Improving maternal folate status to prevent infant neural tube defects: working group conclusions and a framework for action

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As infectious disease control programs achieve increasing success, further reductions in child mortality in low- and middle-income countries (LMICs) will require focused prevention strategies for birth defects and other noninfectious diseases. Neural tube defects (NTDs) can cause early death or lifelong disability. Preventing NTDs provides a feasible, significant opportunity to decrease the toll of birth defects and contribute to further reducing child mortality globally. The Micronutrient Forum convened a technical consultation on Folate Status in Women and Neural Tube Defects Prevention to develop a roadmap to inform and prioritize investments in NTD prevention in LMICs; help guide implementation efforts in terms of the feasibility of interventions and the potential for acceleration; and identify research and knowledge gaps. Here, we describe the impetus for and approach to the consultation and present the conclusions and a framework for developing a roadmap for action to accelerate NTD prevention in LMICs. The framework (1) provides options for action on folate status assessment; (2) outlines a way forward to develop and implement a time-bound global action plan for NTD prevention; and (3) identifies common impediments to NTD prevention, broad strategies to overcome or minimize these impediments, and basic building blocks necessary to accelerate action.

Keywords: neural tube defects; folic acid; birth defects

Introduction

Many countries have made great progress in reducing under-five mortality from infectious diseases like malaria and HIV and from vaccine-preventable diseases like measles and polio. As a result, the prevention of other causes of child mortality has taken on even greater significance to achieve further improvements in child survival. In many countries, birth defects are on the rise as a leading cause of under-five mortality 1 and must be considered in strategies for reaching the health outcomes targeted in the Sustainable Development Goals—Year 2030. 2

Neural tube defects (NTDs) include a group of common and serious congenital anomalies characterized by incomplete closure of the embryonic neural tube, leading to brain and spine anomalies that can lead to death or lifelong disability. 1 Some forms of NTD (anencephaly, craniорachischisis, and encephalocele) are lethal in the newborn period or prenatally. Others (spina bifida and encephalocele) allow for survival but require aggressive multidisciplinary medical and surgical care and impose a heavy toll on the quality of life of the individuals affected and their families. Anencephaly and spina bifida are among the most common NTDs, (each accounting for about 40–45% of all NTDs), with encephalocele constituting the remaining 5–10%. 1,3

NTDs develop during the first 28 days of pregnancy, often before women are aware they are pregnant. Importantly, folate status in women of reproductive age (WRA) is a key determinant of
NTD risk. Folate is the naturally occurring form of this B vitamin in food. Folic acid is the synthetic form used in fortified foods and dietary supplements. In many settings where dietary folate intake is low, folic acid is the largest contributor to folate status and body stores. Improving the folate status of WRA through nutritional interventions can help prevent the majority of NTDs. In 2015, the World Health Organization (WHO) issued guidance on the optimal serum and red blood cell (RBC) folate concentrations in WRA for the prevention of NTDs. An RBC folate concentration above 906 nmol/L in WRA offers the greatest reduction of folate-responsive NTDs. Mandatory fortification of staple foods with folic acid (complemented by folic acid supplementation when access to centrally processed foods is limited) is a proven intervention that improves the folate status of WRA and greatly reduces the risk of having an NTD-affected pregnancy.

The reported prevalence of NTD around the world varies widely because of real differences in incidence (conditioned by different risk factors) but also because of differences in vital registration and surveillance methods. Risk factors that can affect NTD prevalence include geography and socioeconomic, racial–ethnic, and genetic factors; access to and use of folic acid supplements or folic acid–fortified food; preconception education; completeness of case reporting, including among stillbirths; and policies that allow for screening during pregnancy and elective terminations of pregnancy for fetal anomalies (ETOPFA). Prevalence estimates may be affected by what surveillance methods are used (population- versus hospital-based, active versus passive ascertainment, and single-source versus multiple-source systems), the scope of the surveillance (e.g., whether it also includes stillbirths and ETOPFA), and the quality of data sources. For example, hospital-based systems that primarily monitor live births (a common approach in many low- and middle-income countries (LMICs)) would likely underestimate prevalence, especially of NTDs such as anencephaly. In countries with many home births, surveillance is particularly challenging, both for ascertaining congenital anomalies and for many other perinatal health conditions.

Advancing NTD prevention globally presents numerous challenges. Poorer countries in particular are most affected by a high prevalence of NTDs and face the greatest challenges. Implementation of fortification and supplementation tends to be more challenging owing to technical factors (e.g., less centralized food processing and limited industrial capacity, restricted access to supplements). Assessment of folate status is hampered by a lack of dedicated resources and limited availability and use of reliable laboratory methods. Systems to reliably assess and track NTD occurrence are scarce or nonexistent. Finally, particularly in LMICs, NTD prevention efforts compete with other pressing health needs. Strong science- and social-based advocacy at regional and national levels, as well as coordinated action at the global level, is needed to engender the political will required to secure, accelerate, and sustain high-level interest in prevention among global stakeholders.

Our objective here is to describe a technical consultation coordinated by the Micronutrient Forum to assess the global burden of NTDs, determine intervention options, and make actionable recommendations to help direct and prioritize resources for NTD prevention.

Materials and methods

The Bill & Melinda Gates Foundation provided support to the Micronutrient Forum to convene a technical consultation on Folate Status in Women and Neural Tube Defects Prevention. The goals of the consultation were to develop a roadmap for LMICs to better inform and prioritize investments in NTD prevention; to help guide implementation efforts in terms of feasibility of interventions and the potential for acceleration; and to identify the research and knowledge gaps that remain and address any questions on safety and efficacy of folic acid interventions (scoping questions of the consultation were to develop a roadmap for LMICs to better inform and prioritize investments in NTD prevention; to help guide implementation efforts in terms of feasibility of interventions and the potential for acceleration; and to identify the research and knowledge gaps that remain and address any questions on safety and efficacy of folic acid interventions (scoping questions of the consultation are publically available at http://micronutrientforum.org/folate-consultation/).

