Preventing birth defects, saving lives, and promoting health equity: an urgent call to action for universal mandatory food fortification with folic acid

Vijaya Kancherla, Lorenzo D Botto, Laura A Rowe, Nathan A Shlobin, Adrian Caceres, Anastasia Arynchyna-Smith, Kathrin Zimmerman, Jeffrey Blount, Zewdie Kibruyisfaw, Kemel A Ghotme, Santosh Karmarkar, Graham Fieggen, Sylvia Roozen, Godfrey P Oakley Jr, Gail Rosseau, Robert J Berry

July 20, 2021 marked the 30th anniversary of the publication of the landmark trial by the British Medical Research Council showing unequivocally that maternal intake of folic acid (vitamin B_9) starting before pregnancy prevents most cases of infant spina bifida and anencephaly—two major neural tube defects that are severe, disabling, and often fatal. Mandatory food fortification with folic acid is a safe, cost-effective, and sustainable intervention to prevent spina bifida and anencephaly. Yet few countries implement fortification with folic acid; only a quarter of all preventable spina bifida and anencephaly cases worldwide are currently avoided by food fortification. We summarise scientific evidence supporting immediate, mandatory fortification with folic acid to prevent the development of spina bifida and anencephaly. We make an urgent call to action for the World Health Assembly to pass a resolution for universal mandatory folic acid fortification. Such a resolution could accelerate the slow pace of spina bifida and anencephaly prevention globally, and will assist countries to reach their 2030 Sustainable Development Goals on child mortality and health equity. The cost of inaction is profound, and disproportionately impacts susceptible populations in low-income and middle-income countries.

Background

Spina bifida and anencephaly are common neural tube defects. Anencephaly is fatal, and open spina bifida, also known as myelomeningocele, is treatable but not curable, and is associated with an increased risk of child mortality. Many individuals living with spina bifida suffer permanent disability and chronic physical and psychological health complications, requiring lifelong surgical and medical care. Surgical care for spina bifida is expensive, complex, and scarce in many countries due to a shortage of specialised surgeons and multidisciplinary care teams.

An analysis published in 2018 estimated that at least 214 000–322 000 pregnancies worldwide are affected by spina bifida and anencephaly annually, at an average prevalence of about 20 cases per 10 000 births.[1] The burden corresponds to one in every 500 births globally. In low-income and middle-income countries, the prevalence exceeds one in every 100 births. Annually, about 60 000 affected pregnancies are electively terminated after prenatal diagnosis, and another 60 000 result in stillbirths.[1]

Of the few known causes of spina bifida and anencephaly, the most predominant is insufficient concentration of folate in the mother before and during early pregnancy.[2] Diet alone is insufficient to provide the recommended daily intake of folic acid, because a considerable amount of food folate is lost during food processing and cooking.[3] In addition, food folate has poorer bioavailability than folic acid.[4] Folic acid supplement pills are recommended along with a healthy diet. Folic acid is essential for the development of the neural tube in the first 4 weeks of pregnancy, but given that half of all pregnancies worldwide are unplanned,[5] most women are unaware of their pregnancies during this critical window and might not take the recommended intake of folic acid. Health-care providers can generally only prescribe prenatal vitamin supplements when the pregnancy is discovered, typically after the fourth completed week of gestation, at which point it is too late to prevent spina bifida and anencephaly. Supplement programmes also require sustained external funding and continuous educational campaigns; they typically depend on individual behaviours and have low adherence rates.[6]

The solution is to provide adequate folic acid to women of reproductive age in a way that is timely, effective, equitable, and economical; large-scale food fortification meets all these criteria.[7]

Safety and benefits of folic acid food fortification

There is strong evidence of the safety of providing folic acid through the fortification of staple foods.[8] Contrary to concerns raised in the 1970s, folic acid does not mask anaemia caused by vitamin B_{12} deficiency.[9] Evidence of potential adverse effects of circulating unmetabolised folic acid from supplemental folic acid is inconclusive, with no clear evidence pointing to adverse metabolic and clinical effects of high intake.[10] Similarly, claims of potential risks related to cancer, cognitive impairment, diabetes-related disorders, thyroid disease, and hypersensitivity-related outcomes have not been validated.[8] By contrast, food fortification with folic acid is highly effective in safely preventing spina bifida and anencephaly, as proven by multiple studies from different countries.[11,12]

Fortified staple foods have a wide reach. Folic acid consumption, achieved through fortification, would not be limited to people (or countries) who can afford vitamin supplements or receive adequate preconception or

