Double Fortified Salt at Crossroads

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Abstract. Iron Deficiency Anemia (IDA) and Iodine Deficiency Disorders (IDD) are the major public health problems often co-existing in many regions in our country. National Institute of Nutrition (NIN) has promoted the technology of double fortification of common salt with iodine and iron as a strategy to control both deficiencies under food-based approaches. Two other formulations of double fortified salt (DFS) have been subsequently developed by other agencies. NIN formulation & Nutrisalt have a stabilizer/promoter to maintain the stability of iodine in the presence of iron. The Micronutrient Initiative (MI) formulation uses physical separation of iodine by microencapsulation. NIN carried out extensive studies on stability, bioavailability, acceptability, safety and impact (including in community) of DFS. Feasibility both at factory level production and community level implementation have been worked out. MI salt had also undergone stability, acceptability and impact studies. No data is reported on the stability of Nutrisalt except that good stability is claimed in the available reports. In principle, the strategy of double fortification of salt with iron and iodine is sound with uniformly good impact on urinary iodine excretion and prevention of anemia. However, striking increments in hemoglobin (Hb) were not readily demonstrated since the intended purpose of DFS was only to provide iron at maintenance level and not therapeutic level. Complexities in the experimental designs, confounding variables and quality of the ingredients in salts also contributed to difficulties in interpretation of Hb status in studies involving DFS. Along with improvements contemplated in formulation to enhance the stability and bioavailibility, DFS should be able to fulfil the promise and realise its potential in reducing iron and iodine deficiency amongst our poor population in the next few years. **[Indian J Pediatr 2002; 69 (7) : 617-623]**

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Iron Deficiency anemia (IDA) and Iodine Deficiency Disorders (IDD) are the two major micronutrient deficiencies of public health magnitude in India. National Goitre Control Programme and the National Nutritional Anemia Prophylaxis Programmes have been in operation for several decades for the prevention and control of these deficiencies in our country. About 270 million persons were estimated to be at risk of IDDs in India and no state in the country was believed to be free of IDDs in the early 1980s. With the intervention of a vigorous universal salt iodization policy since 1988 the goitre prevalence rates which were well over 20% in many states seem to have decreased close to 10%. On the other hand, about 2/3rds of children and women of child-bearing age, continue to be suffering from nutritional anemia.[1]

Several years ago, National Institute of Nutrition, Hyderabad (NIN) successfully demonstrated iron fortified common salt as a feasible and effective programme to deliver iron to the people. As IDA and IDDs co-exist in many regions, double fortification of salt (DFS) with both iodine and iron was later proposed by NIN to be a simple and inexpensive public health strategy to control iron and iodine deficiencies without a major change in the national health machinery. As per the Government of India policy, the goals set in this regard were, reduction of goitre prevalence to less than 10% and that of IDA in pregnant women to 25% by the year 2000. We do not seem to be anywhere near to achieving these goals, particularly with IDA, and therefore a change in alternative strategies are needed. Thus technology for double fortification of salt with iron and iodine has been successfully developed at NIN using a polyphosphate, sodium hexametaphosphate (SHMP) as a stabilizer.[2] Double fortification as a technology was not simple, as the physical and chemical conditions of the common salt are not conducive for the co-existence of the two micronutrients. While iron is stable in acidic medium, iodine is stable in alkaline conditions. In view of this, there is a need for a barrier to separate the two or a chemical stabilizer needs to be added for brining the nutrients together.[2-8]

The formulation developed by NIN has been tested for its stability, bioavailability, acceptability and impact.[2-4,9-14] Along with these developments propelled by NIN, two other formulations of DFS have also been reported, under the sponsorship of Micronutrient Initiative (MI), Canada, technology for formulation of a DFS in which iodine is encapsulated, to physically separate from the iron source, the ferrous fumarate, has been developed at the University of Toronto, Canada. Reports on the stability, acceptability and impact of this preparation have been

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TABLE 1. Comparative Features of Different Formulations of DFS

