


Global Evidence Base for Large-Scale Food Fortification

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It is my pleasure to share the global evidence base for large-scale food fortification.



Main messages

- Global evidence indicates that
 - Fortification with folic acid (vitamin B9)
 - Improves nutrient intake, nutritional status, and functional outcomes*
 - Does not harm the population
 - Fortification with iodine, iron, and vitamin A
 - Improves nutritional status and functional outcomes*

* Functional outcomes are consequences of adequate or poor nutrition

Image

Through this presentation, I will share the following main messages.

Global evidence indicates that fortification with folic acid improves nutrient intake, nutritional status, and functional outcomes, where functional outcomes are the consequences of adequate or poor nutrition.

Additionally, fortification with folic acid does not harm the population.

Further, fortification with iodine, iron, and vitamin A improves nutritional status and functional outcomes.



Global context: micronutrient deficiencies & strategies to address them

Let's start with the global context in regards to micronutrient deficiencies and strategies to address them.



Micronutrients needed in small quantities for optimum health

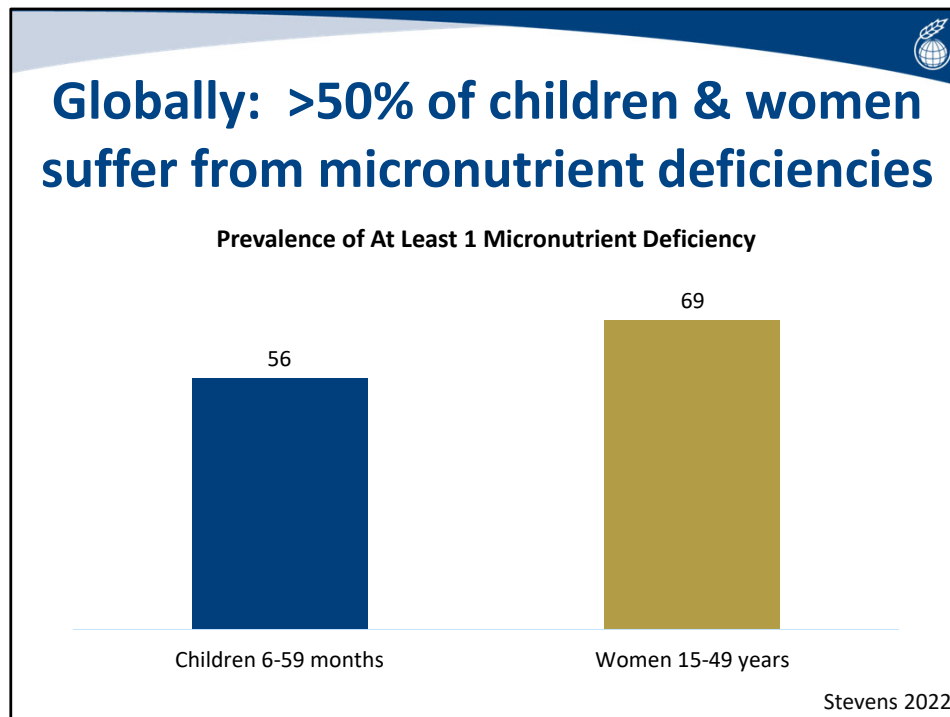
Vitamins (n=14)	Minerals (n=15)	
Biotin	Calcium	Manganese
Choline	Chloride	Molybdenum
Folate	Copper	Phosphorus
Niacin	Chromium	Potassium
Pantothenic acid	Fluoride	Selenium
Pyridoxine	Iodine	Sodium
Riboflavin	Iron	Zinc
Thiamine	Magnesium	
Vitamins A, B12, C, D, E y K		

Pope 2022

Micronutrients are those vitamins and minerals that our body needs in small quantities to function optimally.

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Pope 2022, Nutrition for a Changing World.



At the global level, at least 50% of preschool children and women of reproductive age suffer from one or more micronutrient deficiency.

This suggests that micronutrient deficiencies are a public health problem.

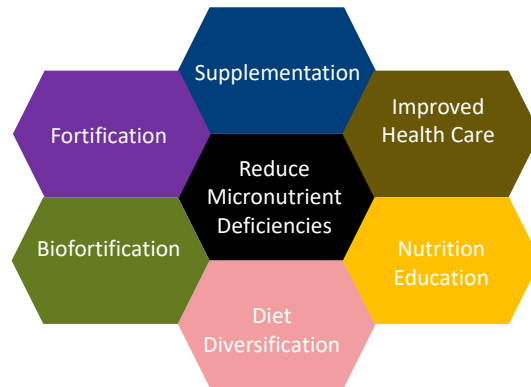
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Stevens GA, Beal T, Mbuya MNN, Luo H, Neufeld LM; Global Micronutrient Deficiencies Research Group. Micronutrient deficiencies among preschool-aged children and women of reproductive age worldwide: a pooled analysis of individual-level data from population-representative surveys. *Lancet Glob Health*. 2022 Nov;10(11):e1590-e1599.



