Original Article

Meta-Analysis of Efficacy of Iron and Iodine Fortified Salt in Improving Iron Nutrition Status

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Abstract

Background: Salt fortification with iron is a potential strategy to increase population-level iron intake. The current evidence regarding double-fortified salt (DFS) in improving iron nutrition status is equivocal. **Objective:** To study the efficacy of DFS as compared to iodine fortified salt (IS) in improving iron nutrition status. **Methods:** Randomized controlled trials comparing DFS and IS until August 2016 were systematically searched across multiple databases to assess for change in mean hemoglobin (Hb), prevalence of anemia, iron deficiency (ID), ID anemia (IDA), serum ferritin, and serum transferrin receptor (TfR). Meta-analysis was performed using R software. **Results:** Of the initial 215 articles retrieved using the predetermined search strategy, data from 10 comparisons of DFS and IS across 8 randomized controlled trials are included. There was significant heterogeneity across included studies and the studies were of low to very low quality as per GRADE criteria. DFS significantly increased mean Hb by 0.44 g/dl (95% confidence interval [CI]: 0.16, 0.71) and significantly decreased anemia (risk difference −0.16; 95% CI: −0.26, −0.06) and ID (risk difference −0.20; 95% CI: −0.32, −0.08) as compared to IS. There was no statistically significant difference in change in ferritin levels (mean difference 0.62 µg/L; 95% CI: −0.12, 1.37), serum TfR levels (mean difference −0.23 mg/dL; 95% CI: −0.85, 0.38), and IDA (risk difference −0.08; 95% CI: −0.28, 0.11). **Conclusion:** DFS is a potentially efficacious strategy of addressing anemia as a public health problem at population level. There is a need for effectiveness trials before DFS can be scaled up in program mode at population level.

Key words: Anemia, dietary/administration and dosage, food fortification, iodine/administration and dosage, iron-deficiency/epidemiology

Introduction

Anemia is one of the most common and intractable public health problems affecting around 2 billion people worldwide.[1] Asia and Africa account for more than 85% of the anemia burden.[2] In 2010, 8.8% of total global disability from all conditions was attributed to anemia.[3] Iron deficiency (ID) is the single most important cause or anemia accounting for about one-third to half of the total anemia.[4] The National Family Health Survey-4 shows that more than half (58.3%) of the children aged 6–59 months, 54% of women in reproductive age 15–49 years, and 22.1% of males aged 15–49 years were anemic in India.[5] ID anemia (IDA) is a leading cause of disability in India[6] with an estimated lifetime intangible loss of 8.3 million disability-adjusted life years in 6–59 months birth cohort, production losses of 24,001 million USD corresponding to 1.3% gross domestic product of India.[7] There is felt a need to explore and identify novel approaches to tackle IDA in the country.

The World Health Organization has proposed a three-pronged strategy for addressing IDA comprising of increased iron intake through dietary diversification, food fortification, and iron supplementation; immunization and control of malaria, hookworm, and schistosomiasis; and prevention and control of nutritional deficiencies such as Vitamin B12, folate, and Vitamin A.[1] Anemia control has been on India's

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policy mandate since 1970 when the erstwhile the National Nutrition Anemia Prophylaxis Programme[8] was launched. However, India is still grappling with high anemia burden.[9] The National Iron Plus Initiative[10] 2013 has heavily focused on iron supplementation for the prevention and cure of anemia mainly in children, adolescents, and women. Strategies such as iron syrups for pediatric age, weekly iron supplementation to adolescents, directly observed iron consumption[11] have been shown to be effective in controlled conditions. However, compliance, effective programmatic implementation, and coverage in remote and underserved areas continue to pose a challenge.[12]

In this context, fortification of staple food vehicles with iron can be one of the strategies to supplement iron intake.[13] Fortification of staple food items that are culturally acceptable, affordable, and available is a potentially useful and scalable intervention. The success of iron fortification of staple food is dependent consumption pattern, effect of the fortificant on the taste and appearance of the food vehicle, shelf life, bioavailability of the iron fortificant, and the baseline iron status of the population.[14,15]

The expert panel of Copenhagen Consensus, 2008 has ranked iron and iodine fortification of salt as one of the most cost-effective interventions available to address the challenge of global malnutrition.[16] Salt is a regularly purchased and consumed entity and therefore, might ensure a daily supply of iron. The unique characteristics of salt and its success story[17] as a vehicle for iodization, render it as one of the most suitable food vehicles for iron fortification as well. Salt-fortification with both iodine and iron has been a long-cherished goal; the process has been slow due to unstable physiochemical properties, unacceptable organoleptic changes, and low bioavailability of the combination. Initial technological concerns regarding the stability of iron and iodine in salt have been now overcome with encapsulation, micro ionization, and addition of stabilizers.

