


**Food Fortification Initiative**  
Enhancing Grains for Healthier Lives



<http://www.pacificstudents.org/wp-content/uploads/2015/09/Women-Today.jpg>

**Fortification with Folic Acid**

Helena Pachón & Karen Codling

Asia-Pacific Conference on Human Genetics  
9 November 2017

I would like to thank Dr. Pornswan for the kind invitation to participate in the congress.

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



## Main Messages

1. Fortification with folic acid reduces the risk of neural tube defects
2. Fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia
3. Fortification with folic acid does not mask vitamin B12 deficiency or cause cancer
4. There are many lessons learned from global experiences to maximize the benefits of food fortification

At the conclusion of this presentation, I hope to convince you that fortification with folic acid reduces the risk of neural tube defects.

And, that fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia.

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

And, there are many lessons from global experiences to maximize the benefits of food fortification.



# Food Fortification

Vitamin & Mineral Premix /  
Fortificants / Compounds

The addition of  
vitamins and minerals  
to foods during their  
processing



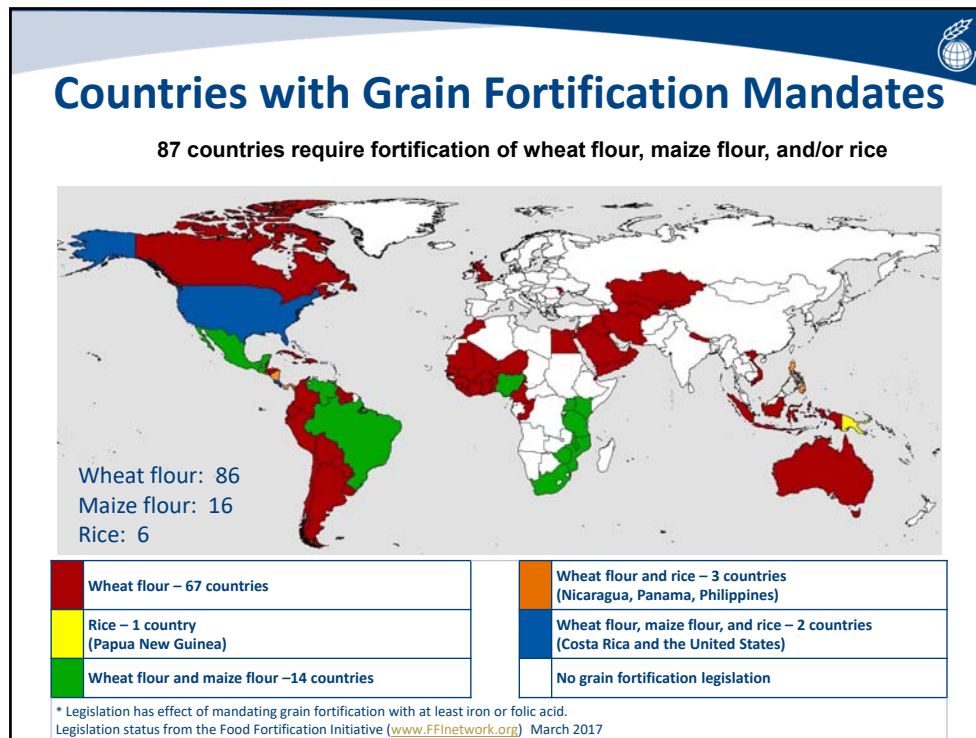
Photo from Mühlenchemie

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 noodles. The bread and noodles will be more nutritious if they have been made with fortified flour.



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](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:

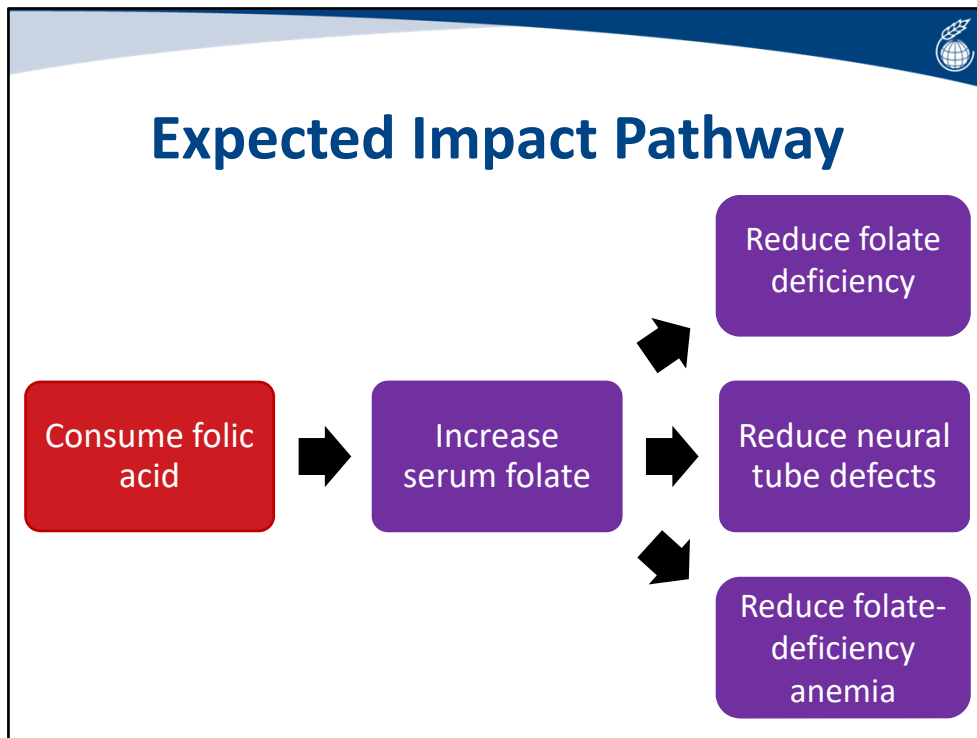
Food Fortification Initiative. Food Fortification Initiative database. 2017.

Exceptions:

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

Maize flour: Venezuela

Rice: Papua New Guinea, Philippines



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.

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

Allow me to show you evidence of these health outcomes.

## Chile: Fortification with Folic Acid Increased Serum Folate

2000: wheat flour fortification with folic acid

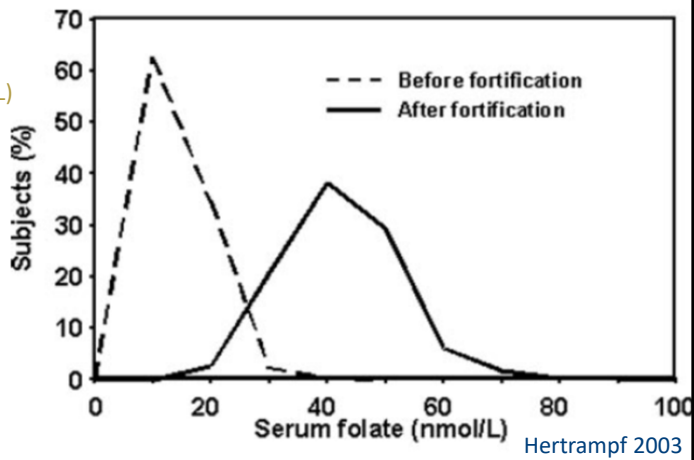
Mean serum folate (nmol/L)

Pre-fortification:

- $9.7 \pm 4.3$

Post-fortification:

- $37.2 \pm 9.5$



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

Researchers assessed serum folate levels in a group of 751 women before and one year after fortification began.

We can see in the dashed line the serum folate distribution before fortification with folic acid, and in the solid line the serum folate distribution one year after fortification began.

Serum folate levels shifted to the right; that is, they increased with fortification. Specifically, mean serum folate levels increased from 9.7 to 37.2 nmol/L after fortification with folic acid.

These data from Chile suggest that fortification with folic acid increases serum folate levels.

## Chile: Fortification with Folic Acid Reduces Neural Tube Defects

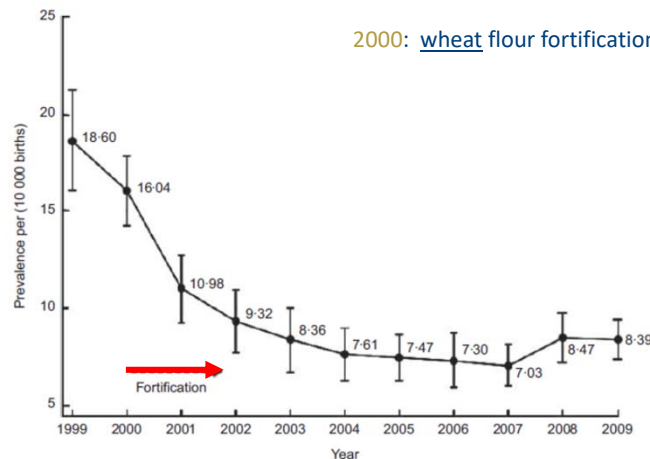


Fig. 2 Prevalence of neural tube defects in Chile, 1999–2009. Values are means with their standard errors represented by vertical bars

Castillo-Lancellotti 2013

As noted in the previous slide, fortification of wheat flour with folic acid began in 2000 in Chile, where the red arrow begins in the figure.