Strategies to prevent & control micronutrient deficiencies

Diverse & Complementary

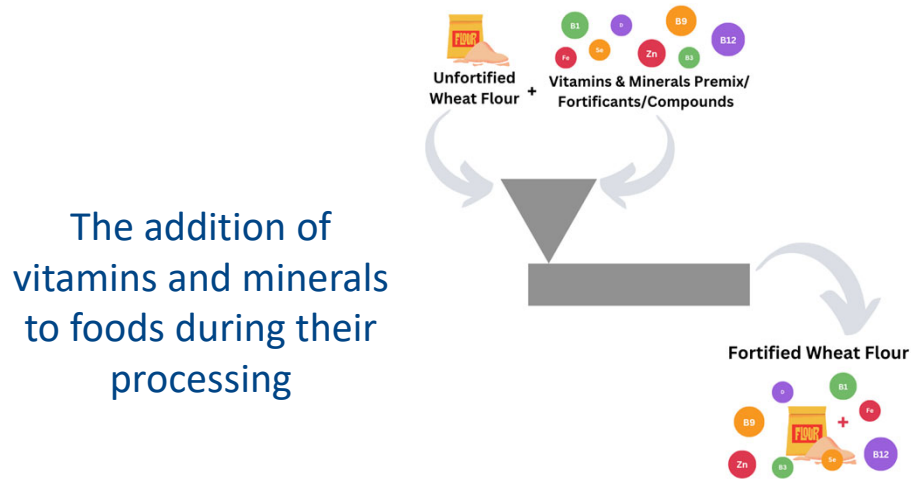


[CLICK TO ADVANCE] This figure has six of the possible strategies that can be used to prevent and control micronutrient deficiencies: starting with supplementation on the top, followed by improved health care, nutrition education, diet diversification, biofortification and fortification.

These strategies are complementary; in some settings, it may be necessary to implement two or more of them to have the desired impact.



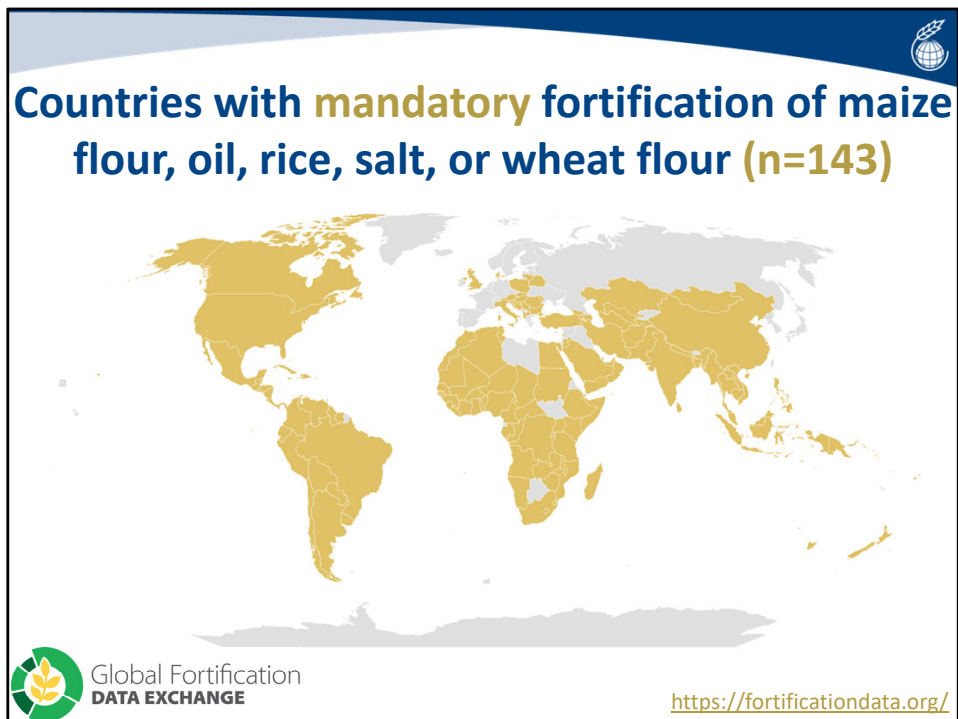
What is food fortification (enrichment)?



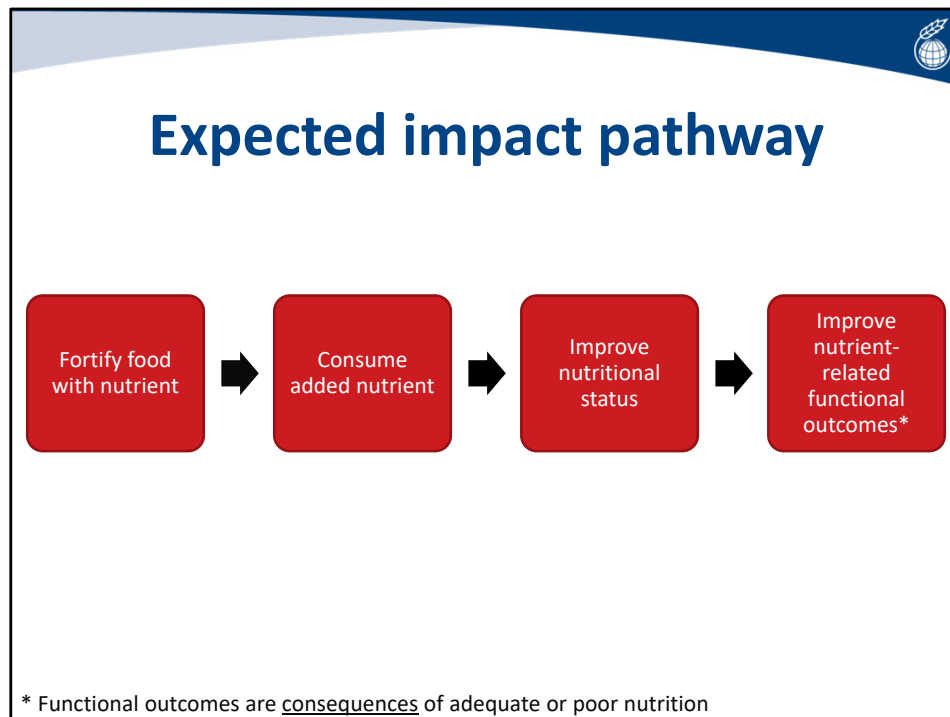
Food fortification, also known as enrichment, is the addition of vitamins and minerals to foods during their processing.

