

# Efficacy of an iron-fortified infant cereal to reduce the risk of iron deficiency anemia in young children in East Cameroon

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## Abstract

Complementary foods in Africa are often poor sources of bioavailable iron. We assessed the efficacy of iron-fortified wheat-based infant cereal (IC) to reduce the risk of iron deficiency anemia in children aged 18–59 months in Cameroon. A 6-month double-blind, cluster-randomized controlled trial was conducted in 2017 among anemic (hemoglobin 7–11 g/dl) but otherwise healthy children. In conjunction with usual diet, children received two 50 g servings/day of a standard, micronutrient-fortified IC (providing 3.75 mg iron/serving;  $n = 106$ ) or the same IC without iron fortification ( $n = 99$ ). Anthropometric measurements, blood sampling, and systematic deworming were performed in all children at baseline (pre-intervention), 3, and 6 months. Mean hemoglobin, ferritin adjusted for C-reactive protein (CRP), serum iron, transferrin saturation, prevalence of anemia, iron deficiency, and iron deficiency anemia as well as anthropometrics were compared between the groups at baseline, 3, and 6 months. Compared to the control group, children consuming the iron-fortified IC had significantly higher baseline-adjusted mean hemoglobin ( $10.0 \pm 1.8$  vs.  $9.7 \pm 1.4$  g/dl, respectively;  $p = .023$ ), ferritin adjusted for CRP ( $16.1 \pm 8.3$  vs.  $9.5 \pm 7.5$   $\mu\text{g/L}$ ,  $p < .001$ ), serum iron ( $14.5 \pm 3.9$  vs.  $11.2 \pm 4.4$   $\mu\text{g/dl}$ ;  $p < .001$ ), and transferrin saturation ( $19.0 \pm 17.4$  vs.  $10.7 \pm 12.5\%$ ;  $p < .001$ ) at 6 months. The prevalence of anemia, iron deficiency, and iron deficiency anemia at 6 months decreased by a larger extent in the iron-fortified group versus controls (all  $p < .01$ ). In addition, at 6 months, children in the iron-fortified group demonstrated higher weight-for-age z-scores ( $p = .016$ ) compared to the control group. Wheat-based IC fortified with 7.5 mg ferrous fumarate administered daily for 6 months improved iron and nutritional status and decreased the prevalence of iron deficiency anemia in children aged 18–59 months in Salapoumbé, Cameroon.

## KEYWORDS

Africa, anemia, cluster-randomized controlled trial, iron fortification, nutritional status, under-five children

Clinical trial registration: Pan African Clinical Trial Registry (PACTR; pactr.org); Registration number: PACTR201802003069111

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## 1 | INTRODUCTION

Anemia and iron deficiency in infants and children can negatively affect growth, cognitive development, academic performance, and immunity (Beard, 2008; Dallman, Siimes, & Stekel, 1980). Anemia affects nearly half of all children under 5 years of age, or about 273 million children, with the highest prevalence found in developing countries (McLean, Cogswell, Egli, Wojdyla, & de Benoist, 2009). In Cameroon, 60% of children under 5 years of age are anemic, mainly due to iron deficiency (Institut National de la Statistique (INS) and ICF International, 2012) although other factors such as malaria, helminth infections, and deficiencies of vitamin B12, vitamin A, or folate may also contribute (Engle-Stone, Aaron, et al., 2017; Loukas et al., 2016). It has been established that iron and other micronutrient deficiencies can be prevented by dietary diversification (i.e., encouraging the consumption of micronutrient-rich foods that may be available but underutilized by the population), supplementation, and fortification of widely consumed foods (Das, Salam, Kumar, & Bhutta, 2013; Eichler, Wieser, Ruthemann, & Brugger, 2012; World Health Organization & Food and Agricultural Organization of the United Nations, 1992). The World Health Organization (WHO) has reported that iron fortification of foods is the best preventive measure of iron deficiency from a cost-effectiveness point of view (Baltussen, Knai, & Sharan, 2004; Horton, 2006). Although several studies have confirmed the efficacy of iron-fortified foods on improving iron status (Bouhouch et al., 2016) and correcting iron deficiency anemia (Andang'o et al., 2007; Sun et al., 2007) in South America, Asia, and Africa, other studies reported mixed or negative results (Assuncao, Santos, Barros, Gigante, & Victora, 2007; Glinz et al., 2015, 2017; Nestel et al., 2004; Rohner et al., 2010). A systematic review of both efficacy and effectiveness trials concluded that consumption of iron-fortified foods results in improved iron status and reduced risk of anemia, yet significant heterogeneity was observed for most outcomes (Gera, Sachdev, & Boy, 2012). Another systematic review of flour fortification programs in 13 countries (none located in Africa) concluded that only limited evidence exists for the effectiveness of iron-fortified flour in reducing anemia prevalence (Pachon, Spohrer, Mei, & Serdula, 2015), perhaps due to variability in program implementation (e.g., compliance, coverage, feasibility in rural settings), iron compound, and iron levels. Together, these results suggest the need for further studies on the efficacy of iron fortification.

Per WHO recommendations, several countries have routinely adopted the strategy of using iron-fortified foods to combat iron deficiency (Nutrition International, 2018). In Africa, 26 of 53 countries including Cameroon have officially adopted iron fortification of cereal flours to reduce the burden of iron deficiency anemia in children (Food Fortification Initiative, 2018). In Cameroon, iron is added to wheat flour as ferrous fumarate (60 mg Fe/kg) (Food Fortification Initiative, 2018). The time and effort to prepare complementary foods from fortified flour rather than from the same foods eaten by older family members, however, may prevent the successful implementation of this policy in all households. For example, in rural

Cameroon, complementary foods are often traditional meals (e.g., maize paste and okra sauce) and made with family staples (potatoes, cassava, rice, beans, and peanuts), with infrequent usage of wheat flour (Mananga, Kana-Sop, Nolla, Tetanye, & Gouado, 2014). Furthermore, the finding that only ~75% of wheat flour samples in Cameroon were actually fortified, plus the lack of improvement in hemoglobin concentration or anemia prevalence in response to wheat flour fortification in Cameroonian children (who commonly receive antihelminthic medications [Institut National de la Statistique (INS) and ICF International, 2012]), suggests that other interventions are needed (Engle-Stone, Nankap, et al., 2017). Nutrient-rich foods that are consistently fortified, convenient to prepare, and readily accepted by young children, such as commercial infant cereal, are important options that can help improve iron consumption during this crucial period of child development. Therefore, we conducted a cluster-randomized controlled trial to evaluate iron fortification of commercial wheat-based infant cereal (IC) to reduce the risk of iron deficiency anemia in young Cameroonian children.

