Food Fortification Initiative

Enhancing Grains for Healthier Lives

Folic Acid Fortification:

Evidence and Global Progress

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Food Fortification Initiative

NAST Roundtable
Discussion on Folic Acid
23 June 2015, Manila

Efficacy of supplementation with folic acid for the prevention of NTDs

Folic acid supplementation prevents NTDs

- Multiple clinical trials, cohort studies and observational trials have conclusively shown that folic acid supplementation prevents NTDs

(Medical Research Council, 1991; Czeizel, 1992; Berry, 1999; Daly, 1995)

- A 2012 Cochrane review confirmed "folic acid supplementation prevents the first and second time occurrence of NTDs”

(De Regil, 2010)

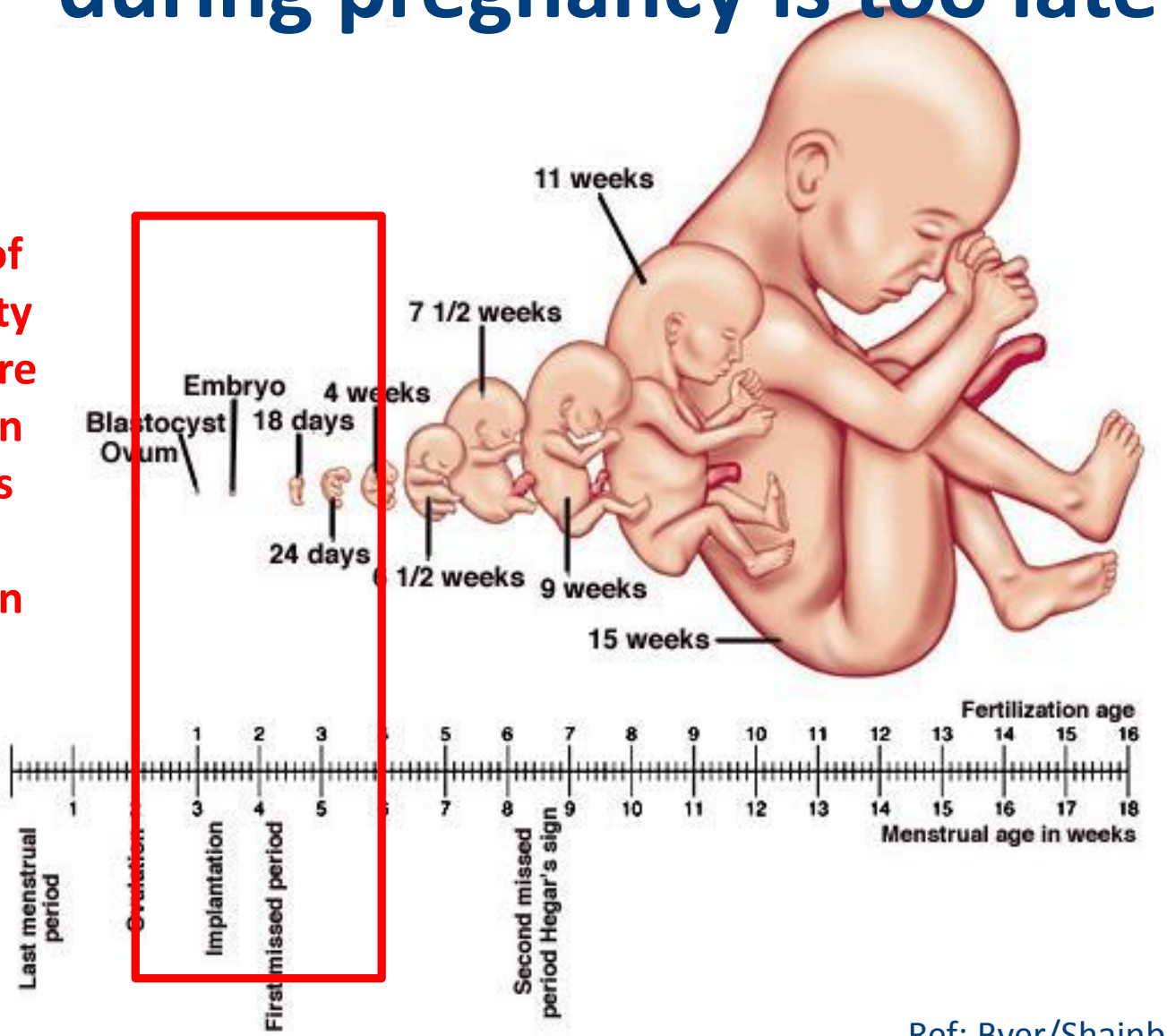
- About 60-85% of NTDs appear to be folic acid dependent (clinical and observational studies)

(Daly, 1995 & 1997; Wald, 1998 & 2001)

Effectiveness of supplementation in prevention of NTDs

Supplementation during pregnancy is too late

Window of opportunity – just before conception to 28 days after conception



Ref: Byer/Shainberg/Galliano, 1999

Achieved coverage of folic acid supplementation

- A review of rates of folic acid supplement use pre-and periconceptually globally found that **supplementation use rarely exceeded 50%**: use ranged from 0.5% to 52%. (Ray, 2004)
- Series of studies from Europe report low awareness and preconception coverage. (Baykan, 2011; Bitzer, 2013; Brough, 2009; Paulik, 2009; Pinto, 2009)
- At least 50% of pregnancies are unintended globally. (Thurnam, 2011)
- Younger women and those from socially economically disadvantaged backgrounds least likely to take supplements. (U. of Nottingham, 2007; Brough, 2009)

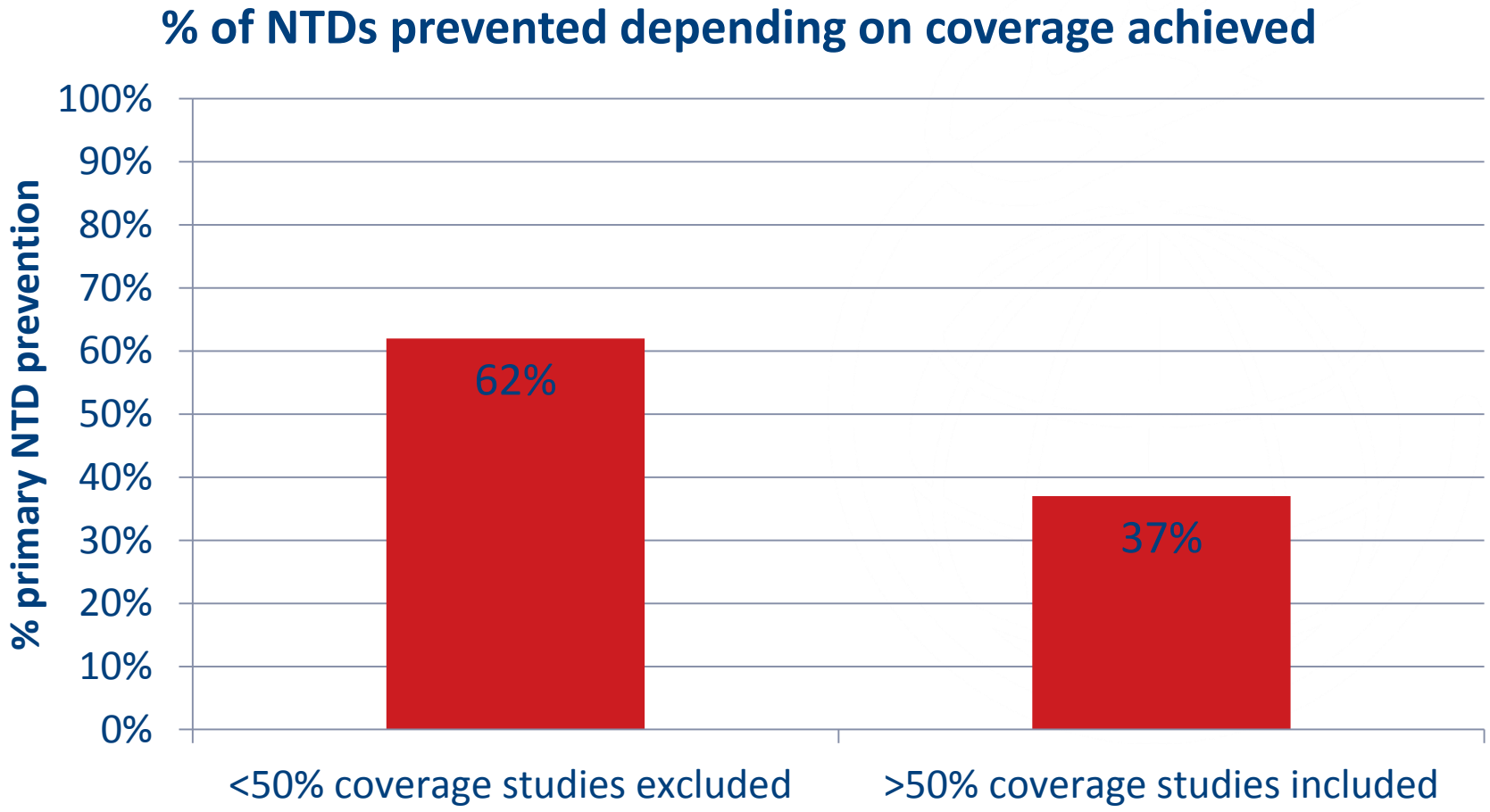
Folic acid supplementation

- Several countries in Europe issued recommendations for folic acid (supplementation and/or diet) in the 1990s
- No discernable improvements in NTD rates were recorded by the end of the decade

