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Changes in Spina Bifida Lesion Level after Folic Acid Fortification in the US

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Abstract

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The authors declare no conflicts of interest.

Objective—To assess whether the severity of cases of spina bifida changed after the institution of mandatory folic acid fortification in the US.

Study design—Six active population-based birth defects programs provided data on cases of spina bifida for 1992-1996 (prefortification period) and 1999-2016 (postfortification period). The programs contributed varying years of data. Case information included both a medical record verbatim text description of the spina bifida diagnosis and spina bifida codes (*International Classification of Diseases, Clinical Modification*, or a modified birth defects surveillance coding system). Comparing the prefortification and postfortification periods, aORs for case severity (upper-level lesions [cervical, thoracic] vs lower-level lesions [lumbar, sacral]) and prevalence ratios (PRs) were estimated.

Results—A total of 2593 cases of spina bifida (out of 7 816 062 live births) met the inclusion criteria, including 573 cases from the prefortification period and 2020 cases from the postfortification period. Case severity decreased by 70% (aOR, 0.30; 95% CI, 0.26-0.35) between the fortification periods. The decrease was most pronounced for non-Hispanic White mothers. Overall spina bifida prevalence declined by 23% (PR, 0.77; 95% CI, 0.71-0.85), with similar reductions seen across the early, mid, and recent postfortification periods. A statistically significant decrease in upper-level lesions occurred in the postfortification period compared with the prefortification period (PR, 0.28; 95% CI, 0.22-0.34), whereas the prevalence of lower-level lesions remained relatively similar (PR, 0.94; 95% CI, 0.84-1.05).

Conclusions—The severity of spina bifida cases decreased after mandatory folic acid fortification in the US. Further examination is warranted to better understand the potential effect of folic acid on spina bifida severity.

In 1992, the US Public Health Service recommended that all women capable of becoming pregnant consume 400 μg of folic acid daily to prevent neural tube defects, such as anencephaly and spina bifida. In 1998, folic acid fortification of enriched cereal grain products became mandatory in the US. Declines in the birth prevalence of neural tube defects were observed immediately after the institution of mandatory toiic acid fortification.[1,2] Several studies have shown that folic acid intervention can impact spina bifida lesion level. A study using Canadian provinces data reported a decrease in the proportion of upper spina bifida (cranial, cervical, and thoracic) from 32% to 13%, concluding that folic acid fortification decreases the risk of more severe spina bifida.[3] Similarly, a EUROCAT-Northern-Netherlands study examining the effect of folic acid supplementation on levels of spina bifida showed protection against cervical/thoracic spina bifida.[4] A study assessing the neurologic function of cases from a southeastern Arizona referral center showed a significant decrease (85%) in thoracic level lesions after fortification.[5]

The location of spina bifida lesions is a critical determinant of outcome and long-term prognosis. Cervical, thoracic, and high lumbar lesion level defects are associated with greater disability and mortality risk compared with sacral and lower lumbar lesions.[6-8] The most useful functional classification for spina bifida is based on the neurologic level of the lesion; 70%-99% of children with thoracic or high lumbar lesions may require orthosis for ambulation and a wheelchair for mobility in adulthood, whereas 94%-100% of children

with low sacral lesions maintain ambulation without braces or support.[9] This difference highlights the importance of lesion level in determining overall functionality and quality of life. However, there are limited data available to assess whether folic acid fortification significantly impacts lesion level in the US. Accurate assessment of this issue is further hindered by the fact that disease classification coding for spina bifida can be nonspecific with respect to the site of the lesion, necessitating a more detailed review on a case-by-case basis. This study was designed to examine patterns of spina bifida lesion level changes after mandatory folic acid fortification in the US using a large population-based database of cases of spina bifida.

Methods

The National Birth Defects Prevention Network issued a call for state birth defects programs' spina bifida lesion data before and after fortification. Eligible programs needed to be able to provide verbatim medical record text descriptions of spina bifida diagnoses. Six programs participated in this study: Arizona, California (covering 8 counties), metropolitan Atlanta (Georgia), Oklahoma, South Carolina, and Utah.

