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# Cost-effectiveness of a folic acid fortification program in Chile

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**Abstract**

*Objective:* Periconceptional intake of folic acid reduces the risk of neural tube defects (NTDs), a frequent birth defect that can cause significant infant mortality and disability. In Chile, fortification of wheat flour with folic acid has resulted in significant reduction in the risk of anencephaly and spina bifida. We investigated the cost-effectiveness implications of this policy.
*Methods:* We conducted an ex-post economic analysis of this intervention. Estimates of the effect of fortification in decreasing NTDs and deaths were derived from a prospective evaluation. The costs of fortification and provision of medical care to children with spina bifida in Chile were based on primary data collection.
*Findings:* The intervention costs per NTD case and infant death averted were I$ 1200 and 11,000, respectively. The cost per DALY averted was I$ 89, 0.8% of Chile's GDP per capita. Taking into account averted costs of care, fortification resulted in net cost savings of I$ 2.3 million.
*Conclusion:* Fortification of wheat flour with folic acid is a cost-effective intervention in Chile, a middle income country in the post-epidemiological transition. This result supports the continuation of the Chile fortification program and constitutes valuable information for policy makers in other countries to consider.


*Keywords:* Folic acid; Fortified food; Cost-effectiveness

## 1. Introduction

Periconceptional intake of folic acid (FA) has been demonstrated to reduce the risk of having a fetus affected with anencephaly or spina bifida by 50–70% [1,2]. Anencephaly and spina bifida are among the most common birth defects contributing to infant mortality and disability. In Chile, they together represent the second most frequent isolated type of birth defect after congenital heart disease [3].

In response to the evidence of a beneficial effect of periconceptional intake of FA, statements from USA,

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Europe [4,5] and FAO/WHO recommended that all women of fertile age should consume 400 μg of FA daily to reduce the risk of NTDs. Several evaluations identified grain fortification as the most cost-effective way to increase consumption of folic acid [6,7]. Studies show that fortification of cereals with FA significantly increases blood folate levels and is associated with reductions in NTDs [8–12].

In Chile, a wheat flour folic acid fortification program showed an increase in blood folate levels [13] and a decrease in the risk of NTDs [14,15]. An ex-post economic evaluation of the program should provide useful information for policy makers in other countries where congenital malformations are an important cause of infant mortality.

## 2. Methods

We compared the strategy of fortification with the baseline alternative of no fortification. Other alternatives directed to increase FA intake such as promoting consumption of supplements were excluded from consideration because they were not in place during the period of evaluation. Consequently, improvements in folate intake and blood folate status and subsequent reductions in the risk of NTDs can best be explained by the implementation of the fortification program.

Birth defects surveillance data were used to evaluate effectiveness in reducing NTD risk in all births (live and fetal deaths) weighting more than 499 g. All estimates were conducted based on pre-fortification and post-fortification incidence rates presented in Table 1. The 95% confidence intervals were used to calculate lower and upper ranges on all estimates presented in the analysis.

In undertaking this cost-effectiveness analysis (CEA), we followed the CEA guidelines provided by the Disease Control Priorities Project supported by the World Health Organization, World Bank, and the U.S. National Institutes of Health [16]. These same guidelines are used in the WHO-CHOICE generalized cost-effectiveness analysis program [17,18]. They call for the calculation of the ratio of intervention costs to numbers of DALYs ("disability adjusted life years") averted. The DALY is a summary measure of premature mortality and morbidity prevented. The guidelines call for use of a 3% discount rate to adjust both DALYs and future year costs and to test the sensitivity of the result to the use of a 0% discount rate for health effect and a 6% discount rate for costs. Because our analysis was conducted using only 1 year of cost data for the intervention, there was no need to discount intervention costs.

In addition, we calculated the averted costs of care from prevention of live births with spina bifida. It is standard practice in cost-effectiveness analyses conducted in industrialized countries to subtract averted costs from intervention costs and divide net costs by units of health outcomes [19,20]. If the net cost is negative, the intervention is said to "dominate" the alternative and to be "cost saving".

