A public health approach for preventing neural tube defects: folic acid fortification and beyond

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In this paper we review the evidence basis for prevention of folic acid–sensitive neural tube defects (NTDs) through public health interventions in women of reproductive age (WRA), the proven vehicles for delivery of folic acid, and what is needed to effectively scale these, and provide a snapshot of potential innovations that require future research. Our primary focus is on the global situation affecting large-scale food fortification (LSFF) with folic acid, in particular the fortification of wheat flour and maize meal. Our overarching conclusion is that folic acid fortification is an evidence-based intervention that reduces the prevalence of NTDs, and that LSFF with folic acid is underutilized. Thus, food fortification with folic acid should be a component of most national public health strategies, in particular where folate status is insufficient and a fortifiable food vehicle, processed by a centralized industry, is consumed regularly by WRA. The evidence shows that there is still much work needed (1) to build the enabling environment and expand programs where there is currently no legislation, (2) to improve the low quality of delivery of existing programs, and (3) to measure and sustain programs by generating new coverage data and demonstrating evidence of impact in low- and middle-income countries.

Keywords: fortification; folic acid; coverage; NTD prevention

Introduction

Neural tube defects (NTDs), a group of severe birth defects resulting from abnormal neural tube (i.e., spinal cord and brain) formation during embryonic development, are associated with fetal and infant mortality, morbidity, severe lifelong disability, psychological maladjustment, and staggering economic costs.³⁻⁵ Globally, more than 260,000 pregnancies are estimated to be affected by NTDs, and of the NTD live births, 75% result in under-5 deaths.² The largest percentage of NTDs are folic acid sensitive,⁴⁻⁵ with much of the NTD burden preventable through consumption of mandatory folic acid–fortified staple food products before conception.⁶

An association between low folate status of women of reproductive age (WRA) and risk of NTD-affected pregnancy was first proposed in 1965.⁷ This hypothesis was substantiated by results of pivotal randomized controlled trials demonstrating the effectiveness of folic acid supplementation before and during early pregnancy (periconceptional) in preventing the recurrence⁴ and first occurrence⁵ of NTDs. These results, published in the early 1990s, were subsequently followed by a recommendation by the U.S. Public Health Service in 1992 that all women capable of becoming pregnant consume 400 μg of folic acid daily to prevent first occurrence of an NTD-affected pregnancy.⁸ This recommendation and others globally⁹⁻¹¹ were supported by a large-scale folic acid intervention study conducted in China that demonstrated the efficacy of a daily periconceptional supplement of 400 μg in preventing a large percentage of NTDs.¹²

To ensure adequate folate status for neural tube closure that occurs in early embryonic development (22–28 days, post conception), a woman should begin folic acid supplementation before becoming pregnant. The recommendation of
400 μg supplemental intake of folic acid daily as a primary public health strategy for the prevention of NTDs, therefore, has limitations as many pregnancies, including up to 50% of all pregnancies in the United States, are unplanned.\textsuperscript{13,14} While public awareness and mass media campaigns have been somewhat effective in increasing knowledge about the importance of folic acid for WRA, overall periconceptional folic acid supplement use continues to be low, especially among high-risk population groups.\textsuperscript{15–17} Among WRA in numerous countries, especially low- and middle-income countries (LMICs), there are many barriers to accessing supplements and compliance with supplement recommendations as such interventions typically require the procurement of micronutrients in a relatively costly prepackaged form, an effective distribution system, and a high degree of consumer compliance. An evaluation of NTD trends in multiple countries indicated that, regardless of form, timing, or intended target, issuing recommendations on folic acid use alone, in the absence of fortification, had no detectable impact on NTD incidence.\textsuperscript{18}

Mandatory folic acid fortification programs have been implemented in many countries to improve folate status of WRA, helping to mitigate issues of high costs, distribution problems, and low compliance associated with supplement use.\textsuperscript{19} In 1996, the United States became the first country to mandate fortification of enriched cereal grain products in an effort to ensure that WRA consumed adequate folic acid in addition to dietary folate, with the program fully implemented in 1998.\textsuperscript{20} The success of mandatory folic acid fortification programs in significantly reducing NTD burden has been documented in many countries following the implementation of mandatory fortification programs.\textsuperscript{21} The mandatory fortification of staple foods with folic acid in LMICs has added benefits in that it uses existing delivery channels, can reach additional WRA, and requires little to no behavior change. In those countries where mandatory fortification will not attain strong coverage, new delivery channels may need to be developed and policies implemented to ensure improved access to folic acid among the most vulnerable WRA.

