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# Short-term daily or weekly administration of micronutrient Sprinkles™ has high compliance and does not cause iron overload in Chinese schoolchildren: a cluster-randomised trial

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## Abstract

*Objectives:* To examine consumption rates and serum ferritin (SF) concentrations (as a marker of safety) among schoolchildren (3–6 years) provided with daily and weekly micronutrients.

*Design and methods:* Micronutrients were provided for one school term (13 weeks) to a kindergarten in northern China as single-dose Sprinkles™ sachets containing 30 mg of iron as encapsulated ferrous fumarate, 5 mg zinc gluconate, 50 mg vitamin C, 300 μg vitamin A, 7.5 μg vitamin $D_3$ and 150 μg folic acid. Sixteen classrooms were randomly assigned to: (1) daily supplements for 5 days a week (daily group); (2) weekly supplements (weekly group); or (3) no supplements (control group). Consumption of sachets was monitored for each child and SF concentrations were measured at the end of study. Random effects general linear models and graphs were used to compare the groups.

*Results:* A total of 415 children from 16 classrooms entered the study. At the end of the study, mean consumption rates per child were 86% (daily group; standard deviation (SD) 12%) and 87% (weekly group; SD 16%). Median SF concentrations were 71 $\mu g\,l^{-1}$ (range 27–292 $\mu g\,l^{-1}$; daily group), 55 $\mu g\,l^{-1}$ (range 11–299 $\mu g\,l^{-1}$; weekly group) and 54 $\mu g\,l^{-1}$ (range 7–327 $\mu g\,l^{-1}$; control group); the overall difference was not significant ($P = 0.06$). However, the daily group was significantly different from the control ($P = 0.02$); daily and weekly groups had higher SF at lower percentiles and similar SF at higher percentiles compared with the control group.

*Conclusion:* The high consumption rates and appropriate SF concentrations in the supplemented groups suggest that a short-term school programme with Sprinkles is an efficient and safe way to provide micronutrients (including iron).

**Keywords**
Micronutrients
Children
Anaemia
Iron deficiency
Cluster-randomised trial
Safety
Sprinkles
China

Iron deficiency (ID) is a common cause of anaemia in China, where prevalence of anaemia varies from 10 to 70% by geographical region[1–6]. In northern China, iron-deficiency anaemia (IDA) is common among infants and children, despite improved quality of food, nutritional status and living conditions[7]. A survey of 42 606 adult males and females aged 18–60 years[8] found that overall 18% were anaemic (mainly due to ID) despite sufficient mean daily iron intake of 24.4 mg per capita; Chinese Recommended Nutrient Intakes for males and females (18–50 years) are 15 and 20 mg $day^{-1}$, respectively. Such results suggest that even high iron intake may not be sufficient to prevent IDA because much of the iron consumed in China comes from food sources with low iron bioavailability. Another reason could be that iron intake is lower among vulnerable subgroups of the population such as young children and women of reproductive age. While public health interventions seem necessary in areas with a high prevalence of anaemia, screening for anaemia is expensive and often not feasible, which makes it difficult for programmes to reach vulnerable individuals. Thus, communities at risk are often targeted, where both anaemic and non-anaemic individuals receive the intervention. However, iron is toxic if too much is ingested[9,10] and ineffective if too little is ingested, thus the supplemented amount of iron must be

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both effective and safe especially for children. In this context, Liu and Liu suggested weekly iron dosing as an effective iron-supplementation programme for China after observing encouraging results for weekly dosing[11]. However, subsequent studies elsewhere showed conflicting results – Beaton and McCabe carried out a pooled analysis which favoured daily over intermittent (weekly) dosing in all settings, except for school programmes and similar controlled settings where both appeared equivalent[12]. This is intuitive since by providing iron supplements in schools, children can be reached specifically and their compliance can be ensured.

