Dual fortification of salt with iodine and iron: a randomized, double-blind, controlled trial of micronized ferric pyrophosphate and encapsulated ferrous fumarate in southern India[1–3]

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ABSTRACT

Background: Dual fortification of salt with iodine and iron could be a sustainable approach to combating iodine and iron deficiencies.

Objective: We compared the efficacy of dual-fortified salt (DFS) made by using 2 proposed contrasting formulas—one fortifying with iron as micronized ground ferric pyrophosphate (MGFePP) and the other with iron as encapsulated ferrous fumarate (EFF)—with the efficacy of iodized salt (IS) in schoolchildren in rural southern India.

Design: After stability and acceptability testing, a double-blind, household-based intervention was conducted in 5–15-y-old children ($n = 458$) randomly assigned into 3 groups to receive IS or DFS with iron as MGFePP or EFF, both at 2 mg/g salt. We measured hemoglobin, iron status, and urinary iodine at baseline, 5 mo, and 10 mo.

Results: Median serum ferritin and calculated median body iron improved significantly in the 2 groups receiving iron. After 10 mo, the prevalence of anemia decreased from 16.8% to 7.7% in the MGFePP group ($P < 0.05$) and from 15.1% to 5.0% in the EFF group ($P < 0.01$). The median urinary iodine concentration increased significantly in the IS and EFF groups ($P < 0.001$) but not in the MGFePP group. Losses of iodine in salt with 1.8% moisture were high for MGFePP, whereas the EFF segregated in salt with 0.5% moisture and caused color changes in some local foods.

Conclusions: Both DFSs were efficacious in reducing the prevalence of anemia and iron deficiency in school-age children. Local salt characteristics should be taken into consideration when choosing an iron fortificant for DFS to achieve optimal iodine stability and color. *Am J Clin Nutr* 2008;88:1378–87.

INTRODUCTION

Iron and iodine deficiencies are widespread and are globally identified as 2 of 4 major preventable risk factors for compromised child development (1–3). Iron and iodine deficiencies often coexist, and iron deficiency anemia (IDA) impairs thyroid metabolism (4–6) and reduces efficacy of iodine prophylaxis (7, 8). Combined intervention strategies are therefore important for successful reduction of both deficiencies. Salt iodization is an effective, well-established intervention strategy (9). The use of salt as a vehicle for iron fortification also may have advantages: it provides a relatively constant daily intake and is one of few regularly purchased food items with central production in areas with iron deficiency (10). However, effective dual fortification of salt with iodine and iron remains a challenge. When iodine and iron are added together, it is difficult to maintain the stability of both while also avoiding color changes and ensuring adequate iron bioavailability (11–15).

Ferric pyrophosphate (FePP) is a water-insoluble white iron compound reported to cause negligible color change when added to salt (16, 17). Although FePP is poorly water-soluble and has modest bioavailability, reducing its particle size increases its absorption (18). Intervention trials in Morocco and Cote d'Ivoire showed that salt fortified with micronized ground FePP (MGFePP) was effective in reducing iron deficiency in children (19–21). An alternative iron compound, ferrous fumarate, has been suggested as a fortificant for dual-fortified salt (DFS) because of its high relative bioavailability (RBV)—100% relative to ferrous sulfate (22–24). A new formulation of encapsulated, agglomerated ferrous fumarate (EFF) has been developed by The Micronutrient Initiative and the University of Toronto (Toronto, Canada). The encapsulation provides a physical barrier between iodine and the salt, its impurities, and the ferrous fumarate (25–28). Despite the potential of EFF, its efficacy as a DFS fortificant has never been studied.

Iron and iodine deficiencies are major public health problems in India; only 51% of Indian households are using adequately iodized salt, and the reported prevalence of anemia is 56% in women of reproductive age, 12–63% in school-age children, and

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[2] Supported by the Micronutrient Initiative, the Swiss Federal Institute of Technology Zurich, and St John's National Academy of Health Sciences. Paul Lohmann GmbH KG (Emmerthal, Germany) provided the iron fortification compound micronized ground ferric pyrophosphate (MGFePP), and The Micronutrient Initiative donated the iron fortification form encapsulated ferrous fumarate (EFF).

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75% in preschool-age children (29–31). Therefore, the aim of the present study was to test the potential of 2 promising alternative DFS formulations, one containing MGFePP and the other containing EFF as iron fortificants, in India. The results are relevant to other countries in which deficiencies of both iodine and iron pose significant public health problems.

SUBJECTS AND METHODS

Study site and subjects

The study was conducted in 18 villages in Anekal Taluk, Bangalore Urban District, Karnataka State, India. The villages are ≈900 m above sea level and are located 35 km from St John's Medical College (SJMC) in Bangalore. SJMC runs a rural health center located in the area, which provides primary health care to villages within a 5-km radius. The study area is not a malaria-endemic area, and the incidence of disease is estimated to be <2% (32). Local families are mostly subsistence farmers. Their diet is monotonous and mainly based on either cooked rice or finger millet (ragi) and a vegetable sauce (sambar) consisting of lentils, vegetables, and spices. The content of animal products in the diet is low. Meals are predominantly prepared at home. A government-funded lunch program provides one rice-based meal/d to children in primary school. The children's breakfasts and dinners are typically prepared at home.

Children for the baseline screening and subsequently the efficacy trial were recruited from 6 schools, 5 primary schools, and 1 high school. The study period was December 2005 through February 2007.

Oral informed consent to carry out the study was obtained from Taluk level officials, school board members, and school headmasters. Written informed consent (or, if the family was illiterate, oral informed consent) was obtained from the parents of the children in door-to-door home visits. Children who had written permission from their parents and who independently assented to participate were invited to join the trial. The study protocol was approved by the ethics committees of SJMC (Bangalore, India) and the Swiss Federal Institute of Technology (Zurich, Switzerland). Permission to carry out the study was obtained from the Principal Secretaries of the Departments of Health, Women and Child Welfare and Education, Government of Karnataka, India.

Salt consumption and iron intake

Total household salt consumption was monitored to estimate salt intake at the beginning and at the end of the study. The household salt container was weighed on 4 consecutive mornings (the first day to establish the baseline and the other 3 d to establish consumption) in separate random samples of 80 households at the beginning of the study and of 85 study households at the end of the study. The amount of salt consumed per day during the 3 d was calculated. This amount was divided by the number of people in the household.

Salt and iron intakes for children 5–15 y old were assessed by 3-d weighed-food records [using previously described procedures (33)] in 36 randomly selected families living in 5 of the 18 study villages. Consumption data were entered into a dietary survey program (NUTRISURVEY software (version 5.0; University of Hohenheim, Stuttgart, Germany). The iron content of the diet was calculated by using values obtained from the Indian food-composition table (34) and the US Department of Agriculture food database (35). Salt and iron intakes were calculated on an individual basis, and averages were calculated for all children and for girls and boys separately.

Fortification of salt

Salt from Tamil Nadu Salt Corporation [(TNSC) Valinokkam, Tamil Nadu, India] was used for the study. The salt is produced in drying ponds from sea water and is washed, dried, and crushed. The unrefined salt used has a milky-white color and is similar in appearance to the salt used by the rural communities involved in the study. The salt has an NaCl content of 98%, a $CaSO_4$ content of 0.16%, and an $MgSO_4$ content of 0.08%.