## 2 | METHODS

This double-blind, cluster-randomized, controlled trial was conducted from February to August 2017 in the locality of Salapoumbé (Cameroon). A random sample of 366 children from the entire locality was initially selected within 30 villages based on local vaccination registers. Further inclusion criteria for this study included age 18–59 months, hemoglobin level between 7 and 11 g/dl and apparent good health. Exclusion criteria were also applied, including iron supplementation in progress per caregiver report, clinical presentation of severe malnutrition (e.g., bilateral pitting edema), diagnosis of any chronic infection (e.g., tuberculosis, HIV), severe acute infection (e.g., severe malaria, pneumonia, meningitis), blood transfusion <3 months prior to enrollment, or allergy/intolerance to cows' milk and/or gluten. From the initial sample of 366 children, 205 were eligible after inclusion and exclusion criteria were applied. Children with weight-for-height z-scores <−3 were not excluded; however, only six of the 205 children had scores <−3 at baseline.

The minimum sample size was calculated for 90% statistical power and  $\alpha$ -level of 5%, with a predicted difference for mean hemoglobin of  $\geq 0.9$  g/dl and a standard deviation 1.48 g/dl (Eichler et al., 2012) in the iron-fortified group between baseline and study completion at 6 months. The minimum sample size was 71 children per group (142 subjects total). To account for dropouts, the entire eligible population of 205 children was enrolled.

The Salapoumbé locality is in the East region of Cameroon that is quite rural and known to be malaria endemic. Salapoumbé is divided by the Lokomo River, which is large and difficult to cross, thus separating the locality into two settlements. The two settlements are generally ethnically comparable in eating habits and customs as well as at the socioeconomic level, notably in terms of literacy and agriculture. Thus, the south and north banks were considered two clusters and the IC (fortified or control) was randomized by cluster.

This design was implemented to minimize treatment crossover due to potential sharing of IC between families located on the same bank of the river.

The batches of IC were manufactured by Nestlé Central and West Africa Ltd. PMB KIA Accra-Ghana according to international cereal fortification standards (Hurrell et al., 2010). Bags of IC were packaged in waterproof plastic and were identical in appearance except for a code (A or B) designating whether the batch was iron-enriched. The code assignment was unknown to researchers and subjects throughout the study period. The random allocation of IC A or B to the south or north bank was performed by the principal investigator by a flip of a coin. All subjects on each bank received the same IC, either A or B. The study team obtained the support of administrative officials and traditional chiefs of the respective villages to ensure monitoring of the correct distribution of the IC lots. Community health workers also verified through periodic home visits that children enrolled in the study were receiving the IC packets corresponding to the randomized area. The manufacturer sent the batch code assignment to the principal investigator after the statistical analysis was complete.

Parents of enrolled children completed a sociodemographic characteristics questionnaire based on a protocol previously validated by the Comité National d'Ethique et de la Recherche pour la Santé Humaine du Cameroun (CNERSH). Data obtained included the vaccination history of the child, the occurrence of illness during the previous 2 weeks, and the child's date of birth. Child anthropometric assessments included weight measurement using an electronic portable scale (SECA LK 5051) with a sensitivity of 0.5 g. The scale was calibrated after every 10 measurements. Length or height was measured using a SECA portable infantometer or stadiometer with an accuracy of 0.1 cm. Immediately after the anthropometric measurements were taken by trained personnel, each child's hemoglobin level was measured with a portable hemoglobinometer (HemoCue 201+). A 3 ml sample of venous blood was collected and centrifuged, and the serum was immediately frozen for analysis by a Biotek EL800X machine to measure levels of ferritin, serum iron, transferrin, and C-reactive protein (CRP). All assays were performed according to manufacturer's instructions. Appropriate procedures (e.g., portable freezers or generators) were used in the field to maintain blood sample quality. Analyses were conducted at the laboratory of the Food and Nutrition Research Center of the Institute of Medical Research and Medicinal Plants Studies of Yaoundé, Cameroon. Serum samples were stored frozen in Salapoumbé (which is partly equipped with generators for rural electrification) and transported frozen to Yaoundé in batches for analysis due to the distance between the sites (>700 km). Anthropometric measurements and biological tests were repeated at 3 and 6 months. In addition, the children had systematic deworming with a mebendazole 500 mg tablet every 3 months.

In addition to their habitual diet, all enrolled children were fed two 50 g servings/day (morning and evening) of the assigned IC by their mothers, who had been previously educated on hygienic measures of IC preparation and administration. The fortified IC was

prepared with previously boiled warm water. The daily ration of 100 g of IC provided 7.5 mg of iron as ferrous fumarate to children in the iron-fortified group; otherwise, the two cereals were identical in terms of appearance, taste, and dietary composition (Table 1). The parents and guardians of the children were provided with IC bags every 15 days on a precise and known date. To guarantee the consumption of the planned quantities of IC for each selected child, each household in the study received additional bags of the same IC intended for all of the enrolled child's siblings. At each date of IC supply, parents were questioned for possible adverse events related to the IC administration.

## 2.1 | Ethics

The study protocol was approved by CNERSH and administrative authorization was received from the Cameroon Ministry of Public Health. The study protocol followed local laws and the Declaration of Helsinki. Prior to data collection, parents of enrolled children signed written informed consent after a detailed explanation of the objectives, nature, and risks of the study. All enrolled children who presented with any comorbid condition during the study received free treatment from study medical staff (nurses or physicians). All children who were not enrolled due to severe anemia or severe malnutrition were referred to the local hospital for routine care (e.g., iron supplementation, blood transfusion, inpatient treatment). At the end of the study after code break, all children in the control group received additional ferrous sulfate for 3 months in accordance with standard guidelines (World Health Organization, 2016); anemic children from either group were referred for treatment.

## 2.2 | Statistical analysis

The primary endpoints of the study were hemoglobin, serum ferritin adjusted to CRP, serum iron, transferrin saturation and prevalence of anemia, iron deficiency, and iron deficiency anemia. Anemia was defined as hemoglobin of <11 g/dl, consistent with the WHO definition of anemia in children under 5 years of age (World Health Organization & Centers for Disease Control and Prevention, 2007). Iron deficiency was defined as serum (unadjusted) ferritin <12 µg/L for a healthy child or <30 µg/L for a child with an infection or inflammation (World Health Organization, 2001; World Health Organization & Centers for Disease Control and Prevention, 2007). Inflammation was defined as CRP >5 mg/L (Engle-Stone, Nankap, Ndjebayi, Erhardt, & Brown, 2013; World Health Organization & Food and Agricultural Organization of the United Nations, 1992). Iron deficiency anemia was defined as a hemoglobin level of <11 g/dl associated with a serum (unadjusted) ferritin level of <12 µg/L in a healthy subject or <30 µg/L in a person with an infection or inflammation (World Health Organization & Centers for Disease Control and Prevention, 2007). Among children with inflammation, the serum

**TABLE 1** Nutrient content per 100 g of wheat-based infant cereal (IC) and corresponding recommended micronutrient intakes

|                                  | Iron-fortified IC | Control IC | RNI (1–3 years) <sup>a</sup> | RNI (4–6 years) <sup>a</sup> |
|----------------------------------|-------------------|------------|------------------------------|------------------------------|
| Energy                           | 420 kcal          | 420 kcal   |                              |                              |
| Fat                              | 10 g              | 10 g       |                              |                              |
| Protein                          | 14.5 g            | 14.5 g     |                              |                              |
| Carbohydrate                     | 68 g              | 68 g       |                              |                              |
| Dietary fiber                    | 2.8 g             | 2.8 g      | ND                           | ND                           |
| Sodium                           | 135 mg            | 135 mg     | <2 g/day                     | <2 g/day                     |
| Calcium                          | 450 mg            | 450 mg     | 500 mg/day                   | 600 mg/day                   |
| Iron                             | 7.5 mg            | 0          | 5.8 mg/day <sup>b</sup>      | 6.3 mg/day <sup>b</sup>      |
| Zinc                             | 5 mg              | 5 mg       | 4.1 mg/day <sup>b</sup>      | 4.8 mg/day <sup>b</sup>      |
| Vitamin A                        | 1,300 IU          | 1,300 IU   | 1,333 IU/day                 | 1,500 IU/day                 |
| Vitamin D                        | 180 IU            | 180 IU     | 200 IU/day                   | 200 IU/day                   |
| Vitamin C                        | 50 mg             | 50 mg      | 30 mg/day                    | 30 mg/day                    |
| Vitamin B <sub>1</sub> (thiamin) | 0.6 mg            | 0.6 mg     | 0.5 mg/day                   | 0.6 mg/day                   |

Note: Recommended intakes of energy, fat, protein, and carbohydrate are not presented because they vary by age, sex, and/or activity level.

Abbreviation: ND, not determined.

<sup>a</sup>Recommended micronutrient intakes (RNI) established by the Food and Agricultural Organization of the United Nations/World Health Organization/United Nations University (Food and Agricultural Organization of the United Nations & World Health Organization, 2001).

<sup>b</sup>Value assumes moderate bioavailability.