Lancet Glob Health 2022

Published Online
May 23, 2022
https://doi.org/10.1016/S2214-109X(22)00213-3

Department of Epidemiology, Center for Spina Bifida Prevention, Rollins School of Public Health, Emory University, Atlanta, GA, USA (V Kancherla PhD, G P Oakley Jr MD, R J Berry MD); **Division of Medical Genetics, Department of Pediatrics, School of Medicine, University of Utah, Salt Lake City, UT, USA** (L D Botto MD); **Food Fortification Initiative, Atlanta, GA, USA** (L A Rowe MPH); **Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA** (N A Shlobin BA); **Department of Neurosurgery, National Children's Hospital of Costa Rica Dr Carlos Saenz Herrera, San José, Costa Rica** (A Caceres MD); **Department of Neurosurgery, Children's of Alabama, University of Alabama at Birmingham, Birmingham, AL, USA** (A Arynchyna-Smith MPH, K Zimmerman BA, J Blount MD); **Department of Neurosurgery, Addis Ababa University, Addis Ababa, Ethiopia** (Z Kibruyisfaw MD); **Translational Neuroscience Research Lab, Faculty of Medicine, Universidad de La Sabana, Chía, Colombia** (K A Ghotme MD); **Department of Neurosurgery, Fundacion Santa Fe de Bogota, Bogota, Colombia** (K A Ghotme); **Department of Paediatric Surgery, Lilavati Hospital and Research Centre, Mumbai, India** (S Karmarkar MCh); **Department of Neurosurgery, Neuroscience Institute, University of Cape Town, Cape Town, South Africa** (G Fieggen MD); **International Federation for Spina Bifida and Hydrocephalus, Brussels, Belgium** (S Roozen PhD);

	Number of people reached (millions)	Expected number of cases of anaemia averted in women of reproductive age	Expected number of NTDs averted	Expected number of deaths under the age of 5 years averted	Expected number of DALYs averted	Expected economic value of DALYs averted (million US$)
India*	553	24 950 107	22 006	20 410	2 198 103	5532
China	1285	28 831 810	14 037	11 681	1 701 396	20 298
Bangladesh	145	3 194 605	4154	3857	369 392	594
Nigeria	109	5 374 530	3731	3519	362 564	2364
Egypt	89	1 896 955	2077	1783	161 352	699
Ethiopia	85	1 695 531	1397	1315	140 088	141
Philippines	81	809 657	1089	954	102 517	537
Angola	9	365 698	816	769	57 522	383
Morocco	32	1 016 226	547	454	66 193	310
Ghana	20	722 468	531	499	54 008	147
Benin	10	503 202	375	354	38 998	64
Indonesia	25	540 840	312	274	35 071	196

Estimates are for mandatory fortification of wheat flour or rice, or both, in selected low-income and middle-income countries in 2019 with a high potential for food fortification.[15] Data are sorted by expected number of NTDs averted. DALYs=disability-adjusted life years. NTDs=neural tube defects (largely comprising spina bifida and anencephaly). *Includes 17 Indian states: Andhra Pradesh, Assam, Bihar, Chhattisgarh, Haryana, Himachal Pradesh, Jharkhand, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Orissa, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh, and West Bengal.

Table: **Estimated annual health and economic benefits of implementing mandatory food fortification with folic acid**

Department of Neurosurgery, School of Medicine and Health Sciences, George Washington University, Washington, DC, USA (G Rosseau MD)

Correspondence to: Dr Vijaya Kancherla, Department of Epidemiology, Center for Spina Bifida Prevention, Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA

vijaya.kancherla@emory.edu

prenatal care. Large-scale fortification of staples with folic acid has resulted in eliminating folate deficiency anaemia in the USA.[13] By helping achieve folate sufficiency in women of reproductive age, fortification has also led to substantial reductions in spina bifida and anencephaly prevalence in many countries (to around 5 per 10 000 births).[11,12] Food fortification is highly cost-effective for national economies by averting health-care and other indirect costs associated with spina bifida and anencephaly.[14] A strong economic argument favours fortification, given that the estimated cost per death averted through mandatory folic acid fortification is US$957 and the cost per disability-adjusted life year is $15, similar to other recommended life-saving interventions such as rotavirus vaccines and insecticide-treated bednets for malaria.[14]

