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 Correll, David Erickson, Janine Goujard, Lorentz Irgens, Paul Merlob, Elisabeth Robert, Csaba Siffel, Claude Stoll, Yoshio 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 folate 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>Live births + stillbirths</th>
<th>Induced abortion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales</td>
<td>1988–96</td>
<td>6,900,000</td>
<td>1042</td>
<td>3055</td>
<td>4097</td>
</tr>
<tr>
<td>France, Central East</td>
<td>1987–96</td>
<td>955,000</td>
<td>192</td>
<td>2195</td>
<td>479</td>
</tr>
<tr>
<td>France, Paris</td>
<td>1987–96</td>
<td>350,000</td>
<td>55</td>
<td>271</td>
<td>326</td>
</tr>
<tr>
<td>France, Strasbourg</td>
<td>1987–95</td>
<td>120,000</td>
<td>15</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>Hungary</td>
<td>1987–96</td>
<td>1,150,000</td>
<td>412</td>
<td>51</td>
<td>463</td>
</tr>
<tr>
<td>Israel</td>
<td>1988–96</td>
<td>28,000</td>
<td>16</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Ireland</td>
<td>1988–96</td>
<td>1,110,000</td>
<td>752</td>
<td>752</td>
<td>1504</td>
</tr>
<tr>
<td>North Netherlands</td>
<td>1988–98</td>
<td>169,000</td>
<td>122</td>
<td>15</td>
<td>137</td>
</tr>
<tr>
<td>Norway</td>
<td>1987–96</td>
<td>768,000</td>
<td>289</td>
<td>105</td>
<td>394</td>
</tr>
<tr>
<td>South America</td>
<td>1988–96</td>
<td>748,000</td>
<td>1208</td>
<td>0</td>
<td>1208</td>
</tr>
<tr>
<td>USA, Atlanta</td>
<td>1988–96</td>
<td>187,000</td>
<td>187</td>
<td>35</td>
<td>222</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>12,078,000</td>
<td>4268</td>
<td>3939</td>
<td>8207</td>
</tr>
</tbody>
</table>

The preventive role of folic acid

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. 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

monitoring into folate supplementation

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, Clark and Fisk and Wild. 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 1995, 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, 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. 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. The preventive role of folic
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 publicis-
ing 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 communi-
cation).

