Effect of daily versus once-weekly home fortification with micronutrient Sprinkles on hemoglobin and iron status among young children in rural Bangladesh

S. M. Ziauddin Hyder, Farhana Haseen, Mizanur Rahman, Méloidy C. Tondeur, and Stanley H. Zlotkin

Abstract

Background. The effectiveness of commonly suggested public health interventions to control childhood iron-deficiency anemia has been low.

Objective. To determine whether iron provided in Sprinkles daily or in a higher dose once weekly affected hemoglobin, serum ferritin levels, and serum transferrin receptor levels, and to determine whether there were differences in the effects of the two regimens.

Methods. In this cluster-randomized, community-based trial conducted in rural areas of Bangladesh, 136 children aged 12 to 24 months with mild to moderate anemia (hemoglobin 70–109 g/L) were randomly allocated to receive Sprinkles daily (12.5 mg of elemental iron, n = 79) or once weekly (30 mg of elemental iron, n = 73) for 8 weeks. Hemoglobin, serum ferritin, and serum transferrin receptor were assessed at the start and end of the intervention.

Results. In both groups, there were significant increases in hemoglobin and serum ferritin and a significant decrease in serum transferrin receptor (p < .01). There were no significant differences between the groups in the increases in hemoglobin (16.1 ± 13.2 g/L for the group receiving Sprinkles daily and 12.3 ± 13.3 g/L for the group receiving Sprinkles once weekly) and serum ferritin (10.6 and 5.7 µg/L, respectively). The decrease in serum transferrin receptor also did not significantly differ between the groups (median, −2.5 and −1.8 mg/L, respectively). The prevalence rates of iron-deficiency anemia, depleted iron stores, and tissue iron deficiency decreased significantly within each group (p < .01), with no significant differences between the groups.

Conclusions. Home fortification of complementary foods with Sprinkles given either daily or once weekly improved iron-deficiency anemia and iron status among young children.

Key words: Bangladesh, children, daily, iron, iron-deficiency anemia, Sprinkles, weekly

Introduction

In South Asia, 55% to 75% of children aged 6 to 59 months have iron-deficiency anemia [1]. The prevalence is believed to be even higher among children younger than 24 months. In Bangladesh, a recent national survey found that 73% of children aged 6 to 24 months in urban areas and 80% of those in the Chittagong Hill Tracts region were anemic [2]. The prevalence of iron-deficiency anemia in the rest of the rural areas was recently estimated to be 68% among children aged 6 to 59 months and 87% among children aged 6 to 24 months [3]. As is the case in many other countries in South Asia, the rice-based complementary foods commonly used in Bangladesh contain low amounts of bioavailable iron and high amounts of phytate, a potent inhibitor of iron absorption [4, 5]. As a result, dietary iron deficiency is generally suggested to be the major cause of anemia [6, 7]. In children, iron-deficiency anemia has significant consequences for health, including adverse effects on cognitive functions and...
Supplementation with iron is the treatment of choice for iron-deficiency anemia. Therefore, the World Health Organization (WHO) recommends blanket iron supplementation in populations with a prevalence of iron-deficiency anemia of 40% or higher [10]. Home fortification with a blend of vitamins and minerals manufactured in powdered form with the trademark name Sprinkles is an innovative strategy to increase the contents of iron and other micronutrients in complementary foods with no appreciable changes in their color, flavor, or taste [11]. Community-based trials conducted to date have demonstrated that once-daily use of Sprinkles containing 12.5 mg of elemental iron (as encapsulated ferrous fumarate) and other micronutrients (vitamin A, zinc, vitamin C, and folic acid) over a 60-day period can treat iron-deficiency anemia in infants and young children aged 6 to 24 months [12–14].

Unlike the control of vitamin A deficiency by distribution of high-dose vitamin A capsules, which is usually done twice a year, treatment and prevention of iron-deficiency anemia requires a longer-term intervention with potentially higher costs. In search of an acceptable and effective strategy, a number of studies have been conducted to compare the efficacy of daily versus intermittent (once or twice weekly) iron supplementation in the prevention and treatment of iron-deficiency anemia [15–21]. Although this is still a controversial topic due to conflicting and limited evidence, most studies conducted in children have shown that weekly administration of an iron intervention is as efficacious as daily administration. Recently, a weekly regimen of ferrous sulfate drops resulted in higher hemoglobin and also higher IQ in children than a daily regimen [22].

