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Estimate of the potential impact of folic acid fortification of corn masa flour on the prevention of neural tube defects

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Abstract

Background—Hispanics in the US have a higher prevalence of neural tube defect (NTD)-affected pregnancies than non-Hispanic whites, and lower median total folic acid (FA) intake. FA fortification of corn masa flour (CMF) is a policy-level intervention for NTD prevention; however, the impact on NTD prevalence has not been estimated.

Methods—We developed a model to estimate the percentage reduction in prevalence of spina bifida and anencephaly that could occur with FA fortification of CMF. Model inputs included estimates of the percentage reduction in prevalence attributed to FA fortification of enriched cereal grain products (ECGP) (1995–1996 vs. 1998–2002), the increase in median FA intake after ECGP fortification, and the estimated increase in median FA intake that could occur with CMF fortification at the same level as ECGP (140μg/100g). We used Monte Carlo simulation to quantify uncertainty. We stratified analyses by racial/ethnic group and rounded results to the nearest 10.

Results—We estimated CMF fortification could prevent 30 Hispanic infants from having spina bifida (95% uncertainty interval: 0,80) and 10 infants from having anencephaly (95% uncertainty interval: 0,40) annually. The estimated impact among non-Hispanic whites and blacks was smaller.

Conclusions—CMF fortification with FA could prevent from 0 to 120 infants, with the most likely value of approximately 40, from having spina bifida or anencephaly among Hispanics, the population most likely to benefit from the proposed intervention. While this estimated reduction is unlikely to be discernible using current birth defect surveillance methods, it suggests an important benefit to the target population.

Keywords

neural tube defects; folic acid; fortification; prevention

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INTRODUCTION

Folic acid (FA) has been demonstrated in randomized-controlled trials (Czeizel, 1998; MRC Vitamin Study Research Group, 1991) and population-based observational studies to prevent neural tube defects (NTDs) if taken periconceptionally (Milunsky et al., 1989; Mulinare et al., 1988; Smithells et al., 1983). The United States mandated that all enriched cereal grain products (ECGP) be fortified with FA to reduce the risk of women having an NTD-affected pregnancy (U.S. Administration, 1996a) resulting in a 36% decrease in the prevalence of spina bifida and a 17% decrease in anencephaly (Centers for Disease Control and Prevention, 2004). In the United States, Hispanics have a higher prevalence of NTD-affected pregnancies than non-Hispanic whites and non-Hispanic blacks (Williams et al., 2005). Relative to non-Hispanic whites, Hispanics in the United States have a lower level of total FA intake (Tinker et al., 2010) and lower concentrations of serum folate and red blood cell folate (Pfeiffer et al., 2007). There have been calls for NTD prevention efforts to focus on the Hispanic population to address this disparity (Fleischman et al., 2011). Efforts to date have focused on behavior change campaigns (Flores et al., 2007); however, these campaigns can be costly, difficult to sustain, and do not typically result in large changes in overall FA consumption (Prue et al., 2010; Schwarz et al., 2008). Therefore, other methods to increase FA intake among this population have been explored, including the policy-level intervention of FA fortification of corn masa flour (CMF), a commodity with higher intake among the Hispanic population than other racial/ethnic groups (Hamner et al., 2009). To assess the potential impact of CMF fortification with FA, we estimated the annual number of NTDs (spina bifida and anencephaly) that could potentially be prevented by this measure in the United States.

METHODS

Model overview

We developed a model to estimate the number of NTDs that could be prevented annually in the United States if CMF were fortified with FA at 140μg/100g, the current level of FA fortification of ECGP in the United States (U.S. Food and Drug Administration, 1996a). We based the model on the ratio of the decrease in NTD prevalence observed after implementation of FA fortification of ECGP relative to the estimated increase in the median daily usual FA intake that occurred after ECGP fortification. We applied this ratio to an estimate of the increase in median daily usual FA intake that could occur if CMF were fortified at the proposed level. We calculated all estimates separately for spina bifida (without anencephaly) and anencephaly and for each of the three largest racial/ethnic groups in the United States (non-Hispanic whites, non-Hispanic blacks and Hispanics).