Because fortification can occur through multiple staple foods, countries can choose to fortify common food vehicles (eg, wheat flour, maize flour, and rice), and many countries have a high potential to fortify staple foods (table). Adapting fortification to diverse dietary patterns allows its benefits to reach a large proportion of the population, including low-income individuals living in areas of high urbanisation and other susceptible groups, and improves global health equity. Building on the success of the almost universal coverage of salt iodisation, double fortification of salt with iodine and folic acid is a promising new avenue in countries lacking large-scale milling infrastructure for grain fortification.[16] Fortification is highly sustainable because it does not depend on continued external funding and pre-established, far-reaching market distribution channels.[7] Fortification leverages the private sector's (eg, food producers) already established distribution channels rather than stressing an often overburdened health-care system. Fortification also does not require complex delivery processes, such as the expensive cold chain and storage infrastructure necessary for global vaccine programmes.

Once fortification is implemented, health and economic benefits continue to accrue annually at no additional setup and operational expense. Multiple micronutrients can be added to staples to address nutritional deficiencies (eg, iron, folic acid, vitamin B_{12}, and more) at a minimal cost increase to governments and food producers. Finally, by averting spina bifida and anencephaly, fortification is able to conserve resources that are otherwise devoted to the diagnosis and care of affected babies and individuals, including costly surgery and rehabilitation. Paediatric neurosurgeons treating spina bifida can be redirected to treat non-preventable neurosurgical conditions, especially in low-income and middle-income countries.

Current status and gaps in global fortification efforts

Mandatory food fortification with folic acid is an effective public health strategy to essentially eliminate folate insufficiency in women of reproductive age and prevent spina bifida and anencephaly.[17] Despite this knowledge, only about 60 countries had chosen to implement effective mandatory fortification of wheat flour, maize flour, or rice, as of the year 2020 (figure). Except for Moldova and Kosovo, no other European country implements mandatory folic acid fortification, resulting in more than 1000 pregnancies affected by spina bifida and anencephaly that are preventable every year in Europe.[18] Many countries in Africa and Asia also do not implement folic acid fortification.

About 215 000 cases of spina bifida and anencephaly could have been averted in 2019 among countries that did not implement folic acid fortification.[19] Additionally, not all countries currently implementing fortification are reaching full prevention potential due to limited implementation or low coverage of fortified food staples, or both.[20] Current gaps in global fortification can be addressed by understanding country-specific challenges, including political will, production infrastructure, monitoring frameworks, and national-level funding, and by identifying viable food staples for fortification.[20] In some countries, such as the UK and Ireland, folic acid fortification has been considered for many years and, although scientific advisory committees have decided to introduce fortification, progress on implementation has been slow.

Compared with a voluntary policy, mandatory fortification creates a more favourable environment for

food producers in terms of competition with domestic and imported goods, enables effective monitoring and measuring of added nutrients to ensure that foods meet national fortification standards and intake requirements, limits the amount of behaviour change required of consumers, and increases the proportion of the population reached. Mandatory folic acid fortification of enriched grain products has been so successful in preventing spina bifida and anencephaly that it was hailed by the US Centers for Disease Control and Prevention as one of the ten greatest public health achievements in 2001–10 in the USA.[21] A policy review of supplementation and fortification concluded that a comprehensive approach that is context-specific and combines both mandatory fortification and targeted supplementation might be most effective in preventing spina bifida and anencephaly.[22]

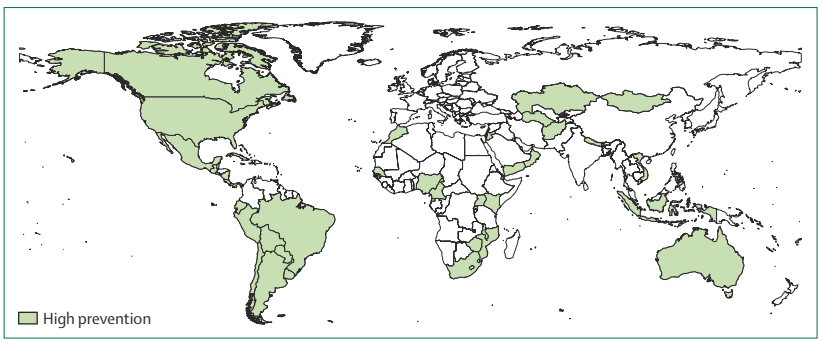

Figure: **Countries with mandatory large-scale food fortification policies for cereal grain achieving optimal prevention of folic acid-preventable spina bifida and anencephaly in the year 2020**
Countries in green provide daily intake of folic acid (>150 µg/day) through mandatory cereal grain (ie, wheat flour, maize flour, or rice) fortification to effectively prevent folic acid-preventable spina bifida and anencephaly. The figure is based on data from the Global Fortification Data Exchange . The adequate daily intake is calculated on the basis of the amount of folic acid fortification in cereal grains (µg/g), the estimated amount (g/day) of cereal grains per person available for consumption, and the proportion of cereal grain that is produced in large-scale industrial mills and fortified with folic acid.