The study prefortification period comprised birth years 1992-1996, and the postfortification period covered birth years 1999-2016. Birth years 1997 and 1998 were not included, to ensure that entire annual birth cohorts were born after full fortification implementation. Programs adjusted the date of pregnancy terminations and fetal deaths for cases to the expected date of delivery to assign the cases to the appropriate study period when possible.

Participating state programs provided deidentified, case-level data based on inclusion/exclusion criteria to the Centers for Disease Control and Prevention (CDC) for central processing and analysis. Case information included both medical record verbatim text description of the spina bifida diagnosis and spina bifida codes, using *International Classification of Diseases, Clinical Modification* (ICD-CM) or the CDC and Prevention/British Pediatric Association (CDC/BPA) coding system. The codes included 741.0 or 741.9 (ICD-9-CM); 741.00-741.99, excluding 741.985 (CDC/BPA); and Q05.0–Q05.9, Q07.01, and Q07.03 (ICD-10-CM). Programs also provided maternal and infant information regarding birth/delivery year, maternal race/ethnicity, maternal age, gestational age at birth/delivery, birth weight, infant sex, pregnancy outcome, vital status (infant death, age in days), and co-occurring birth defects codes.

Case Inclusion/Exclusion

Study case types of spina bifida included myelomeningocele/meningomyelocele, meningocele, spinal rachischisis, and spina bifida not otherwise specified (NOS). These cases are largely due to abnormal primary neurulation and are usually marked by a bulging membrane-covered mass, although occasionally the skin is intact. Rarely the lesion presents as a rachischisis with no sac and exposed neural tissue. Excluded cases were cranial lesions (ie, anencephaly, craniorachischisis, iniencephaly, encephalocele, meningoencephalocele), lipomyelomeningocele/lipomeningomyelocele, dysraphism related to split cord malformations (eg, hydromyelia, diastematomyelia, myelocystocele, syrinx), and spina bifida occulta.

An additional level review conducted by the coauthors was performed centrally to ensure consistent cross-programmatic case inclusion criteria. All codes were also reviewed to exclude cases of spina bifida co-occurring with another neural tube defect, such as anencephaly or encephalocele.

Lesion Level

Programs provided lesion level information based on the highest lesion using best clinical assessment (not radiographic). Cervical or thoracic lesion level cases were assigned as severe upper-level lesions, and cases with lumbar or sacral were classified as less severe lower-level lesions.

Open/Closed Lesions

An open lesion was defined as leaking spinal fluid or membrane covered only (surgical closure required), and a closed lesion was defined as covered by intact skin and not leaking spinal fluid (immediate surgery often not done). An algorithm was used to categorize spina bifida lesions as open or closed based on verbatim description of spina bifida diagnosis details when available (Appendix 1; available at www.jpeds.com).

Isolated/Nonisolated Cases

A code-based algorithm (Appendix 2; available at www.jpeds.com) was used to categorize cases as isolated or nonisolated. Cases of spina bifida were considered isolated if they had no other anomalies related to the primary cause of abnormal neural tube closure or were secondary to the neurologic complications caused by it. These include central nervous system (CNS) anomalies (eg, Chiari malformation, corpus callosum anomalies, hydrocephaly, microcephaly), musculoskeletal defects (eg, hip dysplasia, club foot, other joint deformations or contractures), vertebral anomalies related to the site of the lesion, and urinary tract dysfunction leading to hydronephrosis or reflux. Cases with only additional minor anomalies (eg, preauricular ear tag or other minor skin findings) were considered isolated.

Nonisolated cases had a major structural malformation outside the CNS or a CNS defect unrelated to their spina bifida diagnosis (eg, holoprosencephaly). Complex cases included those with a chromosomal anomaly, even if other malformations were poorly described and those few cases in which an exogenous cause was documented (eg, fetal alcohol syndrome, fetal valproate embryopathy).

Study Design/Analyses

Case data pooled across programs were analyzed using SAS 9.4 (SAS Institute) to calculate prevalence, ORs, prevalence ratios (PRs), and 95% CIs. The generalized estimating approach to logistic (case severity analyses) and log-linear (PR analyses) regression was used to examine associations between fortification period and the outcomes (spina bifida and lesion level), accounting for clustering of cases by state. Additional models included an interaction term between fortification period and variables of interest (maternal race/ethnicity, maternal age, infant sex, and pregnancy outcomes) to examine effect modification

of the association between fortification period and outcomes (Appendix 3; available at www.jpeds.com).