We estimated the expected percentage decrease in the prevalence of each NTD (PD_{CMF}) for each racial/ethnic group using the equation:

$$PD_{CMF} = \left(PD_{ECGP} \Big/ IM_{ECGP} \right) * IM_{CMF} \quad \text{[Equation 1]}$$

where PD_{ECGP} is the percentage decrease in the prevalence of the NTD observed after ECGP fortification; LM_{ECGP} is the increase in the median usual daily FA intake observed after ECGP fortification; and LM_{CMF} is the estimated increase in the median usual daily FA intake with FA fortification of CMF.

We built into the model a threshold level above which additional FA has no additional impact, to account for a woman's baseline level of FA intake. Because this threshold level is unknown, we considered this value uncertain in the modeling effort. We modeled the uncertainty associated with this parameter using a trapezoidal uncertainty distribution with a minimum at 160μg, mode 1 at 210μg, mode 2 at 350μg, and a maximum at 400μg. We incorporated the resulting distribution for the uncertain threshold into the Monte Carlo-based estimation of total uncertainty associated with the estimates described in detail below. We based the lower bound for the distribution of the threshold, 160μg, on the current median usual daily total FA intake among Mexican American women aged 15–44 years who do not use supplements (Hamner et al., 2012) (data were not available for all Hispanics, but Mexican Americans make up approximately 63% of all Hispanics in the United States) (Ennis et al., 2010). Limited available evidence suggests that, on a population level, there may be no additional benefit to increasing FA intake above current consumption amounts (Ahrens et al., 2011; Mosley et al., 2009), in which case fortification of CMF would impact only women with intake below the current median. However, because these studies had small case counts and therefore large uncertainty in their estimates, we considered 400μg as the maximum level for the threshold, as this was the amount used in the largest cohort study demonstrating the preventive effect of FA (Berry and Li, 2002), and it is the amount recommended for all women of childbearing potential by the U.S. Public Health Service (Centers for Disease Control and Prevention, 1992) and the Institute of Medicine (Institute of Medicine, 1998). In a sensitivity analysis, we also considered a maximum level for the threshold of 800μg, as this was the amount used in the first randomized-controlled trial demonstrating the preventive effect of FA on the first occurrence of NTDs (Czeizel and Dudas, 1992) and the upper end of the amount recommended by the U.S. Preventive Services Task Force (U.S. Preventive Services Task Force, 2009).

We estimated the number of pregnancies affected by each NTD ($NTD_{TpostECGP}$) among mothers in each racial/ethnic group with FA intake at or below the sampled threshold level (T) using the following equation:

$$NTD_{TpostECGP} = (p_{NTD} * lb * prop_T) \quad \text{[Equation 2]}$$

Where p_{NTD} is the current racial/ethnic-specific prevalence of the NTD; *lb* is the number of live births in the racial/ethnic group in 2009, and $prop_T$ is the proportion of women of childbearing age in the racial/ethnic group with daily usual FA intake at or below the sampled threshold level.

We estimated the number of each NTD that could potentially be prevented with FA fortification of CMF at the proposed level among each racial/ethnic group using the equation:

$$Number\ of\ NTDs\ prevented = NTD_{TpostECGP} * PD_{CMF} \quad \text{[Equation 3]}$$

(Please see Appendix 1 for numerical example using Equations 1 – 3.)

Model inputs

We identified and utilized inputs (Table 1) if they met the following criteria: 1) published in peer-reviewed journals; 2) provided national-level estimates; 3) provided estimates stratified by the racial/ethnic groups.

NTD prevalence decrease with ECGP fortification (PD_{ECGP})—We used published national estimates for the prevalence of spina bifida and anencephaly before (1995–1996) and after (October 1998–December 2002) fortification of ECGP among non-Hispanic whites, non-Hispanic blacks, and Hispanics (Williams et al., 2005). These post-fortification estimates are the most recent national-level race/ethnicity-specific spina bifida and anencephaly prevalence estimates available in a peer-reviewed publication.