The use of microencapsulated iron Sprinkles™, a new fortification strategy for treating and preventing micronutrient deficiencies, has been shown to be efficacious for treating anaemic infants in their homes[13,14]. However, home delivery of interventions is expensive; thus we embarked upon testing the effectiveness of Sprinkles containing 30 mg of iron provided daily or weekly to healthy children (age 3–6 years) in a school setting in northern China. Six months prior to the study, 450 children (3–6 years) were sampled of whom 21% had haemoglobin (Hb) $<113\,g\,l^{-1}$, presumably due to ID. Thus we presumed a prevalence of IDA of 21%. However, after we had analysed the baseline blood samples from the current study, it became apparent that the prevalence of ID was very low (<5%) in this setting. This meant that the setting was not appropriate to test the effectiveness of iron supplements in reducing ID but provided us a unique opportunity to assess whether consumption of iron, as fortified food, increases the risk of developing iron overload in these children who already had sufficient iron stores. Therefore, we report the consumption rates of daily or weekly iron supplements provided as Sprinkles to children at school and end-of-study serum ferritin (SF) concentrations (an index of iron stores)[15] compared with no supplements; we also examined by tertile of baseline SF concentrations whether the change in SF concentrations in the daily and weekly groups was different across tertiles.

## Methods

### *Study area and participants*

The study took place between March and July 2002 at Xin-shi-dai kindergarten, in Baotou City, Neimenggu Autonomous Region, northern China. The total school population comprised 712 students in the age range of 3–6 years. There were four classrooms for each group of 3-year-olds, 4-year-olds, 5-year-olds and 6-year olds; thus a total of 16 classrooms (4 × 4). Children attended the school 5 days a week where three meals were served every day. Parents had to pay a fee to admit their children in the school; thus this was a relatively wealthy subgroup of the regional population.

### *Study design*

The study was a cluster-randomised clinical trial initially designed to assess the effectiveness of supplementing children at school with Sprinkles for 13 weeks (one school term). One classroom (cluster) in each age group was randomly assigned to one of the three study groups. The three groups were: (1) Sprinkles daily for 5 days a week (daily group); or (2) Sprinkles once a week (weekly group); or (3) no supplementation (control group). With the change in objectives, there were two primary outcomes. The first, which applied only to daily and weekly groups, was the number of sachets consumed by each child out of the total assigned. This was under direct observation of school staff. The second assessed safety through the use of end-of-study SF concentrations as a surrogate measure of iron stores and toxicity[16–18]. Other outcomes were Hb concentrations and ID defined as free erythrocyte protoporphyrin (FEP) $>70\,\mu g\,dl^{-1}$ for children less than 5 years old and $>80\,\mu g\,dl^{-1}$ otherwise.

Our power calculation was based on detecting differences in end-of-study SF concentrations (log-transformed) between the three groups. Assuming a 60–80% participation rate and a 20–40% dropout rate, we estimated that 256–456 children would need to complete the study. Based on classroom size as a cluster, we estimated the number of children per cluster ($m$) in the range of 16–29 and the standard deviation (SD) of SF (log-transformed) for the control group to be 0.8. Assuming a minimal correlation between children in a cluster ($\rho = 0.03$), we obtained a range of adjusted SD for clustering with the following formula:

$$^{\text{cluster-adjusted}}\text{SD} = \sqrt{\text{SD}^2 \times [1 + (m-1)\rho]}.$$

We arbitrarily considered a $15\,\mu g\,l^{-1}$ difference in SF concentrations to be clinically important and assumed a dose–response relationship, i.e. SF concentrations would be lowest in the control group, intermediate in the weekly and highest in the daily group. This corresponded to log means of 3.9, 4.17 and 4.38 for the control, weekly and daily groups, respectively. We estimated that the resulting 85–152 children per group would ensure power of between 84 and 94% ($\alpha = 0.05$) to detect between group differences for SF (log-transformed) concentrations.

Approval was granted by the National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, Beijing, China and the Research Ethics Board at the Hospital for Sick Children, Toronto, Canada. Parent meetings were arranged in the local language to explain the purpose, methods and risks of the study. Consent forms were given and explained to the parents. The sole eligibility criterion was parental consent.

At baseline, information was collected from the parents on sociodemographic and dietary factors using structured questionnaires. Height and weight measurements were recorded and blood samples were taken simultaneously

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for all participating children present at school on that day. Hb was measured in daily and weekly groups only, and involved a finger prick to complete an in-field, direct assay for Hb concentration using a HEMOCUE B-hemoglobin photometer (Hemocue Inc., Angelholm, Sweden). In addition, venous blood (500 μl) was collected from these children for testing of SF and FEP concentrations. For ethical reasons, we did not study controls for baseline biochemical indices as they were not assigned to an intervention.