NTD: neural tube defect

Ref: Botto, 2005

Effectiveness of folic acid supplementation depends on coverage

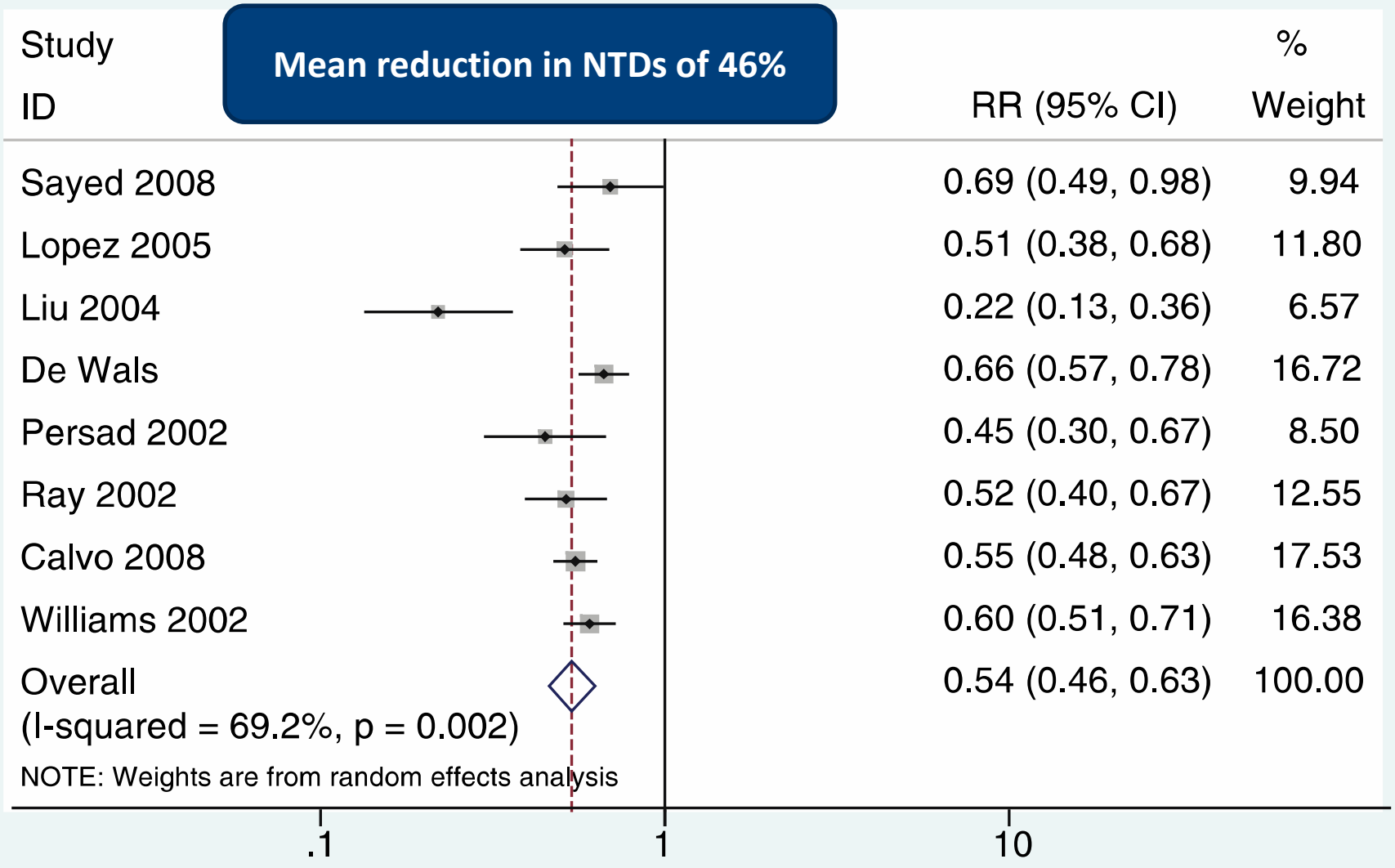


NTD: neural tube defect

Ref: Blencowe, 2010

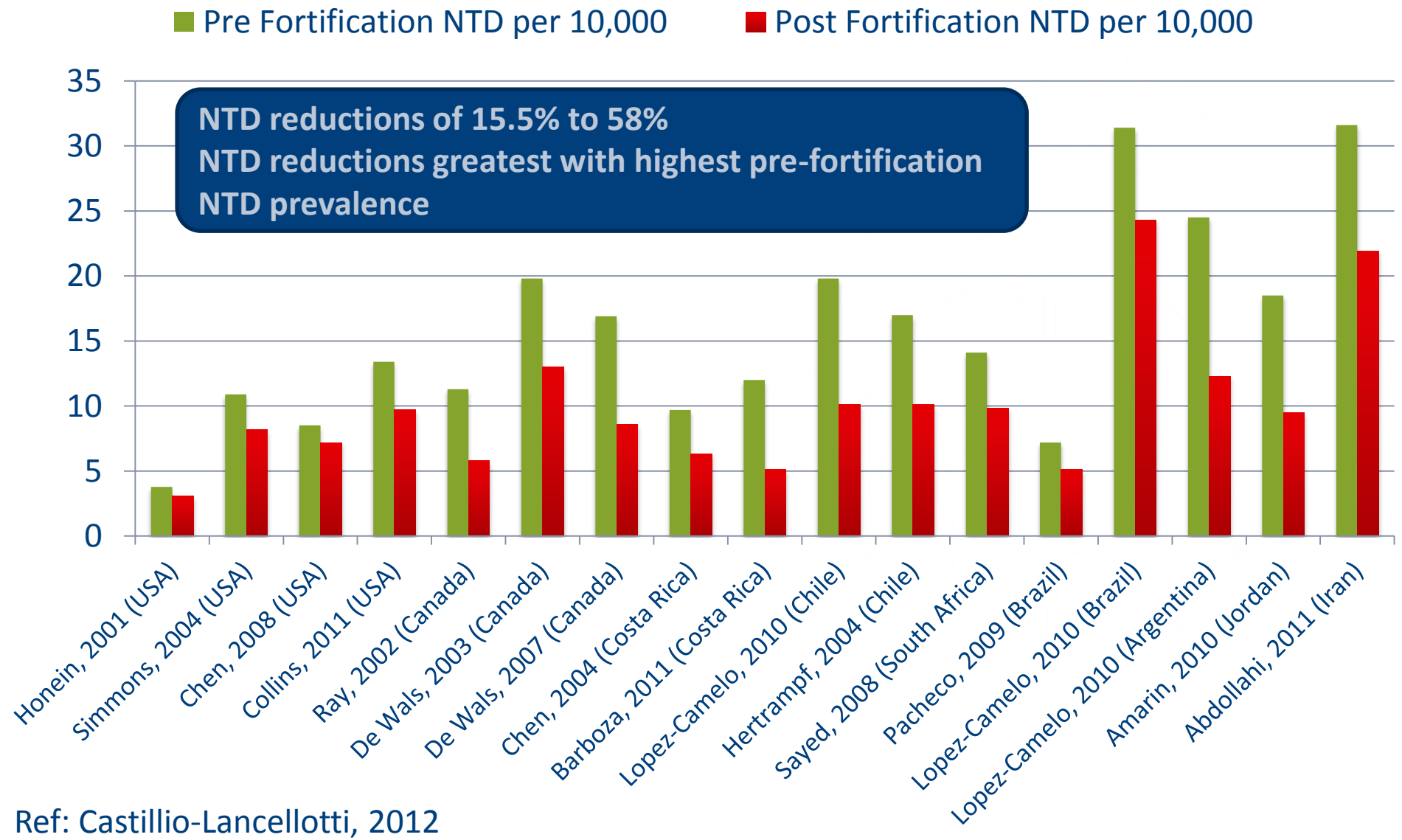
Effectiveness of fortification in prevention of NTDs

