FOLATE TASK TEAM

KNOWLEDGE BRIEF

IMPROVING FOLATE STATUS IN WOMEN OF REPRODUCTIVE AGE TO PREVENT NEURAL TUBE BIRTH DEFECTS

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The Folate Task Team comprises a group of global experts and partners under the leadership of Nutrition International through NTEAM, all joined together to identify priority actions to reduce folate-sensitive neural tube defects, build laboratory capacity for the assessment of folate status, support research in this critical area and to facilitate access to folate-related knowledge products.

NTEAM, as a part of Nutrition International, works with the world community to identify nutrition issues that need championing, bringing together global experts with special perspectives and varied backgrounds, to tackle the issue together.

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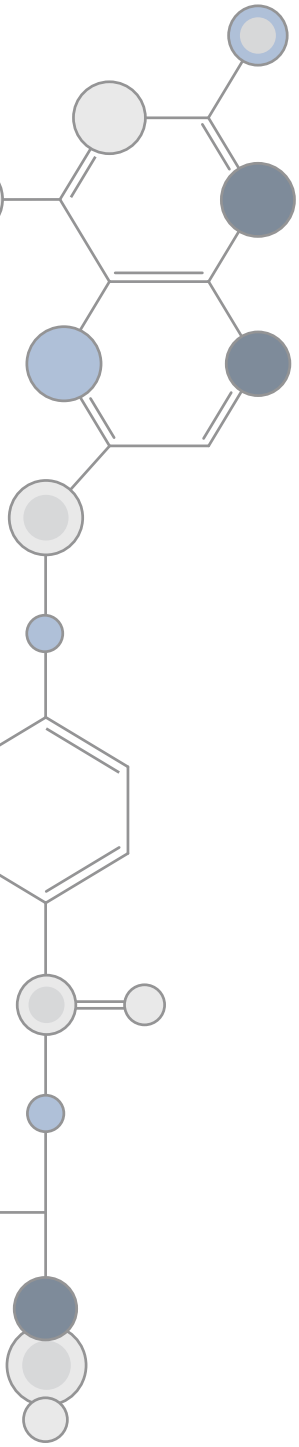
INTRODUCTION

Neural tube defects (NTDs) are made up of a group of severe birth defects (the most common of which are anencephaly[I] and spina bifida[II]) that affect the brain and spine. While anencephaly often results in early death, spina bifida has a varying degree of outcomes. When no treatment is offered, the condition will most likely result in premature death. In contrast, rehabilitation and surgery may allow affected individuals to adjust to this life-long disability with different different degrees of success, but with considerable economic and social costs. NTDs develop within the first 28 days of pregnancy, often before a woman knows she is pregnant. For this reason, it is critical that NTD prevention begins before, and continues throughout, pregnancy.

There is a paucity of high-quality data in the regions of the world with the highest burden, yet based on web-based reviews of birth defect registry databases and systematic literature reviews, and excluding early spontaneous fetal losses and elective terminations of pregnancy, it is estimated that in 2015 there were 260,100 NTD-affected pregnancies worldwide, which resulted in 57,800 still-births and 117,900 under-five deaths.[1] Nearly half of the total estimated NTD-affected birth outcomes in 2015 were estimated to be cases of spina bifida (128,000). While a majority may survive the newborn period, more than three-quarters of those born in low- and middle-income countries die before the age of 5.

On average, 1.86 per 1,000 live births are affected by NTDs around the world. The data show that low- and middle-income countries disproportionately bear the most of this burden:

- Asia 3.0-10.0 per 1,000 live births
- Africa 1.0-2.5 per 1,000 live births
- Europe 0.8-1.5 per 1,000 live births*
- Latin America and the Caribbean 0.4-1.4 per 1,000 live births
- High-income countries with mandatory food fortification 0.5-1.0 per 1,000 live births.[2]

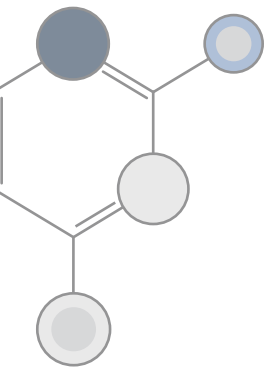


* Access to prenatal screenings and elective terminations of pregnancy for fetal anomalies influence the prevalence of NTDs per live births in most European countries.