The addition of Sprinkles to complementary food as a vehicle to deliver iron and other vitamins and minerals is associated with improved compliance and higher acceptability compared with conventional supplements such as iron drops or syrup [12]. There are, however, no data on the hematologic impact of weekly home fortification with Sprinkles among young children. Thus, there were two primary objectives to this study: to determine whether there was a significant effect on hemoglobin and iron status from a given dose of micro-encapsulated iron-Sprinkles provided daily or a higher dose provided once weekly to mildly and moderately anemic children over an 8-week period; and to determine whether the effect differed between the groups receiving daily and weekly supplementation.

Methods

Study setting, population, and recruitment

The study was carried out from September to December 2003 in Kaligonj Subdistrict, Bangladesh. Kaligonj is an area with around 250,000 inhabitants situated about 30 km northeast of Dhaka, the capital of Bangladesh. It consists of flat agricultural land with a high population density, low literacy rates, high levels of malnutrition, and limited access to health services, all of which make the area comparable to most rural parts of the country [23]. The common diet is composed of rice, vegetables, and lentils, occasionally mixed with fish, milk, poultry, and, less frequently, meat. Malaria is not endemic and no cases of HIV have been reported [24]. The villages in the region are quite homogeneous. For example, in a recently conducted national anemia survey, the mean hemoglobin concentrations did not differ significantly between villages [2].

Eligible subjects were children aged 12 to 24 months with mild to moderate iron-deficiency anemia (70–109 g/L hemoglobin) who had no history of iron supplementation in the past 6 months, had no acute illness, consumed at least one meal of complementary food per day, and were permanent residents of their village.

Meetings were held with parents of potential subjects in the selected villages before the beginning of the baseline survey to inform them about the study. Children were enrolled after one parent gave written informed consent to their participation. Oral informed consent was taken from illiterate parents. The research proposal was approved by the Research Ethics Board of the Hospital for Sick Children, Toronto, and the Bangladesh Medical Research Council of the Ministry of Health, Dhaka.

Study design

The study was an 8-week cluster-randomized trial. The mothers or caregivers and community-based health workers were blinded to the codes on each Sprinkles sachet. However, the code was broken to the research staff to ensure that the active Sprinkles sachets, each containing 30 mg of iron, were used by the weekly-supplementation group on Mondays. Cluster-randomization (randomization by village) was used to avoid any cross-contamination between the two treatment regimens. The 152 children were recruited from 13 villages. A random-numbers table was used to assign seven villages (with 79 children) to the daily regimen and six villages (with 73 children) to the weekly regimen. The composition of the Sprinkles sachets is given in table 1. The dose of iron in the daily Sprinkles sachets (12.5 mg) was based on UNICEF/WHO recommendations [10], whereas the dose in the group receiving Sprinkles weekly was based on previously conducted studies showing the bioavailability and efficacy of a 30-mg dose of iron given as Sprinkles to young children [13, 25, 26]. These doses would have provided 700 and 240 mg of additional iron to each child in the daily and weekly groups, respectively, over the 8-week trial.
TABLE 1. Micronutrient contents of one sachet of Sprinkles (one dose) in the groups receiving daily and weekly supplementation

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Daily</th>
<th>Weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron (encapsulated ferrous fumarate)—mg</td>
<td>12.5</td>
<td>30</td>
</tr>
<tr>
<td>Zinc (zinc gluconate)—mg</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Vitamin A (retinol acetate)—µg</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Folic acid—µg</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Vitamin C—mg</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

period, assuming 100% compliance in each cohort.

All field activities were conducted by the Research and Evaluation Division of the Bangladesh Rural Advancement Committee (BRAC) within its community-based primary health-care program. BRAC is the largest nongovernmental organization in Bangladesh, dedicated to implementing interventions in rural development, health, nutrition, and nonformal primary education. Community health workers from BRAC were responsible for the distribution of Sprinkles and for monitoring their consumption as part of their regular program activities [27]. The community health workers visited each child once a week to document the level of consumption, to motivate the mothers or caregivers, and to address any issue related to the study. The daily group received Sprinkles sachets from Monday through Sunday (7 days a week). The weekly group received “active” Sprinkles on Monday and identical-looking sachets containing placebo Sprinkles for the rest of the week (from Tuesday through Sunday). To ensure high compliance, all mothers or caregivers and their children from both groups were invited to a feeding center every Monday during the 8-week period between 9 AM and 12 noon, and the intake of complementary food mixed with Sprinkles was supervised. Thus, the intake of all active Sprinkles sachets in the weekly group was supervised throughout the entire study period. The packaging of the active and placebo sachets was identical, as was the appearance of their contents. Numerical coding differentiated the active from the placebo sachets.

Before the start of the study, the acceptability of Sprinkles was tested among a group of mothers or caregivers and children from non-study villages by practical demonstrations of the use of Sprinkles and follow-up focus group discussions. In addition to testing the acceptability of Sprinkles, these sessions offered an opportunity to provide hands-on training of the community health workers and interviewers on different aspects of the Sprinkles intervention. The mothers of these children reported good acceptance, with no side effects and no appreciable changes in the color, flavor, or taste of the food.

Data collection

Baseline information on household socioeconomic and demographic characteristics and the children’s complementary feeding practices was obtained from mothers or caregivers by house-to-house interviews using a structured questionnaire. Height and weight were measured as previously described [28]. At the start and end of the intervention, a 1-mL venous blood sample was collected from each child in non-heparin-treated tubes using aseptic techniques. Blood samples were obtained between 9 AM and 12 noon. Hemoglobin concentration was measured with a portable hemoglobin photometer (HemoCue®) by trained technicians using standard techniques as previously described [28, 29]. Serum was separated at the field laboratory office by centrifugation in a portable bench centrifuge (at 3,600 × g for 15 minutes) before storage at −20°C. All serum samples were transported under dry ice to the laboratory at the Hospital for Sick Children, Toronto, Canada, for analysis. Serum ferritin was analyzed by enzyme-linked immunosorbent assay (Diagnostic Products). Serum transferrin receptor was also assessed by enzyme-linked immunosorbent assay (Ramco Laboratories). Baseline and final serum ferritin and serum transferrin receptor concentrations from an individual subject were assayed on the same day to minimize interassay variations.

Data on consumption of Sprinkles were collected once a week by counting the remaining sachets, and compliance was expressed as the total number of sachets consumed divided by the total number recommended for each child. Data on side effects (vomiting, loose stools, and constipation) were collected weekly. The occurrence of vomiting or constipation was defined as at least one episode in the previous 7 days, as reported by the mother or caregiver. Loose stool was defined as at least three episodes within the last 24 hours. The acceptability of the intervention was determined at the end of the intervention by individual interviews using a structured questionnaire.

Sample size calculation

Determination of sample size was based on our primary objectives. The standard deviation of hemoglobin concentration was estimated to be 13 g/L, based on the UNICEF 2004 anemia survey in infants and young children in Bangladesh (personal communications, BRAC Research and Evaluation Division). An alpha of 0.05, a power of 0.80, and a design effect of 2 for cluster randomization were assumed. On the basis of these assumptions, a sample of at least 56 infants per group would be required to detect a 10 g/L difference in hemoglobin concentration within and between groups at 8 weeks of follow-up. On the assumption of
a 20% loss to follow-up, the resulting sample size was determined to be 67 children per group.

**Statistical analysis**

The questionnaires were coded and data were entered by using the SPSSWIN statistical package, version 9.0. Data were verified by checking for consistency and range. SPSSWIN version 11.0 was used for data analysis. Tests of normality for hemoglobin, serum ferritin, serum transferrin receptor, and anthropometric variables were performed by a one-sided Kolmogorov-Smirnov test. Serum ferritin and serum transferrin receptor concentrations were not normally distributed, and therefore these values are presented as medians and percentiles and were analyzed by nonparametric statistics. Height-for-age (stunting, defined as height-for-age < −2 SD), weight-for-age (underweight, defined as weight-for-age < −2 SD), and weight-for-height (wasting, defined as weight-for-height < −2 SD) z-scores were calculated on the basis of the NCHS (US National Center for Health Statistics) reference standard by using EPI-INFO 6 (US Centers for Disease Control and Prevention). The differences in baseline characteristics between the daily and weekly groups were examined by independent t-tests. Changes in hemoglobin concentration from the beginning to the end of the intervention were examined by paired t-tests and compared between the two groups by independent t-tests. Because of the non-normal distribution of serum ferritin and serum transferrin receptor concentrations, the Wilcoxon signed-ranks test was used to assess changes in these measurements from the beginning to the end of the intervention, and the Kruskal-Wallis test was used to compare the effect of the intervention between the two groups. Differences in the prevalence of iron-deficiency anemia were assessed with a chi-square test. Anemia was defined as a hemoglobin concentration less than 110 g/L [30]. A serum ferritin concentration less than 12 µg/L was used as an indicator of depleted iron stores [30], and a serum transferrin receptor concentration greater than 8.5 mg/L was used as an indicator of tissue iron deficiency [31]. Side effects were analyzed as categorical variables. For example, if a child had any episode of constipation over the course of the study, the child was categorized as having constipation. P values less than .05 were considered to indicate statistical significance.

