



Published in final edited form as:

Am J Prev Med. 2016 May ; 50(5 Suppl 1): S74–S80. doi:10.1016/j.amepre.2015.10.012.

Retrospective Assessment of Cost Savings From Prevention: Folic Acid Fortification and Spina Bifida in the U.S.

Scott D. Grosse, PhD¹, Robert J. Berry, MD, MPHTM¹, J. Mick Tilford, PhD², James E. Kucik, PhD, MPH³, and Norman J. Waitzman, PhD⁴

¹National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia

²Department of Health Policy and Management, Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, Little Rock, Arkansas

³Office of the Associate Director for Policy, CDC, Atlanta, Georgia

⁴Department of Economics, University of Utah, Salt Lake City, Utah

Abstract

Introduction—Although fortification of food with folic acid has been calculated to be cost saving in the U.S., updated estimates are needed. This analysis calculates new estimates from the societal perspective of net cost savings per year associated with mandatory folic acid fortification of enriched cereal grain products in the U.S. that was implemented during 1997–1998.

Methods—Estimates of annual numbers of live-born spina bifida cases in 1995–1996 relative to 1999–2011 based on birth defects surveillance data were combined during 2015 with published estimates of the present value of lifetime direct costs updated in 2014 U.S. dollars for a live-born infant with spina bifida to estimate avoided direct costs and net cost savings.

Results—The fortification mandate is estimated to have reduced the annual number of U.S. live-born spina bifida cases by 767, with a lower-bound estimate of 614. The present value of mean direct lifetime cost per infant with spina bifida is estimated to be \$791,900, or \$577,000 excluding caregiving costs. Using a best estimate of numbers of avoided live-born spina bifida cases, fortification is estimated to reduce the present value of total direct costs for each year's birth cohort by \$603 million more than the cost of fortification. A lower-bound estimate of cost savings using conservative assumptions, including the upper-bound estimate of fortification cost, is \$299 million.

Conclusions—The estimates of cost savings are larger than previously reported, even using conservative assumptions. The analysis can also inform assessments of folic acid fortification in other countries.

Address correspondence to: Scott D. Grosse, PhD, National Center on Birth Defects and Developmental Disabilities, CDC, 4770 Buford Highway NE, Mail Stop E-64, Atlanta GA 30341. sgrosse@cdc.gov.

No financial disclosures were reported by the authors of this paper.

Introduction

Periconceptional folic acid intake protects against two neural tube defects (NTDs), spina bifida and anencephaly.^{1,2} The U.S. Food and Drug Administration (FDA) mandated that cereal grain products labeled as enriched after 1997 be fortified with synthetic folic acid at a concentration of 140 μg per 100 g,³ which contributed to a 36% reduction of NTDs between 1996 and 2006.⁴ This article reports updated estimates of economic impacts in order to confirm the value of this policy, inform other potential mandates, and inform policy analyses for other countries considering food fortification.

Economic evaluation findings can help inform policy decisions about the funding of interventions for which evidence of effectiveness can be demonstrated.⁵ Prospective analyses of hypothetical benefits based on the modeling of expected health outcomes should be complemented by retrospective analyses of observed outcomes after a policy has been in place. Three prospective analyses projected 3%–10% reductions in NTDs from the FDA mandate based on models that assumed a threshold intake to reduce NTD risk.^{6–8} The actual reductions in NTDs following fortification costs were much larger, consistent with a dose–response inverse association of NTD risk with red blood cell folate concentration.^{9–11} Annual births with spina bifida or anencephaly were reported to have decreased by 23% between 1995–1996 and 1998–1999.¹² It was projected that fortification resulted in annual direct cost savings of \$143 million in 2002 U.S. dollars, mostly from fewer spina bifida cases.¹²

This analysis was conducted during 2015 and updates cost savings estimates that were published in 2005¹² for changes in costs, inflation, and survival; caregiving time costs; and more recent prevalence estimates. Unlike the previous study, estimates exclude both stillbirths and anencephaly, which is lethal after birth. Results are presented for both a base-case analysis in which all parameters are set to likely values and a worst-case scenario in which parameters are set to values that result in conservative estimates of cost savings.

