Fortification Impact Studies

The goal of this document is to catalogue evidence relating to the impact of mass fortification programs on the prevalence of micronutrient deficiencies.

Although a limited number of robust studies have been conducted to measure the nutritional impact of fortification programs to date, this number is growing. The evidence that does exist speaks for itself in terms of the importance of implementing national fortification programs as one strategy to address the debilitating effects of micronutrient deficiencies. Many of the studies sited in this document are randomized controlled trials conducted on subgroups of populations. These studies may not necessarily point to the successful implementation of a nationwide program but instead to the efficacy of fortificant compounds or fortified food vehicles.

The document is broken down into broad categories by micronutrient and food vehicle used (e.g. iron and maize flour) and into subcategories by country and related study. A preliminary snap-shot is provided in order to give the reader a summary of impact findings related to each category. Abstracts for each identified study can be found in subsequent sections. It is the intent of Project Healthy Children (PHC) to update this document every six to eight months in order to capture current literature.

Table of Contents

Impact Snapshot

Country	Food Vehicle	Micronutrients	Time Period	Study Type	Impact	Source
Kenya	Maize meal porridge	Iron (NaFeEDTA)	5 mos	Randomized controlled trial	High-dose NaFeEDTA improved all measured iron-status indicators. Prevalence of iron deficiency anemia decreased by 89%	Andang'o et al. Lancet, 2007
Venezuela	Maize and wheat flour	Iron (ferrous fumerate)	2 yrs	External evaluation / Population survey	Anemia in children decreased from 19% to 9% and iron deficiency decreased from 37% to 16%	Scrimshaw et al. Micronutrient Initiative, 2001
Bahrain	Wheat and maize flour	Iron and folic acid	11 yrs	Population survey / antenatal surveillance	Anemia among pregnant women dropped from 40% in 1996 to 23% in 2012. NTD prevalence declined from 2.6 / 1000 to 0.9 / 1000 live births.	Flour Fortification Initiative (FFI) newsletter, December 2012
China	Soy sauce	Iron			Anemia dropped by one third	GAIN, 2010
China	Soy sauce	Iron (NaFeEDTA)	18 mos	Randomized, double blind, placebo-controlled trial	Children had significantly higher hemoglobin levels, lower prevalence of anemia, and higher plasma ferritin levels	Chen et al. Food and Nutrition Bulletin, 2005.
Chile	Wheat flour	Folic acid		Population survey	Blood folate levels in women of reproductive age increased 3-4 fold, spina bifida decreased 51%, anencephaly decreased by 46%	Gottlieb and Lopez-Camelo et al. 2005
South Africa	Maize meal, wheat flour			Ecological study	30% decrease in overall neural tube defects, 41.6% decrease in spina bifida	
Canada	Grain products	Folic acid			Neural tube defects fell by 46%	Serdula et al. United Nations University, 2010.
United States	Grain products	Folic acid	5 yrs		Spina bifida decreased by 31%, anencephaly decreased by 16%	Williams et al. M. Teratology, 2002.
Indonesia	MSG	Iron		Controlled field trial	Bitot spots decreased from 12% to 0.2%, linear growth increased, hemoglobin rose by 10g, control	Muhilal et al. J Clin Nutr, 1998.

					children died at ~2 times the rate of program children	
Guatemala	Sugar	Vitamin A	2 yrs	Longitudinal evaluation	Vitamin A deficiency decreased from 22% to 5%	Arroyave et al. J Clin Nutr, 1981.
Tanzania	Salt	Iodine		National cross-sectional survey	Total goiter rate fell from 25% to 6.9%	Assey et al. BMC Public Health, 2009.
Fiji	Salt	Iodine		Sentinel survey	Urinary Iodine Concentration rose from a mean of 26 micrograms/L to a mean of 237 micrograms/L in children and 227 micrograms/L in pregnant women	Ministry of Health Report. ICCIDD 2009 Newsletter.
USA	Enriched Grain Product	Folic Acid	Periconceptional		13% reduced odds of spina bifida was estimated for each 100-µg increase in daily dietary folate equivalent consumed.	Ahrens et al 2011
Australia	Bread	Iodine		Recall Survey (?)	The impact of iodine fortification of bread would be greater for pregnant and postpartum women than has been previously estimated using general population intakes, but additional strategies to increase intakes by these groups are still needed.	Mackerras etal 2010
Brazil	Maize/Wheat Flour	Folic Acid			The reduction in spina bifida birth prevalence in 2006 was 40%, probably related to the food fortification program	Oriolietal 2011
USA	Milk	Vitamin D		Historical	Availability of vitamin D milk increased schooling for the group at highest risk for vitamin D deficiency: African-Americans from cities with low sunlight; increased heights of World War II African-American army enlistees from low sunlight areas by approximately one third of an inch	

Iron and maize / wheat flour

Efficacy of iron-fortified whole maize flour on iron status of school children in Kenya: a randomized controlled trial

Pauline E A Andang'o, Saskia J M Osendarp, Rosemary Ayah, Clive E West, David L Mwaniki, Corine A De Wolf, Rob Kraaijenhagen, Frans J Kok, Hans Verhoef. Lancet 2007; 369: 1799–806

Background: Sodium iron edetic acid (NaFeEDTA) might be a more bioavailable source of iron than electrolytic iron, when added to maize flour. We aimed to assess the effect, on children's iron status, of consumption of whole maize flour fortified with iron as NaFeEDTA or electrolytic iron.