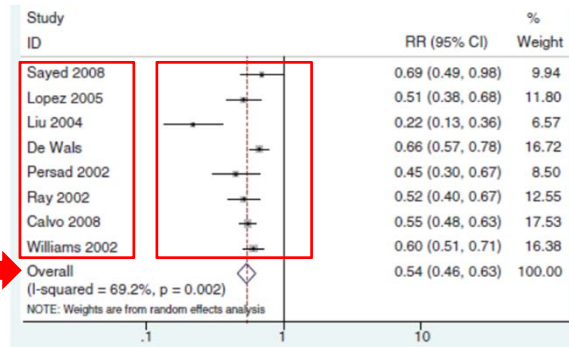
This graph reports the number of neural tube defects per 10,000 births.

From the start of fortification through at least 2007 there was a marked decrease in the number of babies born with neural tube defects, with an increase observed in the last three years of the graph.

These data from Chile suggest that fortification with folic acid reduces neural tube defects.



# 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

Eight studies from Argentina, Canada, Chile, South Africa, USA

**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 eight studies that had measured neural tube defects pre and post-fortification. The studies were from Argentina, Canada, Chile, South Africa, and the USA.

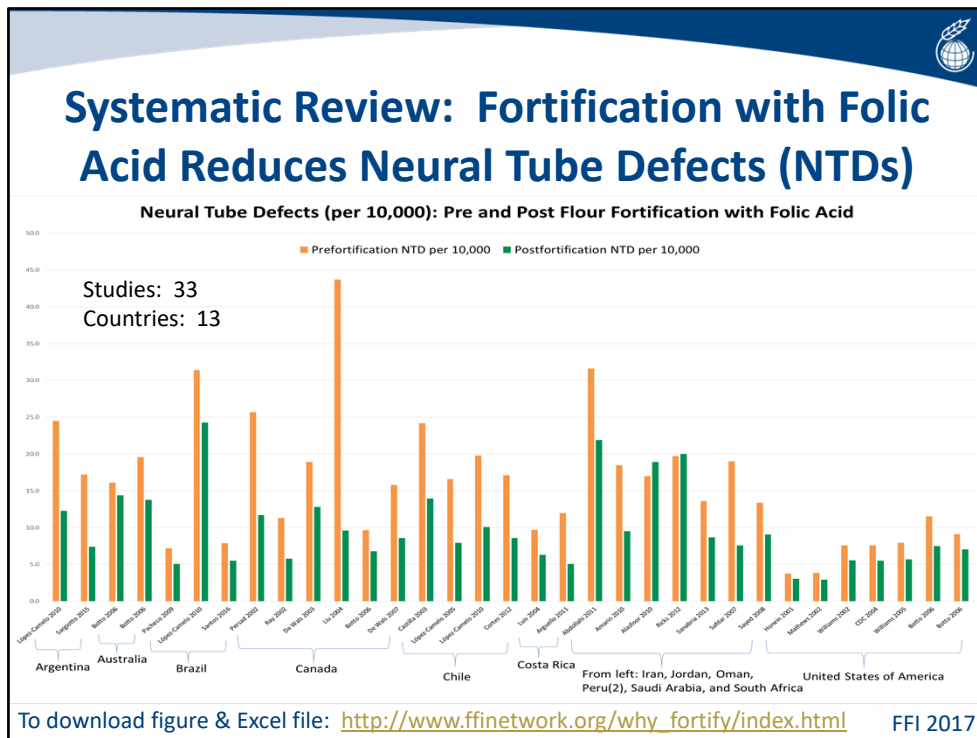
[CLICK TO ADVANCE] All of the data points were to the left of the solid, black, vertical line, which means that fortification reduced neural tube defects in all studies.

[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.



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.

