Time trends in neural tube defects prevalence in relation to preventive strategies: an international study

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Abstract

Objective—To examine time trends in neural tube defects (NTD) prevalence from 1987 to 1996 in relation to the primary prevention policies for folic acid supplementation strategies in different countries.

Design—Retrospective time trends analysis of NTD prevalence.

Setting—11 birth defect registries of congenital malformations participating in the International Clearinghouse for Birth Defects Monitoring System, in the period from 1 July 1987 to 30 June 1996.

Subjects—8207 live births, stillbirths and terminated pregnancies affected by anencephaly or spina bifida registered by the 11 participating centres 1987–1996.

Outcome measures—Prevalence rate ratios based on the annual rates, using the Poisson regression model.

Results—During the study period a significant fall in prevalence rates for all NTD is present in Atlanta (USA), England and Wales, Hungary and Japan, and a significant rise in Norway and South America. After adjusting for the secular trends observed in the earlier years of the study, no significant trend can be attributed to preventive strategies. Data on NTD prevalence are supplemented with information on folate awareness among some of the populations studied.

Conclusion—There is no evidence that, up to the middle of 1996, any change in time trend was attributable to the introduction of national folate supplementation policies. The possible effectiveness of folate supplementation policies for the reduction of NTD clearly needs to be tried and studied for several more years. Considering that in the Western world about 50% of pregnancies are unplanned, a policy that rests on action taken before conception can only have limited success. Strategies based on food enrichment, such as was introduced in the USA from the beginning of 1998, may prove to be more successful.

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support to the hypothesis that folic acid supplements, either alone or in multivitamin preparations, could prevent a high proportion of NTD if taken before and during early pregnancy.^{2 3} The strongest support for the hypothesis came from two large, randomised studies. The UK Medical Research Council⁴ showed that folic acid, 4 mg daily, gave significant protection against recurrences of NTD. Czeizel and Dudas⁵ showed that a multivitamin preparation containing folic acid 0.8 mg protected against the first occurrence of NTD.

After these publications, government health departments in a number of countries began to consider how this new knowledge might be put to practical use by developing public health policies relating to folic acid supplementation.

The purpose of this study, which was carried out by the International Centre for Birth Defects (ICBD) in collaboration with the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS), was to examine time trends in NTD prevalence in relation to folic acid supplementation strategies in different countries.

Methods

Our inquiries into the extent of folic acid supplementation were related to three questions:

- 1 Is there a national policy on folate supplementation?
- 2 If so, how effectively is it being implemented?
- 3 Whether or not there is a national policy, what is actually happening? Are women being encouraged, by health personnel or the mass media, to increase their folic acid intake? How aware are women of folic acid and its relevance to fetal development?

Several of the countries represented by the programmes participating in this study promulgated national policies at different times during the course of this study. In some of these, studies have been undertaken to determine the extent to which their policies are being implemented. To augment this information, the directors of participating programmes were asked to undertake at least one, and preferably two, “folate awareness surveys” to determine what women of childbearing age knew about folic acid, and how many had taken steps to increase their folic acid intake, by taking vitamin pills, by changing their diet, or both, before starting a pregnancy.

Our study of time trends in NTD prevalence was based on birth registries in ICBDMS. This

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A possible link between folic acid deficiency and neural tube defects (NTD) in humans was first proposed by Hibbard and Smithells.¹ Throughout the 1980s, a number of observational and intervention studies gave strong

Table 1 Cases of NTD by registry and period

Programme	Period covered	No of births monitored	NTD cases		Total
			Live births + stillbirths	Induced abortions	
England and Wales	1988–96	6 500 000	1042	3055	4097
France, Central East	1987–96	955 000	192	305	497
France, Paris	1987–96	380 000	53	275	328
France, Strasbourg	1987–95	120 000	15	80	95
Hungary	1987–96	1 150 000	412	51	463
Israel	1988–96	28 000	16	0	16
Japan	1988–96	1 110 000	752	0	752
North Netherlands	1988–96	169 000	122	35	157
Norway	1987–96	568 000	289	103	392
South America	1988–96	748 000	1208	0	1208
USA, Atlanta	1988–96	350 000	167	35	202
Total		12 078 000	4268	3939	8207

was founded in 1974, and links a group of birth defects registries that have reliable records of the prevalence of all major congenital anomalies in the populations they cover. Some are based on defined geographical populations, others on births in one or more hospitals. Their methodologies are not identical but do not change over time, so year on year comparisons of prevalence rates are valid.

