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PRACTICE AND POLICY

Food Fortification Ineffective in Preventing Neural Tube Defects in India due to Regulation Promoting Inadequate Levels of Folic Acid and Vitamin B12

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ABSTRACT

Background: There is a high prevalence of neural tube defects (NTDs) and nutritional anemias that increase the risk of birth defects in India. The current staple food fortification regulations for folic acid and vitamin B12 are ineffective in the country. We provide an evidence-based viewpoint urging for WHO-recommended levels of fortificants (i.e., 1300 mcg of folic acid and 10 mcg of vitamin B12 per kilogram of wheat flour or rice) to be included in the regulation.

Methods: Micronutrient fortified foods are being distributed through various governmental safety-net programs under the National Food Security Act in India. Packaged flour produced by some private companies is fortified.

Results: Food fortification regulation, recommended in 2018 by the Food Safety and Standards Authority of India, allows adding 75–125 micrograms (mcg) of folic acid per kilogram (kg), and 0.75–1.25 mcg of vitamin B12 per kg, as fortificants in wheat flour or rice. These levels are 90% lower than what WHO recommends based on daily consumption of staple foods in India.

Conclusion: Re-setting fortification standards for folic acid and vitamin B12 to levels recommended by the WHO in India will avert thousands of NTD-associated pregnancies each year, as well as morbidity and mortality associated with them.

1 | Micronutrient Deficiencies and Public Health in India

India has successfully spearheaded several food-based initiatives within safety net schemes and programs that address "hidden hunger" in the most vulnerable population in the country.

These initiatives are aimed at addressing micronutrient deficiencies, including those of iron, folate (vitamin B9), and vitamin B12. However, a recent meta-analysis examining studies conducted between years 2015–2020 from various states of India has shown that overall, 37% and 53% of the population in India is folate and vitamin B12 deficient, respectively (Venkatesh et al. 2021). Additionally, the 2016–2019 Comprehensive National Nutrition Survey (CNNS) reported 37% and 31% of adolescents (aged 10–19 years) had folate and vitamin B12 deficiency, respectively (MoHFW 2019). While the Indian Ministry of Health and Family Welfare (MoHFW) continues to respond to nutritional needs through its daily and weekly iron and folic acid (IFA) supplementation programs, the 2019–2021 National Family Health Survey (NFHS-5) has shown that only 44% of mothers in India consumed iron and folic acid supplements for

100 days or more when they were pregnant, and just 26% consumed the same for 180 days or more when they were pregnant (IIPS and ICF 2021).

Maternal folate insufficiency before and during early pregnancy increases the risk of serious birth defects like neural tube defects (NTDs) in the fetus (Crider et al. 2014). Measured through population-based red blood cell (RBC) folate concentrations, maternal folate insufficiency threshold has been recently proposed as a valuable biomarker to assess the risk of NTD in the population (Crider et al. 2014). In populations without vitamin B12 deficiency, folate insufficiency is defined as population RBC folate concentration < 906 nmol/L (Cordero et al. 2015); however, in India, where there is a high prevalence of vitamin B12 deficiency among women of reproductive age (Goh et al. 2023; Finkelstein et al. 2021), the threshold to meet the definition for population RBC folate insufficiency is established at < 748 nmol/L (Fothergill et al. 2023). Mainly, RBC folate surveys conducted among women of reproductive age in Haryana, as well as in Southern India, showed 70%–79% of women of reproductive age (WRA) met the criterion for RBC folate insufficiency (Goh et al. 2023; Finkelstein et al. 2021).

Corresponding to the high prevalence of RBC folate insufficiency in India, meta-analyses and systematic reviews have reported a high prevalence of NTDs (i.e., ~4.0 to 9.5 cases for 1000 births) in the country (Allagh et al. 2015; Bhide et al. 2013; Sinha et al. 2024). Spina bifida, a common type of NTD, causes life-long paralysis associated with bladder and bowel dysfunction, incontinence, and hydrocephalus (Botto et al. 1999). Spina bifida is associated with a high risk of stillbirths and early mortality (Blencowe et al. 2018). Babies affected with anencephaly, another common type of NTD, die during pregnancy or soon after birth (Botto et al. 1999). Given the high burden of morbidity and mortality associated with these conditions, primary prevention should be as much a national public health priority in India as polio eradication was, achieved through determined efforts and commitment at all levels (Solomon 2019; WHO 2024).