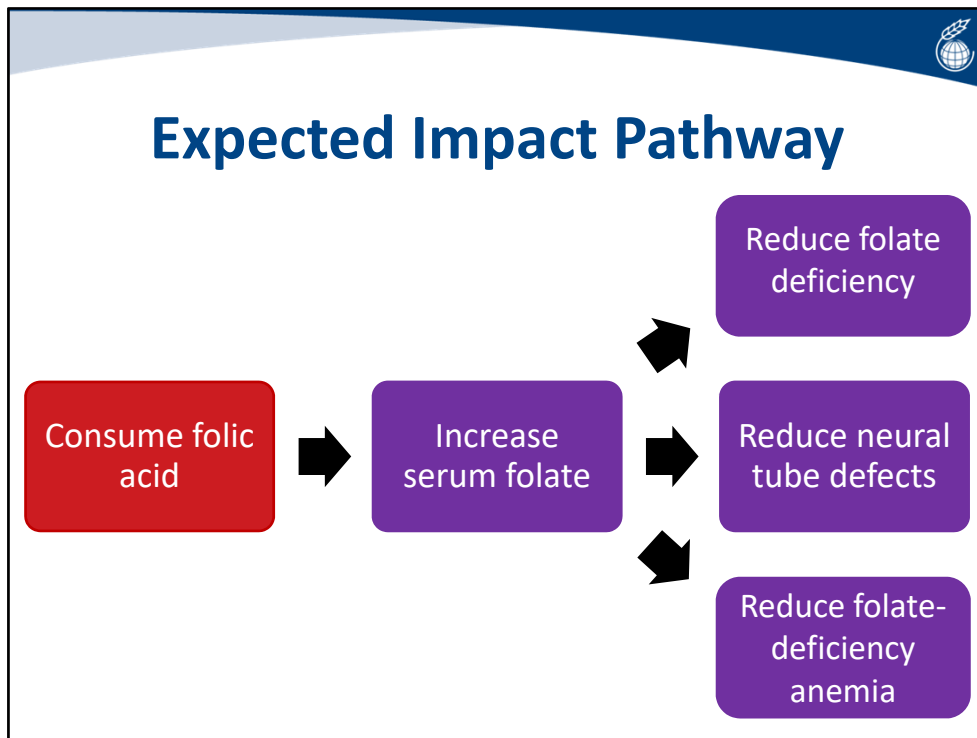
Across the horizontal axis are the 33 studies reviewed. Below each is the name of the 13 countries where the study was completed.

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.

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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](http://www.FFINetwork.org)



We have reviewed data showing that fortification with folic acid leads to an increase in serum folate levels, and to a reduction in neural tube defects.

[CLICK TO ADVANCE] Now, let's look at the evidence for reduced folate deficiency and reduced folate-deficiency anemia, after fortification with folic acid.



## 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 State. 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.

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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

- Food fortification is the addition of vitamins and minerals to foods during their processing
- Adding folic acid in grain fortification is standard practice globally
- Food fortification with folic acid
  - Increases serum folate levels
  - Reduces neural tube defects
  - Reduces folate deficiency
  - Reduces folate-deficiency anemia

To summarize thus far,

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

Adding folic acid in grain fortification is standard practice globally

And, food fortification with folic acid

Increases serum folate levels


Reduces neural tube defects

Reduces folate deficiency, and

Reduces folate-deficiency anemia



I'd like to share further lessons from global experiences with food fortification.



## Costs of Spina Bifida: New Zealand Example

In one year, six adolescents with spina bifida together had:

- 124 operations requiring general anesthesia
- 125 hospital admissions
- 1,066 days as inpatients

<b>Average cumulative cost per adolescent:</b> <b>NZ\$ 944,000</b> (US \$ 733,460)	<b>Total cost:</b> <b>NZ\$ 5,664,000</b> (US \$ 4,400,760)
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Bowkett 2012

Here we have some of the costs associated with neural tube defects.

This study from New Zealand gives you an idea of the type of care that a child with spina bifida requires.

In 1 year, 6 adolescents with spina bifida together had:

- 124 operations requiring general anesthesia
- 125 hospital admissions
- 1,066 days as inpatients

In the red box on the left we see that the average hospital costs through adolescence was NZ \$944,000 or about US \$733,460. This study did not include costs for outpatient treatment, medical devices such as wheelchairs, and the value of the caregivers' time.

Additionally, these teens will continue to require care throughout their lives; this cost is not factored here either.