Monitoring programmes included in this study fall into two categories:

- 1 Those that have data on induced abortions for NTD.
- 2 Those in countries where induced abortion for birth defect is illegal.

Programmes in countries that permit induced abortions but that do not have access to the relevant data have been excluded. The aim of this was to limit the study to registries including all cases of NTD that would have been born if no legal induced abortions had taken place.

For the purposes of this study, NTD were defined as anencephaly and spina bifida. Cases in which the two conditions coexist are classified as anencephaly—that is, no infant or fetus is counted twice.

The time period covered was from 1 January 1988 to 30 June 1996 for live and still births. Induced abortions were recorded from 1 July 1987 to 31 December 1995 on the basis that, had they not been aborted, they would have been born, on average, about six months later. If the gestational age of an aborted fetus was known, a theoretical date of birth was calculated. Time trends were calculated from these data.

Annual time trends were analysed using a regression model. As we are interested in the relation between the number of cases per year over a period of time, allowing for possible confounding factors, the most suitable model is the Poisson regression model.⁶

Using different Poisson models, we estimated the average annual variation in prevalence rates 1988–96 (table 2) and the ratio between the prevalence rates in the two periods before and after 1994, when the folate policies might have begun to produce effects (table 3). However, such ratios do not distinguish the real effect of the policies from the general trend of NTD occurrence. For this purpose we estimated the ratios adjusted for the effect of long term tendency (table 4). The results are

expressed in terms of prevalence rate ratio (PRR). Values of PRR>1 indicate an increase, values of PRR<1 indicate a decrease. (For further statistical details, see appendix)

Results

INQUIRIES INTO FOLATE SUPPELMENTATION
National policies on folate supplementation for prevention of NTD

Recommendations on folate supplementation for the prevention of NTD were first promulgated to the public and the health professions in the USA in September 1992, followed by England and Wales in December 1992. Similar recommendations were made in the Netherlands in November 1993. Hungary followed suit in September 1995. In Israel, a national policy was agreed but was thought not to have been implemented before the end of the study period. Up to that time, Japan, Norway, France and South America had not adopted any national policies on supplementation.

Folate awareness

The existence of a national policy on folate supplementation does not mean that it is necessarily being implemented, or to what extent. The absence of a national policy does not necessarily mean that the public and health professions are not informed about the use of folic acid to prevent NTD and are not using it for this purpose. An attempt was therefore made by most of the participating programmes to determine from representative samples of women of childbearing age (in many cases, women attending antenatal clinics) their knowledge and use of folic acid for NTD prevention.

England and Wales—A number of studies have been carried out by Sutcliffe,⁷ Clark and Fisk⁸ and Wild.⁹ These showed very low levels of awareness in the year after national recommendations had been promulgated, with a significant improvement thereafter. Three studies in the city of Leeds showed that in 1993, 11 (1.8%) of 613 women interviewed at their first antenatal clinic attendance had taken folic acid before conception. The following year this figure had risen to 110 (18.2%) of 603 comparable women. By 1996 the number had increased to 208 (30.6%) of 679 women. (Wild 1997, personal communication)

France—A study in Paris in 1995,¹⁰ showed that 68 (9.3%) of 733 women in maternity hospitals had taken folic acid before pregnancy or during the first month. In 58 of these cases (85%) the folic acid was prescribed by a doctor.

Hungary—Of 105 women interviewed in 1992, seven (6.7%) had taken multivitamins that included folic acid before conception.¹¹ None had taken folic acid alone. It should be mentioned, however, that Hungary contributed the largest number of women of any country participating in the UK Medical Research Council study⁴ on prevention of NTD recurrence, and was the location of the only randomised study of prevention of first occurrence of NTD.⁵ The preventive role of folic

Table 2 Time trend analysis: cases and rates by registry and by year—Anencephaly

	Year																				PRR† (95% CI)
	1988		1989		1990		1991		1992		1993		1994		1995		1996		Total		
	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	
Registry	298	4.28	248	3.59	258	3.64	241	3.43	231	3.34	221	3.26	209	3.13	203	3.12	79	2.42	1988	3.42	0.95 (0.94, 0.97)
England and Wales	14	1.53	18	1.80	22	2.04	24	2.24	23	2.19	23	2.31	25	2.51	17	1.67	7	1.34	173	2.00	1.01 (0.95, 1.07)
France-Central East	18	4.37	14	3.35	22	5.22	26	6.16	21	5.12	13	3.23	15	3.71	22	5.45	5	4.96	156	4.60	1.01 (0.94, 1.08)
France-Paris	5	3.68	6	4.47	8	5.81	8	5.81	11	8.01	7	5.32	5	3.86	6	4.62			56	5.21	1.01 (0.91, 1.13)
France-Strasbourg	25	2.00	13	1.05	13	1.03	26	2.03	3	0.25	4	0.34	10	0.86	10	0.89	3	0.53	107	1.04	0.86 (0.80, 0.94)
Hungary	1	2.69	2	5.01	2	5.34	0	0.00	0	0.00	0	0.00	0	0.00	1	3.55	1	7.39	7	2.54	0.92 (0.68, 1.26)
Israel	89	6.43	67	5.73	63	5.46	56	4.61	36	3.48	32	2.84	39	3.43	30	2.91	7	1.58	419	4.32	0.87 (0.84, 0.91)
Japan	9	7.75	3	1.57	4	2.04	5	2.52	3	1.57	6	3.09	3	1.55	6	3.13	2	2.09	41	2.61	0.92 (0.81, 1.05)
North Netherlands	16	2.76	16	2.67	12	1.95	15	2.45	20	3.31	14	2.33	24	3.97	21	3.46	6	1.93	144	2.80	1.03 (0.97, 1.10)
Norway	29	6.64	36	7.40	47	7.62	39	4.90	86	8.63	96	8.15	99	8.53	95	8.55	60	8.50	587	7.84	1.04 (1.00, 1.08)
South America	12	3.27	7	1.84	9	2.32	9	2.35	8	2.09	11	2.81	3	0.75	9	2.26	6	2.98	74	2.25	0.96 (0.88, 1.06)
USA-Atlanta	516		430		460		449		442		427		432		420		176		3752		
Total																					

*Note: 71 terminated cases from England and Wales, 4 from France-Central East and 5 from France-Paris were excluded because their calculated date of birth was outside the considered period 1.1.88–30.6.96. †PRR = Prevalence rate ratio for annual change according to Poisson regression model.

acid was therefore very well known and had received a good deal of publicity through the media.

Netherlands—A survey of 485 women in their first pregnancies was carried out in 1994, the year after the publication of official advice, and showed that four (0.8%) had taken folic acid during the recommended period.¹² Further surveys were carried out in 1995 and 1996, before and after a national campaign publicising folic acid. In 1996, 96% of well educated women had heard of folic acid, 89% before conception. The corresponding figures for less well educated women were 80% and 64%. These figures were all higher than in the 1995 survey. Folic acid had been taken for the recommended period by 32% of well educated women and 17% of less well educated women. The corresponding figures in 1995 were 10% and 2% (De Walle 1997, personal communication).