Meta analysis of fortification with folic acid



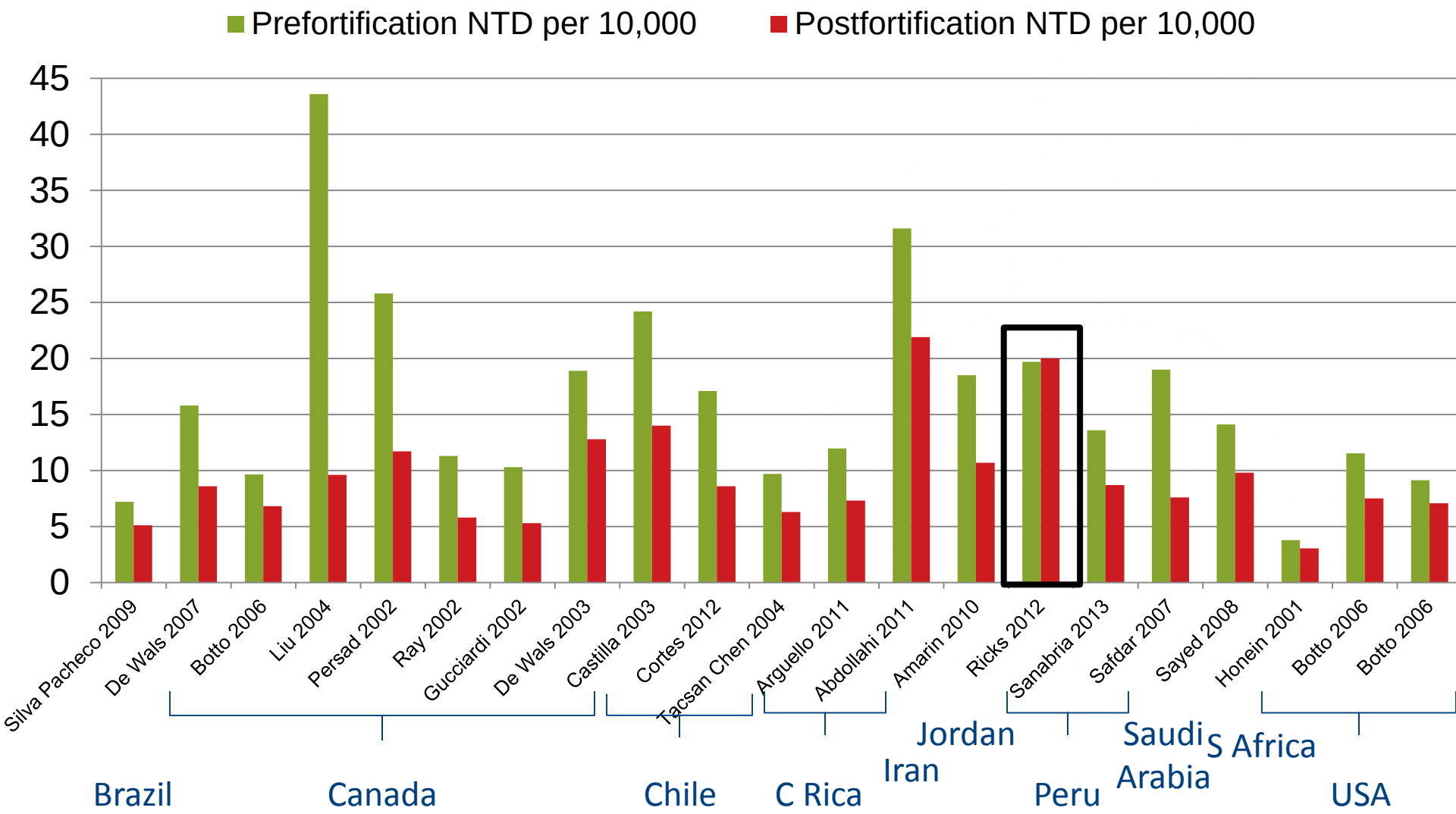
Ref: Blencowe, 2010

Systematic review of fortification with folic acid



Ref: Castillio-Lancellotti, 2012

FFI review of fortification with folic acid



Folic acid in flour ranged from 1.2-2.2 mg/kg

Ref: FFI 2012, updated 2015

USA experience

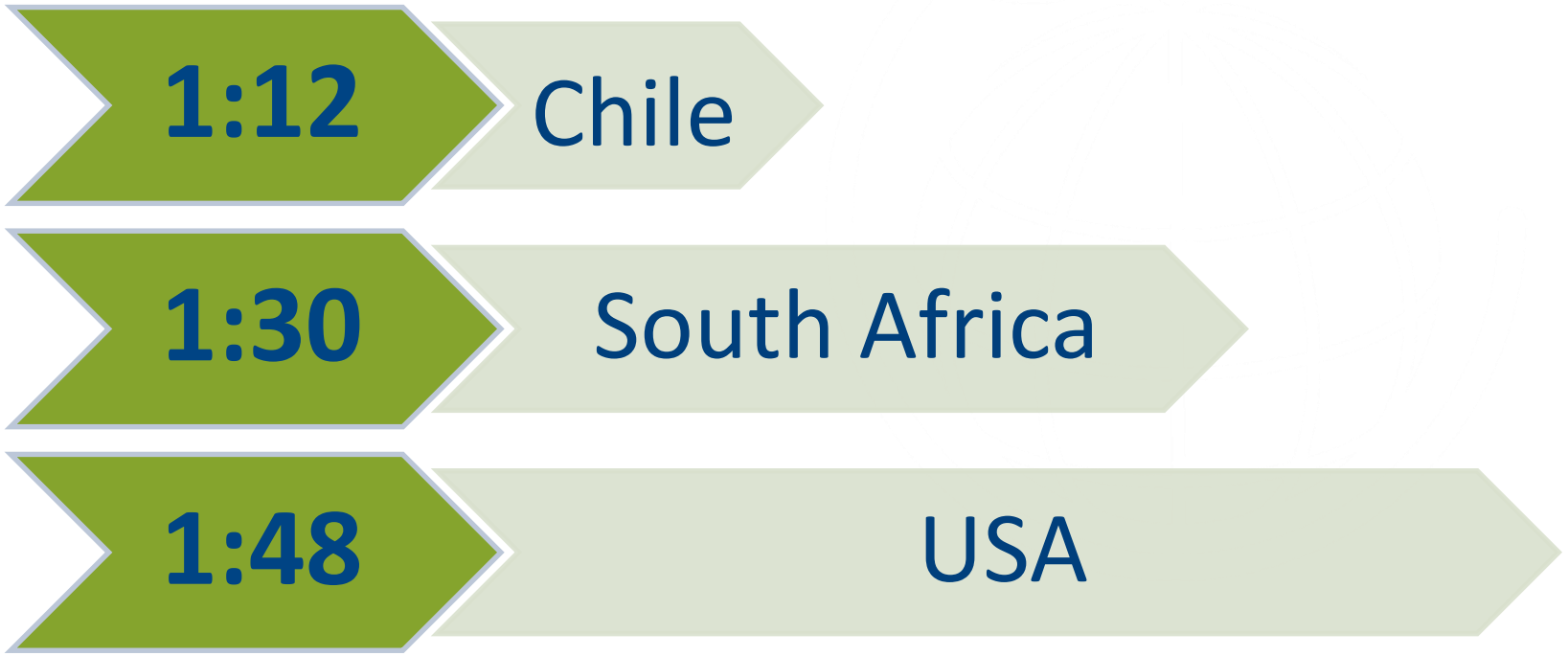
- Mandatory fortification of cereals since 1998 – 140µg folic acid per 100g of grain product labeled as “enriched”
- Multiple studies have shown NTD prevalence decreased and population blood folate increased after fortification
- Recent estimates: NTD prevalence declined from 10.7 to 7 NTDs per 10,000 live births (1995-1996 pre-fortification to 2009-2011 post-fortification) (Williams, 2015)
- 1,122-1,531 less infants born with anencephaly or spina bifida (Williams, 2015)
- RBC assessment suggests 22.8% of women are at risk of NTD (RBC <906nmol/L) (Tinker, 2015)

Ref: Cordero, 2015

Cost-effectiveness of folic acid fortification for prevention of NTDs

- Highly cost-effective

(cost of treatment & rehabilitation vs cost of fortification)



Ref: Grosse 2005, Llanos 2007, Sayed 2008

Evidence for other benefits of fortification with folic acid

Fortification with folic acid reduces folate deficiency & folate-deficiency anemia in older adults

Virtual elimination of folate deficiency & folate-deficiency anemia in adults ≥ 50 years (USA)

Status	Participants (N=1546)
Folate deficiency	2 (0.1%)
Folate-deficiency anemia	1 (<0.1%)

Flour fortification with folic acid began in 1998

Data collected from 2003-2007

Ref: Odewole 2013

Possible health benefits of fortification with folic acid

- Prevention of 13% of neonatal deaths currently attributed to congenital abnormalities in low-income countries. (Blencowe 2010)
- Decreased risk of stroke from treatment of hypertension with folic acid (Huo, 2015)
- Decreased colorectal cancer risk (Gibson, 2011)

Evidence for other benefits of flour fortification

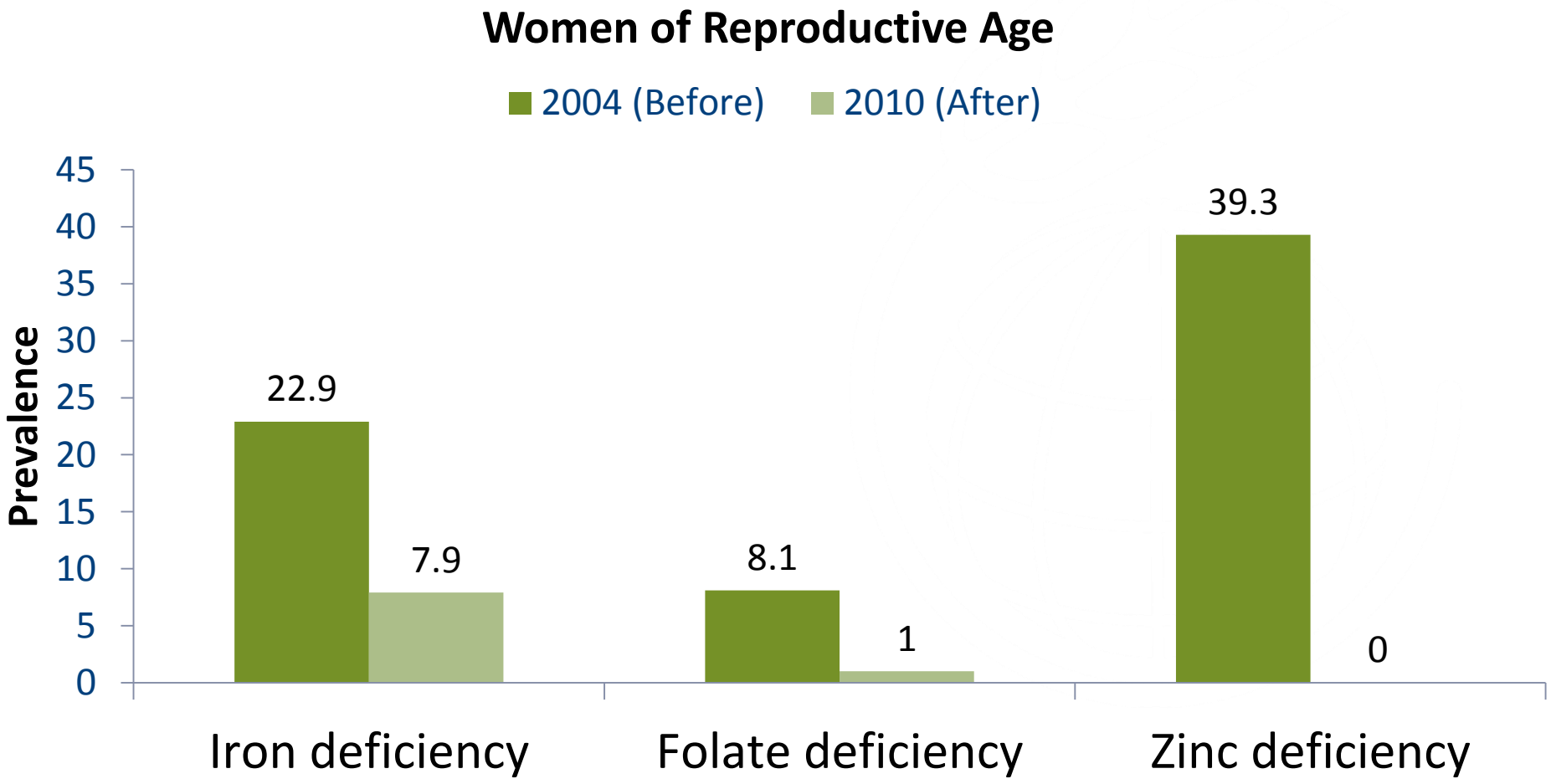
Flour fortification improves other outcomes studied

Outcome	Increased (n)*	Total Evaluated (n)**
Serum ferritin	9	11
Hemoglobin	11	23
Serum zinc	1	1
Serum retinol	0	2

* Increased ferritin, hemoglobin, zinc or retinol in sub-group analyses
** Total number of sub-groups analyzed in large-scale implementation (effectiveness) trials of the impact of flour fortification with different nutrients

Ref: Pachón 2013, updated 2015

Fiji successfully decreased nutrient deficiencies after flour fortification



Iron, folic acid & zinc was added to flour

Ref: Fiji National Food and Nutrition Centre 2010

Safety of folic acid fortification

Safety of folic acid fortification

Cancer

- Studies published between 2007 and Feb 2012: no significant effect on overall cancer incidence in adults
- No evidence of increased childhood cancer; studies in US and Canada have recorded declines in some childhood cancer post fortification
- Meta-analysis of folic acid supplementation on cancer incidence found no increase or decrease of cancer. (Vollset, 2013)

Vitamin B12 masking and cognitive decline in elderly

- Masking addressed by screening for B12 deficiency.
- Pooled data: no evidence folic acid supplementation has negative or positive effect on cognition in elderly.

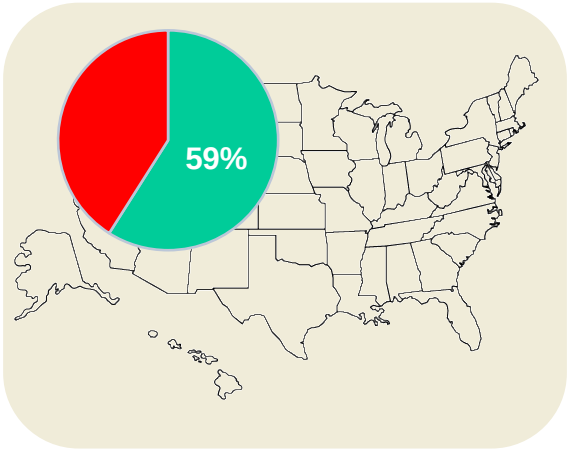
Asthma

- Recent data suggest no association between maternal folic acid supplementation and childhood asthma

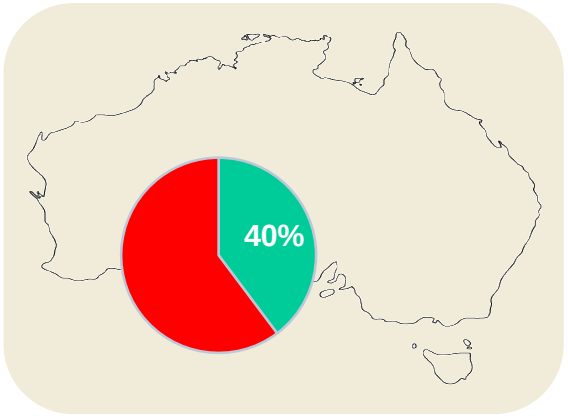
Ref: Ministry for Primary Industries, NZ. August 2012

Fortification provides only a proportion of recommended daily intake

In the **United States**, fortification accounts for **less than two-thirds of the recommended daily intake** of folic acid per day.