However, there is limited scientific evidence on the effect of iron fortification of salt on hematological parameters of anemia. The current meta-analysis attempts to collate and summarize available literature on the efficacy of double-fortified salt (DFS) on iron nutritional parameters. The objectives of the study were to estimate the efficacy of DFS as compared to iodine fortified salt (IS) in improving iron nutrition status as measured by changes in levels of hemoglobin (Hb), serum ferritin (SF), and transferrin receptor (TfR) concentrations and proportion of anemia, ID and IDA.

Materials and Methods

Data sources and search strategy

Literature search using a defined search strategy was performed in PubMed, Web of Science databases, and Cochrane Central Register of Controlled Trials (Search strategy - Supplement 1). Cross-references from all the eligible articles were further searched for relevant studies. The bibliographies of relevant guidelines, reviews, and reports were also searched to identify relevant primary reports. Online searches of major conference proceedings were conducted to identify unpublished literature. All studies published up till August 2016 were included, and no restriction on language was imposed. For studies with missing data or requiring clarification, principal investigators of the studies were contacted.

Study selection and data extraction

Randomized controlled trials comparing (iron and IS) DFS and iodine only fortified salt (IS) across all age and gender groups were included in the review. Uncontrolled trials, nonhuman studies, and articles with incomplete data were excluded from this review. The primary outcome variable was difference in change in mean Hb at baseline and endline in intervention and control groups. Secondary outcome variables were changes in the prevalence of anemia, prevalence of ID, prevalence of IDA, mean SF, and mean serum TfR levels.

Two authors independently ran the search strategy for identifying articles. Titles and abstracts were studied and full text of potentially relevant studies was assessed according to the prespecified inclusion and exclusion criteria. Disagreement on study inclusion was resolved by discussion with a third author. A data extraction form was developed, pilot tested on a small number of selected studies, and necessary changes were incorporated. The following information was extracted: study descriptors (author and year), geographical settings, population characteristics (age and gender distribution), intervention details (sample size, iron form, concentration, and duration of intervention), and data on outcomes (mean and standard deviation [SD] of baseline and endline Hb, prevalence of anemia, ID, IDA, mean SF, and TfR).

Quality assessment

Two reviewers independently assessed the quality of studies included in the review using the Cochrane Risk of Bias tool.[18] Studies were ranked as low, high, or unclear risk of bias across various domains, i.e., random sequence generation, allocation concealment, blinding of participants and persons involved in the study, blinding of outcome assessment, incomplete outcome data, and selective reporting. In addition, for each of the six identified outcomes, Grade assessment was done using GRADEpro GDT software (McMaster University and Evidence Prime Inc., Hamilton, Ontario, Canada)[19] to assess the quality of the evidence generated.

Statistical analysis

Effect size estimation

The effect size was defined as the difference between the standardized mean change in the intervention and control groups. Effect Size estimation of Hb was done as suggested by Morris for Pretest-Posttest Control Group Designs.[20] SF and serum transferrin when summarized as median (range) values and were converted to mean (SD) using the method described by Hozo *et al*.[21] before calculating the standardized mean difference.

Cochran's Q (based on Chi-square test) and I^2 tests were used to assess the heterogeneity of the studies. The heterogeneity of the trials was regarded as low-level when $P < 0.10$ for the Chi-square test and $I^2 < 25\%$. Random effect model was used to calculate pooled effect size as a "substantial" degree of heterogeneity ($I^2 \geq 50\%$) was noted among the included studies. Forest plots showing the point estimate and confidence intervals (CIs) for each study were created. Sensitivity analysis was performed by excluding any study with extreme observations. Egger's linear regression test[22] and rank test[23] were used to assess publication bias. The effect of individual studies on heterogeneity was assessed using graphical method suggested by Baujat *et al*.[24] The statistical tests were performed using the Meta and Metafor package in R version 3.3.0 (Boston, MA, USA).[25] Two-sided $P \leq 0.05$ was considered statistically significant.

Results

Description of studies

A total of 215 relevant studies were retrieved from different databases (web of science = 103, PubMed = 95, and Cochrane library = 17) [Figure 1]. After removing duplicates ($n = 58$), title and abstract of 157 items were screened. Seventy-nine studies were excluded at this stage as 34 were not related to fortification, 24 pertained to iodine fortification only, 7 studies were on iron fortification of foodstuffs other than salt, and 14 studies were nonhuman studies. Full-texts of 78 articles were reviewed for the inclusion criteria of which 70 studies were excluded. The reasons for exclusion at this stage were study design not being randomized controlled trial ($n = 53$), studies only on bioavailability or stability or organoleptic properties ($n = 12$), data incomplete for review and meta-analysis ($n = 3$), and duplicate data already mentioned in studies included in the current review ($n = 2$).

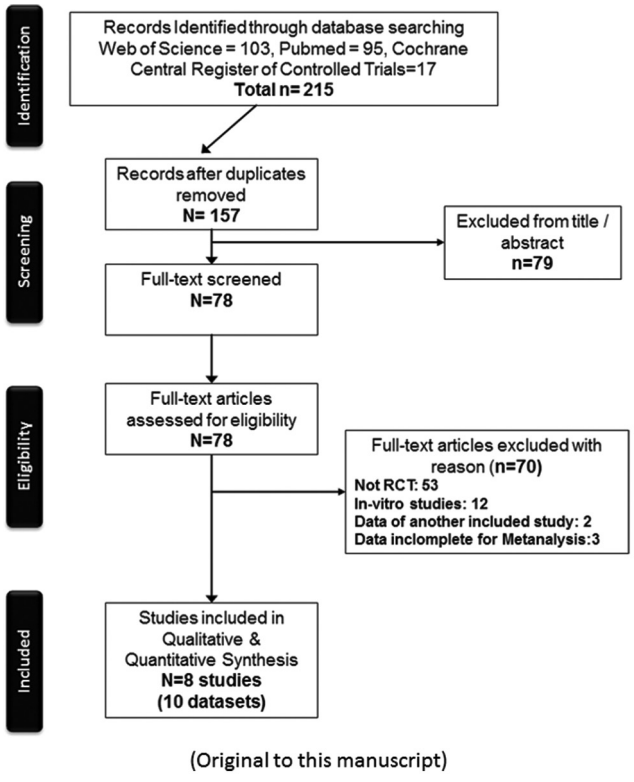

Figure 1: PRISMA flowchart.

Finally, eight studies were included in the review [Table 1]. Out of these, Andersson *et al*.[26] had conducted a three-arm trial comparing two different fortificants for the difference from control-ferric pyrophosphate and ferrous fumarate with controls receiving only iodized salt. Asibey-Berko *et al*.[27] studied DFS intervention in two separate groups, namely nonpregnant, nonlactating mothers, and their under-five children. Thus, 10 studies were effectively available for analysis. Based on the availability of data pertaining to relevant biomarker, 7 studies were pooled for the prevalence of anemia, 6 studies for serum TfR levels, 5 studies for the prevalence of ID, and ferritin levels and 4 for the prevalence of IDA.

Five studies were conducted in India;[26,28-30] two each were from Morocco[31,32] and Ghana[27] and one study was from Ivory Coast.[33] A total of 3219 participants were randomized into DFS intervention group ($n = 1620$) and iodized salt control group ($n = 1591$). A total of seven studies were done in children, two in adult females and one community-based study covered both adults and children. Only three studies had duration of the intervention of 1 year or more. Concurrent deworming was conducted in five studies. The three distinct types of iron compound used for fortifying the DFS were ferrous fumarate (4 studies), ferric pyrophosphate (3 studies), and ferrous sulfate (3 studies).

Risk of bias assessment

More than 50% of studies addressed allocation concealment (5/10), blinding of participants and study personnel (8/10), and incomplete outcome data (7/10). Only one study gave details of random sequence generation. None of the studies gave sufficient information to assess for blinding of outcome assessment [Figure 2].

Publication bias

There was no publication bias [Figure 3] as linear regression test ($P = 0.9263$) and Rank correlation test ($P = 0.7884$) were nonsignificant.