**Results**

**Recruitment**

A total of 263 children aged 12 to 24 months from 13 villages were initially screened (fig. 1). Recorded birth weights were not available for any of them. Of these screened children, 88 were excluded because they were nonanemic (hemoglobin ≥ 110 g/L), 4 were excluded and referred to a nearby clinic to receive appropriate treatment because they were severely anemic (hemoglobin < 70 g/L), 18 were excluded because their parents did not give consent, and 1 was excluded because of an active infection. The remaining 152 children were finally included in the study and randomized by their villages to either the daily or the weekly intervention group. There were no significant differences in age or sex ratio between the excluded and included children. Of the 152 children enrolled at baseline, complete data sets on major outcome measures (hemoglobin, serum ferritin, and serum transferrin receptor concentrations) were available for 136 children: 70 in the daily group and 66 in the weekly group. Reasons for loss to follow-up included movement of one family out of the village, refusal by 14 mothers or caregivers to participate further in the study, and one error in serum separation. The baseline biochemical values of the children lost to follow-up were similar to those of the children who remained in the trial.

![FIG. 1. Trial profile](image-url)
Baseline characteristics

There was no association between village of residence and any of the baseline characteristics. None of the baseline characteristics differed between the daily and weekly groups (table 2). Fifty percent of the children were between 12 and 18 months of age. Forty-eight percent of the mothers or caregivers were illiterate, and 60% of the households had no land, as compared with the national averages of 46% for women's illiteracy and 52% for landlessness in rural Bangladesh. Almost one-third of the children's fathers earned their living by manual labor, an unstable source of income. Despite the WHO recommendation that complementary foods be introduced at the age of 6 months, one-quarter of the study children aged 6 to 24 months received only breastmilk. On the other hand, 23% of the children were weaned before 6 months, some as early as 3 months. Anthropometric indicators (z-scores) suggested poor nutritional status of these children; the prevalence rates of stunting, underweight, and wasting were 32%, 50%, and 24%, respectively. According to the baseline survey, 87% of the study children had received vitamin A capsules within the preceding 6 months, and there was no difference between the groups in the proportion of children receiving the capsules (data not shown).

Effect on biochemical outcomes

After 8 weeks, there were no significant associations between hemoglobin, serum ferritin, or serum transferrin receptor concentrations and village of residence. There were significant increases in hemoglobin and serum ferritin and a decrease in serum transferrin receptor as compared with baseline in both the daily and the weekly groups (p < .001) (table 3). Similar results were observed for changes in hemoglobin, serum ferritin, and serum transferrin receptor when the analysis was repeated on a subset of children with baseline serum ferritin less than 12 µg/L. The changes in hemoglobin and serum ferritin after the intervention did not significantly differ between the daily and the weekly groups (p = .11 and .13 for change in hemoglobin and serum ferritin, respectively). The change in serum transferrin receptor also did not differ between the two groups (p = .11).

