NFI BULLETIN

Bulletin of the Nutrition Foundation of India

Volume 40 Number 2

April 2019

Contextualizing the principles of iron fortification of foods in India

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Introduction

Iron is a vital nutrient for life. It participates in many essential functions in humans like transporting oxygen via haemoglobin to all tissues. Increased demand for iron during child growth, pregnancy and increased loss during reproductive phase in women and adolescents makes them vulnerable to iron deficiency. Habitual intake of diet low in iron and poor bioavailability further aggravates the condition especially in vulnerable segments of the population. The relatively high iron loss combined with dietary inadequacies makes it difficult for Indian women to meet iron requirements, especially during pregnancy. Pregnancy depletes iron stores in order to meet the cost of iron in pregnancy (close to one gram), and replenishment of stores after pregnancy takes a long time. Strategies aimed at correcting iron deficiency should be evidence based and enable vulnerable segments of the population to build adequate iron store to sustain normal haemoglobin status.

Iron stores in vulnerable segments

Physiologically, the sequence of events leading to iron deficiency anaemia (IDA) starts from iron depletion from stores followed by a decrease in transport iron to functional compartments and finally reduced haemoglobin synthesis. This can be assessed by assessing serum ferritin and a value < 12-15 µg/L reflects the first stage of iron depletion which is defined as a condition in which there are no mobilizable iron stores and in which signs of a compromised supply of iron to tissues, including the erythron, are noted. More sustained negative iron balance leads to iron deficiency, lower Hb and iron deficiency anaemia (IDA). Therefore, establishing iron stores is an essential pre-requisite for maintaining haemoglobin and for prevention and correction of IDA. The sequential biological processes provide adequate lag period (as iron stores are always mobilized first to meet increased demand) to intervene and restore positive iron balance throughout the critical phases of childhood and adolescent growth and development and during pregnancy.

Scientific rationale of strategies for prevention and correction of IDA

The main strategies recommended to prevent and correct IDA are:

- improved food consumption and dietary practices,
- food fortification,
- iron supplementation, and
- other public health interventions such as treatment of malaria and hookworm infestations.

Since different stages of iron deficiency exist in a population it is logical to introduce all these interventions simultaneously. However, there is very little data on the impact of comprehensive interventions on iron status and IDA in target groups accessing these interventions.

Iron supplementation programs (both prophylactic and therapeutic) target prevention and reduction in anaemia and are considered as a short term measure[1]. Regular intake of iron supplements are expected to replenish iron stores and restore normal haemoglobin. Introduction of foods fortified with iron, which is considered as a medium term strategy, is a preventive strategy to complement supplementation[2]; if they are introduced in tandem, they are expected to sustain both iron stores and haemoglobin levels. Dietary diversification is a preventive strategy and is a part of comprehensive interventions; but it can function as a standalone strategy only when iron deficiency has been eliminated in the population. The three strategies of dietary diversification, food fortification and supplementation will be effective when combined with functional public health measures which are in place and are implemented well.

The evidence base for introduction of iron supplementation (Table 1)[3-6] and fortification (Table 2)[7-14] are available as systematic reviews and meta-analysis. However, their contextual translational evidence

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base is elusive and hard to produce. This article attempts to consolidate all systematic reviews and meta-analysis and to contextualize their implications in setting country specific iron fortification. Also an attempt has been made to compute the risk of excess iron over Tolerable Upper Limits among 16-17 year old individuals under the existing national programme (WIFS) and concurrent implementation of food fortification (Table 3).

Review of iron supplementation

Due to the increased demand during growth, there is a gradual decline in iron stores as the age advances. Compilation of studies carried out in Indian children under the age of 15 years have shown that by the age of 13-15 years iron stores (serum ferritin 25 μg/L in 2-5 yr olds; 21 μg/L in 6-13 yr olds and 12 μg/L in 13-15 yr olds) get completely depleted[15]. Majority of Indian women enter adult life with negative iron balance and are at risk of developing IDA. In the Intensified National Iron Plus Initiative (I-NIPI) the iron supplementation program has been designed using life cycle approach[16]; if implemented effectively this has enormous potential to reduce IDA.