South America—A survey of 491 women was carried out in 1996 and showed that about 1% had taken folic acid in the first month of pregnancy.¹³

United States—A survey carried out in South Carolina in 1992–1994¹⁴ showed that 6 (8%) of 71 women with a history of previous NTD affected pregnancy had taken folic acid in the periconceptional period. A 1995 study in

Table 3 Time trend analysis: cases and rates by registry and by year—Spina bifida

	Year																				PRR† (95% CI)
	1988		1989		1990		1991		1992		1993		1994		1995		1996		Total		
	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	
Registry																					
England and Wales	324	4.65	273	3.95	252	3.55	275	3.92	234	3.38	215	3.18	167	2.50	216	6.62	82	2.51	2038	3.51	0.94 (0.92, 0.96)
France-Central East	38	4.17	20	2.00	36	3.34	38	3.54	37	3.53	44	4.42	41	4.11	47	4.61	19	3.62	320	3.70	1.04 (1.00, 1.09)
France-Paris	11	2.67	28	6.71	24	5.69	12	2.84	17	4.15	22	5.47	23	5.70	19	4.71	11	10.91	167	4.92	1.05 (0.99, 1.12)
France-Strasbourg	5	3.68	5	3.72	4	2.90	4	2.90	6	4.37	5	3.80	6	4.64	4	3.08			39	3.63	1.01 (0.88, 1.16)
Hungary	85	6.79	61	4.92	51	4.04	52	4.07	25	2.05	26	2.21	24	2.07	18	1.60	14	2.49	356	3.46	0.83 (0.79, 0.87)
Israel	2	5.39	1	2.50	1	2.67	1	3.24	0	0.00	1	3.37	1	3.55	2	7.11	0	0.00	9	3.26	1.06 (0.81, 1.38)
Japan	41	2.96	35	2.99	40	3.47	39	3.21	37	3.58	44	3.90	36	3.17	42	4.07	19	4.30	333	3.44	1.04 (0.99, 1.09)
North Netherlands	13	11.19	14	7.33	20	10.18	22	11.07	14	7.30	7	3.61	9	4.66	10	5.22	7	7.31	116	7.39	0.90 (0.83, 0.98)
Norway	24	4.13	35	5.85	25	4.07	29	4.73	33	5.45	17	2.83	31	5.12	39	6.42	15	4.82	248	4.83	1.02 (0.97, 1.07)
South America	31	7.10	31	6.37	54	8.75	53	6.66	69	6.93	99	8.40	109	9.39	122	10.98	53	7.51	621	8.29	1.05 (1.01, 1.09)
USA-Atlanta	20	5.46	17	4.46	21	5.42	14	3.66	14	3.66	13	3.33	17	4.27	6	1.51	6	2.98	128	3.89	0.90 (0.84, 0.97)
Total	594		520		528		539		486		493		464		525		226		4375		

*Note: 71 terminated cases from England and Wales, 4 from France-Central East and 5 from France-Paris were excluded because their calculated date of birth was outside the considered period 1.1.88–30.6.96. †PRR = Prevalence rate ratio for annual change according to Poisson regression model.

Table 4 Time trend analysis: cases and rates by registry and by year—Anencephaly and Spina bifida