Features/Characteristics	NIN Formulation	MI Formulation	Nutrisalt
I. CHEMICAL FORMULATION			
a) Iodine (ppm) source	30-40 KIO3 or KI[2]	50 KI-potassium iodide	a) *30, Potassium iodate*
b) Iron (ppm), source	1000, Ferrous sulphate	1000, Ferrous fumarate	b) 1000, Iron salt
c) Stabilization of iodine	SHMP	Encapsulation of iodine by dextran	c) Stabilizer and promoter
II LABORATORY STUDIES			
1. Stability/salt quality	Stable upto 9 months with the salt commercially used for iodization[2-4]	Stable for 12 months. Obviously used refined salt.	Data not provided.Published reports claim good stability as vouched by the manufacturer. Salt quality not indicated.
2. Acceptability	Fullfledged acceptability/ organoleptic properties described. No colour or smell. Good acceptability	Develops slight yellow or brown colour with time. Found less acceptable with some foods in all populations studied compared to local salt.	Reports claim acceptability and stability during cooking. No data providing.
3. Bioavailability	Bioavalability of iron and iodine demonstrated in both rats and adult male volunteers. Mean absorption with rice based diet in humans was 6.1% and not different from only iron containing salt. Urinary iodine (μg/24 hr) increased from initial 174 to 181 on 2nd day and not different from iodized salt group.[2]	Bioavailability of iron and iodine demonstrated in rats and adults male and female volunteers.[5,6] Human data: Iron meal 13.5% absorption and inhibition meal 4.0% Urinary iodine equal to those receiving iodized salt.	Not reported
4. Production	Large scale production[13]	Not tested	Not known
III. OPERATIONAL STUDIES			
Feasibility study in community	Two studies confirming the feasibility[3,10]	Two studies confirming the [5] feasibility	One study confirming the feasibility.
Bio Impact 1. Study population	*Study 1* : Tribal village population (AP) *Study 2*: Residential school children, Hyderabad	Mothers and Childrens in Ghana	Tea estate labourers, Valpari, South India.
2. Design	*Study 1*: Single blind placebo controlled *Study 2:* Double blind placebo controlled	Double blind placebo controlled	Double blind placebo controlled.
3. De-worm treatment	No treatment	No treatment	Simultaneously de-wormed
4. Characteristics of beneficiaries	*Study 1:* Tribal population[10] covering pre-adolescent and adolescent boys and girls, and pregnant and lactating women (free living) *Study 2* : School children (captive)[3,4,9]	Mothers and the youngest child above 1 year of age, (free living)	Adults living in high altutude around 2500 meters above the sea level. Captive population

TABLE 1. *Continued*

Features/Characteristics	NIN Formulation	MI Formulation	Nutrisalt
5. Criteria of inclusion	All excluding criticallly ill.	Those having hemoglobin more than 10 g	Only permanently
6. Period of supplement	Two years in both the studies	Eight months	One Year
7. Supply of salt	*Study 1:* Private salt supplier and NIN local supervision. One kg packets placed in 100 kg HDPE bags for tribal study *Study 2:* Manufactured and supplied by a state government enterprise in Chennai placed a HDPE bags containing 50 kg (bulk supply)-Residential school study	Details not provided Supplies provided by the Agency, University of Toronto,Canada & MI	One kg bags in 50 kg HDPE bags. Supplies provided by the Company owning the salt formulation
8. Stability of iodine in programatic conditions	Done	Done	Data not given
9. Impact on iron and iodine status	*Study 1:* Goitre prevalence[4,10] decreased and urinary iodine improved. Gain in Hb. in some groups of the tribals. *Study 2:* Benefited residential[3,4,9] school children both in iron status and iodine status.	Maintain good iodine levels in both children and mothers. Children showed small reduction in prevalence with DFS while the prevalence of anemia increased in controls. Mothers too showed improvement with DFS, though the anemia prevalence at baseline was not comparable to control.	Benefited only in females[7]. De-worming is an important requisite.
IV. Cost	Worked out	Worked out	Rs.4.50/kg
V. Productivity	Not worked out	Not worked out	Measured plucking of tea leaves[7]
VI. Safety issues,, if any, due to components.	Safety of SHMP evaluated[9-12] in rats as well as in children	Perhaps issues are not involved	Not known, if any safety issues are involved.

published earlier.[5,6] Yet another DFS under the trade name 'Nutrisalt' produced by a private enterprise, M/s. Sunder Nutritions Pvt. Ltd. 6 G Century Plaza, 560-562 Mount Road, Chennai-18, India, with a stabilizer is also claimed to be effective.[7,8] A report on the feasibility and impact of this formulation too, has been published recently.[8] In view of the fragile nature of interactions between the two nutrients in the medium of salt, the stability of the DFS and therefore its impact on Hb and iodine status using different formulations is a subject matter of intense interest to scientists, policy makers and public. A brief account of the comparative features of the technology and the bioresponse of these formulations is provided in Table 1. The present review attempts to highlight the salient features of each of the formulations and progress of efforts made to evolve a suitable programme.

FORMULATION: STABILITY

While the salt formulations from NIN and MI have the back up of full laboratory data on stability, absorption and organoleptic evaluation, there is no such data reported on Nutrisalt. Iron content is always stable in salt. However, it could produce colour due to oxidation either during storage or preparation of some foods. Iodine in salt can be labile depending on the conditions. The MI formulation appears to be very stable, but developed mild unacceptable colour in some recipes. It was less acceptable than the conventional salts in different recipes tested in Ghana, Gautemala and Bangladesh.[6] The NIN formulation is very good and had acceptable organoleptic properties. The iodine content is stable upto 6 months.[2,3] In some situations as in residential school study, the iodine content was lower when the quality of salt used for preparing the DFS was not appropriate and the urinary iodine reflected such deterioration in iodine.[3,9] The second factor was that when the supply of DFS is in bulk quantity of 50 kg, the variations are large and the iodine stability was poor as compared to the supplies in 1 kg packets. However, in no situation the salt produced undesirable colour or taste, even when produced in large bulk quantities.[3,4,9,10]

The University of Toronto formulation is obviously based on a refined salt (as no other form of salt is

TABLE 2. Impact of DFS on Iodine Status

Study Group		Goitre prevalence		Median Urinary iodine µg/L			
				Tribal study		Residential school children	
		Initial (%)	Final (%)	Initial	Final	Initial	Final
NIN	IS (Control)	26	16.1	59 (89)	160 (92)*	70 (85)	452 (75)
Study	DFS	28	14.0	116 (104)	155 (67)*	68 (91)	108 (76)

% Prevalence in Urinary Exretion of I

Study Group		Mothers (<1000 µg/L)		Children (<100 µg/L)	
		Initial(%)	Final(%)	Initial(%)	Final(%)
MI	IS (Control)	74.1 (58)	19.0	74.6 (59)	23.7
Study	DFS	68.8 (61)	16.4	87.0 (23)	43.0

Figures in parenthesis indicate sample size
*significantly different from initial

TABLE 3. Estimated Response Time for Obtaining in Increase of 1g of Hemoglobin/dl of Blood Though DFS

1. CONTRIBUTION OF IRON FROM DFS	
Assuming a consumption of 10 g of DFS/day @ 1.0 mg iron/g salt	10 mg iron/day
Considering the intestinal absorption of 3%	available iron is 0.3 mg/day
Over a period of one month the amount absorbed	9 mg iron
2. BLOOD POOL OF HEMOGLOBIN IN THE BODY	
Adult weight	60 kg
Blood volume (10%)	6L
Total Hb to be produced in 6L @ 1 g Hb/dL	60 g
Total amount of iron in 60 g of Hb @ 3.4 mg iron/g Hb	204 mg
3. TIME PERIOD REQUIRED TO INCREASE THE Hb LEVEL BY 1g	
Period for acquiring 204 mg of iron @ 9 mg/month	23 months
Period for increasing of 1g Hb/dL	Approx. 2 years

available) and detailed characteristics of salt have not been described.[6] Similarly the quality of salt used for the preparation of Nutrisalt is not given and no data is reported on the bioavailability of iron and iodine from it.[7,8] In general, the presence of magnesium chloride is deleterious to the stability of iodine in DFS.[6]

All the three studies that are conducted on the effect of DFS on iodine status, have demonstrated a clear improvement in urinary iodine excretion and in one study even on goitre prevalence (Table 2)[3,6,9,10]

Before seriously considering the pros and cons of the impact of DFS on hemoglobin level, it should be noted that the purpose of fortification of salt with micronutrients is prevention of their deficiencies rather than to obtain therapeutic benefits. With the rationale provided in Table 3, about 1g increment in hemoglobin can be obtained with the intervention of DFS only after consumption over a two-year period. Therefore, achieving absolute increments in hemoglobin is more difficult than positive shifts in prevalence of anemia and problems could arise in the interpretation of results obtained on hemoglobin status. It is generally assumed that the iron status of the population, by implication hemoglobin level, is relatively constant over time and the intervention brings about a marked change. However, in many intervention trials this was not found to be true and placebo control groups, on and off, show either an inexplicable decline or increase in hemoglobin levels, posing difficulties of intervention.

The second problem is that randomization of the groups is not completely successful resulting in significant differences in Hb values in between placebo and test groups at the beginning of the study. Many investigators are not familiar that initial Hb levels could be negatively correlated with the increments during recovery. Such data have to be corrected for the differences in the initial values by analysis of co-variance to obtain meaningful conclusions. NIN data after such corrections showed a significant improvement in DFS group.[3,4,9,14]

Scrutiny of results from different DFS studies reveals operation of all such above discrepancies in the final interpretation (Tables 4-6). Studies (NIN) carried out in tribal population, exhibited variable response in hemoglobin in different age and sex groups supplemented with DFS.[3,4,8,10,14] While the increase was significant and positive in males belonging to 14-17 years age group receiving DFS and lactating women, there was no change in females 14-17 year age groups and pregnant women and in the remaining groups 1-5, 6-13 (boys and girls) years. There was a significant increase even in controls and the interpretation of results was difficult (Table 4). A similar situation is also evident in the other two studies.

In the MI study the prevalence of anemia in the mothers was marginally improved by 3.3% with DFS compared to a significant increase by 15.5% in the prevalence of anemia in the controls. The results were not convincing and conclusive as the basal level of anemia in the control group was only 17% as against 35% in the other groups. The data in children was more conclusive with DFS producing a significant decrease in the

TABLE 4. Impact of DFS on Hemoglobin (g/dL) Status (NIN Studies)

Study Group		Children of Different age groups 1-5, 6-13 Boys and Girls	14-17 Years Girls & Pregnant Women	14-17 Years (Boys)		Lactating Women	
Tribal Studies	IS (Control) DFS	Final values are significantly higher than initial values in both control and DFS groups	No significant changes in final values both in control and DFS groups.	Initial	Final	Inital	Final
	IS (Control)			12.4	12.6	10.7	10.9*
	DFS			12.2	13.7*	10.4	10.9*

Study Group		Male		Female		Total		
		Initial	Final	Initial	Final	Initial	Final	% Change
Residential School Children	IS (Control)	11.7	11.6	12.0	10.1	11.9±1.61	10.7*±2.10	-1.1±1.94
	DFS	12.6	12.8	12.0	11.6	12.2±1.55	11.8*±1.98	-0.42**±1.77

*significantly different from intial
**compared to IS

TABLE 5. MI Studies % Prevalence of Anemia (Hb < 12 g/dL)

Control	Mothers (Hb < 12 g/dl)				Children (Hb < 11 g/dl)			
	N	initial	final	% change	N	initial	final	% change
IS	58	18.5	34.0	+15.5	59	53.9	59.0	+5.1
DFS	61	34.0*	37.3	+3.3	23	55.7	34.0	-21.7*

*Initial not comparable

prevalence of anemia by about 22% as against an increase of 5% in the control group and the anemia prevalence at baseline was comparable (53-54%). However, the number of children in these studies were small (Table 5).[6]