In summary, provision of folic acid through food fortification or periconceptional supplementation is an evidence-based intervention shown to reduce the prevalence of NTDs. An appropriate public health goal to reduce NTD risk is to ensure that all WRA obtain sufficient folic acid from fortified foods or supplements to complement dietary folate intake.

**Background to food fortification**

Food systems often fail to sufficiently deliver foods rich in micronutrients, including folate. This failure is due to the availability, access, affordability, and utilization of appropriate foods.\textsuperscript{22} When the food vehicle is processed/produced by centralized industries, fortification of staple foods, and in some instances condiments, is an effective tool within the broader food, nutrition, health, and development agenda to address micronutrient malnutrition.

Food fortification, the practice of adding one or more essential nutrients to improve the nutritional quality of the food supply and provide a public health benefit,\textsuperscript{23} can take several forms, including large-scale mandatory or voluntary fortification.\textsuperscript{6} Large-scale mandatory and voluntary fortification involve the addition of one or more micronutrients to foods commonly consumed by large sectors of the population in an effort to address known deficiencies within the population or a population group.\textsuperscript{6} As the names imply, mandatory fortification is usually mandated and regulated by the government and effected through medium- and large-scale food-processing industries, whereas voluntary fortification, though typically under government regulations or standards, is implemented on a voluntary, often profit-driven basis by food manufacturers or other entities.

Mandatory fortification, which has been implemented in many LMICs where national fortification programs have been enacted, offers greater advantages and benefits for folate-sensitive NTD prevention as compared with voluntary fortification efforts.\textsuperscript{23} Mandatory fortification is appropriate when there is a serious public health need or risk, when consumer knowledge is poor and there are few nutrition education opportunities, and when it can be implemented through a relatively centralized industry processing staple food(s). It generally does not require behavioral changes in consumption or dietary habits, unlike voluntary fortification, which typically relies on the generation of consumer interest and/or demand through marketing initiatives and specific nutrition educational programming. While there may be commercial advantages to voluntary fortification, the many benefits of mandatory
fortification, including a more likely outcome of increased intake of micronutrients across the entire population, make it a preferred choice over voluntary efforts for LMICs.

Mandatory fortification is typically operationalized through mass or large-scale food fortification (LSFF). LSFF utilizes existing common edible products industrially processed within a food system and therefore takes advantage of the shifts in many LMICs toward higher urbanization trends and consumption of diets that contain more processed and fortifiable foods. Alongside continued efforts toward more diverse food systems and balanced diets, food fortification can be a good solution to increase access, including that of marginalized populations, to nutrient-rich food. Fortification of commonly consumed foods can be an effective means of improving dietary quality and nutrition status of WRA during the high-risk periconceptual period. Overall increases in dietary folic acid intake and blood folate concentration, including among WRA, have been reported in a multitude of countries in response to folic acid fortification.

Food fortification, however, should not be considered a stand-alone solution. Rather, it should serve as a highly cost-effective, evidence-based intervention that complements long-term nutrition-specific and nutrition-sensitive strategies to strengthen food systems, increase nutritional diversity in people’s diets, and address nutrient insufficiencies through national systems.

The importance of research underpinning the design of food fortification programs

There is a wide spectrum of choices available for policy makers in the area of food fortification, which include a range of interventions at different steps within the value chain and covering a variety of foods. Here, our focus is on LSFF (i.e., food processed by centralized and relatively large industries), because these interventions can achieve national scale and high coverage in a financially viable way. LSFF of staples and condiments is concentrated in the organized food-processing sector through large- and medium-size industries. It has proven to be both effective and sustainable, while small-scale food fortification does not have the conditions to be economically efficient and has thus not proven to be sustainable.

Mandatory LSFF requires that the specified food vehicle be fortified according to national standards if it is branded and processed centrally. Mandatory fortification allows anyone with access to basic centrally processed staple foods eaten on a regular basis to increase intakes of the nutrients they require. This can be achieved without changes to consumption or feeding habits. Mandatory legislation, when appropriately implemented, creates greater parity for industries to fortify leading to greater coverage (consumption of fortified products), can be easily monitored and enforced, and has greater health impact for entire populations. By providing a higher degree of certainty that a particular food vehicle will contain a predetermined amount of micronutrients, mandatory fortification is more likely to deliver a sustained source of vitamins and minerals for relevant population groups and thus a public health benefit. Mandatory fortification programs can achieve greater impact when implemented within a comprehensive nutrition strategy.