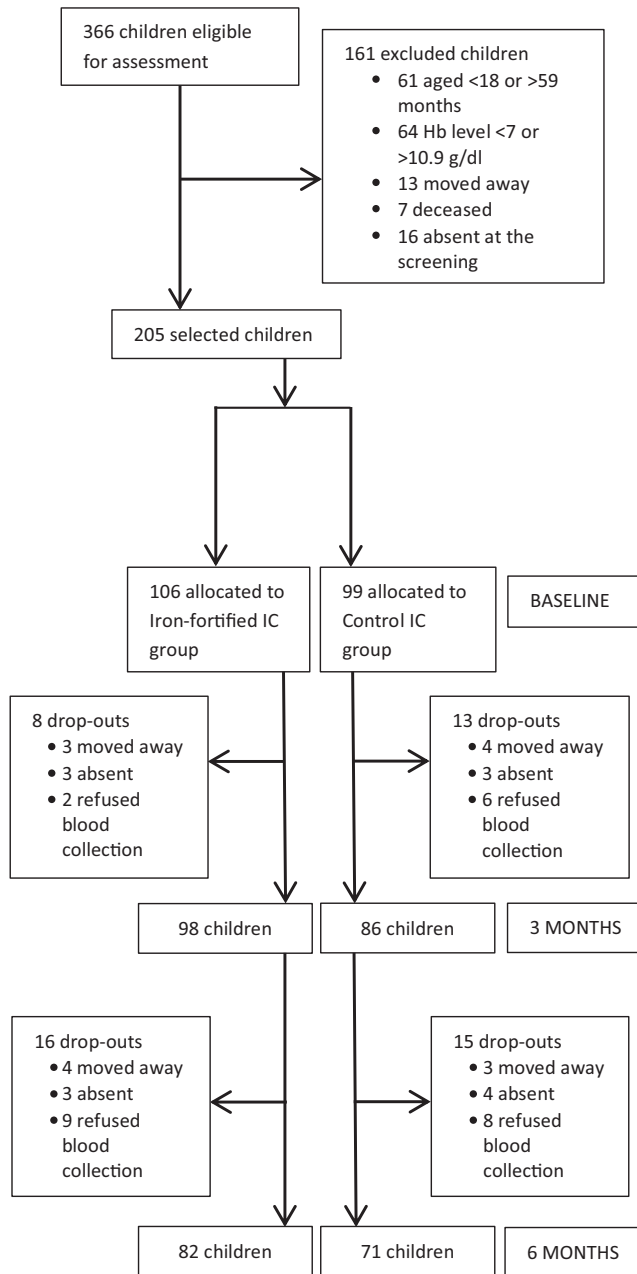
ferritin level was adjusted to CRP using the BRINDA correction as follows:  $\text{ferritin}_{\text{adjusted}} = \text{ferritin}_{\text{unadjusted}} - (\text{CRP regression coefficient}) \times (\text{CRP}_{\text{obs}} - \text{CRP}_{\text{ref}})$  (Namaste, Aaron, Varadhan, Peerson, & Suchdev, 2017). The concentration of  $\text{CRP}_{\text{ref}}$  used in this study was 3.75 mg/L (Engle-Stone et al., 2013). Transferrin saturation was calculated using the total iron-binding capacity (TIBC;  $\text{transferrin} \times 25.1$ ) by the following formula:  $\text{serum iron} \times 100/\text{TIBC}$ , where TIBC is in units of  $\mu\text{mol/L}$ , transferrin in g/L, serum iron in  $\mu\text{mol/L}$ , and transferrin saturation in percent (Beilby et al., 1992; Yamanishi, Iyama, Yamaguchi, Kanakura, & Iwatani, 2003). The secondary endpoints were changes in weight, height, and other anthropometric z-scores.

Analyses were conducted using Epi Info software (version 3.5.4, CDC), WHO Anthro (version 3.2.2, WHO), and SPSS (version 20, SPSS Inc., IBM). The WHO Anthro software was used to calculate weight-for-height, height-for-age, and weight-for-age z-scores in comparison with the WHO standard reference population (World Health Organization, 2006). Descriptive variables for the two groups receiving IC are presented by group and compared using standard *t* tests for continuous measures and chi-square tests for categorical measures. Biomarkers of iron status are presented as unadjusted means and standard deviation. Because these data were non-normally distributed, comparisons between the groups for these measures were done using a nonparametric rank-based ANOVA model at baseline and using a nonparametric rank-based ANCOVA model at 3 and 6 months, including adjustment for the baseline value. Height and weight as well as the z-scores for the anthropometrics

were compared between groups at each time point using a standard parametric ANOVA model (baseline) or ANCOVA model (at 3 and 6 months, again with adjustment for baseline values). Differences between the groups for the prevalence of anemia, iron deficiency, and iron deficiency anemia at baseline, 3, and 6 months were assessed using Fisher's exact test. The threshold of significance was 0.05 for all comparisons.

### 3 | RESULTS

Of the 366 children aged 18–59 months identified in the locality of Salapoumbé, 205 children were included the following: 106 children on the south bank who were cluster-randomized to receive the iron-fortified IC and 99 children on the north bank who received the control IC. Of the 205 children who participated in the study, 153 children were evaluated at the end of the intervention with a similar dropout rate across the two groups (23% in the iron-fortified group and 28% in the control group) (Figure 1). The ICs were well tolerated and no side effects were reported in either group. Table 2 presents the demographic characteristics of the enrolled children. Mean age at enrollment was 32.1 months in the iron-fortified group and 36.1 months in the control group (*p*-value from *t* test = .009) but no other significant differences were seen between the groups for parental profession or education or family size (Table 2). Overall about 41% of the children had infection or inflammation ( $\text{CRP} > 5 \text{ mg/L}$ ) at baseline.



**FIGURE 1** Flow of subject inclusion into trial

The iron, anemia and nutritional status of the enrolled children at baseline, 3 months, and 6 months are presented in Table 3. At baseline, children in the iron-fortified group had significantly lower hemoglobin levels ( $p$ -value from nonparametric ANOVA = .044) and a significantly lower average serum iron level than the control group ( $p = .012$ ). However, the two groups had comparable baseline levels of mean serum ferritin, CRP, and transferrin, mean transferrin saturation, and frequencies of anemia, iron deficiency, and iron deficiency anemia. Mean hemoglobin concentration significantly increased over time in the iron-fortified group ( $p < .001$ ) whereas change over time in the control group was not significant. Compared to the control group, children consuming the iron-fortified IC had significantly higher adjusted mean hemoglobin level ( $10.0 \pm 1.8$  vs.  $9.7 \pm 1.4$  g/dl,