Salt was iodized with potassium iodate (KIO_3) at a concentration of 30 μg I/g salt at the factory. The 2 DFSs were fortified at a level of 2 mg Fe/g salt with *1*) the MGFePP (≈25% Fe, mean particle size of ≈2.5 μm; Paul Lohmann AG, Emmerthal, Germany) or *2*) EFF (≈15% Fe; The Micronutrient Initiative, Ottawa, Canada). The EFF mix includes EFF, soy stearine, titanium dioxide (TiO_2), hydroxypropyl methylcellulose (HPMC), and sodium hexametaphosphate (SHMP) (36).

Homogeneity tests at the factory, measuring iodine and iron content in samples from 6 defined positions in the barrel after each mixing, showed a homogenous mixing and desired level of fortification of iodine and iron in the 3 salts in all batches (data not shown). The salt was packed into white, color-labeled, high-quality 2.5-kg polyethylene plastic bags at the TNSC for household distribution. The salt mixing was done at 3 occasions, 4 mo apart, before and during the study.

The fortification level of 2 mg Fe/g salt was chosen on the basis of an estimated mean per capita salt intake of ≈5 g/d in schoolchildren in meals taken at home and an estimated iron bioavailability of 10% from the diet (37–40). Our goal was to provide ≥0.5 mg absorbed Fe/d to the children in the study. We anticipated the RBV of the MGFePP would be ≈50% compared with ferrous fumarates (39, 40).

During the first 2 mo of the intervention trial, salt with an average grain size of ≤ 2 mm and a moisture content of 0.5% was used. However, in the current field setting, EFF underwent significant segregation in salt with 0.5% moisture during transport from the factory to the study site and during use in the households. In an attempt to reduce segregation of the EFF in the salt with 0.5% moisture, salt with an average grain size of ≤1 mm and a moisture content of 1.8% was introduced. Iron content and iron segregation were measured in salt samples with 0.5% and 1.8% moisture content from all 3 study salts (ie, IS, MGFePP, and EFF) collected after controlled simulation studies, after factory mixing, and in household use. The results showed that adjustment of moisture content from 0.5% to 1.8% effectively resolved the problem of iron segregation of the EFF (data not shown; available on request). Salt with a moisture content of 1.8% was used for the remaining 8 mo of the trial.

Stability testing

Iodine and color-stability testing was performed on the 2 different types of native salts used in the trial, salt with 0.5% mois-

ture and salt with 1.8% moisture. The IS, MGFePP, and EFF salts of the 2 different qualities were locally stored as 2.5-kg batches in closed, high-density, transparent polyethylene bags that were stored indoors under local ambient conditions and out of direct sunlight. After storage for 0, 1, 2, 3, 4, 5, and 6 mo, 50-g aliquots of salt ($n = 6$) were taken and frozen at −20 °C until iodine concentration and color were measured. A 6-mo study was done to approximate the time required for the production, distribution, and consumption of salt in this region.

Color stability was determined by reflectance colorimetry as well as panel (Chroma-Meter CR-310; Minolta AG, Dietikon, Switzerland) visual inspection of unmarked samples side-by-side on white backgrounds as described earlier (17). Reflectance colorimetry was determined by the L value on the Hunter a and b color scale. The color of the IS and DFS at each time-point was compared with IS at baseline, and color lightness (L value) and color difference (ΔE_{ab}) were calculated. For details, see Wegmüller et al (17).

Organoleptic testing

Sensory testing was performed to evaluate potential changes in the color, odor, and taste of foods when the 3 salts were added to local dishes. IS, MGFePP and EFF were added to southern Indian meals prepared by a local cook using traditional recipes at the SJMC rural health center. Each type of salt was added in equal amounts in parallel to separate, otherwise identical pots of commonly consumed foods. The recipes tested were cooked plain rice, chitranna (lemon rice), and rice mixed with vegetable sauce (sambar). The color, odor, and flavor of these foods were assessed by a panel of 18 local women ($\bar{x}$ age: 27 y; range: 18–60 y) using triangle tests (41). During the triangle test, 3 coded samples of each of the 3 dishes were given in random order in a semiprivate setting. The panelists determined which sample differed from the other 2 samples, and they described how the samples differed. One dish with 1 of the 2 iron fortificants (MGFePP or EFF) was tested per day. Each of 2 levels of iron fortification, 1 and 2 mg Fe/g salt, was tested in different daily sessions.

Acceptability testing

Local acceptability of the 2 DFSs compared with IS was measured before the study start and after 10 mo of salt use. Before the study, 100-g samples of IS and the 2 DFS (fortified at the level of 2 mg/g salt) were shown, side-by-side in unmarked, identical clear polyethylene bags placed against a white background, to 50 women ($\bar{x}$ age: 34 y; range: 17–60 y) at a local market. The women answered 4 forced-choice questions on acceptability. At the end of the study, household interviews were conducted with the head of each participating household. Forced-choice questions on patterns of salt use, color and taste acceptability, and overall satisfaction with the salt were asked. Complaints or other self-reported adverse effects of salt were recorded in households at each salt distribution occasion.

Efficacy study

All children between 5 and 18 y old attending grades 1–10 at the 6 schools whose parents gave their informed consent were screened. The baseline screening was conducted alongside the existing annual school health check-up performed by the Department of Community Health Medicine at SJMC (Bangalore) in December 2005 and January 2006. Children were registered, their height and weight were measured, and a spot urine sample was collected for measurement of urinary iodine (UI) concentration. Five milliliters of whole blood was collected by venipuncture into EDTA-containing tubes for measurement of hemoglobin, serum ferritin (SF), zinc protoporphyrin (ZnPP), serum transferrin receptor (TfR), and C-reactive protein (CRP) concentrations. In the 6 schools, a blood sample was obtained from 950 children. With the exclusion of children who provided an insufficient blood volume, 934 children were screened for anemia and iron deficiency.

The inclusion criteria for the double-blind intervention trial were SF < 15 μg/L or TfR > 7.6 mg/L and ZnPP > 40 μmol/mole heme (for SF, *see* Laboratory analysis). TfR was measured at screening if SF was ≥15 μg/L and ZnPP was >40 μmol. Four children with hemoglobin < 8.0 g/dL were excluded and treated with oral iron supplements. The oldest children (grade 10) were not included in the efficacy trial for logistic reasons, because they were to leave school at the end of the academic year. The remaining children from the 6 schools who met the criteria for iron deficiency ($n = 458$) were randomly assigned to 1 of 3 groups to receive IS providing *1*) no fortifying iron, *2*) 2 mg Fe/g salt as MGFePP, or *3*) 2 mg Fe/g salt as EFF. Children living in the same household were randomly assigned to the same group. The 3 salts were randomly assigned 3 different color codes, which were kept by an investigator who was not involved in the study. Both the study investigators and the households were blinded to group assignment.

Salt was distributed to households ($n = 364$) in house-to-house visits every second month for 10 mo. Salt for 2 mo of household consumption was handed over directly to the head of the household. The aim of the study was carefully explained to the participating families, and it was emphasized that the new salt should be used for all cooking and food preparation. Families were instructed to finish an opened salt bag before starting a new one. These messages were reinforced at each of the salt distributions. Each family was asked about family size and livestock in the household. A family with <5 members received two 2.5-kg salt bag; larger families received ≥4 bags according to family size. Two fieldworkers were based in the villages on a full-time basis to ensure constant salt supply to the participating households. The study period was March 2006 through February 2007.

In compliance with current local government recommendations, the routine school health check-up program includes distribution of vitamin A supplements (200 000 IU) and Albendazole (400 mg) (both: Locost, Baroda, India). Vitamin A supplements and Albendazole were distributed to all children by the teachers in the 6 schools the month after the start of the study. At 8 mo, all children were treated with a second dose of Albendazole.

