Fifteen Years of Fortifying With Folic Acid Reduces Birth Defects; Averts Healthcare Expenses

Fifteen years of experience has shown that fortifying flour with folic acid is a reliable method of significantly reducing the incidence of neural tube defects (NTDs) such as spina bifida, anencephaly, and encephalocele. In 1996 Oman was the first country to achieve national scale fortification of flour with folic acid to prevent these permanently disabling or fatal birth defects. Also in 1996, the United States and Canada were beginning to add folic acid to flour, but these larger countries did not achieve nationwide coverage until the end of 1997. By 2008, an estimated 22,000 birth defects were prevented due to this intervention,[1] and by 2011 this form of vitamin B9 was required to be added to flour in 57 countries (see Appendix).

Oman experienced exceptional results as its incidence of spina bifida dropped from an average of 3.17 per 1000 births before fortification to an average of 0.96 per 1000 births after fortification for a 70% reduction.[2] Other studies show a 30 to 60% reduction in NTD rates due to fortification (see Table 1). In addition, fortifying flour with folic acid saves millions of healthcare dollars annually because the cost is minimal compared with the cost of providing surgeries, physical therapy and rehabilitation for children with spina bifida.

All people need folic acid to produce and maintain new cells and decrease the risk of folate deficiency anemia. Women especially need folic acid at least a month before conception and in the early days of pregnancy because the neural tube, which ultimately develops the child's brain and spinal cord, forms within 28 days of conception. Fortified flour adds to the dietary intake of folic acid through staple foods such as bread, tortillas, noodles and pasta.

ADDING FOLIC ACID TO FLOUR

Flour has been fortified with iron and some B vitamins since the 1940s, but adding folic acid to flour did not begin until 50 years later. In 1991, *The Lancet* published a study showing unequivocally that folic acid can prevent NTDs.[3] The study, prepared by Sir Nicholas Wald, professor of environmental and preventive medicine at the Wolfson Institute of Preventive Medicine in London, was a randomized double blind prevention trial conducted at 33 centers in seven countries. One conclusion was that "public health measures should be taken to ensure that the diet of all women who may bear children contains an adequate amount of folic acid."[3]

Dr. Godfrey Oakley, then the director of the U.S. Centers for Disease Control Division of Birth Defects and Developmental Disabilities, had been leading his team to investigate the cause of NTDs. When Wald's research was published, Oakley and the March of Dimes began advocating for folic acid to be added to the U.S. standard for enriched flour. The United States issued this regulation in March 1996, and full implementation was required by January 1998.[4] Oakley is now a research professor of epidemiology at the Rollins School of Public Health at Emory University in Atlanta, Ga.

Also in 1996, countries in the Middle East were considering several public health strategies to improve general nutrition. With encouragement from international organizations, such as the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and the Micronutrient Initiative (MI), fortifying flour with iron and folic acid was one of the interventions being considered. [5] To test the feasibility of flour fortification, Oman Flour Mills began fortifying flour on a trial basis. Oman Flour Mills covered 75% of the market in Oman, and the mill was well-equipped to begin fortification without a major investment. [5] By October 1996 when a regional workshop was held in Oman to consider multiple health interventions, the mill was fortifying flour successfully, and it continues to do so.[5]

Deciding how much folic acid to add to flour to prevent NTDs was a challenge in the early 1990s. Guatemala and El Salvador added folic acid to flour in 1992 to replace the naturally occurring vitamin that was lost in the milling process, however the amounts were not high enough to significantly impact the incidence of NTDs.[6] A key result of the 1996 workshop in Oman was the country's decision to update its wheat flour standard to require folic acid at a minimum of 1.5 parts per million, according to the meetings consensus statement. At a follow up workshop in Beirut in 1998, that became the accepted regional level. The United States and Canada agreed to fortify flour at 1.4 and 1.5 parts per million respectively. Central American countries agreed to fortify with folic acid at a rate of 1.8 parts per million in 2002.[6] Globally recognized recommendations for adding folic acid to wheat flour were published in 2009 with levels ranging from 1 to 5 parts per million based on a country's consumption patterns.[7]

Decrease in Neural Tube Defects

The decrease in the incidence of NTDs attributable to flour fortification varies depending on the amount of folic acid added to flour and the NTD rate prior to fortification. Table 1 provides examples of flour fortification's impact in a variety of settings.

Table 1 Percent decrease in neural tube defects (NTDs) due to fortifying flour with folic acid

Country	NTD prevalence pre-fortification per 1000 births	NTD prevalence post-fortification per 1000 births	Percent decrease in NTD prevalence
Argentina[8]			
spina bifida	1.27	0.66	48
anencephaly	0.86	0.37	57
Brazil[8]			
spina bifida	1.45	1.42	2*
anencephaly	1.12	0.69	38
Canada[9]			
spina bifida	0.86	0.40	53
anencephaly	0.52	0.32	38
Chile[8]			
spina bifida	1.02	0.46	55
anencephaly	0.63	0.37	41
Costa Rica[10]			
spina bifida	0.73	0.29	60
anencephaly	0.37	0.12	68
Iran[11] (all NTDS)	3.16	2.19	31
Oman[2]	3.17	0.96	70
spina bifida	Average 1991-1996	Average 1997-2006	
Saudi Arabia[12] King Abdul-Aziz University Hospital in Jeddah (all NTDS)	1.9	0.76	60
South Africa[13]			
spina bifida	0.93	0.54	42
anencephaly	0.41	0.37	10
United States[14]			
spina bifida	0.50	0.35	30
anencephaly	0.26	0.18	31

**The study in Brazil was for three months, and the authors concluded that a longer period of time was needed to assess fortification's effects.*

Some countries report spina bifida and anencephaly separately; others report all NTDs together, including encephalocele.

Spina bifida is malformation of the spine; anencephaly is malformation of the brain (which is always fatal); encephalocele causes sac-like protrusions of the brain and its membranes that are visible through openings in the skull. The severity of encephalocele varies, depending on its location.

The March of Dimes estimates that more than 300,000 infants worldwide are affected by a NTD annually.[15] With 400 micrograms of folic acid daily at least one month prior to conception and in the early days of pregnancy, 50 to 70% of NTDs may be prevented.[16] Some researchers call these "folic acid preventable spina bifida and anencephaly." A 2008 study estimated that about 22,000 neural tube birth defects were prevented globally due to flour fortification.[1] That figure represented 9% of the estimated folic acid preventable cases of spina bifida and anencephaly.[1] By 2010 more countries were fortifying flour, and an estimated 28,066 birth defects were prevented, for a total of 13.8% of the total number of folic acid preventable spina bifida and anencephaly.[17]

Currently 63 countries require flour fortification, and 57 of those countries include folic acid in the fortification standard. Those 57 countries reported 34.2 million births in 2009 (see Appendix). How many NTDs can be prevented due to flour fortification is difficult to measure precisely because many countries do not have a surveillance system for birth defects. In addition, a minimal number of NTDs will occur even when the mother consumes the recommended amount of folic acid at the appropriate time. Also, the number of pregnancies terminated due to a NTD diagnosis is often not available or not taken into consideration by researchers. However, a few studies have estimated the number of NTDs prevented as a result of flour fortification. These include:

- In Costa Rica the National Children's Hospital treated 105 children with spina bifida in 1995. The country began fortifying wheat and maize flour with folic acid in 1998. The hospital treated 26 children with spina bifida in 2001; fortification was the only intervention conducted during that time period.[18]
- In Chile, fortification is associated with preventing 175 NTDs per year.[19]
- South Africa, approximately 406 cases of spina bifida are prevented annually through fortification.[13]
- In the United States, fortification of flour and breakfast cereals is credited with preventing 1000 NTDs a year.[20]

Economic Impact

The most common NTD is spina bifida which occurs when the spinal cord does not form correctly. In mild cases, permanent loss of some sensation or movement occurs. Severe cases include paralysis and varying degrees of loss of bowel and bladder control. Some spina bifida symptoms can be treated with surgeries and therapy, but spina bifida cannot be cured.

Caring for children with spina bifida can require multidisciplinary medical treatment including surgeries, physical therapy and continence care. Wellington Hospital in New Zealand found that a newborn with spina bifida had undergone surgeries costing NZ$ 680,000 (US$ 569,000) before his second birthday.[21] The hospital's study also found the direct surgery and hospital costs for six teenagers, from their birth, was NZ$ 944,000 (US$ 790,000) per individual.[21] More than 20 years ago, in-hospital care for 1500 patients with one type of spina bifida in Spain was US$ 2.9 million per year.[22] The data collected between 1986 and 1988 did not include prostheses, orthoses and incontinence devices.[22]

The on-going cost to fortify flour with iron, folic acid and other B vitamins is between US$ 2 and US$ 3 per metric ton of flour. Three countries have compared the costs of fortification with the cost of spina bifida treatment and found that fortifying flour is far more economical. They include:

- Chile's cost for fortification compared with the savings in surgical treatment and rehabilitative services for children with spina bifida represented a cost:benefit ratio of 1:12.[23]
- South Africa saved 30 rand for every one rand spent on fortification when it calculated the cost of treating a child with spina bifida during the first three years of life.[24]
- The United States reports annual fortification costs of approximately US$ 3 million. Direct medical costs averted are US$ 145 million per year; consequently, US$ 48 is saved annually for every dollar spent on fortification.[25]

The cost:benefit ratio varies based on the expenses incurred by the country's health care system and the estimated number of NTDs prevented. Anencephaly cases are typically not included in the cost:benefit analysis because this NTD causes the baby to be born without parts of the brain and skull. These children do not live long enough to receive extensive medical care. The value of the caregiver's time is also not included in most economic analysis.

Once the milling infrastructure is in place to fortify flour, it is cost effective to fortify flour with other nutrients in addition to folic acid. Flour is also routinely fortified with iron, thiamine, riboflavin and niacin. Some countries also add vitamin D, vitamin B_{12}, vitamin A and zinc to flour. The economic implications for fortifying with these additional nutrients is not included in the folic acid cost:benefit studies.

Conclusion

When the study showing folic acid's role in preventing NTDs was published 20 years ago, women who might become pregnant were encouraged to consume at least 400 micrograms of this form of vitamin B9 daily. Fortifying flour provides folic acid through commonly consumed staple foods. The 15-year record of this practice shows it is a reliable method of reducing the prevalence of births affected by neural tube defects. The cost of adding folic acid to flour is minimal, especially when compared to the cost of treating children with spina bifida and the immeasurable impact on their families.

Appendix

Countries with mandatory regulation to add folic acid to flour, their population and number of births in 2009

COUNTRY[1]	POPULATION (2010)[2]	ANNUAL BIRTHS (2009)[3]
Argentina	40,412,000	691,000
Australia	22,268,000	270,000
Bahrain	1,262,000	14,000
Barbados	273,000	3,000
Belize	312,000	7,000
Bolivia	9,930,000	262,000
Brazil	194,946,000	3,026,000
Canada	34,017,000	358,000
Cameroon	19,599,000	711,000
Chile	17,114,000	252,000
Colombia	46,295,000	917,000
Costa Rica	4,659,000	76,000
Cote d'Ivoire	19,738,000	729,000
Cuba	11,258,000	116,000
Dominican Republic	9,927,000	224,000
Ecuador	14,465,000	279,000
Egypt	81,121,000	2,029,000
El Salvador	6,193,000	125,000
Fiji	861,000	18,000
Ghana	24,392,000	766,000
Grenada	104,000	2,000
Guadaloupe	461,000	6,000
Guatemala	14,389,000	456,000
Guinea	9,982,000	397,000
Guyana	754,000	13,000
Haiti	9,993,000	274,000
Honduras	7,601,000	202,000
Indonesia	239,871,000	4,174,000
Iran	73,974,000	1,390,000
Iraq	31,672,000	949,000
Jamaica	2,741,000	52,000
Jordan	6,187,000	158,000
Kazakhstan	16,026,000	308,000

Kyrgyz Republic	2,737,000	122,000	
Kuwait	5,334,000	52,000	
Mauritania	3,460,000	109,000	
Mexico	113,423,000	2,021,000	
Morocco	31,951,000	651,000	
Nepal	29,959,000	730,000	
Nicaragua	5,788,000	140,000	
Oman	2,782,000	62,000	
Palestine	4,039,000	150,000	
Panama	3,517,000	70,000	
Paraguay	6,455,000	154,000	
Peru	29,077,000	605,000	
Puerto Rico	3,749,000	52,000	
Qatar	1,759,000	16,000	
Saint Vincent	109,000	2,000	
Saudi Arabia	27,448,000	593,000	
Senegal	12,434,000	476,000	
South Africa	50,133,000	1,085,000	
Tanzania	44,841,000	1,812,000	
Turkmenistan	5,042,000	111,000	
United States	310,384,000	4,413,000	
Uruguay	3,369,000	50,000	
Uzbekistan	27,445,000	558,000	
Yemen	24,053,000	861,000	
TOTAL	**1,722,085,000**	**34,149,000**	*

[1] Flour Fortification Initiative database. Countries are at different stages of implementation.

[2] http://esa.un.org/unpd/wpp/Sorting-Tables/tab-sorting_population.htm

[3] UNICEF(2009).

* How many of these births might have been affected by a neural tube defect without the flour fortification program is difficult to calculate precisely.

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