Draft

The Costs and Benefits of Folic Acid Fortification in the United States: Economic Analysis, Regulatory Action, and Public Health

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Abstract

The United States Food and Drug Administration (FDA) required that as of January 1, 1998, manufacturers of enriched cereal-grain products fortify their products with folic acid to reduce the number of pregnancies affected by a neural tube defect (NTD). Prior to adoption of the regulation in 1996, three economic evaluations projected the net economic benefits or cost savings of folic acid fortification. The expected percentage decline in NTDs in these three studies was between 2.6% and 10.5%. Birth defects surveillance data indicate that since fortification there has been a 20% to 30% decline in births with either spina bifida or anencephaly. We estimate that folic acid fortification is associated with an economic benefit of $425 million per year in the United States and constitutes a major public health success that has resulted from regulatory action.

Introduction

On March 5, 1996, the United States Food and Drug Administration (FDA) required that by January 1, 1998, manufacturers of enriched cereal-grain products fortify their products with 140 micrograms of folic acid per 100 grams of cereal-grain product.[1] This decision invoked the regulatory power of the federal government to ensure that women at risk of becoming pregnant would be provided effective access to a nutrient that can prevent a substantial proportion of neural tube defects (NTDs).[2]

Prior to the adoption of the fortification regulation in 1996, three economic evaluations projected that positive net economic benefits would result from fortification.[3-5] To date, no analysis has evaluated the costs and benefits realized by implementation of fortification. We find that the actual economic benefits substantially exceed the forecasted benefits.

Economic evaluation and the policy process

Economic evaluation plays an important role in translating research findings into practice and policy. Economic evaluations can be either *ex ante*, conducted prior to the adoption of a policy on the basis of results from pilot studies and theoretical assumptions, or *ex post*, carried out after implementation utilizing information on observed outcomes. Only rarely are the findings of ex ante economic analyses compared with the actual results of policies.

Since the Reagan administration, the Executive branch has required federal regulatory agencies to conduct a regulatory impact analysis (RIA) of proposed rules. Under Executive Order 12866 signed in 1993, "significant regulatory actions" are to be accompanied by an assessment of expected costs and benefits.[6]

Two major types of methods of economic evaluation are used to inform policy decisions affecting public health and safety. One is cost-benefit analysis (CBA), also commonly referred to as benefit-cost analysis. A CBA values all outcomes in monetary terms, including deaths and cases of disease averted. The other type of study is cost-effectiveness analysis (CEA). A CEA calculates the ratio of net costs (intervention costs minus medical and other direct costs averted from prevention) to the numbers of health outcomes.[7] Health outcomes can be expressed in natural units (e.g., deaths averted) or in terms of a combined measure such as quality-adjusted life years or QALYs.

Until recently, regulatory analyses have mostly taken the form of CBAs. In contrast, most studies published in medical or public health journals have been CEAs. In September 2003, the Office of Management and the Budget directed agencies to begin using both CEA and CBA, where feasible, "for all major rulemakings for which the primary benefits are improved public health and safety."[8-9]

Economic evaluations do not necessarily determine regulatory decisions. Each federal agency is governed by specific legislation. In particular, the Food, Drug, and Cosmetic Act requires FDA to base regulatory decisions on safety and efficacy.[10] For food additives, FDA follows a safety standard of a reasonable certainty of no harm and does not take into account projected economic benefit..

Folic Acid and Health Outcomes

Between 1981 and 1992, several studies reported that consumption of vitamin supplements containing folic acid prior to conception was associated with a reduction of 50% to 75% of cases of spina bifida and anencephaly.[11-15] More conclusively, a multi-center randomized trial in 1991 demonstrated that folic acid protects against recurrence of

NTD-affected pregnancies.[16] A randomized controlled trial in Hungary in 1992 found that multivitamins containing folic acid have a protective effect on NTDs in women without a previously affected pregnancy.[17]

Based on this evidence, the United States Public Health Service (PHS) issued a recommendation in September 1992 that all women capable of having children consume 400 micrograms per day (mcg/d) of folic acid to reduce the numbers of pregnancies affected by spina bifida and other NTDs.[18] Although folic acid can be obtained through consumption of vitamin supplements, up to 50% of pregnancies are unplanned and the simplest approach to ensuring that women are protected is to routinely add folic acid to commonly consumed foods.