One of the foods that is often fortified is wheat flour.

None of us eat flour, but rather we eat foods made with flour such as bread and pasta. The bread and pasta will be more nutritious if they have been made with fortified flour.



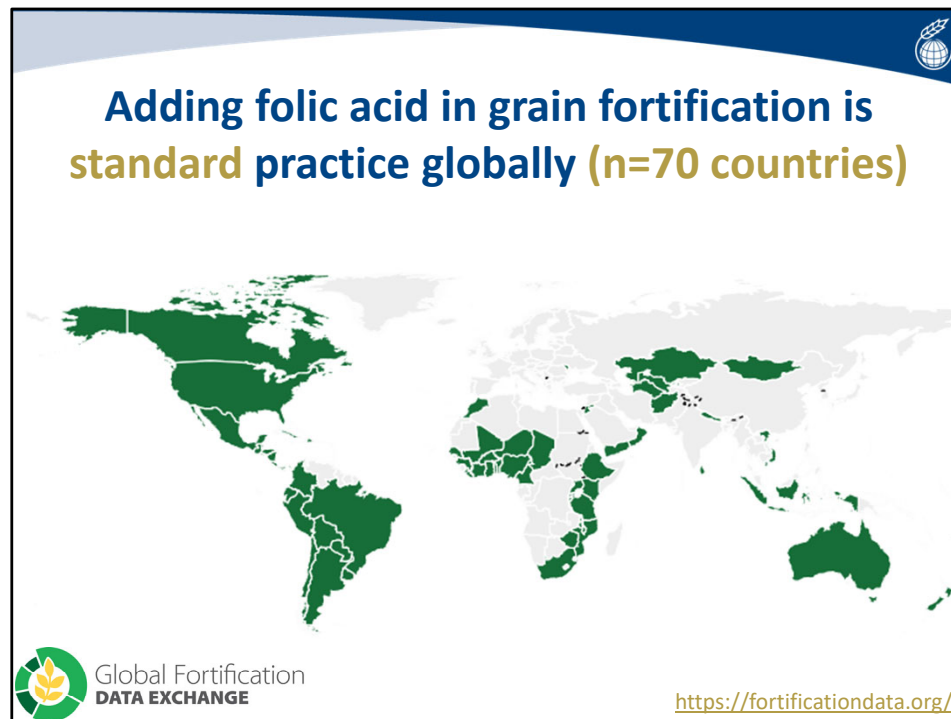
Currently, 143 countries mandate the fortification of maize flour, oil, rice, salt or wheat flour. These are the countries highlighted in yellow in this map.



Why have policy makers mandated fortification in so many countries? Because of the evidence that it improves health outcomes according to this expected impact pathway.

If food is fortified with a nutrient, the consumer gets added nutrients in their diet. This leads to improvements in the person and population's nutritional status and nutrient-related functional outcomes.

I will share these results for the fortification of grains with vitamin B9.

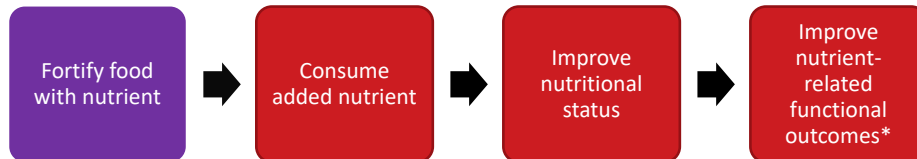


Folic acid is a synthetic form of vitamin B9.

70 countries include folic acid in their wheat flour, maize flour or rice fortification standards.



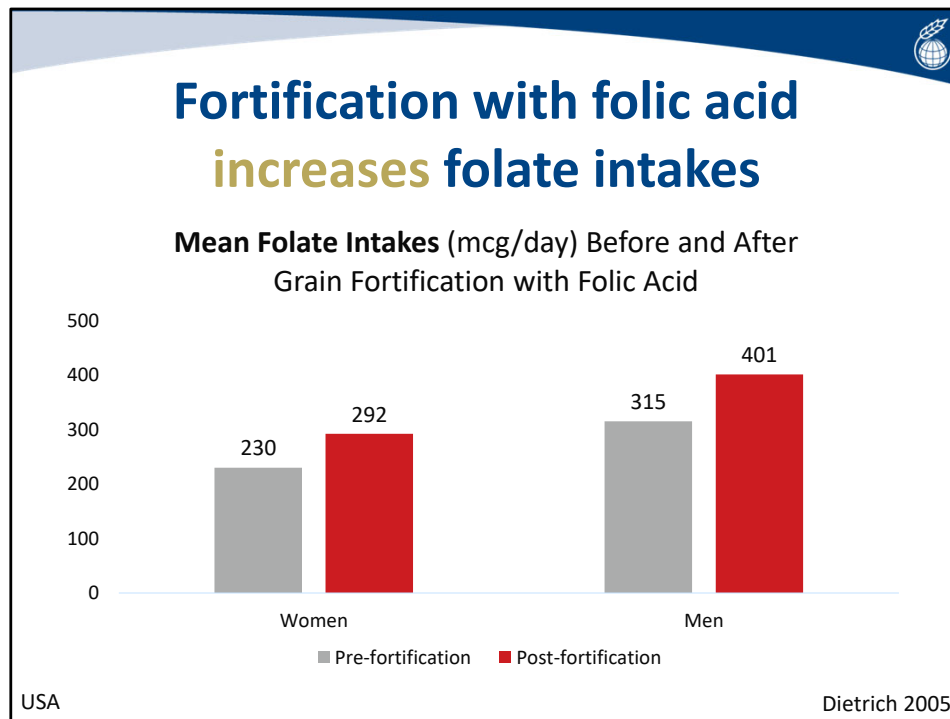
Expected impact pathway



Fortifying grains with folic acid is standard practice globally

* Functional outcomes are consequences of adequate or poor nutrition

In other words, adding folic acid through fortification is a standard practice globally.