Methods: 516 children, aged 3–8 years, from four schools in Marafa, Kenya, were randomly assigned to four groups. All were given the same amount of porridge five times a week. The porridge for one group was made from unfortified whole maize flour; for the other three groups it was fortified with either high-dose NaFeEDTA (56 mg/kg), low-dose NaFeEDTA (28 mg/kg), or electrolytic iron (56 mg/kg). Concentrations of hemoglobin, plasma ferritin, and transferrin receptor were analyzed in samples taken at baseline and at the end of the 5-month intervention. The primary outcome was iron-deficiency anemia. We analyzed data on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT00386074.

Findings: The prevalence of iron-deficiency anemia in children given unfortified flour was 10%. Compared with placebo, the prevalence of iron-deficiency anemia in children given flour fortified with high-dose NaFeEDTA, low-dose NaFeEDTA, and electrolytic iron changed by 89% (95% CI 97% to 49%), 48% (77% to 20%), and 59% (18% to 209%), respectively. Consumption of high-dose NaFeEDTA improved all measured iron-status indicators. Low-dose NaFeEDTA decreased the prevalence of iron deficiency but did not noticeably change the prevalence of anemia. Electrolytic iron did not improve any of these iron-status indicators. Children who were iron-deficient at baseline benefited more from high-dose and low-dose NaFeEDTA than those with sufficient iron at baseline.

Interpretation: Consumption of whole maize flour fortified with NaFeEDTA caused modest, dose-dependent improvements in children's iron status. Fortification with electrolytic iron did not improve their iron status. Therefore, in high-phytate flours, NaFeEDTA is more suitable than electrolytic iron for supplementation of iron in the diet.

Success of the micronutrient fortification of cereal flours in Venezuela

Scrimshaw NS, Guzman MA, Layrisse M, Mendez-Castellano H, Chavez JF, Garcia-Casal MN. Micronutrient Initiative. 2001

Background. This external evaluation of the multiple fortification of cereal flour in Venezuela was supported by the Micronutrient Initiative because of its significance for the global promotion of cereal fortification. Many countries have introduced national cereal micronutrient fortification, but there are almost no outcome evaluations. This report describes the successful use of fortification of cereal flours to reduce iron deficiency and anemia on a national scale.

Situation / Methods. A 1992 national nutrition survey of children 7, 11, and 15 years of age among lower socioeconomic groups that included 78% of the population found a 37% prevalence of iron deficiency and 19% prevalence of anemia in Caracas and similar rates nationwide. This was a significant increase from a similar survey in 1990 and coincided with a deteriorating economic situation. Alarmed nutrition leaders persuaded the government to create a special commission for the enrichment of food that initiated a program to fortify all wheat flour with iron, thiamin, riboflavin, and niacin and all precooked maize flour with these nutrients plus vitamin A.

At the start the maize flour, consumed as “arepas," provided 60 mg of ferrous fumarate per kg and around 15% of dietary energy while the wheat flour supplied 20 mg/kg of ferrous fumarate and about 28% of the energy in socioeconomic groups IV and V.

Findings. When the population of Caracas was re-surveyed in 1994, iron deficiency had decreased to 16% and anemia to 9% in the same socioeconomic and age groups. In 1994 one-third of the ferrous fumarate in the maize flour was replaced with elemental iron to reduce discoloration when arepas were made with hard water. In surveys in Caracas in 1987, 1988, and 1999 iron deficiency continued to decrease as judged by serum ferritin. Anemia rose again but not to 1992 levels. This was believed to be due to a further deterioration of diets with the continuing economic crisis. Between 1992 and 1997, the consumption of cereals, eggs, fat, and sugar decreased. Moreover precooked maize consumption decreased 27%. This was compensated in part by a 23% increase in wheat flour, but with a net decrease in vitamin A intake from fortification, a possible factor in its effectiveness in reducing iron deficiency.

Interpretation. The program was judged to have cut both iron deficiency and anemia in half in the first two years. It also helped to reduce the consequences of decreases in dietary iron and other micronutrients due to a further deterioration in economic status and dietary quality. The cost for the multiple wheat fortification without vitamin A was less than US$0.01/person/year and for the multinutrient maize fortification less than US$0.10/year. The only direct government costs were for monitoring. The program was the result of a strong initiative from the national nutrition community; support at high government levels; and importantly, the cooperation of the milling industry.

Anemia and Neural Tube Birth Defects Decline in Bahrain
Flour Fortification Initiative (FFI) newsletter, December 2012.

Eleven years after beginning its flour fortification program, the Kingdom of Bahrain reports significant declines in anemia among pregnant women and in the prevalence of neural tube birth defects. Anemia among pregnant women dropped from 40% in 1996 to 23% in 2012. The prevalence of neural tube defects declined from 2.6 per 1000 live births to 0.9 per 1000 live births.

The Kingdom began fortifying flour with iron and folic acid in 2001 as one way to address nutrient deficiencies revealed in a 1996 study. In early 2012, the Head of Nutrition Section led the creation of a “Flour Fortification Project Follow-Up.” The committee includes representatives of Bahrain Flour Mills, Ministry of Commerce represented by Consumer Protection Directorate, and the Standardization and Metrology Directorate.

In November 2012, the committee met for a consultation and revealed the data showing improvements in anemia among pregnant women and prevalence of neural tube defects. The data were obtained from health statistics released annually by the Health Information Dictorate-Ministry of Health. The prevalence of anemia and iron deficiency anemia in pregnant women is obtained through the antenatal nutrition surveillance program.

The committee’s next steps will be to review the fortification program's quality assurance, quality control, and monitoring systems. Future directions will be discussed, including the possibility of adding other vitamins and minerals to the country’s wheat flour standard.

Iron and soy sauce

GAIN 2010

Project Overview: In November 2003, GAIN awarded the Food Fortification Office of the Chinese Center for Disease Control and Prevention, in partnership with the National Fortification Alliance and the Chinese Condiment Association, US$3 million to fortify soy sauce with iron. In May 2010, GAIN invested an additional US$1.5 million in the project. In China, soy sauce is an ideal food vehicle for fortification as it is consumed in small consistent quantities by over 70 percent of the total population. Funding will support expansion of the number of production facilities fortifying soy sauce, the establishment of quality control and assurance monitoring systems and increased access to fortified soy sauce by rural low-income communities.

Goal: The goal of the project is to reduce the prevalence of iron deficiency anemia among women of reproductive age by 30% in Zhejinag Province. The project will achieve this goal by fortifying with iron at least 20% of the soy sauce consumed in the province produced by national industrial manufacturers. It also aims to promote iron fortified soy sauce related policy development and create a supportive environment in China to encourage wide production, distribution and consumption of the soy sauce.

Impact: At full scale, the project aims to reach 12.9% of the population with iron fortified soy sauce.

Achievements: In China, data collected from 21 health clinics showed that anemia in women and children dropped by approximately one third following the fortification of soy sauce with iron. The project has also enabled the inclusion of food fortification into Chinese government policy documents on nutrition as well as the continued quality control and monitoring of fortified soy sauce samples from factories. Consumer knowledge about iron fortification has increased as well through social marketing campaigns. As of March 2010, 62.8 million people had access to the iron fortified soy sauce.

Duration: The first phase of the project ended in December 2008. A second phase of the project began in May 2010 to expand the reach of the project to the rural poor through working with small and medium-sized soy sauce producers. The project is expected to be completed in April 2013.

Studies on the effectiveness of NaFeEDTA-fortified soy sauce in controlling iron deficiency: A population-based intervention trial

Junchi Chen, Xianfeng Zhao, Xin Zhang, Shian Yin, Jianhua Piao, Junshen Huo, Bo Yu, Ninq Qu, Qiliang Lu, Shisun Want, Chumming Chen. *Food and Nutrition Bulletin*. Vol. 26,

No. 2. 2005. The United Nations University.

Abstract: The objective of this research was to study the effectiveness of NaFeEDTA-fortified soy sauce for controlling iron deficiency in a high-risk population. This was an 18-month, randomized, placebo-controlled intervention trial in 14,000 residents aged three years or older in Bijie City, Guizhou Province, China, using sodium-iron ethylene diamine tetraacetate (NaFeEDTA)-fortified soy sauce (29.6 mg Fe/100 ml). The study data included measurements of food consumption, hemoglobin, serum ferritin, and serum retinol.

Findings. The results showed that the diet consisted primarily of cereals, fruits, and vegetables, with very little meat. Food consumption remained unchanged during the study period and was similar in the fortified and control groups. The average daily soy sauce consumption of the group consuming the fortified product was 16.4 ml per person, which provided 4.9 mg of iron from NaFeEDTA. At the end of the trial, all age and sex subgroups receiving NaFeEDTA had significantly higher hemoglobin levels, a lower prevalence of anemia, and higher plasma ferritin levels than the controls. The effects became statistically significant after six months of intervention and were maintained throughout the study period (see summary tables below). We conclude that NaFeEDTA-fortified soy sauce was highly effective in controlling iron deficiency and reducing the prevalence of iron-deficiency anemia population.

Folic acid and grain products

Effects of folic acid fortification on spina bifida prevalence in Brazil

Iêda Maria Orioli, Ricardo Lima do Nascimento, Jorge Santiago López-Camelo, Eduardo Enrique Castilla. *Birth Defects Research Part A: Clinical and Molecular Teratology*, Volume 91, Issue 9, pages 831–835, September 2011.

*Background***.** To assess spina bifida birth prevalence changes after folic acid fortification of wheat and maize flours began in Brazil in June 2004.

Methods. Cross-sectional study of Brazilian live births in 2004 and 2006. Spina bifida birth prevalence from the Live Births Information System (SINASC: Sistema de Informações sobre Nascidos Vivos) in a pre-fortified period was compared to a period fortified with folic acid in each state. Observed prevalence rates in 2004 were used to calculate the expected prevalence rates in 2006 under the null hypothesis that both were similar. The observed/expected (O/E) ratios were tested by two-tailed Z-test. To minimize ascertainment differences among states, the O/E ratio of each one of the 27 Brazilian states was adjusted for the number of births with the Mantel-Haenszel statistic.