Any intervention needs to be evaluated for risks of harm. The major concern with adding folic acid to foods is that individuals with undiagnosed vitamin B_{12} deficiency could possibly be delayed in receiving a diagnosis. The fear is that high intakes of folic acid could "mask" the hematologic sign of anemia while allowing neurological damage to proceed untreated.[2] Folic acid shares a metabolic pathway with vitamin B_{12}, and the anemia associated with vitamin B_{12} deficiency can be resolved by increasing the intake of folic acid. Prolonged deficiency of vitamin B_{12} can result in neurological damage which, if left untreated, can be disabling and irreversible.

No direct evidence exists of "masking" of vitamin B_{12} deficiency by folic acid intakes.[19] It is known from older studies that certain individuals with known vitamin B_{12} deficiency who received folic acid alone experienced neurological damage without anemia. The Institute of Medicine has concluded that the lowest level of folic acid intake for which adverse effects have been demonstrated among individuals with vitamin B_{12}

deficiency is 5 milligrams per day (mg/d); due to uncertainty the safe upper level for consumption was set at 1 mg/d due to uncertainty.[20] FDA likewise adopted a level of 1 mg/d as the safe upper level of intake but applied this threshold to total folate intake, not synthetic folic acid alone.[21-22]

Ex ante economic evaluations of folic acid fortification

Three economic evaluations were prepared prior to the 1996 decision to require folic acid fortification of enriched cereal grain products. A CBA was prepared by FDA staff and published in the Federal Register in October 1993.[3] A second CBA was published in 1995 by University of California researchers.[4,23] Third, a CEA was published in 1996 by CDC researchers.[5] Both the California and CDC analyses were presented to the FDA Folic Acid Subcommittee prior to their publication.

The three ex ante economic studies all projected net economic benefits of fortification. Table 1 summarizes the results of the three studies for the then-proposed fortification level of 140 mcg of folic acid per 100 grams of cereal-grain product (140 mcg/100 g). The estimate of net monetary benefit in the two CBA studies was roughly $700 million in the FDA analysis and $100 million in the California analysis. The CDC analysis, which was a CEA, did not calculate net monetary benefit, but did estimate $5 million in direct cost savings. The discrepancy between the FDA and California estimates was driven largely by differences between the willingness-to-pay (WTP) method used in the FDA analysis and the cost-of-illness (COI) method used in the California study. The FDA's approach valued deaths averted according to the estimated average wage premium to compensate for risk of fatal occupational injuries, which at the time was cakulated to be $5 million per death averted.[3] The California approach valued deaths according to lost

productivity in future years discounted to present values using a 5% discount rate, which in 1991 was calculated to be $342,500 at birth.[23]

The three studies utilized similar estimates of the cost of fortification. The annual cost of fortificant was assumed to be $4 million in the FDA and CDC analyses and $3.3 million in the California analysis. All three analyses assumed $2.5 million in analytic testing. The major difference was in the cost of changing food labels. In the FDA analysis this was a one-time cost of $20 million, which was converted to an annualized cost of $800,000 per year in perpetuity in the California analysis and $4.5 million in annualized cost in the CDC study. The California study also assumed that surveillance of adverse effects would be funded at a level of $5 million per year

The analyses differed with regard to the expected costs of adverse effects among adults with undiagnosed vitamin B_{12} deficiency. The FDA analysis assumed no adverse effects with fortification at 140 mcg/100 g. Projections of costs of adverse health effects were much higher in the California study ($16.4 million) than in the CDC study ($350,000). The two studies differed both for the numbers of cases of adverse effects, 500 and 89, respectively, and the average cost per case of neurological damage, $33,500 and $3,900, respectively. The disparity in estimates reflects the lack of accurate information on which to make projections.

Fortification and NTD rates, ex ante and ex post

All three ex ante analyses projected modest percentage reductions in NTD rates that would result from fortification at 140 mcg/100 g. The range of estimates was from 2% to 10% (Table 1). All three analyses assumed that half of NTDs could be prevented if women consumed 400 mcg/d of folic acid or folate and that fortification at 140 mcg/100

g would increase average folic acid intake by 100 mcg/d, but they varied with regard to whether dietary folate intakes are protective and how many women would reach a protective level of intakes.