Effect on intervention

The pooled estimate shows that consumption of DFS increased Hb concentration by 0.44 g/dl (95% CI: 0.16–0.71, $P < 0.01$) in intervention group as compared to control group [Figure 2]. Individually, all studies except one (Wegmuller *et al*.) showed improvement of Hb, ferritin, and transferrin.

Intervention group had a significant reduction in anemia (risk difference −0.16; 95% CI: −0.26, −0.06) and ID (risk difference −0.20; 95% CI: −0.32, −0.08) but not in IDA (risk difference −0.08; 95% CI: −0.28, 0.11) [Figure 2].

Table 1: Characteristics of included randomized controlled trials comparing double fortified salt and iodine fortified salt

Author	Population	Intervention	Control	Outcomes
Sivakumar *et al*., 2001[33]	Age: Schoolchildren 5-15 Country: India Deworming: Not mentioned	*n*=448 (187 male; 261 female) Ferrous sulfate	*n*=352 (153 male; 199 female)	Hb Duration=18 months
Zimmerman *et al*., 2003[34]	Age: 6-15 years old children Country: Morocco Deworming: Not mentioned[a]	*n*=183 (94 male; 89 female) Ferrous sulfate (1 mg/g salt)	*n*=184 (99 male; 85 female)	Hb, SF, ZnPP, and sTfR Duration=9 months
Zimmermann *et al*., 2004[35]	Country: Morocco Age: 6-15 years old children Deworming: Not mentioned[a]	*n*=75 (40 male; 35 female) Ferric Pyrophosphate (2 mg/g salt)	*n*=83 (40 male; 43 female)	Hb, SF, ZnPP, TfR Duration=10 months
Wegmüller *et al*., 2006[36]	Age: School children 5-15 Country: Cote d'Ivoire Deworming done at baseline and 4 months	*n*=60 (male:female not mentioned) Ferric pyrophosphate (3 mg/g salt)	*n*=63	Hb, SF, TfR Duration=6 months
Vinodkumar *et al*., 2007[37]	Age: 10-65 years Country: India Deworming done at baseline, 6 and 12 months	*n*=393 (168 male; 225 female) Ferrous sulfate (1 mg/g salt)	*n*=436 (158 male; 278 female)	Hb Duration=12 months
Asibey-Berko - A, 2007[26]	Country: Ghana Age: 15-45 years nonpregnant, nonlactating females Deworming: Not mentioned	*n*=65 females Ferrous fumarate (1 g/kg salt)	*n*=58 females	Hb[b] Duration=18 months
Asibey-Berko - B, 2007[26]	Country: Ghana Age: 1-5 years children Deworming: Not mentioned	*n*=22 (male:female not mentioned) Ferrous fumarate (1 g/kg salt)	*n*=53	Hb[b] Duration=18 months
Andersson - A, 2008[25]	Country: India Age: 5-18 years school children Deworming done 1 and 8 months after baseline	*n*=130 (82 male; 73 female) Ferric pyrophosphate (2 mg/g salt)	*n*=131 (78 male; 73 female)	Hb, SF, TfR, ZnPP Body iron Duration=10 months
Andersson - B, 2008[25]	Country: India Age: 5-18 years school children Deworming done 1 and 8 months after baseline	*n*=140 (81 male; 71 female) Ferrous fumarate (2 mg/g salt)	*n*=131 (78 male; 73 female)	Hb, SF, TfR, ZnPP Body iron Duration=10 months
Haas *et al*., 2014[39]	Country: India Age: 18-55 years healthy, nonpregnant females Deworming done 4 weeks before baseline and at midpoint	*n*=104 females Ferrous fumarate (1.1 mg/g salt)	*n*=108 females	Hb, MCV, SF, TfR, Vitamin B12, serum folate Duration=10 months

[a]Deworming deemed unnecessary as hookworm prevalence low), [b]The original article by Asibey Berko does not mention the raw data of values. This is however mentioned in the review by Horton who has contacted the author for Hb values and mentioned the same in his review article. SF: Serum ferritin, TfR: Serum transferrin receptor, ZnPP: Zinc protoporphyrin, Hb: Hemoglobin

No significant effect of the intervention was seen on ferritin levels (Standardized Mean Difference 0.62 μg/L; 95% CI, −0.12–1.37) [Figure 3]. Similarly, DFS altered transferrin levels by only −0.23 mg/L (95% CI: −0.85–0.38) but failed to reach statistical significance [Figure 2].