Understanding the potential of fortification for impact among various population groups is important at the design stage. To assist with appropriate design of fortification, one tool that is available is the Fortification Rapid Assessment Tool (FRAT), which was developed in the late 1990s. FRAT helps with the collection and analysis of the data required to select appropriate food vehicles and fortification levels. One limitation of the FRAT approach is that, while the method emphasizes assessing women and children, it does not explicitly assess vulnerability, relying instead on overall consumption patterns by these population groups to select appropriate vehicles. Programs that have not performed intake assessments have generally relied on more indirect assessments, such as estimating per capita consumption based on vehicle production estimates to select vehicles for fortification or used data from household expenditure and consumption surveys.

A more recent tool that was developed and operationalized to help design and monitor performance of national fortification programs is the Fortification Assessment Coverage Toolkit (FACT). The toolkit was designed to assess potential and actual program coverage and utilization, as well as to facilitate the program feedback loop by identifying bottlenecks and barriers to coverage that could and should be addressed during the implementation.
Figure 1. National fortification delivery model. Reprinted from Ref. 59.

phase of the program cycle. Modules can be added with the overall aim of assessing the coverage of specific programs and nutrients (i.e., what can folic acid fortification achieve among at-risk groups?). A weakness found in both FRAT and FACT is that they do not systematically examine the industry layout of the relevant food-processing industry, which could help inform robust regulatory monitoring policies, budgets, and plans. The required evidence generation and collation outlined here are critical steps in establishing the enabling environment required for national fortification. The choice of food vehicle for fortification should not only include considerations on consumption patterns, but also economic analysis and technical feasibility.

Basic steps to building the enabling environment of national food fortification programs

The policy decision to adopt fortification as a public health intervention should be based on strong evidence, demonstrated need as outlined above, and an enabling environment. This first enabling environment phase can be seen as the “build” phase of fortification (Fig. 1) and can be facilitated via a number of good practice steps. For example, a good first step is to establish a national coordinating body for fortification, such as a national food fortification alliance (NFFA). NFFAs can be useful mechanisms allowing different stakeholders to establish roles and responsibilities, coordinate efforts, drive collective decision making, and take shared action.

During this enabling environment phase, it is critical to design a regulatory monitoring framework to deliver consistent and effective monitoring and evaluation and ensure quality assurance and quality control. According to the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO), monitoring is defined as the continuous collection, review, and use of information on program implementation activities for the purpose of identifying problems, such as noncompliance, and informing corrective actions so as to fulfill stated objectives. Further, policy makers should be aware that the overarching policy environment and regulatory framework affect how legislation is developed and implemented. It must be possible to enforce the regulation if the fortification program is going to be effective. Given the differing degrees of industry makeup, government oversight
Figure 2. Reductions in neural tube defects after flour fortification with folic acid was initiated. Reprinted from Ref. 33.

mechanisms, and food regulations, different regulatory monitoring systems are to be expected.

Global status of folic acid fortification: progress and gaps

In the United States, mandatory large-scale fortification of enriched cereal grain products with folic acid was authorized in 1996 and fully implemented in 1998. Within 5 years, the prevalence of NTDs was dramatically reduced to around six per 10,000 pregnancies or fewer, indicating powerful program effectiveness. Fortification of cereal grain products with folic acid became mandatory in several countries soon after, including Canada, Chile, Costa Rica, and South Africa, in an attempt to reach all WRA. These and other fortification efforts have likewise been effective in reducing the prevalence of NTDs in countries where they have been implemented (Fig. 2).

Today, 81 countries, the majority of which are LMICs, mandate the fortification of wheat flour, maize flour, or rice with folic acid specifically (87 mandate wheat flour, maize flour, or rice with any nutrient). While this is substantial progress in terms of scaling a proven intervention, more work remains, even in countries where mandatory fortification is in place. Although 81 countries may have mandated folic acid fortification, we only have evidence of impact in a small number. There is a pressing need to return to countries where there is a mandate and improve delivery and then assess impact.