The WHO recommends that all women, from the moment they begin planning pregnancy and trying to conceive, until 12 weeks of gestation, take supplements with 400 mcg folic acid daily (WHO 2023). However, a large proportion of pregnancies in India, especially in low socio-economic strata, who are at-risk of having NTD-affected pregnancies due to pre-existing micronutrient malnutrition, are unintended (Anand et al. 2023), and would miss the critical window for NTD prevention as it is known that prenatal supplements of vitamins with iron and folic acid are delivered after the critical window, or never delivered in the country (Toivonen et al. 2018).

2 | Sub-Optimal Food Fortification Regulation and the Missed Opportunity to Prevent Neural Tube Defects and Nutritional Anemias in India

Food fortification is known to effectively deliver micronutrients to the population during the critical window for NTD and nutritional anemias prevention (Garrett and Bailey 2018). India has a voluntary fortification policy for wheat flour and rice, with various micronutrients, including folic acid and vitamin B12 (GFDx 2024a). Fortification is currently implemented in foods distributed through various governmental safety-net programs under the National Food Security Act (e.g., Integrated Child Development Scheme (ICDS), Public Distribution System (PDS), and PM-POSHAN in schools) and some fortified packaged flour produced by private companies is available in the market in big cities. The 2018 regulation by the Food Safety and Standards Authority of India (FSSAI) recommends 75–125 micrograms (mcg) of folic acid per kilogram (kg) and 0.75–1.25 mcg of vitamin B12 per kg of wheat flour or rice for fortification (MoHFW 2018). Prior to 2018, fortification standards in India were adhering to the WHO recommendation, including 1300 mcg/kg folic acid and 10 mcg/kg vitamin B12 (Table 1). However, since 2018, when fortification regulations were changed, drastically reducing the amounts of folic acid and vitamin B12 for fortification, India has been missing a remarkable opportunity to prevent NTDs and nutritional anemias by taking an ineffective policy strategy associated with the amounts of folic acid and vitamin B12 allowed for fortification of wheat flour and rice.

In 2020, the Indian Council of Medical Research revised the nutrient requirements for Indians and published new Recommended Dietary Allowances (2020 RDA) for various vitamins, minerals, and amino acids, and the FSSAI has adopted the 2020 RDA which proposes RDA of folic acid for non-pregnant women, children, and men in the range of 110–300 mcg (FSSAI 2021). The 2020 RDA proposed for vitamin B12 ranges between 1.2–2.5 mg for non-pregnant women, children, and men (FSSAI 2021).

Guidance exists for countries to implement effective food fortification, with globally recommended forms and levels of nutrients (WHO and UN FAO 2006; WHO 2022). Specifically, fortification guidance is based on flour extraction rate, chemical form of the fortificant compound, and estimated average per capita wheat flour consumption. Figures 1 and 2 present the amount of folic acid (mcg) and vitamin B12 (mcg) included in a kilogram of fortified wheat flour in countries that implement fortification, respectively. According to the latest fortification data reported by the Global Fortification Data Exchange, the average daily per capita wheat flour consumption in India is 160 g (GFDx 2024a), and at this consumption level, the WHO recommendation points to adding 1300 mcg of folic acid per kg of wheat flour (WHO and UN FAO 2006; WHO 2022). In India, based on the average per capita consumption of 300 g of fortified wheat flour per day (Government of India, National Sample Survey Office 2024; Gupta 2012), folic acid levels in fortification amount to about

TABLE 1 | Regulatory standards for fortification—years 2016 and 2018, Food Safety and Standards Authority of India (FSSAI), Government of India.[a]

Micronutrient	Year 2016	Year 2018
Iron (compounds except NaFeEDTA)	20 mg/kg	28–42.5 mg/kg
Iron (NaFeEDTA)	—	14–21.25 mg/kg
Folic acid	1300 mcg/kg	75–125 mcg/kg
Vitamin B12	10 mcg/kg	0.75–1.25 mcg/kg

Abbreviation: NaFeEDTA = Sodiumferricethylenediaminetetraaceticacid.
[a]Food Safety and Standards Authority of India (FSSAI 2021).