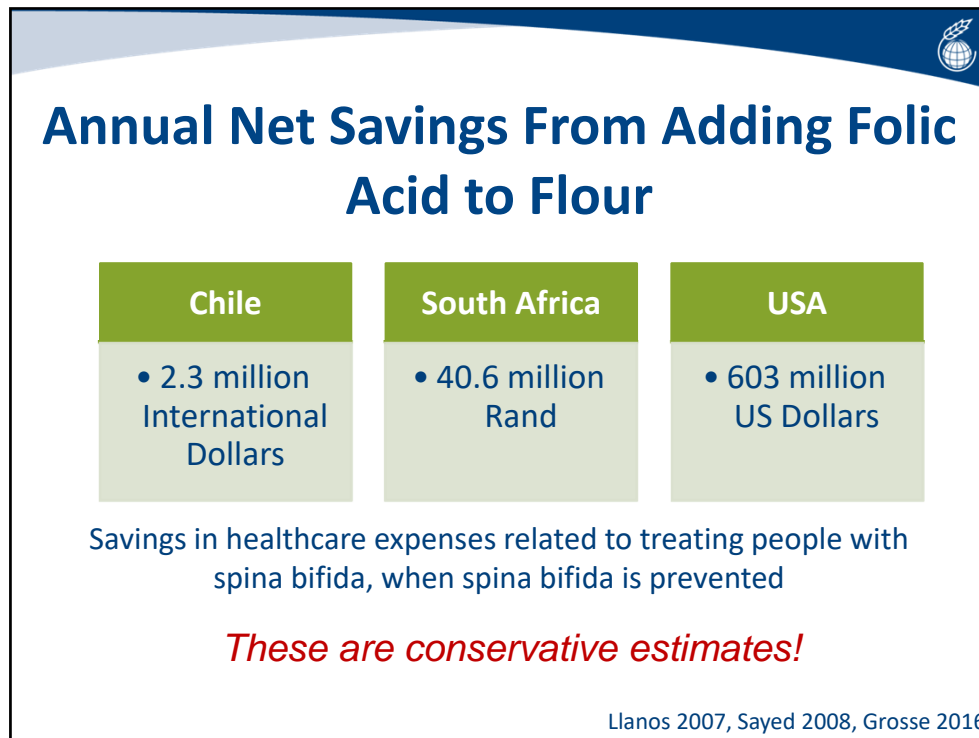
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Source:

Bowkett et. al., Pediatric spina bifida inpatient treatment at Wellington Regional Hospital: a cost analysis of sequential patients. [The New Zealand Medical Journal](#) 124 2012:13-18.

Using the exchange rate effective 1 Jan 2012 (1USD=1.285NZR), NZ\$944,000 is equivalent to USD733,460 and NZ\$5,664,000 is equivalent to USD4,400,760. This is the exchange rate per OANDA.com





Three countries have compared the costs of adding folic acid to flour with the costs of treating people with spina bifida.

Each study showed significant net savings in healthcare expenses when spina bifida is prevented: 2.3 million international dollars in Chile, 40.6 million Rand in South Africa and 603 million US dollars in the USA.

Notice that these are annual savings, so every year of fortification leads to these net savings.

Also note that these are considered conservative estimates. The Chile study only included surgical repair and rehabilitation costs through age 22 years. The South Africa study only used treatment costs during infancy. The US estimate is highest partly because it estimates lifetime costs, and it includes the value of the time required for parents to care for children with spina bifida. Yet the authors of the US study note that they used conservative assumptions.

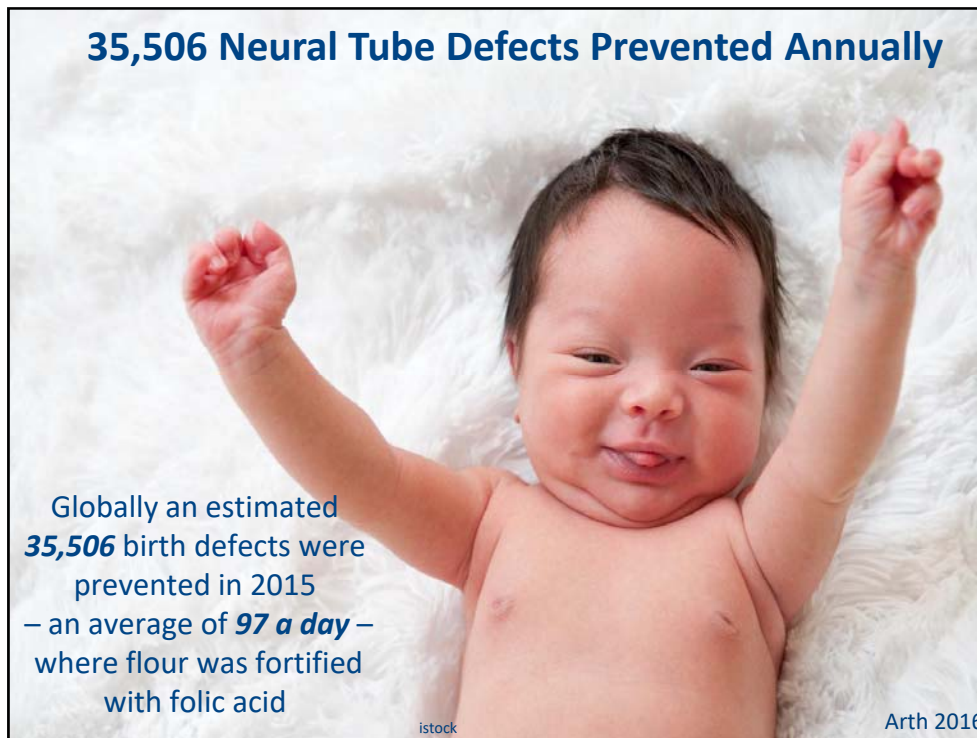
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Source:

Llanos et. al., Cost-effectiveness of a Folic Acid Fortification Program in Chile. [Health Policy](#) 83 2007:295-303.

Sayed et.al., Decline in the Prevalence of Neural Tube Defects Following Folic Acid Fortification and Its Cost-Benefit in South Africa. [Birth Defects Research](#) 82 2008:211-216.

Grosse et. al., Retrospective Assessment of Cost Savings From Prevention. [American Journal of Preventive Medicine](#), 2016.



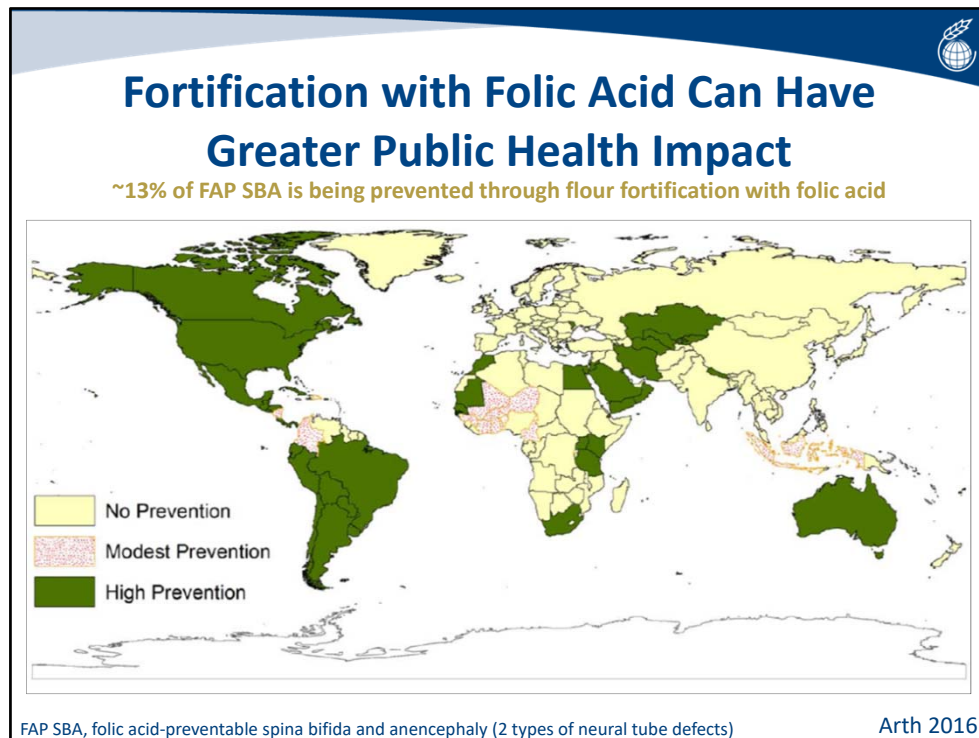
The good news is that an estimated 35,506 birth defects were prevented in 2015 where flour was fortified with folic acid.

This represents an average of 97 babies per day being born free of neural tube defects.

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Source:

Arth A, Kancharla V, Pachón H, Zimmerman S, Johnson Q, and Oakley GP, Jr. (2016), A 2015 Update on folic acid–preventable spina bifida and anencephaly. Birth Defects Research Part A: Clinical and Molecular Teratology.



However, the bad news is that with fortification, we are only preventing about 13% of neural tube defects that could respond to folic acid.

In the map we can see in green those countries with high prevention of folic acid-preventable spina bifida and anencephaly, because they have fortification programs in place.

In yellow are the countries with no prevention because they have no fortification programs.

In dots are the countries with modest prevention because their fortification programs do not have high coverage or high-enough levels of folic acid to prevent neural tube defects.