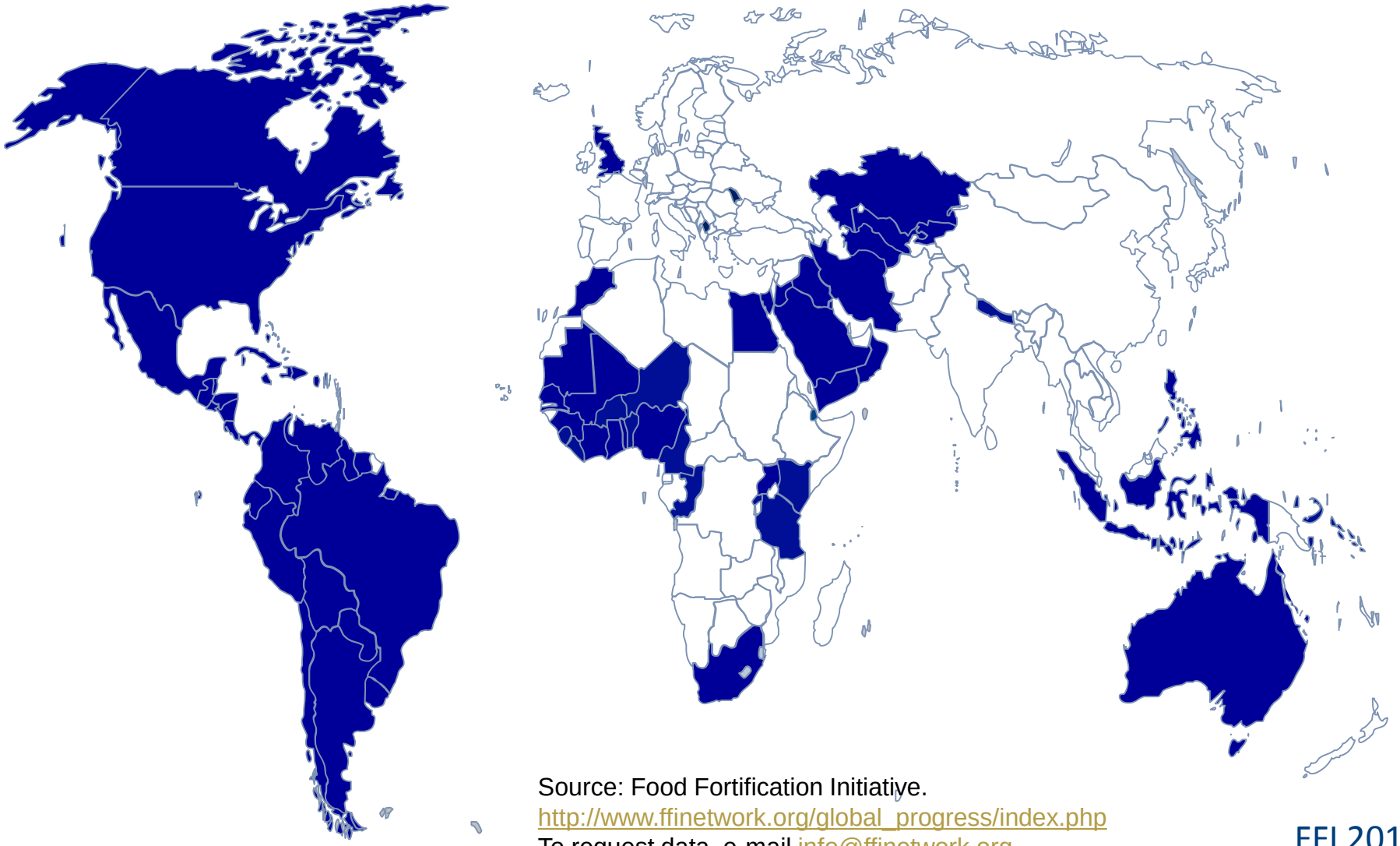
In **Australia**, fortification accounts for **less than half the recommended daily intake** of folic acid per day.



Ref: Dugbaza (2012); Quanhe (2010). Graphic by FFI

Current global status of folic acid fortification

81 countries mandate fortification of wheat flour



Source: Food Fortification Initiative.
http://www.ffinetwork.org/global_progress/index.php
To request data, e-mail info@ffinetwork.org

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Nutrients that must be added to fortified wheat flour

Nutrient	Number of countries (N=81)	Range (mg/kg)
Iron*	80	16.5-105
Folic acid	76	1-3.2
Thiamin (vitamin B1)	62	1.5-15
Riboflavin (vitamin B2)	60	1.3-4.8
Niacin (vitamin B3)	59	13-75
Zinc	25	15-60
Vitamin B12	18	0.0005-0.02
Vitamin B6	17	2.5-18.3
Vitamin A	10	0.5-9
Vitamin D	5	0.01-0.02
Calcium	5	--

* Iron compounds added include electrolytic, ferrous fumarate, ferrous sulfate, NaFeEDTA, reduced
mg/kg is the same as mcg/g is the same as parts per million (ppm)

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Estimate of global prevention of NTDs through flour fortification with folic acid

NTD prev (MoD) x annual births = no of FAPSBA

Wheat/flour consumption (FAO) x folic acid fortification level (FFI) x coverage (FFI) = folic acid provided by fortification

No. of FAPSBA prevented

Folic acid provided	% FAPSBA prevented
20-150µg	25%
151-250µg	50%
2501-350µg	75%
≥350µg	100%

Only 15% of FAPSBA currently being prevented

MOD: March of Dimes FAPSBA: folic acid-preventable spina bifida & anencephaly
Ref: Youngblood 2013

How many NTDs could flour fortification with folic acid prevent in the Philippines?

- Assume NTD rate of 4,560 per year (19/10,000 – March of Dimes)
- Average per capita flour consumption about 58g/day (FAO, 2009)
- Assume fortification at WHO recommended levels – 5µg/g (ppm)
- Assume 100% fortification coverage
- Folic acid provided: about **288µg/day**
- Prevention of about 75% of folic acid preventable NTDs i.e. **2,500 NTDs**

Calculation methodology: Youngblood, 2012

Lessons learnt in achieving optimal impact of fortification with folic acid

Mandatory legislation is necessary

- Does not require social mobilisation or consumer behaviour change
- More likely to achieve high, equitable coverage ➔ public health benefit
- Equalisers costs for industry
- Facilitates safe and effective standard
- Easier to monitor and enforce