The United States introduced mandatory fortification of wheat flour, maize flour and rice with several nutrients, including folic acid.

These bars reflect the mean intake of folate by women on the left, and men on the right, from before fortification in grey to after fortification in red.

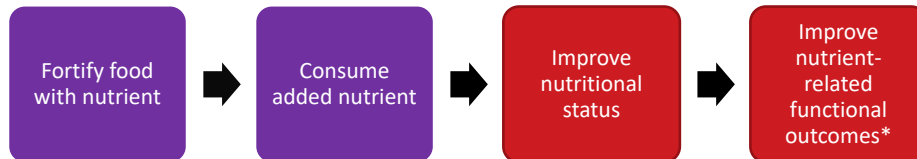
In both groups we can see an increase from the pre- to the post-fortification periods.

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Dietrich M, Brown CJ, Block G. The effect of folate fortification of cereal-grain products on blood folate status, dietary folate intake, and dietary folate sources among adult non-supplement users in the United States. *J Am Coll Nutr.* 2005 Aug;24(4):266-74. doi: 10.1080/07315724.2005.10719474. PMID: 16093404.



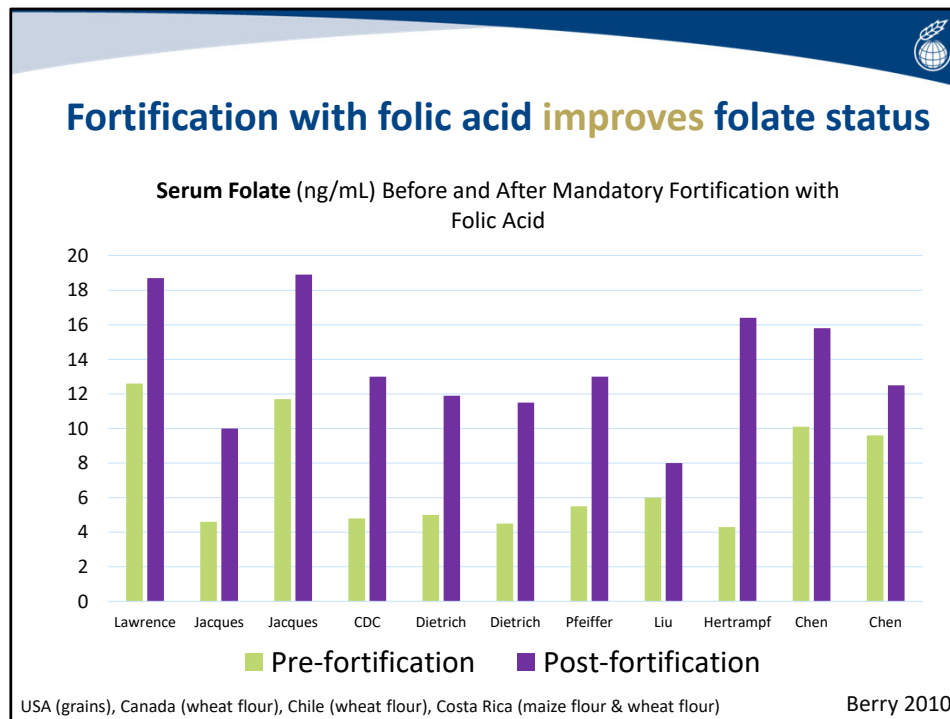
Expected impact pathway



Fortifying grains with folic acid increases folate (vitamin B9) intake

* Functional outcomes are consequences of adequate or poor nutrition

From the previous slide we can conclude that fortifying grains with folic acid leads to an increase in the intake of folate.



This chart has serum folate values before and after countries initiated mandatory fortification of grains with folic acid.

The folate levels before fortification are in green and the levels after fortification are in purple.

Along the horizontal axis, the data are from the USA, Canada, Chile and Costa Rica.

