Iron-containing micronutrient powder provided to children with moderate-to-severe malnutrition increases hemoglobin concentrations but not the risk of infectious morbidity: a randomized, double-blind, placebo-controlled, noninferiority safety trial\textsuperscript{1–3}

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ABSTRACT

Background: A link between the provision of iron and infectious morbidity has been suggested, particularly in children with malnutrition. Two meta-analyses concluded that iron is not harmful, but malnourished children were underrepresented in most available studies.

Objective: This study evaluated the effect of iron-containing micronutrient powder (iron MNP) on infectious morbidities when provided to children with moderate-to-severe malnutrition and anemia.

Design: A randomized, double-blind, placebo-controlled, noninferiority safety trial using a 2-mo course of daily iron MNP or placebo powder (PP) was conducted in 268 Bangladeshi children aged 12–24 mo with moderate-to-severe malnutrition (weight-for-age $z$ score $\leq -2$) and a hemoglobin concentration between 70 and 110 g/L. The primary endpoint was a composite of diarrhea, dysentery, and lower respiratory tract infection episodes (DDL) recorded through home visits every 2 d during the intervention and then weekly for 4 mo. The noninferiority margin was 1.2. Secondary endpoints included hemoglobin and anthropometric changes at 2 and 6 mo. All deaths and hospitalizations were documented. To capture seasonal variation, the study was repeated in the winter and summer with 2 distinct groups. An intention-to-treat analysis of recurrent events was performed by using the univariate Anderson-Gill model.

Results: The baseline characteristics of the subjects were similar. Analysis of phase-aggregated DDL data showed that iron MNP was not inferior to PP (relative risk: 0.81; 95% CI: 0.62, 1.04) and improved hemoglobin concentrations ($P < 0.0001$). We recorded no deaths, and hospitalizations were rare.

Conclusion: Iron MNP is safe and efficacious when provided to children aged 12–24 mo with moderate-to-severe malnutrition and anemia. This trial is registered at clinicaltrials.gov as NCT00530374. *Am J Clin Nutr* 2011;94:585–93.

INTRODUCTION

Malnutrition and iron deficiency (ID) are comorbid conditions, each of which affects large numbers of young children in developing countries (1, 2). For example, >50% of children living in rural Bangladesh have moderate or severe malnutrition (3) and 85% have anemia, most of which is likely due to ID (4). Nutritional interventions (hospital- or community-based) are recommended for malnourished children (5). However, there is confusion about the safety of prescribing ID treatment in a malnourished population.

Because both malnutrition and ID compromise the immune response (6, 7), malnourished, iron-deficient individuals should be predisposed to infection. However, reports that iron supplementation paradoxically increased the risk of infection in children (8–10) triggered intense efforts to investigate this issue: 2 meta-analyses, which summarized the results of these studies, concluded that iron supplementation is not harmful (11, 12). However, because malnourished children were either excluded or absent from most of these studies, the generalizability of this conclusion is limited. We identified 6 studies that did include malnourished children, but all have drawbacks limiting their usefulness (see supplemental Table 1 under “Supplemental data” in the online issue). Convincing evidence regarding the causal link between provision of oral iron and infection susceptibility in the context of malnutrition is thus lacking.

Apparent contradictions between current World Health Organization guidelines reflect this uncertainty. On the one hand, the guidelines for malnourished children requiring hospitalization state that “iron should never be given during the initial phase of treatment” because “it can have toxic effects and may reduce resistance to infection” (13). In contrast, guidelines for ID anemia recommend population-wide oral iron supplementation when the prevalence of anemia is >40%, without mention of nutritional status (14, 15).

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This trial aimed to determine the safety of providing iron (as an iron-containing micronutrient powder) to malnourished Bangladeshi children living in the community. Our primary safety endpoint was the incidence of infectious morbidities, including diarrhea, dysentery, and lower respiratory tract infections.