Sprinkles™ (Ped-Med Ltd, Toronto, Canada) were supplied as single-dose sachets to include: 30 mg of iron as encapsulated ferrous fumarate, 5 mg zinc gluconate, 50 mg vitamin C, 300 μg vitamin A, 7.5 μg vitamin $D_3$ and 150 μg folic acid. Sachets were mixed with a standardised semi-solid meal of rice porridge or *congee* under the supervision of school teachers. Children in the control group were also served the same *congee*, but without Sprinkles. Data on consumption of Sprinkles sachets consisted of each child's record of the number of days that Sprinkles were mixed in his/her bowl of *congee* and that the bowl was entirely eaten by him/her under direct observation of his/her teacher.

At the end of the study, anthropometric and biochemical measures were repeated, using similar procedures as before, except that blood samples were collected from all children including the controls. Children identified to have anaemia at this time were offered additional Sprinkles and referred to a health facility.

Data forms were checked for completeness and face validity before computer entry. Further numerical and logical inconsistencies were addressed upon file transfer to the Toronto centre by sending queries to the field. Research staff from Beijing closely monitored the study and a research assistant from Toronto visited the study site at the time of data collection at baseline and end of the study.

### *Statistical analyses*

Preliminary analyses involved examining the data with histograms and descriptive statistics. We computed *Z*-scores for height-for-age, weight-for-age and weight-for-height[19], and consumption rates by taking the percentage of sachets consumed out of the total assigned per child. Next, we compared groups for end-of-study SF concentrations by using linear random effects regression models that had end-of-study log-transformed SF concentrations as dependent variable, group allocation as independent variable and classroom as random effect, which were extended to test for potential confounding factors such as age, gender, baseline SF concentrations and food consumption. To further examine the group effect we examined percentiles of log-transformed SF concentrations of each group, and carried out a subgroup analysis of the daily and weekly groups by tertiles of their baseline SF concentrations. The latter was an extension of the best-fitting random effects regression model and included tertile as a covariate with an interaction term between the group allocation and tertile. This simultaneously tested whether: (1) the effect on SF concentrations was different between groups; (2) the effect depended upon baseline iron status (tertile); and (3) the effect within a group was different by tertile. Our analyses were based on an intention-to-treat principle and we considered $P < 0.05$ as significant for hypothesis testing. We used SAS (version 8.2; SAS Institute, Inc., Cary, NC, USA) for all statistical and graphical analyses including power calculation.

## Results

### *Participant flow and data for intention-to-treat analysis*

Out of 16 classrooms (clusters), six were assigned to the daily group and five each to weekly and control groups. A total of 712 children were enrolled in the school whose parents were approached to participate in the study at the beginning of the school term in March 2002. As shown in Fig. 1, 297 (42%) children whose parents declined consent were not included in the study. Thus, a total of 415 children were assigned to the daily group ($n = 138$; six clusters), weekly group ($n = 147$; five clusters) or control group ($n = 130$; five clusters). None of the children's parents withdrew their consent during the study.

At the time of enrolment, parents of 316 (76%) children returned questionnaires containing sociodemographic and food frequency information. Anthropometric measurements were collected for 100% of the daily group, 99% of the weekly group and 98% of the control group. At baseline, Hemocue samples (for Hb) were available for 111 (80%) in the daily group and 118 (80%) in the weekly group; and venous blood samples were obtained for 134 (97%) in the daily group and 123 (84%) in the weekly group. For compliance in daily and weekly groups, data were available for 278 (98%) children. At the end of the study, anthropometric measurements were recorded for 116 (84%) in the daily group, 119 (81%) in the weekly group and 109 (84%) in the control group. Hemocue samples were available for 118 (86%) in the daily group, 122 (83%) in the weekly group and 110 (85%) in the control group. Venous blood samples were obtained for 119 (86%) in the daily group, 123 (84%) in the weekly group and 111 (85%) in the control group.

### *Baseline characteristics and iron indices*

At baseline, the demographic characteristics except for gender (Table 1) were similar for children in the three groups; dietary factors (data not shown) were also similar. Very few children (three or fewer) had *Z*-scores $< -2$ for height-for-age, weight-for-age or weight-for-height in any group (Table 1).