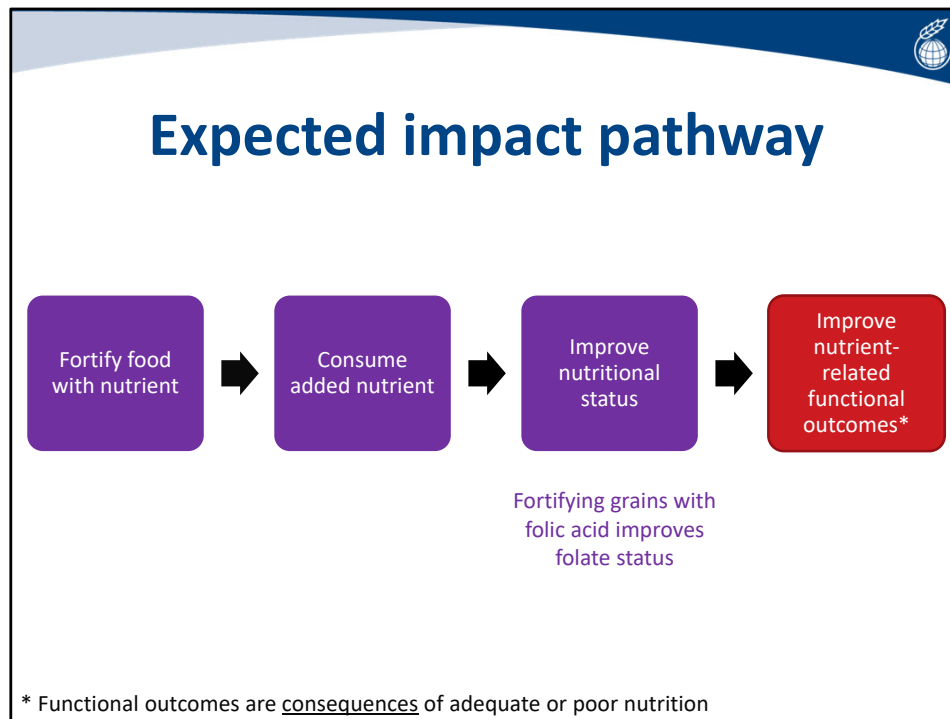
In all of these studies, serum folate increased after folic acid fortification began.

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Two data points from the same publication because different population groups' serum folate data were presented. For example, in Costa Rica, the first set of data are for women from metropolitan areas and the second set are for women in rural areas.

Source:

Berry RJ, Mulinare J, Hamner HC. Folic acid fortification: Neural tube defect risk reduction—a global perspective. In: Folate in Health and Disease (2nd ed), Bailey LB (ed). CRC Press, Boca Raton, 2010.

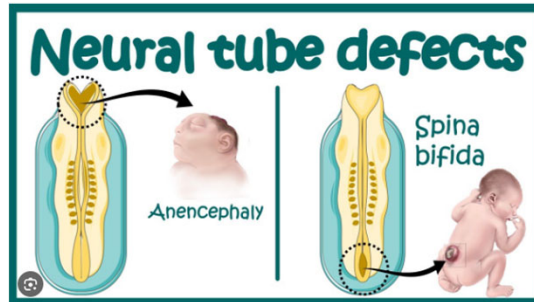


From the previous slide we can conclude that fortifying grains with folic acid improves the folate status of the population.



Neural tube defects and folic acid

Birth defects affecting the brain and spinal cord



[Image](#)

~70% are preventable if the mother has enough folic acid around conception

Blencowe 2018, Czeizel 1992, MRC 1991

Next I will introduce a functional outcome related to insufficient folate status.

Neural tube defects are a type of birth defect that affects the development of a baby's brain and spine. The two most common forms of neural tube defects are pictured in the image.

On the right you have spina bifida which is when the baby's spine is not formed correctly. Spina bifida can be treated, but it cannot be cured, and these children have varying degrees of permanent disability for the rest of their lives.

On the left is anencephaly. This is when the brain is not formed correctly. All babies with anencephaly die before or shortly after birth.

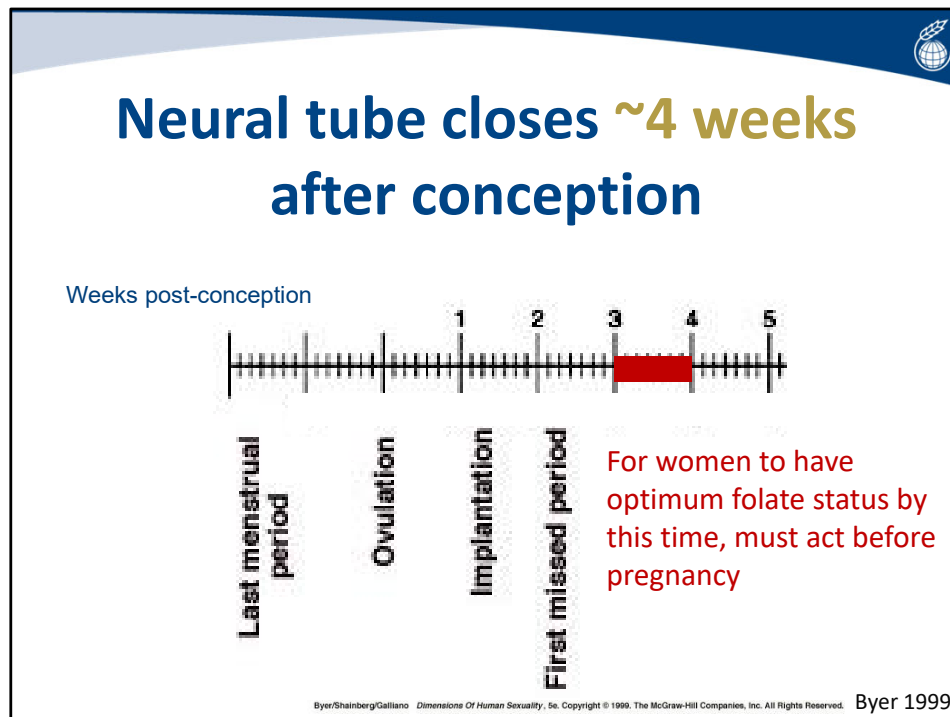
Folic acid can prevent around 70% of these birth defects.

Reference:

Blencowe H, Kancherla V, Moorthie S, Darlison MW, Modell B. Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. *Annals of the New York Academy of Sciences*, 2018.

Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *New England Journal of Medicine* 1992;327(26):1832-5.

MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991;338(8760):131-7.



The neural tube that forms the baby's spine and brain closes between the third and fourth weeks after conception.

One way to prevent neural tube defects is by women having optimum folate status during the first month after conception--before most even know that they are pregnant.

What this means in practice is that to reduce the risk of neural tube defects, we must act before women get pregnant—that is the appeal of fortification.

Image from: <http://raymentspinabifida.blogspot.com/2010/07/learning-about-sb-beginning.html>

Source:

Byer et al. Dimensions of Human Sexuality, 5th edition. McGraw-Hill Companies. 1999.

Fortification with folic acid reduces neural tube defects

1998: wheat flour fortification with folic acid

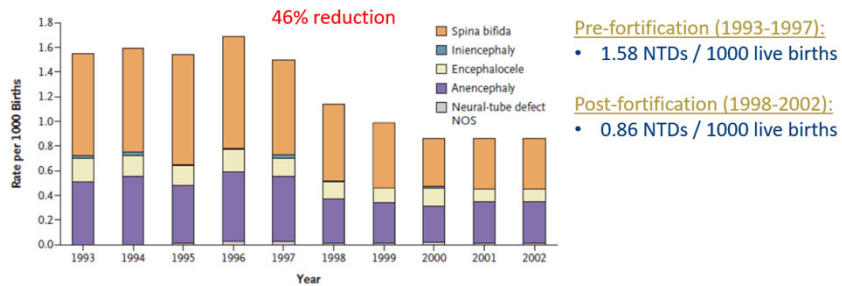


Figure 1. Prevalence of Neural-Tube Defects, According to Diagnostic Category, in Seven Canadian Provinces from 1993 through 2002.

NOS denotes not otherwise specified.

Canada

De Wals 2007

Canada mandated wheat flour fortification with folic acid and other nutrients to begin in 1998.

This graph shows the prevalence of babies with different neural tube defects. For example, orange represents spina bifida and purple represents anencephaly. The height of each bar represents the total number of neural tube defects per 1000 births.

Between 1993 and 2002 along the horizontal axis, there was a 46% reduction in neural tube defects because of fortification with folic acid.

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Source:

Philippe De Wals et al. Reduction in Neural-Tube Defects after Folic Acid Fortification in Canada. N Engl J Med 2007;357:135-42.



Fortification with folic acid **reduces** the odds of neural tube defects

All Neural Tube Defects

Odds Ratio: 0.59 (95% CI: 0.49, 0.70)

n=19,816,008 births (reported in 8 studies)

41% reduction in the odds of neural tube defects after fortification with folic acid

Meta-analysis

Keats 2019

Researchers summarized eight studies like the previous one, with almost 20 million births, and found a 41% reduction in the odds of neural tube defects after fortification with folic acid.

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Source:

Keats EC, Neufeld LM, Garrett GS, Mbuya MNN, Bhutta ZA. Improved micronutrient status and health outcomes in low- and middle-income countries following large-scale fortification: evidence from a systematic review and meta-analysis. *Am J Clin Nutr.* 2019 Jun 1;109(6):1696-1708.

Costa Rica: Fortification with folic acid reduces the severity of open spina bifida

The larger the lesion, the greater the disability and mortality risk

Non-closeable large lesions (>7 cm) **decreased** from 7% to 1% after mandatory fortification with folic acid

Open spina bifida may also be referred to as myelomeningocele (MMC) Caceres 2023

Open spina bifida is the most serious type of spina bifida. A sac of fluid protrudes through an opening in the baby's back. Part of the spinal cord and nerves are in this sac and are damaged.

In open spina bifida, the larger the lesion, the greater the risk of disability and death.

[CLICK TO ADVANCE] Costa Rica mandated the fortification of several foods with folic acid. They measured lesions that are considered too large to close surgically: those greater than 7 cm in size. Non-closeable lesions decreased from 7% to 1% after mandatory fortification.

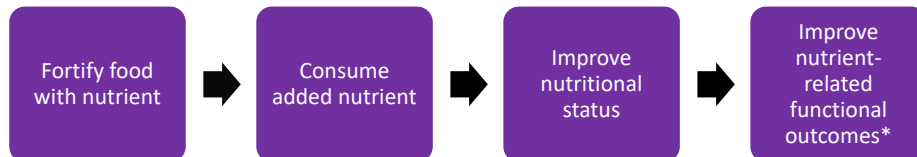
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Caceres, A., Jimenez-Chaverri, A. L., Alpizar-Quiros, P. A., & Wong-McClure, R. (2023). Pre and postnatal care characteristics and management features of children born with myelomeningocele in the post-folate fortification era of staple foods in Costa Rica (2004-2022). *Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery*, 39(7), 1755–1764. <https://doi.org/10.1007/s00381-023-05951-y>

After fortification in Costa Rica, high lumbar cases reduced from 26 to 23% ($P < 0.56$), Middle lumbar cases increased from 43 to 58% ($P < 0.01$). Lower lumbar cases reduced from 25 to 13% ($P < 0.01$). Lesions considered too severe (>7 cm) decreased from 7 to 1%. ($P < 0.01$).