The review of evidence on daily iron supplementation especially in women aged 13-45 yrs have shown high quality evidence for haemoglobin (mean difference Hb 0.53 g/dL) and moderate quality evidence for reduced risk of being iron deficient (RR 0.62) Table 1[6]. These results signify that iron supplementation for short period (3 months) can replenish iron stores and normalize hemoglobin[3]. Iron stores have a prominent function in regulating the rate of absorption.

The scientific rationale of implementation of intermittent or weekly iron folic acid supplementation (WIFS) programme is to prevent anaemia in non-anaemic persons, reduce anaemia and improve iron stores in persons with IDA. However, the quality of evidence base regarding the impact of this strategy ranged from moderate quality evidence for improved Hb-mean difference (MD) of 0.519 g/dL to very low in anaemia risk reduction and in improving ferritin (Table 1)[5]. This may be due to the poor implementation of the programme among participants with high prevalence of anaemia.

Review of iron fortification

Fortification is potentially an effective strategy but evidence for positive impact on IDA from the developing world is scarce. The WHO drew up Guidelines for food fortification which included fortification with iron[2]. Many research studies were undertaken globally on food fortification with iron. There are a total of eight such reviews in literature; three are with multiple vehicles and two on wheat flour and one each related to rice, salt and bio-fortified crops (Table 2)[7-14]. The trials with multiple vehicles and rice and salt have shown an increase in Hb in the range of 0.20-0.64 g/dL; with wheat flour fortification the evidence for reducing iron deficiency among women in reproductive age (WRA) is consistent but on reducing anaemia is limited.

Multiple vehicles: The three reviews wherein multiple vehicles[7-9] and various iron sources including electrolytic iron have been used concluded that consumption of iron fortified foods results in:

- Improvement in weighted mean difference(WMD) in Hb of 0.42 g/dL, increase in serum ferritin of 1.37 μg/L and reduced risk of being anaemic and iron deficient in children[7];
- Improvement in standardized mean difference (SMD) in Hb of 0.55 and 0.64 g/dL, serum ferritin of 0.91 and 0.41μg/L and reduced risk of being anaemic RR 0.55 and 0.68 in children <15 years and WRA, respectively[8];
- Improvement in WMD in Hb of 0.51 g/dL in children <10 years[9].

Wheat flour: The two reviews[10,11] looked at the effectiveness of iron fortification of wheat flour and the conclusions are:

- Reduced prevalence of low ferritin among WRA but impact in terms of reducing prevalence of anaemia is limited in studies

Table-1: Summary of systematic reviews and meta-analysis on iron supplementation

Reference	No of studies	Design	Target group, Supplement and duration	Conclusions
Yakoob and Bhutta (2011)[4]	14 studies on anemia in pregnancy	Daily iron versus no intervention/ placebo	Pregnancy IFA 7 studies on IDA at term	There was a statistically significant 73% reduction in anemia at term (RR = 0.27; 67% reduction in IDA RR0.33
Low et al 2016[6]	67 trials 2 from India	Daily Efficacy 4444 intervention arm, 4064 control arm	Women 13-45 yrs Ferrous sulphate/fumarate/ carbonate/ gluconate/succinate/ glycine sulphate/ sodium citrate Ferric pyro phosphate/ammonium citrate/amino acid chelate Iron polystyrene sulfonate Dose 1-300 mg iron/day Duration 1-24 weeks	High quality of evidence Hb MD 05.53 gms/dl Moderate quality of evidence for anaemia (RR 0.39) and iron deficiency (RR 0.62)
Cembranel et al 2013[5]	13 studies	Daily Effectiveness 4444 intervention arm, 4064 control arm	Women 13-45 yrs Ferrous sulphate Ferric pyro phosphate/ammonium citrate/amino acid chelate Iron polystyrene sulfonate Dose 1-300 mg iron/day Duration 1-24 weeks	Daily was more effective than weekly doses in improving haemoglobin levels (pooled effect Hb 0.56 vs 0.28gms/dl) No decrease in prevalence of anaemia even with daily doses Moderate quality of evidence for anaemia (RR 0.39) and iron deficiency (RR 0.62)
Fernández-Gaxiola, 2019[3]	25 studies involving 10,996	Intermittent	Adolescent and adult menstruating women; Hb 15 studies, 2886; ferritin 7 studies, 1067; risk for anaemia 11 studies, 3135and 3 studies 624 participants	Moderate quality of evidence improved Hb MD 0.519gms/dl Low quality of evidence for reduced risk of having anaemia (RR 0.65) and ferritin MD 7.46 μg/L and risk of having iron deficiency (RR 0.5)

which followed WHO guidelines and used electrolytic iron[10].

