


Food Fortification Initiative
Enhancing Grains for Healthier Lives



<http://apdisciplinestrust.org.nz/wp-content/uploads/2015/05/slider04.jpg>

Evidence Supporting Mandatory Flour Fortification with Folic Acid

Helena Pachón & Karen Codling

Pre-congress Workshop on Birth Defects
Asia-Pacific Conference on Human Genetics
8 November 2017

I would like to thank Dr. Pornswan for the kind invitation to participate in this pre-congress workshop.

I am pleased to make this presentation on behalf of my colleague Karen Codling.



I'm going to start and finish with the main messages I hope you get from this presentation.



1. Fortification with folic acid reduces the risk of neural tube defects

First, fortification with folic acid reduces the risk of neural tube defects.



2. Fortification with folic acid is more effective than dietary diversification or supplementation for reducing the risk of neural tube defects

Second, fortification with folic acid is more effective than dietary diversification or supplementation for reducing the risk of neural tube defects.



3. Mandatory fortification with folic acid is more effective than voluntary fortification for reducing the risk of neural tube defects

Third, mandatory fortification with folic acid is more effective than voluntary fortification for reducing the risk of neural tube defects.



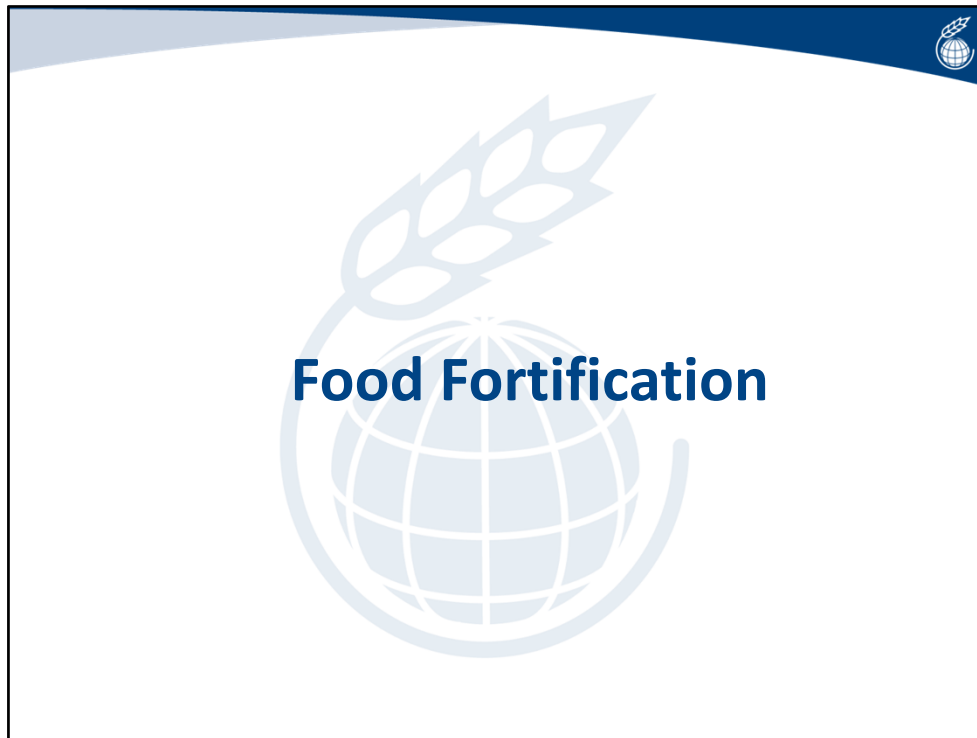
4. Fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia

Fourth, fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia, extending the benefits of fortification to other groups in the population.



5. Fortification with folic acid does not mask vitamin B12 deficiency or cause cancer

Finally, fortification with folic acid does not mask vitamin B12 deficiency or cause cancer.



Let me begin by defining what food fortification is and what it is not.



What is Food Fortification?

The addition of
vitamins and minerals
to foods during their
processing

Vitamin & Mineral Premix /
Fortificants / Compounds



Photo from Mühlenchemie

Food fortification is the addition of vitamins and minerals to foods during their processing.

The mixture of vitamins and minerals has many names: premix, fortificants and compounds. These terms are often used interchangeably.

One of the foods that is often fortified is wheat flour. The premix that is added to flour is itself a dry powder, which makes it easier to mix.

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.



Industrial vs Small-Scale Fortification

“Large modern rice mills in Thailand.”



<http://thumbs.dreamstime.com/z/large-modern-rice-mills-thailand-selection-36063154.jpg>

“A hammer mill is for grinding maize into mealie meal (the staple in every Zambian’s diet).”



<http://www.lipaf.org/wp-content/uploads/hammer-mill.jpg>

FFI definition:

- industrial wheat and maize mills: those with a capacity of at least 20 metric tons a day
- industrial rice mills: those with a production capacity of at least 5 metric tons an hour

FFI 2017

At the Food Fortification Initiative we define industrial wheat and maize mills as those with a capacity of at least 20 metric tons a day, and industrial rice mills as those with a production capacity of at least 5 metric tons an hour.

On the left-hand side, we see a modern rice mill in Thailand with greater than a 5 metric ton per hour capacity.

On the right-hand side, we see a hammer mill used in Zambia which has less than a 20 metric ton per day capacity.

In this presentation, I will focus on industrial-scale fortification, taking places in mills like those observed in Thailand in the photo on the left.

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Source:

“Our focus is fortifying wheat flour, maize flour, and rice in industrial mills. For wheat and maize, this means mills with a capacity of at least 20 metric tons a day. Rice is most easily fortified in mills with a production capacity of at least 5 metric tons an hour. “

<http://www.ffinetwork.org/plan/industry.html>



What Foods are Industrially Fortified?



A book on food fortification by the World Health Organization and FAO lists some of the foods that are commonly fortified at the industrial level.

They include liquid, evaporated and powdered milk, margarine, oil, sugar, wheat flour, soy sauce, maize flour, salt and rice.

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Source:

WHO/FAO. Guidelines on food fortification with micronutrients. 2006.

http://www.who.int/nutrition/publications/guide_food_fortification_micronutrients.pdf

Table 7.10 from WHO/FAO 2006: milk, evaporated milk, powdered milk, margarine, vegetable oil, sugar, wheat flour, pasta, corn masa flour, pre-cooked maize flour, maize meal, soy/fish sauce, salt.

Nutrients Added

Food	A	D	C	B1	B2	B3	B6	B9	B12	Fe	Zn	Ca	I
Milk	X	X											
Margarine	X	X			X	X	X	X					
Oil	X												
Sugar	X												
Wheat flour	X	X		X	X	X	X	X	X	X	X	X	
Maize flour	X			X	X	X	X	X		X			
Soy sauce										X			
Salt										X			X
Rice	X			X		X	X	X	X	X	X		

With a few exceptions, most nutrients can be added to most foods through fortification

WHO/FAO 2006, de Pee 2014

That same book lists the nutrients that are typically added to these foods. Across the top, the nutrients are fat-soluble vitamins A and D. Water-soluble vitamins C, B1, B2, B3, B6, B9 and B12. And the minerals iron, zinc, calcium and iodine. Please note that B9 includes folic acid, which we'll be talking about later.

We can see, for example, that vitamin A is typically added to many foods, while iodine is typically only added to salt.

The main point I want you to take away is that with a few exceptions, most nutrients can be added to most foods through fortification.

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Source:

WHO/FAO. Guidelines on food fortification with micronutrients. 2006.

http://www.who.int/nutrition/publications/guide_food_fortification_micronutrients.pdf

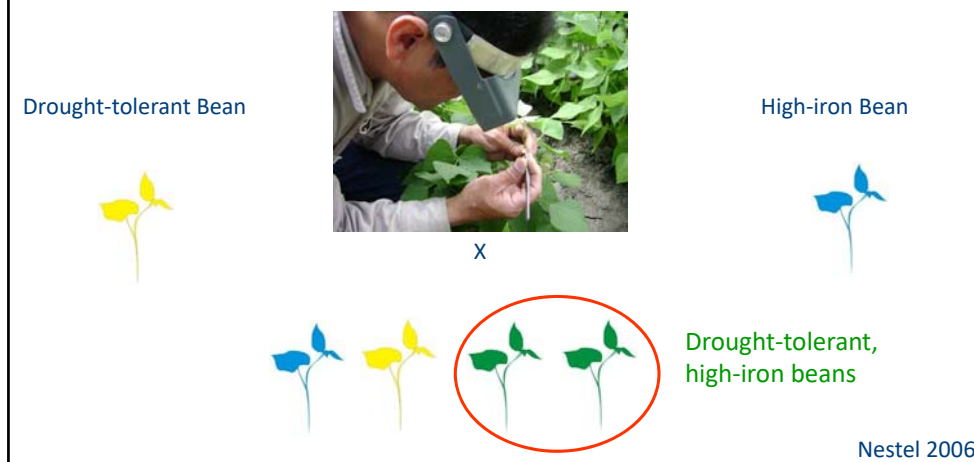
Table 7.10 from WHO/FAO 2006: milk, evaporated milk, powdered milk, margarine, vegetable oil, sugar, wheat flour, pasta, corn masa flour, pre-cooked maize flour, maize meal, soy/fish sauce, salt.

de Pee S. Proposing nutrients and nutrient levels for rice fortification. Ann N Y Acad Sci. 2014 Sep;1324:55-66.



This is NOT Food Fortification

Biofortification: Development of Nutrient-Dense Staple Crops



Other nutrition interventions use the term “fortification” but they are not food fortification. For sake of clarity, let me describe these.

Biofortification is the development of nutrient-dense staple crops using the best conventional breeding practices and modern biotechnology.

[CLICK TO ADVANCE] In this image, we see conventional plant breeding, which is what farmers have been doing for centuries. On the left, we have a variety of bean that is drought tolerant and on the right we have a variety of bean that is high in iron.

[CLICK TO ADVANCE] These two plants are crossed in the field.

[CLICK TO ADVANCE] And they will produce drought-tolerant, high-iron beans.

Biofortification produces a crop that is more nutrient dense.

In comparison, industrial fortification adds nutrients to foods during their processing.

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Source:

Nestel P, Bouis HE, Meenakshi JV, Pfeiffer W. Biofortification of staple food crops. J Nutr. 2006 Apr;136(4):1064-7.



This is NOT Food Fortification

Point-of-Use Fortification

Sprinkles are sachets (like small packets of sugar) containing a blend of micronutrients in powder form, which are easily sprinkled onto foods prepared in the home. Any homemade food can be instantly fortified by adding Sprinkles. Coating of the iron prevents changes to the taste, colour or texture of the food to which Sprinkles are added. Sprinkles were developed by the Sprinkles Global Health Initiative to prevent and treat micronutrient deficiencies among young children and other vulnerable groups at risk.



http://www.sghi.org/about_sprinkles/

Another nutrition intervention uses the term “fortification”: point-of-use fortification.

