Trends in the Postfortification Prevalence of Spina Bifida and Anencephaly in the United States

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BACKGROUND: The prevalence of NTDs in the US declined significantly after mandatory folic acid fortification; however, it is not known if the prevalence of NTDs has continued to decrease in recent years relative to the period immediately following the fortification mandate. **METHODS:** Population-based data from 21 birth defects surveillance systems were used to examine trends in the birth prevalence of spina bifida and anencephaly during 1999–2000, 2001–2002, and 2003–2004. Prevalence data were stratified by non-Hispanic White, non-Hispanic Black, and Hispanic race or ethnicity. Prevalence ratios were calculated by dividing the birth prevalences during the later time periods (2001–2002 and 2003–2004) by the birth prevalences during 1999–2000. **RESULTS:** During 1999–2004, 3,311 cases of spina bifida and 2,116 cases of anencephaly were reported. Hispanic infants had the highest prevalences of NTDs for all years. For all infants, the combined birth prevalences of spina bifida and anencephaly decreased 10% from the 1999–2000 period to the 2003–2004 period. The decline in spina bifida (3%) was not significant; however the decline in anencephaly (20%) was statistically significant. **CONCLUSIONS:** While the prevalences of spina bifida and anencephaly in the United States have declined since folic acid fortification in the food supply began, these data suggest that reductions in the prevalence of anencephaly continued during 2001–2004 and that racial and ethnic and other disparities remain. *Birth Defects Research (Part A) 82:527–532, 2008.* © 2008 Wiley-Liss, Inc.[†]

Key words: spina bifida; anencephaly; neural tube defects; folic acid; fortification

INTRODUCTION

Spina bifida and anencephaly are the most common types of NTDs and result from the failure of the neural tube to close during early embryogenesis. Folic acid supplementation prior to conception and during the first trimester has been shown to reduce the prevalence of spina bifida and anencephaly by 50–70% (MRC, 1991; CDC, 1992a; Czeizel and Dudas, 1992). In 1992, the US Public Health Service released guidelines recommending that all women of childbearing age consume 400 μg of folic acid daily to reduce their risk of an NTD-affected pregnancy (CDC, 1992a). In 1996, the US Food and Drug Administration mandated the addition of folic acid to all enriched cereal grain products by January 1998 (Food and Drug Administration, 1996; Mathews et al., 2002).

The prevalences of spina bifida and anencephaly in the United States have declined significantly since the fortification of enriched grain products with folic acid (Honein et al., 2001; Mathews et al., 2002; Williams et al., 2002, 2005). Estimates of the declines in the prevalences of spina bifida and anencephaly since fortification range from 19–26% (CDC, 2004; Honein et al., 2001; Mathews et al., 2002; Williams et al., 2002). Racial and ethnic variations in the effect of folic acid fortification on the prevalences of spina bifida and anencephaly have also been

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noted, with significantly greater postfortification reductions observed among Hispanic and non-Hispanic White women than among non-Hispanic Black women (Williams et al., 2005). In addition, rates of NTD-affected pregnancies have been consistently higher among Hispanic women in the United States both prior to and after mandatory fortification (Canfield, 1996; Canfield et al., 2006; Ray et al., 2004; Shaw et al., 1997; Williams et al., 2005).

Although Williams et al. (2005) documented declines in the prevalence of spina bifida and anencephaly during 1995–2002, additional years of data are now available from this large, population-based surveillance dataset and can provide important information for assessing long term trends in the postfortification prevalence of these conditions. Furthermore, variations in serum folate concentrations and folic acid intake have been noted in the years since the fortification mandate and may have subsequently influenced recent prevalence data. For example, findings from a recent analysis of data from the 1999–2004 National Health and Nutrition Examination Survey indicate that median serum folate concentrations among women of childbearing age decreased 16% and red blood cell (RBC) folate concentrations decreased 8% from the 1999–2000 period through the 2003–2004 period (CDC, 2007). In addition, current national estimates indicate that the majority of nonpregnant women of childbearing age reported consuming less than the recommended amount of folic acid during 2001–2002 (Yang et al., 2007) and that folate consumption by US women of childbearing age has decreased during 1999–2004 (Quinlivan and Gregory, 2007).