- Based on the odds ratio of prevalence of anaemia among WRA (RR fortified 0.976 vs 0.999 not fortified), each year of flour fortification was associated with a 2.4% decrease in odds ratio of anaemia[11].

Eighty one countries have made fortification of wheat flour alone or in combination with maize flour mandatory. Among these the evidence for reducing iron deficiency among WRA is consistent but on reducing anaemia is limited[11]. This review looked at the implementation of WHO flour fortification recommendations with respect to iron compounds, the dosage and outcomes. Only 2 studies satisfied WHO recommendations with respect to the iron source (electrolytic iron) and concentration (60 mg/kg). There are no studies that evaluated the impact of fortifying high extraction wheat flour with NaFeEDTA, which is the WHO recommended iron source for fortification of atta[2].

Rice: The technology for fortification of rice using extruded rice kernel is relatively new (first study in 2008). The systematic review included 5 RCTs from India and all of them are among children <15 year and used MDM platform. The conclusions of the study are that there was Hb improvement of 0.2 g/dL and about 35% reduction in iron deficiency but no change in risk of anaemia in general population[12].

Salt: About 50% of the studies on impact of fortified salt were carried out in India with 3 types of technologies ($FeSO_4$, encapsulated ferrous fumarate and ferric pyrophosphate)[13]. The conclusions of the study are:

- improvement in SMD of Hb of 0.44 g/dL and ferritin 0.62µg/L,
- anaemia risk reduction ratio of 0.16 and IDA 0.20.

Iron bio-fortified crops

Three types of bio-fortified iron staple foods, rice, pearl millet and bean were developed and they have undergone RCTs in their respective countries of origin. In India a pearl millet variety known[14] as Dhanashakti was introduced in the state of Maharashtra. The study among 12-16 year adolescent girls consuming 200-300 g of pearl millet during lunch and dinner as Bhakri for 4 months revealed the following:

- there was no difference in Hb
- ferritin increased significantly and
- positive impact on cognitive function.

Iron deficiency anaemia: control measures in India

Diet surveys among the rural and urban Indian populations[17] have shown that the habitual intake of iron ranged from 30-70% of ICMR-RDA. Inadequacy of iron is estimated by assessing the difference between habitual iron intake and the RDA; the magnitude of inadequacy varies with age, gender and physiological status. The deficit ranges from 1.6 mg (RDA 17 mg) in adult man to 21.3 mg (RDA 35 mg) in pregnant woman[17]. It is obvious that satisfying a dietary deficit of iron for pregnant women through fortification is not possible; fortified foods should bridge the gap between intake and RDA in all other groups except pregnant women.

The I-NIPI[16] has introduced multi-pronged strategies to bridge the gap between in iron intake and iron requirement. These include iron supplementation programme on a life cycle mode and fortification

Table-2: Summary of reviews, systematic reviews and meta-analysis on iron fortification

Study	No of Studies	Target group	Vehicle	Source of iron	Impact
Gera et al, 2012[7]	60 RCTs: Fe group 11, 750 and control group 9077	70% children and remaining adults	Multiple	ferrous sulphate -28% ;NaFeEDTA -20%; electrolytic iron-13%; ferric pyrophosphate-8%;ferrous fumarate -7%; other sources- 3%	Hb 0.42 g/dL; serum ferritin 1.37 µg/L; reduced risk of anaemia RR 0.59;iron deficient RR 0.48
Das et al , 2013[8]	41 studies 22 UMIC and HIC; 18 LMIC and LIC	43% Infants, preschool and school age; 31% WRA and pregnant women	Multiple	FeSO4-15 NaFeEDTA -7 Other sources	Pooled analysis Infants and pre-school and school age (WRA)- SMD: Hb-0.55(0.64) g/dL, serum ferritin: 0.91 (0.41)µg/L; Anaemia-RR 0.55 (0.68)
Athe et al, (2013)[9]	8 studies 5142 children	children less than 10 years	Multiple	Iron levels 3.5 g to 12.7 mg FeSO4-6, ferrous fumarate -4; NaFeEDTA -3, ferrous bis glycinate-2. other salts-1	WMD Hb- 0.51 g/dL
Pachon et al(2015)[10]	Effectiveness study 13 studies widely implemented for more than a year	Children <15 y (N=14); WRA (N=12)	wheat flour	WHO recommended source for 8 of 13 studies 2 studies met both source and level electrolytic iron and 60 mg/kg	Reducing prevalence of low ferritin among WRA but impact of reducing prevalence of anaemia is limited
Barkley et al (2015)[11]	12 countries with pre post -fortification anaemia prevalence and 20 countries that never fortified	Anaemia trends in non-pregnant women	Wheat -10 Wheat and maize-2	6 Combinations Fe+ B1+B2+B3+B9 in 5 countries Fe+ B1+B2+B3+B9+Zn in 2 countries Fe+ B1+B2+B3+B9+B12 in 2 countries Fe+B9 in 1 country Fe+B9+Zn in 1 country Fe+Vitamin A in 1 country	Odds ratio of prevalence of anaemia in fortified 0.976 vs 0.999 did not fortify. Adjusting for HDI and malaria each year of flour fortification associated with a 2.4% decreased odds ratio of anaemia
WHO (2018)[12]	12 RCTS 5 from India	10 Children <15 yrs 2 non pregnant non lactating women	Rice	6 studies with iron only micronized ferric pyrophosphate 10 studies Zn, vitamin A and folic acid 5 studies provided B-complex vitamins.	Hb0.2 g/dL 35% reduction in iron deficiency No change in Risk of anaemia in general population
Yadav et al (2019)[13]	10 RCTS 50% studies in India	Participants DFS 1620; IS1591 70% children < 15 yr	Salt	FeSO4 Ferrous fumarate Ferric pyrophosphate	Pooled estimate Hb 0.44 g/dL Anaemia risk reduction 0.16 RRR IDA 0.20 SMD ferritin 0.62µg/L
Finkelstein et al (2015)[14]	3 RCTs (rice, pearl millet and bean) 1RCT with pearl millet in India N-122 and 124 4 months	Pearl millet study in India Adolescent girls12-16 yrs consuming 200-300 g	Bio-fortified	86 mg/Kg iron in bio-fortified vs 21-52 mg/kg iron in conventional	No impact on Hb and a positive impact on serum ferritin Can improve cognitive function

SDM Standardized Mean Difference; WRA women of reproductive age; numbers represent number of studies/subjects of multiple foods and bio-fortification. These interventions are being operationalised. Data from research studies will provide useful leads to assess the relative contribution of each of these interventions in correcting anaemia, improving haemoglobin and building up iron stores.

As multiple programmes provide iron, it is important to compute total iron intake from all sources and assess whether it is within the tolerable upper limits (TUL) of iron or not and inform the policy makers and programme officers so that they can appropriately modify the programmes and achieve the target of an annual reduction in anaemia prevalence of 3% envisaged in the Anemia Mukt Bharat[16].

Currently the following strategies are being implemented under I-NIPI[16]:

- Daily and weekly iron supplementation (WIFS) to school children which contributes to 60mg iron/daily or weekly
- Double fortified salt-Iron fortified Iodized salt (providing about 10 mg of iron/day)
- Iron, folic acid and vitamin B12 fortified wheat flour
- Iron, folic acid and vitamin B12 fortified rice

Among the above strategies, WIFS is a standalone program and is a preventive strategy for the non-anaemic population. It has a wider coverage among vulnerable segments of the population. The quality of evidence for WIFS has been reported to vary from very low to moderate[3]. It may work better in populations who have adequate iron store.

Computation of total iron intake

Operationalization of WIFS as part of I-NIPI and concurrent implementation of ICDS and MDM hot cooked food with DFS and iron fortified staple foods will have an additive effect on intake of iron. The combined total daily intake of iron may reach levels above the recommended dietary allowance (RDA) and tolerable upper limits (TUL). Based on the contribution of iron from habitual diets of 8 mg/1000 K Cal and from individual intervention at the current level of fortification, the total iron intake per day among adolescent girls (consuming 350 g of staple food) is about 46 mg/day, which is higher than the RDA of 26 mg and the TUL of 45 mg (Table 3).

Table 3: Computation of risk of excess iron over Tolerable Upper Limits among 16-17 years girls

Source	Intake	Contribution Iron (mg/day)
Habitual diet gms/day[17]	350 g Cereals	13.5*
Bio-fortified Pearl millet gms/day[14]	350@71 mg/kg	24**
Iron fortified iodized salt (DFS)gms/day	10gms	10
Fortified wheat flour/rice gsm/day	350gms @ 40 mg iron/kg	14
Supplementation	Weekly supplementation 400µg folic acid +60 mg iron	8.5
Total intake		46(43)
ICMR-RDA		26
Tolerable Upper Limit		45

Recently, the estimated average intake (EAR) of iron was computed to be 15 mg for WRA in India. Using this EAR the estimated risk of dietary iron inadequacy has decreased substantially[18]. Further it was reported that in 6 states the intake exceeds the TUL in about 20-54% of the WRA when salt fortification delivering 10 mg and 14 mg from supplement (100 mg WIFS) were considered. These estimates suggest that cumulative intake of iron through fortification of multiple products (cereals and salt) can be higher than the RDA and there should be utmost caution in allowing fortification with iron in processed commodities or other food groups.

Introduction of iron fortified salt, wheat and rice in India

Currently, in India wheat, rice and salt have been recommended as vehicles for iron fortification. The levels of iron for wheat and rice fortification is similar and permit additions ranging from a minimum of 33 % to a maximum of 100% of Indian RDA of 17 mg (RDA adult man). The National Institute of Nutrition had developed a technology for fortification of salt with iron and extensively tested its safety and efficacy. A guideline on iron fortified salt and standards was in place in India (PFA) even before the staple food fortification guidelines for wheat and rice came into existence in the country. Since iron intake parallels salt and calorie intake, physically active men who need iron least will take in the most and therefore iron fortification standards have been fixed based on this. Fortification standards were formulated to provide one milligram of iron (and 15 µg of iodine) per gram of salt which provides about 30-60% of RDA of 17 mg of an adult man consuming 5 -10 g salt per day (FSSAI)[19]. Fortification of salt with iron is preferred because:

- unlike fortification of cereals, salt fortification requires only a relatively small volume of the food stuff to be fortified
- Salt consumption is regulated by taste and it is difficult to have too low or too high consumption of salt.
- Currently iodisation of salt is nearly universal and using this platform it will be possible to scale up production, distribution and marketing of DFS.

Conclusion

In India iron fortification is not a standalone strategy to correct iron deficiency. There is a need to improve dietary diversification especially consumption of vitamin C rich fruits along with meals so that iron bioavailability is improved. Based on the available evidence it appears that by optimising the technology of production of fortified foods, ensuring access to fortified food and effective implementation of I-NIPI strategies it will be possible to reduce anaemia; this will enable the country to achieve the targets of POSHAN Abhiyan and World Health Assembly target of 50% reduction of anaemia in WRA by 2025.

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Wheat Flour Fortification With Folic Acid

Prema Ramachandran

Introduction

Folate is a water-soluble vitamin belonging to the B-complex group. Most naturally occurring folates, known as food folates, are pteroylpolyglutamates; bio-availability of food folates is about 50%. Folic acid is the oxidised, stable and metabolically active form of folate. Folic acid functions as a co-enzyme in single-carbon transfers in the metabolism of amino acids and nucleic acids. Folate deficiency is defined as a serum folate concentration <7nmol/L (~3 ng/mL) or a red blood cell folate concentration <315 nmol/L (~140 ng/mL). Synthetic folic acid is used in the preparation of vitamin supplements and fortified food products because of its stability.

Relationship between folic acid deficiency and neural tube defects

Global research studies five decades ago had shown that folic acid deficiency is associated with adverse obstetric outcomes such as an increase in incidence of abortions, placental abruptions, foetal malformations (including neural tube defects) and intra-uterine growth retardation[1-2]. Neural tube defects (NTD) occur when part of the neural tube, which later develops into spinal cord and brain, does not close. Closing normally happens around 24 days after conception. Two common serious NTDs are spina bifida and anencephaly. All infants with anencephaly are stillborn or die shortly after birth; majority of those with spina bifida survive, with lifelong disabilities including paralysis, bowel and bladder incontinence, and other physical handicaps that require lifelong extensive medical, surgical, and nursing care.