**SUBJECTS AND METHODS**

**Study design, sites, and population**

This study was a randomized, double-blind, prospective, placebo-controlled, noninferiority trial aimed at assessing the safety of daily oral iron when provided as a micronutrient powder (iron MNP) to children with moderate-to-severe malnutrition. The powder is used to fortify homemade complementary food. Subjects were selected from 29 villages located in 5 Unions in Mymensingh district (see supplemental Figure 1A and supplemental Table 2 under “Supplemental data” in the online issue). This area has a low prevalence of malaria (0.4%) (16).

To identify potential study subjects, selected villages were screened for children aged 12–24 mo with moderate-to-severe malnutrition, defined as a weight-for-age \( z \) score (WAZ) \( \leq -2 \) based on the National Center for Health Statistics standards. Only one child per household was included to prevent cross-contamination. Exclusion criteria included a hemoglobin concentration <70 or >110 g/L, weight-for-height \( z \) score (WHZ) \( < -3 \), kwashiorrok (defined as evidence of edema), congenital abnormalities, iron supplementation in the previous 6 mo, prior inclusion in a nutrition program, or any chronic illness other than malnutrition. Children excluded because of severe chronic medical conditions were referred to local physicians for treatment.

Ethics review boards at the Hospital for Sick Children (Toronto, Canada), the Bangladesh Medical Research Council (Dhaka, Bangladesh), and the University of Waterloo (Waterloo, Canada) approved the research protocol. A consent form in Bangladesh and the University of Waterloo (Waterloo, Canada) approved the research protocol. A consent form in (Dhaka, Bangladesh) packaged the powders and confirmed the content of both sachet types before delivery. All members of the research team and the family were masked to treatment allocation.

**Random assignment and masking**

The subjects were first stratified by malnutrition level (\( -2 \leq \text{WAZ} < -3 \) and \( \text{WAZ} \leq -3 \)). Then, the eligible children were randomly assigned to either daily iron MNP or placebo powder (PP) by using permuted block assignments (sizes = 4 and 6) generated with Microsoft Excel (Microsoft, Redmond, WA) and the algorithm from www.randomization.com.

The iron MNP content was as follows: microencapsulated iron, 12.5 mg (Descote Ferrous Fumarate 60–Ultra; Particle Dynamics, St Louis, MO); vitamin A, 400 \( \mu \)g retinol equivalents (REs) [acetate; US Pharmacopoeia (USP), Rockville, MD–FCC]; zinc gluconate, 5 mg (USP); vitamin C, 30 mg [ascorbic acid, USP-FCC (Food Chemicals Codex)]; and folate acid, 0.15 mg (USP-FCC). Maltodextran was used as a vehicle. PP contained only the vehicle. No texture or taste difference between the powders was apparent when sprinkled onto complementary foods. Sachets were similar except for labeling with unique codes. Renata Ltd (Dhaka, Bangladesh) packaged the powders and confirmed the content of both sachet types before delivery. All members of the research team and the family were masked to treatment allocation.

**Procedures**

The primary outcome measure was a composite score based on all distinct episodes of diarrhea, dysentery, and lower respiratory tract infections (LRTIs). The composite outcome will hereafter be referred to as DDL. Outcomes were defined as diarrhea, \( \geq 3 \) loose watery stools within 24 h; dysentery, \( \geq 1 \) loose hemorrhagic stool within 24 h; LRTI, cough or difficulty breathing and tachypnea (>40 breaths/min), with or without chest indrawing (17). Fever is not required for any of these standard diagnostic definitions. Episodes were considered to be finished when a child was asymptomatic for >48 h (18).

Infectious morbidity was assessed by using active case detection during the intervention period. More precisely, trained assessors, supervised by a physician, performed a thorough evaluation of each child at home, every other day for 2 mo. During the postintervention period, the same thorough evaluation was performed, but this time on a weekly basis (see supplemental Figure 1b under “Supplemental data” in the online issue). The data set for this period is therefore not as reliable as that of the first 2 mo because it relies more on maternal recall for details about each episode. The protocol was repeated with different subjects over 2 nonoverlapping seasons (winter and summer), hereafter referred to as phase 1 (12/2007–06/2008) and phase 2 (07/2008–01/2009), respectively (see supplemental Figure 1c under “Supplemental data” in the online issue). The trained assessors completed a standardized questionnaire at each visit to elicit specific symptoms of diarrhea, dysentery, and LRTI. Also, axillary temperature was measured twice within 30 min with a mercury thermometer, and the respiratory rate was recorded by counting breaths for 60 s. Fever was defined as 2 recordings of \( \geq 37.2^\circ\text{C} \).