### Table 2. Baseline characteristics of the children included in the study in Kaligonj, Bangladesh

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Daily supplementation (n = 79)</th>
<th>Weekly supplementation (n = 73)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age—mo</td>
<td>17.8 ± 3.6</td>
<td>18.4 ± 3.7</td>
<td>.41</td>
</tr>
<tr>
<td>Male sex—%</td>
<td>52.9</td>
<td>53.0</td>
<td>.56</td>
</tr>
<tr>
<td>Mother literate—%</td>
<td>42.9</td>
<td>53.0</td>
<td>.30</td>
</tr>
<tr>
<td>Landless household—%</td>
<td>58.6</td>
<td>62.1</td>
<td>.73</td>
</tr>
<tr>
<td>Father’s occupation—%</td>
<td></td>
<td></td>
<td>.58</td>
</tr>
<tr>
<td>Manual laborer</td>
<td>31.4</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>Agricultural worker</td>
<td>21.4</td>
<td>28.8</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>25.7</td>
<td>27.3</td>
<td></td>
</tr>
<tr>
<td>Salaried staff</td>
<td>21.4</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>Dietary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complementary food introduced at &gt; 6 mo—%</td>
<td>30.0</td>
<td>24.2</td>
<td>.71</td>
</tr>
<tr>
<td>Breastfed at baseline—%</td>
<td>92.9</td>
<td>86.4</td>
<td>.27</td>
</tr>
<tr>
<td>Anthropometric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length—cm</td>
<td>76.4 ± 3.9</td>
<td>76.7 ± 3.9</td>
<td>.64</td>
</tr>
<tr>
<td>Weight—kg</td>
<td>8.9 ± 1.2</td>
<td>8.8 ± 1.0</td>
<td>.88</td>
</tr>
<tr>
<td>HAZ</td>
<td>−1.50 ± 0.97</td>
<td>−1.57 ± 1.16</td>
<td>.68</td>
</tr>
<tr>
<td>WAZ</td>
<td>−1.85 ± 1.04</td>
<td>−1.94 ± 0.90</td>
<td>.58</td>
</tr>
<tr>
<td>WHZ</td>
<td>−1.31 ± 1.12</td>
<td>−1.41 ± 0.94</td>
<td>.54</td>
</tr>
<tr>
<td>Biochemical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin—g/L</td>
<td>96.5 ± 10.9</td>
<td>97.4 ± 10.9</td>
<td>.63</td>
</tr>
<tr>
<td>Serum ferritin—µg/L &lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.1 (5.5, 13.2)</td>
<td>10.3 (6.7, 16.8)</td>
<td>.23</td>
</tr>
<tr>
<td>Serum transferrin receptor—mg/L &lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.1 (7.1, 12.0)</td>
<td>8.5 (7.0, 10.9)</td>
<td>.46</td>
</tr>
</tbody>
</table>

HAZ, height-for-age z-score; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score

<sup>a</sup> Plus–minus values are means ± SD.

<sup>b</sup> Values are expressed as medians (25th, 75th percentiles).
Effect on iron and anemia status

From baseline to end of the intervention, the prevalence of depleted iron stores (serum ferritin < 12 µg/L) significantly decreased from 66% to 18% in the daily group and from 59% to 27% in the weekly group \((p < .01)\), with no significant difference between the two groups. Similarly, the prevalence of tissue iron deficiency (serum transferrin receptor > 8.5 mg/L) significantly decreased from 60% to 19% in the daily group and from 45% to 21% in the weekly group \((p < .01)\), with no significant difference between the two groups. The anemia cure rate was 54% in the daily group and 53% in the weekly group after the 8-week supplementation period, with no significant difference between the groups.

Compliance

The mean compliance was 91% in the daily group, i.e., on average, the children consumed 91% of the total of 60 sachets of Sprinkles distributed. Since the provision of the active Sprinkles was supervised, compliance with the once-weekly dose of active Sprinkles was 100%. None of the mothers or caregivers reported giving more than one sachet of Sprinkles per day to their children. According to the individual interviews, no caregiver or mother gave the Sprinkles to another child in the household who was not enrolled in the study.

Acceptability and side effects

The intervention was found to be highly acceptable; 91.0% of the mothers or caregivers reported that the Sprinkles caused no change in the smell of the food, 98.6% reported no change in color, and 98.7% reported no change in taste. Eighty-five percent of the mothers or caregivers in the daily group and 90% of those in the weekly group reported that their children's appetites had increased from the preintervention period \((p = .32)\). Episodes of one or more dark stools were reported by 90% and 81% of mothers or caregivers \((p = .16)\) and loose stools by 16% and 32% of mothers or caregivers \((p = .03)\) in the daily and weekly groups, respectively.

Discussion

Our study showed that daily or once-weekly use of micronutrient Sprinkles for 8 weeks significantly increased hemoglobin and iron status indicators and decreased the prevalence of mild to moderate iron-deficiency anemia in children 12 to 24 months of age. There were no significant differences between the daily and the once-weekly groups in any outcome measures.