**TABLE 2** Baseline characteristics of the two groups receiving infant cereal (iron-fortified and control)

|                                  | Iron-fortified IC group (N = 106) | Control IC group (N = 99) | <i>p</i> -value for difference |
|----------------------------------|-----------------------------------|---------------------------|--------------------------------|
| Age (months)                     | 32.1 ± 10.9                       | 36.1 ± 10.8               | .01                            |
| Sex                              |                                   |                           |                                |
| Boys, n (%)                      | 59 (55.7)                         | 49 (49.5)                 | .38                            |
| Girls, n (%)                     | 47 (44.3)                         | 50 (50.5)                 |                                |
| CRP > 5 mg/L, n (%)              | 40 (37.7)                         | 43 (43.4)                 | .41                            |
| Mother's profession              |                                   |                           |                                |
| Civil servant                    | 4 (3.7)                           | 3 (3.0)                   | .92                            |
| Farmer                           | 78 (73.6)                         | 76 (76.2)                 |                                |
| Trader                           | 2 (1.9)                           | 1 (1)                     |                                |
| Homemaker                        | 22 (20.8)                         | 19 (19.8)                 |                                |
| Father's profession              |                                   |                           |                                |
| Civil servant                    | 2 (1.88)                          | 2 (2.0)                   | .91                            |
| Farmer                           | 99 (93.4)                         | 94 (95.0)                 |                                |
| Trader                           | 4 (3.8)                           | 2 (2)                     |                                |
| Fisherman                        | 1 (1)                             | 1 (1)                     |                                |
| Mother's education               |                                   |                           |                                |
| None                             | 70 (66.0)                         | 67 (67.7)                 | .92                            |
| Primary                          | 33 (31.0)                         | 30 (30.3)                 |                                |
| Secondary                        | 3 (3.0)                           | 2 (2.0)                   |                                |
| Father's education               |                                   |                           |                                |
| None                             | 65 (61.3)                         | 60 (60.5)                 | .92                            |
| Primary                          | 26 (24.5)                         | 23 (23.3)                 |                                |
| Secondary                        | 15 (14.2)                         | 16 (16.2)                 |                                |
| Children aged <5 years/household |                                   |                           |                                |
| 1                                | 35 (33.0)                         | 30 (30.0)                 | .34                            |
| 2 or 3                           | 70 (66.0)                         | 65 (65.0)                 |                                |
| >3                               | 1 (1.0)                           | 4 (5.0)                   |                                |

Note: Values are mean ± standard deviation or count (percentages).  $p$ -value for difference computed using standard  $t$  test for continuous measures and chi-square test for categorical measures.

Abbreviation: CRP, C-reactive protein.

respectively;  $p$ -value from nonparametric ANCOVA = .023), ferritin adjusted for CRP ( $16.1 \pm 8.3$  vs.  $9.5 \pm 7.5$   $\mu$ g/L,  $p < .001$ ), serum iron ( $14.5 \pm 3.9$  vs.  $11.2 \pm 4.4$   $\mu$ g/dl;  $p < .001$ ), and transferrin saturation ( $19.0 \pm 17.4$  vs.  $10.7 \pm 12.5\%$ ;  $p < .001$ ) at 6 months. Significant group differences for each of these biochemical measures (except ferritin adjusted for CRP) were also observed at 3 months. The prevalence of children with elevated CRP (>5 mg/L) decreased from 43% to 37% in the control group and from 38% to 15% in the iron-fortified group.

Figure 2 demonstrates that the proportion of children with anemia, iron deficiency, and iron deficiency anemia significantly decreased from baseline to the end of the intervention in the iron-fortified group compared to the control group. During this period, the prevalence of anemia decreased by 34% in the iron-fortified group and by only 15% in the control group ( $p$ -value from

TABLE 3 Iron and nutritional status at baseline, 3, and 6 months, by group

|   | Baseline      | <i>p</i> -value for group difference (ANOVA) | 3 months      | <i>p</i> -value for group difference (ANCOVA) | 6 months      | <i>p</i> -value for group difference (ANCOVA) | <i>p</i> -value for difference over time (paired <i>t</i> test) |
|---|---------------|--|---------------|---|---------------|---|---|
| Hemoglobin (g/L)                                |               |  |               |   |               |   |   |
| Fortified IC                                    | 9.11 ± 1.20   | .044   | 9.60 ± 1.52   | .008  | 10.00 ± 1.80  | .023  | <.001   |
| Control IC                                      | 9.43 ± 1.01   |  | 9.05 ± 1.40   |   | 9.66 ± 1.40   |   | .318  |
| Ferritin (µg/L)                                 |               |  |               |   |               |   |   |
| Fortified IC                                    | 16.57 ± 11.38 | .866   | 22.14 ± 13.32 | .591  | 19.28 ± 6.76  | .007  | .1  |
| Control IC                                      | 15.61 ± 10.61 |  | 21.91 ± 14.42 |   | 16.28 ± 6.21  |   | .478  |
| Ferritin adjusted for C-reactive protein (µg/L) |               |  |               |   |               |   |   |
| Fortified IC                                    | 10.17 ± 6.32  | .913   | 15.58 ± 10.35 | .817  | 16.10 ± 8.29  | <.001   | <.001   |
| Control IC                                      | 10.47 ± 6.81  |  | 16.44 ± 13.21 |   | 9.46 ± 7.51   |   | .614  |
| C-reactive protein (mg/L)                       |               |  |               |   |               |   |   |
| Fortified IC                                    | 6.16 ± 4.88   | .775   | 3.90 ± 3.10   | .720  | 4.27 ± 3.71   | .009  | .005  |
| Control IC                                      | 6.03 ± 4.44   |  | 3.73 ± 2.81   |   | 4.74 ± 2.42   |   | .02   |
| Serum iron (µg/dl)                              |               |  |               |   |               |   |   |
| Fortified IC                                    | 10.40 ± 4.25  | .012   | 13.43 ± 3.37  | <.001   | 14.50 ± 3.90  | <.001   | <.001   |
| Control IC                                      | 11.17 ± 2.75  |  | 12.36 ± 6.17  |   | 11.21 ± 4.42  |   | .982  |
| Transferrin (mg/dl)                             |               |  |               |   |               |   |   |
| Fortified IC                                    | 8.50 ± 7.46   | .851   | 4.95 ± 4.30   | <.001   | 4.72 ± 3.45   | <.001   | <.001   |
| Control IC                                      | 7.30 ± 3.93   |  | 7.05 ± 4.87   |   | 8.27 ± 5.25   |   | .217  |
| Transferrin saturation (%)                      |               |  |               |   |               |   |   |
| Fortified IC                                    | 9.32 ± 9.33   | .317   | 16.10 ± 10.50 | <.001   | 19.00 ± 17.44 | <.001   | <.001   |
| Control IC                                      | 9.10 ± 8.54   |  | 11.80 ± 10.64 |   | 10.70 ± 12.50 |   | .667  |
| Weight (kg)                                     |               |  |               |   |               |   |   |
| Fortified IC                                    | 11.84 ± 2.10  | .20  | 12.76 ± 2.10  | .38   | 13.41 ± 2.06  | .052  | <.001   |
| Control IC                                      | 12.26 ± 2.35  |  | 13.05 ± 2.40  |   | 13.36 ± 2.25  |   | <.001   |
| Height (cm)                                     |               |  |               |   |               |   |   |
| Fortified IC                                    | 86.22 ± 7.63  | .62  | 88.10 ± 7.43  | .35   | 90.00 ± 7.16  | .96   | <.001   |
| Control IC                                      | 85.65 ± 7.80  |  | 88.01 ± 7.72  |   | 88.49 ± 7.20  |   | <.001   |
| Weight-for-age z-score                          |               |  |               |   |               |   |   |
| Fortified IC                                    | -1.04 ± 1.33  | .69  | -0.70 ± 1.29  | .18   | -0.59 ± 1.17  | .016  | ND  |
| Control IC                                      | -1.11 ± 1.17  |  | -1.01 ± 1.09  |   | -1.03 ± 0.94  |   | ND  |