Methods

Avoided Live-born Spina Bifida Cases

Base-case estimates of the reduction in spina bifida cases come from a 2015 CDC analysis of National Birth Defects Prevention Network data for 1995–1996 and 1999–2011. The prevalence of spina bifida among live births, stillbirths, and fetal deaths at 20 weeks registered in eight systems with prenatal ascertainment was reported to have decreased from 6.5 per 10,000 live births pre-fortification to 4.0 per 10,000 live births post-fortification.¹³ For the years 2004–2006, the ratio of live-born cases to all cases was 0.77 in three sites.¹⁴ Applying this ratio to all spina bifida cases, the frequency of live-born cases decreased from 5.04 to 3.10 per 10,000 births, a reduction of 1.94 cases per 10,000 live births. This reduction in birth prevalence, multiplied by 3,952,841 births in 2012,¹⁵ yields an estimated 767 annual affected births avoided as a result of fortification.

To calculate a lower-bound estimate of effectiveness, the number of live-born cases during 1995–1996 was lowered by 5%, to allow for a possibility of a greater proportional decrease

in outcomes other than live birth following fortification. That implies 667 live-born cases avoided each year, which is a 13% lower estimate of effectiveness.

Ready-to-eat (RTE) breakfast cereals accounted for approximately 4.4% of average red blood cell folate concentration among non-pregnant U.S. women aged 12–49 years during 2007–2012 (calculations available on request).¹⁶ RTE cereals are not subject to mandatory fortification with folic acid but may be voluntarily enriched with folic acid up to a limit of 400 μg per serving set by FDA in a food additives standard adopted in 1996.¹⁷ Mean red blood cell folate concentration among U.S. women aged 15–44 years rose by 54.5% between 1988–1994 and 1999–2006.^{18,19} Dividing 4.4% by 54.5% suggests that as much as 8% of the reduction in NTDs following fortification might have been due to voluntary fortification of RTE cereals, which followed the 1996 FDA rule making. The lower-bound estimate of the averted number of live-born cases attributed to the mandatory folic acid fortification component of the FDA policy was reduced by 8%, to 614.

Direct Costs for Live-born Spina Bifida Cases

This analysis follows U.S. cost-effectiveness analysis (CEA) guidelines in using the “societal” perspective and estimating avoided direct costs.²⁰ Direct costs include the difference in both medical and nonmedical services required by individuals with spina bifida and unaffected individuals. In addition, direct costs assessed from the societal perspective include costs incurred by families, which, according to U.S. guidelines, include the opportunity cost of time spent by unpaid family caregivers.²⁰ Two previous U.S. CEAs of folic acid interventions incorporated caregiver time costs.^{7,21} However, because caregiver time costs are excluded from direct costs by some analysts,²² estimates of cost savings that exclude caregiver time costs are also reported.

Estimates of per-person medical costs were adapted from an incidence-based cost-of-illness analysis of lifetime costs for individuals with spina bifida^{23,24} using findings from a subsequent analysis of claims data for adults with spina bifida.^{21,25} The present estimates incorporate improvements in survival among children and adolescents with spina bifida²⁶; survival probabilities beyond age 19 years were assumed to be the same as in the U.S. population. All costs were adjusted for inflation to 2014 U.S. dollars (Table 1).

The estimate of unpaid caregiver time costs comes from a survey in Arkansas during 2001–2002 of annual hours of paid work of primary parental caregivers of children and adolescents with spina bifida and demographically similar parents in the general population.²⁸ That study estimated that each live-born spina bifida case had a discounted present value of avoided lost parental economic output that of approximately \$159,000 in 2005 dollars,²⁸ which was adjusted to 2014 dollars (Table 1) and for increased child survival.

The lifetime direct cost of a live-born spina bifida case in 2014 dollars (rounded to the nearest \$100) is \$791,900, comprising \$513,500 in medical costs, \$63,500 in developmental services and special education costs, and \$214,900 in caregiver time costs (Table 1). Direct costs excluding caregiver time costs amount to approximately \$577,000.