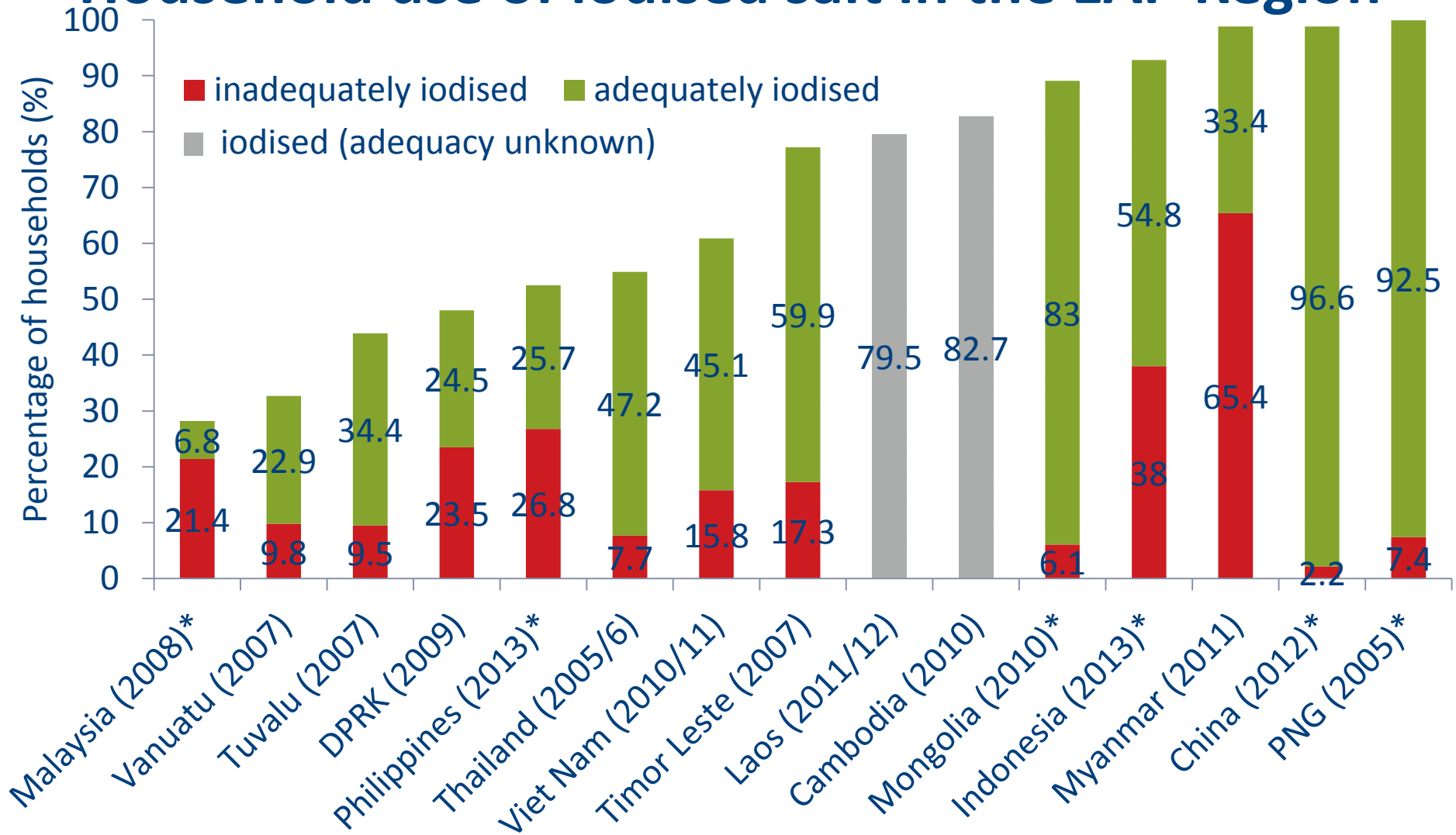
Proportion of industrially milled flour fortified

National legislation for wheat flour fortification	# of countries	Industrial milled flour that is fortified (%)
Mandatory	81	83
Voluntary	15	10

Notes:
Ref: Wheat flour availability - FAO 2010. Excludes countries for which FAO wheat flour availability data is not available and Punjab province in Pakistan
Proportion of industrially milled flour fortified – FFI database
Voluntary: country that fortifies wheat flour but does not have mandatory legislation. Excludes "territories" eg. Puerto Rico

Enforcement is necessary

Household use of iodised salt in the EAP Region



Ref: National surveys such as DHS, MICS, Living Standards, National Nutrition or IDD. Surveys assessing adequately of iodine with a quantitative methodology, such as titration, shown with an asterix *

WHO recommendations

- WHO recommends wheat and maize flour fortification as a **preventative, food-based approach to improve micronutrient status of populations**
- Recommended amounts of iron, **folic acid**, zinc, vitamin A and vitamin B for different levels of consumption

World Health Organization

Recommendations on Wheat and Maize Flour Fortification
Meeting Report: Interim Consensus Statement

PURPOSE

This statement is based on scientific reviews prepared for a Flour Fortification Initiative (FFI) technical workshop held in Stone Mountain, GA, USA in 2008 where various organizations actively engaged in the prevention and control of vitamin and mineral deficiencies and various other relevant stakeholders met and discussed specific practical recommendations to guide flour fortification efforts being implemented in various countries by the public, private and civic sector. This joint statement reflects the position of the World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), The United Nations Children's Fund (UNICEF), Global Alliance for Improved Nutrition (GAIN), The Micronutrient Initiative (MI) and FFI. It is intended for a wide audience including food industry, scientists and governments involved in the design and implementation of flour fortification programs as public health interventions.

BACKGROUND

WHO and FAO published in 2006 the *Guidelines on Food Fortification with Micronutrients* (WHO/FAO, 2006). These general guidelines, written from a nutrition and public health perspective are a source for governments and agencies implementing or considering food fortification and a source of information for scientists, technologists and the food industry. Some basic principles for effective fortification programs along with fortificants' physical characteristics, selection and use with specific food vehicles are described. Fortification of widely distributed and consumed foods has the potential to improve the nutritional status of a large proportion of the population, and neither requires changes in dietary patterns nor individual decision for compliance. Technological issues to food fortification need to be fully resolved especially with regards to appropriate levels of nutrients, stability of fortificant, nutrient interactions, physical properties and acceptability by consumers (WHO/FAO, 2006). Worldwide, more than 600 million metric tons of wheat and maize flours are milled annually by commercial roller mills and consumed as noodles, breads, pasta, and other flour products by people in many countries. Fortification of industrially processed wheat and maize flour, when appropriately implemented, is an effective, simple, and inexpensive strategy for supplying vitamins and minerals to the diets of large segments of the world's population. It is estimated that the proportion of industrial-scale wheat flour being fortified is 97% in the Americas, 31% in Africa, 44% in Eastern Mediterranean , 21% in South-East Asia , 6% in Europe, and 4% in the Western Pacific regions in 2007 (FFI, 2008).

THE FFI SECOND TECHNICAL WORKSHOP ON WHEAT FLOUR FORTIFICATION

Nearly 100 leading nutrition, pharmaceutical and cereal scientists and milling experts from the public and private sectors from around the world met on March 30 to April 3, 2008 in Stone Mountain, GA, USA to provide advice for countries considering national wheat and/or maize flour fortification. This *Second Technical Workshop on Wheat Flour Fortification: Practical Recommendations for National Application* was a follow up to a FFI, the US Centers for Disease Control and Prevention (CDC) and the Mexican Institute of Public Health, first technical workshop entitled "Wheat Flour Fortification: Current Knowledge and Practical Applications," held in Cuernavaca, Mexico in December 2004 (FFI, 2004). The purpose of this second workshop was to provide guidance on national fortification of wheat and maize flours, milled in industrial roller mills (i.e. >20 metric tons/day milling capacity), with iron, zinc, folic acid, vitamin B_{12} and vitamin A and to develop guidelines on formulations of premix based on common ranges of flour consumption. A secondary aim was to agree on the best practices guidelines for premix manufactures and millers. Expert work groups prepared technical documents reviewing published efficacy and effectiveness studies as well as the form and levels of fortificants currently being added to flour in different countries. The full reviews will be published in a supplement of *Food and Nutrition Bulletin* in 2009 and the summary recommendations of this meeting can be found in http://www.sph.emory.edu/wheatflour/atlanta08/ (FFI, 2008).

RECOMMENDATIONS FOR WHEAT AND MAIZE FLOUR FORTIFICATION

Wheat and maize flour fortification is a preventive food-based approach to improve micronutrient status of populations over time that can be integrated with other interventions in the efforts to reduce vitamin and mineral deficiencies when identified as public health problems. However, fortification of other appropriate food vehicles with the same and/or other nutrients should also be considered when feasible. Wheat and maize flour fortification should be considered when industrially produced flour is regularly consumed by large population groups in a country. Wheat and maize flour fortification programmes could be expected to be most effective in achieving a public health impact if mandated at the national level and can help achieve international public health goals. Decisions about which nutrients to add and the appropriate amounts to add to fortify flour should be based on a series of factors including the nutritional needs and deficiencies of the population; the usual consumption profile of "fortifiable" flour (i.e. the total estimated amount of flour milled by

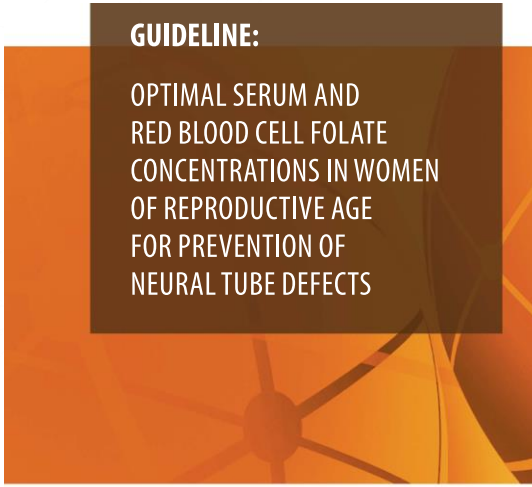
Ref: WHO 2009

Assessing NTD risk

- Serum folate deficiency is an indicator of macrocytic anemia; not NTDs

WHO Guidelines

- Red blood cell folate of reproductive age women should be above 400ng/mL at a population level.
- This threshold is an indicator of folate insufficiency and population risk of NTDs
- It cannot be used for individual risk assessment
- No serum folate threshold is recommended for prevention of NTDs in reproductive age women
- Red blood cell folate should be assessed by microbiological assay for comparison of results across countries



World Health Organization

Folate deficiency vs insufficiency/risk of NTDs

Indicator	Serum/Plasma folate (ng/ml)	Red Blood Cell folate (ng/mL)
Deficient (macrocytic anaemia)	<3	<100
Deficient (homocysteine)	<4	<151
Folate insuficiency/risk of NTD)	N/A	<400

NB. Cut-off values for macrocytic anaemia and folate deficiency based on homocysteine levels are applicable for all age groups.
Cut-off value for folate insufficiency/risk of NTD is only applicable for reproductive age women on a population level
NTD: neural tube defects

Ref: WHO VMNIS, 2015.