Mean Hb concentrations were 128 (SD 13) $g\,l^{-1}$ (daily group) and 131 (SD 11) $g\,l^{-1}$ (weekly group). Median SF concentrations were 46 $\mu g\,l^{-1}$ (range 2.5–264 $\mu g\,l^{-1}$;

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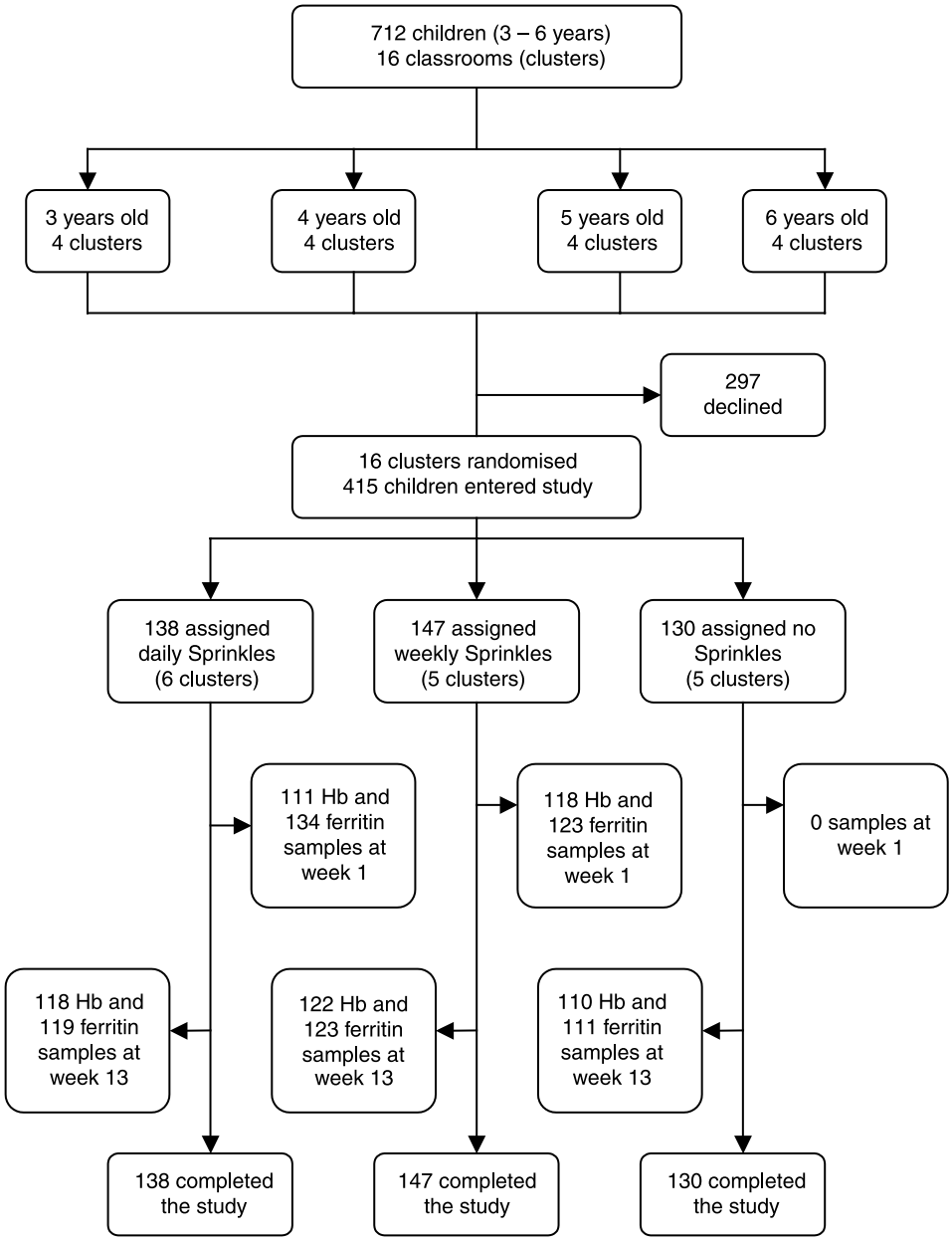


**Fig. 1** Flow chart showing trial profile (Hb – haemoglobin)

**Table 1** Baseline characteristics

| | Group | | |
|---|---|---|---|
| | Daily ($n = 138$) | Weekly ($n = 146$) | Control ($n = 128$) |
| Mean (SD) age (months) | 56 (11) | 58 (11) | 58 (10) |
| Mean (SD) weight (kg) | 18 (3) | 18 (3) | 18 (4) |
| Mean (SD) height (cm) | 107 (7) | 108 (8) | 108 (7) |
| Number (%) boys | 54 (39) | 92 (63) | 80 (62) |
| Number (%) with height-for-age *Z*-score $< -2$ | 2 (1.5) | 1 (0.7) | 1 (0.8) |
| Number (%) with weight-for-age *Z*-score $< -2$ | 3 (2.2) | 1 (0.7) | 1 (0.8) |
| Number (%) with weight-for-height *Z*-score $< -2$ | 3 (2.2) | 0 (0) | 0 (0) |

SD – standard deviation.