Following the full implementation of folic acid fortification in the United States in January 1998, analyses of birth defects surveillance data have estimated substantially larger reductions in NTD, between 20% and 30%. Data on births with spina bifida and anencephaly from programs without prenatal diagnosis indicate a reduction of 23% between 1995-96 and 1998-99, and programs that included information on prenatally ascertained cases recorded a 30% reduction in NTDs.[24]

Why the difference between the projected outcomes and the observed reductions? First, rather than the projected average increase in intake of 100 mcg/d, the average increase in intake in the U.S. adult population may be closer to 200 mcg/d, estimated on the basis of observed changes in serum folate levels.[25] Analysis of folate in enriched foods reveals that certain foods contain more than the expected amount, with enriched bakery products reported to contain 40% to 100% more folic acid than stated.[26] Vitamin supplements and breakfast cereals that are voluntarily enriched with 400 mcg of folic acid per serving may have also contributed, although the contribution of supplements is believed to be quite small. Surveys conducted by the March of Dimes revealed only a small increase during this period in consumption of supplements containing folic acid by women of childbearing age, rising from 28% in 1995 to 32% in 1998 and remaining at that level through 2003.[27-28]

Second, and more importantly, the ex ante economic analyses were all very conservative in epidemiological modeling of the folate-NTD association owing to lack of

information on a dose-response curve. All three analyses assumed that only women consuming =400 mcg/d would have a reduced risk of having a NTD-affected pregnancy. Data from Ireland were subsequently published that showed a dose-response relation between blood folate levels and NTD risk.[29] Based on those data and other assumptions, a 100 mcg/d increase in folic acid consumption would be expected to lead to a reduction in NTD rates in the United States of 13%[25] to 22%[30], while a 200 mcg/d increase would be associated with a 23%[25] to 41%[30] reduction.

The California study projected a greater percentage reduction in NTDs than the CDC study largely because it treated natural folate and synthetic folic acid as equivalently effective. The CDC study conservatively assumed that only synthetic folic acid would provide protection against NTDs. It has long been known that natural folate is limited in bioavailability compared to folic acid. The Institute of Medicine recently concluded that the bioavailability of folic acid is 1.7 times greater than that of dietary folate.[20] Thus, dietary folate has some protective effect against NTDs, but substantially less than that of folic acid.

Canadian authorities also mandated folic acid fortification of flour and pasta in 1998 at 150 mcg/100 g of flour and 240 mcg/100 g of pasta. The reported percentage reductions in NTDs (spina bifida and/or anencephaly) in provinces in the eastern half of Canada are 32% in Quebec,[31] 47% in Ontario,[32] 54% in Nova Scotia,[33] and 78% in Newfoundland,[34] each of which is higher than that reported in the United States. In each province, the post-fortification NTD rate among pregnancies was approximately 1 per 1000, similar to the U.S. rate prior to fortification. The higher the baseline NTD rate, the greater the percentage decline with increased folic acid intakes. Similarly, folic acid

supplementation in a community trial in China resulted in a 81% decline in a northern project area with a high baseline NTD rate and a 41% decline in a southern project area with a low baseline rate, with similar post-supplementation rates in both areas.[35]

Ex post economic evaluation of fortification

We have performed an ex post economic evaluation of folic acid fortification. In line with the OMB guidance recommending that both CEA and CBA be used to evaluate regulatory actions affecting public health, we present estimates in both forms. First, we employ the same COI method used in the California ex ante CBA study. We did not attempt to replicate the FDA analysis, because of concerns about the applicability of the statistical life valuation method. Second, we present calculate the reduction in averted direct costs, which can be directly compared with the CDC ex ante CEA study.