Point-of-use fortification means that you add the nutrients to your food at the time you are going to eat them. The first point-of-use fortification product is known as Sprinkles. As this text says, “Sprinkles are sachets containing a blend of micronutrients in powder form, which are easily sprinkled onto foods prepared in the home.”

This is different from industrial fortification, where the nutrients are added to foods during their processing.

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Source:

http://www.sghi.org/about_sprinkles/



Summary

- Food fortification is the addition of vitamins and minerals to foods during their processing
- Many food products are fortified at industrial scale
- Most nutrients can be added to most foods through industrial fortification
- Biofortification and point-of-use fortification are not the same as food fortification

In summary, food fortification is the addition of vitamins and minerals to foods during their processing.

Many food products are fortified at industrial scale.

Most nutrients (including folic acid) can be added to most foods through industrial fortification.

And biofortification and point-of-use fortification are not the same as food fortification.



Now, I'll begin showing you the evidence that supports each of the main messages.



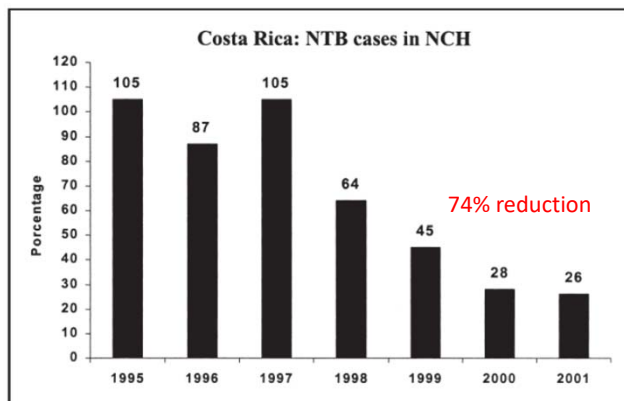
1. Fortification with folic acid reduces the risk of neural tube defects

I will present results from many countries, as well as a meta-analysis and systematic reviews that show that fortification with folic acid reduces the risk of neural tube defects.



Costa Rica: Fortification with Folic Acid Reduces Neural Tube Defects (NTDs)

1997: wheat flour fortification with folic acid 1999: maize flour fortification with folic acid



Pre-fortification (1996-1998):

- 9.7 NTDs / 1000 live births

Post-fortification (1999-2000):

- 6.3 NTDs / 1000 live births

Figure 2. Costa Rica. Neural tube defects cases at National Children's Hospital.

Tacsan Chen 2004

Costa Rica began wheat flour fortification with folic acid in 1997 and maize flour fortification with folic acid in 1999.

[CLICK TO ADVANCE] This graph shows the number of neural tube defect cases reported at the National Children's Hospital between 1995 and 2001. We can observe the downward trend in cases, representing a 74% reduction through fortification with folic acid.

The number of babies born with neural tube defects was reduced from 9.7 per 1000 live births to 6.3 per 1000 live births.

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Source:

Luis Tacsan Chen & Melany Ascencio Rivera. The Costa Rican Experience: Reduction of Neural Tube Defects following Food Fortification Programs. Nutrition Reviews. 2004.

Saudi Arabia: Fortification with Folic Acid Reduces Neural Tube Defects (NTDs)

2001: wheat flour fortification with folic acid

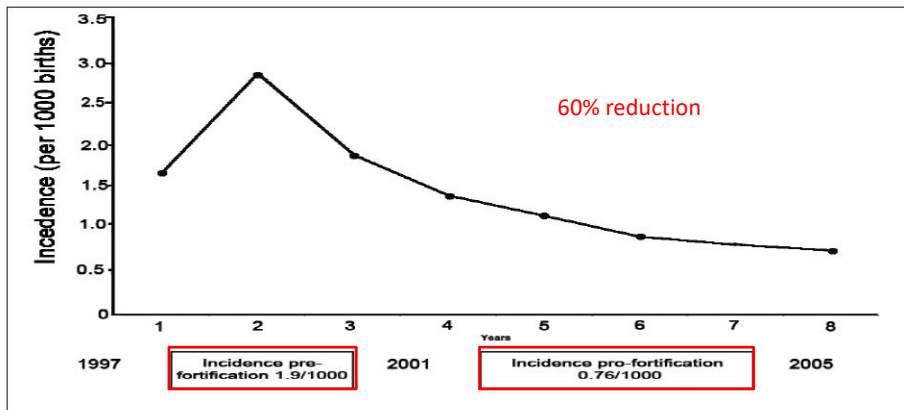


Figure 1 - Incidence of neural tube defects from 1997-2005.

Safdar 2007

Saudi Arabia began wheat flour fortification with folic acid in 2001.

We see in the graph the number of babies with neural tube defects per 1000 births. There is a reduction in this figure from 1997 to 2005.

The pre-fortification period had 1.9 neural tube defects per 1000 births. This declined in the post-fortification period to 0.76 per 1000 births, for a 60% reduction.

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Source:

Osama Y. Safdar. Decline in the incidence of neural tube defects after the national fortification of flour (1997-2005). Saudi Med J 2007.

Canada: Fortification with Folic Acid Reduces Neural Tube Defects (NTDs)

1998: wheat flour fortification with folic acid

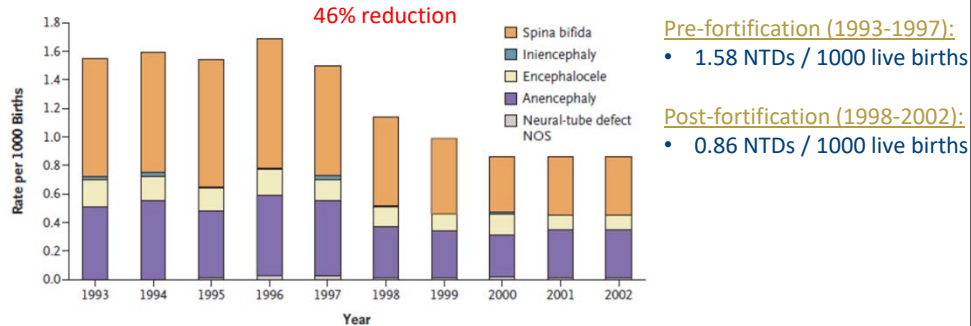


Figure 1. Prevalence of Neural-Tube Defects, According to Diagnostic Category, in Seven Canadian Provinces from 1993 through 2002. NOS denotes not otherwise specified.

De Wals 2007

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

[CLICK TO ADVANCE] This graph shows the prevalence per 1000 births 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.

We can see that in the pre-fortification period there were 1.58 neural tube defects per 1000 live births and this went down in the post-fortification period to 0.86 neural tube defects per 1000 live births, representing a 46% reduction.

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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.

Jordan: Fortification with Folic Acid Reduces Neural Tube Defects

2002: wheat flour fortification with folic acid

Period	Years	Livebirths	NTDs	Rate per 1000	[95% CI]
Before fortification	2000–01	18392	34	1.85	[1.2, 2.4]
Introduction period	2002–04	26286	28	1.07	[0.7, 1.5]
After fortification	2005–06	16769	16	0.95	[0.5, 1.5]

49% reduction

NTDs, neural tube defects

Amarin 2010

Jordan began fortification of wheat flour with folic acid in 2002.

[CLICK TO ADVANCE] They report neural tube defects for three time periods: before fortification, during the early years of fortification (that is, the “introduction period”), and after several years of fortification (called “after fortification”).

Neural tube defects per 1000 live births was reduced from 1.85 to 1.07 to 0.95, for an overall 49% reduction through fortification with folic acid.

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Source:

Amarin, Zouhair O., and Ahmed Z. Obeidat. "Effect of folic acid fortification on the incidence of neural tube defects." Paediatric and perinatal epidemiology 24.4 (2010): 349-351.

Chile: Fortification with Folic Acid Reduces Neural Tube Defects

2000: wheat flour fortification with folic acid

TABLE I. NTD Prevalence Ratios before and after folic acid fortification in Chile, 1999–2009

	Pre-fortification period (1999–2000)		Post-fortification Period (2001–2009)		RR	(95% CI)
	n	Rate/10,000	n	Rate/10,000		
Anencephaly	72	6.0	147	3	0.50	0.38–0.67
Cephalocele	29	2.4	68	1.4	0.58	0.37–0.89
Spina bifida	105	8.7	204	4.2	0.48	0.38–0.6
Total NTDs	206	17.1	419	8.6	0.50	0.42–0.59

NTDs, neural tube defects.

“50% of the potentially new cases of NTDs were prevented [with fortification of wheat flour with folic acid]”

NTDs, neural tube defects

Cortés 2012

In 2000, Chile began wheat flour fortification with folic acid.

[CLICK TO ADVANCE] The number of babies born with neural tube defects was measured in two periods: the pre-fortification period from 1999 to 2000 and the post-fortification period from 2001 to 2009.

In both time periods, three types of neural tube defects and the total number were noted.

We see that in the pre-fortification period 17.1 babies were born with neural tube defects per 10,000 babies born. And this was reduced to 8.6 per 10,000 births in the post-fortification period. And the rate reduction was 50%.

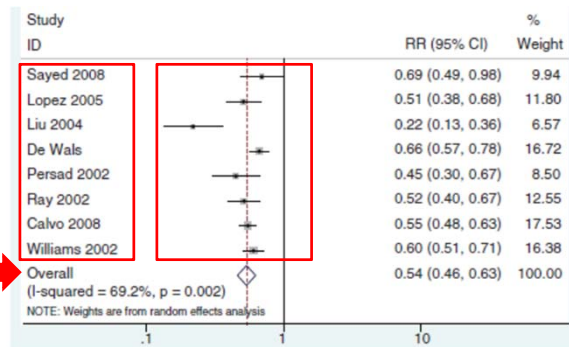
What this means is that 50% of the potentially new cases of neural tube defects were prevented with fortification of wheat flour with folic acid.

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Source:

Cortés F, Mellado C, Pardo RA, Villarroel LA, Hertrampf E. 2012. Wheat flour fortification with folic acid: Changes in neural tube defects rates in Chile. Am J Med Genet Part A. 2012.

Meta-analysis: Fortification with Folic Acid Reduces Neural Tube Defects



Risk Ratio: 0.54

Overall, there was a 46% reduction in the risk of neural tube defects with folic-acid fortification

Figure 3 Meta-analysis (random effects) of the effect of folic acid fortification on primary prevention of neural tube defects. Heterogeneity $\chi^2 = 22.73$ (df = 7), $P = 0.002$, I^2 (variation in RR attributable to heterogeneity) = 69.2%; Estimate of between-study variance $\tau^2 = 0.0295$, Test of RR = 1: $z = 8.01$, $P < 0.001$

Blencowe 2010

Blencowe and colleagues completed a meta-analysis of studies that had measured neural tube defects pre and post-fortification. Eight studies were included.

[CLICK TO ADVANCE] All of the data points were to the left of the solid, black, vertical line, which means that fortification reduced neural tube defects in all studies.