*Health outcomes*: The economic analysis was conducted on the benefits of FA in decreasing the risk

Table 1
Incidence rate and 95% CI of anencephaly, spina bifida and fetal death per 10,000 births during pre-fortification (1999–2000) and post-fortification (2001–2002) evaluation periods, Santiago, Chile

| Health outcome | Pre-fortification ($n = 120{,}636$) | | | Post-fortification ($n = 117{,}101$) | | |
|---|---|---|---|---|---|---|
| | Rate | 95% CI | | Rate | 95% CI | |
| | | Lower | Upper | | Lower | Upper |
| All births[a] | | | | | | |
| Anencephaly | 6.00 | 5.00 | 7.40 | 3.33 | 2.29 | 4.38 |
| Spina bifida | 8.70 | 7.04 | 10.37 | 4.61 | 3.40 | 5.82 |
| Live births[a] | | | | | | |
| Anencephaly | 2.42 | 1.54 | 3.30 | 2.49 | 1.58 | 3.40 |
| Spina bifida | 8.60 | 6.94 | 10.27 | 4.38 | 3.20 | 5.60 |
| Fetal death | 76.40 | 71.17 | 81.02 | 62.00 | 57.49 | 66.51 |

[a] Includes all live births and fetal deaths with birth weight >499 g.

of anencephaly, spina bifida and fetal deaths in all births with weight greater than 499 g. We estimated the incremental cost per case averted extrapolating the incidences of those outcomes before and after fortification (Table 1) to the total number of live births and recorded fetal deaths occurring in the calendar year 2001, that is 259,069 and 1278, respectively [21]. Because of the high fatality rate associated with NTDs we also included cost per infant death averted. Estimates of neonatal deaths were calculated assuming an infant mortality of 18% for spina bifida. Data on spina bifida mortality in the neonatal period was extracted from our registry. Because, the registry did not reveal differences in anencephaly frequency in live births between periods (Table 1) we calculated DALYs averted from the decrease in the number of spina bifida cases among live births.

Children born with spina bifida generally survive for many years depending upon the severity of the lesion. Age-specific death rates were constructed from 1-year survival data from our registry that showed 82% survival at 1 year of age, complemented with data on 20-year survival of patients with spina bifida in a birth cohort from Atlanta (USA) [22].

The number of DALYs averted with the intervention was estimated using methods based on recommendations of the National Burden of Disease Studies and accompanying spreadsheet [23]. DALYs were calculated using a 3% discount rate with age weighting. As recommended, we conducted a one-way sensitivity analysis to assess the impact of assuming a discount rate of 0% and an age weight of 0. We selected the Chilean life table to estimate DALYs. This corresponds to a life expectancy at age 0 of 74 years for men and 80 years for women [24].

To estimate "years of life lived with disability" (YLD) associated with spina bifida, which is a measure that combines morbidity, disability, and perceived quality of life, we used a similar approach to the Australian burden of disease study, where disability weights were constructed based on the severity of the lesion [25]. The high level corresponds to thoracic/high lumbar L1–L2, the medium level comprises lesions affecting lumbar vertebrae L3–L5, and the low level lesion is limited to sacrum. Among Chilean live births with spina bifida, 28% had a high-level lesion, 65% had a medium-level lesion, and 7% had a low-level lesion. DALY weights were those used by the Australian burden of disease study; 0.68, 0.50 and 0.16 for high-, medium-, and low-level lesions, respectively. The resulting average disability weight was 0.53. Average length of life of a child with spina bifida was assumed to be the same as in the 1996 Global Burden of Disease study for the Latin America and Caribbean region that is 63.4 for males and 67.3 for females [26].

### 2.1. Cost

Costs are presented in 2001 international dollars (I$). As recommended by WHO-CHOICE guidelines, costs in dollar terms for goods and services produced in Chile (non-traded goods) were calculated using a purchasing power ratio. To convert the Chilean currency to international dollars we used the purchasing power parity conversion factor taken from World Development Indicators, 298.1. As a comparison, the corresponding official exchange rate in dollars in the same year was 634.9. The dollar cost of internationally traded goods, notably the folic acid used in fortification programs, reflects the import cost and is not transformed by the purchasing power conversion factor.

