Case 16

Prevention of Neural-Tube Defects in Chile

Geographic area: Chile

Health condition: Neural-tube defects (NTDs), the second most common congenital malformation after congenital heart disease, affected about 400 babies in Chile per year in the years before the fortification intervention. The NTD rate of 17.2 per 10,000 live births had been unchanged from 1967 to 1999.

Global importance of the health condition today: Each year, neural-tube defects affect more than 300,000 newborns worldwide. Anencephaly and spina bifida, the two most common NTDs, are important contributors to infant and fetal mortality: all infants with anencephaly are stillborn or die shortly after birth, and those born with spina bifida suffer lifelong disabilities and require extensive medical care.

Intervention or program: Aware of the effect of folic acid on the prevention of neural-tube defects and encouraged by public health experts, the Chilean Ministry of Health introduced new legislation in early 2000 stipulating that all domestically produced wheat flour must be fortified with folic acid. Flour mills began producing, distributing, and marketing wheat flour in compliance with the new legislation, and the government helped to regulate and monitor the quality of fortified flour.

Cost and cost-effectiveness: With existing technologies, the cost of adding folic acid to the pre-mix for fortified flour is approximately 15 cents per ton of wheat flour, making the cost of fortification only 16 cents per woman of reproductive age receiving the target amount of folic acid. With the total cost of rehabilitation for a child affected with spina bifida averaging $100,000, Chile's health system saved an estimated $11 million per year (based on 110 cases in one year).

Impact: Shortly after the fortification legislation was passed, 91 percent of wheat bread was being produced with fortified flour. A year later, blood folate levels in women of reproductive age increased three- to four-fold. Chile's fortification intervention produced a dramatic decrease of the NTD rate—a reduction of approximately 51 percent for spina bifida and 46 percent for anencephaly.

Chile, a country credited for its rapid social and economic progress relative to its Latin American neighbors, again asserted its leadership in public health when in the year 2000 the government successfully implemented the cost-saving fortification of wheat flour with folic acid to prevent neural-tube defects, a congenital malformation. Like other micronutrient programs, the low cost of inputs and the large scale of reach and impact add up to unbeatable cost-effectiveness. In this case, Chile's evidence-based approach to identifying promising interventions, and rapid rollout, resulted in both better health of children and savings to the health system through the prevention of one common type of birth defect, neural-tube defects.

Case drafted by Jessica Gottlieb.

Disabilities as a Health Priority

Birth defects, along with learning, physical, and developmental disabilities of many types, are estimated to affect 10 to 20 percent of children and are increasingly recognized as an important public policy concern in low- and middle-income countries such as Chile, which has the second highest rate of disability prevalence in the region next to Brazil.[1] Recent decades have seen major advances addressing infectious diseases, but few programs focused on the prevention of long-term disabilities. Governments are increasingly seeking ways to provide (often high-cost) support to those children and families affected and, when possible, to prevent the disabilities in the first place. The fortification of pregnant women's staple foods with folic acid has been identified as one of the most viable and cost-effective interventions in low- and middle-income countries to prevent congenital anomalies.[2]

Folic acid fortification has proven successful in countries such as the United States and Canada. Since 1995, the US Centers for Disease Control and Prevention (CDC) has recommended that women of childbearing age consume 400 micrograms of folic acid daily before conception and continuing into pregnancy. Because the synthetic folic acid added to fortified foods is more "bioavailable" or about twice as effective as naturally occurring folate, fortified foods and supplements are preferred to changes in diet. Since 1998, the US Food and Drug Administration (FDA) has mandated that certain foods such as cereals, breads, and pastas be "enriched" or fortified with 140 micrograms of folic acid per 100 grams of grain.[3] A study in 2001 estimated that the folic acid fortification program in the United States contributed to a 19 percent decline in birth prevalence of neural-tube defects.[4]

Neural-Tube Defects

Each year, neural-tube defects (NTDs), the second most common congenital malformation after congenital heart disease, affect more than 300,000 newborns worldwide.[5] NTDs generally occur in the first 28 days of pregnancy when the fetus' neural tube or spine fails to close properly. This results in the incomplete development of the brain, spinal cord, or their protective coverings. Anencephaly and spina bifida are the two most common NTDs and are important contributors to infant and fetal mortality. All infants with anencephaly are stillborn or die shortly after birth. Those born with spina bifida have a chance at surviving, but only with extensive medical care. If infants with spina bifida do survive, they are likely to have severe, lifelong disabilities.