Research Determination

This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy. Where required, participating programs obtained local approval or exemption from their Human Subjects/Institutional Review Board determination process.

Results

A total of 2593 cases of spina bifida from a population of 7 816 062 live births met the study's case inclusion criteria. The prefortification period included 573 cases, with a birth prevalence of 4.07 per 10 000 live births; the postfortification period included 2020 cases, with a birth prevalence of 3.15 per 10 000 live births.

Table I presents selected descriptive characteristics of the spina bifida cases. Non-Hispanic White infants contributed 51.2% of the cases, followed by Hispanic infants, who accounted for 26.6% of the cases. A higher proportion of Hispanic cases was observed during the postfortification period compared with the prefortification period (28.7% vs 19.5%). Most cases (71.7%) occurred among women aged 20-34 years. A slight downward shift occurred in the contribution from women aged <20 years from the prefortification period to the postfortification period (from 14.0% to 10.0%), and the inverse was observed for mothers aged 35 and older (from 9.8% to 14.8%).

Overall, 80.2% of the study cases were live births. The percentage of stillbirth cases remained relatively stable over time, whereas cases from terminations and other nonlive births decreased from the prefortification period to the postfortification period (from 18.9% to 12.2%). Open lesions accounted for 87.6% of all cases, remaining relatively similar prefortification (88.1%) and postfortification (87.4%); a similar finding was observed for closed lesions (8.7% prefortification, 8.4% postfortification). Among all cases, the majority were classified as isolated (74.5%), with 6.6% chromosomal and 16.0% multiple (data not shown).

Most cases of spina bifida involved lower-level lesions (81.3%), most commonly lumbar (Table II). Prefortification and postfortification estimates were 61.4% and 72.0%, respectively, for lumbar level lesions and 7.7% and 11.9% for sacral level lesions. The prevalence of upper-level lesions decreased from 24.6% prefortification to 8.8% postfortification, with decreases in both cervical (from 2.3% to 1.2%) and thoracic (from 22.3% to 7.3%) lesions.

Among cases of spina bifida, the odds of upper-level to lower-level lesions decreased by 70% from prefortification to postfortification (aOR, 0.30; 95% CI, 0.26-0.35) (Table III). The case severity aORs differed significantly by maternal race/ethnicity, with the decrease in non-Hispanic Whites approximately 1.4 times greater than that of non-Hispanic Blacks (aOR, 0.24 vs 0.45), although the 95% CIs overlapped slightly, and by age, with the

decrease among women aged 20-34 years roughly 10.9 times that of women aged <20 years (aOR, 0.24 vs 0.93).

The spina bifida live birth prevalence decreased significantly, with a PR of 0.77 (95% CI, 0.71-0.85) (Table IV; available at www.jpeds.com). The decrease remained similar across the early, mid, and recent postfortification periods. Prevalence of upper-level lesion cases reduced steeply (PR: 0.28, 95% CI: 0.22-0.34), while lower-level lesion prevalence remained similar across fortification periods (PR, 0.94; 95% CI, 0.84-1.05).

In stratified analyses, all maternal race/ethnicity groups examined showed decreases in upper-level lesions between the prefortification and postfortification periods, with the greatest decrease among non-Hispanic White mothers (Table V). Decreases in upper-level lesions were seen among mothers aged 20-34 years and ≥35 years, but not among women aged <20 years. No differences by infant sex were seen.

Discussion

In this large, population-based study of a birth cohort of 7.8 million, the overall prevalence of severe, upper-level lesion cases of spina bifida decreased by 72% after mandatory folic acid fortification in the US, and the prevalence of less severe, lower-level lesions remained relatively stable. Although reductions in severe upper-level lesion cases postfortification were seen among all maternal racial/ethnic groups, decreases were most pronounced among non-Hispanic White women.