Costs obtained from years other than 2001 were adjusted according to the Consumer Price Index variation reported by the Central Bank of Chile. The medical and rehabilitation prices used in this analysis are based on estimates from public hospitals and rehabilitation centers. The reimbursement fees used by these institutions are based on those established by the National Health Fund of Chile (Fondo Nacional de Salud, FONASA). FONASA is the government health insurance provider for approximately 70% of the Chilean population. Therefore, we believe this cost represents the opportunity cost for the public health sector in Chile.

*Cost of fortification*: Program cost was determined by aggregating the cost of adding FA to the flour that is produced and consumed in Chile and the cost of conducting analytic testing to confirm appropriate folic acid levels in fortified products. The implementation of the folic acid fortification program in Chile did not require additional equipment since wheat flour has been fortified with iron and vitamin B complex for the last 30 years. The estimated unit cost is I$ 0.17 per tonnes of grain. Total direct cost was estimated by multiplying the unit cost by the quantity of wheat flour produced in Chile. In 2001 production aimed at domestic demand for human consumption was 1,182,200 tonnes [27], for a total of I$ 201,000. The monitoring system in place for wheat flour fortification under the responsibility of the Institute of Public Health (ISP) includes riboflavin, thiamin, niacin and iron; the added cost of folic acid analysis was estimated as I$ 7700. This cost includes materials, reagents and standards to analyze approximately 400 samples per year. Thus, the total program cost used for this analysis was I$ 208,700.

### 2.2. Framework to calculate averted costs from prevention of NTD

We elected to estimate the economic benefit of fortification restricted to medical, rehabilitation care, and developmental services for which cost data were available. We specifically determined savings from surgical, medical, and rehabilitation costs of live births with spina bifida. Data used in the cost calculations are presented in Table 2.

*Spina bifida cost*: Estimation of averted cost related to neurosurgical treatment of spina bifida patients involved calculating the number of surgeries averted by fortification and the average cost per patient. The number of surgeries prevented was calculated as the number of thoracic/high lumbar and lower lumbar cases averted with the intervention, assuming that all of them undergo surgical closure. The average cost per surgical treatment was constructed from Chilean data on the cost of defect repair and estimates from the literature on the percent undergoing ventriculo-peritoneal (V-P) shunt placement, and risk of infection during the first year of life, with 81% of those undergoing surgery assumed to require a shunt placement and the risk of infection after the first procedure of 10% [28,29]. Surgical cost data came from the Neurosurgical Institute of Santiago, which is a reference center where most cases of spina bifida that are born in the public health system undergo their neurosurgical intervention (Table 2). We determined changes in resource consumption of long-term medical and rehabilitation costs derived from prevention of spina bifida cases at thoracic/high lumbar and lower lumbar sites. Prevention of sacral cases was not included because they represent a very low proportion of spina bifida cases in Chile.

Long-term medical and rehabilitation cost were obtained from the Infant Rehabilitation Institute (TELETON) administrative database, a non-profit private foundation that offers inpatient and outpatient medical services to children and adolescents who are neurologically impaired, up to age 22 years (Table 2). Cost estimates were derived from 1820 patients that received rehabilitation in this institute; medical service claims were adjusted to reflect 2001 FONASA reimbursement rates. Estimation of the average cost per case of thoracic/high lumbar and low lumbar lesion was constructed by aggregating the TELETON cost obtained at different age categories (1–3, 4–6, 7–14, 15–18 and 19–22 years).