	Year																				PRR† (95% CI)
	1988		1989		1990		1991		1992		1993		1994		1995		1996		Total		
	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	cases	rates	
Registry																					
England and Wales	622	8.93	521	7.54	510	7.19	516	7.35	465	6.72	436	6.44	376	5.63	419	6.43	161	4.93	4026	6.93	0.95 (0.93, 0.96)
France-Central	52	5.70	38	3.80	58	5.39	62	5.78	60	5.72	67	6.73	66	6.61	64	6.27	26	4.96	493	5.70	1.03 (1.00, 1.07)
East France-Paris	29	7.04	42	10.06	46	10.91	38	9.00	38	9.27	35	8.70	38	9.41	41	10.16	16	15.87	323	9.52	1.03 (0.98, 1.08)
France-Strasbourg	10	7.36	11	8.19	12	8.71	12	8.71	17	12.38	12	9.13	11	8.50	10	7.69			95	8.85	1.01 (0.92, 1.10)
Hungary	110	8.79	74	5.97	64	5.06	78	6.10	28	2.29	30	2.55	34	2.93	28	2.49	17	3.02	463	4.50	0.84 (0.80, 0.87)
Israel	3	8.08	3	7.51	3	8.02	1	3.24	0	0.00	1	3.37	1	3.55	3	10.66	1	7.39	16	5.80	0.97 (0.78, 1.20)
Japan	130	9.40	102	8.73	103	8.92	95	7.82	73	7.07	76	6.74	75	6.60	72	6.98	26	5.88	752	7.76	0.95 (0.92, 0.97)
North Netherlands	22	18.94	17	8.90	24	12.21	27	13.58	17	8.87	13	6.70	12	6.21	16	8.36	9	9.40	157	10.01	0.91 (0.85, 0.97)
Norway	40	6.89	51	8.52	37	6.03	44	7.18	53	8.76	31	5.16	55	9.09	60	9.88	21	6.75	392	7.63	1.02 (0.98, 1.07)
South America	60	13.74	67	13.77	101	16.37	92	11.57	155	15.56	195	16.55	208	17.92	217	19.53	113	16.01	1208	16.14	1.04 (1.02, 1.07)
USA-Atlanta	32	8.73	24	6.30	30	7.74	23	6.01	22	5.76	24	6.14	20	5.02	15	3.77	12	5.97	202	6.14	0.93 (0.88, 0.98)
Total	1110		950		988		988		928		920		896		945		402		8127		

*Note: 71 terminated cases from England and Wales, 4 from France-Central East and 5 from France-Paris were excluded because their calculated date of birth was outside the considered period 1.1.88–30.6.96. †PRR = Prevalence rate ratio for annual change according to Poisson regression model.

Georgia¹⁵ showed a low level of awareness of the protective effect of folic acid against NTD. A national sample of American woman interviewed in 1995 also showed a low level of awareness of the preventive effect of folic acid.¹⁶

EXAMINATION OF NTD PREVALENCE
Table 1 shows the numbers of cases of NTD by programme. After adjusting the induced abortions to expected dates of birth, as explained above, the numbers of cases and rates are as

shown in tables 2, 3 and 4. Secular trends are evident in some programmes before the introduction of any folate supplementation policies. Over the whole study period, for anencephaly, three programmes (England and Wales, Hungary and Japan) showed a significant fall, while South America showed a significant rise. For spina bifida, a significant fall is seen in Atlanta (USA), England and Wales, Hungary and North Netherlands, while South America again showed a rise. For all NTD, Atlanta, England

Figure 1 Significant downward trends—NTD rates 1988–96.

Table 5 Crude comparison between period before (88–93) and after (94–96) the initiation of strategies of prevention

		Anencephaly PRR (95% CI)	Spina bifida PRR (95% CI)	Anenc and Spina bifida PRR (95% CI)
Registry	Period			
England and Wales	88–96	0.83 (0.75, 0.92)	0.75 (0.67, 0.83)	0.79 (0.73, 0.85)
France–Central East	88–96	0.95 (0.68, 1.32)	1.21 (0.96, 1.52)	1.11 (0.92, 1.34)
France Paris	88–96	1.01 (0.71, 1.44)	1.27 (0.92, 1.76)	1.14 (0.90, 1.45)
France Strasbourg	88–92	0.76 (0.39, 1.46)	1.06 (0.52, 2.19)	0.88 (0.54, 1.43)
Hungary	88–96	0.71 (0.45, 1.13)	0.49 (0.36, 0.65)	0.53 (0.42, 0.68)
Israel	88–96	1.18 (0.22, 6.10)	1.56 (0.38, 6.22)	1.13 (0.36, 3.55)
Japan	88–96	0.60 (0.47, 0.77)	1.11 (0.88, 1.41)	0.81 (0.68, 0.96)
North Netherlands	88–96	0.83 (0.42, 1.66)	0.65 (0.42, 1.01)	0.69 (0.48, 1.01)
Norway	88–96	1.30 (0.92, 1.83)	1.24 (0.95, 1.61)	1.25 (1.02, 1.55)
South America	88–96	1.16 (0.98, 1.36)	1.28 (1.09, 1.49)	1.22 (1.08, 1.36)
USA–Atlanta	88–96	0.73 (0.43, 1.24)	0.67 (0.44, 1.01)	0.69 (0.50, 0.96)

PRR = Prevalence rate ratio for change between 1988–93 and 1994–96 according to Poisson regression model.

and Wales, Hungary, Japan and North Netherlands all show a significant fall, South America a significant rise. There are no other significant changes in prevalence.

