THE IMPORTANCE OF FOLIC ACID FOOD FORTIFICATION TO PREVENT NEURAL TUBE DEFECTS

ADVOCACY BRIEF
ABOUT THE FOLATE TASK TEAM

The Folate Task Team comprises a group of global experts and partners under the leadership of Nutrition International (NI) through NTEAM (Nutrition Technical Assistance Mechanism), 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.

Through NTEAM, NI shares its expertise globally to support the scale-up of nutrition for the most vulnerable. We believe that knowledge, rigorously obtained and generously shared, is key to effective progress for nutrition. NTEAM convenes global experts to tackle key nutrition issues and encourage broad use of knowledge by translating technical information and research into accessible guidance, tools and resources. We also work with countries and agencies, sharing expertise through timely and coordinated technical assistance.
FRAMING THE ISSUE

Neural Tube Defects (NTDs) are a group of congenital anomalies – including anencephaly and spina bifida – which cause brain and spinal malformations in a fetus. NTDs are formed within the first 28 days of a pregnancy, often before a woman knows she is pregnant. While anencephaly often results in early death, spina bifida has a varying degree of outcomes. When no treatment is offered, spina bifida will most likely result in premature death. Rehabilitation and surgery may allow affected individuals to adjust to this life-long disability with different degrees of success, but with considerable individual, economic, and social costs.

Folate insufficiency has been found to be the cause of a majority of NTDs. To reduce the burden of NTDs globally, it is essential for women of reproductive age (WRA) to have sufficient folate status throughout their reproductive age. At minimum, it is critical to have sufficient folate status for three months before they become pregnant and during the first month of gestation. At a population level, the World Health Organization (WHO) recommends WRA have a red blood cell (RBC) folate concentration greater than 906 nmol/L to reduce the risk of having an NTD affected pregnancy.¹

THE BURDEN

On average, 1.86 per 1,000 live births are affected by NTDs around the world. However, there is wide variation in NTD incidence across the globe, and this burden is disproportionately high in low- and middle-income countries in Asia and Africa.

- 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 births²

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

According to web-based reviews of birth defect registry databases and systematic literature reviews, and excluding miscarriages and elective terminations of pregnancy, it has been estimated that in 2015:

- 260,100 pregnancies were affected by NTDs worldwide, which resulted in 57,800 still-births and 117,900 under-five deaths; and
- Nearly half of the total NTDs were estimated to be cases of spina bifida (128,000). While a majority of infants with spina bifida may survive the newborn period, more than three-quarters of those born in low- and middle-income countries will die before the age of 5.³
HOW MUCH FOLATE SHOULD BE CONSUMED

For many populations, it is very difficult to consume enough natural folate in the regular diet to achieve sufficient levels to prevent NTDs.

• The WHO recommends WRA ingest 400 micrograms of folic acid daily, in addition to any folate consumed in their regular diet. At a population level, this intake helps to ensure that WRA have a red blood cell (RBC) folate concentration greater than 906 nmol/L.
• Folate “insufficiency” in a population is defined by WHO as RBC folate concentrations less than 906 nmol/L.
• Food fortification with folic acid has proven to be an effective intervention to ensure WRA consume adequate amounts of folic acid to prevent “insufficiency” before a pregnancy occurs, reducing the risk of NTDs.
• Women who have given birth previously to a child with an NTD may have to take much larger amounts of folate (4 – 5 mg daily) than may be supplied via natural or fortified food, making it necessary to resort to supplementation.

INSUFFICIENT VS. DEFICIENT FOLATE STATUS

Insufficient folate levels are related to an increased risk of NTDs, while deficient folate levels are related to an increased risk of megaloblastic anemia.

Low folate intake gradually leads to folate depletion, which has functional consequences for the body. The initial stages of inadequate folate intake are reflected in low serum folate, followed by a depletion in red blood cell folate, which if continued will then cause changes in the bone marrow (where the red blood cells are produced).

Evidence has shown that insufficient folate intake by WRA increases the risk of NTDs. The WHO recommends that WRA ingest 400 micrograms of folic acid daily from fortified foods or supplements, in addition to any folate consumed in their regular diet. This recommendation is based on evidence that this level of consumption leads to an optimal folate concentration that reduces the risk of NTDs to a minimum.