Laboratory analysis

Salt samples were stored at −20 °C until they were analyzed. Salt color was determined by reflectance colorimetry (Minolta AG) using the Hunter scale (17). Salt iodine concentration was measured with a validated modified Sandell-Kolthoff method

(42). The level of iron fortification in the salt was verified by the standard addition method using flame atomic absorption spectroscopy (SpectrAA-400; Varian Techtron Pty Ltd, Mulgrave, Australia) as reported earlier (17).

Urine samples were aliquoted (2 mL) at the collection site, transported on ice to the laboratory, and frozen at −20 °C until they were analyzed. Whole blood was transported on ice to the laboratory at SJMC. Hemoglobin was measured in whole blood on the day of collection by using an automated counter (AcT8 Coulter Counter; Beckman Coulter, Krefeld, Germany). Blood was centrifuged on the day of collection (3000 rpm, 15 min, room temperature). Serum and washed red blood cells were separated into aliquots (0.5 mL) and frozen at −80 °C until they were analyzed.

All laboratory methods required for the analysis of hemoglobin, ZnPP, SF, TfR, CRP, and UI were established and validated against external control materials at SJMC (Bangalore). ZnPP was measured in washed red blood cells by using a hematofluorometer (Aviv Biomedical, Lakewood, NJ). Lead was measured in a random sample of 67 children to ensure that lead toxicity would not confound the interpretation of elevated ZnPP values (43). Blood lead concentration was measured by anodic stripping voltammetry (ESA Blood Lead Analyzer 3010B; ESA, Chelmsford, MA). The SF concentration at screening was measured by using enzyme immunoassays (Ramco Laboratories Inc, Houston, TX). At the end of the study, we re-measured all samples from all study children by using another immunoassay system (Access 2; Beckman Coulter, Brea, CA). External 3-level control material [World Health Organization (WHO) Standard 80/578; Ramco Laboratories Inc] was used for both methods. Only values from the Access 2 method were used in data analysis and reported here. TfR was measured by using enzyme immunoassays (Ramco Laboratories Inc). CRP was measured by using nephelometry (Turbox; Orion Diagnostica, Espoo, Finland). UI was measured by using the Sandell-Kolthoff reaction as modified by Pino et al (42).

Anemia was defined as hemoglobin concentrations of <12 g/dL in children aged ≥12 y and <11.5 g/dL in children aged 5–11 y (1). SF values from subjects with elevated CRP (CRP ≥ 10 mg/L) were excluded from analysis. Iron deficiency was defined as either an SF concentration of <15 μg/L or a TfR concentration of >7.6 mg/L plus a ZnPP concentration of >40 μmol/mol heme (44–46). IDA was defined as anemia and iron deficiency by the abovementioned criteria. Body iron status was calculated from the ratio of TfR to SF by using the method of Cook et al (47). Only children with normal CRP concentrations were included in the calculation of body iron status. Iron absorption from the 2 DFSs was calculated by comparing the change in body iron status in the treatment and control groups and by estimating the total iron dose given during the study. A blood lead concentration of ≥10 μg/dL was used as to indicate significant lead exposure in the screened children (48). Iodine deficiency was defined as a UI concentration of <100 μg/L (9).

Statistical analysis

Data processing and statistical analysis were done with the use of SPSS software (version 16.0; SPSS Inc, Chicago, IL) and R software (version 2.7.0; R-project; Internet: www.r-project.org). Height-for-age z scores and BMI-for-age z scores were calculated by using WHO references from 2007 (49). Colorimetry data were expressed as mean (SD) L and ΔE_{ab} values (Hunter scale) for each salt (17). The normality of the data was checked before analysis with the Kolmogoroff-Smirnoff test and graphically by evaluating box plots and *Q–Q* plots. Normally distributed data were expressed as means ± SDs. Parameters not normally distributed (ie, ZnPP, SF, TfR, and UI) were expressed as medians (ranges) and were log transformed for comparisons. Two-factor repeated-measures analysis of variance was done to compare the effects of group × time for hemoglobin, ZnPP, SF, TfR, body iron, and UI. Post hoc comparisons were done by using unpaired *t* tests between groups and paired *t* tests within groups. For variables with persisting skewed distribution after log transformation, comparisons were done by using the Mann-Whitney test between groups and Wilcoxon's test within groups (ZnPP and TfR). For variables with significant differences between groups at baseline (SF and body iron), analysis of variance between 2 groups was done for each time-point (5 mo and 10 mo) by using baseline values as covariates. All post hoc comparisons were adjusted for multiple comparisons (Bonferroni correction). A linear mixed-effect model was used to compare the effects of group × time for the binary variables of anemia, iron deficiency, and IDA. Data from children who did not complete the study were not included in the model. The group effect for the binary variables of anemia, IDA, and iron deficiency was tested by using Pearson's chi-square test, and the time effect was tested by using McNemar's test. Significance was set at $P < 0.05$.

RESULTS

Salt consumption and iron intake

The mean salt intake per person in the household was 11.3 ± 5.1 g/d at the beginning of the study, and there was no change in salt consumption over the 10-mo study period. The 3-d weighed food records were completed in 36 families including 67 children 5–15 y old (median age: 10 y). The mean total salt intake for children was 8.3 ± 3.8 g/d, and the average salt intake in the breakfast and dinner meals taken at home was 6.1 g/d (breakfast: 3.2 ± 2.2 g/d; dinner: 2.9 ± 1.9 g/d). Median daily iron intake was 5.7 mg (range: 3.4–16.7) for all 5–15-y-old children, 6.8 mg (range: 3.4–16.7) for boys, and 5.2 mg (range: 2.6–11.4) for girls.

Stability testing

Iodine losses in the MGFePP salt were 44% over the first month of storage and 86% over 6 mo of storage in salt with 1.8% moisture. There was no difference in iodine stability between the EFF and the IS: both salts lost ≈20% of their iodine content after 6 mo. Iodine stability in salt with 0.5% moisture is available on request. Colorimetry showed a difference in color lightness (ie, the L color value on the Hunter scale) between IS and EFF in salt with 0.5% moisture, but not between IS and MGFePP. In salt with 1.8% moisture, there was a difference in color lightness for both DFSs between IS and MGFePP and between IS and EFF. The measured mean (SD) color lightness for IS, MGFePP, and EFF in salt with 0.5% moisture was 89.6 (0.4), 91.6 (0.1), and 81.9 (0.4), respectively, and that in salt with 1.8% moisture was 88.2 (0.3), 83.6 (0.1), and 83.8 (0.6), respectively. The detected difference in color lightness did not change during storage for 6 mo. In salt with 0.5% moisture, the color difference compared with IS (ΔE_{ab}) was ≈1.5 for MGFePP and ≈9.5 for EFF, which indicated a negligible difference in color between the MGFePP

TABLE 1
Acceptability of iodized salt (IS) and the 2 dual-fortified salt (DFS) groups after 10 mo of use[1]

	IS (n = 111)	MGFePP (n = 121)	EFF (n = 113)
The children ate salt every day [n (%)]	111 (100)	121 (100)	113 (100)
The salt was used in the preparation of all foods during cooking and used on the food after preparation [n (%)]	111 (100)	121 (100)	113 (100)
The salt changed the color of foods [n (%)]	4 (4)	32 (26)[2]	67 (59)[2]
The salt color was acceptable in both damp and dry seasons [n (%)]	111 (100)	121 (100)	113 (100)
The taste of the salt was acceptable in all foods [n (%)]	111 (100)	120 (99.2)	113 (100)
The salt was acceptable overall [n (%)]	111 (100)	119 (98.3)	113 (100)

[1] MGFePP, micronized ground ferric pyrophosphate; EFF, encapsulated ferrous fumarate. The numbers and percentages represent the subjects who responded positively for each issue.
[2] Significantly different from IS, $P < 0.001$.