While NTDs are known to be multifactorial conditions, improving the folate[III] status of women of reproductive age (WRA) has proven to reduce the occurrence of NTD-affected pregnancies globally; other causes include genetics and environmental factors. To reduce the burden of NTDs globally, it is essential for WRA to have sufficient folate status before pregnancy occurs. The World Health Organization (WHO) recommends WRA ingest 400 micrograms of folic acid daily from fortified foods or supplements (that is, in addition to the folate already provided by their regular diet) throughout their reproductive age, but at minimum for at least 3 months prior to a pregnancy. One of the most cost-effective and efficient ways to increase folate status in WRA is through large-scale, mandatory food fortification.

ROADMAP FOR ACTION

Between December 2016 and April 2017, the Micronutrient Forum, which was supported by the Bill & Melinda Gates Foundation and hosted by Nutrition International, convened a technical consultation on the *Folate Status of Women and Neural Tube Defect Prevention*.[3] The consultation focused specifically on neural tube defect (NTD) prevention opportunities in low- and middle-income countries, and published a Roadmap for Action that will serve as a guide for harmonized global neural tube defect prevention efforts.[4] The Roadmap was shaped by eight technical reports produced through the consultation, which have now been published as a special Supplement by the Annals of the New York Academy of Sciences (Feb. 2018. Vol. 1414. doi. 10.1111/nyas.13593).



KEY MESSAGES

- In 2015 there were an estimated 260,100 NTD-affected pregnancies worldwide, which resulted in 57,800 stillbirths and 117,900 deaths of children less than five years of age
- Countries in Asia and Africa suffer the highest levels of NTDs per live births:
  - Asia 3.0-10.0 per 1,000 live births
  - Africa 1.0-2.5 per 1,000 live births
  - Europe 0.8-1.5 per 1,000 live births*
  - Latin America and the Caribbean 0.4-1.4 per 1,000 live births
  - High-income countries with mandatory food fortification 0.5-1.0 per 1,000 live births

* Access to prenatal screenings and elective terminations of pregnancy for fetal anomalies influence the prevalence of NTDs per live births in most European countries.

- Folate status is best assessed by using a microbiological assay of red blood cell folate concentration, and this method should be implemented universally to assess folate status in women of reproductive age
- Triple surveillance will ensure that global data on NTDs are standardized and include:
  1. Folate status
  2. NTD prevalence, and
  3. NTD-related health outcomes
- Food fortification with folic acid has successfully reduced NTD prevalence in countries with mandatory fortification policies and coexisting quality assurance mechanisms
- The cost per death averted through food fortification with folic acid is less than other well-accepted and widely implemented lifesaving investments

WHAT WE KNOW

The Role of Folate

How is folate deficiency related to NTDs?

Folate plays a key role in the closure of the neural tube (tissues and bone surrounding the spine and the brain). When folate concentration is below the optimal level recommended during early pregnancy (in the first 28 days), the neural tube is at risk of not closing, resulting in exposure or malformation of the spinal cord or brain. Interventions such as food fortification and supplementation with folic acid before and during this vulnerable stage of pregnancy have proven to be effective in reducing the risk of NTDs by improving women's folate status.

How do we know if women are folate deficient?

The most accurate way to assess folate status is through a laboratory blood test known as the red blood cell (RBC) microbiological assay (MBA).[5] The MBA is recommended by the WHO as the most accurate and reliable laboratory method to assess folate status. The majority of NTDs are caused when folate levels in the population of WRA are below what is known as the optimal level[IV] for NTD prevention during the first weeks of gestation.[6] However, this method is not currently applied consistently in many laboratories, making it difficult to compare results across, and even within, countries. As a result, there is no clear picture of the global burden of folate deficiency and tracking progress of NTD prevention efforts is challenging.

What should we do to improve folate assessment?

Understanding these challenges in folate assessment led the technical consultation on the Folate Status of Women and Neural Tube Defect Prevention to conclude that it is vital to harmonize folate laboratory assessment methods globally.[7] The committee recommendations include:

- Building capacity of lab technicians
- Upgrading technical equipment
- Updating laboratory facilities, and
- Applying the RBC MBA as the universal technique for assessing folate status

Nutrition International is working in collaboration with the CDC to train lab technicians, and harmonize assessment techniques at harmonize assessment techniques at regional laboratories across the globe.

Tracking Neural Tube Defects

How do we track NTD burden?