A core steering group involving the chair and co-chair of the consultation, the funding agency, and the Micronutrient Forum and its hosting institution (Nutrition International) took a multi- and interdisciplinary approach to consider how best to advance NTD prevention globally and in LMICs specifically. The first task of the core steering group was to form an impartial committee with representation from relevant sectors of nutrition and public health. Using a deliberative selection process, more than 45 global experts were considered and 10 members selected across a broad range of technical and
subject matter expertise in the areas of nutrition and nutritional sciences, folate status assessment, clinical pediatrics, epidemiology, economics, policy translation, public health program implementation, and private industry. The committee was convened twice in person and once by teleconference.

The committee was charged with reviewing global data and scientific evidence related to folate status in WRA, NTD burden, and prevention measures. They examined existing data and methods used to estimate the global burden of NTDs; the effectiveness of known interventions to prevent NTDs; and the gaps in knowledge and research of folate status, laboratory methods to assess folate status, and different approaches to NTD prevention. External experts were invited to provide additional perspectives on the actual and potential reach of folic acid fortification, innovative technologies for improving the folate status of WRA, advocacy, and best practices for estimating the current global NTD burden. The committee identified the primary impediments to NTD prevention in LMICs, strategies to mitigate these impediments, and the necessary building blocks to take action in LMICs. Options for action were identified and grouped in a key decisions framework to help guide NTD prevention in LMICs.

The committee considered the evidence and identified eight key technical and scientific areas necessary for NTD prevention. Technical reports were advanced in each of these areas: (1) current knowledge of NTD burden; (2) folate status in WRA; (3) surveillance of birth defects; (4) safety of folic acid interventions; (5) consideration of vitamin B12 status in assessing NTD risk; (6) laboratory harmonization in folate status assessment; (7) food fortification and related innovation for intervention; and (8) the economics of NTD prevention. In addition, two critical knowledge gaps with direct implications for prioritizing investment in NTD prevention were identified: (1) a scarcity of information on the folate status of WRA and (2) lack of consensus on available prevalence estimates on the global burden of NTDs. Eight committee members took lead responsibility for developing the technical reports. Additional reports were commissioned from external experts to address the two critical knowledge gap areas (folate status in WRA and global NTD burden).

The committee discussed the evidence presented in each technical report, and the draft documents were reviewed using a two-phase review process. The first phase comprised peer review of each technical report by subject matter experts (SMEs). Each draft report was reviewed by one to three individuals, with a total of 16 SMEs contributing. The second phase engaged relevant stakeholders to review a full draft of the roadmap for action, including all technical reports. A total of 12 reviewers representing 11 stakeholder organizations participated. Each received background information on the consultation and completed a structured assessment framework, including free-text open-ended feedback. All contributions from both review phases were discussed by the core group and shared with the full committee.

The committee considered all evidence and deliberated on how best to advance NTD prevention and prioritize resources in LMICs. Consideration was given to three thematic areas: (1) folate status assessment of WRA; (2) NTD burden and surveillance; and (3) interventions for NTD prevention. A set of action items and conclusions were agreed upon, leading to a roadmap for action.

The following sections provide an overview of the scope and main conclusions from each thematic area that supported the committee’s final recommendations and framework for action to advance NTD prevention in LMICs.

Results

Folate status of women of reproductive age

Folate status. Acknowledging that the folate status of WRA is a key determinant of NTD risk, the group sought to provide guidance and examples of how best to assess folate status in relation to NTD risk and to evaluate the efficacy of folic acid interventions in LMIC population groups of WRA. The group reviewed the evidence related to selected folate status biomarkers; differentiated between classical folate “deficiency” and folate “insufficiency” as a basis of NTD risk assessment based on assay-matched cutoffs; and provided examples of how the application of the WHO guidelines for optimal blood folate can be used in LMICs as a basis for evaluating current folic acid intervention programs designed to prevent folic acid–sensitive NTDs.

The committee concluded that the lowest incidence of NTDs occurs when the RBC folate concentration is $\geq 906$ nmol/L (or an assay-adjusted
cutoff), and RBC folate values below this threshold should be defined as “insufficient.” This threshold value is not a mean or median value; it is the lowest end of the RBC folate distribution that all women in the population should exceed to achieve optimal NTD risk reduction in the population. The committee supported the recommendation that the analytical method of choice to measure RBC folate concentration should be the microbiologic assay (MBA).

A second report complemented this work by providing a systematic review of folate status in WRA, including publications identified in eight databases published between 2000 and 2014 describing 45 surveys conducted in 39 countries (unpublished data). Given the diversity in methods used to estimate folate status, this review included values for serum or plasma and RBC folate (14 surveys), serum or plasma folate alone (27 surveys), and RBC folate alone (four surveys). There was a wide range of methods and cutoffs used across surveys, making it necessary to adjust the latter in order to compare results across different surveys. Resorting to a simplified classification of folate insufficiency (representing an increased risk of NTD) or folate deficiency (representing an increased risk of megaloblastic anemia or metabolic imbalance), the review found that there is a wide variation in folate deficiency (1–98%) and folate insufficiency (1–100%), with no well-defined trends by income classification of countries. The review also provided evidence that all countries reporting folate status before and after mandatory food fortification found a lower prevalence of folate insufficiency after fortification, although the magnitude of change varied considerably, possibly due to insufficient industry compliance with the national fortification policy and/or limited access of the population to the fortified products.