Our purpose in this study was to apply population-based surveillance data derived from the National Birth Defects Prevention Network (NBDPN) NTD Ascertainment Project to describe the prevalences of spina bifida and anencephaly during the postfortification period (1999–2004) and to compare the prevalences of these birth defects during more recent years (2001–2002 and 2003–2004) with those more closely following the fortification mandate (1999–2000). This unique dataset provides population-based data from 21 birth defects surveillance systems and represents approximately 40% of all US births annually.

MATERIALS AND METHODS

The data used for this study were derived from the NBDPN NTD Ascertainment Project and included quarterly counts of spina bifida and anencephaly cases and the corresponding number of livebirths for 21 programs that participated in the project during 1999–2004 and that met the following criteria: (1) used a surveillance method that identified cases from sources other than birth certificates; (2) reported quarterly cases of anencephaly (ICD-9-CM codes 740.0–740.1) and spina bifida (ICD-9-CM codes 741.0 and 741.9 without 740.0–740.1) from 1999–2004; and (3) reported racial and ethnic data based on maternal race so that the cases and denominators could be stratified into Hispanic, non-Hispanic White, and non-Hispanic Black categories (Williams et al., 2002, 2005).

The birth defects surveillance systems from 20 states and one U.S. commonwealth met the eligibility criteria (Alabama, Arkansas, California, Colorado, Georgia, Hawaii, Illinois, Iowa, Kentucky, Massachusetts, Maryland, New Jersey, New York, North Carolina, Oklahoma, Puerto Rico, South Carolina, Texas, Utah, West Virginia, and Wisconsin) and were included in the analysis. Ten of these states also reported prenatally diagnosed NTD cases.

The study period was divided into three distinct temporal groups, 1999–2000, 2001–2002, and 2003–2004, and quarterly counts of spina bifida, anencephaly, and livebirths were aggregated over the 2-year intervals; small sample sizes precluded evaluation of outcomes on an annual basis. Birth prevalences were calculated as the number of spina bifida and anencephaly cases during the time period of interest per 10,000 livebirths. Prevalence ratios were calculated by dividing the birth prevalences during the later time periods (2001–2002 and 2003–2004) by the birth prevalences during 1999–2000. The 95% CIs for the prevalence ratios were calculated by Poisson regression, with the time intervals included as a classification variable. All analyses were conducted with SAS 9.1 (SAS Institute, Cary, NC) data.

RESULTS

From 1999–2004, 3,311 cases of spina bifida and 2,116 cases of anencephaly were reported. Table 1 shows the birth prevalences of spina bifida and anencephaly during 1999–2004 according to race and ethnicity. Overall, the birth prevalences of spina bifida and anencephaly tended to decrease over the study period. Hispanic infants had the highest prevalences of spina bifida and anencephaly for all time periods, approximately 40% higher than the prevalence among non-Hispanic Black infants and 30% higher than non-Hispanic White infants. While the prevalences of anencephaly and spina bifida were higher among non-Hispanic Black infants in 2001–2002 than in 1999–2000, for 2003–2004 the prevalences of these conditions were lower than for 1999–2000. These discrepancies might have been due to the low number of cases in this group.

The prevalence ratios for the 2001–2002 and 2003–2004 postfortification intervals compared with those for 1999–2000 are shown in Table 2. For all races and ethnicities the prevalences of spina bifida and anencephaly combined significantly decreased (10%) from 1999–2000 to 2003–2004; the decrease among non-Hispanic White infants (11%) was also significant. The largest overall decline in the prevalences of NTDs over the study period (14%) occurred among non-Hispanic Black infants, while Hispanic infants had the smallest decrease (8%); neither of these reductions was statistically significant and may be attributable to small sample sizes. While slightly larger declines in the prevalence of anencephaly were also found in these groups, there were no statistically significant reductions in the prevalence of spina bifida overall or among any racial or ethnic group. With the exception of those for non-Hispanic Black infants, no significant differences were noted in the prevalences of spina bifida and anencephaly from the 2001–2002 period to the 2003–2004 period (data not shown).