The derivation of number of cases prevented of thoracic/high lumbar and low lumbar lesion was based on the extrapolation of spina bifida risk reduction obtained from program evaluation data from hospitals in Santiago (Table 1) to the total number of live births in Chile during 2001; that is 259,069. The distribution of spina bifida level of lesion obtained from our NTD registry was applied to the total live births with spina bifida. We assumed an overall survival probability to age 22

Table 2
Spina bifida related costs used to estimate averted cost

| Health outcome | | | Neurosurgical cost[a] |
|---|---|---|---|
| Cost (I$) | | | 8300 |
| Cost source | | | Neurosurgical Institute |
| Long-term cost per case[b] | Discount rate | | Rehabilitation center |
| | 3% | 6% | |
| Thoracic/high lumbar | I$ 22,500 | I$ 17,400 | TELETON |
| Lower lumbar | I$ 19,500 | I$ 15,200 | |

[a] Neurosurgical cost was composed from the proportion of defect that underwent surgical correction, the proportion requiring VP-shunt placement and risk of infection after first VP-shunt.
[b] Long-term average cost per case according to level of lesion was derived from TELETON database extended to 22 years of age.

of 64% for children with a thoracic/high lumbar lesion and 84% for those with a lower lumbar lesion, derived from the Atlanta spina bifida cohort [22].

## 3. Results

Estimates of the numbers of cases, fetal and infant deaths prevented, and cost-effectiveness ratios for the different health outcomes are presented in Table 3, along with upper and lower bounds for the estimates. These numbers apply the incidence rates from the study sample of hospitals to all births in Chile during 2001. Fortification is calculated to have resulted in 175 averted NTD births per year, including 107 births with spina bifida and 68 with anencephaly. The estimated reduction in the number of live births with spina bifida was slightly greater, 109, as a result of a slight increase in fetal deaths with spina bifida. Fortification was also associated with a reduction of 357 fetal deaths due to all causes and 19 infant deaths due to spina bifida per year. The cost per NTD birth averted was I$ 1200.

Implementation of folic acid fortification in Chile is estimated to have averted 2300 DALYs per year, using age weighting and discounting at 3% per year. Using the lower and upper limit of estimated population relative risk reduction in spina bifida, the range of DALYs averted varies from 2000 to 2500. The reduction was accomplished at an average cost of I$ 89 (range 1$ 101–79) per DALY averted. The results of the sensitivity analysis using the DALY measures of health with a 0% discount rate and without the age weight modulating factor present are shown in Table 3. Because the cost is the same, and the number of undiscounted DALYs averted is greater, the cost per DALY averted is lower I$ 42 per DALY.

### 3.1. Averted cost

Our estimates of numbers of cases prevented and averted costs as a consequence of the intervention are presented in Tables 3 and 4. We estimated that 109 live births with spina bifida were prevented each year nationwide with fortification. We applied the probabilities of surgery and lesion-specific distribution and survival rates described in Section 2. The reduction in cost as a consequence of preventing surgery in 30 and 72 thoracic/high lumbar and lower lumbar cases, respectively, was close to I$ 850,000. Regarding averted long-term costs, we calculated that 20 and 60 cases of thoracic/high lumbar and lower lumbar cases surviving at age 22 years, respectively, would have been prevented. This represents an additional I$ 1.6 (range I$ 1.4–1.8) million in discounted rehabilitation costs avoided. The total reduction in cost was I$ 2.5 (range I$ 2.3–2.8) million, using a 3% discount rate. The net cost savings, after subtracting program cost, was I$ 2.3 (range I$ 2.0–2.6) million. As a ratio, this implies

Table 3
Cost-effectiveness ratios derived from 1 year of FA fortification

| Health outcomes | Cases averted (range) | Cost[a]/case ratio (I$ $\times 10^3$) |
|---|---|---|
| Anencephaly | 68 (62–77) | 3.1 (3.4–2.7) |
| Spina bifida (all births) | 107 (95–125) | 2.0 (2.2–1.7) |
| All NTDs | 174 (157–202) | 1.2 (1.3–1.0) |
| Fetal death | 357 (347–378) | 0.60 (0.60–0.55) |
| Infant death[a] | 20 (17–22) | 11.0 (12.0–9.3) |
| | | DALYs |
| Gains from fortification $\times 10^3$ | | |
| Base case (range)[b] | | 2.3 (2.0–2.5) |
| Sensitivity (range)[c] | | 4.8 (4.2–5.3) |
| Cost (I$)/DALYs averted | | |
| Base case (range)[b] | | 89 (101–79) |
| Sensitivity (range)[c] | | 42 (48–38) |

[a] Infant death averted secondary to prevention of spina bifida cases in live birth, assuming 18% first-year mortality.
[b] Base case assumed 3% discount and age weighting.
[c] Sensitivity analysis based on 0 discount and no age weighting.