[CLICK TO ADVANCE] Overall the risk ratio was 0.54. This means there was a 46% reduction in the risk of neural tube defects with folic-acid fortification.

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Reference: Blencowe H et al. Folic acid to reduce neonatal mortality form neural tube disorders International Journal of Epidemiology. April 2010 (suppl_1):i110-i121.

Eight studies were from Chile, South Africa, Argentina, USA, and Canada.



Systematic Review: Fortification with Folic Acid Reduces Neural Tube Defects

Impact of folic acid fortification of flour on neural tube defects: a systematic review

Setting: Chile, Argentina, Brazil, Canada, Costa Rica, Iran, Jordan, South Africa and the USA.

Results: Twenty-seven studies that met inclusion criteria were evaluated.

Conclusions: Fortification of flour with folic acid has had a major impact on NTD in all countries where this has been reported.

NTD, neural tube defect

Castillo-Lancellotti 2013

A 2013 systematic review assessed the impact of folic acid fortification of flour on neural tube defects.

Studies were obtained from nine countries: Chile, Argentina, Brazil, Canada, Costa Rica, Iran, Jordan, South Africa and the USA.

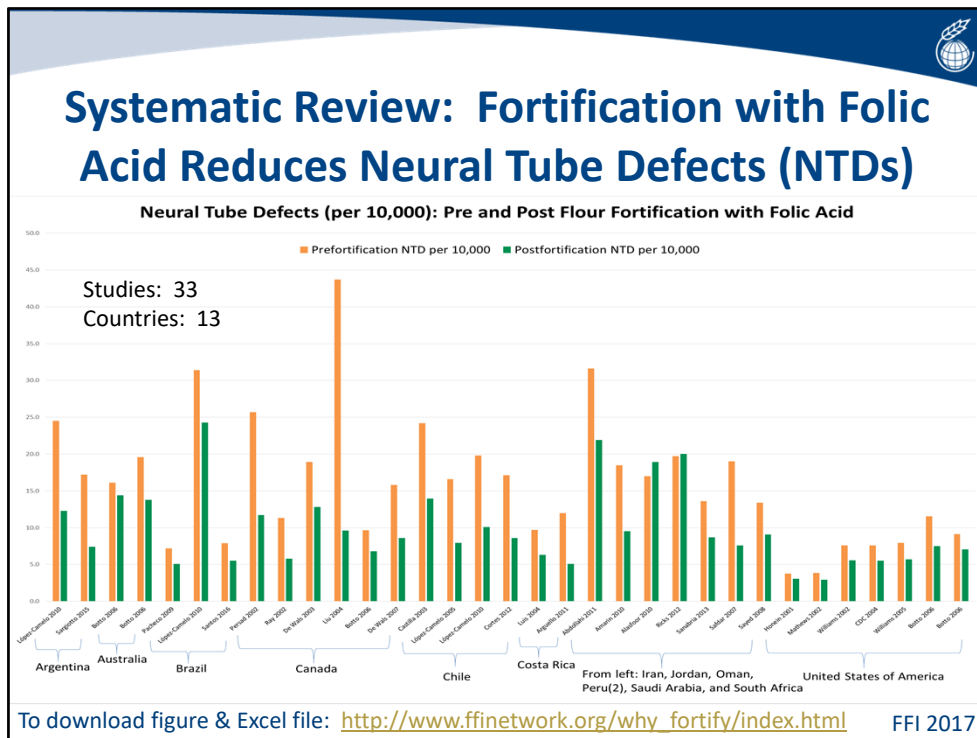
A total of 27 studies were included.

The authors concluded that “Fortification of flour with folic acid has had a major impact on [neural tube defects] in all countries where this has been reported.”

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Source:

Castillo-Lancellotti C, Tur JA, Uauy R. Impact of folic acid fortification of flour on neural tube defects: a systematic review. *Public Health Nutr.* 2013 May;16(5):901-11. doi: 10.1017/S1368980012003576. Review. Erratum in: *Public Health Nutr.* 2013 Aug;16(8):1527



At the Food Fortification Initiative we reviewed countries' experiences with flour fortification with folic acid.

In this graph we have pre-fortification values in orange and post-fortification values in green.

Across the horizontal axis are the 33 studies reviewed. Below each is the name of the 13 countries where the study was completed.

With the exception of two studies (Ricks/Peru, Alasfoor/Oman), there was a reduction in the neural tube defects observed in most studies after fortification with folic acid.

This figure and an Excel sheet with all of these studies summarized, can be downloaded from the FFI website.

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Source:
Food Fortification Initiative (FFI). Fortifying Flour with Folic Acid to Prevent Neural Tube Defects. Atlanta, USA: FFI, 2017. Available from www.FFInetwork.org



Summary

- Fortification with folic acid reduces the risk of neural tube defects
- Supported by pre-post data from countries, meta-analysis and systematic reviews

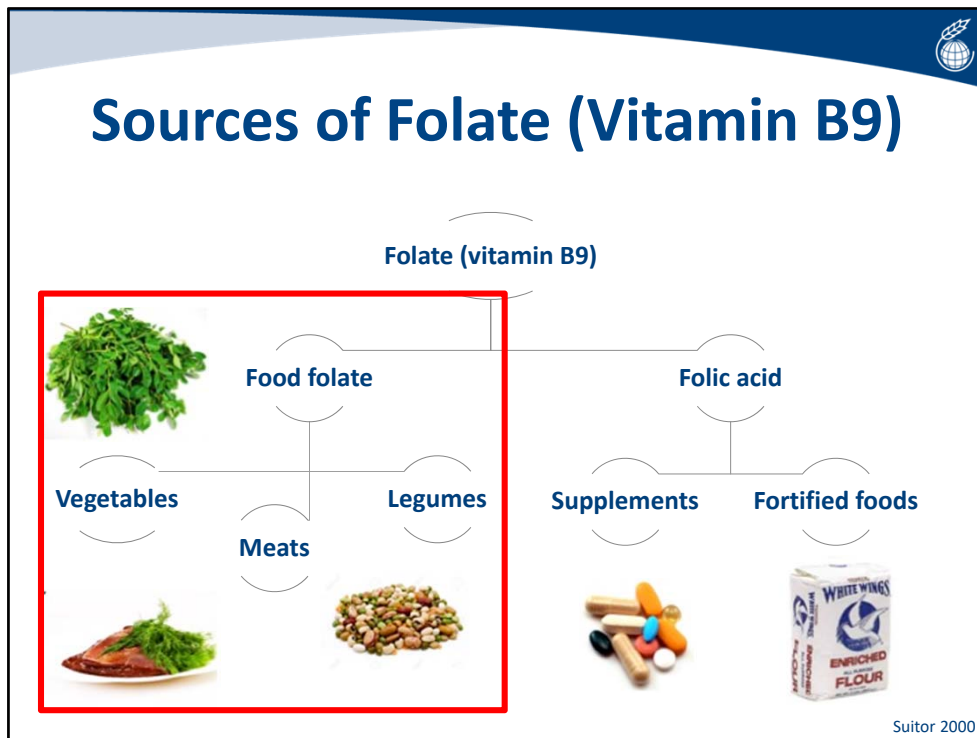
In summary, fortification with folic acid reduces the risk of neural tube defects.

This is supported by pre-post data from countries, a meta-analysis and several systematic reviews.



2. Fortification with folic acid is more effective than dietary diversification or supplementation for reducing the risk of neural tube defects

Now we'll move to the evidence that fortification with folic acid is more effective than dietary diversification or supplementation for reducing the risk of neural tube defects.



The group of vitamins called vitamin B9 includes food folate and folic acid.

Food folate is provided by vegetables, meats and legumes.

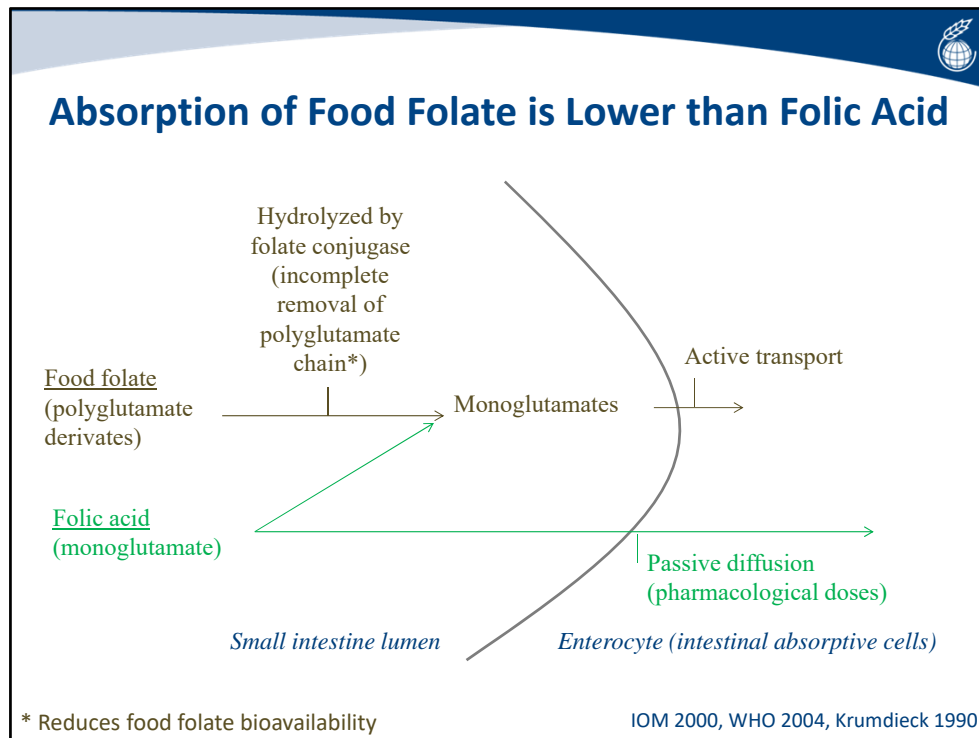
While folic acid is provided by supplements containing folic acid and foods fortified with folic acid.

[CLICK TO ADVANCE] We'll start by looking at food folate.

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Source:

Suitor CW & Bailey LB (2000) Dietary folate equivalents: interpretation and application. Journal of the American Dietetic Association 100: 88–94.



The absorption of food folate is lower than the absorption of folic acid.

This is because food folate is found in the polyglutamate form. In the brush border of the small intestine, folate conjugase hydrolyzes the polyglutamate chain leaving monoglutamates. The incomplete removal of the polyglutamate chain is what contributes to the lower bioavailability of food folate. The monoglutamates are then actively transported into the intestine.

[CLICK FOR ANIMATION] Folic acid, a synthetic form of folate, is found in the monoglutamate form. It does not require modification prior to absorption by the intestine. The monoglutamates can enter through active transport. And if given in pharmacological doses, they passively diffuse across the intestinal mucosa.

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Source:


Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. 2000.

WHO & FAO. Vitamin and mineral requirements in human nutrition, Second edition. 2004.

Krumdieck C. Folic acid. In ME Brown, ed. Present Knowledge in Nutrition. ILSI, Washington DC. 1990.