Significant downward trends in five programmes are shown graphically in figure 1. In four of these programmes, the downward trend has no definable beginning or end. As is to be expected, the programmes with the largest numbers of cases (England and Wales and Japan) show the smoothest curves, and these two programmes are the only ones in which the lowest rate was recorded in the final year of the study (1996). In Hungary, there is a downward trend from 1988 to 1992 and very little change thereafter.

In tables 5 and 6, the years covered in the study have been arbitrarily divided into two periods, 1988–1993 and 1994–1996. These correspond very approximately to periods (1) when supplementation policies could not be expected to have had any significant influence, and (2) when an effect could have been seen in countries that were the first to promulgate policies. Table 5 is a crude comparison. It shows a significant fall in prevalence rates for all NTD from the first to the second period in Atlanta (USA), England and Wales, Hungary and Japan, and a significant rise in Norway and South America. In table 6, the figures have been adjusted to allow for the secular trends observed in the earlier years of the study. The significant trends seen in table 5 are no longer evident apart from the increase in Norway, attributable to an increase in spina bifida.

Table 6 Adjusted for secular trend comparison between period before (88–93) and after (94–96) the initiation of strategies of prevention

		Anencephaly PRR (95% CI)	Spina bifida PRR (95% CI)	Anenc and Spina bifida PRR (95% CI)	Power*
Registry	Period				
England and Wales	88–96	0.99 (0.85, 1.14)	0.95 (0.82, 1.10)	0.97 (0.88, 1.06)	0.99
France–Central East	88–96	0.74 (0.46, 1.20)	1.01 (0.71, 1.43)	0.91 (0.71, 1.15)	0.81
France Paris	88–96	0.99 (0.59, 1.66)	1.18 (0.72, 1.95)	1.09 (0.81, 1.47)	0.37
France Strasbourg	88–92	0.54 (0.22, 1.28)	0.99 (0.35, 2.79)	0.70 (0.40, 1.21)	0.10
Hungary	88–96	1.91 (0.92, 3.95)	1.19 (0.79, 1.79)	1.33 (0.99, 1.80)	0.86
Israel	88–96	8.76 (0.26, 298.31)	2.10 (0.17, 25.54)	2.56 (0.43, 15.05)	0.03
Japan	88–96	1.08 (0.75, 1.54)	0.93 (0.65, 1.31)	1.04 (0.85, 1.28)	0.84
North Netherlands	88–96	1.45 (0.49, 4.27)	1.02 (0.54, 1.94)	1.21 (0.71, 1.77)	0.22
Norway	88–96	1.28 (0.74, 2.20)	1.45 (1.95, 2.21)	1.39 (1.05, 1.83)	0.58
South America	88–96	1.02 (0.80, 1.31)	1.18 (0.93, 1.51)	1.09 (0.95, 1.27)	0.81
USA–Atlanta	88–96	0.77 (0.36, 1.65)	0.96 (0.52, 1.74)	0.88 (0.60, 1.31)	0.39

PRR = Prevalence rate ratio for change between 1988–93 and 1994–96 according to Poisson regression model. *Power for detecting a 25% variation with a two tailed α value of 0.05.

KEY POINTS

- Many studies confirm that folic acid supplements could prevent most NTDs.
- Public health policies relating to folic acid supplementation have been adopted by health authorities in many countries.
- The existence of a national policy does not necessarily imply that it is being implemented.
- The frequency of NTD up to mid-1996 seems not to have been influenced by folate supplements.