Table 4
Cases prevented and cost averted resulting from NTDs prevention based on incidence rate reduction and 95% confidence interval in live birth births

| | Cases prevented | | Savings in millions I$ |
|---|---|---|---|
| Spina bifida live birth | | | |
| Surgical treatment | 102 (90–113)[a] | | 0.9 (0.8–1.0) |
| | Cases surviving at 22 years[b] | Discount | |
| | | 3% | 6% |
| Rehabilitation | | | |
| Thoracic/high lumbar | 19 (17–22) | 0.42 (0.38–0.47) | 0.34 (0.30–0.38) |
| Lower lumbar | 60 (53–67) | 1.2 (1.0–1.3) | 0.90 (0.80–1.01) |
| Total savings | | 2.5 (2.2–2.8) | 2.3 (2.0–2.5) |
| Net saving (minus program cost) | | 2.3 (2.0–2.6) | 2.1 (1.9–2.3) |

[a] Estimates based on thoracic/high lumbar and lower lumbar spina bifida cases prevented.
[b] Estimates performed on a cohort of 109 cases of spina bifida prevented in live birth. For incidence rate, distribution of level of lesion and survival used to estimate cases prevented, refers to Section 2.

average averted costs of 11.8 (range 10.5–13.2) international dollars for every dollar spent on fortification.

## 4. Discussion

A CEA evaluation provides information that allows the health sector to allocate resources to those programs in which the ratio of health benefits of the intervention to costs exceeds alternatives. In this analysis, we utilized data derived from prospectively designed evaluations on NTDs risks, morbidity, and mortality from our NTD registry in combination with cost data from program implementation to estimate cost-effectiveness ratios for health outcomes.

We have conducted a CEA of a wheat flour FA fortification program that had previously been shown to have an effect on improving serum and RBC folate status in the target population as well as reducing the risk of NTDs. This ex-post economic analysis showed that fortification of wheat flour resulted in incremental cost per unit of health benefit that were below the GDP per capita for Chile, which in 2001 was I$ 11,265 [24]. Furthermore, the results showed savings in health expenses that significantly exceeded the investment incurred by the milling industry.

This study has demonstrated that in addition to health benefits there were significant economic benefits associated with the intervention. The World Bank has identified important economic payoffs likely to result from investing in nutrition. Grain fortification with FA is not an exception as revealed by our results and those of others reporting that FA fortification is a cost-saving intervention [30,6].

We compared our estimates of cost per DALY averted to those reported by WHO-CHOICE for the AmrB (South American subregion with low adult and child mortality) on other types of micronutrient fortification. Fortification of a staple food with vitamin A or zinc with 50% coverage was calculated to cost I$ 43 and 79 per DALY averted, respectively [18]. For iron fortification the cost was I$ 214 per DALY [31]. Thus, our finding of I$ 89 per DALY averted is comparable to zinc, higher than vitamin A and lower than iron fortification in the AmrB region.

The Commission on Macroeconomics and Health recently defined interventions that have a cost-effectiveness ratio (CER) of less than three times GDP per capita per DALY as cost effective [32]. The WHO-CHOICE project classifies any intervention with a CER less than average per capita income as "very cost-effective" [18]. In Chile, per capita GDP in 2001 was I$ 11,265. The estimated cost per DALY averted by FA fortification of I$ 75 is less than 1% of per capita income. This cost per DALY averted would be even lower if we were to model improved survival of infants with NTDs associated with FA fortification as has been recently described in the United States [33]. Thus, FA fortification in Chile can be regarded as highly cost-effective by any commonly used criterion.