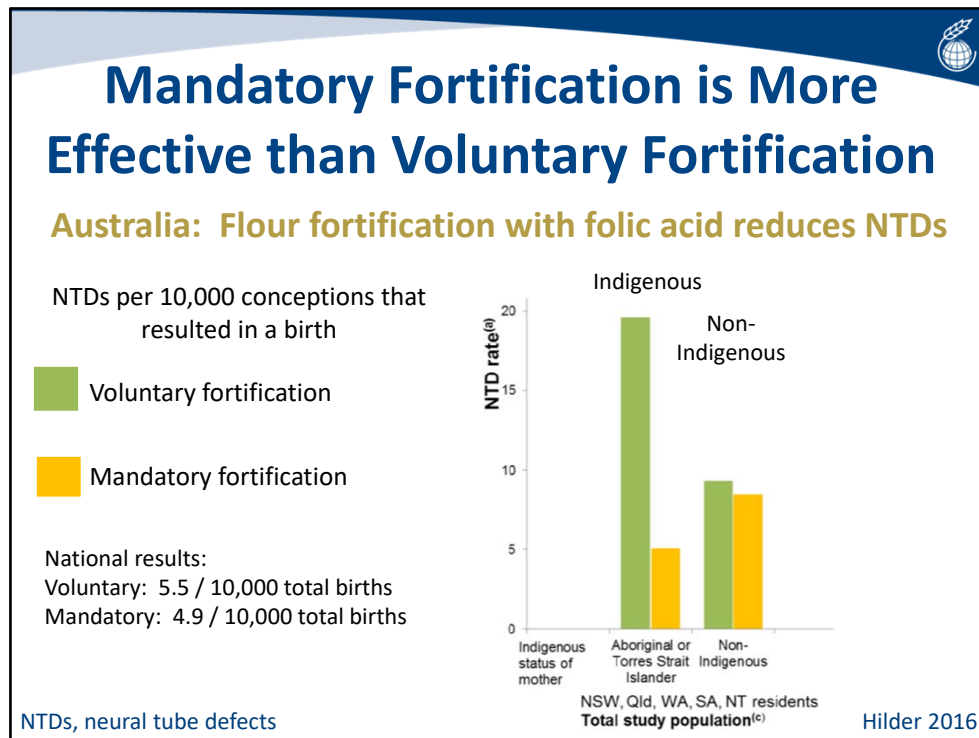
These researchers estimated that 13% of folic acid-preventable spina bifida and anencephaly is being prevented through fortification of flour with folic acid.

The bottom line is we can have a greater public health impact if we can get more countries to fortify their flour or other major food sources with folic acid.

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Source:

Arth A, Kancherla V, Pachón H, Zimmerman S, Johnson Q, and Oakley GP, Jr. (2016), A 2015 Update on folic acid-preventable spina bifida and anencephaly. Birth Defects Research Part A: Clinical and Molecular Teratology.



Another lesson is that mandatory fortification is more effective than voluntary fortification in reducing neural tube defects.

These data are from Australia. 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.

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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

### Notes

(a) NTD rate per 10,000 conceptions that resulted in a birth.

(b) Relative rate is the NTD rate in the standard period relative to the NTD rate in the baseline period.

(c) ‘Total study’ population is all informative conceptions in the study – refer to Table F4.

(d) The group ‘Omitting NSW’ are presented as a sensitivity analysis to assess potential effects of missing data – refer to Table G3.



## 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

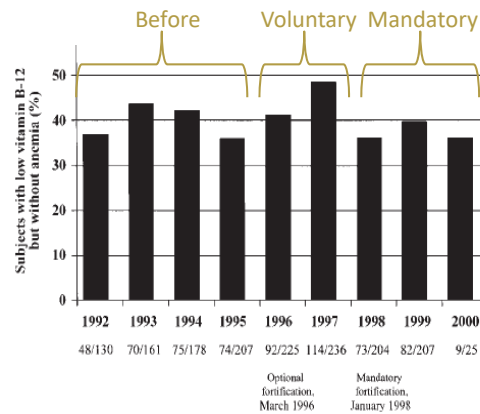


FIGURE 1. Percentages of subjects with low vitamin B-12 concentrations (<258 pmol/L) but without anemia before, during, and after fortification of enriched cereal grains with folic acid. The fractions under the year labels on the x axis indicate the number of subjects without anemia/the number of subjects 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.