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

<table>
<thead>
<tr>
<th>Registry</th>
<th>1988</th>
<th>1990</th>
<th>1992</th>
<th>1994</th>
<th>1996</th>
<th>Total</th>
<th>PRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales</td>
<td>298</td>
<td>4.28</td>
<td>248</td>
<td>3.59</td>
<td>258</td>
<td>3.34</td>
<td>221</td>
<td>3.26</td>
</tr>
<tr>
<td>France-Central East</td>
<td>14</td>
<td>1.53</td>
<td>18</td>
<td>1.80</td>
<td>22</td>
<td>2.04</td>
<td>24</td>
<td>2.24</td>
</tr>
<tr>
<td>France-Paris</td>
<td>18</td>
<td>4.37</td>
<td>14</td>
<td>3.55</td>
<td>22</td>
<td>5.22</td>
<td>26</td>
<td>6.16</td>
</tr>
<tr>
<td>France-Strasbourg</td>
<td>5</td>
<td>5.68</td>
<td>6</td>
<td>4.47</td>
<td>8</td>
<td>8.11</td>
<td>11</td>
<td>8.01</td>
</tr>
<tr>
<td>Hungary</td>
<td>25</td>
<td>2.09</td>
<td>21</td>
<td>3.05</td>
<td>20</td>
<td>3.25</td>
<td>21</td>
<td>3.41</td>
</tr>
<tr>
<td>Israel</td>
<td>1</td>
<td>2.69</td>
<td>1</td>
<td>0.96</td>
<td>2</td>
<td>1.57</td>
<td>2</td>
<td>1.84</td>
</tr>
<tr>
<td>Japan</td>
<td>89</td>
<td>6.43</td>
<td>67</td>
<td>5.37</td>
<td>63</td>
<td>4.86</td>
<td>56</td>
<td>4.38</td>
</tr>
<tr>
<td>North Netherlands</td>
<td>9</td>
<td>7.73</td>
<td>5</td>
<td>1.57</td>
<td>4</td>
<td>2.04</td>
<td>5</td>
<td>2.52</td>
</tr>
<tr>
<td>Norway</td>
<td>16</td>
<td>2.76</td>
<td>17</td>
<td>1.75</td>
<td>11</td>
<td>1.75</td>
<td>15</td>
<td>1.95</td>
</tr>
<tr>
<td>South America</td>
<td>29</td>
<td>6.64</td>
<td>36</td>
<td>7.40</td>
<td>47</td>
<td>7.62</td>
<td>39</td>
<td>4.90</td>
</tr>
<tr>
<td>USA-Atlanta</td>
<td>12</td>
<td>5.27</td>
<td>17</td>
<td>1.84</td>
<td>9</td>
<td>2.39</td>
<td>8</td>
<td>2.09</td>
</tr>
<tr>
<td>Total</td>
<td>516</td>
<td>430</td>
<td>460</td>
<td>444</td>
<td>442</td>
<td>427</td>
<td>432</td>
<td>420</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Registry</th>
<th>1988</th>
<th>1990</th>
<th>1992</th>
<th>1994</th>
<th>1996</th>
<th>Total</th>
<th>PRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales</td>
<td>324</td>
<td>4.65</td>
<td>273</td>
<td>3.99</td>
<td>252</td>
<td>3.55</td>
<td>275</td>
<td>3.38</td>
</tr>
<tr>
<td>France-Central East</td>
<td>38</td>
<td>4.17</td>
<td>20</td>
<td>3.54</td>
<td>36</td>
<td>3.34</td>
<td>38</td>
<td>3.54</td>
</tr>
<tr>
<td>France-Paris</td>
<td>11</td>
<td>2.67</td>
<td>28</td>
<td>6.71</td>
<td>24</td>
<td>5.69</td>
<td>12</td>
<td>2.84</td>
</tr>
<tr>
<td>France-Strasbourg</td>
<td>5</td>
<td>5.68</td>
<td>4</td>
<td>2.04</td>
<td>4</td>
<td>2.52</td>
<td>5</td>
<td>2.52</td>
</tr>
<tr>
<td>Hungary</td>
<td>85</td>
<td>6.79</td>
<td>61</td>
<td>4.92</td>
<td>51</td>
<td>4.04</td>
<td>42</td>
<td>3.80</td>
</tr>
<tr>
<td>Israel</td>
<td>2</td>
<td>5.59</td>
<td>1</td>
<td>2.50</td>
<td>1</td>
<td>2.87</td>
<td>1</td>
<td>2.54</td>
</tr>
<tr>
<td>Japan</td>
<td>41</td>
<td>2.66</td>
<td>35</td>
<td>2.99</td>
<td>40</td>
<td>3.47</td>
<td>38</td>
<td>3.25</td>
</tr>
<tr>
<td>North Netherlands</td>
<td>13</td>
<td>11.14</td>
<td>7.33</td>
<td>20</td>
<td>10.18</td>
<td>22</td>
<td>11.07</td>
<td>14</td>
</tr>
<tr>
<td>Norway</td>
<td>4</td>
<td>4.13</td>
<td>55</td>
<td>8.75</td>
<td>53</td>
<td>8.75</td>
<td>56</td>
<td>8.66</td>
</tr>
<tr>
<td>South America</td>
<td>31</td>
<td>7.10</td>
<td>67</td>
<td>5.67</td>
<td>56</td>
<td>4.95</td>
<td>93</td>
<td>4.59</td>
</tr>
<tr>
<td>USA-Atlanta</td>
<td>20</td>
<td>5.46</td>
<td>17</td>
<td>4.46</td>
<td>21</td>
<td>5.42</td>
<td>14</td>
<td>3.66</td>
</tr>
<tr>
<td>Total</td>
<td>554</td>
<td>520</td>
<td>528</td>
<td>533</td>
<td>486</td>
<td>403</td>
<td>464</td>
<td>425</td>
</tr>
</tbody>
</table>

*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 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...
Anencephaly: PRR (95% CI)  Spina bifida PRR (95% CI)  Anencephaly and Spina bifida PRR (95% CI)  Power

<table>
<thead>
<tr>
<th>Registry</th>
<th>Period</th>
<th>Anencephaly</th>
<th>PRR (95% CI)</th>
<th>Spina Bifida</th>
<th>PRR (95% CI)</th>
<th>Anencephaly and Spina Bifida</th>
<th>PRR (95% CI)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales</td>
<td>1988-93</td>
<td>0.81</td>
<td>(0.75, 0.87)</td>
<td>0.75</td>
<td>(0.70, 0.82)</td>
<td>0.79 (0.73, 0.85)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>France-Central East</td>
<td>1989-96</td>
<td>0.95</td>
<td>(0.90, 1.00)</td>
<td>1.00</td>
<td>(0.96, 1.04)</td>
<td>1.11 (0.99, 1.25)</td>
<td>1.17 (0.99, 1.37)</td>
<td></td>
</tr>
<tr>
<td>France-Pyre</td>
<td>1988-96</td>
<td>1.01</td>
<td>(0.98, 1.04)</td>
<td>1.02</td>
<td>(0.99, 1.05)</td>
<td>1.14 (0.97, 1.35)</td>
<td>1.19 (0.96, 1.46)</td>
<td></td>
</tr>
<tr>
<td>France-Strasbourg</td>
<td>1989-92</td>
<td>0.76</td>
<td>(0.70, 0.82)</td>
<td>1.00</td>
<td>(0.95, 1.05)</td>
<td>0.88 (0.81, 0.96)</td>
<td>0.90 (0.82, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>1988-90</td>
<td>0.71</td>
<td>(0.65, 0.78)</td>
<td>0.69</td>
<td>(0.63, 0.75)</td>
<td>0.75 (0.68, 0.84)</td>
<td>0.79 (0.71, 0.87)</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>1988-96</td>
<td>1.10</td>
<td>(0.88, 1.35)</td>
<td>0.96</td>
<td>(0.75, 1.23)</td>
<td>1.13 (0.96, 1.35)</td>
<td>1.26 (1.00, 1.59)</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>1988-96</td>
<td>0.60</td>
<td>(0.47, 0.77)</td>
<td>1.11</td>
<td>(0.89, 1.41)</td>
<td>0.81 (0.68, 0.95)</td>
<td>0.86 (0.68, 1.06)</td>
<td></td>
</tr>
<tr>
<td>North Netherlands</td>
<td>1988-96</td>
<td>0.83</td>
<td>(0.62, 1.08)</td>
<td>0.65</td>
<td>(0.42, 1.01)</td>
<td>0.49 (0.34, 0.69)</td>
<td>0.50 (0.34, 0.70)</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>1988-96</td>
<td>1.10</td>
<td>(0.92, 1.30)</td>
<td>1.24</td>
<td>(0.96, 1.59)</td>
<td>1.25 (1.02, 1.55)</td>
<td>1.27 (1.02, 1.55)</td>
<td></td>
</tr>
<tr>
<td>North Netherlands</td>
<td>1988-96</td>
<td>1.16</td>
<td>(0.88, 1.50)</td>
<td>1.28</td>
<td>(0.96, 1.70)</td>
<td>1.22 (1.00, 1.55)</td>
<td>1.25 (1.00, 1.55)</td>
<td></td>
</tr>
<tr>
<td>USA-Atlanta</td>
<td>1988-96</td>
<td>0.73</td>
<td>(0.43, 1.26)</td>
<td>0.87</td>
<td>(0.44, 1.41)</td>
<td>0.80 (0.52, 1.25)</td>
<td>0.82 (0.52, 1.30)</td>
<td></td>
</tr>
</tbody>
</table>

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

USA-Atlanta 1988–96 0.77 (0.46, 1.30) 0.84 (0.45, 1.58) 0.87 (0.56, 1.37) 0.60
North Netherlands 1988–96 0.86 (0.67, 1.11) 0.84 (0.65, 1.08) 0.86 (0.65, 1.11) 0.84
USA-Atlanta 1988–96 1.01 (0.60, 1.70) 0.94 (0.55, 1.60) 0.99 (0.60, 1.62) 0.99
North Netherlands 1988–96 1.03 (0.57, 1.93) 0.94 (0.51, 1.76) 0.94 (0.51, 1.76) 0.94
Japan 1988–96 1.07 (0.96, 1.20) 0.94 (0.84, 1.06) 0.94 (0.84, 1.06) 0.94
North Netherlands 1988–96 1.03 (0.57, 1.93) 0.94 (0.51, 1.76) 0.94 (0.51, 1.76) 0.94
USA-Atlanta 1988–96 0.84 (0.51, 1.34) 0.84 (0.51, 1.34) 0.84 (0.51, 1.34) 0.84

Table 7  Crude comparison between period before (88–93) and after (94–96) the initiation of strategies of prevention

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.

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 countries that were the first to promulgate supplementation policies and decreasing in the USA (Atlanta), England and Wales, Hungary, Japan and the Netherlands, and increasing in 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.

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 it seems unlikely that the recommendations have caused the fall. It seems more probable that more affluent countries experience falling NTD 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 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 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 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 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 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 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 the early promulgation of recommendations, but it seems unlikely that the recommendations have caused the fall.
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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Médicale, Hopital de Hautepierre, Strasbourg, France: C Stoll;

for the j-th observation, say

Application of the Poisson models

The Poisson regression is most appropriate for count data, it has only rarely been applied either in epidemiol-

ography or anywhere else. This appendix presents the way in

Appendix

The Poisson regression model, the incidence rate

In the Poisson regression model, the incidence rate for the i-th observation, say \( r_i \), is modelled as

\[ \log \left( \frac{r_i}{1000} \right) = \beta_0 + \beta_1 x_{1,i} + \beta_2 x_{2,i} + \ldots + \beta_k x_{k,i} \]

where \( x_{1,i}, x_{2,i}, \ldots, x_{k,i} \) are the values of the respective independent variables for the i-th observation, with \( x_{k,i} = 0 \) for all observations. 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 NTDS cases among them. Therefore this is not possible as a great number of early miscarried pregnancies are not included in the denominator, and the incidence rate is therefore considered a "corrected" prevalence rate at birth. This is not a perfect estimate of the natural birth prevalence. Some terminated pregnancies wouldmiscarry rather than ending in affected births if they were not terminated, and a substantial proportion of preganncies terminated for NTDs are probably not notified as such.

We are interested in temporal changes that occurred around 1994, when the folic acid policies might have begun to produce effects. For this purpose the general model adopted in this study is the following:

\[ \log \left( \frac{r_i}{1000} \right) = \beta_0 + \beta_1 x_{1,i} + \beta_2 x_{2,i} + \beta_3 x_{3,i} \]

where \( x_{1,i} \) is the time variable (set at 0 for 1988, 1 for 1989 and so on) and \( x_{3,i} \) is a dummy variable that is equal to 1 for years before 1994 and 0 from 1994 onwards. To compare rates, one can easily calculate the PRR, which is the exponential transformation of \( \beta_3 \) for the relevant variable. The PRR shows the variation of the prevalence rate corresponding to one unit change of one independent variable, say \( x_{3,i} \), holding constant all the other variables. 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:

\[ r_i = \exp(\beta_0 + \beta_1 x_{1,i} + \beta_3 x_{3,i}) \]

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:

\[ r_i = \exp(\beta_0 + \beta_1 x_{1,i} + \beta_3 x_{3,i} + \beta_4 x_{4,i}) \]

where \( x_{4,i} \) is a dummy variable that is equal to 1 for years before 1994 and 0 from 1994 onwards.

3) To distinguish the real effect of the policies from the general trend of NTD occurrence (which 2) does not do), we must adjust the time series for the effect of long term trends, represented by the factor \( x_{2,i} \). Therefore the model adopted is:

\[ r_i = \exp(\beta_0 + \beta_1 x_{1,i} + \beta_3 x_{3,i} + \beta_5 x_{5,i}) \]

The relevant PRR, calculated as \( \exp(\beta_5) \), 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. \( \text{e} \)


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