Given the large gaps in global knowledge of folate status among WRA, the committee suggested the following research topical areas: (1) assessment of RBC folate concentration distribution in representative population samples to appropriately evaluate the magnitude of NTD risk globally; (2) the potential use of serum folate concentration as a biomarker for risk reduction (i.e., establish the relationship between serum folate and RBC folate concentrations and then use the optimal value for RBC folate concentration to determine the corresponding threshold for serum folate concentration); (3) dietary assessment that estimates folate intake; and (4) detailed information on existing fortification programs.

Furthermore, the committee recommended that a harmonized MBA should be used to measure RBC folate and produce results that can be compared within and between different populations and over time.

Framework for laboratory harmonization of RBC folate measurements in LMICs and regions.

There remain both analytical and data interpretation challenges to assess folate status. Therefore, ensuring regional technical capacity and harmonization and developing appropriate standards and reference materials for doing so are important to increase the quantity and quality of information on folate status globally and to support NTD prevention programs in LMICs. The report for this section described the challenges in assessing folate status from analytical and data interpretation standpoints and laid out a framework for laboratory harmonization of folate measurements using the MBA via a network of regional resource laboratories.

The committee concluded that the MBA needs to be harmonized through the use of common critical reagents—most importantly the folate calibrator and microorganism—so that it can be used in LMICs to assess folate status in populations. The availability of an MBA kit that contains these critical reagents would greatly facilitate laboratory operations. The committee recommended that a network of regional resource laboratories that are proficient in conducting the folate MBA and willing and able to perform service work for other countries be established as a sustainable way to create an infrastructure where qualified laboratories produce reliable blood folate data. Each resource laboratory would undergo an annual evaluation and certification to verify and document the laboratory’s achievement and maintenance of proficiency in conducting the folate MBA. This would ensure comparability of results across laboratories and over time and allow the use of the same cutoff values to describe folate status in different populations. Furthermore, the committee identified the following research questions: (1) can a stable MBA kit be produced that can be stored refrigerated or even at ambient temperature for at least 1 year; (2) can the harmonized MBA achieve comparable or
better among-laboratory variability (<15% for serum folate and <20% for RBC folate) than commercial protein-binding assays, which currently show among-laboratory coefficients of variability (CVs) of 7–30% for serum folate and 10–50% for RBC folate, depending on the assay kit; (3) can folic acid be used as a calibrator instead of 5-methylTHF if all laboratories use the same microorganism and results are mathematically adjusted to be equivalent to 5-methylTHF calibration; and (4) can RBC folate be accurately assessed from a whole-blood folate measurement without having to separately measure serum folate and hematocrit and by using available hemoglobin data?

Consideration of vitamin \( B_{12} \) in assessing NTD risk. There is a strong biological premise for considering vitamin \( B_{12} \) as well as folic acid in NTD prevention strategies. This is based on the closely interlinked biochemical pathways involving these two vitamins. The report for this section considered two possibilities in the scope of this review: (1) that \( B_{12} \) might have an independent or synergistic role in NTD prevention, such that adding \( B_{12} \) in fortification programs might reduce NTDs further than fortifying with folic acid alone; and (2) that reduction of \( B_{12} \) deficiency among WRA might have an important function in enhancing the capacity of folic acid to prevent NTDs. Two issues concerning the relationship of \( B_{12} \) relative to NTD prevention were considered: (1) whether \( B_{12} \) should be delivered routinely along with folic acid to avoid possible masking of \( B_{12} \) deficiency and (2) whether \( B_{12} \) deficiency is an independent contributor to NTD risk. More research is needed to establish the efficacy of low-dose \( B_{12} \) fortification in WRA and to determine the optimal amount of vitamin \( B_{12} \) to add in a fortification program; possible metabolism of vitamin \( B_{12} \) to biologically inactive compounds by the gut microbiome and potential interactions of vitamin \( B_{12} \) with gut microbiome and parasitic agents, and the influence of genetic variability on vitamin \( B_{12} \) status.

The committee concluded that the known synergy between \( B_{12} \) and folic acid makes it highly probable that fortification with \( B_{12} \) may improve the efficacy of current folic acid–fortification programs to prevent NTDs. The case is much stronger in parts of the world where the \( B_{12} \) status of WRA is low and the probable benefit outweighs any known negative consequences. The committee recommends that, in countries with a high prevalence of \( B_{12} \) deficiency, consideration of \( B_{12} \) inclusion with folic acid should be a priority in NTD prevention efforts. The committee also suggested the following lines of research: an updated systematic review of vitamin \( B_{12} \) status in LMICs and determination of the optimal amount of vitamin \( B_{12} \) to add in a fortification program, with special focus on WRA.

**NTD burden and surveillance**

**Global burden of NTDs.** NTDs are associated with increased risk of stillbirths and contribute to neonatal, infant, and under-five deaths, as well as lifelong disability among affected newborns who survive. Estimates of the prevalence of NTD burden vary globally and are higher in LMICs compared with high-income countries, likely driven at least in part by higher rates of poverty and nutritional inadequacies; however, knowledge about the current global burden of NTDs has been lacking.

The technical report developed a historical perspective and review of the challenges to estimate global prevalence of NTDs. The report identified sources of variability in published literature, including surveillance processes, data quality, risk factors for NTDs, access to health and rehabilitative care, and factors such as preconception education and access to ETOPFA. Taking these issues into consideration, the report provided estimates of NTD prevalence worldwide, with notable differences between developed countries with effective food fortification, mainly in Europe (0.8–1.5 per 1000 total births); countries in Latin America and the Caribbean (0.4–1.4 per 1000 live births); LMICs in Africa (1.0–2.5 per 1000 live births); and LMICs in Asia (3.0–10.0 per 1000 live births). The report also noted that, with effective prevention programs to achieve adequate folate status in the population, it is possible to reach an NTD prevalence of 0.5 per 1000 live births.