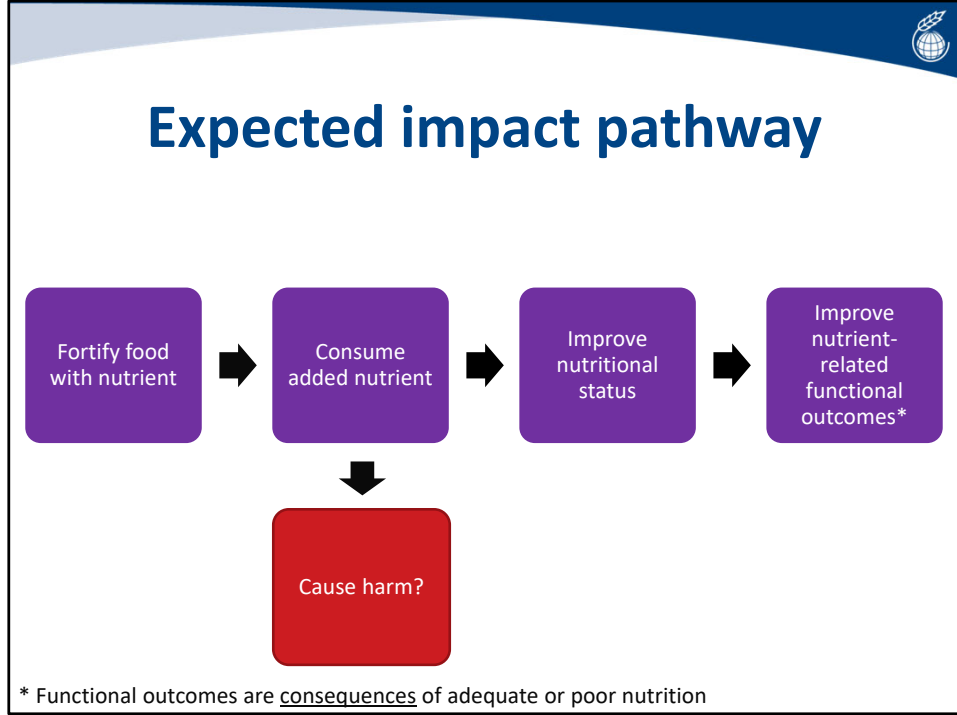
Expected impact pathway




Fortifying grains with folic acid reduces neural tube defects and their severity

* Functional outcomes are consequences of adequate or poor nutrition

From the previous slides we can conclude that fortifying grains with folic acid reduces neural tube defects and their severity.



However, there are concerns that adding too much nutrients to the diet, through fortification, can cause harm.



No evidence of harm from fortification with folic acid

Knowledge gaps in understanding the metabolic and clinical effects of excess folates/folic acid: a summary, and perspectives, from an NIH workshop

“Observations indicating adverse effects from excess folic acid intake, elevated folate status, and unmetabolized folic acid (UMFA) **remain inconclusive**; the data do not provide the evidence needed to affect public health recommendations.”

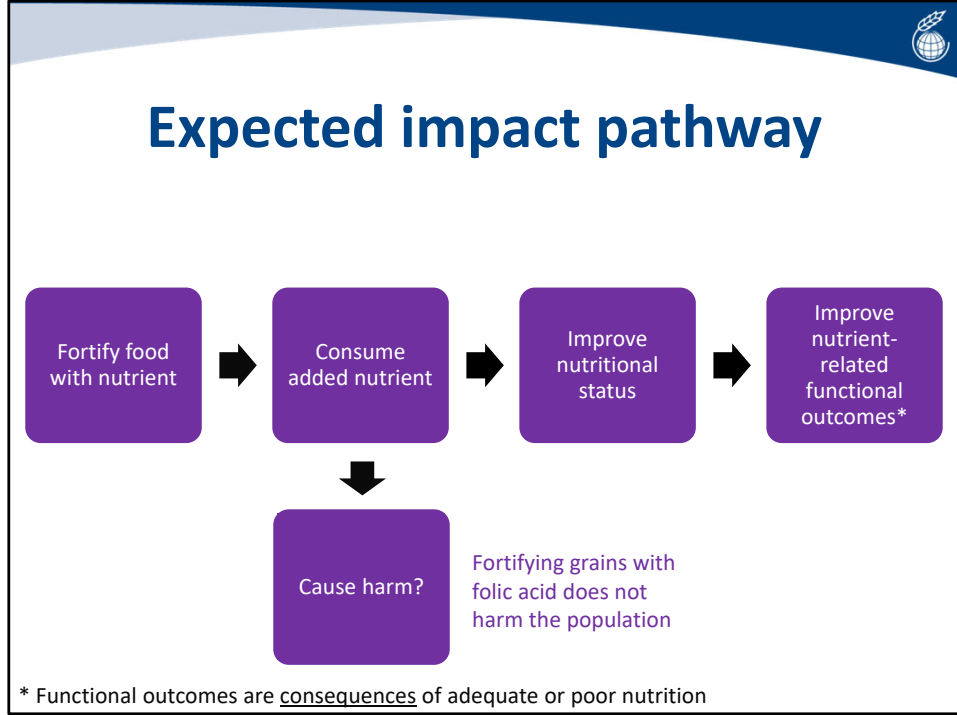
NIH, National Institutes of Health Maruvada 2020

This article summarizes the proceedings of a 2019 expert workshop held at the National Institutes of Health in the United States.

This quote is taken from the abstract: “Observations indicating adverse effects from excess folic acid intake, elevated folate status, and unmetabolized folic acid (UMFA) **remain inconclusive**; the data do not provide the evidence needed to affect public health recommendations.”