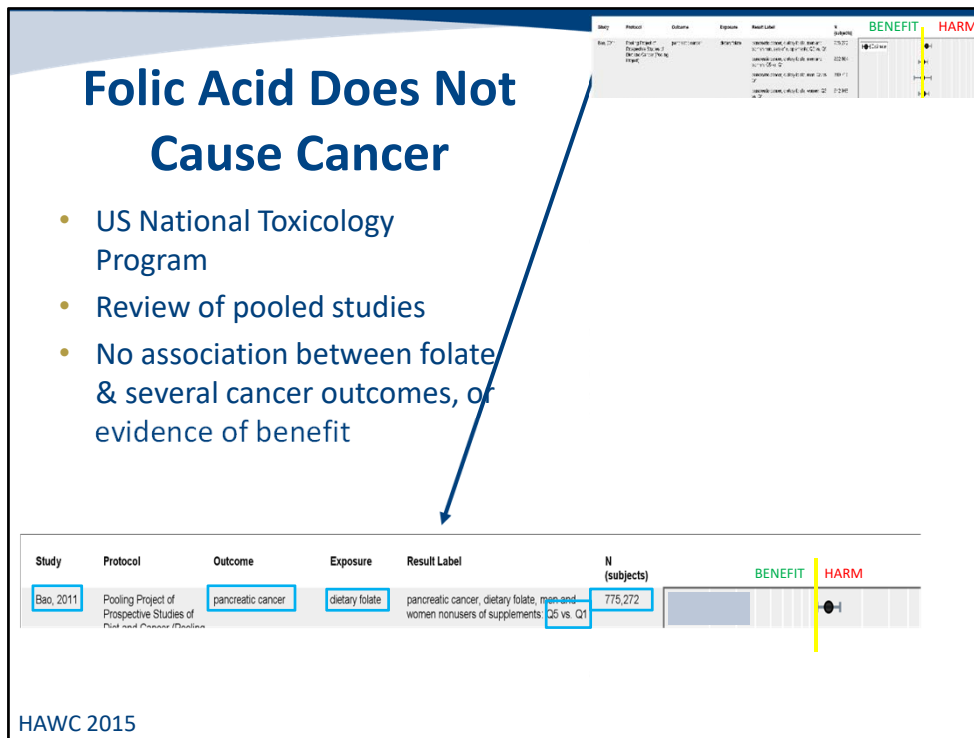
The bars represent the % of people with low vitamin B12 status who were not anemic. If folic acid was masking vitamin B12 deficiency, we would expect an increase, from the “before” to the “mandatory” period, in the prevalence of people with low vitamin B12 status who were not anemic.

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.



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—which included folic acid intake. 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/>



## Food Fortification Does Not Require Consumer Behavior Change

- 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



[https://images-na.ssl-images-amazon.com/images/I/81x2KzYQTL\\_S11500.jpg](https://images-na.ssl-images-amazon.com/images/I/81x2KzYQTL_S11500.jpg)

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](http://www.who.int/nutrition/publications/guide_food_fortification_micronutrients.pdf)





## Summary

- Global experience suggests that
  - The economic benefit of preventing neural tube defects is greater than the cost of flour fortification with folic acid
  - Mandatory fortification with folic acid is more effective than voluntary fortification for reducing the risk of neural tube defects
  - Food fortification does not require consumer behavior change
  - Fortification with folic acid does not mask vitamin B12 deficiency or cause cancer

In summary of the second part of the presentation, global experience suggests that

The economic benefit of preventing neural tube defects is greater than the cost of flour fortification with folic acid

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

In part, this is because women do not need to change their dietary behavior, and Fortification with folic acid does not mask vitamin B12 deficiency or cause cancer.



## Main Messages

1. Fortification with folic acid reduces the risk of neural tube defects
2. Fortification with folic acid can also reduce folate deficiency and folate-deficiency anemia
3. Fortification with folic acid does not mask vitamin B12 deficiency or cause cancer
4. There are many lessons learned from global experiences to maximize the benefits of food fortification

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 can also reduce folate deficiency and folate-deficiency anemia.

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

And, there are many lessons from global experiences to maximize the benefits of food fortification.

For more information:

[www.FFInetwork.org](http://www.FFInetwork.org)

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

<https://twitter.com/FFInetwork>

Join the Food Fortification Initiative group on [Linked In](#)



Food  
Fortification  
Initiative

Enhancing Grains for Healthier Lives

**Contact:**

[Helena.Pachon@emory.edu](mailto:Helena.Pachon@emory.edu)

[Karen.Codling@FFInetwork.org](mailto:Karen.Codling@FFInetwork.org)



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