In an analysis that included averted costs of care resulting from FA fortification, which is consistent with standard CEA methods used in industrialized countries, we calculated that FA fortification is cost saving. That is, it yields net economic benefits in terms of averted direct costs exceeding the costs of the intervention. In particular, it was found that averted costs exceeded intervention cost by a ratio of 11.8:1. This result can be compared with a recently published analysis of FA fortification from the United States, which reported that the reduction in direct cost from fortification exceed the intervention cost by a ratio in excess of 40:1 [28]. Differences in prices and quantity of treatment received by children with spina bifida in the two countries appear to account for the lower ratio of averted cost to intervention cost in the present analysis.

It should be noted that we only considered the direct medical and rehabilitation cost during the first 22 years of life in patients with spina bifida. Categories of cost that were not assessed in this analysis and that have been considered in other economic evaluation of folic acid fortification include costs borne by families, notably unpaid care giving time and the reduction in economic productivity of individuals with spina bifida who experience work disability [6,7,30]. Adult survivors have varying degrees of disability, with up to one third requiring daily care or being unable to live independently [34]. On the other hand, there are program expenses not accounted for, such as money spent on research, public promotion of folic acid consumption, and birth defect surveillance.

We have not estimated costs associated with potential adverse health effects resulting from the masking of the hematologic sign of anemia by high FA intakes. Results of dietary evaluations performed in the target population [13] and in the elderly population [35] showed that the risk of consuming more than 1 mg/day, the upper level (UL) of FA intake established by the U.S. Institute of Medicine, is unlikely. The measured intakes for women in reproductive age and the elderly were below the UL. The only study evaluating the frequency of undiagnosed anemia in people with vitamin $B_{12}$ deficiency following fortification failed to demonstrate an association [36]. We cannot rule out the possibility that some adverse effects might have occurred. A recent case series report from a tertiary care center in Santiago suggests an increase in the number of cases of neurological damage associated with vitamin $B_{12}$ deficiency. However, the presence of anemia was not masked in the studied patients [37].

Conversely, our results may be conservative because we have not modeled a benefit of FA through possible prevention of cardiovascular disease as a result of lowered homocysteine levels [38]. Data from Chile indicate reduced plasma homocysteine levels among Chileans older than 70 years associated with an improvement in FA status following fortification [35]. At present, there is no consensus that folic acid has a causal effect on cardiovascular disease [39]. A new study reports that FA fortification in the United States and Canada has been associated with an improvement in stroke mortality [40]. If this association is confirmed, the economic benefits of FA fortification would be far greater than has been calculated in this or previous studies.

The results of this analysis favor the decision to fortify wheat flour folic acid in a middle income country in epidemiological transition. Whether this experience can be replicated in other developing countries deserves discussion of the factors that may have contributed to the success of the intervention. The long experience of the Chilean milling industry in fortifying wheat flour with iron and vitamin B complex as well as the relatively small number of existing mills facilitated the implementation and control of the program. The extended and high wheat bread consumption by the target population should also be taken into account, as fortification to be successful requires that the target population consume the food that is being fortified.

Another important factor in the success of a public health program is the burden of disease to be reduced. Chile has achieved a significant improvement in infant mortality during the last two decades as a result of a better control of infectious diseases and improvement in economic well being and nutrition of the population. With infant mortality close to 8.0 per 1000 live births, birth defects account for a greater share of infant mortality in Chile than in most developing countries. Likewise, with laws that forbid abortion, we expect a relatively higher contribution of congenital malformations to infant mortality in Chile than in many other countries with a similar level of infant mortality. Reducing the incidence of spina bifida may have contributed to a decrease in neonatal mortality in Chile. Infant mortality decreased to 8.33 per 1000 live birth in 2001 the year immediately after fortification was introduced, from 8.92 per 1000 live birth in year 2000. However, prevention of 20 spina bifida associated infant deaths (Table 3) only accounts for 12% of the observed reduction (0.07/0.59) in infant mortality for the periods.

In conclusion, the results of this economic evaluation strongly support the continuation of fortification of wheat flour with folic acid in Chile. Further, these finding serve as important evidence for policy makers from developing countries that have achieved low infant mortality rated, to consider the implementation of folic acid fortification of cereal grain products.

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