Height-for-age z-score

(Continues)



TABLE 3 (Continued)

|                           | Baseline     | p-value for group difference (ANOVA) | 3 months     | p-value for group difference (ANCOVA) | 6 months     | p-value for group difference (ANCOVA) | p-value for difference over time (paired t test) |
|---------------------------|--------------|--------------------------------------|--------------|---------------------------------------|--------------|---------------------------------------|--|
| Fortified IC              | -1.72 ± 1.95 | .003                                 | -1.67 ± 1.74 | .90                                   | -1.62 ± 1.68 | .42                                   | ND   |
| Control IC                | -2.45 ± 1.53 |                                      | -2.38 ± 1.51 |                                       | -2.60 ± 1.31 |                                       | ND   |
| Weight-for-height z-score |              |                                      |              |                                       |              |                                       |  |
| Fortified IC              | -0.10 ± 1.17 | .001                                 | 0.37 ± 1.19  | .69                                   | 0.51 ± 0.85  | .71                                   | ND   |
| Control IC                | 0.43 ± 1.10  |                                      | 0.56 ± 0.93  |                                       | 0.73 ± 0.77  |                                       | ND   |

Note: Values are unadjusted mean ± standard deviation. *p*-values for difference between fortified IC and control IC groups were calculated using nonparametric ANOVA or ANCOVA model for biochemical measures and standard ANOVA or ANCOVA for anthropometric measures. ANCOVA models include the baseline value as a covariate. *p*-values for difference between baseline and 6-months value were calculated using a paired *t* test.

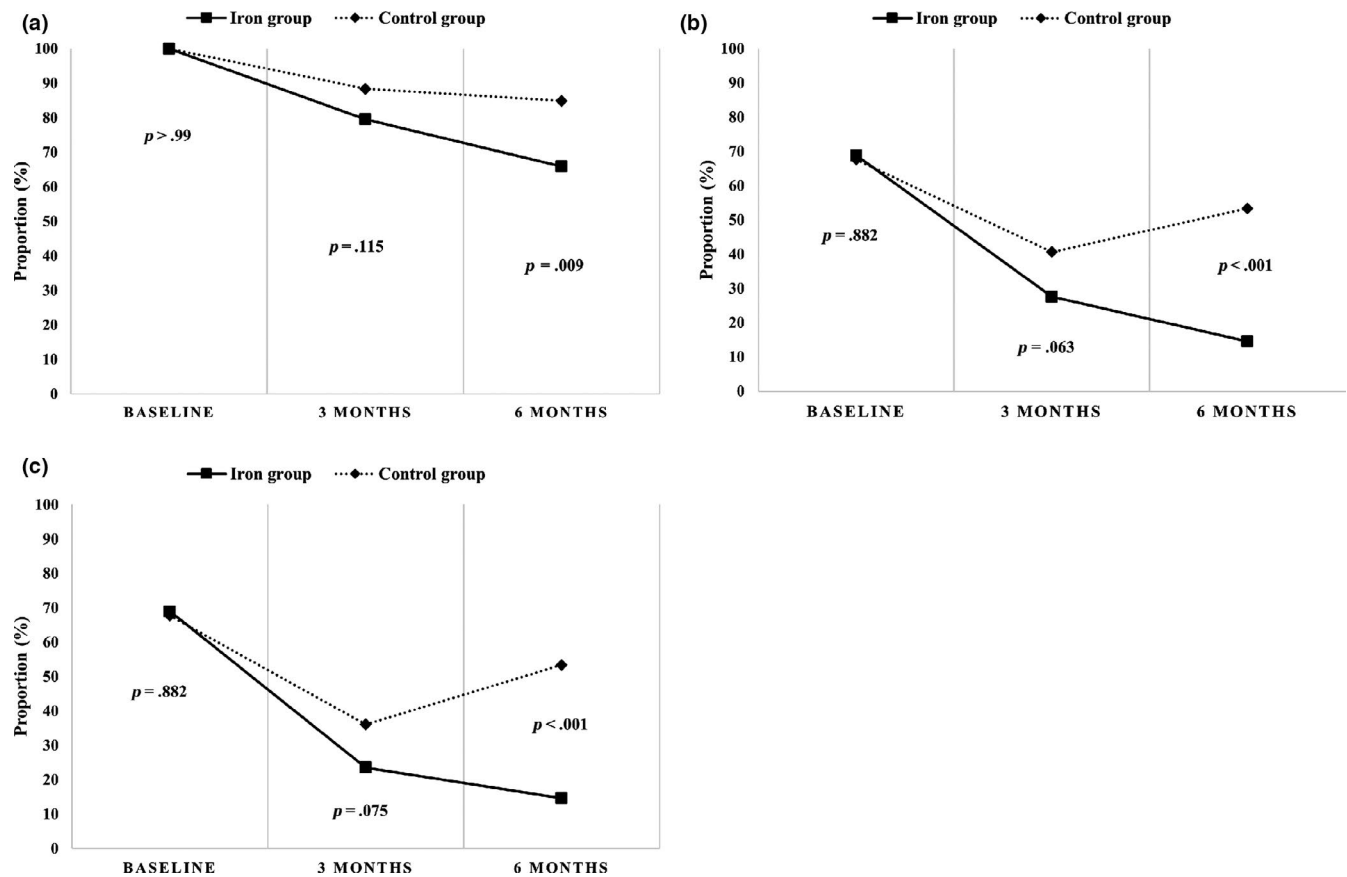
Abbreviation: ND, not determined.