However, there is no significant change in NTD rates in Norway over the whole study period. In 1994 and 1995 (both included in the second period) the rates for both anencephaly and spina bifida were rather higher than usual but fell again in 1996. The rise in rates between the two periods is probably a chance event. For a better evaluation of the results table 6 reports the statistical power for detecting a 25% variation between the two periods with a two tailed α of 0.05. The large sample size allows for a high level of statistical power, but for small registries.

Discussion

The statistically significant falls and rises in NTD prevalence rates from January 1988 to mid-1996 seem to represent continuing secular trends, decreasing in the USA (Atlanta), England and Wales, Hungary, Japan and the Netherlands, and increasing in South America. There is a rough association between significantly falling incidence rates and the early promulgation of recommendations, but it seems unlikely that the recommendations have caused the fall. It seems more probable that more affluent countries experience falling NTD rates and can afford to allocate resources to folate supplementation programmes, while the reverse is true in poor countries. At one time, the British Isles (United Kingdom and Republic of Ireland) had the unenviable reputation of having the highest NTD rates in the world. This distinction now belongs to South and Central America, where poverty coincides with the illegality of pregnancy termination.

There is no convincing evidence that, up to the middle of 1996, any change was attributable to the introduction of national folate supplementation policies. Even in England and Wales, the rate adjusted for secular trend did not decrease significantly between 1988–93 and 1994–96, although the power estimates in table 6 suggest that such a decrease might well have occurred if the uptake of folic acid before conception for the whole county had matched the Leeds figures (18%–31% for 1994–96). It is clear that, where supplementation policies have been promulgated, they take a very long time and a great deal of effort to implement. The possible effectiveness of folate supplementation for the reduction of NTD clearly needs to be tried and studied for several more years. However, recognising that, in the Western

world at least, approximately 50% of pregnancies are unplanned, a policy that rests on action taken before conception can only have limited success. The alternative of fortifying staple foods by adding folic acid to cereal flours, which was mandatory in the USA with effect from 1 January 1998, may prove to be a more successful strategy, provided that the level of enrichment is sufficient.

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Appendix

Application of the Poisson models
The Poisson regression is most appropriate for count data, it has only rarely been applied either in epidemiology or anywhere else. This appendix presents the way in which a time distribution of cases of birth defects can be analysed exploiting the potential of the Poisson regression.

In the Poisson regression model, the incidence rate for the j-th observation, say r_j , (the j-th year in our case) is assumed to be given by $r_j = \exp(\alpha + \beta_1 x_{1,j} + \beta_2 x_{2,j} + \dots + \beta_k x_{k,j})$, where $x_{1,j} + x_{2,j} + \dots + x_k$ are the values of k independent variables in the j-th year. However, dealing with birth defects, the incidence rate at which events occur is not calculable as we cannot know the total number of pregnancies at risk and the total number of NTD cases among them.¹⁷ This is not possible as a great number of early miscarried pregnancies are not registered, or even not recognised as such by the mother. Instead of the incidence rate, we have therefore considered a “corrected” prevalence rate at birth. This is not a perfect estimate of the natural birth prevalence. Some terminated pregnancies would miscarry rather than ending in affected births if they were not terminated, and a substantial proportion of pregnancies terminated for NTDs are probably not notified as such.¹⁸

We are interested in temporal changes that occurred around 1994, when the folate policies might have begun to produce effects. For this purpose the general model adopted in this study is the following: $r_j = \exp(\alpha + \beta_1 x_{1,j} + \beta_2 x_{2,j})$ where $x_{1,j}$ is the time variable (set at 0 for 1988, 1 for 1989 and so on) and $x_{2,j}$ is a dummy variable that is equal to 0 for years before 1994 and 1 from 1994 onwards. To compare rates, one can easily calculate the PRR, which is the exponential transformation of β_j for the relevant variable. The PRR shows the variation of the prevalence rate corresponding to one unit change of

one independent variable, say x_j , holding constant all the other x s.. The rates after and before this change are the ratio's numerator and denominator respectively, so that values of $PRR > 1$ indicate an increase and values of $PRR < 1$ indicate a decrease.

