Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe

(Updated version December 2009)

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EUROCAT receives funding from the European Union, in the framework of the Public Health Programme
WHO Collaborating Centre for the Epidemiology Surveillance of Congenital Anomalies
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We thank Barbara Norton for secretarial support. We thank Nicky Armstrong, Araceli Busby, Helen Dolk and Maria Loane for their contribution to a previous report which is updated here. We thank Ruth Greenlees for providing data from the EUROCAT database.
We thank the registry staff and health professionals across Europe who provided data on neural tube defects for this Report.

EUROCAT is supported by the Public Health Programme of the European Commission.
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Austria
Belgium
Croatia
Denmark
Finland
France
Germany
Hungary
Ireland
Italy
Malta
Netherlands
Norway
Poland
Portugal
Slovenia
Spain
Sweden
Switzerland
Ukraine
United Kingdom
Recommendations

1) European countries could prevent most neural tube defects in planned pregnancies by putting in place an official policy recommending periconceptional folic acid supplementation and taking steps to ensure that the population are aware of the benefits of supplementation and the importance of starting supplementation before conception.

2) European countries should review their policies regarding folic acid fortification and supplementation taking into account available information on benefits and hazards of both. They should pay special attention to results of studies done post mandatory fortification in countries that have introduced it.

3) As many pregnancies are unplanned, European countries could achieve more effective prevention of neural tube defects by additionally introducing fortification of a staple food with folic acid. The particular objectives of this policy would be preventing neural tube defects among women who do not plan their pregnancy, and reducing socio-economic inequalities in neural tube defect prevalence.

4) Health effects of supplementation and fortification should be monitored, and policies should be reviewed periodically in light of the findings.

5) The European population should be covered by high quality congenital malformation registers which collect information about affected pregnancies (livebirths, stillbirths and terminations for fetal abnormality). One important use for the information would be to assess the effect of folic acid supplementation and fortification on NTD rates as well as rates of other congenital malformations.
Summary

Background
This Special Report 2009 reviews progress in developing and implementing public health policies to raise periconceptional folate status in European countries up to the end of 2007. Data on the prevalence of neural tube defects from 20 countries was analysed to determine the extent to which neural tube defects had been prevented. Our findings were disappointing and prompted us to make a number of recommendations including fortifying a staple food with folic acid. This recommendation is already under consideration by many governments.

Methods
The EUROCAT network has currently 43 population-based congenital anomaly registries in 20 European countries collaborating in the epidemiological surveillance of congenital anomalies. NTD cases (including livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis) were extracted from the EUROCAT Central Registry database for 1980-2007 and prevalence rates were calculated. In addition, representatives from 21 countries participating in or interested in joining EUROCAT provided information about policy, health education campaigns and surveys of folic acid supplement uptake in their country.

Results
By January 2005, 15 of the 20 countries contributing data to this report had introduced an official policy advising women to take periconceptional folic acid supplementation. Four countries (Austria, Belgium, Croatia, Germany) have no official government policy at the time of writing, although professional groups within them advise supplementation.

Half the countries have launched some type of health education campaign so that the information about the protective effect of folic acid can reach women directly rather than uniquely through health professionals.

We found that the majority of women surveyed are still not taking folic acid supplements periconceptionally. Only in the Netherlands and Denmark is the periconceptional use of folic acid above 30%, the other countries not reaching 10%. Mandatory fortification of a staple food (usually flour) with folic acid has been
seriously considered in eight countries contributing to this report (Denmark, Germany, Ireland, Northern Netherlands, Norway, Poland, Switzerland, and the UK). As of November 2009 food fortification with folic acid had not been implemented in any European country although it is now widespread in North and South America and in several countries in the Middle East.

Despite all measures taken to date, the majority of women in all countries surveyed are not taking folic acid supplements prior to and for the first weeks after conception.

This study shows a declining trend for anencephaly in the years 1992-2007, but not for spina bifida. We focused on this time period because all the folic acid advice and campaigns started after 1992.