A complementary report on this section focused on estimating the global and regional prevalence of NTDs for the year 2015 using updated information from birth defects registries and current literature. The authors estimate that 260,100 NTD-affected pregnancies occurred in 195 countries (uncertainty interval 213,800–322,000), reflecting a prevalence of 1.86 (1.53–2.30) per 1000 live births, resulting
in 117,900 (81,100–148,500) under-five deaths and 57,800 (35,000–88,600) stillbirths.

The committee identified several research needs on this topic, including quantification of all pregnancy outcomes affected by NTDs, including assessment of stillbirths and elective terminations of pregnancy associated with NTDs, as well as affected live births, and information on mortality associated with NTDs among live births, including both early deaths in infancy and reduced life expectancy due to later deaths to which NTDs contribute.

The committee concluded that the estimated global prevalence of NTD-affected pregnancies is large, and affected pregnancies are continuing to number in hundreds of thousands globally, disproportionately affecting families in LMICs. Nonexistent or deficient surveillance programs make NTDs invisible to policy makers, despite the sizeable emotional and economic impact of NTDs on families and society. Well-designed population-based birth defect surveillance systems that examine all pregnancy outcomes (including live births, stillbirths, and ETOPFA) are necessary to understand the total prevalence of NTDs in a country and to evaluate prevention programs. Blood folate surveys of WRA can also be used as a strategy to predict the NTD burden.

**Rethinking surveillance for NTD prevention.**

There is a strong practical argument for assessing and tracking concurrently the health impact of NTDs (e.g., birth prevalence and survival) together with their main cause, namely, the degree of folate insufficiency in the population. Ideally, information would derive from robust population-based tracking systems that capture all pregnancy outcomes using multiple data sources. However, a review of available information showed that many LMICs lack even basic data or vital registration systems capable of continuously generating reliable information on birth defects. This technical report considered a framework for surveillance specifically targeted at supporting and accelerating NTD prevention in LMICs.

The ideal system (“triple surveillance”) would collect information from cause to effect by integrating population surveillance of blood folate concentrations, NTD birth prevalence (among all pregnancy outcomes), and health outcomes in children born with NTDs (e.g., morbidity, mortality, disability, and quality of life). Different countries may be at different stages of preparedness and ability to implement such a surveillance system. Successful deployment of effective surveillance will require several elements: (1) adapting surveillance to local priorities and systems; (2) focusing on key data and avoiding “recreational” data collection; (3) maximally leveraging existing health care and data systems; (4) showing the usefulness of the data for prevention and care; (5) devising innovative approaches (e.g., population-based sample surveys); and (6) developing regional expertise and networks to help build and leverage high-end skills (e.g., clinical case review and epidemiologic analysis) and share findings.

The committee concluded that, by providing reliable, up-to-date estimates of the burden of disease and the potential benefits of prevention, surveillance can help increase awareness, inform policies, and track the effect of interventions. The committee recognized different challenges to be addressed in order to implement these activities, which often fall under the coordination of different specialists: epidemiologists concerned with birth defects; nutritionists focusing on nutritional status assessment and related surveys; and clinicians addressing health outcomes. However, the committee also supported the view that redesigning surveillance with the goal of NTD prevention has the potential of accelerating the pace of prevention of NTDs. These prevention efforts ideally need to incorporate an element of ongoing assessment to foster maximal effectiveness and to demonstrate benefits and address remaining gaps. The committee identified the following research questions as the basis of topical areas to address: How do actual rates of NTDs compare with the estimated models used so far?, and Does the severity and distribution of NTD types correlate with overall NTD prevalence?

**Interventions for NTD prevention**

**Large-scale fortification of staple foods and related innovations.** Food fortification with folic acid is a cost-effective intervention with the potential to cover the majority of the population in many countries. However, much work is needed to build new programs and improve industry compliance and effective coverage of existing programs. Information is needed on the reach and effectiveness of folic acid fortification, and novel approaches should be considered to reach WRA, either through...
new fortification vehicles or other technologies where high coverage is not achievable through current programs.

The report on this section considered the steps needed to effectively scale up food fortification programs for NTD prevention and provided a snapshot of relevant innovations currently under development. Details on the global situation and gaps in coverage of large-scale food fortification (LSFF) with folic acid were provided; opportunities to prevent NTD through rice fortification with folic acid were considered; and research gaps and public health policy concerns related to potential folic acid fortification of additional commodities (e.g., salt, sugar) to expand the reach to WRA were discussed.

Given that fortification plays a central role in NTD prevention strategies, it is important to distinguish between mandatory and voluntary fortification. Mandatory fortification offers greater advantages and benefits to NTD prevention than voluntary fortification efforts. Mandatory fortification sets national standards and provides the population with access to folic acid in regularly consumed staple foods without requiring behavioral changes in food consumption or dietary habits. In contrast, according to the WHO’s Guide on Food Fortification with Micronutrients, voluntary fortification is less likely to increase intakes of micronutrients across an entire population. Mandatory fortification has been legislated in most LMICs where national fortification programs have gone to scale.