(light beige) and the IS (milky white) and a slight difference in color between the EFF (light gray) and the IS. In salt with 1.8% moisture, the ΔE_{ab} was ≈9.5 for MGFePP and ≈5.6 for EFF, which indicated a more pronounced difference in the yellow color between the MGFePP (light yellow) and the IS (milky white) and a less pronounced difference between the gray color in the EFF and the IS. The EFF had visually detectable small gray specks that were evenly distributed through the crystals of salt with 1.8% moisture. Storage for 6 mo did not further enhance any color differences between MGFePP or EFF and IS.

Organoleptic testing

In the triangle testing comparing IS with MGFePP and EFF, there was no detectable difference in color, odor, or taste (or all 3) between the fortified salts in any of the traditional foods, except for EFF in plain rice fortified at 2 mg Fe/g salt ($P < 0.05$). When added to the water used in cooking rice, EFF produces small black spots on the surface of the cooked rice grains. The specks were visible to the eye and were detected by 72% of the women.

Acceptability testing

Most of the women interviewed in acceptability testing before the study (62%) would choose IS as their first choice, but almost all of the women (98%) would consider buying their second choice. Women would be willing to pay, on average, 5 rupees/kg for a salt that was good for their health, which is 2–3 rupees more per kilogram than the locally available noniodized salt but 2–5 rupees less than the cost of 7–10 rupees/kg for the high-end refined IS. (As of December 2005, 1 rupee = $0.0218.) All of the women detected a color difference between the 3 salts. Seventy percent of the women said the salt containing MGFP was "dim" or "yellow," and 76% said the EFF salt was "dirty."

The results of interviews performed in all households after 10 mo of household salt use are shown in **Table 1**. All surveyed households rated the 3 salts as acceptable. However, 26% of the households using MGFePP and 59% of the households using EFF noted a slight color change in ≥1 food (mainly vegetable curry) when the respective salts were added. Similar observable color changes to cooked foods were self-reported during the bimonthly salt distribution in 2%, 7%, and 17% of households using IS, MGFePP, and EFF, respectively.

Efficacy trial

The characteristics of screened children are shown in **Table 2**. Of the 934 children who were screened, 458 were enrolled in the efficacy trial and randomly allocated to the 3 intervention groups (**Figure 1**). Age, sex ratio, and anthropometric characteristics of the children at baseline after random assignment in the IS, MGFePP, and EFF groups are given in **Table 3**. Baseline characteristics for hemoglobin and the iron status indicators are shown in **Table 4**. There were no significant between-group differences in any of the baseline characteristics except the SF concentration and the body iron status (*see* Table 4). A total of 401 children completed the study; the overall drop-out rate was 5.7% at 5 mo and 12.4% at 10 mo (Figure 1). The dropouts were due to *1*) migration (39%); *2*) school dropouts (30%), and *3*) final school examinations (32%). When the children who dropped out the study were compared by group with those who completed, no significant differences were observed in baseline hematologic characteristics or in iron status indicators (data not shown). However, children who dropped out between 5 mo and 10 mo were generally older than the children who completed the study ($P < 0.01$).

The changes in hemoglobin concentration and iron status indicators in the 3 groups are shown in Table 4. The hemoglobin concentration improved significantly in all groups over the 10-mo study, but it was significantly ($P < 0.01$) higher in the EFF

TABLE 2
Characteristics of the children in 6 schools in the baseline screening used to select subjects for the efficacy trial[1]

	Value
Age (y)	12.0 ± 2.9[2]
Weight (kg)	27.7 (11.9–68.6)[3,4]
Height (m)	1.37 ± 0.16[5]
Height-for-age z score	-1.71 ± 0.96[5]
BMI-for-age z score	-1.64 ± 1.10[6]
Hemoblobin (g/dL)	12.8 (5.6–16.7)
Zinc protoporphyrin (μg/mol heme)	46 (18–537)
Serum ferritin (μg/L)	12.8 (0.6–199.2)[7]
Prevalence of anemia [n (%)]	115 (12.3)
Prevalence of iron deficiency [n (%)]	543 (58.1)[7]
Prevalence of iron deficiency anemia [n (%)]	95 (10.2)[7]
Blood lead (μg/dL)[8]	2.6 (0.2–15.4)

[1] n = 934 [male: n = 483 (51.7%); female: n = 451 (48.3%)].
[2] $\bar{x}$ ± SD (all such values).
[3] Median; range in parentheses (all such values).
[4–6] Missing values: [4] n = 24, [5] n = 26, [6] n = 27.
[7] Serum ferritin was measured with enzyme immunoassays (Ramco Laboratories Inc, Houston, TX).
[8] Measured in a subsample of 67 children.