This population-based study used spina bifida case information extracted from medical records collected by active birth defects registries during prefortification (1992-1996) and postfortification (1999-2016) periods. Verbatim text summarizing spina bifida diagnoses allowed detailed analyses of open/closed lesions and case classification. In addition, central review of cases ensured consistent application of case inclusion/exclusion criteria, especially for the excluded cases (eg, lipomyelomeningocele/lipomeningomyelocele, dysraphism related to split cord malformations). Although the precise embryologic basis for the excluded anomalies is unclear, the mechanisms involved appear to be distinct from the more common forms of spina bifida.[10] For lipomeningomyelocele specifically, this distinction is further supported by evidence from Hawaii and Canada that folic acid fortification did not influence the prevalence of these defects; thus, they appear to be folate-insensitive.[11,12] Spina bifida occulta, the asymptomatic defect in the posterior arches of a single vertebra, rarely causes disabilities or symptoms, and is not monitored in US population-based birth defects surveillance registries. Even with the case exclusion criteria for some subtypes, the overall postfortification prevalence reported in this study is only slightly lower than the US national estimate for spina bifida (3.15 vs 3.6 per 10 000 live births).[13]

Our study findings are consistent with those of others that classified motor function level of spina bifida cases (eg, thoracic, high lumbar, mid lumbar, low lumbar, sacral), comparing children born in prefortification and postfortification periods. Using data from a southeastern Arizona children's referral center, the authors observed an 85% decrease in the proportion of thoracic level lesions occurring in the postfortification period.[4] The proportion of high

and mid lumbar functional lesions remained relatively unchanged, but low lumbar and sacral lesions increased. However, the clinic-based setting precluded assessment of the absolute prevalence at birth by lesion level, and changes in clinic referral patterns might have changed over the study period.

In another study using neural tube defect data from 7 Canadian provinces, the proportion of upper-level lesion defects decreased from 31.9% to 13.0% between the prefortification and full implementation periods.[12] Excluding Quebec births, which had a higher proportion of cases of unknown lesion level, birth prevalence for both upper and lower lesions decreased after fortification (upper, from 2.54 to 0.43/10 000; lower, from 4.22 to 2.25/10 000). By the time of full fortification implementation, the Canadian rates were similar to our study rates.[12] Differences are expected given the populations under study. A key factor might be demographic differences between the populations, with these Canadian provinces having a higher number of individuals with Celtic and French ancestry, a higher background risk of spina bifida prefortification, and fewer African Americans. In addition, the Canadian study did not exclude cases unlikely to be due to primary neurulation defects, such as diastematomyelia or lipomeningomyelocele.

It is unclear whether folic acid fortification contributed to changing cases of spina bifida from upper to lower lesion levels or simply attenuated the severity of folate-sensitive spina bifida cases. The possibility of etiologic heterogeneity between upper- and lower-level lesions is noted given demographic differences, such as sex ratio, mean maternal age, family history, and frequency of associated anomalies. Although the findings are inconsistent and the number of cases available for analysis is relatively small, there is some evidence that upper-level lesions have a higher frequency of associated anomalies and positive family history/recurrence risks.[14-18]

Geographical variation also seems to exist, with British Isles populations with higher rates of spina bifida having larger proportions of upper-level lesions than those seen in continental Europe.[19] A similar variation was also noted in the Canadian study.[12] Moreover, the differences in the proportion of upper-level lesions also disappeared, indicating that the impact of fortification in reducing upper-level lesions was greatest in those areas with the highest rates.[12] Less information is available on specific ethnic differences in proportions of upper-level and lower-level lesions, but a California study indicated that Hispanic White women, who had the highest overall risk ratios for neural tube defects, also had higher risk ratios for upper spina bifida lesions.[17]

Geographic variation can reflect differences in the ethnic backgrounds of populations, cultural practices with respect to diet or cooking techniques and their impact on folate levels, and other environmental risk factors. Thus, the greater impact of folic acid fortification on upper-level lesions might be related to an amelioration of relative folate insufficiency owing to underlying genetic factors influencing general spina bifida rates. Likewise, proportions of cases related to different underlying embryologic mechanisms that cause spina bifida and their sensitivity to folic acid fortification might depend on the site of the lesion. For example, thoracic lesions are usually myelomeningoceles that are folate-sensitive, whereas lipomeningomyeloceles are usually low-level defects that are not.[12] Meningoceles are

frequently sacral, but their sensitivity to folic acid has not been studied in depth. A study from a population-based surveillance program of cases from 1968 to 1980 noted that cases with closed lumbosacral defects, likely meningoceles, had a different risk profile from those with upper-level lesions or open lumbosacral defects, none with a positive family history.[16]

