ORIGINAL ARTICLE

Reduction in Neural-Tube Defects after Folic Acid Fortification in Canada

Philippe De Wals, Ph.D., Fassiatou Tairou, M.Sc., Margot I. Van Allen, M.D., Soo-Hong Uh, M.Sc., R. Brian Lowry, M.D., Barbara Sibbald, M.Sc., Jane A. Evans, Ph.D., Michiel C. Van den Hof, M.D., Pamela Zimmer, M.H.S.A., Marian Crowley, M.N., Bridget Fernandez, M.D., Nora S. Lee, M.Sc., and Theophile Niyonsenga, Ph.D.

ABSTRACT

BACKGROUND

In 1998, folic acid fortification of a large variety of cereal products became mandatory in Canada, a country where the prevalence of neural-tube defects was historically higher in the eastern provinces than in the western provinces. We assessed changes in the prevalence of neural-tube defects in Canada before and after food fortification with folic acid was implemented.

METHODS

The study population included live births, stillbirths, and terminations of pregnancies because of fetal anomalies among women residing in seven Canadian provinces from 1993 to 2002. On the basis of published results of testing of red-cell folate levels, the study period was divided into prefortification, partial-fortification, and full-fortification periods. We evaluated the relationship between baseline rates of neural-tube defects in each province and the magnitude of the decrease after fortification was implemented.

RESULTS

A total of 2446 subjects with neural-tube defects were recorded among 1.9 million births. The prevalence of neural-tube defects decreased from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full-fortification period, a 46% reduction (95% confidence interval, 40 to 51). The magnitude of the decrease was proportional to the prefortification baseline rate in each province, and geographical differences almost disappeared after fortification began. The observed reduction in rate was greater for spina bifida (a decrease of 53%) than for anencephaly and encephalocele (decreases of 38% and 31%, respectively).

CONCLUSIONS

Food fortification with folic acid was associated with a significant reduction in the rate of neural-tube defects in Canada. The decrease was greatest in areas in which the baseline rate was high.

From Laval University, Quebec, QC (P.D.W., F.T.); the University of British Columbia, Vancouver (M.I.V.A.); British Columbia Ministry of Health, Victoria (S.-H.U.); Alberta Health and Wellness, Calgary (R.B.L., B.S.); the University of Manitoba, Winnipeg (J.A.E.); Dalhousie University, Halifax, NS (M.C.V.H.); the IWK Health Centre, Halifax, NS (P.Z.); Health Science Centre, St. John's, NL (M.C., B.F.); Food Directorate, Health Canada, Ottawa (N.S.L.) — all in Canada; and Robert Stempel School of Public Health, Florida International University, Miami (T.N.). Address reprint requests to Dr. De Wals at the Département de Médecine Sociale et Préventive, Université Laval, Pavillon de l'Est, Local 1110, 2180, Chemin Sainte-Foy, Quebec, QC G1K 7P4, Canada, or at philippe.dewals@msp.ulaval.ca.

N Engl J Med 2007;357:135-42.

The benefit of folic acid supplementation during the periconception period in reducing the risk of neural-tube defects in offspring has been demonstrated both in experimental and in observational studies.[1] Fortification of many cereal-food products became mandatory in the United States on January 1, 1998, and the Canadian milling industry started fortification early in 1997, to meet the U.S. requirements for imported flour.[2] On November 11, 1998, fortification with folic acid of all types of white flour, enriched pasta, and cornmeal became mandatory in Canada.[3] The goal of fortification was to increase by approximately 30 to 70% the average intake of folic acid among women of childbearing age without posing a risk to the general public.[3] Higher levels of fortification were not adopted because of concern about exceeding the recommended daily upper intake level of 1000 μg for adults.[1]

We conducted our study to assess changes in the prevalence of neural-tube defects associated with food fortification with folic acid throughout Canada. Since there was known to be a geographical gradient in the prevalence of neural-tube defects at birth, with higher rates in the eastern provinces than in the western provinces,[4] we also tested the hypothesis that the magnitude of the effect of folic acid fortification would vary directly with the baseline rate of the defect.