The committee concluded that much work is still needed to build the enabling environment and expand programs in countries where there is no relevant legislation; to improve the coverage and quality of existing programs; and to monitor the coverage and quality of these programs and measure their impact. Considering the coverage limitations of fortifiable cereal grains in many countries, it is important to invest in further research of potential new vehicles to enhance scale-up of the delivery of folic acid. The overarching conclusion is that LSFF should be a component of most national public health strategies, particularly where there is a fortifiable food vehicle consumed regularly by the majority of the population and produced by a reasonably small number of production facilities. Several research topics based on the following questions were suggested by the committee: (1) do new vehicles for folic acid fortification offer significant opportunities to decrease NTD prevalence (new vehicles may include rice, fish sauce, salt, and sugar); (2) what are the drivers of political and business commitment for folic acid fortification and how can they be leveraged and constraints overcome; (3) what combination of incentives and penalties can be applied to ensure folic acid fortification according to standards, and what are their predicted effects; (4) what combination of regulatory monitoring improvements will lead to greater auditing and inspection of folic acid–fortified foods, which will in turn improve compliance with relevant standards with the greatest cost-effectiveness; and (5) what innovative, field-friendly technologies can be developed to better quantitate folic acid in fortified foods and/or blood folate in individuals consuming fortified foods?

Safety of folic acid. The safety of folic acid intake above the upper level (UL) remains a subject of debate. This report reviewed the evidence for the safety of folic acid fortification based primarily on the very thorough assessments conducted by the U.S. National Toxicology Program in 2015, the UK Scientific Advisory Committee on Nutrition in 2016, and other scientific literature published since these reports were released.

The committee concluded that the totality of scientific evidence fully supports the benefits of mandatory folic acid fortification in NTD prevention. Furthermore, there is no evidence of any adverse consequences resulting from existing mandatory folic acid–fortification programs that have been implemented in many countries. Given that current folic acid–fortification programs have been shown to support public health in populations and that the exposure levels are informed by and adherent to the precautionary principle (i.e., evaluating and monitoring folic acid interventions in terms of intended benefits and safety), the committee recommended support of folic acid fortification as a proven intervention to improve the folate status of the population. However, additional research is needed to assess health effects of folic acid supplement use when intake levels exceed the UL. In terms of potential research areas, the committee identified the following priorities based on the recommendations from the NTD report. First, they advocated supporting ongoing genome-wide association studies to identify genetic risk alleles associated with risk
for folic acid–responsive NTDs, identifying environmental exposures that put women at risk for folic acid–responsive NTDs, and fundamental science to elucidate the molecular pathways involved in neural tube closure defects. Second, they recommended conducting preclinical studies to test the hypothesis that conditions, including age, preexisting neoplasia, and/or genetics, may sensitize cells to cancers at folic acid exposure levels above the UL and not at levels that exceed the highest levels of human exposure observed in free-living populations. Preclinical studies are needed to determine if and how elevated folic acid intake above the UL exacerbates vitamin B\textsubscript{12} deficiency at the levels of metabolism, cellular physiology, and human pathogenesis.

**Economics of prevention: making the investment case for folic acid fortification.** Securing resources for NTD prevention remains a major hurdle at national and global levels and depends heavily on making the investment case for NTD prevention in LMICs to national and global stakeholders. There is compelling evidence that NTDs can be prevented through mandatory folic acid fortification, but efforts to do so often compete with other potential health investments. This technical report focused on building an investment case for folic acid fortification comparing the costs and benefits of folic acid fortification relative to alternative life-saving investments and informed estimates of the financing required for implementation. Costs associated with folic acid fortification included (1) “upfront” costs associated with the introduction of folic acid fortification, such as acquiring hardware required for adding the micronutrient premix to the food vehicle, training staff on the use of this machinery, establishing systems for monitoring industry compliance, and implementing related communication activities (i.e., social marketing); and (2) ongoing or recurrent costs, such as the cost of the premix, labor associated with adding the premix to the selected product, and monitoring industry compliance. Drawing from cost calculations in a scenario such as South Africa, the report estimates costs per death averted over a 10-year period, assuming 1,000,000 births per year, ranging between U.S. $1915 in the most conservative scenario (i.e., where there are limited existing fortification activities, so upfront costs are higher) and $319 in the most optimistic one (i.e., where some foods are already fortified, so initial costs are lower). Finally, the report provides estimates of folic acid fortification on averted disability-adjusted life years (DALYs). For this part, the report based its estimates on cost estimates in Zambia, assuming 670,000 live births per year. Taking as a base figure a hypothetical calculation of $14.90 US per DALY averted, the estimates range from $9.93 in a high-effectiveness scenario to $29.80 in a low-effectiveness one. Overall, the study concludes that folic acid fortification compares favorably with other well-recognized life-saving interventions, like insecticide-treated bed nets and rotavirus vaccine.

The report recognizes that more precise estimates will require better data on the costs of implementing fortification and on the costs of improving compliance where regulations are already in place.

On the basis of these findings and building on previous research, which has estimated that the return on investment of folic acid fortification programs varies from 11.8:1 in Chile to 30:1 in South Africa, the committee concluded that there is a strong economic argument for mandatory folic acid fortification. It is likely that folic acid fortification will yield a positive return on investment for societies and prevent many thousands of child deaths. The committee strongly advised that countries invest in prevention of NTDs through proven folic acid prevention programs. The committee recommended that the investment case for folic acid fortification be raised as a further argument to support government-level decisions on starting or enhancing fortification programs. In terms of research, the committee suggested the need to focus on better data on costs of introducing mandatory fortification for countries already fortifying with some micronutrients but not folic acid and for countries where there is little or no mandatory fortification.

**The way forward: a framework for developing a roadmap for action**

Outlining the steps for developing and implementing a roadmap was an integral part of the committee deliberations. After considering the available technical and scientific evidence, the committee proposed a conceptual framework to (1) identify options for folate status assessment and (2) outline a path to develop and implement a time-bound action plan for NTD prevention in LMICs. In developing the framework, the committee considered common impediments to NTD prevention in LMICs; ways
to mitigate or minimize these impediments; and the basic building blocks to advance NTD prevention in LMICs. The committee applied these considerations to three thematic areas: (1) folate status assessment of WRA; (2) assessment of NTD burden and ongoing surveillance; and (3) interventions for NTD prevention.