One sachet was administered daily to each child for 2 mo. Clear instructions for storage and use with complementary feeding were provided to parents before randomization (19). Families were asked to keep all empty sachets. The trained assessors counted the sachets every week as a measure of adherence to the intervention.

Details pertaining to all hospital admissions or deaths were recorded, as were all encounters with local health care workers or doctors. Episodes of prolonged fever of unknown origin, defined as fever lasting \( > 10 \) d with no apparent source, were also noted.

An independent data safety monitoring committee performed an interim safety analysis after the first phase. The protocol stipulated that the study would be stopped if 1 of the 2 arms were associated with significantly more adverse outcomes.

The main secondary efficacy outcomes were the effect of iron MNP on hemoglobin and growth variables over time. Hemoglobin was measured at baseline, 2 mo, and 6 mo by using portable HemoCue photometers (Angelholm, Sweden) per the manufacturer’s recommendations. Anthropometric data were recorded at the same time: weight (within 0.1 kg) was obtained with a Salter balance (Salter Scales, Tonbridge, Kent, United Kingdom), and height (within 0.1 cm) was measured while the subjects were recumbent. Sociodemographic information about the subjects, their parents, and their family dwelling was collected at baseline.

**Noninferiority margin**

The noninferiority margin on the relative risk scale (MNP compared with PP) was denoted by \( \Delta \) and is “a threshold that is defined as an acceptable difference in the value of the response
parameter between the tested treatment and a standard agent” (20) The margin $\Delta$ should be chosen as the largest relative risk (RR) that one would be willing to accept with the use of the new treatment. Ideally, $\Delta$ should be derived from both statistical reasoning by using information available from the relevant literature, but also primarily from clinical judgment (21). Investigators must rely on the latter when no historical data are available.

For this study, a $\Delta$ value of 1.2 was used for 2 reasons: 1) as clinicians, we believed that it was reasonable to accept an increase of up to 20% in infections above and beyond what is observed in the community (or with placebo) to maximize the opportunity for infants to benefit from iron MNP, and 2) a $\Delta$ value of 1.2 fitted within the range of what is considered an acceptable margin (typically between 10% and 20%) (22). What does this mean concretely for the children? It would mean that if a child were expected to have 5 infectious episodes within a 6-mo period, only an average of 1 additional infection would be tolerated during that time frame for children in the iron MNP group. As a result of the uncertainty associated with ascertaining $\Delta$, we decided to use active-case detection to minimize as much as possible the likelihood of missing any significant infections associated with the use of iron MNP (when compared with PP). It is important to note that, for this trial, noninferiority between the treatment arms would be concluded only if the value of the upper bound of the RR (95% CI) is $<1.2$. We refer interested readers to a recent review on the topic for more details (23).

Sample size calculation

Sample size calculation was based on annual data from 2 studies conducted in Bangladesh that included few malnourished children (17, 24). Our conservative estimate was that Bangladeshi children would have $\geq7$ episodes of diarrhea, dysentery, or LRTIs in any 6-mo period. We calculated the SD for each infection category from Mitra (17), and these were then combined to generate a composite SD for the composite primary outcome. The sample size was calculated with National Council for Social Studies-Power Analysis and Sample Size (NCSS-PASS, 2006; Kaysville, UT) by using a $\Delta$ value of 1.2; 168 subjects would achieve 80% power to detect noninferiority by using a one-sided, 2-sample $t$ test. The actual difference between means was assumed to be 0.05 (ie, the expected effect sizes for both groups would be within 5% of each other), and $z$ was set at 0.05. After adding 10% for loss to follow-up and dropouts, and another 30% to account for seasonal differences between phases 1 and 2, the target sample size was 240 children (ie, $\approx60$ per group per season).