There are substantial regional and ethnic variations in the prevalence of NTD. Global epidemiological data do not show any significant association between folate deficiency and NTD; but a number of genetic polymorphisms which affect folate pathways and metabolism have been shown to be associated with an increased risk for NTDs. It has been hypothesised that epigenetic mechanisms may be involved in the aetiology of NTD and that the presence of elevated folate receptor antibodies would limit folate transport to the early embryo thus affecting its development[3]. Changes in DNA methylation that lead to over-expression of genes involved in auto-immunity[3] have been linked to the development of NTD. Disruption of DNA methylation in animal models suggests that DNA methylation may also play a role in neural tube closure[3-6].

Folic acid supplementation for prevention of neural tube defects

A rigorous double-blind randomised controlled trial supported by the UK Medical Research Council showed that giving a pharmacological dose of 4mg of folic acid daily [twenty times the

Recommended Dietary Allowance (RDA)] to women with a history of previous offspring with NTD, reduced the recurrence by 72%[7]. Subsequent studies showed that peri-conceptional folic acid supplementation in women who have had no previous history of delivering infants with NTD resulted in some reduction in NTD in this group also, but that the magnitude of reduction was lower[8]. Subsequent published studies showed that this reduction could be achieved with lower doses of folic acid supplementation[9,10]. Based on these data, programmes for peri-conceptional folic acid supplementation (400µg daily) for primary prevention or prevention of recurrence of NTD were initiated in several countries. In 1991, the Centers for Disease Control and Prevention recommended that women with a history of a prior NTD-affected pregnancy should consume 4000 µg of folic acid daily starting at the time they begin planning a pregnancy[11]. In the US over 50% of pregnancies are unplanned, and compliance was poor. Compliance with peri-conceptional folic acid supplementation was even lower in women who were planning to conceive and did not have any previous history of NTD.

Fortification of wheat flour with folic acid

In view of the difficulties in ensuring peri-conceptional supplementation with folic acid, several countries took up food fortification for the prevention of NTD. Wheat flour was identified as the food to be fortified with folic acid because it was universally used. Wheat flour processing in many developed countries is done on industrial scale and universal fortification can be achieved. Processed wheat flour and its products (biscuits, cakes and other processed food) are consumed by a large percentage of the population.

Mandatory fortification of wheat flour with varying levels of folic acid was attempted in different countries (Table 1). Even in countries where it was made mandatory, compliance with fortification was suboptimal. The US is the only country which has implemented mandatory fortification very well for over two decades and has achieved substantial reduction in NTD. In most countries the fortification was voluntary and coverage remained very low. An evaluation of NTD trends in countries with voluntary fortification revealed no significant changes since the recommendations were enacted, because of low coverage.

US experience with mandatory wheat flour fortification

In the US, a mandatory wheat flour fortification programme has been formulated and implemented well for the past two decades[12]. USA has set up an excellent monitoring system for the implementation of the wheat fortification programme and to track changes in the incidence of NTD and any potential adverse consequences of such fortification on the general population. The reported coverage under the programme has been near-universal[13]. Studies using various methodologies have shown that since the implementation of folic acid fortification in 1998, there has been a 19%-32% reduction in the prevalence of NTDs in US. There are approximately 3.7 million births per year in the US; of these 3000 infants are born with NTD. It has been estimated that about 1300 NTDs are prevented per year as a result of the mandatory fortification of wheat flour which ensured that folic acid is consumed by nearly all pregnant women (the target group). However, due to mandatory fortification, over 320 million persons from general population (non-target population) have been consuming four times the RDA levels of folic acid.

A review of all the available data from the US suggests that:

- a proportion of NTDs occur despite folic acid fortification, and
- a prevalence of 5-6 cases per 10,000 pregnancies represents the lowest prevalence that is achievable through current folic acid fortification practices.

It was assumed the continued high folic acid consumption above the RDA level will not have any adverse consequences because:

- excessive folic acid consumed will be excreted in urine, and
- the Tolerable Upper Limit for folic acid is higher than the current wheat flour fortification of 400µg per day.

Available data from US national surveys indicate that there has been a fall in folic acid deficiency in the country, and that currently the RBC folic acid levels in the US population are substantially higher than what they were two decades ago. The latter findings suggest that the fortification of wheat flour with folic acid has resulted in a substantial rise in RBC folate; there may be other metabolic alterations, some of which may have an adverse health impact in the non-target population. It has been documented that folic acid fortification could mask symptoms of vitamin B12 deficiency and precipitate neurological complications associated with vitamin B 12 deficiency. The possibility that high folic acid levels might increase the risk of cardiovascular diseases is a potential area of concern. There have been reports that excessive folic acid may promote the progression of pre-malignant and malignant lesions but these have not been confirmed.

Experiences of other countries

Canada, South Africa, Costa Rica, Chile, Argentina, and Brazil are other countries which had implemented mandatory fortification of wheat flour and have reported decline in the incidence of NTDs (19%-55%) since the initiation of folic acid fortification[13]. Many countries have not implemented mandatory folic acid fortification because of:

- problems in reaching all the population with the fortified product,
- cost of such universal fortification,

Table 1 Level of folic acid fortification in different countries

Country	Level	Year of implementation
USA	140µg/100g	1998
Canada	150µg/100g	1998
Costa Rica	180µg/100g	1998
Chile	220µg/100g	2000
South Africa	150µg/100g	2003

- variation in prevalence of NTD,
- lack of effective monitoring systems for monitoring reduction in NTD and potential adverse consequences in non-target populations, such as masking the B12 deficiency, increase in cardiovascular diseases, and cancer, and
- the belief that consumers should be given the choice of whether they want to consume fortified wheat.

Indian situation

Earlier studies in India in pregnant women had shown that folic acid deficiency was widespread. However, more recent studies have reported lower prevalence of folic acid deficiency. There are substantial inter-regional differences. Some small scale studies have documented biochemical changes such as rise in homocysteine associated with folic acid supplementation, suggesting that folic acid supplementation may be associated with adverse health consequences.

Available data on the prevalence of NTD in India is meagre, and even the reported data are from studies that are inadequate in terms of sampling frame and sample size. A meta-analysis of the data has shown that, at the national level, the prevalence is 4.5/1000. The prevalence is lowest in Eastern India 1.1/1000 and highest in northern India 7.7/1000[14]. The reasons for the differences between regions are not known but similar variations have been known to occur between adjacent countries - England and Ireland or different regions in large countries, e.g., China.

Problems in rolling out wheat flour fortification for NTD prevention in India

NTD prevention requires therapeutic levels (four times RDA levels) of fortification with folic acid. It may not be desirable to expose the general population to long term consumption of such high levels of folic acid. The main cereals consumed by Indians are wheat and rice. Over half the population does not consume wheat flour on a daily basis. Only about 20% of the wheat flour is industrially processed and can be readily fortified. Given these constraints, mandatory fortification is not possible. Voluntary fortification will reach too small a proportion of the population and may not result in a significant reduction in NTD. On the other hand, the potential adverse health consequences of such supplementation, namely, masking vitamin B12 deficiency, higher homocysteine levels and increasing CVD risk in the general population, may be there. India is yet to build up effective monitoring systems for assessing beneficial effects on target populations (reduction in NTD incidence) and potential adverse health consequences in the non-target population.

Table 2 FSSAI notifications on wheat flour fortification (fortificant/kg)

FSSAI notification 2016		FSSAI draft notification 2018	
		Ferrous citrate or Ferrous lactate or Ferrous sulphate or Ferric pyrophosphate or electrolytic iron or Ferrous fumarate or Ferrous BisGlycinate	28 to 42.5mg
Na iron EDTA	20mg	Na iron EDTA	14 to 21.25 mg
Folic acid	1300 µg	Folic acid	75 µg to 125 µg
VitaminB12	10 µg	VitaminB12	0.75 µg to 1.25 µg

Wheat flour fortification with iron, folic acid and vitamin B12

Anaemia is a major public health problem globally and in India. Low intake of vegetables rich in iron and folate is the major factor responsible for the high prevalence of anaemia. Over time there has been very little change in the prevalence of iron deficiency, some reduction in the prevalence of folate deficiency, and perhaps some increase in Vitamin B12 deficiency. In 2006, the WHO published Guidelines for fortification of wheat[15] with iron, folic acid and vitamin B12 (for prevention of both anaemia and neural tube defects). Fortification of iron was at about one-third of the RDA but folic acid and vitamin B12 were higher than RDA. Systematic reviews of the global wheat flour fortification with iron, folic acid and vitamin B 12 suggest such fortification had only limited effectiveness in reducing prevalence of anaemia[16].