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daily group) and 45 $\mu g\,l^{-1}$ (range 7.7–156 $\mu g\,l^{-1}$; weekly group) (Table 2). The prevalence of ID was 1% and 4% for the daily and weekly groups, respectively (data not shown).

### *Primary outcomes: consumption rates and SF concentrations*

The total number of Sprinkles sachets provided per child was 65 (daily group) and 13 (weekly group); the average number of Sprinkles sachets consumed per child over the 13-week period was 56 (SD 8) for the daily group and 11 (SD 2) for the weekly group, corresponding to a mean consumption rate per child of 86% (daily group; SD 12%) and 87% (weekly group; SD 16%). For the daily group, all children consumed at least 22 sachets (one-third of maximum total); 96% consumed at least 32 sachets (one-half of maximum); 95% consumed at least 42 sachets (two-thirds of maximum); 40% consumed at least 58 sachets (nine-tenths of maximum) and no child consumed all sachets. For the weekly group, 98% of children consumed at least four sachets (one-third of maximum total); 94% consumed at least seven sachets (one-half of maximum); 91% consumed at least nine sachets (two-thirds of maximum); 66% consumed at least 11 sachets (nine-tenths of maximum) and 34% children consumed all sachets (Fig. 2).

Median SF concentrations (Table 2) at the end of study were 71 $\mu g\,l^{-1}$ (range 27–292 $\mu g\,l^{-1}$; daily group), 55 $\mu g\,l^{-1}$ (range 11–299 $\mu g\,l^{-1}$; weekly group) and 54 $\mu g\,l^{-1}$ (range 7–327 $\mu g\,l^{-1}$; control group). The overall difference in log-transformed SF concentrations between the three groups was not significant ($P = 0.06$), although the daily group had significantly higher concentrations than the control group ($P = 0.02$). Percentile–percentile (PP) plots showed that there were greater differences between the three groups below the 60th percentile; the daily group had higher SF concentrations than the weekly and control groups. However, above the 60th percentile the three groups appeared similar (Fig. 3). Examination by tertiles revealed that the daily and weekly groups had significant changes in SF concentrations for all tertiles except for the highest tertile of the weekly group; however, we found that there were no significant differences between the two groups ($P = 0.08$), changes in SF concentrations did not depend significantly upon tertile ($P = 0.82$), and the magnitude of change in SF concentrations for a group did not differ significantly across tertiles ($P = 0.45$) (Table 3).

### *Secondary outcomes*

At the end of the study, mean Hb concentrations were 128 (SD 10) $g\,l^{-1}$ (daily group), 127 (SD 10) $g\,l^{-1}$ (weekly group) and 128 (SD 9) $g\,l^{-1}$ (control group) (Table 2); the differences between groups were not significant. Prevalence of ID was 0.8% for the daily, 3% for the weekly and 3% for the control group.

On measures of anthropometric indices, we did not observe any significant differences among groups (data not shown). In the daily group, one child had height-for-age *Z*-score $< -2$ and one child had both weight-for-age and weight-for-height *Z*-scores $< -2$. No child had *Z*-scores $< -2$ in the weekly group and only one child in the control group had weight-for-height *Z*-score $< -2$.

There were no reported side-effects such as staining of teeth, metallic taste or stomach upset. Direct observations by research staff suggested that children did not comment on any change in the taste of the Sprinkles-served *congee* and accepted it well (Fig. 4).

## Discussion

Despite global declarations to control anaemia and ID, the estimated number of individuals with ID and IDA has

**Table 2** Effect of Sprinkles™ on iron indices

| | | Daily group | Weekly group | Control group | *P* overall |
|---|---|---|---|---|---|
| Haemoglobin ($g\,l^{-1}$) | *n* | 109 | 103 | 108 | |
| | Mean (SD) | | | | |
| | Baseline | 128 (13) | 131 (11) | – | – |
| | End of study | 128 (10) | 127 (10) | 128 (9) | 0.94* |
| | *P* for change | 0.73 | 0.002 | – | – |
| Ferritin ($\mu g\,l^{-1}$) | *n* | 115 | 107 | 111 | |
| | Median (range) | | | | |
| | Baseline | 46 (2.5–264) | 45 (7.7–156) | – | – |
| | End of study | 71[a] (27–292) | 55[ab] (11–299) | 54[b] (6.9–327) | 0.06† |
| | *P* for change | <0.0001 | <0.0001 | – | – |