Increase in FA intake with ECGP fortification (LM_{ECGP})—We used published national estimates for the median daily usual total folate intake (naturally-occurring food folate and synthetic FA) among women aged 15–44 years before (1988–1994) and after (1999–2000) fortification of ECGP, for each of the three racial/ethnic groups included in the analysis (Bentley et al., 2006). For the estimate of FA intake among Hispanics, we used data on Mexican Americans, as these estimates were all that were available. These estimates include intake from naturally-occurring food folate and synthetic FA from fortified foods and supplements. The difference in the estimates of median intake before and after implementation of ECGP fortification can most likely be attributed only to increases in synthetic FA from fortified ECGP.

Increase in FA with fortification of CMF (LM_{CMF})—We estimated the current median daily usual total FA intake in the United States and the median daily usual total FA intake with fortification of CMF with FA at the modeled level of 140μg/100g among women age 15–44 years, by race/ethnicity, using data from the 2001–2008 National Health and Nutrition Examination Study (NHANES) (Hamner et al., 2009).

Estimate of NTDs potentially preventable with additional FA ($NTD_{TpostECGP}$)—We derived model inputs for the post fortification prevalence of each NTD among each racial/ethnic group (p_{NTD}) based on published estimates (Williams et al., 2005). We obtained the number of live births for each racial/ethnic group (*lb*) in 2009 from the National Vital Statistics Report (Martin et al., 2011). We estimated the percentage of women aged 15–44 years in each racial/ethnic group with usual daily total FA intake at or below the range of possible threshold values ($prop_T$), in intervals of 10 μg (i.e. 160 μg,…400 μg) using data from the 2001–2008 NHANES (National Health and Nutrition Examination Survey (a–d), 2012); please see table in Appendix 2 for values. Methods for estimation of the percentiles are described in detail elsewhere (Tinker et al., 2010).

Monte Carlo simulation

Uncertainty distributions for all model inputs, with the exception of the threshold FA level described above, were assumed to be normal with means and standard deviations set to the corresponding estimates from each of the data sources (Table 1). We used the previously described trapezoidal distribution to model uncertainty associated with the FA threshold value. We imposed certain restrictions on the samples drawn in the Monte Carlo simulations: 1) correlation was induced between pre- and post-fortification NTD prevalence by restricting the Monte Carlo sample for the possible post-fortification prevalence to be equal to or less than the pre-fortification prevalence; 2) similarly, samples for the post-fortification median usual daily FA intake were restricted to be equal to or exceed the corresponding Monte Carlo sample for the pre-fortification intake.

We estimated uncertainty in model outputs using a Monte Carlo sampling approach in which 10,000 random draws were selected from each of the assumed uncertainty distributions for the model inputs, subject to the constraints above. We calculated the estimated reduction in NTDs due to CMF for each draw of the input parameters resulting in 10,000 realizations for the model output reflecting uncertainty in the estimates due to lack of knowledge concerning the input parameters. We summarized the resulting estimated uncertainty distribution for the number of each NTD prevented using the median of the distribution of the 10,000 estimates produced in the Monte Carlo process and a 95% uncertainty interval composed of the 2.5th and 97.5th percentile values of this distribution. We rounded all estimates to the nearest 10.

RESULTS

Using the model described above, we estimated that among Hispanics fortification of CMF with FA in the United States at 140μg/100g could prevent from 0 to 120 infants, with the most likely value of approximately 40, from having spina bifida or anencephaly (Table 2). An estimated median value of 30 infants could be prevented from having spina bifida (95% uncertainty interval: 0, 80) and 10 infants from having anencephaly (95% uncertainty interval: 0, 40), resulting in prevalence decreases of 6% (95% uncertainty interval: 0, 19%) and 4% (95% uncertainty interval: 0, 15%), respectively, among Hispanic women able to benefit from additional FA intake (i.e. above the modeled threshold value). For non-Hispanic whites, we estimated that CMF fortification with FA could result in a 2% reduction in the prevalence of spina bifida (95% uncertainty interval: 0, 12%) and a 1% reduction in the prevalence of anencephaly (95% uncertainty interval: 0, 10%), preventing a median value of 10 infants from having spina bifida (95% uncertainty interval: 0, 90) and 10 infants from having anencephaly (95% uncertainty interval, 0, 50). Smaller reductions were estimated for non-Hispanic blacks, with less than 5 infants estimated to be prevented from having spina bifida or anencephaly (95% uncertainty intervals: 0, 20 and 0, 10, respectively), equating to approximately 1% reductions in the prevalence of each of these neural tube defects (95% uncertainty intervals: 0, 13% and 0, 10%, respectively). Increasing the maximum level at which additional FA intake no longer impacts NTD prevalence from 400μg/day to 800μg/day had little effect on the estimates (Table 3).

DISCUSSION

Evaluation of effectiveness is a key component when considering the impact of any public health intervention. The modeling approach described here can be useful in defining the anticipated outcome of an intervention such as CMF fortification. In the case of mandatory FA fortification of ECGP, in which there was a 27% decrease in the overall prevalence of NTDs, the impact of fortification could be demonstrated using birth defects surveillance data (Centers for Disease Control and Prevention, 2004). Because the target population for CMF fortification is much smaller, the estimates from the model used in this analysis suggest a much more modest decrease in the prevalence of spina bifida and anencephaly with FA fortification of CMF, resulting in a prevented number of NTDs that, although important and of benefit to the target population, is unlikely to be observable using current methods for birth defect surveillance.

The use of supplements containing FA is the factor most strongly associated with women of childbearing age achieving the recommended level of FA intake (Tinker et al., 2010), but efforts to increase supplement use are expensive and difficult to maintain over time. Fortification of staple food products is a means of increasing FA intake across a population without requiring sustained behavior change. However, there are many populations in addition to Hispanic women for which a higher prevalence of NTDs has been observed compared to the general population, including women taking antiepileptic medications (Jentink et al., 2010a; Jentink et al., 2010b) and those who are obese (Stothard et al., 2009) or have diabetes (Correa et al., 2008). FA fortification of CMF would address only the increased prevalence observed among infants born to Hispanic women, and would only impact those NTDs susceptible to additional FA.

FA fortification of CMF is an intervention designed not only to reduce the prevalence of NTDs, but also aimed at reducing the difference in NTD prevalence among Hispanics relative to non-Hispanic whites. Many examples exist of interventions designed to address a health disparity and when planning such an intervention, it is important to understand the potential magnitude of the impact among different groups. The Racial and Ethnic Approaches to Community Health (REACH) is an intervention designed to improve diabetes-related outcomes among African Americans and Latinos using lifestyle interventions specifically tailored to these groups (Two Feathers et al., 2005). The Well-Integrated Screening and Evaluation for WOMen Across the Nation (WISEWOMAN) screens for cardiovascular disease risk factors and implements lifestyle interventions for women of low socioeconomic status (Will et al., 2004). In these interventions a geographically-restricted population received the intervention, and therefore evaluation could be done directly. However, a population-level intervention such as the Women, Infant, and Children (WIC) program, which serves mothers and children of low socioeconomic status, uses population-based surveillance data to demonstrate an effect in reducing infant mortality overall and reducing disparities in infant mortality between African Americans and whites (Khanani et al., 2010). For CMF fortification, surveillance data are unlikely to be able to detect these modest changes in the NTD prevalence, so models such as the one presented here can be useful for demonstrating theoretically how a proposed intervention might impact a recognized disparity.

There are other examples of modeling the potential impact of interventions on the prevention of specific birth defects. Gilboa et al. estimated the potential impact on the prevalence of spina bifida and cleft palate if valproic acid and carbamazepine, antiepileptic drugs, were not used during pregnancy (Gilboa et al., 2011). They estimated that 45 infants could be born each year without spina bifida if neither valproic acid nor carbamazepine were used during pregnancy (95% uncertainty interval: 0, 115). Taylor et al. estimated the potential reduction in NTD prevalence with universal use of FA-fortified oral contraceptives in the United States (Taylor et al., 2011). They estimated that spina bifida could be prevented in 168–300 pregnancies and anencephaly could be prevented in 125–226 pregnancies.

A major strength of the model-based estimates presented here is that we used published race/ethnicity-specific estimates, and the uncertainty associated with those values, as inputs allowing propagation of this lack of knowledge through to the estimates of CMF fortification impact. However, the presented estimates have a number of limitations that should be considered. First, we assumed that all CMF was fortified with FA at the modeled level of 140μg/100g CMF. If CMF producers were not required to fortify (i.e. voluntary fortification) and decided not to fortify their product or if the level of fortification was lower, the estimated impact of fortification would decrease. Second, surveillance systems tend to underestimate birth defects with high termination and fetal death rates, such as spina bifida and anencephaly (Cragan and Gilboa, 2009). The rate of terminations among pregnancies affected by these defects may differ among women of different racial and ethnic groups (Parks et al., 2011). Third, for FA intake below the threshold of 400μg, we assumed a linear relationship between the decrease in spina bifida and anencephaly prevalence with increasing median FA intake was assumed. Uncertainty due to variation of the true relationship below the threshold from this linear assumption was not addressed in the uncertainty estimation. Fourth, the relationship between FA intake and NTD prevalence likely differs between racial/ethnic groups because of different distributions of genetic markers which affect folate metabolism (e.g. methyltetrahydrofolate reductase genotype). These differences could not be taken into account. Fifth, although we included a threshold level of intake above which there was assumed to be no additional benefit of FA, we were not able to incorporate the potential difference in NTD prevalence among women “susceptible” to FA-sensitive NTDs and those who were not, based on their estimated FA intake into the model. Sixth, except for the uncertainty surrounding the threshold level, the Monte Carlo simulation conducted took into account sampling error only. Finally, while a Monte Carlo approach was used to reflect the impact of model input uncertainty on the uncertainty of the final estimates, the approach did not consider uncertainty due to the choice of a particular model. While the model used in the estimation is logical and straightforward, uncertainty due to the correctness of the model itself could not be addressed.

Under the assumptions of the model, we estimated that annually in the United States, about 40 infants (95% uncertainty interval: 0, 120) born to Hispanic mothers could be prevented from having an NTD because of fortification of CMF with FA. Another 20 infants could potentially be prevented from having an NTD among non-Hispanic white mothers (95% uncertainty interval: 0, 140), a population for whom this intervention would not be

specifically designed, but who could nevertheless benefit from it. Although these decreases may be difficult to detect using current surveillance data, over a ten year period, the model suggests that approximately 600 infants who would have been born with spina bifida or anencephaly could be born without these conditions. Anencephaly, a universally fatal condition, can be devastating to families who are affected. Spina bifida remains a debilitating lifelong condition that can severely impact the health and well-being of those affected and their families (Grosse et al., 2009). Given that the average total lifetime direct cost of a child born with spina bifida is $560,000 (2003 dollars) (Gross et al., 2008), an additional 40 babies being born healthy each year could provide substantial financial return on investment to fortify CMF with FA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Data inputs and sources for estimated number of neural tube defects (NTDs) that could be prevented with fortification of corn masa flour

	Race/ethnic group	Spina bifida	Anencephaly	Data Source
Prevalence of NTD/10,000 live births before mandatory folic acid fortification of ECGP (95% CI)[a]	Hispanic	6.49 (5.73, 7.25)	3.85 (3.26, 4.43)	Williams et al. *Pediatrics* 2005 (8)
	Non-Hispanic white	5.13 (4.77, 5.49)	2.79 (2.52, 3.05)	
	Non-Hispanic black	3.57 (2.98, 4.16)	1.98 (1.55, 2.42)	
Prevalence of NTD/10,000 live births after mandatory folic acid fortification of ECGP (95% CI)[a]	Hispanic	4.18 (3.87, 4.49)	2.84 (2.58, 3.09)	Williams et al. *Pediatrics* 2005 (8)
	Non-Hispanic white	3.37 (3.18, 3.56)	1.98 (1.84, 2.13)	
	Non-Hispanic black	2.90 (2.56, 3.24)	1.80 (1.53, 2.06)	
Increase in the median daily usual total folate[b] intake with folic acid fortification of ECGP (95% CI)[c]	Mexican American[c]	156μg (87 μg, 225μg)		Bentley et al. *American Journal of Public Health* 2006 (26)
	Non-Hispanic white	116μg (47 μg, 185μg)		
	Non-Hispanic black	101μg (32 μg, 170μg)		
Increase in the median daily usual total folic acid intake with folic acid fortification of corn masa flour (95% CI)[e]	Mexican American[c,d]	41μg (0μg, 90μg)		Hamner et al. *Public Health Nutrition* 2012 (17)
	Non-Hispanic white	11μg (0μg, 46μg)		
	Non-Hispanic black	11μg (0μg, 57μg)		
Annual number of live births	Hispanic	1,041,239		Martin et al. *National Vital Statistics Reports* 2010 (45)
	Non-Hispanic white	2,267,817		
	Non-Hispanic black	623,029		