The Food Safety and Standards Authority of India (FSSAI) had issued comprehensive draft Food Safety Standards (Fortification of Foods) Regulations 2016 which included standards for the wheat flour fortification with iron, folic acid and vitamin B12. The fortification with iron was at about one-third of the RDA but folic acid and vitamin B12 were several folds higher than RDA (Table 2).

Subsequently the standards were reviewed and revised in 2018 taking into account:

- the data on impact of mandatory fortification of wheat flour with folic acid on NTD incidence from USA and other countries,
- the data on potential adverse consequences of high folic acid intake by general population reported in the last two decades,
- the impact of use of wheat flour fortified with iron, folic acid and vitamin B12 on Hb levels in developing countries,
- the current data on prevalence of anaemia in India,
- global SDG targets, and
- National Nutrition Goals identified by National Nutrition Strategy, 2017.

The revised draft Food Safety Regulations of FSSAI[17] in which wheat flour is to be fortified with about one third of the RDA of iron, folic acid and vitamin B12 (Table 2) has been placed in public domain for comments. Fortification at this level is expected to reduce the gap between current intake and requirement of these three nutrients in the segments with low intake and at the same time not exceed the RDA in other segments of the population who are consuming their required amount of these nutrients. As both folic acid and Vitamin B12 are provided, health hazards associated with fortification of wheat flour with only folic acid will not arise.

There have been no major publications from large-scale studies in India on the impact of wheat flour fortification on Hb levels. Currently there are ongoing studies on populations consuming wheat flour fortified with iron at 1/3rd RDA and high levels of folic acid and Vitamin B12. It is expected that in future there will also be studies on the effectiveness of wheat fortified at 1/3rd RDA for iron as well as folic acid and B12. Once the data on the impact of the consumption of fortified wheat containing similar levels of iron and different levels of folic acid and vitamin B12 on Hb are available, these can be reviewed and appropriate recommendations for wheat flour fortification can be evolved.

Summary and conclusion

Global epidemiological data have shown that a number of genetic polymorphisms which affect folate pathways and metabolism, are associated with an increased risk for NTDs. Peri-conceptional folic acid supplementation results in a substantial reduction in NTD especially in women with previous history of delivery of an infant with NTD; but coverage under peri-conceptional folic acid supplementation is very low even in developed countries. In an attempt to ensure that all pregnant women consume high folic acid during peri-conception period, many developed countries embarked on fortification of universally consumed wheat flour with folic acid.

Mandatory fortification of wheat flour with folic acid has been in vogue in the US since 1998 and data from USA had provided valuable insights into the extent of the NTD reduction due to peri-conceptional consumption of fortified flour by women (target groups) as well as the potential adverse consequences of sustained high intake of folic acid in the non-target general population.

Global data have shown that near-universal use of fortified wheat flour is necessary in order to achieve significant reduction in the incidence of NTD. Indians consume wheat and rice as major cereals. Over half the population does not consume wheat flour on a daily basis. Only about 20% of wheat flour is industrially processed and could be fortified. Voluntary fortification of wheat flour will reach only a small proportion of the population. In view of these constraints it is not possible to currently initiate a wheat flour fortification programme for reduction of NTD in India.

Anaemia due to low intake of iron, folate, and vitamin B 12 is a major public health problem in India. FSSAI has notified standards for fortification of wheat flour with iron, folic acid and vitamin B 12 at one third the RDA, so that the gap between the dietary intake and requirement of these nutrients can be minimised. Studies assessing the impact of consumption of wheat fortified with these three nutrients on Hb levels and prevalence of anaemia are needed to provide leads regarding optimal level of fortification.

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Dr.Prema Ramachandran, Director NFI, participated in the NITI Aayog – IFPRI workshop "A Common Vision for Tackling Malnutrition in India: Building on Data, Evidence and Expert Opinion" on March 29-30, 2019

Edited by Dr. Anshu Sharma for the Nutrition Foundation of India, C-13, Qutab Institutional Area, New Delhi - 110016, website : www.nutritionfoundationofindia.res.in
Designed & Printed by Himanshi Enterprises