METHODS

STUDY SUBJECTS

The study population included live births, stillbirths, and terminations of pregnancies because of fetal anomalies among women residing in 7 of the 10 Canadian provinces and none of the territories from 1993 to 2002. Denominator numbers were provided by provincial vital-statistics offices. The total numbers of live births and stillbirths recorded in each participating province are shown in Table 1. In the province of Quebec, many high-risk pregnancies in the Outaouais region are referred to hospitals situated in the province of Ontario. Since outcomes from these pregnancies were unavailable, we excluded all births from the Outaouais region, which represented less than 5% of the total births in the province.

In each province, the identification of subjects with neural-tube defects relied on multiple sources (Table 1). Codes that were checked in provincial databases included the categories for infants with neural-tube defects in the *International Classification of Diseases, 9th Revision* (ICD-9: 740.0 to 742.0) and *10th Revision* (ICD-10: Q00, Q01, and Q05) and for women with a fetus affected by a central-nervous-system malformation (ICD-9: 655.0; ICD-10: O35.0). Medical records of subjects with suspected neural-tube defects were reviewed

Table 1. Total Number of Live Births and Stillbirths to Women Residing in Seven Canadian Provinces (1993–2002) and Primary Sources for the Identification of Subjects with Neural-Tube Defects.

Province	Total No. of Births	Sources for Identification
Newfoundland and Labrador	54,528	Newfoundland and Labrador Provincial Medical Genetics Program, provincial live-birth and stillbirth notification forms, maternal–fetal medicine referrals to the single tertiary care unit in the province
Nova Scotia	100,875	Provincial Perinatal Database and IWK Health Centre Fetal Anomaly Database
Prince Edward Island	15,723	Same as for Nova Scotia
Quebec	765,567	Provincial hospital administrative database MedEcho and infant-death and stillbirth certificates
Manitoba	153,686	Clinical and outcome databases of the Manitoba Maternal Serum Screening Program, the Genetics Prenatal Diagnosis Program, and the Genetics and Metabolism Program of the Winnipeg Regional Health Authority
Alberta	378,728	Stillbirth and infant-death certificates and the Provincial Congenital Anomaly Surveillance System supplemented by a survey of all maternity hospitals and children's treatment centers
British Columbia	440,634	Provincial Health Status (Congenital Anomaly) Registry, Vancouver BC Women's and Children's Health Centre databases (including the Provincial Medical Genetics Programme), the Spina Bifida Clinic, the Perinatal Diagnosis and Treatment Centre, the Fetal Diagnostic Services Clinic, and Victoria Hospital records (including the Fetal Pathology Service, the Medical Genetics Clinic, and the Perinatology and Spina Bifida Clinic)
All provinces	1,909,741	

by experienced medical archivists or specially trained research assistants. According to the province being studied, 95 to 100% of records could be found and reviewed. Medical diagnoses were reviewed by one of the authors.

The neural-tube defects of subjects were classified according to the nomenclature proposed by Nevin and Weatherall.[5] The main categories were anencephaly (including acrania, craniorachischisis, and exencephaly), spina bifida or meningomyelocele (including a spinal defect not otherwise specified), iniencephaly, encephalocele, and any neural-tube defect not otherwise specified. We excluded subjects with occult spinal dysraphism, including spina bifida occulta, thickened filum terminale, diastematomyelia, caudal regression syndrome, intradural lipoma, lipomeningomyelocele, split notochord, and other forms of myelodysplasia. This category of mainly caudal defects may be embryologically distinct from myelomeningocele,[6] and a substantial proportion of persons with such defects are diagnosed late in childhood or even adulthood.[7] Ethical approvals and authorizations to review medical records were obtained in accordance with provincial jurisdictions.

FOLATE SUPPLEMENTATION

The level of fortification with folic acid in Canada is 0.15 mg per 100 g of flour or cornmeal (U.S. level, 0.14 mg per 100 g) and 0.20 to 0.27 mg per 100 g of pasta (the same as the U.S. level). In the United States, but not in Canada, the level of fortification for rice is 0.154 mg per 100 g up to a maximum of 0.308 mg per 100 g; the level for corn grits and farina is 0.15 mg per 100 g. Breakfast cereals may be enriched up to 400 μg per serving in the United States and up to 60 μg per serving in Canada. Results of biochemical tests in a large Ontario laboratory have shown that red-cell folate levels in the population started to increase in April 1997 and reached a plateau in February 1999.[8] Given this finding and assuming that there is no beneficial effect of folic acid after the first trimester of pregnancy,[9] we considered that all term births before September 30, 1997, occurred during the prefortification period, those between October 1, 1997, and March 31, 2000, occurred during the partial-fortification period, and those after March 31, 2000, occurred during the full-fortification period. Thus, term births in the full-fortification period were conceived after the mother had been exposed to full fortification for at least 5 months, which was assumed to be sufficient to attain an equilibrium in folate status.[10] A large proportion of pregnancies affected by neural-tube defects were terminated or were preterm births. Therefore, to prevent any classification bias, a theoretical birth date was calculated for each subject, assuming a gestation of 40 weeks (the date of the birth or abortion minus the length of gestation in weeks plus 40 weeks).

STATISTICAL ANALYSIS

Prevalence rates for neural-tube defects were calculated as the sum of subjects with the defect in live births, stillbirths, and induced abortions, divided by the number of total live births and stillbirths. Confidence intervals of rates, ratios, and differences were calculated by an exact method. The chi-square test and the Cochran–Armitage test for linear trend in proportions were performed, with the statistical significance level set at 0.05 in two-sided tests. The relationship between the baseline rate of neural-tube defects in each province and the magnitude of the decrease after fortification began was modeled by testing a series of linear, exponential, and power functions. A weight equal to the inverse of the variance of the estimated difference in rate was assigned to each observation. A constraint was that we assumed that no risk reduction would be observed in situations in which the baseline rate of neural-tube defects was 0.6 per 1000 births or less. We based this assumption on data regarding residual risk observed in several regions in China in which women received daily supplementation of folic acid at a dose of 400 μg.[11] The predicted residual error sum square coefficient and the coefficient of determination were used to assess statistical fit and to select the best model. The data were analyzed with the use of SAS software, version 8.1 (SAS Institute).

RESULTS

STUDY SUBJECTS

During the study period, we identified 2446 subjects with neural-tube defects. The distribution of subjects according to diagnostic category and pregnancy outcome is shown in Table 2. Of pregnancies affected by neural-tube defects, 60% were terminated after prenatal diagnosis. Spina bifida was the most frequently recorded anomaly (53% of total subjects), with anencephaly representing approximately a third of subjects with neural-tube defects (34%). The overall ratio of anencephaly to spina bifida was 0.65, and there was no significant variation of this ratio during the study years.

The prevalence of neural-tube defects at birth according to the diagnostic category and year is shown in Figure 1. The obvious pattern is a stable rate from 1993 through 1997, followed by a decrease from 1998 through 2000 and stabilization thereafter. There was no significant downward trend during the prefortification years from 1993 through 1997, either in the whole data set or in any of the participating provinces.

As shown in Table 3, the overall prevalence of neural-tube defects at birth decreased from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full-fortification period, a 46% reduction (95% confidence interval, 40 to 51). The magnitude of the decrease was higher for spina bifida (53%) than for either anencephaly (38%, P=0.02) or encephalocele (31%, P=0.03).

The reductions in the prevalence of neural-tube defects in each province after folic acid fortification began are shown in Table 4. The data show a clear east-to-west gradient both in the prefortification rates of defects and in the magnitude of rate reduction after fortification was fully implemented. After full implementation, geographical differences in rates almost disappeared.