Even though the absolute effect of home fortification with Sprinkles on hemoglobin and iron status

### TABLE 3. Concentrations of hemoglobin, serum ferritin, and serum transferrin receptor at the beginning and end of the intervention in children aged 12 to 24 months given 12.5 mg of iron daily or 30 mg of iron once weekly in Sprinkles for 8 weeks

<table>
<thead>
<tr>
<th>Biochemical measure</th>
<th>All children</th>
<th>Children with &lt; 12 µg/L serum ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily</td>
<td>Weekly</td>
</tr>
<tr>
<td></td>
<td>supplementation((n = 70))</td>
<td>supplementation((n = 66))</td>
</tr>
<tr>
<td>Hemoglobin—g/L(^a)</td>
<td>96.8 ± 10.8</td>
<td>97.0 ± 10.9</td>
</tr>
<tr>
<td>Beginning</td>
<td>112.9 ± 10.9</td>
<td>109.3 ± 12.0(^b)</td>
</tr>
<tr>
<td>End</td>
<td>16.1 ± 13.2</td>
<td>12.3 ± 13.3</td>
</tr>
<tr>
<td>Change</td>
<td>.11</td>
<td>18.2 ± 13.1</td>
</tr>
<tr>
<td>Serum ferritin—µg/L(^c)</td>
<td>8.1 (5.5, 13.2)</td>
<td>10.3 (6.7, 16.8)</td>
</tr>
<tr>
<td>Beginning</td>
<td>19.5 (14.1, 27.3)(^d)</td>
<td>18.4 (11.5, 26.1)</td>
</tr>
<tr>
<td>End</td>
<td>10.6 (4.6, 16.0)</td>
<td>5.7 (1.5, 14.4)</td>
</tr>
<tr>
<td>Change</td>
<td>.11</td>
<td>11.3 (4.9, 14.5)</td>
</tr>
<tr>
<td>Serum transferrin receptor—mg/L(^c)</td>
<td>9.0 (7.1, 12.0)</td>
<td>8.1 (7.0, 10.9)</td>
</tr>
<tr>
<td>Beginning</td>
<td>6.2 (5.5, 7.9)(^d)</td>
<td>6.5 (5.6, 8.0) (^d)</td>
</tr>
<tr>
<td>End</td>
<td>−2.5 (−5.0, −0.8)</td>
<td>−1.8 (−3.5, −1.2)</td>
</tr>
<tr>
<td>Change</td>
<td>.11</td>
<td>−3.4 (−5.8, −1.6)</td>
</tr>
</tbody>
</table>

\(^a\) Values are expressed as means ± SD.
\(^b\) Values from beginning to end are significantly different \((p < .01, \text{paired} \ t\text{-test})\).
\(^c\) Values are expressed as medians (25th, 75th percentiles).
\(^d\) Values from beginning to end are significantly different \((p < .01, \text{Wilcoxon signed-ranks test})\).
indicators could not be assessed in the absence of a placebo group, it is unlikely that the observed increase in hemoglobin and improvements in iron status would have occurred to the same extent had no intervention been provided. Indeed, in Bangladesh, weaning practices are very poor and the most commonly eaten weaning foods are made from plain rice or rice-based cereals (suji), which are poor sources of bioavailable iron and zinc [32]. Another likely limitation of our study may be correction of iron-deficiency anemia due to the use of time-dependent statistics; i.e., some of the improvements in hemoglobin and iron status in both groups could have resulted from spontaneous correction of iron-deficiency anemia as the children grew older. However, the intervention period was relatively short (2 months), and little or no improvement would be expected without an intervention within this limited period.

To the best of our knowledge, this is the first study comparing daily and once-weekly home fortification with powdered micronutrients in anemic young children. A previous study was conducted on daily and weekly use of Sprinkles in nonanemic school-aged children in China [33]. The children in the present study may be considered representative of children in the rest of the rural plains of Bangladesh with respect to diet, caregivers’ practices, and socioeconomic and nutritional status [34]. Rice is the major staple food in Bangladesh, and is commonly used to prepare complementary foods [34]. Since Sprinkles was mixed into rice-based complementary foods, the study results may also be applicable to many other rice-eating developing countries. Unlike the children in many studies comparing daily and weekly administration of iron, the children in our study were not dewormed at the start of the intervention, since the prevalence of hookworm is relatively low in the study area and there are no general recommendations to deworm children under 2 years of age [35].

