Regular consumption of a complementary food fortified with ascorbic acid and ferrous fumarate or ferric pyrophosphate is as useful as ferrous sulfate in maintaining hemoglobin concentrations >105 g/L in young Bangladeshi children

Lena Davidsson, Shafiqual Alam Sarker, Kazi Asif Jamil, Shamima Sultana, and Richard Hurrell

ABSTRACT

Background: Non-water-soluble iron compounds have been reported to be less well absorbed than ferrous sulfate in young children, and concern has been raised about their usefulness as food fortificants.

Objective: The objective was to evaluate the usefulness of ferrous fumarate and ferric pyrophosphate, compared with ferrous sulfate, in maintaining hemoglobin concentrations >105 g/L in Bangladeshi children.

Design: Two hundred thirty-five children aged 7–24 mo (hemoglobin >105 g/L) were randomly assigned in a double-blind study to receive an infant cereal fortified with ferrous fumarate, ferric pyrophosphate, or ferrous sulfate. One serving of cereal (9.3 mg Fe; molar ratio of ascorbic acid to iron of 3:1) was consumed per day, 6 d/wk, for 9 mo. Blood samples were drawn at 4.5 and 9 mo.

Results: Raw data were reformatted, and a “time to event” was calculated that corresponded to reaching the following thresholds: hemoglobin <105 g/L, plasma ferritin <12 μg/L, or plasma C-reactive protein >10 mg/L at baseline, 4.5 mo, or 9 mo. Data were censored when children did not reach the threshold or were lost to follow-up. A Kaplan-Meier approach was used to compare the 3 groups. No statistically significant differences were observed for hemoglobin <105 g/L (P = 0.943), plasma ferritin <12 μg/L (P = 0.601), or plasma C-reactive protein >10 mg/L (P = 0.508).

Conclusions: Contrary to earlier concerns, these results do not indicate differences in usefulness between water-soluble and non-water-soluble iron compounds in maintaining hemoglobin concentrations and preventing iron deficiency. These data will be important in the development of food-fortification strategies to combat anemia and iron deficiency in highly vulnerable population groups.


INTRODUCTION

The high return on investments related to the addition of micronutrients to food was recently recognized by the Copenhagen Consensus (1), and iron fortification of regularly consumed foods is generally considered a cost-effective nutritional intervention to prevent iron deficiency (2, 3). However, the practical problems associated with the addition of iron to foods are numerous (4). In particular, when iron is added to cereal foods as water-soluble, highly bioavailable compounds such as ferrous sulfate, the soluble iron rapidly catalyzes fat oxidation resulting in organoleptically unacceptable rancid products. Furthermore, water-soluble iron compounds can cause unacceptable color reactions during storage and food preparation. Thus, food manufacturers are often obliged to use water-insoluble iron compounds to fortify foods, and fortification compounds such as elemental iron powders and ferric pyrophosphate are widely used to fortify cereal flours and infant cereals. These compounds do not dissolve completely in gastric juice and are usually significantly less well absorbed than ferrous sulfate (5). Ferrous fumarate on the other hand, although almost insoluble in water, readily dissolves in the gastric juice and has been shown to be equally well absorbed as ferrous sulfate in healthy Western adults (6, 7). Because ferrous fumarate is not water soluble, it causes relatively few sensory problems in fortified foods and is therefore an interesting food fortificant for large-scale food-fortification programs. Iron bioavailability from ferrous fumarate has been shown to be significantly higher than from ferric pyrophosphate in European infants (8), and this compound is currently used to fortify blended cereal flours for food aid programs, commercial infant cereals in Europe, and in the encapsulated form as the iron fortificant in “in-home-fortification” strategies (9). However, our recent study in young Bangladeshi children (10) reported that ferrous fumarate was only ∼30% as well absorbed as ferrous sulfate. A study in Mexican children reported similar findings (11), and it has been suggested that lower gastric acid output in infants and young children—
particularly in developing countries where gastric acid secretion might be lowered because of *Helicobacter pylori* infection—may decrease the solubility of ferrous fumarate in the gastric juice, resulting in lower absorption. It is therefore possible that fortification strategies directed at infants and young children, which use ferrous fumarate, may result in less than optimal benefits. Clearly, there is a need to carefully evaluate the usefulness of iron compounds with different physicochemical characteristics added to foods as a public health strategy to combat iron deficiency during early life (12).