Few known measures can treat problems resulting from the failure of the neural tube to close, and dealing with the problem on a population level requires preventive interventions. As demonstrated in the United States and Canada, consumption of the B vitamin folic acid before conception and during early pregnancy can significantly reduce the number of NTDs occurring in newborns. Large-scale interventions have been found to reduce the prevalence of NTDs by as much as 50 percent.

An Ounce of Prevention

In Chile, one quarter to one third of all health care costs for catastrophic events occur in the neonatal period and represent the single largest demand on health care.[6] Catastrophic health conditions such as congenital malformations not only are a burden on the nation's health care system, but also represent a substantial proportion of the household's income and are rarely covered sufficiently by insurance plans. At very low cost, Chile's decision to fortify wheat flour to prevent children from being born with neural-tube defects relieved a tragic and expensive burden on families and on the Chilean health care system.

In spite of recent declines in Chile's infant mortality rate, the rate of congenital malformations went unchanged in the years prior to the fortification intervention. About 400 babies affected with NTDs were born in Chile each year, and the NTD rate of 17.2 per 10,000 live births was unchanged from 1967 to 1999.[7]

NTD rates in the United States before its fortification interventions were significantly lower than those in Chile. This difference can be attributed, in part, to low consumption in Chile of the vegetables and fresh fruits containing naturally occurring folate, as well as cooking habits.[8] In addition, families in the United States and other countries may choose to terminate pregnancies upon prenatal diagnosis of NTDs, but termination of pregnancies for any reason is forbidden by law in Chile.

High prevalence of NTDs implies not only high mortality, particularly for anencephaly, but also extremely high costs of clinical care and management for complications of spina bifida. In addition to the physical and emotional tolls upon the family, surgery, clinical care, and rehabilitation for each spina bifida patient is estimated to cost about US$120,000 in Chile from birth to 18 years of age.[9]

The Development of an NTD Prevention Strategy

In Chile, where folate supplements and fortified breakfast cereals and other commercial products are out of reach for most income groups, it was necessary to develop a new method of reaching pregnant women with folic acid. "Aware of the effect of folic acid on the prevention of neural-tube defects, in 1997 a group of academics from Chile's Institute of Nutrition and Food Technology convinced authorities from the Ministry of Health to convene a working group to evaluate the feasibility of implementing folic acid fortification to prevent NTDs," says Eva Hertrampf, one of the leading academics from the institute, known as INTA. The working group, composed of academics (pediatricians, nutritionists, geneticists, food technologists), industry representatives (millers, premix vendors, pharmacists), and professionals from the Ministry of Health (representatives from the nutrition unit, monitoring, and primary child care programs) recommended that Chile adopt the fortification of wheat flour with folic acid to prevent NTDs. As later happened in Mexico with milk fortification (see Box 16–1), strong evidence was marshaled by the research community to support the government's decision to introduce an important nutrition intervention.

Wheat flour fortification appeared to be the best option for a number of reasons. First, wheat flour is a staple food in Chile; 90 percent of it is consumed as bread. It is estimated that Chileans eat about 160 g of wheat flour per day, the equivalent of eight slices of wheat bread.[7] Second, Chilean mills have been fortifying wheat flour with micronutrients since the 1950s and even before that with baking aids and whiteners.[10] These early experiences with fortification were important for both economic and technical reasons. Because the mills were already equipped with the requisite equipment, it was much less costly to introduce folic acid to the premix for flour at the time the new fortification intervention was introduced. The Ministry of Health also had quality controls in place since 1967 when it became mandatory to fortify flour with iron. A national laboratory controls quality by randomly sampling wheat flour for analysis on a regular basis.