Our findings are similar to those of other community- and school-based studies from Bolivia, China, Indonesia, and Vietnam. Among children ranging from 6 months to 13 years of age, twice- or once-weekly administration of iron for 2 to 4 months had similar effects on hemoglobin concentration as daily administration [15–17, 21]. In contrast to our results, several other studies in infants and young children (with ages ranging from 2 months to 6 years) found that daily administration of iron over periods ranging from 6 weeks to 3 months resulted in greater changes in hemoglobin concentration than once- or twice-weekly administration [36–38]. However, direct comparisons between the present study and other studies are difficult to make because of differences in study populations, types of iron compounds and doses, delivery systems (home fortification vs. medicinal supplementation), and duration of the interventions.

The prevalence of depleted iron stores and tissue iron deficiency significantly decreased from baseline to the end of the intervention in both groups, with no significant differences between the groups. Two studies comparing weekly and daily administration did not find any significant differences between treatment groups in serum ferritin concentration at the end of the study [17, 20], a result similar to that of our study. In contrast, Sungthong et al. reported greater iron stores (higher serum ferritin) in primary schoolchildren receiving daily doses of iron than in those receiving weekly doses [19]. An explanation for these conflicting results is not readily apparent, but the differences are most likely due to differences in the populations of children studied, the dose and form of iron used, the duration of the intervention, or a combination of these factors.

After 8 weeks of home fortification, about 45% of the children in both groups remained anemic. There are several possible explanations for this lack of response. A dose of 2 to 3 mg of elemental iron per kilogram of body weight is recommended to correct iron-deficiency anemia [39]. The duration of our study was probably shorter than that required to achieve an optimum response, and hence the average weekly iron doses of 87.5 mg in the daily group and 30 mg in the weekly group might not have been high enough to correct all cases of iron-deficiency anemia. It is also possible that the cause of the anemia in some children was some chronic disease rather than iron deficiency [40]. These children would not have been expected to respond to an iron intervention.

In the present study, loose stools were reported more frequently in the weekly group. Black-colored stools were also common, but vomiting and constipation were rare. Since there was no placebo group, it is not possible to attribute these adverse effects to the intervention alone. Nevertheless, to understand and explain compliance with the intervention, we believe it is still informative to record this type of information when providing an iron intervention. It is well known that the failure of most supplementation programs is at least partly due to low compliance [41] and that gastrointestinal side effects are often thought to be partly responsible for the low compliance [30]. In the current study, it is possible that the weekly 30-mg dose of iron was too high as a single dose for such a moderately malnourished population, leading to loose stools in some cases. However, the occurrence of adverse effects did not appear to affect compliance to a great extent, since compliance was high in both groups.

The study results need careful interpretation because of the limited sample size. A post hoc power analysis was conducted to examine whether inadequate sample size could have accounted for the observed lack of difference in mean hemoglobin concentration between groups. On the basis of the variance and differences
observed between groups, at least 193 subjects per
group (a total of 386 including a design effect of 2)
would have been needed to detect a significant
difference. Therefore, with a larger sample we might have
found a difference between the two administration
regimens. However, an additional post hoc power
analysis indicated that the present study was adequately
powered (100%) to detect a clinically significant
within-group difference of 10 g/L at a significance level
of .05 and a standard deviation of 13.3 g/L.

In conclusion, home fortification with micronutri-
ent Sprinkles providing 12.5 mg of elemental iron
daily or 30 mg once weekly improved hemoglobin
and iron status indicators in young children aged 12
to 24 months. There were no differences in the degree
of improvement between groups, although because of
the limited sample size, we cannot definitively conclude
that the effect was similar in both groups. A less fre-
frequent administration schedule for Sprinkles, such as
the weekly regimen studied here, may be more benefi-
cial from a public health perspective due to decreased
program costs, increased convenience, and possibly
less demanding organizational and administrative
efforts. However, further studies, including large-
scale effectiveness trials, are warranted to understand
the relative benefits and limitations of weekly versus
daily administration of Sprinkles in infants and young
children.

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Competing interests

Dr. Stanley Zlotkin owns the intellectual property rights
to micronutrient Sprinkles. Any profit from the licens-
ing of Sprinkles production, after expenses, is donated
to the Hospital for Sick Children Foundation.

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