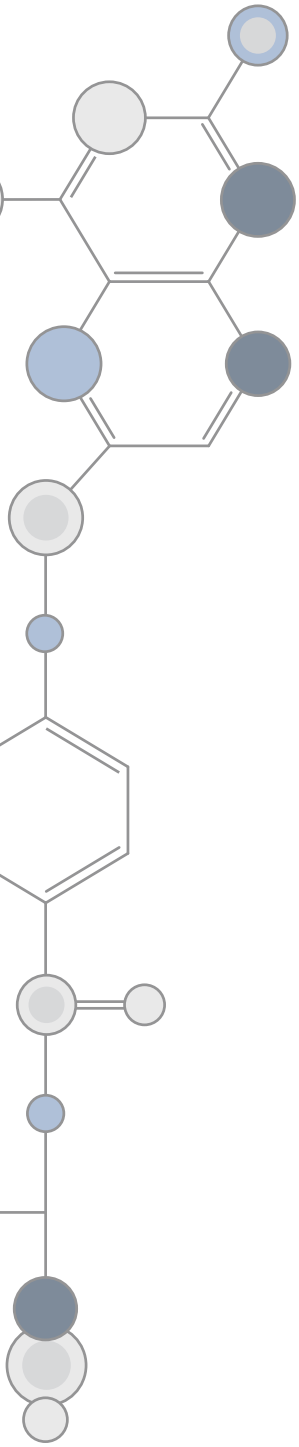
There are significant challenges in collecting and monitoring data on birth defects in general and NTDs specifically. These include:

- Historical data from around the world are limited
- Methods used for collecting information are not standardized and vary greatly
- Data collection methods do not always account for all NTD-affected pregnancy outcomes (including live births, neonatal death, stillbirths and elective terminations of pregnancies for fetal anomalies)

Therefore, it is essential to improve data collection on birth defects and surveillance systems to monitor the prevalence, and successful prevention, of NTDs worldwide and specifically in low- and middle-income countries.

As with folate assessment, the consultation worked to identify a practical and comprehensive approach to track NTD burden and impact of prevention efforts. The result was a recommendation for countries to consider a triple surveillance[8] approach, which includes surveillance of:

- Folate status
- NTD prevalence, and
- NTD-related health outcomes



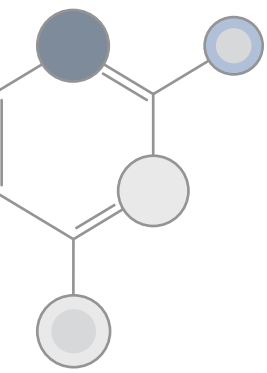
What steps can countries take to implement triple surveillance?

First, countries can conduct harmonized determinations of folate status in WRA to assess the NTD risk in a population, and then identify and implement appropriate interventions. Second, adequate birth registration systems must be implemented to track all NTD-affected pregnancy outcomes, including stillbirths and elective terminations, as specified above. This will ensure that the true magnitude of NTD prevalence is documented and available to policy-makers and public health care professionals. If the true prevalence of NTD remains unknown, the problem of NTDs becomes invisible to policy-makers. Third, the health outcomes of babies born with these birth defects need to be recorded to help countries monitor the impact of prevention efforts and remain informed on the needs of those affected and their families.

How Food Fortification Pays Off

What is needed for effective NTD prevention through food fortification?

Food fortification has the potential to reach the majority of a country's population when implemented under the right policy environment, i.e. when it utilizes food vehicles, or food types, that are consumed by a majority of the target population, is mandatory, is conducted through large-scale food-processing industries, and is properly regulated with effective monitoring.[9] Many countries have found fortifying cereal grains – such as wheat flour, maize flour and rice – with folic acid to be the most effective food vehicles to reach the majority of their population. However, further research is necessary to create opportunities to expand fortification beyond traditional food vehicles to others such as bouillon cubes, salt, sugar and fish sauce for other countries or target populations where the traditional food vehicles have limited consumption, particularly by populations at high risk of micronutrient deficiencies.[9] For example, for Indigenous Guatemalans or Aborigines in Australia whose diets do not typically include fortified food vehicles that the rest of the



majority population consume, such as wheat or maize flour and grains.[2]

Mandatory food fortification with folic acid has proven to be feasible, economical, and an effective intervention to reduce the risk of NTDs in countries that have implemented it, including in Canada, the United States, Costa Rica, South Africa, Guatemala, Indonesia, Vietnam and others.[9,10] In many countries NTDs have been consistently reduced to 0.5-1.0 per 1,000 live births after fortification programs have been properly implemented.[11] However, many low- and middle-income countries have mandated national fortification programs with little consistency in enforcement and quality assurance. More widely applied policies towards mandatory fortification developed in tandem with quality assurance mechanisms will ensure more people have access to nutrient-rich foods that can improve folate levels in WRA.

