, through the use of a biomarker that remains elevated longer than CRP such as α1-acid glycoprotein)[29] would be required to discern the effect of recurrent or extended bouts of malaria infection on iron status.

In addition to the effect of inflammation on iron biomarkers, iron absorption is inhibited by febrile and asymptomatic malaria parasitemia,[30] and constant exposure to infection can result in anemia of chronic inflammation.[31] This inhibitory action may be driven by an innate immune response as a means to withhold iron from invading pathogens, such as malarial parasites, which require iron for growth.[32,33] Doherty et al[34] documented significant inhibition of oral iron absorption among 18- to 36-month-old Gambian children with malarial infection (compared with those with iron deficiency anemia alone), and return to near-normal absorption levels approximately 15 days after successful antimalarial treatment. The authors concluded that the efficacy of supplemental iron may be limited if administered within 2 weeks of malaria treatment.[34] In Ghana, the administration of iron or iron status measurements were not scheduled to coincide with malaria diagnoses or treatments; thus, the full potential effects of the intervention on improving iron status may not have been realized. Perhaps future studies should explore the feasibility of incorporating a modified iron administration schedule, particularly in settings in which iron deficiency anemia and anemia due to malaria infection are known to coexist.

Several other limitations of our study should be noted. First, insecticide-treated bed nets were provided to all participants, and according to our adherence results, were well used. Malaria bite rates may be higher in areas in which bed nets are not available. This study did not explore whether similar outcomes would have been achieved had insecticide-treated bed nets not been supplied or used. Second, we facilitated prompt treatment for malaria and other infections as soon as they were detected. It is thus difficult to predict the effect of a MNP with iron if treatment for malaria or other infections was not available. Third, the interpretation of iron status of the participants as well as its association with malaria infection would have been more robust had we included measurement of α1-acid glycoprotein as a reflection of long-term inflammation and hepsidin as a measure of iron availability at the cellular level. However, with a limited budget, we had to prioritize biochemical markers of iron status. Lastly, our subgroup analyses should be considered exploratory in nature because the overall and per-subgroup sample sizes were not adequate to allow effect power estimations of 80% or greater.

The findings from the current study not only address a gap in the literature, but also have potentially important policy implications for countries like Ghana that have not implemented iron supplementation or fortification as part of anemia control programs in part due to the joint recommendation from the WHO and UNICEF.[6] For ethical reasons, we ensured that all participants were not denied existing malaria prevention (insecticide-treated bed nets) or malaria treatment. As such, our results most likely can be applied to other malaria-endemic settings in which similar malaria control measures are in place. Overall, given our findings and the new WHO guidelines recommending iron fortification for the prevention and treatment of anemia among children younger than 2 years (in whom the prevalence of anemia is ≥20%),[8,35] there should be renewed interest and consideration for implementing iron fortification in Ghana as part of the national nutrition policy.

Since the publication of the 2006 joint recommendation from the WHO and UNICEF on the limited use of iron in malaria-endemic regions, a systematic review[22] has been published supporting the use of iron supplements in malaria-endemic regions when regular malaria surveillance and treatment services are also provided. Thus, the WHO recently updated its recommendation and advises that in malaria-endemic areas, the provision of iron should be implemented in conjunction with measures to prevent, diagnose, and treat malaria.[36] The results of the current study are consistent with the conclusion of the systematic review and provide further evidence about the provision of iron in malaria-endemic regions.

ARTICLE INFORMATION

Author Contributions: Dr Zlotkin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Zlotkin, Newton, Aimone, Owusu-Agyei.
Acquisition of data: Newton, Aimone, Azindow, Amenga-Etego, Tchum, Owusu-Agyei.
Analysis and interpretation of data: Newton, Aimone, Tchum, Mahama, Thorpe, Owusu-Agyei.
Drafting of the manuscript: Newton, Aimone, Owusu-Agyei.
Critical revision of the manuscript for important intellectual content: Zlotkin, Newton, Aimone, Azindow, Amenga-Etego, Tchum, Mahama, Thorpe, Owusu-Agyei.
Statistical analysis: Aimone, Tchum, Mahama, Thorpe, Owusu-Agyei.
Obtained funding: Zlotkin, Aimone.
Administrative, technical, or material support: Zlotkin, Newton, Tchum, Owusu-Agyei.
Study supervision: Zlotkin, Newton, Aimone, Azindow, Tchum, Owusu-Agyei.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Zlotkin reported having intellectual property rights to his invention known as Sprinkles, which includes (1) patent rights for the United States and Canada, which are held by Ped-Med Limited (a Canadian corporation of which Dr Zlotkin is the sole shareholder) and (2) trademark rights in various jurisdictions to the name Sprinkles, which are held by either Ped-Med Limited or the Sprinkles Global Health Initiative Inc (a Canadian not-for-profit corporation of which Dr Zlotkin is a member); receiving grant funding and support for travel expenses from the National Institutes of Health; serving on a scientific advisory committee for Danone; providing expert testimony for the Ministry of the Attorney General of Ontario; receiving institutional grants from the Saving Lives at Birth Foundation and the Muskoka Initiative Consortium; receiving payment for lectures from

Nutreo and the government of Colombia; holding a North American patent on micronutrient powders; having a nonexclusive agreement on micronutrient powders with New GPC Ltd in Guyana; and receiving institutional funding from the United Nations Children's Fund for consultation meetings related to micronutrient powders. Mss Aimone and Azindow and Messrs Tchum and Owusu-Agyei reported receiving institutional grant funding from the National Institutes of Health. No other author reported disclosures.

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