Existing support and resources for implementing and evaluating fortification

Implementing effective fortification programmes requires buy-in from governments and the food industry. Successful global fortification programmes require: (1) science-based advocacy for global coordination; (2) technical assistance to champions enabling fortification; (3) technical support to food producers; and (4) policy guidance to governments regarding monitoring, enforcement, and evaluation of the effectiveness of programmes, including using well established biomarkers to confirm folate adequacy in the target populations.

In 2006, WHO and the UN Food and Agricultural Organization published guidelines to assist countries in implementing fortification based on national food consumption patterns and globally recommended forms of nutrients.[23] Several organisations are working to build political will for fortification through science-based advocacy, including the Center for Spina Bifida Prevention, the Food Fortification Initiative, Nutrition International, and the Global Alliance for Improved Nutrition. These organisations aid governments in assessing need, relevance, and feasibility of fortification; implementing fortification, including optimising the design and harmonising efforts with other regional or national nutrition initiatives; assessing the quality and reach of fortified foods in the population; and evaluating cost-effectiveness and nutritional impact.

Tools exist for establishing birth defect surveillance systems[24] and standard folate testing laboratories.[25] Periodic monitoring of blood folate concentrations in women of reproductive age can be integrated into existing Demographic Health Survey questionnaires or periodic national nutritional surveys. Blood folate concentrations increase within a few weeks after fortified food is consumed, swiftly informing policy makers of the effectiveness of fortification in the target population. Additionally, thresholds for optimal blood folate concentrations for spina bifida and anencephaly prevention have been elucidated recently to guide prevention (>400 ng/mL or >906 nmol/L in red blood cells; and >25·5 nmol/L in plasma).[26,27]

For more on the **Global Fortification Data Exchange** see www.fortificationdata.org

Stakeholder support and predictors of success

The International Federation for Spina Bifida and Hydrocephalus, representing people with spina bifida and hydrocephalus and their families worldwide, published a policy statement in 2005 supporting mandatory food fortification.[28] In 2010, the World Health Assembly adopted resolution WHA 63.17 on birth defects, recommending that all member nations promote equitable access to food fortification strategies.[29] In 2015, the North American Teratology Society published a resolution urging all governments to prevent spina bifida and anencephaly by 2024 through mandatory fortification of staple foods with the recommended amount of folic acid.[30] In 2018, the Folate Task Team, a group of global experts and partners under the leadership of Nutrition International, published a position statement supporting food fortification.[31] In 2020, the G4 Alliance, a federation of nearly 70 global surgery organisations in 160 countries, convened stakeholders to advocate for a World Health Assembly resolution on fortification with folic acid. In 2021, the International Society for Pediatric Neurosurgeons, the largest and most diverse paediatric neurosurgical society in the world, passed a resolution advocating for food fortification with folic acid globally.[32]

Fortification has been successful in most Latin American countries due to: (1) country champions; (2) active partnerships between the government, academia, industry, and civil society; (3) fortification of foods that are consumed by nutritionally susceptible populations in adequate amounts; (4) the use of adequate amounts of bioavailable fortificants; (5) institutional research capacity; and (6) effective monitoring and quality control measures.

Smarter Futures, a public–private–civic partnership, is working to bring together the milling industry,

governments, and development partners to support the implementation of national flour fortification programmes, to improve the nutritional quality of wheat flour and maize flour in Africa. As a case study, Costa Rica has effectively implemented folic acid fortification of multiple staples. Public health and medical sectors collaborated with policy makers to pass and enforce successful fortification legislation.

An urgent call to action for a World Health Assembly resolution on mandatory folic acid food fortification

According to the Global Fortification Data Exchange, more than 100 countries do not currently have folic acid fortification programmes. Attempts to establish food fortification programmes in these countries have often been met with requests for more research or a lack of political will, stating that spina bifida and anencephaly prevention is not a priority for national public health action. These hurdles have resulted in more than 4 million preventable cases of spina bifida and anencephaly globally in the 30 years since the British Medical Research Council's landmark trial publication providing unequivocal evidence on folic acid.[2] There are sufficient, high-quality data on the safety and effectiveness of fortification for policy makers to swiftly implement fortification.[33] Knowledge and guidance exist to assist governments and the food industry in successfully implementing fortification, but bringing fortification to scale globally has been difficult due to a lack of resources. Global spina bifida and anencephaly prevention is a missed opportunity, which can be remedied by concerted global action to overcome fortification barriers.