Many factors in isolation or combination might cause a reduced prevalence of severe lesions, including fortification/supplementation, elective termination rates, and/or improved prenatal diagnosis and treatment. However, supplementation use among women of reproductive age in the US has been limited. Wong et al[20] reported a decrease in daily multivitamin consumption from 32.7% in 2006 to 23.6% in 2016 among women of reproductive age. Unfortunately, our study was unable to document maternal periconceptional folic acid supplement use. Although supplementation is an important folic acid source, the generally low percentage of women reporting daily supplementation intake is not expected to drive the population-level shift in lesion level changes.

The initiation of folic acid fortification in the US occurred concurrently with improved prenatal screening and diagnosis and surgical prenatal lesion repair. Historically, spina bifida elective termination rates have ranged from 20% to 63%.[21] Although some underascertainment of prenatally diagnosed cases is expected, interestingly, the contribution of terminations and nonlive birth cases in this study was greater for upper-level lesion cases than for lower-level lesion cases during the prefortification period, but this difference disappeared postfortification. It can be postulated that the greater postnatal mortality and morbidity associated with upper lesions might have influenced some families' decisions concerning termination of pregnancy, especially in the prefortification period when such defects were more prevalent. However, it is unlikely that the opportunity for prenatal surgery would have made a major impact on upper-level lesions, as such surgery is very rarely performed on fetuses with these lesion levels.[22]

The study has several limitations. Our analysis unveiled shortcomings in relying on diagnostic codes. The ICD-9-CM coding scheme does not allow easy coding of the lesion level, whereas CDC/BPA coding may include the site of lesion (cervical, thoracic, lumbar, or sacral) as a criterion for some specific codes but not for all cases. Also, lack of an ICD-10-CM code for lipomeningocele required an additional case verbatim review to ensure consistent cross-case exclusion. Although information on complexity, severity, and stage can be challenging, this study used the combination of codes, especially more specific CDC/BPA codes, and verbatim clinical case information to ensure more complete clinical information on lesion level and determine categorized lesions as "open" or "closed".

Likewise, records could not determine children's functional outcomes, which are indirect indicators of severity. A potential approach could link birth defects registry data with follow-up clinic data. Furthermore, a lack of preconception and prenatal folic acid data did not allow for further analyses of folic acid intake.

The ratio of isolated to complex cases varies depending on the precise definitions used. Historically, approximately 75%-85% of cases have been considered isolated. However, this varies with respect to the level of lesion, with high defects (above L1) having a higher

rate of associated anomalies than lower-level defects.[14,23,24] In addition, there is evidence that the proportion of isolated defects has decreased since the introduction of folic acid food fortification, indicating the spina bifida lesions in complex cases, such as those with chromosomal, single gene and other patterns of multiple malformations, may be less folate-sensitive.[24,25]

Finally, over time, case ascertainment within and among programs contributing study cases could vary. This analysis adjusted for program and accounted for potential clustering. Although the overall severity finding in this study is consistent with other published studies, our study highlights differences by maternal race/ethnicity in changes in spina bifida severity between prefortification and postfortification periods.

A major strength of this study is that, given its size in terms of numbers of cases and detailed clinical case review using both codes and verbatim text, it has the potential to address other important questions with respect to spina bifida epidemiology. Although the classification of cranial neural tube defects is relatively straightforward, the classification of spinal defects is much more complex, and there are limited data on the distribution of specific subtypes prefortification and postfortification. Given that our study was able to overcome the nonspecificity issue of certain codes and identify both lesion level and type of spina bifida, these data could inform further exploration of more precise subtype differences with respect to characteristics of the infant, including associated malformations and sex differences, and presence of risk factors, including genetic and epigenetic factors and exposures during pregnancy.

In conclusion, a steep reduction in the overall prevalence of cases of severe upper-level lesion spina bifida was observed after the institution of mandatory folic acid fortification in the US, while the overall prevalence of less severe lower-level lesions remained relatively unchanged. Further examination is warranted to better understand the magnitude and mechanism of the potential effect of folic acid on spina bifida severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

BPA	British Pediatric Association
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system

ICD-CM	*International Classification of Diseases, Clinical Modification*
NOS	not otherwise specified
PR	Prevalence ratio

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Table I.