Conclusions

- Extensive global evidence on effectiveness and safety of prevention of NTDs through fortification with folic acid
- Fortification more effective than supplementation because of the need to reach women pre-conception
- Out of 81 countries with mandatory wheat flour fortification, the Philippines is one of only five without folic acid fortification
- Modeled data suggests mandatory wheat flour fortification could prevent 75% of folic-acid preventable NTDs, at current levels of consumption
- Mandatory legislation, regulatory monitoring (enforcement) and impact evaluation are necessary

For More Information

www.FFInetwork.org

www.Facebook.com/FFInetwork

https://twitter.com/FFINetwork

Join the Food Fortification Initiative group on Linked In

E-mail: karen.codling@ffinetwork.org

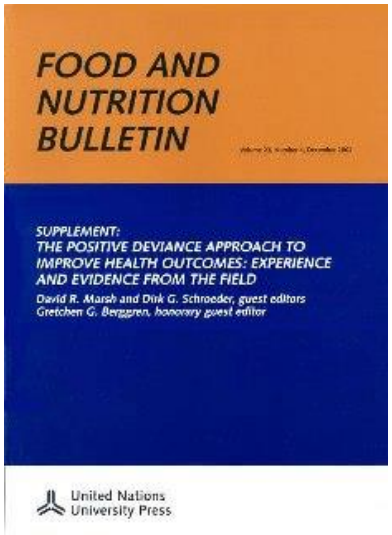
Additional slides

Equivalent of 400 µg of folic acid

To get the equivalent of 400 micrograms of folic acid a day, eat:

- 4 slices of beef liver or
- 44½ medium ripe tomatoes or
- 14½ cups of raw broccoli or
- 17½ cups of orange juice or
- 5½ cups of black beans or
- 200 medium red apples or
- 19½ cups of raw green beans

Ref: US CDC (2010)



Mandatory fortification of flour with folic has proved to be one of the most successful public health interventions in reducing the prevalence of NTD-affected pregnancies

Expanding the number of developed and developing countries with folic acid flour fortification has tremendous potential to safely eliminate most folic acid-preventable NTDs

Fortification of flour with folic acid

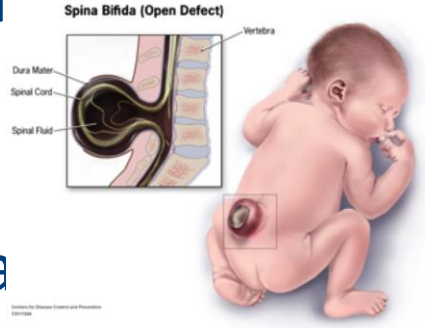
Folic Acid Working Group: Robert J. Berry, Lynn Bailey, Joe Mulinare, and Carol Bower

Conclusions: *NTDs remain an important cause of perinatal mortality and infantile paralysis worldwide. Mandatory fortification of flour with folic acid has proved to be one of the most successful public health interventions in reducing the prevalence of NTD-affected pregnancies. Most developing countries have few, if any, common sources of folic acid, unlike many developed countries, which have folic acid available from ready-to-eat cereals and supplements. Expanding the number of developed and developing countries with folic acid flour fortification has tremendous potential to safely eliminate most folic acid-preventable NTDs.*

Ref: Folic Acid Working Group, 2010

What is a Neural Tube Defect (NTD)?

- Birth defect affecting the brain and cord
- Neural tube fa close
- Neural tissue may be exposed and susceptible to damage
- Can lead to permanent disability or death



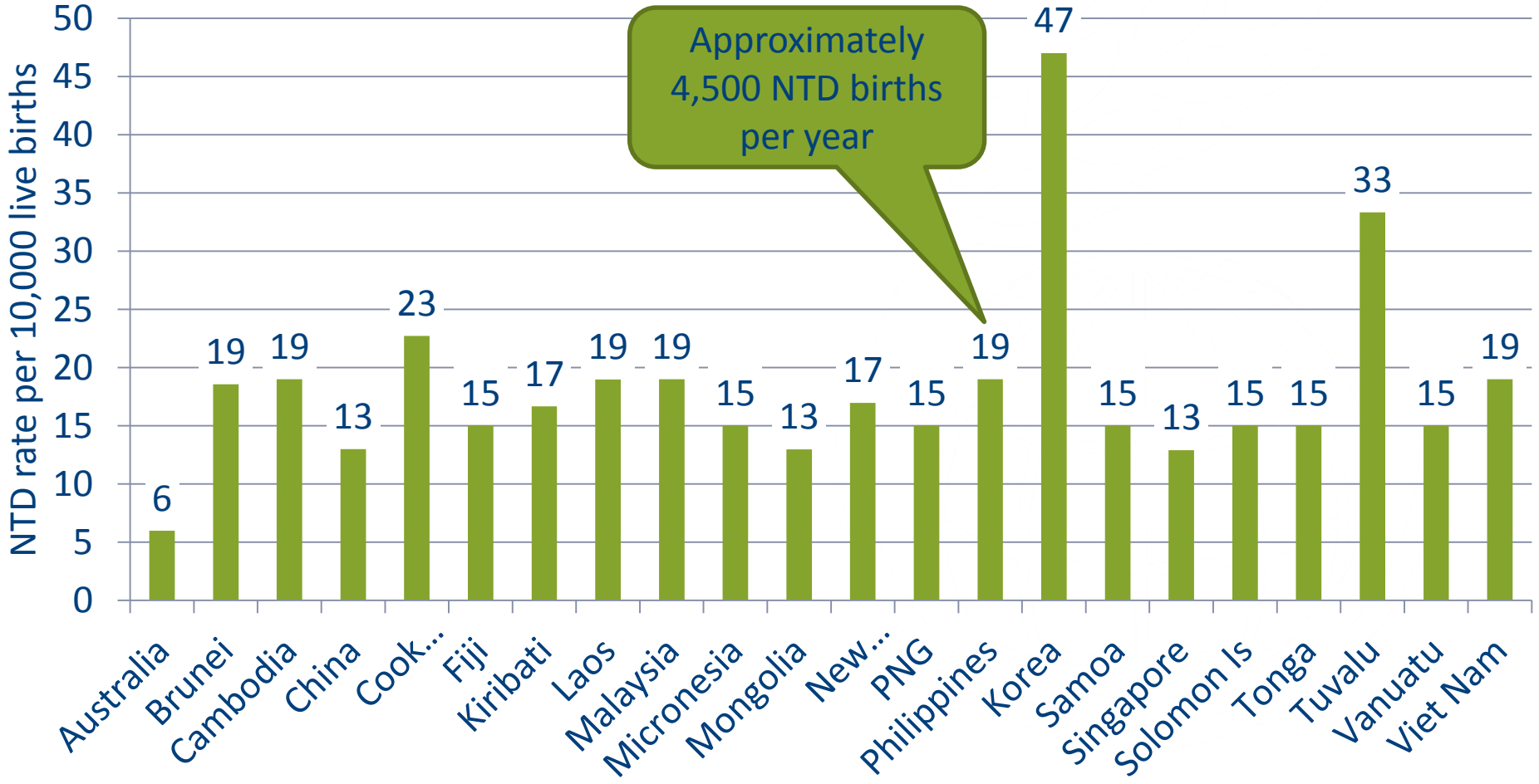
Spina Bifida

Anencephaly

Encephalocele

Ref: Blencowe et al. Folic acid to reduce neonatal morality from neural tube disorders. International Journal of Epidemiology 2010; 39 (Suppl 1), i110-21. Illustrations: US Centres for Disease Contol

