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Special Report:

Special Report:

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

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RECOMMENDATIONS

EUROCAT data reveal the lack of substantial decline in neural tube defect prevalence in Europe in the last decade. Even countries which have pursued supplementation policies relatively actively have found a limited preventive impact. Therefore, EUROCAT strongly recommends the following:

1) Countries should review their policies regarding folic acid fortification and supplementation, taking account of WHO Europe recommendations.
2) 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.
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

Approximately 4000 pregnancies every year in Europe result in a livebirth, stillbirth or termination of pregnancy of a baby/fetus affected by Neural Tube Defects (NTD), mainly anencephaly and spina bifida. Periconceptional folic acid supplementation has been shown over a decade ago to be an effective method of preventing potentially two thirds of cases. In this Report we review progress in the last decade in European countries in terms of developing and implementing public health policies to raise periconceptional folate status, and analyse data on the prevalence of neural tube defects from 36 congenital anomaly registries in 17 countries to determine the extent to which neural tube defects have been prevented up to the year 2000.

Methods

EUROCAT is a network of 36 congenital anomaly registries in Europe collaborating in the epidemiological surveillance of congenital anomalies. Representatives from seventeen countries participating in EUROCAT provided information about policy, health education campaigns and surveys of folic acid supplement uptake in their country. NTD rates (including livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis) were extracted from the EUROCAT Central Registry database for 1980-2000.

Results

At the beginning of 2002, an official governmental recommendation that women planning a pregnancy should take 0.4 mg of folic acid supplementation daily was in operation in nine of the seventeen countries. The earliest countries to introduce an official supplementation policy were the UK, Ireland and Netherlands in 1992-3 and the latest were Spain and France in 2000-2001. In the remaining eight participating countries, no official government recommendation about supplementation was in place, however, professional bodies within a subset had in fact recommended supplementation, and two countries had an official policy of encouraging women to increase their dietary intake of folate periconceptionally. Only seven countries had official health education initiatives: UK, Ireland, France, Poland, Netherlands, Norway and Denmark. Despite all measures taken to date, the majority of women in all countries surveyed are not taking folic acid supplements periconceptionally. The situation regarding low uptake of supplementation advice is reflected in the lack of a clear decline in the prevalence of neural tube defects across Europe. Nevertheless, there was some evidence that in countries with a

supplementation policy, a small decline in prevalence had taken place. In UK and Ireland, it was difficult to distinguish any effect of supplementation policy against the background of a strongly declining NTD prevalence throughout the 1980s, predating folic acid advice.

Conclusion

The potential for preventing NTDs by periconceptional folic acid supplementation is still far from being fulfilled in Europe. Only a public health policy including folic acid fortification of staple foods is likely to avoid widening socio-economic inequalities in NTD prevalence and result in large scale prevention of NTD.

Part I

Overview

1. Introduction

Across the 15 member states of the European Union an estimated 4000 pregnancies are affected by Neural Tube Defects (NTD) each year. Evidence of a possible association between *folic acid* and neural tube defects has been described in the scientific literature for more than three decades (Scott et al, 1995). Since the early 1980s a number of intervention trials examining the effects of periconceptional folic acid on the incidence 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) Vitamin Study (MRC Vitamin Study Research Group, 1991). On the basis of this trial, it was estimated that improving folate status sufficiently could result in the prevention of over two-thirds of all NTD.

This report examines the periconceptional folic acid policies and implementation strategies across Europe since 1991 and the reported prevalence rates of neural tube defects up to the year 2000. Contributions from EUROCAT (European Surveillance of Congenital Anomalies) members representing 17 countries 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 neural tube defects up to the year 2000 is examined in relation to policies on folic acid supplementation across Europe.

Although there is increasing evidence to suggest that folic acid may also protect against other congenital anomalies this 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. Background

2.1 What are neural tube defects?

The development of the brain and spinal cord is observable at approximately 18 days after conception as a localised thickening of cells collectively known as the neural plate. Following elongation and subsequent formation of the neural tube, closure at the midbrain/cervical region occurs at about day 21 and closure at the cephalic end at around day 26. The closed neural tube then stimulates the development of the bony structures of the vertebral column and the skull. The group of congenital malformations known as NTD are the collective set of malformations which occur if the bone fails to form above any unclosed region of the neural tube. One of the main difficulties regarding the prevention of neural tube defects lies in the fact that NTD occur before most women know they are pregnant.

The location of the defect along the neuraxis determines the specific anomaly presented: ie. if the cephalic end of the tube is affected, the outcome is the lethal condition anencephalus, or more rarely encephalocele or iniencephalus. If any of the remainder is affected, the outcome is spina bifida. Most neonates with spina bifida and encephalocele survive but the vast majority have lifelong moderate or severe disability.

2.2 Geographic, temporal and socio-economic variation in the prevalence of NTD

There is marked geographic variation in the prevalence of NTD (Little and Elwood, 1992) with the UK and Ireland having exhibited the highest rates in Europe for many decades (Penrose, 1957; EUROCAT Working Group, 1991). There has been a decline in many parts of the world in the prevalence of neural tube defects. This decline appears to have begun earlier in some places than in others, for example: 1950s in the Netherlands (Romijn and Treffers, 1983), and 1970s in the UK (Kadir et al, 1999). While since the early 1980s the decline in birth prevalence in UK and Ireland is partly due to prenatal diagnosis and selective termination of affected pregnancies, decreasing prevalence is still seen when terminated pregnancies are included (EUROCAT Working Group 91).

Data are available from several countries up to the mid-1970s which demonstrate a higher prevalence of NTD in babies of women of low socio-economic status: Britain (Elwood and Nevin, 1973; Anderson et al, 1958), Australia (Field, 1978), Finland (Hemminki et al, 1981) and

the USA (Naggan and MacMahon, 1967). There is little epidemiologic evidence concerning the relationship between socio-economic status and NTD more recently (Vrijheid et al, 2000).

2.3 What is Folic Acid?

The term folate refers to a family of compounds which have common vitamin activity and have a double aromatic ring of a pteridine attached to a *p*-aminobenzoate and a glutamate.

Folic acid (pteroyl glutamic acid) is the synthetic form of folate (one of the B-vitamin group). It is highly bioavailable, stable to heat exposure (eg. during cooking), and not present in nature.

In order that folic acid can function as a co-enzyme for cell growth and multiplication, it must be converted *in vivo* to the natural forms – first to the dihydro and subsequently the tetrahydro form (Scott & Weir, 1994).

2.4 Sources of Folate

While folate is found in a wide variety of foods (Table 1), there is no particularly good source, with the exception of liver. The folate-rich foods shown in the table do not necessarily contribute the most to overall intakes of folate in a population (McNulty, 1997). The main food sources of folate consumed in the UK (as determined in the Dietary and Nutritional Survey of British adults) are shown in Figure 1 below. The paucity of foods eaten on a regular basis which are folate-rich leads to a problem in achieving the higher folate status necessary to reduce the risk of development of NTD in the fetus during pregnancy (Cuskelly et al, 1996). Cruciferous vegetables (cabbage, cauliflower, broccoli) are rich in natural folates; however, few women have sufficiently high intakes of these foods to offer optimal protection for the fetus. This is compounded by the fact that natural food folates are only half as bioavailable as folic acid which is assumed to be 100% available (Gregory et al, 1991).

Some of the mean daily dietary intakes of folate for women, as quoted in the country-specific chapters in Part II, are as follows: 248 μg in Denmark, 102 μg folic acid equivalent in Germany 252 μg in Spain, 275 μg in Switzerland, and 213 μg in the UK.

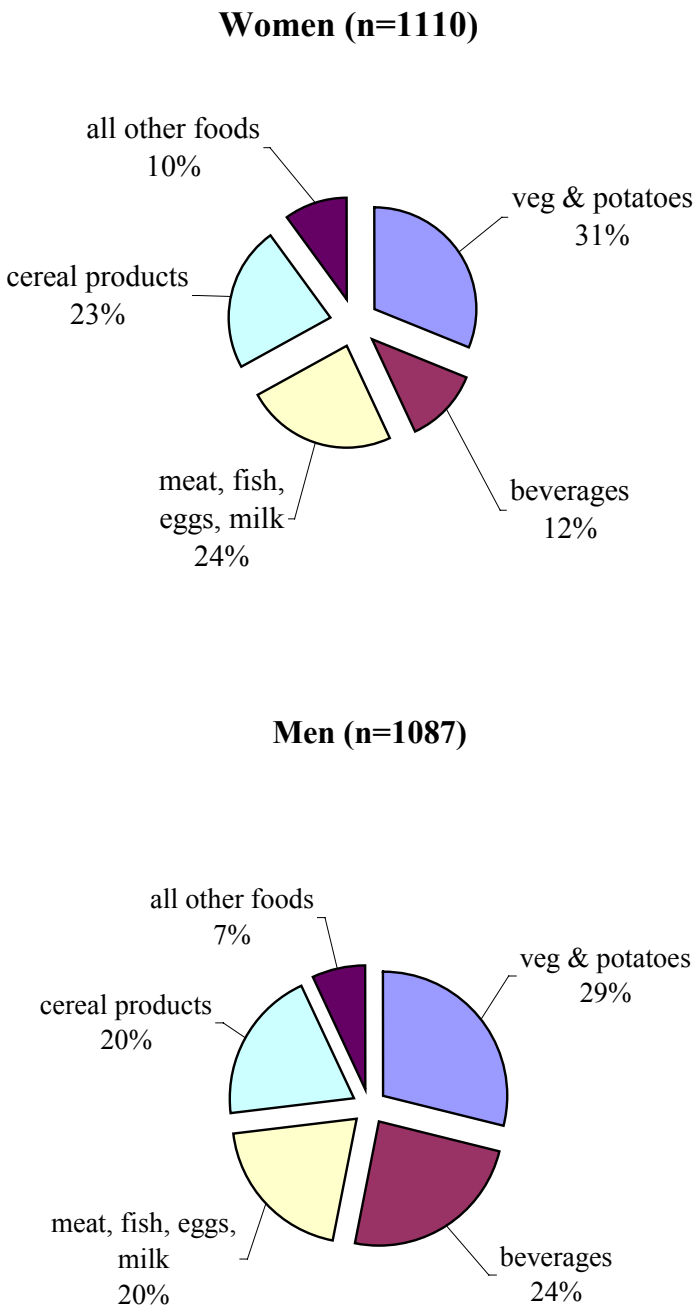
Table 1: Folate content of selected foods* (μg of folate per usual serving) (Holland et al 1991)