Statistical analyses

The main analysis examined the primary outcome (DDL) recorded during the intervention and postintervention periods, from both phases (phase-aggregated data). Other exploratory analyses were similarly performed on phase- and period-specific data. Recurrent events analyses were used to estimate the relative risk (RR) of DDL when the iron MNP group was compared with the PP group. The expected number of DDL episodes was evaluated by using the Nelson-Aalen estimate, a nonparametric estimate of the average (or equivalently the mean, or expected) cumulative number of events over time. This method is used routinely to analyze recurrent infections because it effectively deals with subjects followed for different lengths of time. By taking into account the at-risk period for each subject, the calculation of the number of observed events is more meaningful. It is important to note that the term “RR” is used here in its generic sense, as was done by some of the pioneers in the field of time-to-event analysis (25). Indeed, our estimates are not true hazard ratios given that subjects have multiple recorded events.

Two types of regression analyses were conducted to estimate treatment effects, reported as the RR of DDL (iron MNP relative to PP) along with its corresponding 95% CIs (26). The first regression analysis was based on the Andersen-Gill model, with robust variance estimates. The Andersen-Gill model is an extension of the Cox regression model used to analyze recurrent event data (ie, it deals with the fact that each patient may experience more than one event over time) (27). It makes use of the number and times of events. The robust variance estimate is used to ensure tests and CIs are valid even if there is a strong association between event times within patients (28). It is therefore analogous to a generalized estimating equation type of analyses used routinely in dealing with longitudinal or clustered data. The second regression analysis involved a semiparametric negative binomial model (mixed Poisson), which provides an estimate of the association within patients, or equivalently the heterogeneity in event rates between patients (29). It does this by introducing random effects that are patient-specific. Note that subjects’ recurrent event processes are censored at the time of loss to follow-up, as is customarily done in survival analysis. Both the Nelson-Aalen and Andersen-Gill methods allow patients to drop out of the risk set and back in again over the course of observations. Details pertaining to any hospitalizations were included in the analysis only if caused by DDL, without weighting. Because the results for both regression analyses agreed very closely with each other, only the former is reported. A conclusion of noninferiority was possible only if the upper bound of the 95% CI fell entirely below the $\Delta$ value of 1.2. Only the intention-to-treat analysis is presented. Initial hemoglobin concentrations ($\leq90$ or $>90$ g/L) and the number of live children (as a continuous variable) were also included in the model. The software used for these analyses is R (version 2.11.10), with the Survival package (version 2.36–4), both of which are available at http://CRAN.R-project.org).

Changes in hemoglobin and anthropometric variables were analyzed by using Wilcoxon’s test between the iron MNP and PP groups. These analyses were done by using JMP software (version 9.0, 1989–2010; SAS Institute Inc, Cary, NC). Test results were considered significant if $P < 0.05$.

RESULTS

In phases 1 and 2, nearly 4000 households were screened: 81% of eligible children were assessed, and 34% met the entry criteria (Figure 1). No between-group differences in baseline characteristics were noted whether phases were analyzed separately or together (Table 1). The only between-phase differences noted were more prevalent stunting in phase 1 (defined as a height-for-age
Early dropouts after randomization but before the intervention started were rare (5/268; 1.9%; Figure 1). Of the subjects who started the intervention, loss to follow-up was documented in 7 of 134 (5.2%) children from the iron MNP group and 11 of 129 (8.5%) children from the PP group. The baseline characteristics of these subjects were similar to those who finished the trial (see supplemental Table 6 under “Supplemental data” in the online issue). The 2-mo intervention was completed by 92% of subjects, and data were obtained for the entire 6 mo for 90%. The number of successful planned home visits was 95% for both groups. No statistically significant between-group differences were identified for all of the above variables (Table 3). Weekly counting of empty sachets by the trained assessors yielded an estimate of 100% adherence.

A trend toward lower infectious morbidity was noted when data from the full 6-mo period was compiled (primary outcome), favoring iron MNP (RR: 0.80; 95% CI: 0.62, 1.04; Figure 2). This result, consistent with a conclusion of noninferiority with a prespecified δ of 1.2 (Figure 3), was unchanged when hemoglobin status (≤90 or >90 g/L) or number of children per family (as a continuous variable) was included in the analytic model: hemoglobin status (RR: 0.83; 95% CI: 0.65, 1.08) and number of children per family (RR: 0.81; 95% CI: 0.63, 1.04). The incidence rates of infections were lower than expected in

![Flow diagram illustrating the number of children screened, excluded, and randomly assigned and the temporal pattern of dropouts for each group. Combined data from both phases are presented; for phase-specific details, see supplemental Figure 2 under “Supplemental data” in the online issue. The numbers in parentheses indicate the number of sachets consumed before loss to follow-up; the underlined numbers indicate data from phase 1 subjects. Iron MNP, iron-containing micronutrient powder; PP, placebo powder.](https://academic.oup.com/ajcn/article-abstract/94/2/585/4597933/588)
both groups (see supplemental Table 7 under “Supplemental data” in the online issue). When the 6-mo data were analyzed independently for each phase (subgroup analysis), the composite primary outcome was lower for the iron MNP group in phase 1 (RR: 0.66; 95% CI: 0.46, 0.93; see supplemental Figure 3b under “Supplemental data” in the online issue). In this case, iron MNP was protective in phase 1 (RR: 0.45; 95% CI: 0.26, 0.77), and a similar trend was observed in phase 2 (RR: 0.77; 95% CI: 0.50, 1.20).

There were no episodes of prolonged fever, no deaths, and short hospital admissions for 2 infants in each group (see supplemental Table 8 under “Supplemental data” in the online issue). No diagnosis of malaria was recorded. No between-group differences were found in the incidence of febrile episodes (P = 0.50; data not shown) or in the mean axillary temperature trends (P = 0.08; supplemental Figure 5 under “Supplemental data” in the online issue). Additional data on patterns of health care utilization are also available (see supplemental Tables 9 and 10 under “Supplemental data” in the online issue).

Whereas baseline hemoglobin was similar between groups (Table 1), hemoglobin was higher for subjects randomly assigned to iron MNP (P < 0.0001) at 2 mo (Table 4). The same trend was observed after 6 mo (P = 0.03, both phases combined). Importantly, an increase in hemoglobin over baseline was noted at 2 and 6 mo in subjects who received PP (P < 0.0001).

Measured heights and weights were comparable between groups at all time points (see supplemental Figure 4 under “Supplemental data” in the online issue). The only exception was higher weights at 60 d for subjects from phase 2 randomly assigned to iron MNP (P = 0.026)—an effect that did not persist to the end of the trial (P = 0.458). A difference in daily weight gain was observed when both phases were combined, which favored the iron MNP group.

### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Characteristic and phase no.</th>
<th>Comparison group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of live children per family (n)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>First-born child (n [%])</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (2–8)</td>
</tr>
<tr>
<td>2</td>
<td>3 (2–8)</td>
</tr>
<tr>
<td>Polio vaccine and vitamin A at last immunization (n [%])</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>61 (93.9)</td>
</tr>
<tr>
<td>2</td>
<td>64 (100)</td>
</tr>
<tr>
<td>Antihelminthic treatment in the past 3 mo (n [%])</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30 (46.2)</td>
</tr>
<tr>
<td>2</td>
<td>27 (42.2)</td>
</tr>
</tbody>
</table>

### Table 1

Sociodemographic, anthropometric, and laboratory characteristics of the study participants.

<table>
<thead>
<tr>
<th>Characteristic and phase no.</th>
<th>Comparison group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of subjects</td>
<td>Iron MNP PP</td>
</tr>
<tr>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>Male sex [n (%)]</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34 (52.3)</td>
</tr>
<tr>
<td>2</td>
<td>33 (46.5)</td>
</tr>
<tr>
<td>Age (mo)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17.7 ± 3.9</td>
</tr>
<tr>
<td>2</td>
<td>17.9 ± 2.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.7 ± 0.7</td>
</tr>
<tr>
<td>2</td>
<td>7.8 ± 0.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>73.4 ± 3.5</td>
</tr>
<tr>
<td>2</td>
<td>74.1 ± 3.2</td>
</tr>
<tr>
<td>WAZ, weight-for-age z score</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−2.8 (−3.1, −2.6)</td>
</tr>
<tr>
<td>2</td>
<td>−2.8 (−3.2, −2.5)</td>
</tr>
<tr>
<td>WHZ, height-for-age z score</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−2.5 (−3.0, −2.2)</td>
</tr>
<tr>
<td>2</td>
<td>−2.4 (−3.0, −1.9)</td>
</tr>
<tr>
<td>Baseline hemoglobin concentration (g/L)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>96.3 ± 9.7</td>
</tr>
<tr>
<td>2</td>
<td>94.2 ± 10.5</td>
</tr>
<tr>
<td>Baseline hemoglobin concentration ≤90 g/L [n (%)]</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16 (24.6)</td>
</tr>
<tr>
<td>2</td>
<td>21 (29.6)</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 2
Maternal sociodemographic and family-dwelling characteristics

<table>
<thead>
<tr>
<th>Characteristic and phase no.</th>
<th>Iron MNP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families for whom data were collected [n (%)]</td>
<td>65 (100.0)</td>
<td>64 (100.0)</td>
</tr>
<tr>
<td>Maternal age (y)</td>
<td>24.8 ± 6.0⁷</td>
<td>25.1 ± 5.2</td>
</tr>
<tr>
<td>Maternal weight (kg)</td>
<td>40.3 ± 5.2</td>
<td>39.5 ± 5.2</td>
</tr>
<tr>
<td>Maternal duration of education (y)⁵</td>
<td>2 (0–10)</td>
<td>0 (0–9)</td>
</tr>
<tr>
<td>Maternal literacy (%)</td>
<td>28 (43.1)</td>
<td>27 (42.2)</td>
</tr>
<tr>
<td>Familial monthly income (US$)⁵,⁶</td>
<td>45 (18–179)</td>
<td>45 (18–149)</td>
</tr>
<tr>
<td>Size of dwelling’s main room (m²)³,⁷</td>
<td>15 (11, 20)</td>
<td>15 (12, 20)</td>
</tr>
<tr>
<td>Tube well near dwelling [n (%)]</td>
<td>44 (67.7)</td>
<td>45 (70.3)</td>
</tr>
<tr>
<td>Sanitary toilet near dwelling [n (%)]</td>
<td>15 (23.1)</td>
<td>15 (23.4)</td>
</tr>
</tbody>
</table>

¹ Iron MNP, iron-containing micronutrient powder; PP, placebo powder.
None of the other between-group comparisons were significant unless noted otherwise (for all exact \( P \) values and details on paternal data, see Supplemental Table 4 under “Supplemental data” in the online issue).
² Mean ± SD (all such values).
³ \( P = 0.02 \) (t test).
⁴ Data are from 61 mothers.
⁵ Values are medians; ranges in parentheses.
⁶ The monetary exchange calculation used to normalize US dollars was 1 US$ = 67 Takas.
⁷ Values are medians; 25th, 75th quartiles in parentheses.

(P = 0.002; see supplemental Table 11 under “Supplemental data” in the online issue), but this effect was no longer noticeable at the end of the trial (\( P = 0.22 \)). Monthly gain in length and daily weight gain were near normal values for children aged 12–24 mo in both groups during the intervention period (10–20 mm/mo and 7–9 g/d, respectively; see supplemental Table 11 under “Supplemental data” in the online issue). However, these benefits were again short-lived because both rates slowed down considerably in the postintervention period (\( P = 0.01 \)).

DISCUSSION

This is the first trial specifically designed to address the safety of providing iron-containing MNP to anemic children with moderate-to-severe malnutrition. The results show that iron MNP provided daily for 2 mo is efficacious in terms of the hemoglobin response and noninferior to placebo in terms of infectious morbidity (composite of DDL) over a 6-mo period. In fact, a trend toward a protective effect of iron MNP was observed in the 4-mo period that followed the intervention. Furthermore, it did not increase the likelihood of hospitalization or mortality.