There was a proportional relationship between the baseline rate in each province and the absolute reduction in the rate after fortification was implemented (Fig. 2). The best fit was provided by a linear function, indicating a risk reduction proportional to prefortification rates and starting at a prefortification rate value of 0.6 per 1000 births, below which our model assumed that no further reduction was possible. (Data regarding absolute numbers of neural-tube defects according to specific diagnoses and provinces are available in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

DISCUSSION

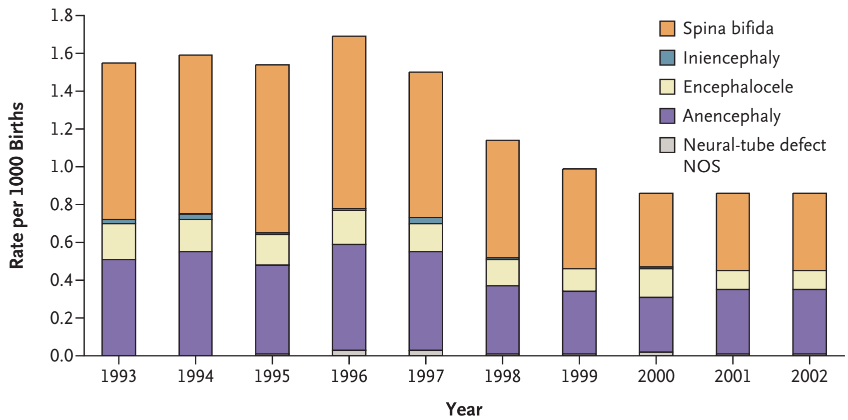
We found that food fortification with folic acid was associated with a significant reduction in neural-tube defects in Canada. Furthermore, the risk reduction appeared greatest in regions in which the rates were highest before the fortification program was implemented.

Achieving a high level of identification of subjects with neural-tube defects in a geographically defined population was possible in seven provinces, representing 55% of the total births in the country. Previous reports regarding Canadian data have showed similar reductions in rates.[2,12-16] Our study extends those observations with the use of standard methods to obtain a comprehensive assessment from the Atlantic to the Pacific coasts and multiple sources for identification of subjects. Published data from Ontario[16] were used to complement the observations in the other seven Canadian provinces, as indicated in Figure 2. Validation studies performed in Quebec and British Columbia, the two largest participating provinces, have indicated a high level of identification of subjects with neural-tube defects, equal to or higher than 92%, with no substantial change during the study years.[17-19]

A marked decrease in prevalence rates was observed from 1997 through 2000, corresponding to the initiation of food fortification in Canada.

Table 2. Subjects with Neural-Tube Defects, According to Diagnostic Category and Pregnancy Outcome, in Seven Canadian Provinces from 1993 through 2002.

Diagnostic Category	Pregnancy Outcome			
	Induced Abortion	Stillbirth	Live Birth	Total
Anencephaly	668	67	95	830
Encephalocele	160	8	115	283
Iniencephaly	19	2	2	23
Spina bifida	595	35	656	1286
Unspecified neural-tube defect	24	0	0	24
All neural-tube defects	1466	112	868	2446



	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
All neural-tube defects	1.55	1.59	1.55	1.69	1.50	1.14	0.99	0.86	0.86	0.86
Spina bifida	0.83	0.84	0.89	0.91	0.77	0.62	0.53	0.39	0.41	0.41
Iniencephaly	0.02	0.03	0.01	0.01	0.03	0.01	0.00	0.01	0.00	0.00
Encephalocele	0.19	0.17	0.16	0.18	0.15	0.14	0.12	0.15	0.10	0.10
Anencephaly	0.51	0.55	0.47	0.56	0.52	0.36	0.33	0.29	0.34	0.34
Neural-tube defect NOS	0.00	0.00	0.01	0.03	0.03	0.01	0.01	0.02	0.01	0.01

Figure 1. Prevalence of Neural-Tube Defects, According to Diagnostic Category, in Seven Canadian Provinces from 1993 through 2002.