Fisher's exact test = .009) (panel A). Iron deficiency decreased by 79% in the iron-fortified group and 21% in the control group ( $p < .001$ ) (panel B). The prevalence of iron deficiency anemia at baseline, 3, and 6 months was 68.9%, 23.5%, and 14.6%, respectively, in the iron-fortified group and 67.7%, 36.1%, and 53.4% in the control group ( $p < .001$ ) (panel C).

At baseline, both groups were comparable in weight, height, and weight-for-age z-scores, while the iron-fortified group had higher height-for-age and lower weight-for-height z-scores than the control group (Table 3). The study population as a whole was mildly to moderately undernourished at baseline, with approximately 56% of children stunted (height-for-age z-score  $< -2$ ) and 25% underweight (weight-for-age z-score  $< -2$ ); only 3% of the children were wasted (weight-for-height z-score  $< -2$ ). At the end of the intervention, the iron-fortified group had a very small (~50 g) but borderline significant higher weight gain (*p*-value from ANCOVA = .052) and a significantly higher weight-for-age z-score ( $p = .016$ ) compared to the control group (Table 3). Height, height-for-age, and weight-for-height z-scores were similar in both groups at the end of the intervention. The overall proportion of stunted and underweight children decreased to 52% and 11%, respectively, at the end of the intervention, with no children considered to be wasted; however, anthropometry measures were missing for 27% of the population.

## 4 | DISCUSSION

This study found that in addition to their usual diet, daily consumption of wheat-based IC fortified with 7.5 mg iron as ferrous fumarate among children under 5 years of age improved hemoglobin levels and indicators of iron status and decreased the prevalence of anemia, iron deficiency, and iron deficiency anemia as compared to the control group consuming the same IC without iron. Hemoglobin levels of children in the iron-fortified group significantly increased by  $0.89 \pm 1.87$  g/dl compared to an increase of  $0.23 \pm 1.74$  g/dl in the control group (note that children in the iron-fortified group had lower hemoglobin levels than the control group at baseline). These results are comparable to the increase in hemoglobin and reduction in iron deficiency anemia observed in a Kenyan study of children aged 3–8 years who received high-dose (56 mg/kg) of NaFeEDTA-enriched maize flour five times per week (Andang'o et al., 2007) and in an Indian study of children aged 6–15 years who received a daily portion of wheat flour fortified with 6 mg of the same iron compound (Muthayya et al., 2012). In addition, a recent study in children aged 6–12 months in India using a similar but rice-based IC (providing 3.75 mg iron/day as ferrous fumarate) fed for 6 months showed better iron status and reduced risk for anemia and iron deficiency in association with more favorable neurodevelopmental scores (Awasthi et al., 2020). However, our results showed greater efficacy than those reported in another study in India in which children aged 6–13 years received a daily portion of rice fortified with 20 mg iron as



**FIGURE 2** Prevalence of anemia (panel a), iron deficiency (panel b), and iron deficiency anemia (panel c) in both groups at baseline, 3, and 6 months. Comparisons between groups by Fisher's exact test

micronized ground ferric pyrophosphate (Moretti et al., 2006) and a study in children aged 6–14 years in Côte d'Ivoire who received biscuits fortified with 20 mg electrolytic iron four times per week (Rohner et al., 2010). This difference could be explained by the fact that the fortified IC in the present study also provided vitamin C, known to promote gut iron absorption (de Almeida et al., 2003), and vitamin A, the deficiency of which decreases the absorption of iron (Hurrell & Egli, 2010). Differences in results may also be due in part to the varied iron fortificant compounds used in the studies, which have different bioavailabilities (Hurrell & Egli, 2007), as well as variability in the population characteristics including age, baseline iron status, and inflammation.

In addition, in the present study, significant increases in mean serum iron, CRP-adjusted ferritin, and transferrin saturation were observed in the iron-fortified group, and at the end of the intervention, there were significant decreases in the prevalence of anemia, iron deficiency, and iron deficiency anemia in the iron-fortified group. These results are comparable to those described in the study done in India with NaFeEDTA-enriched wheat flour (Muthayya et al., 2012). In contrast, the results differ from those in long-term studies conducted in preschoolers (age 9–71 months) and older children (age 6–11 years) in Sri Lanka (Nestel et al., 2004) and in children under age 6 years in Brazil (Assuncao et al., 2007) that demonstrated no effect of iron-fortified wheat flour on

hemoglobin or anemia. While low hemoglobin status may be due to other factors besides low iron intake and thus an inadequate biomarker to test the efficacy of iron fortification, this difference could also be explained by the fact that the population of the present study consisted exclusively of anemic children, whereas the proportion of anemic children was 8% and 30%, respectively, in the other two clinical trials. Furthermore, the results may differ because the fortificant used in the previously mentioned trials was electrolytic iron, known to have a lower bioavailability than ferrous fumarate, which was used in the present study (Hurrell et al., 2010; Walter, Pizarro, Boy, & Abrams, 2004). The nonsignificant improvement in hemoglobin levels and indicators of iron status (ferritin, serum iron, and transferrin) and the equally nonsignificant decrease in the prevalence of anemia, iron deficiency, and iron deficiency anemia in the control group is unlikely to be due to the cluster randomization, and such a finding has been described in other studies in India (Muthayya et al., 2012) and Côte d'Ivoire (Rohner et al., 2010). These changes in the control group may be related to the vitamin C and vitamin A content of the control IC or to systematic deworming, known for its beneficial effect on reducing digestive parasites and improving absorption of iron from the usual diet (Dreyfuss et al., 2000; Stoltzfus, Dreyfuss, Chwaya, & Albonico, 1997). The increase of iron deficiency and iron deficiency anemia prevalence between midpoint and endpoint in the



control group could be explained by the lack of iron supplementation in children recovering from mild malnutrition during the first 3 months of intervention (Macdougall, Moodley, Eyberg, & Quirk, 1982; Velasquez Rodriguez et al., 2007).