We excluded NTD-affected pregnancies not ending in live birth because of the relatively low direct costs and difficulties with the attribution of indirect costs, as well as the issue of costs associated with replacement births. Birth defects surveillance data indicate reductions each year of approximately 612 births affected by NTDs following fortification, including 520 with spina bifida and 92 with anencephaly.[24]

Not all the reduction in NTDs can be attributed to fortification, since some contribution presumably has come from increases in use of vitamin supplements and of consumption of breakfast cereals with 400 mcg of folic acid per serving. Our base case analysis assumes that the observed reduction in NTD births is due entirely to fortification, which sets an upper bound to the benefit estimate, which is varied in a sensitivity analysis

Our updated estimates of the costs of spina bifida are described in a book chapter devoted to that topic.[36] The cost estimates use a 3% discount rate to adjust projected

lifetime costs in future years to present value, which is the current standard in public health. In 2002 dollars, the lifetime cost associated with a birth with spina bifida is estimated at $636,000. Of this amount, $279,000 represents lifetime direct costs, mostly medical, and do not include caregiving time costs. For anencephaly, the total cost is $1,020,000, including $1,014,000 in indirect costs[37] and $6,000 in average hospital costs for births with anencephaly[5] updated to 2002 prices.

The actual cost of fortification is lower than was projected in the ex ante analyses. No evidence exists that food manufacturers are spending additional money on analytic testing of enriched cereal-grain products because of folic acid. Likewise, surveillance of adverse effects was not funded. The cost of food label changes was presumably lowered by the fact that manufacturers were given an 18-month window in which to change nutrition labels. Finally, the cost of bulk folic acid is now lower than it was in the early 1990s; the estimated cost per ton of flour is one third lower than that estimated in the California study (Peter Ranum, MS, oral communication, August 7, 2004). This indicates an estimated annual folic acid fortificant cost of $2.2 million. The sum of fortificant cost and an annualized cost of $800,000 for nutrition label changes yields an estimate of total fortification costs of $3 million per year.

We have not calculated costs associated with possible adverse health effects because of the absence of evidence that adverse effects have occurred. Although higher than projected intakes of folic acid presumably put more people at risk, the projections likely overstated the number of people at risk. Empirical post-fortification information is limited. A study conducted in one U.S. health care system found no reduction in diagnoses of anemia among people with vitamin B_{12} deficiency following fortification, as

would have been expected if masking had occurred.[38] We cannot rule out the possibility that some adverse effects might have occurred, although it seems likely that alert clinicians would have detected this if it were a widespread phenomenon.

Our findings are summarized in Table 2. Following the CBA approach, the total economic benefit from reduction in the number of NTDs following folic acid fortification is estimated to be $425 million per year. Subtracting fortification cost of $3 million per year, the net monetary benefit is $422 million. This compares with an estimate of $94 million in the California study. We do not have data on costs associated with possible cases of masked anemia of vitamin B_{12} deficiency.

For our CEA estimates, we calculated direct cost estimates. Our preliminary estimate is that the averted costs of care for children born with spina bifida amount to $145 million per year. Subtracting $3 million for fortification yields net cost savings of $142 million per year, which compares with an estimate of $5 million in cost savings from the CDC ex ante study. The latter study also projected that there would be an annual gain of 898 QALYs resulting from fortification, which included projected gains from prevention of termination of pregnancies. Including only the QALY gains from the prevention of births with spina bifida or anencephaly and using the same per-person QALY weights as in the previous CDC study, we project that each year's birth cohort gains 10,234 QALYs as a result of folic acid fortification.

These estimates imply savings in averted direct costs of more than 40 dollars for every dollar on average spent on fortification. This does not take into account money spent on research, public promotion of folic acid consumption, or evaluation through birth defects surveillance. Nonetheless, few public health interventions, other than

immunizations, are found to be cost saving in terms of lower total costs of care including the cost of the intervention.[39] Folic acid fortification is unusual among public health interventions in the magnitude of economic benefits.

Sensitivity analyses

Our analysis is subject to two major areas of uncertainty. One is the lack of information on potential, undocumented cases of neurological damage secondary to untreated pernicious anemia. We have presented an analysis based on the best available data, which provides no evidence of an increase in such cases. If adverse effects had indeed occurred to the extent modeled in the California ex ante analysis, our estimates of net benefits and cost savings would be reduced by $25 million each, leaving net benefit at $400 million per year and cost savings at $117 million. This sensitivity analysis indicates that our estimates of economic benefit do not substantially depend on this factor.