NOS denotes not otherwise specified.

Distribution of fortified food started at the beginning of 1997, and by the end of that year, the entire milling industry had adopted fortification in anticipation of the coming mandatory requirements in the United States and Canada.[2] This finding was also consistent with the observed increase in red-cell folate levels in the population of Ontario.[8] In Newfoundland, a nutritional survey showed no significant change in dietary habits from 1997 through 2001, with the average daily intake of naturally occurring folate remaining the same at the end of the period as it was at the beginning.[12]

In contrast to the reduction in rates of neural-tube defects observed after dietary fortification, there was no significant change in the prevalence rate between 1993 and 1997, when expert committees and Health Canada recommended daily folic acid supplementation with or without multivitamins for pregnant women.[2] Other data suggest that these recommendations were not routinely followed. Health surveys that were performed periodically in Quebec showed no substantial change in the use of vitamin supplements among nonpregnant women between the ages of 18 and 40 years during the period from 1987 through 1998.[2] During the period of our study, results from two surveys among pregnant women in Quebec showed no substantive change in the use of vitamin supplements either before conception (27.5% in 1997–1998 and 31.6% in 1999–2000) or before the 12th week of pregnancy (36.0% in 1997–1998 and 30.6% in 1999–2000).[20,21] Among a random sample of nonpregnant women of reproductive age in Greater Vancouver, only 25.7% reported taking daily vitamins in 1998–1999.[22]

A study comparing folate levels in women of childbearing age before and after the implementation of food fortification in Ontario found geometric mean levels of red-cell folate of 527 nmol per liter before food fortification and 741 nmol per liter after fortification was implemented, with serum vitamin B_{12} levels remaining unchanged.[23] On the basis of the increase in serum folate levels reported in Ontario, it was estimated that the fortification program increased daily folic acid consumption by 150 μg.[24] However, in blood samples collected at prenatal clinics in Newfoundland, there was a marked increase in serum folate and a slight but significant increase in serum vitamin B_{12} levels from 1992–1996 to 1998–2002, suggesting that dietary changes or increased consumption of vitamin supplements may have contributed to the substantial reduction in the rate of neural-tube defects observed in this province after food fortification was implemented.[13]

Table 3. Prevalence of Neural-Tube Defects per 1000 Births, According to Diagnostic Category and Fortification Period.*

Diagnostic Category	Prefortification	Partial Fortification	Full Fortification	Rate Ratio†	Difference in Rate‡
	rate (95% confidence interval)				
Anencephaly	0.52 (0.45 to 0.58)	0.38 (0.28 to 0.44)	0.32 (0.24 to 0.38)	0.62 (0.52 to 0.74)	0.20 (0.13 to 0.26)
Encephalocele	0.17 (0.09 to 0.23)	0.12 (0.06 to 0.19)	0.12 (0.06 to 0.18)	0.69 (0.51 to 0.93)	0.05 (0.01 to 0.09)
Iniencephaly	0.02 (0.01 to 0.08)	0 (0 to 0.07)	0.002 (0 to 0.06)	0.10 (0.01 to 0.74)	0.02 (0.01 to 0.03)
Spina bifida	0.86 (0.80 to 0.92)	0.57 (0.50 to 0.63)	0.40 (0.35 to 0.46)	0.47 (0.40 to 0.55)	0.45 (0.37 to 0.53)
Unspecified neural-tube defect	0.014 (0.01 to 0.08)	0.01 (0 to 0.07)	0.012 (0.01 to 0.07)	0.85 (0.33 to 2.22)	0.002 (−0.01 to 0.01)
All neural-tube defects	1.58 (1.48 to 1.64)	1.09 (1.01 to 1.15)	0.86 (0.80 to 0.92)	0.54 (0.49 to 0.60)	0.72 (0.61 to 0.84)

* The fortification periods that were studied were as follows: prefortification: January 1, 1993, to September 30, 1997; partial fortification, October 1, 1997, to March 31, 2000; full fortification, April 1, 2000, to December 31, 2002.
† The ratio is the comparison of the full-fortification rate to the prefortification rate.
‡ The difference is the prefortification rate minus the full-fortification rate.