Descriptive characteristics of spina bifida cases by fortification period

Characteristics	Total cases (N = 2593)				Prefortification, 1992-1996 (N = 573)				Postfortification, 1999-2016 (N = 2020)			
	Upper	Lower	Total*	% of total cases	Upper	Lower	Total*	% of total cases	Upper	Lower	Total*	% of total cases
Participating program (years with case data)												
AZ (1992-1996; 1999-2016)	70	492	614	23.7	34	105	144	25.1	36	387	470	23.3
CA (1992-1996; 1999-2016)	49	383	455	17.6	19	71	100	17.5	30	312	355	17.6
MACDP (1992-1996; 1999-2016)	40	283	351	13.5	20	57	83	14.5	20	226	268	13.3
OK (1994-1996; 1999-2013)	44	223	304	11.7	19	52	75	13.1	25	171	229	11.3
SC (1992-1996; 1999-2016)	84	403	507	19.6	37	83	125	21.8	47	320	382	18.9
UT (1994-1996; 1999-2016)	31	325	362	14.0	12	32	46	8.0	19	293	316	15.6
Total	318	2109	2593	—	141	400	573	—	177	1709	2020	—
Race/ethnicity												
White, non-Hispanic	162	1090	1328	51.2	87	230	332	57.9	75	860	996	49.3
Black, non-Hispanic	38	240	300	11.6	11	37	52	9.1	27	203	248	12.3
Hispanic	79	570	691	26.6	25	82	112	19.5	54	488	579	28.7
Asian/Pacific Islander	6	30	38	1.5	1	4	6	1.0	5	26	32	1.6
American Indian/Alaskan native	12	77	101	3.9	4	18	22	3.8	8	59	79	3.9
Total *	318	2109	2593	—	141	400	573	—	177	1709	2020	—
Maternal age												
<20 y	61	206	281	10.8	19	59	80	14.0	42	147	201	10.0
20-34 y	208	1541	1860	71.7	101	274	391	68.2	107	1267	1469	72.7
35+ y	32	294	355	13.7	9	41	56	9.8	23	253	299	14.8
Total *	318	2109	2593	—	141	400	573	—	177	1709	2020	—
Pregnancy outcome †												
Live births	249	1718	2080	80.2	104	305	429	74.9	145	1413	1651	81.7
Stillbirths	17	110	156	6.0	6	25	36	6.3	11	85	120	5.9
Terminations/other nonlive births	52	279	355	13.7	31	70	108	18.8	21	209	247	12.2
Total *	318	2109	2593	—	141	400	573	—	177	1709	2020	—
Infant sex												
Male	161	1083	1326	51.1	71	195	282	49.2	90	888	1044	51.7

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Characteristics	Total cases (N = 2593)				Prefortification, 1992-1996 (N = 573)				Postfortification, 1999-2016 (N = 2020)			
	Upper	Lower	Total*	% of total cases	Upper	Lower	Total*	% of total cases	Upper	Lower	Total*	% of total cases
Female	147	959	1182	45.6	65	195	275	48.0	82	764	907	44.9
Total *	318	2109	2593	—	141	400	573	—	177	1709	2020	—
Open/closed lesion												
Open	263	1892	2271	87.6	124	358	505	88.1	139	1534	1766	87.4
Closed	44	164	220	8.6	14	31	50	8.7	30	133	170	8.4
Total *	318	2109	2593	—	141	400	573	—	177	1709	2020	—
Infant death‡												
Living, no known death	185	1492	1756	84.4	81	276	369	86.0	104	1216	1387	84.0
Known death	61	166	258	12.4	22	28	58	13.5	39	138	200	12.1
Total *	249	1718	2080	—	104	305	429	—	145	1413	1651	—
Age at infant death§												
Early neonatal (<7 d)	33	78	133	51.6	11	12	29	50.0	22	66	104	52.0
Late neonatal (7-27 d)	4	20	29	11.2	0	6	7	12.1	4	14	22	11.0
Postneonatal (28-364 d)	16	36	55	21.3	6	3	10	17.2	10	33	45	22.5
Total *	61	166	258	–	22	28	58	–	39	138	200	–
Birth weight by gestational age¶												
Small for gestational age	44	291	374	16.7	13	62	81	16.5	31	229	293	16.7
Appropriate for gestational age	154	1143	1357	60.5	65	198	272	55.5	89	945	1085	61.9
Large for gestational age	26	159	196	8.7	11	29	41	8.4	15	130	155	8.8
Total *	278	1826	2242	—	121	343	490	—	157	1483	1752	—