When the analysis was restricted to the 10 states that reported prenatally ascertained cases, a statistically significant decline (prevalence ratio 0.83; 95% CI: 0.73–0.93) in spina bifida and anencephaly combined was noted during 2003–2004 compared with 1999–2000 (data not shown). While no significant decreases in spina bifida

Table 1
Post-Fortification Prevalences of Spina Bifida and Anencephaly by Race and Ethnicity, 1999–2004

	1999–2000		2001–2002		2003–2004	
	No. cases	Prevalence (per 10,000)	No. cases	Prevalence (per 10,000)	No. cases	Prevalence (per 10,000)
All races and ethnicities						
Spina bifida	1,111	3.51	1,102	3.43	1,098	3.39
Anencephaly	782	2.47	692	2.15	642	1.98
Total	1,893	5.98	1,794	5.58	1,740	5.37
Non-Hispanic White						
Spina bifida	582	3.30	562	3.24	549	3.22
Anencephaly	385	2.19	310	1.79	280	1.64
Total	967	5.49	872	5.02	829	4.86
Non-Hispanic Black						
Spina bifida	138	3.06	142	3.15	117	2.64
Anencephaly	75	1.66	92	2.04	63	1.42
Total	213	4.72	234	5.19	180	4.05
Hispanic						
Spina bifida	329	4.23	348	4.13	373	4.17
Anencephaly	253	3.25	237	2.81	246	2.75
Total	582	7.48	585	6.93	619	6.91

were noted during the study period, the birth prevalences for anencephaly were observed to have decreased significantly. Small sample sizes precluded further stratification by race or ethnicity.

DISCUSSION

Following a 31% decline in the prevalence of spina bifida and a 16% decline in the prevalence of anencephaly in the immediate postfortification period (October 1998–December 1999) (Williams et al., 2002), spina bifida and anencephaly prevalence rates declined 10% from 1999–2004. Whether this continued decline is due to a long-term trend of decreasing rates of NTDs, increased supplement use, dietary changes, or mandatory fortification cannot be elucidated in this analysis. Because the declines in the prevalences of spina bifida and anencephaly in the years immediately following mandatory fortification of enriched cereal grain products have been well described in the literature, we evaluated changes in more recent years (2001–2004) relative to those more proximal to the fortification mandate (1999–2000).

It is unclear why a significant decline in the prevalence of anencephaly was noted during the study period while the decline for spina bifida was much smaller and not statistically significant. The same pattern was evident in the states that included prenatally ascertained cases and for the majority of the individual states. This may lend support to the concept that anencephaly and spina bifida do not necessarily share the same risk factors and may therefore be etiologically heterogeneous (Khoury et al., 1982; Sever, 1995). Further research is needed to determine potential causes of this trend.

Several potential explanations could account for the relatively stable prevalence patterns for anencephaly and spina bifida in the US. In the early stages of fortification during the late 1990s, more than the anticipated level of folate might have entered the food supply. The finding that serum folate levels have fallen in recent years among women of all reproductive ages and racial and ethnic groups could reflect this pattern (CDC, 2007). Pfeiffer et al. (2007) compared National Health and Nutrition Examination Survey data for 1999–2000, 2001–2002, and 2003–2004 with those for 1988–1994 and found that the

Table 2
Prevalence Ratios and 95% CI for Selected Pre- and Postfortification Intervals Compared to 1999–2000