Results. The reduction in spina bifida birth prevalence in 2006 was 39% (O/E = 0.61; 95% confidence interval [CI], 0.55-0.67), and 40% (O/E = 0.60; 95% CI, 0.53–0.68), after adjusting for state birth number. This reduction was significant ($p < 0.0001$), and heterogeneous among states ($\chi^2 = 72.96$; $p < 0.0001$).

Conclusion. Using SINASC data, there was a significant reduction in spina bifida birth prevalence in Brazil, probably related to the folic acid food fortification program.

Folic Acid Intake and Spina Bifida in the Era of Dietary Folic Acid Fortification

Ahrens, Katherine; Yazdy, Mahsa M.; Mitchell, Allen A.; Werler, Martha M.
Epidemiology September 2011 - Volume 22 - Issue 5 - pp 731-737.

Background. The US Food and Drug Administration (FDA) mandated that enriched grain products be fortified with folic acid by 1998. We evaluated whether intake of folic acid from supplements and diet was associated with a reduction in spina bifida in the setting of folic acid fortification.

Methods. Data were collected as part of the Slone Birth Defects Study from 1998 to 2008. Mothers of infants with and without birth defects were interviewed within 6 months of delivery about pregnancy exposures, including details of diet and vitamin intake. Dietary natural folate and synthetic folic acid from fortification were combined into a single, weighted measure—dietary folate equivalent. Periconceptional folic acid supplementation and dietary folate consumption were

compared between 205 mothers of spina bifida cases and 6357 mothers of nonmalformed controls. Relative risks of a spina bifida-affected birth were estimated with odds ratios (ORs) and 95% confidence intervals (CIs).

Results. Spina bifida was not associated with regular folic acid supplementation (≥4 days per week) either around the time of conception (adjusted OR = 1.1 [95% CI = 0.74–1.7]) or initiated in early pregnancy (0.79 [0.54–1.2]). After adjustment for confounders, a 13% reduced odds of spina bifida was estimated for each 100-µg increase in daily dietary folate equivalent consumed.

Conclusions. In the setting of folic acid fortification of grains, our data suggest that folic acid supplementation does not appear to offer further benefit for reducing risk of spina bifida. Rather, the folate-associated benefit on spina bifida risk was found with increasing amounts of dietary folic acid consumed, regardless of folic acid supplementation level.

Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States
Williams LJ, Mai CT, Edmonds LD, Shaw GM, Kirby RS, Hobbs CA, Sever LE, Miller LA, Meaney FJ, Levitt M.Teratology 2002; 66: 33-39.

Background: In 1992, the United States Public Health Service recommended that all women of childbearing age consume 400 micrograms of folic acid daily. The Food and Drug Administration authorized the addition of synthetic folic acid to grain products in March 1996 with mandatory compliance by January 1998. The impact of these public health policies on the prevalence of neural tube defects needs to be evaluated. We sought to determine the prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification.

Methods: Twenty-four population-based surveillance systems were used to identify 5,630 cases of spina bifida and anencephaly from 1995-99. Cases were divided into three temporal categories depending on whether neural tube development occurred before folic acid fortification (January 1995 to December 1996), during optional fortification (January 1997 to September 1998), or during mandatory fortification (October 1998 to December 1999). Prevalence for each defect were calculated for each time period. Data were also stratified by programs that did and did not ascertain prenatally diagnosed cases.

Results: The prevalence of spina bifida decreased 31% (prevalence ratio [PR] = 0.69, 95% confidence interval [CI] = 0.63-0.74) from the pre- to the mandatory fortification period and the prevalence of anencephaly decreased 16% (PR = 0.84, 95% CI = 0.75-0.95). Stratification by prenatal ascertainment did not alter results for spina bifida but did impact anencephaly trends.

Conclusions: The decline in the prevalence of spina bifida was temporally

associated with folic acid fortification of US grain supplies. The temporal association between fortification and the prevalence of anencephaly is unclear.

Prevention of Neural Tube Defects in Chile

Gottlieb J. Center for Global Development. *Case Study #16: Prevention of Neural-Tube Defects in Chile*.

Background. In 2001, researchers at the University of Chile's Institute of Nutrition and Food Technology collaborated with the University of Florida to undertake an impact evaluation with support from the Pan American Health Organization (PAHO), the March of Dimes, the CDC, and the Chilean Ministry of Health. The researchers considered two outcomes: bread folate content and folate status in women of childbearing age, and one impact: frequency of NTD in the population.

Methods. Bread folate content was measured by testing the folic acid content of bread at 50 randomly selected bakeries in the capital, Santiago, three and six months after the mandate to fortify with folic acid. Through folate extraction methods, the researchers determined that shortly after the 2000 mandate by the Ministry of Health, 91% of bread sampled was produced with fortified flour.