NH, non-Hispanic; *AZ*, Arizona; *CA*, California; *MACDP*, Metropolitan Atlanta Congenital Defects Program; *OK*, Oklahoma; *SC*, South Carolina; *UT*, Utah.

*Total includes unknown/missing.

†Stillbirths include pregnancy losses at ≥20 wks of gestation. Terminations and other nonlive births include pregnancy losses before 20 wks of gestation.

‡Vital status of cases with live births (see “Overall pregnancy outcome” in this table).

§Age at death for liveborn cases with known infant deaths (see “Overall infant death, known death” in this table).

¶Birth weight not included n = 351; missing or invalid combination, n = 315; Fenton measurements done using the Kramer method (https://pubmed.ncbi.nlm.nih.gov/11483845).

Table II.

Spina bifida cases by lesion level, pregnancy outcome, and fortification period

	Total cases					Prefortification period					Postfortification period				
Lesion level	**LB**	**SB**	**NLB**	**Total**	**% of total cases**	**LB**	**SB**	**NLB**	**Total**	**% of total cases**	**LB**	**SB**	**NLB**	**Total**	**% of total cases**
Upper*	249	17	52	318	12.3	104	6	31	141	24.6	145	11	21	177	8.8
Cervical	25	6	7	38	1.5	7	—	5	13	2.3	18	5	—	25	1.2
Thoracic	221	10	45	276	10.6	97	5	26	128	22.3	124	5	19	148	7.3
Lower*	1718	110	279	2109	81.3	305	25	70	400	69.8	1413	85	209	1709	84.6
Lumbar	1498	75	231	1806	69.6	270	17	65	352	61.4	1228	58	166	1454	72.0
Sacral	211	32	42	285	11.0	32	7	5	44	7.7	179	25	37	241	11.9
Total†	2080	156	355	2593	—	429	36	108	573	—	1651	120	247	2020	—

LB, live births; *NLB*, terminations and other nonlive births (including pregnancy losses before 20 wk of gestation); *SB*, stillbirths (pregnancy losses at 20 or more wk of gestation).

*Upper lesion level cases include cervical, thoracic, and upper not otherwise specified (NOS). Upper NOS contributed to <0.2% of upper-level cases. Lower lesion level cases include lumbar, sacral, and lower NOS. Lower NOS contributed to <0.7% of lower-level cases.

†Total includes lesion level NOS and unknown/missing.

Table III.

Severity ORs for the odds of upper- to lower-level spina bifida lesions in the postfortification period compared with prefortification for selected characteristics

Characteristics	aOR (95% CI)*	*P* value
Total cases	0.30 (0.26-0.35)	
Maternal race/ethnicity		
White, non-Hispanic	0.24 (0.18-0.32)	Referent
Black, non-Hispanic	0.45 (0.31-0.65)	.0002
Hispanic	0.34 (0.25-0.47)	.04
Maternal age		
<20 y	0.93 (0.62-1.40)	.00001
20-34 y	0.24 (0.19-0.30)	Referent
35+ y	0.40 (0.19-0.84)	.13
Infant sex		
Female	0.33 (0.24-0.46)	Referent
Male	0.29 (0.20-0.41)	.63
Pregnancy outcome		
Live birth (referent)	0.31 (0.25-0.37)	Referent
Nonlive birth	0.29 (0.21-0.40)	.78

P values are from the pairwise testing of aORs against each referent group for maternal race/ethnicity, maternal age, infant sex, or pregnancy outcome.

*Adjusted for state program.

Table IV.