Implications of Changes in Composition of Spina Bifida Births

Average cost per live-born spina bifida case may have changed with fortification, which was accompanied by increases in the proportion of cases of non-isolated spina bifida^{29,30} and decreases in the proportion of cases with upper-level (cervical or thoracic) lesions.^{30,31} Estimates of costs for subtypes of spina bifida, including by lesion level, were not available. Post-infancy hospitalization costs for children with spina bifida who have another major birth defect are roughly 1.5 times greater than for isolated spina bifida (E Radcliff, University of South Carolina, personal communication, 2014). Upper-level lesions are associated with higher parental time costs. If death during childhood is more common in upper-level spina bifida cases, as has been suggested,⁷ fortification may have contributed to a disproportionate reduction in infant and child deaths. For a sensitivity analysis, the estimates of direct medical and service costs were adjusted downward by 10% to reflect the possible impacts of more than proportional reduction in deaths, as spina bifida-associated costs associated with those infants who survive as a result of fortification should be subtracted from averted costs of live-born cases assuming no difference in survival rates.

Fortification Costs

The incremental cost of fortification is the product of the quantity of grain product and the unit cost of adding folic acid to the premix, which mills use to fortify enriched grain products. The cost of folic acid was estimated to be \$0.10–0.15 per metric ton of flour in 2013, \$0.20–0.30 per metric ton in 2014, and, owing to a shortage in early 2015, close to \$1.00 per ton as of May 2015 (Q Johnson, Quican, Inc., personal communication, 2015). With roughly 20 million metric tons of enriched foods, the estimated total cost of folic acid fortification each year was approximately \$2–3 million in 2013, \$4–6 million in 2014, and \$20 million in 2015. Those figures compare with previous estimates of \$3–4 million.^{7,12} The base-case model uses \$4 million and the worst-case scenario assumes \$20 million per year.

Results

The base-case estimate of the total direct cost averted each year is \$607 million, or \$442 million excluding caregiver time costs (Table 2). That assumes 767 averted live-born spina bifida cases and a constant cost per live-born case. With a lower-bound estimate of 614 live-born cases averted by mandatory fortification and the cost per live-born case lowered by 10%, the “worst-case” estimate of avoided direct costs is \$438 million overall or \$319 million excluding parental caregiver time costs.

The base-case estimate of net cost savings, after subtracting the estimate of \$4 million incremental cost of folic acid fortification from the estimate of averted direct costs, is \$603 million including the lost value of parental employment due to added caregiving responsibilities as is recommended, or \$438 million excluding caregiver time costs. Using lower-bound estimates of live-born cases and costs averted, which exclude parental caregiving costs, and using the upper bound estimate of \$20 million in fortification costs, net cost savings in the worst-case scenario is estimated to be \$299 million per year.

Discussion

Based on estimates presented here, fortification has had a larger societal return on investment than previously estimated. The base-case net cost savings estimate of \$607 million in 2014 dollars is 3.1 times larger than the previous estimate,¹² which is equivalent to \$195 million in 2014 dollars. The increase is explained by three differences in assumptions. First, the estimate of per-person incremental medical costs with spina bifida is 59% higher than the previous estimate in inflation-adjusted dollars, based on more complete expenditure data for adults with spina bifida²⁵ and increases in survival among children with spina bifida.²⁶ Second, the base-case inclusion of caregiver time costs as is recommended in U.S. CEA guidelines²⁰ raised the per-person direct cost estimate by 37%. Third, the estimated number of annual live-born cases of spina bifida avoided is 47% larger compared with the previous analysis. That analysis relied on published prevalence estimates from passive birth defects surveillance systems with less complete and accurate ascertainment compared with active surveillance programs that routinely ascertain prenatally diagnosed cases, including fetal deaths.

Exclusion of unpaid caregiving costs from the base-case analysis reduces the estimate of cost savings. However, reduction in caregiver time costs is an important “spillover” benefit to other family members, and exclusion of such effects can understate the economic impact of prevention.³² Even in the worst-case scenario using estimates that are least favorable to fortification, net cost savings are estimated at almost \$300 million per year. That estimate, which excludes lost parental productivity owing to caregiving responsibilities, takes into account the additional cost of spina bifida–associated care for infants who in the absence of fortification would have died. It has been argued by some that unrelated lifetime medical costs should also be included for avoided deaths.³³

The base-case estimates of costs savings may be conservative. In particular, individuals with thoracic or higher lumbar lesions may not be subject to significantly higher mortality. In a population-based 2001–2002 survey of Arkansas families with children and adolescents with spina bifida, 24.5% had upper-level lesions, which did not vary significantly by age.^{28,34} Unpublished cross-sectional data from the National Spina Bifida Patient Registry³⁵ indicate that upper-level lesions are very common among adolescents and adults with spina bifida born prior to 1999 and less common among younger children (R Valdez on behalf of the CDC National Spina Bifida Patient Registry team, personal communication, 2014).