Findings. Ten months after the fortification mandate, a study was conducted on the folate status of 605 women of reproductive age in Santiago. Researchers discovered a three- to four-fold increase in blood folate levels in these women, demonstrating that consumption of a food staple fortified with folic acid effectively improves folate status. As expected, the women in the study indicated that they did not consume other foods fortified with folic acid or supplements because they were culturally unacceptable, scarce, and economically infeasible. The increases in folate levels can thus be attributed to the introduction of folic acid in the wheat flour they regularly consume. Nearly half of women of reproductive age were at risk of folate deficiency before the fortification intervention, but very few neared these levels after the intervention.

In spite of encouraging results from these intermediate outcomes, the real impact of the folic acid fortification program was determined by measuring the prevalence of neural-tube defects in the Chilean population. A surveillance system for congenital malformations had been in place in Chile for more than 30 years and was able to provide data on some births, but not enough. In 1999, the CDC helped finance a hospital-based surveillance system in nine public hospitals to register NTDs. Because nearly all deliveries occur in institutional settings, this new system was able to account for 25% of all births in Chile. Evidence from both surveillance sources indicated that NTD rates were at 17 per 10,000 live births before fortification. After wheat flour fortification with folic acid was mandated in 2000, the surveillance demonstrated a dramatic decrease of the NTD rate in Chile to 10 per 10,000 live births – an approximate 51% decrease for spina bifida and 46% decrease for anencephaly.

Interpretation. To determine whether this observed decrease could be attributed to the folic acid fortification program or a pre-existing trend, a group of Brazilian researchers who have conducted a congenital malformation surveillance study

since the 1980s in Latin America analyzed their findings. Based on a population survey (see Lopez-Camelo et al. study below) from two pre-fortification periods (1982–1989 and 1990–2000), the researchers determined that NTD prevalence rates were not decreasing in Chile before the mandate to fortify wheat flour with folic acid. In addition, the rates of decrease after fortification are comparable to decreases in prevalence in other countries with folic acid fortification programs such as Canada and the United States.

Reduction of birth prevalence rates of neural tube defects after folic acid fortification in Chile
Lopez-Camelo JS, Orioli IM, da Graca Dutra M, et al. Am J Med Genet A 2005; 135: 120-125.

Background. To verify whether the decreasing neural tube defects birth prevalence rates in Chile are due to folic acid fortification or to pre-existing decreasing trends, we performed a population survey using a network of Estudio Colaborativo Latino Americano de Malformaciones Congenitas (ECLAMC, Latin American Collaborative Study of Congenital Malformations) maternity hospitals in Chile, between the years 1982 and 2002.

Methods. Within each maternity hospital, birth prevalence rates of spina bifida and anencephaly were calculated from two pre-fortification periods (1982-1989 and 1990-2000), and from one fortified period (2001-2002). There was no historical trend for spina bifida birth prevalence rates before folic acid fortification, and there was a 51% (minimum 27%, maximum 66%) decrease in the birth prevalence rates of this anomaly in the fortified period. The relative risks of spina bifida were homogeneous among hospitals in the two period comparisons. There was no historical trend for the birth prevalence of anencephaly comparing the two pre-fortified periods, but the relative risks were heterogeneous among hospitals in this comparison.

Findings. There was a 42% (min 10%, max 63%) decrease in the birth prevalence rate of anencephaly in the fortified period as compared with the immediately pre-fortified period, with homogeneous relative risks among hospitals.

Interpretation. Within the methodological constraints of this study we conclude that the birth prevalence rates for both spina bifida and anencephaly decreased as a result of folic acid fortification, without interference of decreasing secular trends.

Decline in the prevalence of neural tube defects following folic acid fortification and its cost-benefit in South Africa.
Abdul-Rauf Sayed, David Bourne, Robert Pattinson, Jo Nixon, Bertram Henderson.

Background: In October 2003 South Africa embarked on a program of folic acid fortification of staple foods. We measured the change in prevalence of NTDs

before and after fortification and assessed the cost benefit of this primary health care intervention.

Methods: Since the beginning of 2002 an ecological study was conducted among 12 public hospitals in four provinces of South Africa. NTDs as well as other birth defect rates were reported before and after fortification. Mortality data were also collected from two independent sources.

Results: This study shows a significant decline in the prevalence of NTDs following folic acid fortification in South Africa. A decline of 30.5% was observed, from 1.41 to 0.98 per 1,000 births (RR = 0.69; 95% CI: 0.49-0.98; p = .0379). The cost benefit ratio in averting NTDs was 46 to 1. Spina bifida showed a significant decline of 41.6% compared to 10.9% for anencephaly. Additionally, oro-facial clefts showed no significant decline (5.7%). An independent perinatal mortality surveillance system also shows a significant decline (65.9%) in NTD perinatal deaths, and in NTD infant mortality (38.8%).

Conclusions: The decrease in NTD rates post fortification is consistent with decreases observed in other countries that have fortified their food supplies. This is the first time this has been observed in a predominantly African population. The economic benefit flowing from the prevention of NTDs greatly exceeds the costs of implementing folic acid fortification.

Reduction in neural-tube defects after folic acid fortification in Canada
De Wals P, Tairou F, Van Allen MI, et al. New Engl J Med 2007; 357: 135-142.

Background: In 1998, folic acid fortification of a large variety of cereal products became mandatory in Canada, a country where the prevalence of neural-tube defects was historically higher in the eastern provinces than in the western provinces. We assessed changes in the prevalence of neural-tube defects in Canada before and after food fortification with folic acid was implemented.