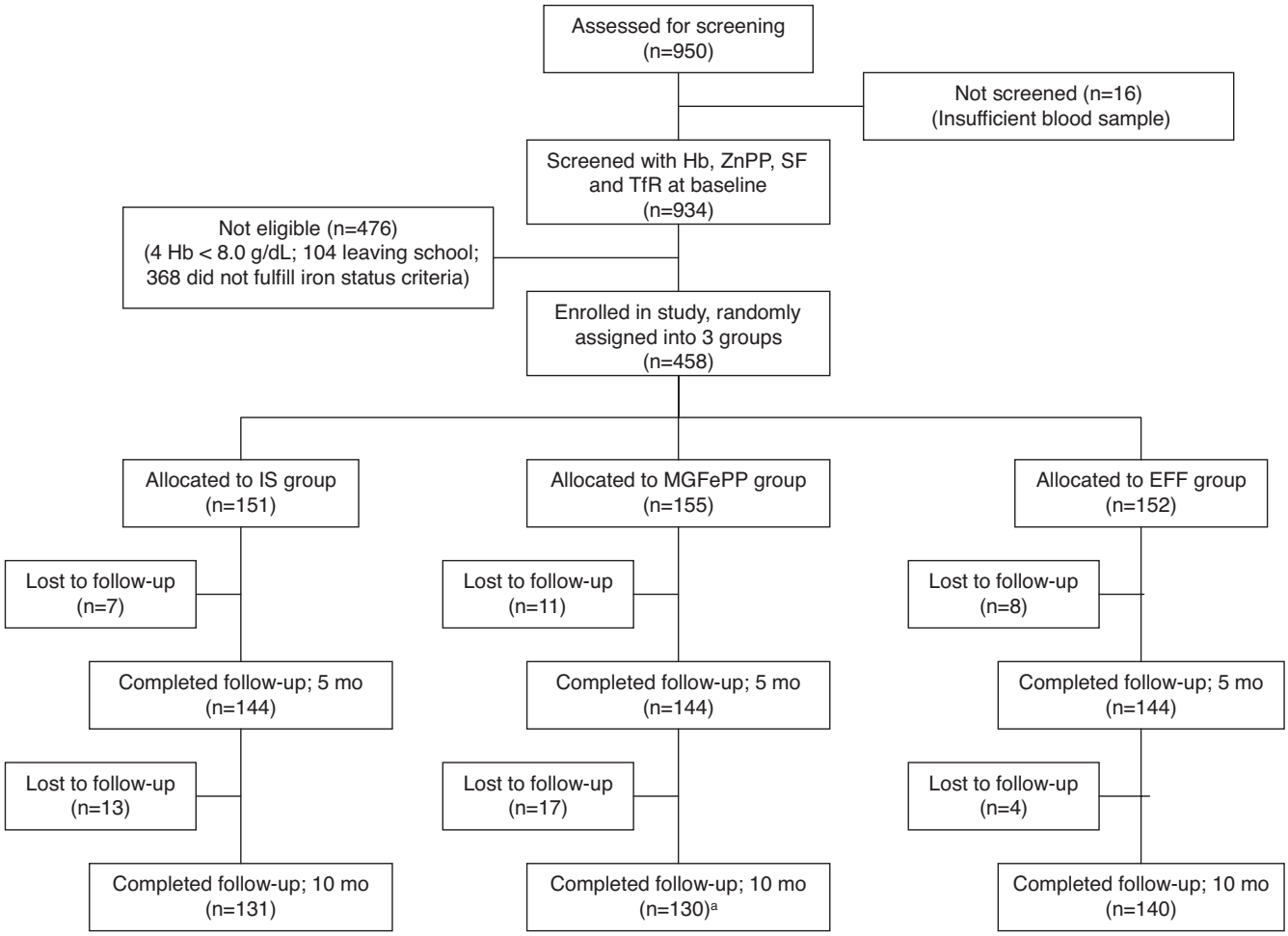

FIGURE 1. Efficacy study profile. Hb, hemoglobin; IS, iodized salt; MGFePP, micronized ground ferric pyrophosphate; EFF, encapsulated ferrous fumarate; ZnPP, zinc protoporphyrin; SF, serum ferritin; TfR, transferrin receptor. [a]Three children who were absent at midpoint completed follow-up at 10 mo.

group than in the IS group. Both groups receiving iron significantly improved their SF and body iron status from baseline ($P < 0.001$) and as compared with the IS group ($P < 0.001$). TfR increased in the control group ($P < 0.001$), but did not change in the 2 iron groups. There was no difference in the prevalence of elevated CRP values between the 3 intervention groups at any time point (data not shown). Because of the adverse color changes that occurred in cooked foods, 17% of households ($n = 20$) in the EFF group stopped using the EFF salt for short periods at some point during the trial. Salt consumption was resumed, however, after the beneficial health effects of iron added to the salt were explained. At 10 mo, noncompliant children ($n = 23$) had lower SF concentrations ($P < 0.05$) and body iron status ($P < 0.05$) than did compliant children.

TABLE 3
Age, sex, and anthropometric characteristics of the children in the iodized salt (IS) group and the 2 dual-fortified salt (DFS) groups at baseline[1]

	IS ($n = 151$)	MGFePP ($n = 155$)	EFF ($n = 152$)
Age (y)	11.2 ± 2.9[2]	11.7 ± 2.8	11.6 ± 2.8
Male:female (n)	78:73	82:73	81:71
Height (kg)	27.4 ± 8.8	28.7 ± 8.8	28.6 ± 9.2
Height (m)	1.33 ± 0.16	1.36 ± 0.16	1.36 ± 0.16
Height-for-age z score	−1.73 ± 0.97	−1.76 ± 0.95	−1.77 ± 0.83
BMI-for-age z score	−1.59 ± 1.05	−1.59 ± 1.07	−1.66 ± 1.15

[1] MGFePP, micronized ground ferric pyrophosphate; EFF, encapsulated ferrous fumarate. There were no significant differences between the 3 groups.
[2] $\bar{x}$ ± SD (all such values).

The prevalence of anemia and iron deficiency with or without anemia is shown in **Figure 2**. Compared with baseline, the prevalence of anemia decreased over 5 and 10 mo from 16.8% to 13.2% and 7.7% ($P < 0.05$), respectively, in the MGFePP group; from 15.1% to 9.0% ($P < 0.05$) and 5.0% ($P < 0.01$), respectively, in the EFF group; and from 19.2% to 13.2% and 14.5% (NS), respectively, in the IS group. The prevalence of iron deficiency dropped over 5 and 10 mo from 56.6% to 39.7% ($P < 0.05$) and 32.8% ($P < 0.001$), respectively, in the MGFePP group; from 52.4% to 30.8% ($P < 0.001$) and 34.6% ($P < 0.01$), respectively, in the EFF group; and from 68.2% to 66.4% and 68.0% (NS), respectively, in the IS group. The prevalence of IDA dropped over 5 and 10 mo from 15.2% to 9.9% and 6.4% ($P < 0.05$), respectively, in the MGFePP group; from 11.7% to 5.3%

TABLE 4
Changes in hemoglobin and iron status indicators in the iodized salt (IS) group and the 2 dual-fortified salt (DFS) groups over 10 mo[1]

	IS	MGFePP	EFF
Hemoblobin (g/L)			
Baseline	12.4 ± 1.2[2] [151]	12.7 ± 1.1 [155]	12.6 ± 1.1 [152]
5 mo	12.7 ± 1.3[3] [144]	13.1 ± 1.2[4] [144]	13.0 ± 1.1[4] [144]
10 mo	13.0 ± 1.4[4,5] [131]	13.3 ± 1.2[4,6] [130]	13.4 ± 1.1[4,5,7] [140]
Zinc protoporphyrin (μg/mol heme)			
Baseline	53 (24–341) [151][8]	48 (22–399) [155]	49 (22–537) [152]
5 mo	47 (21–352)[4] [142]	42 (21–312)[4,9] [140]	40 (18–450)[4,7] [136]
10 mo	45 (22–379)[4] [131]	38 (20–207)[4,7] [130]	37 (19–340)[4,10] [140]
Serum ferritin (μg/L)			
Baseline	11.7 (1.7–52.3) [148]	13.3 (1.9–75.4)[9] [144]	14.4 (1.9–30.7)[7] [145]
5 mo	11.9 (1.7–115.7) [141]	17.1 (2.2–79.0)[4,7] [140]	20.2 (1.8–71.8)[4,10,11] [133]
10 mo	11.6 (1.9–43.2) [125]	19.7 (2.6–61.0)[4,10] [125]	19.3 (2.5–54.8)[4,10,12] [132]
Transferrin receptor (mg/L)			
Baseline	6.0 (2.9–17.6) [151]	5.5 (3.5–17.6) [154]	5.6 (3.0–15.6) [152]
5 mo	6.2 (2.1–21.8)[3] [143]	5.7 (3.4–26.2)[9] [143]	5.5 (2.8-16.8)[7] [144]
10 mo	6.4 (3.6–16.8)[4,12] [131]	5.8 (3.5-30.6)[10] [130]	5.6 (2.9-16.0)[10] [140]
Body iron (mg/kg)			
Baseline	1.1 (−9.5 to 6.9) [148]	1.7 (−7.2 to 8.4) [143]	2.0 (−9.0 to 5.3)[9] [145]
5 mo	1.0 (−10.1 to 9.8) [140]	2.8 (−8.7 to 9.2)[3,9] [139]	3.3 (−9.6 to 8.1)[4,10] [133]
10 mo	1.1 (−9.3 to 6.1) [125]	3.1 (−8.7 to 8.8)[4,10] [125]	3.2 (−7.5 to 6.8)[4,10] [132]

[1] MGFePP, micronized ferric pyrophosphate; EFF, encapsulated ferrous fumarate. Significant time × group interactions were observed for hemoglobin ($P < 0.05$), zinc protoporphyrin (P ____), serum ferritin ($P < 0.001$), transferrin receptor ($P < 0.01$), and body iron ($P < 0.001$).
[2] $\bar{x}$ ± SD; *n* in brackets (all such values).
[3,4] Significantly different from baseline: [3]$P < 0.01$, [4] $P < 0.001$.
[5,6,12] Significantly different from 5 mo: [5]$P < 0.001$, [6] $P < 0.01$, [12] $P < 0.05$.
[7,9,10] Significantly different from IS group at the same time-point: [7]$P < 0.01$, [9] $P < 0.05$, [10] $P < 0.001$.
[8] Median (range) (all such values).
[11] Significantly different from MGFePP group at the same time-point, $P < 0.05$.

($P < 0.05$) and 3.8% ($P < 0.001$), respectively, in the EFF group; and from 16.9% to 12.8% and 15.2% (NS), respectively, in the IS group.

The median UI was significantly higher in the IS and the EFF groups at 10 mo than at baseline ($P < 0.001$), but it did not change significantly in the MGFePP group (**Table 5**). Median UI was significantly lower in the MGFePP ($P < 0.001$) and EFF ($P < 0.05$) groups at 10 mo than in the IS group. The proportion of children with UI concentrations of <100 μg/L was higher in the MGFePP group at 10 mo than in the IS group ($P < 0.01$) or the EFF group ($P < 0.05$).

DISCUSSION

Inadequate dietary intake of iron and poor iron bioavailability likely were the main causes of the high prevalence of iron deficiency in children in the study area. The mean additional iron intake supplied by the DFS in the breakfast and dinner meals prepared at home was 12 mg/d. Fortification with 2 mg Fe/g salt was estimated to be sufficient to reduce the prevalence of inadequate iron intake in the study area from 66% to the recommended level of 2–3% (40). By comparing the total dose of ≈3.7 g Fe supplied over the 10-mo trial with the mean change in body iron status, iron absorption was calculated to 0.9% for MGFePP and 1.1% for EFF. Iron absorption is dependent on many different factors, including iron content and bioavailability of the diet, bioavailability of the iron fortificant, and iron status at baseline (16, 50, 51). The calculated absorption for MGFePP was slightly lower in the current study than in earlier efficacy studies of MGFePP, in which absorption was estimated at 2–3% (19–21, 33). Salt was mainly added to vegetable sauce (sambar) and to water for rice preparation. It is possible that part of the water-insoluble MGFePP and poorly water-soluble EFF iron also was lost in food preparation. The addition of EFF to DFS was tested for the first time in the present study. Although the bioavailability of the iron in EFF was expected to be twice that of the iron in MGFePP, our findings show a similar overall absorption and response in iron status for the 2 groups. Encapsulation and agglomeration of the ferrous fumarate may have reduced its bioavailability (28, 52). The intake of iron from the DFS was not under supervision, and the design of the study approaches that of a community-based effectiveness study (53).

In the present field setting, EFF underwent significant segregation in salt with 0.5% moisture during transport from the factory to the study site and during use in the households. Segregation of added iron was eliminated by matching the salt grain size to EFF (≤1 mm) and by increasing the moisture content to 1.8%. However, increasing the moisture content to 1.8% increased the yellow coloration of the MGFePP salt and resulted in visually detectable gray specks on the EFF salt.

No changes to the color, taste, or appearance of local southern Indian dishes were detected for MGFePP in sensory testing. We previously showed that DFS containing MGFePP does not react with the food matrix, even at high concentrations (17, 19, 21). In both Morocco and the Cote d'Ivoire, MGFePP had a taste and appearance in cooked food and local dishes comparable to that of plain IS. However, in acceptability testing in the present study, 26% of households reported color changes to cooked food. The EFF developed black flecks on cooked rice grains. The house-

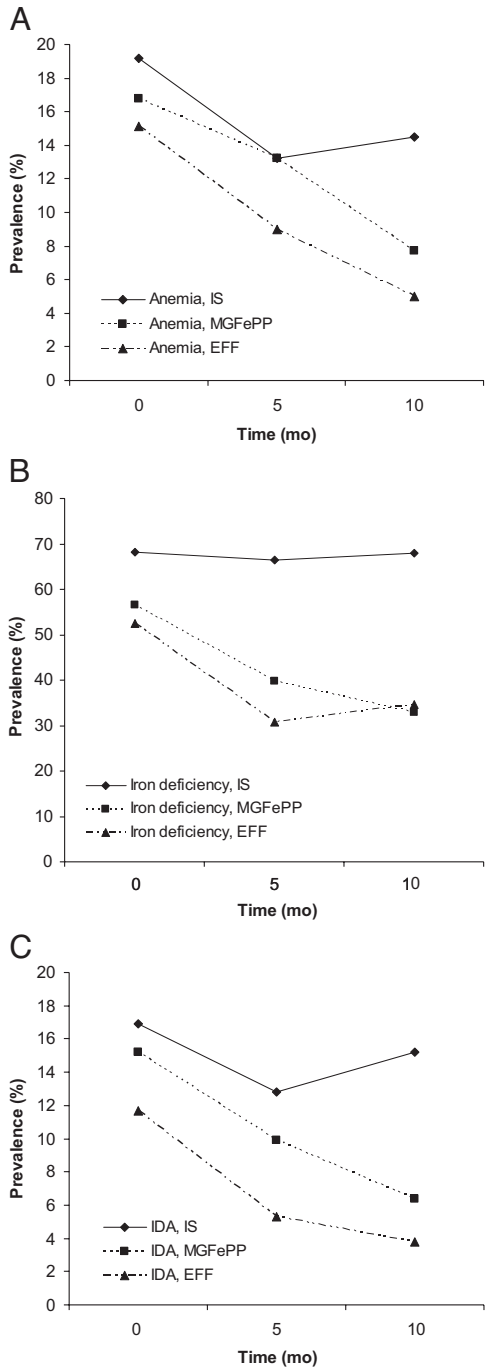

FIGURE 2. The prevalence of anemia (A), iron deficiency (B), and iron deficiency anemia (IDA) (C) in children receiving iodized salt (IS) or dual-fortified salt (DFS) with micronized ground ferric pyrophosphate (MGFePP) or encapsulated ferrous fumarate (EFF) for 10 mo. In comparison with those who received IS, the prevalence of anemia was lower at 10 mo in those who received EFF ($P < 0.05$), the prevalence of iron deficiency was lower at both 5 and 10 mo in those who received MGFePP or EFF ($P < 0.001$), and the prevalence of iron deficiency anemia was lower at 10 mo in those who received MGFePP ($P < 0.05$) and at both 5 and 10 mo in those who received EFF ($P < 0.05$ and $P < 0.01$, respectively). In the IS, MGFePP, and EFF groups, respectively, *n* for anemia = 151, 144, and 131; 155, 144, and 130; and 152, 144, and 140 at baseline, 5 mo, and 10 mo, respectively; *n* for iron deficiency = 151, 140, and 125; 155, 140, and 125; and 152, 133, and 132 for baseline, 5 mo, and 10 mo, respectively; and *n* for IDA = 148, 140, and 125; 144, 140, and 125; and 145, 133, and 132 at baseline, 5 mo, and 10 mo, respectively. A significant time × group interaction was observed for anemia ($P < 0.05$), iron deficiency ($P < 0.01$), and IDA ($P < 0.001$).

holds using EFF also reported color changes to sambar, in the form of floating black specks. The specks may be due to the melting of the encapsulation during cooking, which results in the exposure of the natural color of ferrous fumarate. Despite observable color changes, DFSs containing either MGFePP or EFF were found to be acceptable for household use. It is possible that families accepted the observed color and sensory changes because of the explained health benefits of consumption and because the salt was given free of charge.