There are three critical areas that must be addressed if folic acid fortification is to be fully utilized to prevent NTDs moving forward: (1) targeted advocacy to build and expand programs where there is no legislation, (2) poor compliance according to national standards of current programs, and (3) low coverage of current folic acid fortification programs.

First, targeted advocacy is required to build and expand folic acid fortification programs. Today, there remain 62 LMICs that do not have mandatory folic acid fortification, yet these countries meet general criteria for establishing this intervention. This estimate is based on 2017 legislation data from the Food Fortification Initiative; consumption data based on FAO food availability for rice, maize meal, or wheat flour using the WHO-recommended minimum consumption pattern of 75 g/day to allow sufficient fortificant coverage of micronutrient needs of WRA; and 2017 World Bank classifications for low-, medium-, and high-income countries. Implementation research would be required to ascertain which of these 62 countries do not industrially mill or import the majority of their grains and thus consume “unfortifiable” grain products.

In addition, on the basis of 2015 estimates from the Food Fortification Initiative (FFI), the percent
Table 1. Global data on fortifiable and fortified wheat flour, maize flour, and rice: 2015

|                      | Wheat flour, metric tons | Maize flour, metric tons | Rice, \(^a\) metric tons |
|----------------------|--------------------------|--------------------------|---------------------------|
| **Worldwide**        |                          |                          |                           |
| Available            | 349,765,488              | 87,803,467               | 371,704,171               |
| Industrially milled  | 286,640,416              | 12,445,717               | 230,333,404               |
| Fortified            | 80,667,513               | 7,218,545                | 1,789,082                 |
| % Fortified          | 28.1%                    | 58.0%                    | 0.8%                      |
| **LMICs with \(\geq 75\) g/c/day availability** |                          |                          |                           |
| Available            | 252,454,313              | 41,088,118               | 323,830,574               |
| Industrially milled  | 192,784,284              | 9,224,401                | 214,318,585               |
| Fortified            | 37,912,274               | 6,298,563                | 143,000                   |
| % Fortified          | 19.7%                    | 68.3%                    | 0.1%                      |

\(^a\)Because rice fortification using hot extrusion technology requires high start-up costs and marginally higher maintenance costs, a clear understanding of the market feasibility and industry layout is important before undertaking national or regional mandatory rice fortification programs. Public subsidy and distribution systems likely provide the most feasible way to scale up rice fortification in the short term.

Data are from Ref. 36 and represent 236 countries worldwide and 75 LMICs (low- and middle-income countries) for wheat, 34 LMICs for maize flour, and 45 LMICs for rice.

of global fortifiable wheat flour (industrially processed) that is currently fortified in LMICs with \(\geq 75\) g/c/day availability (consumption) is only 19.7% (Table 1). Furthermore, the proportion of fortifiable maize flour and rice that is currently fortified in these countries is only 68% and 0.1%, respectively. “Industrially processed” means that it is milled in wheat and maize mills that have a capacity of at least 20 metric tons a day.\(^36\) Rice is most feasibly fortified in mills with a production capacity of at least 5 metric tons an hour.\(^36\) These figures provide baseline estimates, which would need to be updated following further design and implementation research to scale up folic acid fortification in order to ensure that all fortifiable food vehicles are fortified with folic acid, thus maximizing the opportunity to improve coverage and reduce folic acid–sensitive NTDs. This is important before designing the interventions in each of these 62 countries.

Second, in terms of the delivery of existing national programs, available data indicate ongoing issues with the quality of fortification. For example, based on single-sample testing of fortified foods in a range of national mandatory programs in LMICs, only 50% of the samples adhered to national standards.\(^37\) While single-sample testing is not the optimal way to test the performance of programs, in the absence of other data it provides an inference on ongoing quality issues that can adversely affect the potential for impact. These quality issues persist due to several factors. A 2015 survey among regulatory agencies and industry found that there is a perceived political risk in taking regulatory action against non-compliance in the food industry.\(^37\) Related issues include the frequent absence of effective government and industry incentives, follow-up action that is not transparent and objective, and a lack of clarity in the structure and role of government authority vis-à-vis regulatory monitoring and enforcement. It is important that mandatory legislation is underpinned with strong regulatory measures to ensure the quality of fortified foods.