Krumdieck 1990

"Dietary folates, most of which are polyglutamyl derivatives, undergo hydrolysis to monoglutamates before appearing in the mesenteric blood. The requirement for hydrolysis decreases the availability of folypolyglutamates compared with that of folic acid. Intraluminal polyglutamate hydrolysis is catalyzed by an intestinal enzyme found in the brush border. This brush border pteroylpolyglutamate hydrolase (BB-PPH) is an exo-peptidase that cleaves the polyglutamyl chain one residue at a time starting from the carboxyl end."



To Prevent NTDs without Folic Acid, Women Need 450 mcg of Dietary Folate Equivalents (DFEs) Daily

	DFE mcg ²
23 spears cooked asparagus	460
4 cups cooked okra	540
4 cups raw spinach	440
2 cups cooked black beans	420
2 slices of beef liver	370
6 cups orange juice	480
48 fresh strawberries	480
4.5 cups cooked broccoli	450

“It is difficult for a woman to eat enough natural food folate to prevent neural tube defects.”

WHO recommendations to prevent neural tube defects: folic acid (primarily)

NTD, neural tube defect Marchetta 2015, Suitor 2000, WHO 2007

Some people want to rely only on food folate to prevent neural tube defects. Without folic acid, women would need 450 micrograms of dietary folate equivalents daily to reduce the risk of a pregnancy being affected by a neural tube defect. This is very difficult to achieve on a daily basis as it would require women to eat, for example, 23 spears of asparagus daily, or 4 cups of okra daily.

Therefore, at present, WHO recommends that women primarily take folic acid as a way to prevent neural tube defects.

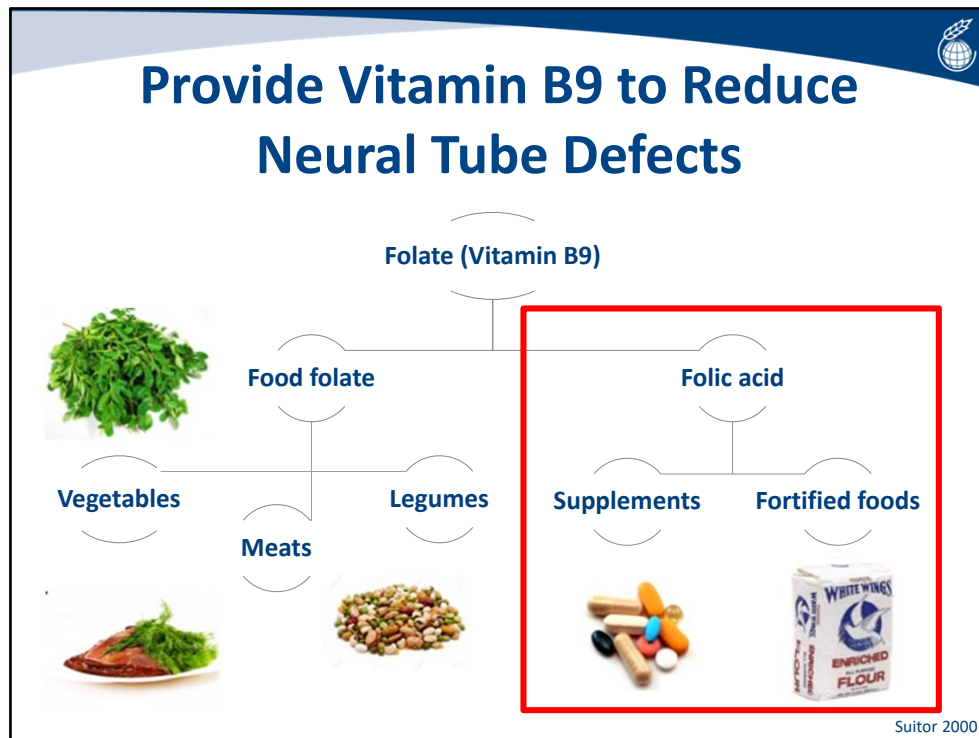
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Source:

Marchetta et al. Assessing the association between natural food folate intake and blood folate concentrations: a systematic review and Bayesian meta-analysis of trials and observational studies. [Nutrients](#). 2015 10;7(4):2663-86.

Suitor & Bailey. Dietary folate equivalents: Interpretation and application. [Journal of the American Dietetic Association](#), 2000 100(1):88-94.

WHO. Prevention of neural tube defects. Standards for Maternal and Neonatal Care. 2007.



Let's turn to folic acid.

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Source:

Suitor CW & Bailey LB (2000) Dietary folate equivalents: interpretation and application. *Journal of the American Dietetic Association* 100: 88–94.

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In comparison, folic acid is a synthetic form of vitamin B9.

It is better absorbed by the body than food folate.

We get folic acid in two ways: dietary supplements containing folic acid, and foods fortified with folic acid.

Folic Acid Supplements Reduce Neural Tube Defects

- Women planning a pregnancy were given daily
 - Folic acid and other nutrients (vitamin group), or
 - Other nutrients (trace-element group)



Table 3. Congenital Malformations, According to Study Group.

MALFORMATION	VITAMIN GROUP	TRACE-ELEMENT GROUP	<i>P</i> = 0.029
	<i>number</i>		
Neural-tube defect	0	6	

Czeizel 1992

The original studies that showed that folic acid reduced neural tube defects were completed by giving women dietary supplements.

Here are the results of the first study to show that folic acid supplements given daily to women reduce the first occurrence of a neural tube defect.

Specifically, women planning a pregnancy were given on a daily basis one of two supplements: a supplement containing folic acid and other nutrients, or a supplement containing other nutrients.

[CLICK TO ADVANCE] The table shows that at the end of the study, women receiving the folic acid had no pregnancies affected by neural tube defects, while among women who did not consume folic acid supplements, six had pregnancies affected by this congenital anomaly.

Therefore, we know that if taken, folic acid supplements reduce the risk of neural tube defects.

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Source:

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

Women planning a pregnancy were randomly assigned to receive a single tablet of a vitamin supplement (containing 12 vitamins including 0.8 mg folic acid) or a trace-element supplement daily for at least one month before conception and until the date of the second missed menstrual period or later. Congenital malformations were significantly more prevalent in the group receiving the trace-element supplement than in the vitamin-supplement group (22.9 per 1000 vs 13.3 per 1000, $p=0.02$). There were six cases of neural tube defects in the group receiving the trace-element supplement than in the vitamin-supplement group ($p=0.029$).



Folic Acid Supplement Use is Low Before and During Early Pregnancy

- Assessed in 49 studies from 22 countries
- Peri-conceptual use ranged from:
 - 0.5% (Italy)
 - 52% (Netherlands)

In practice, peri-conceptual folic acid supplement use is low, even after mass media campaigns to increase use

Ray 2004

Unfortunately, in practice, folic acid supplement use is low in the period before and during early pregnancy, known as the pre-conceptual period.

These are the results of a review of 49 studies carried out in 22 countries.

Folic-acid supplement use before and during early pregnancy ranged from 0.5% in Italy to 52% in The Netherlands.

So at best, 50% of women are taking folic acid supplements around the time of conception.

To prevent neural tube defects, we need for 100% of women to be getting adequate folic acid around the time of conception.

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Source:

Ray JG, Singh G & Burrows RF (2004) Evidence for suboptimal use of periconceptual folic acid supplements globally. *British Journal of Obstetrics & Gynaecology* 111: 399–408.



Many Pregnancies are Unplanned

“Almost half of all pregnancies worldwide, estimated to be over 100 million annually, are unintended or mistimed.”



<http://www.istockphoto.com/2011/01/14/stock-photo/27581483>

If women are not planning pregnancy, they may not take supplements in peri-conceptual period

Thurman 2011

A further complication is that many pregnancies are unplanned.

Thurman and colleagues report that almost 50% of all pregnancies worldwide are unintended or mistimed.

So, if women are not planning a pregnancy, they may not take folic-acid supplements in the peri-conceptual period, when they can do the most good.

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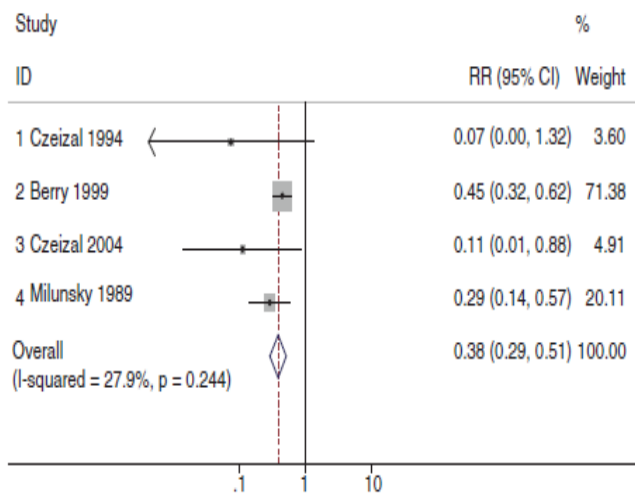
Source:

Thurman AR, Clark MR & Doncel GF (2011) Multipurpose prevention technologies: biomedical tools to prevent HIV-1, HSV-2, and unintended pregnancies. *Infectious Diseases in Obstetrics & Gynecology* **2011**: 1–10.



High Coverage of Supplement Use

62% Reduction in the First Occurrence of Neural Tube Defects (NTDs)



A meta-analysis of studies with **>50% folic-acid supplementation coverage** estimated a **62% reduction** in the risk of first occurrence of NTDs due to supplementation

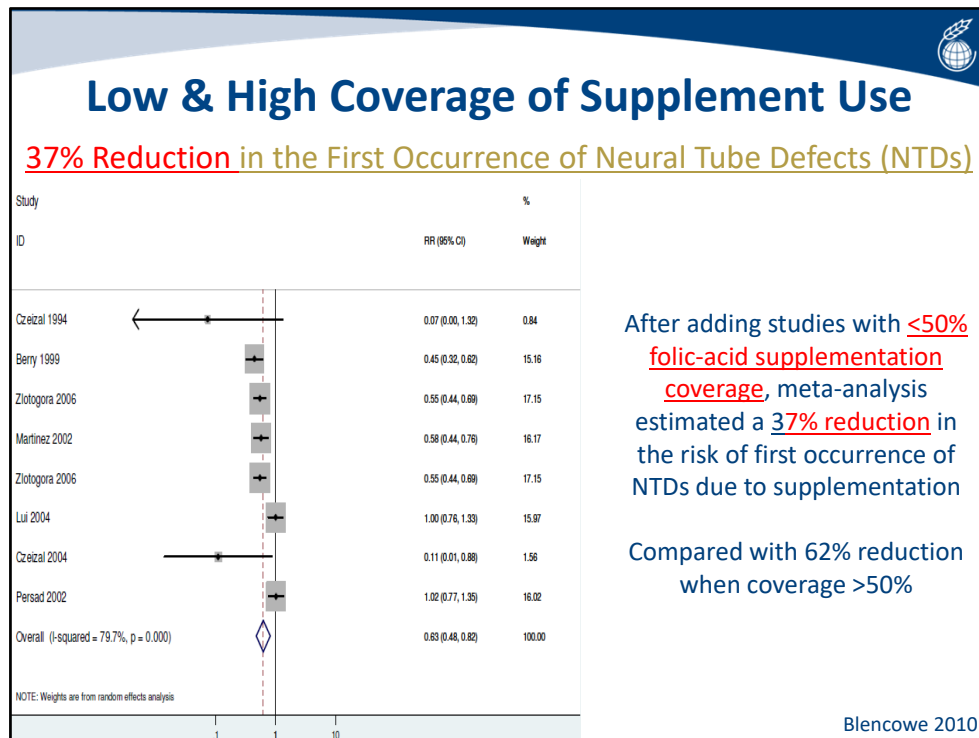
Blencowe 2010

When folic acid supplement use is high, the reduction in neural tube defects is high. These are the results of a meta-analysis of four studies where more than 50% of women took the folic-acid supplement. In these studies, the relative risk was 0.38, indicating that folic-acid supplementation led to a 62% reduction in the risk of first occurrence of neural tube defects.