Table 4. Prevalence of Neural-Tube Defects per 1000 Births, According to Fortification Period.*

Province	Prefortification	Partial Fortification	Full Fortification	Rate Ratio†	Difference in Rate‡
	rate (95% confidence interval)				
Newfoundland and Labrador	4.56 (3.78 to 5.35)	1.42 (0.80 to 2.21)	0.76 (0.48 to 1.31)	0.17 (0.09 to 0.32)	3.80 (2.89 to 4.71)
Prince Edward Island	2.08 (1.23 to 3.23)	1.06 (0.33 to 2.58)	0 (0 to 0.06)	0 (0 to 0.62)	2.08 (1.20 to 2.96)
Nova Scotia	2.72 (2.29 to 3.14)	1.32 (0.91 to 1.87)	1.26 (0.86 to 1.81)	0.46 (0.31 to 0.68)	1.46 (0.83 to 2.09)
Quebec	1.77 (1.61 to 1.95)	1.27 (1.19 to 1.45)	0.97 (0.79 to 1.16)	0.55 (0.47 to 0.65)	0.80 (0.61 to 0.99)
Manitoba	1.54 (1.25 to 1.84)	0.88 (0.61 to 1.19)	0.93 (0.64 to 1.24)	0.61 (0.42 to 0.88)	0.62 (0.20 to 1.02)
Alberta	1.12 (0.91 to 1.31)	0.73 (0.63 to 0.91)	0.67 (0.59 to 0.86)	0.60 (0.46 to 0.79)	0.45 (0.23 to 0.67)
British Columbia	0.96 (0.78 to 1.15)	1.08 (0.88 to 1.26)	0.75 (0.66 to 0.93)	0.78 (0.60 to 1.00)	0.21 (0.01 to 0.42)

* The fortification periods that were studied were as follows: prefortification: January 1, 1993, to September 30, 1997; partial fortification, October 1, 1997, to March 31, 2000; full fortification, April 1, 2000, to December 31, 2002.
† The ratio is the comparison of the full-fortification rate to the prefortification rate.
‡ The difference is the prefortification rate minus the full-fortification rate.

A previous study assessed the effect of folic acid fortification in the United States, using eight population-based surveillance systems that identified subjects with neural-tube defects that had been diagnosed prenatally.[25] In that study, the combined prevalence rate of anencephaly and spina bifida was 1.06 per 1000 births in 1995–1996, before fortification, and 0.76 per 1000 births in 1999–2000, after fortification was implemented, a 28% reduction. This decrease is less than the one we report in Canada: 46% for all neural-tube defects and 48% for anencephaly and spina bifida combined. The higher baseline rate in Canada may have contributed to the difference, but other factors could also play a role, including differences in ethnic distribution, eating habits, use of vitamin supplements, and the prevalence of other risk factors for neural-tube defects, such as maternal obesity and diabetes.[26,27]

We found a greater reduction in rates in regions with a higher baseline prevalence of neural-tube defects than in regions with a lower prevalence. The greatest reduction in birth prevalence was observed in Newfoundland and Labrador, which had a difference in rate of 3.80 per 1000 births, as compared with British Columbia, which had a difference in rate of 0.21 per 1000 births. These results are consistent with the findings of a study in China showing a more pronounced effect of prenatal folic acid supplementation in the northern part of the country, where the baseline rate of neural-tube defects (4.9 per 1000 births)