What are the safety concerns of folic acid food fortification?

The WHO recommends 400 micrograms (µg)/day of folic acid be consumed by WRA in addition to folate naturally present in foods, within a maximum (also known as the upper intake level) of 1000 µg/day.[12] Concerns regarding the safety of consuming folic acid through food fortification have been considered and studied. As a result, a comprehensive review of the published literature has shown no adverse health consequences from mandatory fortification programs.[12] Mandatory fortification programs have been occurring for over two decades in several high-income countries, including in North America.[13,14] Women who have previously given birth to a child with an NTD may have to take much larger amounts of folic acid (4 to 5 mg daily) than may be supplied via natural or fortified food, making it necessary to resort to supplementation.

What are the costs of NTD prevention through food fortification?

There are two sets of costs associated with food fortification—upfront and ongoing.[15] Upfront costs include: purchasing the micronutrient (e.g. folic acid); equipment to add the proper amount of folic acid when processing wheat and grains; training staff at mills; and, setting up mechanisms for monitoring and evaluation. Ongoing costs include: labour and utilities; testing and compliance; retraining; monitoring and evaluation; and marketing. Further costs may be associated to advocacy and education activities.

The average cost per NTD-death averted through food fortification has been estimated to an equivalent of US $957, whereas the cost per death averted by the rotavirus vaccine is US $3,015, and US $2,770 per death averted by insecticide-treated bed nets and other malaria prevention interventions.[15] Additional research has found that life-time costs for an individual living with spina bifida can range between US $100,000 and US $700,000 depending on the country of residence and access to services including healthcare, education and caregivers.[15]

WHAT'S NEXT?

Nutrition International, supported by the Bill & Melinda Gates Foundation, has convened a Folate Task Team. The purpose of this task team is to coordinate a global effort to act upon the Roadmap for Action and provide technical expertise in the effort to reduce NTDs.

Next steps include:

- Facilitating access to the scientific and technical consultation of the Roadmap for Action and folate-related knowledge products
- Conducting a landscape analysis to prioritize countries where actions to reduce folate-sensitive neural tube defects are needed and likely to show impact
- Building laboratory capacity in a selected number of low- and middle-income countries to harmonize assessment of folate status, and
- Supporting research to further inform the activities required to implement the global action plan

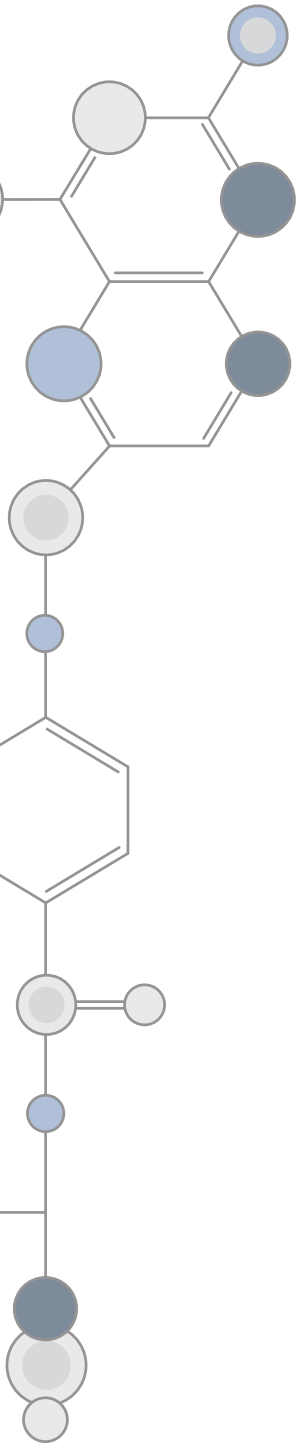
TAKE AWAY MESSAGES

FOR DECISION-MAKERS

- Low- and middle-income countries face the highest levels of NTDs globally
- Mandatory food fortification with folic acid is the most impactful and economically viable investment to overcome this burden
- In countries already mandating fortification, enhanced monitoring and evaluation of programs will help ensure industry compliance and quality of fortified foods, making sure that target populations are receiving fortified foods
- Fortifiable food vehicles must be taken into consideration, where in some areas target populations do not consume traditional foods and require fortification of other food types such as salt, sugar and bouillon cubes
- Improved “triple surveillance” will highlight the true burden of NTDs, including the number of pregnancies affected, the health outcomes of babies born with NTDs and the impact of care on society
- Published literature has shown no adverse health consequences as a result of mandatory fortification programs implemented for decades in many countries
- The cost of NTD prevention compares favourably to other life-saving interventions such as the rotavirus vaccine and insecticide-treated bed nets to control malaria
- The average cost per NTD-death averted is less than the cost of public health services to care for an individual afflicted with an NTD