Policy Implications

This retrospective analysis amplifies previous U.S. estimates of the economic benefits of mandatory folic acid fortification of cereal grain products labeled as enriched at the level of 140 μg per 100 g. However, despite that policy, U.S. Hispanic women with origins in Mexico and Central America consume fewer fortified foods and their children have elevated NTD prevalence.³⁶ Fortifying corn masa flour (dry alkali-processed maize flour³⁷), which is disproportionately consumed by less-aculturated Mexican American women,³⁶ could reduce the number of cases of NTDs in the U.S. by approximately 40 per year (range, 0–120).^{38,39} A CEA of corn masa fortification requires additional modeling, including

estimates of the numbers of avoided live-born spina bifida cases as well as the costs of fortifying corn masa flour.

The findings presented here could inform policy analyses for countries considering folic acid fortification. Although fortification has variable impacts on NTDs depending on folate status and NTD prevalence, which foods are fortified and at what level, and consumption of fortified foods, it has been a success in several countries.^{40–44} Incomplete data on costs of care for spina bifida can result in conservative estimates of avoided costs. For example, a CEA of fortification in Chile concluded that fortification was cost saving, although only the subset of surgical repair and rehabilitation costs through age 22 years were included (present value per birth of approximately \$20,000 in 2007 dollars).⁴⁵ A South African CEA calculated cost savings based on estimated treatment costs during infancy.⁴⁶ Therefore, the published estimates of cost savings from fortification in Chile and South Africa were very conservative. A newly published study estimated the potential cost savings from a hypothetical fortification policy in Germany, which reported that reducing spina bifida births by 40%–50% would save €26–33 million per year in direct costs.⁴⁷ That study adjusted the U.S. estimate of lifetime medical costs used in the present study²⁵ downward by 47% to account for lower healthcare costs in Germany.

Limitations

This analysis has several limitations. First, it relies on estimates of changes in the birth prevalence of spina bifida from eight surveillance systems located in different parts of the U.S. It is common not to report SEs or CIs for birth defects surveillance estimates because ascertainment biases are presumed greater in magnitude than random errors resulting from sampling variability.⁴⁸ The analysis used estimates from surveillance systems with prenatal ascertainment to minimize under-ascertainment.¹⁴ Although the resulting estimates of numbers of total cases with spina bifida are more robust than previous estimates, uncertainty in these parameter estimates was taken into account through sensitivity analyses to develop lower-bound or worst-case estimates.

The base-case analysis attributed all of the decline in live-born cases of spina bifida and associated direct costs to fortification. The assumption that the change in prevalence was not influenced by increased consumption of folic acid supplements is consistent with the absence of change in the use of folic acid-containing supplements by U.S. adults during the study period.⁴⁹ The assumption that changes in the frequency of elective termination of fetuses with spina bifida did not contribute to the decrease in the prevalence of live-born cases in the present analysis is consistent with the finding that the decrease in total spina bifida cases between 1995–1996 and 1998–2006 was greater in systems that included prenatal ascertainment of terminations and early fetal deaths than in systems without prenatal ascertainment.^{13,50}

Other potential limitations include the exclusion of non-NTD health outcomes. CEAs should include all health outcomes for which there is evidence of impact, both benefits and harms. Prospective economic assessments of fortification projected that folic acid fortification could “mask” vitamin B-12 deficiency, delay diagnosis, and adversely affect the neurologic status of older adults who have low vitamin B status.^{6,7,51} However, post-fortification empirical

evidence did not bear out those fears.^{44,52–54} Likewise, subsequent concerns that additional folic acid might increase the incidence of colorectal cancer were not confirmed.^{55,56}