Three particular models have been estimated, including the general one:

- (1) For studying the general tendency of the prevalence rates during the study period, the model adopted is $r_j = \exp(\alpha + \beta_1 x_{1,j})$ and the relevant PRRs estimate the average annual variation in prevalence rates during the period.
- (2) For studying initially the temporal changes occurring around 1994, when the folate policies might have begun to produce effects, the model used is $r_j = \exp(\alpha + \beta_2 x_{2,j})$. Here, the PRR compares the prevalence rates before 1994 with the rates from 1994 onwards.
- (3) To distinguish the real effect of the policies from the general trend of the NTD occurrence (which (2) does not do), we must adjust the time series for the effect of long term trends, represented by the factor x_1 . Therefore the model adopted is $r_j = \exp(\alpha + \beta_1 x_{1,j} + \beta_2 x_{2,j})$. The relevant PRR, calculated as $\exp(\beta_2)$, indicates how much larger or smaller the prevalence rates are before and after 1994, given the secular trend.

Maximum likelihood estimates of the parameters are obtained using the Poisson function of the STATA software.¹⁹

1 Hibbard BM, Smithells RW. Folic acid metabolism and human embryopathy. *Lancet* 1965;i:1254.
2 Smithells RW, Sheppard S, Schorah CJ, *et al.* Possible prevention of neural tube defects by periconceptional vitamins supplementation. *Lancet* 1980;i:339-40.
3 Seller MJ, Nevin NC. Periconceptional vitamin supplementation and the prevention of neural tube defects in South East England and Northern Ireland. *J Med Genet* 1984;21:325-30.
4 Medical Research Council Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council vitamin study. *Lancet* 1991;338:131-7.
5 Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;327:1832-5.
6 Dobson AJ. *An introduction to generalized linear model.* London: Chapman and Hall, 1990: 42-6.
7 Sutcliffe M, Schorah CJ, Perry A, *et al.* Prevention of neural tube defects. *Lancet* 1993;342:1174.
8 Clark NAC, Fisk NM. Minimal compliance with the Department of Health recommendation for routine folate prophylaxis to prevent neural tube defects. *Br J Obstet Gynaecol* 1994;101:709-10.
9 Wild J, Schorah CJ, Maude K, *et al.* Folate intake in young women and their knowledge of pre-conceptional folate supplementation to prevent neural tube defects. *Eur J Obstet Gynecol* 1996;70:185-9.
10 De Vigan C, Raoult B, Vodovar V, *et al.* Prévention de l'anencéphalie et du spina bifida par l'acide folique: situation en région parisienne. *Bulletin épidémiologique hebdomadaire* 1996; N 15/96.
11 Czeizel AE, Susánszky E. Diet intake and vitamin supplement use of Hungarian women during the pre-conception period. *Int J Vitam Nutr Res* 1994;64:300-5.
12 De Jong-van den Berg LTW, Cornel MC, Tymstra T, *et al.* Folate prophylaxis in pregnancy. *Lancet* 1995; 346:1227-8.
13 Castilla EE, Dutra MG. Folate awareness among South American woman. *Lancet* 1997;349:735.
14 Centers for Disease Control (USA). Prevention program for reducing risk for neural tube defects-South Carolina, 1992-1994. *MMWR* 1995;44:141-2.
15 Centers for Disease Control (USA). Knowledge about folic acid and use of multivitamins containing folic acid among reproductive-aged women-Georgia, 1995. *MMWR* 1996; 45:793-5.
16 Centers for Disease Control (USA). Knowledge and use of folic acid by women of childbearing age-United States, 1995. *MMWR* 1995;44:716-18.
17 Marino B, Mastroiacovo P, Dallapiccola B. *Cardiopatie Congenite e Sindromi Genetiche.* Milan: Mcgraw-Hill, 1995:28-30.
18 Cuckle HS, Wald NJ, Cuckle PM. Prenatal screening and diagnosis of neural tube defects in England and Wales in 1985. *Prenat Diagn* 1989; 9:393-400.
19 StataCorp. *Stata Statistical Software. Release 4.0* College Station, TX: Stata Corporation, 1995.