FOR RESEARCHERS

- The RBC MBA provides the most reliable assessment of folate status in a population and should be universally applied by properly trained laboratory technicians, allowing for meaningful comparisons within and between different populations
- There is a need to collect complete and reliable NTD data accounting for all pregnancy outcomes including: live births,



neonatal deaths, stillbirths, and elective terminations of pregnancies for fetal anomalies
- Complementary strategies to folic acid fortification of traditional food vehicles and supplementation must be found to cover hard-to-reach populations, particularly in low- and middle-income countries

FOR THE PUBLIC

- NTDs develop within the first 28 days of pregnancy, often before a woman knows she is pregnant
- Maintaining sufficient levels of folate in WRA before and during pregnancy is key to reducing the risk of an NTD-affected pregnancy
- Consuming foods fortified with folic acid is a practical solution for attaining and maintaining the necessary levels of folate to reduce NTD risk

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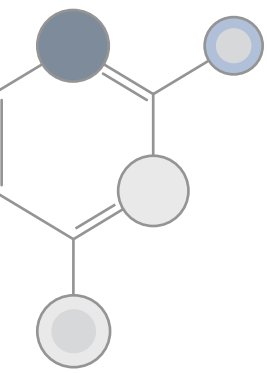

their comprehensive review of the Report of the Roadmap for Action: Center for Spina Bifida Prevention, Rollins School of Public Health, Emory University; CDC-National Center on Birth Defects and Developmental Disabilities; CDC-National center for Chronic Disease Prevention and Health Promotion; International Federation of Spina Bifida and Hydrocephalus; March of Dimes; Micronutrient Forum, Steering Committee; Nutrition International (Africa region); Nutrition International (India office); Scaling Up Nutrition; WHO-South-East Asia Regional Office – Newborn, Child and Adolescent Health; and WHO-South-East Asia Regional Office – Nutrition.

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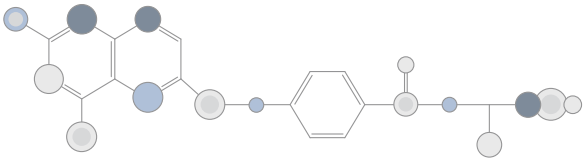

ENDNOTES

I. Anencephaly: A birth defect in which parts of the brain and skull of a baby are not formed during pregnancy.[16] https://www.cdc.gov/ncbddd/birthdefects/anencephaly.html
II. Spina Bifida: Occurs when the neural tube does not close all the way, and can happen anywhere along the spine.[17] https://www.cdc.gov/ncbddd/spinabifida/facts.html
III. Folate is a B vitamin that occurs naturally in food. Folic acid is the synthetic form used to fortify foods or make supplements.
IV. The optimal level of folate for NTD prevention is 906 nmol/L determined in red blood cells.

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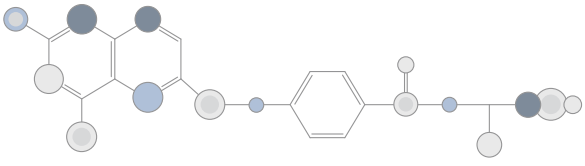

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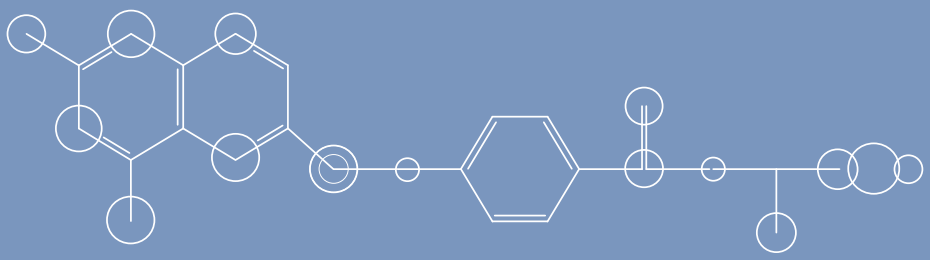

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