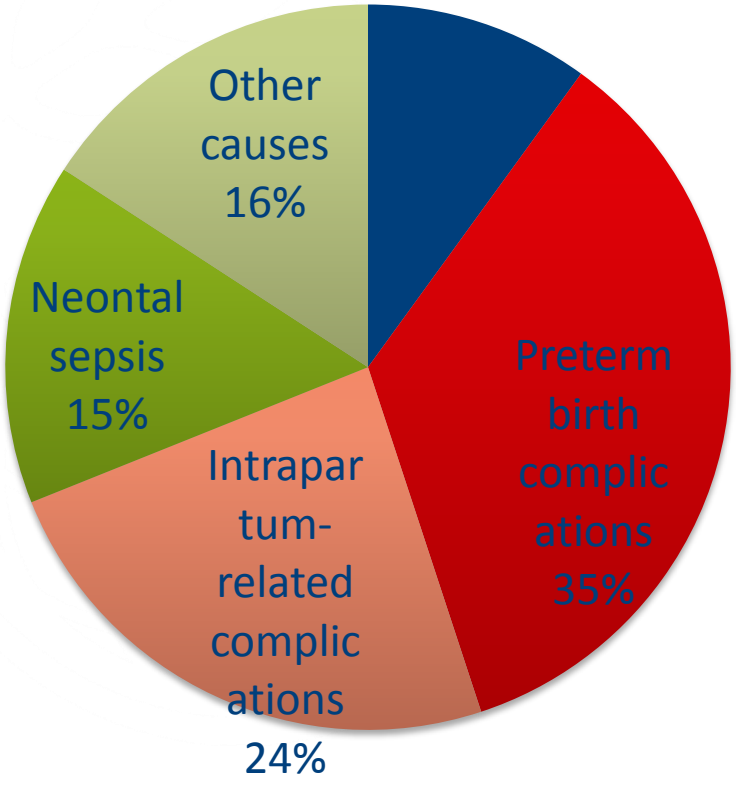
NTD rate per 10,000 births in the Western Pacific



Ref: March of Dimes Global Report on Birth Defects, March of Dimes Birth Defects Foundation, New York 2006. NTD rate calculated from estimated number of affected births, based on 2001 annual births data

2010 World Health Assembly Resolution on Birth Defects

- Promote primary prevention and improve the health of children with congenital anomalies
- Most common congenital anomalies: heart defects, neural tube defects, Down syndrome
- Primary prevention: vaccination, adequate provision of iodine ***or folic acid through fortification of staple foods or provision of supplements***, antenatal care



Causes of Neonatal Death.
Adapted from WHO 2000-2013 Child Causes of

Folic acid fortification status in the region

Country	Legislation status	Food	Nutrients
Australia	Mandatory	Bread flour	Folic acid
Fiji	Mandatory	Wheat flour	Folic acid, iron, zinc
Indonesia	Mandatory	Wheat flour	Folic acid, iron, zinc, B1, B2
Philippines	Mandatory	Wheat flour	Iron, vitamin A
Malaysia	Planning	Wheat flour	Folic acid, iron
Mongolia	Planning	Wheat flour	Folic acid, iron, vitamin D + others?
Nepal	Mandatory	Wheat flour from roller mills	Folic acid, iron vitamin A
New Zealand	Voluntary	Bread flour	Folic acid

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Current achievements of folic acid fortification

~15% of FAPSBA is being prevented through folic acid fortification programs (wheat & maize)

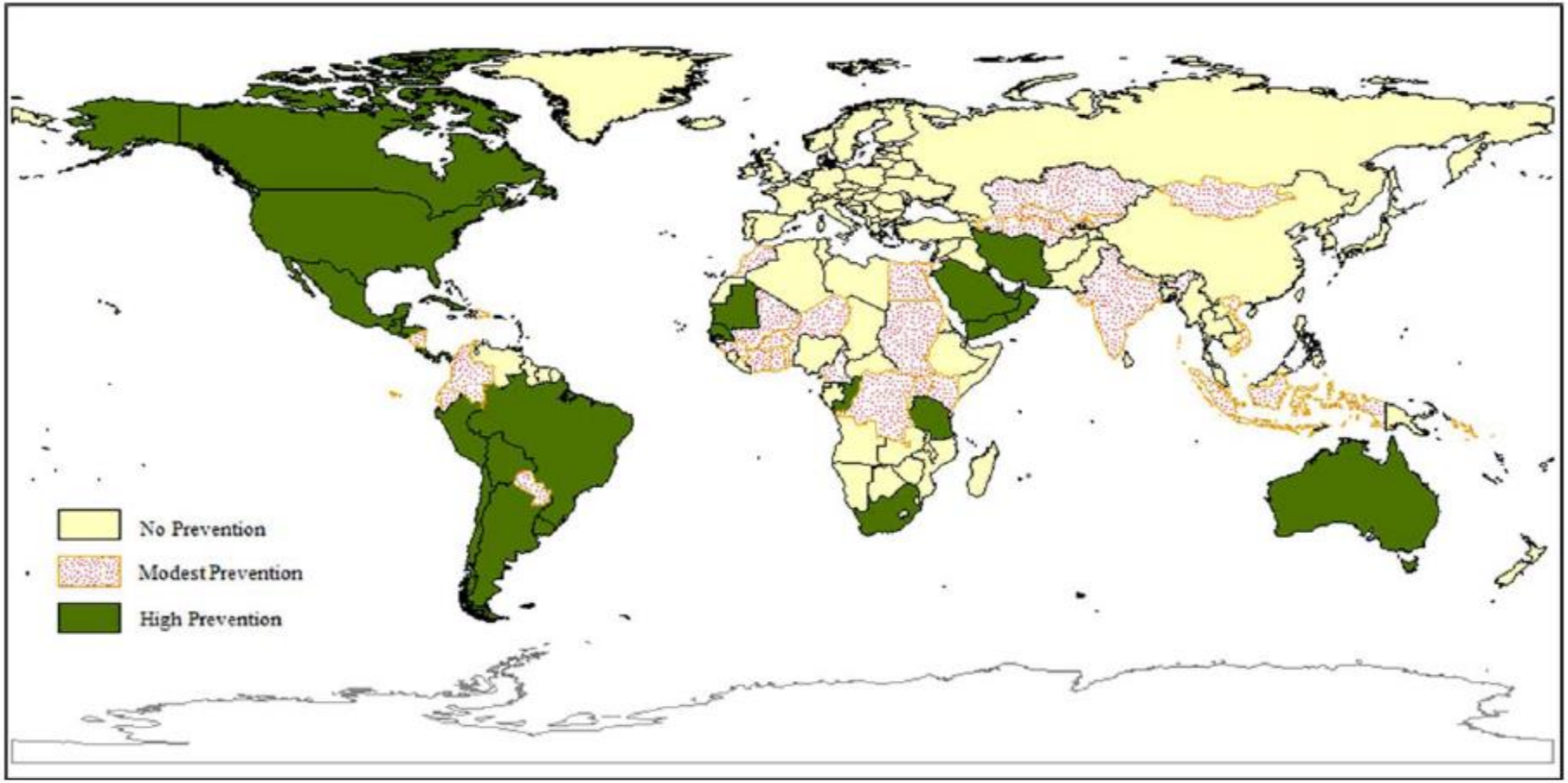

Figure 1. The status of global prevention of folic acid–preventable spina bifida and anencephaly (model II), 2012.

FAPSBA, folic acid-preventable spina bifida and anencephaly

Youngblood 2013

Folic Acid Intake Recommendations for NTD prevention

Country/Agency	Who	What	How much	Duration	Previous NTD-pregnancy
WHO	Women trying to conceive	Folic acid supplement	400ug/day	2 months prior to 12 weeks post	5,000ug
US	Women capable of becoming pregnant	Fortified foods or supplements	400ug/day	Begin planning pregnancy	4,000ug
New Zealand	Women planning pregnancy	Registered folic acid supplements & folate rich and fortified foods	800ug/day	4 weeks prior and f12 weeks after	5,000ug