A significant decline in prevalence of NTD since 1992 was found in Ireland, but not in the UK. In Continental Europe (excluding Southern Europe), in spite of the significant decrease in NTD prevalence in Northern Netherlands, the decrease for all registries combined is slight and non-significant. In South Europe the decline in NTD prevalence since 1992 was significant.

While livebirth NTD prevalence has decreased considerably in countries without a folic acid supplementation policy due to the increase in prenatal diagnosis and subsequent termination of affected pregnancies, the total prevalence has not significantly decreased. Reduction of livebirth prevalence is still relying more on prenatal screening and termination than on primary prevention with folic acid supplementation. In order to distinguish between decreases in prevalence due to primary prevention and those due to prenatal screening, information on terminations of pregnancy is essential.

The existence of an expanded network of congenital anomaly registries in Europe, collecting data on affected livebirths, stillbirths and terminations of pregnancy, is vital to track progress towards the prevention of NTDs. Information on NTD prevalence should be supplemented where possible by surveys of uptake of periconceptional folic acid supplementation in the population, and by monitoring of serum levels of folic acid.
Conclusion

The potential for preventing NTDs by periconceptional folic acid supplementation is still far from being fulfilled in Europe. In order to achieve a reduction in NTD prevalence, new efforts are needed in all countries to implement a combined strategy to increase folate status by dietary means, increase uptake of folic acid supplements periconceptionally, and to increase availability and identification of fortified foods. Mandatory fortification could improve folate status of all women of childbearing age, substantially reduce NTD prevalence, and reduce socio-economic inequalities in NTD prevalence. Additional benefits such as reduced specific cancer occurrence and cognitive decline have also been reported, although these have not been supported by randomised controlled trials.

As countries change their policies and practices regarding prevention of NTD, continued monitoring of NTD prevalence is vitally important. This requires data from population based registers of congenital anomalies with high ascertainment of cases among livebirths, stillbirths and termination of pregnancy for fetal anomaly
Part I

Overview of Neural Tube Defects
1. Introduction

Across Europe, an estimated 4,500 pregnancies are affected by Neural Tube Defects (NTD) each year. Evidence of a possible association between folic acid and NTD has been described in the scientific literature for more than three decades (Scott, Weir, & Kirke 1995). Since the early 1980s a number of intervention trials examining the effects of periconceptional folic acid on the prevalence of NTD have been published, with the first unambiguous evidence of the effectiveness of periconceptional folic acid coming in 1991 on the publication of the results of the Medical Research Council (MRC 1991). On the basis of this trial, it has been estimated that improving folate status sufficiently would result in the prevention of 72% of all NTD.

This report is an updated version of the EUROCAT NTD Report by the same name published in 2005 and focuses on periconceptional folic acid policies and implementation strategies across Europe since 1991 and the reported prevalence rates of NTD until 2007. Contributions from EUROCAT (European Surveillance of Congenital Anomalies) members representing 21 countries (20 countries with new data) are included in the form of chapters describing policy and practice in their respective countries in relation to: periconceptional folic acid supplementation, dietary advice, food fortification and women’s knowledge about the advice and compliance with recommendations. These are set within the context of laws relating to termination of pregnancy for fetal abnormality and of what is known about the proportion of pregnancies that are planned. The prevalence of NTD up to the end of 2007 is examined in relation to policies on folic acid supplementation across Europe. Furthermore, since 2005 a variable on folic acid intake has been added to the set of data all registries are sending to the Central registry. This report will show, for the first time, the periconceptional folic acid intake among women giving birth to malformed infants in several registries. The report will focus on NTD, as it is for this group of anomalies that the body of evidence for the protective effect of folic acid is strongest.
2. The Public Health Response to Evidence Concerning the Protective Effect of Folic Acid

2.1 Periconceptional Folic Acid Policies in European Countries

Table 1 summarises periconceptional folic acid supplementation policies around Europe. For more detail, the reader is advised to look at individual country chapters in Part II of this Report.

By January 2005, 15 of the 20 countries contributing data to this report had introduced an official policy advising women to take periconceptional folic acid supplementation. The first governments to formulate such a policy were in the Netherlands (1992), UK (1992) and Ireland (1993). Portugal recommends that health workers should educate women about the benefits of folic acid; Malta recommend raising folate status by dietary means only and four countries (Austria, Belgium, Croatia, Germany) have no official government policy at the time of writing, although professional groups within them advise supplementation.

The recommendation for periconceptional folic acid supplements in most countries is for a daily dose of 0.4 to 0.5 mg (except in Poland, where it is 1.0 mg, and Portugal, where no dose is specified). Higher doses, of 4 or 5 mg daily, are usually recommended for women who have had a previous pregnancy affected by an NTD. Some countries also have special recommendations for women on anticonvulsant therapy.

Half the countries have launched some type of health education campaign (Table 1) so that the information about the protective effect of folic acid can reach women directly rather than uniquely through health professionals. This is particularly important as folic acid supplementation must start before conception and therefore before the consultation of health professionals during pregnancy. The details of these campaigns can be found in Part 2. There is little evidence as to how often health education campaigns need to be repeated for a sustained effect.
2.2 Uptake of Recommendations to Take Periconceptional Folic Acid Supplements

Surveys of the use of folic acid supplements periconceptionally in European countries are summarised in Table 1. Details are given in the individual country chapters in Part 2 of this report. Details of the methodology of each survey, where available, are given in Part 2, and figures shown in Table 1 should be interpreted in the light of these details.

Table 1: Current¹ Folic Acid Supplementation Policy in European Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Periconceptional Folic Acid Policy</th>
<th>Year current policy introduced</th>
<th>Health education campaign</th>
<th>Year of study</th>
<th>% Women Using Folic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Unofficial</td>
<td>1998</td>
<td>No</td>
<td>1998</td>
<td>24% some part of advised period 10% for entire advised period</td>
</tr>
<tr>
<td>Belgium</td>
<td>Unofficial - Being prepared</td>
<td>-</td>
<td>Being prepared</td>
<td>2006</td>
<td>48% some part of advised period 24% for entire advised period</td>
</tr>
<tr>
<td>Croatia</td>
<td>Unofficial - Unofficial</td>
<td>-</td>
<td>Unofficial</td>
<td>2003</td>
<td>69% some part of advised period 20% for entire advised period</td>
</tr>
<tr>
<td>Denmark</td>
<td>Official</td>
<td>1997</td>
<td>1999 and 2001</td>
<td>2000-2</td>
<td>22% of women who planned pregnancies took supplements at correct time</td>
</tr>
<tr>
<td>Finland</td>
<td>Official</td>
<td>2004</td>
<td>Unofficial</td>
<td>2000</td>
<td>19% took FA before or in early pregnancy</td>
</tr>
<tr>
<td>France</td>
<td>Official</td>
<td>2000</td>
<td>2000 and 2004</td>
<td>?</td>
<td>30% some part of advised period 10% for entire advised period</td>
</tr>
<tr>
<td>Germany</td>
<td>Unofficial</td>
<td>1994</td>
<td>No</td>
<td>2000</td>
<td>4.3% for entire advised period</td>
</tr>
<tr>
<td>Hungary</td>
<td>Official</td>
<td>1996</td>
<td>Ongoing</td>
<td>2006</td>
<td>69% of pregnant women</td>
</tr>
<tr>
<td>Italy</td>
<td>Official</td>
<td>2004</td>
<td>2004 regional</td>
<td>2007</td>
<td>Depends very much on the region, range: 3-21%</td>
</tr>
<tr>
<td>Malta</td>
<td>Dietary</td>
<td>1994</td>
<td>No</td>
<td>2000</td>
<td>74% some part of advised period 15% for entire advised period</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Official</td>
<td>1993</td>
<td>1995</td>
<td>2005</td>
<td>80% some part of advised period 51% for entire advised period</td>
</tr>
<tr>
<td>Poland</td>
<td>Official</td>
<td>1997</td>
<td>Yes, but no date given</td>
<td>2005</td>
<td>70% some part of advised period 11% for entire advised period</td>
</tr>
<tr>
<td>Portugal</td>
<td>Official</td>
<td>1998</td>
<td>No</td>
<td>2005</td>
<td>24% for entire advised period</td>
</tr>
</tbody>
</table>

¹Current refers to the most recent period of study or policy implementation available at the time of the survey.
In all countries other than Netherlands, only a minority of women were found to have taken folic acid supplements during the entire advised periconceptional period. The highest uptake in the studies was recorded in Netherlands, UK, Switzerland, Norway and Hungary with 30-51% periconceptional uptake. Since these are the results of specific studies, we added an extra variable to EDMP to assess folic acid intake for each woman. In 2.3 the results are shown.

It should be noted that the countries in which the highest uptake rates were found were those with official health education initiatives.

There is evidence that women of higher social status are more likely to know of the benefits of taking supplemental folic acid and to be aware of the correct timing (de Walle, van der Pal-de Bruin, & de Jong- van den Berg 1998; Sayers et al. 1997; US Department of Health and Human Services 1993), potentially leading to widening of socio-economic inequalities in NTD prevalence.

### 2.3 Monitoring of Intake of Folic Acid

Since 2005 EUROCAT has added an extra variable to the data entry programme of EUROCAT in order to have more information on the periconceptional intake of folic acid for individual cases. The results are shown in the graph hereunder. In general over the years 2005-2007 the following registries had some information on the use of folic acid periconceptionally: Denmark (Odense), Italy (Tuscany and Emilia Romagna), Ireland (Dublin and SE Ireland), Northern Netherlands, Switzerland (Vaud), Croatia (Zagreb), S

<table>
<thead>
<tr>
<th>Country</th>
<th>Official Start Year</th>
<th>Official End Year</th>
<th>Unofficial Start Year</th>
<th>Unofficial End Year</th>
<th>Folic Acid Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slovenia</td>
<td>1998</td>
<td></td>
<td>2007</td>
<td></td>
<td>88% some part of advised period, 31% for entire advised period</td>
</tr>
<tr>
<td>Spain</td>
<td>2001</td>
<td>2002</td>
<td>2007</td>
<td></td>
<td>71% some part of advised period, 17% for entire advised period</td>
</tr>
<tr>
<td>Sweden</td>
<td>1996</td>
<td>No</td>
<td>1997</td>
<td></td>
<td>8% some part of advised period</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1996</td>
<td>2008</td>
<td>2003</td>
<td></td>
<td>98% some part of advised period, 37% for entire advised period</td>
</tr>
<tr>
<td>UK</td>
<td>1992</td>
<td>1995</td>
<td>2002</td>
<td></td>
<td>45% periconceptionally</td>
</tr>
<tr>
<td>Ukraine</td>
<td>2002</td>
<td></td>
<td>Unofficial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Policy as of December 2007
2. Recommended dose is as supplements unless otherwise stated
Portugal, Belgium (Antwerp), Spain (Basque country) and Germany (Saxony Anhalt).

We restricted the figure (Figure 1) to include the 9 registries with information on folic acid for more than 20% of their cases (periconceptional use, some use or no use).

**Figure 1:** Use of folic acid, 2005-2007 (only for registries with 20% or more data on Folic Acid)

The figure shows that of the nine registries that have some information on uptake, the uptake is very disappointing. The Northern Netherlands and Odense (Denmark) have the highest percentage women taking folic acid in the periconceptional period, 4 weeks before conception till 8 weeks after. Figure 2 shows the NTD prevalence rates shown for these 2 countries. This is the prevalence excluding chromosomal anomalies because it is thought that folic acid has the potential to be protective for multifactorial malformations, not for chromosomal anomalies.
Figure 2: Total Prevalence Neural Tube Defects (Excl Chromosomal) for Denmark (Odense) and Northern Netherlands, 1992-2007

There is a significant decreasing trend in the Netherlands ($\chi^2=5.1$, $p=0.02$) but not in Denmark ($\chi^2=0.52$, $p=0.47$).

The 7 other registries reported less than 10% periconceptional use of folic acid, so the overall uptake is very low. In 2005-2007 there were in total 41,516 cases with congenital malformations in the database. For 5,628 (13.6%) folic acid information is known and the mothers of 969 (2.3%) cases took folic acid in the periconceptional period. These numbers are too small to do a reliable statistical analysis.

In the near future we will publish the results of a survey we did in all the registries about the amount of information GPs, hospitals and midwives are collecting routinely on folic acid intake before and during pregnancy.

2.4 Fortification of Food with Folic Acid

Mandatory fortification of a staple food (usually flour) with folic acid has been seriously considered in eight countries contributing to this report (Denmark, Germany, Ireland, Northern Netherlands, Norway, Poland, Switzerland, and the UK) and the case for it is still being reviewed. As of November 2009 food fortification with folic acid had not been implemented in any European country.
although it is now widespread in North and South America and in several countries in the Middle East.

Food voluntarily fortified with folic acid (mainly breakfast cereals) is available in many European countries. In a study investigating the effects of consumption of folic acid-fortified bread compared with folic acid tablets, bread was found to be equally effective in increasing folate status as indicated by both increased red cell and serum folate concentrations (Armstrong NC. et al. 2001). However, it may be difficult for women to identify foods fortified with folic acid and to determine the amount in relation to their needs due to limitations/restrictions on food labelling.


NTD prevalence rates over time by country can be found in the Country Specific Chapters of Part 2. Registry descriptions can be found on our new website address: http://eurocat.bio-medical.co.uk. Most registries are population-based and register affected fetuses / babies in livebirths, stillbirths from 20 weeks gestation and terminations of pregnancy for fetal abnormality. Laws in each country regarding whether and until what gestational age termination of pregnancy for fetal abnormality is legal are summarised in Table 2.

Table 2: Laws Regulating Termination of Pregnancy for Fetal Abnormality

<table>
<thead>
<tr>
<th>Country</th>
<th>Is it Legal?</th>
<th>Gestational Age Limit for Non-Lethal Serious Anomalies</th>
<th>Gestational Age Limit for Lethal Anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Belgium</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Croatia</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Denmark</td>
<td>Yes</td>
<td>Before viability</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Finland</td>
<td>Yes</td>
<td>24 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>France</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Hungary</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Ireland</td>
<td>No</td>
<td>Not legal</td>
<td>Not legal</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>Before viability</td>
<td>Before viability</td>
</tr>
<tr>
<td>Malta</td>
<td>No</td>
<td>Not legal</td>
<td>Not legal</td>
</tr>
<tr>
<td>Country</td>
<td>Eligibility</td>
<td>Weeks</td>
<td>Upper Limit</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes</td>
<td>24</td>
<td>No upper</td>
</tr>
<tr>
<td>Norway</td>
<td>Yes</td>
<td>18</td>
<td>No upper</td>
</tr>
<tr>
<td>Poland</td>
<td>Yes</td>
<td>&lt;23</td>
<td>&lt;23</td>
</tr>
<tr>
<td>Portugal</td>
<td>Yes</td>
<td>24</td>
<td>No upper</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Yes</td>
<td>No</td>
<td>No upper</td>
</tr>
<tr>
<td>Spain</td>
<td>Yes</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Sweden</td>
<td>Yes</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Yes</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>UK</td>
<td>Yes</td>
<td>No</td>
<td>No upper</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Yes</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

Information as of April 2008
1 Except Northern Ireland

3.1 Methods

Data for all cases of NTD were extracted from the EUROCAT Central Registry database 1980-2007.

Total prevalence rates were calculated as the number of affected livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis divided by the total number of births (live and still) in the registry population. Livebirth prevalence rates were calculated as the number of affected livebirths divided by the total number of livebirths in the registry population.

Prevalence rates are given for anencephalus, spina bifida and all NTD combined. Cases with both anencephalus and spina bifida were classified as having anencephalus.

The χ² for trend was used to test if prevalence was significantly decreasing or increasing in time. Logistic regression was used in which the year of birth was taken as independent variable for decreasing or increasing prevalence. The test was done only for the total prevalence and total prevalence without chromosomal anomalies whenever appropriate. We did not test livebirth prevalence as the influence of prenatal testing and termination of pregnancy is becoming more important every year. Livebirth prevalence is not a reliable measure for discussing the role of folic acid prevention.

Further details of methods can be found in the original EUROCAT special report (2003) on the Prevention of Neural Tube Defects by Periconceptional
3.2 Results

Figure 3 shows a significantly decreasing prevalence of NTD from 1980 and onwards. In the beginning of the nineties it became clear from the MRC study (1991) and Czeizel’s Hungarian study (Czeizel 1993) that folic acid had a preventive effect on NTDs. That was the impetus for launching campaigns in several European countries. An effect of folic acid is therefore to be expected from 1992 onwards and not before. As the main focus in this report is the effect of periconceptional folic acid we tested the prevalence for significance from 1992 onwards.

Figure 3: All Registries: Total (In- and Exclusive Chromosomal Anomalies) and Livebirth Prevalence Rates for Neural Tube Defects

The total prevalence for NTDs for all registries included in this report is significantly decreasing from 1992 onwards. Over the years 1992-2007 \( \chi^2 \) for trend =10.9, \( p=0.001 \). For the non-chromosomal NTDs \( \chi^2 \) for trend =9.3,
p=0.002. The figures below show whether this is due to spina bifida, anencephaly or both.

**Figure 4:** All Registries: Total (In- and Exclusive Chromosomal Anomalies) and Livebirth Prevalence Rates for Spina Bifida

In figure 4 for the years 1992-2007 the \( \chi^2 \) for trend = 1.1, \( p=0.29 \), the odds ratio (OR) for year of birth is 0.997 (95% CI: 0.991-1.003), therefore no significant decrease in trend for spina bifida over the years 1992-2007. For the non-chromosomal spina bifida \( \chi^2 \) for trend = 0.31, \( p=0.58 \).
Figure 5: All Registries: Total (In- and Exclusive Chromosomal anomalies) and Livebirth Prevalence Rates for Anencephaly

Figure 5 shows a significantly (slightly) decreasing trend for anencephaly over the years 1992-2007, $\chi^2$ for trend = 6.4, $p=0.012$, the odds ratio (OR) for year of birth is 0.991 (95% CI: .984-.998). For the non-chromosomal anencephaly $\chi^2$ for trend = 6.9, $p=0.009$. This decrease might be real but can also be caused by the fact that anencephaly is diagnosed earlier in pregnancy in recent years and therefore less notified to the registries.

Figure 6 shows the total NTD prevalence for all countries in three time periods.
The decrease in prevalence is most significant in Ireland. In May 2006, The Food Safety Authority of Ireland (FSAI) and the Irish Department of Health & Children (DoHC) recommended fortification of all bread (with the exception of minor bread products) on a mandatory basis with folic acid at a level which provides 120 µg per 100g of bread as consumed. It is mentioned earlier that no EU country has mandatory food fortification with folic acid. However, this was not implemented, and in 2008, the FSAI recommended postponement of fortification, following preparatory studies by the implementation group which showed that the rate of NTD affected births had decreased further. In addition, there had also been a significant increase in folic acid intake in the Irish diet as a result of increased voluntary fortification by food producers in recent years. Furthermore, although termination of pregnancy is forbidden in Ireland, there is always the possibility of terminations abroad.

Another country worth mentioning is the UK. The UK, together with Ireland was the country with historical high rates for NTDs. In the recent period of 2005-2007 the prevalence is now of the same order as France, Belgium, Malta, Denmark, Austria and Norway.
The chapter on France in the second part of this report shows that it is especially the registry of Isle de la Reunion that has high prevalences over the years 2002-2007. This registry is one of the overseas departments of France and is the outermost region of the European Union. It is located in the Indian Ocean, east of Madagascar. The population is different genetically and environmentally from Europe, so there is no reason to expect the prevalence to be similar to that of other French registries.

NTD prevalence has changed over time, so regions with a high prevalence in the past do not necessarily continue to have a high prevalence. Figure 7 shows how the prevalences are changing in different parts of Europe.

**Figure 7:** Total Prevalence for Neural Tube Defects for Several Regions in Europe

![Graph showing total prevalence for Neural Tube Defects for several regions in Europe](image)

Countries belonging to ‘South Europe’ are: Italy, Croatia, Portugal, Malta and Spain. “Continental Europe” is represented by France, Belgium, Switzerland, Northern Netherlands, Denmark, Germany, Austria, Norway, Poland, Hungary, Ukraine and Finland. Regions or countries that show a statistically declining trend after 1992 are Ireland (p<.001) and Southern Europe (p<.001).
In the beginning of this report we showed in which countries public health campaigns about folic acid have taken place (Table 1). Figure 8 compares the NTD prevalence for countries that have had a campaign to encourage folic acid use with those that have not had a campaign. The countries that had a campaign (between 1992-2007) are: Ireland, UK, France, the Netherlands, Denmark, Spain, Norway, Poland and Hungary. There was no significant decline in prevalence in either group. This was tested for the whole period of 1992-2007. However, it is clear from the picture that the lines come together in recent years and that especially in countries with a public health campaign the decline from 2003 onwards is obvious. For example in 2007 there is a significant decline of 20% (OR=.80, 95% CI: .68-.95) in countries with a public health campaign. We also commented before (figure3) that the total prevalence for NTDs for all registries is significantly decreasing from 1992 onwards.

Figure 8: Total NTD Prevalence in Countries with and without a Public Health Campaign

Total NTD prevalence in countries with and without a public health campaign
3.3 Discussion

This study shows a declining trend for NTDs in the years 1992-2007, driven by the decline in anencephaly. We focused on this time period because all the folic acid advice and campaigns started after 1992.

In Ireland it is difficult to distinguish the effect of the folic acid supplementation policy on NTD prevalence rates from the decline in prevalence starting well before the implementation of national policy. It is possible that one explanation for this decline may be the increasing folate content of the Irish diet starting before the national policy. However, since 1992 the decline has continued, probably because of voluntarily fortified foods and better use of folic acid supplementation.

In the UK registries participating in this study there has been no decline since 1992.

In Continental Europe (excluding Southern Europe), in spite of the significant decrease in NTD prevalence rates in Northern Netherlands, the decrease for all registries combined is slight and non-significant.

In South Europe the decline in prevalence since 1992 was significant. The explanation for this could be increased consumption of folate rich / fortified food and /or use of periconceptional folic acid supplementation, but it is also known that increased socio-economic status decreases the risk for NTD.

While live birth NTD prevalence has decreased considerably in countries without a folic acid supplementation policy due to the increase in prenatal diagnosis and termination of affected pregnancies in these countries, the total prevalence has not significantly decreased. This emphasizes two points. Firstly, reduction of livebirth prevalence is still relying more on prenatal screening and termination than on primary prevention with folic acid supplementation. Secondly, in order to distinguish between decreases in prevalence due to primary prevention and those due to prenatal screening, information on terminations of pregnancy is essential.
The existence of an expanded network of congenital anomaly registries in Europe, collecting data on affected livebirths, stillbirths and terminations of pregnancy, is vital to track progress towards the prevention of NTDs. Information on NTD prevalence should be supplemented where possible by surveys of uptake of periconceptional folic acid supplementation in the population, and by monitoring of serum levels of folic acid.

This study showed that registries have only little or no information about whether the mother actually took folic acid periconceptionally. This is disappointing. Apparently the perceived need for monitoring this is low. Specific studies on this topic in contributing countries showed that only a minority of women took supplements during the entire advised period.

Overall in Europe, some progress has been made in the primary prevention of NTDs. This is especially true for anencephaly and for specific countries like the Netherlands and Ireland. Southern Europe decreased significantly while continental Europe only had a minor decrease in NTD prevalence. It is very difficult to estimate how many affected pregnancies in Europe are being prevented by use of folic acid. There is still room for improvement, especially since the percentage of unplanned pregnancies is still high. Therefore, folic acid fortification of staple foods might be an option to achieve significant prevention of NTDs.