Methods: The study population included live births, stillbirths, and terminations of pregnancies because of fetal anomalies among women residing in seven Canadian provinces from 1993 to 2002. On the basis of published results of testing of red-cell folate levels, the study period was divided into pre-fortification, partial-fortification, and full-fortification periods. We evaluated the relationship between baseline rates of neural-tube defects in each province and the magnitude of the decrease after fortification was implemented.

Results: A total of 2446 subjects with neural-tube defects were recorded among 1.9 million births. The prevalence of neural-tube defects decreased from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full-fortification period, a 46% reduction (95% confidence interval, 40 to 51). The magnitude of the decrease was proportional to the pre-fortification baseline rate in each province, and geographical differences almost disappeared after fortification began. The observed reduction in rate was greater for spina bifida (a decrease of

53%) than for anencephaly and encephalocele (decreases of 38% and 31%, respectively).

Conclusions: Food fortification with folic acid was associated with a significant reduction in the rate of neural-tube defects in Canada. The decrease was greatest in areas in which the baseline rate was high.

Vitamin A and MSG

Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial

Muhilal, Dewi Permeisih, Yanyan R Idjradinata, Muherdiyantiningsih, Darwin Karyadi.
Am J Clin Nutr 1998;48:1271-6.

Background / Conclusion: In a controlled trial, fortification of commercially marketed monosodium glutamate (MSG) with vitamin A improved serum vitamin A levels of young children and the vitamin A content of breast milk of lactating women in Indonesia. These improvements in vitamin A indices were accompanied by dramatic changes in health and anthropometric status.

Findings. During the course of the study, the prevalence of Bitot's spots among children in program villages fell progressively from 1.2% at base line to 0.2% one month after introduction of the fortified product *(p* < 0.001); xerophthalmia rates in control villages remained essentially unchanged. Linear growth was greater among program than among control children at every age. Hemoglobin levels among program children rose by 10 g, from 113 ± 16 g/L at base line to 123 ± 16 by 5 mo (p < 0.001); they remained essentially unchanged among children of control villages. Preschool children in control villages died at 1.8 times the rate of children in program villages.

Vitamin A and sugar

Vitamin A sugar fortification in Central America: Experience and lessons learned. MOST, USAID.
Jose O. Mora, Omar Dary , Doris Chinchilla, Guillermo Arroyave. MOST, The USAID Micronutrient Project. August 2000.

Background. The effectiveness of sugar fortification has been demonstrated through biological indicators (WHO, 1996) obtained from national surveys conducted between 1995 and 1998 in El Salvador, Guatemala, and Honduras. These surveys indicate a significant reduction in the prevalence of VAD among preschool-aged children as compared to previous surveys.

Findings / Interpretation. The prevalence of low serum retinol (less than 20 µg/dl) in the mid-1990s was <10% in El Salvador, 16% in Guatemala, and 13% in Honduras, as compared with 44%, 26%, and 40%, respectively, during the mid-1960s. These improvements can reasonably be credited to sugar fortification, given that there was no significant improvement in socioeconomic indicators and that population coverage by other specific interventions (e.g., supplementation) was extremely low. Moreover, additional evidence from the 1995 survey in Guatemala mentioned earlier confirms the link with fortified sugar: the prevalence of VAD was significantly lower among the population that consumed only fortified sugar, as opposed to those who consumed mainly *panela* or brown sugar loaf (unfortified). The impact of sugar fortification has been somewhat less impressive on children under two years of age, possibly because this group consumes less sugar.

In Costa Rica, sugar fortification between 1975 and 1980 achieved a noteworthy reduction in the prevalence of VAD, from 33 to <2 percent. Fortification was suspended in 1981, and by 1996 the prevalence of VAD had increased to 9%.

The Effect of vitamin A fortification on sugar on the serum vitamin A levels of preschool Guatemalan children: A longitudinal evaluation
Guillermo Arroyave, Lisa A. Mejia, JR Aguilar. *Am. J. Clin. Nuir.* 34: 41-49, 1981.

Background: Based on the Guatemalan program of vitamin A fortification of sugar [introduced by the Institute of Nutrition of Central American and Panama (INCAP) in 1975], a longitudinal evaluation on serum retinol levels of preschool-aged children was performed.

Methods. Five consecutive surveys executed every 6 months were examined, considering only children who were surveyed more than once. Thus, the changes in their serum retinol after the intervention were evaluated.

Findings. Natural dietary vitamin A remained unchanged throughout. Addition of retinyl palmitic to sugar increased significantly the intake of vitamin A ($p < 0.001$).

After 1 yr of fortification 76% of the children experienced an elevation of retinol. All those with initial values <20 micrograms/dl showed an increase. Mean values increased significantly, particularly for children below 20 micrograms/dl whose levels changed from 16.2 ± 2.9 to 30.2 ± 9.7 ($P < 0.00001$). Those between 20 to 29 micrograms/dl increased from 24.9 ± 3.2 to 30.1 ± 8.1 ($p < 0.0003$). Similar results were obtained after 2 yr.

Conclusion. The results indicated the effectiveness of the program in raising serum retinol levels.