	Prevalence ratio (2001–2002/1999–2000)	95% CI	Prevalence ratio (2003–2004/1999–2000)	95% CI
All races and ethnicities				
Spina bifida	0.98	0.90–1.06	0.97	0.89–1.05
Anencephaly	0.87	0.79–0.96	0.80	0.72–0.89
Total	0.93	0.87–0.99	0.90	0.84–0.96
Non-Hispanic White				
Spina bifida	0.98	0.87–1.10	0.98	0.87–1.09
Anencephaly	0.82	0.70–0.95	0.75	0.64–0.88
Total	0.91	0.83–1.00	0.89	0.81–0.97
Non-Hispanic Black				
Spina bifida	1.03	0.81–1.30	0.86	0.67–1.10
Anencephaly	1.23	0.90–1.66	0.86	0.31–1.19
Total	1.10	0.91–1.32	0.86	0.70–1.05
Hispanic				
Spina bifida	0.98	0.84–1.13	0.99	0.85–1.14
Anencephaly	0.86	0.72–1.03	0.85	0.71–1.01
Total	0.93	0.83–1.04	0.92	0.83–1.04

prevalence of low serum folate concentrations (<6.8 nmol per liter) among women of childbearing age declined from 20.6% before to 0.8% after fortification; however, the prevalence of low serum folate concentrations remained unchanged during the postfortification period (1999–2004). Levels of folic acid in breads and pasta appear to have decreased over time since 1998 (Johnston and Tamura, 2004), at least in part because the amount lost during processing was found to be less than originally estimated. This finding could also be attributed to products being overfortified when fortification was first initiated. A second potential explanation holds that folic acid fortification and folic acid public health campaigns did not reach certain subgroups of women. Williams et al. (2005) examined racial- and ethnic-specific trends in spina bifida and anencephaly prevalences from before to after folic acid fortification, and found that while declines occurred for non-Hispanic White, non-Hispanic Black, and Hispanic women, spina bifida and anencephaly prevalence rates for Hispanic women remain at higher levels. The proportion of women of reproductive age with low RBC folate levels has also been shown to vary by ethnicity (CDC, 2007). National population-based surveys of women of reproductive age have demonstrated variation in the proportion of women taking folic acid supplements daily, with non-Hispanic White women having the highest rates and non-Hispanic Black and Hispanic women having somewhat lower rates (Green-Raleigh et al., 2006; Yang et al., 2007). Younger women, those with less formal education, and those with lower annual household income also were less likely to take folic acid supplements daily (Green-Raleigh et al., 2006).

The prevalence of risk factors for NTDs such as maternal diabetes (Becerra et al., 1990; Cabrera et al., 2004) and obesity (Waller et al., 2007) may have changed during the study period and thus impacted the trends presented in this report; however, these data were not available for this analysis. Findings from other studies indicate that while national estimates of the prevalence of diagnosed diabetes increased from 1988–1994 through 1999–2002, the increase was not statistically significant among women (Cowie et al., 2006). In addition, national rates of obesity remained constant for women during 1999–2004 (Ogden et al., 2006).

Changes in the use of supplements containing folic acid and eating habits also could have contributed to the observed trends. Overall, the proportion of women of childbearing age who reported using a dietary supplement containing folic acid remained relatively unchanged during the 1995–2005 period (CDC, 2005). However, findings from a nationally representative study suggested that two-thirds of nonpregnant women of reproductive age in the US consumed <400 μg of folic acid daily during 2001–2002, and the proportion of women consuming the recommended amount via supplements or fortified foods varied significantly by race and ethnicity (Yang et al., 2007). Furthermore, folate intake among women of childbearing age in the US has decreased during 1999–2004, most notably among women with the highest folate status (Quinlivan and Gregory, 2007). Among other dietary trends, carbohydrate avoidance made popular through low carbohydrate diets (e.g., the Atkins diet) could have led to decreased daily consumption of food products such as breads and pastas, resulting in lower folic acid intake. Finally, historical trends in NTDs have to some extent reflected the temporal differences in rates of prenatal ascertainment of NTDs, or in rates of pregnancy terminations following an antenatal diagnosis of an NTD-affected pregnancy. Improvements in state-level surveillance of prenatally diagnosed NTDs could have led to improved ascertainment, biasing results toward no decrease in NTD rates (Cragan et al., 1995; Peller et al., 2004; Schechtman et al., 2002; Velie and Shaw, 1996). However, data from the NBDPN NTD Ascertainment Project indicate that the prenatal ascertainment of NTDs was stable during the postfortification years (1999–2004) covered in this study (data not shown). Because the completeness of prenatal ascertainment varies considerably across surveillance programs (Cragan et al., 1995), we do not report data stratified by prenatal ascertainment. When a dichotomous variable indicating whether a program ascertained cases prenatally was included in the log-linear models, no significant changes were observed in the prevalence ratios.