The overall aim of the study was to evaluate the usefulness of 2 non-water-soluble iron fortificants, ferrous fumarate and ferric pyrophosphate, as compared with ferrous sulfate, to maintain hemoglobin concentrations >105 g/L in Bangladeshi infants and young children.

**SUBJECTS AND METHODS**

The study protocol was reviewed and approved by the Ethical Review Committee at ICDDR,B and at the Swiss Federal Institute of Technology, Zurich. Parents were informed about the aims and procedures of the study, and informed consent was obtained from at least one parent.

**Study population**

Infants and young children (7–24 mo; *n* = 235; hemoglobin >105 g/L) were recruited at the ICDDR,B clinic in Nandipara—a periurban area 12 km from Dhaka City. Recruitment started on October 2003 and was completed in June 2006. Exclusion criteria included systemic infection or an apparent inflammatory process, hemoglobin <105 g/L, or a very low weight for age (<70%, National Centre for Health Statistics). Recruited children were randomly assigned to 3 groups to receive an infant cereal fortified with ferrous fumarate (group A), ferric pyrophosphate (group B), or ferrous sulfate (group C). Recruitment of 78–79 children per group was based on a power calculation for comparisons of independent binomial proportions (α level: 0.025; power: 0.80), assuming attrition of ≤30%. The study design was double-blind; all cereal products were coded, and the codes were kept at Nestlé Switzerland and not broken until all data evaluation had been completed.

All children with low hemoglobin (<105 g/L), diagnosed during the screening study, were treated with medicinal iron according to standard treatment (ferrous sulfate drops; 2 mg Fe/kg daily) for 2 mo. Doses of medicinal iron were administered by health care workers under close supervision of the investigators. Infants and young children with a diagnosis of low hemoglobin at the 4.5- and 9-mo follow-up during the study were treated according to the abovementioned standard protocol and were excluded from the study.

**Iron-fortified infant cereal**

Each serving consisted of 25 g dry infant cereal based on wheat flour and cow milk, and produced especially for this study by Nestlé Ltd, Bangladesh (Nestlé, Vevey, Switzerland). The infant cereal was similar to a commercial product, Cérélac, but was produced in different batches and was fortified with 3 different iron compounds—ferrous fumarate, ferric pyrophosphate, or ferrous sulfate—at a higher fortification level (9.3 mg/25 g dry cereal). Iron compounds were purchased from Paul Lohmann GmbH KG, Emmersthal, Germany. Ascorbic acid was added at a molar ratio of 3 to 1 relative to added iron. A premix containing other vitamins (folate, biotin, niacin, pantothenic acid, thiamine, and vitamins E, A, B-6, B-12, and D), minerals (calcium as calcium carbonate), and trace elements (zinc as zinc sulfate and iodine) was added at amounts used for the production of commercial Cérélac.

Seven batches of each fortified infant cereal (product A with added ferrous fumarate, product B with ferric pyrophosphate and product C with ferrous sulfate) were produced during the duration of the intervention study and stored frozen at Nestlé Ltd (Bangladesh) to prevent fat oxidation. Each batch was analyzed for iron, ascorbic acid, calcium, vitamin A, fat, protein, and moisture and was tested for microbiological quality and organoleptic properties at Nestlé Switzerland, according to standard protocols.

Infant cereal products were transported to ICDDR,B at regular intervals, and weighed servings (25 g) were prepared by ICDDR,B staff. Individual servings of fortified infant cereals were prepared by mixing with hot water immediately before each child was fed. Servings were administered by health care workers under close supervision by field supervisors. Intake data were monitored regularly by one of the investigators. One serving of cereal was fed to each child daily 6 d/wk for 9 mo. Intake was monitored weekly and, if needed, servings of fortified cereals were fed for 7 d/wk to compensate for days when the child was sick or absent. In addition to the iron-fortified infant cereal, the infants consumed their habitual diets.

**Blood analyses**

Venous blood samples (2 mL) were drawn into EDTA-treated tubes at the ICDDR,B clinic in Nandipara by one of the investigators (SS) during the screening study and after 4.5 and 9 mo of intervention.

Hemoglobin was measured with the cyanmethemoglobin method by using Danam Excell 22 (Danam Electronics, Dallas, TX) at ICDDR,B within 8 h of blood sampling. Quality control was monitored by using standard control samples (low, medium, and high values) from Drew Scientific Ltd (Cumbria, UK) and through interlaboratory comparisons organized by the College of American Pathologists.

Plasma was separated within 4 h at ICDDR,B and kept frozen (−20°C). Plasma samples were transported frozen to Zurich, where plasma ferritin and C-reactive protein (CRP) as an acute phase reactant were analyzed as single measurements by using automated solid-phase, 2-site chemiluminescent immunometric assays (Inmulite One; Diagnostic Products Corporation, Los Angeles CA). Circulating transferrin receptor (TfR) concentrations were measured in duplicate by enzyme-linked immunosorbent assay with a commercial kit (Ramco Laboratories, Stafford TX). Analyses were repeated if duplicates differed by >10%. Commercial quality-control materials (ferritin and CRP: EURO/Diagnostic Products Corporation, Llamberis, United Kingdom; TfR: Ramco Laboratories, Stafford, TX) were analyzed in parallel with each assay.

**Morbidity**

Mothers were asked about recent illness every 2 wk. A study physician (SS) interviewed the mothers, examined the children, and provided treatment as needed.
Dietary intake and anthropometric measures

A questionnaire was used to collect information on breastfeeding and descriptive data on habitual dietary intake. Body weight, length, and height were measured at baseline and after 4.5 and 9 mo of intervention. National Center for Health Statistics Growth Curves for Children (US series 11, no. 165; DHEW publication no. 78–1650) were used to calculate weight-for-age z scores (WAZ), weight-for-height z scores (WHZ), and height-for-age z scores (HAZ).

Stool antigen test for H. pylori infection

Stool specimens were collected at recruitment and tested for the presence of Helicobacter pylori antigen with a polyclonal commercial kit (H. pylori antigen EIA; catalog no. 740096; Novitech, Freiburg, Germany).

Statistical analysis

Raw data were reformatted, and a “time to event” was calculated that corresponded to reaching the following thresholds: hemoglobin <105 g/L, plasma ferritin <12 μg/L, or elevated CRP (>10 mg/L) at baseline, 4.5 mo, or 9 mo. Data were censored for children not reaching these thresholds or lost to follow-up, and the time-to-event value was set to 2.25 (baseline to 4.5 mo) or 6.75 (4.5 mo to 9 mo). Iron deficiency, defined as a plasma TfR concentration >8.5 mg/L, was very rare and thus not included in the analysis. A Kaplan-Meier approach was used to compare the 3 groups.

Kruskal-Wallis tests were used to evaluate changes in z scores from baseline to 4.5 mo and 9 mo. Pearson’s chi-square test was used to evaluate morbidity data between the intervention groups, comparing the proportion of children reporting illnesses during the first (baseline to 18 wk) or second (20–36 wk) part of the intervention. To preserve an overall statistical significance, Bonferroni adjustment was applied for each comparison to baseline. S-PLUS 7.0 for Windows (Insightful Corp, Seattle, WA) was used for all statistical analyses.

RESULTS

The initial screening study, based on venous blood samples drawn from 556 children 6–18 mo of age, showed a very high prevalence of anemia; 90% of children were anemic (hemoglobin <110 g/L). The cutoff for hemoglobin was consequently lowered to 105 g/L, and the age range was expanded to include children up to 24 mo of age. These changes to the study protocol were reviewed and approved by the ethical committee at ICDDR,B. A total of 1239 infants and young children were screened for hemoglobin concentration. All children with low hemoglobin (<105 g/L) were excluded from the study and treated with medicinal iron.

A total of 235 infants and young children (110 boys and 125 girls; hemoglobin >105 g/L) were enrolled into the study (Figure 1). Children were randomly assigned into 3 groups, with 78–79 children per group. All children had been introduced to the family diet and/or traditional, homemade, complementary foods such as milk suji (rice powder and cow milk), khichuri (rice and legumes), cow milk, seasonal fruit, or eggs at the time of enrollment. A large majority of the children (82% in group A, 79% in group B, and 86% in group C) were breastfed at recruitment. Breastfeeding rates were still high after 4.5 mo (80% in group A, 79% in group B, and 86% in group C) and 9 mo of intervention (77% in group A, 71% in group B, and 74% in group C). Twenty-five children (11%) were wasted (WHZ < −2), 73 children (31%) were underweight (WAZ < −2), and 61 children (26%) were stunted (HAZ < −2) at baseline.

More than 60% of enrolled children (48–49 children per group) maintained a hemoglobin concentration >105 g/L at the end of the 9-mo intervention study. Seventeen to nineteen children per group were excluded because of the development of a hemoglobin concentration below the cutoff level (<105 g/L) (Table 1, Figure 1). Other reasons for exclusion included migration and noncompliance with the study protocol.

The total number of servings was 216 during the 9-mo intervention. All children who completed the study consumed 77% of servings. The number of servings consumed during the 9-mo intervention was 212.9 ± 7.0 (group A; n = 48), 211.8 ± 10.3 (group B; n = 49), and 214.6 ± 3.5 (group C; n = 48). All 7 batches of infant cereal were microbiologically safe and organoleptically acceptable. The nutrient contents (per 100 g dry cereal) were as follows: 37.9 ± 1.4 (product A), 39.1 ± 1.4 (product B), and 36.7 ± 16 (product C) mg Fe; 225.0 ± 7.4 (product A), 221 ± 3.7 (product B), and 223.6 ± 8.4 (product C) mg ascorbic acid; 14.2 ± 0.9 (product A), 14.3 ± 1.0 (product B), and 14.3 ± 1.0 (product C) g protein; 389 ± 17 (product A), 387 ± 14 (product B), and 389 ± 17 (product C) mg Ca; and 2.8 ± 0.11 (product A), 3.0 ± 0.4 (product B), and 2.7 ± 0.2 (product C) mg Zn.

The proportions of children with biological indicators below (hemoglobin and plasma ferritin) or above (plasma TfR and CRP) established cutoffs at baseline, 4.5 mo, and 9 mo are presented in Table 1. No statistically significant difference was observed between the 3 groups in the time to event (baseline, 4.5 mo, or 9 mo) in the development of low hemoglobin (<105 g/L; chi-square test = 0.1, df = 2, P = 0.943), iron deficiency (plasma ferritin <12 μg/L; chi-square test = 1.0, df = 2, P = 0.601), or elevated CRP (>10 mg/L; chi-square test = 1.4, df = 2, P = 0.508). Iron deficiency, defined as a plasma TfR concentration >8.5 mg/L, was very rare [2–8 children per group at baseline and only one child at follow up (4.5 mo)], and thus was not included in the analysis.

The Kruskal-Wallis tests indicated no significant differences between groups when changes in WAZ, WHZ, and HAZ were compared from baseline to 4.5 mo and from baseline to 9 mo (data not shown). Morbidity data were grouped in 2 periods: baseline to 18 wk and 20 to 36 wk (Table 2). Respiratory infections and diarrhea were most common. Pearson’s chi-square tests were performed to test whether the percentage of children with reported symptoms differed between groups. None of the tests were statistically significant. Stool specimens were collected from 199 children and were tested for the presence of H. pylori antigen. Less than half (41%) of these samples were positive.

DISCUSSION

Contrary to expectations based on short-term bioavailability studies in children in Bangladesh and Mexico (10, 11), the results from this study indicate no difference in the ability of water-
soluble and non-water-soluble iron compounds to maintain hemoglobin concentrations >105 g/L in Bangladeshi infants and young children. These results thus contribute important new information on the usefulness of ferrous fumarate and ferric pyrophosphate as food fortificants in nutritional interventions targeted to infants and young children in developing countries. It should be stressed, however, that both iron and ascorbic acid were added at relatively high levels. The iron-fortification level was ≈4 times higher than in most commercial complementary foods, and ascorbic acid was added at a relatively high molar ratio to iron (ie, 3:1) instead of the recommended molar ratio of 2:1. It is unknown whether, at lower levels of iron fortification, the different iron compounds would be equally useful. The strategy adopted by the World Health Organization food-fortification guidelines (13) is to recommend the addition of twice the amount of iron from ferric pyrophosphate as from ferrous sulfate because it is 50% less well absorbed. It is important to note that ferrous sulfate was used only as a positive control in this study. The practical difficulties involved in using this freely water-soluble and thus highly reactive iron compound prohibit the feasibility of using ferrous sulfate to fortify infant cereal products. In the intervention study in Nandipara, these problems were overcome by introducing a relatively short shelf-life of the fortified product and storage at low temperature. This approach would obviously not be feasible in large-scale food-fortification programs.

Because food fortification is a strategy to prevent—not to cure—nutritional deficiencies, the present study was designed to evaluate the usefulness of different iron compounds in the prevention of anemia in infants and young children, and the evaluation was primarily based on the ability to maintain a hemoglobin concentration >105 g/L during the 9-mo intervention. The extremely high prevalence of anemia in this study population, 90% during the initial screening based on a hemoglobin concentration <110 g/L, and the consistently high prevalence after modifying the cutoff level to a hemoglobin concentration <105 g/L (80%), clearly indicate the urgent need to develop effective strategies to address this public health problem. The children participating in this study thus represent a small proportion of young children living in resource-poor settings in periurban Dhaka. Approximately one-third of these children were iron deficient on the basis of low plasma ferritin and/or elevated transferrin receptor concentrations at baseline. The importance of supplying additional dietary iron to this vulnerable population group was clearly shown because 50% of the children enrolled in this study (>60%) were able to maintain a hemoglobin concentration >105 g/L during the nutritional intervention, and very few children were iron deficient after 4.5 mo (0–5% to 6% per group) and after 9 mo (0–4% per group) of intervention.

The importance of food fortification targeted to infants and young children has been emphasized repeatedly as an approach to help meet nutritional requirements during vulnerable periods of rapid growth and development, for example, by Lutter and Rivera (14). The results of the present study provide new data to
TABLE 1
Proportion of children with biological indicators below or above established cutoffs at baseline and after the 4.5- and 9-mo consumption of a complementary food fortified with ferrous fumarate, ferric pyrophosphate, or ferrous sulfate.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Group A: ferrous fumarate</th>
<th>Group B: ferric pyrophosphate</th>
<th>Group C: ferrous sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin &lt;105 g/L [n/total n (%)]</td>
<td>0/79 (0)</td>
<td>0/78 (0)</td>
<td>0/78 (0)</td>
</tr>
<tr>
<td>4.5 mo</td>
<td>13/73 (17.8)</td>
<td>15/69 (21.7)</td>
<td>14/68 (20.6)</td>
</tr>
<tr>
<td>9 mo</td>
<td>5/53 (9.4)</td>
<td>4/53 (7.5)</td>
<td>3/51 (5.9)</td>
</tr>
<tr>
<td>Plasma ferritin &lt;12 µg/L [n/total n (%)]</td>
<td>16/71 (22.5)</td>
<td>15/69 (21.7)</td>
<td>19/66 (28.8)</td>
</tr>
<tr>
<td>4.5 mo</td>
<td>0/59 (0)</td>
<td>3/54 (5.6)</td>
<td>1/53 (1.9)</td>
</tr>
<tr>
<td>9 mo</td>
<td>0/44 (0)</td>
<td>1/48 (2.1)</td>
<td>2/47 (4.3)</td>
</tr>
<tr>
<td>Plasma transferrin receptor &gt;8.5 mg/L [n/total n (%)]</td>
<td>8/74 (10.8)</td>
<td>5/68 (7.4)</td>
<td>2/68 (2.9)</td>
</tr>
<tr>
<td>4.5 mo</td>
<td>0/58 (0)</td>
<td>1/54 (1.8)</td>
<td>0/54 (0)</td>
</tr>
<tr>
<td>9 mo</td>
<td>0/48 (0)</td>
<td>0/49 (0)</td>
<td>0/48 (0)</td>
</tr>
<tr>
<td>Plasma C-reactive protein &gt;10 mg/L [n/total n (%)]</td>
<td>10/74 (13.5)</td>
<td>7/69 (10.1)</td>
<td>8/68 (11.8)</td>
</tr>
<tr>
<td>4.5 mo</td>
<td>3/60 (5.0)</td>
<td>2/54 (3.7)</td>
<td>2/54 (3.7)</td>
</tr>
<tr>
<td>9 mo</td>
<td>4/48 (8.3)</td>
<td>5/49 (10.2)</td>
<td>3/48 (6.2)</td>
</tr>
</tbody>
</table>

1 No statistically significant differences (Kaplan-Meier approach) were observed between the 3 intervention groups in the “time to event” (baseline, 4.5 mo, or 9 mo) in reaching the following thresholds: hemoglobin <105 g/L (P = 0.943), plasma ferritin <12 µg/L (P = 0.601), or elevated C-reactive protein (>10 mg/L; P = 0.508). Iron deficiency, defined as a plasma transferrin receptor concentration >8.5 mg/L, was very rare and thus not included in the analysis.

Iron fortificants targeted to young children

IRON FORTIFICANTS TARGETED TO YOUNG CHILDREN

Support the regular consumption of iron-fortified complementary foods to maintain hemoglobin concentrations and to prevent iron deficiency in this age group. The observation that no statistically significant differences were found between ferrous fumarate, ferric pyrophosphate, and ferrous sulfate support the continued use of non-water-soluble iron compounds in food-fortification programs targeted to infants and young children. In support of our findings, a recent study in South Africa showed a significant decrease in anemia (from 45% to 17%) in infants consuming 11 mg Fe/d, as ferrous fumarate, added to a maize-meal porridge (15).

However, although the present study provides evidence of the usefulness of non-water-soluble iron compounds as well as ferrous sulfate in food-fortification programs targeted to infants and young children, it is important to note that ∼20% of children developed low hemoglobin (<105 g/L) after 4.5 mo and an additional 6–9% of children had low hemoglobin at the end of the study. These data clearly highlight the importance of a holistic approach to combating anemia. Although our study does not provide any information on the etiology of anemia in the study population, it can be assumed that nutritional deficiencies, in addition to iron deficiency and infections, contributed to the development of low hemoglobin. The infant cereal products fed to the children participating in this study were based on high-quality raw materials, including cow milk, and were fortified with a wide range of nutrients, including folate and vitamin B-12. The importance of these vitamins in the etiology of anemia in this age group is not well established; however, recent data from Malawi highlighted the importance of vitamin B-12 deficiency in the etiology of severe anemia in young children (16), and it can be assumed that the dietary intake of vitamin B-12 would be low in this setting because the intake of animal-source foods is very limited. The small contribution of folate (5.5 µg) and vitamin B-12 (0.19 µg) provided by each serving of fortified infant cereal might not have been sufficient under these conditions.

TABLE 2
Morbidity during the first (baseline to 18 wk) and second (20–36 wk) part of the intervention providing regular consumption of a complementary food fortified with ferrous fumarate, ferric pyrophosphate, or ferrous sulfate.

<table>
<thead>
<tr>
<th>Illness</th>
<th>Group A: ferrous fumarate</th>
<th>Group B: ferric pyrophosphate</th>
<th>Group C: ferrous sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>29/480 (6.0)</td>
<td>24/490 (4.9)</td>
<td>30/480 (6.2)</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>69/480 (14.4)</td>
<td>71/490 (14.5)</td>
<td>72/480 (15.0)</td>
</tr>
<tr>
<td>Skin infections</td>
<td>57/432 (13.2)</td>
<td>51/437 (11.7)</td>
<td>57/428 (13.3)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>2/480 (0.4)</td>
<td>0/490</td>
<td>1/480 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>3/432 (0.7)</td>
<td>0/437</td>
<td>0/428</td>
</tr>
</tbody>
</table>

1 Data are reported as a proportion of the total number of observations. No statistically significant differences were observed between the intervention groups in the proportion of children reporting illnesses during the first or second part of the intervention (Pearson’s chi-square test).
Infections are known to represent an important factor in the etiology of anemia (17). We monitored data on morbidity, and plasma CRP concentrations were measured as an indicator of the inflammatory response to infections. As can be expected for children of this age group, living in a resource-poor setting, respiratory infections were reported most frequently. Elevated CRP concentrations were observed in 10–14% of children at baseline, 4–5% at 4.5 mo, and 6–10% at 9 mo. The effect of asymptomatic *H. pylori* infection on the etiology of anemia is unclear, and conflicting data have been presented (18, 19). In this study, ≈40% of children were infected. This finding agrees with a previous study in Nandipara, reporting 50% *H. pylori* infection in this age group (20).

Our previous study of iron bioavailability from ferrous fumarate and ferrous sulfate in preschool children with and without *H. pylori* infection was implemented in the same community as the present study. In both infected and noninfected children, relative bioavailability of ferrous fumarate was ≈30% (10). The results of the present study provide no evidence to discourage the use of ferrous fumarate or ferric pyrophosphate as food fortificants targeted to infants and young children. However, it is important to stress that, in the previous study (10), all children had iron deficiency anemia, and the relative bioavailability of ferrous fumarate might have been influenced by their poor iron status, as has been reported in women (21). The observation that adaptive up-regulation of iron absorption is more effective for ferrous sulfate than for a non-water-soluble iron compound (21) highlights the importance of careful consideration of iron status of the target population. Also, it is important to emphasize that, in the previous study (10), all children were infected with *H. pylori*.

A complementary food providing ≈9 mg Fe/d with ascorbic acid added at 3:1 molar ratio to iron as ferrous fumarate or ferric pyrophosphate was shown to be as useful as ferrous sulfate at preventing the development of low hemoglobin concentrations (<105 g/L) in young Bangladeshi children.

We are indebted to all children participating in this study. Excellent assistance was provided by health workers and other staff at the ICDDR,B clinic in Nandipara. In particular, the dedicated work by Rekha Chanda, Rawnack Ara, Azmira Begum, and Shihbna Sarker is gratefully acknowledged. We express our gratitude to SS Rana and his colleagues at the Sripur Factory (Bangladesh) and Josep Burri (Nestlé Product Technology Center, Orbe, Switzerland) for excellent cooperation. We gratefully acknowledge the excellent technical assistance of Christophe Zeder (ETH Zurich).

The authors’ responsibilities were as follows—LD and RH: designed the study; SAS, KAJ, and SS: responsible for the implementation of the study in Bangladesh; and LD: responsible for the overall data analysis and writing of the manuscript. All authors reviewed the study protocol and contributed to the preparation of the manuscript. No conflicts of interest were declared.

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