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DUAL FORTIFICATION OF SALT WITH IRON AND IODINE IN WOMEN AND CHILDREN IN RURAL GHANA

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ABSTRACT

Objective: To test the efficacy of double-fortified salt (DFS) on the anaemia and iodine deficiency (ID) status of women and their children.

Design: Double-blind randomised controlled trial.

Setting: Sekyere West District of Ghana.

Subjects: In this eight-month trial, mildly anaemic or non-anaemic, non-pregnant, non-lactating women were randomised into three groups receiving: DFS plus weekly placebo (n = 61); iodised salt plus weekly 70 mg iron supplement (n = 65); or iodised salt (IS) plus weekly placebo (control group, n = 58). Correspondingly, their mildly anaemic and non-anaemic children aged 1-5 years were randomised into two groups receiving either the DFS (n = 23) or IS alone (control group, n = 59).

Results: At the end of the intervention, prevalence of anaemia in women remained unchanged in the DFS or IS plus weekly iron supplement group, but significantly increased by 19.5% in the control group (P = 0.039). In children, prevalence of anaemia in the DFS group significantly decreased by 21.7% (P = 0.025) while no change was observed in the control group. ID decreased significantly in all groups of women (P < 0.001) and children (P < 0.05), with no difference among groups of women and children.

Conclusion: While the use of DFS prevented anaemia in women, it had a significant role in both the prevention and treatment of anaemia in children. Both the DFS and IS significantly reduced ID in women and children to a similar degree.

INTRODUCTION

The World Health Organization estimates that worldwide two billion people suffer from anaemia and that approximately 50% of all anaemia can be attributed to iron deficiency (1). Women of child-bearing age and young children are at highest risk of iron deficiency anaemia (IDA). It has recently been estimated that 76% of Ghanaian children 6-59

months old have some level of anaemia, including 23% of children who are mildly anaemic, 47% who are moderately anaemic, and 6% who are severely anaemic (2). Prevalence of anaemia among children is higher in rural areas (80%) than in urban areas (68%). In addition, recent estimates show that 45% of women aged 15-49 years are anaemic, with 35% being mildly anaemic, 9% moderately anaemic, and less than 1% severely anaemic (2).

About 1.6 billion people live in parts of the world where naturally-occurring iodine is not available in sufficient quantities to prevent iodine deficiency disorders (IDD) (3,4). In Ghana, goiter is present in 18% of the population (5). Fortification of salt with iodine has been the most widespread and effective preventative tool against IDD since 1920. However, in Ghana, it is estimated that approximately 50% of households use iodised salt (4,5).

Anaemia and iodine deficiency co-exist in many areas of the world. In addition, recent evidence from West Africa demonstrated that impaired iron status impacts on the effectiveness of iodine prophylaxis in areas where goiter is endemic (6). Thus, a method that delivers both iron and iodine simultaneously would be a practical means of prevention in areas where anaemia and goiter are highly prevalent. Iron fortification of salt (7-14) has been shown to be efficacious in preventing anaemia (15,16). Further work with more bioavailable and organoleptically undetectable iron salts is warranted and common table salt could be used as a vehicle for 'double-fortification'.

Research to produce a stable and acceptable double-fortified salt (DFS) has been conducted over the past 20 years in a number of countries (7,17). An impediment to its successful use has been the reaction between iron and iodine resulting in loss of the latter from the salt, reduced bioavailability of the iron, an unacceptable brown discoloration of the salt and altered flavour of the food to which the salt is added. The Micronutrient Initiative and researchers at the University of Toronto, Canada have designed a salt fortified with both iron and iodine, which is stable for at least one year (3,18) and is very simple and inexpensive to produce on a large-scale (19). This DFS was specifically designed to provide an adequate amount of iodine to treat and prevent iodine deficiency and an adequate amount of iron to prevent iron deficiency if consumed on a daily basis and in sufficient amounts (19). The iodine in this salt is encapsulated with dextrin, protecting it from chemical reactions with the iron. Researchers have already demonstrated good bioavailability of iron and iodine from this salt in healthy human volunteers (19). Past research on DFS products demonstrated that they are more efficacious in improving both iron and iodine status as compared to iodised salt alone (12,13). However, no studies have previously shown the efficacy of DFS as compared to iodised salt given with a weekly iron supplement in improving both iron and iodine status. The objective of this study was

to test the efficacy of common table salt fortified with ferrous fumarate and dextrin-coated potassium iodide on anaemia and iodine deficiency status of mildly anaemic and non-anaemic non-pregnant women and children.