There was also indication that nutritional status improved after 6 months of intervention with a small but borderline significant higher weight gain ( $p = .052$ ) and a significantly higher increase in weight-for-age z-score ( $p = .016$ ) in the iron-fortified group compared to the control group. Mean weight-for-age z-score at 6 months remained below but moved closer to the WHO median in the fortified group compared to controls. These findings are confirmatory for the beneficial effect of iron fortification of wheat-based IC on the nutritional status of children, as demonstrated in other studies (Aukett, Parks, Scott, & Wharton, 1986; Barth-Jaeggi et al., 2015; Briend, Hoque, & Aziz, 1990). This beneficial effect may be due to iron stimulation of appetite in children (Lawless, Latham, Stephenson, Kinoti, & Pertet, 1994; Sachdev, Gera, & Nestel, 2005; Stoltzfus et al., 2004). In addition, the proportion of underweight children in the overall study population decreased from 25% to 11%, likely due to the energy content of the ICs. The high proportion of stunting observed in our population has been observed previously (Pondy, 2016) and is likely due to both poor growth resulting from low dietary diversity and the infrequent inclusion of meats and eggs as complementary foods, as well as overestimation based on the use of WHO growth charts, which are likely nonrepresentative standards for ethnic groups who reside in this area of Cameroon and who generally have a shorter stature (Funk et al., 2019). Growth charts specific for this population are not yet available.

Although the amount of iron provided by the fortified cereal was relatively small, our group has previously reported a pattern of complementary feeding in Cameroon that consists mostly of traditional and indigenous foods such as corn gruel, potato puree, banana, and other starch-based foods that lack diversity and do not meet the dietary iron needs of growing children (Kana-Sop et al., 2013). While fish is also commonly consumed, the amount eaten by children is generally insufficient to cover their iron needs (Kana-Sop et al., 2013). The median intake of fortified wheat flour by children aged 12–59 months in Cameroon has been reported to be 31 g/day, representing an intake of 1.86 mg/day of iron from this food source (Engle-Stone, Nankap, et al., 2017). Therefore, the iron provided by the fortified IC (7.5 mg/day) likely represented a sizable proportion of total daily intake.

An important limitation of this study is that only two clusters were randomized, and thus, the differences observed at the end of the study between the clusters located north and south of the river could theoretically be due to differences in living conditions in the two areas; however, as the two areas are largely comparable in terms of customs, diet, level of literacy, and agro-pastoral activities, this seems to be an unlikely explanation of the results observed. Moreover, the lack of assessment of malaria in both groups during the intervention did not permit us to conclude on the safety of iron fortification in this endemic malaria area as shown in other studies (Prentice, Verhoef, & Cerami, 2013; Zlotkin et al., 2013). However, the iron concentration of the IC (3.75 mg/serving) is much

lower than that of micronutrient powders (12.5 mg/serving) previously associated with increased risk of hospitalization and mortality in malaria-endemic areas (Sazawal et al., 2006). This lower iron dose within a food matrix is unlikely to promote the appearance of plasma nontransferrin bound iron that can enhance bacterial virulence (Brittenham, 2012). The lack of information on compliance or the amount of cereal consumed is an additional study limitation. Finally, no formal adjustment for multiplicity was performed to account for multiple primary endpoints (seven parameters). However, if a Bonferroni correction is applied ( $p$ -value of interest =  $.05/7$  or  $.00714$ ), differences between groups for six of the seven endpoints remain statistically significant at study end, with only hemoglobin no longer significant. Adjusting for multiplicity does not change the overall interpretation of the study results.

The strengths of the study include the rural setting and subject selection process, which resulted in a study population that is generally representative of this area of Cameroon and other regions of Africa. In addition, the cluster-randomized design helped minimize treatment “contamination” between intervention and control participants, which can reduce the apparent effectiveness of an intervention (Torgerson, 2001).

## 5 | CONCLUSION

In conclusion, these results suggest that daily consumption of micronutrient-fortified IC enriched with 7.5 mg of iron as ferrous fumarate for 6 months improved hemoglobin and iron status and decreased the prevalence of anemia, iron deficiency, and iron deficiency anemia in children under 5 years of age in a malaria-endemic setting, in which it is more difficult to demonstrate a positive effect due to the high infection rate. In addition, the children receiving the iron-fortified IC had improved growth parameters. Given that most households in this region consume wheat flour, a geographically expanded program of iron fortification of affordable cereals in association with other public health interventions, such as prevention of malaria and promotion of immunization, could help to prevent and correct iron deficiency anemia and improve nutritional status in the locality of Salapoumbé, and possibly throughout Cameroon and beyond.

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## CONFLICT OF INTEREST

NPH is employed by Société des Produits Nestlé SA. No other author has any conflict of interest to report.

## ETHICAL APPROVAL

This study was approved by the Comité National d'Ethique et de la Recherche pour la Santé Humaine du Cameroun, and administrative authorization was received from the Cameroon Ministry of Public Health.

## INFORMED CONSENT

Written informed consent was obtained from the parents of all study participants.

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