Chicken liver (grilled or fried)	500
Asparagus (*Asparagus officinalis*)	193
Fortified breakfast cereal	83
Spinach (Spinacia oleracea)	81
Broccoli (*Brassica oleracea botrytis asparagoides*)	54
Green beans	50
Marmite	40
Orange juice	32
Baked beans	30
Fruit yoghurt	24

* **Note that 100 μg of food folate is equivalent to 50 μg folic acid** (Suitor 2000)

In terms of changes over time, data from the UK National Food Survey indicate that average dietary folate intakes in Britain have increased substantially since the mid 1980s (the current average daily intake is 311μg for men and 213μg for women) coinciding with the increased proportion of breakfast cereal manufacturers introducing voluntary fortification with vitamins (including folic acid) between the years 1985 and 1991. In addition, bread voluntarily fortified with folic acid first became available in the UK in 1991. National food survey data suggest that steady increases occurred in the consumption of fruit juice and fruits in British households during the past three decades (Rayner et al, 1998).

Figure 1: Main Food Sources of Folate in the UK (MAFF 1994)



2.5 Folic Acid and Neural Tube Defects: the evidence for a protective effect

The possibility that maternal folate status might be implicated in NTD was raised in 1965 when Hibbard and Smithells showed that a test indicating lack of folate or disturbed folate metabolism (the FIGLU test) was more often positive in women carrying a fetus with an NTD than in controls (Hibbard and Smithells, 1965). This finding stimulated a number of studies investigating the role of folic acid in relation to NTDs.

a) Recurrence studies

In 1980 Smithells et al reported on a multicentre (5 UK centres) non-randomised prospective trial of periconceptional multivitamin supplementation (including 0.36 mg folic acid per day) for the prevention of recurrence of NTD (i.e. mothers who have had a baby with NTD having another baby with NTD). This study found a statistically significant difference between the recurrence risk in supplemented women (0.6%) and that of the controls (5.0%). The lack of randomisation made interpretation of these results difficult. Laurence et al (1981) reported on the results of another intervention study for the prevention of recurrence of NTD. This was a small randomised controlled trial in which the study group took 4mg folic acid daily while the control group took a placebo. While supplemented women had fewer recurrences, the small size and methodological weaknesses left the question still open.

The MRC vitamin study (1984-1991) conclusively demonstrated a substantial reduction of the incidence of NTD with periconceptional folic acid treatment (4 mg daily). This was an international, multi-centre, double-blind randomised trail involving 33 centres of which 17 were in the UK (MRC Vitamin Study Research Group, 1991). The recurrence rate in the folic acid groups was 1.0% and in the non folic acid groups it was 3.5%, yielding an odds ratio of 0.29 (95% CI: 0.12-0.71). This represents a 71% protective effect of folic acid for recurrence among women with a previously affected pregnancy.

b) Occurrence studies

Since 95% of NTD are first occurrences rather than recurrences (Department of Health (DOH), 1992), the results in 1992 of the randomised controlled occurrence trial (folic acid content 0.8mg daily) carried out in Hungary were very important. Czeizel and Dudás published the first results in 1992 with further analysis following in 1993 and 1996. There were no NTD in the multivitamin group and six in the trace element group

(Fisher's exact p=0.014). Although unlikely to alter the conclusions of this study, it must be pointed out that the design of the trial does not allow the contribution of the various components of the vitamin tablet administered to be distinguished as there were only two arms (vitamin supplement including folic acid, other vitamins and trace elements versus a trace elements only arm). A large intervention trial in China also showed a protective effect of folic acid supplementation (Berry et al, 1999).

In addition to the intervention trials, there have been a number of observational studies. A protective effect of folic acid or dietary folate was found by most of them (Mulinare et al, 1988; Milunsky et al, 1989; Bower and Stanley, 1989; Werler et al, 1993). One study (Mills et al, 1989) did not find a protective effect of folic acid. While the overwhelming body of literature is supportive of the positive role of folic acid for the prevention of NTD, more cautious views have also been expressed (Kalter 2000, Kallen 2002)

There is increasing evidence to suggest that folic acid may also protect against other congenital anomalies such as orofacial clefts (Tolarova and Harris 1995, Shaw et al, 1995a, 1998; Hayes et al 1996, Czeizel et al, 1999; Mills et al 1999, Werler et al, 1999; Itikala et al, 2001), cardiac defects (Shaw et al, 1995b; Botto et al, 1996; Scanlon et al 1998, Botto et al, 2000), urinary tract defects (Li et al, 1995; Werler et al, 1999) and limb reduction defects (Shaw et al, 1995b; Yang et al, 1997),

There is good evidence that a polymorphism (version) of a gene encoding a critical enzyme involved in folate metabolism, methylenetetrahydrofolate reductase (MTHFR), is associated with the risk of NTD (van der Put et al, 1995; van der Put et al, 1996, Wald and Noble 1999). This is a very good example of a gene-nutrient interaction, where the absence of an environmental factor (either folate or folic acid) combined with a specific variant gene (MTHFR) can cause a NTD. In terms of the biochemical effects of the polymorphisms of MTHFR, homozygotes show reduced enzymatic activity (Frosst et al, 1995) and this leads to low serum and red cell folate (Molloy et al, 1997) and increased levels of plasma homocysteine (Kang et al, 1993; Frosst et al, 1995; Engbersen et al, 1995; Kluijtmans et al, 1996). The percentage of homozygosity of MTHFR measured in various populations are described elsewhere (Fletcher and Kessling, 1998, Botto and Yang 2000). It has been proposed that folic acid supplementation prevents NTD by partially correcting the lower activity of the variant form

of the enzyme (Whitehead et al, 1995; Shaw et al, 1998b). However, the benefits of increasing folate status are not only confined to women with an MTHFR mutation.

3. The Public Health Response to evidence concerning the protective effect of folic acid

3.1 Possible methods of increasing folate status

There are three possible ways in which the recommendation of increasing folate status in women of childbearing age can be achieved:

(i) Increased intake of foods naturally rich in folate

(ii) Folic acid supplementation

(iii) Folic acid fortification of food

Cuskelly et al (1996) addressed the question of the relative effectiveness of these three options in an intervention study in healthy young women. They measured change in red cell folate concentration (considered to be the best indicator of folate status) in response to a 12-week study in which women were randomly assigned to one of the following groups: a) folic acid supplements (400μg per day), b) folic acid-fortified food (400μg per day), c) dietary advice (qualitative) or d) no supplements, folic acid-fortified foods or advice. Although women in all four intervention groups increased their folate/folic acid intakes, this change was reflected in increased folate status in *only* those women assigned to folic acid supplements or fortified food.

In order to achieve the recommended extra 400μg, a 3-fold increase in typical intakes of the vitamin would be required (approximately 200 μg per day in women; Subar et al, 1989; Gregory et al, 1990; Irish Universities Nutrition Alliance, 2001). Achieving this target by food folates alone would require major dietary modifications unlikely to be accomplished by most women planning a pregnancy, not to mention those women not planning to become pregnant (McNulty et al, 2000).

McKillop et al (2002) indicated the importance of cooking method, especially for green vegetables, a particularly good source of folate. Boiling was found to decrease the folate content to 49% and 44% of the original amount for spinach and broccoli respectively. Steaming of spinach and broccoli, in contrast, resulted in no significant decrease in folate content. Thus, dietary changes would need to concern not only foods eaten but cooking method.

3.2 Policies regarding increasing periconceptional folate status in European countries

In Part II of this Report, the recommendations of governments in Europe ("official policy") as well as professional and other associations ("unofficial policy") are described. A summary is given in Table 2.

The first governments to formulate a policy concerning folic acid supplementation were Netherlands (1992), UK (1992) and Ireland (1993). Seven more countries had introduced an official policy of folic acid supplementation by 2001, two of these countries (France and Spain) as late as 2000-2001. Two countries (Malta and Finland) recommended raising folate status by dietary means only. Five countries (Austria, Belgium, Croatia, Germany and Italy) had no official policy at the time of writing.

Recommendations for periconceptional folic acid supplements were for a dose of 0.4 to 0.5 mg (except Poland: 1.0 mg and Portugal: no specified dose) daily for women planning a pregnancy. It is usually recommended that supplementation begin at least a month prior to conception and continue for the first three months of pregnancy. Higher doses 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.

Seven countries launched some type of health education campaign (Table 2) so that the information about the protective effect of folic acid could 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 II. There is little evidence as to how often health education campaigns need to be repeated for a sustained effect.

Mandatory fortification of staple food with folic acid has been considered by governments in some countries contributing to this report (eg. Denmark, Switzerland, Ireland and UK) and the case for it is still being reviewed. Implementation of food fortification is currently being planned for the Lubin Province in Poland where there are approximately 30, 000 births per year.

Food voluntarily fortified with folic acid (mainly breakfast cereals) is available in many regions (for example, breakfast cereal, bread and milk in Ireland and flour in Germany). In a recent 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 et al, 2001). It may be difficult in some countries 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.

Table 2: Current[1] Folic Acid Supplementation Policy in European Countries

Country	Periconceptional Folic Acid Supplementation Policy [2]					Selection of recent studies of folic acid use described in the Country-Specific chapters	
	Status	Date	Low risk women	Women with previously affected pregnancy	Health Education Campaign	Year of study	% Women Using Folic Acid
Netherlands	Official	1992	0.5 mg	4 mg	1995	1998	63% some of advised period 36% for entire advised period
UK	Official	1992	0.4 mg	4 mg	1995	2001	45% preconceptionally
Ireland	Official	1993	0.4 mg	5 mg	1993 and 2000/2001 with NI	1997-8	30% preconceptionally
Denmark	Official	1997	0.4 mg	5 mg	1999 and 2001	1999	17% at GA <5 weeks
Poland [3]	Official	1997	1.0 mg	4 mg	No date given	2001	19% of all women aged 18-45 13% of non-pregnant women aged 18-45
Norway [4]	Official	1998	0.4 mg	4 mg	1998 (website)	2000	46% before or during the first 3 months of pregnancy
France	Official	2000	0.4 mg	4 mg	2000	1999	1% at recommended time (1 month before until 2 months after conception)
Malta	Official	1994	Women planning a pregnancy should increase dietary intake of folate		No	1999	15% periconceptionally, a further 59% at GA <12 weeks
Finland [5]	Official	1995	dietary	4 mg	No	2000	19% preconceptionally and in early pregnancy
Switzerland	Official	1996	0.4 mg	4 or 5 mg	No		
Portugal	Official	1998	Health workers should educate women about benefits of folic acid		No		
Spain	Official	2001	0.4 mg	4 mg	No	2000	4.5% at recommended time
Germany	Unofficial	1994	0.4 mg	4 mg	No	2000	4.3% preconceptionally
Austria	Unofficial	1998	0.4 mg	4 mg	No	1998	10% at GA <12 weeks
Belgium	Unofficial	-	0.4 mg	4 mg	No		
Croatia	Unofficial	-	0.4 mg	4 mg	No		
Italy	None	-	-	-	No	1999	3% periconceptionally

1. Policy as of June 2002 see Part II: Country-specific Chapters for full details
2. Recommended dose is as supplements unless otherwise stated
3. Poland recommends that all women of child bearing age take a supplement of 0.4 mg, increasing to 1 mg when planning a pregnancy.
4. Norway recommends >0.4 mg for moderate risk women (see Norwegian chapter for details).
5. Finland recommends 0.4 mg folic acid supplementation for moderate risk women (see Finnish chapter for details).

3.3 The uptake by women of recommendations to take periconceptional folic acid supplements

Surveys in European countries of the use of folic acid supplements periconceptionally are described in Part II, and summarised in Table 2. A fully informative survey needs to be based on a representative sample of pregnant women, distinguishing any use of folic acid (which may start too late, after the pregnancy is recognized) from use which starts preconceptionally and continues for the recommended length of time. Details of the methodology of each survey, where available, are given in Part II, and figures shown in Table 2 should be interpreted in the light of these details.

In all countries (Table 2), a minority of women were taking folic acid supplements during the entire advised periconceptional period. The highest uptake was recorded in Netherlands, UK and Ireland with 30-45% periconceptional uptake. Extremely low uptakes of less than 5% were found in France, Spain, Germany and Italy. It should be noted that the countries in which the highest uptake rates were found were those with official health education initiatives.

The low uptake of periconceptional folic acid supplements may be because a large proportion of women do not plan their pregnancies and of those who do plan the pregnancy, many are either unaware of the benefits of periconceptional folic acid, unaware of when they should take it or disinclined to take it (Clark and Fisk 1994; Scott et al, 1994; de Walle et al, 1999). It has been shown that women often modify their behaviour only after pregnancy has been confirmed and this usually occurs after the critical embryonic development of the neural tube is complete (Morin et al, 2002). Surveys have also shown that women believe if they "eat well" they do not need additional folic acid.

Estimates of the proportion of pregnancies which are 'planned' in different countries are shown in Table 3. Since surveys which have asked women whether their pregnancy was planned have not generally employed a definition of "planned", it is difficult to make meaningful comparisons of reported pregnancy planning behaviour between countries. The concept of 'planning' needed in relation to periconceptional folic acid supplementation refers to a conscious decision to stop contraception together with consideration by the woman of possible health and lifestyle changes needed to achieve conception and/or a healthy pregnancy. It may or may not include a

consultation with a health professional. The concept of pregnancy 'planning' held by women almost certainly differs from this, and is influenced by social status and cultural factors.

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 (Food and Drug Administration, 1996; Sayers et al 1997; de Walle et al, 1998), potentially leading to widening of socio-economic inequalities in NTD prevalence.

Table 3: Proportion of pregnancies thought to be 'planned'*

Country	**Estimated proportion of pregnancies which are planned**
Belgium	about 50%
Denmark	more than 50%
Finland	about 85%
Germany	about 65-70%
Ireland	40-45 %
Netherlands	about 85%
Norway	less than 75%
Poland	10-20%
Portugal	low
U.K.	about 60%

*Information as of June 2002, source: Country Specific chapters of Part II. No information for Austria, Croatia, France, Italy, Malta, Spain or Switzerland.

4. NTD prevalence rates in Europe 1980-2000: to what extent has perinconceptional folic acid supplementation prevented NTD in Europe?

4.1 Introduction

In this section, EUROCAT data on the prevalence of NTD in Europe from 1980 to 2000 are examined in relation to folic acid supplementation policy in different countries.

Further detail on NTD prevalence rates can be found in the Country Specific Chapters of Part II, and in Appendix 3, and further detail on statistical analysis can be found in Appendix 2.

4.2 Methods

Data for all cases of NTD were extracted from the EUROCAT Central Registry database 1980-2000 for 33 registries in 18 countries (Table 4).

Descriptions of registries can be found in Appendix 5. The majority of registries are population-based. The majority of registries register cases in livebirths, stillbirths and terminations of pregnancy. Table 5 summarises laws in each country regarding whether termination of pregnancy for fetal abnormality is legal, and the upper gestational age limit. A few registries have experienced problems with the ascertainment of terminations of pregnancy (Table 4) and these registries were excluded from statistical analyses. An analysis of the ratio spina bifida to anencephaly was undertaken to explore whether there may have been further underascertainment of terminations of pregnancy, which would be revealed by underascertainment of anencephaly relative to spina bifida (Appendix 4). The results are shown in Table 4. However, registries with high spina bifida to anencephaly ratios without other evidence of underascertainment of terminations were not excluded from statistical analysis.

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.

Prevalence rates for all NTD were calculated, as well as anencephalus and spina bifida separately. Spina bifida excludes cases associated with anencephalus.

Data from UK and Ireland were analysed separately from data from the rest of Europe due to the historically higher prevalence of NTD in UK and Ireland, and the well documented steep decline in prevalence in UK and Ireland prior to the 1990s (EUROCAT Working Group 91).

Policy with regard to periconceptional folic acid supplementation was categorised as follows (Table 4):

A. Official supplementation policy plus health education campaign
B1. Official supplementation policy without health education campaign
B2. Official policy relating only to increasing folic acid by dietary means.
C. Unofficial or no policy
D. No policy, years prior to 1992 when results of randomised trials had not yet been disseminated.

Full details of policy can be found in Part Two.

Analyses were performed as follows:

1. Graphical presentation of total NTD prevalence rates per region, with arrows showing year of supplementation policy introduction
2. Prevalence rate ratio analysis by policy type, comparing total prevalence 1998-2000 to prevalence in 1989-1991 and 1989-1994, using Mantel-Haenzel stratification for registries. The first of these baseline periods was to predate the randomised trial results, the second to increase the statistical power for comparisons in small registries, and to check for stability of results using different baselines. Only registries with data spanning at least the period 1991 to 1999, and with good ascertainment of terminations of pregnancy, were entered into this analysis (see Table 4). Registries were grouped by policy type in 1999.
3. Poisson regression, modelling NTD total prevalence in relation to year, year^2, registry, interaction of year and registry, interaction of year^2 and registry and policy type. Policy type was analysed in four levels (combining C and B2 above) and three levels (combining A and B1, and combining C and B2 above). Policy type was attributed to each year of analysis starting in the year following the introduction of the policy. All registries with data spanning

at least 1995-99, and with good ascertainment of terminations of pregnancy, were entered into the analysis. Full details of this statistical analysis are presented in Appendix 2.

Table 4: EUROCAT population included in prevalence rate ratio (PRR) and Poisson regression statistical analyses

Country	Registry	No. of births / year (approx)	Years of data	Years with missing (M) or incomplete (I) data for Terminations of Pregnancy **	PRR analysis (1989-2000) Yes/No	Poisson regression analysis (1980-2000) Yes/No	Policy type from 1992 to 2000†
Austria	Styria	11,000	1985-1999	High SB:Anen ratio **	Yes	Yes	C
Belgium	Antwerp	12,000	1990-1999	-	Yes	Yes	C
	Hainaut	12,000	1980-1999	-	Yes	Yes	C
Bulgaria *	Bulgaria	10,000	1996-1999	-	No	Yes	C
Croatia	Zagreb	6,000	1983-2000	High SB:Anen ratio **	Yes	Yes	C
Denmark	Odense	5,500	1980-2000	-	Yes	Yes	C until 1997 A from 1998
Finland	Finland	57,000	1993-2000	-	No	Yes	C until 1995 B2 from 1996
France	Central East France	100,000	1980-2000	M:1980-1985, High SB:Anen ratio **	Yes	Yes	C
	Paris	39,000	1981-2000	-	Yes	Yes	C
	Strasbourg	14,000	1982-2000	-	Yes	Yes	C
Germany	Mainz	3,000	1990-1999	-	Yes	Yes	C
	Saxony-Anhalt	14,000	1987-2000	-	Yes	Yes	C
Ireland	Dublin	21,000	1980-2000	TOP illegal	Yes	Yes	C until 1993 A from 1994
	Galway	2,500	1981-1999	TOP illegal	Yes	Yes	C until 1993 A from 1994
Italy	Campania	50,000	1996-2000	-	No	Yes	C
	Emilia Romagna	25,000	1981-2000	M:1981-1989, I:1990-2000	No	No	C
	North East Italy	55,000	1981-1999	M:1981-1988	Yes	Yes	C
	South East Sicily	15,000	1991-2000	M:1991-2000	No	No	C
	Tuscany	26,000	1980-2000	-	Yes	Yes	C

Country	Registry	No. of births / year (approx)	Years of data	Years with missing (M) or incomplete (I) data for Terminations of Pregnancy **	PRR analysis (1989-2000) Yes/No	Poisson regression analysis (1980-2000) Yes/No	Policy type from 1992 to 2000†
Malta	Malta	4,000	1986-2000	TOP illegal	Yes	Yes	C until 1994 B2 from 1995
Netherlands	Northern Netherlands	20,000	1981-2000	-	Yes	Yes	B1 to 1994, A from 1995
Norway	Norway	60,000	1980-2000	I:1980-1998	No	Yes	C to 1997, A from 1998
Poland	Poland	159,000	2000	M:2000	No	No	A in 2000
Portugal	Southern Portugal	18,000	1990-2000	-	Yes	Yes	C until 1998 B1 from 1999
Spain	Asturias	6,000	1990-1999	-	Yes	Yes	C
	Barcelona	12,000	1992-1999	-	No	Yes	C
	Basque Country	17,000	1990-2000	-	Yes	Yes	C
	ECEMC (Madrid)	100,000	1980-1999	TOP illegal before 1985, M:1985-1999	No	No	C
Switzerland	Vaud	7,500	1997-2000	-	Yes	Yes	C until 1996 B1 from 1997
U.K.	Glasgow	10,000	1980-1999	-	Yes	Yes	B1 until 1995 A from 1996
	Mersey	27,000	1995-1999	-	No	Yes	B1 in 1995 A from 1996
	North West Thames	47,000	1991-2000	-	Yes	Yes	B1 until 1995 A from 1996
	Wales	32,000	1998-2000	-	No	Yes	A

* No country specific chapter for Bulgaria
** See Appendix 4. A high SB:Anen ratio may, but does not necessarily, reflect underascertainment of terminations of pregnancy
*** Years where termination data was missing (M) or incomplete (I) where excluded from PRR analysis and Poisson regression analysis
† For the purposes of any analysis the year in which any policy or education campaign can have an affect on births is the year *following* the introduction of the new policy/education campaign: thus Denmark, for example, introduced an official policy of supplementation in 1997, and is hence coded as classification A from 1998.
Policy type A = official supplementation policy and health education campaign, Policy type B1 = official supplementation policy without health education campaign, Policy type B2 = official policy relating only to increasing folate by dietary means, Policy type C = unofficial or no policy

Table 5: Laws regulating termination of pregnancy for fetal abnormality*

Country	Is it legal?	Gestational age limit for non lethal serious anomalies	Gestational age limit for lethal anomalies
Austria	yes	no upper limit	no upper limit
Belgium	yes	24 weeks	24 weeks
Croatia	yes	24 weeks	no upper limit
Denmark	yes	24 weeks (usually)	no upper limit
Finland	yes	24 weeks	24 weeks
France	yes	no upper limit	no upper limit
Germany	yes	no upper limit	no upper limit
Ireland	no	illegal	illegal
Italy	yes	24 weeks	24 weeks
Malta	no	illegal	illegal
Netherlands	yes	24 weeks	no upper limit
Norway	yes	18 weeks	no upper limit
Poland	yes	viability	no upper limit
Portugal	yes	24 weeks	no upper limit
Spain	yes	22 weeks	22 weeks
Switzerland	yes	24 weeks	24 weeks
U.K. [1]	yes	no upper limit	no upper limit

* Information as of June 2002

1. Except Northern Ireland

4.3 Results

a) Graphical presentations

The total prevalence rate for all registries in UK and Ireland combined declined from 47.1 per 10,000 births in 1980 to 13.6 per 10,000 in 2000 (Figure 2). The total prevalence rate for other European regions combined is relatively stable over the period 1980-2000 at around 7-9 per 10,000 (Figure 2), although some variation is seen (see Appendix 2).

Graphs of prevalence rates per registry 1980-2000, indicating the introduction of policies in each country, are shown in Figures 3 to 6. It should be noted that yearly rates are often based on small numbers, and thus much of the yearly variation in rates seen is chance variation. The key to each graph shows the approximate numbers of births per year covered by the registry. Yearly rates in the smaller registries (such as Galway, Malta, Odense, Asturias, Barcelona, Vaud) are based on particularly small numbers. Graphical presentation shows no clear impact of supplementation policy on prevalence rate, nor any clear tendency for total prevalence to decrease during the 1990s. Details of relevant factors affecting yearly rates in individual countries can be found in the registry descriptions in Appendix 5.

b) Prevalence Rate Ratio analysis

Registries in UK and Ireland, all of Policy Type A in 1999, showed an overall prevalence rate ratio of 0.82 (95%CI 0.68-0.98) compared to the 1989-91 baseline (Table 6). Only two other European registries had Policy Type A: Odense and Northern Netherlands. There was evidence of a decrease in rate in Northern Netherlands but not Odense, and combined the PRR was 0.73 (95% CI 0.54-0.99) compared to the 1989-91 baseline. Two registries had an official supplementation policy without health education initiative (B1): Southern Portugal and Vaud. There was some evidence of a decrease in rate in Southern Portugal, but confidence intervals were wide and the two registries combined showed no decrease in rate. Overall, there was weak evidence of a decrease in rate in areas of mainland Europe with folic acid supplementation policy (PRR = 0.79, 95%CI 0.61-1.01). Thirteen registries had no official supplementation policy in place before the year 2000.

Overall, the PRR was 1.00 (95%CI 0.90-1.11) compared to the 1989-91 baseline, showing no evidence of a decrease in rate.

c) Regression Analysis

The Poisson regression analysis had the advantage, compared to the prevalence rate ratio analysis, of being able to use data on the precise year the policy was introduced, using all the data rather than selected years, and modelling the underlying decline pre-1991, thus asking whether the introduction of policy led to any *additional* decline to that already occurring. The full results are given in Appendix 2.

Table 7 summarises the results for different policy types. Analysis of UK and Ireland taking into account the pre-existing decline in rates suggests there was no additional decline in prevalence after the introduction of supplementation policy.

The results for European countries which introduced a supplementation policy suggest, like the prevalence rate ratio analysis, that there was a decline in rate associated with policy introduction (RR=0.67, 95%CI 0.47-0.97). Nevertheless, removing policy type from the model was not statistically significant (see Appendix 2), suggesting that the overall evidence for an effect of supplementation policy on NTD prevalence is weak.

Analysing policy in four levels, where the fourth level was a supplementation policy accompanied by a health education campaign, did not provide any evidence that health education had an additional effect in lowering NTD prevalence, either in UK and Ireland, or in other European countries.

The regression analysis, like the PRR analysis, shows that there was no decline in rate after 1992 in countries where no policy regarding folic acid supplementation was introduced.

Figure 2: NTD total prevalence rates per 10,000 births for Europe 1980-2000 and 95% confidence intervals (upper points: UK and Ireland, lower points: rest of Europe)

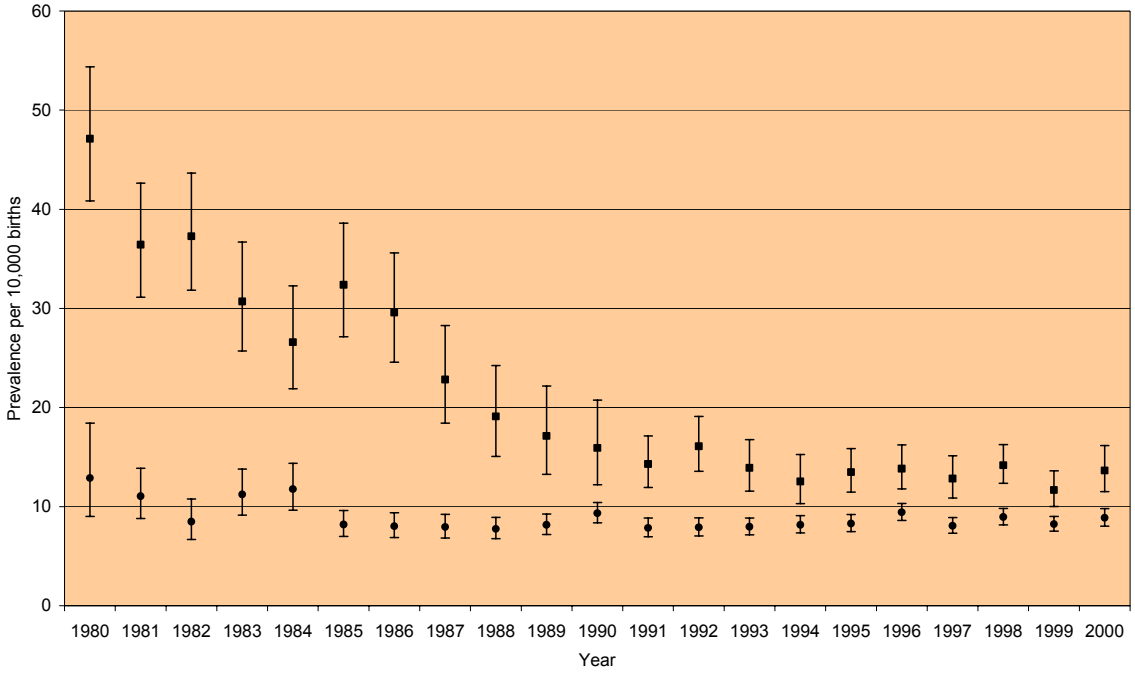
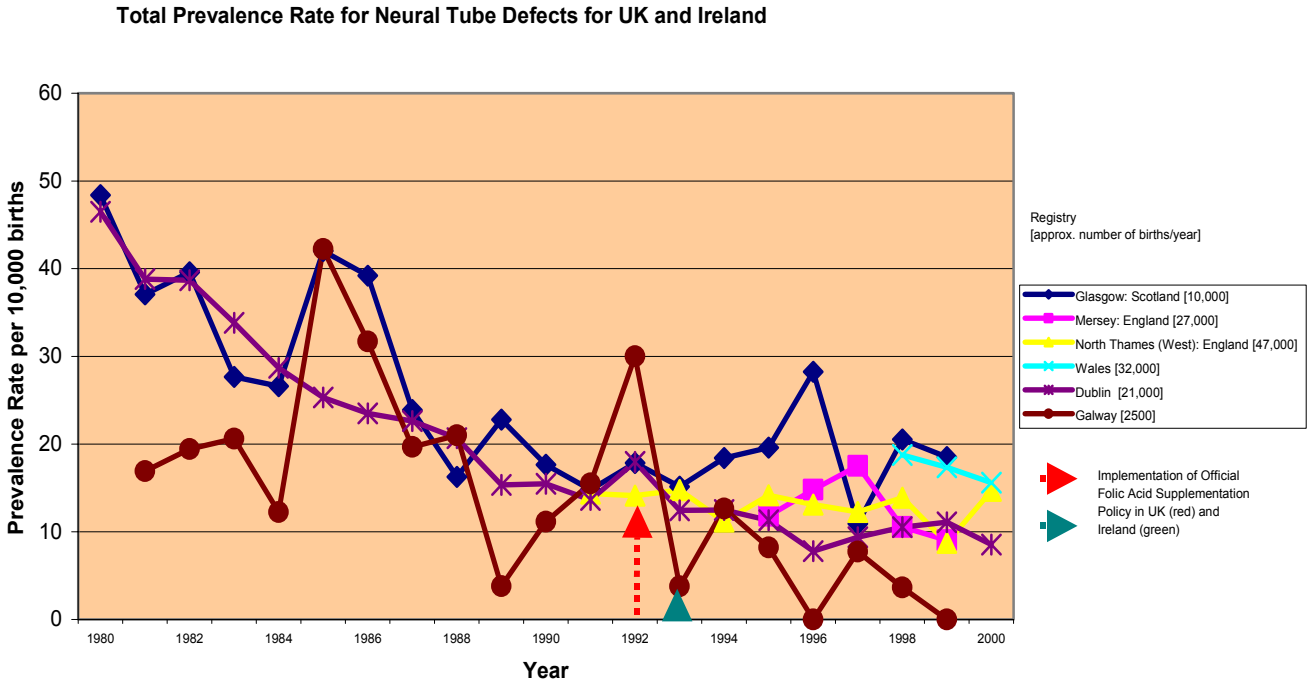
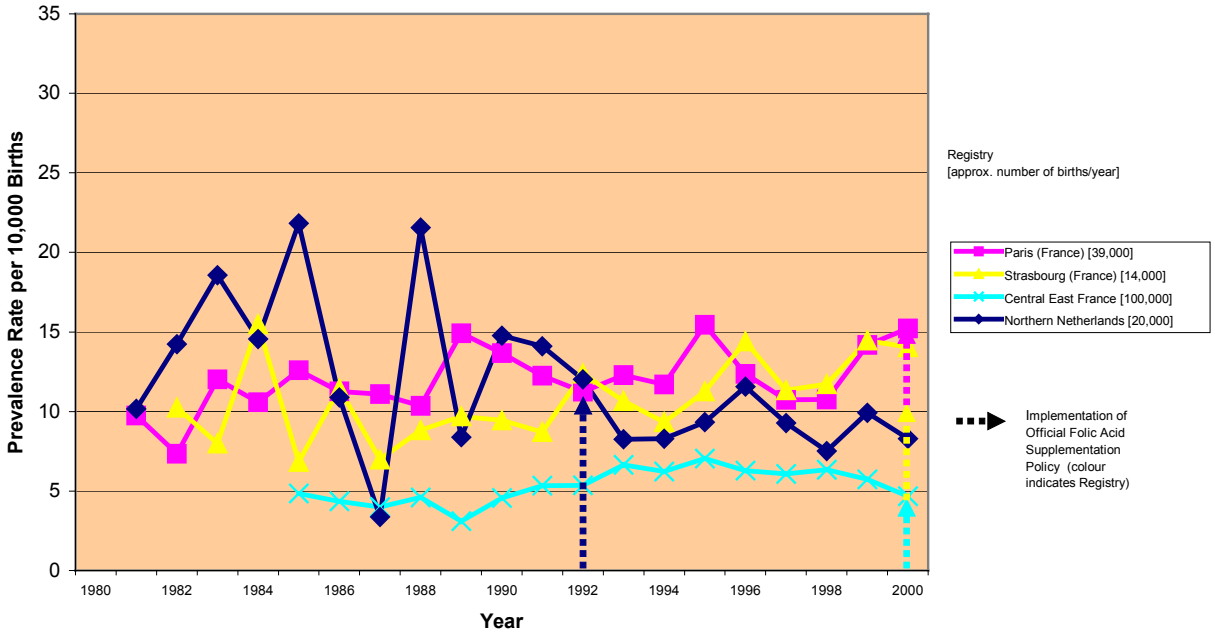


Figure 3: Registries with an official policy for folic acid supplementation in conjunction with a health education campaign by the year 2000 (Policy Type A)



Total Prevelance Rate for Neural Tube defects for France (Central East France, Paris and Strasbourg) and Northern Netherlands



Total Prevalence Rate for Neural Tube Defects for Denmark (Odense), Norway and Poland

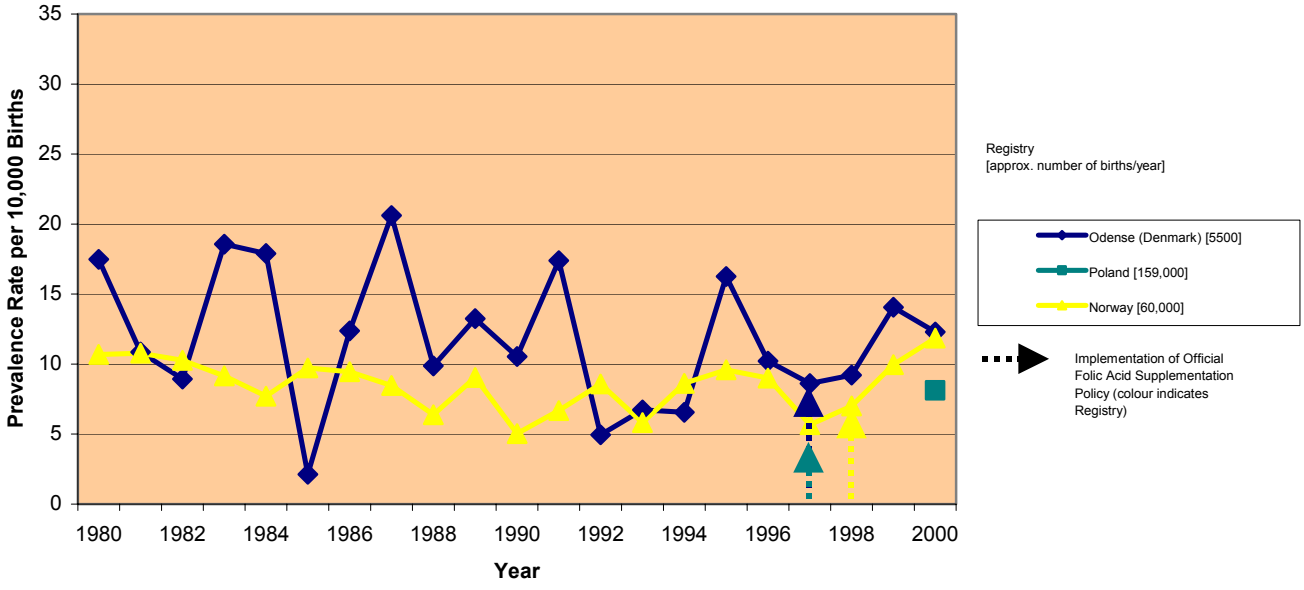


Figure 4: Registries with an official folic acid supplementation policy without a health education campaign (Policy Type B1)

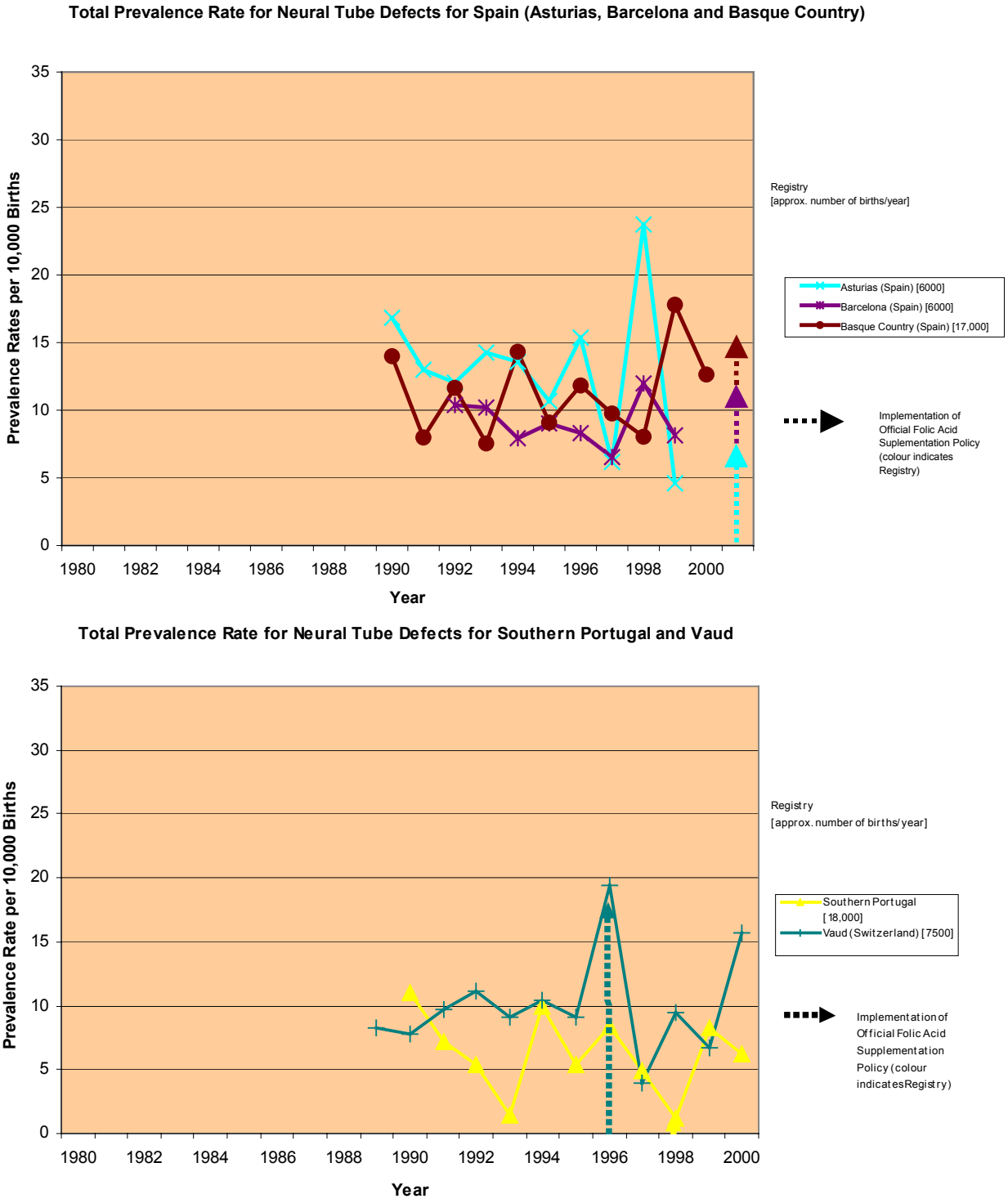


Figure 5: Registries with an official policy to encourage increased dietary folate without health education campaign (Policy Type B2)

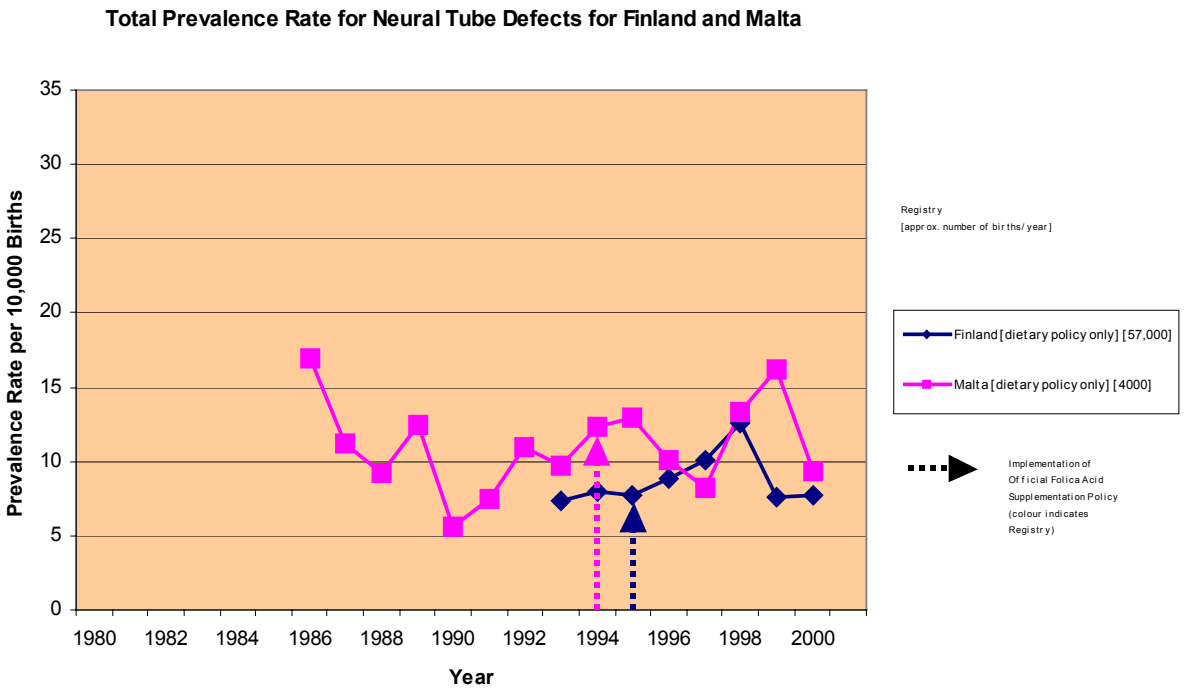
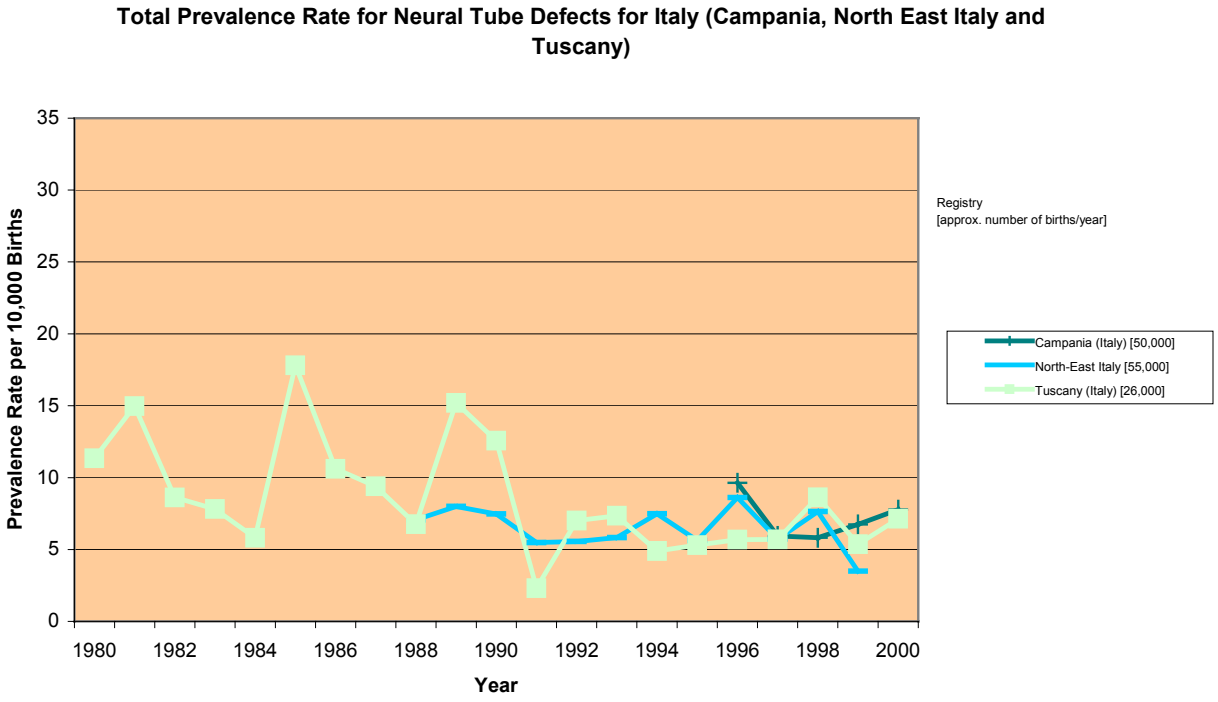
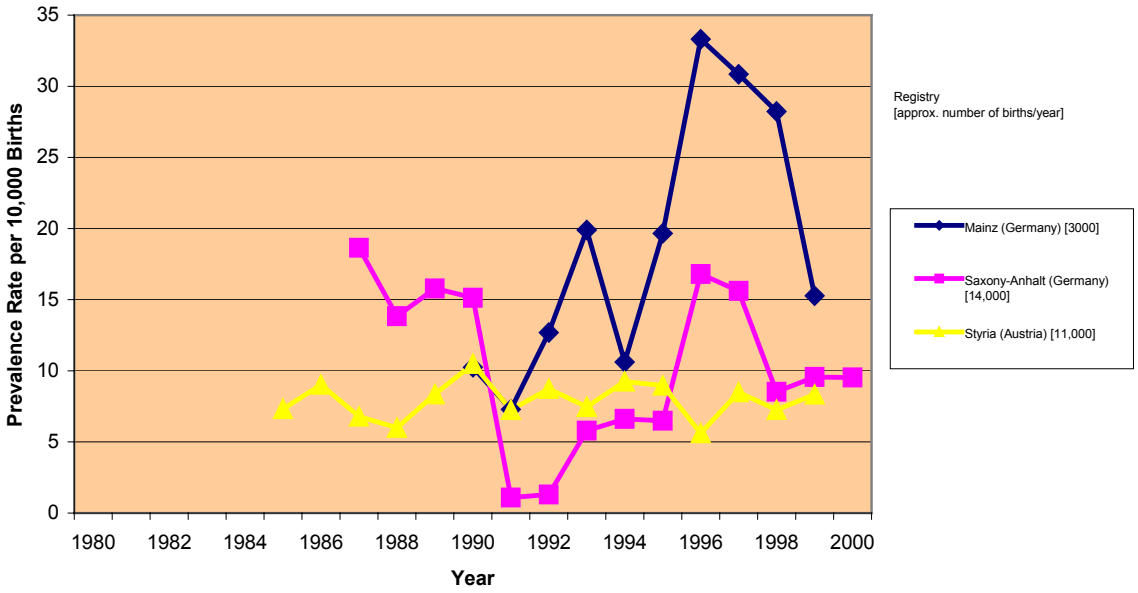


Figure 6: Registries with no official folic acid supplementation policy or health education campaign (Policy Type C)



Total Prevalence Rate for Neural Tube Defects for Germany (Mainz and Saxony-Anhalt) and Austria (Styria)



Total Prevalence Rate for Neural Tube Defects for Belgium (Antwerp and Hainaut) and Croatia (Zagreb)

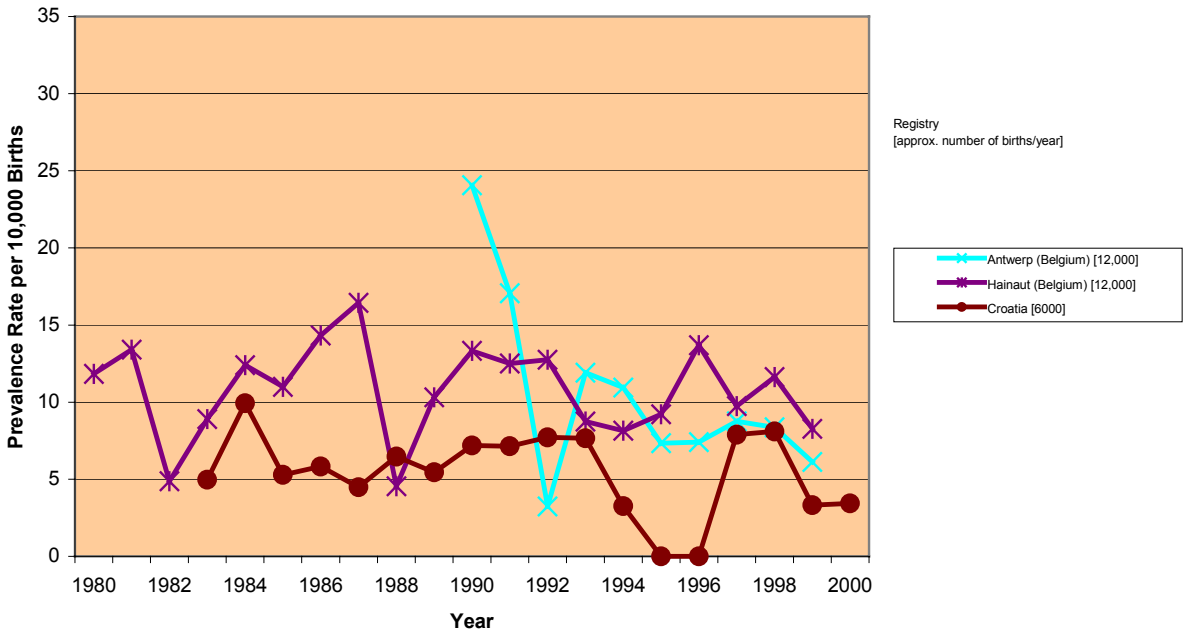


Table 6: Ratio of Total Prevalence (PRR) 1998–2000 to (i) 1989–1991 and (ii) 1989-1994

Overall:

	1989 - 1991		1989 - 1994		1998 - 2000		Compared with 1989 - 1991	Compared with 1989 - 1994
Regions	Total Number of Cases	Rate per 10,000 Births	Total Number of Cases	Rate per 10,000 Births	Total Number of Cases	Rate per 10,000 Births	PRR (CI) ‡	PRR (CI) ‡
UK & Ireland	231	14.41	573	14.69	277	10.96	0.82 (0.68-0.98)*	0.85 (0.74-0.99)*
Mainland Europe with FA supplementation Policy	126	10.99	228	9.24	124	9.11	0.79 (0.61-1.01)	0.90 (0.72-1.12)
Mainland Europe without FA supplementation Policy	700	10.50	1428	9.73	725	10.44	1.01 (0.91-1.12)	1.03 (0.94-1.13)

Policy Type A: Official Folic Acid Supplementation Policy in conjunction with Health Education Initiative

	1989 - 1991		1989 - 1994		1998 - 2000		Compared with 1989 - 1991	Compared with 1989 - 1994
Registry	Total Number of Cases	Rate per 10,000 Births	Total Number of Cases	Rate per 10,000 Births	Total Number of Cases	Rate per 10,000 Births	PRR (CI) ‡	PRR (CI) ‡
UK & Ireland								
Total	231	14.41	573	14.69	277	10.96	0.82 (0.68-0.98)*	0.85 (0.74-0.99)*
Total: UK	137	16.37	387	15.67	213	15.98	0.93 (0.74-1.17)	0.95 (0.80-1.13)
Total: Ireland	94	12.46	186	13.70	64	5.95	0.65 (0.47-0.89)**	0.65 (0.49-0.86)**
N Thames (West) (England)	68	14.37	257	13.59	174	12.42	0.86 (0.65-1.14)	0.91 (0.75-1.11)
Glasgow (Scotland)	69	18.36	130	17.75	39	19.54	1.06 (0.72-1.58)	1.10 (0.77-1.57)
Dublin (Ireland)	86	14.80	166	14.57	63	10.04	0.68 (0.49-0.94)*	0.69 (0.52-0.92)*
Galway (Ireland)	8	10.12	20	12.83	1	1.85	0.18 (0.02-1.46)	0.14 (0.02-1.08)*
Mainland Europe								
Total	96	13.11	162	10.38	72	10.24	0.73 (0.54-0.99)	0.87 (0.66-1.15)
Odense (Denmark)	23	13.75	34	9.76	20	11.89	0.87 (0.48-1.58)	1.22 (0.70-2.12)
Northern Netherlands	73	12.46	128	11.00	52	8.58	0.69 (0.48-0.98)*	0.78 (0.57-1.08)

Policy Type B: Official Folic Acid Supplementation or Dietary Policy without a Health Education Initiative

	1989 - 1991		1989 - 1994		1998 - 2000		Compared with 1989 - 1991	Compared with 1989 - 1994
Registry	Total Number of Cases	Rate per 10,000 Births	Total Number of Cases	Rate per 10,000 Births	Total Number of Cases	Rate per 10,000 Births	PRR (CI) ‡	PRR (CI) ‡
Dietary only								
Malta	14	8.57	31	9.72	17	12.96	1.51 (0.75-3.07)	1.33 (0.74-2.41)
Supplementation								
Total							0.94 (0.60-1.47)	0.96 (0.66-1.39)
Southern Portugal	10	9.08	22	6.76	28	5.31	0.58 (0.28-1.20)	0.79 (0.45-1.37)
Vaud (Switzerland)	20	8.65	44	9.45	24	10.66	1.23 (0.68-2.23)	1.13 (0.69-1.85)

Policy Type C: No Official Folic Acid Supplementation Policy or Health Education Initiative before 2000

	1989 - 1991		1989 - 1994		1998 - 2000		Compared with 1989 - 1991	Compared with 1989 - 1994
Registry	Total Number of Cases	Rate per 10,000 Births	Total Number of Cases	Rate per 10,000 Births	Total Number of Cases	Rate per 10,000 Births	PRR (CI) ‡	PRR (CI) ‡
Total	686	10.65	1397	9.73	708	10.25	1.00 (0.90-1.11)	1.02 (0.93-1.12)
Styria (Austria)	35	8.68	69	8.58	17	7.79	0.90 (0.50-1.60)	0.91 (0.53-1.54)
Antwerp (Belgium)	17	20.17	40	12.07	26	7.24	0.36 (0.20-0.66)***	0.60 (0.37-0.98)*
Hainaut (Belgium)	49	12.05	87	11.03	24	9.94	0.83 (0.51-1.34)	0.90 (0.57-1.42)
Croatia	14	6.58	26	6.43	9	5.00	0.76 (0.33-1.75)	0.78 (0.36-1.66)
Central East France	137	4.37	321	5.20	168	5.61	1.29 (1.03-1.61)*	1.08 (0.90-1.30)
Paris (France)	152	13.61	279	12.69	156	13.41	0.99 (0.79-1.23)	1.06 (0.87-1.29)
Strasbourg (France)	38	9.28	81	10.03	56	13.42	1.45 (0.96-2.18)	1.34 (0.95-1.88)
Mainz (Germany)	7	8.73	24	12.15	15	22.00	2.52 (1.03-6.17)*	1.81 (0.95-3.45)
Saxony (Germany)	47	12.09	57	9.35	38	9.28	0.77 (0.50-1.18)	0.99 (0.66-1.50)
North East Italy	105	6.96	199	6.63	61	5.58	0.80 (0.58-1.10)	0.84 (0.63-1.12)
Tuscany (Italy)	26	10.01	74	7.35	55	7.04	0.70 (0.44-1.12)	0.96 (0.68-1.36)
Asturias (Spain)	23	14.92	51	13.96	18	14.02	0.94 (0.51-1.74)	1.00 (0.59-1.72)
Basque Country (Spain)	36	11.00	89	11.08	65	12.89	1.17 (0.78-1.76)	1.16 (0.84-1.60)

‡Chi-square *p<0.05; **p<0.01; ***p<0.001
Prevalence rate ratios presented are relative risks with Taylor series confidence limits and stratified analyses presented are Mantel-Haenszel weighted relative risks with Greenland/Robins confidence limits (Epi Info, 2000).