A major drawback to the use of the MGFePP identified in the present study is the lack of iodine stability in salt with 1.8% moisture. Most households in the study area did not use IS before the study start, and the only source of iodine for children at baseline was the IS provided at the midday meal served at the schools. Over the 10-mo study, UI increased significantly in the IS and EFF groups but not in the MGFePP group. Iodine losses in IS are accelerated by the presence of salt impurities and high salt moisture, as well as by reducing agents in the salt, including ferrous ions (25, 54). We tested iodine stability (KIO_3) in the 2 DFSs. In salt with 1.8% moisture, MGFePP lost 86% of its iodine concentration over 6 mo of storage. Two storage studies of FePP added to Moroccan (<1% moisture content) and Ivorian (1.6% moisture content) salts show losses of ≈20% in the Moroccan salt and ≈65% in the Ivorian salt over 6 mo of storage, which confirms the lower iodine stability in salt with higher moisture content than in drier salt (17, 19). In the present study, iodine losses with the EFF were ≈20% in salt with 1.8% moisture and were comparable to those with IS. Thus, the encapsulation and agglomeration of the ferrous fumarate together with a stabilizing agent in the EFF was successful in minimizing iodine losses, as was also shown under humid conditions in Kenya and Nigeria (27, 55). Similar acceptable iodine stability has been shown with encapsulated MGFePP added to triple-fortified salt (20).

Other potential formulas of iron have been developed for DFS in India. Ferrous sulfate chelated with the stabilizer sodium hexametaphosphate, malic acid, and the absorption promoter sodium dihydrogen phosphate show good color and iodine stability in salt with low moisture content and low content of impurities (13, 56–58). With its high bioavailability, ferrous sulfate may be another promising option for DFS in high-quality salt.

The 2 iron compounds tested for DFS in the current study, MGFePP and EFF, equally improve iron status in children and reduce the prevalence of anemia and iron deficiency. Both fortificants are commercially available at roughly comparable cost per kilogram. However, neither of these 2 DFS formulations is an ideal fortificant under all conditions. MGFePP has superior sensory qualities and does not segregate, but it causes unacceptable iodine losses in salt with higher moisture content. When it is to be used in moist salt, MGFePP may be encapsulated to prevent iodine losses. EFF has higher bioavailability, but causes observable sensory changes in moist salt and in foods when used in cooking. It segregates in dry salt but has excellent iodine stability in both dry and wet salt. Therefore, salt quality should be considered when an optimal iron fortificant for DFS is being chosen.

DFS has been suggested as a potential iron intervention strategy when salt production is largely centralized and when a quality-control systems for IS is already in place and could easily be expanded to include quality control for iron. Using salt as a condiment for fortification of micronutrients other than iodine has recently been questioned (59). However, replacing IS with DFS in existing, well-functioning, supervised feeding programs

TABLE 5
Changes in urinary iodine concentrations in the in the iodized salt (IS) group and the 2 dual-fortified salt (DFS) groups over 10 mo[1]

	IS	MGFePP	EFF
Urinary iodine (μg/L)[2]			
Baseline	182 (8–857)[3] [150]	143 (7–697) [154]	133 (12–817) [154]
5 mo	290 (25–966)[4] [142]	171 (18–788)[5] [140]	242 (30–1114)[4,6] [140]
10 mo	355 (33–1223)[4,7] [126]	166 (17–723)[5] [125]	252 (14–1156)[5,6,8] [125]
Proportion <100 μg/L (%)			
Baseline	29.3 [150]	35.1 [154]	37.5 [154]
5 mo	12.0[9] [142]	17.1[9] [140]	15.0[4] [140]
10 mo	11.9[9] [126]	26.4[10] [125]	15.6[11] [125]

[1] MGFePP, micronized ground ferric pyrophosphate; EFF, encapsulated ferrous fumarate. *n* in brackets (all such values).
[2] Significant time × treatment interaction, $P < 0.001$.
[3] Median; range in parentheses (all such values).
[4,9] Significantly different from baseline: [4]$P < 0.001$, [9] $P < 0.01$.
[5,8,10] Significantly different from the IS group: [5]$P < 0.001$, [8] $P < 0.05$, [10] $P < 0.01$.
[6,11] Significantly different from the MGFePP group: [6]$P < 0.001$, [11] $P < 0.05$.
[7] Significantly different from 5 mo, $P < 0.01$.

such as school midday meal programs, integrated child development services programs, and public food distribution systems similar to those that are in place in India still may be a cost-effective way to reach population groups that are vulnerable to both iodine and iron deficiencies.

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REFERENCES

1. World Health Organization, United Nations Children's Fund, United Nations University. Iron deficiency anaemia. Assessment, prevention and control. Geneva, Switzerland: World Health Organization, 2001 (WHO/NHD/01.3).
2. Walker SP, Wachs TD, Gardner JM, et al. Child development: risk factors for adverse outcomes in developing countries. Lancet 2007;369:145–57.
3. de Benoist B, McLean E, Andersson M, Rogers L. Iodine deficiency in 2007: global progress since 2003. Food Nutr Bull (in press).
4. Beard JL, Borel MJ, Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anemia. Am J Clin Nutr 1990;52:813–9.
5. Beard JL, Brigham DE, Kelley SK, Green MH. Plasma thyroid hormone kinetics are altered in iron-deficient rats. J Nutr 1998;128:1401–8.
6. Zimmermann MB. The influence of iron status on iodine utilization and thyroid function. Annu Rev Nutr 2006;26:367–89.
7. Zimmermann M, Adou P, Torresani T, Zeder C, Hurrell R. Persistence of goiter despite oral iodine supplementation in goitrous children with iron deficiency anemia in Cote d'Ivoire. Am J Clin Nutr 2000;71:88–93.
8. Hess SY, Zimmermann MB, Adou P, Torresani T, Hurrell RF. Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Cote d'Ivoire. Am J Clin Nutr 2002;75:743–8.
9. World Health Organization, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. 3rd ed. Geneva, Switzerland: World Health Organization, 2007.
10. Cook JD, Reusser ME. Iron fortification: an update. Am J Clin Nutr 1983;38:648–59.
11. Rao BS, Vijayasarathy C. Fortification of common salt with iron: effect of chemical additives on stability and bioavailability. Am J Clin Nutr 1975;28:1395–401.
12. Narasinga Rao BS. Fortification of salt with iron and iodine to control anaemia and goitre: development of a new formula with good stability and bioavailability of iron and iodine. Food Nutr Bull 1994;15:32–9.
13. Nair KM, Brahmam GN, Ranganathan S, Vijayaraghavan K, Sivakumar B, Krishnaswamy K. Impact evaluation of iron & iodine fortified salt. Indian J Med Res 1998;108:203–11.
14. Zimmermann MB, Zeder C, Chaouki N, Saad A, Torresani T, Hurrell RF. Dual fortification of salt with iodine and microencapsulated iron: a randomized, double-blind, controlled trial in Moroccan schoolchildren. Am J Clin Nutr 2003;77:425–32.
15. Ranganathan S, Karmarkar MG. Estimation of iodine in salt fortified with iodine & iron. Indian J Med Res 2006;123:531–40.
16. Hurrell RF. Fortification: overcoming technical and practical barriers. J Nutr 2002;132(suppl):806S–12S.
17. Wegmüller R, Zimmermann MB, Hurrell RF. Dual fortification of salt with iodine and encapsulated iron compounds: stability and acceptability testing in Morocco and Côte d'Ivoire. J Food Sci 2003;68:2129–35.
18. Fidler MC, Walczyk T, Davidsson L, et al. A micronised, dispersible ferric pyrophosphate with high relative bioavailability in man. Br J Nutr 2004;91:107–12.
19. Zimmermann MB, Wegmueller R, Zeder C, et al. Dual fortification of salt with iodine and micronized ferric pyrophosphate: a randomized, double-blind, controlled trial. Am J Clin Nutr 2004;80:952–9.
20. Zimmermann MB, Wegmueller R, Zeder C, et al. Triple fortification of salt with microcapsules of iodine, iron, and vitamin A. Am J Clin Nutr 2004;80:1283–90.
21. Wegmuller R, Camara F, Zimmermann MB, Adou P, Hurrell RF. Salt dual-fortified with iodine and micronized ground ferric pyrophosphate affects iron status but not hemoglobin in children in Cote d'Ivoire. J Nutr 2006;136:1814–20.
22. Hurrell RF, Furniss DE, Burri J, Whittaker P, Lynch SR, Cook JD. Iron fortification of infant cereals: a proposal for the use of ferrous fumarate or ferrous succinate. Am J Clin Nutr 1989;49:1274–82.
23. Christofides A, Asante KP, Schauer C, Sharieff W, Owusu-Agyei S, Zlotkin S. Multi-micronutrient Sprinkles including a low dose of iron provided as microencapsulated ferrous fumarate improves haematologic