Third, coverage of existing folic acid fortification programs is low in LMICs with mandates. Between 2014 and 2016, FACT coverage surveys were completed in seven countries fortifying maize and/or wheat flour with folic acid. From the studied countries (all of them in Africa, with the exception of the Indian state of Rajasthan), only two country programs—South Africa maize flour fortification and Senegal wheat flour fortification—achieved a coverage percentage of at least \(\geq 40\%\) for more than one vulnerable group.\(^38\) In these coverage surveys, vulnerability was defined using a composite indicator of poverty, poor women’s dietary diversity score, and rural residence and was not focused on identifying the risk of insufficient folate status. Additionally, the FACT coverage surveys found that, on average across all these countries, 35% of wheat flour consumed was fortifiable, while only 18.5% of the flour was fortified (any level). For maize flour, 48% consumed fortifiable maize flour and only 29% of the maize flour available was fortified (any level). Coverage was generally higher among urban populations and lower among at-risk population groups. Table 2 presents the relevant FACT data sets.

The aforementioned gaps in legislation, quality, and coverage of folic acid fortification programs present a critical opportunity to scale up and improve this proven intervention. This in turn can help improve intakes of folic acid among hundreds of millions of WRA in LMICs who may be at risk of having a pregnancy affected by folic acid–sensitive NTDs.
Table 2. FACT raw coverage of wheat flour and maize flour at the household level by country

|                | Uses vehicle, % (95% CI) | Vehicle is fortifiable, % (95% CI) | Vehicle is fortified, % (95% CI) |
|----------------|--------------------------|-------------------------------------|----------------------------------|
| **Wheat flour**|                          |                                     |                                  |
| Côte d’Ivoire, Abidjan | 54.7 (50.1–59.6)         | 10.2 (7.5–13.1)                     | NA                               |
| India, Rajasthan | 83.2 (79.5–86.5)         | 7.1 (5.6–9.1)                       | 6.3 (4.8–7.9)                    |
| Nigeria, Kano    | 83.9 (81.5–86.3)         | 83.8 (81.4–86.2)                    | 22.7 (20.0–25.5)                 |
| Nigeria, Lagos   | 14.2 (11.8–16.5)         | 13.8 (11.5–16.1)                    | 5.4 (3.8–6.9)                    |
| Senegal          | 81.8 (76.2–86.6)         | 81.5 (75.5–86.4)                    | 51.2 (44.7–57.2)                 |
| South Africa, Eastern Cape | 25.2 (16.3–34.1) | 25.2 (16.3–34.1) | 16.3 (10.0–23.7) |
| South Africa, Gauteng | 4.3 (1.8–7.6) | 4.3 (1.8–7.6) | 0.8 (0.0–2.3) |
| Tanzania         | 51.5 (44.5–58.5)         | 50.5 (43.3–57.7)                    | 33.1 (27.5–38.7)                 |
| Uganda           | 11.2 (7.7–14.7)          | 10.6 (7.6–13.6)                     | 8.5 (5.7–11.4)                   |
| **Maize flour**  |                          |                                     |                                  |
| Nigeria, Kano    | 77.1 (74.4–79.9)         | 11.0 (9.0–13.1)                     | 1.7 (0.9–2.6)                    |
| Nigeria, Lagos   | 12.2 (10.0–14.4)         | 2.9 (1.8–4.0)                       | 0.2 (0.0–0.5)                    |
| South Africa, Eastern Cape | 98.7 (96.5–100.0) | 98.7 (96.5–100.0) | 86.8 (80.0–92.4) |
| South Africa, Gauteng | 95.6 (90.4–98.6) | 95.4 (90.3–98.4) | 77.4 (69.8–94.9) |
| Tanzania         | 93.0 (89.7–96.4)         | 36.6 (29.2–44.0)                    | 2.5 (1.3–3.7)                    |
| Uganda           | 91.8 (87.7–96.0)         | 42.4 (32.7–52.1)                    | 6.5 (3.3–9.7)                    |

In 2015, modeling was completed to estimate the potential impact of folic acid fortification of flour on the annual prevention of NTDs for 18 LMICs for which fortified food data were available. To estimate the current and future prevalence of NTDs, the model used the methodology of Youngblood et al. with several modifications. Data from a systematic review of global NTD prevalence were utilized. The proportion of the population reached by industrially milled flour was estimated on the basis of consumption and coverage data taken from FACT/GAIN (Global Alliance for Improved Nutrition) survey data as well as the FFI. The model assumed that populations consuming adequate amounts of wheat flour fortified with folic acid will have an NTD prevalence of approximately six per 10,000. Using this methodology, the final estimates of additional NTDs that could be averted by fortification of fortifiable (industrially milled) wheat flour in these 18 LMICs were determined. If all wheat flour (both industrially milled and locally milled) in these countries could be fortified with folic acid, there is a potential to prevent 103,000 births with NTDs annually in these 18 LMIC countries alone.