We propose 3 explanations for these results. First, recent pharmacokinetic studies in pregnant women showed that supplementation or treatment with microencapsulated iron resulted in lower peak plasma iron concentrations when compared with tablets (30). Because the iron source used in this study (ferrous fumarate) is similarly microencapsulated, we posit that the lack of increased infectious morbidity may have been explained by a reduction in iron bioavailability to pathogens. Second, it is possible that zinc, which is included in standard MNP, may have mitigated the “negative” potential of iron. Indeed, zinc supplementation hastens recovery from acute diarrhea or respiratory episodes (31). Because the recurrent event analysis used in this study takes into account both frequency and duration of episodes, these properties of zinc could have positively influenced our outcome. Of note, neither folic acid nor vitamin A appear to affect the incidence or severity of these infectious morbidities (31); there are no data for vitamin C. Finally, the previously observed negative effects of the provision of iron to malnourished infants may have been overestimated because the data originated from uncontrolled studies (8, 9).

The trend toward a protective effect of iron MNP, noted during the intervention period of phase 1, may reflect important between-phase differences at 3 levels: intervention, subjects, and exposures.

TABLE 3
Retention patterns and adherence to study protocol

<table>
<thead>
<tr>
<th>Characteristic and phase no.</th>
<th>Iron MNP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early dropouts, loss to follow-up and retention</td>
<td>1</td>
<td>2/mo</td>
</tr>
<tr>
<td>Early dropouts, after random assignment, before intervention</td>
<td>2/65 (3.1)</td>
<td>1/64 (1.6)</td>
</tr>
<tr>
<td>Retention to end of intervention, 2 mo</td>
<td>62/63 (98.4)</td>
<td>60/63 (95.2)</td>
</tr>
<tr>
<td>Retention to end of trial, 6 mo</td>
<td>60/63 (95.2)</td>
<td>58/63 (92.1)</td>
</tr>
<tr>
<td>Planned home visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of successful home visits</td>
<td>2839/2898 (98.0)</td>
<td>2819/2898 (97.3)</td>
</tr>
<tr>
<td>Number of subjects who missed ≤1/30 home visits during the intervention period</td>
<td>59/62 (95.2)</td>
<td>54/60 (90.8)</td>
</tr>
<tr>
<td>Number of subjects who missed ≤2/46 home visits during the entire 6-mo trial</td>
<td>58/60 (96.7)</td>
<td>52/58 (89.7)</td>
</tr>
</tbody>
</table>

¹ Iron MNP, iron-containing micronutrient powder; PP, placebo powder.
² \( P = 0.018 \) (Fisher’s exact test, 2-tailed).
First, only systematic, phase-specific deviations from the intervention plan could account for such effects. We believe that this hypothesis is not supported by the data because the effect of iron MNP on hemoglobin was similar in both phases. Second, the distinctive phase-specific effects noted may be explained, at least in part, by some striking and unexpected between-phases differences identified in the subjects characteristics: stunting was more common in subjects from phase 1, the group that also appears to be more impoverished based on many between-phase differences in key socioeconomic indicators. This raises the possibility that the positive effects of iron MNP on hematologic and anthropometric outcomes were likely attributable to the intensity of the intervention periods but were significantly reduced during the postintervention periods. This may have been because the mothers from both groups were equally likely to change their feeding behavior after receiving education on appropriate complementary feeding before the trial. In addition, a substantial proportion of the positive effects of iron MNP on hemoglobin and anthropometric outcomes were likely attributable to the intensity of the follow-up itself (35). In retrospect, the primary outcome was probably not immune to this trial effect either and may explain in part why the overall incidence rates of infections were lower than anticipated in both groups. It is critical to realize, however, that had historical controls been used in lieu of a PP arm for the intervention groups, including many UNICEF-supported micronutrient projects around the world. Second, iron MNPs are taste-neutral and, unlike iron drops or syrup, do not stain children’s’ teeth. The acceptability of iron MNP has been shown in diverse settings (19, 33). Third, excellent bioavailability of the microencapsulated iron in the iron MNP has been shown in infants (34).

Few data have documented the effect of iron supplementation on iron stores in malnourished children. In this study, hemoglobin was used as the sole surrogate for iron status because of community concerns about excessive bloodletting. As expected, hemoglobin significantly increased with iron MNP compared with PP. The largest effects were noted immediately after the interventions, and hemoglobin was still significantly above baseline at the end of the trial. A similar trend was observed with PP, albeit of lesser magnitude. We concluded that a 60-d regimen of iron MNP likely helped replenish iron stores in malnourished children.