After assessing the effect of individual studies on heterogeneity[24] [Supplement 5], a sensitivity analysis was performed excluding Zimmerman *et al*. 2004 which gave a pooled estimate of 0.33 (95% CI: 0.18, 0.49).

Discussion

The current review shows that with consumption of DFS, Hb levels significantly improved the risk of anemia and ID reduced in the controlled settings of the trials included in the review. However, there was no significant effect on serum transferrin, ferritin levels, and the risk of IDA in the studies included in the review. Gera *et al*.[13] have shown that in principle food fortification can lead to significant improvements in various indicators of iron nutrition. The current review gives further evidence for using salt as a potential fortificant for not only iodine but also iron. The results of the study support the scientific rationale behind the introduction of DFS as part of the public funded nutrition program. However, larger effectiveness trials of greater methodological rigor are required to establish the feasibility of DFS in program mode.

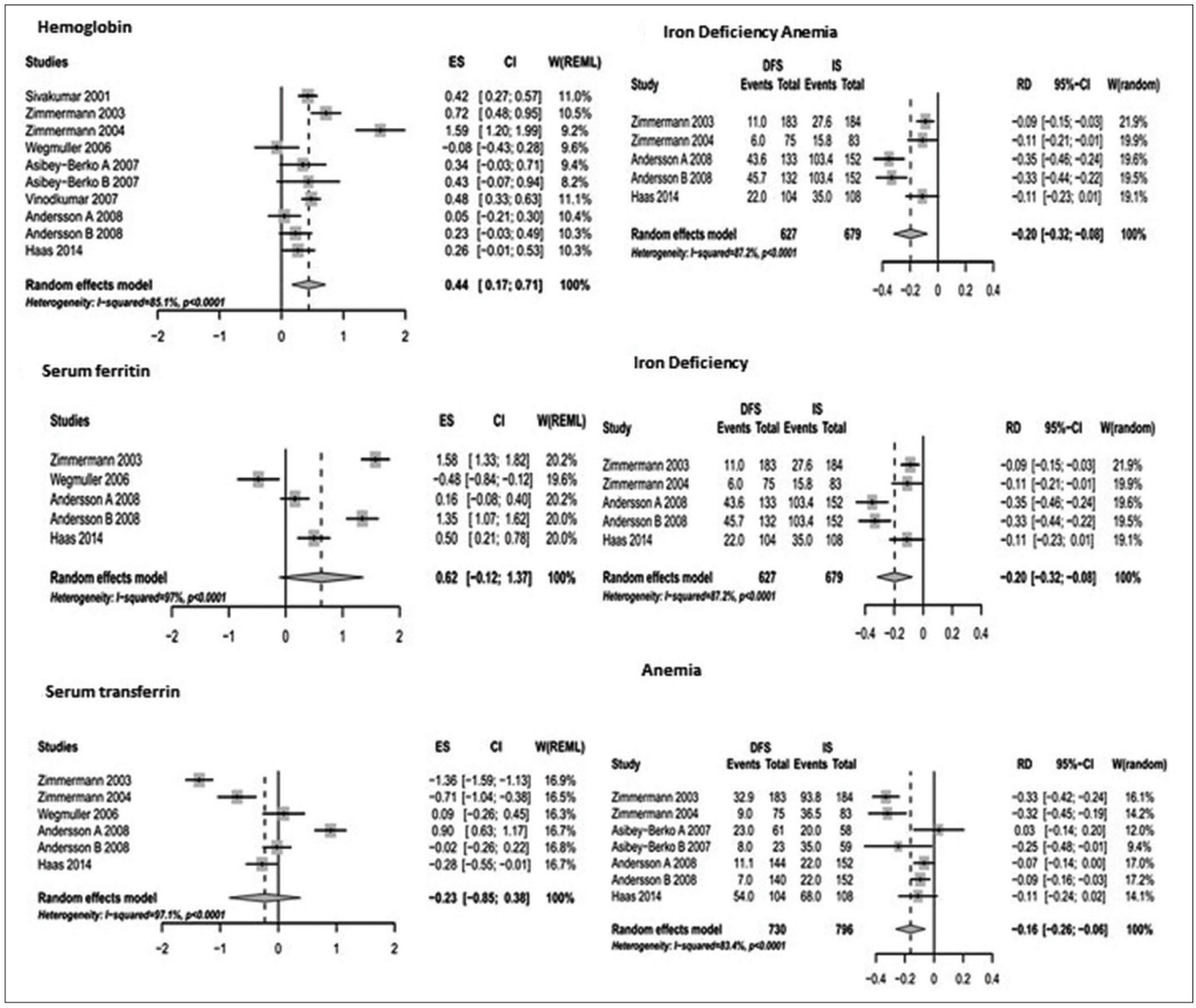

Figure 2: Forrest plot.