Mandatory food fortification with folic acid will protect pregnancies from spina bifida and anencephaly, prevent associated death and disability, and conserve and redirect already meagre surgical manpower and health-care resources. We make an urgent call to action for the World Health Assembly to pass a resolution for universal mandatory folic acid fortification of staple foods. This resolution will accelerate the pace of global prevention of severe and fatal birth defects, support equitable food fortification in all countries, and assist countries in reaching their 2030 Sustainable Development Goals on child mortality and health equity.

Contributors

All authors contributed equally to the conceptualisation, literature search, and writing, review, and editing of the manuscript. VK and LAR created the table. VK created the figure.

Declaration of interests

We declare no competing interests.

Acknowledgments

We acknowledge the G4 Alliance and the International Society for Pediatric Neurosurgery for their leadership in this call to action and thank the following partner organisations for their endorsement of this proposed World Health Assembly resolution for mandatory fortification of staple foods with folic acid (listed in alphabetical order): Center for Spina Bifida Prevention at Emory University; Food Fortification Initiative; Global Alliance for Prevention of Spina Bifida-F; International Clearinghouse for Birth Defects Surveillance and Research; International Federation for Spina Bifida and Hydrocephalus; the Latin American Pediatric Neurosurgery Association; and Nutrition International. We thank Kaustubh Wagh and Pretty Priyadarshini for assisting with the creation of the figure. We also thank Pedram Maleknia for assisting in reviewing and editing the manuscript.

References

1 Blencowe H, Kancherla V, Moorthie S, Darlison MW, Modell B. Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. *Ann N Y Acad Sci* 2018; **1414:** 31–46.

2 MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991; **338:** 131–37.

3 Marchetta CM, Devine OJ, Crider KS, et al. Assessing the association between natural food folate intake and blood folate concentrations: a systematic review and Bayesian meta-analysis of trials and observational studies. *Nutrients* 2015; **7:** 2663–86.

4 Bailey LB, Stover PJ, McNulty H, et al. Biomarkers of nutrition for development–folate review. *J Nutr* 2015; **145:** 1636S–80S.

5 Bearak J, Popinchalk A, Ganatra B, et al. Unintended pregnancy and abortion by income, region, and the legal status of abortion: estimates from a comprehensive model for 1990–2019. *Lancet Glob Health* 2020; **8:** e1152–61.

6 Toivonen KI, Lacroix E, Flynn M, et al. Folic acid supplementation during the preconception period: a systematic review and meta-analysis. *Prev Med* 2018; **114:** 1–17.

7 Zimmerman S, Baldwin R, Codling K, et al. Mandatory policy: most successful way to maximize fortification's effect on vitamin and mineral deficiency. *Indian J Community Health* 2014; **26:** 369–74.

8 Field MS, Stover PJ. Safety of folic acid. *Ann N Y Acad Sci* 2018; **1414:** 59–71.

9 Berry RJ. Lack of historical evidence to support folic acid exacerbation of the neuropathy caused by vitamin B12 deficiency. *Am J Clin Nutr* 2019; **110:** 554–61.

10 Maruvada P, Stover PJ, Mason JB, et al. Knowledge gaps in understanding the metabolic and clinical effects of excess folates/folic acid: a summary, and perspectives, from an NIH workshop. *Am J Clin Nutr* 2020; **112:** 1390–403.

11 Atta CA, Fiest KM, Frolkis AD, et al. Global birth prevalence of spina bifida by folic acid fortification status: a systematic review and meta-analysis. *Am J Public Health* 2016; **106:** e24–34.

12 Castillo-Lancellotti C, Tur JA, Uauy R. Impact of folic acid fortification of flour on neural tube defects: a systematic review. *Public Health Nutr* 2013; **16:** 901–11.

13 Odewole OA, Williamson RS, Zakai NA, et al. Near-elimination of folate-deficiency anemia by mandatory folic acid fortification in older US adults: reasons for geographic and racial differences in stroke study 2003–07. *Am J Clin Nutr* 2013; **98:** 1042–47.

14 Hoddinott J. The investment case for folic acid fortification in developing countries. *Ann N Y Acad Sci* 2018; **1414:** 72–81.