Iodine and Bread

Estimating the impact of mandatory fortification of bread with iodine on pregnant and post-partum women

Mackerras, Dorothy, Jennifer Powers, Boorman, Deborah Loxton, Graham G Giles. *J Epidemiol Community Health* 2011;65:1118-1122.

Background. Iodine deficiency has re-emerged in Australia. Pregnant and breastfeeding women need higher iodine intakes (estimated average requirements: 160 µg/day and 190 µg/day) than non-pregnant women (100 µg/day) because iodine is critical for early infant development. The impact of iodine fortification of bread on women's iodine intake is evaluated by reproductive status using 2003 Australian Longitudinal Study on Women's Health (ALSWH) food frequency data and projected onto 1995 National Nutrition Survey (NNS) daily food consumption data for women of child-bearing age.

Methods. Recent iodine analyses of Australian foods were combined with reported intakes of key foods to estimate iodine intake before and after fortification for 665 pregnant, 432 zero to 6 months postpartum, 467 seven to 12 months postpartum and 7324 non-pregnant women. Differences in mean iodine intake between these groups were projected onto NNS estimates of total iodine intake for women of child-bearing age.

Results. Pregnant and postpartum women reported eating more bread than did non-pregnant women. Mean iodine intakes (µg/day before; and after fortification) from key foods were higher in pregnant (78; 124), 0–6 months postpartum (75; 123) and 7–12 months postpartum (71; 117) than in non-pregnant women (65; 103). Projecting ALSWH results onto the NNS yields total mean iodine intakes of 167, 167, 160 and 146 for the same groups.

Conclusion. Current iodine intakes are well below dietary recommendations. The impact of iodine fortification of bread would be greater for pregnant and postpartum women than has been previously estimated using general population intakes, but additional strategies to increase intakes by these groups are still needed.

Iodine and salt

Tanzania national survey on iodine deficiency: impact after twelve years of salt iodization

Assey VD, Peterson S, Kimboka S, Ngemera D, Mgoba C, Ruhiye DM, Ndossi GD, Greiner T, Tylleskar T. *BMC Public Health*. 9:319, 2009.

Background. In many low-income countries, children are at high risk of iodine deficiency disorders, including brain damage. In the early 1990s, Tanzania, a country that previously suffered from moderate to severe iodine deficiency, adopted universal salt iodization (USI) as an intervention strategy, but its impact remained unknown.

Methods. We report on the first national survey in mainland Tanzania, conducted in 2004 to assess the extent to which iodated salt was used and its apparent impact on the total goitre prevalence (TGP) and urinary iodine concentrations (UIC) among the schoolchildren after USI was initiated. In 2004, a cross-sectional goitre survey was conducted; covering 140,758 schoolchildren aged 6 - 18 years were graded for goitre according to new WHO goitre classification system. Comparisons were made with district surveys conducted throughout most of the country during the 1980s and 90s. 131,941 salt samples from households were tested for iodine using rapid field test kits. UIC was determined spectrophotometrically using the ammonium persulfate digestion method in 4523 sub-sampled children.

Results. 83.6% (95% CI: 83.4 - 83.8) of salt samples tested positive for iodine. Whereas the TGP was about 25% on average in the earlier surveys, it was 6.9% (95%CI: 6.8-7.0) in 2004. The TGP for the younger children, 6-9 years old, was 4.2% (95%CI: 4.0-4.4), n = 41,965. In the 27 goitre-endemic districts, TGP decreased from 61% (1980s) to 12.3% (2004). The median UIC was 204 (95% CF: 192-215) µg/L. Only 25% of children had UIC <100 µg/L and 35% were ≥ 300 µg/L, indicating low and excess iodine intake, respectively.

Conclusion. Our study demonstrates a marked improvement in iodine nutrition in Tanzania, twelve years after the initiation of salt iodization program. The challenge in sustaining IDD elimination in Tanzania is now two-fold: to better reach the areas with low coverage of iodated salt, and to reduce iodine intake in areas where it is excessive. Particular attention is needed in improving quality control at production level and perhaps the national salt iodization regulations may need to be reviewed.

Elimination of iodine deficiency in Fiji

Ministry of Health Report, Fiji. *ICCIDD Newsletter*. December 2009.

Background. In 1994, UNICEF worked with the Ministry of Health, the Ministry of Education and WHO to survey iodine status in Fiji. The survey was done in three

areas on the island of Viti Levu (Ba, Sigatoka and Suva). It found that the prevalence of goiter as determined by ultrasound and palpation in school children and pregnant women in Viti Levu was ca. 45%. The mean urinary iodine (UI) concentration in 15 schools in the Ba, Sigatoka, and Suva areas ranged from 2-94 µg/L, with an average value of 26 µg/L, indicating moderate-to-severe IDD. It also reported that salt iodine levels were insufficient and ranged from <0.01 to 3.21 mg/100g salt.