SD – standard deviation.
* Random effects linear model with haemoglobin as dependent variable, group allocation and gender as independent variables and classrooms as random effects; model includes baseline haemoglobin as a covariate for comparing daily and weekly groups.
† Random effects linear model with log-transformed serum ferritin as dependent variable, group allocation and gender as independent variables and classrooms as random effects; model includes baseline serum ferritin as a covariate for comparing daily and weekly groups.
[a,b]Groups with different superscript letters are significantly different from each other; daily group is significantly different from the control group ($P = 0.02$).

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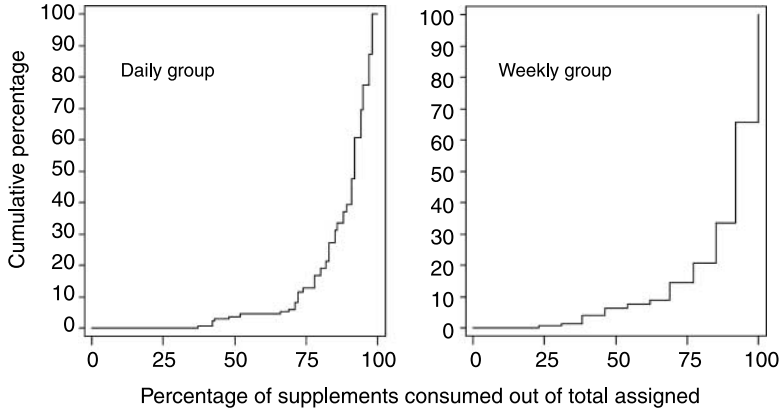


**Fig. 2** Cumulative histograms of compliance. Ninety per cent of the children in both groups consumed at least 75% of the total assigned sachets

increased by as much as 30% between 1990 and 2000[20]. The ineffectiveness of preventive intervention programmes using iron supplements (usually as ferrous sulfate) is often attributed to limited ability to reach the target population, and (when reached) to poor compliance with the intervention. School-based interventions using new and more acceptable forms of iron may improve the efficiency and effectiveness of prevention programmes provided that the intervention is safe for all recipients; i.e. supplementation does not increase risk of iron overload (and toxicity) in individuals who already have sufficient iron stores. This study was originally conceived and conducted to test the effectiveness of microencapsulated iron (Sprinkles). It had progressed beyond 6 weeks with no reported problems when results for Hb, SF and FEP from the baseline assessment unexpectedly indicated that the participating children already had sufficient iron stores. In such children absorbed iron from supplements would not cause further increments in Hb; however, this iron could accumulate in the body and result in excess iron stores. SF concentration $>300\,\mu g\,l^{-1}$ in the absence of infection or other inflammatory conditions is generally suggestive of increased iron stores, but not iron overload. Thus, we assessed whether consumption rates were high and whether any child was at risk of iron overload. We found that the mean consumption rate was 86% among supplemented children during the 13-week study period (one school term) and supplementation did not increase SF concentrations above $300\,\mu g\,l^{-1}$. The only SF value that was $>300\,\mu g\,l^{-1}$ in this study was in a child in the control group who had an SF concentration of $327\,\mu g\,l^{-1}$ (Table 2). Thus, a short-term intervention at school was not only an efficient means for daily provision of micronutrients (as microencapsulated iron Sprinkles), but importantly was also safe.

Our results are consistent with findings elsewhere of higher compliance in a school setting. The primary reason why the consumption rate in both groups was not 100% was related to a child's attendance at school. If a child was absent from school, no mechanism was in place to replace the Sprinkles sachet that was not consumed. Thus, the lack of perfect compliance was not related to a lack of motivation by the teachers. On the other hand, as per observations of the research staff, children demonstrated discipline and obedience to teachers' instructions and ate all their food.