MATERIALS AND METHODS

Study setting and recruitment: The study was conducted from December 1997 to August 1998 in the agrarian region of Sekyere West District of Ghana. At the time of the study, the district had a high rate of IDD (prevalence of goiter: 29.3% and mean urinary iodine: 27 µg/L (20) and a reported anaemia prevalence of over 60% from hospital reports. The district, in the Ashanti region of Ghana, is located in a mountainous zone about 1400 feet above sea level. It has a population of about 169,000 (District Health Administration; Sekyere West District Statistics, Ghana 1997). Ecologically, it is located at the beginning of a transition zone where thick forests begin to give way to Savannah as one travels northwards. The region experiences peak rains around June, followed by a smaller peak in October each year. The district is served by one major hospital, located at Mampong (district capital). Most villages receive occasional visits from public health nurses, district nutritionists or other health workers. While 51% of the population are women, those of child-bearing age constitute about 20% of the population.

Seventeen villages were randomly selected from a cluster of villages around Mampong. Mother-child pairs were recruited from two clusters of nine rural villages. Field workers randomly chose homes in each village and recruited mother and child dyads who satisfied the inclusion criteria and gave informed consent to participate. A woman met the inclusion criteria if she was healthy, non-pregnant, non-lactating, of child-bearing age (15-45 years), cared for a child 1-5 years of age and prepared family meals herself. Women were excluded if they were unwilling to take supplemental (supplement or placebo) tablets required for the study, uncertain about availability for the study throughout the eight-month intervention period, or had a haemoglobin concentration (Hb) <100 g/L during the baseline visit. Excluded women were given nutrition counselling. A child qualified for inclusion in the study if aged between 1-5 years, was healthy and had Hb ≥ 100 g/L. Anaemic children were treated. Anyone with severe anaemia was referred to the local hospital.

Ethics approval for the study was obtained from the Research Ethics Board at the Hospital for Sick Children (Toronto, Canada), from the Ethics Review Committee of the International Development Research Centre, from the Scientific Ethics Committee, Ghana Medical School (Korle Bu) and from the Regional Health Directorate, Ashanti. Recruited women gave written informed consent for themselves and their children to participate in the study by fingerprinting a consent form.

Study design: Eligible women and target child dyads were invited to a local centre for baseline blood screening. Women meeting the inclusion criteria were randomised by assignment to red, yellow or green-labeled salt packages. This resulted in three groups receiving: (i) iodised salt (IS) plus a weekly placebo (control group); (ii) IS plus a weekly 70 mg iron supplement; and (iii) double-fortified salt (DFS) plus a weekly placebo for eight months. Children meeting the inclusion criteria were not specifically randomised, but received the same salt as their corresponding mother (DFS or IS). Children did not receive supplement or placebo tablets.

Salt was given to the women on the day of confirmation for inclusion in the study. They were provided with an excess amount of salt, 4 kg salt in four 1 kg sachets, in a covered tupperware (plastic) container and were asked to use the salt for the entire household as they normally would. This quantity was estimated to last up to about three months. Each family was visited weekly by a research worker to monitor salt usage and health status. Salt supplies were replenished in 1kg sachets when needed. All subjects, field staff, technicians and data analysts were blinded to group assignments.

Women were excluded from the study if they became pregnant during the study, but were allowed to keep any unused salt. Any women or children who developed or still had anaemia or iodine deficiency at the end of the study were treated.

Salt preparation and intake: The absorption of iron from the DFS was previously documented in healthy adults and it was concluded that the iodine from the salt was readily available and absorbable. In addition, the DFS was found to be stable even after 12 months of storage under differing environmental conditions (19).

The salt contained 1000 ppm iron (1g/kg) as ferrous fumarate and 50 ppm iodine (50 mg/kg) as

potassium iodide. Based on a pilot project completed in anticipation of the current study, it was assumed that the average daily intake of salt was 10 g per person per day. Thus, the DFS was estimated to provide 70 mg of iron per week.

