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

Aldo Rosano, Dick Smithells, Laura Cacciani, Beverley Botting, Eduardo Castilla, Martina Corred, David Erickson, Janine Goujard, Lorentz Irgens, Paul Merlob, Elisabeth Robert, Csaba Sifet, Claude Stoll, Yoshiro Sumiyoshi

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.


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 folic acid 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 folic acid supplementation policies. The possible effectiveness of folic acid 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.

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
Table 1  Cases of NTD by registry and period

<table>
<thead>
<tr>
<th>Programme</th>
<th>Period covered</th>
<th>No of births monitored</th>
<th>NTD cases</th>
<th>Linear trend (%)</th>
<th>Logarithmic trend (%)</th>
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<tr>
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<td>192</td>
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<tr>
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<td>53 000</td>
<td>53</td>
<td>3055</td>
<td>4907</td>
</tr>
<tr>
<td>France, Strasbourg</td>
<td>1987–95</td>
<td>120 000</td>
<td>15</td>
<td>3055</td>
<td>4907</td>
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<tr>
<td>Hungary</td>
<td>1987–96</td>
<td>1 150 000</td>
<td>412</td>
<td>3055</td>
<td>4907</td>
</tr>
<tr>
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<td>28 000</td>
<td>16</td>
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<tr>
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<td>289</td>
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<tr>
<td>South America</td>
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<td>187</td>
<td>3055</td>
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<td>Total</td>
<td></td>
<td>12 078 000</td>
<td>4268</td>
<td>3055</td>
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</table>

Results

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.1

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.)

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 study in Paris in 1995,10 showed that 69 (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.

France—Of 105 women interviewed in 1995,11 showed that 68 (9.3%) of 733 women in maternity hospitals had taken folate 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.12 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 study on prevention of NTD recurrence, and was the location of the only randomised study of prevention of first occurrence of NTD.13 The preventive role of folic acid...
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. 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.

**United States**—A survey carried out in South Carolina in 1992–1994 showed that 6% of 71 women with a history of previous NTD affected pregnancy had taken folic acid in the periconceptional period. A 1995 study in

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

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<tr>
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*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 3: Time trend analysis: cases and rates by registry and by year—Spina bifida

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*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.
Georgia 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.

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...
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 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 over the first period and a significant rise for the second period (the rates for both anencephaly and spina bifida were rather higher than usual in the second period) the rates for both anencephaly and spina bifida were rather higher than usual in the second period). However, recognizing that, in the Western Hemisphere, the US represents the longest period of five years during which supplementation policies were implemented, it seems not to have been influenced by folate supplementation.

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 with a power 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 distinction between significant 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 trends 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, recognizing that, in the Western Hemisphere, the US represents the longest period of five years during which supplementation policies were implemented, it seems not to have been influenced by folate supplements.

### Table 5

<table>
<thead>
<tr>
<th>Registry</th>
<th>Period</th>
<th>Anencephaly, PRR (95% CI)</th>
<th>Spina Bifida, PRR (95% CI)</th>
<th>Anencephaly and Spina Bifida, PRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales</td>
<td>1988–93</td>
<td>0.83 (0.75, 0.92)</td>
<td>0.75 (0.67, 0.85)</td>
<td>0.78 (0.73, 0.85)</td>
</tr>
<tr>
<td>France-Central East</td>
<td>1988–96</td>
<td>0.95 (0.88, 1.03)</td>
<td>1.22 (1.06, 1.42)</td>
<td>1.11 (0.92, 1.34)</td>
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<tr>
<td>France-Pays</td>
<td>1988–96</td>
<td>1.01 (0.72, 1.41)</td>
<td>1.27 (0.92, 1.76)</td>
<td>1.14 (0.90, 1.45)</td>
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<td>France-Strasbourg</td>
<td>1988–92</td>
<td>0.76 (0.59, 1.01)</td>
<td>1.05 (0.72, 1.51)</td>
<td>0.88 (0.54, 1.43)</td>
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<td>Hungary</td>
<td>1988–90</td>
<td>0.87 (0.70, 1.10)</td>
<td>0.80 (0.65, 0.95)</td>
<td>0.85 (0.62, 1.00)</td>
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<td>Japan</td>
<td>1988–94</td>
<td>1.18 (0.92, 1.50)</td>
<td>1.55 (1.20, 2.01)</td>
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<td>South America</td>
<td>1988–96</td>
<td>1.11 (0.92, 1.35)</td>
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<td>0.73 (0.63, 1.26)</td>
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**PRR** = Prevalence ratio rate for change between 1988–93 and 1994–96 according to Poisson regression model.