15 Kancherla V, Chadha M, Rowe L, et al. Reducing the burden of anemia and neural tube defects in low- and middle-income countries: an analysis to identify countries with an immediate potential to benefit from large-scale mandatory fortification of wheat flour and rice. *Nutrients* 2021; **13:** 244.

16 Kancherla V, Tsang B, Wagh K, Dixon M, Oakley GP Jr. Modeling shows high potential of folic acid-fortified salt to accelerate global prevention of major neural tube defects. *Birth Defects Res* 2020; **112:** 1461–74.

17 Centeno Tablante E, Pachón H, Guetterman HM, Finkelstein JL. Fortification of wheat and maize flour with folic acid for population health outcomes. *Cochrane Database Syst Rev* 2019; **7:** CD012150.

18 Morris JK, Addor MC, Ballardini E, et al. Prevention of neural tube defects in Europe: a public health failure. *Front Pediatr* 2021; **9:** 647038.

19 Kancherla V, Wagh K, Pachón H, Oakley GP Jr. A 2019 global update on folic acid-preventable spina bifida and anencephaly. *Birth Defects Res* 2021; **113:** 77–89.

20 Mkambula P, Mbuya MNN, Rowe LA, et al. The unfinished agenda for food fortification in low- and middle-income countries: quantifying progress, gaps and potential opportunities. *Nutrients* 2020; **12:** 354.

21 US Centers for Disease Control and Prevention. Ten great public health achievements—United States, 2001–10. *MMWR Morb Mortal Wkly Rep* 2011; **60:** 619–23.

22 Shlobin NA, LoPresti MA, Du RY, Lam S. Folate fortification and supplementation in prevention of folate-sensitive neural tube defects: a systematic review of policy. *J Neurosurg Pediatr* 2020; **27:** 294–310.

23 WHO, UN Food and Agriculture Organization. Guidelines on food fortification with micronutrients. Nov 25, 2006. https://www.who.int/publications/i/item/9241594012 (accessed Dec 7, 2021).

24 WHO, Centers for Disease Control and Prevention, International Clearinghouse for Birth Defects. Birth defects surveillance: a manual for programme managers, second edn. Geneva: World Health Organization, 2020.

25 Pfeiffer CM, Zhang M, Jabbar S. Framework for laboratory harmonization of folate measurements in low- and middle-income countries and regions. *Ann N Y Acad Sci* 2018; **1414:** 96–108.

26 Cordero AM, Crider KS, Rogers LM, Cannon MJ, Berry RJ. Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects: World Health Organization guidelines. *MMWR Morb Mortal Wkly Rep* 2015; **64:** 421–23.

27 Chen MY, Rose CE, Qi YP, et al. Defining the plasma folate concentration associated with the red blood cell folate concentration threshold for optimal neural tube defects prevention: a population-based, randomized trial of folic acid supplementation. *Am J Clin Nutr* 2019; **109:** 1452–61.

28 International Federation of Spina Bifida and Hydrocephalus. Policy statement on prevention of neural tube defects and mandatory food fortification. June 28, 2005. https://www.ifglobal.org/publications/if-policy-statement-on-prevention-of-neural-tube-defects-and-mandatory-food-fortification/ (accessed Feb 28, 2022).

29 WHO. 63rd World Health Assembly. Agenda item 11.7: birth defects. May 21, 2010. http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R17-en.pdf (accessed June 30, 2021).

30 Smith MA, Lau C. A resolution on folic acid fortification. *Birth Defects Res A Clin Mol Teratol* 2015; **103:** 1–2.

31 Folate Task Team. The policy environment for folic acid interventions to prevent NTDs: understanding supplementation, and laying the groundwork for fortification. April, 2020. https://www.nutritionintl.org/wp-content/uploads/2020/04/FFT_Policy-Environment-for-folic-acid-interventions.pdf (accessed Feb 28, 2022).

32 Caceres A, Blount JP, Messing-Jünger M, Chatterjee S, Fieggen G, Salomao JF. The International Society for Pediatric Neurosurgery resolution on mandatory folic acid fortification of staple foods for prevention of spina bifida and anencephaly and associated disability and child mortality. *Childs Nerv Syst* 2021; **37:** 1809–12.

33 Martinez H, Pachón H, Kancherla V, Oakley GP Jr. Food fortification with folic acid prevents spina bifida and anencephaly: a need for paradigm shift in evidence evaluation for policy-making. *Am J Epidemiol* 2021; **190:** 1972–76.