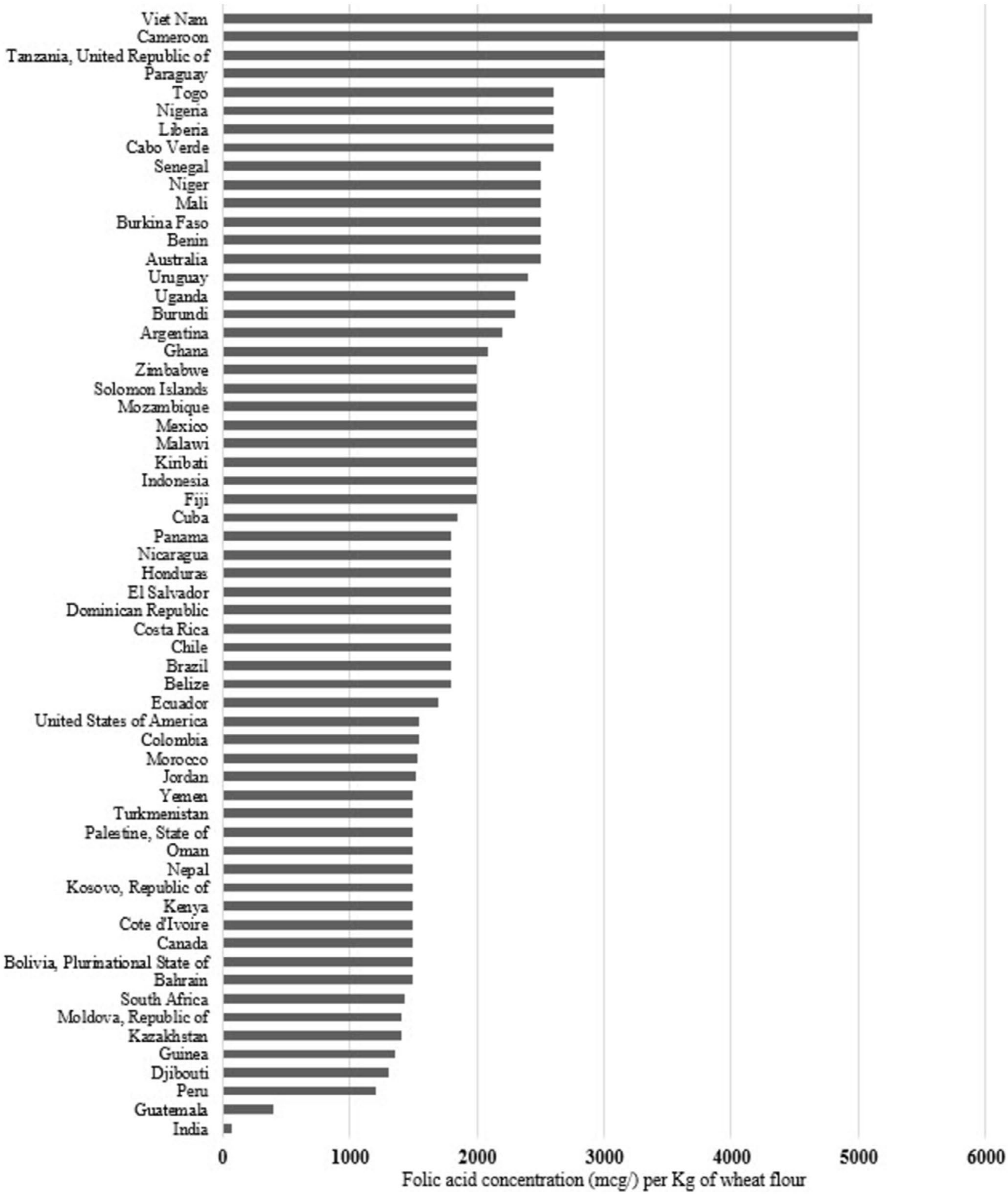

FIGURE 1 | Folic acid (mcg/kg) levels in fortified wheat flour in countries that implement folic acid fortification, based on Food Safety and Standards Authority of India Fortification Standard approved in 2018. INDIA: Year 2018 when regulatory standards changed for folic acid fortification level in India by the Food Safety and Standards Authority of India (FSSAI), Government of India (Ministry of Health and Family Welfare (MoHFW), Food Safety and Standards Authority of India (FSSAI) 2018.

400 mcg per day, which meets the recommended daily level of folic acid to prevent NTDs. The adequate vitamin B12 level for wheat flour fortification in India would be 10 mcg per kg (WHO and UN FAO 2006; WHO 2022). As stated above, this guidance was followed by India prior to the year 2018. However, the current regulations by FSSAI in India, allowing 75–125 mcg/kg of folic acid and 0.75–1.25 mcg/kg of vitamin B12 for wheat flour and rice fortification (Table 1) are 90% lower than the guidance,

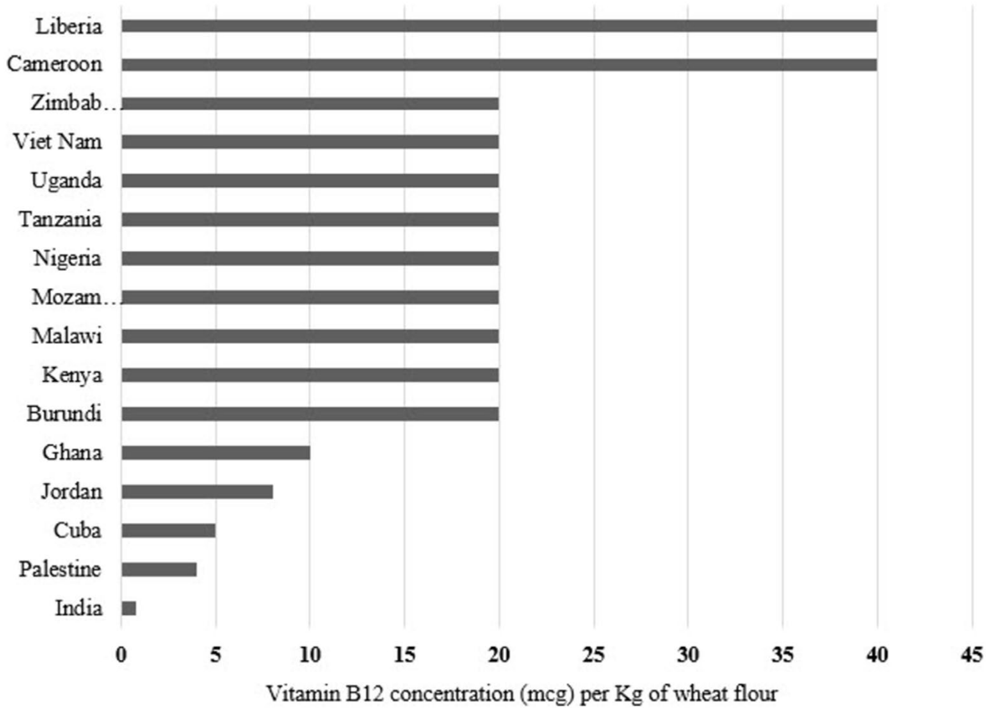

FIGURE 2 | Vitamin B12 (mcg/kg) levels in fortified wheat flour in countries that implement vitamin B12 fortification, based on Food Safety and Standards Authority of India Fortification Standard approved in 2018. INDIA: Year 2018 when regulatory standards changed for vitamin B12 fortification level in India by the Food Safety and Standards Authority of India (FSSAI), Government of India (Ministry of Health and Family Welfare (MoHFW), Food Safety and Standards Authority of India 2018).

and thus ineffective in achieving any prevention of folate insufficiency or deficiency, as well as vitamin B12 deficiency. For comparison, other countries (e.g., Kazakhstan and Mongolia) that consume similar amounts of wheat flour as compared to India (i.e., ~160–175 g/capita/day) are implementing food fortification with recommended levels of folic acid to fortified staples (i.e., 1300–1400 mcg of folic acid per kg of wheat flour) (GFDx 2024b). The main reason for lowering the fortification levels for folic acid and vitamin B12 in India in 2018 was that regulators did not elect to use more than 30%–50% of the recommended RDA for these micronutrients in the country. Their focus while setting the updated standards was only anemia, and not the high prevalence of NTDs and vitamin B12 levels in the population.