In January 2000, the Chilean Ministry of Health introduced new legislation stipulating that folic acid must be added to the premix. The level of mandated folic acid, 2.2 mg/kg, was tailored to the target group for the intervention. If women of childbearing age consumed the estimated average amount of fortified wheat flour, they would receive the 400 μg/day of folic acid recommended for the prevention of NTDs.

The government, the food industry, and the mills each played a part in the rollout of the legislative mandate. The mills had the most immediate role in implementing folic acid fortification. Thanks to their early involvement in the decision to fortify wheat flour and the small size of the milling community, little advocacy by the health authorities was required to turn the legislative mandate into action. The food industry was responsible for producing, distributing, and marketing wheat flour in compliance with the regulations of the government. To ensure the effectiveness of the fortification intervention and to continually inform program design, the government was charged with the responsibility of regulating and monitoring the quality of fortified flour.

Evaluating the Impact of the Fortification Program

With much of the current impact data on folic acid fortification derived from the United States and Canada, the Chilean intervention offered an opportunity to measure program impact in a middle-income country. The evaluation of Chile's experience was important not only to Chilean authorities, but also to neighboring Latin American countries that could utilize the results to pursue similar fortification programs.

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 Organiza-

Box 16–1

The Influence Potential of Evidence: Milk Fortification in Mexico

As with wheat flour fortification, Chile was a regional leader in milk fortification. In the 1980s, Chile began fortifying milk with iron and distributing it to infants with the result of significant reductions in anemia.[11] This experience was one of the influences behind a recent decision in Mexico to fortify milk with micronutrients to address observed problems in child malnutrition.

In 1999, the results of a national nutrition survey in Mexico signaled a serious problem: Despite significant investments in health and nutrition throughout the 1990s, a large share of Mexican children, especially those in rural and primarily indigenous areas, still suffered from malnutrition. One in four children suffered from anemia, and up to half of children exhibited signs of other micronutrient deficiencies.

These research findings helped influence decision making by government leaders. When presented with the poor nutrition findings, the Ministry of Health decided to coordinate with the Ministry of Social Development, which was responsible for many poverty reduction programs that had nutrition components. Knowing of successful milk fortification programs, public health researchers seized this opportunity to recommend that the Social Development Ministry take advantage of an existing milk distribution program and fortify the milk with micronutrients.

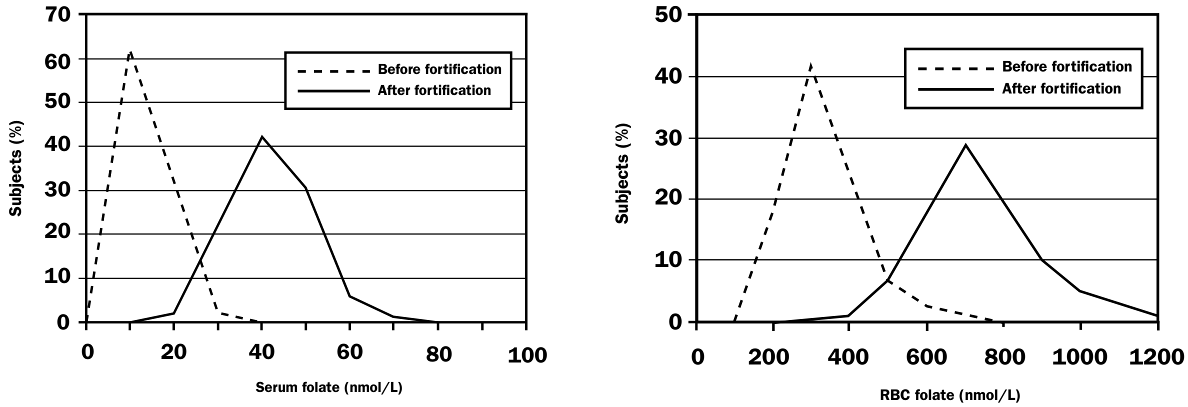
For 30 years, the Community Milk Supply Program (Programa de Abasto Social de Leche), implemented by the Liconsa company, had provided subsidized milk to as many as 4.6 million Mexican children. As a result of the collaboration between the public health researchers and the two government ministries, a fortification component was added to the Liconsa milk distribution program in late 2002. The new program, *Liconsa fortificada*, distributed fortified milk with appropriate amounts of iron, zinc, vitamin C, and folic acid to compensate for the deficiency of these micronutrients in children's diets. Beneficiaries of the program were chosen according to socioeconomic and demographic studies that focused on geographic zones with a high prevalence of malnutrition. Early results of the program indicate a decrease in the prevalence of anemia from 27 to 17 percent and the prevalence of iron deficiency from 20 to 4 percent among children aged 12–24 months who consumed the fortified milk.[12]