If inadequate folate intake persists, this insufficiency turns into a folate deficiency. Folate deficiency is defined by the Institute of Medicine in the United States on the basis of the amount of folate required to maintain physiological folate levels in red blood cells. Megaloblastic anemia is caused by these low levels of folate which affect the formation of red blood cells and hemoglobin concentration in them. This is the basis for the estimated average requirement, on which the recommended dietary allowance (RDA) is based.
FOOD FORTIFICATION WITH FOLIC ACID

Large-scale food fortification with folic acid has proven to be an effective intervention to reduce the risk of NTDs in countries which have implemented mandatory fortification programs, such as Canada, the United States, Costa Rica, South Africa, Oman and others.

- In all of these countries, the incidence of NTDs have been consistently reduced to 0.5-0.6 per 1,000 live births after fortification and effective monitoring programs were implemented.

For countries with a relatively low prevalence of NTDs, it is feasible to reach an NTD threshold of 0.5 per 1,000 live births through mandatory folic acid fortification of appropriately selected foods. Food fortification has the potential to reach the majority of the target population when implemented following the right practices; i.e., when it is mandatory; regulated; conducted through large-scale food-processing facilities; effectively monitored; and utilizes staple foods that are already consumed by a majority of the target population.

THE INVESTMENT CASE

Food fortification with folic acid has proven to be a rewarding economic investment. This investment includes two groups of costs - upfront and on-going- which include purchasing folic acid, updating milling machinery, training, marketing, monitoring and evaluation, testing, and compliance. Further costs may be required for advocacy and education activities.

The benefits of mandatory folic acid food fortification largely outweigh the costs. Investing in food fortification with folic acid also compares favorably to other lifesaving interventions:

- Average cost per NTD-death averted: US $957
- Average cost per death averted through insecticide-treated bed nets: US $2,770
- Average cost per death averted by rotavirus vaccine: US $3,015

SAFETY OF FOLIC ACID

Concerns related to the safety of folic acid often include questions related to the potential increased risk of cancer and the risk of “masking” an underlying vitamin B₁₂ deficiency.

There is no evidence that folic acid consumed in fortified foods increases the risk of any type of cancer. In fact, there is strong evidence that low folate status promotes development of cancer, and in the US, where food fortification with folate acid has been mandatory for two decades, it has actually been found that the risk of different types of cancer has progressively declined post-fortification.
Since both vitamin B\textsubscript{12} and folate are required to make DNA, a deficiency of either impairs the division of RBCs. This leads to megaloblastic anemia, which is characterized by larger and fewer cells. This type of anemia will respond to therapeutic doses of either B\textsubscript{12} or folic acid. The term “masking” refers to a potential delay in diagnosis and treatment of a vitamin B\textsubscript{12} deficiency due to the initial reversal of anemia when therapeutic doses of supplemental folic acid are given to a vitamin B\textsubscript{12}-deficient patient. A differential diagnosis depends on evaluations of blood folate and vitamin B\textsubscript{12} prior to treatment, a routine clinical practice. There is no evidence that consumption of folic acid in fortified foods has resulted in any cases of misdiagnosed or “masking” of a vitamin B\textsubscript{12} deficiency in the US. However, given that the metabolism of folic acid and vitamin B\textsubscript{12} are closely linked, for populations at high-risk of vitamin B\textsubscript{12} deficiency, such as vegetarians or the elderly, relatively high intakes of folic acid may mask signs of B\textsubscript{12} deficiency, like anemia. In these cases, it is necessary to increase vitamin B\textsubscript{12} intake, which can be achieved by direct supplementation or by adding this vitamin to the fortified food.

**KEY MESSAGES**

- It is estimated that in 2015 there were 260,100 pregnancies affected by NTDs, worldwide.
- Folate insufficiency is associated with increased risk of NTD. Folate deficiency is associated with megaloblastic anemia.
- NTDs form within the first 28 days of a pregnancy, often before a woman knows she is pregnant.
- In order to reduce the risk of folate-sensitive NTDs, women of reproductive age must have sufficient folate status at least three months prior to conception and throughout the first month of pregnancy.
- In most settings it may be almost impossible for women to ingest enough natural folate from dietary sources to effectively reduce the risk of NTDs.
- Mandatory fortification with folic acid can significantly reduce the prevalence of NTDs, and it is a low-cost, high impact, lifesaving nutrition intervention.
- Published literature has shown no adverse public health consequences from large-scale mandatory folic acid fortification programs.
ENDNOTES