No clear effect of iron MNP on growth variables was noted. In fact, analysis of anthropometric data showed that, in both phases and for all intervention groups, growth rates were near normal during the intervention periods but were significantly reduced during the postintervention periods. This may have been because the mothers from both groups were equally likely to change their behavior after receiving education on appropriate complementary feeding before the trial. In addition, a substantial proportion of the positive effects of iron MNP on hemoglobin and anthropometric outcomes were likely attributable to the intensity of the follow-up itself (35). In retrospect, the primary outcome was probably not immune to this trial effect either and may explain in part why the overall incidence rates of infections were lower than anticipated in both groups. It is critical to realize, however, that had historical controls been used in lieu of a PP arm for the statistical analyses, we may have overestimated the effects of iron MNP on these outcomes.

One of the major strengths of this study was the quality of data gathered during the intervention. Most previous studies relied solely on maternal recall over periods ranging from weeks to months. This study addressed this weakness by using more frequent home visits combined with direct observation of each child during the intervention.
child by trained assessors. As a result, the duration and timing of each infection episode was more precisely delineated. Another strength was the use of statistical analyses of repeated measures for the primary outcome. Most previous studies compared the sum of all episodes occurring in each group, an approach that is suboptimal because it fails to recognize that recurrent episodes experienced over time by one subject are dependent events. A repeated-measure analysis is more appropriate because it takes this issue into account. Finally, the combination of excellent subject retention rates, few missed home visits, and good adherence to treatment schedule enhanced the reliability of the data set.

Several limitations need to be highlighted. First, our findings are only generalizable to anemic children with moderate-to-severe malnutrition who live in areas where the prevalence of malaria is not high. Second, we cannot rule out that other micronutrients included in iron MNP—namely zinc, folate, vitamin A, and vitamin C—may have modulated the effects of iron on the outcomes. Third, the use of a 2-phase design proved to be a double-edge sword: whereas it increased data heterogeneity, it provided a reliable, seasonally adjusted data set. Finally, we recognize that every-other-day home visits during the entire 6-mo period would have resulted in less data heterogeneity.

The safety of interventions on vulnerable subjects is paramount. Although not explicit in the literature, evidence regarding the safety of iron use in children with malnutrition and ID anemia is lacking. Because of mixed messages distilled from 3 World Health Organization publications on the topic (13–15), confusion exists among those responsible for implementation of nutrition programs in areas where malnutrition and ID anemia are prevalent. Results from the current study support the conclusion that provision of iron MNP to malnourished children is not only safe, but may be beneficial in reducing the risk of infection while also improving hemoglobin status.

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The authors’ responsibilities were as follows—ML, SHZ, ZH, FH, QSI, MP, FA, and MAK: designed the research; QSI, MP, FA, and MAK: conducted the research; ML, SHZ, QSI, MP, FA, and MAK: designed and optimized the database; ML, SHZ, RJC, and HS: analyzed the data; ML and SHZ: wrote the manuscript; and SHZ: had primary responsibility for the final content. All authors read and approved the final manuscript. The two funding bodies (Thrasher Research Fund and HH Heinz Company Foundation) were not involved in the design, implementation, analysis, and/or interpretation of the data. SHZ had beneficial interests in certain intellectual property rights to his invention known as “Sprinkles.” These interests include 1) patent rights in various jurisdictions to the name “Sprinkles,” which are held by either Ped-Med Limited (a Canadian corporation of which SHZ is the sole shareholder) and 2) trade-mark 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 SHZ is a member). ML received two travel grants (in 2005 and 2006) from the Rockefeller/Evans International Health Fund/International Health Elective Scholarship from the University of Toronto during the early parts of this project; while working on the manuscript, ML was supported by a Howard Hughes Medical Institute research fellowship from July 2009 until June 2010 and then by a postdoctoral fellowship from KRES/CKF/CIHR; ML is part of the Investigative Medicine PhD training program and the Yale Center for Clinical Investigation at Yale University School of Medicine (New Haven, CT). None of the remaining authors had competing interests.

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