Folic acid might also have had other favorable outcomes. In U.S. and Canadian data, the incidence of one rare cancer, Wilms tumor, decreased by 20%–26% following fortification.^{57,58} By contrast, although U.S. folic acid fortification was followed by significant reductions in selected non-NTD birth defects,⁵⁹ no significant reductions were observed in other countries.^{42,60} There is also a possibility, not confirmed, that folic acid fortification might have reduced the risk of stroke; an epidemiologic analysis found a roughly 10 percentage point additional reduction in stroke mortality in the U.S. during 1998–2002.⁶¹ Folic acid supplements, at higher doses, have been reported to reduce the occurrence of stroke by approximately 10% in areas with low folic acid intakes,^{62,63} and a recent trial found that folic acid supplements (800 µg per day) significantly reduced the risk of first stroke among Chinese adults with hypertension.⁶⁴

These findings are conservative as a measure of the economic benefit of folic acid fortification because they do not include either intangible benefits such as knowing that women and infants are protected from harm or the avoided “indirect” costs of lost productivity resulting from premature death and disability. Previous analyses that used the present value of average lifetime productivity to value averted deaths reported that the total economic benefit of NTD prevention is much larger than the reduction in direct costs alone.^{12,23} However, productivity measures understate the economic benefit of avoided deaths⁶⁵ and do not capture the economic benefits of avoided pregnancy outcomes other than live birth.⁶⁶

Conclusions

Fortification with folic acid is effective in preventing NTDs and saves hundreds of millions of dollars each year. The present estimates of cost savings are larger than in previous analyses owing to more complete counting of averted cases, costs, and inflation. Economic evaluation should form part of an iterative process in which assumptions are reassessed and updated as needed. Retrospective evaluations previously confirmed that the magnitude of benefit was even larger than had been assumed prior to fortification. The new evidence presented here warrants consideration by decision makers in other parts of the world who might consider fortification policies to reduce the occurrence of NTDs.

Acknowledgments

The authors acknowledge Krista Crider, Peggy Honein, Cara Mai, Joe Mulinare, and Sarah Tinker for substantive comments on previous versions of the manuscript.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

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Table 1

Parameter Estimates and Sources

Parameter	Point estimate	Sources
Prevalence of spina bifida in 1995-1996 in systems with prenatal ascertainment	6.5 per 10,000 births	13
Prevalence of spina bifida in 1999-2011 in systems with prenatal ascertainment	4.0 per 10,000 births	13
Percentage of live births among spina bifida cases in systems with prenatal ascertainment during 2004-2006	77.0%	14
Annual births in 2012	3,952,841	15
Ready-to-eat breakfast cereals share of average RBC folate concentration among non-pregnant U.S. women aged 12-49 years during 2007-2012	4.4%	16
Increase in mean RBC folate concentration among U.S. women aged 15-44 years between 1988-1994 and 1999-2006	54.5%	18
Base-case fortification cost	\$4 million	Expert opinion
Worst-case fortification cost	\$20 million	Expert opinion
Cost components for live-born infants with spina bifida (present value, 2014 U.S. dollars, rounded to nearest 100)		
Medical	\$513,500 ^a	25,27
Special education and developmental services	\$63,500 ^b	24
Parental time cost	\$214,900 ^c	28
Total	\$791,900	–
Excluding caregiver time cost	\$577,000	–

RBC, Red blood cell.

^aAdjusted for inflation using the Bureau of Economic Analysis Personal Consumption Expenditures health care deflator, available at www.bea.gov/, Table 2.3.4, Price Indexes for Personal Consumption Expenditures by Major Function (series DHLTRG).

^bAdjusted for inflation using the Bureau of Labor Statistics Employment Cost Index for state and local government employees employed in educational services, available from www.bls.gov/web/eci/echistrynaics.pdf, Table 7.

^cAdjusted for inflation using the Bureau of Labor Statistics Employment Cost Index for all civilian workers, available from www.bls.gov/web/eci/echistrynaics.pdf, Table 4.

Table 2

Summary of Annual Averted Direct Costs and Cost Savings (2014 U.S. dollars)

Scenario	Number of live births averted	Total direct cost per birth with spina bifida averted (nearest \$100)	Total direct cost averted (nearest \$100,000)	Cost savings (reduction in direct costs, nearest \$100,000)
Base-case	767	791,900	607.3 million	603.3 million
	767	577,000 ^a	442.4 million ^a	438.4 million ^a
Worst case	614	712,700	437.5 million	417.5 million
	614	519,300 ^a	318.8 million ^a	298.8 million ^a

^aExcluding caregiver time costs

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