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Source:

Blencowe H, Cousens S, Modell B, Lawn J. Folic acid to reduce neonatal mortality from neural tube disorders. *International Journal of Epidemiology* 2010;39:i110–i121.



After adding studies with <50% folic-acid supplementation coverage, meta-analysis estimated a 37% reduction in the risk of first occurrence of NTDs due to supplementation

Compared with 62% reduction when coverage >50%

When there is a mix of low and high coverage of folic-acid supplement use, the reduction in neural tube defects is lower.

The meta-analysis from the previous slide was changed to include studies with supplementation coverage less than 50%, which reflects supplementation coverage globally. There, the relative risk was 0.63, indicating that supplement use only reduced by 37% the risk of first occurrence of neural tube defects.

This compares with a 62% reduction when supplementation coverage was greater than 50%. Therefore, the efficacy of an intervention is not enough, it must have broad coverage in order to have a public-health impact.

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Source:

Blencowe H, Cousens S, Modell B, Lawn J. Folic acid to reduce neonatal mortality from neural tube disorders. *International Journal of Epidemiology* 2010;39:i110–i121.



Supplementation Recommendations Alone are Not Effective

- Compared NTD levels before and after recommendations were issued for folic acid supplementation (~1992)
- 13 birth defects registries; 9 European countries + Israel
- “The issuing of recommendations on folic acid [supplementation] was followed by no detectable improvement in the trends of incidence of neural tube defects.”

**All women capable of becoming pregnant should be encouraged to take folic acid supplements
AND consume food fortified with folic acid**

NTD, neural tube defect

Botto 2005

The evidence suggests that we need to use the combination of folic acid supplementation and fortification with folic acid, to ensure women have optimum folate status during the peri-conceptual period.

[CLICK TO ADVANCE] A study compared neural tube defect levels before and after recommendations were issued for folic acid supplementation use by women in 1992.

[CLICK TO ADVANCE] They used data from 13 birth defects registries, which encompassed 9 European countries and Israel.

[CLICK TO ADVANCE] The researchers concluded that “The issuing of recommendations on folic acid [supplementation] was followed by no detectable improvement in the trends of incidence of neural tube defects.”

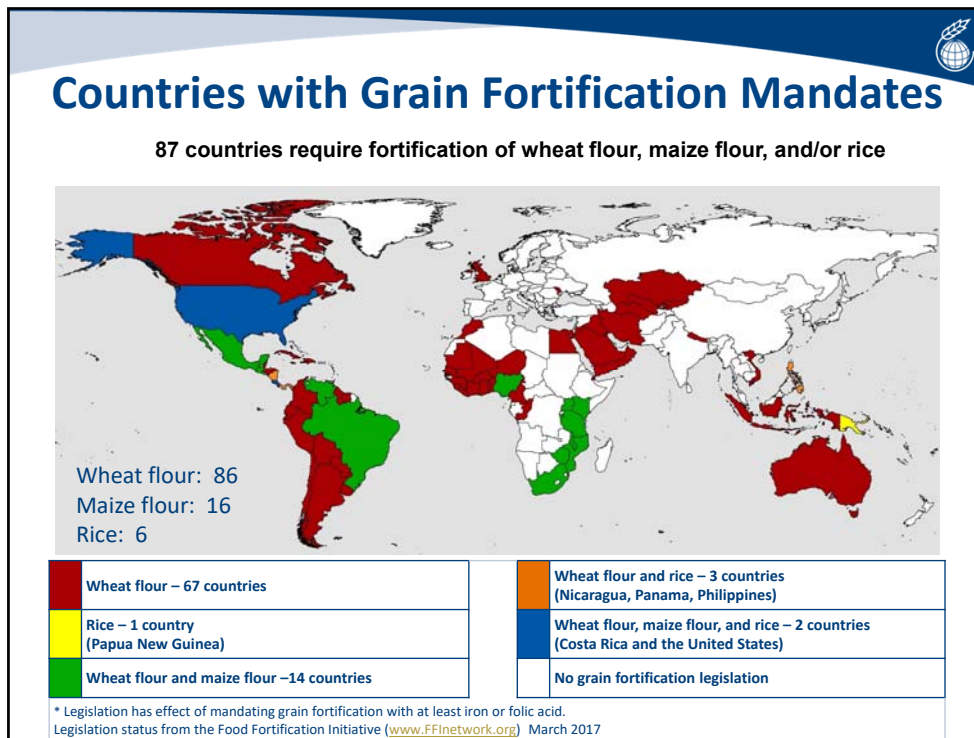
[CLICK TO ADVANCE] Please allow me to clarify, that we should continue to encourage all women capable of becoming pregnant to take supplements containing folic acid.

In addition, we need to make sure women enter pregnancy with good folate status. For that, we will look to food fortified with folic acid.

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Source:

Botto LD, Lisi A & Robert-Gnansia E (2005) International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? British Medical Journal 330: 571.



This map represents the countries that have passed legislation that mandates the fortification of the three most commonly consumed grains in the world: wheat flour, maize flour and rice.

Currently 86 countries mandate fortification of wheat flour.

Of these, 16 countries also mandate fortification of maize flour.

And, a total of 6 countries mandate fortification of rice.

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Source:

Food Fortification Initiative. Global progress.

http://ffinetwork.org/global_progress/index.php



Adding Folic Acid in Grain Fortification is Standard Practice Globally

- Mandate fortification with folic acid
 - Wheat flour: 81 of 86 countries
 - Maize flour: 15 of 16 countries
 - Rice: 4 of 6 countries
- Folic acid levels required
 - Wheat flour: 0.5-3.3 mg/kg
 - Maize flour: 0.5-2.6 mg/kg
 - Rice: 1-3.08 mg/kg



mg/kg = parts per million (ppm)

FFI 2017

Most of the countries that mandate fortification of wheat flour, maize flour or rice, require that folic acid be added to the grain.

The amount of folic acid added to these grains ranges from 0.5-3.3 mg/kg, or parts per million.

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Source:

Food Fortification Initiative. Food Fortification Initiative database. 2017.

Exceptions:

Wheat flour: Congo, Philippines, Venezuela, Viet Nam, United Kingdom

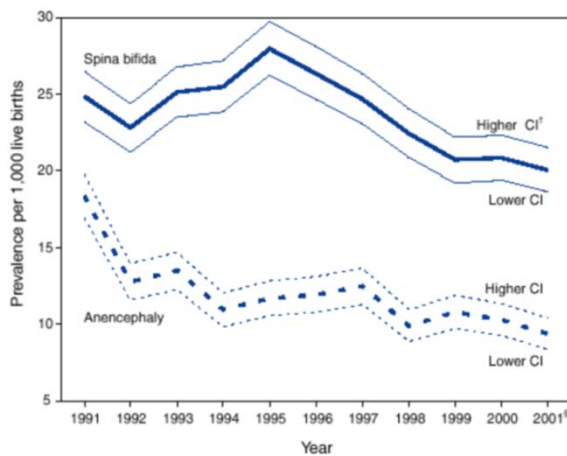
Maize flour: Venezuela

Rice: Papua New Guinea, Philippines



USA: Fortification with Folic Acid Reduces Neural Tube Defects

FIGURE. Spina bifida and anencephaly prevalence — United States, 1991–2001*



1998: grain fortification with folic acid

Matthews 2002

As shown earlier, countries such as the USA, which fortify food with folic acid, have experienced a decrease in the number of babies born with neural tube defects, such as spina bifida and anencephaly, after mandating fortification with folic acid.

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Source:

Mathews TJ et al. Spina Bifida and Anencephaly Prevalence --- United States, 1991--2001. MMWR 2002.



Advantages of Food Fortification

- Women consume food fortified with folic acid without any need for behavior change
- Extra folic acid will improve women's folate status
- Women with unplanned pregnancies will have optimal folate status to prevent NTDs

NTDs, neural tube defects

WHO/FAO 2006

The main advantage of fortification is that the foods selected for fortification are those consumed by the target population, such as women of childbearing age. These women are not asked to change their behavior.

Instead, as they continue to eat these foods, which are now fortified with folic acid, they will get extra folic acid in their diet.

And this extra folic acid will improve their folate status, so that even women who don't plan their pregnancies, can have an optimum folate status to prevent neural tube defects.

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Source:

WHO/FAO. Guidelines on food fortification with micronutrients. 2006.

http://www.who.int/nutrition/publications/guide_food_fortification_micronutrients.pdf



Summary

- Food folate is less well absorbed than folic acid
- Difficult for women to consume the amount of food folate needed daily to reduce NTDs
- Folic acid supplements reduce NTDs, if they are taken around time of conception & they have high coverage
- Fortification with folic acid is more effective than dietary diversification or supplementation for reducing the risk of neural tube defects

NTDs, neural tube defects

In summary, food folate is less well absorbed than folic acid.

And it is difficult for women to consume the amount of food folate needed daily to reduce neural tube defects.

Folic acid supplements reduce the risk of neural tube defects, if they are taken around the time of conception and they have high coverage.

Fortification with folic acid is more effective than dietary diversification or supplementation for reducing the risk of neural tube defects.



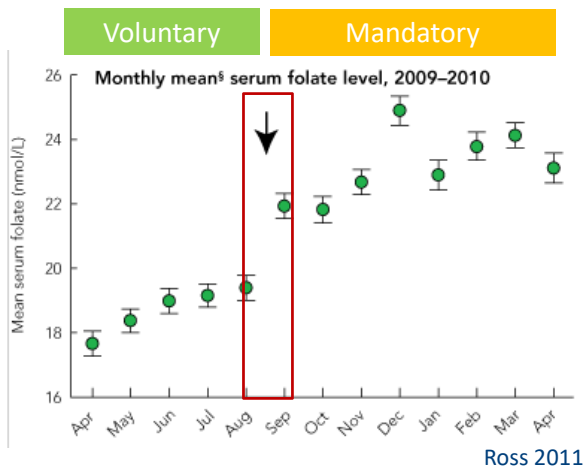
3. Mandatory fortification with folic acid is more effective than voluntary fortification for reducing the risk of neural tube defects

Let's look at evidence that mandatory fortification with folic acid is more effective than voluntary fortification for reducing the risk of neural tube defects.