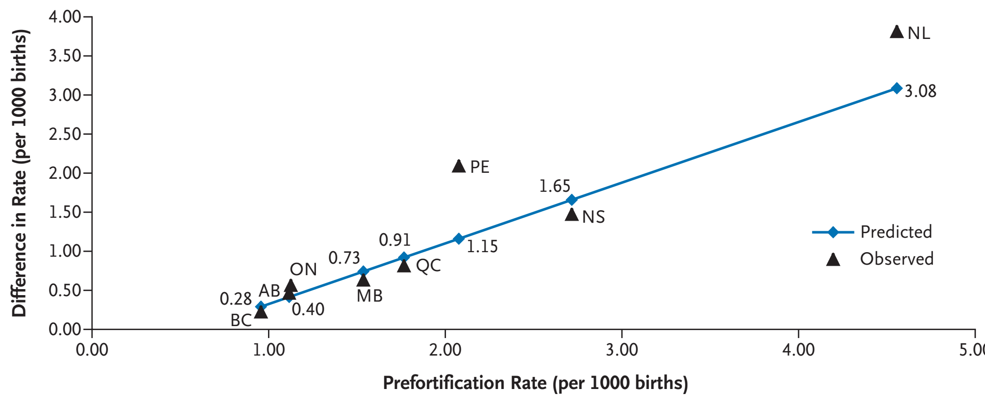


Figure 2. Decrease in the Rate of Neural-Tube Defects after Folic Acid Fortification Was Implemented, According to Baseline Prevalence in Canadian Provinces.

Rates are expressed as the absolute difference between the period before folic acid fortification and the period after full fortification. The model that best fit the observations was provided by a linear model predicting the difference in rates as −0.466 plus 0.7767 times the prefortification rate. BC denotes British Columbia, AB Alberta, MB Manitoba, QC Quebec, PE Prince Edward Island, NS Nova Scotia, NL Newfoundland and Labrador, and ON Ontario. Data for Ontario refer only to subjects with anencephaly and spina bifida born to women undergoing maternal serum screening from 1994 through 2000 and were not used to compute the prediction line.

was higher than that in the southern part (1.0 per 1000 births). Ultimately, a birth prevalence of 0.6 neural-tube defects per 1000 births was observed among women who received daily supplementation of 400 μg of folic acid in both regions.[11]

A simple linear function best represented the relationship between the baseline prevalence of neural-tube defects in a region and the magnitude of the decrease in the rate after fortification was implemented. This model might be used to predict the effect of a food-fortification program providing an average level of additional daily intake of 150 μg of folic acid, as estimated in Canada.[24] In Canada, the current rate of neural-tube defects ranges from 0.7 to 1.3 per 1000 births, with an average of 0.9 per 1000 births. Since not all cases of neural-tube defects can be prevented, the potential for further improvement would be smaller than that reported in our study but might be as much as 30% for a residual risk of 0.6 per 1000 births. Validation of our model is warranted in other settings.

Marked reductions in rates of neural-tube defects have occurred across Canada after fortification of food with folic acid was implemented. Decisions regarding the optimal level of food fortification and the types of foods to be enriched must take into account both safety, especially for seniors who may have unrecognized B_{12} deficiency,[28] and the goal of maximizing the reduction in neural-tube defects.

Supported by a grant (MOP-57904) from the Canadian Institutes of Health Research.

No potential conflict of interest relevant to this article was reported.

We thank Health Canada and the Public Health Agency of Canada for logistic assistance and Martine Six and Manale Ouakki at the Quebec University Hospital Research Centre for their help in the collection and analysis of data.

REFERENCES

1. Institute of Medicine. Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press, 1998: 196-305.
2. De Wals P, Rusen ID, Lee NS, Morin P, Niyonsenga T. Trends in prevalence of neural tube defects in Quebec. Birth Defects Res A Clin Mol Teratol 2003;67:919-23.
3. Canada Gazette part II: regulatory impact analysis statement, SOR/98-550. 1998;132(24):3029-33.
4. Little J, Elwood M. Geographical variation. In: Elwood JM, Little J, Elwood JH, eds. Epidemiology and control of neural tube defects. New York: Oxford University Press, 1992:96-145.
5. Nevin NC, Weatherall JAC. Illustrated guide to malformations of the central nervous system at birth. Edinburgh: Churchill Livingstone, 1983.
6. Lemire RJ. Neural tube defects. JAMA 1988;259:558-62.
7. Pacheco-Jacome E, Ballesteros MC, Jayakar P, Morrison G, Ragheb J, Medina LS. Occult spinal dysraphism: evidence-based diagnosis and treatment. Neuroimaging Clin N Am 2003;13:327-34.
8. Ray JG, Vermeulen MJ, Boss SC, Cole

DE. Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada. Can J Public Health 2002;93:249-53.

9. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. N Engl J Med 1999;341:1509-19.

10. Caudill MA, Cruz AC, Gregory JF III, Hutson AD, Bailey LB. Folate status response to controlled folate intake in pregnant women. J Nutr 1997;127:2363-70.

11. Berry RJ, Li Z, Erickson JD, et al. Prevention of neural tube defects with folic acid in China. N Engl J Med 1999;341:1485-90. [Erratum, N Engl J Med 1999;341:1864.]

12. Liu S, West R, Randell E, et al. A comprehensive evaluation of food with folic acid for the primary prevention of neural tube defects. BMC Pregnancy Childbirth 2004;4:20.

13. House JD, March SB, Ratnam MS, Crowley M, Friel JK. Improvements in the status of folate and cobalamin in pregnant Newfoundland women are consistent with observed reductions in the incidence of neural tube defects. Can J Public Health 2006;97:132-5.

14. Crane JMG, Sun C, Hutchens D, Crowley M. The epidemiology of neural tube defects in Newfoundland and Labrador. J Soc Obstet Gynaecol Can 2001;23:510-4.

15. Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. CMAJ 2002;167:241-5.

16. Ray JG, Meier C, Vermeulen MJ, Boss S, Wyatt PR, Cole DEC. Association of neural tube defects and folic acid food fortification. Lancet 2002;360:2047-8.

17. De Wals P, Trochet C, Pinsonneault L. Prevalence of neural tube defects in the province of Quebec, 1992. Can J Public Health 1999;90:237-9.

18. Tairou F, De Wals P, Bastide A. Validity of death and stillbirth certificates and hospital discharge summaries for the identification of neural tube defects in Quebec City. Chronic Dis Can 2006;27:120-4.

19. Van Allen MI, Boyle E, Thiessen P, et al. The impact of prenatal diagnosis on neural tube defect (NTD) pregnancy versus birth incidence in British Columbia. J Appl Genet 2006;47:151-8.

20. Morin P, De Wals P, St-Cyr-Tribble D, Niyonsenga T, Payette H. Pregnancy planning: a determinant of folic acid supplements use for the primary prevention of neural tube defects. Can J Public Health 2002;93:259-63.

21. Morin P, De Wals P, Noiseux M, Niyonsenga T, St-Cyr-Tribble D, Tremblay C. Pregnancy planning and folic acid supplement use: results from a survey in Quebec. Prev Med 2002;35:143-9.

22. French MR, Bar SI, Levy-Milne R. Folate intakes and awareness of folate to prevent neural tube defects: a survey of women living in Vancouver, Canada. J Am Diet Assoc 2003;103:181-5.

23. Ray JG, Vermeulen MJ, Boss SC, Cole DE. Increased red cell folate concentrations in women of reproductive age after Canadian folic acid food fortification. Epidemiology 2002;13:238-40.

24. Quinlivan EP, Gregory JF III. Effect of food fortification on folic acid intake in the United States. Am J Clin Nutr 2003;77:221-5.

25. Spina bifida and anencephaly before and after folic acid mandate — United States, 1995–1996 and 1999–2000. MMWR Morb Mortal Wkly Rep 2004;53:362-5.

26. Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. JAMA 1996;275:1093-6.

27. Velie EM, Shaw GM, Malcoe LH, et al. Understanding the increased risk of neural tube defect-affected pregnancies among Mexico-born women in California: immigration and anthropometric factors. Paediatr Perinat Epidemiol 2006;20:219-30.

28. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 2007;85:193-200.