The variations in the prevalence of spina bifida and anencephaly by race/ethnicity documented in this report have been identified previously (Williams et al., 2005). A number of possible explanations for these differences have been described and include genetic factors (Esfahani et al., 2003), differences in folic acid consumption (Yang et al., 2007), and variations in NTD risk factors such as diabetes (Becerra et al., 1990; Cabrera et al., 2004) and obesity (Waller et al., 2007).

Our study was limited by the secondary nature of the data analyzed. Although it has been suggested that declines in the prevalence of spina bifida and anencephaly in the postfortification period may be the continuation of a long-term progressive decline that started long before the mandatory fortification of enriched cereal grain products (CDC, 1992b; Besser et al., 2007), we were unable to evaluate this hypothesis because the surveillance data used for this analysis are only available from 1995–2004. While many of the state-based surveillance programs included in this analysis use active case-finding methods, data for a number of these programs were limited to passively ascertained data, in several instances focusing only on cases identified among liveborn infants (National Birth Defects Prevention Network, 2004). When we limited our analysis to those states that included prenatally ascertained cases in their prevalence data, the observed trends were similar to those reported here. Our data were also limited by an inability to account for factors known or suspected to influence the prevalence of NTDs, including maternal diabetes, obesity prior to pregnancy, presence of polymorphisms associated with folate metabolism, or a prior pregnancy affected by an NTD. Due to its cross-sectional nature, we could not impute causality from these data. However, the 20 states and one US commonwealth who contributed data to this report accounted for 40% of all births in the US during 1999–2004; thus, this analysis provides the most comprehensively ascertained national data on NTDs that are currently available.

CONCLUSIONS

Our findings provide important information regarding trends in the prevalence of spina bifida and anencephaly during the postfortification era and facilitate further evaluation of the effect of recently noted declines in serum

and RBC folate levels among women of childbearing age during the study period. While the prevalences of spina bifida and anencephaly in the US have declined since folic acid fortification in the food supply began, reductions in prevalences have been smaller than anticipated based on the findings of two randomized trials (Czeizel and Dudas, 1992; MRC, 1991), and racial and ethnic and other disparities remain. When considered in the context of recent reports of declining folate status among US women of reproductive age (CDC, 2007; Pfeiffer et al., 2007), the findings presented in this report suggest that subsequent decreases in the prevalence of spina bifida and anencephaly may continue to be smaller than predicted as they approach the nadir of folic acid preventable NTDs. Additional public health efforts might be necessary to further reduce the prevalences of spina bifida and anencephaly in the US, especially among Hispanics, younger women of reproductive age, and those with less formal education or lower household incomes. Efforts to educate women, children in elementary and secondary schools, and health care providers concerning the importance of daily consumption of supplements that include folic acid, as well as increasing intakes of fortified grains and other healthy foods, must continue. Further research is also needed to explore factors that can influence the prevalences of spina bifida and anencephaly and explain the observed trends. Surveillance programs providing rapid ascertainment of rare health outcomes such as NTDs will enable continued monitoring of trends and identify progress towards national public health objectives.

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