In the third study, too, the problems of interpretation arose because of four factors.[8] As a matter of principle in subjects having a mean (± SD) initial hemoglobin of 9.56± 1.74 (males) and 8.48±2.00 (females), there exists a sizeable segment of severely anemic adults who should receive therapeutic supplementation but not regeneration of Hb through fortified salt. As the author confirms a large proportion of the study population suffers from hookworm infestation causing severe anemia, doubts arise as to the suitability of the population to test the impact of DFS (Table 6A). There was no significant difference in the hemoglobin levels due to DFS in non-dewormed sub-group and the effect was only found in the de-wormed individuals. This was confirmed by productivity reflected by the quantity of tea leaves plucked/day not being influenced by the iron component of the salt. It was only the combined effect of de-worming and salt with iron that had raised the productivity in one group (1.1 kg/day) (Table 6B). The third variable which gives rise to a problem of interpretation is the mean increase in the hemoglobin level was significantly higher in the experimental group (1.28 g/dL) compared to the control groups (0.77 g/dL), and it was concluded by the authors that the DFS has improved the hemoglobin status (Table 6A). This conclusion is not justified as the authors agreed that initial hemoglobin level of the control group 9.2 vs experimental 8.9 g/dL are not comparable and the initial hemoglobin levels were earlier shown to have negative relationship with increments in NIN residential school study.[3,4] The fourth factor is that the Nutrisalt study was conducted in adults who were permanently living in high altitude. It is very well known that populations living in high altitudes have different levels of affinity of hemoglobin to oxygen and the therapeutic response to treatment may not be similar, particularly when additional factors like de-worming are interacting with the consumption of DFS.

The Nutrisalt study is the only study which attempted cost benefit analysis of intervention with DFS (Table 6B).[8] There are two difficulties in the interpretation of these results, one is error of calculation which can be corrected, the other is the error of interpretation due to the variations in response based on the initial values as described earlier. While the total cost for salt were calculated for 450 beneficiaries consuming on an average 10g/salt/day for one year @ Rs.4.50/kg works out to Rs.7290/year, this cost was compared with the benefits in terms of enhanced work output calculated for 1000 subjects as 330 tonnes (@ 1.1 kg/day of increased output of tea leaves in DFS group over 250 days in a year). In addition when the benefit was demonstrated by a combination of DFS and deworming, the cost of DFS only was included and not the cost of deworming. On the contrary, according to their own data, if DFS was consumed by the non-dewormed people, there was a drop of 0.9 kg/day in tea leaves output.

If all the variables are taken into account, there are mainly two studies in children which confirm the beneficial effects of DFS in preventing anemia and improving the urinary excretion of iodine. In one study (NIN) a significant proportion of children (preadolescent) receiving DFS showed lesser percentage of anemia compared to the controls. These observations were duplicated in the MI study carried out in children (under

TABLE 6. Nutrisalt Study

A. Mean Hemoglobin (Hb) Values (g/dL) In Different Groups

Group	Total Group								
	Male			Female					
	N	initial	final	N	initial	final	initial	final	% change
is control	158	9.7	10.3	250	8.9	9.7	9.22	9.99	0.77
DFS	155	9.6	10.4	230	8.5	11.0	8.91	10.1*	1.27*

B. Mean (Hb) Values and Productivity of Tea Leaves

Salt	Non-Dewormed Group			Dewormed Group			Significance of Variables on Hb and productivity
	Hb (g/dL)		Productivity	Hb (g/dL)		Productivity	
	initial	final	(kg/day)	Initial	Final	(kg/day)	
IS (control)	9.30	9.95	24.2	9.1	10.0	25.1	1. deworing not significant 2. Effect of iron not significant
DFS	8.96	10.0	23.3	8.9	10.4	26.2	3. Interaction, effect of both iron and deworming significant on both Hb status and productivity

2 years) from Ghana. The NIN salt formulation has also been found to be absolutely safe both from experimental and clinical studies[11,12] and large scale factory production has been demonstrated.[13]

While drawing firm positive conclusions about the impact of DFS, circumspection points that the impact of DFS is not as readily demonstrated as with other interventions like iron supplementation or iron fortified salt on Hb status. It is worth looking into the possible counteracting effect the presence of iodine has on utilization of iron from DFS. Unless we ensure the quality and the chemical purity of the ingredients, the stability of iodine in DFS can be at risk. It is, therefore, logical to conclude that the basic philosophy of double fortification of salt with iron and iodine is sound. Uncertainties regarding the components used in fortification have to be removed and the methodology that is employed for evaluation has to be more rigorous than in other investigations. On the other hand, it is important to improve the technology further and present a formulation which could withstand the fluctuations in the quality of supplies. It is heartening to note that both NIN and MI have charted such a course of action and the day may not be too far when an ideal double fortified salt could bring us closer to eliminating iodine deficiency and reducing iron deficiency from amongst the poor populations.

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