Table 1 summarizes the primary challenges identified in each thematic area, as well as recommendations to overcome these challenges and frame action. Challenges are grouped under three main headings: technical; market, economic, and behavioral/resources; and political and legal. The challenges identified are not exhaustive but rather indicative of the primary impediments to NTD prevention in LMIC settings. Suggestions to overcome these challenges are offered as potential strategies that can be considered for a broad approach rather than specific actions, which will have to be tailored to the specific environment where they may be applied. Topline mitigations of impediments include the following.

The first such mitigation would be to promote and support the use of an MBA kit to evaluate folate status in the population, coupled with adequate training and standardization of laboratory technicians to ensure data quality. Given the need to maintain proficiency in the laboratory procedures, and given that folate assessments at the population level in a specific country (or region) are not conducted often enough for technicians to maintain accuracy, the committee proposed to build a network of regional laboratories that may process samples from different settings. Following a “train-the-trainers” approach, this model would also allow for expanding capacities to other laboratories, as well as addressing subadequate technical expertise regarding field activities, laboratory measurement, quality assurance, interpretation, and data analysis.

A second mitigation would be to promote a phased approach to surveillance tailored to the country context to overcome limited availability in surveillance expertise, limited or no civil registration system (birth and deaths), competing needs (high mortality from other health conditions), no data for advocacy, and implementation and compliance issues with fortification.

Finally, work to prioritize, regulate, enable, validate, educate, network, train, and survey (PREVENTS) can enhance knowledge and capacity and help build the political will necessary for sustainable prevention.

Table 2 summarizes recommendations for action in each thematic area, with each recommendation seen as a building block necessary to set the stage for action. Among the first actions recommended by the committee was to establish a task group (secretariat) that will guide development and implementation of the activities required to implement the roadmap. This technical group will take on tasks including information translation and dissemination; technical assistance with folate status assessment (including establishing a network of regional resource laboratories) and identification of appropriate food/condiment vehicles for fortification; advocacy with policy makers to promote folate status assessment, birth defects surveillance and appropriate intervention programs; coordination of different stakeholders; and selected research to fill some of the salient knowledge gaps. This group will benefit from the advice of a multidisciplinary expert advisory group and will aim to work directly with national stakeholders and partners to advance the NTD prevention agenda. The focus of action will be in LMICs, and a proper landscape analysis will be needed to identify which countries are ready to proceed. Once countries are identified and initial contacts established, it will be necessary to focus on building the enabling environment for legislation, implementation, and monitoring of interventions. As mentioned before, there is also a need to build up infrastructure, particularly related to determination of folate status and NTD surveillance, as well as management of fortification programs.

Table 3 summarizes next steps, namely actionable activities in each of the three proposed thematic areas that the committee identified as critical to implement the roadmap for action. These include exploring the need, feasibility, costs, timeline, and management of laboratory and surveillance networks; harmonization of technical capacity and data (e.g., folate levels and NTD burden); and determining a country’s “state of readiness” for bringing NTD prevention efforts to scale, starting with the identification of a potential food vehicle to be fortified, assessing the minimum potential coverage of fortification via existing or proposed vehicles, and exploring (if warranted) the intersection of fortification with an innovative technology agenda.
Table 1. Primary challenges (technical, constrained resources, political and legal) to advancing NTD prevention in low- and middle-income countries and recommendations for overcoming these challenges, by the three major thematic areas necessary for future action as identified by the consultation.

| Folate status assessment in women of reproductive age | NTD burden and surveillance | Interventions for NTD prevention | Overcoming challenges and framing action |
|-------------------------------------------------------|-----------------------------|---------------------------------|-----------------------------------------|
| | Challenges | Overcoming challenges and framing action | Challenges | Overcoming challenges and framing action | Challenges | Overcoming challenges and framing action |
| Technical | • Inadequate technical expertise regarding field activities, laboratory measurement, quality assurance, interpretation, and data analysis and interpretation | • Train for all aspects and availability of laboratory procedures | • Limited surveillance expertise | • Articulate feasible options targeted to different local typologies (e.g., civil data/registration infrastructure (birth and deaths)); healthcare systems (providers and medical records); magnitude of home versus hospital births, birth defect activities in place (surveillance, prevention, and care) | • Insufficient knowledge and capacity among industry and government |
| | • Inadequate number of laboratories conducting recommended MBA | • Make an MBA kit available to country laboratories to help address access and budget barriers | • Limited or no civil registration (birth and deaths) in country | • Pilot to test tools and processes, evaluate/assess, and recalibrate and expand | • Infrastructure capacity |
| | | • Continue efforts to develop simple field technologies to assess folate status | • Few resources dedicated to surveillance designed to capture NTDs | | • Lack of pre- and postsurveillance in the health, food, and medical arenas |
| | | • Build a network of regional laboratories to enhance capacity (train-the-trainers) and increase availability of folate status assessment to help guide prevention | • Competing needs and priorities (high mortality for other health issues) | | • Implementation and compliance issues with fortification |
| | | | • No country-specific data for advocacy | | |
| | | | | | |
| Constrained resources (market, economic, and behavioral) | • Engage in political advocacy with policy makers to describe folate status data as an intermediate success measure for ultimate NTD reduction, to secure resources, necessary supplies, equipment, and training | • Limited financial incentives for surveillance without industry support/engagement | • Focus on the value of high-quality information to guide and direct prevention efforts | • Fragmentation of food processing industry |
| | • Inadequate laboratory equipment for folate assessment | | • Sampling design; good data from a few areas are better than lots of noisy/biased data from an entire country | | • Economic viability |
| | • Difficulties procuring necessary supplies to effectively and consistently assess folate status | | | | • Consumer behavior and education |
| | • Difficulty hiring and retaining qualified staff | | | | |
| | • No budget allocated for nutritional surveillance | | | | |

