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 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.

Methods

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

1. Is there a national policy on folic acid 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.

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

The strongest support for the hypothesis came from two large, randomised studies. The UK Medical Research Council showed that folic acid, 4 mg daily, gave significant protection against recurrences of NTD. Czeizel and Dudas showed that a multivitamin preparation containing folic acid 0.4 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 Monitoring Systems (ICBDMS), was to examine time trends in NTD prevalence in relation to folic acid supplementation strategies in different countries.

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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>Live births + stillbirths</th>
<th>Induced abortions</th>
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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 fell into two categories:
1. Those that had 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)

### Results

**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 Frat\(^8\) 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 1989, 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. The folate knowledge study was done as a part of the Hungarian 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.\(^12\) The preventive role of folic...
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. [PPR] = 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 women 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 Nether-
lands all show a significant fall, South America
a significant rise. There are no other significant
changes in prevalence.

Significant downward trends in five pro-
gress 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
correspond 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
France-Central East (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 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>
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<td>England and Wales</td>
<td>88–93</td>
<td>0.83 (0.75, 0.92)</td>
<td>0.92 (0.75, 0.92)</td>
<td>0.79 (0.73, 0.85)</td>
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<td>France-Central East</td>
<td>88–96</td>
<td>0.95 (0.68, 1.32)</td>
<td>1.27 (0.92, 1.76)</td>
<td>1.19 (0.92, 1.54)</td>
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<td>South America</td>
<td>88–96</td>
<td>1.16 (0.98, 1.30)</td>
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<td>USA-Atlanta</td>
<td>88–96</td>
<td>0.73 (0.49, 1.24)</td>
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PRR = Prevalence rate ratio for change between 1988–93 and 1994–96 according to Poisson regression model.

### Table 6

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<th>Anencephaly PRR (95% CI)</th>
<th>Spina Bifida PRR (95% CI)</th>
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<td>0.90 (0.85, 1.14)</td>
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<tr>
<td>Hungary</td>
<td>88–96</td>
<td>1.03 (0.52, 1.84)</td>
<td>1.15 (0.70, 1.79)</td>
<td>1.13 (0.59, 1.65)</td>
</tr>
<tr>
<td>Israel</td>
<td>88–96</td>
<td>0.76 (0.26, 2.09)</td>
<td>2.10 (0.17, 25.54)</td>
<td>2.56 (0.45, 15.05)</td>
</tr>
<tr>
<td>Japan</td>
<td>88–96</td>
<td>0.78 (0.75, 1.44)</td>
<td>0.83 (0.50, 1.31)</td>
<td>1.04 (0.65, 1.20)</td>
</tr>
<tr>
<td>North Netherlands</td>
<td>88–96</td>
<td>1.45 (0.43, 4.77)</td>
<td>1.02 (0.54, 1.94)</td>
<td>1.21 (0.71, 1.77)</td>
</tr>
<tr>
<td>Norway</td>
<td>88–96</td>
<td>1.26 (0.74, 2.10)</td>
<td>1.45 (0.95, 2.16)</td>
<td>1.39 (0.87, 1.98)</td>
</tr>
<tr>
<td>South America</td>
<td>88–96</td>
<td>1.02 (0.30, 3.11)</td>
<td>1.18 (0.93, 1.51)</td>
<td>0.95 (0.72, 1.27)</td>
</tr>
<tr>
<td>USA-Atlanta</td>
<td>88–96</td>
<td>0.77 (0.56, 1.01)</td>
<td>0.94 (0.52, 1.78)</td>
<td>0.80 (0.60, 1.11)</td>
</tr>
</tbody>
</table>

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

### 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 Nether-
lands, and increasing in South America.

There is a rough association between signifi-
cantly 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 attribut-
able to the introduction of national folate sup-
plementation 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 country had matched
the Leeds figures (18%–31% for 1994–96). It
is clear that, where supplementation policies
have been promulgated, they have taken a very
time and a great deal of effort to implement.

The possible effectiveness of folate supple-
tmentation for the reduction of NTD clearly needs
to be tried and studied for several more years.

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% varia-
tion between the two periods with a two tailed
p value of 0.05. The large sample size allows for
a high level of statistical power, but for small reg-

### Key Points

- Many studies confirm that folic acid sup-
  plements 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.
Neural tube defects prevalence and preventive strategies

The prevalence and associated risk factors for neural tube defects (NTDs) are important for public health policy. This study provides an overview of the current understanding of NTD prevalence and preventive strategies. The data presented include a review of epidemiological studies and the implementation of public health policies to reduce NTD incidence. The discussion covers the role of folic acid supplementation in preventing NTDs, as well as other strategies such as genetic counseling and prenatal diagnosis. The implications for public health and future research directions are also highlighted.

Conflicts of interest: none.

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Appendix

Application of the Poisson models

The Poisson regression model is most appropriate for count data, but it may be applied either as epidemiological or another type. This appendix presents the way in which a time distribution of cases of birth defects can be analyzed, using a linear model that is assumed to be given by

\[ y_{i,j} = \exp(\beta_0 + \beta_1 x_{i,j} + \ldots + \beta_k x_{i,k}) \]

where \( y_{i,j} \) is the observed count in the ith region, the jth year, \( x_{i,j} \) is the value of the jth covariate in the ith region, \( x_{i,j} \) is the time variable (set at 0 for 1988, 1 for 1994), and \( \beta_k \) are the coefficients of the covariates. The rates after and before this change are the prevalence rates before 1994 with the rates from 1994 onwards.

(1) To distinguish the real effect of the policies from the general trend of NTD occurrence (which (2) does not completely stop), we must adjust the time series for the effect of long-term trends, represented by the factor \( \alpha_i \). Therefore the model adopted is \( r_i = \exp(\beta_0 + \beta_2 x_{i,j} + \alpha_i) \). 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 NTD occurrence (which (2) does not completely stop), we must adjust the time series for the effect of long-term trends, represented by the factor \( \alpha_i \). Therefore the model adopted is \( r_i = \exp(\beta_0 + \beta_2 x_{i,j} + \alpha_i) \). Here the PRR compares the prevalence rates before 1994 with the rates from 1994 onwards.

(4) To distinguish the real effect of the policies from the general trend of NTD occurrence (which (2) does not completely stop), we must adjust the time series for the effect of long-term trends, represented by the factor \( \alpha_i \). Therefore the model adopted is \( r_i = \exp(\beta_0 + \beta_2 x_{i,j} + \alpha_i) \). Here the PRR compares the prevalence rates before 1994 with the rates from 1994 onwards.