Mandatory Fortification is More Effective than Voluntary Fortification

Fortification with folic acid increases serum folate

- Voluntary fortification began in 1995 in Australia
- Mandatory wheat flour fortification began in September 2009
- Analysis of 20,592 blood samples



Australia introduced voluntary fortification of wheat flour with folic acid in 1995. Then, mandatory fortification was implemented as of September 2009.

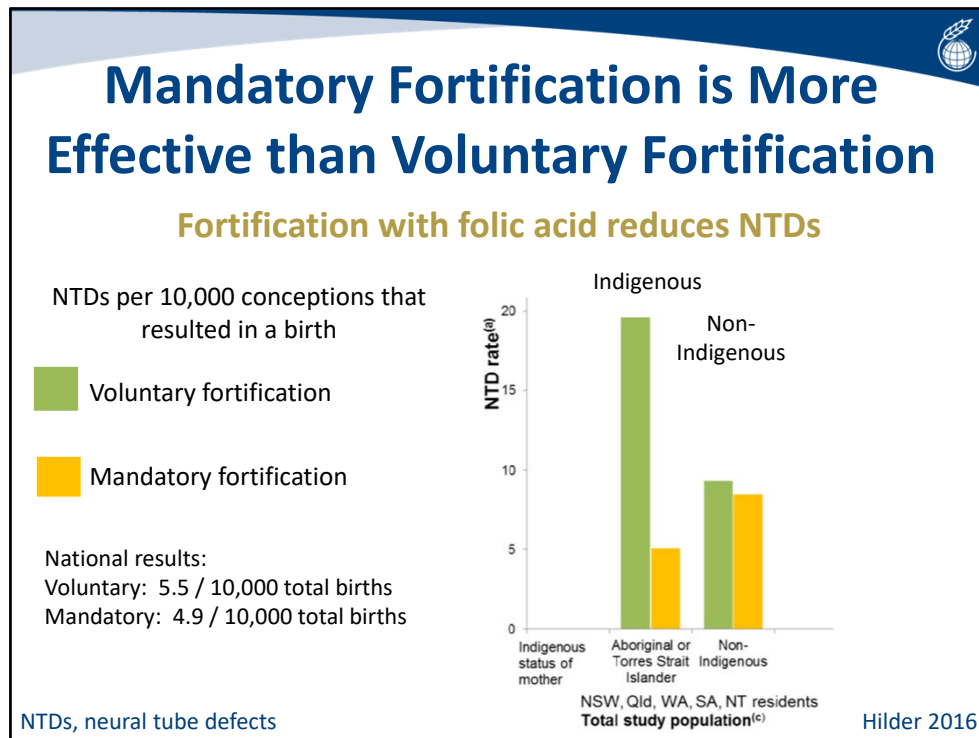
When folic acid is consumed, serum folate levels increase in individuals.

This slide has the mean serum folate levels in 20,000 blood samples. You can see that the mean levels increased when the country passed from voluntary to mandatory fortification.

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Source:

D. Ross et. al., The impact of mandatory fortification of flour with folic acid on the blood folate levels of an Australian population. *The Medical Journal of Australia*. 2011.



Consistent with the previous slide, after serum folate levels increased in Australia, the birth prevalence of neural tube defects decreased.

In this slide, the first two bars refer to indigenous women and the next two bars refer to non-indigenous women.

The green bars refer to the voluntary fortification period and the yellow bars refer to the mandatory fortification period.

At the national level, there was a reduction in the birth prevalence of neural tube defects between the voluntary and mandatory periods: 5.5 versus 4.9/10,000 total births.

This difference is most pronounced in the indigenous women who experienced a large reduction in neural tube defects from approximately 20/10,000 in the voluntary period to 5/10,000 in the mandatory period.

Mandatory fortification reduced neural tube defects in the most vulnerable population.

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Source:
 Hilder S. Neural Tube Defects in Australia, 2007–2011: Before and after implementation of the mandatory folic acid fortification standard. The University of New South Wales, 2016.

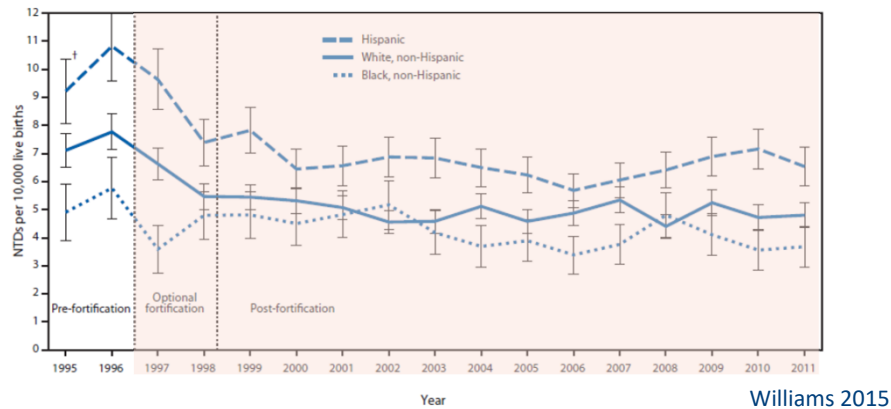
“Three time periods were therefore selected for this study and applied to conceptions: a ‘baseline’ period before mandatory fortification commenced until the end of December 2008; a ‘transition’ period from January 2009 to the end of September 2009; and a ‘standard’ period from the beginning of October 2009 to the end of March 2011, during which the fortification standard was mandated.”

Indigenous: 19.6 versus 5.1
 Non-indigenous: 9.3 versus 8.5

Mandatory Fortification is More Effective than Voluntary Fortification

1996: grain fortification with folic acid optional 1998: grain fortification with folic acid mandatory

FIGURE. Prevalence of neural tube defects (NTDs) (anencephaly and spina bifida) before and after mandatory folic acid fortification, by maternal race/ethnicity — 19 population-based birth defects surveillance programs,* United States, 1995–2011



In the USA, several grains are fortified with folic acid: wheat flour, maize flour and rice.

[CLICK TO ADVANCE] In the country, there was a two-year period of voluntary fortification in 1996 and 1997.

[CLICK TO ADVANCE] Then, fortification with folic acid became mandatory in 1998.

[CLICK TO ADVANCE] This graph has the number of neural tube defects per 10,000 live births for three population groups: Hispanics in the top-most line, Whites in the solid blue line and Black Americans in the bottom-most line.

As observed in Australia, the reduction in neural tube defects has been greater during the mandatory fortification period than it was in the voluntary fortification period.

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Source:

Williams J et al. Updated Estimates of Neural Tube Defects Prevented by Mandatory Folic Acid Fortification — United States, 1995–2011. MMWR 2015.



Summary

- Mandatory fortification is more effective than voluntary fortification in
 - Increasing serum folate levels
 - Reducing neural tube defects (especially among most vulnerable)

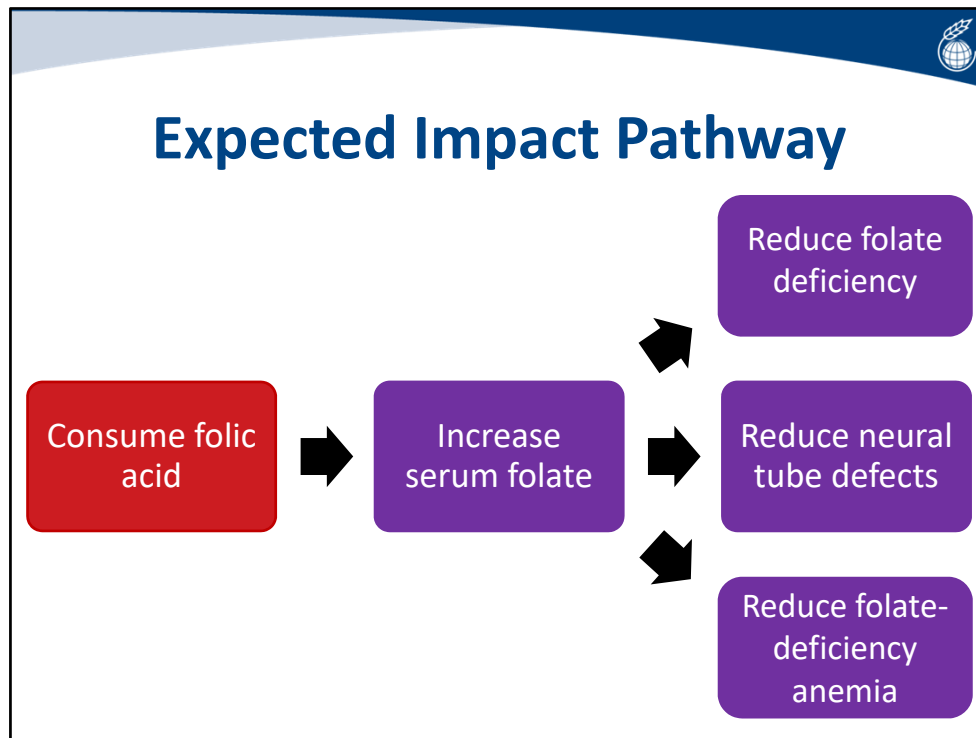
NTDs, neural tube defects

In summary, mandatory fortification with folic acid is more effective than voluntary fortification in increasing serum folate levels, and in reducing neural tube defects (especially among the most vulnerable).



4. Fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia


Fourth, fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia, extending the benefits of fortification to other groups in the population.



We expect that when people consume folic acid from any source, it will increase their serum folate levels. And, in women of childbearing age, this will lead to a reduction in neural tube defects. We saw data from Australia showing this.

[CLICK TO ADVANCE] For women and other members of the population, increased serum folate can also reduce folate deficiency and reduce folate-deficiency anemia.

We will see evidence for these two latter outcomes.



Fortification with Folic Acid is Associated with Reduced Folate Deficiency

Country	Age range	Sample size	Folate deficiency
Canada	6-79 years	5248	<1%
Chile	Women of childbearing age	605	0%
Fiji	Women 15-45 years	869	1%
USA	≥ 50 years	1546	0.1%

Colapinto 2011, Hertrampf 2003, Odewole 2013, National Food and Nutrition Centre 2010

Data from several countries suggest that fortification with folic acid virtually eliminates folate deficiency.

These data are from Canada, Chile, Fiji, and the United States. The population studied varied by country: it was females and males 6-79 years of age in Canada, women of childbearing age in Chile and Fiji, and women and men 50 years of age and older in the United States.

In all of these settings, after fortification with folic acid began, 1% or fewer had folate deficiency.