Table 7: Rate Ratios (RR) of neural tube defects according to policy type: results of Poisson regression analysis

	RR *	95% CI	p value
Europe (excluding UK/Ireland)			
Baseline (D)	1.0	-	-
Dietary or no policy compared with pre-1992	0.97	(0.86 - 1.10)	0.66
Supplementation with or without education campaign compared with pre 1992	0.67	(0.47 - 0.97)	0.03
Baseline (D)	1.0	-	-
Dietary or no policy compared with pre-1992	0.98	(0.87 - 1.12)	0.80
Supplementation without education campaign compared with pre-1992	0.65	(0.45 - 0.95)	0.03
Supplementation with education campaign compared with pre-1992	0.89	(0.51 - 1.57)	0.70
UK/Ireland			
Baseline (D)	1.0	-	-
Dietary or no policy compared with pre-1992	1.12	(0.91 - 1.39)	0.28
Supplementation with or without education campaign compared with pre-1992	1.14	(0.86 - 1.51)	0.37
Baseline (D)	1.0	-	-
Dietary or no policy compared with pre-1992	1.14	(0.92 - 1.42)	0.24
Supplementation without education campaign compared with pre-1992	1.14	(0.86 - 1.52)	0.36
Supplementation with education campaign compared with pre-1992	1.22	(0.85 - 1.76)	0.29

*** All rate ratios adjusted for year (linear and quadratic), registry and interaction between year and registry**

4.4 Discussion

In UK and Ireland it is difficult to distinguish the effect of periconceptional 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 British and Irish diet (see Sources of Folate above). Total prevalence rates in UK and Ireland were 18% lower in 1998-2000 compared to 1989-1991. This would be the level of decline expected if less than 30% of women were taking supplements periconceptionally in the latter period, consistent with the evidence from surveys of folic acid use (Section 3.3). However, results are sensitive to the model of decline assumed. No effect of policy on NTD prevalence, whether or not accompanied by a health education campaign, was established.

In the rest of Europe, there was some weak evidence of an overall decrease in prevalence following the introduction of supplementation policy (Netherlands, Denmark, Portugal, Switzerland and Norway taken as a group), with a point estimate of 33% decrease in rates.

There was no decrease in countries where no policy was introduced before 2000 (Austria, Belgium, Bulgaria, Croatia, France, Germany, Italy, Spain) or in countries introducing a dietary policy only (Finland, Malta).

The wide confidence intervals around total prevalence rates show that it is very difficult to demonstrate policy-related declines in prevalence in regional populations until a number of years have elapsed. Data from different regions needs to be combined, but may of course obscure regional or national differences in the success of policy implementation.

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 neural tube defects. 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.

Overall in Europe, despite the considerable promise of primary prevention of NTD by raising folic acid levels periconceptionally, little progress has been made, and few of the 4,000 affected pregnancies every year in Europe are being prevented.

4.5 Conclusion

In countries without a policy regarding folic acid supplementation, there has been no discernible decrease in the total prevalence of neural tube defects.

In countries with a policy to recommend periconceptional folic acid supplementation, there is evidence of some decrease in prevalence, but to a disappointing degree compared to the potential for prevention. In UK and Ireland, it is not clear if the decrease in prevalence is simply a continuation of the pre-existing decline in prevalence already evident in the 1980s.

5. The case for fortification of staple foods in Europe

The previous section has shown the disappointing progress of NTD prevention in Europe, even in countries which have a clear policy implemented by a health education campaign.

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 receive or respond to health promotion messages and especially for the large proportion of pregnancies in many countries which are unplanned. Fortification is likely to be a more cost-effective option for preventing NTD than supplementation policy, since a supplementation policy requires a health education campaign more extensive and effective and possibly more frequent than those implemented so far. Fortification of staple foods with folic acid may have additional health benefits unrelated to reproduction. For example, there is evidence that optimal folate status may have a role in the prevention of cardiovascular disease via plasma homocysteine-lowering (Boushey et al, 1995), and possibly in the prevention of certain cancers (Branda and Blickenderfer, 1993; Kim et al, 1997; Jacob et al, 1998; Choi and Mason, 2000).

In the US, mandatory fortification of enriched grain products at a level of 1.4 μg per g of product (Food and Drug Administration, 1996) was introduced in 1998. This level of fortification was projected to result in an additional 100 μg per day of folic acid in the

population intake. Studies carried out subsequent to the introduction of fortification report increased levels of folic acid in serum from 4.8 ng/ml before fortification to 14.8 ng/ml after fortification (Centers for Disease Control and Prevention, 2000). Choumenkovitch et al (2002) estimated that folic acid intake increased by a mean of 190 (95% CI: 176-204) μg per day for non-supplement users and total folate intake increased by a mean of 323 (95% CI: 296-350) μg dietary folate equivalents per day using data collected from participants of the Framingham Offspring Cohort Study. As manufacturers of breakfast cereal have also increased the fortification level in many products in recent years in the US, it is not clear how much of the rise in folate status is due to mandatory fortification and how much to the increase in voluntary fortification which was introduced. A 19% lowering of NTD rates in the US since the introduction of mandatory fortification has been reported (Honein et al, 2001). Further analysis of NTD prevalence rates during the transition to mandatory folic fortification in the US indicate that the decline in spina bifida was temporally associated with fortification of grain supplies. The temporal association between fortification and the prevalence of anencephalus is, however, unclear (Williams et al, 2002). Additional calls have been made for a further increase in the level of fortification (Oakley, 1999), however, others have urged that more information should be available regarding both the benefits and drawbacks of current levels of mandatory fortification before this should be considered (Mills, 2000).

Mandatory fortification has also been introduced in Canada, and in many countries in Central and South American and the Middle East. In Canada and Chile increased serum folate levels have been found following the introduction of mandatory fortification (Hirsch et al, 2002; Ray et al, 2002) and a study in Nova Scotia, Canada has shown a decrease of more than 50% in the prevalence of NTD following fortification (Persad et al 2003).

Why has there been reluctance in Europe to proceed to mandatory food fortification? We believe this stems from two factors:

(i) lack of recognition of the public health importance of NTD, to the extent that some countries have not developed a policy regarding primary prevention to date, and others have been exceedingly slow to do so.

(ii) the possibility of health risks related to raising the population folic acid status. There has been concern regarding the potential risk of masking the symptoms of pernicious anaemia caused by vitamin B_{12} deficiency. If undiagnosed, there is potential for

irreversible neurological damage in those at high risk of this deficiency, namely the elderly (Savage and Lindenbaum, 1995).

We would argue that NTD do represent an important public health issue. Spina bifida carries a high lifetime burden to the affected individual and family and a high economic cost for services. In addition to individuals surviving with spina bifida, there are large numbers of terminations of pregnancy and perinatal losses as a result of NTD, causing great distress (Stratham 2003, Van Mourik 2003) and using health service resources. Four thousand pregnancies in Europe every year result in a fetal loss or baby with a neural tube defect. In view of the mounting evidence regarding the beneficial effects of folic acid for the prevention of other congenital anomalies, cardiovascular disease and cancer, the public health benefit of fortification could potentially be even greater than the prevention of the majority of NTD.

The issue of potential harm caused by fortification has been widely discussed. It is argued that B_{12} deficiency can be diagnosed simply with or without the presence of anaemia (Bower and Wald, 1995). Other potential problems which have been discussed include: the effects on folate antagonistic drugs (mainly anti-convulsants), zinc malabsorption and hypersensitivity reactions. There have also been some reports of possible increases in twinning associated with periconceptional folic acid (Czeizel et al, 1994; Werler et al, 1997; Ericson et al, 2001). Most of the women in these studies used multivitamins and not folic acid alone. The increased occurrence of multiple births was not supported in another early, randomised trial of folic acid (Kirke et al, 1992) and has not been confirmed in a more recent, large population-based cohort study with folic acid in China (a country with a normally low twinning rate) (Li et al, 2003) or a recent US study (Shaw et al 2003).

6. Conclusions

- The evidence that the majority of NTD are preventable by increasing folate status before conception is very strong. Evidence is also accumulating that the protective effect may extend to other congenital anomalies.
- Government response to this evidence has been variable in Europe. Many countries have been slow to introduce policies, and some still have no policy regarding raising periconceptional folate status.

- Most countries contributing to this report have not implemented health education campaigns designed to reach all women before conception.
- The majority of women in countries surveyed are not taking folic acid supplements periconceptionally.
- In countries without a policy regarding folic acid supplementation, there has been no discernible decrease in the total prevalence of neural tube defects.
- In countries with a policy to recommend periconceptional folic acid supplementation, there is evidence of some decrease in prevalence, but to a disappointing degree compared to the potential for prevention. In UK and Ireland it is not clear if the decrease in prevalence is simply a continuation of the pre-existing decline in prevalence already evident in the 1980s.
- 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 as the chief method of reducing the number of infants affected by this most serious group of congenital anomalies. It should be remembered that termination of pregnancy for fetal abnormality is extremely traumatic for the parents.
- In order to achieve a reduction in NTD prevalence, renewed 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
  - introduce mandatory folic acid fortification of staple foods
- Clear responsibilities within the health service for delivering preconceptional health education need to be identified.
- The objective of preventing the majority of NTD is unlikely to be achieved without mandatory fortification of staple foods, which 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 socioeconomic inequalities in NTD prevalence.
- As countries change their policies and practices regarding prevention of NTD, continued monitoring of NTD prevalence is vitally important, using the data of population based registers of congenital anomalies with high ascertainment of cases among livebirths, stillbirths and termination of pregnancy for fetal abnormality

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