Data collection: Venous blood samples were obtained from the women and their children at baseline and eight months, and assessed for Hb on site. Hb was measured with a portable HEMOCUE B-haemoglobin photometer (HemoCue®, Angelholm, Sweden) by trained technicians using standard techniques as previously described (21, 22). Blood smears from each visit were checked for malaria parasites and the presence of sickle cell trait was determined from one of the blood samples. At each of these sampling times, about 20 ml of urine was collected from both women and their children, preserved with 0.1 ml concentrated acetic acid and kept on ice until frozen at -20°C . Urine samples were analysed for iodine by using the method by Dunn *et al* (23) at the laboratory of the University of Ghana (certified by the Program Against Micronutrient Malnutrition). For each analyses, three quality control samples (low, medium and high levels) were analysed. Data were checked with Multiscala software which compared assay quality control values against target values. It rejected or accepted an assay on the basis of Westgard rules.

A field worker visited each home once a week for eight months to assess acceptability of the salt, encourage compliance with salt and weekly iron supplement usage, and check the health of the subjects including incidence of malaria, constipation, diarrhoea (defined as three or more watery stools per day), other gastrointestinal disorders, and pregnancy.

Sample-size determination: Sample-size calculations were performed based on our two main outcomes, Hb and urinary iodine (UI) concentrations. Based on a previous study by Punnonen *et al* (24) in which the SD for Hb was 13 g/l for healthy adults and 19 g/l for adults with IDA and because our adult subjects were either mildly anaemic or healthy, we estimated that between 26-50 subjects per group would be sufficient to detect a 10 g/l difference in Hb concentration on the basis of a Type I Error set at 0.05 and a 0.8 probability of detecting a true difference between baseline and eight months. In addition, based on data from the National Iodine Deficiency Disorders (IDD)

survey (20), the mean urinary excretion of iodine was expected to be $27 \pm 47 \mu\text{g}/\text{l}$. Normal UI concentrations are above $100 \mu\text{g}/\text{l}$. Therefore, assuming a SD of 47 and a desired change of $73 \mu\text{g}/\text{l}$ the sample size was estimated to be seven subjects per group. Assuming a 50% dropout rate due to unforeseen reasons such as non-compliance with the interventions, refusal to provide blood samples, becoming pregnant, or moving from the area, we planned to include 100 women per group.

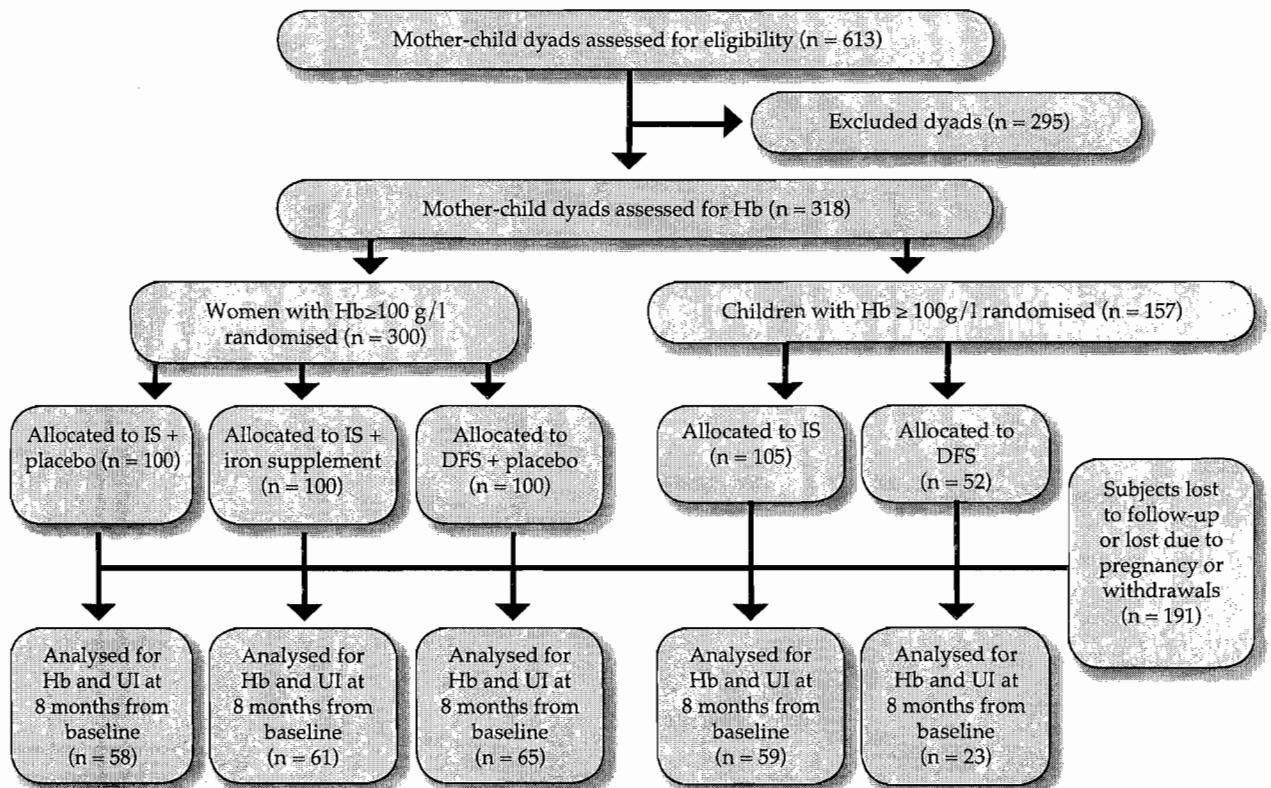
Data analysis: Clinical definitions of anaemia and iodine deficiency as recommended by the WHO were adopted for analysis (25). Anaemia was defined as $\text{Hb} < 120 \text{ g}/\text{l}$ in women and $\text{Hb} < 110 \text{ g}/\text{l}$ in children. Iodine deficiency was defined as UI concentration $< 100 \mu\text{g}/\text{l}$ (23). Non-normally distributed data (skewed) were log-transformed for analyses. McNemar's test for paired data was used to compare the proportions of anaemic and iodine deficient subjects between baseline and the end of the study. Mean baseline Hb and UI values were compared to 8th month values using

paired t-test. Mean baseline values were compared between groups by using ANOVA or student's t-test. Analysis was conducted using SAS version 6.12 (SAS Institute, Inc., Carey, NC). The acceptable level of statistical significance for all tests was $p < 0.05$.

RESULTS

Three hundred ninety mothers with children satisfied all preliminary inclusion criteria during screening. Less than 6% of the 318 women who attended the baseline visit were excluded while about 50% of the children were excluded on the basis of their Hb concentration. Therefore, a total of 300 women and 157 children were included in the study (Figure 1). Only 2.5% of subjects tested positive for malaria parasites throughout the study, which did not have a significant impact on Hb or iodine parameters. Malaria was more common in children (3.5-8.2%) compared to their mothers (0.6-0.9%). Loss to follow-up occurred for the following reasons: pregnancy; relocation from study area; and withdrawal of mother from study.

Figure 1
Trial profile



DFS = Double Fortified Salt; Hb = Haemoglobin Concentration; IS = Iodised Salt; UI = Urinary Iodine Concentration

Table 1
Baseline characteristics of subjects

Characteristic	Subjects	DFS + weekly placebo group*	IS + weekly iron supplement group	IS + weekly placebo group (Control)*
Study sub-sample				
^a Age (years)	Women (n = 150)	28.46 ± 8.17	31.78 ± 6.45	28.66 ± 8.38
	Children (n = 110)	3.0 ± 1.0	–	3.0 ± 1.0
Study completers				
^a Haemoglobin (g/l)	Women (n = 184)	125 ± 12	122 ± 11	127 ± 11
	Children (n = 82)	109 ± 11	–	110 ± 9.0
^b Urinary Iodine (µg/l)	Women (n = 184)	22.2 ± 116	70.1 ± 169	34.1 ± 207
	Children (n = 82)	39.3 ± 77.0	–	67.4 ± 176

DFS = Double Fortified Salt; IS = Iodised Salt; * Weekly placebo used by mothers only; ^aValues expressed as mean ± SD; ^bValues expressed as median ± SD

Table 2
Change in prevalence of anaemia and iodine deficiency (%) from baseline to the end in women

		DFS + weekly placebo group (n = 61)	IS + weekly iron supplement group (n = 65)	IS + weekly placebo group (Control) (n = 58)
% anaemia (n)	Baseline	21 34.4	23 35.4	11 19.0
	End	23 37.7	24 36.9	20 34.5
	%change	+3.3	+1.5	+15.5
	*P-value	0.59	0.84	0.039
% iodine deficiency (n)	Baseline	42 68.8	46 70.8	43 74.1
	End	10 16.4	16 24.6	11 19.0
	%change	-52.4	-46.2	-55.1
	*P-value	<0.001	<0.001	<0.001

DFS = Double Fortified Salt; IS = Iodised Salt; ^a McNemar's paired test

Baseline characteristics. Baseline characteristics including age, and Hb and UI concentrations were not significantly different among the groups at baseline (Table 1). Overall, 86% of women and 65% of children at baseline were screened for sickle cell trait. It was found that 9.2% of subjects were found to be positive for sickle cell. Sickle status was not related to baseline Hb or UI excretion.

Anaemia outcomes: In the IS control group, anaemia prevalence (Hb < 120 g/l) in women significantly increased from 19% at baseline to 34.5% at the end of the study (P = 0.039) (Table 2). In contrast, no significant changes occurred in the DFS group with an anaemia prevalence of 34.4% at baseline

and 37.7% at the end (P = 0.59) or in the IS plus iron supplement group with an anaemia prevalence of 35.4% at baseline and 36.9% at the end (P = 0.84).

Anaemia prevalence in children (Hb < 110 g/l) at baseline was 54.2% in the IS control group and 56.5% in the DFS group (Table 3). By the end of the study there was no significant change in the prevalence rate in the IS control group with 59.3% of the children being anaemic (P = 0.49). In contrast, the prevalence rate significantly decreased to 34.8% in the DFS group (P = 0.025). The change in anaemia rate was significantly different between the two groups (P = 0.05).

Iodine deficiency outcomes: The prevalence (UI < 100 µg/l) in women significantly dropped from 74.1% at

Table 3

Change in prevalence of anaemia and iodine deficiency (%) in children

		DFS (n = 23)	IS (Control) (n = 59)
% anaemia(n)	Baseline	13 56.5	32 54.2
	End	8 34.8	35 59.3
	% change	-21.7	+ 5.1
	^a P-value	0.025	0.49
% iodine deficiency (n)	Baseline	20 87.0	44 74.6
	End	10 43.5	14 23.7
	% change	-43.5	-50.9
	^a P-value	0.012	<0.001

DFS = Double Fortified Salt; IS = Iodised Salt; ^aMcNemar' s paired test

baseline to 19.0% at the end of the study ($P < 0.001$) in the IS control group, from 68.8% to 16.4% ($P < 0.001$) in the DFS group and from 70.8% to 24.6% in the IS plus iron supplement group ($P < 0.001$) (Table 2). The drop was similar in magnitude between groups ($P = 0.46$).

Iodine deficiency prevalence in children at baseline was 74.6% in the IS control group and 87.0% in the DFS group (Table 3). By the end of the study, prevalence rates decreased significantly to 23.7% ($P < 0.001$) and 43.5% ($P = 0.012$) in the IS control and DFS groups, respectively. The decrease in prevalence was similar in both groups ($P = 0.124$).

Side effects. No adverse side effects such as nausea, vomiting or epigastric discomfort were reported by parents during the weekly monitoring visits. In addition, tremors or signs of hyperthyroidism were not reported.

Acceptability: The DFS had a slightly darker colour compared to normal iodised salt. The difference in colour was only noticeable if the salts were compared, side by side. Over the eight-month study period 2.7% of the women in the DFS group reported a darkening of plantain when fried with DFS. The taste of the food to which the DFS was added did not change and the food remained acceptable.

DISCUSSION

In the current study, after eight months of intervention the prevalence of anaemia in women in the double-fortified salt group was not significantly different

than the control group. With regards to iodine deficiency, a significant reduction was found in all groups of women, with no significant difference among the groups. In children, anaemia prevalence decreased significantly in the double-fortified salt group over the eight-month intervention. Similar to their mothers, a significant decrease in iodine deficiency was found in both groups of children, with no significant difference between the groups.

Daily urinary excretion of iodine closely reflects iodine intake and has been used as a measure of iodine status (26). Using urinary iodine as the primary measure to define iodine deficiency, a significant reduction in iodine deficiency was observed in all groups of women and children. This suggests that the dextrin-coating present in the double-fortified salt did not interfere with the availability of iodine and that the iodine was absorbed in adequate amounts to reverse iodine deficiency in these population groups. Since dextrin is soluble in water or dilute acid, these results are not unexpected.