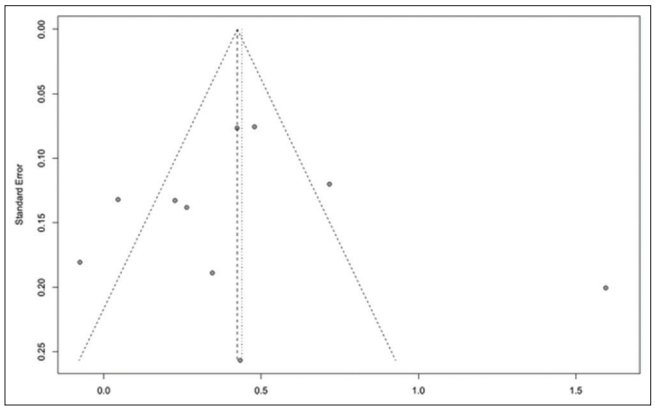

Figure 3: Funnel plot.

The individual trials may not have conclusively established the efficacy of DFS in improving the iron status of the study subjects primarily due to the shorter duration of the studies. Factoring in the bioavailable iron from DFS and the requirement of iron for improving iron nutrition status, it has been estimated that a duration of at least 2 years is required before a change of 1 g of Hb can be observed after DFS consumption. However, most of the available studies are of much shorter duration (<1 years).

The iron fortificants used in various studies ranged from ferric pyrophosphate, ferrous fumarate, and ferrous sulfate. However, the formulation type did not have a significant effect on the intervention effect size [supplement 3]. Most bioavailable fortificant is water-soluble ferrous sulfate, but it also causes organoleptic problems, such as precipitation and changes in color and flavor.[34] Ferrous fumarate although a relatively water-insoluble compound, however, dissolves adequately in gastric juice and is almost as bioavailable as the freely water-soluble fortificants except in cases of reduced gastric acid generation like mucosal atrophy from protein-energy malnutrition[35] or bacterial-induced gastritis.[36] Indians have a

comparatively lower basal acid output compared to the western population, and this could, therefore, be a reason for low bioavailability if fumarate salts are used for fortification. Ferric pyrophosphate is poorly soluble in both water and gastric juice, however, it has been shown that particle-size reduction and encapsulation improves bioavailability.[37] Similarly, sodium iron EDTA (NaFeEDTA) has been demonstrated to have good iron bioavailability[38] Identifying the ideal iron compound, and the formulation for DFS will enable scaling up of the program, and further research is warranted. Very few studies are currently available to undertake a meaningful comparative analysis of different iron compounds and formulations used for DFS.

With a mean salt consumption of 10 g/day per person and fortification standard of 1 mg iron per gram salt, DFS is likely to provide nearly 60% of recommended dietary allowance for iron in adults.[39] Thus, DFS can significantly contribute to dietary iron requirement, and if consumed over a long period in maintaining adequate iron stores. Currently, however, there is limited evidence from effectiveness trials to support the introduction of DFS in the national public health program. There is a potential danger of iron overload especially if combined with parallel interventions like iron supplementation and in certain special subgroups like patients with hemoglobinopathies.

The strength of this review includes a large collated sample size resulting in highly precise pooled estimate. There was no observed publication bias, which further increased the validity of our estimate. Grade analysis and assessment of the quality of evidence were generated with respect to each of the outcomes considered in the review (Supplement 4). Limitations of the review included the significant heterogeneity that could not be explained substantially by prespecified subgroups. In most of the included studies randomization procedures were poorly reported and also the overall quality assessed as per Grade criterion varied from very low to low.

DFS is a potentially efficacious strategy of addressing anemia at the population level. However, considering the paucity of effectiveness trials, it may be too early to introduce DFS program in program mode. Further research will be prudent to substantiate effectiveness, nationwide scalability with quality assurance and cost implications of DFS as a strategy to address IDA.

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Conflicts of interest

There are no conflicts of interest.

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