Prevalence and PRs for spina bifida cases by lesion level and fortification period

Lesion level fortification period	No. of cases	No. of live births	Birth prevalence per 10 000 (95% CI)	PR (95% CI)	*P* value
All spina bifida cases *					
Prefortification (1992-1996)	573	1 407 707	4.07 (3.74-4.42)	Referent	Referent
Postfortification, overall (1999-2016)	2020	6 408 355	3.15 (3.02-3.29)	0.77 (0.71-0.85)	<.0001
Early postfortification period (1999-2004)	669	2 136 303	3.13 (2.90-3.38)	0.77 (0.69-0.86)	<.0001
Mid postfortification period (2005-2010)	787	2 331 761	3.38 (3.14-3.62)	0.83 (0.74-0.92)	.0006
Recent postfortification period (2011-2016)	564	1 940 291	2.91 (2.67-3.16)	0.71 (0.64-0.80)	<.0001
Upper lesion level cases					
Prefortification (1992-1996)	141	1 407 707	1.00 (0.84-1.18)	Referent	Referent
Postfortification, overall (1999-2016)	177	6 408 355	0.28 (0.24-0.32)	0.28 (0.22-0.34)	<.0001
Early postfortification period (1999-2004)	75	2 136 303	0.35 (0.28-0.44)	0.35 (0.26-0.46)	<.0001
Mid postfortification period (2005-2010)	61	2 331 761	0.26 (0.20-0.34)	0.26 (0.19-0.35)	<.0001
Recent postfortification period (2011-2016)	41	1 940 291	0.21 (0.15-0.29)	0.21 (0.15-0.30)	<.0001
Lower lesion level cases					
Prefortification (1992-1996)	400	1 407 707	2.84 (2.57-3.13)	Referent	Referent
Postfortification, overall (1999-2016)	1709	6 408 355	2.67 (2.54-2.80)	0.94 (0.84-1.05)	.25
Early postfortification period (1999-2004)	564	2 136 303	2.64 (2.43-2.87)	0.93 (0.82-1.06)	.26
Mid postfortification period (2005-2010)	660	2 331 761	2.83 (2.62-3.05)	1.00 (0.88-1.13)	.95
Recent postfortification period (2011-2016)	485	1 940 291	2.50 (2.28-2.73)	0.88 (0.77-1.00)	.06

P values are for pairwise testing of the PR against the referent group for each period stratification.

* All cases include unknown lesion level.

Table V.

Adjusted PRs (postfortification to prefortification periods) of spina bifida cases by lesion level by maternal race/ethnicity, maternal age, and infant sex

	All spina bifida cases*		Upper lesion level cases		Lower lesion level cases	
Characteristics	**APR, 95% CI**	***P* value**	**APR, 95% CI**	***P* value**	**APR, 95% CI**	***P* value**
Total	0.77 (0.69-0.86)	—	0.28 (0.23-0.33)	—	0.93 (0.81-1.07)	—
Maternal race/ethnicity						
White, non-Hispanic	0.74 (0.62-0.87)	Ref	0.21 (0.17-0.27)	Ref	0.91 (0.79-1.06)	Ref
Black, non-Hispanic	1.23 (1.10-1.37)	<.0001	0.64 (0.46-0.89)	<.0001	1.42 (1.25-1.60)	<.0001
Hispanic	0.81 (0.72-0.90)	0.10	0.31 (0.26-0.38)	0.003	0.93 (0.83-1.05)	0.67
Maternal age						
<20 y	0.77 (0.62-0.96)	0.65	0.68 (0.45-1.02)	<.0001	0.77 (0.60-0.97)	0.04
20-34 y	0.79 (0.68-0.94)	Ref	0.23 (0.20-0.26)	Ref	0.98 (0.82-1.16)	Ref
35+ y	0.93 (0.67-1.30)	0.40	0.45 (0.18-1.13)	0.12	1.08 (0.86-1.35)	0.58
Infant sex						
Female	0.72 (0.58-0.89)	Ref	0.28 (0.19-0.42)	Ref	0.85 (0.70-1.04)	Ref
Male	0.81 (0.69-0.95)	.46	0.28 (0.22-0.36)	.98	0.99 (0.78-1.26)	.39

APR, adjusted PR (ratio of prevalence postfortification to prevalence prefortification, adjusted for state program).

P values are for the pairwise testing of APR against each referent group for maternal race/ethnicity, maternal age, or infant sex.

*All cases include unknown lesion level.