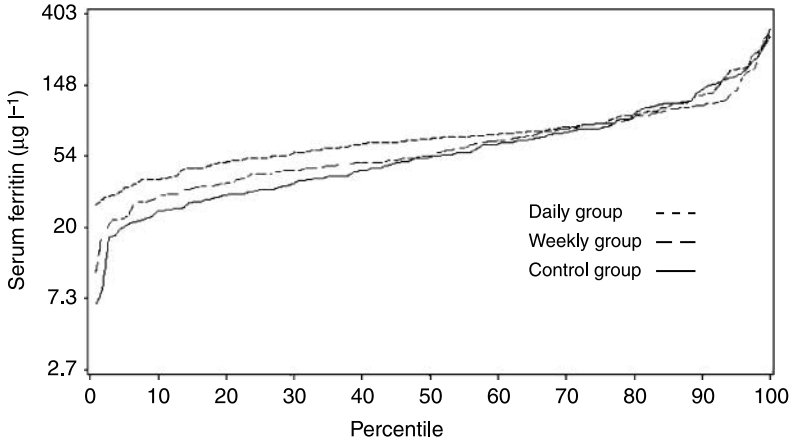


**Fig. 3** Percentiles of serum ferritin concentrations (plotted on a log scale). Children in the daily and weekly groups below the 60th percentile have higher ferritin concentrations than the control group; there is no difference between groups above the 60th percentile

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**Table 3** Serum ferritin concentrations ($\mu g\,l^{-1}$) for daily and weekly groups by tertile

| | Tertile* | | | | | | *P*-values† | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 (lowest) | | 2 | | 3 (highest) | | | | |
| | Daily group ($n = 41$) | Weekly group ($n = 30$) | Daily group ($n = 28$) | Weekly group ($n = 44$) | Daily group ($n = 46$) | Weekly group ($n = 33$) | *P* for group effect | *P* for tertile effect | *P* for interaction |
| Median (range) | | | | | | | | | |
| Baseline | 29 (2.5–37) | 26 (8–37) | 44 (38–53) | 45 (38–53) | 75 (53–264) | 81 (53–156) | | | |
| End of study | 61 (27–164) | 51 (11–115) | 65 (32–238) | 78 (22–299) | 80 (30–292) | 80 (18–182) | 0.08 | 0.82 | 0.45 |
| Mean (SE) | | | | | | | | | |
| Change | 38 (4.3) | 25 (4.5) | 32 (8.4) | 33 (9.1) | 16.5 (8.1) | −0.55 (7.6) | | | |
| *P* for change | <0.001 | <0.001 | 0.008 | 0.008 | 0.04 | 0.94 | | | |

SE – standard error.
* Tertiles of baseline serum ferritin concentrations: 1, $<37.5\,\mu g\,l^{-1}$; 2, 37.51–52.69 $\mu g\,l^{-1}$; 3, $>52.69\,\mu g\,l^{-1}$.
† Random effects linear model with end-of-study log-transformed serum ferritin as dependent variable, group allocation, baseline serum ferritin and gender as independent variables, tertile as a covariate, an interaction term between group allocation and tertile, and classrooms as random effects.

Monitoring of side-effects was quite simple in the school environment. According to the teachers who served the meals, as well as direct observations from the research staff on site, children accepted the *congee*-with-Sprinkles with no complaints and reported no side-effects. In fact, after a short acclimatisation period, children added the Sprinkles to their *congee* on their own (under supervision by the teachers) and enjoyed the process (Fig. 4). Therefore, a rice-based *congee* seems to be an appropriate vehicle to administer Sprinkles to Chinese schoolchildren.

It has been demonstrated in rats that net iron absorption with intermittent iron dosing was equivalent to daily dosing[21]. However, conflicting results observed in humans are partly attributable to differences in the ratio of iron demand and supply for different age groups and the level of control over study participants. Thus, our results are not comparable to those of Ekstrom and colleagues, who showed in Bangladeshi pregnant women that daily supplementation would be expected to have a greater short-term impact on Hb than weekly supplementation, but both might be equivalent over the longer term[22]. Similarly, our results for change in SF are not comparable to the pooled pre-school cohort of Beaton and McCabe[12], where baseline geometric mean ferritin was only 23 $\mu g\,l^{-1}$ compared with a geometric mean of 45 $\mu g\,l^{-1}$ in our study.