Abbreviations: ECGP = enriched cereal grain products; CI = confidence interval

[a] Standard error estimates were not provided in the referenced publication; they were therefore estimated under a Poisson assumption using the equation: $\sqrt{number\ of\ NTDs/(number\ of\ live\ births)^2}$

[b] "Total folate" includes sum of naturally-occurring food folate and synthetic folic acid, with no adjustment for differences in bioavailability

[c] The term "Hispanic" is used for rates of NTDs, because that is how the data were collected in the cited publication. However, folic acid intake data that can be generalized to the US population are only available for Mexican Americans. Mexican Americans make up approximately 63% of all Hispanics in the United States (18).

[d] Standard error estimates were not provided in the reference publication. For purposes of the Monte Carlo simulation a conservative estimate of 25 μg was used for the standard error of each estimate of the median usual daily folic acid intake. This value was selected based on external estimates of median usual daily folic acid intake by race/ethnicity using NHANES data. The equation used to estimate the standard error for the difference between the estimates was $\sqrt{SE(median_1)^2+SE(median_2)^2}$

[e] Lower bound set to 0 because fortification with folic acid was assumed to have a non-negative impact on intake.

Table 2

Estimated annual number of pregnancies affected by spina bifida and anencephaly prevented by fortification of corn masa flour at the modeled level[a]

Race/ethnicity	Estimated annual number of pregnancies affected in the U.S. (95% uncertainty interval)	Estimated annual number of defects potentially prevented with corn masa flour fortification[b] (95% uncertainty interval)	Estimated potential percentage decrease in prevalence with corn masa flour fortification (95% uncertainty interval)
Hispanic			
Spina bifida	435 (403, 467)	30 (0, 80)	6.3 (0, 18.6)
Anencephaly	296 (269, 321)	10 (0, 40)	4.4 (0, 14.7)
Non-Hispanic white			
Spina bifida	765 (722, 806)	10 (0, 90)	1.7 (0, 12.2)
Anencephaly	449 (417, 482)	10 (0, 50)	1.4 (0, 10.2)
Non-Hispanic black			
Spina bifida	180 (159, 201)	<5 (0, 20)	1.1 (0, 13.0)
Anencephaly	108 (90, 125)	<5 (0, 10)	0.5 (0, 9.7)

[a] 140 μg folic acid per 100 g corn masa flour

[b] Estimates rounded to the nearest 10

Table 3

Results of sensitivity analysis allowing the threshold level for the effect of folic acid to be as high as 800μg: Estimated annual number of pregnancies affected by spina bifida and anencephaly prevented by fortification of corn masa flour at the modeled level[a]

Race/ethnicity	Estimated annual number of defects potentially prevented with corn masa flour fortification[b] (95% uncertainty interval)	Estimated potential percentage decrease in prevalence with corn masa flour fortification (95% uncertainty interval)
Hispanic		
Spina bifida	30 (0, 100)	7.8 (0, 23.0)
Anencephaly	20 (0, 50)	5.5 (0, 17.7)
Non-Hispanic white		
Spina bifida	20 (0, 130)	2.3 (0, 17.5)
Anencephaly	10 (0, 70)	1.9 (0, 14.6)
Non-Hispanic black		
Spina bifida	<5 (0, 30)	1.4 (0, 15.4)
Anencephaly	<5 (0, 10)	0.6 (0, 11.8)

[a] 140 μg folic acid per 100 g corn masa flour

[b] Estimates are rounded to the nearest 10