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Source:

Calapinto et al. Folate status of the population in the Canadian Health Measures Survey. *Canadian Medical Association Journal*, 183(2):E100-6, 2011.

Hertrampf et al. Consumption of folic acid-fortified bread improves folate status in women of reproductive age. *Journal of Nutrition*. 2003.

National Food and Nutrition Centre. Impact of iron fortified flour in child bearing age (CBA) women in Fiji, 2010 report. Suva: National Food and Nutrition Centre; 2012.

Odewole et al. Near-elimination of folate-deficiency anemia by mandatory folic acid fortification in older US adults: Reasons for Geographic and Racial Differences in Stroke study 2003–2007. *American Journal of Clinical Nutrition*, 98(4):1042-7, 2013.

Fiji completed a national nutrition survey in 2004, before flour fortification was initiated, and then again in 2010, after flour fortification had been implemented for about 5 years. Wheat flour fortification in Fiji is compulsory with at least iron, folic acid and zinc.

This graph shows the prevalence of (from left to right) iron deficiency, folate deficiency and zinc deficiency in women of reproductive age. The green bar shows the prevalence before fortification began and the gray bar shows the prevalence after fortification was started.

We can see that the prevalence of iron deficiency decreased from 22.9% to 7.9%, the prevalence of folate deficiency decreased from 8.1% to 1% and the prevalence of zinc deficiency decreased from 39.3% to 0% after fortification began.

Several additional analyses completed by the researchers lead us to believe that it is very likely that flour fortification contributed to these important declines in nutrient deficiency.

Source: National Food and Nutrition Centre. Impact of iron fortified flour in child bearing age (CBA) women in Fiji, 2010 report. Suva: National Food and Nutrition Centre; 2012.

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Studies were cross-sectional in Canada and USA, pre-post cross sectional in Fiji, and prospective in Chile.



Fortification with Folic Acid is Associated with Reduced Folate-deficiency Anemia

Country	Age range	Sample size	Folate-deficiency anemia
USA	≥ 50 years	1546	<0.1%

Flour fortification with folic acid began in 1998
Data collected from 2003-2007

Odewole 2013

These are data on folate-deficiency anemia. They come from the USA where Odewole and colleagues studied 1546 persons aged 50 years and older from 2003 to 2007. This was 5 to 9 years after fortification with folic acid was made mandatory in the USA.

In this cross-sectional survey, they identified 1 person with folate-deficiency anemia. Therefore, with folic-acid fortification, folate-deficiency anemia was virtually eliminated in older adults.

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Source:

Odewole et al. Near-elimination of folate-deficiency anemia by mandatory folic acid fortification in older US adults: Reasons for Geographic and Racial Differences in Stroke study 2003–2007. *American Journal of Clinical Nutrition*, 98(4):1042-7, 2013.



Summary

- Flour fortification with folic acid
 - Increases serum folate
 - Reduces neural tube defects
 - Reduces folate deficiency
 - Reduces folate-deficiency anemia
- Benefits apply to
 - Total population that consumes fortified flour

NTDs, neural tube defects

To summarize, flour fortification with folic acid increases serum folate, reduces neural tube defects, reduces folate deficiency, and reduces folate-deficiency anemia.

These benefits apply to the total population that consumes fortified flour.



5. Fortification with folic acid does not mask vitamin B12 deficiency or cause cancer

Finally, let me share with you the evidence that fortification with folic acid does not mask vitamin B12 deficiency or cause cancer.



Fortification with Folic Acid Does Not Mask Vitamin B12 Deficiency

- Concern: Folic acid could mask vitamin B12 deficiency by ameliorating anemia while allowing neurological damage to progress
- Study premise: Persons with low vitamin B12 status and no anemia are most likely to be detrimentally affected by excessive folic acid intake
- Study question: Did prevalence of persons with low vitamin B12 status and no anemia change between pre and post folic-acid fortification periods?

Mills 2003

One of the questions we are asked is if fortification with folic acid masks vitamin B12 deficiency.

The concern stems from the fact that both folate deficiency and vitamin B12 deficiency are manifested as megaloblastic anemia. Therefore, if a person is truly vitamin B12 deficient and only folic acid is administered, the anemia will be ameliorated, but the person will continue to have vitamin B12 deficiency, and with it, neurological damage can progress.

So, these researchers surmised that people with low vitamin B12 status and no anemia are most likely to be detrimentally affected by excessive folic acid intake. That is, with greater folic acid, they will not progress to getting anemia; however with their low vitamin B12 status, they may progress to developing vitamin B12 deficiency.

So, the researchers assessed if the prevalence of persons with low vitamin B12 status and no anemia changed between pre and post folic-acid fortification periods.

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Source:

Mills JL et al. Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr* 2003;77:1474-7.

Fortification with Folic Acid Does Not Mask Vitamin B12 Deficiency

Fortification

- USA
- Fortification with folic acid: before, voluntary, mandatory

Population

- Patients at Veterans Affairs Medical Center in Washington DC
- 53-75 years of age

Sample

- n=1785

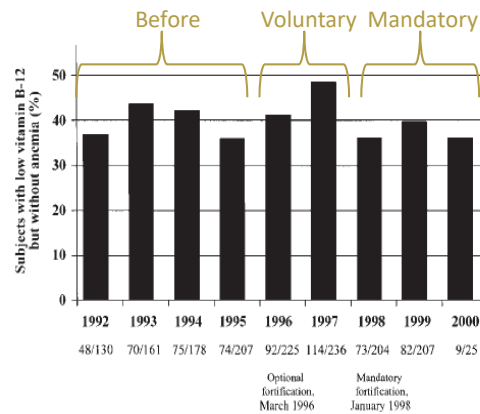


FIGURE 1. Percentages of subjects with low vitamin B-12 concentrations (<258 pmol/L) but without anemia before, during, and after fortification of enriched cereal grains with folic acid. The fractions under the year labels on the x axis indicate the number of subjects without anemia/the number of subjects with a low vitamin B-12 concentration. The percentage of subjects without anemia was not significantly different between the 3

Mills 2003

The graph has data from 1785 patients aged 53 to 75 years who were seen at the Veterans Affairs Medical Center in Washington DC from 1992 to 2000. 1992-1995 corresponds to the period before mandatory fortification with folic acid was begun in the USA, 1996-1997 corresponds to the voluntary fortification period, and 1998 forward corresponds to the period when mandatory fortification was in effect.

The bars represent the % of people with low vitamin B12 status who were not anemic. If folic acid was masking vitamin B12 deficiency, we would expect an increase, from the “before” to the “mandatory” period, in the prevalence of people with low vitamin B12 status who were not anemic.

In the graph we see that the prevalence did not change across the three fortification periods. These data from Mills suggest that folic-acid fortification does not increase the masking of vitamin B12 deficiency.

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Source:

Mills JL et al. Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr* 2003;77:1474-7.



Fortification with Folic Acid Does Not Mask Vitamin B12 Deficiency

- Concern: Folic acid could mask vitamin B12 deficiency by ameliorating anemia or macrocytosis, while allowing neurological damage to progress
- Study premise: Persons with low vitamin B12 status and no anemia (or no macrocytosis) are most likely to be detrimentally affected by excessive folic acid intake
- Study questions:
 - Did prevalence of persons with vitamin B12 deficiency and no anemia change between pre- and post folic-acid fortification periods?
 - Did prevalence of persons with vitamin B12 deficiency and no macrocytosis change between pre- and post folic-acid fortification periods?

Macrocytosis: enlarged red blood cells

Qi 2014

Another study from the USA, published 11 years after the Mills study, aimed to answer the same question.

The concern is the same: if a person is truly vitamin B12 deficient and only folic acid is administered, their anemia or macrocytosis (meaning enlarged red blood cells) will be improved, but the person will continue to have vitamin B12 deficiency, and with it, neurological damage can progress.

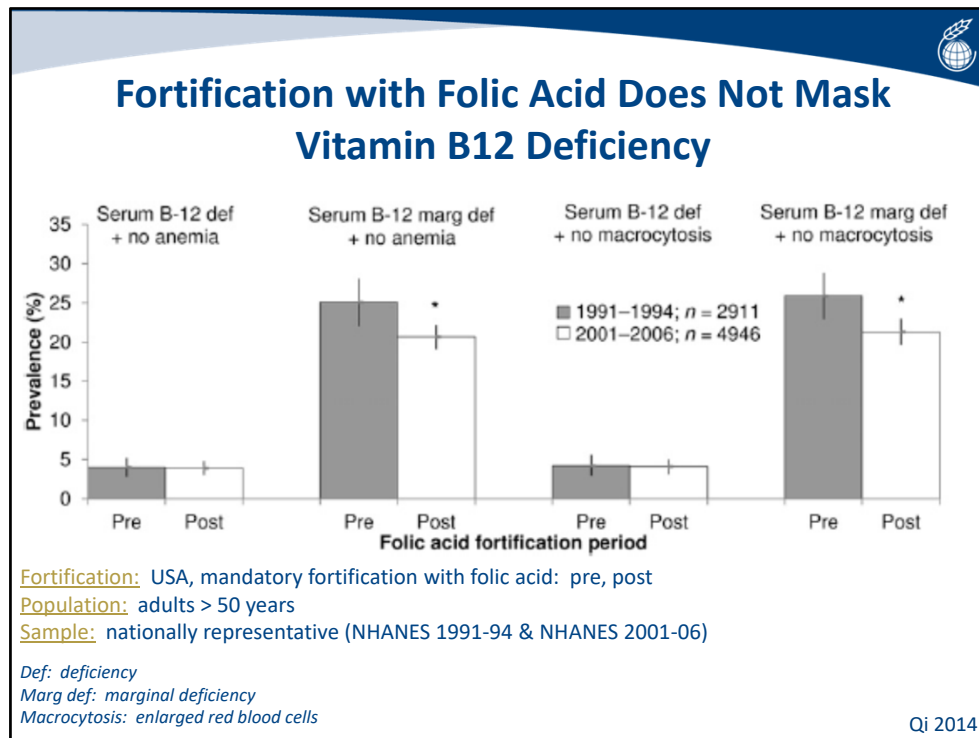
The study premise is that people with low vitamin B12 status and no anemia are most likely to be detrimentally affected by excessive folic acid intake. The same is true for people with low vitamin B12 status and no macrocytosis.

So, the researchers assessed if the prevalence of persons with vitamin B12 deficiency and no anemia changed between pre and post folic-acid fortification periods. And, if the prevalence of persons with vitamin B12 deficiency and no macrocytosis changed between pre and post folic-acid fortification periods.

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Source:

Yan Ping Qi, Ann N. Do, Heather C. Hamner, Christine M. Pfeiffer, and Robert J. Berry. The prevalence of low serum vitamin B-12 status in the absence of anemia or macrocytosis did not increase among older U.S. adults after mandatory folic acid fortification. *J. Nutr.* 144: 170–176, 2014.



This slide has the main results from this study.