At the end of the study, the daily group had higher SF concentrations at lower percentiles compared with weekly and control groups, and similar concentrations at higher percentiles (Fig. 3). This observation supports the existence of a feedback mechanism by which the body down-regulates iron absorption when its stores are sufficient. These findings are consistent with those of Hallberg and colleagues, who suggested that normal subjects are not at risk of developing iron overload from iron-fortified diets[23]. However, the amount of iron used in this study was high in relation to the amount routinely used in fortified foods, the duration of intervention was very short and young children were studied. Thus our results are not generalisable to fortification programmes of staple foods which are meant to be used by all age groups of the population for an indefinite period of time. The significant increase in SF concentrations in children from the highest tertile of baseline SF in the daily group as opposed to no increase in the weekly group, and lack of effect of tertile on change or magnitude of change, suggests that chronic consumption at a daily dose of 30 mg of iron may eventually overwhelm the physiological feedback mechanism and iron may accumulate to reach toxic levels.

Although SF concentration is a measure of body iron stores and hence iron overload, its use as such is subject to limitations: SF concentrations rise in the presence of infection and inflammatory conditions[24–26]; and SF concentrations may vary physiologically as iron is mobilised to various body iron compartments[27]. Thus, a rise in SF concentration does not always indicate iron

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**Fig. 4** Two of the participating children eating *congee* at school

overload and serial measurements of SF concentrations may be required to rule out iron overload[25]. Furthermore, there is no established cut-off level of SF concentration to diagnose iron overload in children: Milman[28] defined moderate iron overload in healthy adults as SF concentrations in the range of 300–800 $\mu g\,l^{-1}$ and major iron overload as SF $>800\,\mu g\,l^{-1}$; Siimes and colleagues[29] observed that 95% of 486 normal children (aged 6 months to 15 years) had SF concentrations in the range of 7–142 $ng\,ml^{-1}$ ($1\,ng\,ml^{-1} = 1\,\mu g\,l^{-1}$) and seven children in the same age range with thalassaemia major (a disease characterised by iron overload subsequent to multiple blood transfusions) had SF concentrations in the range of 590–1830 $ng\,ml^{-1}$. Although we did not screen for the presence of infection or inflammation through simultaneous determination of C-reactive protein, as SF concentrations in this study were well below these reference ranges they indicate neither infection/inflammatory condition nor iron overload.

The participation refusal rate of 42% seemed high. We believe that parents declined participation primarily because of their reluctance to have blood collected from their children, although we did not specifically ask for reasons of refusal. The fact that no child dropped out of the study suggests that refusal was not related to the addition of Sprinkles to the food. However, this refusal caused an imbalance in the distribution of children by gender in the study groups – the daily group had more girls than the other two groups. We believe this inequality has no impact on our conclusions because gender is not a factor in iron metabolism and regulation in this age group, and we adjusted for gender differences in our statistical analyses. Similarly, we do not believe that the absence of biochemical indices in the control group at baseline would have any impact on our conclusions. Hb and SF concentrations at baseline were similar in the daily and weekly groups; we have no reason to believe that Hb and SF concentrations at baseline were significantly different in the control group.

There are a number of clear advantages to partnering with schools in a nutrition programme. For example, it facilitates the integration of nutritional education into the curriculum, leads to improved compliance with the intervention, promotes a sense of participation or ownership by the students in their own health, and is associated with a reduction in overhead costs for distribution. The only disadvantage is that success is related to school enrolment and attendance. This might be a major limitation in developing countries with a relatively limited number of schools that have meal-serving facilities and also limited day-care facilities for children $<2$ years of age who are at the highest risk of ID. Nevertheless, in certain countries like India, Sprinkles can be incorporated into existing programmes such as the 'Anganwadi' programmes to reach these children[30]. However, there are other likely shortfalls in teacher motivation and compliance when such an approach is made operational. In this trial as in most pilot studies, there was motivation and reinforcement. Here teacher compliance was closely monitored and was complete, and supplies were always on hand; these are unrealistic expectations for operational programmes. The trial should be seen as one establishing feasibility and short-term safety of Sprinkles in a school setting but not addressing effectiveness.

In conclusion, short-term daily school-administered Sprinkles sachets containing 30 mg of elemental iron is an efficient and safe strategy to deliver micronutrients (including iron) to young children. Independent of whether the intervention was administered daily or

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weekly, all children received the intervention with no evidence of iron overload.

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*Conflict of interest:* S.Z. owns the intellectual property rights to micronutrient Sprinkles™. There are no other competing interests.

*Author contributions:* S.Z. and S.Y. conceived the study. S.Z., C.S., S.Y. and W.S. participated in designing the study. M.W and Q.Y. participated in acquisition of data. W.S. analysed the data and wrote the first draft of the paper. G.T. participated in the data analysis. All researchers contributed to the preparation of and approved the paper.

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