Continued
Recognizing that the framework does not provide a complete global action plan and does not identify specific strategic objectives, the committee conceptualized an implementation strategy that can be advanced in two phases. Phase 1 will establish a group with technical expertise to leverage influence, align funding and program implementation, tap into existing networks, and set the stage for implementation at the national level. The group will seek to advance implementation at both national and global scales and will enlist, foster, and coordinate stakeholder and partner engagement. In addition, the expert group will pursue laboratory harmonization toward establishing a standardized approach to prevention (e.g., folate assessment) and will prioritize and guide opportunities to address known gaps in research and knowledge. Phase 2 will engage multiple stakeholders to move forward with global and country-level actions, focused on creating and disseminating “global public goods” (e.g., scientific advocacy, technical support, program and research priorities) around the consequences of folate insufficiency and folic acid fortification. The country-level component will prioritize LMICs for intervention options based on country interest, presence of implementation partners, population size, and regional representation (i.e., Africa and Asia), including both countries with or without mandatory folic acid fortification policies and existing programs.

Discussion

Preventing NTDs presents a significant and incompletely realized opportunity to decrease the toll of birth defects and childhood mortality globally. Most NTDs worldwide are preventable through nutritional interventions, such as mandatory folic acid fortification, that improve the folate status in the population and particularly among WRA. However, implementing interventions globally has challenges: identifying and addressing them systematically is necessary to accelerate and scale up NTD prevention.

Among the major strengths of this technical consultation was the multi- and interdisciplinary approach followed by the core group, which brought together a cadre of highly recognized experts in

Table 1. Continued

| Folate status assessment in women of reproductive age | NTD burden and surveillance | Interventions for NTD prevention |
|---|---|---|
| Challenges | Overcoming challenges and framing action | Challenges | Overcoming challenges and framing action | Challenges | Overcoming challenges and framing action |
| Political and legal | | | |
| • Transfer of specimens and data between laboratories | • Build existing laboratory infrastructure | • Little to no interest in the topic | Take the long-term as well as the short-term view: | • Fraud and petty corruption | Employ a “PREVENTS” approach* |
| • Geopolitical positions | • Provide examples of legal agreements for materials transfers | • Lack of appreciation on the value of NTD surveillance | • Early deliverables: data for baseline and advocacy | • Challenges with prioritization | |
| • Delayed access to data to monitor public health progress | • Effectively plan to anticipate potential barriers | • Competing priorities with more “visible” issues | • Build for the future: countries transition to mature systems (more in-hospital births, better care leading to survival, and higher priority for birth defect evaluation and interventions) | • Lack of leaders and champions | |
| • Advocate for action and investment | • Advocate for investment and action can be considered to overcome the impediments | • Lack of birth defects advocacy groups or champions | | • Limited to no budget availability | |
| | | | | • Legal frameworks | |

*The PREVENTS approach is to: Prioritize NTD prevention and fortification by establishing the need to improve population nutrient intake; Regulate fortification through appropriate standards, legislation, and oversight; Enable (establish standards and appropriate legislation, set program goals, build partnerships, develop marketing and communication strategies, target advocacy efforts, set up enforcement framework, procure, and develop a monitoring system); Validate refers to concerns regarding issues around NTDs as well as those of food fortification; Educate on the benefits of folic acid fortification; Network and coordinate with multiple stakeholders; Train industry to support quality assurance and compliance; Survey (set up surveillance to monitor compliance, safety, and success).
their fields to focus on a well-defined problem and develop a tangible roadmap for action. The dedicated commitment of the committee members, as well as of the SME and stakeholder reviewers, facilitated meeting tight deadlines and maintaining a streamlined, focused process. Likewise, engaging in a comprehensive review process served as an effective way to share the scope and activities of the technical consultation, allowed for invaluable feedback, and further strengthened this work by facilitating inputs and the buy-in of the proposed roadmap by external groups.

At the outset of the consultation, it was recognized that current global data on folate status and NTD prevalence were lacking. The folate status of WRA was virtually unknown in many countries, and effective birth defects surveillance was largely absent in many countries, so most of the available NTD prevalence data were based on model estimations. The consultation aimed at addressing some of these knowledge gaps by systematically reviewing and integrating information from multiple sources, studies, and publications to provide updated data on both folate status of WRA and the global burden of NTDs. Information on population folate status remains an important area for NTD prevention efforts, both to identify high-risk populations and to help generate political will to invest in effective interventions. However, our review showed that population-based information on folate status is generally unavailable globally, particularly in LMICs (unpublished data). We also learned that, among the scant number of surveys that do exist in low-income countries, the results are not comparable, as different methods of assessing folate status were used (unpublished data). The committee strongly endorsed the need to obtain better information on folate status of WRA, which will require the use of appropriate laboratory methods to assess folate status and correct interpretation of the data to help support NTD prevention efforts. The new estimations for global NTD prevalence for 195 countries for the year 2015 provide a needed update on this figure and underscore the magnitude of the problem, calling for a more dedicated effort to prevent these conditions.