However, the fortification standard should consider the high burden of NTDs in India, and it is well-documented through meta-analyses and systematic reviews of several studies (Allagh et al. 2015; Bhide et al. 2013; Sinha et al. 2024); and more recently, biomarker-based NTD risk estimation in the population (Finkelstein et al. 2021). Additionally, the perception of harm associated with high levels of folic acid may have driven the decision to reduce the fortification standards in India in 2018. The amount of folic acid introduced through large-scale food fortification is not at a high level but rather implemented at levels below the RDA (expecting folic acid is available through various sources including diet, supplement pills, and any fortified foods), as presented in the WHO guidelines for food fortification. Field and Stover (2018) have reviewed the current evidence on the safety of folic acid and confirmed that no conclusive evidence exists on adverse effects from the levels of folic acid used in mandatory folic acid fortification, on outcomes such as cancer, cognition issues related to interactions with vitamin B12 deficiency, hypersensitivity-elated outcomes, thyroid- and diabetes-related disorders. Additionally, evidence from systematic reviews and meta-analyses, including studies done in many countries with existing mandatory folic acid fortification programs, implemented at WHO-recommended levels of folic acid, confirms that folic acid fortification safely supports public health in the population (Field and Stover 2018).

An additional consideration for folate metabolism in the body involves a single nucleotide polymorphism at the methylene tetrahydrofolate reductase (MTHFR) gene (667 C to T transition), and this has been associated with reduced RBC concentrations depending on the level of folic acid intake (Crider et al. 2011). A study by Crider et al. (2014) examined the effect of MTHFR genotype and low folate intake on RBC folate levels, and reported that low folate intake, MTHFR genotype, or both, can increase the risk of NTDs due to their impact on lowering blood folate concentrations. Populations in India where there is a higher prevalence of MTHFR T allele would require additional folate (or folic acid) to reach RBC folate threshold levels (~1000 nmol/L) for prevention of NTDs; however, Crider et al. (2014) also concluded that, "similar risks of NTDs would be expected for two populations with similar distributions of RBC folate concentrations regardless of genotype" (Crider et al. 2014).

The beneficial impact of folic acid-fortified wheat flour was demonstrated in a well-conducted population-based study in Haryana, showing that the blood folate levels were raised above the threshold needed to prevent NTDs (Duggal and Das 2023). This shows that raising the fortification standards to WHO-recommended levels, and implementing food fortification at a large scale, will have a large scope for improving micronutrient levels in the population and preventing NTDs and other micronutrient deficiencies significantly.

3 | Recommendation for Effective Food Fortification Policy and Regulation in India

Staple food fortification with WHO recommended levels folic acid and vitamin B12 is the way forward for India to prevent nutritional anemias in the population, and prevent folate insufficiency among WRA during the critical window of the pregnancy (i.e., before and during early pregnancy), and thus preventing life-threatening NTDs in their offspring. The current national regulations on the amount of folic acid and vitamin B12 permitted to be added to fortified wheat flour and rice are remarkably below the WHO recommendations. This is a time-sensitive issue for India as rice fortification is being scaled up nationally. India is missing an opportunity to prevent NTDs and nutritional anemias in the population through existing fortification guidelines. A modeled analysis based on year 2015 births alone in India showed that folic acid interventions would have prevented about 116,070 cases of folic acid-associated NTDs, and an associated 101,565 under-five deaths; and prevention of these birth defects nationally through food fortification had the potential to reduce neonatal, infant, and under-five mortality by 10.2%, 8.9%, and 8.3%, respectively, in the year 2015 alone (Kancherla and Oakley 2018). It is an inefficient use of the national resources and should be a matter of urgency for policy makers and food regulators to improve blood folate and vitamin B12 concentrations in the population, and especially, WRA. Reverting fortification standards for folic acid and vitamin B12 to levels recommended by the WHO, along with sustained implementation and monitoring of fortification, is bound to prevent thousands of NTD-associated stillbirths, elective terminations of pregnancies, and neonatal, infants and under-five deaths and associated life-long morbidity and disability in the survivors that will continue to occur each year, as well as morbidity and lost productivity associated with nutritional anemias. The beneficial impact will be visible as soon as an optimal fortification program, abiding by the recommended standards, is implemented. This change will positively contribute towards India's 2030 Sustainable Development Goals on health promotion and mortality prevention.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest. Two of the authors (P.B., S.K.D.) are employed with the Food Fortification Initiative (FFI). FFI helps country leaders promote, plan, implement, monitor or evaluate fortification of wheat flour, maize flour and rice.

Data Availability Statement

The data reported in the manuscript are from the public domain. Global Fortification Data Exchange: Country-specific levels of 2022 folic acid fortification levels (Available at: https://fortificationdata.org/list-of-countries-for-the-food-fortification-dashboard/; Accessed on August 1, 2024).

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