Mandatory fortification with folic acid has been introduced in around 50 countries worldwide as a strategy to help women increase their folate levels. Reports from the US and Canada have shown an effective and significant decline in NTDs (De Wals et al. 2007; Godwin et al. 2008; Williams et al. 2005). Heseker et al. reported that countries with mandatory folic acid fortification achieved a significant decrease in the prevalence of NTD. He concludes in his study that the degree of reduction in NTD prevalence in a population is related to the baseline NTD prevalence. This decline was independent of the amount of folic acid administered and reveals a „floor effect” for folic acid preventable NTDs. Thus, not all cases of NTDs are preventable by increasing folate intake (Heseker et al. 2009). At the moment, mandatory fortification of folic acid is not
implemented in Europe. Fortification of staple foods with folic acid would provide a more effective means of ensuring an adequate intake, especially for those groups of women who are unlikely to plan their pregnancies or to receive or respond to health promotion messages. Fortification together with supplementation is likely to be a more cost-effective option than supplementation only for preventing NTD, since a supplementation only policy requires a health education campaign more extensive and effective and possibly more frequent than those implemented so far.

In Europe there has been reluctance to proceed to mandatory food fortification which we believe stems from two factors:

1) Lack of recognition of the public health importance of neural tube defects, possibly because the great majority of NTD pregnancies are now terminated, rendering them invisible to all but the family affected.

2) The possibility of health risks related to raising the population folic acid status. (Cornel, de Smit, & den Berg 2005)

There has been concern regarding the potential risk of masking the symptoms of pernicious anaemia caused by vitamin B₁₂ deficiency. If undiagnosed, there is potential for irreversible neurological damage in those at high risk of this deficiency, namely the elderly. However, it is argued that B₁₂ deficiency can be diagnosed simply with or without the presence of anaemia (Bower & Wald 1995). Furthermore, the masking of pernicious anaemia, which has concerned people at a theoretical level, has not been observed in countries with mandatory fortification of flour with folic acid.

Evidence continues to mount about the beneficial effects of folic acid for the prevention of other congenital anomalies. The evidence regarding effects of folic acid on cancer is not conclusive. Although there is evidence that folic acid may be protective against the development of new cancers, there is concern at the possibility that it may promote the development of undiagnosed premalignant and malignant lesions. The European Food Safety Authority summary report wrote: “There are currently insufficient data to allow a full
quantitative risk assessment of folic acid and cancer or to determine whether there is a dose-response relationship or a threshold level of folic acid intake associated with potential colorectal cancer risk. The evidence regarding the effects of folic acid on cardiovascular disease is also inconclusive. Observational studies suggested that high intakes of folic acid were associated with a lower risk of CVD but randomised trials have not confirmed these findings (ESCO 2009).

4. Conclusions

- The evidence that most NTD are preventable by increasing folate status before conception is very strong
- Government response to this evidence has been variable in Europe. Some countries have been slow to introduce policies while others very actively promote periconceptional folic acid supplementation
- The majority of women in countries surveyed are still not taking folic acid supplements periconceptionally
- Most countries have implemented some type of health education campaign designed to reach women before conception. However, there are still five countries that have had no campaigns at all. No difference was found in the decrease in NTD prevalence between countries with and without a campaign
- There is a decreasing trend of anencephaly over the years 1992-2007 which is significant but falls short of expectations; the prevalence of spina bifida is not declining
- There is an immense challenge facing those involved in public health and the care of prospective mothers to replace termination of pregnancy with primary prevention by folic acid as the chief method of reducing the number of infants affected by this very serious group of congenital anomalies
- In order to achieve a reduction in NTD prevalence, new efforts are needed in all countries to implement a combined strategy to:
  - increase folate status by dietary means
  - increase uptake of folic acid supplements periconceptionally
  - increase availability and identifiability of fortified foods
• The possibility of preventing the majority of NTD through mandatory fortification of a staple food has not yet been introduced by any of the countries surveyed. Mandatory fortification could improve folate status of all women of childbearing age, substantially reduce NTD prevalence, and reduce socio-economic inequalities in NTD prevalence. Suggestions for additional benefits such as reduced specific cancer occurrence and cognitive decline are also made. However, evidence for this is not supported by randomised controlled trials

• As countries change their policies and practices regarding prevention of NTD, continued monitoring of NTD prevalence is vitally important. This requires data from population based registers of congenital anomalies with high ascertainment of cases among livebirths, stillbirths and termination of pregnancy for fetal anomaly
5. References

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