### Table 6

<table>
<thead>
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<th>Registry</th>
<th>Period</th>
<th>Anencephaly, PRR (95% CI)</th>
<th>Spina Bifida, PRR (95% CI)</th>
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<td>1988–93</td>
<td>0.90 (0.85, 0.95)</td>
<td>0.98 (0.92, 1.04)</td>
<td>0.97 (0.92, 1.02)</td>
</tr>
<tr>
<td>France-Central East</td>
<td>1988–96</td>
<td>0.74 (0.61, 0.91)</td>
<td>1.01 (0.75, 1.43)</td>
<td>0.91 (0.75, 1.13)</td>
</tr>
<tr>
<td>France-Pays</td>
<td>1988–96</td>
<td>0.99 (0.95, 1.03)</td>
<td>1.18 (1.01, 1.39)</td>
<td>1.09 (1.05, 1.14)</td>
</tr>
<tr>
<td>France-Strasbourg</td>
<td>1988–92</td>
<td>0.54 (0.22, 0.89)</td>
<td>0.98 (0.93, 1.03)</td>
<td>0.70 (0.63, 0.79)</td>
</tr>
<tr>
<td>Hungary</td>
<td>1988–96</td>
<td>1.01 (0.63, 1.57)</td>
<td>1.00 (0.70, 1.37)</td>
<td>1.13 (0.96, 1.55)</td>
</tr>
<tr>
<td>Israel</td>
<td>1988–94</td>
<td>0.76 (0.26, 2.58)</td>
<td>2.50 (0.75, 8.78)</td>
<td>2.56 (0.45, 15.0)</td>
</tr>
<tr>
<td>Japan</td>
<td>1988–96</td>
<td>1.06 (0.95, 1.15)</td>
<td>1.05 (0.95, 1.11)</td>
<td>1.04 (0.95, 1.12)</td>
</tr>
<tr>
<td>Japan</td>
<td>1988–96</td>
<td>1.09 (0.95, 1.24)</td>
<td>1.05 (0.95, 1.12)</td>
<td>1.04 (0.95, 1.12)</td>
</tr>
<tr>
<td>North Netherlands</td>
<td>1988–96</td>
<td>1.43 (0.90, 2.27)</td>
<td>1.20 (0.80, 1.72)</td>
<td>1.33 (0.96, 1.81)</td>
</tr>
<tr>
<td>Norway</td>
<td>1988–96</td>
<td>1.28 (0.79, 2.02)</td>
<td>1.45 (0.95, 2.12)</td>
<td>1.59 (1.05, 2.35)</td>
</tr>
<tr>
<td>South America</td>
<td>1988–96</td>
<td>1.02 (0.80, 1.31)</td>
<td>1.08 (0.80, 1.46)</td>
<td>1.00 (0.80, 1.27)</td>
</tr>
<tr>
<td>USA-Atlanta</td>
<td>1988–96</td>
<td>0.77 (0.61, 1.0)</td>
<td>0.80 (0.62, 1.03)</td>
<td>0.80 (0.60, 1.03)</td>
</tr>
</tbody>
</table>

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

At 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.

International Centre for Birth Defects, Rome Study: A Rosano, D Smithells, L Cacciani; Office for National Statistic, London: Folic Acid Fortification, ECLAMC-Departamento de Genética-Instituto Osvaldo Cruz, Brazil: E Castilla; Department of Obstetrics and Gynaecology, University of Groningen, the Netherlands: C Geirard; Division of Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, USA; Department of Neonatology, Rabin Medical Center, Belinson Medical Birth Registry of Norway, Bergen, Norway: L Irgens; Service de Génetique Médicale, Hopital de Hautepierre, Strasbourg, France: C Stoll; Japan Association of Obstetricians and Gynecologists, Tokyo, Japan; Y Sumiyoshi.

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The prevalence rate corresponding to one unit change of the relevant variable. The PRR shows the variation of the prevalence rate corresponding to one unit change of the relevant variable. The PRR shows the variation of the prevalence rate corresponding to one unit change of the relevant variable. The PRR shows the variation of the prevalence rate corresponding to one unit change of the relevant variable. The PRR shows the variation of the prevalence rate corresponding to one unit change of the relevant variable. The PRR shows the variation of the prevalence rate corresponding to one unit change.
A Rosano, D Smithells, L Cacciari, B Botting, E Castilla, M Cornel, D Erickson, J Goujard, L Irgens, P Merlob, E Robert, C Siffel, C Stoll and Y Sumiyoshi

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