Research gaps: other potential fortifiable vehicles and innovations

On the basis of current data and research, the mandatory fortification of maize meal and wheat flour with folic acid offers the greatest opportunity for strong coverage that is also cost-effective. Fortification of rice and other vehicles offers the opportunity to reach new individuals, particularly in countries where consumption of centralized processed food vehicles is high. Many questions and gaps in knowledge remain, however, related to additional or alternative folic acid fortification opportunities, including the following.

Expansion of rice fortification

Rice is a staple in many countries and regions, including Southeast Asia, which has the highest reported median prevalence (1.58 per 1000) of NTDs of any region worldwide based on a recent systematic review. Worldwide, less than 1% of fortifiable rice is currently being fortified. In India, folic acid could be added to the heavily subsidized rice made available to the poor throughout the country. In West Africa, rice fortified with folic acid could reach an estimated 130 million, largely owing to imports of rice supplies from Asia. Further research is required in both regions to assess the market feasibility of rice fortification as well as to understand who consumes the fortifiable rice
vehicle (by target group and by vulnerability) and where it is consumed (urban/rural). Likely, the most feasible way to scale up rice fortification with folic acid in the short term is through public subsidy and through public distribution systems, such as school meal programs that reach adolescent girls and government-run subsidized distribution of staple foods.

Salt and sugar as fortification vehicles

There may be additional opportunities to fortify vehicles other than these three cereal grains (maize flour, wheat flour, and rice). For example, it appears to be technically feasible to fortify salt and sugar with folic acid, and this may offer an opportunity to reach millions more in countries where cereal grains are not consumed at high levels or the grain milling industry is not conducive to fortification. A feasibility study in Guatemala examined folic acid fortification of both salt and sugar.45 Even in the presence of encapsulated ferrous fumarate as an iron fortificant, samples retained >80% folic acid in salt and approximately 70% in sugar samples after 9 months of storage at 40 °C and 60% relative humidity. Although there were no noticeable changes in organoleptic characteristics, further organoleptic testing as well as economic analysis of the use of folic acid in salt and sugar is needed. Moreover, as one limitation of these matrixes may be segregation (separation) of folic acid particles from the crystal of salt and sugar, further research in this area is also required.

Double fortification of salt with folic acid and iodine may also offer opportunities in some contexts. A recent publication outlined a new stable formulation of salt fortified with both folic acid and iodine that utilizes a single solution sprayed onto salt using standard salt iodization infrastructure and equipment.16 After fortification and 12 months of storage at ambient conditions, the formulations prepared using refined salt retained >80% of the folic acid and >90% of the iodine. For fine-grained salt, the appearance is likely acceptable owing to the pale, even dispersion of color; however, for coarse-grained salt, organoleptic issues may arise owing to unevenness of folic acid distribution, which needs to be addressed.

However, the cost sensitivity of salt fortifications must be considered. Low-income consumers are highly sensitive to the costs of the product; thus, before mandatory folic acid fortification of salt, cost sensitivity studies would be required, and, once a program is implemented, strong enforcement is needed to ensure a level playing field among producers. Furthermore, while salt iodization has been a tremendous success to date, there remain quality and coverage issues in some countries, and adding an additional nutrient to the salt fortification process may be challenging for a country’s salt industry and government to undertake.

Finally, health concerns related to salt and sugar fortification must be taken into account. There are a number of caveats that must be considered before the fortification of salt—and its derivative bouillon cubes—and sugar with folic acid is selected as an intervention to reduce folate-sensitive NTDs. Notably, as high salt consumption has been linked to high blood pressure and cardiovascular disease risk, salt reduction initiatives have been developed in various countries and promoted by the WHO as a strategy in the prevention of noncommunicable diseases.47 Thus, the use of salt as the vehicle for new fortification initiatives other than iodine and fluoride has been repeatedly discouraged by the WHO owing to the potential for confusing public health messages around salt reduction.48 However, the WHO has produced guidance on implementing complementary salt reduction and salt iodization programs.49 Similarly, although controversial, excessive sugar consumption has been associated with the development and/or prevalence of numerous metabolic disorders, including cardiovascular disease, type 2 diabetes, dyslipidemia, and obesity.50 Using it as a vehicle for fortification should be limited to mandated programs and related public health messaging should be carefully constructed.