tion, 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 type of impact—the frequency of NTD in the population. 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 percent of bread sampled was produced with fortified flour.

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

Figure 16–1

Serum (A) and red blood cell folate (B) levels in women of reproductive age before and after folic acid fortification, Santiago, Chile, 1999–2001.[13]



Source: Chor-ching Goh (2002). Reprinted with permission from the UNU *Food and Nutrition Bulletin* 2002;23:280–291.

consume (see Figure 16–1). 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 percent 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 percent decrease for spina bifida and 46 percent decrease for anencephaly.[a]

a Rates included the prevalence of the main three types of NTD: anencephaly, encephalocele, and spina bifida. Encephalocele decreased by only 26 percent, which explains the greater decreases in anencephaly and spina bifida.

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 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.[14]

At Almost No Cost

Thanks to existing technologies, the cost of adding folic acid to the pre-mix for fortified flour is very low, approximately 15 cents per ton of wheat flour. The cost of fortification was only 16 cents per woman of reproductive age receiving the target amount of folic acid. This implies that two cases of NTDs prevented per year would recover the annual fortification cost of folic acid.[9] With NTDs being cut by more than 40 percent per year, the fortification intervention more than paid for itself.

Adding an average of less than 0.5 percent to the retail price of wheat flour, this cost was easily absorbed by the milling industry. Because the mills already had most of the machinery and quality controls in place, relatively little overhead cost was associated with the addition of folic acid to the other micronutrients already used in fortification processes. The considerable cost of research, data collection, and information-sharing needed to support Chile's fortification intervention was made possible by contributions from donor agencies and benefited many beyond Chile's borders. With the milling industry taking on the minor costs of fortification and the total cost of rehabilitation for a child affected with spina bifida averaging $100,000, Chile's health system saved an estimated $11 million per year (based on 110 cases in one year).[15]

A Success Built on Partnership

Key to Chile's success in its folic acid fortification program was a strong alliance among partners in the public and private sectors. This exemplary public-private partnership was fostered by a clear understanding of roles and responsibilities as well as a strong sense of the imperative to collaborate to achieve effective planning, implementation, and sustainability of the program.

The government provided the enabling legislation and the regulatory apparatus to support micronutrient fortification in the public and private sectors. Academics at the national level contributed to the success through advocacy, monitoring, and impact evaluation efforts. And the milling industry enabled fortification through advanced technological capacity. Collaboration between partners was positively influenced by existing linkages between the research community and public health agencies in Chile. The private sector also has a long history of supporting research and development and interacting with legislators.

Chile's success has been contagious. "The long tradition of fortification in Chile inspired ALIM," says Hertrampf, referring to the Latin American Association of Industrial Millers, established in 1982 to harmonize quality procedures and combat unfair competitive practices. Spurred by advocates within PAHO, the US Agency for International Development, the World Bank, and UNICEF, ALIM advanced the fortification agenda in 1997 when its association millers agreed to support the mandatory fortification of wheat flour.

Chile's recent success with folic acid fortification continues to inspire. In 2001, Argentina adopted mandatory fortification of wheat flour with folic acid. And in October 2003, Chile's Institute of Human Nutrition and Food Technology cosponsored a conference with PAHO and the CDC to standardize and strengthen similar programs in neighboring countries. Since then, almost every Latin American country has implemented a regulation to fortify wheat flour with folic acid.

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