Study design. Due to the high costs required for a large-scale cross-sectional survey, a smaller sentinel survey was done. Sentinel districts were chosen because they had moderate or severe IDD in the 1994 study before implementation of salt iodization. The study included the following: *c*ollection of spot urine samples from school children (8-12 years) and pregnant women, structured interview of pregnant women regarding diets and knowledge , structured interview of school children regarding demographics and knowledge, and semi-quantitative assessment of iodine level of salt samples brought by the school children from their homes

In addition to the original schools in the 1994 study, the study also included schools and the antenatal clinics from Labasa to assess IDD in north Fiji. The survey included 18 schools and 4 antenatal units from Ba, Sigatoka, Suva and Labasa. The urinary iodine levels were measured at the Endocrinology Laboratory at Westmead Hospital, in Sydney, Australia. A total of 979 urine samples from school children and 292 urine samples from pregnant women were analyzed, while 883 samples of salt were tested for iodine.

School children in Fiji are clearly iodine sufficient with a median UI of 237 µg/ L (83.6% had no IDD). Also, only 4% of the population had a UI less then 50 µg/L. However, knowledge about the importance of iodine was low: the majority (78.6%) of the children didn't know if iodine was important while 12.7% said iodine wasn't important and 8.7% said iodine was important for health. Similar results were obtained from the questionnaire for pregnant mothers. Of the 883 salt samples tested, 98.4% (868) met the current Fiji mandated standards (minimum 15 ppm), when tested using rapid test kits. UI results for pregnant women clearly indicate they are iodine sufficient with a median UI of 227 µg/L (88.4% had no IDD).

Conclusions. This was the first follow up study to evaluate the effect of the USI program in Fiji since its implementation in 1996. The implementation of USI has been highly effective. Another recent study by health inspectors and dieticians using MBI test kits for determining salt iodine levels in various areas of Fiji and found that 99.6% of the 3890 samples randomly selected at household levels had adequate iodine content of above 15ppm. These results are similar to results of this study where 98.4% of salt was adequately iodized.

Iron and Iodine in Salt (i.e. double-fortified salt)

Dual fortification of salt with iron and iodine in women and children in rural Ghana
Asibey-Berko E, Zlotkin SH, Yeung GS, Nti-Nimako W, Ahunu B, Kyei-Faried D, Johnston JL, Tondeur MC, Manner V. East Africa Medical Journal. 2007 Oct:84(10):473-80.

Objective. To test the efficacy of double-fortified satl (DFS) on the anemia and iodine deficiency (ID) status of women and their children.

Design. Double-blind randomized controlled trial in Sekyere West District of Ghana. In this eight-month trial, mildly anemic or non-anemic, non-pregnant, non-lactating women were randomized into three groups receiving: DFS plus weekly placebo (n = 61); iodized salt plus weekly 70 mg iron supplement (n = 65); or iodized salt (IS) plus weekly placebo (control group, n = 58). Correspondingly, their mildly anemic and non-anemic children aged 1-5 years were randomized into two groups receiving either the DFS (n = 23) or IS alone (control group, n = 59).

Results: At the end of the intervention, prevalence of anemia in women remained unchanged in the DFS or IS plus weekly iron supplement group, but significantly increased by 19.5% in the control group (P = 0.039). In children, prevalence of anemia in the DFS group significantly decreased by 21.7% (P = 0.025) while no change was observed in the control group. ID decreased significantly in all groups of women (P < 0.001) and children (P < 0.05), with no difference among groups of women and children.

Conclusion. While the use of DFS prevented anaemia in women, it had a significant role in both the prevention and treatment of anaemia in children. Both the DFS and IS significantly reduced ID in women and children to a similar degree.

Vitamin D and Milk

Nutrition and development: The case of vitamin D milk
Doctoral Thesis by Schwab, Benjamin B., Ph.D., The University of Wisconsin, Madison, 2011.

Background. Micronutrient deficiencies reduce the health of children and risk impeding human capital investments critical for economic development. While the developed world has largely eliminated the most pernicious of these deficiencies, they remain widespread in poorer countries. This study looks at the effects of the introduction of fortified milk, which contributed to the decline of one such micronutrient deficiency in the United States: vitamin D. At the time of vitamin D milk's introduction in the early 1930s, vitamin D deficiency, manifested most prominently in the form of rickets, affected large numbers of children. Despite the lack of a government mandate, Vitamin D milk spread steadily throughout the 1930s. The product's success owed greatly to the support of the medical establishment. Indeed, patent holders on fortification technology and dairies marketing the milk actively worked to promote their product through medical professionals in hopes of stimulating consumer demand.

Methods and Findings. Using previously unexamined historical sources, I compile and introduce an original dataset describing the rollout of vitamin D fortified milk across the United States throughout the decade. Vitamin D milk appeared earliest in large markets, but quickly became available in a range of cities. I then use this dataset to examine the impact of fortified milk on schooling and health outcomes. The gradual expansion of vitamin D milk, along with natural variation in susceptibility to vitamin D deficiency due to geographic and racial factors, permits the identification of fortification's impact from other regional and temporal trends. Using a difference-in-difference-in-difference (DDD) estimator, I find that the availability of vitamin D milk increased schooling for the group at highest risk for vitamin D deficiency: African-Americans from cities with low sunlight. A variety of sensitivity tests supports the validity of the results. Similarly, vitamin D milk's availability increased heights of World War II African-American army enlistees from low sunlight areas by approximately one third of an inch. The results indicate that large-scale food fortification initiatives merit further consideration from economists and policy makers concerned with achieving development outcomes.