Potential for fortification of fish sauce

Other vehicles have been considered for folic acid fortification, including fish sauce in Vietnam.51 No studies yet appear available on this intervention showing organoleptic results, bioavailability, or efficacy.

Fortified blended foods

Fortified blended foods (FBFs) are specialized blends of partially precooked and milled cereals, soy, beans, and pulses fortified with micronutrients.52 Corn soy blend (CSB) is the main blended food distributed, but wheat soy blend is also used. FBFs are designed to provide protein supplements and to prevent and address nutritional deficiencies in
food assistance programs. CSB formulations typically contain 110–170 μg of folic acid per 100 g. The reach, coverage, and potential impact of FBFs among WRA are unknown.

**Biofortification**

Biofortification, the process of increasing the nutritional quality of food crops through metabolic engineering (the redirection of one or more enzymatic reactions to produce new compounds in an organism) or conventional plant breeding, may provide an option for improving folate status of WRA. Little work, however, has been done in this area. Enhancing the folate content of foods through biofortification would require considerable financial investment, research, and implementation time and is outside the current mandate of organizations focused on such efforts. Furthermore, as increased consumption of food folate has not been shown to be an effective means to enhance folate status relative to folic acid, the focus needs to be on addition of folic acid to foods consumed on a regular basis.

**Bioavailability/efficacy to enhance folate status**

Efficacy and effectiveness studies for new fortification vehicles are needed. For example, although stability studies related to fortification of salt and sugar have been conducted, the bioavailability of folic acid added to these vehicles remains to be determined. Likewise, additional research is required to determine if the consumption of these potential new fortified food products or condiments is an effective means to enhance folate status, particularly in WRA. These types of studies were conducted with cereal grain products and provided the evidence basis for large-scale folic acid fortification of these staple food products.

**Improved efficacy with vitamin B₁₂?**

Low folate concentrations and increased risk for NTDs have been reported for WRA characterized as vitamin B₁₂ deficient or marginally deficient in several studies. As vitamin B₁₂ is intimately associated with the metabolic function of folate, it is likely that fortification with vitamin B₁₂ could improve the efficacy of current folic acid fortification programs in the prevention of folate-sensitive NTDs in countries with a high prevalence of vitamin B₁₂ deficiency. More research is needed to establish the feasibility and effectiveness of low-dose vitamin B₁₂ fortification.

**Summary and conclusions**

The trend of establishing national mandatory folic acid fortification programs has led to 81 countries, at present, mandating this intervention. While this is substantial progress, there are three critical gaps that need to be addressed to ensure that LSFF with folic acid is fully utilized in LMICs moving forward to prevent folate-sensitive NTDs: (1) the need to build and expand the enabling environment and enlarge programs where there is currently no legislation, (2) the necessity of improving existing programs of low quality, and (3) the need to measure and sustain programs by generating new coverage data and evidence of the impact of folic acid fortification in LMICs.

Furthermore, since there may be limitations to folic acid coverage of fortifiable cereal grains in many countries, it is important to invest in further research to provide the evidence base to support new, large-scale delivery vehicles. In addition to establishing the stability of folic acid in proposed new products, the positive impact of consumption of these new fortified products on folate status must be confirmed, and obstacles affecting the feasibility of manufacturing these products at affordable prices in LMICs must be overcome. To ensure that the addition of folic acid to currently consumed food commodities does not lead to increased consumption of other nutrients associated with negative health consequences (e.g., sodium and sugar), it is important to demonstrate that consumption of recommended quantities of the newly fortified products would be efficacious in enhancing folate status in WRA in LMICs.

LSFF with folic acid is a cost-effective, evidence-based intervention proven to prevent folic acid–sensitive NTDs, complement long-term strategies to strengthen food systems, increase nutritional diversity, and reduce folate deficiency. The overarching conclusion is that LSFF with folic acid is underutilized and should be a component of national public health strategies to address folate insufficiency associated with NTD risk where there is a fortifiable food vehicle consumed regularly by a majority of the population and processed by centralized industries.
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Competing interests

The authors have no competing interests.

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