A second area of uncertainty is the number of NTDs prevented that can be attributed to mandatory folic acid fortification. As noted, multivitamin supplement use increased from 28% of women of reproductive age in 1995 to 32% in 1999, a small increase. In the absence of information on the consumption of folic acid from foods voluntarily enriched at higher levels (e.g. certain breakfast cereals), we cannot calculate the relative contribution. For the purpose of sensitivity analysis, we assumed that 20% of the observed decrease in NTDs might be due to other sources of increased folic acid intake. On the basis of this assumption, our estimates of net benefit and net cost savings would be reduced to $340 million and $116 million, respectively.

Discussion

Ex post economic evaluations are underutilized in the regulatory arena. Because they are not required, few economic analyses are conducted after a regulation is adopted. Public health policy making could be enhanced by the ongoing economic evaluation of policies, regulatory or otherwise. Certain policies turn out to be less effective and cost-beneficial than expected, whereas other policies, including folic acid fortification, are revealed to have generated substantially more economic benefits than anticipated.

Three independent economic evaluations all concluded that folic acid fortification at 140 mcg/100 g would yield net economic benefits or cost savings,[3-5] a conclusion confirmed by subsequent evidence. The FDA choice of level of fortification was not based on calculations of net economic benefit but on the basis of the safety standard that no group of people would be likely to be harmed. The FDA in 1996 cited the California team's projection of 500 annual adverse effects from fortification at 140 mcg/100 g but chose not to take this into account in projecting the costs and benefits of fortification.

The decrease in numbers of NTDs following fortification was greater than that projected by the ex ante analyses. In part, this probably reflects a higher level of folic acid intakes than expected. The greater reduction in NTD numbers also reflects the conservative nature of the models used to project declines in numbers of NTDs from increased folic acid intakes. Economic evaluations in public health depend on epidemiologic data and assumptions, which play a crucial role in determining the magnitude of cost-benefit or cost-effectiveness.

Estimates of net benefit depend on how costs and benefits are calculated. We have followed the COI method of valuation of health outcomes, which is a conservative

approach to valuing health outcomes. Use of the WTP method could lead to a higher estimate of economic benefit of fortification, but validated WTP estimates for the prevention of lethal or disabling congenital conditions are not available. Several of the advantages and limitations of each health valuation approach have been reviewed.[7,9]

We have presented an analysis based on the best available data regarding outcomes following folic acid fortification. Although alert clinicians have not detected an unusual occurrence of neurological damage due to untreated pernicious anemia, conclusive evidence would require systems to monitor this outcome. Nonetheless, our sensitivity analysis indicates that even if adverse effects had occurred to a larger extent than seems likely, it would have a very small effect on our estimates of net economic benefit.

In conclusion, folic acid fortification has proven to be a public health success story in the United States and Canada. The net economic benefit and cost savings resulting from the prevention of these deadly and disabling birth defects far surpass estimates prepared prior to the implementation of fortification in the United States. For every dollar that has been spent on folic acid fortification in the United States, at least 40 dollars will be saved in avoiding the costs of providing care to children with spina bifida who instead were born healthy as a result of their mothers' consumption of fortified foods prior to conception. This does not take into account the prevention of anguish to parents who lose a child to death from spina bifida or anencephaly. By any measure, folic acid fortification provides excellent value and a remarkable return on investment. Other industrialized countries could benefit by following the lead of the United States and Canada in adopting folic acid fortification of cereal grain products.

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Table 1. Summary of Ex Ante Economic Evaluations of Folic Acid Fortification at 140 µg/100 g

Study (currency year)	# NTDs averted (% reduction)	# cases neurological damage	Benefit from NTD prevention	Fortification costs	Adverse health effects costs	Net benefit
FDA (not stated)	116 (4.6%)	0	$651m-$786m	$27m	NA	$624m-$759m
California (1991)	304 (10.5%)	500	$121.5m	$10.5m	$16.4m	$93.6m
CDC (1993)	89 (2.3%)	89	$16.1m	$11m	$350,000	$4.7m

Table 2. Summary of Ex Post Economic Evaluation of Folic Acid Fortification at 140 µg/100 g in 2002 dollars

NTD-affected births	# NTDs averted	Total cost per NTD birth (direct cost)	Total benefit	Net benefit (minus $3m in cost)	Total direct cost	Cost savings (minus $3m in cost)
Spina Bifida	520	$636,000 ($279,000)	$331m		$145m	
Anencephaly	92	$1,020,000 ($6,000)	$94m		$1m	
Both	612		$425m	$422m	$146m	$143m