indices in anaemic children: a randomized clinical trial. Matern Child Nutr 2006;2:169–80.
24. Sattarzadeh M, Zlotkin SH. Iron is well absorbed by healthy adults after ingestion of double-fortified (iron and dextran-coated iodine) table salt and urinary iodine excretion is unaffected. J Nutr 1999;129:117–21.
25. Diosady LL, Alberti JO, Ramcharan K, Mannar MG. Iodine stability in salt double-fortified with iron and iodine. Food Nutr Bull 2002;23:196–207.
26. Diosady LL, Alberti JO, Mannar MGV. Microencapsulation for iodine stability in salt fortified with ferrous fumarate and potassium iodide. Food Res Int 2002;35:635–42.
27. Oshinowo T, Diosady L, Yusufali R, Laleye L. Stability of salt double-fortified with ferrous fumarate and potassium iodate or iodide under storage and distribution conditions in Kenya. Food Nutr Bull 2004;25:264–70.
28. Zimmermann MB. The potential of encapsulated iron compounds in food fortification: a review. Int J Vitam Nutr Res 2004;74:453–61.
29. Rao B. Anaemia and micronutrient deficiency. Natl Med J India 2003;16:46–50.
30. Muthayya S, Thankachan P, Zimmermann MB, et al. Low anemia prevalence in school-aged children in Bangalore, South India: possible effect of school health initiatives Eur J Clin Nutr 2007;61:865–9.
31. International Institute for Population Sciences (IIPS) and Macro International. National Family Health Survey (NFHS-3), 2005-2006: India. Mumbai, India: IIPS, 2007.
32. Sitalakshmi S, Srikrishna A, Devi S, Damodar P, Mathew T, Varghese J. Changing trends in malaria—a decade's experience at a referral hospital. Indian J Pathol Microbiol 2003;46:399–401.
33. Moretti D, Zimmermann MB, Muthayya S, et al. Extruded rice fortified with micronized ground ferric pyrophosphate reduces iron deficiency in Indian schoolchildren: a double-blind randomized controlled trial. Am J Clin Nutr 2006;84:822–9.
34. Gopalan C, Ramasastry BV, Balasubramaniam SC, Narasinga Rao BS, Deosthale YG, Pant KC, eds. Nutritive value of Indian foods. Hyderabad, India: National Institute of Nutrition (ICMR), 1989.
35. US Department of Agriculture. USDA national nutrient database for standard reference, release 19, 2006. Internet: http://www.ars.usda.gov/nutrientdata (accessed 20 August 2006).
36. The Micronutrient Initiative. Double fortified salt premix: product description. Ottawa, Canada: The Micronutrient Initiative, 2005.
37. Rao BSN, Vijayasarathy C, Prabhavathi T. Iron absorption from habitual diets of Indians studied by the extrinsic tag technique. Indian J Med Res 1983;77:648–57.
38. FAO/UN. Requirements of vitamin A, iron, folate and vitamin B12. Report of a Joint FAO/WHO Expert Consultation. Rome, Italy: Food and Agriculture Organization of the United Nations, 1988. (FAO Food and Nutrition Series no. 23.)
39. Wegmuller R, Zimmermann MB, Moretti D, Arnold M, Langhans W, Hurrell RF. Particle size reduction and encapsulation affect the bioavailability of ferric pyrophosphate in rats. J Nutr 2004;134:3301–4.
40. Allen L, de Benoist B, Dary O, Hurrell R. Guidelines on food fortification with micronutrients. 2nd ed. Geneva, Switzerland: World Health Organization and Food and Agriculture Organization of the United Nations, 2006.
41. Meilgaard M, Civille GV, Carr BT. Sensory evaluation techniques. Boca Raton, FL: CRC Press, 1991.
42. Pino S, Fang SL, Braverman LE. Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. Clin Chem 1996;42:239–43.
43. Labbe RF, Vreman HJ, Stevenson DK. Zinc protoporphyrin: a metabolite with a mission. Clin Chem 1999;45:2060–72.
44. World Health Organization, Centers for Disease Conrol and Prevention. Assessing the iron status of populations. Report of a joint technical consultation on the assessment of iron status at the population level. Geneva, Switzerland: World Health Organization, 2004.
45. Hastka J, Lasserre JJ, Schwarzbeck A, Strauch M, Hehlmann R. Washing erythrocytes to remove interferents in measurements of zinc protoporphyrin by front-face hematofluorometry. Clin Chem 1992;38:2184–9.
46. Zimmermann MB, Molinari L, Staubli-Asobayire F, et al. Serum transferrin receptor and zinc protoporphyrin as indicators of iron status in African children. Am J Clin Nutr 2005;81:615–23.
47. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. Blood 2003;101:3359–64.
48. Harvey B, ed. Managing elevated blood lead levels among young children: recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention. Atlanta, GA: Centers for Disease Control and Prevention, 2002.
49. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660–7.
50. Hurrell RF. How to ensure adequate iron absorption from iron-fortified food. Nutr Rev 2002;60:S7–15.
51. Moretti D, Zimmermann MB, Wegmuller R, Walczyk T, Zeder C, Hurrell RF. Iron status and food matrix strongly affect the relative bioavailability of ferric pyrophosphate in humans. Am J Clin Nutr 2006;83:632–8.
52. Liyanage C, Zlotkin S. Bioavailability of iron from micro-encapsulated iron sprinkle supplement. Food Nutr Bull 2002;23:133–7.
53. Hurrell RF. Iron fortification: its efficacy and safety in relation to infections. Food Nutr Bull 2007;28:S585–94.
54. Diosady LL, Mannar VMG, Stone T. Stability of iodine in iodized salt used for the correction IDD. Food Nutr Bull 1997;18:388–96.
55. Oshinowo T, Diosady LL, Yusufali R, Wesley A. An investigation of the stability of double fortified salt during storage and distribution in Nigeria. Int J Food Eng 2007;3:article 13.
56. Ranganathan S. Fortification of common salt with iron—use of polyphosphate stabilizers. Food Chem 1992;45:263–7.
57. Vinodkumar M, Rajagopalan S, Bhagwat IP, et al. A multicenter community study on the efficacy of double-fortified salt. Food Nutr Bull 2007;28:100–8.
58. Ranganathan S, Karmarkar MG, Krupadanam M, et al. Stability of iodine in salt fortified with iodine and iron. Food Nutr Bull 2007;28:109–15.
59. World Health Organization. Reducing salt intake in populations: report of a WHO forum and technical meeting, 5-7 October 2006, Paris, France. Geneva, Switzerland: World Health Organization, 2007.