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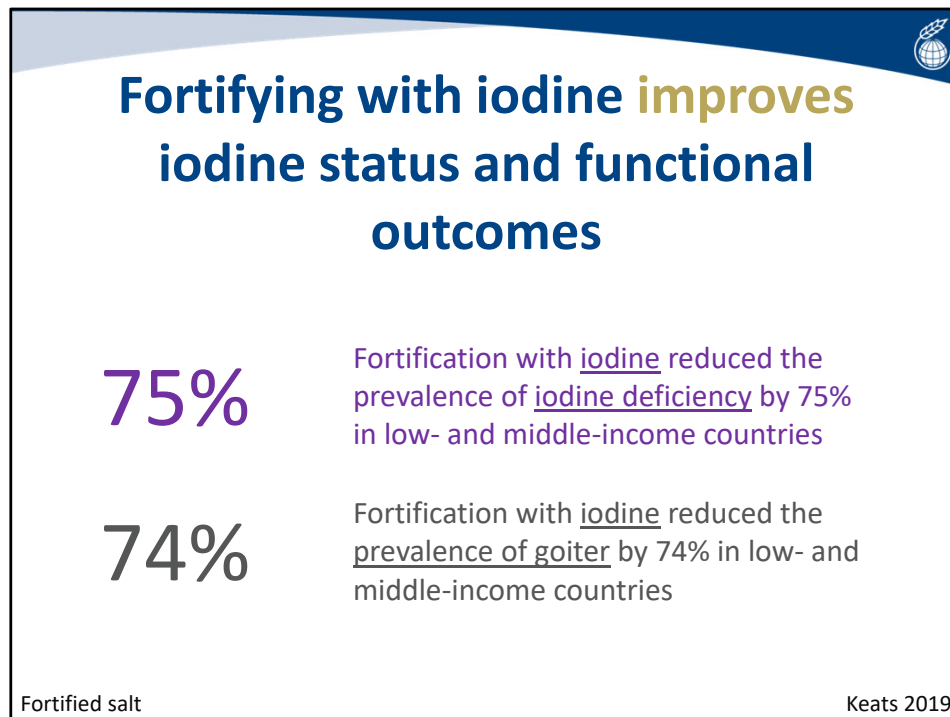
Maruvada P, Stover PJ, Mason JB, et al. Knowledge gaps in understanding the metabolic and clinical effects of excess folates/folic acid: a summary, and perspectives, from an NIH workshop. *Am J Clin Nutr.* 2020;112(5):1390-1403.



In other words, there is no evidence that fortifying grains with folic acid harms the population.



Next I will share the health impact of fortification with other nutrients.



A meta-analysis by Keats and colleagues revealed that fortification of salt with iodine in low- and middle-income countries reduced the prevalence of iodine deficiency and the prevalence of goiter by approximately 75%.

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Source:

Keats EC, Neufeld LM, Garrett GS, Mbuya MNN, Bhutta ZA. Improved micronutrient status and health outcomes in low- and middle-income countries following large-scale fortification: evidence from a systematic review and meta-analysis. *Am J Clin Nutr.* 2019 Jun 1;109(6):1696-1708.



Fortifying with iron **improves** iron status and functional outcomes

58%

Fortification with iron reduced the prevalence of iron deficiency by 58% in low- and middle-income countries

34%

Fortification with iron reduced the prevalence of anemia by 34% in low- and middle-income countries

Fortified fish sauce, maize flour, milk, rice, soy sauce, wheat flour


Keats 2019

Similarly, fortification with iron in low- and middle-income countries reduced the prevalence of iron deficiency by 58% and anemia prevalence by 34%. The fortified foods included in the analysis were fish sauce, maize flour, milk, rice, soy sauce and wheat flour.

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Source:

Keats EC, Neufeld LM, Garrett GS, Mbuya MNN, Bhutta ZA. Improved micronutrient status and health outcomes in low- and middle-income countries following large-scale fortification: evidence from a systematic review and meta-analysis. *Am J Clin Nutr.* 2019 Jun 1;109(6):1696-1708.



Fortifying with vitamin A improves vitamin A status

**0.31
mcg/dl**

Fortification with vitamin A increased serum retinol levels by 0.31 mcg/dl, indicating an improvement in vitamin A status, in low- and middle-income countries

Fortified maize flour, oil, sugar Keats 2019

Finally, fortification of maize flour, oil and sugar with vitamin A increased serum retinol levels by 0.31 mcg/dl, indicating an improvement in vitamin A status in low- and middle-income countries.

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Source:

Keats EC, Neufeld LM, Garrett GS, Mbuya MNN, Bhutta ZA. Improved micronutrient status and health outcomes in low- and middle-income countries following large-scale fortification: evidence from a systematic review and meta-analysis. *Am J Clin Nutr.* 2019 Jun 1;109(6):1696-1708.



Main messages

- Global evidence indicates that
 - Fortification with folic acid (vitamin B9)
 - Improves nutrient intake, nutritional status, and functional outcomes*
 - Does not harm the population
 - Fortification with iodine, iron, and vitamin A
 - Improves nutritional status and functional outcomes*

* Functional outcomes are consequences of adequate or poor nutrition [Image](#)

In conclusion, global evidence indicates that fortification with folic acid improves nutrient intake, nutritional status, and functional outcomes, where functional outcomes are the consequences of adequate or poor nutrition.

Additionally, fortification with folic acid does not harm the population.

Further, fortification with iodine, iron, and vitamin A improves nutritional status and functional outcomes.

We hope that this body of evidence is helpful for policy making in countries.

For more information:

www.FFInetwork.org

[www.Facebook.com/FFInetwork](https://www.facebook.com/FFInetwork)

<https://twitter.com/FFInetwork>

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Enhancing Grains for Healthier Lives

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Thank you.