Though mandatory folic acid fortification is an effective intervention for NTD prevention, obstacles to policy adoption and program implementation remain, making it challenging to deliver adequate levels of folic acid to populations. It is fair to recognize that fortification policies do exist in a number of LMICs, but there is an urgent need to implement these interventions at a large scale and in a sustained manner and in countries with the highest expected burden. One of the key drivers for adopting and scaling up folic acid fortification is demonstrating the investment case for fortification to drive the political will to invest in it among a myriad of other competing priorities. Our review highlights that investment

Table 2. Recommendations (building blocks) to move to action on each of the three thematic areas identified by the consultation

| Folate status assessment in women of reproductive age | NTD burden and surveillance | Interventions for NTD prevention |
|------------------------------------------------------|-----------------------------|---------------------------------|
| • Establish a folate task group (secretariat) to steer the implementation of the roadmap, supported by an expert advisory group | • Set realistic goals and timelines for accurate and meaningful tracking | • Establish a need |
| • Generate kit components needed by resource laboratories | • Engage advocacy groups that play a vital role in realizing action | • Build the enabling environment |
| • Identify potential resource laboratories | • Use preliminary data for advocacy purposes and longer-term outcome data to evaluate the impact of interventions | • Legislate |
| • Train-the-trainers and continued training and development | • Consider action that is in step with the country context (e.g., infrastructure, capacity, and development) to realize sustainable long-term prevention | • Implement the programs |
| • Conduct landscape analysis to identify countries which may be prioritized to start working with | | • Set up surveillance systems to monitor compliance, safety, and success |
Table 3. Immediately actionable areas for roadmap implementation on each of the three thematic areas identified by the consultation

| Folate status assessment in women of reproductive age | NTD burden and surveillance | Interventions for NTD prevention |
|--------------------------------------------------------|-----------------------------|----------------------------------|
| • Explore the need, feasibility (technical and political), costs, timeline, and management of a laboratory network | • Explore the need, feasibility (technical and political), costs, timeline, and management of NTD surveillance network | • Consider any “quick wins” for fortification that could be mapped out and applied to prioritize countries where near-term resources and efforts can be applied |
| • Consider two laboratories per WHO region to help assuage any political issues of sending samples between countries and make the network more manageable | • Develop practical, tiered surveillance solutions addressing typical challenges in LMICs, including scarcity or lack of registration systems and health records, varying proportions of home births, and lack of specialized medical training | • Prioritize assessment of a country’s “state of readiness” |
| • Further consider what may be needed to include folate in nutritional assessments and whether support for harmonization of laboratory assessment should be broadened to general nutritional status and multiple micronutrients, rather than focused on folate assessment only | • Explore innovative approaches to potential challenges, including the use of population sampling, point-of-care photography, and distance-based training to streamline the process and ensure quality | • Explore the minimum potential coverage of a fortification vehicle to motivate a related fortification program as well as the maximum number of production sites to reach an identified level of coverage |
| | • Explore collaborations with existing health surveillance systems (neonatal, pediatrics, nutritional, woman, and child) to minimize start-up costs, promote sustainability, and increase the use of data for multiple stakeholders | • Facilitate understanding of how best to guide countries in fortification vehicle selection, including listing all appropriate vehicles for folic acid fortification, and connect that with a technology agenda. |
| | • Develop a regional network to share harmonized surveillance data and identify regional differences | • Consider a step-wise approach: |
| | • Build into surveillance a process for timely dissemination of information to support the advocacy agenda | (1) identify the feasibility of fortification; |
| in folic acid fortification makes sound fiscal sense, with demonstrated health impact economic estimates on cost per death averted through mandatory fortification and cost per DALY.20 | | (2) identify specific fortification vehicles and delivery platforms to reach the target population; and |
| The proposed framework for action to advance NTD prevention in LMICs requires an application of some key principles: (1) pursuing harmonization on advocacy and implementation to maximize and leverage resources, strengthen impact, and develop a standardized approach to prevention where appropriate (e.g., folate assessment methods, stakeholder and donor engagement); (2) implementing evidence-based interventions (i.e., food fortification) and improving the coverage and quality of those interventions already launched; (3) exploring innovative strategies and identifying new entry points for prevention to achieve maximum effective coverage, acceleration, and sustainability of prevention efforts; (4) engaging national-level stakeholders from the outset and providing a toolbox of options that can be tailored to specific country needs and capacity; and (5) effective coordination and collaboration among partners to achieve common goals. | | (3) explore potential pharmacologic or other technological approaches to delivering folic acid and any related program feasibility. |
| Research and knowledge gaps were identified across the full spectrum of scientific and program areas necessary for folate assessment and NTD prevention. Prioritizing and identifying opportunities to fill these gaps is of primary importance and will require strong engagement with global and national organizations already engaged in these efforts. | | |
small committee, some subject matter areas may have been only partially represented. For example, representation of those affected by NTDs would have contributed first-hand insights into the consequences of NTDs for survivors and related advocacy efforts. Also, we recognize that the proposed framework provides a way forward toward implementing a global action plan but does not present a detailed roadmap, as the plan does not provide country-specific strategic objectives, a timeline for achieving these objectives, or specific roles and tasks to be taken by individual agencies and stakeholder groups.

In spite of these caveats, the work of the committee underscored three basic issues: the high global prevalence of NTD-affected pregnancies; the urgent need to tackle this burden with effective prevention strategies known to prevent the majority of NTDs; and the low priority currently given to NTD prevention in many countries. Inaction continues to contribute to the significant emotional and economic impact on families and society at large. There is an urgency to advance and accelerate NTD prevention activities in LMICs. The proposed roadmap for action can help provide a clear path forward to help direct and prioritize investments, advance resource mobilization, and garner the political will to accelerate NTD prevention in LMICs. As we found throughout this process, there is very strong interest among the various stakeholders in nutrition and public health to advance NTD prevention.

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Competing interests

The authors declare no competing interests.

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