We have four groups of individuals represented, starting from the left, those with vitamin B12 deficiency and no anemia, those with marginal vitamin B12 deficiency and no anemia, then those with vitamin B12 deficiency and no macrocytosis, and on the far right, those with marginal vitamin B12 deficiency and no macrocytosis.

The gray bars represent the period before mandatory fortification with folic acid in the USA and the white bars represent the period after mandatory fortification.

If folic acid was masking vitamin B12 deficiency, we would expect an increase in any of these groups during the post-fortification period.

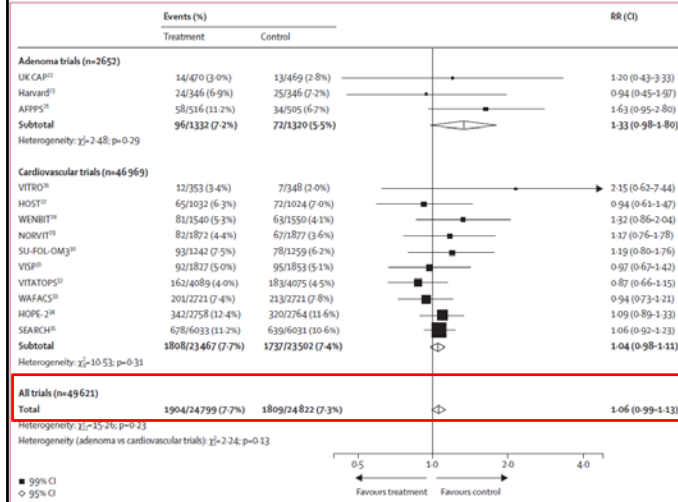
We see that there was no change in the prevalence for the first and third groups, where people had vitamin B12 deficiency. And there was a significant decrease in the prevalence of the second and fourth groups. Because there was no increase in people with low B12 status and either no anemia or no macrocytosis, these results suggest there is no masking of vitamin B12 deficiency by fortification with folic acid.

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Source:

Yan Ping Qi, Ann N. Do, Heather C. Hamner, Christine M. Pfeiffer, and Robert J. Berry. The prevalence of low serum vitamin B-12 status in the absence of anemia or macrocytosis did not increase among older U.S. adults after mandatory folic acid fortification. *J. Nutr.* 144: 170-176, 2014.

Folic Acid Does Not Cause Cancer



Supplementation

- n ~50,000
- Received folic acid or placebo
- Treatment ≥ 1 y
- Provided (median) 2000 mcg folic acid/d
- Calculated the cancer incidence rate ratio (RR)

Figure 1: Effects of folic acid allocation on overall first cancer incidence
 RR=rate ratio. The black squares denote the RRs and horizontal lines the 99% CIs. Each square has an area inversely proportional to the variance of the log of the RR. The diamonds represent the summary estimates and their corresponding 95% CIs. * $p<0.07$. † $p<0.20$. ‡ $p<0.10$.

Vollset 2013

The next question we are asked is if folic acid causes cancer.

This study is one of the latest meta-analyses on the effect of folic-acid supplementation on cancer incidence. Data from adenoma trials and cardiovascular trials were pooled for a total of ~50,000 individuals who had been randomly assigned to receive folic acid or a placebo.

The folic acid provided ranged from 500 mcg per day to 40,000 mcg per day. The median amount provided in the trials was 2,000 mcg folic acid per day, which is 5 times higher than the recommended amount for women of childbearing age.

The authors calculated the cancer incidence rate ratio, which appears as RR in the right-hand column of the table.

7.7% of the individuals who received folic acid were diagnosed with cancer, compared with 7.3% of those who received the placebo. The rate ratio was 1.06. Since the confidence interval included 1.0, the data suggest that folic-acid supplementation does not increase the incidence of cancer.

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Source:

Vollset SE et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50 000 individuals. Lancet January 25, 2012. [http://dx.doi.org/10.1016/S0140-6736\(12\)62001-7](http://dx.doi.org/10.1016/S0140-6736(12)62001-7).

Folic Acid Does Not Cause Cancer

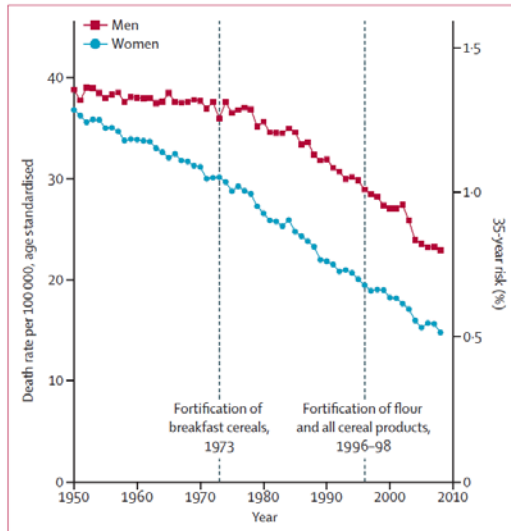


Figure 4: Annual mortality from colorectal cancer in the USA, 1950-2008, at ages 35-69 years

Vollset 2013

Fortification

- Annual mortality from colorectal cancer
- USA
- 1950-2008
- Voluntary fortification with folic acid (1973, 1996-1997)
- Mandatory fortification with folic acid (1998+)

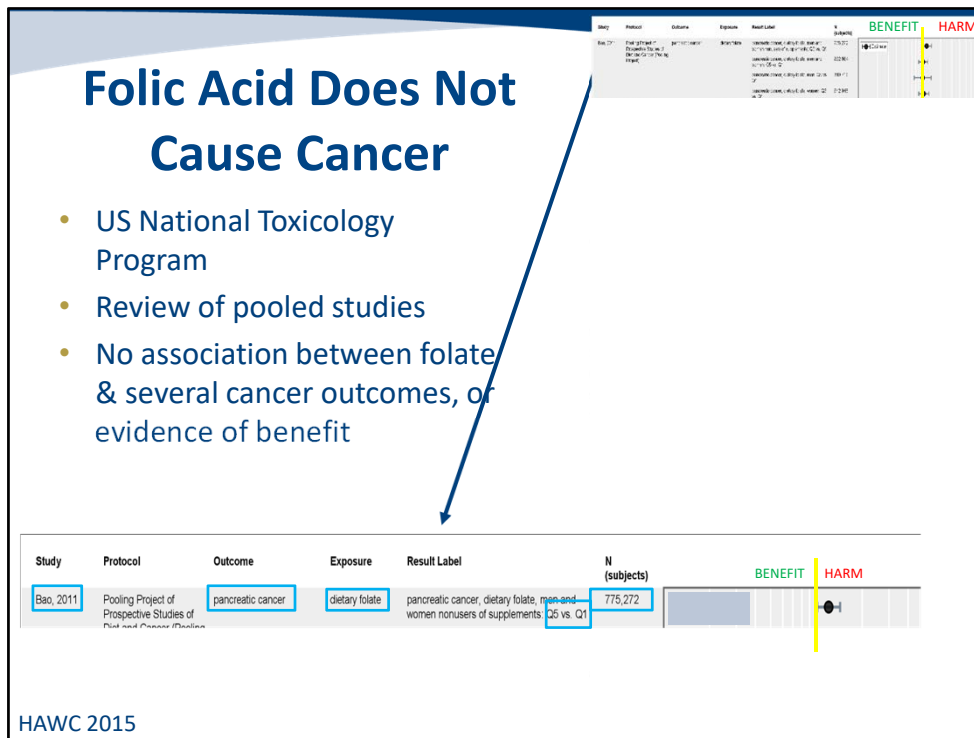
The same authors reviewed data on the annual mortality in the USA from colorectal cancer from 1950 to 2008, which is the timeline that appears along the x-axis. They note in the dashed vertical lines that voluntary fortification of breakfast cereals began in 1973 and that fortification of grains with folic acid began in voluntary fashion in 1996 and became mandatory in 1998. The data are presented for women in blue and men in red.

It's clear from the graph that the downward trend in annual deaths from colorectal cancer has not changed since the introduction of voluntary and mandatory fortification with folic acid in the USA. These data suggest that folic-acid fortification does not cause death from colorectal cancer.

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Source:

Vollset SE et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50 000 individuals. Lancet January 25, 2012. [http://dx.doi.org/10.1016/S0140-6736\(12\)62001-7](http://dx.doi.org/10.1016/S0140-6736(12)62001-7).



In 2015 the US National Toxicology Program conducted a review of pooled studies. These studies had themselves pooled data that looked at the relationship between folate intake and several cancer outcomes.

If the estimate and its confidence interval are below 1, that means that folate benefited the study participants—they had fewer cases of cancer than a comparison group. In other words, if the estimate and confidence interval are to the left of the yellow vertical line in the graph, folate was beneficial.

If the estimate and its confidence interval are above 1 (and to the right of the yellow line), that means that folate harmed the study participants—they had more cases of cancer than a comparison group.

And if the estimate and its intervals include 1, that means there is no evidence of harm or benefit of folate on cancer.

[CLICK TO ADVANCE] For example, the top-most data point on this forest plot is a study by Bao published in 2011. The outcome they studied was pancreatic cancer. And the exposure they studied was dietary folate; specifically they compared people with the highest versus the lowest quintile of dietary folate intake—this included intake from folic acid. They had data on 775,272 individuals. It's hard to see but the interval fell on 1, suggesting that there is no association between dietary folate and pancreatic cancer.

[CLICK TO ADVANCE] When we look down the graph, we see that all estimates either included 1 or were to the left of 1, suggesting there was no association between folate and cancer, or that folate was associated with fewer cancer cases compared to a comparison group.

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Source:
Health Assessment Workspace Collaboration (HAWC). Draft-all pooled studies. 2015.
<https://hawcproject.org/summary/data-pivot/assessment/94/draft-all-pooled-studies/>



Summary

- Fortification with folic acid does not mask vitamin B12 deficiency
- Folic acid supplements do not cause cancer
- Fortification with folic acid does not cause cancer

In summary, fortification with folic acid does not mask vitamin B12 deficiency.

Folic acid supplements do not cause cancer.

And, fortification with folic acid does not cause cancer.



Main Messages (1)

1. Fortification with folic acid reduces the risk of neural tube defects
2. Fortification with folic acid is more effective than dietary diversification or supplementation for reducing the risk of neural tube defects
3. Mandatory fortification with folic acid is more effective than voluntary fortification for reducing the risk of neural tube defects

In closing, I hope to have convinced you that fortification with folic acid reduces the risk of neural tube defects.

And that fortification with folic acid is more effective than dietary diversification or supplementation for reducing the risk of neural tube defects.

Additionally, mandatory fortification with folic acid is more effective than voluntary fortification for reducing the risk of neural tube defects.



Main Messages (2)

4. Fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia
5. Fortification with folic acid does not mask vitamin B12 deficiency or cause cancer

Fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia, and thus extend the benefits of fortification to other groups in the population.

And, fortification with folic acid does not mask vitamin B12 deficiency or cause cancer.

For more information:

www.FFInetwork.org

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For more information, you can contact the Food Fortification Initiative through social media, and Karen and me through email. Thank you.