In the current study, both the double-fortified salt and iodised salt plus weekly iron supplement prevented non-anaemic women from becoming anaemic when compared to the iodised salt control group (iodised salt plus placebo). As weekly home visits were conducted to ensure compliance throughout the study, it is unlikely that this level of compliance would be seen in real life settings. In addition, for unknown reasons, baseline randomisation of the women in this study was unsuccessful. Indeed, the prevalence of anaemia at baseline was significantly lower in the control group when compared to the two other groups, but was similar for all three groups at the end

of the study. The significant increase in anaemia in the control group may have been a result of regression to the mean, rather than a true worsening of anaemia status. Thus, although suggestive, the data does not definitively show a protective effect against mild anaemia of the double fortified salt or the iodised salt plus weekly iron supplement when compared to the control.

Salt is an excellent vehicle for both iron and iodine fortification in settings where iron and iodine deficiencies co-exist. Observations made by the field workers during the study indicated that acceptance of the different salts was good. In addition, acceptability surveys revealed that in a few cases (2.7%) the double fortified salt had a slightly darker colour than iodised salt, which appeared to darken the plantains. It is noteworthy that in Ghana some cooking pots have been known to have the same effect on plantain and have posed no problem. In addition, a previous study on the same salt demonstrated no appreciable changes in the flavor or palatability of the meals when the salt was added (19). Therefore, the salt would most likely be well accepted if distributed on a large-scale in Ghana.

Previous reports suggest that the average Ghanaian adult consumes about 10 g of salt per day and that salt is widely used in this area of the world (19, 20, 27). Thus, on average, women would consume 10 mg of iron and 500 μ g of iodine per day from the double-fortified salt used in the current study. Ingestion of the salt would therefore provide about 55% of the recommended dietary allowance (RDA) for iron and about 330% of the RDA for iodine if 10 g of salt were consumed in a day (28). None of the general adverse side-effects (eg. nausea, vomiting and epigastric discomfort) occasionally reported by women using iron supplements were reported in this study (29). In addition, tremors or signs of hyperthyroidism (associated with high iodine consumption) were not reported. This suggests that, as a delivery system for both iron and iodine, double fortification of salt would be well accepted and effective. However, the community effectiveness of the double fortified salt in treating and preventing iodine deficiency and anaemia still needs to be determined.

As salt is added to the family pot during the cooking process, children would receive the lowest amount of salt since children, presumably, would eat a smaller amount of food (containing the salt) than adults in the household. Thus, given the positive outcomes

in the children, the results of the current study are quite encouraging considering the high prevalence of anaemia among young children found in Ghana as well as other African nations (50% of children were excluded based on their low haemoglobin concentrations at baseline in the current study). Since the prevalence of anaemia decreased significantly in the children receiving the double fortified salt, it could be assumed that enough salt was consumed and enough iron was absorbed to meet some of the demands for growth in the preschool-aged children in the study. However, the double fortified salt may not solve the problem of anaemia and iodine deficiency for the entire population. Indeed, infants and young children (6-24 months of age) are at particularly high risk for anaemia and iodine deficiency but do not consume salt in sufficient amounts for it to be an effective fortification vehicle. Thus, encouraging dietary diversification, supplementation and fortification programmes as well as parasite control strategies are all important components of the solution to control the problems of anaemia and iodine deficiencies in developing countries.

In conclusion, while the use of double-fortified salt prevented anaemia in women, it had a significant role in both the prevention and treatment of anaemia in children. With regards to iodine deficiency, both the double-fortified salt and iodised salt significantly reduced the prevalence in women and children to a similar degree. Subsequent to the research reported here, the MI and the University of Toronto, Canada have further refined the formulation by encapsulating ferrous fumarate instead of the iodine. This has facilitated the production of DFS in developing countries because the encapsulated iron premix can be easily blended with locally produced iodised salt without disruption to the existing salt industry practices. It is believed that the research reported here is relevant to understanding the efficacy of double fortified salt on the nutritional status of African populations. Further research is needed to investigate the efficacy and effectiveness of the salt double fortified with iron and iodine in different populations, climates and ecological conditions in anticipation of large-scale distribution.

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