

Citation:

Williams LJ, Mai CT, Edmonds LD, Shaw GM, Kirby RS, Hobbs CA, Sever LE, Miller LA, Meaney FJ, Levitt M. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. *Teratology*. 2002 Jul; 66 (1): 33-39.

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Study Design:

Trend study

Class:

D - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

 POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine if the prevalence of spina bifida (SB) and anencephaly (AN) declined during the transition to mandatory fortification of United States of America (USA) enriched grain products with folic acid.

Inclusion Criteria:

The Neural Tube Defect Surveillance/Folic Acid Education Committee of the National Birth Defects Prevention Network (NBDPN) designed an NTD reporting system based on data collected from population-based birth defects surveillance programs. Programs were included if they:

- Ascertain cases from sources other than birth certificates
- Submit data from January, 1995 through December, 1999 for counts of pregnancies affected by SB and AN
- Provide annual prevalence of SB and AN in 1995 and 1996
- Report data from 1997 to 1999 by quarter of birth: First quarter, January through March; second quarter, April through June; third quarter, July through September; fourth quarter, October through December. Programs were asked to adjust for expected date of delivery for pregnancy terminations and fetal deaths.

Exclusion Criteria:

Programs that did not have data for the entire study period.

Description of Study Protocol:

- *Recruitment*: 24 programs (13 without prenatal ascertainment and nine with prenatal ascertainment)
- *Design*: Trend study
- *Statistical analysis*: Prevalence ratios (PRs) were calculated by dividing the prevalence from the mandatory fortification period by the prevalence from the pre-fortification period. The Taylor Series method was used to calculate 95% CI for the PRs. Data were analyzed using the Statistical Analysis Battery for Epidemiological Research (SABER).

Data Collection Summary:**Timing of Measurements**

1995 to 1999 separated into three time periods:

- Pre-fortification (1995 to 1996)
- Optional fortification (first quarter 1997 to last quarter 1998)
- Mandatory fortification (fourth quarter 1998 to fourth quarter 1999).

Dependent Variables

- Prevalence, calculated by the number of SB and AN cases per 10,000 births
- Prevalence of SB and AN
- Prevalence ratios (PRs) = ratio of prevalence from the mandatory fortification period and prevalence from the pre-fortification period.

Independent Variables

Time period.

Description of Actual Data Sample:

- *Attrition:* Total births, 1995 to 1999 (8,596,853)
- *Location:* 24 states in the USA, including Arkansas, California, Colorado, Delaware, Florida, Georgia, Hawaii, Iowa, Illinois, Kentucky, Maryland, Michigan, Missouri, North Carolina, New Jersey, New York, Oklahoma, Puerto Rico, South Carolina, Texas, Utah, Washington, West Virginia and Wisconsin.

Summary of Results:

Table 1. Prevalence of SB and AN for all 24 Participating Programs

	Pre-fortification: January 1995 to December 1996			Optional Fortification: January 1997 to September 1998			Mandatory Fortification: October 1998 to December 1999			PR (Pre-vs. Mandatory)	95% CI
	Total Births	% US Births	Prevalence (per 10,000)	Total Births	% US Births	Prevalence (per 10,000)	Total Births	% US Births	Prevalence (per 10,000)		
SB	3,127,161	40.14	5.15	3,063,265	44.77	4.22	2,406,427	48.74	3.54	0.69	0.36 to 0.74
AN	3,127,161	40.14	2.43	3,063,265	44.77	2.04	2,406,427	48.74	2.05	0.84	0.75 to 0.95

Table 2. Prevalence of SB and AN for Programs With and Without Ascertainment

	Pre-fortification			Optional Fortification			Mandatory Fortification			PR (Pre-vs. Mandatory)	95% CI
	Total Births	% US Births	Prevalence (per 10,000)	Total Births	% US Births	Prevalence (per 10,000)	Total Births	% US Births	Prevalence (per 10,000)		
SB programs with prenatal ascertainment	735,156	9.44	6.68	651,146	9.52	5.41	473,348	9.59	4.04	0.60	0.51 to 0.71
SB programs without prenatal ascertainment	2,173,379	27.90	4.7	2,267,745	33.14	3.90	1,785,684	36.16	3.40	0.72	0.65 to 0.80
AN programs with prenatal ascertainment	735,156	9.44	4.18	651,146	9.52	3.44	473,348	9.59	3.36	0.80	0.66 to 0.97

AN program without prenatal	2,173,379	27.90	1.86	2,267,745	33.14	1.69	1,785,684	36.16	1.63	0.87	0.75 to 1.02
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Other Findings

- Prevalence of SB and AN during from the pre-fortification to the mandatory fortification period decreased: 31% for SB (PR=0.69, 95% CI = 0.63 to -0.74) and 16% for AN (Pr=0.84, 95% CI=0.75 to 0.95)
- The prevalence of SB decreased 40% (PR=0.60, 95% CI=0.51 to 0.71) among the nine programs with prenatal ascertainment and 28% (PR=0.72, 95% CI=0.65 to 0.80) among the 13 programs without prenatal ascertainment
- The decline in the prevalence of AN remained significant among programs with prenatal ascertainment (PR=0.80, 95% CI=0.66 to 0.97) and programs without prenatal ascertainment showed no significant decline (PR=0.85, 95% CI=0.975 to 1.02)
- No decline was observed from the optional to the mandatory fortification period.

Author Conclusion:

The transition from pre-fortification to mandatory fortification of the US food supply with folic acid was temporally associated with a decline in the prevalence of SB, though the association was unclear for AN.

Reviewer Comments:

Authors assert that ascertainment methodology was not consistent across the 24 programs.

- *Many used intensive ascertainment where staff directly abstracted records from various data sources, including hospitals, laboratories and clinics*
- *Others relied on reports from hospitals, other health care facilities and private physicians, to obtain case information.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	Was the research question clearly stated?	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	Was the selection of study subjects/patients free from bias?	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes

2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	Were study groups comparable?	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	Was method of handling withdrawals described?	???
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	???
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	Was blinding used to prevent introduction of bias?	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	N/A

6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	Were outcomes clearly defined and the measurements valid and reliable?	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	Are conclusions supported by results with biases and limitations taken into consideration?	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	Is bias due to study's funding or sponsorship unlikely?	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes