

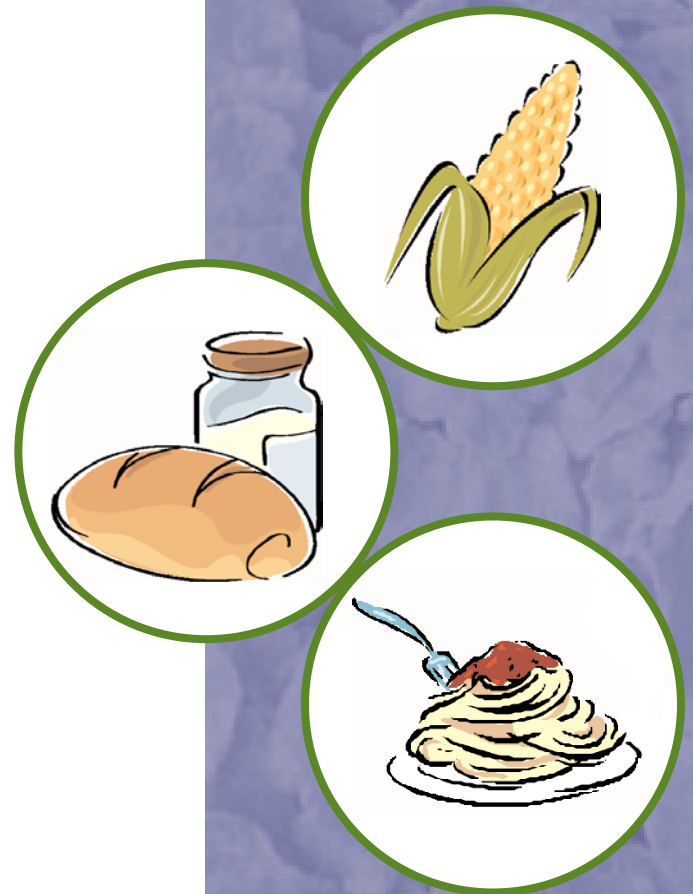


# Evaluation of **Food Fortification with Folic Acid** for the Primary Prevention of Neural Tube Defects

## Executive Summary

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1997–2003





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This study was granted full ethics approval by research ethics boards at Memorial University of Newfoundland and at Queen's University. All study subjects gave written informed consent prior to participation in this study.

## Background

**N**EURAL TUBE DEFECTS (NTDs) ARE BIRTH DEFECTS RESULTING FROM THE FAILURE OF NEURAL TUBE

closure during early development of the human embryo. The 1997 Canadian national NTD rate was 0.75 per 1,000 births (live births and stillbirths), down from 1.16 per 1,000 in 1989 (Health Canada, 2000). The rates tend to be higher in the eastern provinces than in the west (Persad et al. 2002; Gucciardi et al. 2002; Crane et al. 2001). Historically, Newfoundland has had one of the highest rates in North America with a reported average yearly incidence rate for 1976-1997 of 3.4 per 1,000 births (including live births, stillbirths and fetuses from pregnancies terminated after a prenatal diagnosis of an NTD) (Crane et al. 2001).

Evidence from a number of studies has demonstrated that periconceptual use of vitamin supplements containing folic acid reduces the risk of NTDs (Laurence et al. 1981; Smithells et al. 1983; MRC Vitamin Study Research Group 1991; Czeizel and Dudas 1992). Although the mechanism of action of this nutrient in influencing the risk of NTDs is poorly understood, the evidence of the benefit of folic acid has led many health organizations since late 1992 to recommend periconceptual folic acid supplementation, at a level of 400 µg/day for low risk women (CDC 1992; Health Canada 1993; Canadian Task Force on the Periodic Health Examination 1994).

Because of concern that public education campaigns alone would not be effective in achieving optimal periconceptual folic acid intake for the majority of women, food fortification with folic acid was proposed as a strategy to ensure that all women of childbearing

age increase their dietary intake of this vitamin. In March 1996 the US Food and Drug Administration (FDA) announced that it would permit addition of folic acid to enriched flour and other enriched cereal grain products, and that this addition would be mandatory as of January 1998. The level of fortification was set at 0.14 mg folic acid per 100 g of cereal grain product. It was determined that at this level of fortification, the intake of folate (from all sources) for the target and the general population would be kept below 1,000 µg/day, which was deemed to be the safe upper limit. This level of fortification was estimated to increase the average daily intake of folic acid in women of childbearing age by about 100 µg (Food and Drug Administration 1996).

Subsequent to the US decision, Canada followed suit, permitting folic acid fortification at an equivalent level in December 1996 (addition of folic acid to white flour and enriched pasta and cornmeal at 0.15 mg folic acid per 100 g of flour and 0.20 mg folic acid per 100 g of pasta). In Canada, fortification became mandatory in November 1998 (Canada Gazette 1998).

The question of whether folic acid fortification of grain products poses any serious health risk has been controversial. The main concern has been the potential masking of vitamin B<sub>12</sub> deficiency, a condition that affects 10-15% of the population over age 60 (Institute of Medicine 1998; Balk and Russell 1999). Increased folic acid intake may correct the haematologic signs of vitamin B<sub>12</sub> deficiency, thus delaying diagnosis and treatment of the condition while its attendant neurologic manifestations progress. Seniors may be at particular risk since the incidence of vitamin B<sub>12</sub> deficiency increases with age.

Thus, Health Canada undertook a population based study to evaluate the effectiveness of the public health strategy of food fortification with folic acid and to determine possible adverse effects resulting from fortification.

## Objectives and Methods

**T**HE STUDY WAS A MULTI-SITE POPULATION BASED STUDY CARRIED OUT IN TWO PHASES; THE FIRST phase took place prior to mandatory fortification, from November 1997 to March 1998 and the second phase took place after fortification had been implemented for two years, from November 2000 to March 2001.

Because of the high rates of NTDs in Newfoundland, an urban (St. John's) and a rural (Clarenville, Port Blandford, Random Island area) location in this province were chosen as sites for this study. A third site in southeastern Ontario (counties of Frontenac and Lennox & Addington, including the city of Kingston) was also chosen.

### Study objectives

The objectives of this study were:

- To determine knowledge and consumption of folic acid supplements, pre- and post-fortification, in women of childbearing age (19-44 years).
- To determine dietary intake of folate pre- and post-fortification in women of childbearing age and in seniors ( $\geq 65$  years).
- To determine blood folate and vitamin B<sub>12</sub> status in women of childbearing age and in seniors pre- and post-fortification.
- To determine whether the incidence of NTDs in Newfoundland declined following fortification.

**Table 1** shows schematically the framework including objectives and sampling of subjects for this study.

### Data collection

Through random telephone surveys in the three sites, non-pregnant women of childbearing age (19-44 years) and who spoke English were recruited. In the initial telephone survey, women were asked about their use of vitamin supplements and knowledge of the importance of folic acid for reducing the risk of NTDs or for fetal development. Questions about likelihood of pregnancy and demographic characteristics were asked in order to assess whether these factors influenced knowledge and behaviour.

Women who completed the initial telephone survey were screened for their eligibility for the dietary and blood assessments. Women who were not taking supplements containing folic acid were eligible to participate. Seniors were recruited in the same manner as the sample of women, but were drawn only from St. John's, Newfoundland. Seniors age 65 or over, not diagnosed with vitamin B<sub>12</sub> deficiency or anaemia and not taking vitamin B<sub>12</sub> or supplements containing folic acid, were eligible for dietary and blood sample assessments.

In order to determine intakes of naturally occurring folate (the form of the vitamin found naturally in foods) pre and post fortification, and dietary intakes of folic acid (the synthetic form of the vitamin) post fortification, a Willett food frequency dietary questionnaire (Willett et al. 1987) was administered to subjects during an in-person interview by trained personnel. There were some modifications to the questionnaire to include common Newfoundland foods and to ensure that all foods high in folate were included. The dietary questionnaire was used to estimate an average frequency of consumption of 124 food items over the previous period of one year. The Willett food frequency dietary questionnaire is well validated (Willett et al. 1988) and proved easy to administer for this sample population.

The women and senior participants were also asked to provide a sample of blood in order to determine blood folate and vitamin B<sub>12</sub> status, pre- and post-fortification. Laboratory tests for complete blood count (CBC), red blood cell (RBC) folate, serum folate, creatinine, vitamin B<sub>12</sub>, plasma homocysteine (HCY) and methylmalonic acid (MMA) were conducted at the laboratories of the Health Care Corporation of St. John's.

In order to examine temporal changes in the incidence of NTDs in Newfoundland, data for 1976 to 2001 were compiled by the Newfoundland and Labrador Medical Genetics Program. NTD cases include anencephaly, spina bifida and encephalocele diagnosed in live births, stillbirths and fetuses from pregnancies terminated after a prenatal diagnosis of an NTD.

## Data analysis

Data collected from these sites were compared between Phase I and Phase II. Data from the blood analyses were tested for normality with the Komogorov-Smirnov test, and the Shapiro-Walk test when the number of data points was less than 50. Differences between groups were tested using the non-parametric Kruskal-Wallis test and the Mann-Whitney U test or Student's t-test. The distributions of plasma MMA, plasma HCY, serum folate, RBC folate and serum vitamin B<sub>12</sub> were skewed. Values were therefore log transformed to give an approximate normal distribution for estimation of geometric mean and confidence intervals. Unless otherwise stated, all laboratory values presented in this paper are geometric means and 95% confidence intervals (CI). Differences in the frequency of high or low results based on reference values were tested by Pearson chi-square statistics.

Incidence of NTDs was defined as the number of above described NTD cases, divided by the total number of live births, stillbirths, and pregnancy terminations for an NTD (termed as "births" hereafter). First we examined the temporal trend in annual incidence of NTDs from 1976 to 2001 using 3-year moving average rates, then we focused on comparison of the incidence data for the most recent

11 years, identified as pre-supplementation (1991-1993), pre-fortification (1994-1997) and post-fortification (1998-2001). We regard the year 1997 as a transition period, or partial fortification period, since fortification of white flour and enriched pasta and cornmeal was *permitted* in Canada as of December 1996 (Canada Gazette 1996). Thus we also analysed the incidence data using 1994-1996 as a pre-fortification period.

All data for this study were entered into SPSS (the Statistical Package for Social Sciences) Rel. 10.0 after the end of each phase. Data from the dietary interviews were analyzed using Epi-Info (Version 6.04d), while the laboratory data and the data about knowledge and use of supplements were analyzed using SPSS.

## Study Results and Interpretation

### Knowledge and use of folic acid supplements

There was a significant increase from Phase I to Phase II in the proportion of women aged 19-44 who knew the importance of folic acid in Newfoundland (two sites combined) (from 33% to 46%,  $p < 0.001$ ) and in Kingston, Ontario (from 36% to 51%,  $p < 0.001$ ). The proportion of women taking a vitamin supplement containing folic acid increased significantly between the two time periods in Newfoundland (from 17% to 28%,  $p < 0.003$ ), but increased non-significantly in Kingston, Ontario (from 33% to 39%,  $p > 0.05$ ) (**Table 2**). In Ontario, the proportion of women who reported taking supplements with at least 400µg folic acid per dose increased between Phase I and Phase II (from 17% to 26%,  $p < 0.005$ ) (data available in full report). Information about folic acid dosage was not collected in Newfoundland.

In the Phase II Newfoundland sample, women who were trying to conceive or who were sexually active and not using birth control were more likely to be taking supplements containing folic acid than women who were using birth control or who had taken permanent measures to prevent pregnancy (see full report). There was a 37 percentage points increase in use of supplements containing folic acid among women with a chance of pregnancy in Phase II in Newfoundland ( $p = 0.02$ ). Although there was also an increase in the Ontario sample, the results were not statistically significant (**Table 3**).

This study suggests that the message to take folic acid is not getting through to enough women of childbearing age, despite a range of national and local educational initiatives, including development and dissemination of Canadian clinical practice guidelines (Canadian Task Force on the Periodic Health Examination 1994), well-publicized national conferences and local public health campaigns. Although we have shown some increase over three years in folic acid supplement use, considerable room for improvement remains.

### Dietary assessment

There was no statistically significant change in the average daily intake of naturally occurring folate among either women aged 19-44 or seniors between Phase I and Phase II ( $p = 0.19$  and  $p = 0.18$ , respectively). Seniors generally had dietary folate intake slightly higher than women of childbearing age. In Phase II, the average daily intake of naturally occurring folate was 290 µg/day for seniors and 260 µg/day for women aged 19-44 (data available in full report).

The implementation of mandatory fortification resulted in an average dietary intake of 70 µg/day of folic acid in women aged 19-44, and 74 µg/day of folic acid among seniors. It is noteworthy that for the women the average daily folic acid intake due to food fortification was less than the approximately 100 µg that was previously predicted for women of childbearing age (Food and Drug Administration 1996, Turner and McCourt 1998). The maximum dietary intake of folic acid due to fortification for an individual woman was 235 µg/day, and for an individual senior was 219 µg/day (data available in full report).

Income was a significant predictor of folate intake. Both women of childbearing age and seniors living in households with income below the Low Income Cutoff (LICO) had lower folate intake. A detailed examination of the dietary sources of folate for the women of childbearing age showed that the difference in consumption for those below the LICO was due solely to lower consumption of naturally occurring folate and not due to less consumption of cereal grain products that were the target for fortification with folic acid.

The dietary folic acid intake due to fortification did not exceed the Tolerable Upper Intake Level (UL) of 1,000 µg folic acid/day (Institute of Medicine 1998) for any of the participants. It is important to note that this part of the study excluded persons taking vitamin supplements containing folic acid. While it was not possible to estimate the proportion of people



in the general population who may be consuming more than 1,000 µg/day of folic acid from fortification and supplementation combined, it is likely that this proportion is small. The average dietary intake and maximum intake of folic acid due to fortification were 70 µg/day and 235 µg/day, respectively, for women aged 19-44 years, and 74 µg/day and 219 µg/day, respectively, for seniors. The average folic acid dose in folic acid containing over-the-counter supplements marketed in Canada is about 350 µg/day (Health Canada unpublished information).

### Blood analysis — folate

For all sites combined, mean serum folate and RBC folate increased significantly from Phase I to Phase II in both women of childbearing age and seniors ( $p < 0.001$ ). For both age groups, there was a corresponding decrease in mean plasma HCY levels post fortification (**Tables 4 and 5**).

The results of this study provide strong evidence of improved blood folate status in women aged 19-44 following mandatory fortification with folic acid. Among seniors, the improvements in folate indices and the moderate decrease in mean plasma HCY are a positive result, especially with regard to risk of cardiovascular disease.

### Blood analysis — vitamin B<sub>12</sub>

There was a significant increase in mean vitamin B<sub>12</sub> levels in women of childbearing age and seniors between Phases I and II ( $p = 0.020$  and  $p < 0.001$ , respectively) (**Tables 4 and 5**). Prior to mandatory fortification the proportion of seniors in this study with low vitamin B<sub>12</sub> (<133 pmol/L) was 18.8%. Following fortification the proportion of elderly with low vitamin B<sub>12</sub> levels declined to 11.8% ( $p = 0.032$ ) (data available in full report).

In vitamin B<sub>12</sub> deficiency, plasma MMA is usually elevated. Plasma MMA is believed to be a better indicator of vitamin B<sub>12</sub> status at the tissue level than serum vitamin B<sub>12</sub> levels are. In this study, no significant changes were seen in mean plasma MMA levels for women of childbearing age from all sites or for seniors between Phases I and II (**Tables 4 and 5**). However, there was an increase in the proportion of

women of childbearing age with MMA values above the upper reference value of 0.37 µmol/L. Also, for the Newfoundland sample of women, there was a statistically significant increase in mean plasma MMA. There was no significant change in the proportion of abnormal MMA values in seniors (data available in full report).

Among seniors, the results showed no significant difference in mean haemoglobin concentrations, mean corpuscular volume (MCV), or proportion with abnormally high MCV (>99 fL) or low haemoglobin (<120 g/L) concentrations (data available in full report).

These results show no evidence of a deterioration in vitamin B<sub>12</sub> status among seniors. Furthermore, there is no evidence of improved folate status resulting in masking of the haematological manifestations of vitamin B<sub>12</sub> deficiency among seniors as a group. There was no evidence of deteriorating vitamin B<sub>12</sub> status among young women participants based on vitamin B<sub>12</sub> measurements. The upward trend in plasma MMA levels and higher proportion of abnormal values among young women is being further evaluated.

It is unlikely that this is a direct effect of folic acid fortification and this observation is not consistent with any known effects of folic acid on vitamin B<sub>12</sub> status.

### Incidence of NTDs

Prior to 1998, the annual incidence rate of NTDs in Newfoundland varied greatly over time, with the lowest rate of 2.72 per 1,000 births in 1978, and the highest rate of 5.02 per 1,000 births in 1995. The average incidence rate of NTDs between 1976 and 1997 was 3.40 per 1,000 births. A drop is seen in 1998, in which the rate of NTDs was 1.60 per 1,000 births, from 3.06 per 1,000 births in the previous year. The decreasing trend continued after 1998 (**Figure 1**).

The incidence of NTDs for the years 1991-2001 is presented in three periods in **Table 6**. The mean annual incidence was 4.35 per 1,000 births during 1991-1993 and 5.02 per 1,000 births during 1994-1996 (1994-96 vs 1991-93, relative risk [RR] 1.15, 95% CI 0.86-1.54,  $p = 0.95$ ), and 4.37 per 1,000 births during 1994-1997 (1994-97 vs 1991-93, RR 1.01, 95% CI 0.76-1.34,  $p = 0.54$ ). The total annual

incidence of NTDs fell by 78% after the implementation of folic acid fortification, from an average of 4.36 per 1,000 births during 1991-1997 to 0.96 per 1,000 births during 1998-2001 (RR 0.22, 95% CI 0.14-0.35,  $p < 0.0001$ ). It is worthwhile to note that there has been no significant increase in the proportion of NTDs from terminated pregnancies since 1994.

The 65% increase in the proportion of women in the Newfoundland sample who were taking vitamin supplements containing folic acid, from 17% in Phase I to 28% in Phase II, suggests that an increasing trend in folic acid supplementation may have played a role in the declining NTD rate in Newfoundland. In this study it was not possible to determine the individual contribution of supplementation and fortification to the trend in NTDs.

## Limitations

There are several limitations in this study. We have documented the incidence of NTDs among live births, stillbirths and terminated pregnancies known to have an NTD. It was not possible to include NTDs that may have occurred in pregnancies that resulted in a spontaneous abortion or a termination that occurred for reasons other than a congenital anomaly.

This study, as with other studies of fortification in Canada, was challenged by the fact that there was no precise date when exposure to food fortification with folic acid began. The addition of folic acid to white flour and enriched pasta and cornmeal was permitted as of December 1996. Although this requirement did not come into force in Canada until late 1998, the Phase I (November 1997 to March 1998) subjects of our study may have consumed at least some food fortified with folic acid. This would result in an underestimate of improvements in blood folate status due to fortification, and might lead us to miss adverse effects on vitamin B<sub>12</sub> status. On the other hand, the fact that we observed such marked improvements in blood folate status leads us to conclude that there was a real increase in exposure to folic acid through fortification over the study period.

Another limitation of this study is the possible underestimation of folic acid intake due to fortification. Our calculations were based on the assumption that manufacturers are fortifying flour at the required level.

It has been suggested that allowance for “overages” is resulting in higher amounts in the affected products (Choumenkovitch et al. 2002). Also, for enriched pasta, the required level of fortification is from a minimum of 0.20 mg/100 g pasta to a maximum of 0.27 mg/100 g. In our calculations we assumed the minimum level of fortification.

The sampling procedure showed a Phase I 60% and Phase II 65 % response rate for the dietary questionnaire and blood sampling among women aged 19-44 years in Newfoundland, with no difference between urban and rural response rates. In contrast, the response rates for Ontario were 28% for Phase I and 37% for Phase II (data available in full report). Thus the results in Newfoundland may better reflect the province’s women of childbearing age compared to Ontario’s results. These findings may not be representative of the rest of Canada because of population differences in factors such as genetic background and dietary behaviour. These differences may also affect the generalizability of the NTD incidence results.

The sample response rate for the dietary questionnaire and blood sampling in seniors was 45% both in Phase I and in Phase II (see full report). Many of the refusals to participate were due to illness of the eligible person. Furthermore, seniors residing in long term care settings were not included. Thus our sample population of seniors may be healthier than the general population age 65 and over in Newfoundland.

## Conclusions

### Primary findings

- The implementation of food fortification with folic acid has been accompanied by a marked decrease (78%) in the incidence of NTDs in Newfoundland. Increased use of folic acid supplements may also have played a role in the declining NTD rate. It was not possible to determine the separate contributions of fortification and supplementation.
- At the current levels of food fortification with folic acid, there is no evidence of a deterioration in vitamin B<sub>12</sub> status among seniors. Furthermore, there is no evidence of improved folate status resulting in masking of the haematological manifestations of vitamin B<sub>12</sub> deficiency among seniors as a group.

### Secondary findings

- Although there has been an increase in women's knowledge and use of folic acid supplements, in Phase II of our study only about one-half of the women of childbearing age were aware of the importance of folic acid. Approximately one-third were taking supplements containing folic acid in Phase II.
- The results of this study highlight the need to re-examine strategies for improving women's understanding of the link between periconceptional folic acid intake and NTD prevention.
- As a result of fortification, there have been significant improvements in blood folate status among women of childbearing age and seniors.

### Recommendations

- Continue food fortification with folic acid at currently mandated levels.
- Continue public health efforts to promote awareness of the importance of folic acid supplementation by women of childbearing age.
- Initiate studies to quantify the independent contribution of fortification and supplementation to rates of NTDs.
- Continue monitoring of possible adverse health outcomes of fortification, particularly in seniors and children.
- Assess changes in NTDs post fortification in areas with lower incidence rates.

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## Tables and Figures

**Table I: Framework for a two-phase, multi-site study to examine the effects of food fortification with folic acid**

Content	Study objective	Sample**	Location
I. Knowledge and intake of folic acid supplements	Determine knowledge and consumption of folic acid supplements, pre- and post-fortification	Non-pregnant women of childbearing age (19-44 years)	St. John's Rural Newfoundland Kingston, Ontario
II. Dietary assessment*	Determine dietary intake of folate, pre- and post-fortification	A) Non-pregnant women of childbearing age (19-44 years), not taking supplements containing folic acid;	St. John's Rural Newfoundland Kingston, Ontario
III. Blood analysis*	Determine blood folate and vitamin B12 status, pre- and post-fortification	B) Seniors (65 years or older) not taking supplements containing folic acid or B12 supplements and not diagnosed with anaemia	St. John's only
IV Rates of NTDs	Determine incidence of NTD-affected pregnancies, pre- and post-fortification	Provincial population	Province of Newfoundland and Labrador

\* For each phase, the same sample of women and seniors were analyzed in Components II and III.

\*\* Sampling was done separately for Phases I and II.

**Table 2: Knowledge and use of supplements containing folic acid**

	Newfoundland		Ontario	
	Phase I	Phase II	Phase I	Phase II
Participants (n)	469	443	481	451
Knowledge (%)	32.8	45.6*	35.6	51.2*
Use of supplements (%)	17.1	28.0*	33.0	38.8

\* Increase from Phase I to Phase II is statistically significant.

**Table 3: Use of supplements containing folic acid by likelihood of pregnancy**

Likelihood of pregnancy	Newfoundland				Ontario			
	Phase I		Phase II		Phase I		Phase II	
	Number	% users	Number	% users	Number	% users	Number	% users
Not using birth control	50	18.0	33	54.5*	53	41.5	38	50.0
Using birth control	202	19.8	200	27.0	224	29.4	172	40.6
No chance	198	11.1	193	20.7	199	34.2	236	35.6
Information not available	19	47.4	17	70.6	5	60.0	5	40.0
Total	469	17.1	443	28.0	481	33.0	451	38.8

\* Increase from Phase I to Phase II is statistically significant.

**Table 4: Laboratory data (geometric mean and 95% confidence interval) for young women participants (age 19-44 years) for Phase I and Phase II**

Characteristics	Phase I	Phase II	p value*
Total participants (n)	322	305	—
Serum folate (nmol/L)	14.4 (13.9 - 15.0)	19.0 (18.4 - 19.7)	<0.001
RBC Folate (nmol/L)	647 (627 - 669)	796 (769 - 824)	<0.001
Plasma HCY (μmol/L)	10.0 (9.6 - 10.4)	8.9 (8.6 - 9.2)	<0.001
Serum vitamin B12 (pmol/L)	188 (180 - 197)	199 (191 - 207)**	0.02
Plasma MMA (μmol/L)	0.18 (0.17 - 0.19)	0.20 (0.18 - 0.21)**	0.169

\* Significance test of difference between Phase I and Phase II is based on non-parametric Mann-Whitney U test.

\*\* The distribution of log-transformed data failed when tested for normality by the Komogorov-Smirnov test for  $p < 0.05$ .

**Table 5: Laboratory data (geometric mean and 95% confidence interval) for senior participants (age 65 or over) for Phase I and Phase II**

Characteristics	Phase I	Phase II	p value*
Total participants (n)	202	186	—
Serum folate (nmol/L)	14.8 (14.0 - 15.6)	23.0 (22.0 - 24.1)	<0.001
RBC Folate (nmol/L)	745 (713 - 779)	916 (873 - 961)**	<0.001
Plasma HCY (µmol/L)	13.6 (13.0 - 14.2)**	12.3 (11.7 - 12.9)**	0.001
Serum vitamin B12 (pmol/L)	183 (173 - 194)	216 (202 - 231)	<0.001
Plasma MMA (µmol/L)	0.24 (0.22- 0.27)**	0.26 (0.24 - 0.28)	0.229

\* Significance test of difference between Phase I and Phase II is based on non-parametric Mann-Whitney U test.

\*\* The distribution of log-transformed data failed when tested for normality by the Komogorov-Smirnov test for p <0.05.

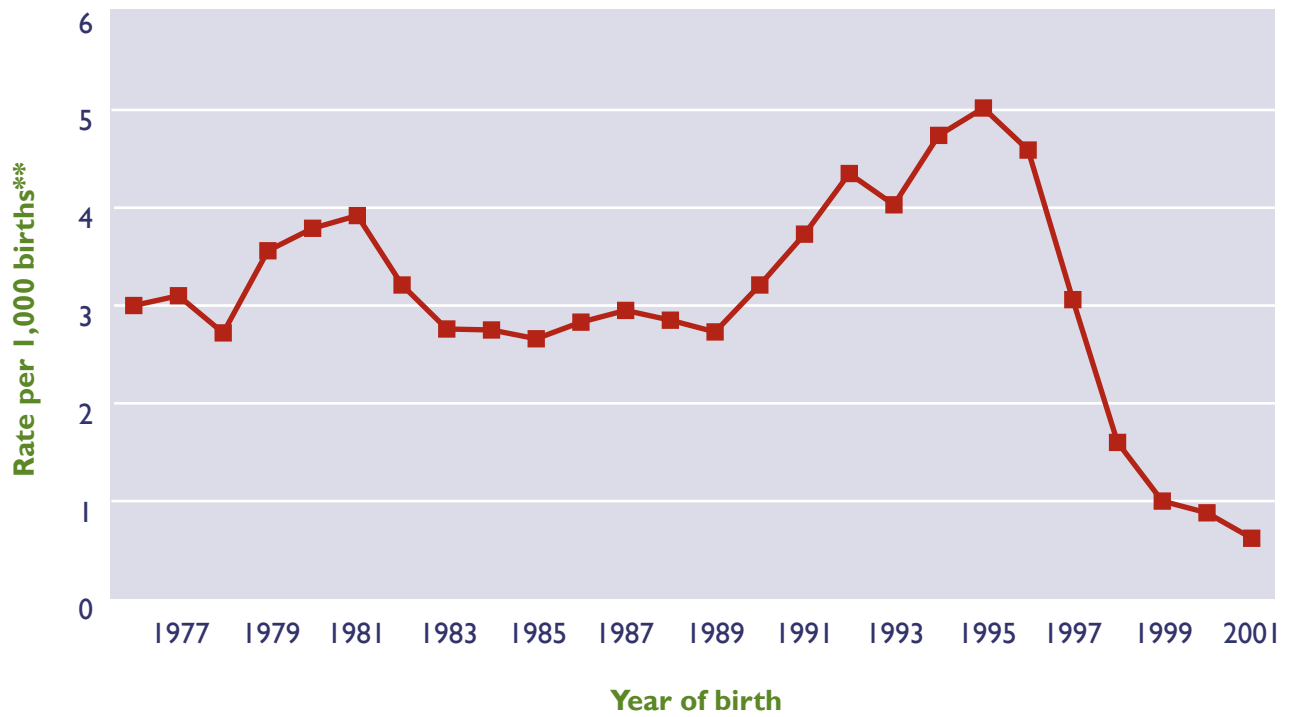
**Table 6: Incidence of neural tube defects (NTDs) in Newfoundland before folic acid supplementation (1991-1993), prior to folic acid fortification (1994-1997) and after fortification (1998-2001)**

Year	Number of cases of NTDs			Total number of births*	Average incidence per 1,000 births per year
	In live births and stillbirths	In terminated pregnancies	Total		
Pre-supplementation 1991-1993	50	40	90	20,711	4.35
Pre-fortification 1994-1997	53	50	103	23,592	4.37
Post-fortification 1998-2001	8	11	19	19,816	0.96

\* The total number of births includes live births, stillbirths and terminations for NTD.



**Figure 1: Incidence of NTDs in Newfoundland, 1976 to 2001 (3-year moving average rates)\***



\* The rate for 1976 is a 2-year average based on data for 1976 and 1977 and the rate for 2001 is a 2-year average based on data for 2000 and 2001.

\*\* Live births, stillbirths and terminations for NTDs.