Eurocat

European Surveillance of Congenital Anomalies

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WHO Collaborating Centre for the Epidemiology Surveillance of Congenital Anomalies

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.

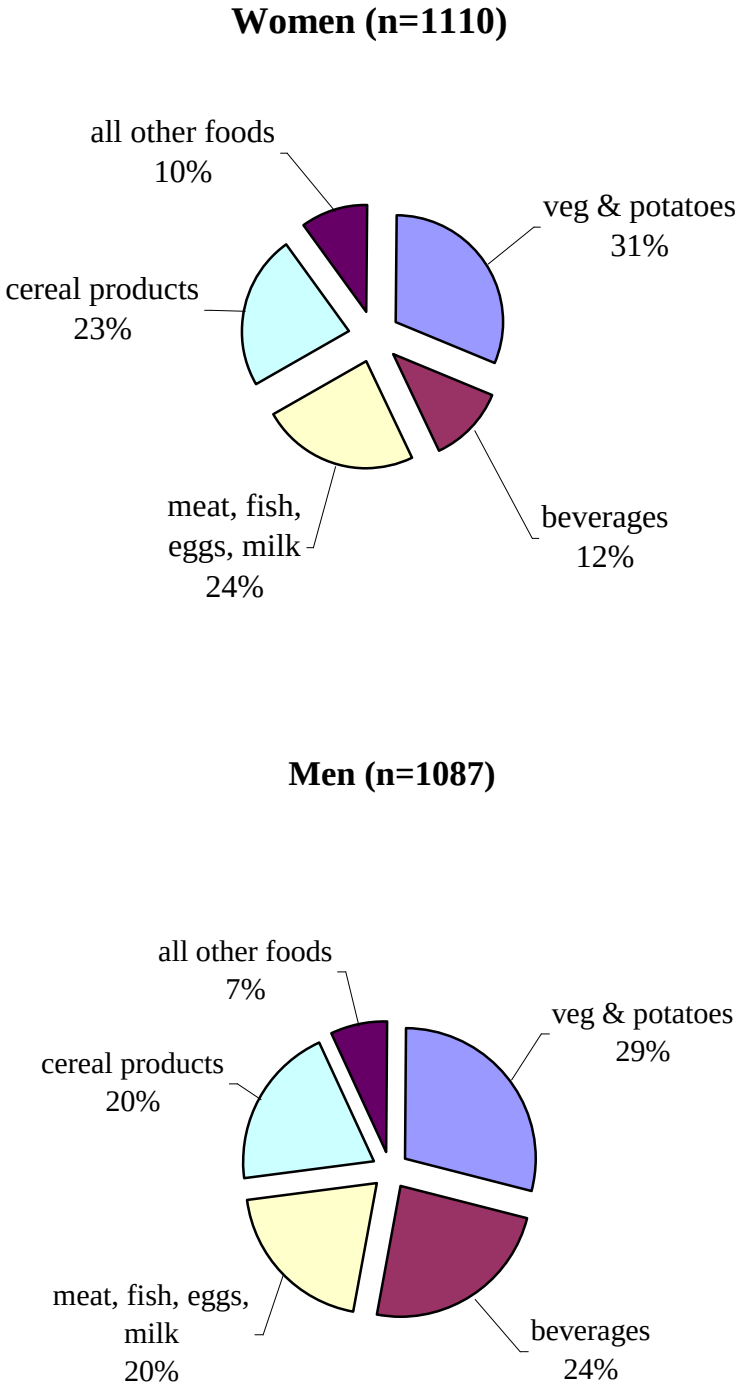
Table 1: Folate content of selected foods* (μg of folate per usual serving) (Holland et al 1991)

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)

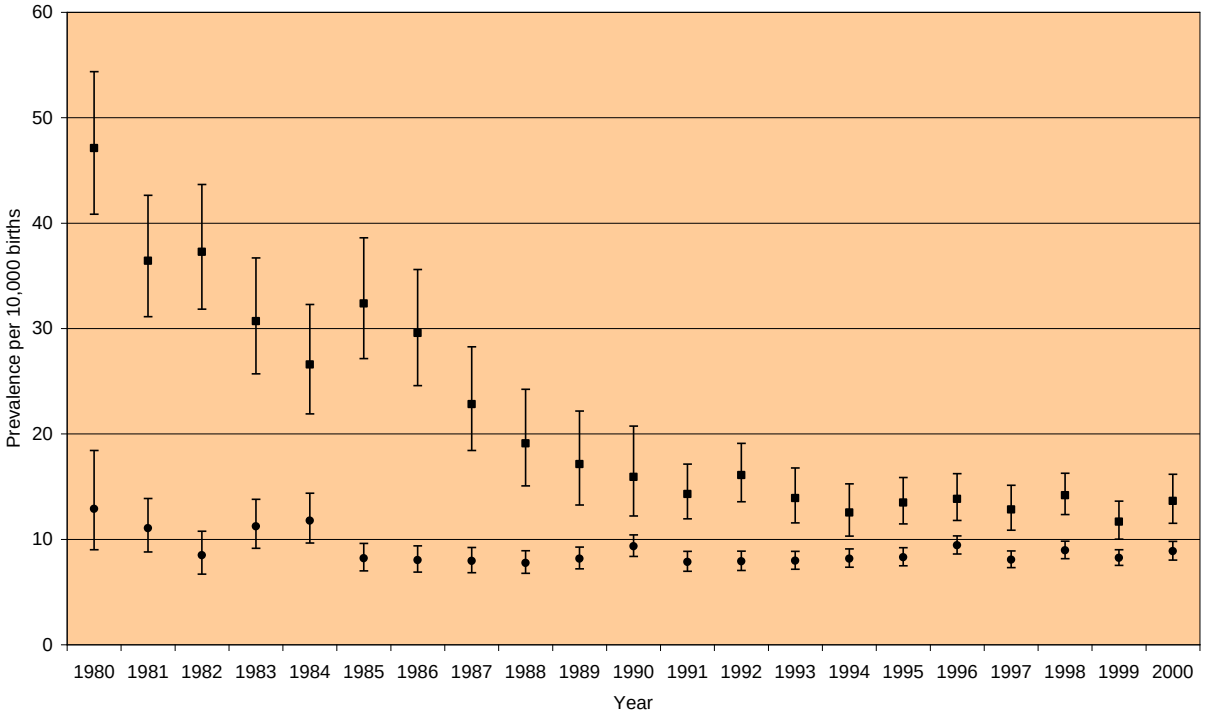
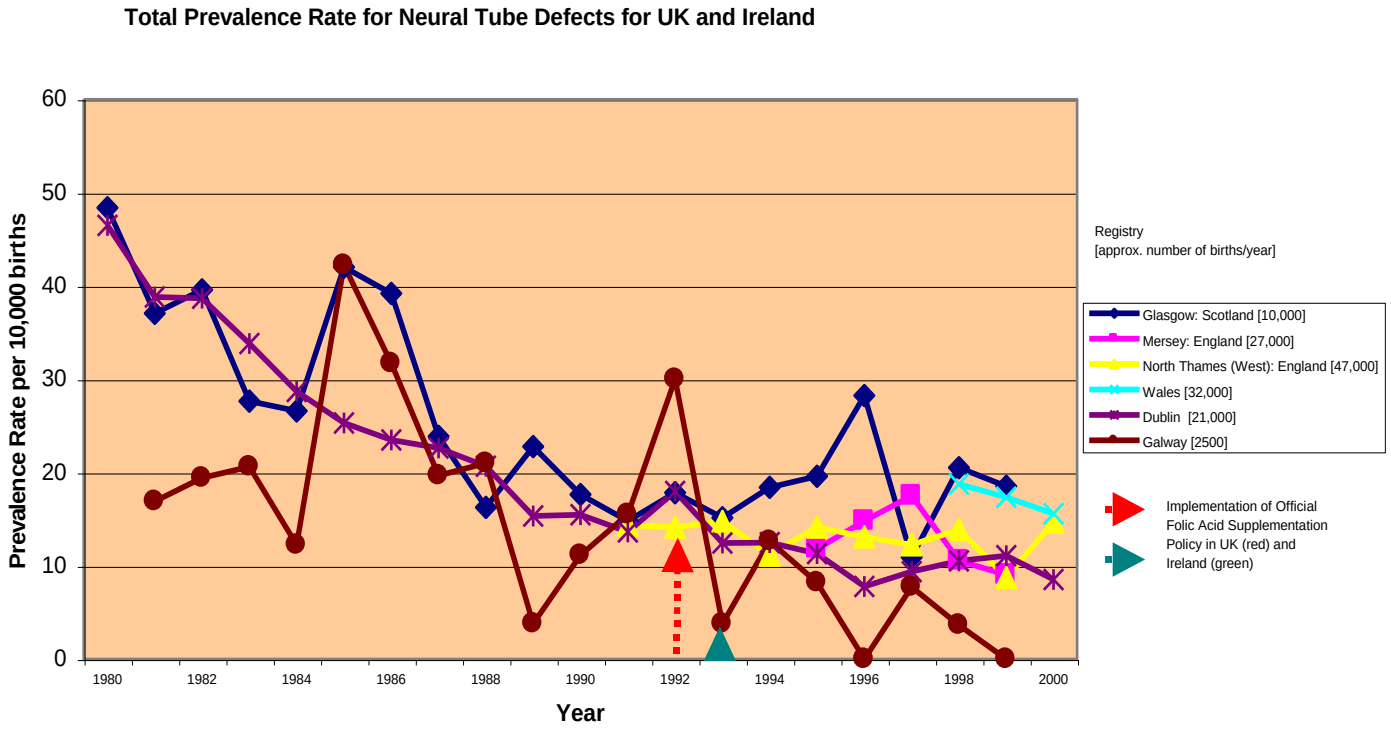
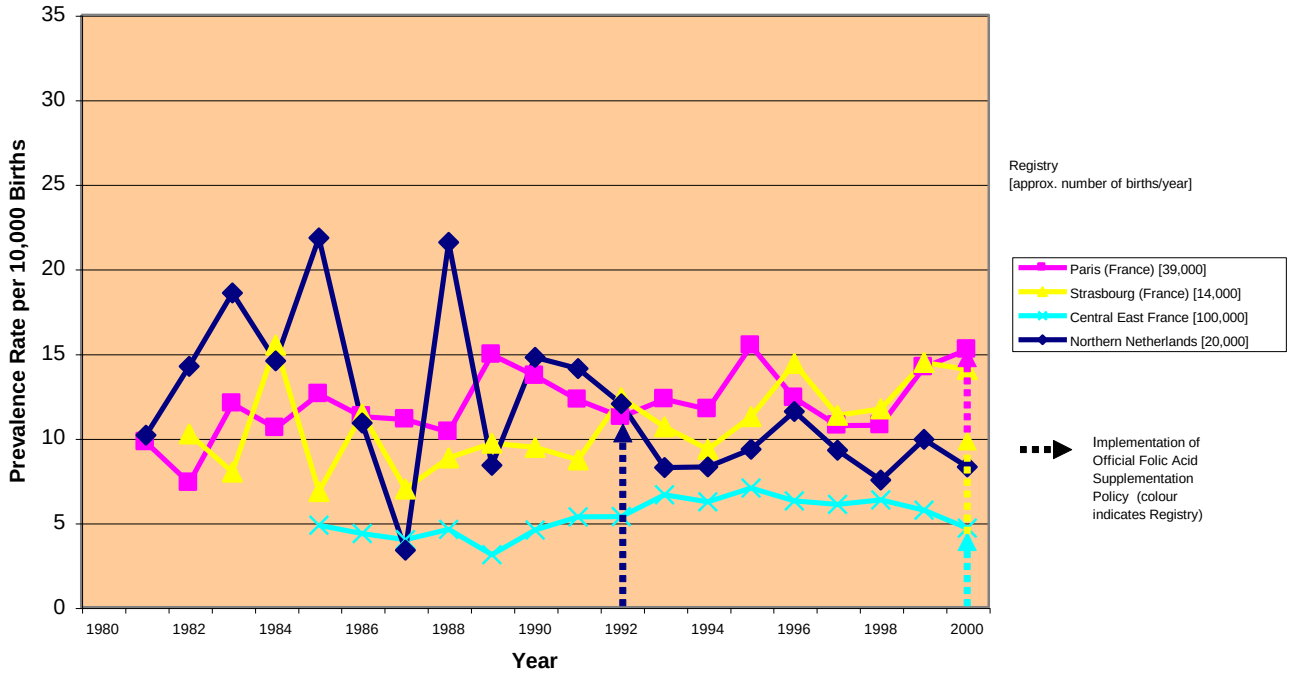


Figure 3: Registries with an official policy for folic acid supplementation in conjunction with a health education campaign by the year 2000 (Policy Type A)



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

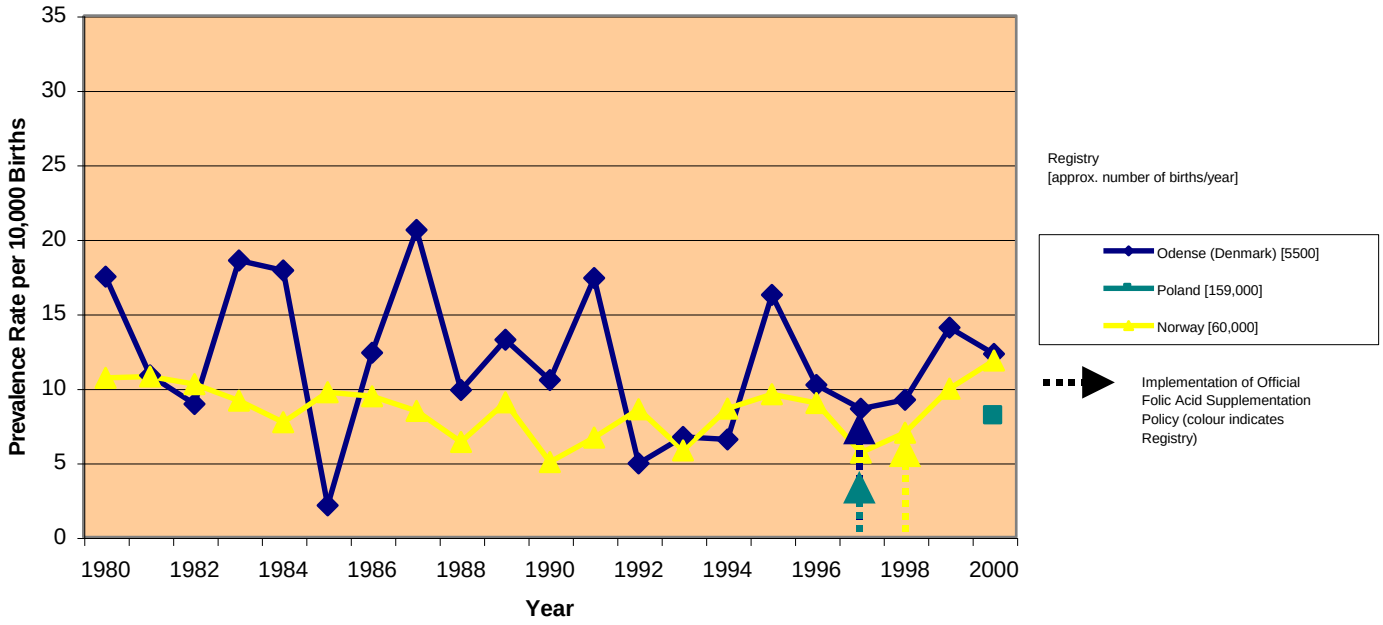


Figure 4: Registries with an official folic acid supplementation policy without a health education campaign (Policy Type B1)

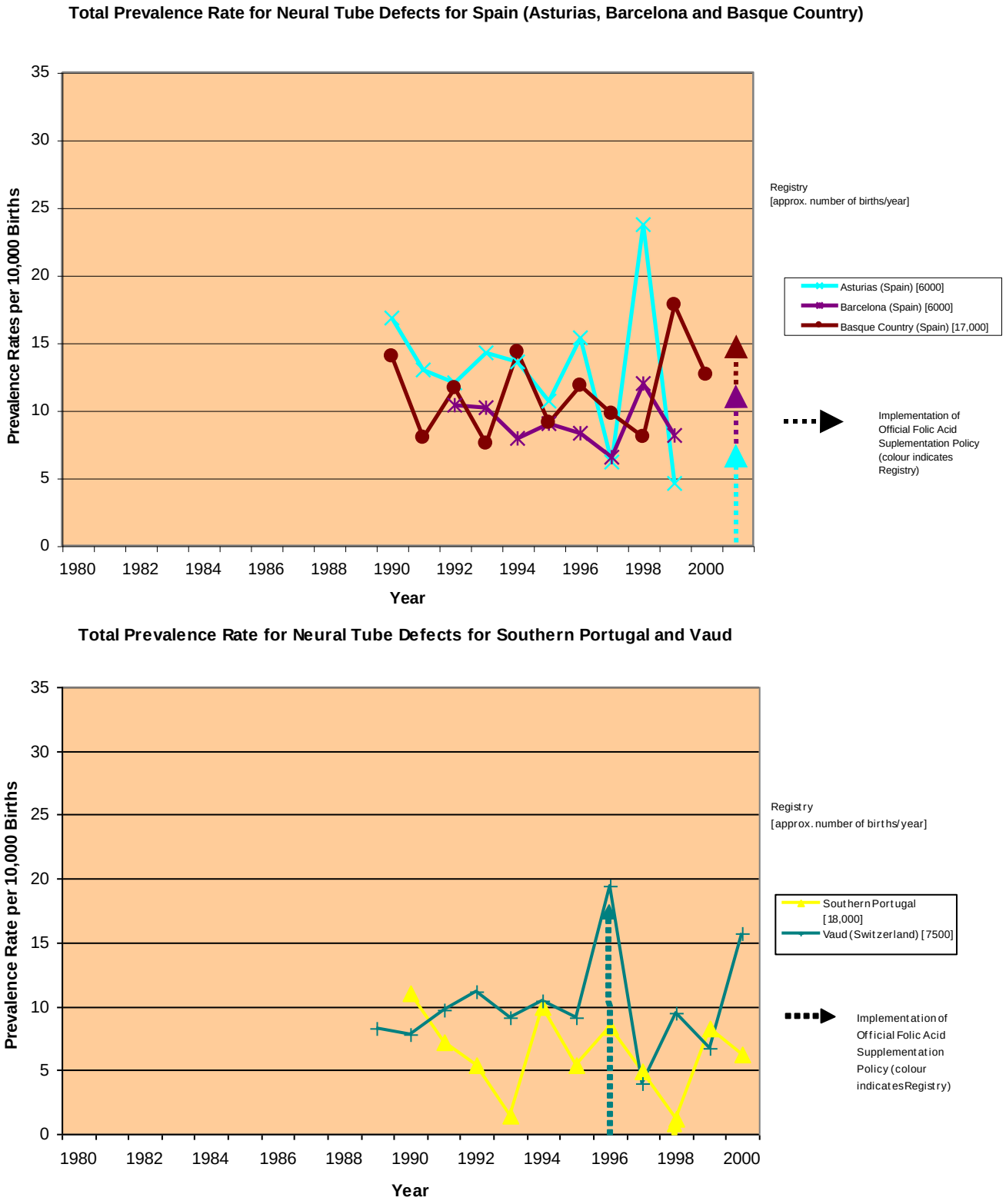


Figure 5: Registries with an official policy to encourage increased dietary folate without health education campaign (Policy Type B2)

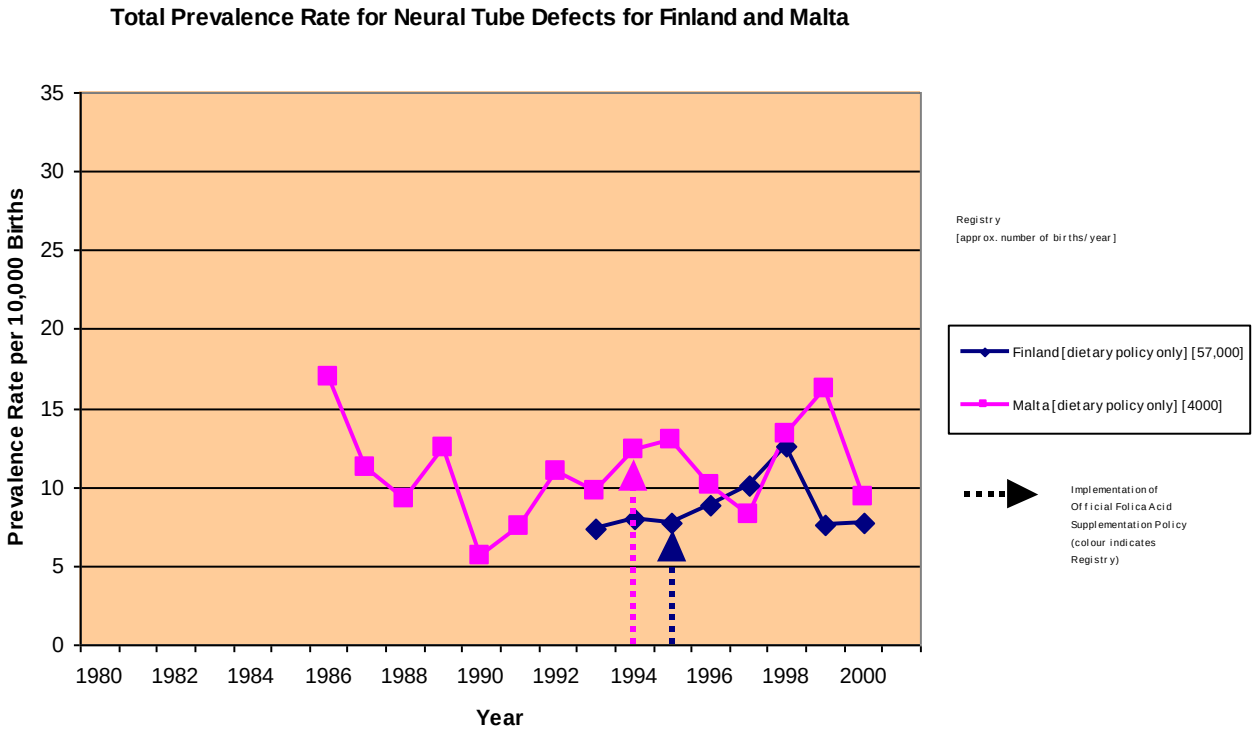
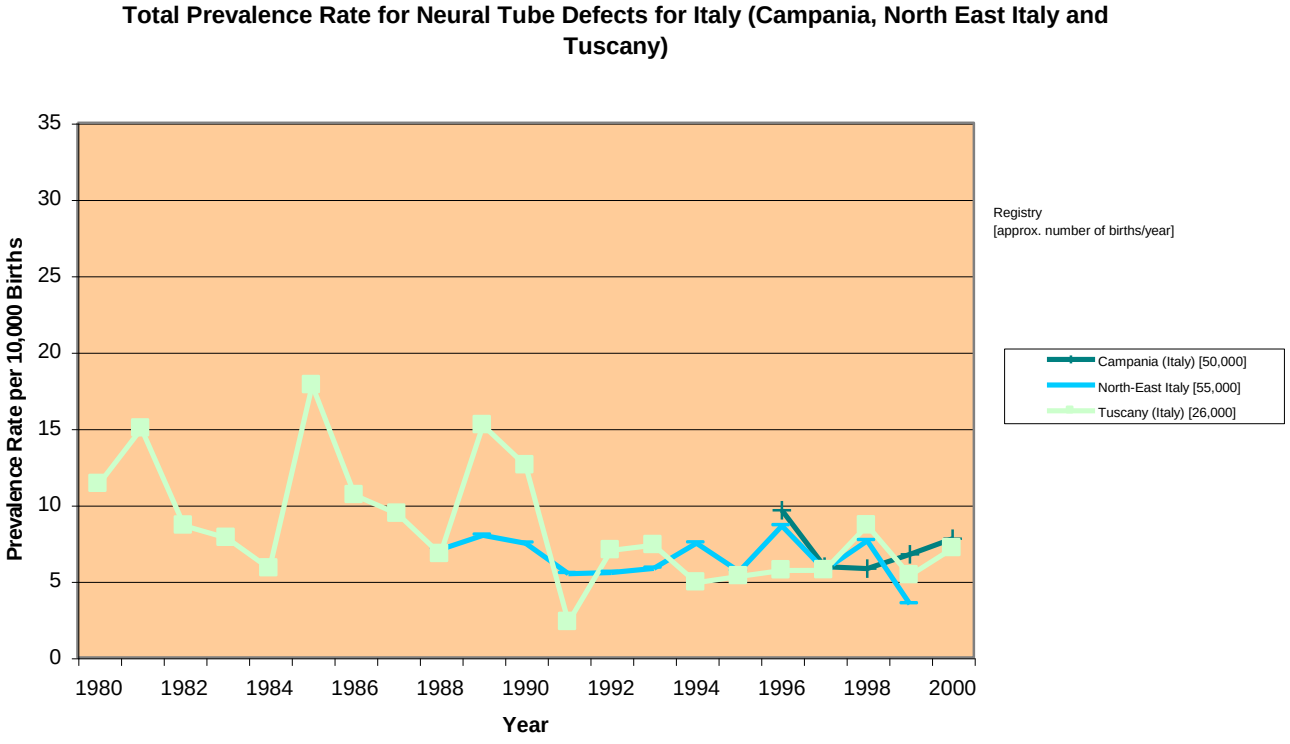
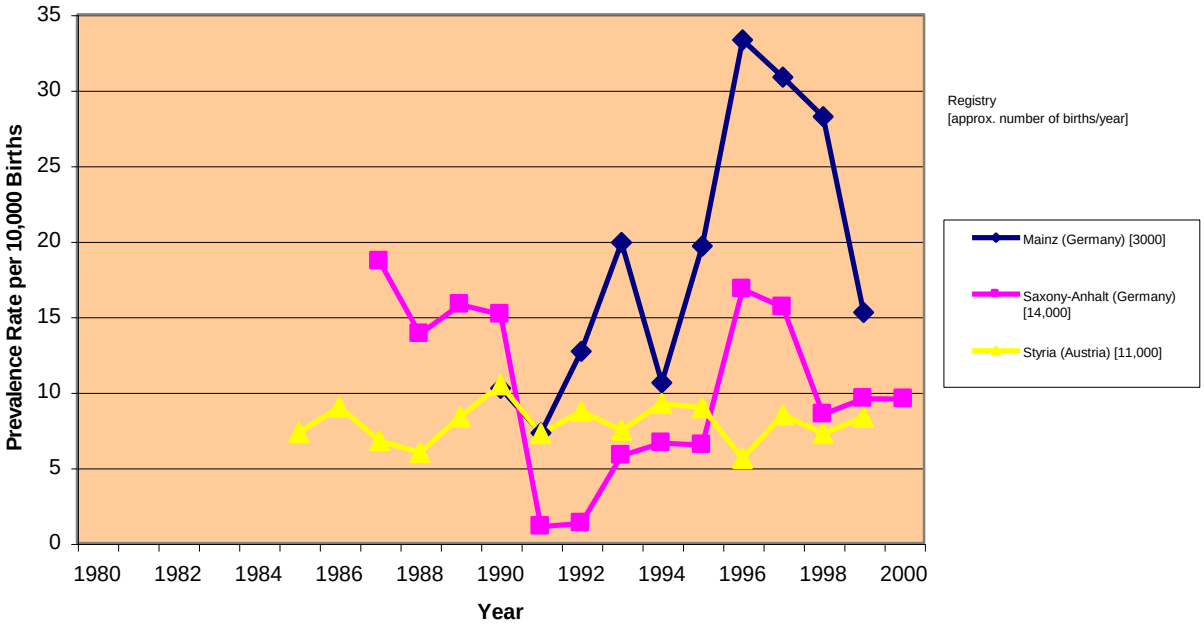


Figure 6: Registries with no official folic acid supplementation policy or health education campaign (Policy Type C)



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)

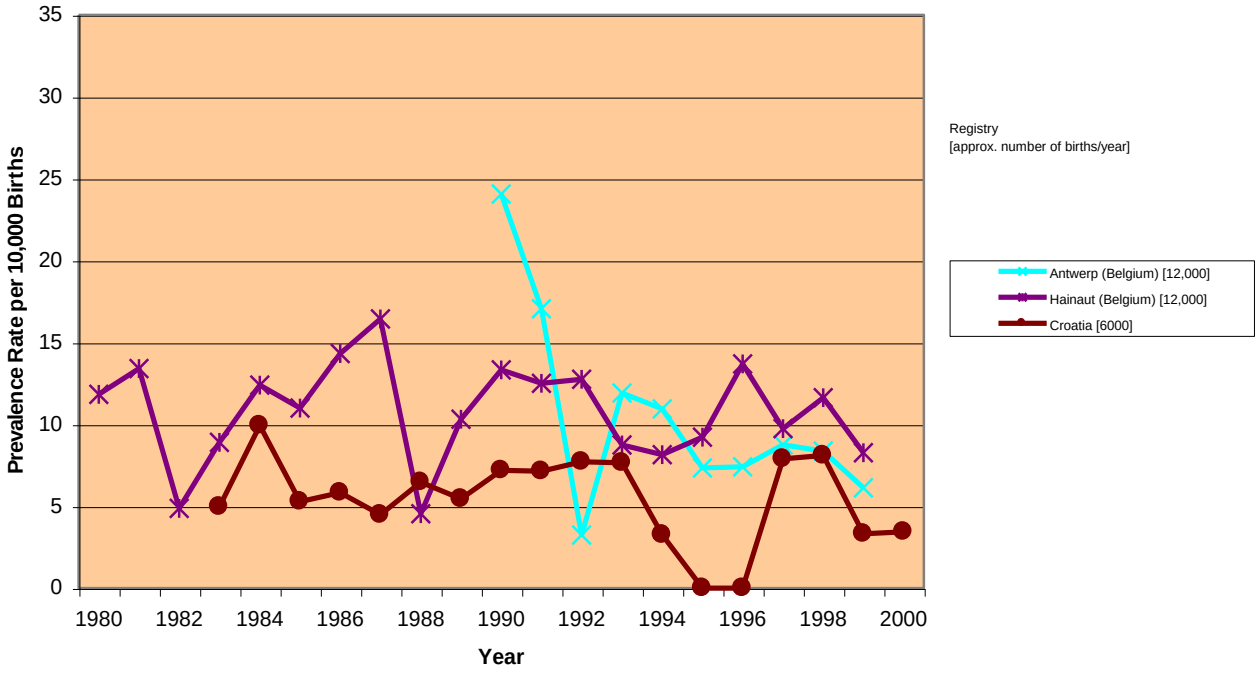


Table 6: Ratio of Total Prevalence (PRR) 1998–2000 to (i) 1989–1991 and (ii) 1989-1994

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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Part II

Country-Specific Chapters

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR AUSTRIA

Prof Andrea Berghold, Prof Häusler

Folic Acid Supplementation Policy

In Austria, there is no official government recommendation for periconceptional folic acid supplementation, but a recommendation was published by the Austrian Pediatric Society and the Austrian Society of Prenatal and Perinatal Medicine in 1998 (A Pollak, 1998). They recommended that all women wishing to become pregnant should take periconceptional folic acid supplementation of 0.4 mg per day before conception. Women who were already pregnant should start taking folic acid supplementation during the first four weeks of gestation and continue until the 8th week. For women with a high risk for recurrence of a neural tube defect, a periconceptional folic acid supplementation of 4 mg per day was recommended.

Food Fortification Policy

There is no official food fortification policy in Austria, but as in many other countries, food companies voluntarily fortify some breakfast cereals, malted drinks and some other foods.

Health Education Initiatives

No official health education initiative to inform women about the role of folic acid in reducing the risk for neural tube defects has been carried out and none is planned for the near future in Austria.

Knowledge and Uptake of Folic Acid

A study carried out in the obstetric unit of St Pölten hospital in Lower Austria, (K Zwiauer, 2000) looked at knowledge and uptake of periconceptional folic acid supplementation among recently delivered women. All women whose babies were born between 1.12.1997 and 31.3.1998 were included in the study. They were interviewed using a standardized questionnaire. 238 women participated in the study and 234 questionnaires were used for the analysis. 57 (24%) women used folic acid; however 33 out of 57 did not start use until after the 12th week of gestation. 61 out of 161 (38%) who answered this question knew of the preventive effect of folic acid in respect of fetal neural tube defects.

Proportion of Pregnancies that are Planned

The proportion of pregnancies that are planned in Austria is unknown.

Laws Regarding Termination of Pregnancy

Termination of pregnancy is allowed irrespective of gestational age, if the pregnancy poses a serious threat to the pregnant woman's physical or mental health, or if there is a serious possibility that the child will be mentally or physically handicapped. However, in the case of non-lethal malformations, most doctors in Austria agree to terminate pregnancies only before viability (< 25 weeks gestational age). In the case of lethal malformations they will agree to terminate pregnancies after viability.

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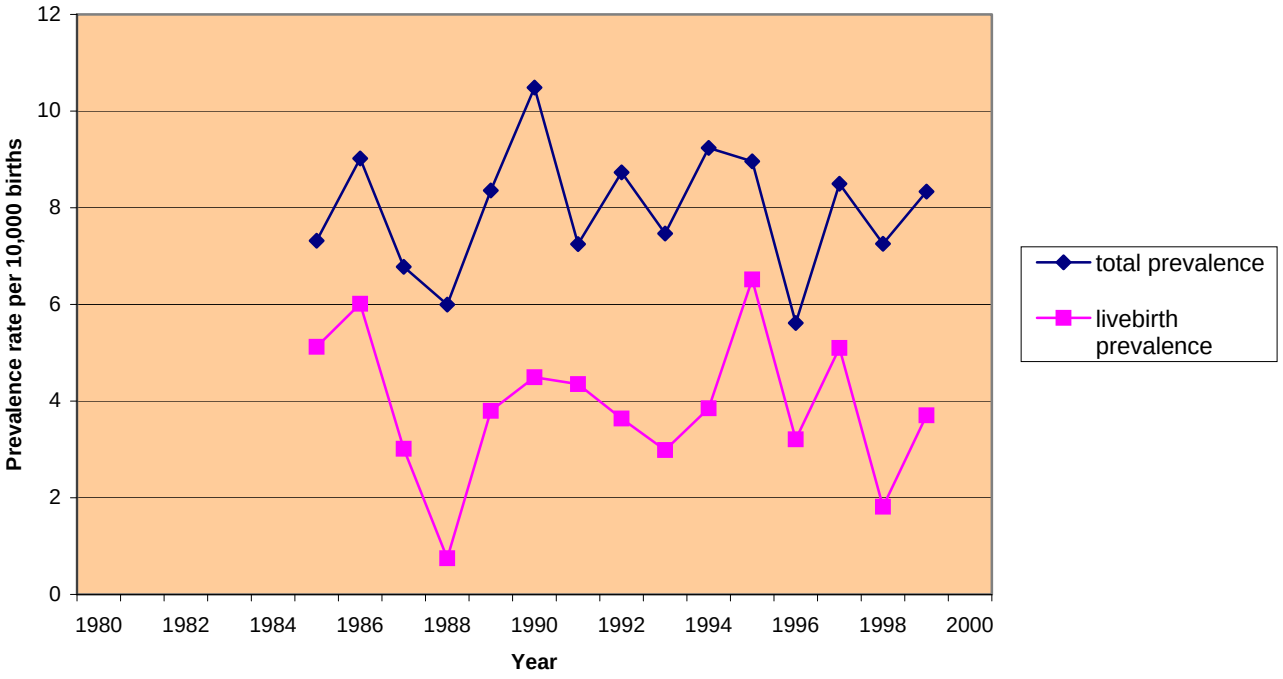
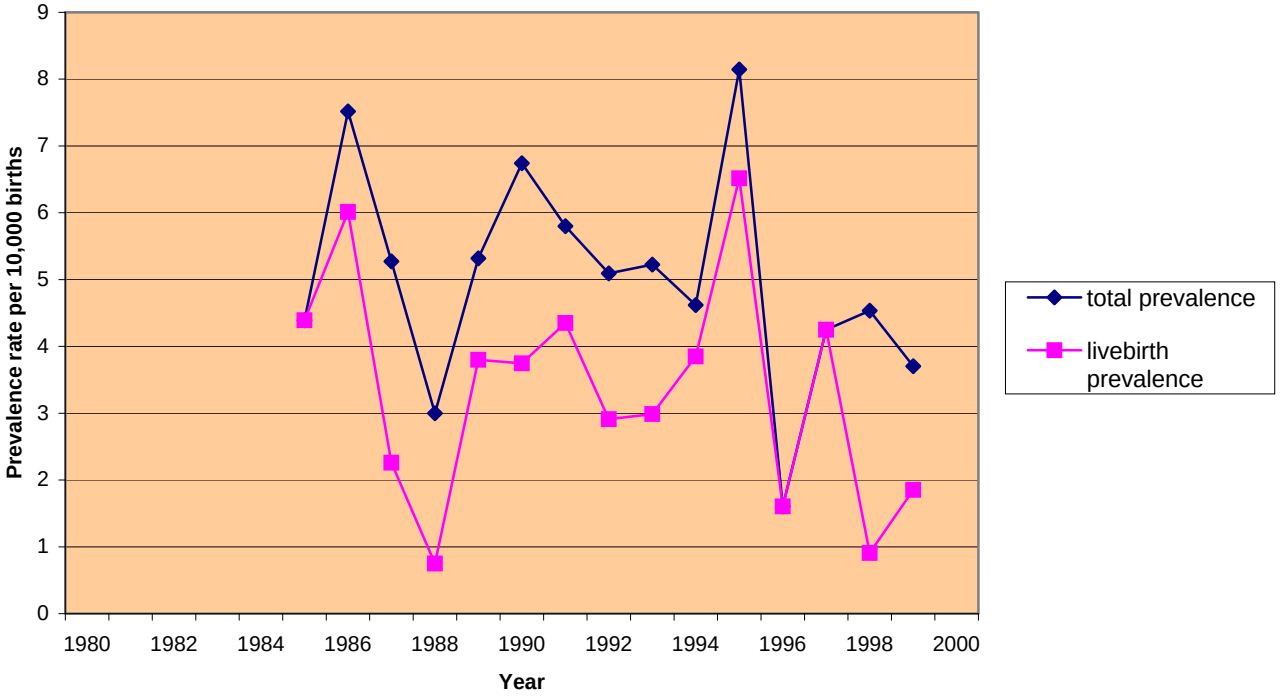
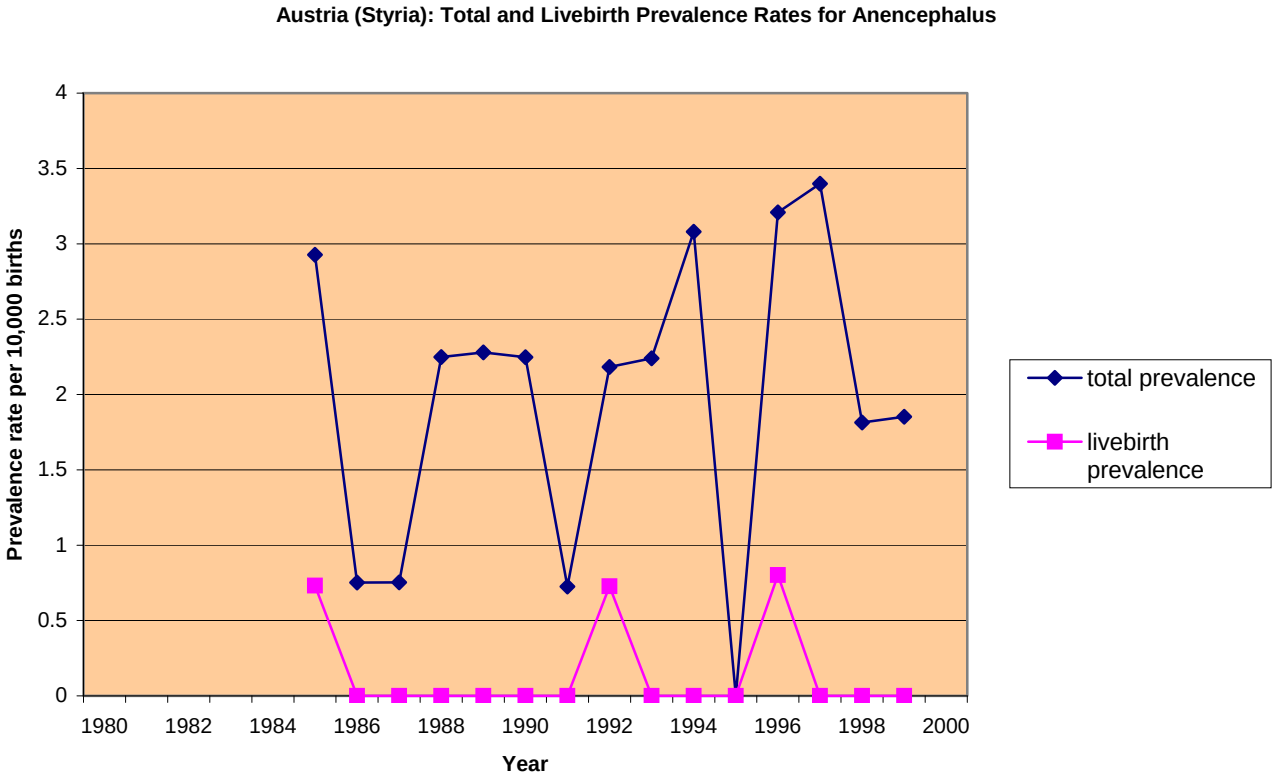
Zwiauer K, Groll D, Weissensteiner M (**2000)** "Folsäuresubstitution bei Schwangeren: Ergebnisse einer regionalen Untersuchung im Raum St. Pölten" *Pädiatrie/Pädologie*, Vol 6, pp 14-17.

Austria (Styria): Total and Livebirth Prevalence Rates for Neural Tube Defects



Austria (Styria): Total and Livebirth Prevalence Rates for Spina Bifida




Austria (Styria): Total and Livebirth Prevalence Rates for Anencephalus
Prevalence rate per 10,000 births
4
3.5
3
2.5
2
1.5
1
0.5
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR BELGIUM

Prof Yves Gillerot

Folic Acid Supplementation Policy

In Belgium there is no official recommendation for periconceptional folic acid supplementation. However, the unofficial policy is for all women planning a pregnancy to take 0.4 mg folic acid daily and for women at high risk of having a pregnancy affected by a neural tube defect to take 4 mg of folic acid daily. This should be taken 2 or 3 weeks before conception and during the first 3 months of pregnancy.

Food Fortification Policy

No information provided

Health Education Initiatives

A representative of ONE (Office de la naissance et de l'enfance (Office of Birth and Childhood)) said that since the prevalence of neural tube defects in Belgium continues to be rather low, a campaign to ensure that more women take periconceptional folic acid supplementation is probably not necessary and is not justified for costs/benefits reasons.

Knowledge and Uptake of Folic Acid

No information provided

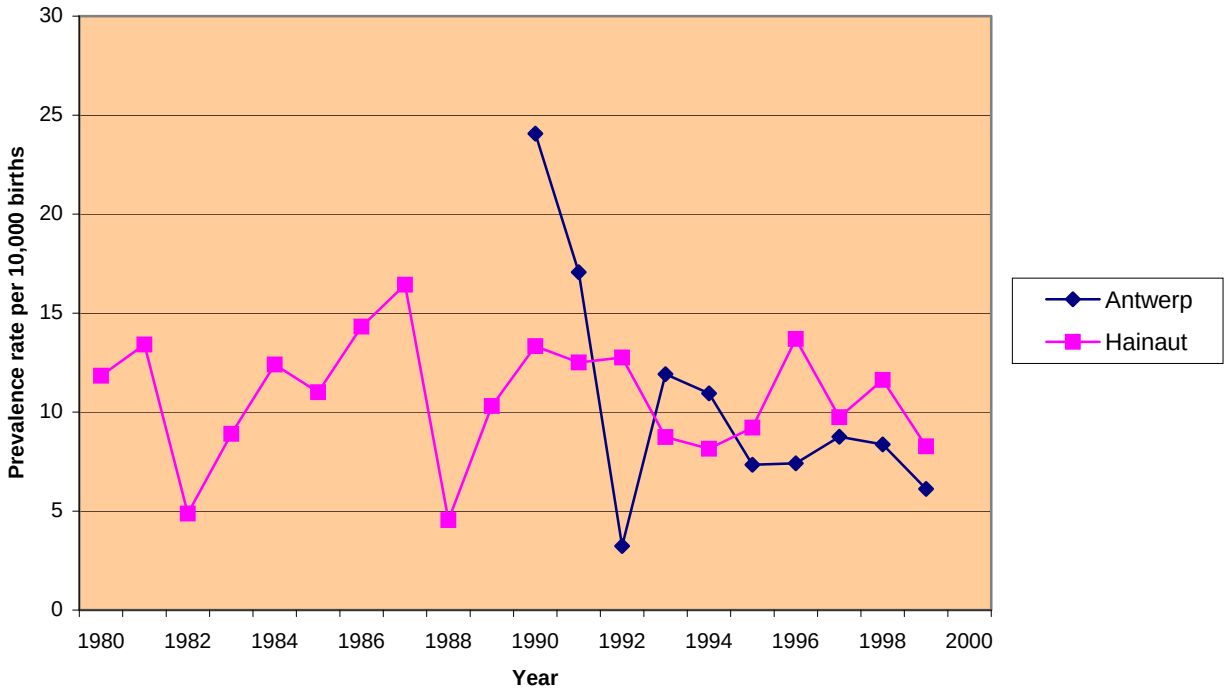
Proportion of Pregnancies that are Planned

No information provided

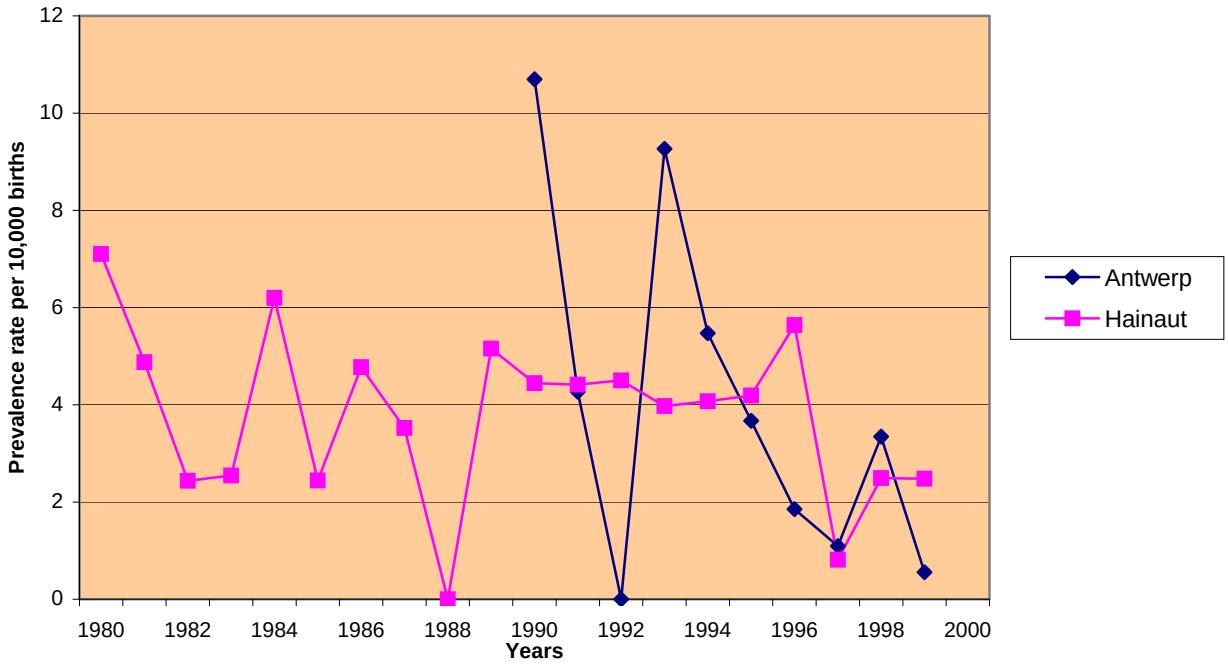
Laws Regarding Termination of Pregnancy

Termination of pregnancy for fetal abnormality is legal up to the gestational age of 24 weeks.

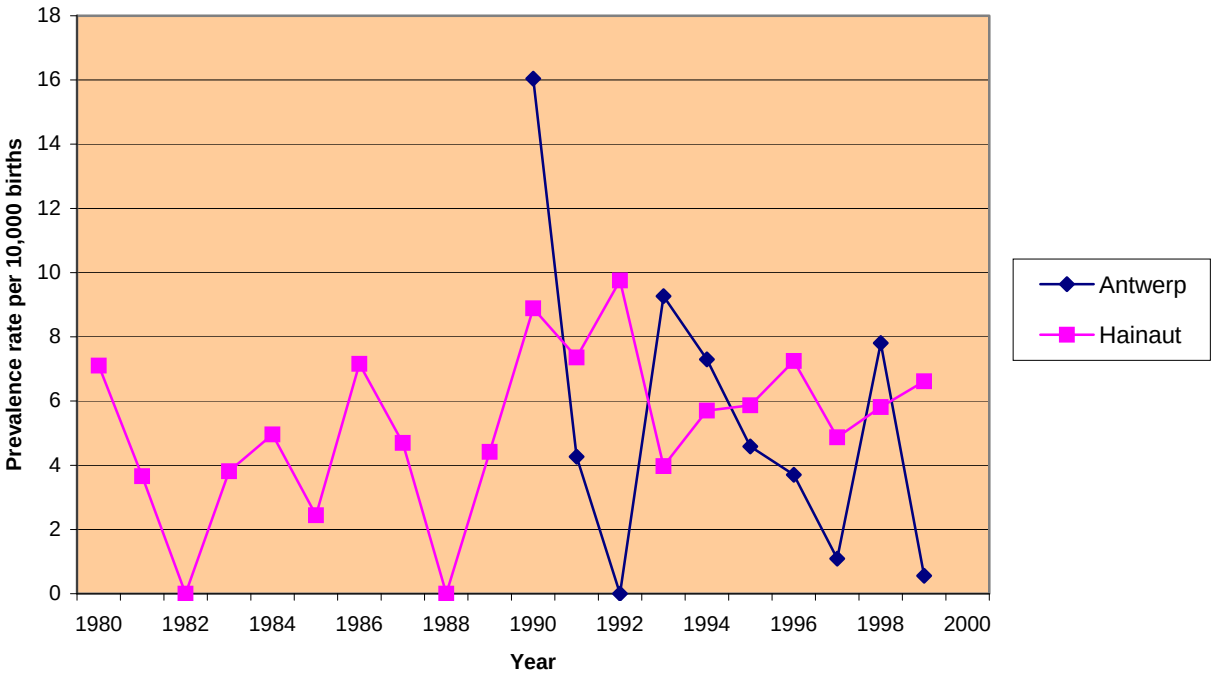
Belgium (Antwerp and Hainaut): Total Prevalence Rates for Neural Tube Defects



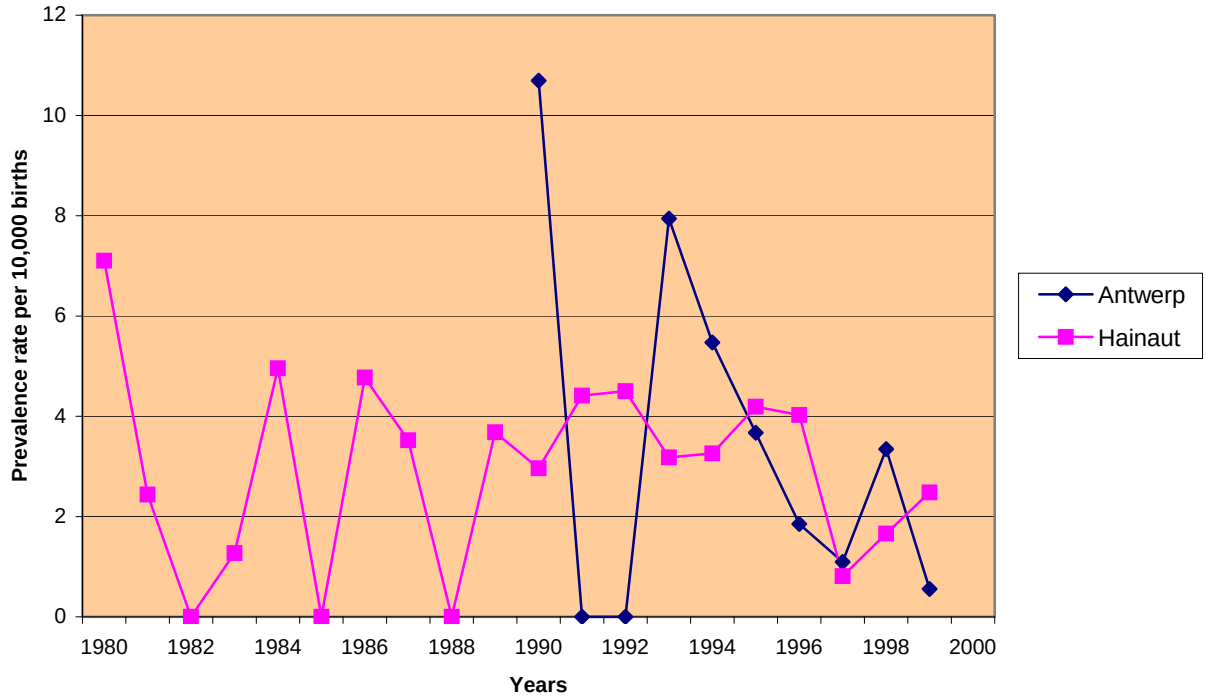
Belgium (Antwerp and Hainaut): Livebirth Prevalence Rate for Neural Tube Defects



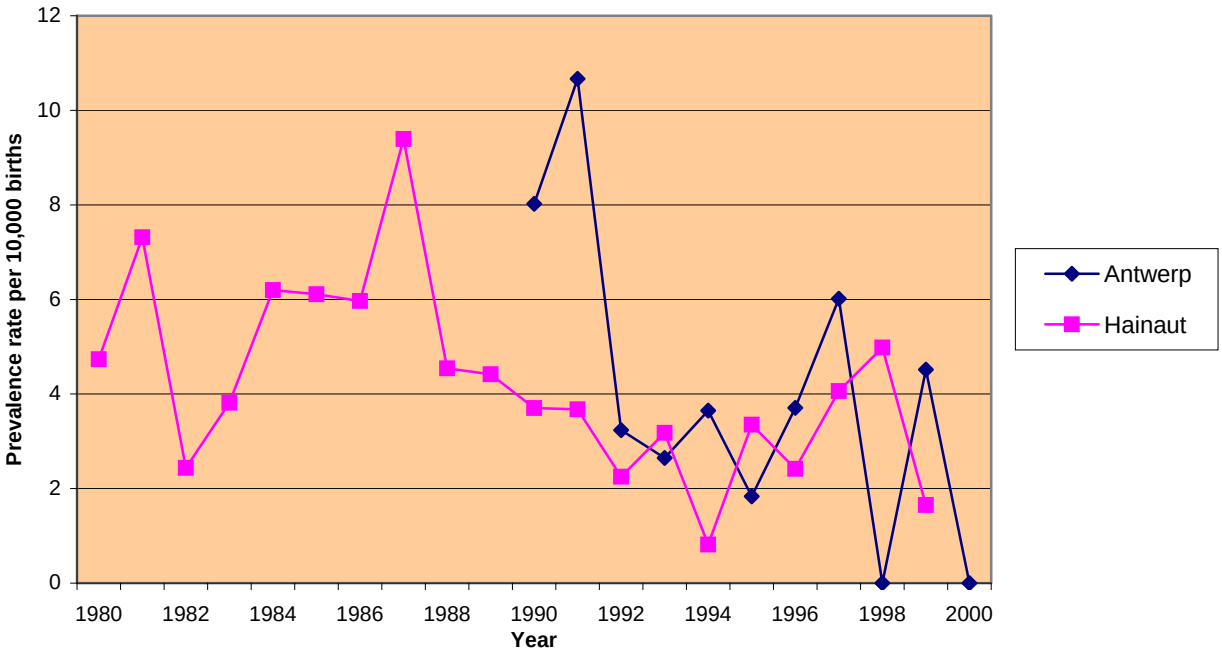
Belgium (Antwerp and Hainaut): Total Prevalence Rates for Spina Bifida



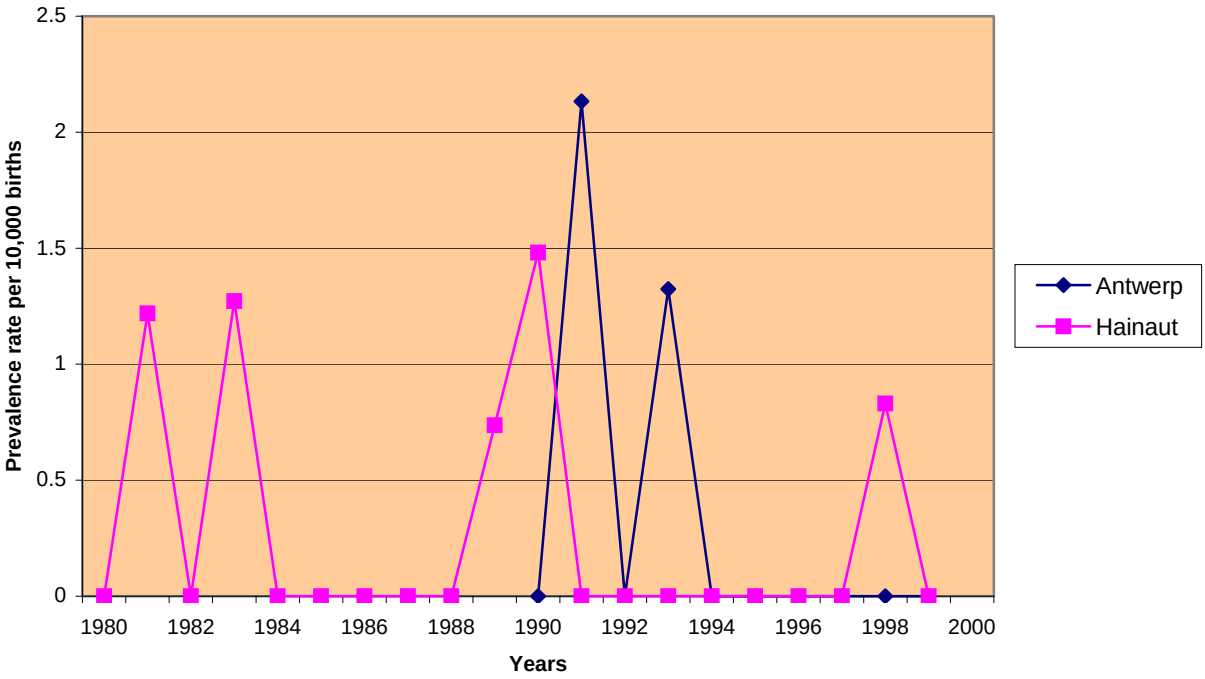
Belgium (Antwerp and Hainaut): Livebirth Prevalence Rate for Spina Bifida



Belgium (Antwerp and Hainaut): Total Prevalence Rates for Anencephalus



Belgium (Antwerp and Hainaut): Livebirth Prevalence Rate for Anencephalus



REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR CROATIA

Dr Ingeborg Barisic, Dr Romana Gjergja

Folic Acid Supplementation Policy

There is no official folic acid supplementation policy in Croatia and none is being planned. Most gynecologists and pediatricians in Croatia advise every woman to take folic acid (0.4 mg per day) at least 4 weeks before starting a pregnancy until the 12th week of pregnancy. For women who have had a previous pregnancy affected by a neural tube defect, the dosage is 4 mg per day for the above-mentioned period. There are few folic acid supplementation products: TWINLAB Folic acid caps (800 μg) or Folic plus (800 μg) etc. There is no funding for folic acid products during pregnancy; pregnant women have to pay for it themselves.

Food Fortification Policy

There is no mandatory food fortification in Croatia. Of course, one can get fortified food from other European countries, and it is not prohibited to have and to sell it in shops, but there are no statistics or studies on that issue.

Health Education Initiatives

There is no official health education initiative in Croatia, but there are many initiatives by the media (TV, Internet, journals, gynecologists and pediatricians, especially private ones). An example is in the Maternity Unit "Sveti Duh" in the city of Zagreb; there is a "Club of pregnant women" and they discuss their habits and nutrition during the pregnancy. A major function of that Club is to educate women about healthy nutrition, for instance, the importance of taking ample folic acid. The Internet page is: http:// klubtrudnica.net/trudnoca
There are some useful Croatian sites on the Internet:
http://www.medika.hr/?URL=foli&L=h
http://agram89.com/folic.htm
http://hrana.com/suplementi/vita_folna kis.htm
http://poliklinika-harni.hr/teme/trud/4_Ishr.htm

Knowledge and Uptake of Folic Acid

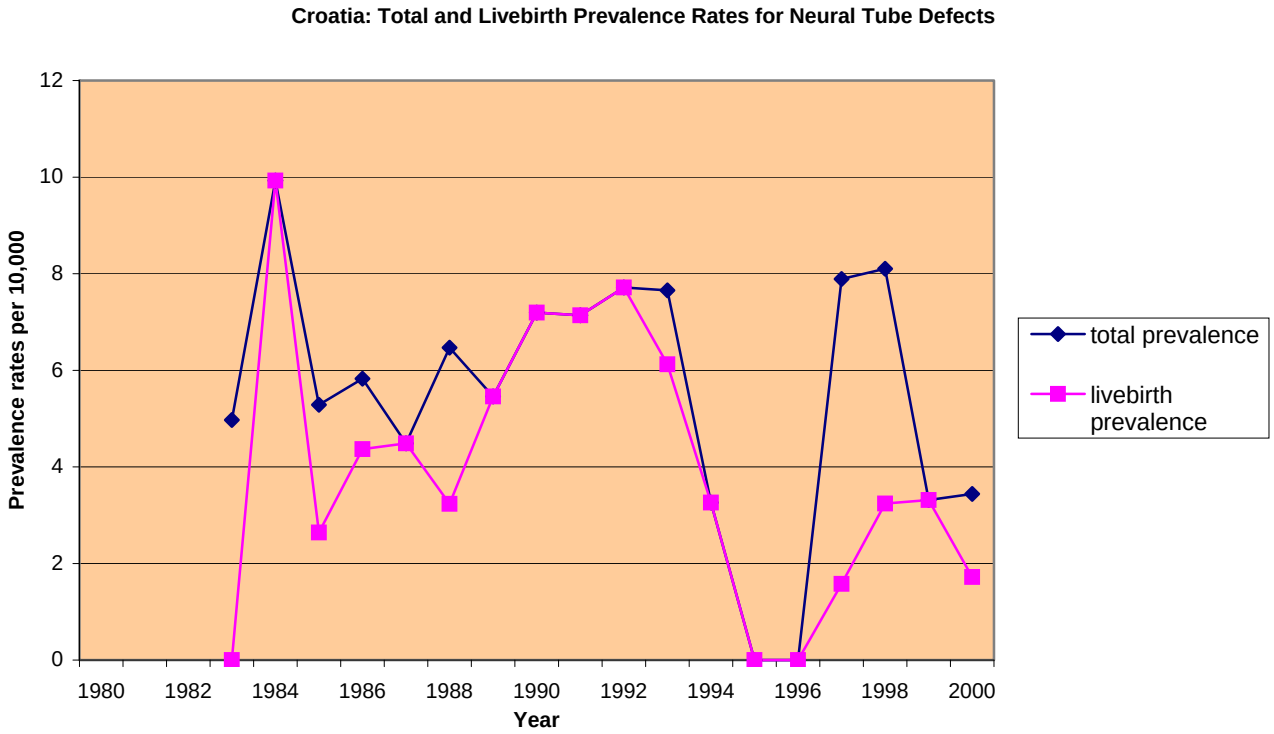
So far, there are no studies of awareness in the childbearing population or among health professionals of recommendations regarding folic acid supplementation, uptake of advice regarding folic acid supplementation, or percent of planned pregnancies. There are some studies of dietary habits and vitamin supplementation, but only considering anaemia in childhood etc. Pregnant women in Croatia are aware of the importance of vitamins and minerals during the pregnancy. It is planned in the near future to administer a questionnaire to pregnant women (and later among doctors), in Croatia (at least in the city of Zagreb), concerning their knowledge about the role of folic acid during the pregnancy.

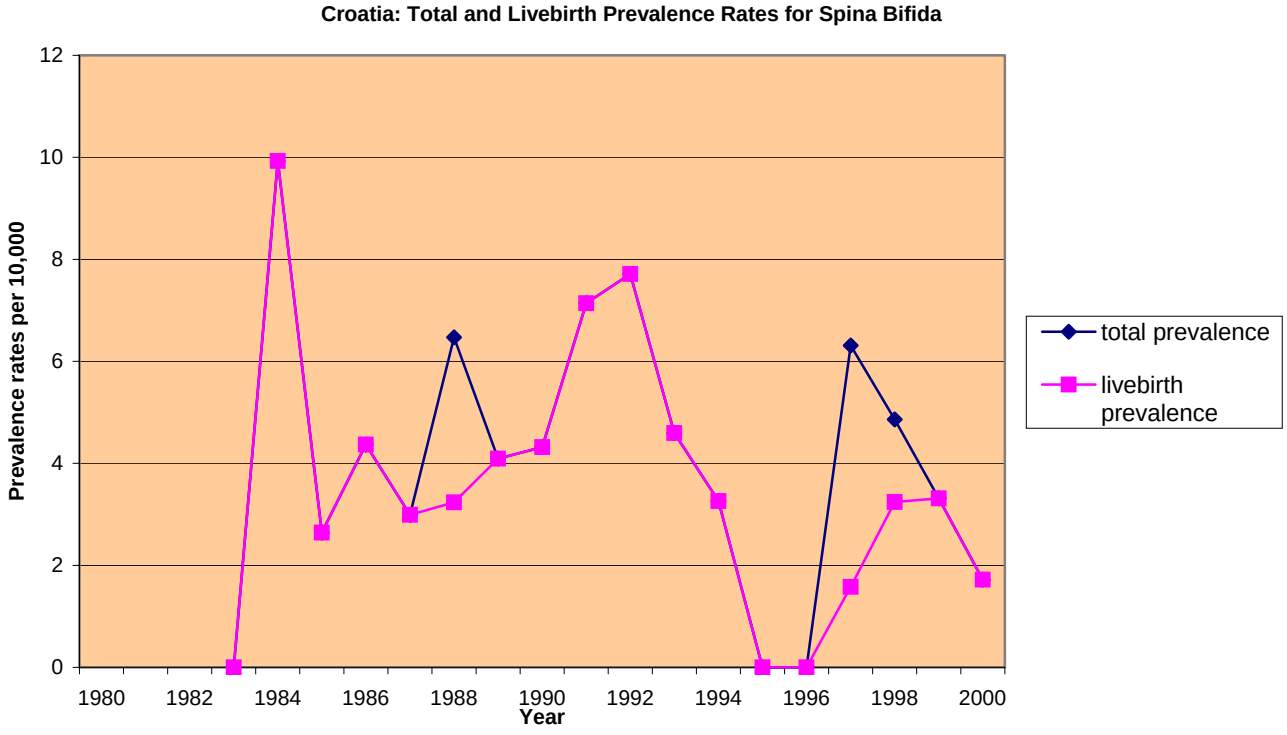
Proportion of Pregnancies that are Planned

No information provided

Laws Regarding Termination of Pregnancy

Termination of pregnancy for fetal abnormality is legal up to 24 weeks of gestation in Croatia. After 24 weeks gestation it is not legal, but if a life-threatening anomaly is found on ultrasound scan after 24 weeks, there is some possibility of termination of pregnancy if it is approved by the Hospital Commission.


Croatia: Total and Livebirth Prevalence Rates for Neural Tube Defects
Prevalence rates per 10,000
0
2
4
6
8
10
12
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence


Croatia: Total and Livebirth Prevalence Rates for Spina Bifida
Prevalence rates per 10,000
0
2
4
6
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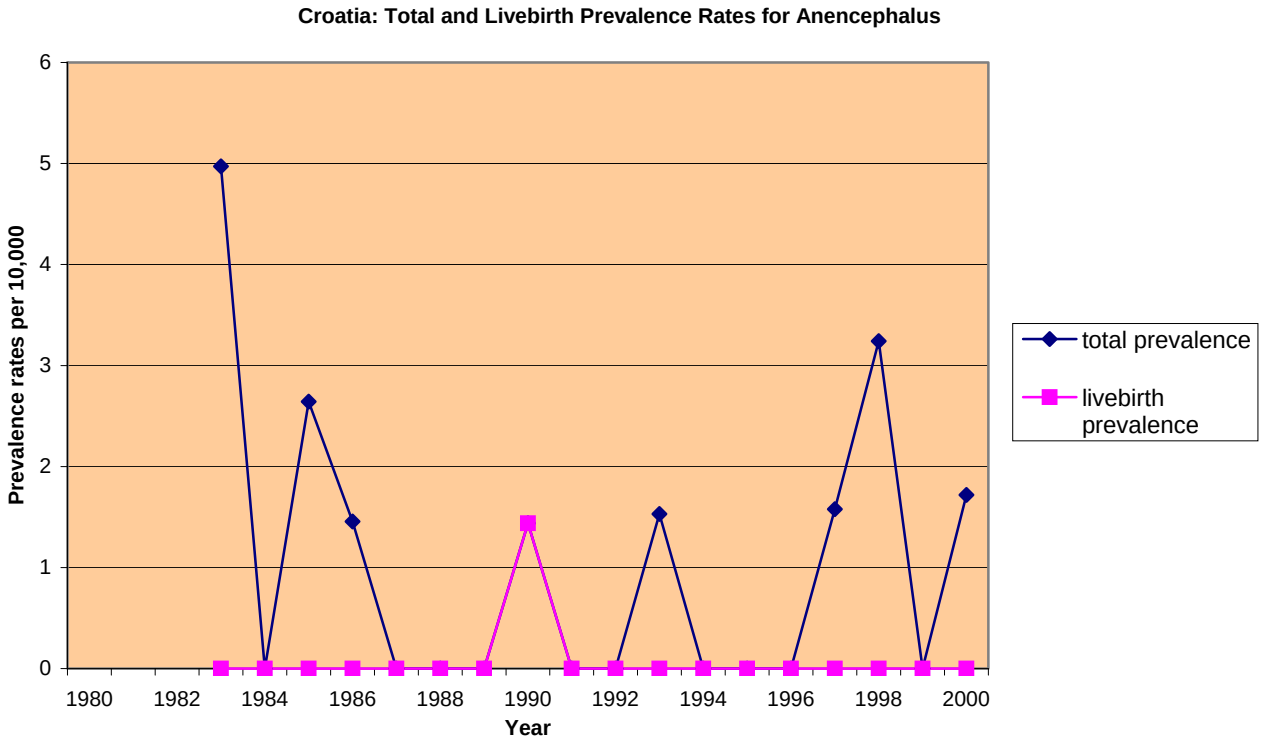
12
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence


Croatia: Total and Livebirth Prevalence Rates for Anencephalus
Prevalence rates per 10,000
0
1
2
3
4
5
6
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR DENMARK

Dr Marianne Christiansen

Folic Acid Supplementation Policy

The official folic acid supplementation policy in Denmark was introduced in March 1997 by the Danish Veterinary and Food Administration. It is as follows: Women planning a pregnancy are recommended to take a multivitamin tablet or a folic acid tablet containing 400 μg of folic acid per day, or to take in 400 μg of folic acid per day through diet, if possible. In the official recommendations, it is mentioned that for practical reasons the recommendation is to take a folic acid supplementation of 400 μg per day since achieving 400 μg of folic acid through the diet would require a change of diet for most women. The supplementation should begin when the pregnancy is planned and continue until 3 months of gestation. Women with increased risk of having a pregnancy with a neural tube defect due to malabsorption, long-term use of certain medications, diabetes mellitus or neural tube defects in relatives are recommended a folic acid supplementation of 400 μg per day through multivitamin / folic acid tablets**.** Women who have previously had a fetus with a neural tube defect, who themselves have a neural tube defect or whose partner has a neural tube defect are recommended to take 5 mg of folic acid per day. This supplementation is recommended from when the pregnancy is planned and until 2 months of gestation.

The official policy was declared by the Danish Veterinary and Food Administration after a working group had made a report on the issue (1). The official policy differs slightly from the recommendations given in the report regarding the time period in which the pregnant women should take supplementation. The policy is also stated in the Directives of Antenatal and Maternity Care given by the Danish National Board of Health 1998 (2).

Food Fortification Policy

There is no official food fortification policy in Denmark but this issue is under consideration at a very early stage. The Danish Veterinary and Food Administration is considering establishing a new working group to re-evaluate this issue (personal communication, the Danish Veterinary and Food Administration).

Health Education Initiatives

There is an official health education initiative in Denmark to inform women about the role of folic acid in reducing the risk for neural tube defects: The Danish Veterinary and Food Administration have had press releases with information about the policy, the first was on March 3., 1997, another on June 11, 1999. Folders addressing women planning pregnancy have been published by the Danish Veterinary and Food Administration and distributed to the general practitioners, the specialists in gynecology and obstetrics, the gynecological/ obstetrical departments of the Danish hospitals, pharmacies and drugstores. The folders were first distributed in 1999 and again in 2001. In 2001 the number of distributed folders was 105,000 (the number of total births in Denmark per year is approximately 65,000). There have been no paper or television advertisements, but the issue has been covered in some newspaper articles, television programs about health issues and in magazines concerning health, pregnancy and children. The initiative is still ongoing.

Knowledge and Uptake of Folic Acid

No papers have been published in Denmark concerning the awareness in the child-bearing population of recommendations regarding folic acid supplementation or the uptake of advice regarding folic acid supplementation. The issue however is one among many other issues investigated in a major study "The Danish National Birth Cohort" (3) which is an ongoing study. Some preliminary results from the Danish National Birth Cohort have been published as an abstract and presented at a Congress on Food Science (called the LMC Congress) in Copenhagen 17-18 January 2001 by scientists from the Danish Epidemiology Science Centre, Statens Serum Institut, Copenhagen, and the Research Department of Human Nutrition, Copenhagen (4). The heading of the abstract was "Do women planning pregnancy follow the advice to take folate?" The participants in the survey are pregnant women who are recruited in gestational week 5-10 at the first visit to their GP. Thirty percent of all pregnant women in Denmark participate. At entry the women are asked to fill in an entry form containing information on age, date of last menstrual period, and use of drugs and dietary supplements. The participants in this particular investigation were selected in the period from January 1998 to December 1999, N=3559. The results showed that 14 % of the whole study group reported use of 400 μg folic acid or more per day in gestation week 1-5. There was a significantly higher intake in 1999 (17%) compared to 1998 (12%), but further analyses will be performed to control for social classes. The conclusion was that the frequency of folate use

among pregnant women was low. Looking at the months separately, no clear rise in folate use was detectable which could be directly attributed to the campaign (press release and folders) which took place in June 1999.

Regarding the dietary habits of women of child bearing age, the working group under the Veterinary and Food Administration (1) have calculated the intake of folate in Denmark using data from the Danish Dietary Survey performed in 1995. The results were that women of child bearing age in Denmark have a mean intake of 248 μg folate per day through the diet; only 5% get 400 μg or more.

An intervention study on the influence of folic acid supplement on the outcome of pregnancies in the county of Funen was done in the period 1983 to 1986, which is long before the official policy was introduced. These results were published in 1999 (5, 6, 7). In this project all pregnant women resident in the county of Funen were offered free folic acid in different dosages when pregnant or planning a pregnancy. Information was provided by health personnel, by advertisements in the press and by mailed folder to the age group 18-35 years. In a total of 14,021 pregnancies 10,494 pregnant women (74.8%) had folic acid supplement. 8184 women took part in a double-blind randomised trial between two different dosages, namely 1.0 mg and 2.5 mg. A further 2310 women had a supplement of folic acid without being randomised. Three groups were defined: an early start group in which folic acid supplement was started no later than 7 weeks from the last period, a middle start group in which folic acid supplementation was started 8-11 weeks from the last period, and a late start group in which folic acid supplementation was started after 12 weeks or more. The early start group comprised 5345 children (37.7%) including 1562 (11%) with start before the last menstrual period. In the middle start group there were 3193 children (22.5%) and in the late start group 2091 (14.7%). The study looked at the influence of folic acid supplement on birth weight, incidence of preterm labour and congenital anomalies. It was concluded that a supplement of 1.0 mg folic acid had the same effect on birth weight and preterm labour as a supplement of 2.5 mg, that is a slight increase of birth weight and a decrease in the incidence of preterm labour, infants with low birth weight and those small for gestational age. No dose-dependant differences between the doses 1.0 mg and 2.5 mg were found in congenital

anomalies, but children whose mothers started folic acid supplement before the 7th week of pregnancy showed a significantly lower prevalence of the malformations which develop in the first 7 weeks when compared to pregnancies with a later start of supplement.

The above mentioned study is one of the only studies published on periconceptional folic acid in Denmark so far. The study area was Funen County, which is covered by the EUROCAT registry. As mentioned, the study took place more than 15 years ago although it was only recently published. Looking at the preliminary results from the Danish Birth Cohort (4) it seems as if the awareness and / or acceptance of taking periconceptional folic acid among the study population from Funen County in the 1980s was quite high compared with the acceptance or awareness among all pregnant women today after the official recommendation has been implemented. Of course, the data are not very comparable.

Proportion of Pregnancies which are Planned

No national study has been published from Denmark on the proportion of planned pregnancies. In the Danish version of the report done by the working group under the Danish Veterinary and Food Administration (1) it is assumed that the number is a little higher than in the United States where approximately half of the pregnancies are planned, since compliance with contraception in Denmark is rather high. However a regional study in Denmark was published in 2001 (8): The study population (N=3516) was recruited among pregnant women attending Odense University Hospital, Funen County (the region covered by the EUROCAT register), in the period November 1994-January 1996. In this study 68% of the women with accepted pregnancies stated that the pregnancy was planned. The representativity of this study sample was judged by comparing the age distribution and the parity profile of the women in the study population with the national figures. No pronounced difference was found, indicating that the study sample can be considered a representative sub sample of the Danish population.

Laws Regarding Termination of Pregnancy

Women in Denmark have the right to have a termination of pregnancy before 12 weeks of gestation. After 12 weeks of gestation a woman can have her pregnancy terminated without special permission if it is necessary to avoid danger to her life. For other specified indications, one of these being anomalies of the fetus, the woman can have her pregnancy

terminated after obtaining permission from a certain committee of two doctors and an employee at the Social Centre (one committee in each County). There is no upper limit of gestation, but the law states that if the fetus is presumably viable, permission can only be given if the fetus suffers from a severe anomaly.

References:

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The Danish National Board of Health: Directives of Antenatal and Maternity Care (**1998)**

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Ulrich M, Kristoffersen K, Rolschau J, Grinsted P, Schaumburg E, Foged N **(1999)**, "The influence of folic acid supplement on the outcome of pregnancies in the county of Funen in Denmark. Part II. Congenital anomalies. A randomised study" *Eur J Obsted Gynecol Reprod Biol*, Vol 87, No 2, pp 111-113

Ulrich M, Kristoffersen K, Rolschau J, Grinsted P, Schaumburg E, Foged N **(1999)**, "The influence of folic acid supplement on the outcome of pregnancies in the county of Funen in Denmark. Part III. Congenital anomalies. An observational study" *Eur J Obsted Gynecol Reprod Biol*, Vol 87, No 2, pp 115-118

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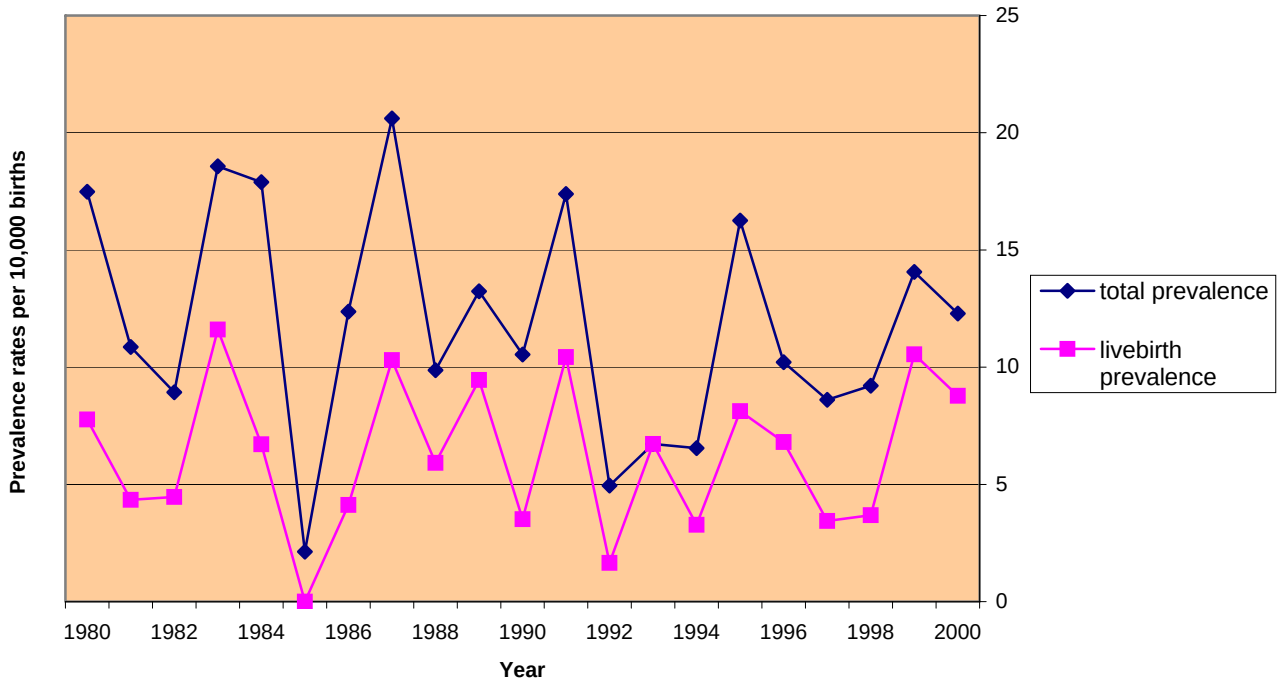
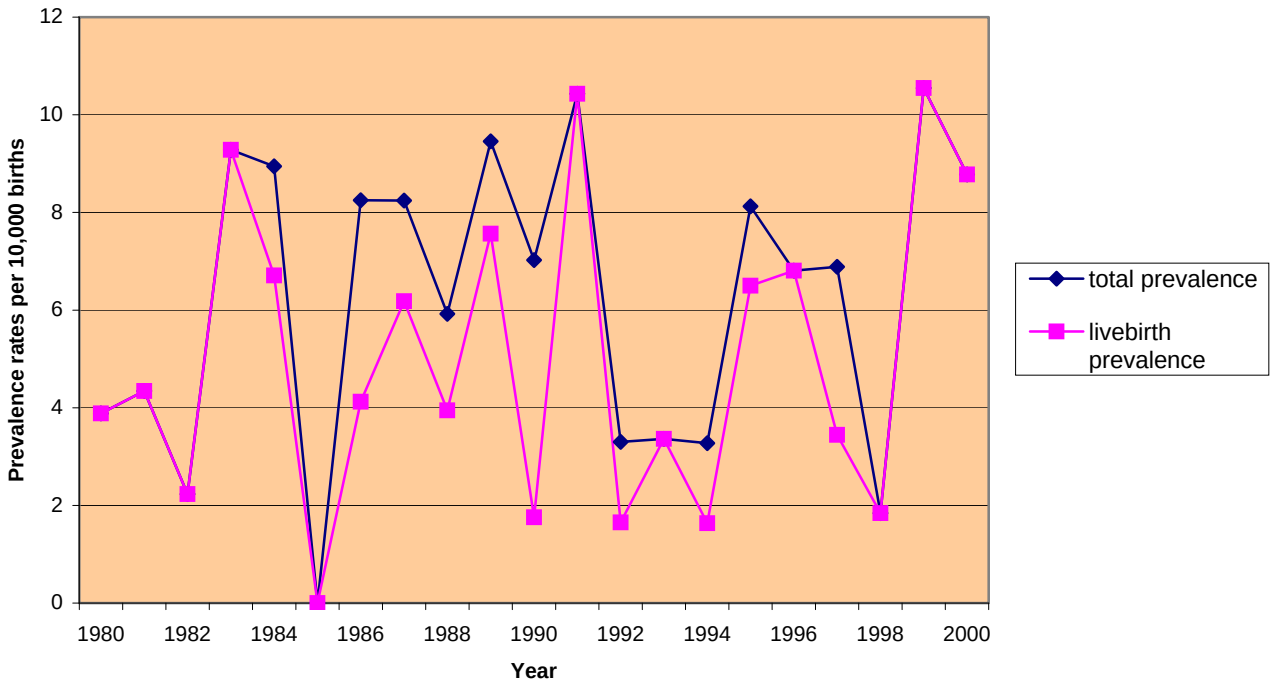
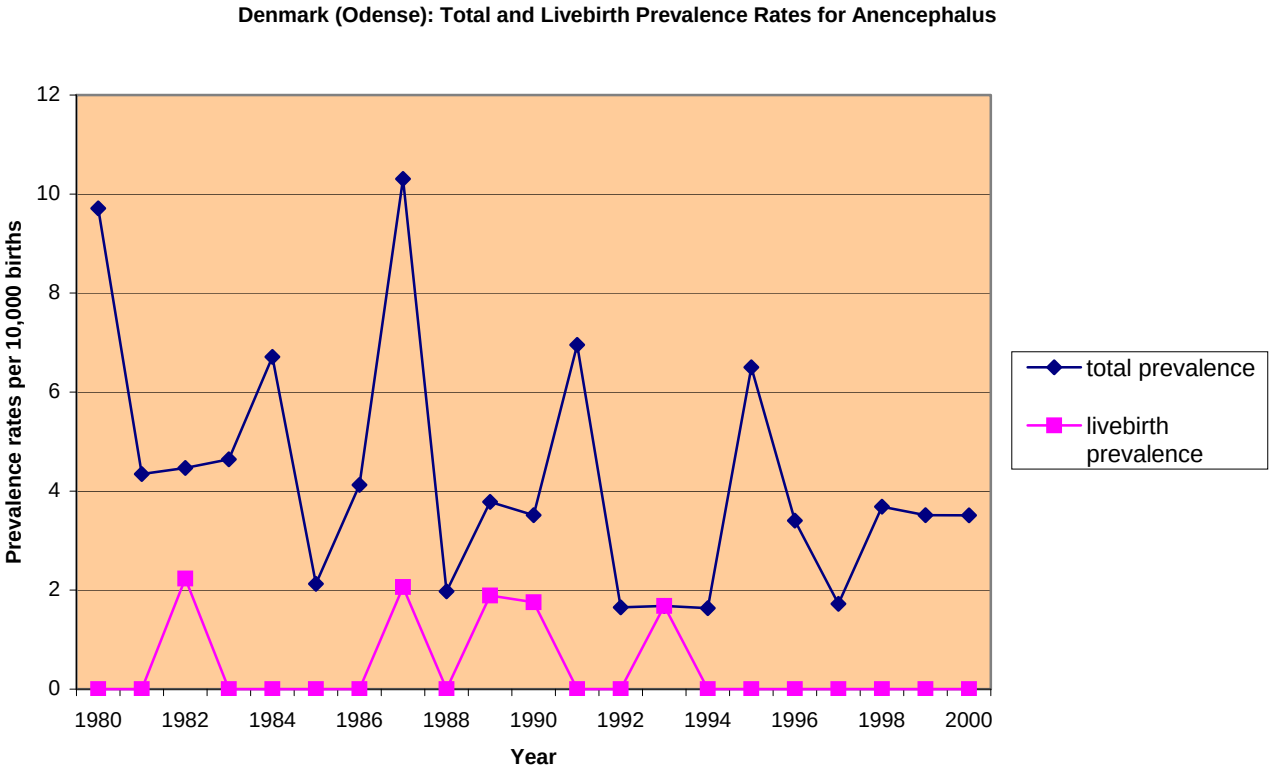
Denmark (Odense): Total and Livebirth Prevalence Rates for Neural Tube Defects



Denmark (Odense): Total and Livebirth Prevalence Rates for Spina Bifida




Denmark (Odense): Total and Livebirth Prevalence Rates for Anencephalus
Prevalence rates per 10,000 births
12
10
8
6
4
2
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR FINLAND

Dr Annukka Ritvanen

Folic Acid Supplementation Policy

The randomised, international study published by the UK Medical Research Council (MRC) in 1991 confirmed the results of the previous non-randomised studies carried out in the UK in the 1980's that folic acid prevented the majority of recurrencies of neural tube defects (NTD). The Hungarian randomised intervention study of Czeizel and Dúdas in 1992 showed that periconceptional use of a folic acid supplement significantly reduced the occurrence of NTD.

In the light of these studies, the Finnish Ministry of Social Affairs and Health set up an expert group to prepare a national recommendation which was issued in 1995 (Sosiaali-ja terveysministerion asiantuntijaryhma, 1995). It was sent to all medical professionals, health care centers, hospitals and pharmaceutical companies. The recommendation was also published in the leading Finnish scientific medical paper in 1996 (STM, 1996). This official recommendation for supplementation has three sections:

1. To prevent first occurrence NTD - all women planning or undergoing a pregnancy are recommended to include an adequate amount of diverse food in their diet to obtain at least 0.4 mg folic acid daily. Use of vitamin supplements containing folic acid in order to prevent NTD is normally not necessary. This recommendation is being modified at present by the expert group of the Ministry of Social Affairs and Health.

2. To prevent first occurrence of NTD - in a few special situations women who plan a pregnancy and who may for various reasons have potential deficiency of folic acid, should take a daily supplememt of 0.4 mg folic acid as tablets periconceptionally (starting 4 weeks before conception and continuing until the end of the 12th week of pregnancy). These special situations are: in connection with antiepileptics (phenytoin , barbiturates, valproate and carbamazepine treatment), long-term use of sulphonamides, intestinal malabsorption diseases like coeliac disease etc., abundant use of alcohol, very unbalanced diet, insulin dependent diabetes, clomiphene, and with neural tube defects among more distant relatives.

3. To prevent NTD recurrence - for women with high risk of fetal NTD who are planning a pregnancy, a daily supplement of 4 mg folic acid as tablets is recommended periconceptionally (ie from 4 weeks prior to conception until the end of the 12th week of pregnancy).

The recommendation published by the National Research and Development Centre for Welfare and Health STAKES in 1999 was approximately the same as the official folate / folic acid supplementation recommendation from 1995, but it also said that women planning a pregnancy or in early pregnancy who use folate rich food products to a lesser degree or who do use folate rich food but who want to make sure to get adequate daily amounts of folic acid, can use a daily supplement of 0.4 mg folic acid as tablets periconceptionally (Stakes, 1999).

Food Fortification Policy

Fortification of food products with folic acid was not considered justifiable in Finland (1995).

Fortification of food products with folic acid has been monitored by the National Food Agency with the support of the Ministry of Social Affairs and Health and under the direction of a broad-based group of experts. The report of the expert group was published in December 2001: it did not recommend fortification of basic food products with folic acid (Elintarvikevirasto, 2001).

Health Education Initiatives

There has been no health education initiative on folic acid supplementation in Finland, but information is being given at schools and by the maternity clinics and child welfare clinics. The issue has been widely presented in women's magazines.

Folic Acid Knowledge and Uptake

A study was carried out in year 2000 in 114 public maternity clinics around Finland. A public health nurse or a midwife completed a questionnaire with the women during their first visit to the maternity clinic. 547 women participated in the study (6% refused). The women had their first antenatal visit on average during the ninth gestational week. 65% of the women had heard about folic acid, young and less educated women less often than others.

The women had got information on the effect of folic acid on pregnancy and fetuses from newspapers and magazines, public maternity clinics and health care centres, and from schools and other educational institutions. Drug advertisements and friends were more important information sources than were doctors and pharmacists. 10% of women knew about the effects of folic acid on pregnancy and the foetus. 29% of women could list at least one food product containing folic acid. 45% of women had used at least one preparation containing vitamins and / or trace elements before and / or in early pregnancy. 34% of women had consumed a folic acid supplement and out of these 19% before pregnancy or before and in early pregnancy (A. Ritvanen, S. Sihvo, 2003).

Proportion of Pregnancies which are Planned

Women (n=547) were interviewed by the midwife / nurse during their first prenatal care visit. Data were collected during a month's period in 114 maternity centres in Finland in Spring 2000. 6% of the women refused to participate and two thirds of the questionnaires were returned. The average time for the first prenatal care visit was 9 weeks. Between 37% and 86% of the pregnancies were planned, depending on the interpretation of the concept of "planned". Most (60%) of the women changed their life style in early pregnancy. However, 75% of the changes were made only after the woman found out about her pregnancy. (S. Sihvo, A. Ritvanen, E. Hemminki 2002).

What women thought about getting pregnant prior to the pregnancy, by age of mother (%)

	< 25	25-29	30-34	≥ 35	All
I wished to get pregnant as soon as possible	33	39	41	32	37
I thought the pregnancy may begin by its own time	48	53	47	45	49
I wished to get pregnant later	9	4	2	5	5
I didn't want to get pregnant	4	1	3	3	2
I didn't think about it	3	3	4	9	4
Getting pregnant or the time was not important	4	1	3	6	3

Laws Regarding Termination of Pregnancy

Termination of pregnancy is allowed up to 12 weeks gestation for many indications by permission of one or two doctors and up to 20 weeks by special permission of the National Authority for Medicolegal Affairs. If the mother's life is in danger, the pregnancy can be terminated at any gestational age.

Termination for fetal abnormality can be done up to 24 weeks only by special permission of the National Authority for Medicolegal Affairs.

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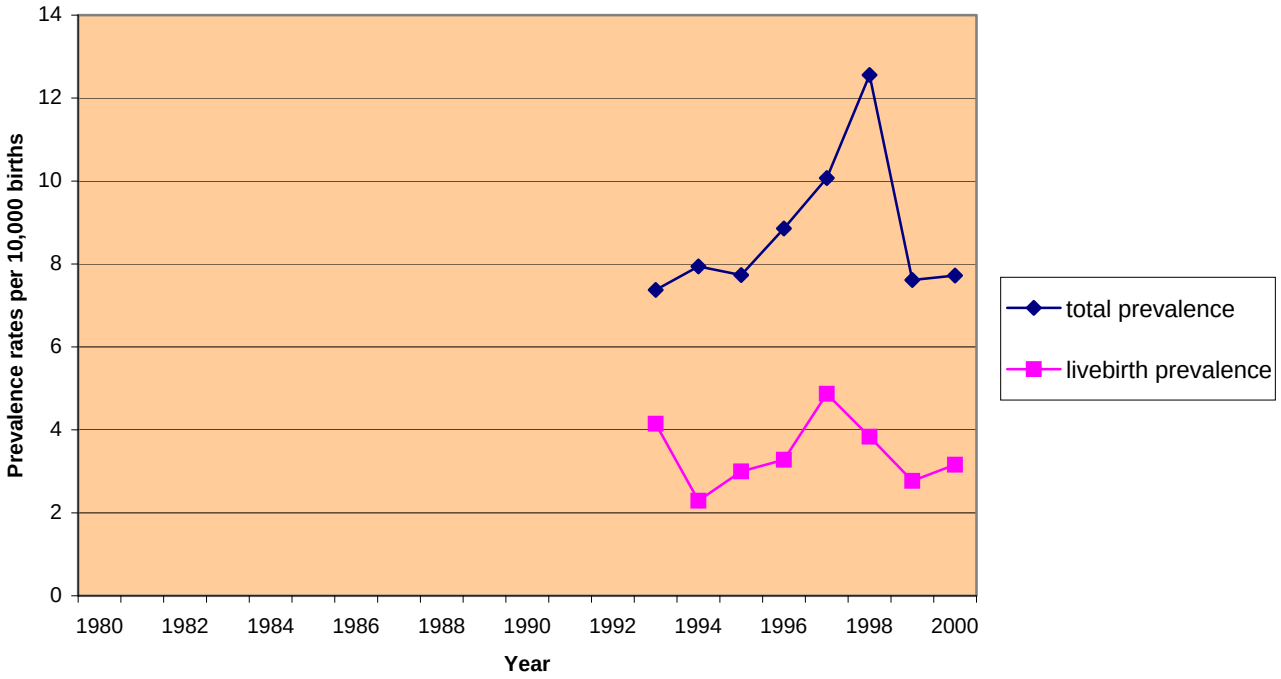
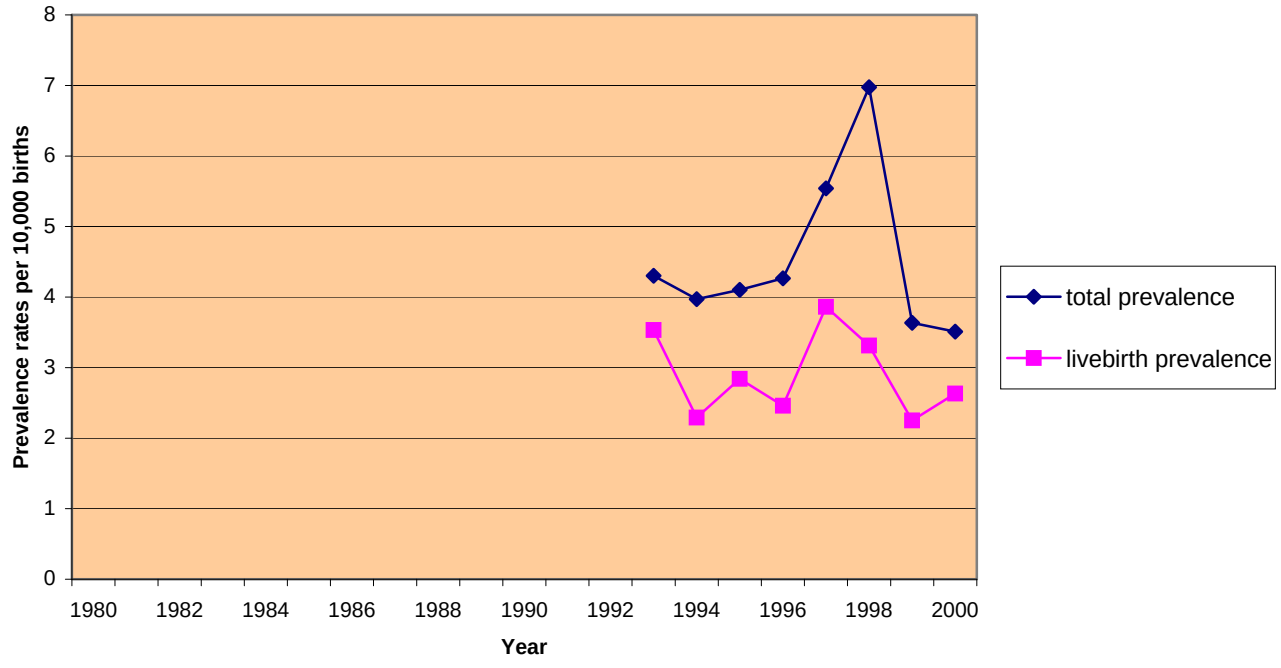
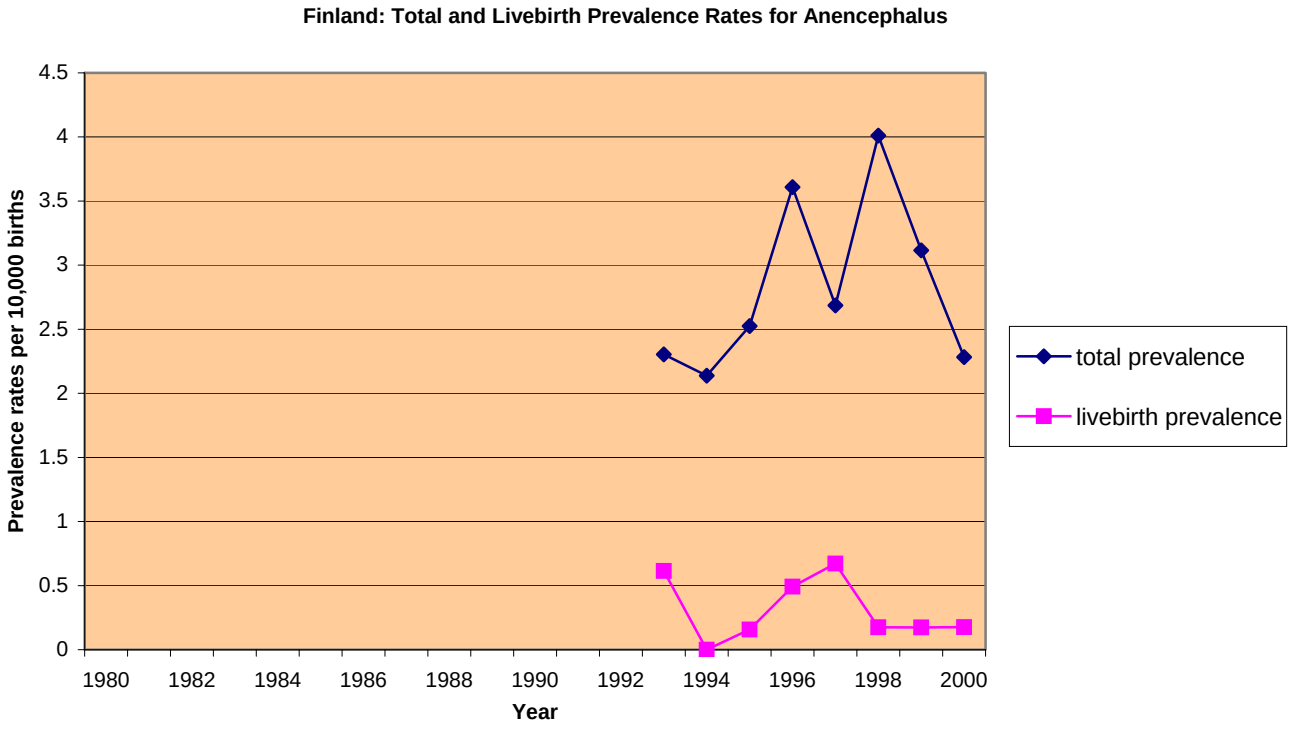
Finland: Total and Livebirth Prevalence Rates for Neural Tube Defects



Finland: Total and Livebirth Prevalence Rates for Spina Bifida




Finland: Total and Livebirth Prevalence Rates for Anencephalus
Prevalence rates per 10,000 births
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR FRANCE

Dr Janine Goujard

Policy on Folic Acid Supplementation

In 1995, the French Pediatric Society published a recommendation to pregnant women to take a daily dose of 0.2 mg daily of folic acid supplements. They also advised women of child-bearing age to increase folate intake through diet.

A second awareness was raised in 1997 by the National College of Obstetrics and Gynecology. They advised the same folic acid supplementation level of 0.2 mg daily during the periconceptional period, reinforcing the position of the French Pediatric Society. The folic acid status of the French women was considered to be good. However, encouragement was given for a multi-vitamin therapy at a daily dose of 400 μg of folic acid in high-risk situations (teenagers, discontinuation of oral contraception, alcoholic women, women of low social economic class).

In 1999, the State Secretary of Health set up an expert group to prepare national recommendations which were issued in August 2000. The advice was a daily dose of 0.4 mg of folic acid from 4 weeks before conception to 8 weeks after conception. For anti-epileptic treated women, the recommendation was 5 mg folic acid daily.

Food Fortification Policy

There is no mandatory food fortification. However, some fortified breakfast cereals are available (around 160-170 mg /100 g, more for “Cornflakes: 300 mg /100 g”) in most supermarkets.

Health Education Initiatives

In 2000, recommendations for a diet rich in folate, calcium, iodine and iron were made in an illustrated leaflet addressed to women of child-bearing age. In this booklet, there is a small paragraph for women planning pregnancy, saying that folic acid is needed to “prevent intra uterine growth retardation and various severe malformations of the baby “.

Knowledge and Uptake of Folic Acid

Two studies using the same protocol were done in public and private obstetric units in Paris in 1995 and 1999. The 1999 study (2) carried out on 735 women interviewed 2 or 3 days after the delivery showed that 55.1 % (405/735) had heard of folic acid but most often with no knowledge of its effect. 24.3% (177/728) reported the use of one of the products containing folic acid (with or without additional multivitamins or minerals) present on a list with the pictures of the boxes. But only 1.0% (8/735) took the folic acid in the recommended period. Even these results were better than those of the 1995 survey (1) in which only 0.5 % - 3/733- took folic acid during the recommended period. Clearly, the messages from the "non official" recommendations issued in the country in 1995 and 1997 were not heard.

Laws Regarding Termination of Pregnancy

There is no upper gestational age limit on termination of pregnancy for fetal abnormality with approval by experts if "there is a high probability that the fetus is affected by a particularly severe condition with no effective therapy available at the time of prenatal diagnosis" (law of July 1994).

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Additional Reading: Three chapters in books addressed to the French medical establishment have been written

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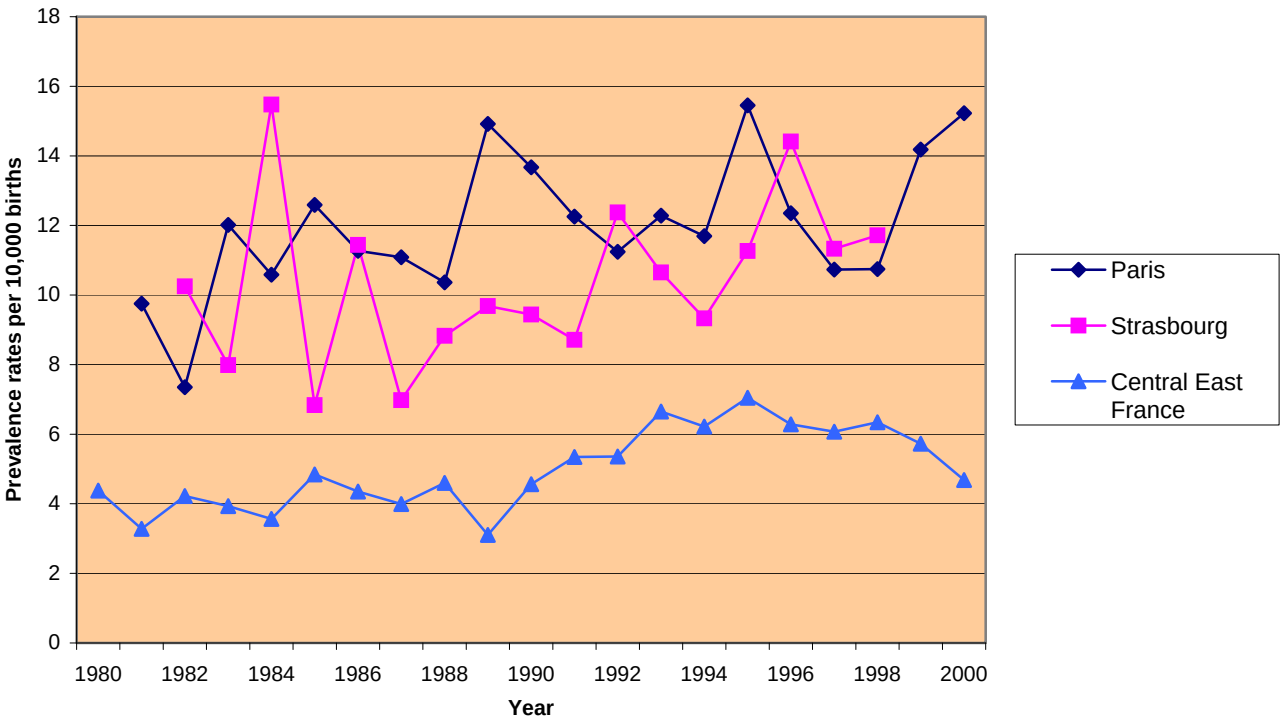
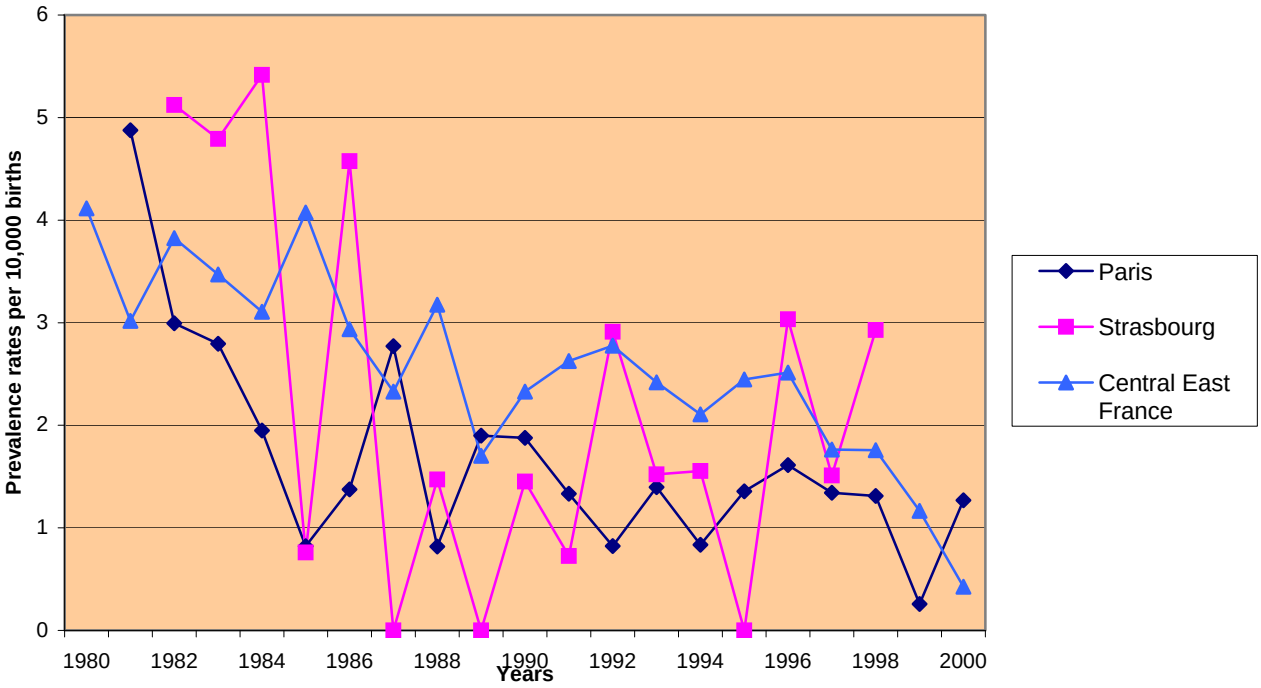
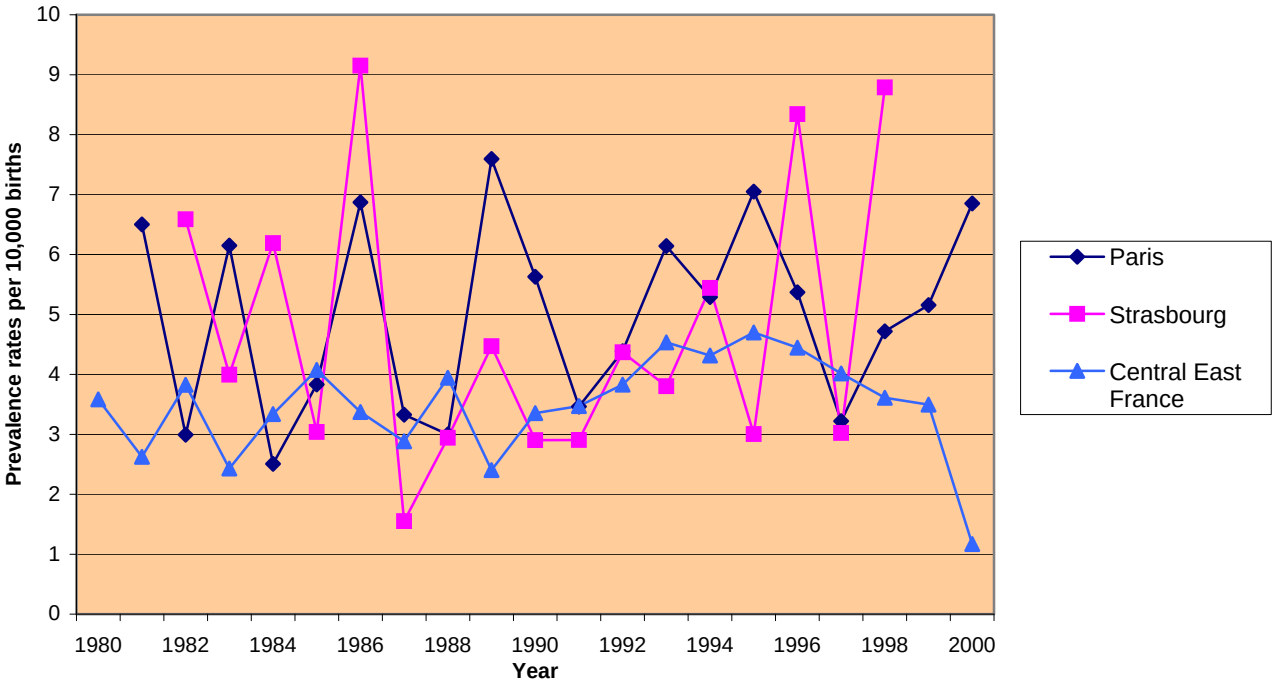
France (Central East France, Paris and Strasbourg): Total Prevalence Rate for Neural Tubes



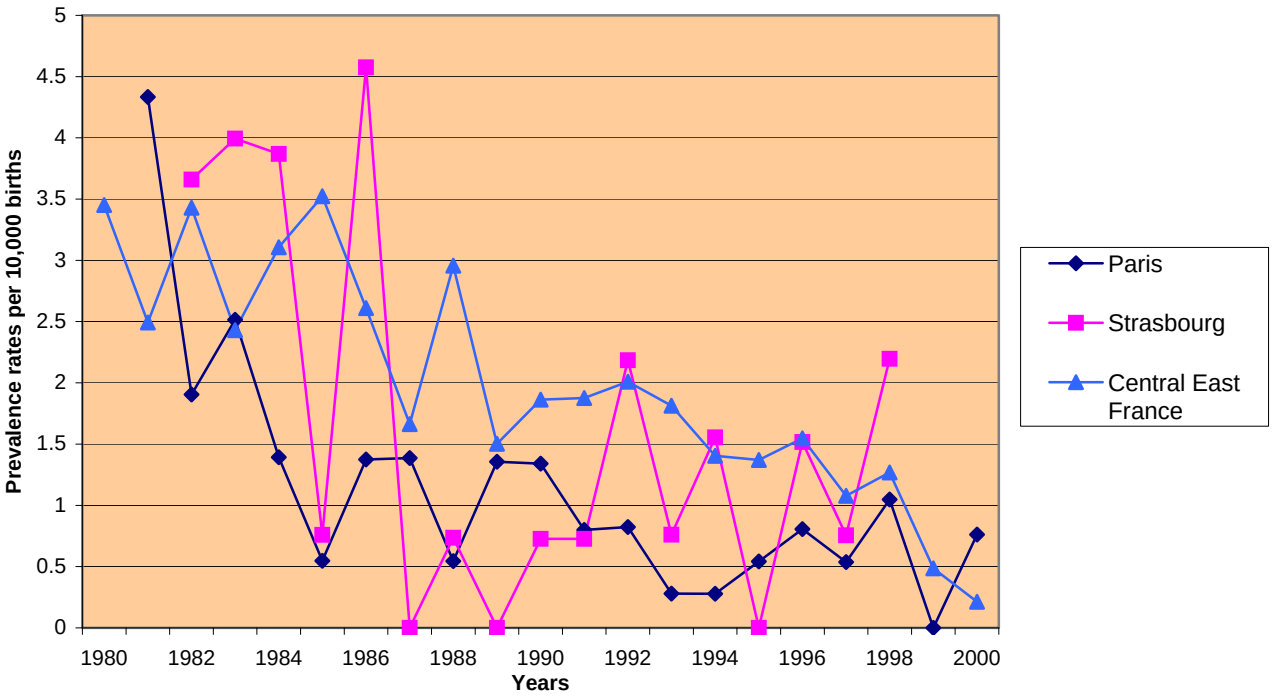
France (Central East France, Paris and Strasbourg): Livebirth Prevalence Rate for Neural Tube Defects



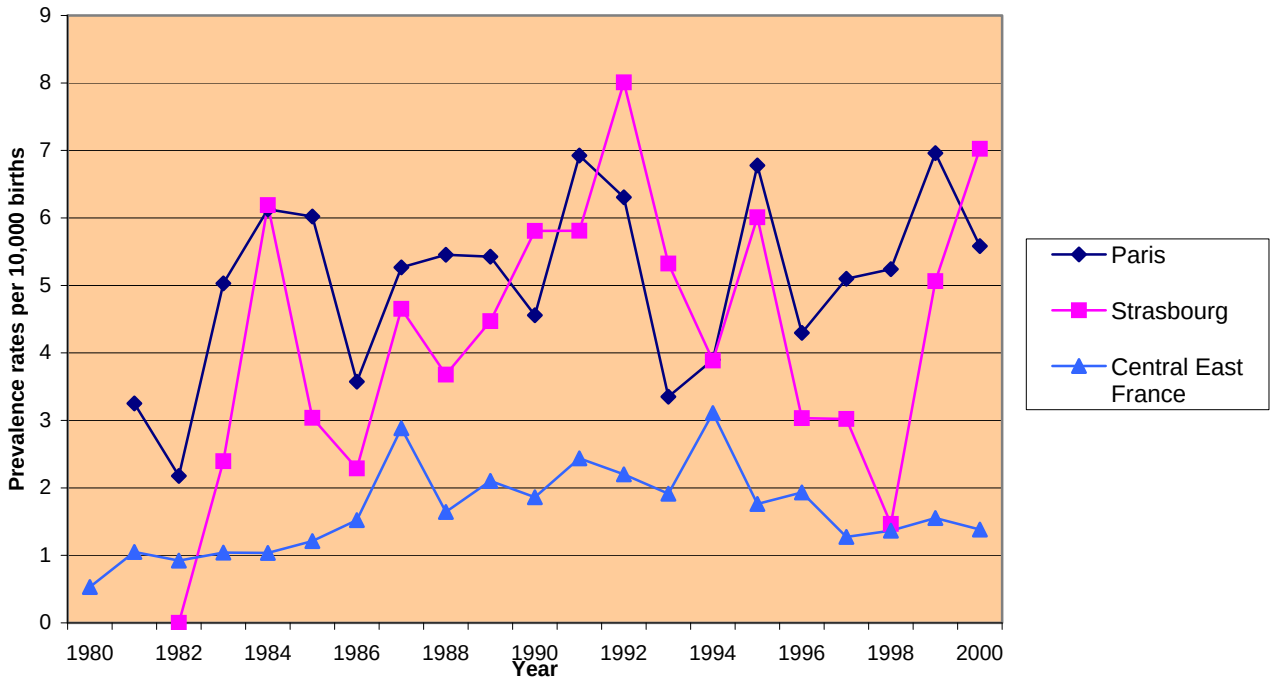
France (Central East France, Paris and Strasbourg): Total Prevalence Rate for Spina Bifida



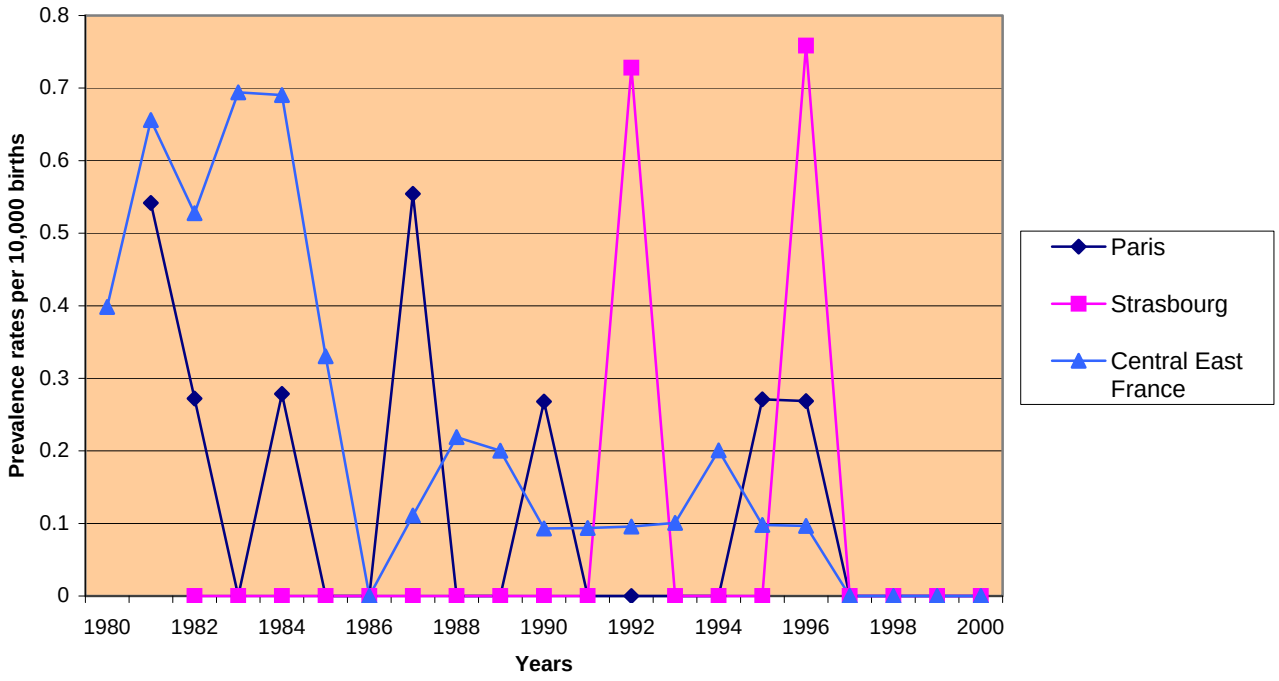
France (Central East France, Paris and Strasbourg): Livebirth Prevalence Rate for Spina Bifida



France (Central East France, Paris and Strasbourg): Total Prevalence Rate for Anencephalus



France (Central East France, Paris and Strasbourg): Livebirth Prevalence Rate for Anencephalus



REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR GERMANY

Prof Volker Steinbicker, Dr Christine Rösch

Folic Acid Supplementation Policy

While many bodies have made recommendations regarding folic acid intake for women planning a pregnancy, there are no official government guidelines on this point.

In 1991 the German Nutrition Society (Deutsche Gesellschaft für Ernährung) published "Recommendations for nutrient intake" which advised 150 μg of folate equivalent daily for adolescents and adults, and 300 μg daily for pregnant women (Deutsche Gesellschaft fur Ernahrung, 1991).

In 1994/95 recommendations published by the German Nutrition Society, the German Society of Obstetrics and Gynecology, the German Society of Human Genetics, the German Society of Pediatrics and Adolescent Medicine, and the German Society of Neuropediatrics advised 400 μg folic acid daily for women wishing a child, and 4000 μg of folic acid daily for women with a previous pregnancy affected with a neural tube defect (NTD). The recommendations specified a period starting four weeks prior to pregnancy and lasting till the end of the first trimester (B Koletzko 1994, B Koletzko 1995a and 1995b).

In 2000 the Societies of Nutrition in Germany (DGE), Austria (ÖGE) and Switzerland (SVE, SGE) published "Reference values for nutrient intake" for the German-speaking countries (Deutsche Gesellschaft fur Ernahrung 2000).

Table 1: Reference values for folic acid intake (Deutsche Gesellschaft fur Ernahrung 2000)

Age groups	Folic acid (μg equivalent daily)
Infants	
0 – 4 months	60
4 – 12 months	80
Children	
1 – 4 years	200
4 – under 7 years	300
7 – under 10 years	300
10 – under 13 years	400
13 – under 15 years	400
Adolescents and adults	
15 – under 19 years	400
19 – under 25 years	400
25 – under 51 years	400
51 – under 65 years	400
65 years and elder	400
Pregnant women	600
Nursing women	600

Food Fortification Policy

In Germany folic acid is classified as a supplementary food, and hence does not fall under drug approval requirements. The *Nährwertkennzeichnungsverordnung* (Nutritive Declaration Regulation) (Thamm 1999) stipulates that 100 g of grain may be fortified with up to 15 per cent of the recommended daily dose of 200 μg of folic acid. However, the maximum daily intake must not exceed three times the recommended daily dose (i.e. 600 μg folic acid).

A major problem in marketing foodstuffs enriched with folic acid is that it is not allowed to refer to potentially beneficial effects on health for advertisement purposes, e.g. "... contributes to the prevention of NTD". (*Lebensmittel- und Bedarfsgegenstandsgesetz* (Law on Foodstuffs and Articles of Consumption) (Thamm 1999).

Among the medical societies in Germany, only the Society of Pediatrics and Adolescent Medicine has published a recommendation for cereal grains enriched with folate (B Koletzko 2000). Some foodstuffs are fortified with folic acid, such as bread, cereal grains and fruit juice. However, there is still no official list in Germany.

On 8 May 2000, a meeting of experts took place in Berlin where the necessity of improving the measures for preventing NTD was discussed. Participants in the meeting included physicians, representatives of malformation registries, politicians, representatives of the food industry, consumer federations, scientists, pharmaceutical firms, and others. However, this meeting failed to establish a common position regarding the fortification of food with folic acid. Instead, the participants decided to form a working group to this end. To date, this working group has not been founded.

Health Education Initiatives

There has been no official health education initiative. Departments of the Federal Ministry of Health, Federal Ministry of Consumer Protection, food and agriculture, and the German Nutrition Society are aiming at improving health knowledge and awareness of the population. Although they have all studied the effects of folic acid intake, a concerted action for improving knowledge in this field has not been launched to date.

Knowledge and Uptake of Folic Acid in Women

- In 2000 a study was performed by Mrs Egen from Munich, comprising two inquiries: (i) during the first inquiry 346 newly delivered women were interviewed in 1996, (ii) the second inquiry interviewing 402 women was performed in 1998. Between 1996 and 1998 an information campaign had taken place. The study results revealed a periconceptional folic acid intake of 400 µg per day in seven women (2%) in 1996, whereas this number was 20 (5%) in 1998 (Egen 1999).

- In the Federal State of Saxony-Anhalt an inquiry was held in maternity hospitals in 1998. A total of 567 women were interviewed after childbirth about whether they had taken folic acid prior to or after confirmed conception. Only 34 women (6%) reported to have taken folic acid prior to conception. A second inquiry was conducted in 2000, comprising a total of 1,224 newly delivered women. The total number of women, who had taken folic acid prior to conception, amounted to only 53 (4.3%) (Heinz 2001).

Knowledge and Practice of Health Care Professionals in Recommending a Supplementary Folic Acid Intake

Gynecologists

- In 1998 Malformation-Monitoring Saxony Anhalt performed an anonymous inquiry among 234 gynecologists regarding pre- and post conceptional administration of folic acid. The questionnaire was returned by 104 gynecologists (44.4%). 76.9% of them said they would administer folic acid after confirmation of conception, whereas 87.5% would recommend preconceptional intake.
- In 1996 a total of 27 gynecologists in Munich were interviewed about their attitude to prophylactic folic acid. Nine gynecologists (38%) recommended taking folic acid preconceptionally, two (8%) recommended taking folic acid at the beginning of pregnancy, four (17%) recommended taking folic acid only in cases with a family history of NTD, whereas nine (37%) did not give any recommendation at all.
- Following an intervention campaign in 1998, 20 (74%) recommended taking preconceptional folic acid, four gynecologists (15%) recommended taking folic acid with the beginning of pregnancy and three (11%) only in case of a family history of NTD (N = 27) (Egen 2000).

Pharmacists

- In 1996 Mrs Egen interviewed 21 pharmacists in Munich about their recommendations for prophylactic folic acid. Eight pharmacists (38%) recommended taking folic acid in the beginning of pregnancy, whereas five pharmacists (24%) did not give any recommendation, and eight pharmacists (38%) recommended a periconceptional intake (Egen 2000).

- In 2000 Malformation-Monitoring Saxony-Anhalt conducted an anonymous inquiry among 598 pharmacists with regard to prophylactic folic acid. Only 104 (17.4%) of the interviewed pharmacists returned the questionnaire, of which 82 pharmacists (79%) recommended both a pre- and post-conceptional folic acid intake. Twelve pharmacists (11.5%) recommended taking folic acid preconceptionally, and eight pharmacists (7.7%) recommended it only in the post-conceptional phase. Two pharmacists (1.8%) did not give any recommendation at all (Kastner 2001).

Nutritional Habits and Other Supplementary Vitamins

- The German Food Consumer Study (Nationale Verzehrstudie 1991) found that the average daily folic acid intake for women was 90 μg folic acid equivalent while for men it was 110 μg folic acid equivalent. The recommended reference value was 150 μg (Heseker 1992).
- The Bavarian Food Consumer Study (Bayerische Verzehrstudie 1995) found that the average daily folic acid intake for women was 80 μg folic acid equivalent (Bayerisches Staatsministerium fur Ernahrung, Landwirtschaft und Forsten1997).
- In the German National Health Interview and Examination Survey (Bundesgesundheitssurvey 1999, Mensink 1998), a total of 1,266 women between 18 and 40 years of age were interviewed. The average daily folic acid intake was 119 μg free folic acid equivalent. The daily intake of 80.6 % of all women was less than 150 μg folic acid. 8.1 % of women in the western federal states (N = 1,231) and 5.5% women in the eastern federal states (N=601) between 18 and 45 years of age were taking multivitamin tablets. 0.6 % were taking folic acid tablets (Heinz 2001).
- The German Nutrition Report 2000 (Ernährungsbericht 2000) (Ernahrungsbericht 2000) stated that the daily intake of folic acid among women was 102.5 μg equivalent. About 70 to 80 % of all people in Germany take less folic acid than recommended.

Women's Sources of Information about Folic Acid

The German National Health Interview and Examination Survey (n = 562) (Bundesgesundheitssurvey 1999, Mensink 1999) found that women heard from the following sources:

- 29.3% physicians
- 28.1% journals

- 14.8% TV
- 9.1% friends
- 8.5% newspapers
- 7.1% health insurance
- 3.1% radio

Egen (1999) interviewed 35 women and found they heard from the following sources:

- 77% gynaecologists
- 14% self-information
- 6% professionals
- 3% genetic counselling

Investigations in Saxony-Anhalt (2000) (Heinz 2001) found that women heard from the following sources:

Sources of information	Prior to pregnancy		During pregnancy	
	N = 227	Rate In percent	N = 1,057	Rate in percent
Physicians	137	60.4	784	74.2
Radio/ TV/ journals	44	19.4	51	4.8
Books	33	14.5	61	5.7
Friends	30	13.2	47	4.4
Others	17	7.5	28	2.7
Partner	13	5.7	28	2.6
Relatives	13	5.7	25	2.4
Pharmacists	11	4.8	27	2.6
Information centre	0	0	6	0.6

Proportion of Pregnancies which are Planned

- Mrs Egen conducted a study comprising 131 newly delivered women, of which 94 women (72%) confirmed that they had planned their pregnancy. In 1998 Mrs Egen interviewed 118 newly delivered women. Out of them 80 women (68%) had planned their pregnancy (Egen 1999).
- In 1998 a study was performed in Saxony-Anhalt, comprising 567 newly delivered women who were asked whether or not their pregnancy had been intended. A total of 391 (69%) of the women confirmed that their pregnancy had been planned. Again, in 2000 a study was conducted in Saxony-Anhalt in the course of which 1,224 newly delivered women were interviewed. 806 (66%) answered that their pregnancy had been planned.
- From October 1997 to March 1999 the first German Health Survey was carried out (German National Health Interview and Examination Survey) (Bundesgesundheitssurvey 1999, Mensink 1998). One point of this study was "Subjective Statements on the Daily Intake of Drugs from Selected Drug Groups". For women between 18 and 45 years of age the following ranking of drug use was established: (i) in the western federal states 30% oral contraceptives, 11.5% thyroid drugs, 8.1% vitamins; (ii) in the eastern federal states 47% oral contraceptives, 10% thyroid drugs, 5.5% vitamins (Knopf 1999).

Molecular-Genetic Investigations

Under the German National Health Interview and Examination Survey (Bundesgesundheitssurvey 1999) 994 women were checked for the presence of a C677T mutation. 421 women (42.4%) did not show any mutation. 455 women (45.7%) were heterozygous and 118 (11.9%) were homozygous for the C677T mutation. These women exhibited a significantly higher homocysteine level (Thamm, M – personal information).

Laws Regarding Termination of Pregnancy

In Germany, termination of pregnancy is allowed irrespective of gestational age, if the pregnancy poses a serious threat to the pregnant woman’s physical or mental health, or if the fetus is affected by malformations.

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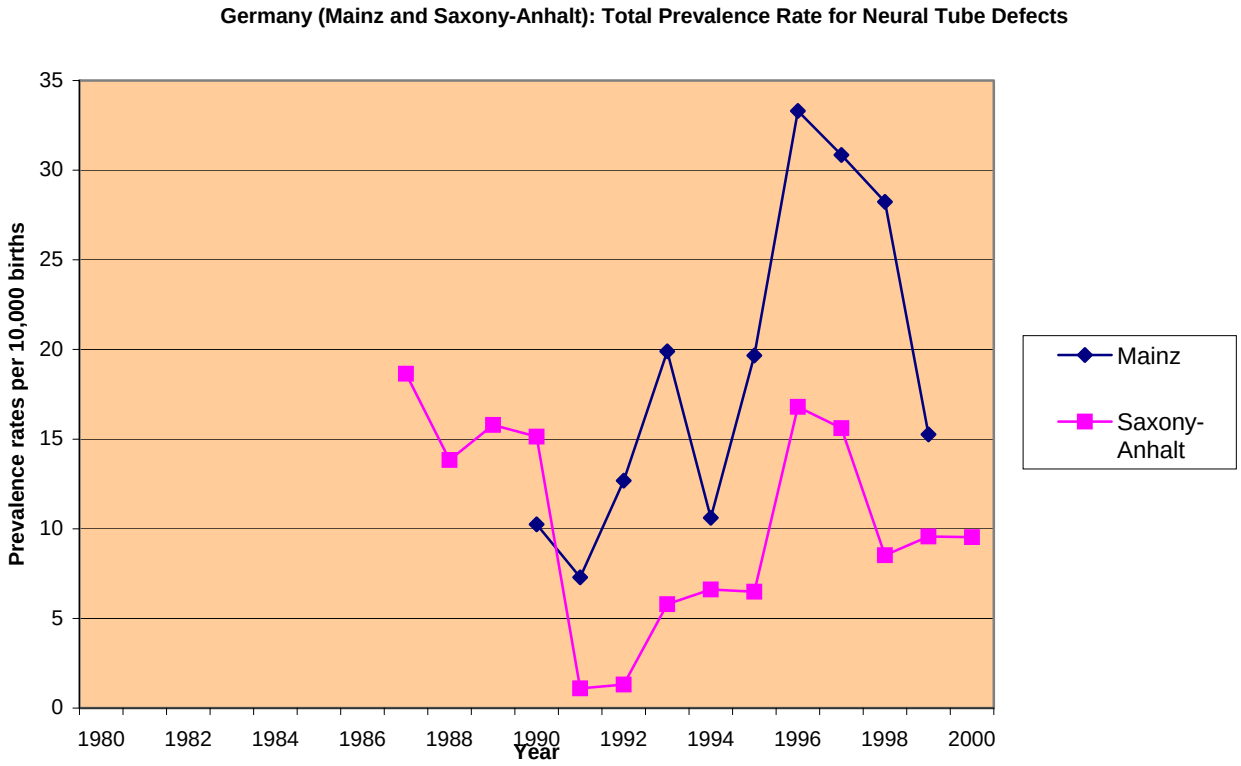
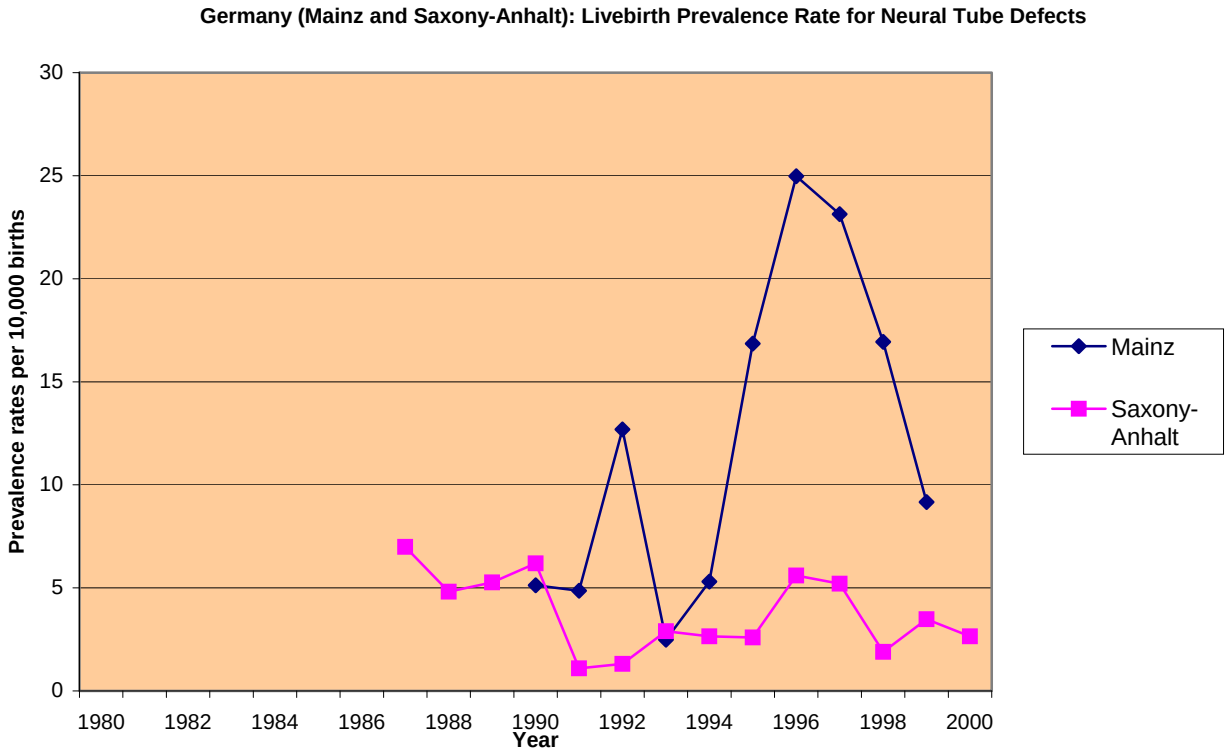
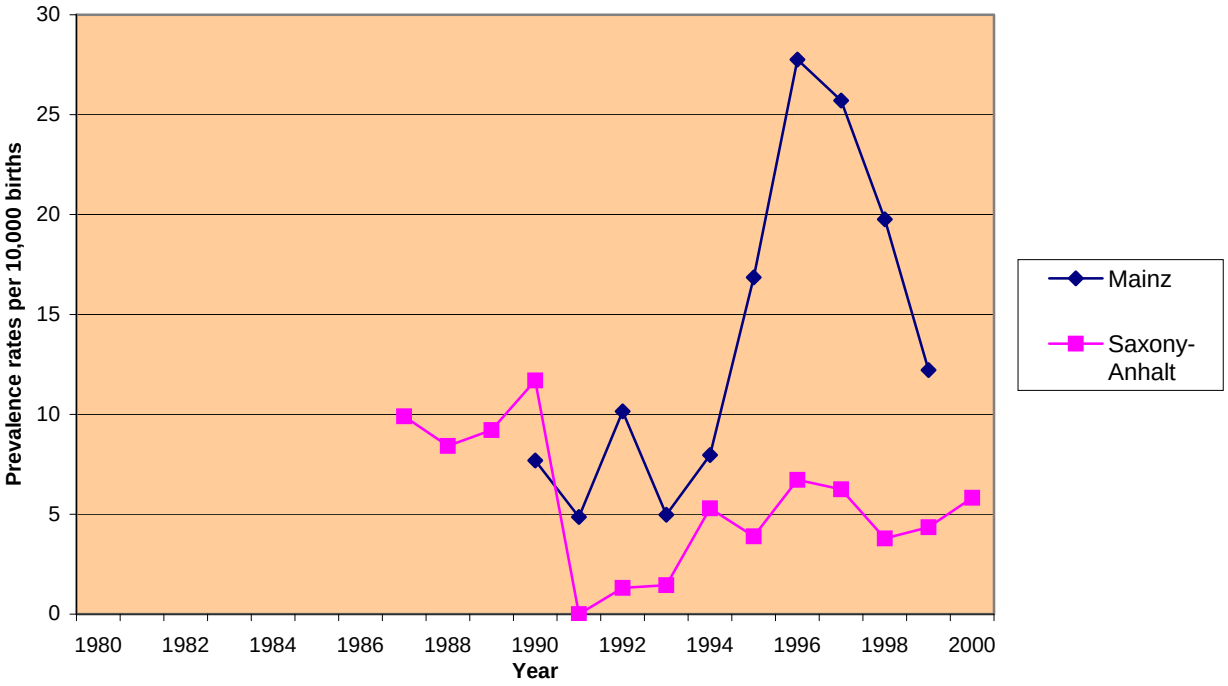

Germany (Mainz and Saxony-Anhalt): Total Prevalence Rate for Neural Tube Defects
Prevalence rates per 10,000 births
0
5
10
15
20
25
30
35
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
Mainz
Saxony-Anhalt

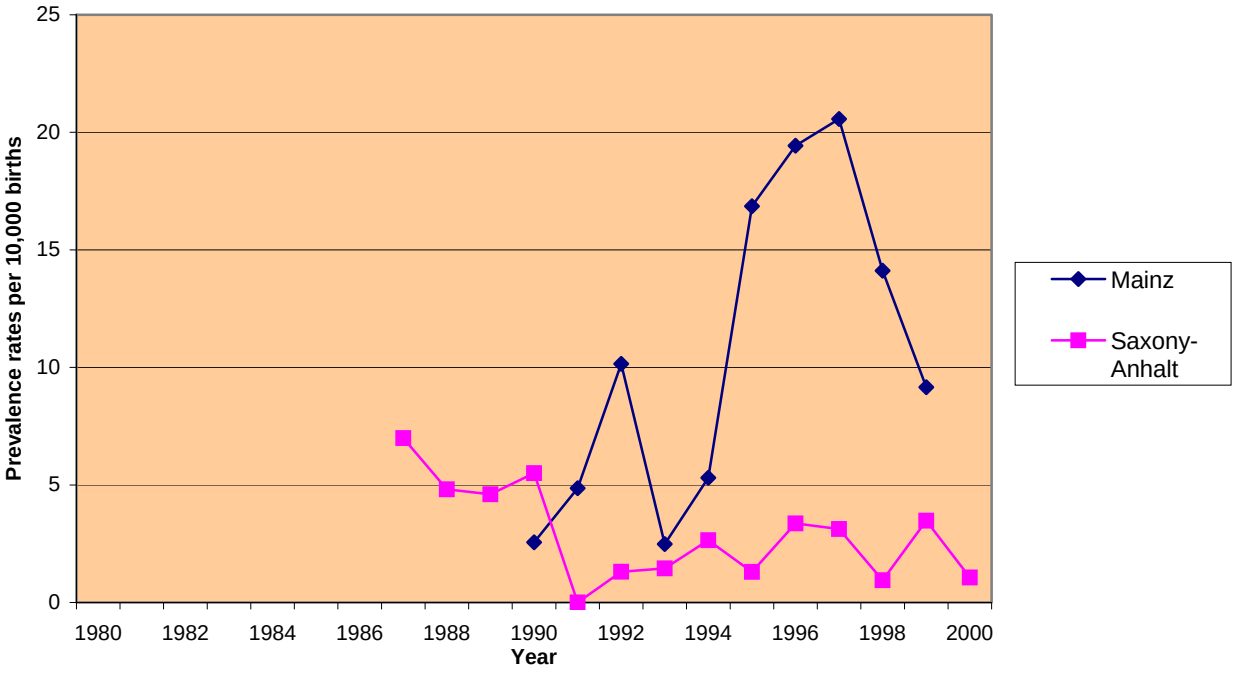

Germany (Mainz and Saxony-Anhalt): Livebirth Prevalence Rate for Neural Tube Defects
Prevalence rates per 10,000 births
0
5
10
15
20
25
30
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
Mainz
Saxony-Anhalt

check data

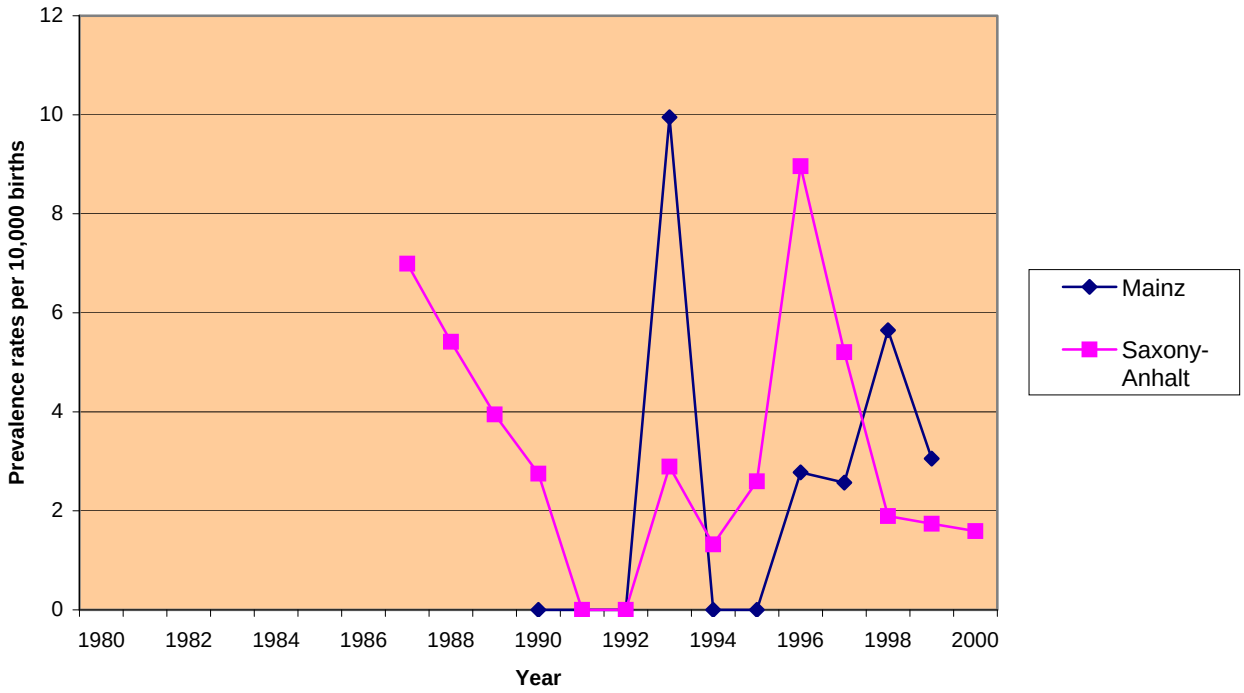
Germany (Mainz and Saxony-Anhalt): Total Prevalence Rate for Spina Bifida



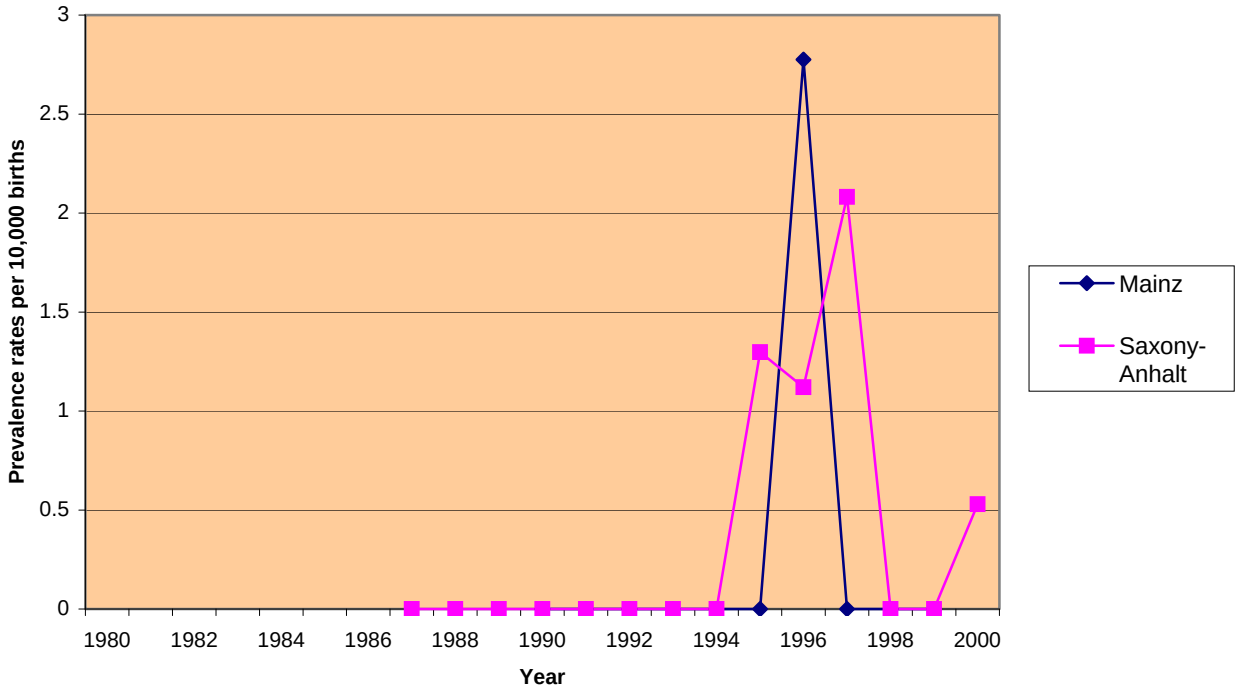
Germany (Mainz and Saxony-Anhalt): Livebirth Prevalence Rate for Spina Bifida



Germany (Mainz and Saxony-Anhalt): Total Prevalence Rate for Anencephalus



Germany (Mainz and Saxony-Anhalt): Livebirth Prevalence Rate for Anencephalus



REPORT ON FOLIC ACID SUPPLEMENTATION FOR REPUBLIC OF IRELAND

Dr Robert McDonnell

Folic Acid Supplementation Policy

Recommendations were made by the Irish Department of Health in 1993 that if there is any possibility of pregnancy, a woman should take an additional 400 μg of folic acid daily prior to conception and during the first twelve weeks of pregnancy. The preferred means of supplementation is by a daily folic acid tablet. The policy is promoted through the Department's Health Promotion Unit by way of leaflets and promotion campaigns.

Food Fortification Policy

Voluntary fortification of foods (particularly cereal and milk) by food producers has been in existence for a number of years. Although there is no mandatory food fortification of staple foods at present, the Food Safety Advisory Board of Ireland (an official body) in a 1998 report[1] to the Minister for Health recommended that food fortification should be considered as a complimentary measure to supplementation (rather than an alternative). However, a recent and ongoing controversy on the fluoridation of water supplies has not provided an ideal scenario for the mandatory fortification of foods at this stage.

Health Education Initiatives

A folic acid promotional campaign has been in operation since the official recommendations on folic acid came into being in 1993. The most recent high profile promotion of folic acid consisted of a joint cross-border initiative between the Departments of Health in the Republic of Ireland and Northern Ireland in late 2000 and early 2001. This was a media campaign lasting some months with prime-time television and radio advertisements, and also involved daily newspapers. At a more local level, health promotion units and public health departments in the regional health boards undertake promotion of folic acid through a variety of channels, generally on an on-going basis. The Health Promotion Unit of the Irish Department of Health has undertaken much of this work at a national level.

Folic Acid Knowledge and Uptake

There have been studies on folic acid awareness and uptake since 1995. The table below summarises the results of studies (Milner et al 1996, Sayers et al 1997, McDonnell et al 1999a and 1999b, McDonnell et al 2000, O'Leary et al 2001) of women attending their first ante-natal visit in maternity hospitals in Dublin. The sample sizes in the studies from 1996-2000 were of 300 respondents each, using the same questionnaire, with core questions as shown in the table. In addition, there was also a community survey of women of child-bearing age in 1995 (Sayers et al 1997) in Dublin. This showed that 63% had heard of folic acid but less than 3% were currently taking it. These studies mainly asked about daily folic acid tablet intake, without explicitly asking about vitamin intake.

Studies of Folic Acid Knowledge and Uptake in Ireland 1995-1999

Year	1995	1996	1997	1998	1999	2000
Heard of folic acid	50%	54%	76%	88%	91%	92%
Knew folic acid can prevent spina bifida NTD	25%	21%	44%	57%	64%	67%
Took folic acid periconceptionally	5%	6%	16%	21%	22%	18%

There has also been a study of folic acid in another health board region of Ireland (Howell et al 1997), in the north-east, with similar findings. A national study (unpublished) of folic acid knowledge and use was undertaken in 1997/98. This showed that 93% or women had heard of folic acid and 75% knew it could prevent NTD; 30% had taken folic acid or a vitamin containing folic acid before pregnancy, (approximately 23% in the form of folic acid tablets and 7% as multivitamin preparations).

Although there has not been a survey among health care professionals, it is likely that virtually all are aware of the recommendations considering the high profile folic acid promotion campaigns that have taken place, and the high level of knowledge among women of child-bearing age, the source of which is frequently a health professional.

Proportion of Pregnancies which are Planned

The studies in the above table showed that the proportion of women planning their pregnancy has been stable from 1995-1999 at 40-45%.

Laws Regarding Termination of Pregnancy

Termination of pregnancy is not legal in Ireland except in the most extreme circumstances. It is never allowed because of fetal abnormality. The number of women who may go abroad for terminations because of fetal abnormality is not known.

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Sayers G, Scallan E, Mc Donnell R, Johnson Z. **(1997)** Knowledge and use of periconceptional folic acid among ante-natal patients. Irish Med Journal; Vol 90, No 6, pp 236-238.

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McDonnell R, Johnson Z, Doyle A, Sayers G. **(1999)** Determinants of folic acid knowledge and use among antenatal women. Journal of Public Health Medicine; Vol 21, pp 145-49.

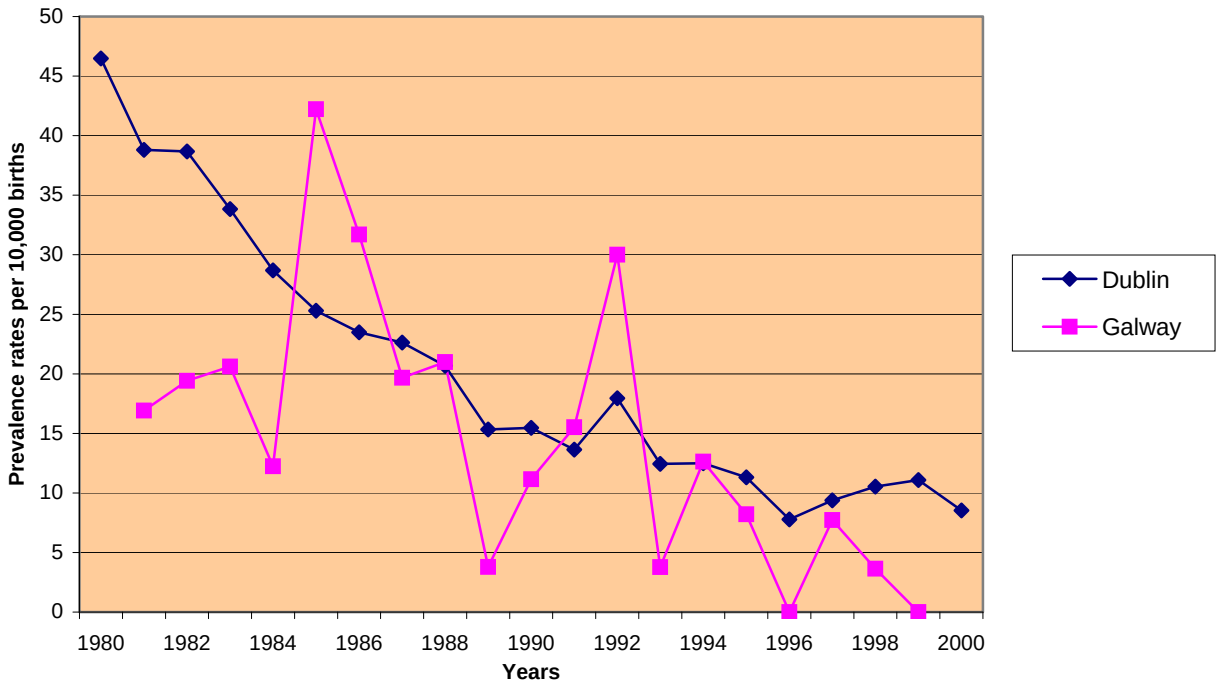
Mc Donnell R, Ward M, O'Leary M. **(2000)** Trends in knowledge and use of folic acid in the five year period 1996-2000. 6th European Symposium on the prevention of congenital anomalies. Catania, Sicily.

O'Leary M, Mc Donnell R, Johnson H. **(2001)** Folic acid and prevention of Neural Tube Defects in 2000: Improved awareness – low periconceptional uptake. Irish Medical Journal; Vol 94, No 6, pp 180-182.

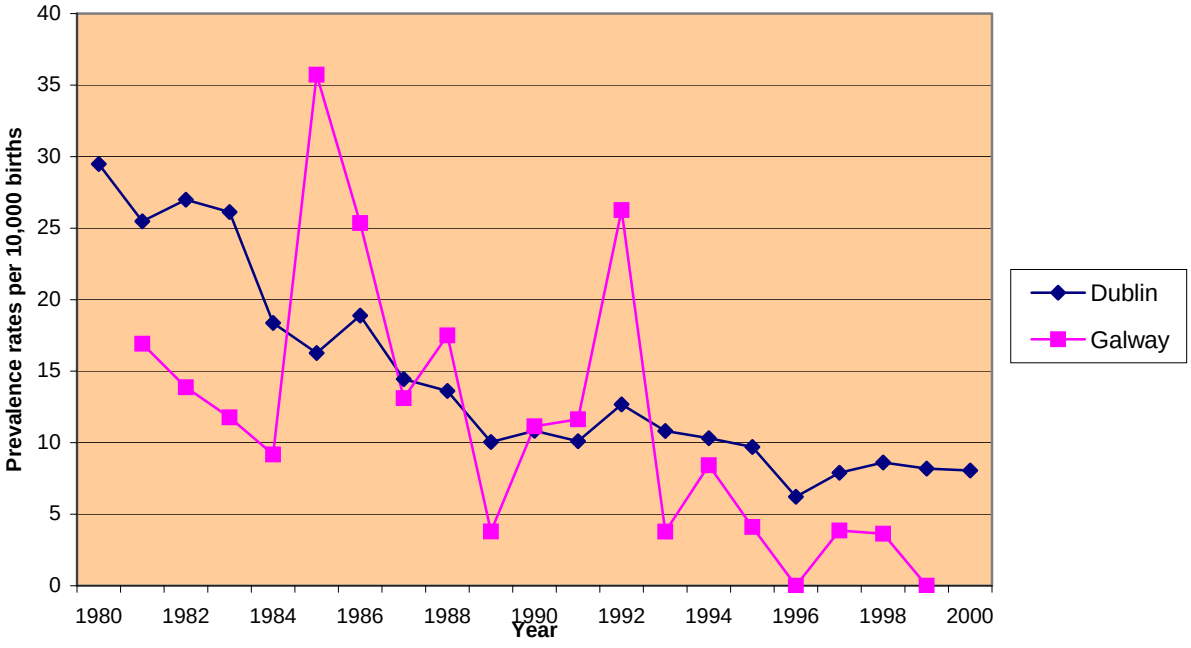
Sayers G, Hughes N, Scallan E, Johnson Z. **(1997)** A survey of knowledge and use of folic acid among women of child bearing age in Dublin. Journal of Public Health Medicine; Vol 19, No 3, pp 328-332.

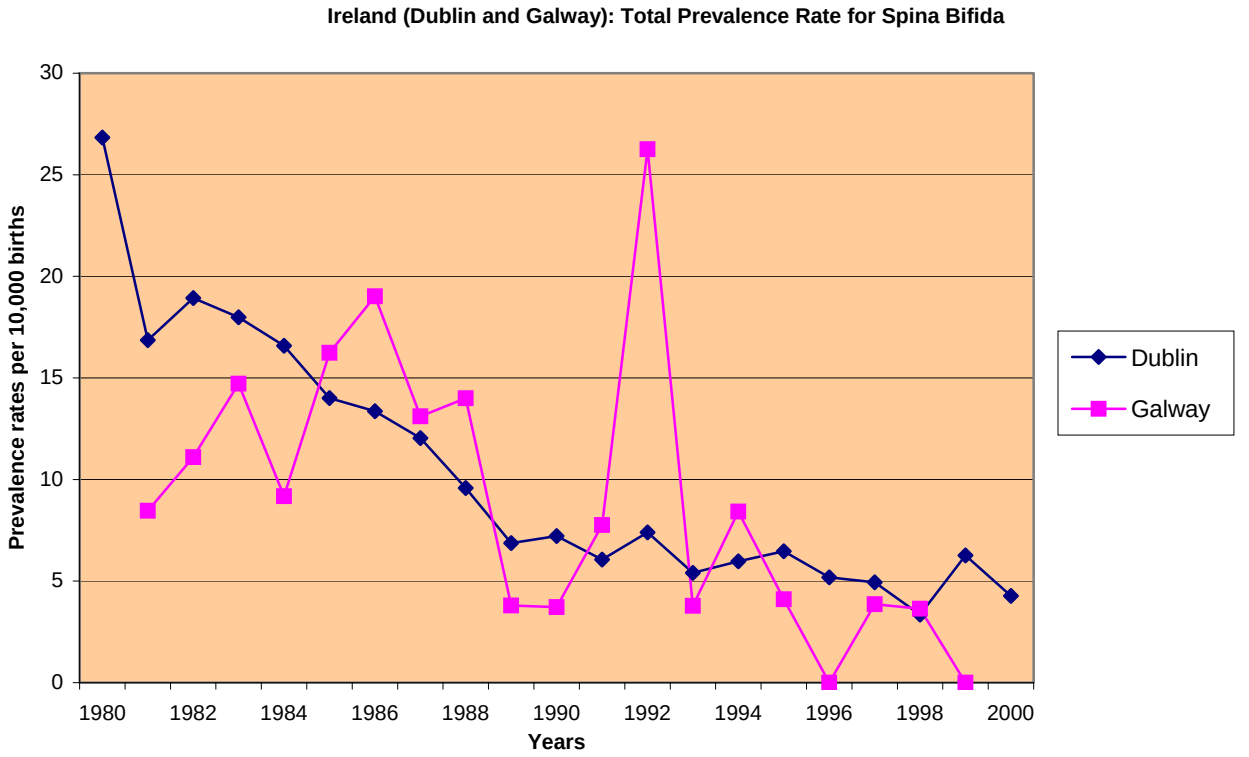
Howell F, Bedford D, O'Keffe B, Corcoran R. **(1997)** Folic acid and prevention of neural tube defects. Lancet; Vol 350, No 9078, pp 664-5.

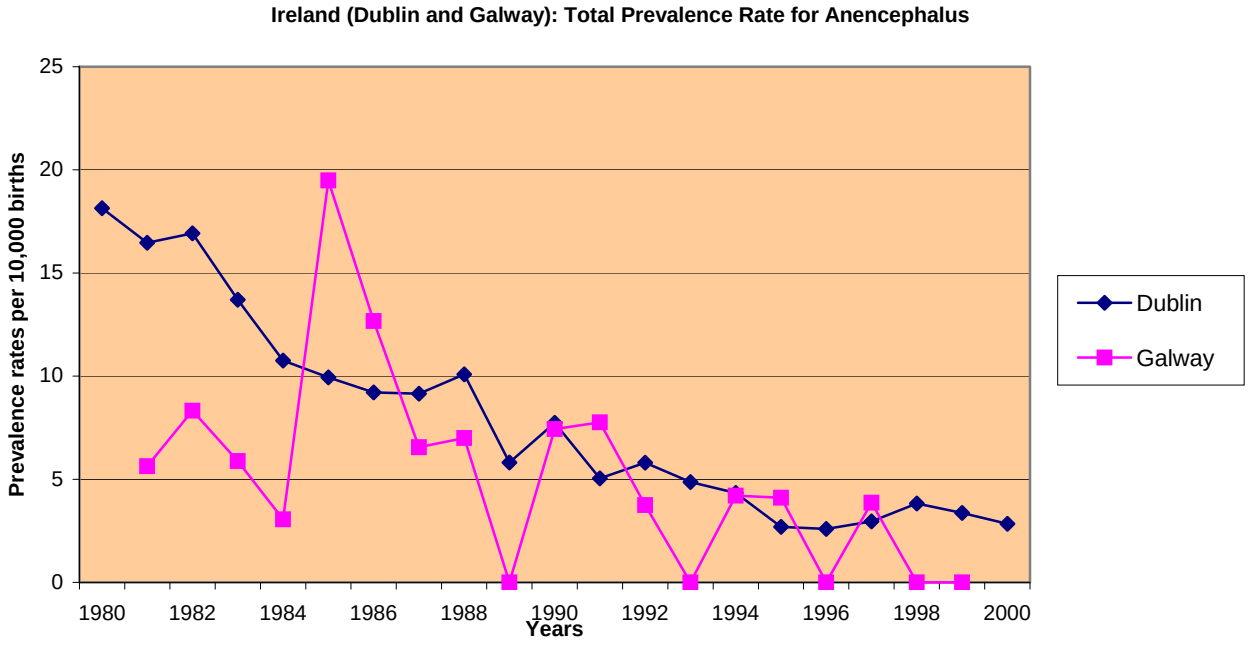
Ireland (Dublin and Galway): Total Prevalence Rate for Neural Tube Defects



Ireland (Dublin and Galway): Livebirth Prevalence Rate for Neural Tube Defects




Ireland (Dublin and Galway): Total Prevalence Rate for Spina Bifida
Prevalence rates per 10,000 births
30
25
20
15
10
5
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Years
Dublin
Galway


Ireland (Dublin and Galway): Total Prevalence Rate for Anencephalus
Prevalence rates per 10,000 births
25
20
15
10
5
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Years
Dublin
Galway

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR ITALY

Prof E Calzolari, Dr G Cocchi, Dr A J Neville

Folic Acid Supplementation Policy

There is not a guideline or official recommendation for folic acid supplementation in Italy. When considering the factors to be assessed in a decision to introduce a preventative health policy, the size of the problem must be weighed against safety and efficacy. The lack of policy in Italy is a reflection of the low neural tube defect (NTD) prevalence in the country, the wide use of prenatal diagnosis, and the political and economic problems related to aging taking priority on the public health agenda. It appears there is no balance between cost/effectiveness in the implementation of a folic acid policy. See details in report of BIOMED II (Goujard 2001).

Folic acid supplements are on sale in Italian pharmacies. 0.4mg alone is the dose for some preparations, but higher doses (5 to 15mg tablets) are available on prescription. The 0.4mg dose is also available as part of a multivitamin pill (Litrison-Roche), whilst lower doses are included in other multivitimin pills available over the counter. Combinations of 0.4mg or 0.8mg of folic acid combined with ferritin and B12 are also available (Ferrolin, Ferrotre)

Food Fortification Policy

There is not an official food fortification policy. There are food products on sale which are enriched with folate or folic acid derivatives, eg Kellogg Cornflakes and other breakfast cereals, cereal bars (eg Cerealix, Barilla) but there are no recommendations. In Italy there is nothing comparable to the USA Food and Drug Administration (FDA) to manage or introduce a policy. Food additives are regulated at a national level by a Ministerial Decree (27.02.96 no. 209) which recognises the CE directives.

Health Education Initiatives

There is not, and has not been, an official health education initiative in Italy. Some scientific societies such as the Society of Gynecologists and Obstetricians have published advice and recommendations in their bulletins but not in an official manner. Prescribing habits for folic acid vary widely within the country.

Knowledge and Uptake about Folic Acid

To our knowledge no national epidemiological studies have been conducted.

At a regional level the following studies have been reported:

1. A study was conducted at the Obstetric Clinic of Bologna (Cocchi et al 2000)) on the percentage of women who had correctly consumed folic acid in the periconceptional period. In the early part of the study 3.5% of women took folic acid correctly; a year later 5% did so.

2. Details of the study entitled "Primary prevention of neural tube defects: lack of information about folic acid supplementation in Italy: Emilia-Romagna region" (Cocchi 2000) looked at knowledge and uptake of folic acid. *Objective*: To detect the level of knowledge of women of childbearing age about the ability of folic acid (FA) supplementation to reduce the risk of having a pregnancy affected by neural tube defects (NTD). To administer an ad hoc questionnaire prepared in relation to the goals of the BIOMED Project and conduct a survey in Bologna (one of the centres of the IMER Registry, Italy) on the policy of consuming FA before conception (at least 2 months) and in the first quarter after conception. *Design*: An educational campaign about the health benefits of periconceptional consumption of FA and reduction of the risk of NTD. *Participants*: A sample of women in hospital for delivery during November and December 1999. The questionnaire, in Italian, was given to 302 women with healthy babies who were randomly selected. The collected information included data about maternal age, parity, education, smoking use, knowledge of the effect of FA and of food intake, changes in diet during pregnancy, and consumption of FA or a FA-containing multivitamin, specifically related to the period of consumption. *Main outcome measures*: Number of women who were aware of the FA recommendations, number who were aware of what FA is, who advised them about the benefits of FA, and when FA should be taken. *Results*: The same doctor interviewed 302 women in the 2-month period. Only 9 women (2.9%) took FA correctly, in the perinatal period. These 9 women tended to be informed by their gynecologist about FA preventive effect for NTD, tended to have a higher education level (university) (χ^2=8.920; 2 gdl; p=0.0012) and tended to be older (> 30 years) (χ^2=9.364; 2 gdl; p=0.009). *Conclusions*: These results demonstrate the lack of

medical information in Italy about the preventive effect of FA and the necessity of carrying out information campaigns addressed to gynecologists, general practitioners and to all women in childbearing age

3. In Sicily a study (Ginecol 1999) was carried out on periconceptional folic acid intake by Sicilian couples at increased risk of NTD. The authors conclude that pregnant Sicilian women at risk for recurring NTD interviewed by the authors were not aware of the possible prevention of NTD using folic acid supplements during the periconceptional phase. In the study period, January 1997 until December 1998, 18 couples were identified as being at risk for recurring NTD. A further 15 couples showed a positive family history for NTD. Of 11 planned pregnancies, none of the pregnant women took folic acid during the periconceptional phase. A similar level of ignorance was found in a study conducted by the Emilia Romagna region (2). Details of this study:"Periconceptional folic acid intake by Sicilian couples at a risk of recurrence of NTD" BACKGROUND AND AIM: The authors aimed to evaluate the frequency with which pregnant Sicilian women with a high risk of recurring neural tube defects (NTD) attending the Ultrasonography and Prenatal Diagnosis Clinic in the Department of Diagnosis and Treatment at Ospedale S. Bambino in Catania were aware of the preventive effect of folic acid supplements during the periconceptional period and whether they therefore took folic acid supplements before the next pregnancy. *METHODS*: All pregnant women undergoing ultrasonography between January 1997 and December 1998 were interviewed. It was noted whether any earlier offspring had suffered from NTD or whether relatives (sisters, brothers, parents) had suffered from a NTD. They were also asked whether they knew about the preventive effect of periconceptional folic acid supplements on the development of NTD, whether their pregnancy was planned and whether they had taken periconceptional folic acid supplements and, if so, at what dose. *RESULTS*: Eighteen couples were identified as being at risk for recurring NTD: 3 cases had an earlier pregnancy resulting in NTD (2 cases of spina bifida and 1 case of anencephalus) with a negative family history for NTD; a further 15 couples showed a positive family history for NTD. None of the women were aware of the preventive effect of folic acid supplements during the periconceptional period on the development of NTD. Out of 11 planned pregnancies, none of the pregnant women took folic acid during the periconceptional phase. CONCLUSIONS: Pregnant Sicilian women at risk for

recurring NTD interviewed by the authors were not aware of the possible prevention of NTD using folic acid supplements during the periconceptional phase.

Laws Regarding Termination of Pregnancy

Voluntary termination of pregnancy became legal in Italy in 1984. Termination because of a congenital anomaly can be done until gestational age of 23-24 weeks. A psychiatric report is required. Termination of pregnancy is allowed only in NHS hospitals, not in private clinics.

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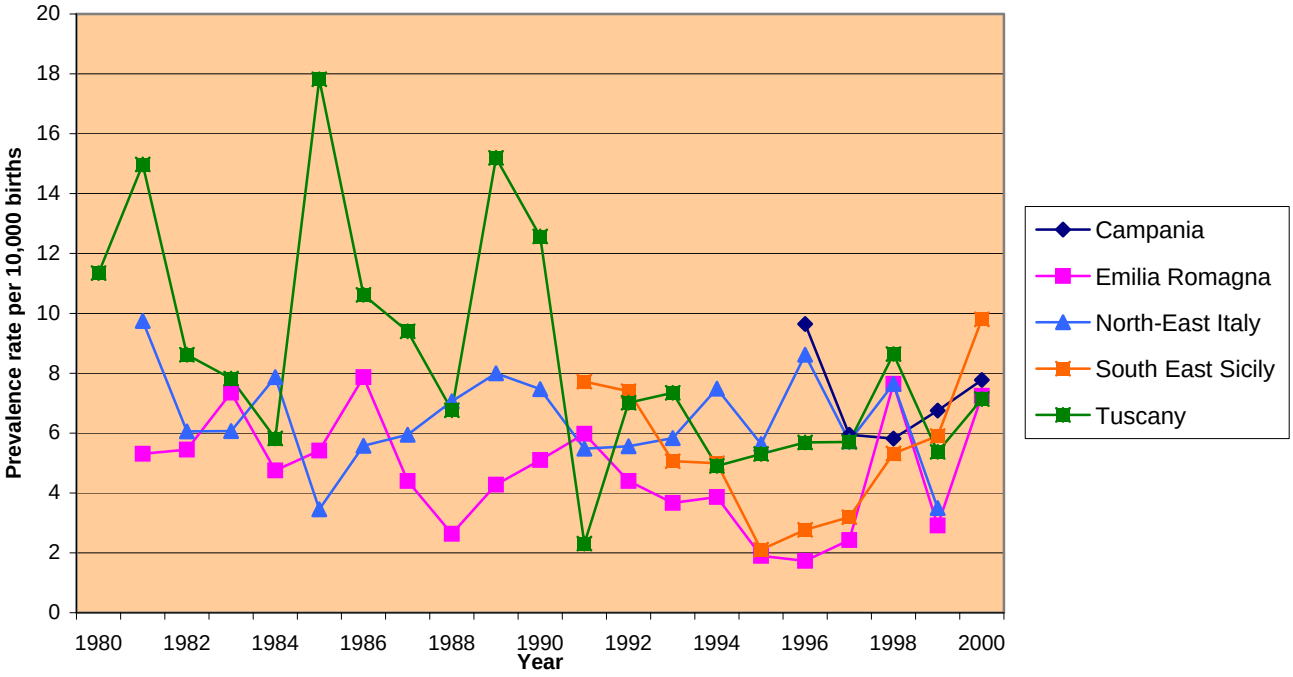
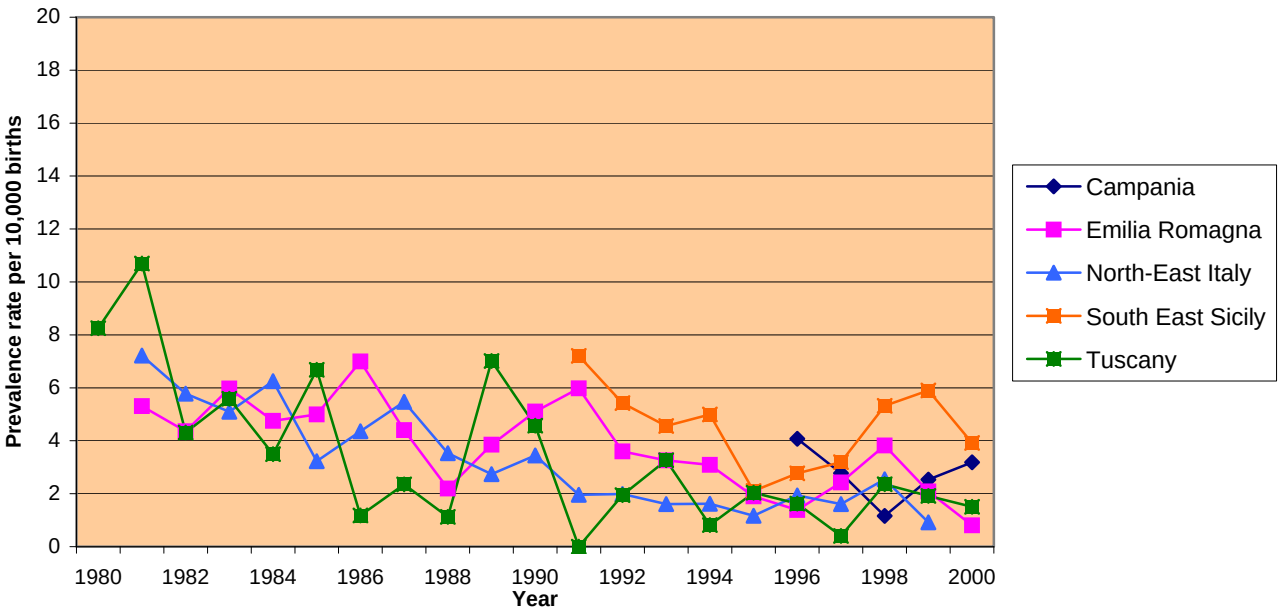
2. Guido Cocchi, S. Gualdi, P.M.A. Mammoliti, L. Piccolo, C. **(2000)** Primary prevention of neural tube defects: lack of information about folic acid supplementation in Italy: Emilia-Romagna region; La RosaInstituto Clinico di Pediatria Preventiva e Neonatologia, Università degli studi di Bologna, Italy, Supported by Grants of EC: NTD & Primary prevention strategies: European Medical Research Concerted Action. Biomed 2. 1st International Symposium on Prevention and Epidemiology of Congenital Malformations.Cardiff, September 15-16. Frontiers in Fetal Health Vol 2, pp 9-11
3. Minerva Ginecol **(1999)** [Periconceptional folic acid intake by Sicilian couples at a risk of recurrence of NTD][Article in Italian] Pepe F, Pepe P, Grillo S, Insolia G. I Divisione di Diagnosi e Cura Ambulatorio di Ecografia e Diagnosi Prenatale, Ospedale di Maternita S. Bambino, Catania.Vol 51, No 10, pp 399-401

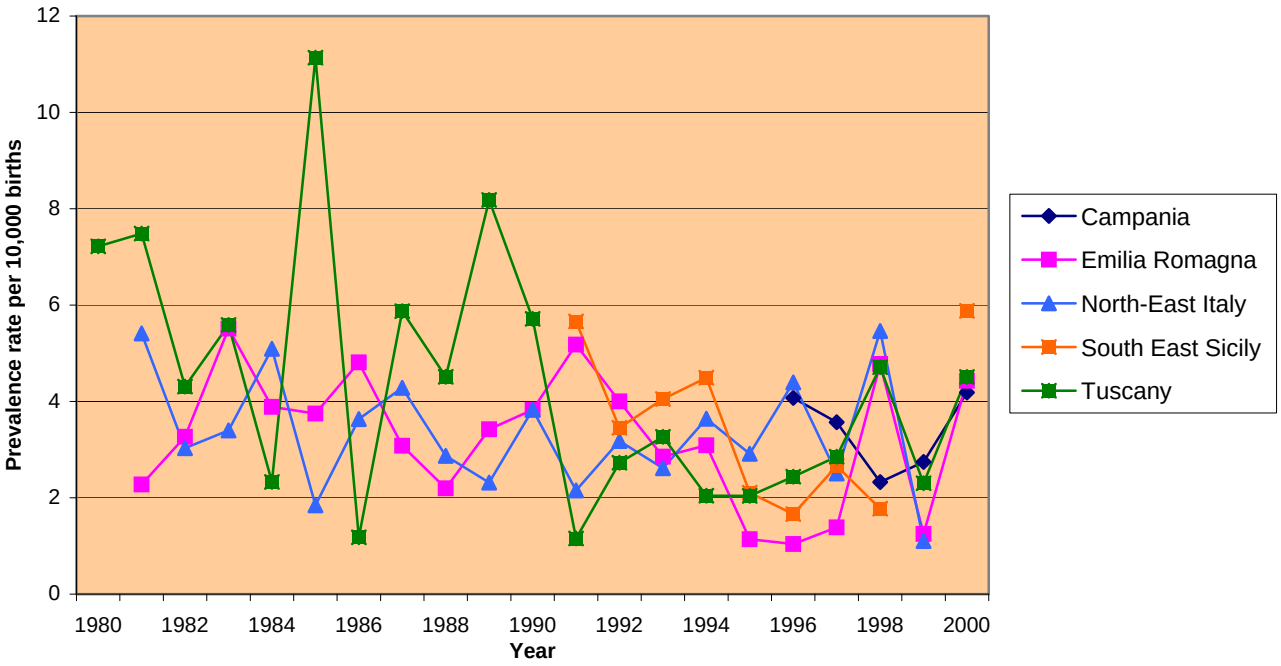
Italy (Campania, Emilia Romagna, North East Italy, South East Sicily and Tuscany): Total Prevalence Rate for Neural Tube Defects



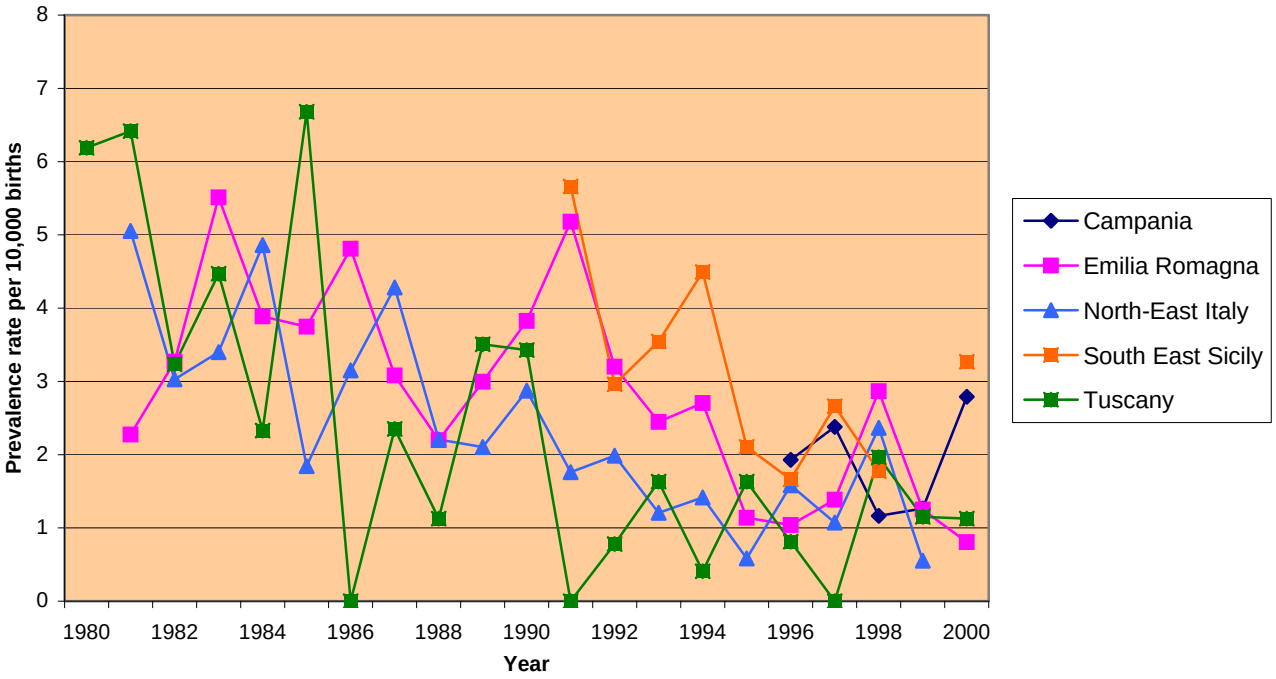
Italy (Campania, Emilia Romagna, North East Italy, South East Sicily and Tuscany): Livebirth Prevalence Rate for Neural Tube Defects



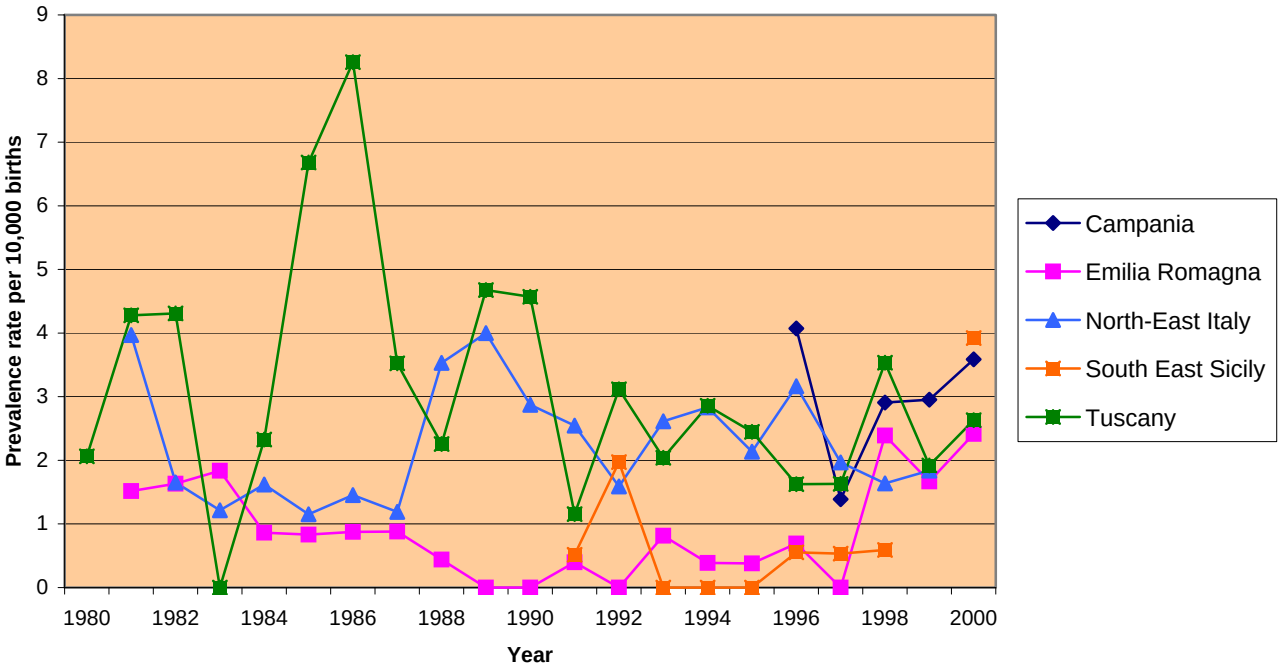
Italy (Campania, Emilia Romagna, North East Italy, South East Sicily and Tuscany): Total Prevalence Rate for Spina Bifida



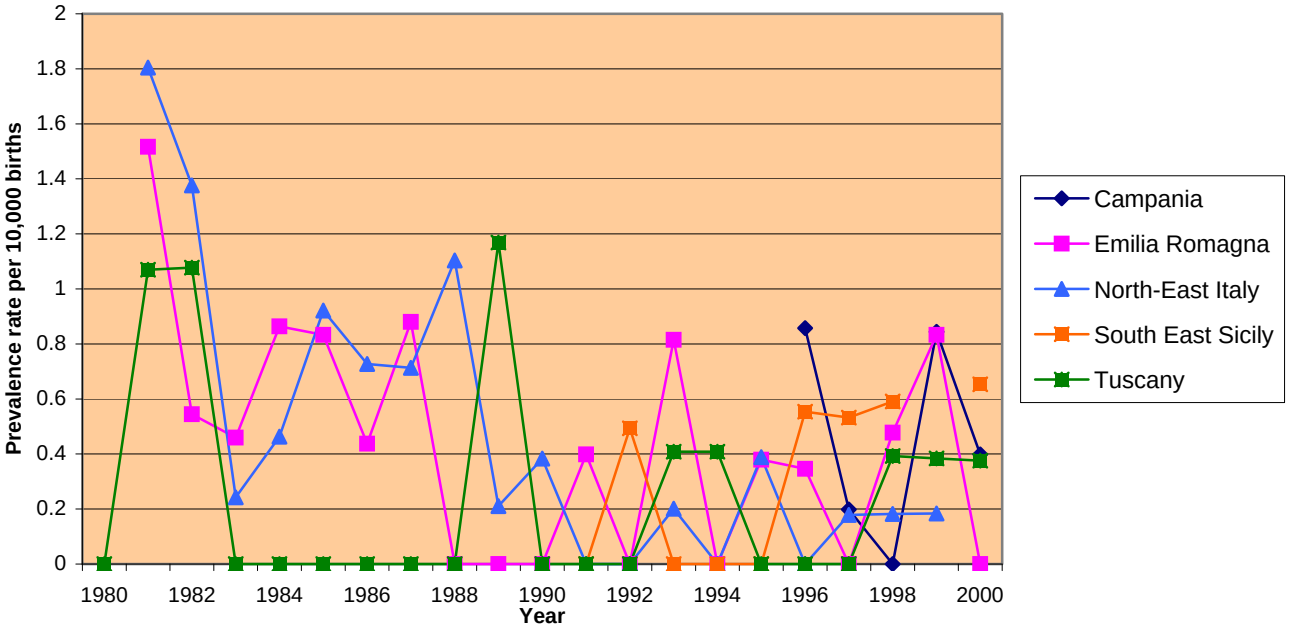
Italy (Campania, Emilia Romagna, North East Italy, South East Sicily and Tuscany): Livebirth Prevalence Rate for Spina Bifida



Italy (Campania, Emilia Romagna, North East Italy, South East Sicily and Tuscany): Total Prevalence Rate for Anencephalus



Italy (Campania, Emilia Romagna, North East Italy, South East Sicily and Tuscany): Livebirth Prevalence Rate for Anencephalus



REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR MALTA

Dr Miriam Gatt

Folic Acid Supplementation Policy

In Malta an official policy regarding increasing folate in the diet was introduced in 1994. The policy advises that pregnant women and women intending to become pregnant should increase their intake of foods rich in folate. This is a Department of Health Circular No. 36/94

Food Fortification Policy

There is no official food fortification policy and none is being planned. However, a wide variety of imported fortified cereals and malted drinks are available. Cereals are relatively expensive locally and may not be accessible to people of all income brackets. Fortified breads are not readily available.

Health Education Initiatives

No official Department of Health Promotion campaigns have been undertaken, but GPs, gynecologists, midwives and organised antenatal courses inform women of the benefits of folic acid. The official dietary policy mentioned above was aimed to inform and educate health professionals. A health promotion officer is currently (2002) presenting his postgraduate research investigating the needs of a national health promotion campaign to raise awareness of the benefits of periconceptional folic acid supplementation among sexually active Maltese women of childbearing age. This research utilises the data collected during a folic acid survey conducted in 1999-2000 as part of the needs assessment [1]. It is envisaged that following the results of this research, a health promotion campaign regarding periconceptional folic acid will be launched officially in Malta.

Folic Acid Awareness and Uptake

A study regarding folic acid awareness in Maltese mothers was undertaken between October 1999 and February 2000 (Gatt 1999). The results were published as a report from the Malta Congenital Anomalies Register . Of the mothers interviewed in the study, 72% had known that folic acid was important in pregnancy. 15% of mothers took folic acid supplementation prior to pregnancy; another 59% of mothers started folic acid after conception but before 12

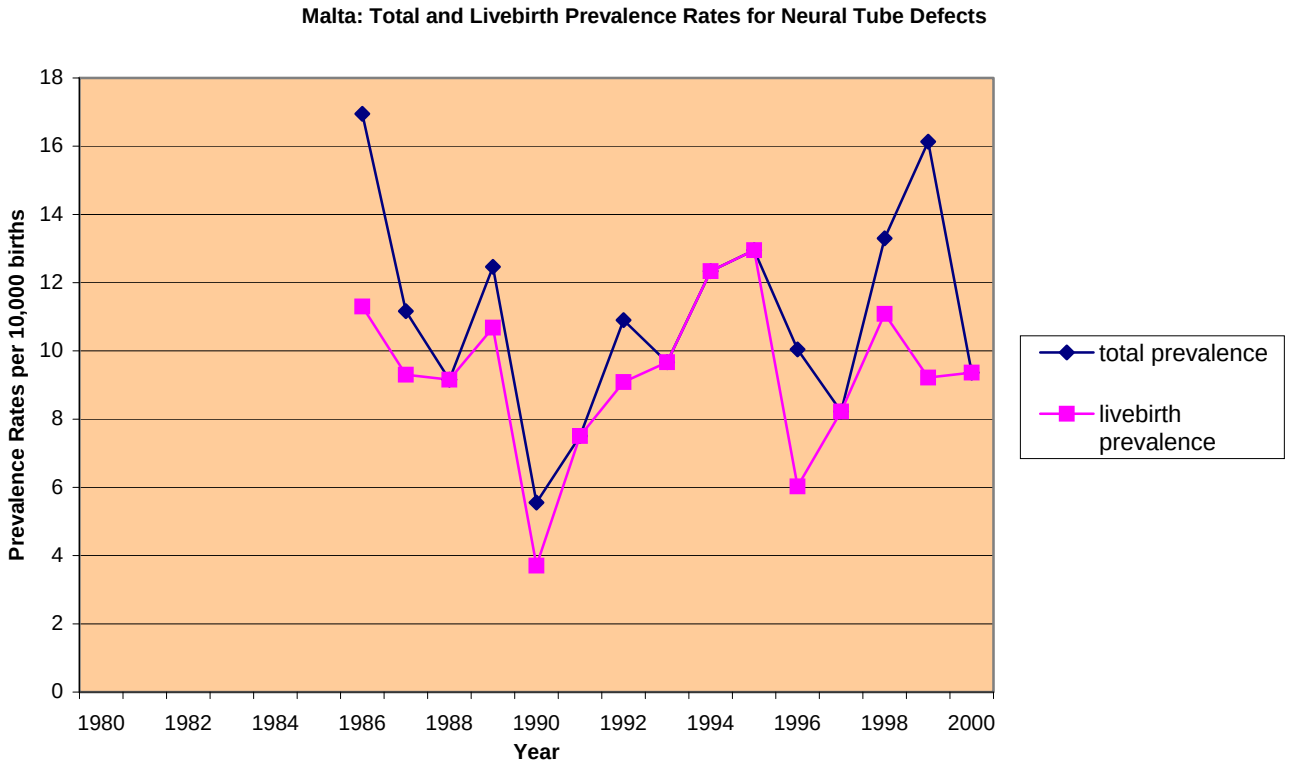
weeks of gestation. 35% said that they had changed their diet during pregnancy, increasing their folate intake.

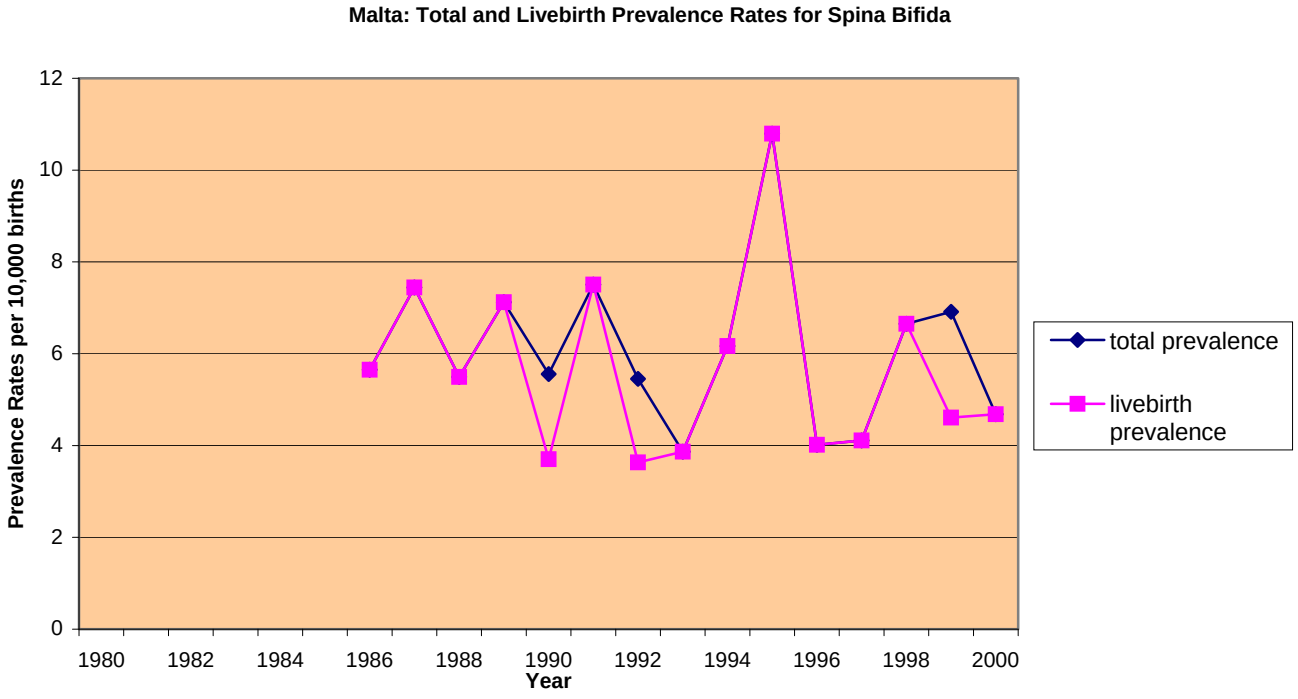
Laws Regarding Termination of Pregnancy

In Malta, termination of pregnancy is not legal.

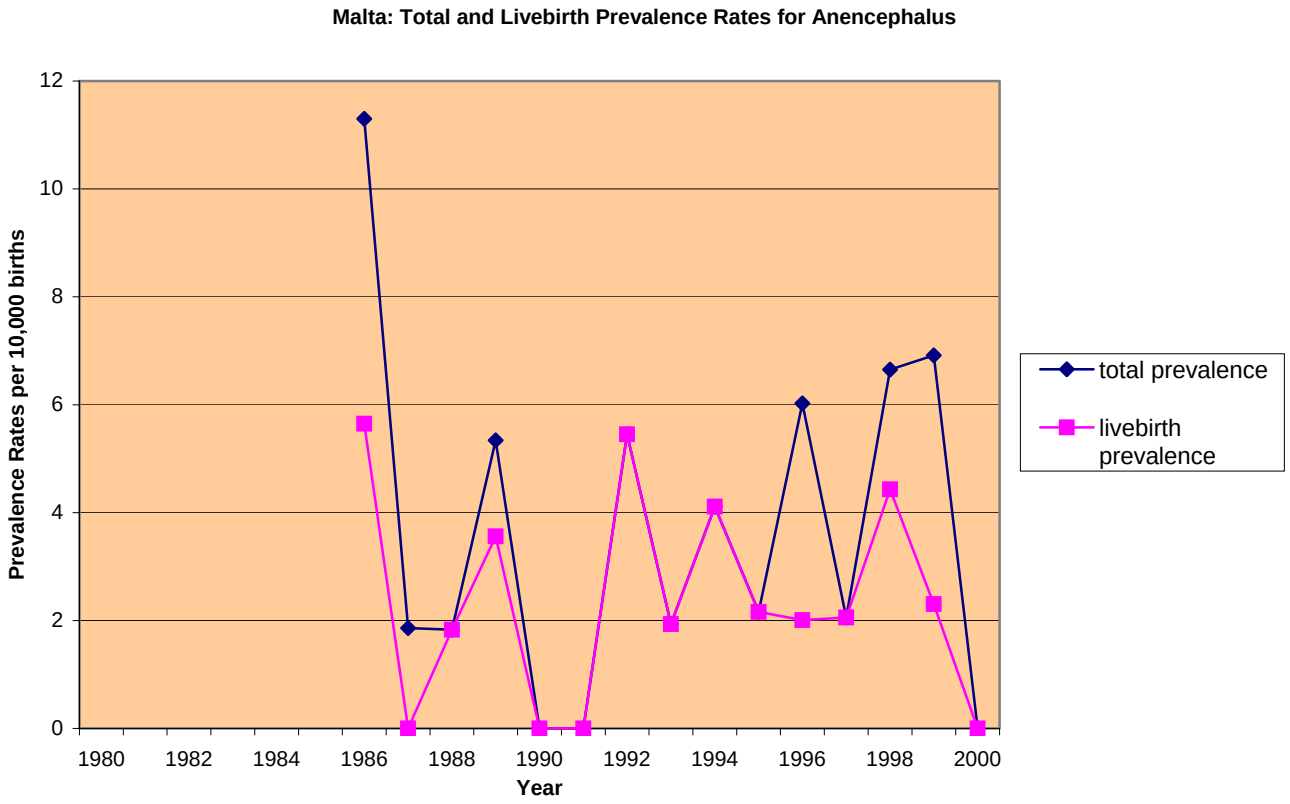
References:

Gatt M **(1999)** Periconceptional Folic Acid Supplementation in Malta, in 'Half Yearly Report of Malta Congenital Anomalies Register, Malta Congenital Anomalies Registry, Department of Health Information.





† Where only one line appears, the total prevalence and the live birth prevalence are the same.


Malta: Total and Livebirth Prevalence Rates for Anencephalus
Prevalence Rates per 10,000 births
12
10
8
6
4
2
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR THE NETHERLANDS

Dr HEK de Walle

Folic Acid Supplementation Policy

In 1993 the official Dutch advice was that all women wishing to become pregnant should take a folic acid supplement of 0.5 mg per day. The official status for that policy was the Ministry of Health Welfare and Sports (Gezondheidsraad/Voedingsraad 1993)).

Food Fortification Policy

Since 1996 different types of food have been fortified with vitamins and minerals in the Netherlands. For example, extra calcium is added to milk and vitamins are added to (expensive brands of) marmalade. Folic acid was not on the list of vitamins because of the risk of masking a vitamin B_{12} deficiency; only restoration was possible.

The likelihood of appropriate fortification of food with folic acid in the Netherlands is further decreased after the publication of a recent report of the Dutch Health Council.(2000) They did not advise fortification of staple foods such as flour, but only products that can be specifically aimed at the target-population: women who want to become pregnant. No suggestions were made as to what these products could be or what the recommended amount of folic acid to be added to these products would be.

Health Education Initiatives

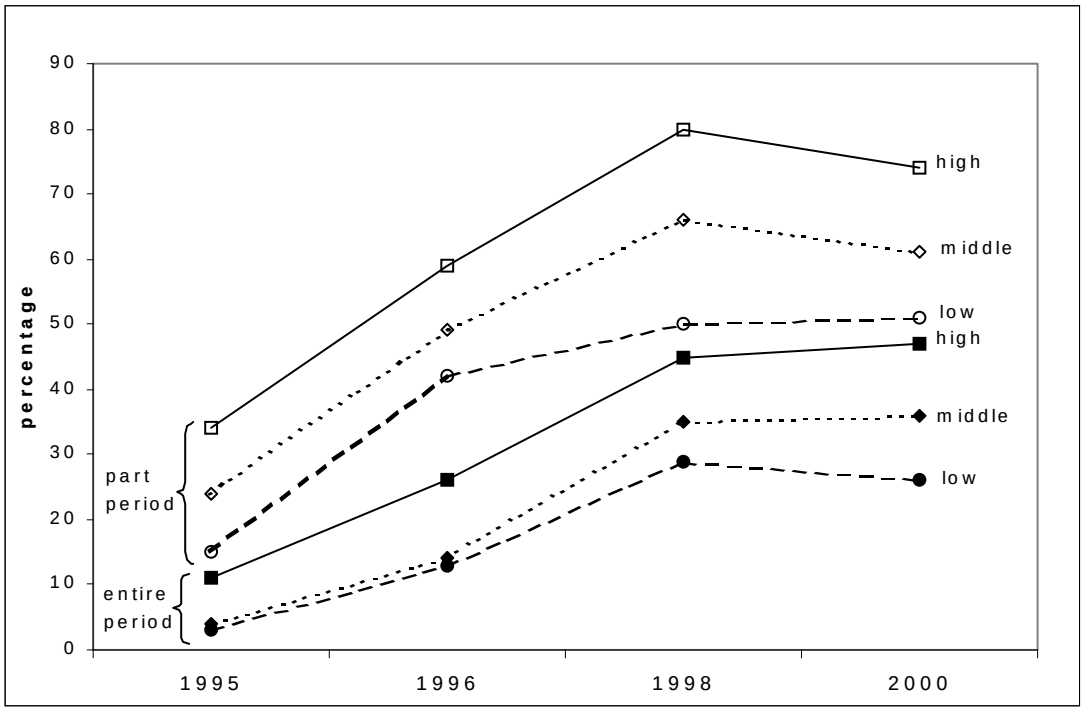
A campaign was aimed at all women of childbearing age but with a special emphasis on reaching women with a low socioeconomic status. General targets of the campaign were that 70% of women planning a pregnancy should know the recommended period to use folic acid and that 65% of women who knew of the advice before pregnancy should use folic acid during the entire recommended period(Voorlichtingsbureau voor de voeding 1994). This campaign was carried out in 1995.

Folic Acid Awareness and Uptake

The level of knowledge increased satisfactorily in the five years after the campaign. However, the percentage that used it in the advised period did not follow the same trend. Figure 1 shows how socioeconomic status is related to use of folic acid during the last five years in which we did the four surveys (de Jong-van den Berg et al 1998, de Walle et al 1999,

de Walle et al 1998, De Walle et al 1999). It is clear that the target that 65% of the women who were aware of the folic acid advice before their pregnancy should use folic acid during the entire recommended period is not reached in any of the surveys (36% of women surveyed in 1999 used folic acid during the entire recommended time. Socioeconomic differences with respect to knowledge and use of folic acid remained statistically significant in all the surveys. This means that another goal of the public campaign, the reduction of socioeconomic differences with respect to the use of folic acid, was not reached. It is disappointing to conclude this was also true in the regions where an extra intervention was made to reach women with a low education. Striking examples are the billboards with the folic acid message, which were placed in public areas and in buses. The more highly educated women remembered this information much better than the group for whom it was intended.

Figure 1 The use of folic acid in the three educational groups (low, middle, high) either in part of the period (3 lines at the top) or during the entire advised period *(3 lines at the bottom).*



Proportion of Pregnancies which are Planned

The Netherlands has a high percentage of planned pregnancies (Vennix 1990). In our surveys the percentage of planned pregnancies was high (around 85%) and it was not related to the

socioeconomic status of the respondents. However, the concept of "planned" in the way the respondents are using it might be different from the way it is interpreted by researchers.

Our study shows that in the Northern Netherlands, in 2000, women were aware of the importance and the correct time frame of using folic acid. However, not all of them took folic acid in the periconceptional period. This was not because of a negative attitude towards taking folic acid but, according to the most often mentioned reason, because although the pregnancy was planned they conceived sooner than expected.

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de Walle HEK, van der Pal KM, de de Jong-van Den Berg LTW, Schouten J, de Rover CM, Buitendijk SE et al **(1998)**. Periconceptional folic acid in The Netherlands in 1995. Socioeconomic differences. J Epidemiol Community Health, Vol 52, No 12, pp 826-827.

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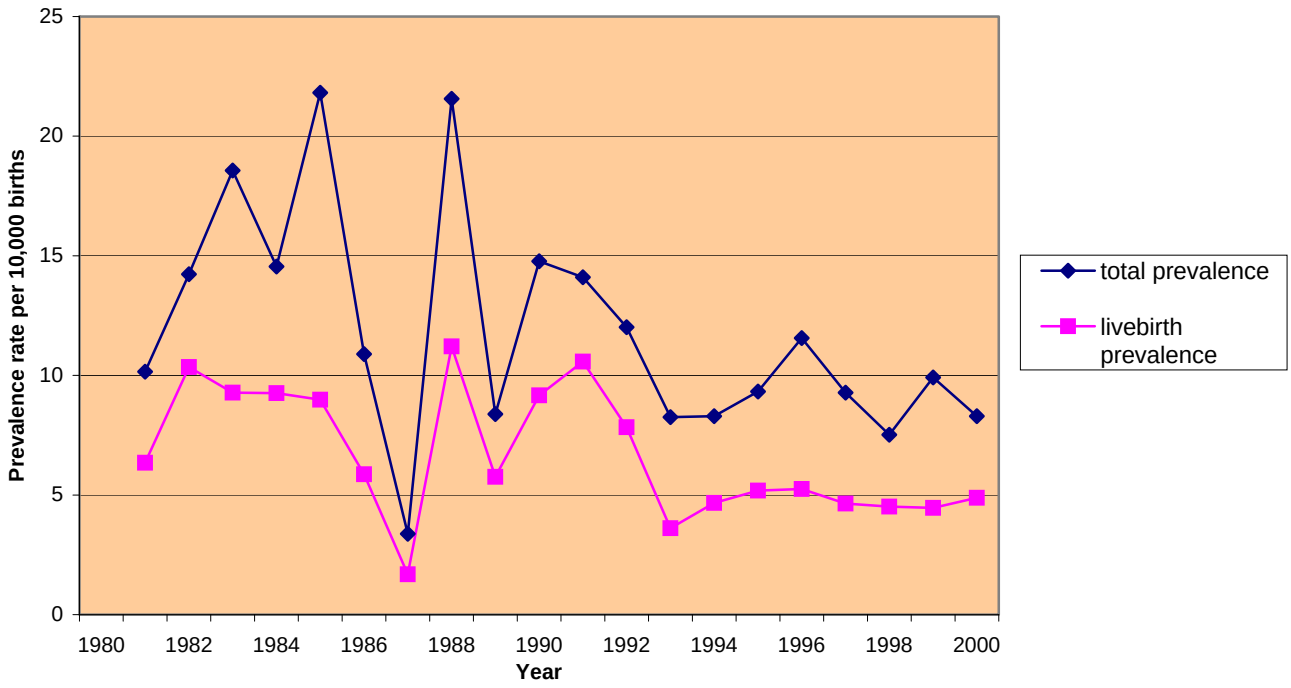
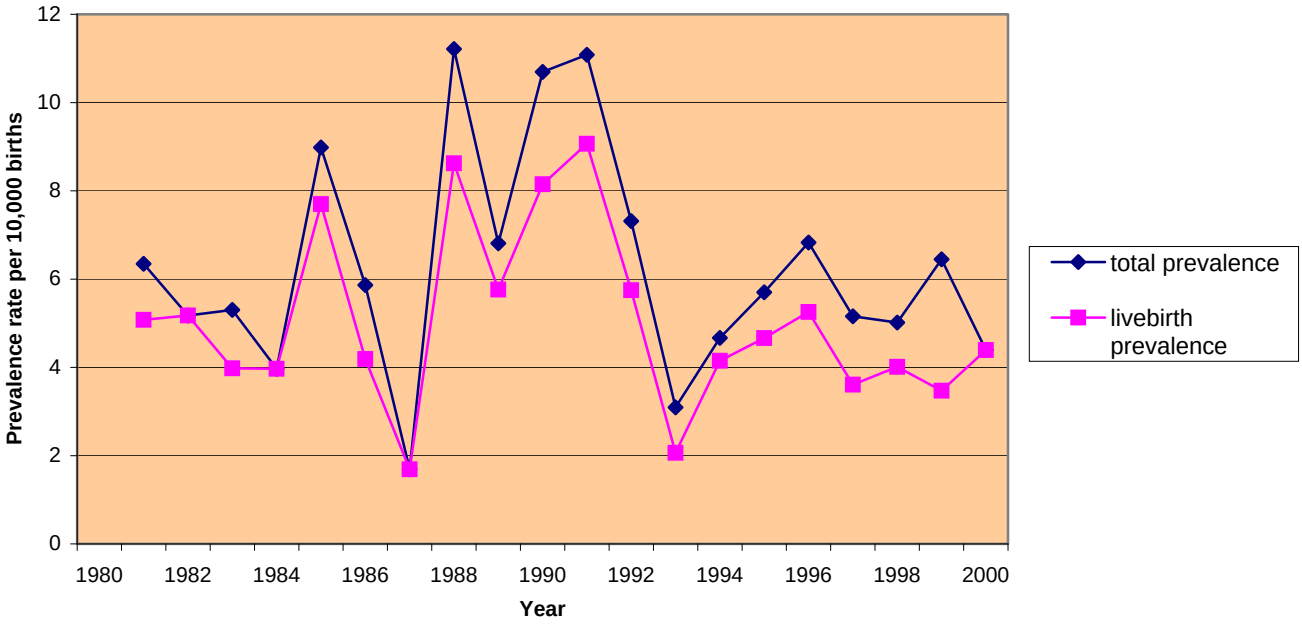
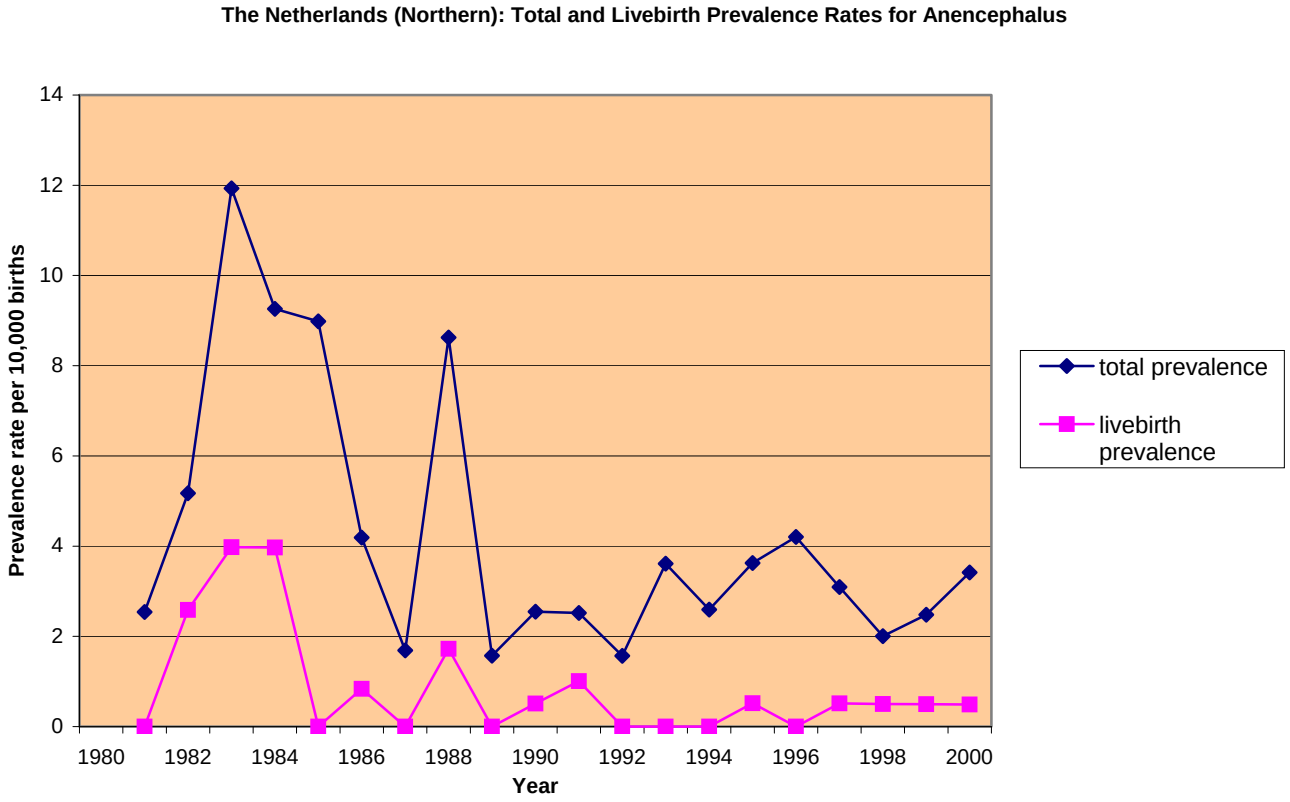
The Netherlands (Northern): Total and Livebirth Prevalence Rates for Neural Tube Defects



The Netherlands (Northern): Total and Livebirth Prevalence Rates for Spina Bifida




The Netherlands (Northern): Total and Livebirth Prevalence Rates for Anencephalus
Prevalence rate per 10,000 births
14
12
10
8
6
4
2
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION IN NORWAY

Anne Kjersti Daltveit dr.ph

Folic Acid Supplementation Policy

The official folic acid supplementation policy in Norway is that women who are planning a pregnancy or who may become pregnant are recommended to have a total intake of at least 400 μg of folic acid per day. Since an intake of 400 μg through the diet is unlikely to be achieved by many women, and since there are reasons to believe that supplementation is more efficient than diet in reducing the risk, the practical recommendation is to take a folic acid supplement of 400 μg per day. The supplementation should begin prior to the first month before conception and continue until 2-3 months of gestation.

Women with an increased need for folic acid due to disease or medication (eg anti-epileptic medication), and women with neural tube defects in their own or their partner's family, are recommended to confer with the their doctor about a supplement of more than 400 μg per day. The supplementation should begin prior to the first month before conception and continue until 2-3 months of gestation.

Women who have previously had a fetus with a neural tube defect as well as women who themselves or their partner have a neural tube defect are recommended to take 4 mg of folic acid supplement per day. The supplementation should begin prior to the first month before conception and continue until 2-3 months of gestation.

After the first 2-3 months of pregnancy, pregnant and breastfeeding women are recommended to have a total intake of folic acid of 400 μg per day. It is suggested that a common level of dietary intake of folic acid among Norwegian women in the child-bearing age is about 200 μg per day. It is therefore recommended that women continue with a folic acid supplement of 200 μg per day during the last 6 months of pregnancy and during the breastfeeding period.

Women of child-bearing age are recommended to have a dietary intake of folic acid of 300 μg per day. With the exception of recommendations regarding pregnancy and breastfeeding, child-bearing women are not recommended to take folic acid supplementation.

The above recommendations were issued in the Spring of 1998 by the National Council on Nutrition and Physical Activity (1998). Before 1998, the official recommendations were those issued by the Board of Health in February 1993. These first recommendations did not recommend the use of supplements for any women other than those at risk of recurrence, but stated that women of child-bearing age should consume 400 μg through their diet.

Food Fortification Policy

There is no policy in Norway to fortify food with folic acid. A working group was established in 1997 by the National Council on Nutrition and Physical Activity to suggest recommendations and means of increasing the intake of folic acid among women of child bearing age. The working group's recommendation was not to implement food fortification with folic acid: it maintained that women should be recommended to have a supplementary intake of folic acid in connection with pregnancy (Rapport nr. 1/1998). Further decisions on food fortification policy will depend on current knowledge and uptake of advice regarding folic acid supplementation in the childbearing population. If a beneficial effect of folic acid supplementation on the general population (i.e. related to heart disease) is documented, this will also be an inducement to implement food fortification.

Health Education Initiatives

An official Health Education Initiative began in Norway in Autumn 1998 to inform women about the role of folic acid in reducing the risk for neural tube defects. The Norwegian Agency for Health and Social Welfare (formerly National Council on Nutrition and Physical Activity) has a public web site (1998). At the web site there is information on the occurrence of neural tube defects in Norway, recommended daily intake of folic acid, contents of folic acid in different foods, when to take supplementation of folic acid in connection with pregnancy, potential side effects related to high intake of vitamin A through multivitamin supplementation, and needs for special groups such as epileptic women.

Leaflets published by the Norwegian Agency for Health and Social Welfare (formerly National Council on Nutrition and Physical Activity) are distributed to women by general practitioners, specialists in gynecology and obstetrics, midwives, health care centres for

mother and child, drugstores, and pharmacies. Also posters and post cards are distributed, and there have been advertisements in women's magazines and other relevant magazines.

Health personnel are requested to inform women about folic acid and pregnancy at the time of giving guidance on contraceptive devices, doing pregnancy tests, removing an intrauterine device, selling of pregnancy tests, and selling of contraceptive devices. The Norwegian Agency for Health and Social Welfare has distributed a guide for health personnel with these items.

Folic Acid Awareness and Uptake

One paper was published in Norway concerning the awareness in the child bearing population of recommendations regarding folic acid supplementation and the uptake of advice regarding folic acid supplementation (Vollset & Lande 2000). After the recommendations were issued in the Spring of 1998, a random sample of 1500 Norwegian women of reproductive age was selected for study during the autumn 1998. Among the 1500 women, telephone interviews were carried out with 1146 women (Vollset & Lande 2000). A repeat study was done in 2000, in which telephone interviews were carried out with 1218 women. Results from this repeat study are not yet published, but some results are referred to here.

The folic acid recommendation issued by the National Council on Nutrition and Physical Activity in March 1998 was known by 22% of women in 1998 increasing to 32% in 2000. Supplementation with folic acid before conception or early in pregnancy, when that pregnancy was less than one year ago, was reported by 10% of women in 1998 increasing to 46% in 2000. Intention to follow the recommendations on folic acid supplementation in a future pregnancy was reported by 56% of women in 1998 increasing to 68% in 2000. Intention to follow recommendations on folate rich food in a future pregnancy was reported by 75% of women in 1998 and again in 2000. The women were also asked about other vitamin supplementation. Supplementation of other vitamins or minerals before or early in pregnancy among women in whom the last pregnancy was less than one year ago, was reported by (numbers for 2000 in parenthesis) 57% (79%) for any vitamin or mineral supplementation, 29% (30%) for multivitamins, 5% (11%) for vitamin B, 28%(20%) for iron, and 21% (32%) for cod liver oil.

Proportion of Pregnancies which are Planned

There is little knowledge in Norway about the proportion of pregnancies that are planned. In the Norwegian Cohort Study (www.fhi.no), preliminary unpublished data show that 76% of the pregnancies were planned. The response rate in this study was about 50%, and we believe that the proportion of planned pregnancies is lower in the total population than that reported in the Norwegian Cohort Study.

Laws Regarding Termination of Pregnancy

Induced abortion is legal at a woman's request up to 12 completed weeks of gestation. Induced abortion is legal on specified medical and social indications above 12 completed weeks and up to18 completed weeks, and the decision is made by an abortion board. After 18 completed weeks, induced abortion is legal if the pregnancy represents a serious risk to the mother, or if the fetus suffers from a condition incompatible with life. In those cases there is no gestational age limit.

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Anbefalinger og virkemidler for økt folatinntak blant kvinner i fertil alder. Rapport nr. 1/1998. Oslo:Statens ernæringsråd, **1998**.

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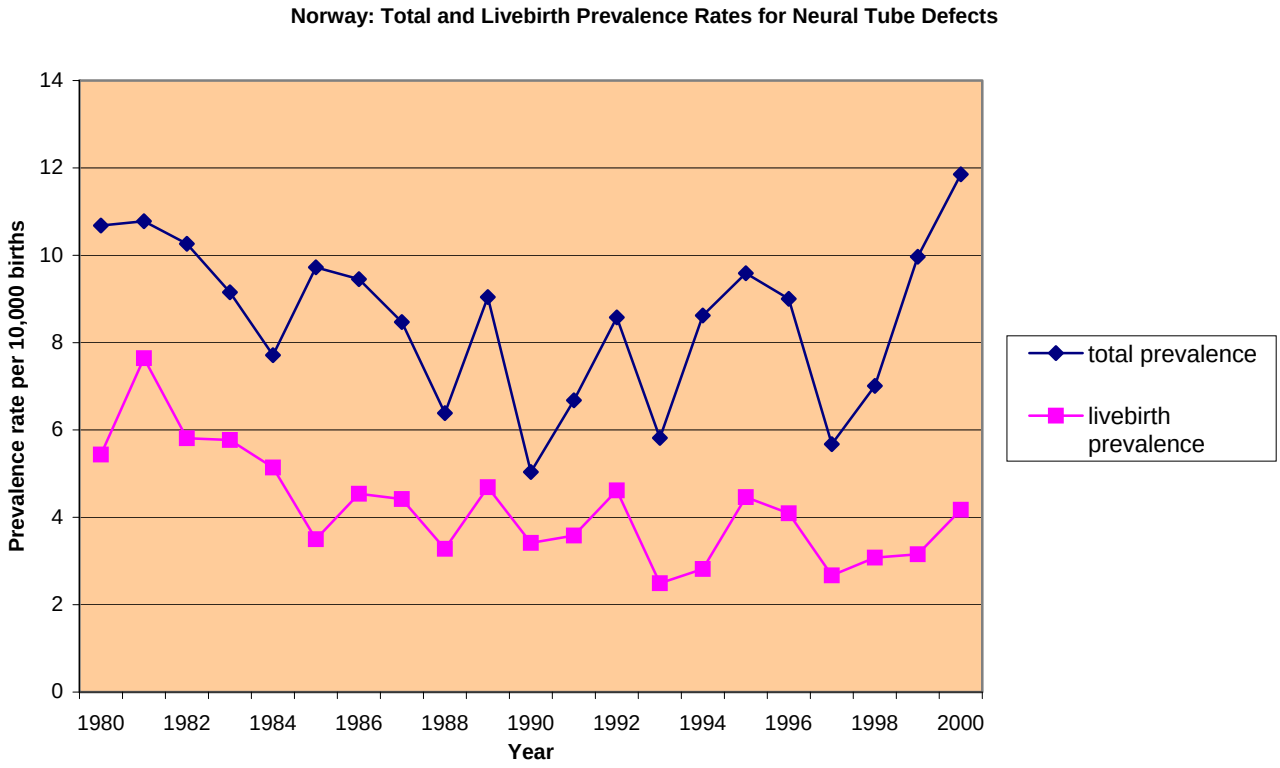
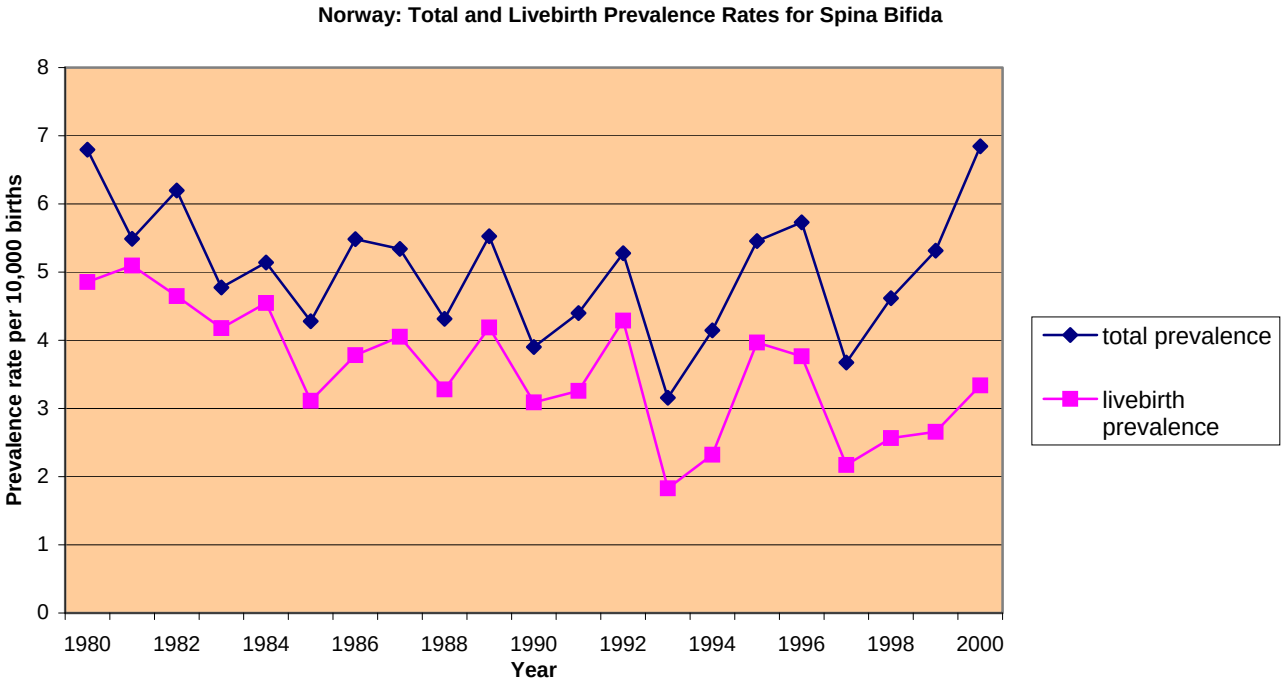
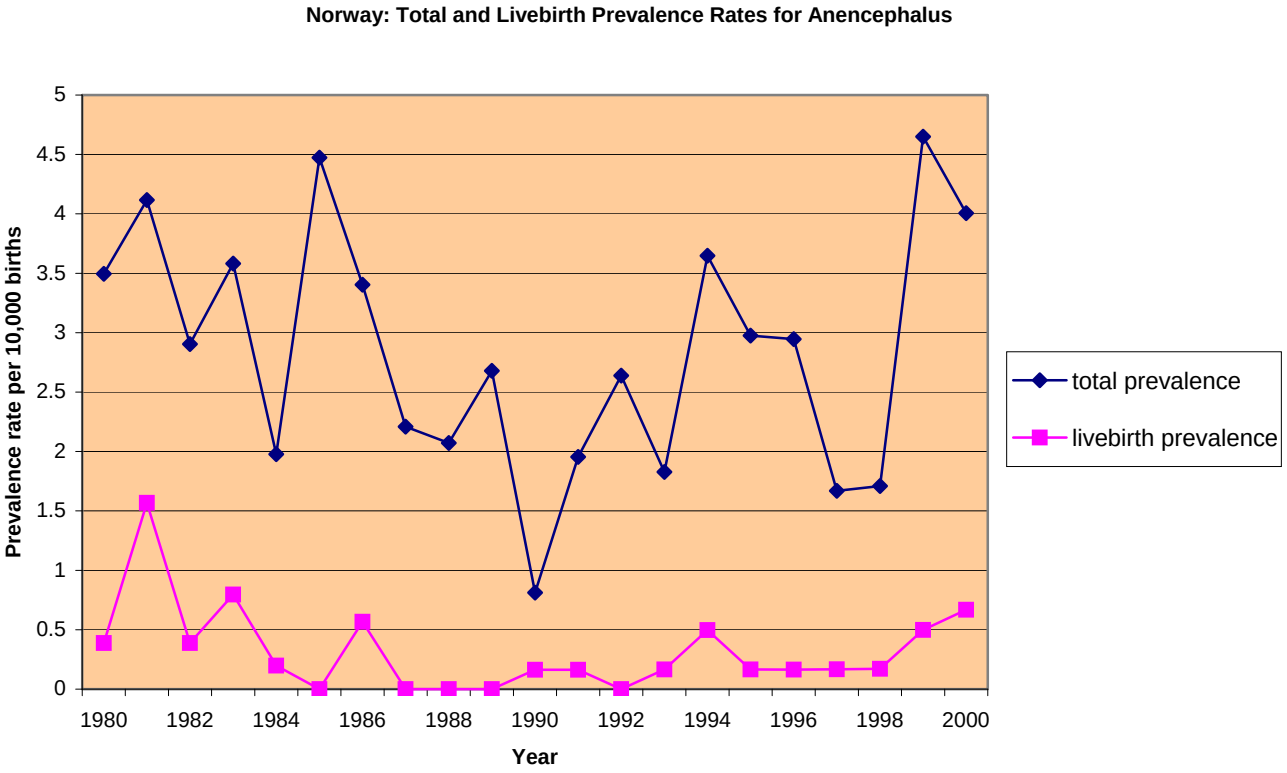
www.fhi.no


Norway: Total and Livebirth Prevalence Rates for Neural Tube Defects
Prevalence rate per 10,000 births
0
2
4
6
8
10
12
14
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence


Norway: Total and Livebirth Prevalence Rates for Spina Bifida
Prevalence rate per 10,000 births
0
1
2
3
4
5
6
7
8
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence


Norway: Total and Livebirth Prevalence Rates for Anencephalus
Prevalence rate per 10,000 births
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR POLAND

Dr Anna Latos-Bielenska

Folic Acid Supplementation Policy

Since 1997 there has been a nation wide government program regarding periconceptional folic acid supplementation. The program "Primary Prophylaxis of Neural Tube Defects", is headed by Professor Zbigniew Brzezinski, from the Department of Epidemiology, Institute of Mother and Child, Warsaw.

Food Fortification Policy

Food fortification is planned for the Lublin Province in which there are approximately 30,000 births per year.

Health Education Initiatives

An educational program is aimed at women, health care professionals and children over fifteen years of age.

Knowledge and Uptake of Folic Acid

In 1999, folic acid supplementation was taken by 15% of women aged 18-45; by 11% of non-pregnant women between those ages; and by 9% of women under 20 years of age.

In 2001, folic acid supplementation was taken by 19% of women aged18-45; by 13% of non-pregnant women between those ages, and by 16% of women under 20 years of age. Thus, folic acid supplementation rates had gone up for all three categories within the space of two years. (Report on realization of program of primary prophylaxis of neural tube defects in 1997-2001, Institute of Mother and Child, Warsaw 2000).

57% of women took other vitamin supplements.

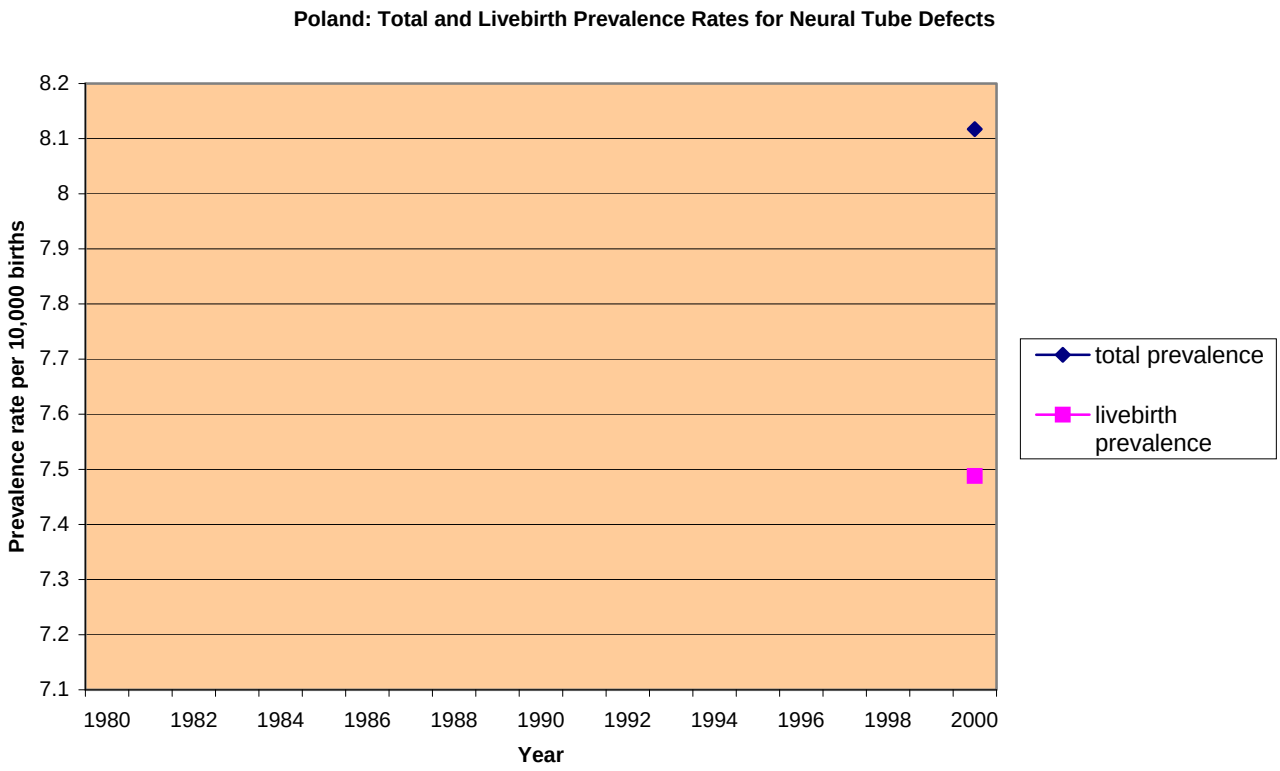
Proportion of Pregnancies which are Planned

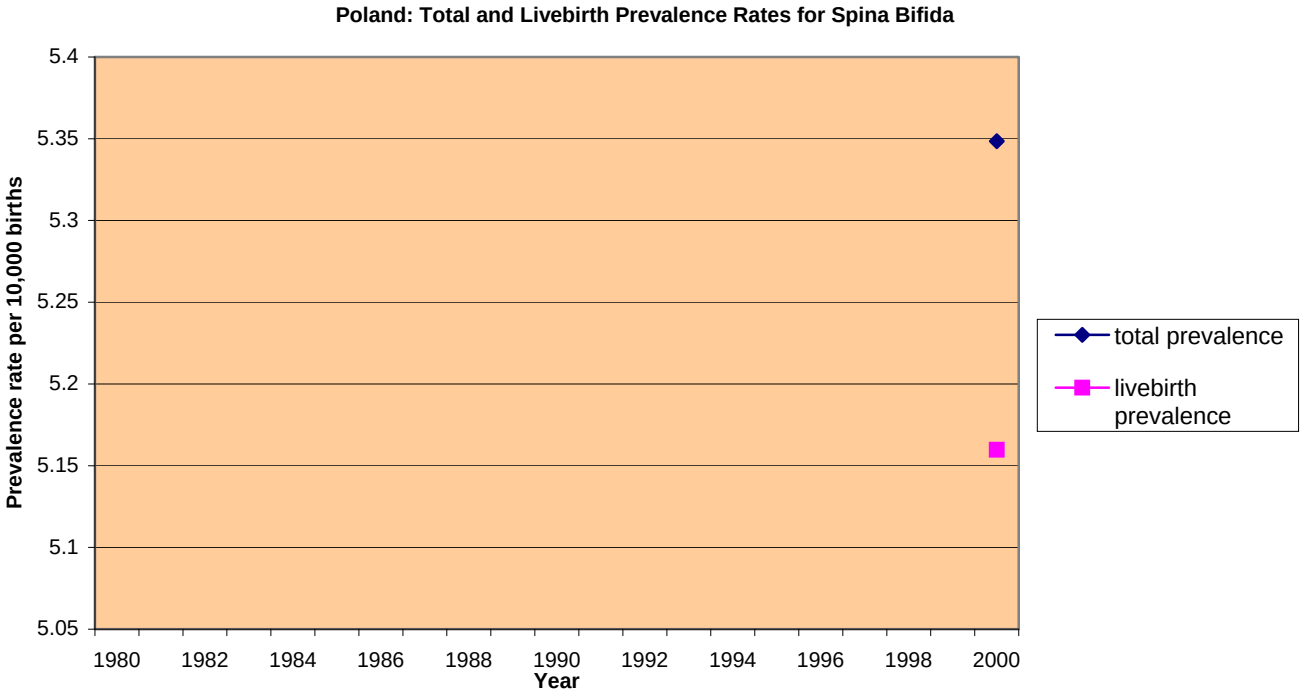
The proportion of pregnancies which are planned in Poland is low.

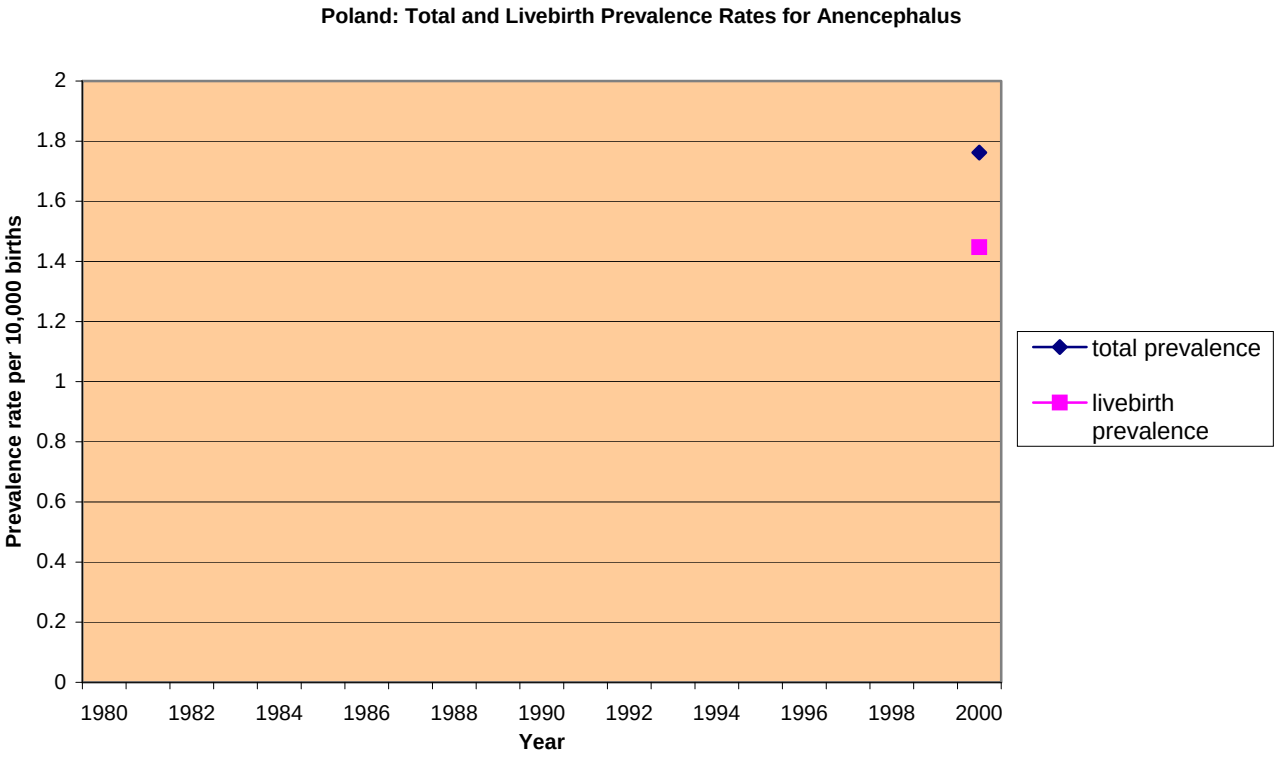
References

Zbigniew Brzezinski, Report on realization of program of primary prophylaxis of neural tube defects in 1997-2001.

Program of primary prophylaxis of neural tube defects, Institute of Mother and Child, Warsaw, **2002**.


Poland: Total and Livebirth Prevalence Rates for Neural Tube Defects
Prevalence rate per 10,000 births
8.2
8.1
8
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence


Poland: Total and Livebirth Prevalence Rates for Spina Bifida
Prevalence rate per 10,000 births
5.4
5.35
5.3
5.25
5.2
5.15
5.1
5.05
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence


Poland: Total and Livebirth Prevalence Rates for Anencephalus
Prevalence rate per 10,000 births
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR PORTUGAL

Dr Paula Braz

Folic Acid Supplementation Policy

There is a recommendation from the Directory of Health "Directory of Health guideline number 2/DSMIA" to all health care professionals, to inform the childbearing population about the importance of folic acid. There is no information about dosage. This policy was introduced in March 1998

Food Fortification Policy

There is no food fortification policy, but one of the most important commercial firms in Portugal for milk products (Mimosa) decided three years ago to fortify milk with 50µg/100ml of folic acid.

Health Education Initiatives

There is no official health education initiative, but the recommendation from the Directory of Health in March 1998, suggested that general practitioners should inform their female patients about the importance of folic acid supplementation.

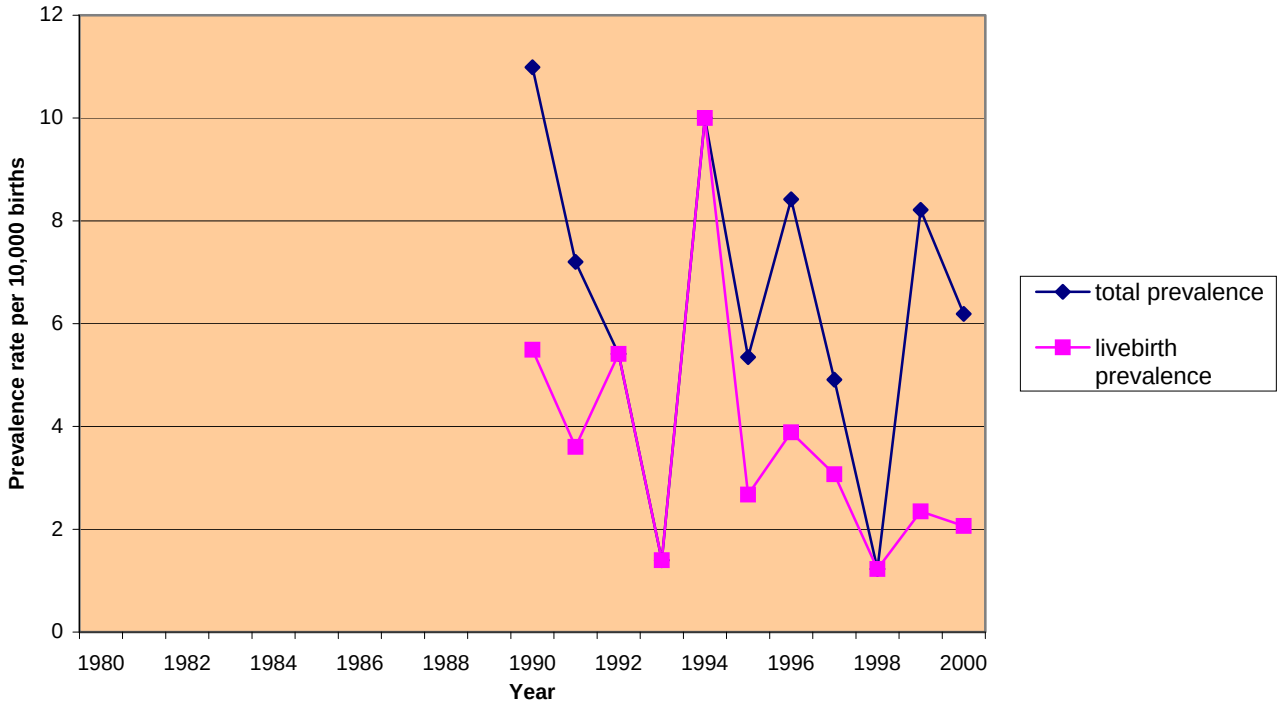
Knowledge and Uptake of Folic Acid

To our knowledge there are no studies in the Portuguese population.

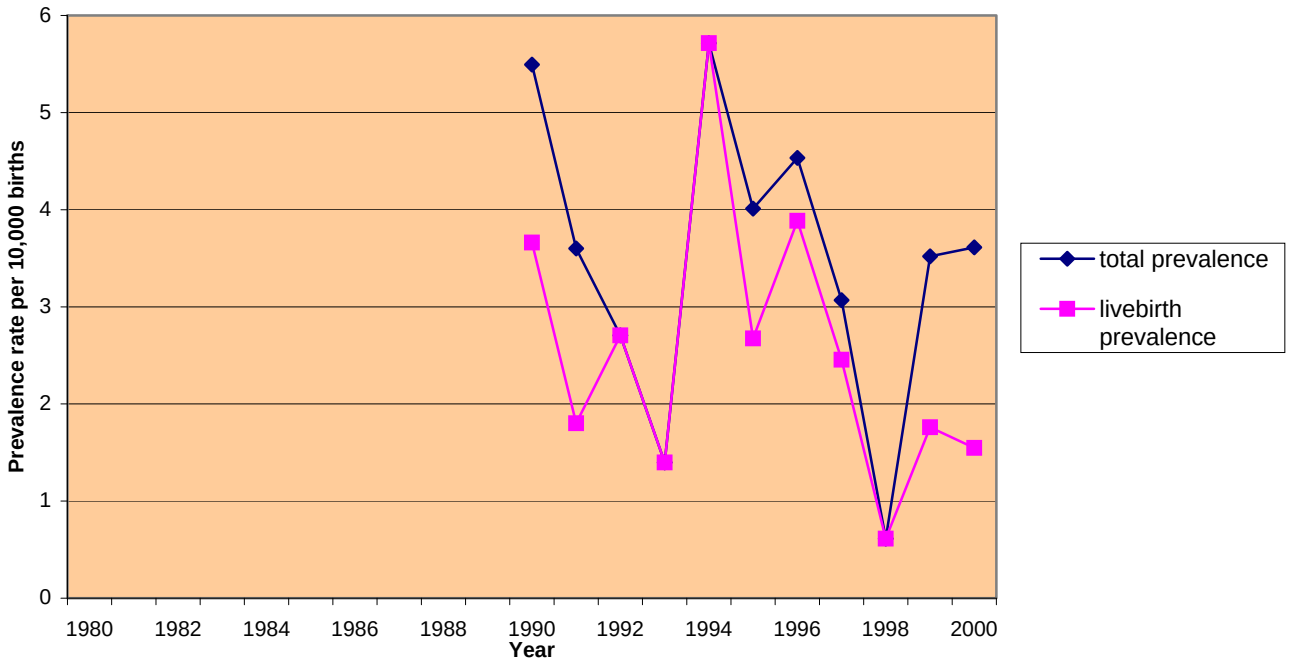
Laws Regarding Termination of Pregnancy

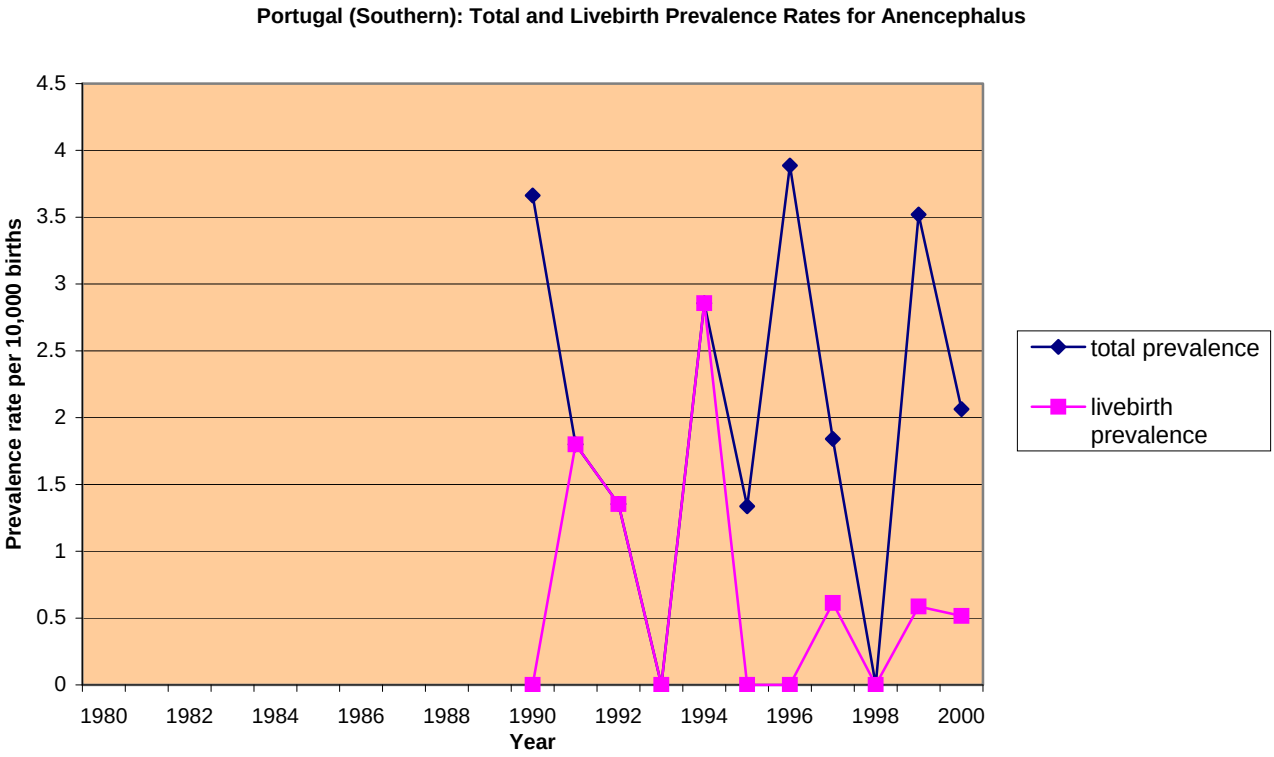
Termination of pregnancy is legal in Portugal until 24 weeks gestation for major congenital anomalies, rape, and risk to the mother's health. It is legal up to term if an anomaly is incompatible with life. There is a technical committee in each obstetric unit in which terminations are performed which decides in each case if the procedure is legal.

Portugal (Southern): Total and Livebirth Prevalence Rates for Neural Tube Defects



Portugal (Southern): Total and Livebirth Prevalence Rates for Spina Bifida




Portugal (Southern): Total and Livebirth Prevalence Rates for Anencephalus
Prevalence rate per 10,000 births
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION IN SPAIN

Dr Blanca Gener

Folic Acid Supplementation Policy

The most recent official recommendations from the Ministry of Health regarding folic acid supplementation in order to reduce the risk of having a child affected with an NTD was published in 2001 (*Dirección General de Salud Publica. Mº de Sanidad y Consumo. Int Ter Sist Nac Salud 2001, Vol 25, pp 66-67).* These recommendations stated that all women who are considering a pregnancy and have no family history of NTD should take 0.4 mg per day of folic acid at least one month before conception and during the first three months of pregnancy. Those women who have already had a child affected with NTD should take a dose of 4 mg per day of folic acid at least one month before conception and during the first three months of pregnancy. In addition, the Ministry of Health recommends that any pregnant woman should consume food rich in folic acid. The daily requirements of folic acid in a pregnant woman's diet are estimated to be 400 μg, twice that of a non pregnant woman (200 μg). A table with the content of folic acid in certain foods is also available.

The 2001 recommendations replaced those published in 1998, which had targeted only those women who had previously had a child affected with an NTD.

In addition to government recommendations, the Spanish Society of Gynecology and Obstetrics (SEGO) is very interested in promoting the preconceptional care of women. Special stress is laid on supplementation with folic acid. It should start at least one month before conception, and continue until 10-12 weeks of gestation. The specific recommendations are detailed below.

- All women with a low risk of having a fetus affected with NTD should take 0.8 mg ay of folic acid, besides ensuring they have a balanced diet.
- All women with high risk of having a fetus affected with NTD, should take at least 4mg per day of folic acid, besides ensuring they have a balanced diet.

- It is advisable to avoid the use of multivitamin tablets in order to achieve the expected doses of folic acid, because an excess of other vitamins (e.g. vitamins A and D) could be dangerous both for the fetus and the mother.

Food Fortification Policy

For the moment there is no specific official food fortification policy. However, there is voluntary food fortification with folic acid. In Spain most breakfast cereals are fortified by food companies.

Knowledge and Uptake of Folic Acid

In Spain, the average daily intake of folic acid in the adult female population is estimated at: 252 (103) μg (Aranceta et al 1994). The average daily intake of folic acid in pregnant women is estimated at: 258 (89) μg (Aranceta et al 1994). 10% of women in Spain are at risk of having a diet without enough folic acid.

In the Basque country the daily intake of folic acid in the adult female population is estimated to be 212 (108) μg (Aranceta et al 1994). 14% of adult females have suboptimal levels of serum folate. 25.7% of adult females have suboptimal levels of red cell folate. The percentage of women of reproductive age with inadequate intake of folic acid is 25%.

[1]indicates the standard deviation of the mean folic acid intake.

"Folates and vitamin B12 in pregnant women**"**. Ballesteros G, Muñoz P, Lopez M.E., De Miguel J.R. Prog Obstet Ginecol 1999, Vol 42, pp 543-557.

Study design: A prospective observational serial prevalence study to determine levels of red cell folate and serum levels of folate and vitamin B12 in a sample group of 406 pregnant women in Cantabria (Spain), distributed by areas and health care centres related to their number of births in 1993. All the women underwent an analytical determination upon beginning prenatal care. Some 94,5% had a second and 84,2% a third such determination. For each of the vitamins the values obtained were analysed for their distribution and correlation with respect to gestational age, considering the incidence of supplementation and the moment in which it took place. Results: Folate

and vitamin B12 levels in the sample group were comparable throughout the gestation period with figures published in other studies, and generally higher. However, in the first trimester, only 12% had optimum folate levels to prevent NTD, whereas levels in 68,2% of the women involved risks of NTD greater than those in other population groups.

"Primary prevention of neural tube defects in the population served by a reference hospital". Gilbert M.J., Juncosa N, Martín I. Prog Obstet Ginecol 2000, Vol 43, pp 13-20.

Study design: Retrospective descriptive study of 651 mothers attended in the Hospital Son Dureta in Palma de Mallorca (Balear Isles) during the second trimester in 1998. Results: Folic acid supplementation was used by 381 pregnant women (58,5%). Only 4,5% of the prescribed preventions were sufficient and they were more frequent in private medicine (12%) than in public medicine (3,4%) ($p= 0.036$). 85,2 % of midwifes and 45,7% of gynecologists recommended prophylaxis when the mother first attended the antenatal clinic or before ($p<0.001$).

Laws Regarding Termination of Pregnancy

Termination of pregnancy in Spain is allowed up to 22 weeks of gestation if the fetus is expected to be born with severe physical or intellectual defects (unspecified). Two doctors must sign that any of those indications is present.

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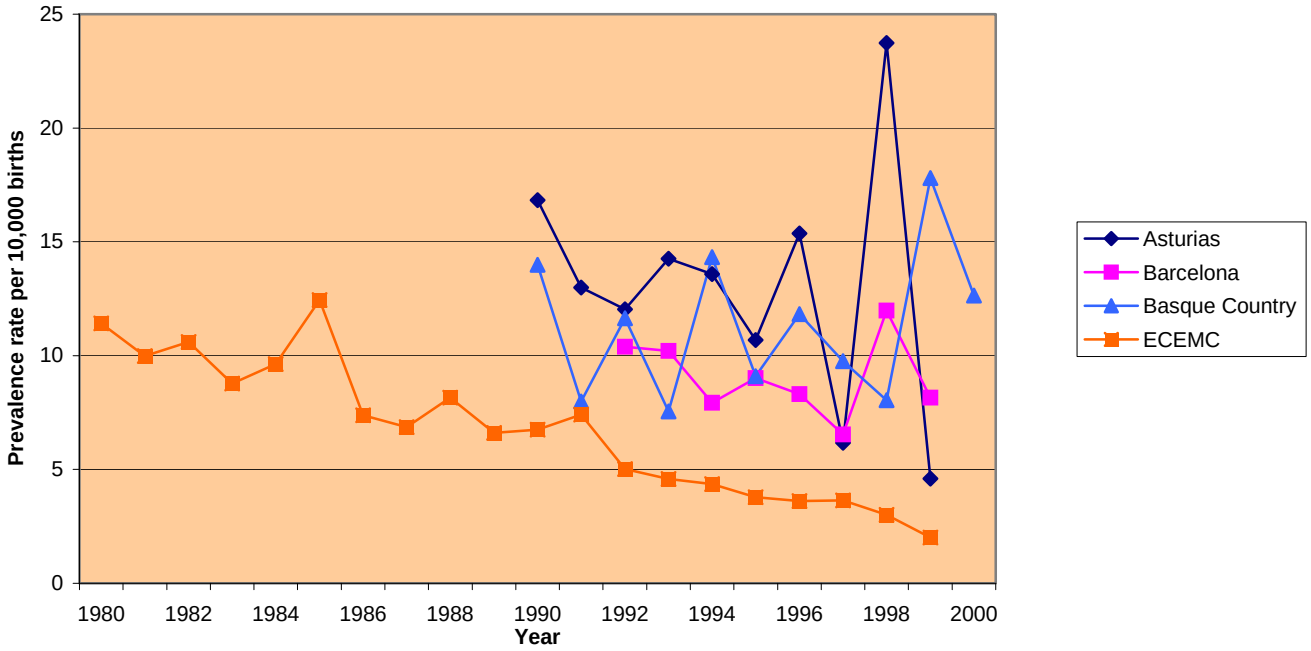
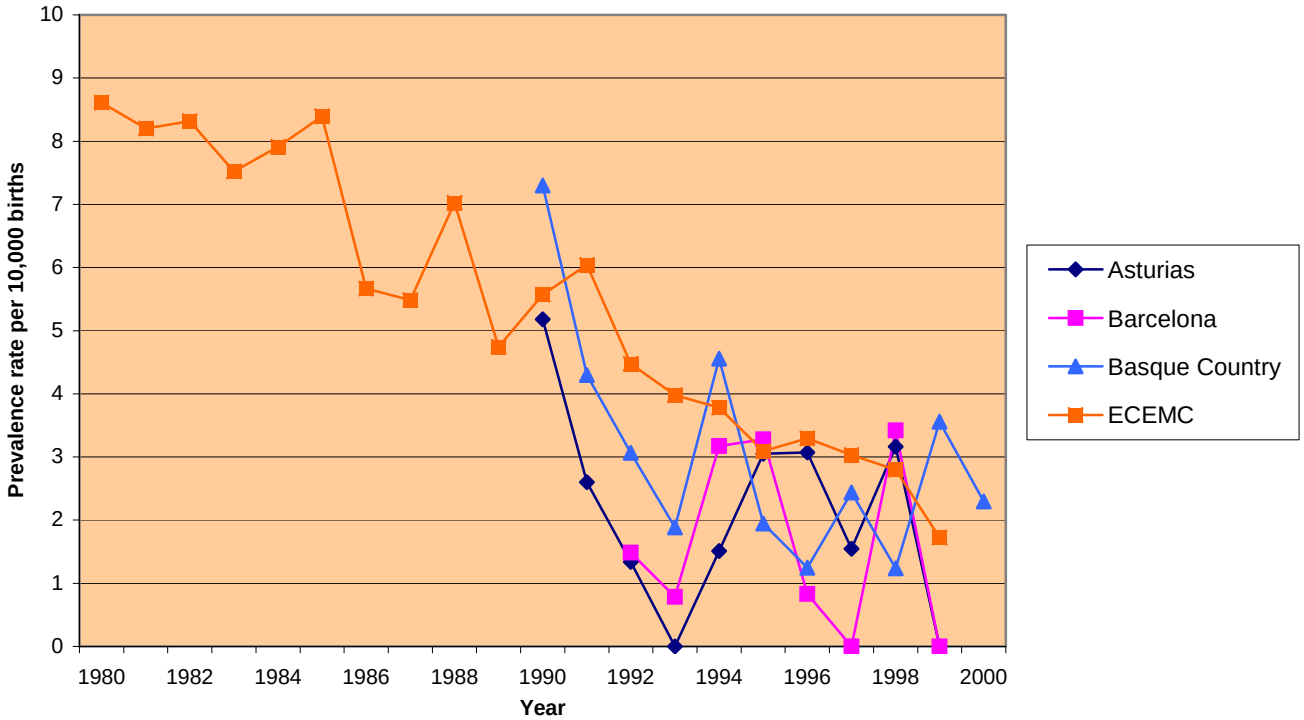
Spain (Asturias, Barcelona, Basque Country and ECEMC): Total Prevalence Rate* for Neural Tube Defects

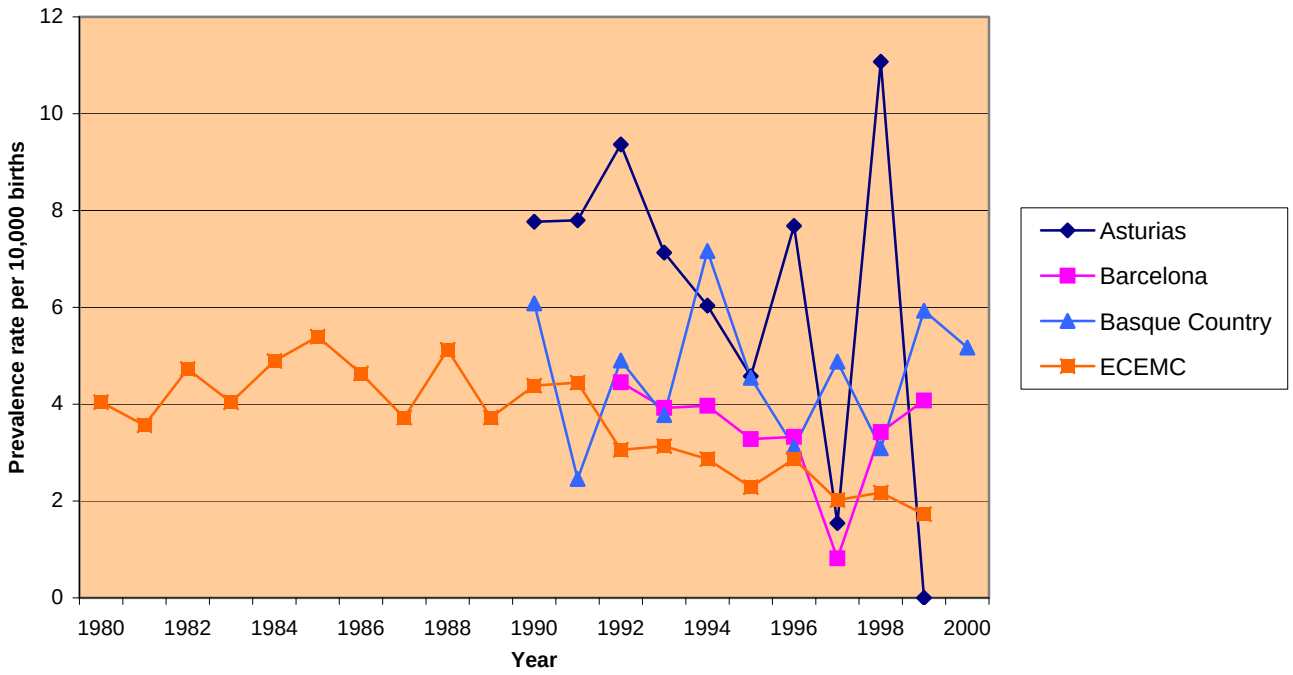


*Data for the ECEMC registry do not include pregnancies that were terminated.

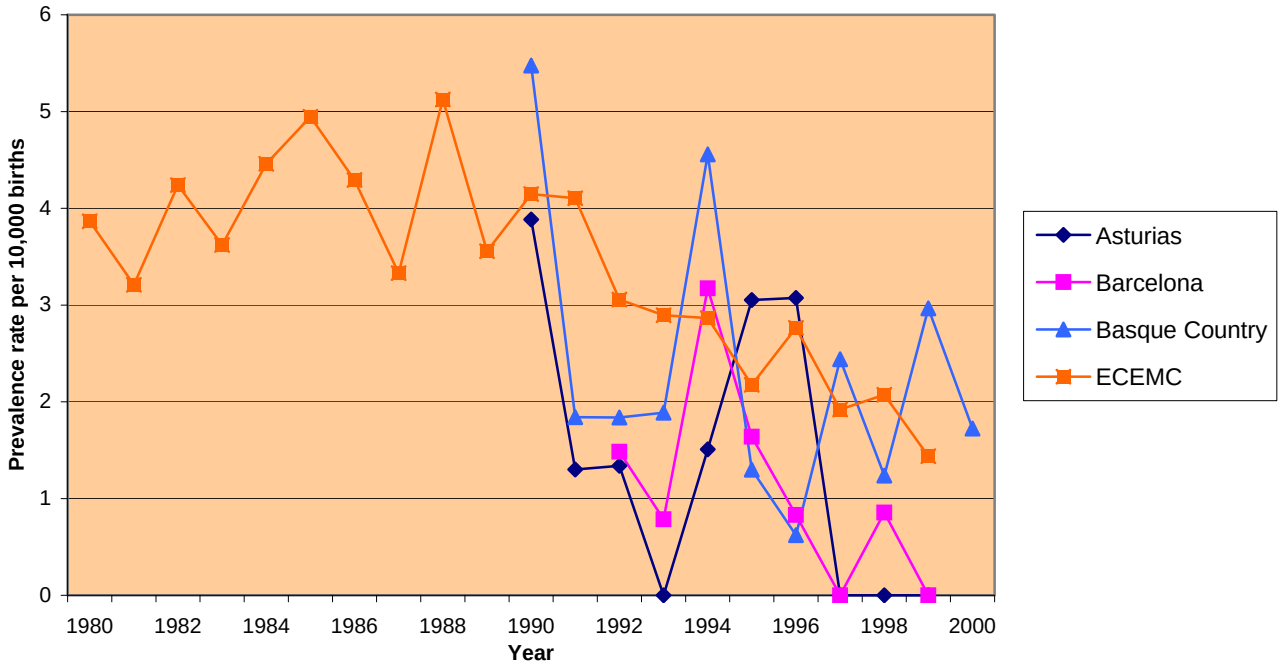
Spain (Asturias, Barcelona, Basque Country and ECEMC): Livebirth Prevalence Rate for Neural Tube Defects



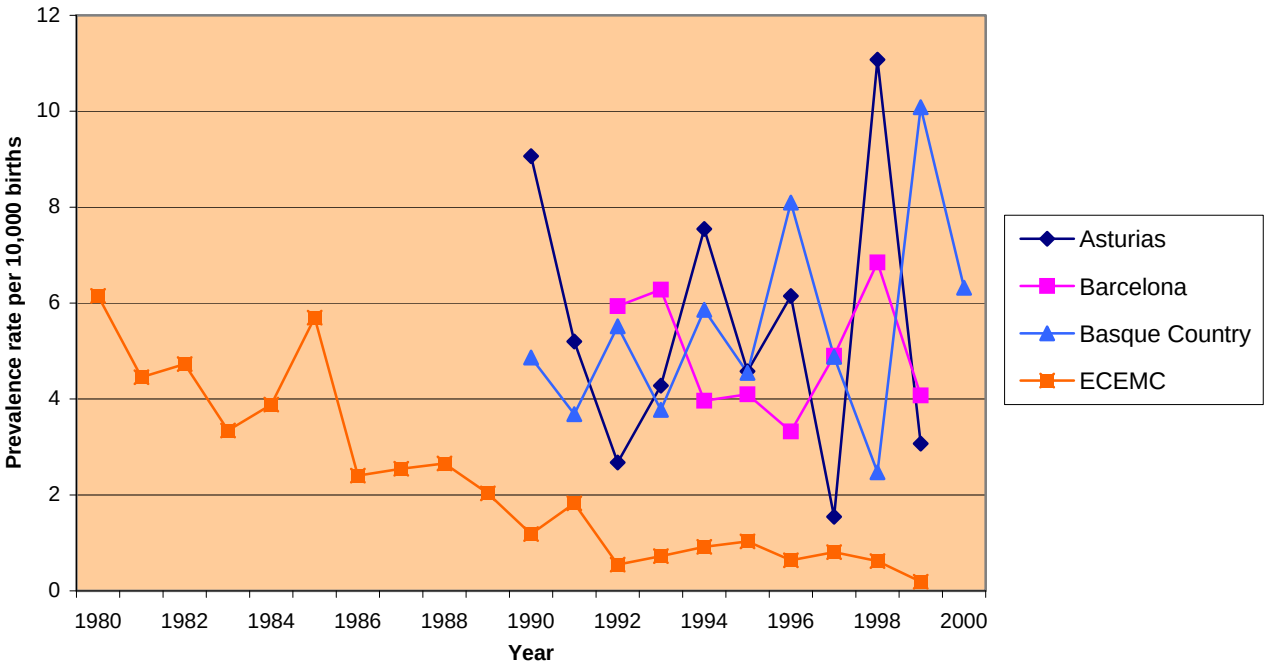
Spain (Asturias, Barcelona, Basque Country and ECEMC): Total Prevalence Rate for Spina Bifida



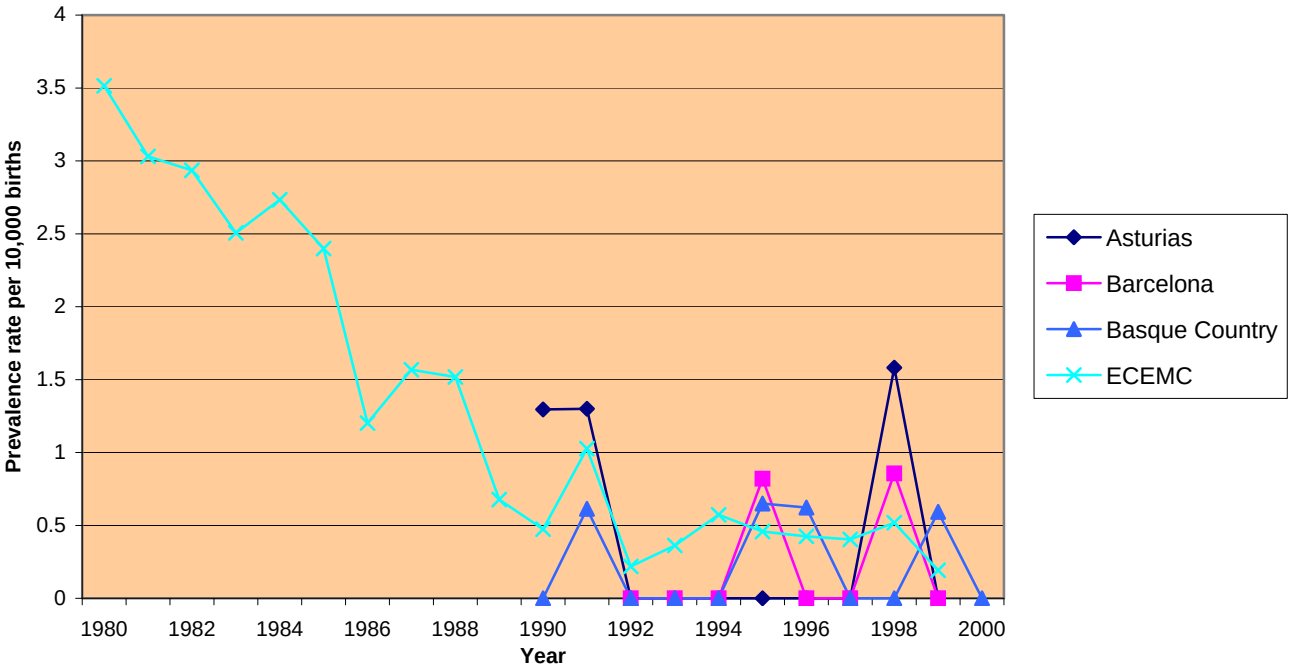
Spain (Asturias, Barcelona, Basque Country and ECEMC): Livebirth Prevalence Rate for Spina Bifida



Spain (Asturias, Barcelona, Basque Country and ECEMC): Total Prevalence Rate for Anencephalus



Spain (Asturias, Barcelona, Basque Country and ECEMC): Livebirth Prevalence Rate for Anencephalus



REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR SWITZERLAND

Dr Marie-Claude Addor

Switzerland is a federal country comprising 26 cantons. Most responsibilities in the health field are vested in the Cantonal Public Health Services. On the federal level, there is a Federal Office of Public Health whose guidelines now have a large audience and are used as the legal basis.

Folic Acid Supplementation Policy

In the early 1990s, the Public Health Officer for the canton of Vaud, at the request of the University Department of Gynecology and Obstetrics, asked the Federal Office of Public Health to support the idea of a national recommendation concerning folic acid and the prevention of neural tube defects (NTD).

The current recommendations (2002) for primary prevention are as follows:

- 0.4 mg folic acid supplementation (with or without other vitamins) should be taken daily from four weeks before conception until twelve weeks after.
- All women of child bearing age without safe contraception should consume a folate rich diet (fresh fruits and vegetables, whole grain products and fortified food eg cereals and breakfast beverages).
- Women who have had a previous pregnancy affected by a neural tube defect are advised to take the following supplements periconceptionally:
    - 4-5 mg folic acid daily, monopreparation (Folvite, Ac. Folicum, Foli-Rivo)
    - polyvitamins = 0.4-1 mg folic acid (vit A ≤ 8000 Ul)

Food Fortification Policy

In 1997, Wiederkehr et al submitted to the Swiss representative assembly a proposal for the mandatory fortification of flour with folic acid for the prevention of neural tube defects.

Since 2000, the Federal Office of Public Health has been studying the folate situation in Switzerland (3) and a working group of the Swiss Nutrition Council has submitted a report for the Federal Government with scientific recommendations, published in 2002(4).
The current recommendation regarding fortification is that flour should be fortified on a mandatory basis by 3 mg folic acid and 10 micrograms of vitamin B12 per kg of flour in order to obtain a supplementary daily intake of folic acid of 275 micrograms and about 1 microgram of B12 per day. This is the most efficacious, sure and economic way to prevent NTD.

It should be noted that this recommendation is supported by the Swiss Nutrition Council but not yet by the Federal Office of Public Health. The fortification with folic acid of other foods is under re-evaluation. The potential benefits of folic acid in the Swiss population have now been evaluated and this knowledge will influence the official federal policy for folic acid fortification in Switzerland. At the moment the Federal Office of Public Health is considering the next steps to be taken.

Health Education Initiatives

A working group of the Federal Office of Public Health is preparing a booklet and a leaflet for women in childbearing age. Some booklets, edited by pharmacists "vitamin info" are available in waiting rooms of gynaecologists.

Uptake and Knowledge of Folic Acid.

The percentage of pregnancies that are planned in Switzerland is very low and there are very few "preconceptional consultations". Awareness in the child bearing population of the recommendations regarding folic acid supplementation is still poor.

In Switzerland, the daily dietary intake of folate has been estimated to be 275 μg or even less.

Laws Regarding Termination of Pregnancy

Termination of pregnancy is legal up to 24 weeks gestation. Thereafter, it is not legal for any indication.

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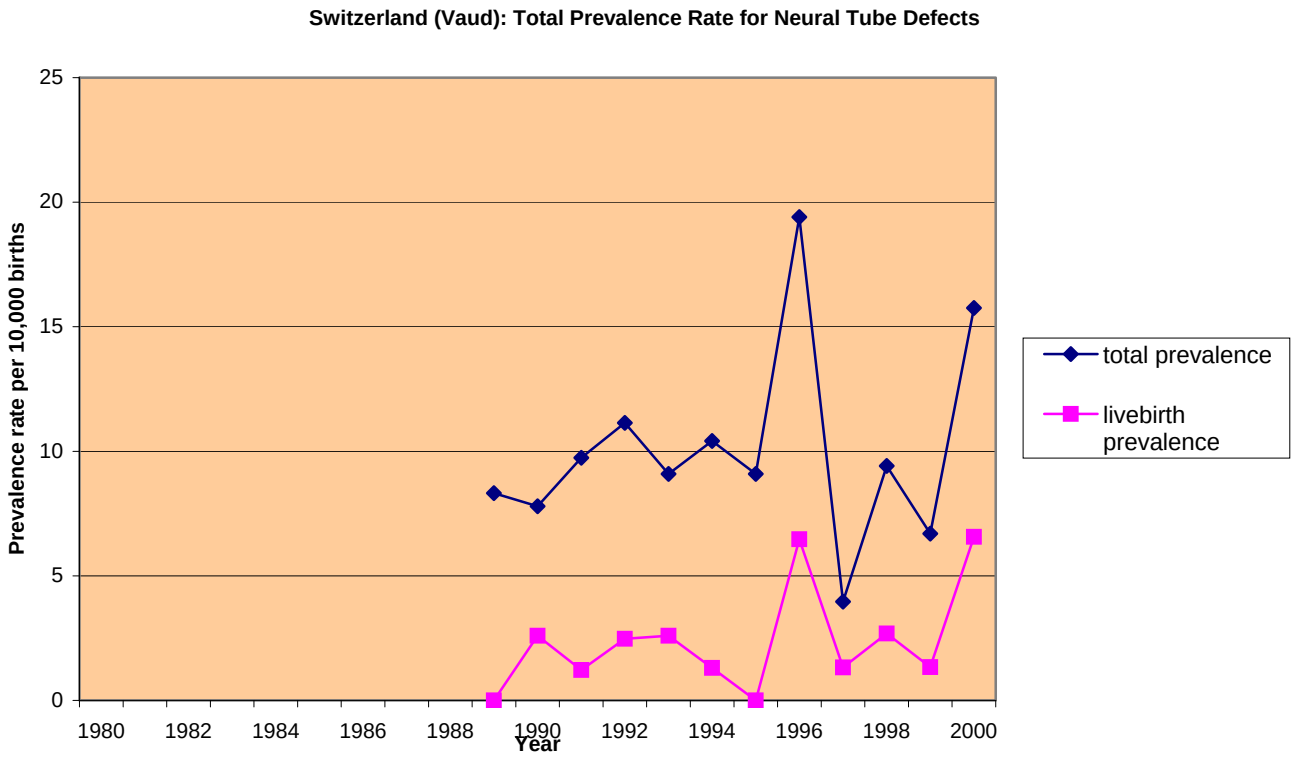
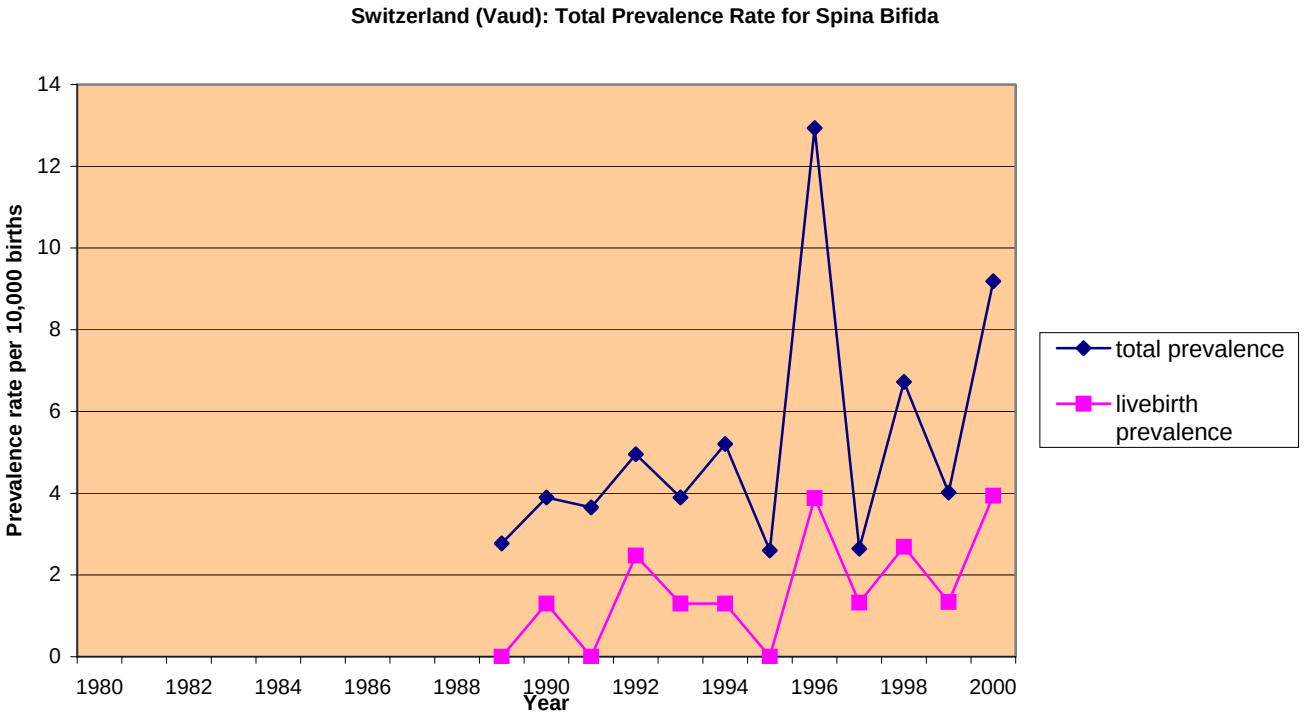
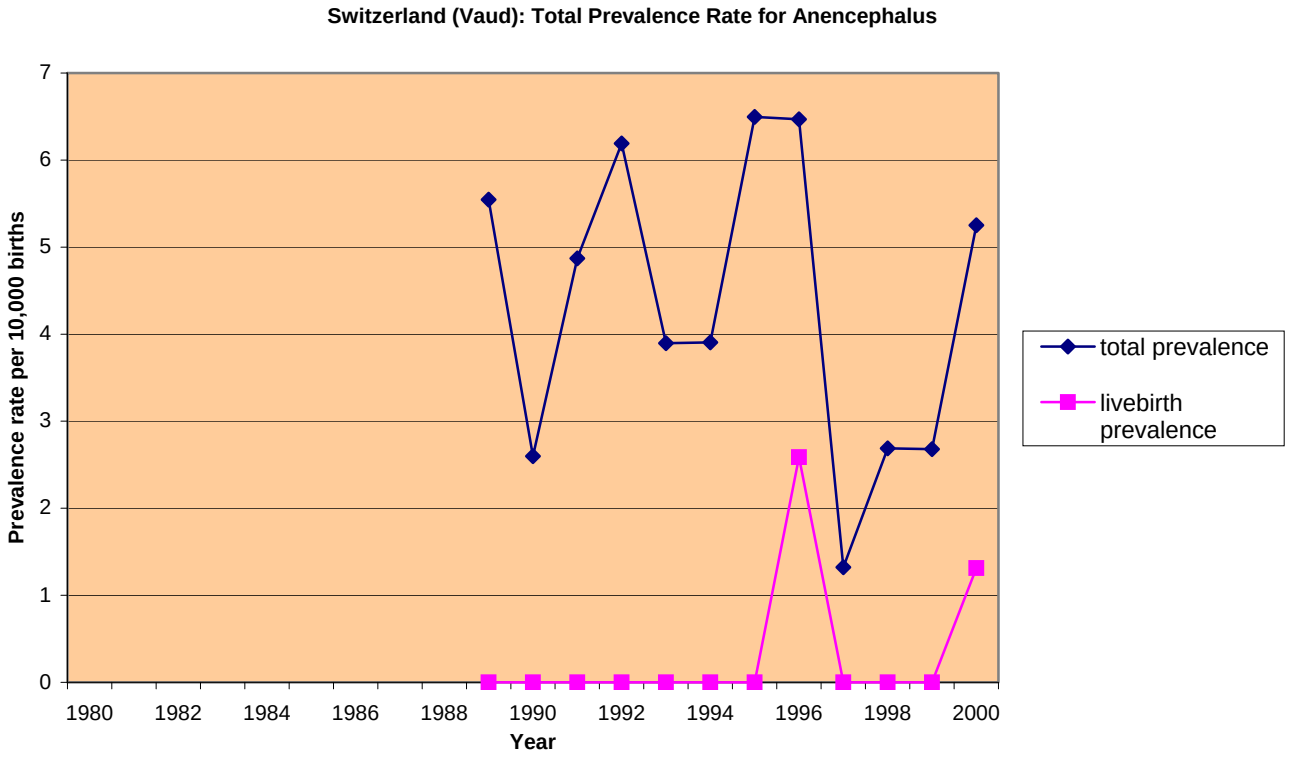

Switzerland (Vaud): Total Prevalence Rate for Neural Tube Defects
Prevalence rate per 10,000 births
25
20
15
10
5
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence


Switzerland (Vaud): Total Prevalence Rate for Spina Bifida
Prevalence rate per 10,000 births
14
12
10
8
6
4
2
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence


Switzerland (Vaud): Total Prevalence Rate for Anencephalus
Prevalence rate per 10,000 births
0
1
2
3
4
5
6
7
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
Year
total prevalence
livebirth prevalence

REPORT ON PERICONCEPTIONAL FOLIC ACID SUPPLEMENTATION FOR THE UNITED KINGDOM

Dr Grace Edwards

Folic Acid Supplementation Policy

The link between folate deficiency in pregnancy and neural tube defects was first reported in the United Kingdom by Hibbard and Smithells in 1968. A randomised control trial funded by The Medical Research Council, UK, confirmed that improving folic acid status periconceptionally in women who had had a previous child with a neural tube defect reduced the recurrence risk in that pregnancy (MRC Vitamin Study research Group 1991). As a result, in 1992 the Department of Health in conjunction with the Scottish Office, the Welsh Office and the Northern Ireland office produced a report recommending that folic acid supplementation should be taken by all women contemplating pregnancy (Department of Health 1992). The report recommended that all women take 400 μg of folic acid per day when planning a pregnancy. Women who have had a baby with a previous neural tube defect are advised to take 5 mg per day before conception and until 12 weeks of pregnancy.

Food Fortification Policy

There is no mandatory fortification of food in the United Kingdom. However, most breakfast cereals have been fortified voluntarily with vitamins and minerals such as B vitamins, including folic acid, and iron for many years, although there is no standardised amount and there are varying levels of fortification with folic acid.

Since the original work of Hibbard and Smithells there has been increasing debate on the fortification of flour with folic acid. A recent report on the role of folic acid in preventing neural tube defects was published by the Committee of Medical Aspects of Food and Nutrition (COMA 2000). This report concluded that by fortifying flour with folic acid, a significant proportion of neural tube defect affected births could be prevented. The report looked at both the benefits and possible risks of folic acid intake and concluded that:

- Universal fortification of flour with folic acid at 240 μg per 100 grams in food products as consumed would reduce the risk of a neural tube defect in unborn babies and children by 41% without resulting in unacceptably high intakes in any group of the population

- Women who could become pregnant should continue to be advised to take a diet rich in folate and take folic acid supplementation.

However, there is no consensus on the introduction of a food fortification programme without a controlled field trial. The main concern is that fortification may mask megaloblastic anaemia in people with vitamin B12 deficiency (Wharton & Booth 2001). A recent review for the Cochrane collaboration looked at four trials of supplementation involving 6425 women. The review concluded that periconceptional folate supplementation has a strong protective effect against neural tube defects. Consensus regarding the relative benefits and risks of fortifying basic foodstuffs such as flour remain unresolved (Lumley et al 2000), in spite of recognition of the success of food fortification in the US which has reduced the rate of neural tube defects from 37.8 per 100,000 livebirths before fortification to 30.5 per 100,000 livebirths following fortification, representing a 19% decline (Wise 2001, Honein et al 2001). A public consultation was undertaken in the United Kingdom. In May 2002, the Food Standards Agency recommended that mandatory fortification should not be implemented.

Health Education Initiatives

In 1995 a UK campaign led by the Health Education Authority (HEA) was launched to improve folate status awareness in women of child bearing age. This campaign highlighted ways of improving folate status before conception and up to 12 weeks of pregnancy by increasing folic acid intake from foods and supplements. This was a large and expensive campaign with advertisements on television, in newspaper, magazines and professional journals. Although the campaign raised awareness in women from 9% in 1995 to 68% in 1998, only 38% of women surveyed in 1998 took folic acid around the time of conception (Health Education Authority 1998).

It should be noted that Northern Ireland was not covered by the television advertising campaign launched by the HEA in 1995. However, a Northern Ireland television advertising campaign was broadcast as part of a public information initiative developed by the Health Promotion Agency for Northern Ireland and launched in 1998.

Knowledge and Uptake of Folic Acid

Studies undertaken in the UK found that approximately half of women sampled were unaware of when they should take folic acid and of what effect it had. Work by Sens *et al 2001* studied the knowledge, attitude and practice of pregnant women regarding periconceptional folic acid intake. A total of 300 women were sampled. Knowledge of the correct timing of folic acid intake was present in only 76% and was more likely in those women with a higher educational status. Less than half of the women (44.6%) had taken folic acid in the preconceptional period (Sens et al 2001). Other research by Mathews *et al 1998* studied 969 randomly selected primigravida at 16 weeks gestation, found similar results and noted that women who are young, are of low educational status and are smokers were least likely to take folic acid (Mathews et al 1998). Although periconceptional supplementation with folic acid has been shown to be effective, the rate of decline in the true incidence of neural tube defects has slowed. Supplementation may not be taken at the appropriate time, or may not be taken by women who are at greatest risk (Mathews et al 1998).

Some work has been undertaken in the United Kingdom to measure the changes in folate consumption. Murphy et al found that dietary folate consumption had increased by 1.6% per annum in Scotland and 1.4% in England from 1980 to 1996. This increase was thought to have been linked with the introduction of folate fortification of cereals (Murphy et al 2000).

In Northern Ireland anecdotal evidence from antenatal clinics indicates an increase in uptake of folic acid supplements.

Proportion of Pregnancies which are Planned

A study by While (1990) found that up to one out of every three livebirths are unplanned (While 1990). These findings were supported by research in Merseyside, England (2000) where forty percent of women reported that their pregnancies were unplanned (Edwards 2001), and by research in other parts of Britain (McGovern et al 1997).

Laws Regarding Termination of Pregnancy

Under the 1967 Abortion Act (amended in 1990) abortion is legal in England, Scotland and Wales at gestational age up to 24 weeks provided that two doctors certify that a woman's mental or physical health (or that of her children) is at greater risk if she continues with the pregnancy than if she has a termination. There is now no gestational age limit for termination of pregnancy because of serious fetal abnormality or because there is a risk of permanent injury to a woman's health or life. The 1967 Abortion act does not apply in Northern Ireland.

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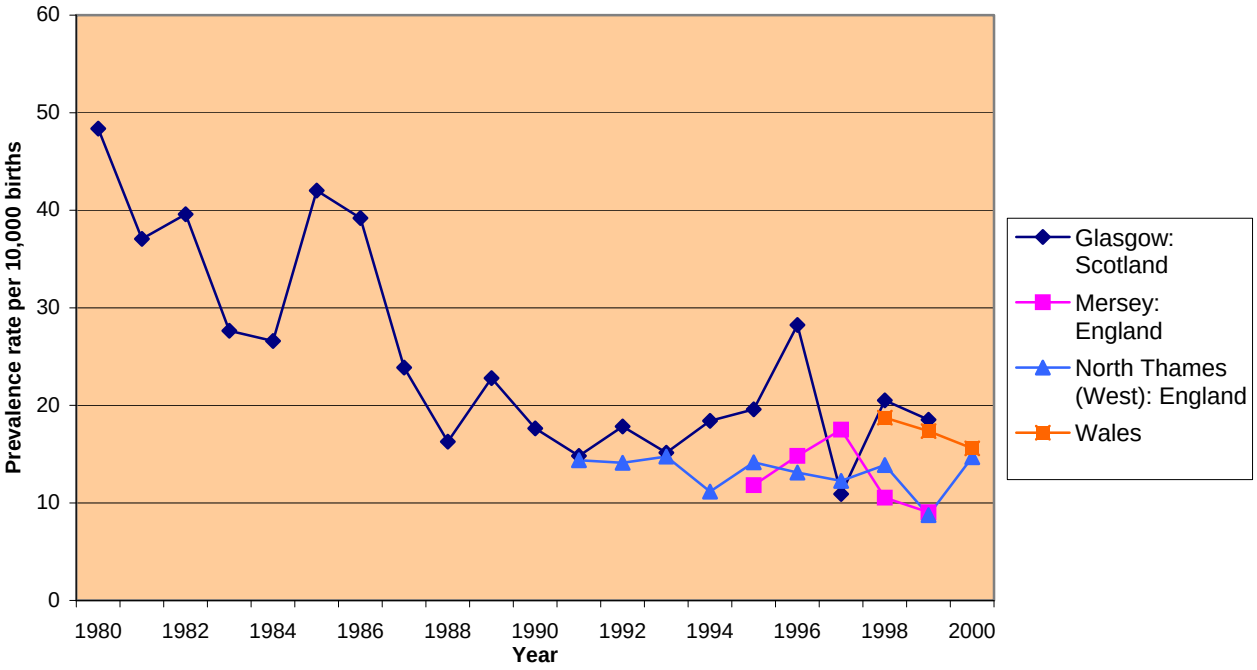
Thanks to Margaret Slane of the Health Promotion Agency in Northern Ireland and Margaret Boyle, Senior Medical Officer, Department of Health, Social Services and Personal Safety Northern Ireland for their input about the situation in Northern Ireland.

United Kingdom (Glasgow, Mersey, North Thames (West) and Wales): Total Prevalence Rate for Neural Tube Defects



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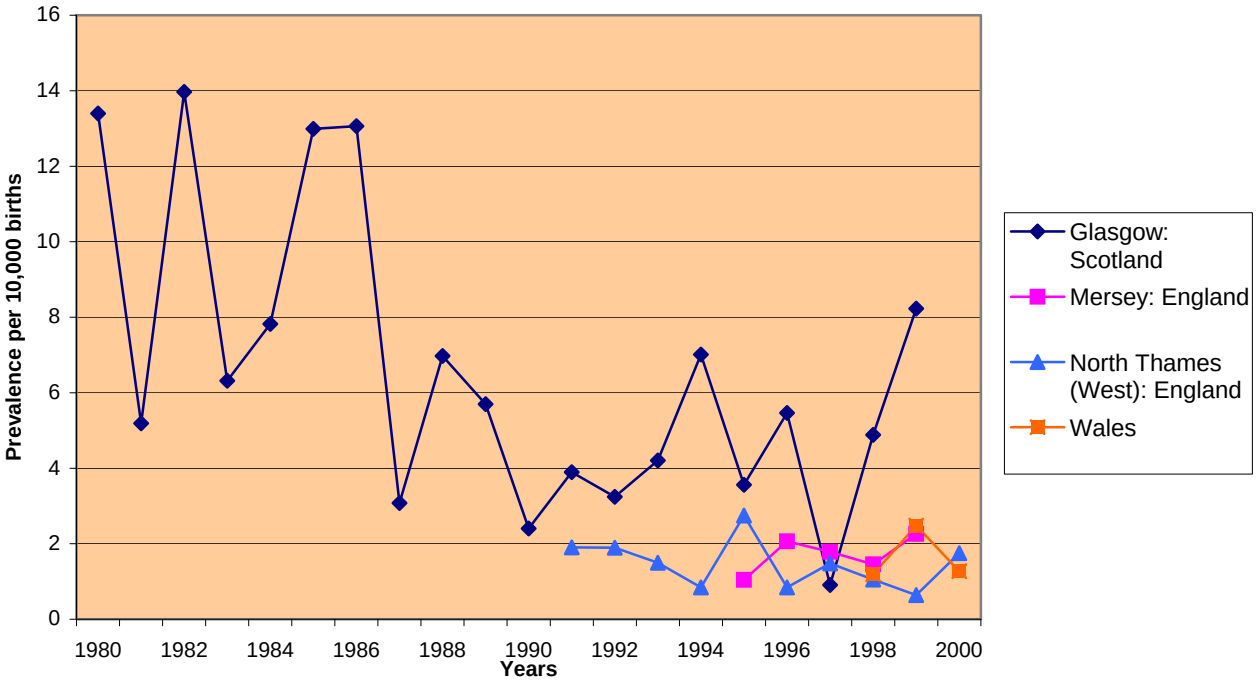
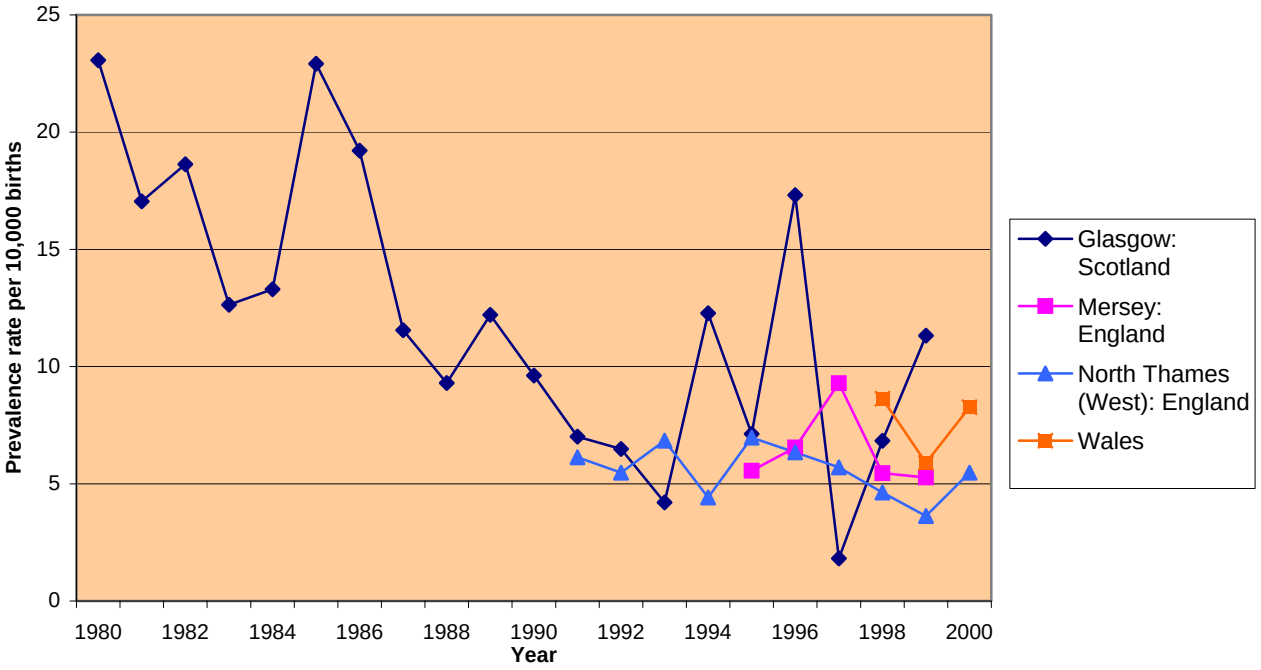


United Kingdom (Glasgow, Mersey, North Thames (West) and Wales): Total Prevalence Rate for Spina Bifida



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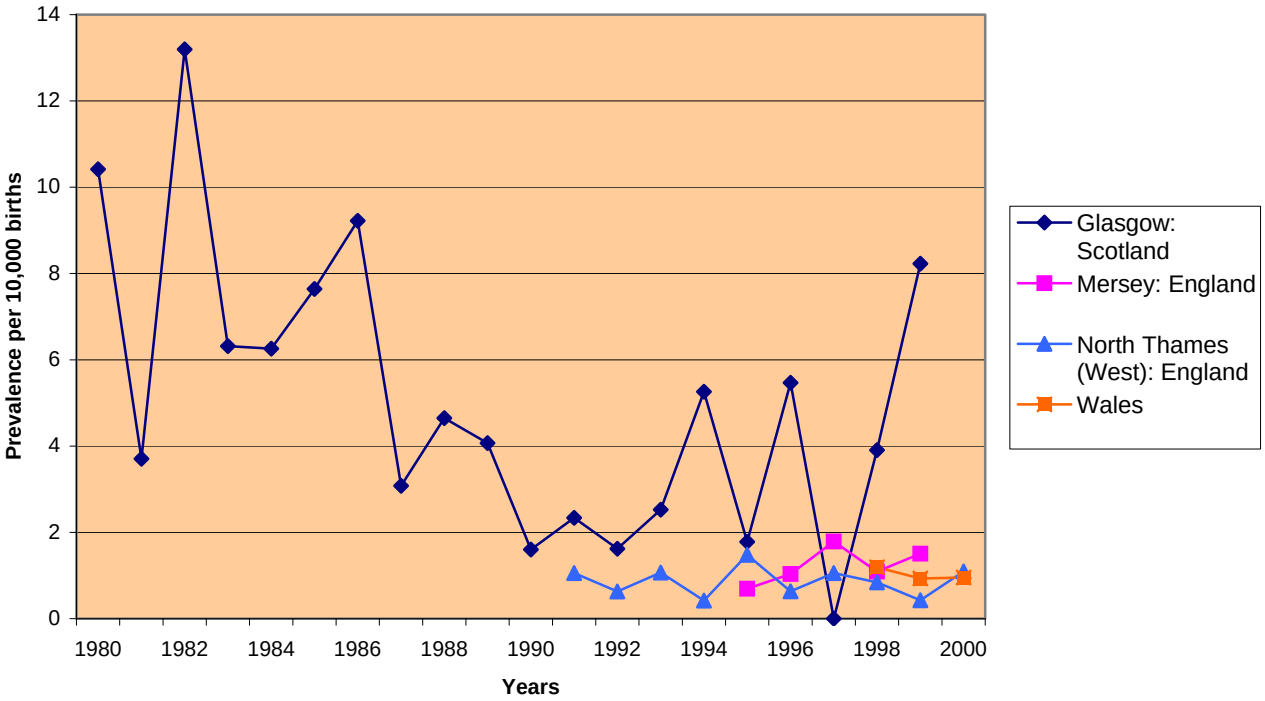
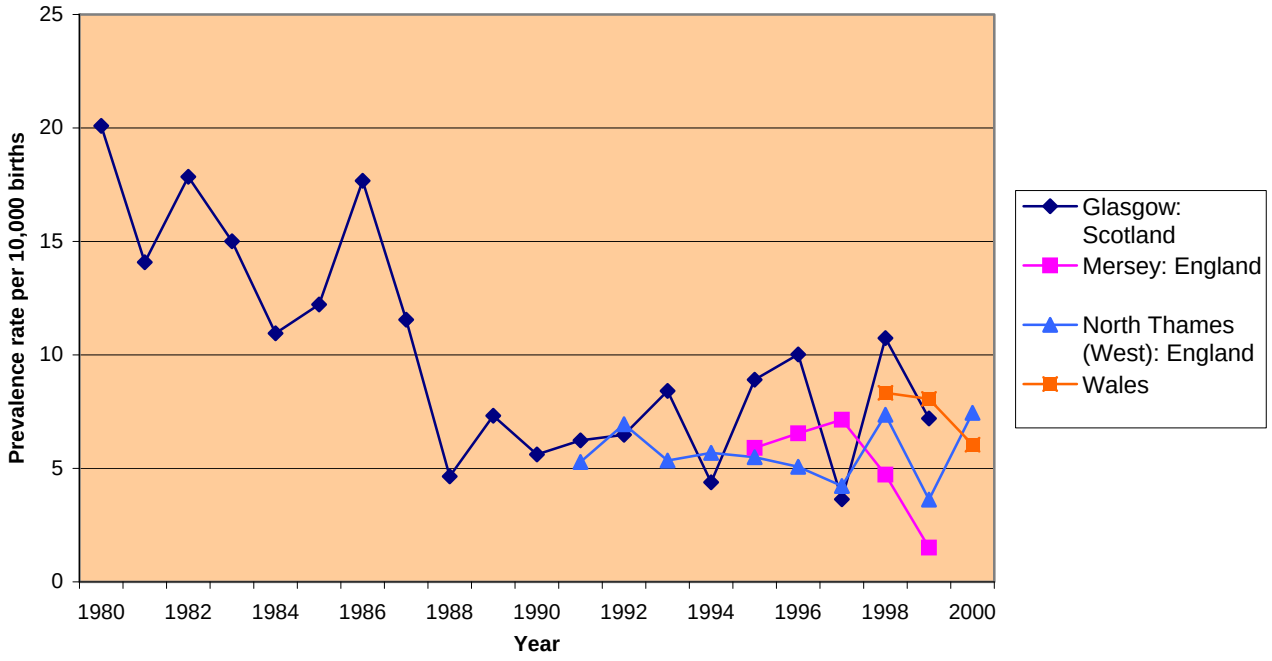
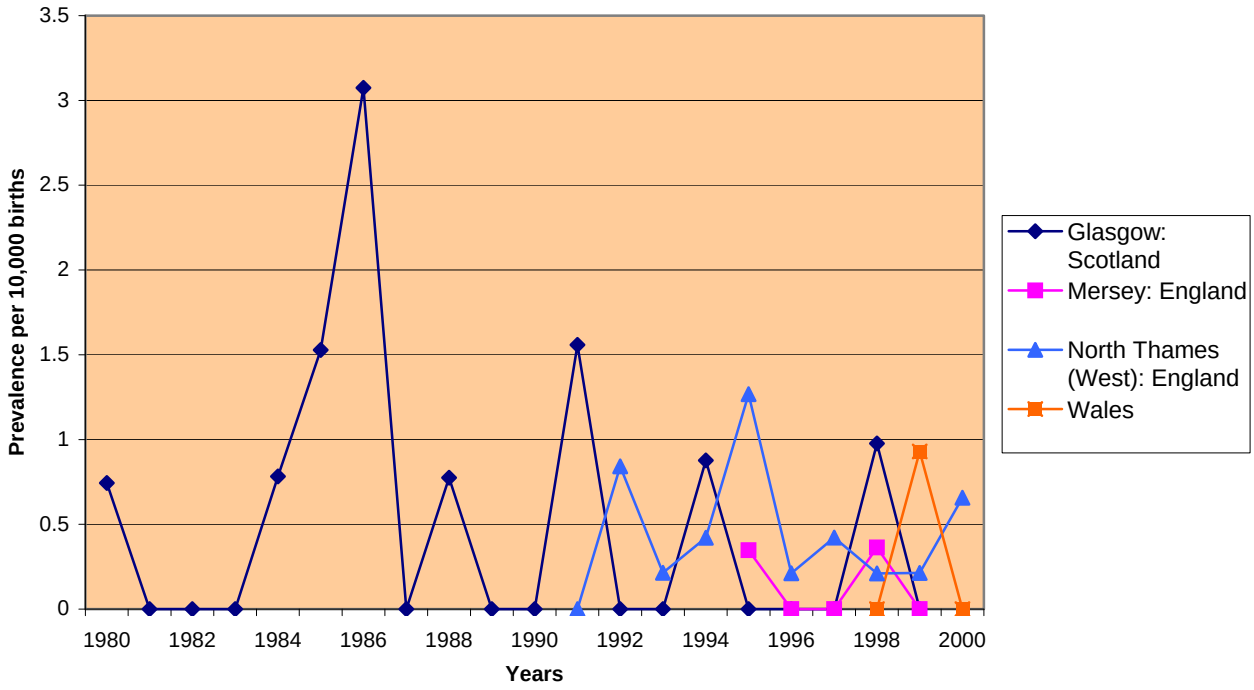


United Kingdom (Glasgow, Mersey, North Thames (West) and Wales): Total Prevalence Rate for Anencephalus



United Kingdom (Glasgow, Mersey, North Thames (West) and Wales): Livebirth Prevalence Rate for Anencephalus



Part III

Appendices

Appendix 1

Definition and ICD codes of Neural Tube Defects, Anencephaly and Spina Bifida

(Extract from EUROCAT Guide 1.2)

Subgroup	**ICD9-BPA**	**ICD10-BPA**	**Exclusions**
Neural Tube Defects: Neural tube defects include Anencephalus, encephalocele, spina bifida and iniencephaly	7400-7420	Q00,Q01, Q05, Q070	
Anencephalus and similar: Absence or deficiency of a major portion of the cranial vault, the covering skin and the brain tissue	7400-7401	Q000 and Q001	
Spina Bifida: Midline defect of the osseous spine usually affecting the posterior arches resulting in a herniation or exposure of the spinal cord and/or meninges	7410, 7419	Q050-Q059, Q070	Exclude association with Anencephalus

Appendix 2

Methods and Results of Poisson Regression Analysis

METHODS

The analysis included all registries and years for which data were available on the prevalence of neural tube defects (including information on induced abortions). Table A2 shows the years of data and the folic acid policy codes used for the analysis. Registries were analysed in two separate groups: UK plus Ireland and Continental Europe. Neural Tube Defect total prevalence rates are calculated by dividing the number of cases (liveborn, fetal deaths from 20 weeks gestation, or induced abortions following prenatal diagnosis) by the number of births. Neural tube defect total prevalence rates per 10,000 births were calculated for individual registries, by year, and by folic acid policy code. Folic acid policy codes were:

A= official policy of folic acid supplementation plus health education campaign
B1=official of folic acid supplementation policy with no education campaign
B2=official policy of encouraging diet rich in folate with / without an education campaign
C = no policy or education campaign
D = pre 1992 data: this code represents births which took place in years prior to conclusion evidence being available about the role of folic acid in the prevention of neural tube defects; thus distinguishing these years from code C in which although there was no policy in the country clinicians and some individuals may have been aware of the benefit of taking folic acid supplements.

The analysis was undertaken using two folic acid policy classifications, the first essentially examines whether folic acid supplementation affects NTD rates, and the second examines the possible additional effect of an education campaign on the folic acid supplementation policy. In these analyses dietary folate has been classified as equivalent to no policy:

Analysis 1 (3 levels):

- D
- C and B2 combined
- A and B1 combined

Analysis 2 (4 levels):

- D
- C and B2 combined
- B1
- A

Prevalence rates and 95% confidence intervals were calculated in Stata (Stata Statistical Software, Release 7.0, College Station, TX: Stata Corporation) using the tabrate command (authors David Clayton, MRC Biostatistical Research Unit, Cambridge, Michael Hills, London School of Hygiene and Tropical Medicine, London) which calculates exact Poisson confidence intervals (Hamilton 1990; Hoel 1984). Chi squared tests for heterogeneity and trend were also performed in STATA using the tabrate command.

Poisson regression was used to model the effect of folic acid supplementation policy on NTD rate. Incident rate ratios were obtained for the effect of policy on the NTD rate using pre 1992

years as the baseline (RR = 1.0) controlling for the effect of registry, year (as both a linear and quadratic term) and any interaction between registry and year. Likelihood ratio tests were performed to assess the significance of registry, year and their interaction in the model and to test for the effect of policy on the NTD rate.

Table A2.1: Years of data by Registry and Policy Type for the years for which NTD data were available

Registry	Country	Policy Type* (relevant years)				
		A	**B1**	**B2**	**C**	**D**
Antwerp	Belgium	-	-	-	1993-1999	1990-1992
Asturias	Spain	-	-	-	1993-1999	1990-1992
Barcelona	Spain	-	-	-	1993-1999	1992
Basque Country	Spain	-	-	-	1993-2000	1990-1992
Bulgaria	Bulgaria	-	-	-	1996-1999	-
Campania	Italy	-	-	-	1996-2000	-
Central East France	France	-	-	-	1993-2000	1985-1992
Croatia	Croatia	-	-	-	1993-2000	1983-1992
Dublin	Ireland	1994-2000	-	-	1993	1980-1992
Finland	Finland	-	-	1996-2000	1993-1995	-
Galway	Ireland	1994-1999	-	-	1993	1981-1992
Glasgow	UK	1996-1999	1993-1995	-	-	1980-1992
Hainaut	Belgium	-	-	-	1993-1999	1980-1992
Mainz	Germany	-	-		1993-1998	1990-1992
Malta	Malta	-	-	1995-2000	1993-1994	1986-1992
Mersey	UK	1996-1999	1995	-	-	-
North Thames (West)	UK	1996-1999	1993-1995	-	-	1991-1992
North-East Italy	Italy	-	-	-	1993-1999	1988-1992
Northern Netherlands	Netherlands	1996-2000	1993-1995	-	-	1981-1992
Norway	Norway	1999-2000	-	-	-	-
Odense		1998-2000	-	-	1993-1997	1980-1992
Paris	France	-	-	-	1993-2000	1981-1992
Saxony-Anhalt	Germany	-		-	1993-2000	1987-1992
Southern Portugal	Portugal	-	1999-2000	-	1993-1998	1990-1992
Strasbourg	France	-	-	-	1993-2000	1982-1992
Styria	Austria	-	-	-	1993-1999	1985-1992
Tuscany	Italy	-	-	-	2000	1980-1992
Vaud	Switzerland	-	1997-2000	-	1996	1989-1992
Wales	UK	1998-2000	-	-	-	-

* **A**= folic acid supplementation + health education; **B1**=folic acid supplementation, no education; **B2**= diet rich in folate +/- education; **C** = no policy or education; **D** = pre 1992 data before MRC vitamin study.

Results

Univariate Analysis

Prevalence Rates by year and policy type

The NTD rate showed a consistent decline across years from 47.12 in 1980 to only 13.65 in 2000, less than a third of the 1980 rate. This decline was statistically significant ($p<0.001$) (Table 3).

Table A2.2: NTD Total Prevalence (per 10,000 births) by registry, UK and Ireland only, Chi^2 for heterogeneity 192.53 $p<0.001$

Registry	Cases	Births	Prevalence (95% CI)
Dublin	940	441654	21.28 (19.97-22.69)
Galway	84	54509	15.41 (12.44-19.09)
Glasgow	627	243634	25.74 (23.80-27.83)
North Thames (West)	618	471189	13.12 (12.12-14.19)
Mersey	179	139867	12.80 (11.05-14.82)
Wales	168	97325	17.26 (14.84-20.08)

The prevalence of NTDs by policy type is shown in Table A2.4. The trend in prevalence across policy type levels is also significant ($p<0.001$).

Table A2.3: NTD total prevalence by year, UK and Ireland only, Chi^2 for trend 460.43, $p<0.001$

Year	Cases	Births	Prevalence	(95%	CI)
1980	188	39898	47.12	(40.84 -	54.36)
1981	155	42547	36.43	(31.12 -	42.64)
1982	154	41310	37.28	(31.83 -	43.66)
1983	121	39410	30.70	(25.69 -	36.69)
1984	102	38363	26.59	(21.90 -	32.28)
1985	124	38299	32.38	(27.15 -	38.61)
1986	112	37876	29.57	(24.57 -	35.59)
1987	84	36806	22.82	(18.43 -	28.26)
1988	68	35596	19.10	(15.06 -	24.23)
1989	58	33839	17.14	(13.25 -	22.17)
1990	55	34555	15.92	(12.22 -	20.73)
1991	118	82539	14.30	(11.94 -	17.12)
1992	131	81431	16.09	(13.56 -	19.09)
1993	111	79781	13.91	(11.55 -	16.76)
1994	100	79720	12.54	(10.31 -	15.26)
1995	146	108323	13.48	(11.46 -	15.85)
1996	151	109153	13.83	(11.79 -	16.23)
1997	140	109180	12.82	(10.87 -	15.13)
1998	202	142546	14.17	(12.35 -	16.27)
1999	162	138815	11.67	(10.01 -	13.61)
2000	134	98191	13.65	(11.52 -	16.17)

Table A2.4: NTD prevalence (per 10,000 births) by folic acid code, UK and Ireland only, Chi^2 for trend code group 1: 307.21 p<0.001, and code group 2: 284.38, p<0.001

Code	Cases	Births	Prevalence	(95%	CI)
Code Group 1:					
D	1339	501038	26.73	(25.33 -	28.20)
B2 and C	155	102567	15.11	(12.91 -	17.69)
A and B1	1122	844573	13.29	(12.53 -	14.09)
Code Group 2:					
D	1339	501038	26.73	(25.33 -	28.20)
B2 and C	155	102567	15.11	(12.91 -	17.69)
B1	284	204915	13.86	(12.34 -	15.57)
A	838	639658	13.10	(12.24 -	14.02)

The NTD rate in continental Europe in contrast to the UK and Ireland registries does not show a consistent decline over time (Table A2.6) ; 1980 and 1981 have slightly higher rates but thereafter the rates fluctuate around 7-9 per 10,000 births with no notable trend (p=0.39, 1980-2000).

Table A2.5: NTD prevalence (per 10,000 births) by registry, Continental Europe, Chi^2 for heterogeneity 579.63, p<0.001

Registry	Cases	Births	Prevalence	(95%	CI)
Hainaut (Belgium)	232	214340	10.82	(9.52 -	12.31)
Odense (Denmark)	131	111970	11.70	(9.86 -	13.89)
Paris (France)	887	738666	12.01	(11.24 -	12.83)
Tuscany (Italy)	254	333133	7.63	(6.74 -	8.62)
(Northern Netherlands	341	308594	11.05	(9.94 -	12.29)
Strasbourg (France)	275	254048	10.83	(9.62 -	12.18)
Vaud (Switzerland)	93	92089	10.10	(8.24 -	12.38)
Croatia	59	109070	5.41	(4.19 -	6.98)
Malta	83	75626	10.98	(8.85 -	13.61)
North-East Italy	402	619204	6.49	(5.89 -	7.16)
Southern Portugal	79	131991	5.99	(4.80 -	7.46)
Antwerp (Belgium)	98	109002	8.99	(7.38 -	10.96)
Basque Country (Spain)	203	178583	11.37	(9.91 -	13.04)
Asturias (Spain)	90	68897	13.06	(10.63 -	16.06)
Saxony-Anhalt (Germany)	185	161920	11.43	(9.89 -	13.20)
Mainz (Germany)	70	37616	18.61	(14.72 -	23.52)
Barcelona (Spain)	90	99248	9.07	(7.38 -	11.15)
Finland	423	486577	8.69	(7.90 -	9.56)
Styria (Austria)	153	192348	7.95	(6.79 -	9.32)
Bulgaria	72	38257	18.82	(14.94 -	23.71)
Campania (Italy)	176	246252	7.15	(6.17 -	8.29)
Central East France	850	1588618	5.35	(5.00 -	5.72)
Norway	131	120122	10.91	(9.19 –	12.94)

The prevalence rates of NTD by policy type are shown in Table A2.7. There is no significant trend in prevalence by policy however for either code group (p=0.63, p=0.20).

Table A2.6: NTD prevalence (per 10,000 births) by year, Continental Europe, Chi^2 for trend 0.71, p=0.39

Year	Cases	Births	Prevalence	(95%	CI)
1980	30	23293	12.88	(9.01 -	18.42)
1981	74	66952	11.05	(8.80 -	13.88)
1982	68	80102	8.49	(6.69 -	10.77)
1983	91	80984	11.24	(9.15 -	13.80)
1984	96	81543	11.77	(9.64 -	14.38)
1985	154	187626	8.21	(7.01 -	9.61)
1986	161	200568	8.03	(6.88 -	9.37)
1987	171	215396	7.94	(6.83 -	9.22)
1988	204	262819	7.76	(6.77 -	8.90)
1989	239	292700	8.17	(7.19 -	9.27)
1990	321	343429	9.35	(8.38 -	10.43)
1991	266	338666	7.85	(6.97 -	8.86)
1992	289	365438	7.91	(7.05 -	8.88)
1993	334	419546	7.96	(7.15 -	8.86)
1994	344	421082	8.17	(7.35 -	9.08)
1995	358	431266	8.30	(7.48 -	9.21)
1996	467	495164	9.43	(8.61 -	10.33)
1997	406	503303	8.07	(7.32 -	8.89)
1998	449	501867	8.95	(8.16 -	9.81)
1999	464	563604	8.23	(7.52 -	9.02)
2000	391	440823	8.87	(8.03 -	9.79)

Table A2.7: NTD prevalence (per 10,000 births) by folic acid code, continental Europe, Chi^2 for trend code group 1: 0.24, p=0.63, and code group2: 1,62, p<0.20

Code	Cases	Births	Prevalence	(95%	CI)
Code Group 1:					
D	1875	2174078	8.62	(8.24 -	9.02)
B2 and C	3182	3818080	8.33	(8.05 -	8.63)
A and B1	320	324013	9.88	(8.85 -	11.02)
Code Group 2:					
D	1875	2174078	8.62	(8.24 -	9.02)
B2 and C	3182	3818080	8.33	(8.05 -	8.63)
B1	77	88049	8.75	(7.00 -	10.93)
A	243	235964	10.30	(9.08 -	11.68)

Regression analysis

Table A2.8 shows the results of the multivariate analysis for continental Europe and UK plus Ireland separately. The three level analysis in continental Europe shows a decreasing trend in the rate of NTD by policy type, with a significant rate ratio of 0.67 in the policy type A and B1 combined (ie. policy with or without education campaign) compared with years in which there was no intervention. In the four level analysis the additional effect of an education campaign is associated with a (non-significant) increase in the rate ratio compared with the group with folic acid supplementation policy and no education campaign. The likelihood ratio tests show that whilst the association between year and NTD rate is not significant ($p>0.5$), both linear and quadratic year and the interactions between linear and quadratic year and registry are significant in the model ($p<=0.02$) as is the effect of registry (<0.001). Removing policy from the model does not significantly alter the model either for the 3 level model ($p=0.097$) or the 4 level model ($p=0.096$).

The analysis of NTD and policy for the UK and Ireland shows an increase in NTD prevalence by policy type ($p<?$) although this is not significant in any one policy group compared to the pre-1992 baseline. In these countries the association between year and NTD rate is significant ($p<0.001$) and likelihood ratio tests indicate that year and the interaction between year and registry is also significant for both linear and quadratic year ($p<0.01$). Removing policy from the model does not have a significant effect (likelihood ratio tests for the 3 level model=0.53 and for the 4 level model $p= 0.65$).

Table A2.8: Multivariate analysis results (all rate ratios adjusted for year [linear and quadratic], registry and any interaction between year and registry).

Europe			
Cases	**RR**	**95% CI**	**p value**
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

Appendix 3

NTD, Anencephaly and Spina Bifida:

Number of cases by type of birth[1], population (births), total prevalence rate and livebirth prevalence rate[2] (per 10,000 births) by year and registry: 32 EUROCAT registries, 1980-2000

[1] Fetal deaths from 20 weeks gestation (including stillbirths), induced abortion following prenatal diagnosis

[2] For simplicity livebirth prevalence rates have been calculated using all births as denominators

Table A3.1: Neural Tube Defects: Number of cases by type of birth[1], population (births), total prevalence rate and livebirth prevalence rate (per 10,000 births) by year and registry: 32 EUROCAT registries, 1980-2000

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Styria (Austria)																							
total cases						10	12	9	8	11	14	10	12	10	12	11	7	10	8	9		153	153
livebirths						7	8	4	1	5	6	6	5	4	5	8	4	6	2	4		75	75
fetal deaths						0	0	1	0	1	2	1	4	1	0	1	0	0	0	1		12	12
induced abortions						3	4	4	7	5	6	3	3	5	7	2	3	4	6	4		66	66
population:						13663	13303	13276	13340	13161	13349	13794	13744	13395	12988	12276	12465	11768	11026	10800		192348	192348
Total Prevalence						7.32	9.02	6.78	6.00	8.36	10.49	7.25	8.73	7.47	9.24	8.96	5.62	8.50	7.26	8.33		7.95	7.95
Livebirth Prevalence						5.12	6.01	3.01	0.75	3.80	4.49	4.35	3.64	2.99	3.85	6.52	3.21	5.10	1.81	3.70		3.90	3.90
Antwerp (Belgium)																							
total cases											9	8	2	9	12	8	8	16	15	11		98	98
livebirths											4	2	0	7	6	4	2	2	6	1		34	34
fetal deaths											2	1	0	0	1	0	0	0	0	0		4	4
induced abortions											3	5	2	2	5	4	6	14	9	10		60	60
population:											3740	4688	6180	7555	10964	10899	10796	18282	17930	17968		109002	109002
Total Prevalence											24.06	17.06	3.24	11.91	10.94	7.34	7.41	8.75	8.37	6.12		8.99	8.99
Livebirth Prevalence											10.70	4.27	0.00	9.27	5.47	3.67	1.85	1.09	3.35	0.56		3.12	3.12
Hainaut (Belgium)																							
total cases	10	11	4	7	10	9	12	14	4	14	18	17	17	11	10	11	17	12	14	10		232	232
livebirths	6	4	2	2	5	2	4	3	0	7	6	6	6	5	5	5	7	1	3	3		82	82
fetal deaths	0	5	0	2	0	2	2	1	0	2	5	2	1	0	2	0	0	0	1	0		25	25
induced abortions	4	2	2	3	5	5	6	10	4	5	7	9	10	6	3	6	10	11	10	7		125	125
population:	8449	8204	8209	7862	8066	8182	8380	8518	8805	13579	13503	13595	13328	12583	12273	11933	12416	12314	12044	12097		214340	214340
Total Prevalence	11.84	13.41	4.87	8.90	12.40	11.00	14.32	16.44	4.54	10.31	13.33	12.50	12.76	8.74	8.15	9.22	13.69	9.75	11.62	8.27		10.82	10.82
Livebirth Prevalence	7.10	4.88	2.44	2.54	6.20	2.44	4.77	3.52	0.00	5.16	4.44	4.41	4.50	3.97	4.07	4.19	5.64	0.81	2.49	2.48		3.83	3.83
Bulgaria																							
total cases																	16	17	23	16		72	72
livebirths																	9	9	6	8		32	32
fetal deaths																	5	2	7	4		18	18
induced abortions																	2	6	10	4		22	22
population:																	9908	9004	9177	10168		38257	38257
Total Prevalence																	16.15	18.88	25.06	15.74		18.82	18.82
Livebirth Prevalence																	9.08	10.00	6.54	7.87		8.36	8.36

Neural Tube Defects (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Croatia																							
total cases				2	4	2	4	3	4	4	5	5	5	5	2	0	0	5	5	2	2	57	59
livebirths				0	4	1	3	3	2	4	5	5	5	4	2	0	0	1	2	2	1	43	44
fetal deaths				2	0	1	1	0	2	0	0	0	0	0	0	0	0	2	0	0	0	8	8
induced abortions				0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	3	0	1	6	7
population:				4023	4029	3784	6867	6686	6183	7329	6948	7003	6481	6532	6135	6280	6435	6337	6170	6033	5815	103255	109070
Total Prevalence				4.97	9.93	5.29	5.82	4.49	6.47	5.46	7.20	7.14	7.71	7.65	3.26	0.00	0.00	7.89	8.10	3.32	3.44	5.52	5.41
Livebirth Prevalence				0.00	9.93	2.64	4.37	4.49	3.23	5.46	7.20	7.14	7.71	6.12	3.26	0.00	0.00	1.58	3.24	3.32	1.72	4.16	4.03
Odense (Denmark)																							
total cases	9	5	4	8	8	1	6	10	5	7	6	10	3	4	4	10	6	5	5	8	7	124	131
livebirths	4	2	2	5	3	0	2	5	3	5	2	6	1	4	2	5	4	2	2	6	5	65	70
fetal deaths	4	3	1	1	1	0	3	2	0	1	1	2	1	0	1	1	1	2	1	0	1	26	27
induced abortions	1	0	1	2	4	1	1	3	2	1	3	2	1	0	1	4	1	1	2	2	1	33	34
population:	5148	4604	4478	4309	4471	4698	4849	4852	5066	5287	5694	5752	6059	5946	6108	6153	5875	5807	5429	5689	5696	106274	111970
Total Prevalence	17.48	10.86	8.93	18.57	17.89	2.13	12.37	20.61	9.87	13.24	10.54	17.39	4.95	6.73	6.55	16.25	10.21	8.61	9.21	14.06	12.29	11.67	11.70
Livebirth Prevalence	7.77	4.34	4.47	11.60	6.71	0.00	4.12	10.31	5.92	9.46	3.51	10.43	1.65	6.73	3.27	8.13	6.81	3.44	3.68	10.55	8.78	6.12	6.25
Paris (France)																							
total cases		36	27	43	38	46	41	40	38	55	51	46	41	44	42	57	46	40	41	55	60	827	887
livebirths		18	11	10	7	3	5	10	3	7	7	5	3	5	3	5	6	5	5	1	5	119	124
fetal deaths		10	7	11	5	7	12	3	4	6	4	2	2	2	1	0	0	0	2	4	2	82	84
induced abortions		8	9	22	26	36	24	27	31	42	40	39	36	37	38	52	40	35	34	50	53	626	679
population:		36917	36741	35781	35902	36536	36384	36080	36672	36866	37302	37541	36469	35819	35918	36884	37237	37272	38160	38785	39400	699266	738666
Total Prevalence		9.75	7.35	12.02	10.58	12.59	11.27	11.09	10.36	14.92	13.67	12.25	11.24	12.28	11.69	15.45	12.35	10.73	10.74	14.18	15.23	11.83	12.01
Livebirth Prevalence		4.88	2.99	2.79	1.95	0.82	1.37	2.77	0.82	1.90	1.88	1.33	0.82	1.40	0.84	1.36	1.61	1.34	1.31	0.26	1.27	1.70	1.68
Strasbourg (France)																							
total cases			14	10	20	9	15	9	12	13	13	12	17	14	12	15	19	15	16	20	20	255	275
livebirths			7	6	7	1	6	0	2	0	2	1	4	2	2	0	4	2	4	2	2	52	54
fetal deaths			2	2	2	1	2	3	2	0	2	0	1	0	1	0	1	2	2	0	0	23	23
induced abortions			5	2	11	7	7	6	8	13	9	11	12	12	9	15	14	11	10	18	18	180	198
population:			13662	12519	12924	13166	13112	12895	13595	13425	13775	13770	13736	13148	12865	13313	13185	13237	13656	13827	14238	239810	254048
Total Prevalence			10.25	7.99	15.48	6.84	11.44	6.98	8.83	9.68	9.44	8.71	12.38	10.65	9.33	11.27	14.41	11.33	11.72	14.46	14.05	10.63	10.82
Livebirth Prevalence			5.12	4.79	5.42	0.76	4.58	0.00	1.47	0.00	1.45	0.73	2.91	1.52	1.55	0.00	3.03	1.51	2.93	1.45	1.40	2.17	2.13

Neural Tube Defects (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Mainz (Germany)																							
total cases											4	3	5	8	4	7	12	12	10	5		70	70
livebirths											2	2	5	1	2	6	9	9	6	3		45	45
fetal deaths											1	0	0	0	1	1	1	1	1	0		6	6
induced abortions											1	1	0	7	1	0	2	2	3	2		19	19
population:											3903	4113	3941	4020	3769	3560	3603	3890	3542	3275		37616	37616
Total Prevalence											10.25	7.29	12.69	19.90	10.61	19.66	33.31	30.85	28.23	15.27		18.61	18.61
Livebirth Prevalence											5.12	4.86	12.69	2.49	5.31	16.85	24.98	23.14	16.94	9.16		11.96	11.96
Saxony-Anhalt (Germany)																							
total cases								32	23	24	22	1	1	4	5	5	15	15	9	11	18	167	185
livebirths								12	8	8	9	1	1	2	2	2	5	5	2	4	5	61	66
fetal deaths								6	2	1	3	0	0	1	1	0	0	0	0	0	0	14	14
induced abortions								14	13	15	10	0	0	1	2	3	10	10	7	7	13	92	105
population:								17165	16623	15202	14536	9123	7633	6910	7557	7707	8928	9606	10554	11500	18876	143044	161920
Total Prevalence								18.64	13.84	15.79	15.13	1.10	1.31	5.79	6.62	6.49	16.80	15.62	8.53	9.57	9.54	11.67	11.43
Livebirth Prevalence								6.99	4.81	5.26	6.19	1.10	1.31	2.89	2.65	2.60	5.60	5.21	1.90	3.48	2.65	4.26	4.08
Dublin (Ireland)																							
total cases	123	99	96	79	64	56	51	47	41	29	30	27	34	23	23	21	15	19	22	23	18	922	940
livebirths	78	65	67	61	41	36	41	30	27	19	21	20	24	20	19	18	12	16	18	17	17	650	667
fetal deaths	45	34	29	18	23	20	10	17	14	10	9	7	10	3	4	3	3	3	4	6	1	272	273
induced abortions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
population:	26460	25510	24822	23352	22312	22131	21708	20768	19830	18914	19393	19800	18933	18491	18412	18550	19288	20257	20887	20746	21090	420564	441654
Total Prevalence	46.49	38.81	38.68	33.83	28.68	25.30	23.49	22.63	20.68	15.33	15.47	13.64	17.96	12.44	12.49	11.32	7.78	9.38	10.53	11.09	8.53	21.92	21.28
Livebirth Prevalence	29.48	25.48	26.99	26.12	18.38	16.27	18.89	14.45	13.62	10.05	10.83	10.10	12.68	10.82	10.32	9.70	6.22	7.90	8.62	8.19	8.06	15.46	15.10
Galway (Ireland)																							
total cases		6	7	7	4	13	10	6	6	1	3	4	8	1	3	2	0	2	1	0		84	84
livebirths		6	5	4	3	11	8	4	5	1	3	3	7	1	2	1	0	1	1	0		66	66
fetal deaths		0	2	3	1	2	2	2	1	0	0	1	1	0	1	1	0	1	0	0		18	18
induced abortions		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
population:		3546	3604	3397	3268	3079	3155	3051	2858	2636	2691	2578	2666	2645	2375	2436	2534	2588	2747	2655		54509	54509
Total Prevalence		16.92	19.42	20.61	12.24	42.22	31.70	19.67	20.99	3.79	11.15	15.52	30.01	3.78	12.63	8.21	0.00	7.73	3.64	0.00		15.41	15.41
Livebirth Prevalence		16.92	13.87	11.78	9.18	35.73	25.36	13.11	17.49	3.79	11.15	11.64	26.26	3.78	8.42	4.11	0.00	3.86	3.64	0.00		12.11	12.11

Neural Tube Defects (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Campania (Italy)																							
total cases																	45	30	30	32	39	176	176
livebirths																	19	14	6	12	16	67	67
fetal deaths																	1	1	3	2	0	7	7
induced abortions																	25	15	21	18	23	102	102
population:																	46658	50458	51568	47397	50171	246252	246252
Total Prevalence																	9.64	5.95	5.82	6.75	7.77	7.15	7.15
Livebirth Prevalence																	4.07	2.77	1.16	2.53	3.19	2.72	2.72
Emilia Romagna (Italy)																							
total cases		7	10	16	11	13	18	10	6	10	12	15	11	9	10	5	5	7	16	7	18	198	216
livebirths		7	8	13	11	12	16	10	5	9	12	15	9	8	8	5	4	7	8	5	2	172	174
fetal deaths		0	2	3	0	1	2	0	1	1	0	0	0	1	1	0	0	0	0	2	1	14	15
induced abortions		0	0	0	0	0	0	0	0	0	0	0	2	0	1	0	1	0	8	0	15	12	27
population:		13189	18364	21769	23155	24016	22868	22726	22760	23380	23524	25095	25002	24533	25886	26359	28873	28859	20928	24003	24839	445289	470128
Total Prevalence		5.31	5.45	7.35	4.75	5.41	7.87	4.40	2.64	4.28	5.10	5.98	4.40	3.67	3.86	1.90	1.73	2.43	7.65	2.92	7.25	4.45	4.59
Livebirth Prevalence		5.31	4.36	5.97	4.75	5.00	7.00	4.40	2.20	3.85	5.10	5.98	3.60	3.26	3.09	1.90	1.39	2.43	3.82	2.08	0.81	3.86	3.70
North-East Italy																							
total cases		27	22	25	34	15	23	25	32	38	39	28	28	29	37	29	49	32	42	19		573	573
livebirths		20	21	21	27	14	18	23	16	13	18	10	10	8	8	6	11	9	14	5		272	272
fetal deaths		7	1	4	7	1	5	0	3	6	2	1	2	0	1	1	1	1	1	0		44	44
induced abortions		0	0	0	0	0	0	2	13	19	19	17	16	21	28	22	37	22	27	14		257	257
population:		27708	36321	41195	43202	43401	41265	42048	45307	47515	52205	51093	50340	49735	49443	51486	56869	55908	54939	54364		894344	894344
Total Prevalence		9.74	6.06	6.07	7.87	3.46	5.57	5.95	7.06	8.00	7.47	5.48	5.56	5.83	7.48	5.63	8.62	5.72	7.64	3.49		6.41	6.41
Livebirth Prevalence		7.22	5.78	5.10	6.25	3.23	4.36	5.47	3.53	2.74	3.45	1.96	1.99	1.61	1.62	1.17	1.93	1.61	2.55	0.92		3.04	3.04
South East Sicily (Italy)																							
total cases												15	15	10	10	4	5	6	9	10	15	84	99
livebirths												14	11	9	10	4	5	6	9	10	6	78	84
fetal deaths												1	4	1	0	0	0	0	0	0	0	6	6
induced abortions																					9	0	9
population:												19430	20273	19746	20031	18986	18054	18795	16922	16942	15304	169179	184483
Total Prevalence												7.72	7.40	5.06	4.99	2.11	2.77	3.19	5.32	5.90	9.80	4.97	5.37
Livebirth Prevalence												7.21	5.43	4.56	4.99	2.11	2.77	3.19	5.32	5.90	3.92	4.61	4.55

Neural Tube Defects (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Tuscany (Italy)																							
total cases	11	14	8	7	5	16	9	8	6	13	11	2	18	18	12	13	14	14	22	14	19	235	254
livebirths	8	10	4	5	3	6	1	2	1	6	4	0	5	8	2	5	4	1	6	5	4	86	90
fetal deaths	3	4	1	0	0	1	0	0	0	2	0	0	1	0	0	0	1	0	1	0	1	14	15
induced abortions	0	0	3	2	2	9	8	6	5	5	7	2	12	10	10	8	9	13	15	9	14	135	149
population:	9696	9350	9281	8948	8592	8980	8477	8511	8869	8556	8751	8657	25670	24504	24487	24520	24606	24535	25468	26059	26616	306517	333133
Total Prevalence	11.34	14.97	8.62	7.82	5.82	17.82	10.62	9.40	6.77	15.19	12.57	2.31	7.01	7.35	4.90	5.30	5.69	5.71	8.64	5.37	7.14	7.67	7.62
Livebirth Prevalence	8.25	10.70	4.31	5.59	3.49	6.68	1.18	2.35	1.13	7.01	4.57	0.00	1.95	3.26	0.82	2.04	1.63	0.41	2.36	1.92	1.50	2.81	2.70
Malta																							
total cases							9	6	5	7	3	4	6	5	6	6	5	4	6	7	4	79	83
livebirths							6	5	5	6	2	4	5	5	6	6	3	4	5	4	4	66	70
fetal deaths							3	1	0	1	1	0	1	0	0	0	2	0	1	3	0	13	13
induced abortions							0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
population:							5310	5375	5461	5617	5400	5328	5503	5172	4863	4633	4978	4864	4511	4339	4272	71354	75626
Total Prevalence							16.95	11.16	9.16	12.46	5.56	7.51	10.90	9.67	12.34	12.95	10.04	8.22	13.30	16.13	9.36	11.07	10.98
Livebirth Prevalence							11.30	9.30	9.16	10.68	3.70	7.51	9.09	9.67	12.34	12.95	6.03	8.22	11.08	9.22	9.36	9.25	9.26
Northern Netherlands																							
total cases		8	11	14	11	17	13	4	25	16	29	28	23	16	16	18	22	18	15	20	17	324	341
livebirths		5	8	7	7	7	7	2	13	11	18	21	15	7	9	10	10	9	9	9	10	184	194
fetal deaths		2	1	2	2	2	2	1	3	1	6	3	1	2	1	1	2	2	3	2	3	39	42
induced abortions		1	2	5	2	8	4	1	9	4	5	4	7	7	6	7	10	7	3	9	4	101	105
population:		7877	7731	7542	7559	7792	11936	11847	11595	19093	19635	19853	19140	19387	19283	19296	19033	19397	19941	20167	20490	288104	308594
Total Prevalence		10.16	14.23	18.56	14.55	21.82	10.89	3.38	21.56	8.38	14.77	14.10	12.02	8.25	8.30	9.33	11.56	9.28	7.52	9.92	8.30	11.25	11.05
Livebirth Prevalence		6.35	10.35	9.28	9.26	8.98	5.86	1.69	11.21	5.76	9.17	10.58	7.84	3.61	4.67	5.18	5.25	4.64	4.51	4.46	4.88	6.39	6.29
Poland																							
total cases																					129		129
livebirths																					119		119
fetal deaths																					10		10
induced abortions																							0
population:																					158923		158923
Total Prevalence																					8.12		8.12
Livebirth Prevalence																					7.49		7.49

Neural Tube Defects (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Southern Portugal																							
total cases											6	4	4	1	7	8	13	8	2	14	12	67	79
livebirths											3	2	4	1	7	4	6	5	2	4	4	38	42
fetal deaths											0	2	0	0	0	2	1	0	0	0	1	5	6
induced abortions											3	0	0	0	0	2	6	3	0	10	7	24	31
population:											5461	5554	7391	7152	7000	14959	15439	16293	16312	17047	19383	112608	131991
Total Prevalence											10.99	7.20	5.41	1.40	10.00	5.35	8.42	4.91	1.23	8.21	6.19	5.95	5.99
Livebirth Prevalence											5.49	3.60	5.41	1.40	10.00	2.67	3.89	3.07	1.23	2.35	2.06	3.37	3.18
Asturias (Spain)																							
total cases											13	10	9	10	9	7	10	4	15	3		90	90
livebirths											4	2	1	0	1	2	2	1	2	0		15	15
fetal deaths											0	0	1	0	0	0	0	0	0	0		1	1
induced abortions											9	8	7	10	8	5	8	3	13	3		74	74
population:											7722	7693	7474	7012	6626	6553	6507	6473	6321	6516		68897	68897
Total Prevalence											16.84	13.00	12.04	14.26	13.58	10.68	15.37	6.18	23.73	4.60		13.06	13.06
Livebirth Prevalence											5.18	2.60	1.34	0.00	1.51	3.05	3.07	1.54	3.16	0.00		2.18	2.18
Barcelona (Spain)																							
total cases													14	13	10	11	10	8	14	10		90	90
livebirths													2	1	4	4	1	0	4	0		16	16
fetal deaths													1	1	0	1	1	1	1	2		8	8
induced abortions													11	11	6	6	8	7	9	8		66	66
population:													13477	12738	12609	12199	12031	12240	11684	12270		99248	99248
Total Prevalence													10.39	10.21	7.93	9.02	8.31	6.54	11.98	8.15		9.07	9.07
Livebirth Prevalence													1.48	0.79	3.17	3.28	0.83	0.00	3.42	0.00		1.61	1.61
Basque Country (Spain)																							
total cases											23	13	19	12	22	14	19	16	13	30	22	181	203
livebirths											12	7	5	3	7	3	2	4	2	6	4	51	55
fetal deaths											1	0	0	0	1	1	0	1	0	0	1	4	5
induced abortions											10	6	14	9	14	10	17	11	11	24	17	126	143
population:											16438	16291	16316	15891	15357	15397	16060	16397	16169	16859	17408	161175	178583
Total Prevalence											13.99	7.98	11.65	7.55	14.33	9.09	11.83	9.76	8.04	17.79	12.64	11.23	11.37
Livebirth Prevalence											7.30	4.30	3.06	1.89	4.56	1.95	1.25	2.44	1.24	3.56	2.30	3.16	3.08

Neural Tube Defects (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Vaud (Switzerland)																							
total cases										6	6	8	9	7	8	7	15	3	7	5	12	81	93
livebirths										0	2	1	2	2	1	0	5	1	2	1	5	17	22
fetal deaths										0	0	0	0	1	0	1	0	0	0	0	0	2	2
induced abortions										6	4	7	7	4	7	6	10	2	5	4	7	62	69
population:										7212	7697	8211	8076	7700	7683	7697	7730	7562	7438	7465	7618	84471	92089
Total Prevalence										8.32	7.80	9.74	11.14	9.09	10.41	9.09	19.40	3.97	9.41	6.70	15.75	9.59	10.10
Livebirth Prevalence										0.00	2.60	1.22	2.48	2.60	1.30	0.00	6.47	1.32	2.69	1.34	6.56	2.01	2.39
Glasgow (UK:Scotland)																							
total cases	65	50	51	35	34	55	51	31	21	28	22	19	22	18	21	22	31	12	21	18		627	627
livebirths	18	7	18	8	10	17	17	4	9	7	3	5	4	5	8	4	6	1	5	8		164	164
fetal deaths	13	9	3	1	0	3	2	2	0	1	2	1	2	2	0	5	1	3	1	1		52	52
induced abortions	34	34	30	26	24	35	32	25	12	20	17	13	16	11	13	13	24	8	15	9		411	411
population:	13438	13491	12884	12661	12783	13089	13013	12987	12908	12289	12471	12831	12339	11883	11407	11227	10976	10997	10239	9721		243634	243634
Total Prevalence	48.37	37.06	39.58	27.64	26.60	42.02	39.19	23.87	16.27	22.78	17.64	14.81	17.83	15.15	18.41	19.60	28.24	10.91	20.51	18.52		25.74	25.74
Livebirth Prevalence	13.39	5.19	13.97	6.32	7.82	12.99	13.06	3.08	6.97	5.70	2.41	3.90	3.24	4.21	7.01	3.56	5.47	0.91	4.88	8.23		6.73	6.73
Mersey (UK:England)																							
total cases																34	43	49	29	24		179	179
livebirths																3	6	5	4	6		24	24
fetal deaths																1	0	3	4	1		9	9
induced abortions																30	37	41	21	17		146	146
population:																28786	29031	27983	27514	26553		139867	139867
Total Prevalence																11.81	14.81	17.51	10.54	9.04		12.80	12.80
Livebirth Prevalence																1.04	2.07	1.79	1.45	2.26		1.72	1.72
North Thames (West) (UK:England)																							
total cases												68	67	69	53	67	62	58	66	41	67	551	618
livebirths												9	9	7	4	13	4	7	5	3	8	61	69
fetal deaths												3	2	4	3	8	4	3	1	3	4	31	35
induced abortions												56	56	58	46	46	54	48	60	35	55	459	514
population:												47330	47493	46762	47526	47324	47324	47355	47549	46874	45652	425537	471189
Total Prevalence												14.37	14.11	14.76	11.15	14.16	13.10	12.25	13.88	8.75	14.68	12.95	13.12
Livebirth Prevalence												1.90	1.90	1.50	0.84	2.75	0.85	1.48	1.05	0.64	1.75	1.43	1.46

Neural Tube Defects (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Wales (UK)																							
total cases																			63	56	49	119	168
livebirths																			4	8	4	12	16
fetal deaths																			0	2	1	2	3
induced abortions																			59	46	42	105	147
population:																			33610	32266	31449	65876	97325
Total Prevalence																			18.74	17.36	15.58	18.06	17.26
Livebirth Prevalence																			1.19	2.48	1.27	1.82	1.64
Total (Full Member Registries)																							
total cases	218	263	254	253	243	262	274	254	236	276	339	357	390	350	350	392	509	437	539	480	528	6676	7204
livebirths	114	144	153	142	128	117	142	117	100	108	145	147	143	119	125	123	150	133	144	137	221	2631	2852
fetal deaths	65	74	49	49	41	41	46	39	32	33	41	27	35	19	20	28	25	28	34	33	26	759	785
induced abortions	39	45	52	62	74	104	86	98	104	135	153	183	212	212	205	241	334	276	361	310	279	3286	3565
population:	63191	150396	176097	183358	186263	202517	210627	226785	229872	250061	294138	359123	387664	379259	381565	419413	486839	498478	522435	522385	527240	6130466	6657706
Total Prevalence	34.50	17.49	14.42	13.80	13.05	12.94	13.01	11.20	10.27	11.04	11.53	9.94	10.06	9.23	9.17	9.35	10.46	8.77	10.32	9.19	10.01	10.89	10.82
Livebirth Prevalence	18.04	9.57	8.69	7.74	6.87	5.78	6.74	5.16	4.35	4.32	4.93	4.09	3.69	3.14	3.28	2.93	3.08	2.67	2.76	2.62	4.19	4.29	4.28
Associate Member Registries																							
Finland																							
total cases														48	52	49	54	60	72	44	44	379	423
livebirths														27	15	19	20	29	22	16	18	148	166
fetal deaths														1	2	2	4	5	2	1	1	17	18
induced abortions														20	35	28	30	26	48	27	25	214	239
population:														65098	65480	63368	60965	59569	57345	57782	56970	429607	486577
Total Prevalence														7.37	7.94	7.73	8.86	10.07	12.56	7.61	7.72	8.82	8.69
Livebirth Prevalence														4.15	2.29	3.00	3.28	4.87	3.84	2.77	3.16	3.45	3.41
Central East France																							
total cases	33	25	32	34	31	44	40	36	42	31	49	57	56	66	62	72	65	62	65	59	44	961	1005
livebirths	31	23	29	30	27	37	27	21	29	17	25	28	29	24	21	25	26	18	18	12	4	497	501
fetal deaths	2	2	3	4	4	3	2	1	2	0	2	0	2	2	0	1	0	0	1	3	0	34	34
induced abortions						4	11	14	11	14	22	29	25	40	41	46	39	44	46	44	40	430	470
population:	75332	76220	75813	86433	86904	90825	91950	90191	91303	99858	107370	106607	104480	99249	99674	102153	103440	102090	102483	102982	93963	1895357	1989320
Total Prevalence	4.38	3.28	4.22	3.93	3.57	4.84	4.35	3.99	4.60	3.10	4.56	5.35	5.36	6.65	6.22	7.05	6.28	6.07	6.34	5.73	4.68	5.07	5.05
Livebirth Prevalence	4.12	3.02	3.83	3.47	3.11	4.07	2.94	2.33	3.18	1.70	2.33	2.78	2.78	2.42	2.11	2.45	2.51	1.76	1.76	1.17	0.43	2.62	2.52

Neural Tube Defects (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Norway																							
total cases	55	55	53	46	39	50	50	46	37	54	31	41	52	35	52	58	55	34	41	60	71	944	1015
livebirths	28	39	30	29	26	18	24	24	19	28	21	22	28	15	17	27	25	16	18	19	25	473	498
fetal deaths	27	16	23	17	13	23	18	12	12	13	6	8	7	8	11	11	11	5	9	12	7	262	269
induced abortions	0	0	0	0	0	9	8	10	6	13	4	11	17	12	24	20	19	13	14	29	39	209	248
population:	51495	51021	51642	50258	50576	51416	52885	54313	57936	59712	61523	61386	60636	60166	60306	60488	61092	59896	58482	60215	59907	1135444	1195351
Total Prevalence	10.68	10.78	10.26	9.15	7.71	9.72	9.45	8.47	6.39	9.04	5.04	6.68	8.58	5.82	8.62	9.59	9.00	5.68	7.01	9.96	11.85	8.31	8.49
Livebirth Prevalence	5.44	7.64	5.81	5.77	5.14	3.50	4.54	4.42	3.28	4.69	3.41	3.58	4.62	2.49	2.82	4.46	4.09	2.67	3.08	3.16	4.17	4.17	4.17
ECEMC (Spain)																							
total cases	65	56	65	63	67	83	43	35	43	39	57	65	46	38	38	33	34	36	29	21		956	956
livebirths	49	46	51	54	55	56	33	28	37	28	47	53	41	33	33	27	31	30	27	18		777	777
fetal deaths	16	10	14	9	12	27	10	7	6	11	10	12	5	5	5	6	3	6	2	3		179	179
induced abortions	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		0	0
population:	56910	56102	61333	71812	69513	66720	58245	51051	52686	59046	84379	87708	91607	82925	87239	87372	94044	98945	96490	104337		1518464	1518464
Total Prevalence	11.42	9.98	10.60	8.77	9.64	12.44	7.38	6.86	8.16	6.61	6.76	7.41	5.02	4.58	4.36	3.78	3.62	3.64	3.01	2.01		6.30	6.30
Livebirth Prevalence	8.61	8.20	8.32	7.52	7.91	8.39	5.67	5.48	7.02	4.74	5.57	6.04	4.48	3.98	3.78	3.09	3.30	3.03	2.80	1.73		5.12	5.12
Total (Associate Member Registries)																							
total cases	153	136	150	143	137	177	133	117	122	124	137	163	154	187	204	212	208	192	207	184	159	3240	3399
livebirths	108	108	110	113	108	111	84	73	85	73	93	103	98	99	86	98	102	93	85	65	47	1895	1942
fetal deaths	45	28	40	30	29	53	30	20	20	24	18	20	14	16	18	20	18	16	14	19	8	492	500
induced abortions	0	0	0	0	0	13	19	24	17	27	26	40	42	72	100	94	88	83	108	100	104	853	957
population:	183737	183343	188788	208503	206993	208961	203080	195555	201925	218616	253272	255701	256723	307438	312699	313381	319541	320500	314800	325316	210840	4978872	5189712
Total Prevalence	8.33	7.42	7.95	6.86	6.62	8.47	6.55	5.98	6.04	5.67	5.41	6.37	6.00	6.08	6.52	6.76	6.51	5.99	6.58	5.66	7.54	6.51	6.55
Livebirth Prevalence	5.88	5.89	5.83	5.42	5.22	5.31	4.14	3.73	4.21	3.34	3.67	4.03	3.82	3.22	2.75	3.13	3.19	2.90	2.70	2.00	2.23	3.81	3.74
Total (All Registries)																							
total cases	371	399	404	396	380	439	407	371	358	400	476	520	544	537	554	604	717	629	746	664	687	9916	10603
livebirths	222	252	263	255	236	228	226	190	185	181	238	250	241	218	211	221	252	226	229	202	268	4526	4794
fetal deaths	110	102	89	79	70	94	76	59	52	57	59	47	49	35	38	48	43	44	48	52	34	1251	1285
induced abortions	39	45	52	62	74	117	105	122	121	162	179	223	254	284	305	335	422	359	469	339	383	4068	4451
population:	246928	333739	364885	391861	393256	411478	413707	422340	431797	468677	547410	614824	644387	686697	694264	732794	806380	818978	837235	847701	738080	11109338	11847418
Total Prevalence	15.02	11.96	11.07	10.11	9.66	10.67	9.84	8.78	8.29	8.53	8.70	8.46	8.44	7.82	7.98	8.24	8.89	7.68	8.91	7.83	9.31	8.93	8.95
Livebirth Prevalence	8.99	7.55	7.21	6.51	6.00	5.54	5.46	4.50	4.28	3.86	4.35	4.07	3.74	3.17	3.04	3.02	3.13	2.76	2.74	2.38	3.63	4.07	4.05

Table A3.2: Spina Bifida: Number of cases by type of birth, population (births), total prevalence rate and livebirth prevalence rate (per 10,000 births) by year and registry: 32 EUROCAT registries, 1980-2000

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Styria (Austria)																							
total cases						6	10	7	4	7	9	8	7	7	6	10	2	5	5	4		97	97
livebirths						6	8	3	1	5	5	6	4	4	5	8	2	5	1	2		65	65
fetal deaths						0	0	1	0	1	1	1	2	1	0	0	0	0	0	0		7	7
induced abortions						0	2	3	3	1	3	1	1	2	1	2	0	0	4	2		25	25
population:						13663	13303	13276	13340	13161	13349	13794	13744	13395	12988	12276	12465	11768	11026	10800		192348	192348
Total Prevalence						4.39	7.52	5.27	3.00	5.32	6.74	5.80	5.09	5.23	4.62	8.15	1.60	4.25	4.53	3.70		5.04	5.04
Livebirth Prevalence						4.39	6.01	2.26	0.75	3.80	3.75	4.35	2.91	2.99	3.85	6.52	1.60	4.25	0.91	1.85		3.38	3.38
Antwerp (Belgium)																							
total cases											6	2	0	7	8	5	4	2	14	1		49	49
livebirths											4	0	0	6	6	4	2	2	6	1		31	31
fetal deaths											1	0	0	0	1	0	0	0	0	0		2	2
induced abortions											1	2	0	1	1	1	2	0	8	0		16	16
population:											3740	4688	6180	7555	10964	10899	10796	18282	17930	17968		109002	109002
Total Prevalence											16.04	4.27	0.00	9.27	7.30	4.59	3.71	1.09	7.81	0.56		4.50	4.50
Livebirth Prevalence											10.70	0.00	0.00	7.94	5.47	3.67	1.85	1.09	3.35	0.56		2.84	2.84
Hainaut (Belgium)																							
total cases	6	3	0	3	4	2	6	4	0	6	12	10	13	5	7	7	9	6	7	8		118	118
livebirths	6	2	0	1	4	0	4	3	0	5	4	6	6	4	4	5	5	1	2	3		65	65
fetal deaths	0	1	0	1	0	1	1	1	0	1	5	2	0	0	2	0	0	0	1	0		16	16
induced abortions	0	0	0	1	0	1	1	0	0	0	3	2	7	1	1	2	4	5	4	5		37	37
population:	8449	8204	8209	7862	8066	8182	8380	8518	8805	13579	13503	13595	13328	12583	12273	11933	12416	12314	12044	12097		214340	214340
Total Prevalence	7.10	3.66	0.00	3.82	4.96	2.44	7.16	4.70	0.00	4.42	8.89	7.36	9.75	3.97	5.70	5.87	7.25	4.87	5.81	6.61		5.51	5.51
Livebirth Prevalence	7.10	2.44	0.00	1.27	4.96	0.00	4.77	3.52	0.00	3.68	2.96	4.41	4.50	3.18	3.26	4.19	4.03	0.81	1.66	2.48		3.03	3.03
Bulgaria																							
total cases																	10	10	13	10		43	43
livebirths																	9	8	5	8		30	30
fetal deaths																	1	1	2	1		5	5
induced abortions																	0	1	6	1		8	8
population:																	9908	9004	9177	10168		38257	38257
Total Prevalence																	10.09	11.11	14.17	9.83		11.24	11.24
Livebirth Prevalence																	9.08	8.88	5.45	7.87		7.84	7.84

Spina Bifida (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Croatia																							
total cases				0	4	1	3	2	4	3	3	5	5	3	2	0	0	4	3	2	1	44	45
livebirths				0	4	1	3	2	2	3	3	5	5	3	2	0	0	1	2	2	1	38	39
fetal deaths				0	0	0	0	0	2	0	0	0	0	0	0	0	0	2	0	0	0	4	4
induced abortions				0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	2	2
population:				4023	4029	3784	6867	6686	6183	7329	6948	7003	6481	6532	6135	6280	6435	6337	6170	6033	5815	103255	109070
Total Prevalence				0.00	9.93	2.64	4.37	2.99	6.47	4.09	4.32	7.14	7.71	4.59	3.26	0.00	0.00	6.31	4.86	3.32	1.72	4.26	4.13
Livebirth Prevalence				0.00	9.93	2.64	4.37	2.99	3.23	4.09	4.32	7.14	7.71	4.59	3.26	0.00	0.00	1.58	3.24	3.32	1.72	3.68	3.58
Odense (Denmark)																							
total cases	2	2	1	4	4	0	4	4	3	5	4	6	2	2	2	5	4	4	1	6	5	65	70
livebirths	2	2	1	4	3	0	2	3	2	4	1	6	1	2	1	4	4	2	1	6	5	51	56
fetal deaths	0	0	0	0	0	0	2	0	0	0	0	0	0	0	1	0	0	2	0	0	0	5	5
induced abortions	0	0	0	0	1	0	0	1	1	1	3	0	1	0	0	1	0	0	0	0	0	9	9
population:	5148	4604	4478	4309	4471	4698	4849	4852	5066	5287	5694	5752	6059	5946	6108	6153	5875	5807	5429	5689	5696	106274	111970
Total Prevalence	3.89	4.34	2.23	9.28	8.95	0.00	8.25	8.24	5.92	9.46	7.02	10.43	3.30	3.36	3.27	8.13	6.81	6.89	1.84	10.55	8.78	6.12	6.25
Livebirth Prevalence	3.89	4.34	2.23	9.28	6.71	0.00	4.12	6.18	3.95	7.57	1.76	10.43	1.65	3.36	1.64	6.50	6.81	3.44	1.84	10.55	8.78	4.80	5.00
Paris (France)																							
total cases		24	11	22	9	14	25	12	11	28	21	13	16	22	19	26	20	12	18	20	27	343	370
livebirths		16	7	9	5	2	5	5	2	5	5	3	3	1	1	2	3	2	4	0	3	80	83
fetal deaths		4	3	5	1	4	8	0	0	3	1	0	0	1	0	0	0	0	1	2	1	33	34
induced abortions		4	1	8	3	8	12	7	9	20	15	10	13	20	18	24	17	10	13	18	23	230	253
population:		36917	36741	35781	35902	36536	36384	36080	36672	36866	37302	37541	36469	35819	35918	36884	37237	37272	38160	38785	39400	699266	738666
Total Prevalence		6.50	2.99	6.15	2.51	3.83	6.87	3.33	3.00	7.60	5.63	3.46	4.39	6.14	5.29	7.05	5.37	3.22	4.72	5.16	6.85	4.91	5.01
Livebirth Prevalence		4.33	1.91	2.52	1.39	0.55	1.37	1.39	0.55	1.36	1.34	0.80	0.82	0.28	0.28	0.54	0.81	0.54	1.05	0.00	0.76	1.14	1.12
Strasbourg (France)																							
total cases			9	5	8	4	12	2	4	6	4	4	6	5	7	4	11	4	12	13	10	120	130
livebirths			5	5	5	1	6	0	1	0	1	1	3	1	2	0	2	1	3	2	2	39	41
fetal deaths			2	0	0	0	2	0	1	0	1	0	0	0	1	0	1	0	1	0	0	9	9
induced abortions			2	0	3	3	4	2	2	6	2	3	3	4	4	4	8	3	8	11	8	72	80
population:			13662	12519	12924	13166	13112	12895	13595	13425	13775	13770	13736	13148	12865	13313	13185	13237	13656	13827	14238	239810	254048
Total Prevalence			6.59	3.99	6.19	3.04	9.15	1.55	2.94	4.47	2.90	2.90	4.37	3.80	5.44	3.00	8.34	3.02	8.79	9.40	7.02	5.00	5.12
Livebirth Prevalence			3.66	3.99	3.87	0.76	4.58	0.00	0.74	0.00	0.73	0.73	2.18	0.76	1.55	0.00	1.52	0.76	2.20	1.45	1.40	1.63	1.61

Spina Bifida (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Mainz (Germany)																							
total cases											3	2	4	2	3	6	10	10	7	4		51	51
livebirths											1	2	4	1	2	6	7	8	5	3		39	39
fetal deaths											1	0	0	0	0	0	1	1	1	0		4	4
induced abortions											1	0	0	1	1	0	2	1	1	1		8	8
population:											3903	4113	3941	4020	3769	3560	3603	3890	3542	3275		37616	37616
Total Prevalence											7.69	4.86	10.15	4.98	7.96	16.85	27.75	25.71	19.76	12.21		13.56	13.56
Livebirth Prevalence											2.56	4.86	10.15	2.49	5.31	16.85	19.43	20.57	14.12	9.16		10.37	10.37
Saxony-Anhalt (Germany)																							
total cases								17	14	14	17	0	1	1	4	3	6	6	4	5	11	92	103
livebirths								12	8	7	8	0	1	1	2	1	3	3	1	4	2	51	53
fetal deaths								2	2	1	2	0	0	0	1	0	0	0	0	0	0	8	8
induced abortions								3	4	6	7	0	0	0	1	2	3	3	3	1	9	33	42
population:								17165	16623	15202	14536	9123	7633	6910	7557	7707	8928	9606	10554	11500	18876	143044	161920
Total Prevalence								9.90	8.42	9.21	11.70	0.00	1.31	1.45	5.29	3.89	6.72	6.25	3.79	4.35	5.83	6.43	6.36
Livebirth Prevalence								6.99	4.81	4.60	5.50	0.00	1.31	1.45	2.65	1.30	3.36	3.12	0.95	3.48	1.06	3.57	3.27
Dublin (Ireland)																							
total cases	71	43	47	42	37	31	29	25	19	13	14	12	14	10	11	12	10	10	7	13	9	470	479
livebirths	63	39	44	39	32	28	27	21	16	10	13	10	13	10	11	12	9	9	7	11	9	424	433
fetal deaths	8	4	3	3	5	3	2	4	3	3	1	2	1	0	0	0	1	1	0	2	0	46	46
induced abortions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
population:	26460	25510	24822	23352	22312	22131	21708	20768	19830	18914	19393	19800	18933	18491	18412	18550	19288	20257	20887	20746	21090	420564	441654
Total Prevalence	26.83	16.86	18.93	17.99	16.58	14.01	13.36	12.04	9.58	6.87	7.22	6.06	7.39	5.41	5.97	6.47	5.18	4.94	3.35	6.27	4.27	11.18	10.85
Livebirth Prevalence	23.81	15.29	17.73	16.70	14.34	12.65	12.44	10.11	8.07	5.29	6.70	5.05	6.87	5.41	5.97	6.47	4.67	4.44	3.35	5.30	4.27	10.08	9.80
Galway (Ireland)																							
total cases		3	4	5	3	5	6	4	4	1	1	2	7	1	2	1	0	1	1	0		51	51
livebirths		3	4	4	3	5	6	3	4	1	1	2	6	1	2	0	0	1	1	0		47	47
fetal deaths		0	0	1	0	0	0	1	0	0	0	0	1	0	0	1	0	0	0	0		4	4
induced abortions		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
population:		3546	3604	3397	3268	3079	3155	3051	2858	2636	2691	2578	2666	2645	2375	2436	2534	2588	2747	2655		54509	54509
Total Prevalence		8.46	11.10	14.72	9.18	16.24	19.02	13.11	14.00	3.79	3.72	7.76	26.26	3.78	8.42	4.11	0.00	3.86	3.64	0.00		9.36	9.36
Livebirth Prevalence		8.46	11.10	11.78	9.18	16.24	19.02	9.83	14.00	3.79	3.72	7.76	22.51	3.78	8.42	0.00	0.00	3.86	3.64	0.00		8.62	8.62

Spina Bifida (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Campania (Italy)																							
total cases																	19	18	12	13	21	62	83
livebirths																	9	12	6	6	14	33	47
fetal deaths																	0	0	1	0	0	1	1
induced abortions																	10	6	5	7	7	28	35
population:																	46658	50458	51568	47397	50171	196081	246252
Total Prevalence																	4.07	3.57	2.33	2.74	4.19	3.16	3.37
Livebirth Prevalence																	1.93	2.38	1.16	1.27	2.79	1.68	1.91
Emilia Romagna (Italy)																							
total cases		3	6	12	9	9	11	7	5	8	9	13	10	7	8	3	3	4	10	3	11	140	151
livebirths		3	6	12	9	9	11	7	5	7	9	13	8	6	7	3	3	4	6	3	2	131	133
fetal deaths		0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	2	2
induced abortions		0	0	0	0	0	0	0	0	0	0	0	2	0	1	0	0	0	4	0	9	7	16
population:		13189	18364	21769	23155	24016	22868	22726	22760	23380	23524	25095	25002	24533	25886	26359	28873	28859	20928	24003	24839	445289	470128
Total Prevalence		2.27	3.27	5.51	3.89	3.75	4.81	3.08	2.20	3.42	3.83	5.18	4.00	2.85	3.09	1.14	1.04	1.39	4.78	1.25	4.43	3.14	3.21
Livebirth Prevalence		2.27	3.27	5.51	3.89	3.75	4.81	3.08	2.20	2.99	3.83	5.18	3.20	2.45	2.70	1.14	1.04	1.39	2.87	1.25	0.81	2.94	2.83
North-East Italy																							
total cases		15	11	14	22	8	15	18	13	11	20	11	16	13	18	15	25	14	30	6		295	295
livebirths		14	11	14	21	8	13	18	10	10	15	9	10	6	7	3	9	6	13	3		200	200
fetal deaths		1	0	0	1	0	2	0	0	0	1	0	1	0	0	0	0	0	0	0		6	6
induced abortions		0	0	0	0	0	0	0	3	1	4	2	5	7	11	12	16	8	17	3		89	89
population:		27708	36321	41195	43202	43401	41265	42048	45307	47515	52205	51093	50340	49735	49443	51486	56869	55908	54939	54364		894344	894344
Total Prevalence		5.41	3.03	3.40	5.09	1.84	3.64	4.28	2.87	2.32	3.83	2.15	3.18	2.61	3.64	2.91	4.40	2.50	5.46	1.10		3.30	3.30
Livebirth Prevalence		5.05	3.03	3.40	4.86	1.84	3.15	4.28	2.21	2.10	2.87	1.76	1.99	1.21	1.42	0.58	1.58	1.07	2.37	0.55		2.24	2.24
South East Sicily (Italy)																							
total cases												11	7	8	9	4	3	5	3		9	50	59
livebirths												11	6	7	9	4	3	5	3		5	48	53
fetal deaths												0	1	1	0	0	0	0	0		0	2	2
induced abortions																					4	0	4
population:												19430	20273	19746	20031	18986	18054	18795	16922		15304	152237	167541
Total Prevalence												5.66	3.45	4.05	4.49	2.11	1.66	2.66	1.77		5.88	3.28	3.52
Livebirth Prevalence												5.66	2.96	3.55	4.49	2.11	1.66	2.66	1.77		3.27	3.15	3.16

Spina Bifida (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Tuscany (Italy)																							
total cases	7	7	4	5	2	10	1	5	4	7	5	1	7	8	5	5	6	7	12	6	12	114	126
livebirths	6	6	3	4	2	6	0	2	1	3	3	0	2	4	1	4	2	0	5	3	3	57	60
fetal deaths	1	1	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	1	4	5
induced abortions	0	0	1	1	0	4	1	3	3	2	2	1	5	4	4	1	4	7	7	3	8	53	61
population:	9696	9350	9281	8948	8592	8980	8477	8511	8869	8556	8751	8657	25670	24504	24487	24520	24606	24535	25468	26059	26616	306517	333133
Total Prevalence	7.22	7.49	4.31	5.59	2.33	11.14	1.18	5.87	4.51	8.18	5.71	1.16	2.73	3.26	2.04	2.04	2.44	2.85	4.71	2.30	4.51	3.72	3.78
Livebirth Prevalence	6.19	6.42	3.23	4.47	2.33	6.68	0.00	2.35	1.13	3.51	3.43	0.00	0.78	1.63	0.41	1.63	0.81	0.00	1.96	1.15	1.13	1.86	1.80
Malta																							
total cases							3	4	3	4	3	4	3	2	3	5	2	2	3	3	2	44	46
livebirths							3	4	3	4	2	4	2	2	3	5	2	2	3	2	2	41	43
fetal deaths							0	0	0	0	1	0	1	0	0	0	0	0	0	1	0	3	3
induced abortions							0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
population:							5310	5375	5461	5617	5400	5328	5503	5172	4863	4633	4978	4864	4511	4339	4272	71354	75626
Total Prevalence							5.65	7.44	5.49	7.12	5.56	7.51	5.45	3.87	6.17	10.79	4.02	4.11	6.65	6.91	4.68	6.17	6.08
Livebirth Prevalence							5.65	7.44	5.49	7.12	3.70	7.51	3.63	3.87	6.17	10.79	4.02	4.11	6.65	4.61	4.68	5.75	5.69
Northern Netherlands																							
total cases		5	4	4	3	7	7	2	13	13	21	22	14	6	9	11	13	10	10	13	9	187	196
livebirths		4	4	3	3	6	5	2	10	11	16	18	11	4	8	9	10	7	8	7	9	146	155
fetal deaths		1	0	0	0	0	2	0	1	1	2	2	0	1	0	0	1	0	0	0	0	11	11
induced abortions		0	0	1	0	1	0	0	2	1	3	2	3	1	1	2	2	3	2	6	0	30	30
population:		7877	7731	7542	7559	7792	11936	11847	11595	19093	19635	19853	19140	19387	19283	19296	19033	19397	19941	20167	20490	288104	308594
Total Prevalence		6.35	5.17	5.30	3.97	8.98	5.86	1.69	11.21	6.81	10.70	11.08	7.31	3.09	4.67	5.70	6.83	5.16	5.01	6.45	4.39	6.49	6.35
Livebirth Prevalence		5.08	5.17	3.98	3.97	7.70	4.19	1.69	8.62	5.76	8.15	9.07	5.75	2.06	4.15	4.66	5.25	3.61	4.01	3.47	4.39	5.07	5.02
Poland																							
total cases																					85		85
livebirths																					82		82
fetal deaths																					3		3
induced abortions																							0
population:																					158923		158923
Total Prevalence																					5.35		5.35
Livebirth Prevalence																					5.16		5.16

Spina Bifida (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Southern Portugal																							
total cases											3	2	2	1	4	6	7	5	1	6	7	37	44
livebirths											2	1	2	1	4	4	6	4	1	3	3	28	31
fetal deaths											0	1	0	0	0	0	0	0	0	0	1	1	2
induced abortions											1	0	0	0	0	2	1	1	0	3	3	8	11
population:											5461	5554	7391	7152	7000	14959	15439	16293	16312	17047	19383	112608	131991
Total Prevalence											5.49	3.60	2.71	1.40	5.71	4.01	4.53	3.07	0.61	3.52	3.61	3.29	3.33
Livebirth Prevalence											3.66	1.80	2.71	1.40	5.71	2.67	3.89	2.46	0.61	1.76	1.55	2.49	2.35
Asturias (Spain)																							
total cases											6	6	7	5	4	3	5	1	7	0		44	44
livebirths											3	1	1	0	1	2	2	0	0	0		10	10
fetal deaths											0	0	1	0	0	0	0	0	0	0		1	1
induced abortions											3	5	5	5	3	1	3	1	7	0		33	33
population:											7722	7693	7474	7012	6626	6553	6507	6473	6321	6516		68897	68897
Total Prevalence											7.77	7.80	9.37	7.13	6.04	4.58	7.68	1.54	11.07	0.00		6.39	6.39
Livebirth Prevalence											3.89	1.30	1.34	0.00	1.51	3.05	3.07	0.00	0.00	0.00		1.45	1.45
Barcelona (Spain)																							
total cases													6	5	5	4	4	1	4	5		34	34
livebirths													2	1	4	2	1	0	1	0		11	11
fetal deaths													0	1	0	0	0	0	0	1		2	2
induced abortions													4	3	1	2	3	1	3	4		21	21
population:													13477	12738	12609	12199	12031	12240	11684	12270		99248	99248
Total Prevalence													4.45	3.93	3.97	3.28	3.32	0.82	3.42	4.07		3.43	3.43
Livebirth Prevalence													1.48	0.79	3.17	1.64	0.83	0.00	0.86	0.00		1.11	1.11
Basque Country (Spain)																							
total cases											10	4	8	6	11	7	5	8	5	10	9	74	83
livebirths											9	3	3	3	7	2	1	4	2	5	3	39	42
fetal deaths											0	0	0	0	0	1	0	1	0	0	0	2	2
induced abortions											1	1	5	3	4	4	4	3	3	5	6	33	39
population:											16438	16291	16316	15891	15357	15397	16060	16397	16169	16859	17408	161175	178583
Total Prevalence											6.08	2.46	4.90	3.78	7.16	4.55	3.11	4.88	3.09	5.93	5.17	4.59	4.65
Livebirth Prevalence											5.48	1.84	1.84	1.89	4.56	1.30	0.62	2.44	1.24	2.97	1.72	2.42	2.35

Spina Bifida (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Vaud (Switzerland)																							
total cases										2	3	3	4	3	4	2	10	2	5	3	7	41	48
livebirths										0	1	0	2	1	1	0	3	1	2	1	3	12	15
fetal deaths										0	0	0	0	1	0	0	0	0	0	0	0	1	1
induced abortions										2	2	3	2	1	3	2	7	1	3	2	4	28	32
population:										7212	7697	8211	8076	7700	7683	7697	7730	7562	7438	7465	7618	84471	92089
Total Prevalence										2.77	3.90	3.65	4.95	3.90	5.21	2.60	12.94	2.64	6.72	4.02	9.19	4.85	5.21
Livebirth Prevalence										0.00	1.30	0.00	2.48	1.30	1.30	0.00	3.88	1.32	2.69	1.34	3.94	1.42	1.63
Glasgow (UK:Scotland)																							
total cases	31	23	24	16	17	30	25	15	12	15	12	9	8	5	14	8	19	2	7	11		303	303
livebirths	14	5	17	8	8	10	12	4	6	5	2	3	2	3	6	2	6	0	4	8		125	125
fetal deaths	5	5	2	0	0	2	2	1	0	0	1	0	0	0	0	2	1	0	1	0		22	22
induced abortions	12	13	5	8	9	18	11	10	6	10	9	6	6	2	8	4	12	2	2	3		156	156
population:	13438	13491	12884	12661	12783	13089	13013	12987	12908	12289	12471	12831	12339	11883	11407	11227	10976	10997	10239	9721		243634	243634
Total Prevalence	23.07	17.05	18.63	12.64	13.30	22.92	19.21	11.55	9.30	12.21	9.62	7.01	6.48	4.21	12.27	7.13	17.31	1.82	6.84	11.32		12.44	12.44
Livebirth Prevalence	10.42	3.71	13.19	6.32	6.26	7.64	9.22	3.08	4.65	4.07	1.60	2.34	1.62	2.52	5.26	1.78	5.47	0.00	3.91	8.23		5.13	5.13
Mersey (UK:England)																							
total cases																16	19	26	15	14		90	90
livebirths																2	3	5	3	4		17	17
fetal deaths																1	0	1	2	1		5	5
induced abortions																13	16	20	10	9		68	68
population:																28786	29031	27983	27514	26553		139867	139867
Total Prevalence																5.56	6.54	9.29	5.45	5.27		6.43	6.43
Livebirth Prevalence																0.69	1.03	1.79	1.09	1.51		1.22	1.22
North Thames (West) (UK:England)																							
total cases												29	26	32	21	33	30	27	22	17	25	262	262
livebirths												5	3	5	2	7	3	5	4	2	5	41	41
fetal deaths												2	0	1	1	2	1	1	0	1	0	9	9
induced abortions												22	23	26	18	24	26	21	18	14	20	212	212
population:												47330	47493	46762	47526	47324	47324	47355	47549	46874	45652	471189	471189
Total Prevalence												6.13	5.47	6.84	4.42	6.97	6.34	5.70	4.63	3.63	5.48	5.56	5.56
Livebirth Prevalence												1.06	0.63	1.07	0.42	1.48	0.63	1.06	0.84	0.43	1.10	0.87	0.87

Spina Bifida (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Wales (UK)																							
total cases																			29	19	26	48	74
livebirths																			4	3	3	7	10
fetal deaths																			0	0	0	0	0
induced abortions																			25	16	21	41	62
population:																			33610	32266	31449	65876	97325
Total Prevalence																			8.63	5.89	8.27	7.29	7.60
Livebirth Prevalence																			1.19	0.93	0.95	1.06	1.03
Total (Full Member Registries)																							
total cases	117	128	121	132	122	127	157	128	113	143	186	179	193	166	186	201	256	206	267	215	286	3368	3629
livebirths	91	94	102	103	99	82	105	89	71	80	108	109	100	77	98	91	109	98	103	92	156	1906	2057
fetal deaths	14	17	10	10	7	10	21	10	9	13	18	10	8	8	7	7	7	10	10	9	6	215	221
induced abortions	12	17	9	19	16	35	31	29	33	50	60	60	85	81	81	103	140	98	154	114	122	1247	1349
population:	63191	150396	176097	183358	186263	202517	210627	226785	229872	250061	294138	359123	387664	379259	381565	419413	486839	498478	522435	505443	527240	6159176	6640764
Total Prevalence	18.52	8.51	6.87	7.20	6.55	6.27	7.45	5.64	4.92	5.72	6.32	4.98	4.98	4.38	4.87	4.79	5.26	4.13	5.11	4.25	5.42	5.47	5.46
Livebirth Prevalence	14.40	6.25	5.79	5.62	5.32	4.05	4.99	3.92	3.09	3.20	3.67	3.04	2.58	2.03	2.57	2.17	2.24	1.97	1.97	1.82	2.96	3.09	3.10
Associate Member Registries																							
Finland																							
total cases														28	26	26	26	33	40	21	20	200	220
livebirths														23	15	18	15	23	19	13	15	126	141
fetal deaths														1	1	1	3	2	1	1	0	10	10
induced abortions														4	10	7	8	8	20	7	5	64	69
population:														65098	65480	63368	60965	59569	57345	57782	56970	429607	486577
Total Prevalence														4.30	3.97	4.10	4.26	5.54	6.98	3.63	3.51	4.66	4.52
Livebirth Prevalence														3.53	2.29	2.84	2.46	3.86	3.31	2.25	2.63	2.93	2.90
Central East France																							
total cases	27	20	29	21	29	37	31	26	36	24	36	37	40	45	43	48	46	41	37	36	11	689	700
livebirths	26	19	26	21	27	32	24	15	27	15	20	20	21	18	14	14	16	11	13	5	2	384	386
fetal deaths	1	1	3	0	2	3	1	1	2	0	1	0	2	1	0	1	0	0	1	2	0	22	22
induced abortions						2	6	10	7	9	15	17	17	26	29	33	30	30	23	29	9	283	292
population:	75332	76220	75813	86433	86904	90825	91950	90191	91303	99858	107370	106607	104480	99249	99674	102153	103440	102090	102483	102982	93963	1895357	1989320
Total Prevalence	3.58	2.62	3.83	2.43	3.34	4.07	3.37	2.88	3.94	2.40	3.35	3.47	3.83	4.53	4.31	4.70	4.45	4.02	3.61	3.50	1.17	3.64	3.52
Livebirth Prevalence	3.45	2.49	3.43	2.43	3.11	3.52	2.61	1.66	2.96	1.50	1.86	1.88	2.01	1.81	1.40	1.37	1.55	1.08	1.27	0.49	0.21	2.03	1.94

Spina Bifida (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Norway																							
total cases	35	28	32	24	26	22	29	29	25	33	24	27	32	19	25	33	35	22	27	32	41	559	600
livebirths	25	26	24	21	23	16	20	22	19	25	19	20	26	11	14	24	23	13	15	16	20	402	422
fetal deaths	10	2	8	3	3	6	8	5	4	5	5	4	1	1	4	5	6	2	6	4	3	92	95
induced abortions	0	0	0	0	0	0	1	2	2	3	0	3	5	7	7	4	6	7	6	12	18	65	83
population:	51495	51021	51642	50258	50576	51416	52885	54313	57936	59712	61523	61386	60636	60166	60306	60488	61092	59896	58482	60215	59907	1135444	1195351
Total Prevalence	6.80	5.49	6.20	4.78	5.14	4.28	5.48	5.34	4.32	5.53	3.90	4.40	5.28	3.16	4.15	5.46	5.73	3.67	4.62	5.31	6.84	4.92	5.02
Livebirth Prevalence	4.85	5.10	4.65	4.18	4.55	3.11	3.78	4.05	3.28	4.19	3.09	3.26	4.29	1.83	2.32	3.97	3.76	2.17	2.56	2.66	3.34	3.54	3.53
ECEMC (Spain)																							
total cases	23	20	29	29	34	36	27	19	27	22	37	39	28	26	25	20	27	20	21	18		527	527
livebirths	22	18	26	26	31	33	25	17	27	21	35	36	28	24	25	19	26	19	20	15		493	493
fetal deaths	1	2	3	3	3	3	2	2	0	1	2	3	0	2	0	1	1	1	1	3		34	34
induced abortions																							0
population:	56910	56102	61333	71812	69513	66720	58245	51051	52686	59046	84379	87708	91607	82925	87239	87372	94044	98945	96490	104337		1518464	1518464
Total Prevalence	4.04	3.56	4.73	4.04	4.89	5.40	4.64	3.72	5.12	3.73	4.38	4.45	3.06	3.14	2.87	2.29	2.87	2.02	2.18	1.73		3.47	3.47
Livebirth Prevalence	3.87	3.21	4.24	3.62	4.46	4.95	4.29	3.33	5.12	3.56	4.15	4.10	3.06	2.89	2.87	2.17	2.76	1.92	2.07	1.44		3.25	3.25
Total (Associate Member Registries)																							
total cases	85	68	90	74	89	95	87	74	88	79	97	103	100	118	119	127	134	116	125	107	72	1975	2047
livebirths	73	63	76	68	81	81	69	54	73	61	74	76	75	76	68	75	80	66	67	49	37	1405	1442
fetal deaths	12	5	14	6	8	12	11	8	6	6	8	7	3	5	5	8	10	5	9	10	3	158	161
induced abortions	0	0	0	0	0	2	7	12	9	12	15	20	22	37	46	44	44	45	49	48	32	412	444
population:	183737	183343	188788	208503	206993	208961	203080	195555	201925	218616	253272	255701	256723	307438	312699	313381	319541	320500	314800	325316	210840	4978872	5189712
Total Prevalence	4.63	3.71	4.77	3.55	4.30	4.55	4.28	3.78	4.36	3.61	3.83	4.03	3.90	3.84	3.81	4.05	4.19	3.62	3.97	3.29	3.41	3.97	3.94
Livebirth Prevalence	3.97	3.44	4.03	3.26	3.91	3.88	3.40	2.76	3.62	2.79	2.92	2.97	2.92	2.47	2.17	2.39	2.50	2.06	2.13	1.51	1.75	2.82	2.78
Total (All Registries)																							
total cases	202	196	211	206	211	222	244	202	201	222	283	282	293	284	305	328	390	322	392	322	358	5343	5676
livebirths	164	157	178	171	180	163	174	143	144	141	182	185	175	153	166	166	189	164	170	141	193	3311	3499
fetal deaths	26	22	24	16	15	22	32	18	15	19	26	17	11	13	12	15	17	15	19	19	9	373	382
induced abortions	12	17	9	19	16	37	38	41	42	62	75	80	107	118	127	147	184	143	203	134		1611	1611
population:	246928	333739	364885	391861	393256	411478	413707	422340	431797	468677	547410	614824	644387	686697	694264	732794	806380	818978	837235	830759	738080	11138048	11830476
Total Prevalence	8.18	5.87	5.78	5.26	5.37	5.40	5.90	4.78	4.65	4.74	5.17	4.59	4.55	4.14	4.39	4.48	4.84	3.93	4.68	3.88	4.85	4.80	4.80
Livebirth Prevalence	6.64	4.70	4.88	4.36	4.58	3.96	4.21	3.39	3.33	3.01	3.32	3.01	2.72	2.23	2.39	2.27	2.34	2.00	2.03	1.70	2.61	2.97	2.96

Table A3.3: Anencephalus: Number of cases by type of birth, population (births), total prevalence rate and livebirth prevalence rate (per 10,000 births) by year and registry: 32 EUROCAT registries, 1980-2000

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Styria (Austria)																							
total cases						4	1	1	3	3	3	1	3	3	4	0	4	4	2	2		38	38
livebirths						1	0	0	0	0	0	0	1	0	0	0	1	0	0	0		3	3
fetal deaths						0	0	0	0	0	0	0	1	0	0	0	0	0	0	1		2	2
induced abortions						3	1	1	3	3	3	1	1	3	4	0	3	4	2	1		33	33
population:						13663	13303	13276	13340	13161	13349	13794	13744	13395	12988	12276	12465	11768	11026	10800		192348	192348
Total Prevalence						2.93	0.75	0.75	2.25	2.28	2.25	0.72	2.18	2.24	3.08	0.00	3.21	3.40	1.81	1.85		1.98	1.98
Livebirth Prevalence						0.73	0.00	0.00	0.00	0.00	0.00	0.00	0.73	0.00	0.00	0.00	0.80	0.00	0.00	0.00		0.16	0.16
Antwerp (Belgium)																							
total cases											3	5	2	2	4	2	4	11	0	8		41	41
livebirths											0	1	0	1	0	0	0	0	0	0		2	2
fetal deaths											1	1	0	0	0	0	0	0	0	0		2	2
induced abortions											2	3	2	1	4	2	4	11	0	8		37	37
population:											3740	4688	6180	7555	10964	10899	10796	18282	17930	17968		109002	109002
Total Prevalence											8.02	10.67	3.24	2.65	3.65	1.84	3.71	6.02	0.00	4.51		3.77	3.76
Livebirth Prevalence											0.00	2.13	0.00	1.32	0.00	0.00	0.00	0.00	0.00	0.00		0.18	0.18
Hainaut (Belgium)																							
total cases	4	6	2	3	5	5	5	8	4	6	5	5	3	4	1	4	3	5	6	2		86	86
livebirths	0	1	0	1	0	0	0	0	0	1	2	0	0	0	0	0	0	0	1	0		6	6
fetal deaths	0	3	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0		5	5
induced abortions	4	2	2	2	5	4	5	8	4	4	3	5	3	4	1	4	3	5	5	2		75	75
population:	8449	8204	8209	7862	8066	8182	8380	8518	8805	13579	13503	13595	13328	12583	12273	11933	12416	12314	12044	12097		214340	214340
Total Prevalence	4.73	7.31	2.44	3.82	6.20	6.11	5.97	9.39	4.54	4.42	3.70	3.68	2.25	3.18	0.81	3.35	2.42	4.06	4.98	1.65		4.01	4.01
Livebirth Prevalence	0.00	1.22	0.00	1.27	0.00	0.00	0.00	0.00	0.00	0.74	1.48	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83	0.00		0.28	0.28
Bulgaria																							
total cases																	6	5	10	6		27	27
livebirths																	0	0	1	0		1	1
fetal deaths																	4	0	5	3		12	12
induced abortions																	2	5	4	3		14	14
population:																	9908	9004	9177	10168		38257	38257
Total Prevalence																	6.06	5.55	10.90	5.90		7.06	7.06
Livebirth Prevalence																	0.00	0.00	1.09	0.00		0.26	0.26

Anencephalus (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Croatia																							
total cases				2	0	1	1	0	0	0	1	0	0	1	0	0	0	1	2	0	1	9	10
livebirths				0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1
fetal deaths				2	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	4
induced abortions				0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	2	0	1	4	5
population:				4023	4029	3784	6867	6686	6183	7329	6948	7003	6481	6532	6135	6280	6435	6337	6170	6033	5815	103255	109070
Total Prevalence				4.97	0.00	2.64	1.46	0.00	0.00	0.00	1.44	0.00	0.00	1.53	0.00	0.00	0.00	1.58	3.24	0.00	1.72	0.87	0.92
Livebirth Prevalence				0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.44	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.09
Odense (Denmark)																							
total cases	5	2	2	2	3	1	2	5	1	2	2	4	1	1	1	4	2	1	2	2	2	45	47
livebirths	0	0	1	0	0	0	0	1	0	1	1	0	0	1	0	0	0	0	0	0	0	5	5
fetal deaths	4	2	1	0	1	0	1	2	0	1	1	2	1	0	0	1	1	0	1	0	1	19	20
induced abortions	1	0	0	2	2	1	1	2	1	0	0	2	0	0	1	3	1	1	1	2	1	21	22
population:	5148	4604	4478	4309	4471	4698	4849	4852	5066	5287	5694	5752	6059	5946	6108	6153	5875	5807	5429	5689	5696	106274	111970
Total Prevalence	9.71	4.34	4.47	4.64	6.71	2.13	4.12	10.31	1.97	3.78	3.51	6.95	1.65	1.68	1.64	6.50	3.40	1.72	3.68	3.52	3.51	4.23	4.20
Livebirth Prevalence	0.00	0.00	2.23	0.00	0.00	0.00	0.00	2.06	0.00	1.89	1.76	0.00	0.00	1.68	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.47	0.45
Paris (France)																							
total cases		12	8	18	22	22	13	19	20	20	17	26	23	12	14	25	16	19	20	27	22	353	375
livebirths		2	1	0	1	0	0	2	0	0	1	0	0	0	0	1	1	0	0	0	0	9	9
fetal deaths		6	3	5	3	0	3	3	2	2	0	2	1	1	1	0	0	0	0	1	1	33	34
induced abortions		4	4	13	18	22	10	14	18	18	16	24	22	11	13	24	15	19	20	26	21	311	332
population:		36917	36741	35781	35902	36536	36384	36080	36672	36866	37302	37541	36469	35819	35918	36884	37237	37272	38160	38785	39400	699266	738666
Total Prevalence		3.25	2.18	5.03	6.13	6.02	3.57	5.27	5.45	5.43	4.56	6.93	6.31	3.35	3.90	6.78	4.30	5.10	5.24	6.96	5.58	5.05	5.08
Livebirth Prevalence		0.54	0.27	0.00	0.28	0.00	0.00	0.55	0.00	0.00	0.27	0.00	0.00	0.00	0.00	0.27	0.27	0.00	0.00	0.00	0.00	0.13	0.12
Strasbourg (France)																							
total cases			0	3	8	4	3	6	5	6	8	8	11	7	5	8	4	4	2	7	10	99	109
livebirths			0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	2	2
fetal deaths			0	2	1	1	0	3	1	0	1	0	1	0	0	0	0	0	0	0	0	10	10
induced abortions			0	1	7	3	3	3	4	6	7	8	9	7	5	8	3	4	2	7	10	87	97
population:			13662	12519	12924	13166	13112	12895	13595	13425	13775	13770	13736	13148	12865	13313	13185	13237	13656	13827	14238	239810	254048
Total Prevalence			0.00	2.40	6.19	3.04	2.29	4.65	3.68	4.47	5.81	5.81	8.01	5.32	3.89	6.01	3.03	3.02	1.46	5.06	7.02	4.13	4.29
Livebirth Prevalence			0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.73	0.00	0.00	0.00	0.76	0.00	0.00	0.00	0.00	0.08	0.08

Anencephalus (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Mainz (Germany)																							
total cases											0	0	0	4	0	0	1	1	2	1		9	9
livebirths											0	0	0	0	0	0	1	0	0	0		1	1
fetal deaths											0	0	0	0	0	0	0	0	0	0		0	0
induced abortions											0	0	0	4	0	0	0	1	2	1		8	8
population:											3903	4113	3941	4020	3769	3560	3603	3890	3542	3275		37616	37616
Total Prevalence											0.00	0.00	0.00	9.95	0.00	0.00	2.78	2.57	5.65	3.05		2.39	2.39
Livebirth Prevalence											0.00	0.00	0.00	0.00	0.00	0.00	2.78	0.00	0.00	0.00		0.27	0.27
Saxony-Anhalt (Germany)																							
total cases								12	9	6	4	0	0	2	1	2	8	5	2	2	3	53	56
livebirths								0	0	0	0	0	0	0	0	1	1	2	0	0	1	4	5
fetal deaths								3	0	0	1	0	0	1	0	0	0	0	0	0	0	5	5
induced abortions								9	9	6	3	0	0	1	1	1	7	3	2	2	2	44	46
population:								17165	16623	15202	14536	9123	7633	6910	7557	7707	8928	9606	10554	11500	18876	143044	161920
Total Prevalence								6.99	5.41	3.95	2.75	0.00	0.00	2.89	1.32	2.60	8.96	5.21	1.90	1.74	1.59	3.71	3.46
Livebirth Prevalence								0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.30	1.12	2.08	0.00	0.00	0.53	0.28	0.31
Dublin (Ireland)																							
total cases	48	42	42	32	24	22	20	19	20	11	15	10	11	9	8	5	5	6	8	7	6	364	370
livebirths	12	15	18	17	7	6	12	7	10	5	7	6	4	6	5	2	3	4	5	3	5	154	159
fetal deaths	36	27	24	15	17	16	8	12	10	6	8	4	7	3	3	3	2	2	3	4	1	210	211
induced abortions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
population:	26460	25510	24822	23352	22312	22131	21708	20768	19830	18914	19393	19800	18933	18491	18412	18550	19288	20257	20887	20746	21090	420564	441654
Total Prevalence	18.14	16.46	16.92	13.70	10.76	9.94	9.21	9.15	10.09	5.82	7.73	5.05	5.81	4.87	4.34	2.70	2.59	2.96	3.83	3.37	2.84	8.66	8.38
Livebirth Prevalence	4.54	5.88	7.25	7.28	3.14	2.71	5.53	3.37	5.04	2.64	3.61	3.03	2.11	3.24	2.72	1.08	1.56	1.97	2.39	1.45	2.37	3.66	3.60
Galway (Ireland)																							
total cases		2	3	2	1	6	4	2	2	0	2	2	1	0	1	1	0	1	0	0		30	30
livebirths		2	1	0	0	4	2	1	1	0	2	1	1	0	0	1	0	0	0	0		16	16
fetal deaths		0	2	2	1	2	2	1	1	0	0	1	0	0	1	0	0	1	0	0		14	14
induced abortions		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
population:		3546	3604	3397	3268	3079	3155	3051	2858	2636	2691	2578	2666	2645	2375	2436	2534	2588	2747	2655		54509	54509
Total Prevalence		5.64	8.32	5.89	3.06	19.49	12.68	6.56	7.00	0.00	7.43	7.76	3.75	0.00	4.21	4.11	0.00	3.86	0.00	0.00		5.50	5.50
Livebirth Prevalence		5.64	2.77	0.00	0.00	12.99	6.34	3.28	3.50	0.00	7.43	3.88	3.75	0.00	0.00	4.11	0.00	0.00	0.00	0.00		2.94	2.94

Anencephalus (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Campania (Italy)																							
total cases																	19	7	15	14	18	55	73
livebirths																	4	1	0	4	2	9	11
fetal deaths																	1	1	2	2	0	6	6
induced abortions																	14	5	13	8	16	40	56
population:																	46658	50458	51568	47397	50171	196081	246252
Total Prevalence																	4.07	1.39	2.91	2.95	3.59	2.80	2.96
Livebirth Prevalence																	0.86	0.20	0.00	0.84	0.40	0.46	0.45
Emilia Romagna (Italy)																							
total cases		2	3	4	2	2	2	2	1	0	0	1	0	2	1	1	2	0	5	4	6	34	40
livebirths		2	1	1	2	2	1	2	0	0	0	1	0	2	0	1	1	0	1	2	0	19	19
fetal deaths		0	2	3	0	0	1	0	1	0	0	0	0	0	1	0	0	0	0	2	1	10	11
induced abortions		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	4	0	5	5	10
population:		13189	18364	21769	23155	24016	22868	22726	22760	23380	23524	25095	25002	24533	25886	26359	28873	28859	20928	24003	24839	445289	470128
Total Prevalence		1.52	1.63	1.84	0.86	0.83	0.87	0.88	0.44	0.00	0.00	0.40	0.00	0.82	0.39	0.38	0.69	0.00	2.39	1.67	2.42	0.76	0.85
Livebirth Prevalence		1.52	0.54	0.46	0.86	0.83	0.44	0.88	0.00	0.00	0.00	0.40	0.00	0.82	0.00	0.38	0.35	0.00	0.48	0.83	0.00	0.43	0.40
North-East Italy																							
total cases		11	6	5	7	5	6	5	16	19	15	13	8	13	14	11	18	11	9	10		202	202
livebirths		5	5	1	2	4	3	3	5	1	2	0	0	1	0	2	0	1	1	1		37	37
fetal deaths		6	1	4	5	1	3	0	3	3	1	1	1	0	1	1	1	1	1	0		34	34
induced abortions		0	0	0	0	0	0	2	8	15	12	12	7	12	13	8	17	9	7	9		131	131
population:		27708	36321	41195	43202	43401	41265	42048	45307	47515	52205	51093	50340	49735	49443	51486	56869	55908	54939	54364		894344	894344
Total Prevalence		3.97	1.65	1.21	1.62	1.15	1.45	1.19	3.53	4.00	2.87	2.54	1.59	2.61	2.83	2.14	3.17	1.97	1.64	1.84		2.26	2.26
Livebirth Prevalence		1.80	1.38	0.24	0.46	0.92	0.73	0.71	1.10	0.21	0.38	0.00	0.00	0.20	0.00	0.39	0.00	0.18	0.18	0.18		0.41	0.41
South East Sicily (Italy)																							
total cases												1	4	0	0	0	1	1	1		6	8	14
livebirths												0	1	0	0	0	1	1	1		1	4	5
fetal deaths												1	3	0	0	0	0	0	0		0	4	4
induced abortions																					5	0	5
population:												19430	20273	19746	20031	18986	18054	18795	16922		15304	152237	167541
Total Prevalence												0.51	1.97	0.00	0.00	0.00	0.55	0.53	0.59		3.92	0.53	0.84
Livebirth Prevalence												0.00	0.49	0.00	0.00	0.00	0.55	0.53	0.59		0.65	0.26	0.30

Anencephalus (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Tuscany (Italy)																							
total cases	2	4	4	0	2	6	7	3	2	4	4	1	8	5	7	6	4	4	9	5	7	87	94
livebirths	0	1	1	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	1	1	1	7	8
fetal deaths	2	3	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	9	9
induced abortions	0	0	2	0	2	5	7	3	2	3	4	1	7	4	6	6	4	4	7	4	6	71	77
population:	9696	9350	9281	8948	8592	8980	8477	8511	8869	8556	8751	8657	25670	24504	24487	24520	24606	24535	25468	26059	26616	306517	333133
Total Prevalence	2.06	4.28	4.31	0.00	2.33	6.68	8.26	3.52	2.26	4.68	4.57	1.16	3.12	2.04	2.86	2.45	1.63	1.63	3.53	1.92	2.63	2.84	2.82
Livebirth Prevalence	0.00	1.07	1.08	0.00	0.00	0.00	0.00	0.00	0.00	1.17	0.00	0.00	0.00	0.41	0.41	0.00	0.00	0.00	0.39	0.38	0.38	0.23	0.24
Malta																							
total cases							6	1	1	3	0	0	3	1	2	1	3	1	3	3	0	28	28
livebirths							3	0	1	2	0	0	3	1	2	1	1	1	2	1	0	18	18
fetal deaths							3	1	0	1	0	0	0	0	0	0	2	0	1	2	0	10	10
induced abortions							0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
population:							5310	5375	5461	5617	5400	5328	5503	5172	4863	4633	4978	4864	4511	4339	4272	71354	75626
Total Prevalence							11.30	1.86	1.83	5.34	0.00	0.00	5.45	1.93	4.11	2.16	6.03	2.06	6.65	6.91	0.00	3.92	3.70
Livebirth Prevalence							5.65	0.00	1.83	3.56	0.00	0.00	5.45	1.93	4.11	2.16	2.01	2.06	4.43	2.30	0.00	2.52	2.38
Northern Netherlands																							
total cases		2	4	9	7	7	5	2	10	3	5	5	3	7	5	7	8	6	4	5	7	104	111
livebirths		0	2	3	3	0	1	0	2	0	1	2	0	0	0	1	0	1	1	1	1	18	19
fetal deaths		1	1	2	2	1	0	1	2	0	2	1	0	1	0	1	1	2	2	2	3	22	25
induced abortions		1	1	4	2	6	4	1	6	3	2	2	3	6	5	5	7	3	1	2	3	64	67
population:		7877	7731	7542	7559	7792	11936	11847	11595	19093	19635	19853	19140	19387	19283	19296	19033	19397	19941	20167	20490	288104	308594
Total Prevalence		2.54	5.17	11.93	9.26	8.98	4.19	1.69	8.62	1.57	2.55	2.52	1.57	3.61	2.59	3.63	4.20	3.09	2.01	2.48	3.42	3.61	3.60
Livebirth Prevalence		0.00	2.59	3.98	3.97	0.00	0.84	0.00	1.72	0.00	0.51	1.01	0.00	0.00	0.00	0.52	0.00	0.52	0.50	0.50	0.49	0.62	0.62
Poland																							
total cases																					28		28
livebirths																					23		23
fetal deaths																					5		5
induced abortions																					0		0
population:																					158923		158923
Total Prevalence																					1.76		1.76
Livebirth Prevalence																					1.45		1.45

Anencephalus (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Southern Portugal																							
total cases											2	1	1	0	2	2	6	3	0	6	4	23	27
livebirths											0	1	1	0	2	0	0	1	0	1	1	6	7
fetal deaths											0	0	0	0	0	2	1	0	0	0	0	3	3
induced abortions											2	0	0	0	0	0	5	2	0	5	3	14	17
population:											5461	5554	7391	7152	7000	14959	15439	16293	16312	17047	19383	112608	131991
Total Prevalence											3.66	1.80	1.35	0.00	2.86	1.34	3.89	1.84	0.00	3.52	2.06	2.04	2.05
Livebirth Prevalence											0.00	1.80	1.35	0.00	2.86	0.00	0.00	0.61	0.00	0.59	0.52	0.53	0.53
Asturias (Spain)																							
total cases											7	4	2	3	5	3	4	1	7	2		38	38
livebirths											1	1	0	0	0	0	0	0	1	0		3	3
fetal deaths											0	0	0	0	0	0	0	0	0	0		0	0
induced abortions											6	3	2	3	5	3	4	1	6	2		35	35
population:											7722	7693	7474	7012	6626	6553	6507	6473	6321	6516		68897	68897
Total Prevalence											9.07	5.20	2.68	4.28	7.55	4.58	6.15	1.54	11.07	3.07		5.52	5.52
Livebirth Prevalence											1.30	1.30	0.00	0.00	0.00	0.00	0.00	0.00	1.58	0.00			0.44
Barcelona (Spain)																							
total cases													8	8	5	5	4	6	8	5		49	49
livebirths													0	0	0	1	0	0	1	0		2	2
fetal deaths													1	0	0	1	0	1	1	1		5	5
induced abortions													7	8	5	3	4	5	6	4		42	42
population:													13477	12738	12609	12199	12031	12240	11684	12270		99248	99248
Total Prevalence													5.94	6.28	3.97	4.10	3.32	4.90	6.85	4.07		4.94	4.94
Livebirth Prevalence													0.00	0.00	0.00	0.82	0.00	0.00	0.86	0.00		0.20	0.20
Basque Country (Spain)																							
total cases											8	6	9	6	9	7	13	8	4	17	11	87	98
livebirths											0	1	0	0	0	1	1	0	0	1	0	4	4
fetal deaths											0	0	0	0	1	0	0	0	0	0	1	1	2
induced abortions											8	5	9	6	8	6	12	8	4	16	10	82	92
population:											16438	16291	16316	15891	15357	15397	16060	16397	16169	16859	17408	161175	178583
Total Prevalence											4.87	3.68	5.52	3.78	5.86	4.55	8.09	4.88	2.47	10.08	6.32	5.40	5.49
Livebirth Prevalence											0.00	0.61	0.00	0.00	0.00	0.65	0.62	0.00	0.00	0.59	0.00	0.25	0.22

Anencephalus (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Vaud (Switzerland)																							
total cases										4	2	4	5	3	3	5	5	1	2	2	4	36	40
livebirths										0	0	0	0	0	0	0	2	0	0	0	1	2	3
fetal deaths										0	0	0	0	0	0	1	0	0	0	0	0	1	1
induced abortions										4	2	4	5	3	3	4	3	1	2	2	3	33	36
population:										7212	7697	8211	8076	7700	7683	7697	7730	7562	7438	7465	7618	84471	92089
Total Prevalence										5.55	2.60	4.87	6.19	3.90	3.90	6.50	6.47	1.32	2.69	2.68	5.25	4.26	4.34
Livebirth Prevalence										0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.59	0.00	0.00	0.00	1.31	0.24	0.33
Glasgow (UK:Scotland)																							
total cases	27	19	23	19	14	16	23	15	6	9	7	8	8	10	5	10	11	4	11	7		252	252
livebirths	1	0	0	0	1	2	4	0	1	0	0	2	0	0	1	0	0	0	1	0		13	13
fetal deaths	7	3	0	1	0	0	0	1	0	0	1	1	1	2	0	2	0	1	0	1		21	21
induced abortions	19	16	23	18	13	14	19	14	5	9	6	5	7	8	4	8	11	3	10	6		218	218
population:	13438	13491	12884	12661	12783	13089	13013	12987	12908	12289	12471	12831	12339	11883	11407	11227	10976	10997	10239	9721		243634	243634
Total Prevalence	20.09	14.08	17.85	15.01	10.95	12.22	17.67	11.55	4.65	7.32	5.61	6.23	6.48	8.42	4.38	8.91	10.02	3.64	10.74	7.20		10.34	10.34
Livebirth Prevalence	0.74	0.00	0.00	0.00	0.78	1.53	3.07	0.00	0.77	0.00	0.00	1.56	0.00	0.00	0.88	0.00	0.00	0.00	0.98	0.00		0.53	0.53
Mersey (UK:England)																							
total cases																17	19	20	13	4		73	73
livebirths																1	0	0	1	0		2	2
fetal deaths																0	0	2	2	0		4	4
induced abortions																16	19	18	10	4		67	67
population:																28786	29031	27983	27514	26553		139867	139867
Total Prevalence																5.91	6.54	7.15	4.72	1.51		5.22	5.22
Livebirth Prevalence																0.35	0.00	0.00	0.36	0.00		0.14	0.14
North Thames (West) (UK:England)																							
total cases												25	33	25	27	26	24	20	35	17	34	266	266
livebirths												0	4	1	2	6	1	2	1	1	3	21	21
fetal deaths												1	1	2	1	5	3	1	0	2	3	19	19
induced abortions												24	28	22	24	15	20	17	34	14	28	226	226
population:												47330	47493	46762	47526	47324	47324	47355	47549	46874	45652	471189	471189
Total Prevalence												5.28	6.95	5.35	5.68	5.49	5.07	4.22	7.36	3.63	7.45	5.65	5.65
Livebirth Prevalence												0.00	0.84	0.21	0.42	1.27	0.21	0.42	0.21	0.21	0.66	0.45	0.45

Anencephalus (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Wales (UK)																							
total cases																			28	26	19	54	73
livebirths																			0	3	0	3	3
fetal deaths																			0	1	1	1	2
induced abortions																			28	22	18	50	68
population:																			33610	32266	31449	65876	97325
Total Prevalence																			8.33	8.06	6.04	8.20	7.50
Livebirth Prevalence																			0.00	0.93	0.00	0.46	0.31
Total (Full Member Registries)																							
total cases	86	102	97	99	95	101	98	100	100	96	110	130	147	128	124	152	194	156	210	191	188	2550	2704
livebirths	13	28	30	23	16	19	26	16	20	11	18	16	16	14	13	19	19	14	19	19	39	369	408
fetal deaths	49	51	35	36	30	24	22	27	20	14	16	15	19	10	9	17	16	12	19	22	17	463	480
induced abortions	24	23	32	40	49	58	50	57	60	71	76	99	112	104	102	116	159	130	172	150	132	1684	1816
population:	63191	150396	176097	183358	186263	202517	210627	226785	229872	250061	294138	359123	387664	379259	381565	419413	486839	498478	522435	505443	527240	6113524	6640764
Total Prevalence	13.61	6.78	5.51	5.40	5.10	4.99	4.65	4.41	4.35	3.84	3.74	3.62	3.79	3.38	3.25	3.62	3.98	3.13	4.02	3.78	3.57	4.17	4.07
Livebirth Prevalence	2.06	1.86	1.70	1.25	0.86	0.94	1.23	0.71	0.87	0.44	0.61	0.45	0.41	0.37	0.34	0.45	0.39	0.28	0.36	0.38	0.74	0.60	0.61
Associate Member Registries																							
Finland																							
total cases														15	14	16	22	16	23	18	13	124	137
livebirths														4	0	1	3	4	1	1	1	14	15
fetal deaths														0	0	0	1	1	1	0	1	3	4
induced abortions														11	14	15	18	11	21	17	11	107	118
population:														65098	65480	63368	60965	59569	57345	57782	56970	429607	486577
Total Prevalence														2.30	2.14	2.52	3.61	2.69	4.01	3.12	2.28	2.89	2.82
Livebirth Prevalence														0.61	0.00	0.16	0.49	0.67	0.17	0.17	0.18	0.33	0.31
Central East France																							
total cases	4	8	7	9	9	11	14	26	15	21	20	26	23	19	31	18	20	13	14	16	13	324	337
livebirths	3	5	4	6	6	3	0	1	2	2	1	1	1	1	2	1	1	0	0	0	0	40	40
fetal deaths	1	3	3	3	3	3	1	3	3	2	0	0	0	0	0	0	1	0	0	0	0	26	26
induced abortions						5	13	22	10	17	19	25	22	18	29	17	18	13	14	16	13	258	271
population:	75332	76220	75813	86433	86904	90825	91950	90191	91303	99858	107370	106607	104480	99249	99674	102153	103440	102090	102483	102982	93963	1895357	1989320
Total Prevalence	0.53	1.05	0.92	1.04	1.04	1.21	1.52	2.88	1.64	2.10	1.86	2.44	2.20	1.91	3.11	1.76	1.93	1.27	1.37	1.55	1.38	1.71	1.69
Livebirth Prevalence	0.40	0.66	0.53	0.69	0.69	0.33	0.00	0.11	0.22	0.20	0.09	0.09	0.10	0.10	0.20	0.10	0.10	0.00	0.00	0.00	0.00	0.21	0.20

Anencephalus (Cont'd)

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	1980-1999	1980-2000
Norway																							
Total cases	18	21	15	18	10	23	18	12	12	16	5	12	16	11	22	18	18	10	10	28	24	313	337
livebirths	2	8	2	4	1	0	3	0	0	0	1	1	0	1	3	1	1	1	1	3	4	33	37
Fetal deaths	16	13	13	14	9	15	9	5	8	7	1	3	5	7	6	5	5	3	2	8	4	154	158
induced abortions	0	0	0	0	0	8	6	7	4	9	3	8	11	3	13	12	12	6	7	17	16	126	142
population:	51495	51021	51642	50258	50576	51416	52885	54313	57936	59712	61523	61386	60636	60166	60306	60488	61092	59896	58482	60215	59907	1135444	1195351
Total Prevalence	3.50	4.12	2.90	3.58	1.98	4.47	3.40	2.21	2.07	2.68	0.81	1.95	2.64	1.83	3.65	2.98	2.95	1.67	1.71	4.65	4.01	2.76	2.82
Livebirth Prevalence	0.39	1.57	0.39	0.80	0.20	0.00	0.57	0.00	0.00	0.00	0.16	0.16	0.00	0.17	0.50	0.17	0.16	0.17	0.17	0.50	0.67	0.29	0.31
ECEMC (Spain)																							
Total cases	35	25	29	24	27	38	14	13	14	12	10	16	5	6	8	9	6	8	6	2		307	307
livebirths	20	17	18	18	19	16	7	8	8	4	4	9	2	3	5	4	4	4	5	2		177	177
Fetal deaths	15	8	11	6	8	22	7	5	6	8	6	7	3	3	3	5	2	4	1	0		130	130
induced abortions																						0	0
population:	56910	56102	61333	71812	69513	66720	58245	51051	52686	59046	84379	87708	91607	82925	87239	87372	94044	98945	96490	104337		1518464	1518464
Total Prevalence	6.15	4.46	4.73	3.34	3.88	5.70	2.40	2.55	2.66	2.03	1.19	1.82	0.55	0.72	0.92	1.03	0.64	0.81	0.62	0.19		2.02	2.02
Livebirth Prevalence	3.51	3.03	2.93	2.51	2.73	2.40	1.20	1.57	1.52	0.68	0.47	1.03	0.22	0.36	0.57	0.46	0.43	0.40	0.52	0.19		1.17	1.17
Total (Associate Member Registries)																							
Total cases	57	54	51	51	46	72	46	51	41	49	35	54	44	51	75	61	66	47	53	64	50	1068	1118
livebirths	25	30	24	28	26	19	10	9	10	6	6	11	3	9	10	7	9	9	7	6	5	264	269
Fetal deaths	32	24	27	23	20	40	17	13	17	17	7	10	8	10	9	10	9	8	4	8	5	313	318
induced abortions	0	0	0	0	0	13	19	29	14	26	22	33	33	32	56	44	48	30	42	50	40	491	531
population:	183737	183343	188788	208503	206993	208961	203080	195555	201925	218616	253272	255701	256723	307438	312699	313381	319541	320500	314800	325316	210840	4978872	5189712
Total Prevalence	3.10	2.95	2.70	2.45	2.22	3.45	2.27	2.61	2.03	2.24	1.38	2.11	1.71	1.66	2.40	1.95	2.07	1.47	1.68	1.97	2.37	2.15	2.15
Livebirth Prevalence	1.36	1.64	1.27	1.34	1.26	0.91	0.49	0.46	0.50	0.27	0.24	0.43	0.12	0.29	0.32	0.22	0.28	0.28	0.22	0.18	0.24	0.53	0.52
Total (All Registries)																							
Total cases	143	156	148	150	141	173	144	151	141	145	145	184	191	179	199	213	260	203	263	255	238	3584	3822
livebirths	38	58	54	51	42	38	36	25	30	17	24	27	19	23	23	26	28	23	26	25	44	633	677
Fetal deaths	81	75	62	59	50	64	39	40	37	31	23	25	27	20	18	27	25	20	23	30	22	776	798
induced abortions	24	23	32	40	49	71	69	86	74	97	98	132	145	136	158	160	207	160	214	200	172	2175	2347
population:	246928	333739	364885	391861	393256	411478	413707	422340	431797	468677	547410	614824	644387	686697	694264	732794	806380	818978	837235	830759	738080	11092396	11830476
Total Prevalence	5.79	4.67	4.06	3.83	3.59	4.20	3.48	3.58	3.27	3.09	2.65	2.99	2.96	2.61	2.87	2.91	3.22	2.48	3.14	3.07	3.22	3.23	3.23
Livebirth Prevalence	1.54	1.74	1.48	1.30	1.07	0.92	0.87	0.59	0.69	0.36	0.44	0.44	0.29	0.33	0.33	0.35	0.35	0.28	0.31	0.30	0.60	0.57	0.57

Appendix 4

Ascertainment of Terminations of Pregnancy (TOP)

In Dublin, Galway and Malta, terminations of pregnancy for fetal anomaly are illegal – in these registries numbers of IA are "0" and these registries are included in total prevalence rates across registries. In addition, terminations were illegal in ECEMC (Spain) before 1985. Terminations of pregnancy were legal but information about terminations of pregnancy was not available to Poland in 2000, South East Sicily up to 1999, ECEMC-Spain from 1985 to 1999, North East Italy before 1988, and Central East France before 1985. In Emilia Romagna, data on terminations were not available until 1989, recording was very incomplete between 1989 and 1993, and since 1994, ascertainment of IA has improved. In Norway registration of all abortions induced after prenatal diagnosis of a congenital anomaly was introduced on 1st December 1998, prior to this some of these cases may be missing. Numbers of cases of terminations and total prevalence rates for these registries are represented by "-" where the data were missing or severely incomplete for the entire period referred to in the Table.

Table A4 and Figure A4 give additional indications regarding the possibility of underascertainment of terminations of pregnancy in other registries. Since the proportion of anencephaly cases which are terminations of pregnancy following prenatal diagnosis is generally much greater than the proportion of spina bifida cases which are terminations, high spina bifida:anencephaly ratios may suggest that terminations have been selectively underascertained, particularly when associated with a lower NTD prevalence that the average for the region (Figure A5). However, other explanation may also apply

Table A4: Spina bifida cases, Anencephalus cases and spina bifida to Anencephalus ratio (SB:ANEN) with NTD prevalence per 10,000 births rate for 1980 – 1999

	80-84	85-89	90-94	95-99	Total 80-99	NTD Rate 80-99
Styria (Austria)						
Spina bifida total cases		34	37	26	97	
Anencephalus total cases		12	14	12	38	
Spina Bifida : Anencephalus		2.83	2.64	2.17	2.55	7.95
Antwerp (Belgium)						
Spina bifida total cases			23	26	49	
Anencephalus total cases			16	25	41	
Spina Bifida : Anencephalus			1.44	1.04	1.20	8.99
Hainaut (Belgium)						
Spina bifida total cases	16	18	47	37	118	
Anencephalus total cases	20	28	18	20	86	
Spina Bifida : Anencephalus	0.80	0.64	2.61	1.85	1.37	10.82
Bulgaria						
Spina bifida total cases				43	43	
Anencephalus total cases				27	27	
Spina Bifida : Anencephalus				1.59	1.59	18.82
Croatia						
Spina bifida total cases	4	13	18	9	44	
Anencephalus total cases	2	2	2	3	9	
Spina Bifida : Anencephalus	2.00	6.50	9.00	3.00	4.89	5.52
Odense (Denmark)						
Spina bifida total cases	13	16	16	20	65	
Anencephalus total cases	14	11	9	11	45	
Spina Bifida : Anencephalus	0.93	1.45	1.78	1.82	1.44	11.67
Paris (France)						
Spina bifida total cases	66	90	91	96	343	
Anencephalus total cases	60	94	92	107	353	
Spina Bifida : Anencephalus	1.10	0.96	0.99	0.90	0.97	11.83

Table A4 (Cont'd)

	80-84	85-89	90-94	95-99	Total 80-00	NTD Rate 80-00
Strasbourg (France)						
Spina bifida total cases	22	28	26	44	120	
Anencephalus total cases	11	24	39	25	99	
Spina Bifida : Anencephalus	2.00	1.17	0.67	1.76	1.21	10.63
Mainz (Germany)						
Spina bifida total cases			14	37	51	
Anencephalus total cases			4	5	9	
Spina Bifida : Anencephalus			3.50	7.40	5.67	18.61
Saxony-Anhalt (Germany)						
Spina bifida total cases		45	23	24	92	
Anencephalus total cases		27	7	19	53	
Spina Bifida : Anencephalus		1.67	3.29	1.26	1.74	11.67
Dublin (Ireland)						
Spina bifida total cases	240	117	61	52	470	
Anencephalus total cases	188	92	53	31	364	
Spina Bifida : Anencephalus	1.28	1.27	1.15	1.68	1.29	21.92
Galway (Ireland)						
Spina bifida total cases	15	20	13	3	51	
Anencephalus total cases	8	14	6	2	30	
Spina Bifida : Anencephalus	1.88	1.43	2.17	1.50	1.70	15.41
Campania (Italy)						
Spina bifida total cases				62	62	
Anencephalus total cases				55	55	
Spina Bifida : Anencephalus				1.13	1.13	7.15
Emilia Romagna (Italy)						
Spina bifida total cases	30	40	47	23	140	
Anencephalus total cases	11	7	4	12	34	
Spina Bifida : Anencephalus	2.73	5.71	11.75	1.92	4.12	4.45
North-East Italy						
Spina bifida total cases		24	78	90	192	
Anencephalus total cases		35	63	59	157	
Spina Bifida : Anencephalus		0.69	1.24	1.53	1.22	6.41

Table A4 (Cont'd)

	80-84	85-89	90-94	95-99	Total 80-00	NTD Rate 80-00
South East Sicily (Italy)						
Spina bifida total cases			35	15	50	
Anencephalus total cases			5	3	8	
Spina Bifida : Anencephalus			7.00	5.00	6.25	4.86
Tuscany (Italy)						
Spina bifida total cases	25	27	26	36	114	
Anencephalus total cases	12	22	25	28	87	
Spina Bifida : Anencephalus	2.08	1.23	1.04	1.29	1.31	7.67
Malta						
Spina bifida total cases		14	15	15	44	
Anencephalus total cases		11	6	11	28	
Spina Bifida : Anencephalus		1.27	2.50	1.36	1.57	11.07
Northern Netherlands						
Spina bifida total cases	16	42	72	57	187	
Anencephalus total cases	22	27	25	30	104	
Spina Bifida : Anencephalus	0.73	1.56	2.88	1.90	1.80	11.25
Poland						
Spina bifida total cases						
Anencephalus total cases						
Spina Bifida : Anencephalus						
Southern Portugal						
Spina bifida total cases			12	25	37	
Anencephalus total cases			6	17	23	
Spina Bifida : Anencephalus			2.00	1.47	1.61	5.95
Asturias (Spain)						
Spina bifida total cases			28	16	44	
Anencephalus total cases			21	17	38	
Spina Bifida : Anencephalus			1.33	0.94	1.16	13.06
Barcelona (Spain)						
Spina bifida total cases			16	18	34	
Anencephalus total cases			21	28	49	
Spina Bifida : Anencephalus			0.76	0.64	0.69	9.07

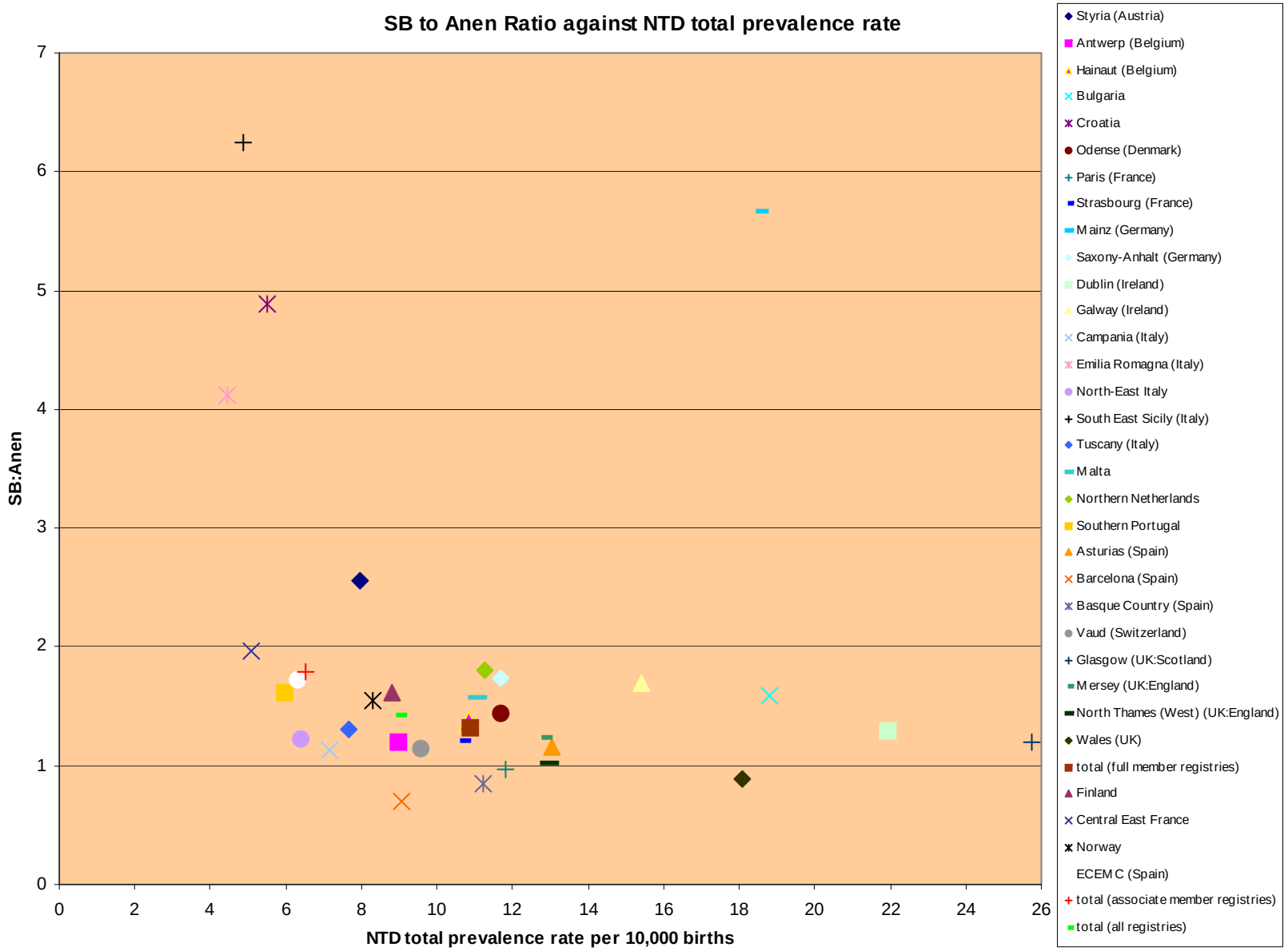
Table A4 (Cont'd)

	80-84	85-89	90-94	95-99	Total 80-00	NTD Rate 80-00
Basque Country (Spain)						
Spina bifida total cases			39	35	74	
Anencephalus total cases			38	49	87	
Spina Bifida : Anencephalus			1.03	0.71	0.85	11.23
Vaud (Switzerland)						
Spina bifida total cases		2	17	22	41	
Anencephalus total cases		4	17	15	36	
Spina Bifida : Anencephalus		0.50	1.00	1.47	1.14	9.59
Glasgow (UK:Scotland)						
Spina bifida total cases	111	97	48	47	303	
Anencephalus total cases	102	69	38	43	252	
Spina Bifida : Anencephalus	1.09	1.41	1.26	1.09	1.20	25.74
Mersey (UK:England)						
Spina bifida total cases				90	90	
Anencephalus total cases				73	73	
Spina Bifida : Anencephalus				1.23	1.23	12.80
North Thames (West) (UK:England)						
Spina bifida total cases			108	129	237	
Anencephalus total cases			110	122	232	
Spina Bifida : Anencephalus			0.98	1.06	1.02	12.95
Wales (UK)						
Spina bifida total cases				48	48	
Anencephalus total cases				54	54	
Spina Bifida : Anencephalus				0.89	0.89	18.06
total (full member registries)						
Spina bifida total cases	558	627	910	1145	3240	
Anencephalus total cases	450	475	613	853	2391	
Spina Bifida : Anencephalus	1.24	1.32	1.48	1.34	1.36	10.90

Table A4 (Cont'd)

	80-84	85-89	90-94	95-99	Total 80-00	NTD Rate 80-00
Associate Member Registries						
Finland						
Spina bifida total cases			54	146	200	
Anencephalus total cases			29	95	124	
Spina Bifida : Anencephalus			1.86	1.54	1.61	8.82
Central East France						
Spina bifida total cases	126	154	201	208	689	
Anencephalus total cases	37	87	119	81	324	
Spina Bifida : Anencephalus	3.41	1.77	1.69	2.57	2.13	5.07
Norway						
Spina bifida total cases	145	138	127	149	559	
Anencephalus total cases	82	81	66	84	313	
Spina Bifida : Anencephalus	1.77	1.70	1.92	1.77	1.79	8.31
ECEMC (Spain)						
Spina bifida total cases	135	131	155	106	527	
Anencephalus total cases	140	91	45	31	307	
Spina Bifida : Anencephalus	0.96	1.44	3.44	3.42	1.72	6.30
Total (Associate Member Registries)						
Spina bifida total cases	406	423	537	609	1975	
Anencephalus total cases	259	259	259	291	1068	
Spina Bifida : Anencephalus	1.57	1.63	2.07	2.09	1.85	6.51
Total (All Registries)						
Spina bifida total cases	964	1050	1447	1754	5215	
Anencephalus total cases	709	734	872	1144	3459	
Spina Bifida : Anencephalus	1.36	1.43	1.66	1.53	1.51	8.93

Figure A4:


SB to Anen Ratio against NTD total prevalence rate
SB:Anen
NTD total prevalence rate per 10,000 births
0
1
2
3
4
5
6
7
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Styria (Austria)
Antwerp (Belgium)
Hainaut (Belgium)
Bulgaria
Croatia
Odense (Denmark)
Paris (France)
Strasbourg (France)
Mainz (Germany)
Saxony-Anhalt (Germany)
Dublin (Ireland)
Galway (Ireland)
Campania (Italy)
Emilia Romagna (Italy)
North-East Italy
South East Sicily (Italy)
Tuscany (Italy)
Malta
Northern Netherlands
Southern Portugal
Asturias (Spain)
Barcelona (Spain)
Basque Country (Spain)
Vaud (Switzerland)
Glasgow (UK:Scotland)
Mersey (UK:England)
North Thames (West) (UK:England)
Wales (UK)
total (full member registries)
Finland
Central East France
Norway
ECEMC (Spain)
total (associate member registries)
total (all registries)

Appendix 5

EUROCAT Registry Descriptions by Registry

Styria (Austria)
Styrian Malformation Registry

History and funding: The registry was set up in 1986 following the Chernobyl disaster. It registers fetuses/babies with congenital anomalies born after January 1st 1985. The registry has been a member of EUROCAT since 1995. It is funded by research grants provided by the Styrian government on an annual basis.

Population coverage: The registry covers all births to residents of the province of Styria (Population-based I = All mothers resident in defined geographic area) which amounts to a total of approximately 11,000 births annually.

Sources of ascertainment: The registry operates as a research programme with voluntary participation of hospitals. Information is actively gathered from 49 sources and reports are requested once per year. Sources consist of 34 minor or major obstetric hospitals, 1 cytogenetic laboratory, 2 pathology services, 11 child health services, including specialised departments for diagnosis and treatment, and free practicing midwives. The main record forms are filled out by medical doctors at the reporting source and are sent to the registry. Six sources have to be visited for data collection by a member of the registry. 48% of cases are reported by more than one source. In the remaining 52% of cases, only one source provided data. Fetuses/babies with anomalies are registered if diagnosed before birth, at birth or during the first year of life.

Terminations of pregnancy: Terminations of pregnancy following prenatal diagnosis of congenital anomaly are registered. Termination of pregnancy is legal in all cases for Socioeconomic reasons up to 12 weeks and thereafter, if serious psychological or health problems for mother or the fetus were to be expected. If a non-lethal congenital anomaly is diagnosed, most obstetricians in Austria would follow the maternal wish for TOP only up to 24 WG+0. Non-viable forms of congenital anomalies may be terminated at any stage of gestation. The official policy regarding prenatal diagnosis is: pregnant women are offered 2 ultrasound scans (16-20 and 30-34 weeks' gestation) according to a booklet called 'Mother-child passport'. More scans are done in most cases.

Stillbirth and early fetal deaths: Stillbirths with congenital anomaly are registered. Stillbirth definition is: late fetal death from a Crown Foot Length>=35cm and from 01.01.95 a limit of >=500g has been introduced by law. There is no lower gestational age or weight limit for registration of congenital anomaly in early fetal deaths/spontaneous abortions. Autopsy rates in 1999 were are as follows: stillbirths 63, induced abortions 68%, early neonatal deaths (0-7 days) 70% (estimate), later deaths 1 week to 1 year 70% (estimate) and deaths with congenital anomaly 64%.

Exposure data availability: Exposure information (e.g. maternal occupation, intake of drugs or illnesses during pregnancy) is not available. Data about techniques of prenatal screening (ultrasound, serum markers) and prenatal diagnosis are not systematically collected. Maternal residency is recorded and can be used for evaluating the sub-regional pattern of birth defects.

Denominators and controls information: Information on all births is available from birth certificates, gathered by Statistics Austria.

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Antwerp (Belgium)

History and funding: The registry began with a pilot study on procedures for registration of congenital anomalies in 1989. In 1990 the registry formally started in a region in Antwerp. Since 1997, the whole province of Antwerp has been covered. The registry is developed in collaboration with the provincial government and the university of Antwerp. The program is funded by the provincial government of Antwerp. The Registry has been a member of EUROCAT since1990.

Population coverage: The registry covers about 18,000 births annually, these are all births in the province of Antwerp (about 15% of the births in Belgium, Population-based I = All mothers resident in defined geographic area).

Sources of ascertainment: Reports are actively collected from maternity, Pediatric, and neonatologic units by registry staff who visit each maternity and neonatal unit in the covered region. There are a total of 23 participating hospitals. The midwife gives the basic information of children born with congenital anomalies. Further information is gathered from the Gynecologist and Pediatrician. Information about the parents is obtained from the general practitioners. The Gynecologist also reports cases to the registry if an anomaly is prenatally detected. If an anomaly is detected after the stay in the maternity hospital the Pediatrician reports it to the head nurse of the Pediatric ward. A check is made to ascertain whether the case has already been notified. Clinical geneticists, surgeons, pathologists and the Pediatrician of the centre of metabolic diseases are also contacted for more information. In 1996, the Child Welfare centres, an important notifier underwent re-organisation and computerisation, leading to a deficit of notifications that year. All cases of congenital anomaly diagnosed prenatally or in the first year of birth are registered. Reporting by hospitals and health workers is voluntary.

Termination of pregnancy: Termination of pregnancy is registered. Termination of pregnancy is legal under 13 weeks. If congenital anomaly is diagnosed, the upper gestational age for termination is 23 to 24 weeks.

Stillbirth definition and early fetal deaths: The stillbirth definition for denominators is: a baby which is not viable with a gestational age of >180 days. Stillbirths are registered. Early fetal deaths/spontaneous abortions are registered. Autopsy rates are as follows: stillbirths 75% (estimate), induced abortions 61%, neonatal deaths (0-7 days) unknown, later deaths 1 week to 1 year unknown and deaths with congenital anomaly 48%.

Exposure data availability: Exposure information: includes: maternal drug use maternal smoking and alcohol abuse, maternal and paternal diseases and family history, parental occupation.

Denominators and controls information: Background data on births are retrieved from the population databases of the local authorities and from the study centre for perinatal epidemiology in the Flanders region. Controls are not included in the registry, but data can be ascertained for specific studies.

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Hainaut (Belgium)

History and funding: The registry of Hainaut-Namur was initiated in 1978 and it started in 1979. It has been a member of EUROCAT since the beginning. From 1979 to 1990, it was located at the School of Public Health of the Catholic University of Louvain (Brussels). Since 1990, it was integrated into the Centre of Human Genetics of the Institute of Pathology and Genetics of the Institute of Pathology and Genetics (Loverval – Belgium). As a part of the Institute of Pathology and Genetics of Loverval, it is supported by an annual grant front the Institute of Research in Pathology and Genetics of Loverval. From 2001 it is also partly supported by the Ministry of Public Health of Wallonia.

Population coverage: The registry annually covers approximately 12,000 births in the provinces of Hainaut (south) and Namur (Population-based II = All mothers delivering within defined geographic area, irrespective of place of residence), which represents about 11% of all births in Belgium.

Sources of ascertainment: Delivery units, neonatal and Pediatric departments divided into 13 hospitals. All cytogenetic, genetic and pathological data including the examination of aborted fetuses are regionally concentrated in the Institute of Pathology and Genetics of Loverval. Children with malformations are registered up to one year of age.

Termination of pregnancy: Termination of pregnancy is legal up to 12 weeks of gestation. If a congenital anomaly is diagnosed, the upper gestational age limit for termination is approximately 24 weeks. Theoretical access to information is available on all cases of termination of pregnancy as they are registered, however, in practice ascertainment is slow to process.

Stillbirth definition and early fetal deaths: Stillbirth definition is: 28 weeks (or 180 days). Stillbirths are registered. Early fetal deaths/spontaneous abortions are included if the gestational age is greater than or equal to 20 weeks (weight is not a factor). Early fetal deaths/spontaneous abortions are registered. Autopsy rates are as follows: stillbirths 52% for all cases (95% of cases of malformations), induced abortions virtually 100%, early neonatal deaths (0-7 days) 52% for all cases (95% of cases of malformations), later deaths 1 week to 1 year unknown and deaths with congenital anomaly 48% in 1992-94 compared with 25% in 1982.

Exposure data availability: Exposure information: All that concerns information of maternal diseases during pregnancy, maternal drugs, occupations and genetic data is available.

Denominators and controls information: Background data on births are available from national and regional institutes of statistics. It is also based on our own statistics in collaboration with the ONE (Office de la Naissance et de l'Enfance).

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Bulgaria
Sofia Registry of Congenital Anomalies (SORCA)

History and funding: The registry started in 1995 when it became a member of EUROCAT in 1996. The registry is organised by the Bulgarian Society of Human Genetics and Sofia Municipality, and was supported by the State and private sponsors until 2001. The registry is not currently funded.

Population coverage: The registry covers all mothers resident in the region of Sofia (Population-based III = All mothers delivering in defined geographic area excluding non-residents of that area) and covers approximately 10,000 births annually.

Sources of ascertainment: The registry covers livebirths up to 1-year life, stillbirths and terminations of pregnancy. In practice, cases are notified by: obstetricians, neonatologists, Pediatricians, and pathologists. However, according to the Ministry of Health Act, every physician is allowed to notify by telephone or special form. Birth certificates do not include notification of congenital anomaly whereas death certificates do and are used as a source. Developmental screening clinics and child health centres are used as a source of notification of congenital anomaly.

Terminations of pregnancy: Termination of pregnancy is legal, with an upper gestational age limit of 12 weeks without special permission and up to 20 weeks with permission. If a congenital anomaly is diagnosed, the upper gestational age limit for termination is 27 weeks. The timing of termination depends on the severity of the defect. The Information Group (registry leader, two Pediatricians and a midwife) has full access to the data relating to invasive prenatal diagnosis carried out in the Genetic Centre in Sofia.

Stillbirth definition and early fetal deaths: Stillbirth definition is death at 20 or more weeks of gestation with no evidence of life after delivery. Stillbirths are registered. Early fetal deaths/spontaneous abortions are registered and included if the gestational age is less than 20 weeks.

Exposure data availability: Exposure information: Information about maternal drug use, maternal diseases, maternal occupation, and obstetric history is available for cases.

Denominators and controls information: Denominators are available from the Statistics unit of the regional health centre of Sofia municipality, the Ministry of Health and the statistics units of Sofia maternity clinics.

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Croatia

History and funding: The project started as a pilot investigation in 1982 and began formally as a registry in 1983 when it also joined EUROCAT. Until the end of 2000 we did not have any local funding, collection and transmission of data were on voluntary basis. From the year 2000 we have received funding from Ministry of Science and Technology and as a public health project we are in process of applying for funding from the Ministry of Health.

Population coverage: The registry is population based (Population-based I: All mothers resident in defined geographic area) and covers approximately 6000 annual births, up to 12% of births in Croatia (cities Rijeka, Varazdin, Koprivnica and region Pula).

Sources of ascertainment: Data are actively collected from four Delivery Units in the cities of Rijeka, Varazdin, Koprivnica and region Pula by neonatologists and Gynecologists. Birth certificates include notification of congenital anomaly and are used as a source. Death certificates also allow for notification of congenital anomaly and are used as a source. Children can be registered up to the first week of life.

Termination of pregnancy: Termination of pregnancy is legal and the upper gestational age limit set for termination is 24 weeks for all reasons. Terminations of pregnancy with congenital anomaly are not completely ascertained, but ascertainment has improved since 1996.

Stillbirth definition and early fetal deaths: Stillbirth definition is: 22 completed gestational weeks/500g weight. Stillbirths and early fetal deaths/spontaneous abortions are registered. Autopsy rates are as follows: stillbirths 90-100%, induced abortions 100%, early neonatal deaths (0-7) days 90-100%, later deaths 1 week to 1 year 90-100% and deaths with congenital anomaly 100%.

Exposure data availability: Exposure information: information on maternal drug use, maternal and paternal diseases and occupations, outcome of previous pregnancies is available for almost all malformed cases.

Denominators and controls information: Information on all births is available from the birth certificates.

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Odense (Denmark)
Registry of Funen County

History and funding: The registry started in 1979 and joined the EUROCAT network from the beginning of EUROCAT. The registry has been approved by the "Data Tilsynet" as a private registry for the purpose of research. There is no specific funding except private funding for computer equipment.

Population coverage: The registry covers Funen County (island of Funen with surrounding small islands) situated in the middle of Denmark (Population-based I = All mothers resident in defined geographic area). The total number of births per year in Funen County is around 6,000.

Sources of ascertainment: The registry is based on active case finding. Data for the registry includes hospital records from obstetric and Pediatric departments, birth notifications, deaths certificates, post-mortem examinations and data from the cytogenetic laboratory. For livebirths, late diagnosed cases are included up to the age of seven years.

Terminations of pregnancy: Termination of pregnancy is legal and the upper gestational age limit is 12 weeks without special permission. After 12 weeks of gestation induced abortion can be performed after permission from a local committee. If a congenital anomaly is diagnosed, the upper gestational age for termination is usually 24 weeks (24 to 28 weeks possible if survival is impossible). Terminations of pregnancy for fetal malformations are registered.

Stillbirth definition and early fetal deaths: Stillbirths include fetal deaths with gestational age ≥ 28 weeks. Stillbirths and fetal deaths/spontaneous abortions from 20 weeks are registered. The autopsy rate in stillbirths is 70% but is declining over the years.

Exposure data availability: Exposure information: Parental occupation, maternal smoking and medication during first trimester, maternal illness before and during pregnancy.

Denominators and controls information: Data on births per year and maternal age distribution covering Funen county is available from National Danish Statistics.

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Paris (France)

History and funding: The programme was initiated in 1975, but the registry began formally in 1981. It has also been a member of EUROCAT since 1982. The registry is part of a research unit of INSERM (National Institute of Health and Medical Research). The registry has been officially recognised by the French National Committee of Registries, and is renewed for four years (2001-2004) and partially supported by an annual grant from INSERM and Institut de la Veille Sanitaire (Institute for Health Surveillance).

Population coverage: The registry is population-based III (includes all mothers delivering in defined geographic area excluding non-residents of that area) and covers 38,000 annual births (about 5% of all births in France), that is, all births (live and stillbirths of 22 weeks or more) and terminations of pregnancy in the population of Greater Paris delivering in Paris maternity units. The estimation of the coverage of the registry is around 95%. The percentage of non-residents delivering within the registry area was 9.5% in 1998.

Sources of ascertainment: Notification to the registry is voluntary. Reports are actively collected from delivery units, Pediatric departments, cytogenetic laboratories, and pathology departments. Terminations of pregnancy are included. Case information is also received from the health certificates of the first week of life and this is the maximum age at diagnosis. Birth certificates include notification of congenital anomaly and are used as a source of notification.

Termination of pregnancy: Termination of pregnancy is legal and there is no upper gestational age limit for termination after diagnosis of congenital anomaly.

Stillbirth definition and early fetal deaths: Stillbirths of 22 weeks after the last menstrual period or more are registered. Early fetal deaths/spontaneous abortions are registered and included when the gestational age is 16 weeks. Autopsy rates in 1998 were as follows: 86% in stillbirths, 90% in induced abortions, 70% in early neonatal deaths (0-7 days) and no data are available for later deaths except from specific studies. All autopsies are carried out by fetopathologists.

Exposure data availability: Information on maternal drug use, maternal and paternal diseases and occupations, outcome of previous pregnancies, is available for the malformed cases.

Denominators and controls information: Background data on births are available from the National Institute of Statistics (INSEE).

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Strasbourg (France)
Strasbourg Prospective Study of Congenital Malformations.

History and funding: The registry was started in 1979 and became a member of EUROCAT in 1982. The programme is a research program, recognised by the local health authorities and funded by Social Security, Ministry of Health and INSERM.

Population coverage: The registry is population-based III and includes all mothers delivering in the covering area excluding non-residents. 3.5% of non-residents gave birth in the covered hospitals and 2% of the residents delivery outside the area. The geographic area covered by the Registry is the "departement du Bas-Rhin", Northeastern France, including Strasbourg, an urban area, and rural areas around Strasbourg. The registry covers about 13,500 births which represents approximately 2% of all births in France.

Sources of ascertainment: Registration is active. Sources of information are multiple including reports obtained from Pediatricians examining the newborn infants, hospital discharge records, maternity records, fetal ultrasound screening, laboratory records (cytogenetic, molecular, pathology) and specialised departments. Birth certificates include notification of congenital anomaly and are also used as a source of notification. The maximum age at diagnosis is between 2 and 5 years of age.

Termination of pregnancy: Termination of pregnancy is legal and there is no upper gestational age limit set for either social terminations or terminations as a result of diagnosis of a congenital anomaly. Terminations of pregnancy are registered.

Stillbirth definition and early fetal deaths:
Before 1993 stillbirths were defined as 180 days and since 1993 the definition has been set at 22 weeks of gestation. There is no limit, with regard to either gestational age or weight which impedes notification of a fetal death/spontaneous abortion to the register. Both stillbirths and fetal death/spontaneous abortions are registered. Autopsy is refused by about 10% of parents in cases not involving a congenital anomaly. Rates were as follows in 1994: in stillbirths 94%, in induced abortions 94%, in early neonatal deaths (0-7 days) 94%, in later deaths 1 week to 1 year 94% and 80% in deaths with congenital anomaly.

Exposure data availability: Detailed information on various exposures is obtained by interview of the mothers of the malformed infants and their controls. The children are followed to the age of one year.

Denominators and controls information: General demographic information is obtained from the National Institute of Statistics. Further information is obtained from Social Security Records and Health Sheets. A control infant is selected for each malformed one: the next infant of the same sex as the proband born at that hospital.

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Mainz (Germany)

History and funding: The Mainz Model was launched in 1990. The aim of this screening project was to determine prevalences and etiological causes of congenital birth defects. The registry and its associated research is funded by the Ministry of Health of the Federal Republic of Germany from 1990-1995 and by the Ministry of Labour, Social Affairs and Health of Rhineland-Palatine from 1990 until now. The Registry joined EUROCAT in 1992.

Population coverage: The registry covers births in three maternity hospitals which serve the Mainz district of Rhineland-Palatinate in SW Germany with approximately 3,300 births per year. Births to non-residents of the area are excluded (population-based III).

Sources of ascertainment: The registry employs three Pediatricians specially trained in clinical genetics, neonatalology and pediatric ultrasonography who examine each baby born in the participating hospitals twice within the first week of life. Routine sonography of hips and kidneys are performed. For particular indications (e.g. microcephaly or heart murmur) further ultrasound examinations of heart, brain and other investigations are made. Both major and minor anomalies are recorded according to a standard examination protocol, but only major anomalies are transmitted to the EUROCAT Central Registry. Information concerning stillbirths is obtained from pathology reports. Information concerning terminations of pregnancy is obtained from pathology reports and from the one centre in the district doing the final prenatal diagnosis. Cases of Microcephaly are not transmitted to EUROCAT Central Registry.

Termination of pregnancy: Terminations of pregnancy following prenatal diagnosis are registered. Induced abortion for social reasons is legal but not done in the Mainz region. Terminations of pregnancy for fetal malformation are performed in one of the hospitals. It is relatively common for prenatal diagnosis of major malformation not to result in a decision to terminate the pregnancy. 60% of terminations have an autopsy examination.

Stillbirth definition and early fetal deaths: The official stillbirth definition in Germany is a baby born with no signs of life weighing >=500g. The registry records information on all fetal deaths (including both stillbirths and spontaneous abortions) from 16 weeks gestation. Autopsy rates were as follows in 1995: in stillbirths 70%, in induced abortions 70%, in early neonatal deaths (0-7 days) 55%, in later deaths 1 week to 1 year - not applicable and in deaths with congenital anomaly – not known.

Exposure data availability: Exposure information on the EUROCAT form is obtained for both malformed and non-malformed babies from the pregnancy pass filled out throughout pregnancy and data collected by midwives 6-8 weeks before birth. Additional exposure data is held which is not transmitted to EUROCAT. Drugs are ATC coded.

Denominators and controls information: There is comparable information on all non-malformed babies in the population from the same process of Pediatric examination and information gathering. The number of births is taken from this database. Information on the total number of fetal deaths from 16 weeks is available and included in “stillbirth” statistics.

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Saxony-Anhalt (Germany)

History and Funding: The registry started in 1980. The years 1980-89 were funded by Ministry of Health of former German Democratic Republic. The years 1990-92 were funded by the Academy of Medicine, Magdeburg whereas the period between 1993 and 1995 was sponsored by the Ministry of Health, Federal Republic of Germany. Since 1995, the registry has been funded by the Ministry of Labour, Women, Health and Social Security of the Federal State of Saxony-Anhalt. The registry joined EUROCAT in 1992.

Population Coverage: The registry started in 1980 in the city of Magdeburg with about 4,000 annual births. After it there was a successive enlargement of the registry from 1981 to 1986. In 1981 we expanded to include some counties around the city of Magdeburg and this process continued until 1987 when we registered the whole district (about 17,000 births per year). Then we had a stable system from 1987 to 1989 and in 1990 there was a dramatic political change. Since the reunification there has been a two-third decrease in the number of births in the so-called new federal states. After the reunification, a similar process of territorial enlargement took place. In year 2000, registration expanded to the entire Federal State of Saxony-Anhalt, with about 19,000 annual births, 21 counties and three major cities.

By comparison to 1987, currently we survey a much larger area in our registry with approximately twice as many inhabitants (2.7 million) but the births rate is the same as the 1980s. Registration concerns deliveries within surveyed region excluding non-residents (Population-based III).

Sources of ascertainment: About 80 health institutions in 2000 including obstetric clinics, maternity hospitals, neonatal and pathological departments, prenatal diagnostic departments, children's hospitals report fetuses/infants with malformations. Until 1990, registration extended to diagnoses made in the first year of life. Subsequently, the time period for registration was restricted to the first week of life.

Terminations of pregnancy: Terminations of pregnancy ("medical indication") have no time limitation by law in Germany. We have had complete information about terminations of pregnancy after prenatal diagnosis of fetal malformations since 1987.

Stillbirth definition and early fetal deaths: Stillbirths and spontaneous abortions with malformations from 16 weeks gestation are registered. The stillbirth definition has been >=500 g from 1.4.94 and >= 1000g before 1994.

Exposure data availability: Maternal and paternal occupation, drugs in pregnancy (ATC coded), alcohol, nicotine, drug abuse.

Denominators and controls information: Statistics on the total number of births comes from Statistical Office Saxony-Anhalt. There is the opportunity to exclude non-residents mothers with assistance of the postal code. A woman who gives births outside of Saxony-Anhalt but is a resident here is included in the statistics. The denominators include only livebirths and stillbirths. Information about maternal age for all births is available only at the level of the entire state of Saxony-Anhalt.

Information is also reported about two control infants per malformed child. The two control infants, theoretically, are those born directly before and directly after the malformed child. The information about the control children is the same as malformed because a standardised documentation sheet is used.

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Dublin (Ireland)
Dublin EUROCAT Registry

History and funding: Register began in September 1979 and joined EUROCAT in 1980. The Registry is located within the Public Health Department of Eastern Regional Health Authority. Staffing includes a full time nurse/researcher and a part time secretary plus a part-time public health specialist and a part-time epidemiologist. Funding is provided by the Department of Health through the Eastern Regional Health Authority. There is a Steering Committee comprising specialists from each of Maternity and Pediatric Hospitals in the catchment plus a representative from the Department of Health.

Population coverage: The Registry is population-based I which includes all mothers resident in the Eastern Regional Health Authority of Ireland covering the counties of Dublin, Wicklow and Kildare. In 1999, less than 3% of resident mothers delivered outside the registry area. About one third (21,000 births) of all births in Ireland occur in this area.

Sources of ascertainment: All live and stillbirths are covered. Information collected by developmental screening clinics, child health centres, social allowances and health visitors are used as sources of notification. Birth certificates and death certificates do not include notification of congenital anomaly. Children with congenital anomaly are included in the registry when diagnosed up to the age of 5 years.

Termination of pregnancy: Abortion is illegal in Ireland.

Stillbirth definition and early fetal deaths: Babies born without signs of life with a gestational age of >=24 weeks or a weight of >=500g are registered. Early fetal deaths/spontaneous abortions are not registered. *National* autopsy rates only were available for 1999 for the following: stillbirths 50-60% and early neonatal deaths (0-7 days) 50-60%. There has been a decrease in the proportions having an autopsy due to controversy arising from the issue of consent – from about 70-80% in 1997 to 50-60% in 1999.

Exposure data availability: For each malformed infant reported, limited information is given on certain exposures.

Denominators and controls information: Denominator data are supplied by the government body - the Central Statistics Office. No information is available on controls.

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Galway (Ireland)

History and funding: Funding for the registry is provided nationally by the Department of Health and the Western Health Board. The Registry joined EUROCAT in 1981.

Population coverage: The registry is population-based I and includes all mothers resident in the County of Galway. The registry covers a total of about 3,000 births per year which represents 5% of all births in the Republic of Ireland.

Sources of ascertainment: Death certificates allow for the notification of a congenital anomaly, however, birth certificates do not. Notifications of children who are diagnosed up to the age of 5 years are included in the registry database.

Termination of pregnancy: Termination of pregnancy is illegal in the Republic of Ireland.

Stillbirth definition and early fetal deaths: The official definition of stillbirth is: a baby who shows no sign of life with a gestational age of >=24 weeks or weight of >= 500g. All stillbirths are registered. Early fetal deaths/spontaneous abortions are considered as such at a gestational age of 24 weeks and are included in the register if the birthweight is 500g. Autopsy rates for 1994 were: 90% in stillbirths, 70% in early neonatal deaths (0-7 days), 70% in later deaths 1 week to 1 year, 70% in deaths with congenital anomaly.

Additional exclusions and exposure data availability: No information was supplied on this section for the report.

Denominators and controls information: No information was supplied on this section for the report.

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Campania (Italy)
Birth Defects Registry of Campania

History and funding: The registry started in 1991. The programme is a surveillance programme supported by grants from Regional Health Authorities. The Registry joined EUROCAT in 1997.

Population coverage: The registry is hospital-based with participating hospitals distributed in Campania, a region of southern Italy where Naples is the main city. Initially 38 hospitals reported and the annual number of births was 38,000. At the present time, 80 hospitals participate, covering just over 60,000 annual births, approximately 90% of all births in Campania region which is approximately 8% of all births in Italy.

Sources of ascertainment: Participation was voluntary up to 1995 but became mandatory from 1996 onwards. Report forms are obtained from delivery units, Pediatric clinics and all divisions that care for babies with birth defects at the participating hospitals. From 1994, a report form has been introduced to record anomalies diagnosed from induced abortions. From 2002 sonographers and pathologists send notification to the Registry. Birth certificates include notification of congenital anomaly (after 2000) as do death certificates and both are used as a source of notification. Formerly notification occurred up to 1 year of life, but in current practice there is no age limit for diagnosis.

Termination of pregnancy: Termination of pregnancy is legal with an upper gestational age limit of 180 days for all reasons including a diagnosis of congenital anomaly. Terminations of pregnancy are registered.

Stillbirth definition and early fetal deaths: Any baby born without signs of life after 180 gestational days may be classified as stillborn and is included in the register. Hence any baby born without signs of life at less than or equal to 180 days is classified as an early fetal death/spontaneous abortion. Autopsy rates are as follows: 100% in stillbirths, 100% in induced abortions and about 90% in deaths with congenital anomaly. There were no figures available for early neonatal deaths or deaths between 1 week and 1 year.

Exposure data availability: For each malformed infant reported, information is given on certain exposures, including maternal drug usage and parental occupation. From 2002 information on induced abortions and controls are available. Information on all births from birth certificates is available.

Denominators and controls information: The ISTAT – National Institute of Statistics – is the source of birth statistics. Only demographic information is available on controls.

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Emilia Romagna (Italy)
Emilia-Romagna Registry of Congenital of Malformations

History and funding: The registry started in 1978 in a few hospitals, has increased in size, and now includes 35 delivery units (2001). The programme is recognised and financed by the Emilia Romagna region and the Ministry of Scientific Research. The Registry joined EUROCAT in 1980.

Population coverage: The programme is population-based II and includes all mothers delivering within the region of Emilia Romagna, irrespective of place of residence (about 95% of all births in the Emilia-Romagna region) and covers approximately 24,000 annual births per year. Approximately 10% of non resident mothers are thought to deliver within the defined geographic region.

Sources of ascertainment: Hospital participation is voluntary. Reporting is carried out by both neonatologists and Pediatricians during the first week of the infant's life. Notification of congenital anomaly is recorded up to 1 week (after 1 week for selected malformations e.g. Downs Syndrome, cardiovascular defects, cleft palate). Selected malformations are followed up. An information exchange between Cytogenetic Laboratories, Pathology Services and Health Services has been established.

Termination of pregnancy: Termination of pregnancy became legal in Italy in 1978. At present the usual upper gestational age limit is 12 weeks and 23-24 weeks if a congenital anomaly is diagnosed. A psychiatric report is required for termination in the latter category. Data on induced abortions was not available to the IMER Registry until 1989. Between 1989 and 1993, recording was very incomplete due to difficulties in obtaining the data from the centres. Since 1994, ascertainment of IA has improved, but the data were still under revision of closure of the database of this Report.

Stillbirth definition and early fetal deaths: Stillbirths of 28 weeks or more gestation are included. The lower gestational age limit for inclusion of fetal deaths/spontaneous abortions is: less than 28 weeks of gestation (with no lower weight limit exclusion criteria). The autopsy rates for 1999 were: <10% in stillbirths, <5% in induced abortions, ~90% in early neonatal deaths (0-7 days), ~90% in later deaths 1 week to 1 year and ~90% in deaths with congenital anomaly.

Exposure data availability: Detailed exposure information is obtained by interviews of the mothers of malformed infants.

Denominators and controls information: Some general demographic information is known for all births in the area (e.g. mean maternal and paternal ages, percentage of mothers 35 years or older). For each participating hospital, the number of livebirths and stillbirths are known. A good information exchange has been established with regional health services. For each malformed infant, a control is chosen (the baby born before or after the malformed case in the same hospital) and its mother is interviewed in a similar way to the mothers with a registered baby.

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North-East (Italy)
North East Italy Registry of Congenital Malformations

History and funding: The Registry was established in 1980 to include Veneto and Friuli Venezia Giulia regions. Trentino Alto Adige region was added in 1990. The Registry became a member of EUROCAT in 1985. The programme is partly run by privately funded research organisations and partly by Regional Health Authorities.

Population coverage: The registry is population-based II and so it includes all mothers delivering within the Veneto, Friui-Venezia, Giulia and Trentino-Alto Adige Regions, irrespective of place of residence. Reports are obtained from 78 participating hospitals, with a total of approximately 54,000 annual births. The estimated proportion of non-resident mothers giving birth in the covered hospitals is 1.8% (calculated using controls).

Sources of ascertainment: Reporting is voluntary and they are obtained on specific forms from delivery units, induced abortion units, Pediatric, cardiology, ophthalmology and pathology departments, regional induced abortion database and cytogenetic laboratories. Thirty-two selected malformations are recorded within 7 days from birth (as of 1st July 1991 postnatal registration up to 3 years of age is limited to cardiovascular and ophthalmologic anomalies only). In terminated fetuses all anomalies are recorded. From 1st January 2000 we are now registering all congenital anomalies adopting the EUROCAT list of exclusions (revised 1985). Up to 1999 we did not register cases of: microcephaly, arhinencephaly/ holoprosencephaly, cystic kidney disease, indeterminate sex, diaphraghmatic hernia, Patau syndrome (Trisomy 13), Edward syndrome (Trisomy 18). The following anomalies were not coded according to EUROCAT standard and therefore are included in total case counts but not tabulated separately: common arterial truncus, transposition of the great vesssels (complete), congenital absence, atresia and/or stenosis of duodenum, congenital absence, atresia and/or stenosis of other specified parts of the small intestine.

Termination of pregnancy: Termination of pregnancy is legal under normal circumstances up to 12 weeks of gestation and up to 26 weeks if a fetal anomaly is diagnosed. Most terminations in the latter category, however, are carried out before 22 weeks. The recording of induced abortions for embryo-fetal anomaly was established on 1st July 1988. A form is completed in the hospital where the pregnancy is terminated by a Gynecologist.

Stillbirth definition and early fetal deaths: The official stillbirth definition: is a gestational age of >=28 weeks. Death certificates do not always allow for notification of congenital anomaly as a cause of death and they are not used as a source of information for registration. Autopsy rates quoted for 1994 were: 44% in stillbirths, 74% in induced abortions, 60% in early neonatal deaths, (0-7 days) with congenital anomaly. If no information was found on the death certificate then it was assumed that an autopsy was not performed.

Exposure data availability: Detailed information on various exposures, including maternal or paternal occupation, diseases and drug use is obtained by interview of the mothers at the birth of the malformed infants and their controls.

Denominators and controls information: Some epidemiological background data of all births are available. For each participating hospital the number of livebirths and stillbirths by sex and number of twin pairs are known. Information on controls are available – two control infants are selected for each malformed one.

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South East Sicily (Italy)
Sicilian Registry of Congenital Malformations

History and funding: The Registry started in 1991 and became a member of EUROCAT in 1997. The registry collaborates with other Italian Registries under supervision of the Italian National Institute of Health in Rome. The programme is supported at local level by A.S.MA.C, the Sicilian association for congenital malformation prevention.

Population coverage: It is hospital based and includes all mothers delivering in selected hospitals, irrespective of place of residence. The registry collaborates with four southeast provinces of the nine Sicilian provinces, (with a covering rate higher than 75% per year) which represented about one third of all births in Sicily with approximately 17,000 births per year.

Sources of ascertainment: Reports are obtained from delivery units, Pediatric units and other specialist departments. Congenital anomaly is registered up to and after 1 year of birth. The following anomalies are not coded according to EUROCAT standard and therefore not tabulated separately: cleft lip with or without palate, cleft palate, bilateral renal agenesis.

Termination of pregnancy: Termination of pregnancy is legal and the upper limit is usually 12 weeks, rising to 24 weeks if a congenital anomaly is diagnosed. Terminations of pregnancy following prenatal diagnosis are registered when notified, but ascertainment is currently still very incomplete. Registered terminations have been excluded from this Report.

Stillbirth definition and early fetal deaths: Stillbirths are registered as such if the gestational age is >180 days. Early fetal deaths/spontaneous abortions are not included. Although deaths due to congenital anomaly can be recorded on a death certificate, this information is not used as a source of notification. Autopsy rates were not reported.

Exposure data availability: For each malformed reported (livebirth, stillbirth and voluntary abortion), information is given on certain exposures, including maternal drug usage and parental occupation.

Denominators and controls information: Up to now no information on controls is available.

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Tuscany (Italy)
Tuscany Registry of Congenital Defects

History and funding: The registry started in 1979 in the province of Florence and from 1992 in the whole Tuscany region. The Registry is a surveillance programme included in the Regional Statistics System; it is formally recognised and supported by the Tuscany Region Health Authority. The Registry joined EUROCAT in 1979.

Population coverage: The programme is population-based I which includes all mothers resident in the Region of Tuscany. It involves all the regional hospitals and the coverage is around 95% of all births in the Tuscany region (approximately 3.5 million inhabitants and 26,000 births per year). Exchanges between regional informative systems indicate that approximately 0.2% of resident mothers gave birth in a hospital outside Tuscany in 1999.

Sources and ascertainment: Multiple sources are used to ascertain malformed infants; records are obtained from all obstetrical and maternity units, Pediatric departments, neonatal and Pediatric surgery units, prenatal diagnostic centres and pathology services. Mothers are interviewed by using a standardised questionnaire. Malformed babies diagnosed within the first year of life are also registered.

Termination of pregnancy: Termination of pregnancy became legal in Italy in 1978. Termination of pregnancy is legal when there is no possibility of autonomous life for the fetus. The Italian law (L.N. 194/78) lays down that termination is allowed in the case of diagnosis of serious fetal pathology which may detrimentally affect the woman's physical or psychological health. Induced abortions after prenatal diagnosis of birth defects are systematically included. Data for induced abortions first became available in 1982. Early ascertainment, however, was incomplete.

Stillbirth definition and early fetal deaths: The official definition of stillbirth in this registry is: 180 gestational days. Fetal deaths of 20 weeks or more gestation are systematically included if the weight is >=500g. Autopsy rates in 1999 were: ~60% in stillbirths, ~30% in induced abortions, ~50% in early neonatal deaths (0-7 days), ~30% in later deaths 1 week to 1 year and ~50% in deaths with congenital anomaly.

Exposure data availability: Maternal and paternal occupation, life-style, and Socioeconomic characteristics are obtained by interviews of mothers of malformed infants.

Denominators and controls information: Vital statistics and other epidemiological information is obtained by the birth medical records collected by the Regional Bureau of Statistics. Selected information is obtained from the control material collected.

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Malta
Malta Congenital Anomalies Register

History and funding: The register started in 1985 as a research project of the University of Malta. It started as a hospital-based register collecting data regarding congenital anomalies diagnosed in babies born at the main general hospital. It became a member of EUROCAT in 1986. Funding for the research project was stopped in 1995 and in 1997 the Department of Health Information resumed the functions of the registry increasing coverage to all hospitals on the islands making it a population-based register. The registry is now run and funded by the Government Department of Health Information. The aim of the Registry is to provide accurate epidemiological information regarding the occurrence of congenital anomalies in Malta and Gozo.

Population coverage: The registry is population-based I: covering all resident mothers in Malta, Gozo and Comino and presently covers about 4,300 births per year. The number of resident mothers giving birth in a hospital outside the area is considered to be negligible as Malta is an island and population movement is limited. It is unlikely that mothers will go abroad to give birth. It is precisely for this reason that the registry is thought to cover close to 100% of births.

Sources of ascertainment: Reporting is voluntary. Several new sources of information have been used since 1997 and the registry has back-dated its information to include these sources of information from 1993. For this reason data since 1993 may be considered most complete and reliable. The registry now employs active data collection from multiple sources including: labour, postnatal and nursery wards, cardiac laboratory records, genetics clinic records, National Mortality Register, National Obstetric Systems database, Hospital Activity Analysis database, National Cancer Register and the hypothyroid screening programme. Voluntary reporting by doctors is also available. These sources cover the whole population of the Maltese Islands. Babies with a congenital anomaly may be diagnosed and registered up to 1 year of age. Minor anomalies (as defined by EUROCAT) are not registered unless occurring in combination with other major defects.

Termination of pregnancy: Termination of pregnancy is illegal in Malta.

Stillbirth definition and early fetal deaths: The official definition of stillbirth is: a baby born with no signs of life at gestational age of 22 weeks or more, of a birth weight equal to or greater than 500g. Stillbirths are registered. All early fetal deaths of 20 weeks gestation and over which have been diagnosed as having a congenital anomaly are included. Autopsy rates for 1999 were as follows: 55% in stillbirths, 6% in early neonatal deaths (0-7 days), 20% in later deaths 1 week to 1 year and 50% in deaths with a congenital anomaly aged 0-1 years of age.

Exposure data availability: Information regarding maternal disease and exposure to medicinal drugs, smoking, alcohol and drug abuse as well as parental occupation are collected for all malformed infants.

Denominators and controls information: Epidemiological background data on all births are available from the National Obstetric Information Systems (NOIS) database and the National Statistics Office (NSO).

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Northern Netherlands
EUROCAT Registration Northern Netherlands

History and funding: The programme started in 1981, and became a member of EUROCAT in that year. The programme is funded by the Dutch Ministry of Public Health, Welfare and Sports. The registry is carried out in the Department of Medical Genetics of the University of Groningen.

Population coverage: The registry is population-based I which includes all mothers resident in the Provinces of Groningen, Friesland and Drenthe. In the beginning the programme covered 7,500 births annually when it covered the province of Groningen and the northern part of the province of Drenthe. Coverage was gradually increased to 19,000 births annually in the provinces from 1989 onwards. Home deliveries (30% of births per year) are included and it is estimated that only a few percent of resident mothers would give birth outside the defined registry area.

Sources of ascertainment: Obstetricians, Pediatricians, clinical geneticists, surgeons, general practitioners, midwives, well-baby clinics, pathologists and the national obstetric registry send information to the registry on a voluntary basis. Registry personnel are actively involved in data collection. There are no age limits are applied regarding maximum age at diagnosis and if new information becomes available on infants born in 1981 or later, the files are updated.

Termination of pregnancy: Termination of pregnancy is legal. There is no specified upper gestational age limit for termination written in law –viability is the criterion. In practice 22 weeks is the usual upper limit unless a child has a lethal (or almost lethal) condition. In the case of diagnosis of congenital anomaly, there is no upper limit.

Stillbirth definition and early fetal deaths: Stillbirths are registered and the official stillbirth definition is: a gestational age of >=24 weeks. There are no age or weight limits for inclusion of early fetal deaths/spontaneous abortions. Autopsy rates in year were not given.

Exposure data availability: Since 1997 parents have been asked to fill out a questionnaire including questions on occupational activities, smoking, alcohol and drug use. In addition, data from community pharmacies are used to collect maternal drug exposure data.

Denominators and controls information: General statistics are available from the Dutch Central Bureau of Statistics (CBS).

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Poland
The Polish Registry of Congenital Malformations

History and Funding
The Polish Registry of Congenital Malformations has been in operation since 1997. It was founded as a scientific project ordered by the Polish Ministry of Health and financed by the State Committee for Scientific Research. Since July 1, 2000 it has been part of the Government Programme of Monitoring and Primary Prophylaxis of Congenital Malformations in Poland. As part of this Programme the Registry provides the Polish Ministry of Health with important information needed in health care management.

Population Coverage
The PRCM is a population based registry of Type I (all mothers resident in defined geographic area). Until 2001 PRCM covered 9 provinces of Poland: Pomorskie, Zachodniopomorskie, Warmińsko-Mazurskie, Kujawsko-Pomorskie, Wielkopolskie, Lubuskie, Łódzkie, Dolnośląskie and Opolskie. In 2001 the Śląskie Province (Silesia) was added, and in 2002 the Lubelskie and Podkarpackie Regions joined the Registry. With these newly added regions the Registry covers 12 of 16 provinces of Poland: 73.6% of the area of Poland (230,091 km^2) with the population of 27,815,601 (72.0%), and about 267,300 births (life and stillbirths) per year (70.27%) (2002).

Sources of Ascertainment
Reporting is recommended by the Ministry of Health (as an official Government Programme) and consists of multi-source reporting. The sources include: delivery unit staff, ultrasound staff, postnatal ward staff, Pediatric intensive care unit staff, foetal medicine unit staff, Pediatricians, post-mortem reports, regional genetic and cytogenetic services, and Pediatric cardiology referral centres. The main source of information is a double sided notification form filled up by a physician responsible for diagnosing the malformation. The notification forms are sent immediately to the PRCM Central Working Group. Birth certificates do not record congenital anomaly. Death certificates allow for notification of congenital anomaly as a cause of death and they are therefore used as a source. The maximum age at diagnosis is 24 months.

Termination of Pregnancy
Although termination of pregnancy is legal, it can only be performed by a physician when: 1) a pregnancy poses danger to health or life of the pregnant woman; 2) prenatal diagnosis or other medical evidence indicates high probability of serious and irreversible damage to a fetus or its untreatable life-threatening disease; 3) there is a plausible suspicion the pregnancy has arisen from a prohibited act. The upper gestational limit for termination of a congenital anomaly affected pregnancy is viability. Although the termination of pregnancy is legal, in Poland there is a public pressure not to perform such a procedure and that is why the availability of information on pregnancy terminations is rather low as there is no central registry for the IAs. Hence the registry currently does not register terminations of pregnancy following prenatal diagnosis

Stillbirth Definition and Early Fetal Deaths
The official stillbirth definition is as follows: foetal death (stillbirth) is a death prior to the complete expulsion or extraction of a product of conception from a mother, irrespective of pregnancy duration; the death is indicated by the fact that after separation the fetus does not breathe, or shows no other evidence of life, such as heart beating, pulsation of the umbilical cord or definite movement of voluntary muscles. For statistical purposes we include all fetuses weighing at least 500 grams at the moment of birth, having reached the 22nd week of gestational age, if the weight is unknown, or reaching 25cm of the body length (crown-heel).
We do not include early foetal deaths or spontaneous abortions. Autopsy rates vary between regions or even between health care units, the ranges for performance are as follows: stillbirths 10-30%, early neonatal deaths 20-30%, later deaths 1 week to 1 year 10-20% and deaths with congenital anomaly 30-40%.

Data Availability
The following data is gathered by way of registration forms, although its availability may be limited, depending on the source of registration: chronic illness in mother, pregnancy induced conditions in mother, acute maternal illness during pregnancy, therapeutic and recreational drugs taken during pregnancy, invasive tests in pregnancy, folic acid use in pregnancy, smoking habits, alcohol use, mother's obstetric history as well as the county of residence, family history of congenital malformations, and genetic conditions in family members, father's and mother's occupational and environmental hazards, father's and mother's education.

Denominators and Controls Information
Information on all births (live & stillbirths) is available from birth certificates, gathered by the Central Statistical Office of Poland. No information is available on controls.

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Southern Portugal

History and funding: The registry started in 1990 and became a member of EUROCAT then. The registry is funded by the National Institute of Health.

Population coverage: The registry is population-based and includes all mothers resident in Algarve, Alentejo, Setubal and part of Santaren. It covers approximately 18 000 births annually (representing 14% of total births in Portugal).

Sources and ascertainment: Pediatricians and obstetricians are responsible for case notification in each region up to the end of the neonatal period. Other sources of ascertainment are fetal pathology, pediatric cardiology, cytogenetic laboratories and clinical genetics services. Data are validated at central level in Lisbon.

Termination of pregnancy: Termination of pregnancy is legal up to 24 weeks gestation and requires the permission of a technical committee. There is no upper gestational age limit for terminations for non-viable anomalies.

Stillbirth definition: The definition of stillbirth in Southern Portugal is: a gestational age of 22 weeks or a birthweight of 500g. Stillbirths and terminations as a result of diagnosis of congenital anomaly are included in the registry. Most fetuses in the covered area have an autopsy performed.

Exposure data availability: Information about maternal drug use, maternal diseases, maternal occupation, and obstetric history is available for cases.

Denominators and controls information: Demographic information is available from the National Statistic Office.

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Asturias (Spain)

History and funding: The registry started in 1990 and became a member of EUROCAT in 1992. The registry is situated in the Epidemiology Unit of the Regional Public Health Department which provides accommodation and computer facilities.

Population coverage: The registry is population-based III which covers all mothers delivering in Asturias in Northern Spain excluding non-residents of that area. In 1999, 1.5 % of non-resident mothers gave birth in the covered hospitals of Asturias. The registry covers approximately 6,500 births annually.

Sources and ascertainment: Case forms are collected from pathology units, biochemical and cytogenic laboratories, neonatology and Pediatric units, obstetricians, geneticists, death certificates and hospital discharge forms. The registry covers livebirths up to five years of age.

Termination of pregnancy: Termination of pregnancy is legal up to 12 gestational weeks in the case of sexual assault and no upper limit for maternal illness. If a congenital anomaly is diagnosed, the upper gestational limit is 22 weeks with an additional stipulation that two specialised medical reports are completed. Terminations of pregnancy have been registered since the registry's inception.

Stillbirth definition and early fetal deaths: The official stillbirth definition is: a gestational age of 26 weeks and these are registered. The registry definition for denominators is 22 weeks or a birthweight >=500g. Early fetal deaths/spontaneous abortions are defined as a gestational age of 20 weeks or a birthweight of 500g but these are not registered. Autopsy rates in 1999 were as follows: 84% in stillbirths, <50% in induced abortions, 60% in early neonatal deaths (0-7days) % in later deaths 1 week to 1 year unknown and 92% deaths with congenital anomaly.

Exposure data availability: Information about maternal drug use, maternal diseases, and obstetric history is available for cases.

Denominators and controls information: Denominators are available from the Asturias Natural Population Movement Statistics.

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Barcelona (Spain)
Barcelona Birth Defects Registry (Registro de Defectos Congénitos de Barcelona: REDCB).

History and funding: The programme was initiated in 1990 and reached a population based status by 1992, when it became a member of EUROCAT. The registry is part of the Health Information Service in the Municipal Institute of Public Health of Barcelona. It is partially funded by national research grants.

Population coverage: The registry is population-based I which includes all mothers resident in the city of Barcelona, Catalonia. The registry covers about 12 500 births annually which represents about 3% of all births in Spain.

Sources of ascertainment: General information on cases and controls as well as clinical information on cases is collected using questionnaires specifically made for the registry. An interview of the mother is the main source of general information. Delivery units, Pediatric departments, cytogenetic laboratories, pathology departments, prenatal diagnosis units, etc. are the sources of clinical information. Since 1995, the register has incorporated most Pediatric cardiology services to its coverage.

Termination of pregnancy: Termination of pregnancy is legal with an upper gestational age limit of 22 weeks for all reasons including diagnosis of a congenital anomaly following prenatal screening. Data about techniques of prenatal screening and diagnosis are systematically collected

Stillbirth definition and early fetal deaths: The official definition of stillbirth is: a gestational age of 22 weeks or more. Earlier fetal deaths are not recorded. Autopsy rates in 1994 were as follows: 71% in stillbirths, unknown in induced abortions, 57% in early neonatal deaths, unknown in later deaths 1 week to 1 year and 78% in deaths with a congenital anomaly.

Exposure data availability: Information on maternal drug use, maternal and paternal diseases and occupations, is available for cases and controls.

Denominators and controls information: Background data on births are available from birth certificates and the Barcelona perinatal mortality registry. A random sample (not case-matched) of about 2% of the babies expected in each maternity unit is selected.

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Basque Country (Spain)
Registry of Congenital Anomalies of the Basque Country (RACAV)

History and funding: Registration of congenital anomalies in the Basque Country started on January 1st 1990. The Registry became a EUROCAT member in September 1990. The registry is financially supported by the Health Department of the Basque Government.

Population coverage: The registry is located in the Basque Country region, in northern Spain, covering a geographic area of 7260 Km^2, and a population of 2,250,000 inhabitants. It is a population-based III registry which therefore includes all mothers delivering in the Basque Country excluding any non-residents. The total number of annual births is about 16,000. It is estimated that 1-2% of outside resident mothers deliver in the covered hospitals.

Sources of ascertainment: Reporting is voluntary. There is an active search for cases (livebirths, stillbirths and induced abortions) through multiples sources of information: Neonatal Units, Specialist Pediatrics Departments, Cytogenetics and Pathology laboratories, Hospital discharge records and private maternity hospitals. The maximum age at diagnosis routinely reported to the registry is one year of age.

Termination of pregnancy: Termination of pregnancy is legal for certain indications, including prenatal diagnosis of severe anomaly with an official upper gestational age limit of 22 weeks. In practice there is no upper limit in the main public maternity hospitals, although in some the cases are officially registered as stillbirths. The private maternity hospitals send such mothers to the public hospitals or abroad (to the UK). Data about techniques of prenatal screening and diagnosis are systematically collected.

Stillbirth definition and early fetal deaths: The official definition of stillbirth in the Basque Country is: a gestational age of 22 weeks or a birthweight of 500g. Postmortem examination rates are highly variable in the region. About 90% of autopsies in stillbirths and neonatal deaths were performed in the public maternity hospitals (the remaining 10% of parents did not give permission). Autopsy following induced abortion usually depends upon the condition of the fetus.

Exposure data availability: Information on maternal drug use, maternal and paternal diseases, outcome of previous pregnancies and assisted conception is available.

Denominators and controls information: Statistics are provided by the Basque Statistics Institute (EUSTAT).

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Vaud (Switzerland)
Registry of Switzerland

History and funding: The registry of Switzerland was originally set up in 1988, and also became member of EUROCAT in 1988. Different cantonal registries sent their data to the central registry in Lausanne. The aim at the beginning was to cover the whole country (80,000 births/year). In the first years of activity, 30% - 81% of births were surveyed. For financial reasons, many cantons had to stop this activity and in 1993, the Swiss registry covered 50% of all births in Switzerland. In 1998, the following cantons were included in the programme: Zurich, Fribourg, Argovie, Tessin, Vaud, Valais, Neuchâtel and Jura. The registry is located in the Division of Medical Genetics of the University hospital in Lausanne. The registry has formerly been associated with members from the Swiss Academy of Medical Sciences and from the Swiss Society of Pediatrics. The system is financed by the Swiss Federal Agency for Statistics for the central registry and by the cantonal health department for some cantonal registries. As the level of ascertainment was quite heterogeneous between the local cantonal registries and their activities fluctuating according to the years (cf prevalence rate <200 per 10,000), it was decided in January 2002 to restrict the registration in canton of Vaud only and to change the name of the Registry: Registry of Vaud (Switzerland).

Population coverage: The registry is population-based I and as such it covers all mothers resident in the canton of Vaud. The percentage of mothers delivering in a hospital outside the registry area is not known precisely although it is thought to be very low. The registry covers about 9% of all births in Switzerland (approximately 7,500 births annually). The changing coverage is detailed above.

Sources of ascertainment: Reporting is voluntary. Active case finding and multiple sources of information are used: delivery units; Pediatric departments; cytogenetic and genetic counseling and pathology unit. Data about different methods of prenatal diagnosis are collected (ultrasound, serum markers, cytogenetic and molecular). There is no upper age limit for registration of a child with a malformation.

Termination of pregnancy: Termination of pregnancy is legal up to 12 weeks gestation under most circumstances but this limit is extended to 24 gestational weeks if a congenital anomaly is diagnosed. In the latter circumstance, additional permission must be granted by two further physicians. Induced abortions following prenatal diagnosis are included in the register.

Stillbirth definition and early fetal deaths: The official stillbirth definition is: a gestational age of >= 27 weeks or length >=30cm and these are included in the register. Early fetal deaths/spontaneous abortions are included if they are 20 gestational weeks or more with no weight restrictions. Autopsy statistics were not available.

Exposure data availability: Information on maternal occupations and diseases, maternal drug use, outcome of previous pregnancies is available for the malformed infants.

Denominators and controls information: Background data on births are available from the Swiss Federal Agency for Statistics and from Service Cantonal de Recherche et d'Information Statistique (SCRIS).

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Username: eurocat, password: tropic

Glasgow (UK: Scotland)
Greater Glasgow NHS Board Congenital Anomalies Register

History and funding: The Glasgow Register of Congenital Malformations was founded in 1972 under the auspices of the Social Pediatric and Obstetric Research Unit and jointly administered by the University of Glasgow and the Corporation of Glasgow. It became a member of EUROCAT in 1978. The first full year for which standardised notifications were made was 1979. Greater Glasgow NHS Board (formerly Greater Glasgow Health Board) funds the Register. The Register had three initial objectives: the detection of epidemics, the calculation of prevalence rates and the epidemiological investigation of selected malformations. The objectives were broadened after joining EUROCAT to include the evaluation of preventive and therapeutic measures.

Population coverage: Population based I: the reference population is defined as all births (live and still) to women resident in the Greater Glasgow NHS Board area irrespective of the place of birth. Livebirths, stillbirths of 24 weeks gestation or more, spontaneous and induced abortions are included. In 2000, 3% of Greater Glasgow NHS livebirths were delivered outwith the study area and 18% of Scottish births resided in Greater Glasgow NHS Board area (Source: General Register Office for Scotland). From 1972 to March 1974 the Registry population and geographic area was defined by the boundaries of the former City of Glasgow. Following the reorganisation of the National Health Service in 1974, the Greater Glasgow Health Board assumed responsibility for the Register. Consequently the population under observation was enlarged by 35% to accommodate those areas formerly outside the boundaries of the City of Glasgow which were included within the area of the newly created Greater Glasgow Health Board. Annual number of births within Greater Glasgow has dropped from 13,500 in 1979 to 9,500 in 2000.

Sources of ascertainment: Notification is voluntary. Sources available are: Hospital discharge data, Health visitor immunisation consent forms, Inborn errors of metabolism screening programme, Child health surveillance programme, Death & stillbirth registration, Regional medical genetics department, Regional pathology department. Maternal and Pediatric hospital case records are viewed to confirm each case. Two useful sources are no longer available: Pediatric discharge letters are no longer sent to registry staff due to the closure of participating Pediatric units and perinatal summaries - an important early source for terminations for fetal abnormality – were sent by one maternity hospital for a number of years but this has ceased. The time-delay in ascertainment is a growing problem. This is partly due to the above-mentioned loss of earlier notifications but also due to time constraints on medical records staff who pull hospital case records for the registry worker to view. Due to reorganization of medical records in some hospitals, a delay in obtaining 1998 and 1999 data was experienced, leading to deficits in the prevalence rates for those years in this Report. Around 20% of cases in 2000 were reported by more than one source of information. There is no time limit for registration or for updating diagnostic detail. Cases with antenatal false positive screening results that do not have a congenital anomaly are not recorded.

Terminations: Termination of pregnancy became legal in the United Kingdom in 1967 (Abortion Act). Termination for fetal malformation is legal up to 24 weeks gestation. Information on terminations is now mainly obtained by viewing post mortem reports in regional medical genetics department.

Stillbirth definition and early fetal deaths: The official stillbirth definition is: fetal death after 24 completed weeks. Stillbirths and infant deaths are routinely notified to the register where at least one cause of stillbirth/death is a congenital anomaly. There is no lower gestational age or weight limit. Autopsy rates are not known.

Exposure data availability: No information available.

Denominators and controls information: Data on births is available from the Registrar General for Scotland. Mid-year estimates are published by the middle of the year following. The number of births (live and still) is available by maternal age and by month of birth for the population from1983. These figures are produced by analysing birth and child record files from a quarterly download based on current status of residence and not initial status at birth. As a result the denominator data will therefore vary from quarter to quarter and will never correspond to the Registrar General's figures. Demographic/exposure information on controls is not collected.

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Mersey (UK: England)
Mersey Congenital Anomaly Survey

History and funding: In 1992 a fetal anomaly survey was initiated in the former Mersey region. Its aim was to assess the effectiveness of antenatal diagnosis. However, this survey proved difficult to establish and anomalies were under reported. In 1995 the survey linked to CESDI (Confidential Enquiry into Stillbirths and Deaths in Infancy), became the responsibility of the CESDI Regional Co-ordinator and was relaunched as the Congenital Anomalies Survey. Funding is obtained from various sources which is bid for annually. The registry joined EUROCAT in 1995.

Population coverage: The registry is population-based II All mothers delivery in a defined geographic area, irrespective of place of residence, the number of women from outside Mersey accounts for around 8-10% of all anomalies. The Survey covers Merseyside and Cheshire with about 27,000 annual births. Despite many national boundary changes, the survey has maintained its boundaries since 1995.

Sources of Ascertainment: Reporting is voluntary. The survey records all anomalies which: (a) are first detected antenatally, at birth or termination of pregnancy, or during the first year of life (b) involve a structural, metabolic, endocrine or genetic defect in the child/fetus. The survey relies on multi source ascertainment and has developed an extensive network of health professionals, obstetricians, Pediatricians, midwives, neonatal nurses, pathologists and ultrasonographers. There is also close collaboration with CESDI, the Regional Cytogenetic department, the Royal Liverpool Children's Hospital Alder Hey including the cleft lip and palate unit and birth and death district notification. This network has ensured our local ascertainment is better than national statistics. Birth certificates do not include notification of congenital anomaly.

Termination of pregnancy: Termination of pregnancy is legal and there is a statutory requirement for registration. The upper gestational age limit is 24 weeks, however, if a congenital anomaly is diagnosed this upper gestational age limit no longer applies.

Stillbirth definition and early fetal deaths: Stillbirth definition is: any baby born after 24 completed weeks of gestation that shows no sign of life. Stillbirths and fetal deaths/spontaneous abortions are registered. There is no lower gestational age limit for inclusion of early fetal deaths/spontaneous abortions although in practice the registry is notified of very few spontaneous abortions. Autopsy rates are as follows: stillbirths 32%, induced abortions 47%, early neonatal deaths (0-7 days) 23%, later deaths 1 week to 1 year 45% and deaths with congenital anomaly 37%.

Exposure data availability: Exposure Information: No information on exposure is collected other than self reported information on smoking, alcohol and drug intake during pregnancy.

Denominators and controls information: Denominator data is supplied in an aggregated format by each hospital within Mersey. No control cases are currently collected.

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North Thames (West) (UK: England)
North Thames (West) Congenital Malformation Register

History and funding: Case registration began on 1 January 1990 and EUROCAT reporting began in 1996. Data transmission to ONS (the Office for National Statistics) began on 1 January 2000. The registry is an active member of BINOCAR (British Isles Network of Congenital Anomaly Registers) and FOCAL (Follow-up of Congenital Anomalies Long Term). Registry data continues to be used in many collaborative research projects as well as for local audit of prenatal screening and diagnostic programmes. The registry is funded by our regional Genetics Commissioning Group.

Population coverage: This is a hospital based registry (all mothers delivering in selected hospitals, irrespective of place of residence) which covers 16 obstetric units in the North West Thames area (North West London, Hertfordshire and Bedfordshire) that together had about 47,000 births in 2000 and represents 7% of all births in England. Ninety-nine percent of births occur in hospital and 15% of resident mothers gave birth in a hospital outside the area in 2000 (data from the Office of National Statistics).

Sources and ascertainment: Reporting is voluntary and consists of multi-source reporting. Sources include: delivery suite staff, ultrasound staff, post natal ward staff, Pediatric intensive care unit staff, fetal medicine unit staff, Pediatricians, post mortem reports, cytogenetic reports, computerised obstetric records, CESDI (Confidential Enquiry on Stillbirths & deaths in Infancy), regional genetic service notes, serum screening for Down Syndrome programme, notifications to Office for National Statistics, Pediatric cardiology referral centre. Birth certificates do not include notification of congenital anomaly. Registration covers fetuses with prenatally diagnosed anomalies, affected fetuses spontaneously lost from 16 weeks gestation, and babies diagnosed before their first birthday in the case of structural anomalies and at any time in the case of chromosome anomalies. Ascertainment is poor for cardiac defects that are not prenatally diagnosed. The registry has excluded, since 1993, babies in whom the main diagnosis is hypospadias, polydactyly, syndactyly (as reflected in lower total prevalence rates – see Table A0.ALL), and in 1996 the registry stopped registering cases where the main diagnosis was talipes. Ascertainment was generally low in 1999.

Termination of pregnancy: Termination of pregnancy is legal up to 24 weeks of gestation but if a congenital anomaly is diagnosed this can be extended with no limit if the malformation is serious. In addition, if the termination is carried out after 22 weeks and the condition is not lethal, a fetocide is usually performed prior to induction of labour. Access to information about the termination is available if performed due to a congenital anomaly. Information is collected on how and when anomalies were diagnosed, the indication for any invasive tests that were done and why prenatal karyotyping was not done.

Stillbirth definition and early fetal deaths: The official stillbirth definition is: a child born with no signs of life after complete expulsion from the mother after the 24th week of pregnancy (there is no weight limit). All stillbirths with anomalies are registered. Early fetal deaths/spontaneous abortions with structural anomalies are registered; those with chromosome anomalies are registered if the gestational age at delivery is at least 16 weeks or if the karyotype abnormality was prenatally diagnosed. Autopsy rates were as follows in 2000: 66% in stillbirths, 47% in induced abortions (some autopsies not done include early terminations of pregnancy with dilatation and curettage), 46% in early neonatal deaths (0-7 days), 59% in later deaths 1 week to 1 year and 66% in deaths with congenital anomaly.

Exposure data availability: Chronic illness in mother, pregnancy induced condition in mother, acute maternal illness during pregnancy, therapeutic and recreational drugs taken around conception and during pregnancy, invasive tests in pregnancy, smoking habits, alcohol abuse and post code of residence.

Denominators and controls information: As the numerator is hospital based, the denominator is the births and terminations of pregnancies in the contributing hospitals. There is a computerised database in which information is stored on all births similar to that which we have on the births on our register.

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Wales (UK)
Congenital Anomaly Register and Information Service (CARIS)

History and funding: Data collection commenced on 1st January 1998 and includes any baby where pregnancy ended after this date. CARIS joined EUROCAT in 1998. CARIS is based at Singleton Hospital, Swansea and is funded by the National Assembly for Wales. CARIS aims to collect data which can be used to describe the pattern of congenital anomalies across Wales. This should help:

- Build up and monitor the picture of congenital anomalies in Wales
- Assess interventions intended to help prevent or detect congenital anomalies
- Plan and co-ordinate provision of health services for affected babies and children
- Assess possible clusters of birth defects and their causes

Population coverage: The registry covers the entire country of Wales (Population-based I = All mothers resident in defined geographic area) with an annual number of births of around 32,000.

Sources of ascertainment: Reporting is voluntary. The Register relies upon multi-source reporting including: antenatal clinics, delivery units, pediatric departments, ophthalmology, cytogenetics, pathology and regional; centers of pediatric surgery. Each delivery unit has a nominated co-ordinator to help ensure good reporting and chase for further details. CARIS staff also visit units to help with data collection. Registration covers all fetuses with prenatally diagnosed anomalies. There is no lower age of cut off, so the fetal losses and early terminations with anomalies are registered. All live born babies with structural anomalies are registered if diagnosed before their 1st birthday, but all chromosomal anomalies are registered, even if diagnosed later. Data exchange with the Mersey Register is also important as babies needing specialist services in North Wales are referred to Liverpool.

Termination of pregnancy: Termination of pregnancy is legal up to 24 weeks of gestation. Terminations of pregnancy are registered. If congenital anomaly is diagnosed, there is no upper gestational age limit for termination in cases of major anomaly.

Stillbirth definition and early fetal deaths: Stillbirth definition: 24 weeks gestation (late fetal death after 23 completed weeks of gestation). Stillbirths of 24 weeks or more gestation are registered. Early fetal deaths/spontaneous abortions have no lower limit for inclusion on the register (earliest cases recorded go down to 8 weeks gestation. Autopsy rates were not given.

Exposure data availability: Exposure information: Information on maternal drug use, maternal and paternal diseases and occupations, outcome of previous pregnancies is available. Folic acid supplementation before and during pregnancy is also collected.

Denominators and controls information: Denominator data is obtained from the Office for National Statistics.

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Finland

History and funding: The registry was established in 1963 and regular monitoring started in 1977. In 1998 the registry became an associate member of EUROCAT. The registry system (data collection etc) has been changed twice, in 1985 and in 1993. The activities of the Registry are regulated by specific laws and statutes affecting national healthcare registers which hold personal data. It is run and financed by STAKES, the governmental National Research and Development Centre for Welfare and Health (under the Ministry of Social Affairs and Health).

Population coverage: The registry is national and population-based I: all mothers resident in defined geographic area. All births in Finland are covered, representing approximately 58 000 births annually. As a research project selective terminations for fetal reasons and spontaneous abortions with malformations have also been included since 1993.

Sources and ascertainment: Notification to the registry is compulsory. Reports are obtained from delivery units, neonatal, Pediatric and pathology departments, death certificates and cytogenetic laboratories. Case information is also received from the national Medical Birth Register, Abortion Register and Hospital Discharge Register. The diagnoses of the malformation cases received from other sources are confirmed from the hospitals. Information on malformations is principally collected up to 1 year of age, but later information is also included. Aggregated data is transmitted to EUROCAT.

Termination of pregnancy: Termination of pregnancy is legal. Termination of pregnancy for fetal reasons (congenital anomaly, other birth defect or disease) can only be granted by a special permission from the National Authority for Medicolegal Affairs (TEO). At the gestational age of >20+0 to ≤24+0 weeks, termination can only be granted by TEO's permission when a severe fetal malformation or disease has been detected by reliable prenatal diagnostics.

Stillbirth definition and early fetal deaths: Prior to 1987, stillbirths of 28 weeks or more were registered. At present, stillbirths of at least 22 weeks of gestation or 500g of birth weight are registered. All notified early fetal deaths have been registered since 1993 but are only included for transmission to EUROCAT if > 20+0 gestational weeks.

Exposure data availability: Until 1986, extensive exposure information was obtained from maternity health centres and by personal interview for selected malformations and their controls. In 1987-1992 only parental occupation was reported. Exposure information, like maternal occupation, medication, X-rays and diseases, etc., has been obtained since 1993. Some exposure information on all births is also available in the Medical Birth Register since 1987.

Denominators and controls information: Epidemiological background data are available on all births in the Medical Birth Register and in the Statistics Finland.

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Central East France
Central-East France Register of Congenital Malformations.

History and funding: The registry began in 1973 within the Rhone-Alps area -the Auvergne region was added in 1983, the Jura area in 1985, the Côte d'Or & Nièvre in 1989 and Saône-et-Loire in 1990. In 1998 the registry was split up and the Auvergne region, became financially independent, under the responsibility of Christine Francannet. The collaboration between Auvergne and the rest of the FCE-registry is maintained and common results are published. The Registry joined EUROCAT as an associate member in 1999. Until 1991, 90% of the funding was provided by an insurance company. The system currently has multiple sources of funding: 33% from an insurance company (GROUPMA), 13% from the Ministry of Health, 5% from local health authorities, 10% from specific epidemiological studies, 13% from the French National Electricity Agency, and 26% from contracts with drug companies for the surveillance of their products with respect to potential teratogenic effects. The registry was set up to monitor birth defects.

Population coverage: The registry is population-based II where all mothers delivering within defined geographic area, irrespective of place of residence. Approximately 1.5% of non-resident mothers deliver within the registry area. Mothers living in the defined area who are later transferred outside the area for delivery because of prenatal diagnosis of malformation made in the defined are included as well. The registry covers the Rhône-Alps region, Auvergne region, plus 4 departments: Côte d'Or, Jura, Nièvre, Saône-et-Loire with approximately 104,000 births annually (90,000 from 200), which represents about 14% of all births in France. The geographic regions have changed over time as follows: Rhône-Alps from 1976 onwards, Auvergne from 1983 to 1999 (from 2000, Auvergne still uses the same database, but the registry is separated from an administrative point of view), Jura from 1985 onwards, Côte d'Or and Nièvre from 1989 onwards and Saône-et-Loire from 1990 onwards.

Sources of ascertainment: Notification to the registry is voluntary. Reports are received from multiple sources: Pediatric records, cytogenetic laboratory,pathology laboratory, child health services, specialized departments for medical genetics, orthopaedics, cardiology, Pediatric surgeons, midwives, birth notifications, maternity unit records. Active registration is performed by midwives in the large units in which a lot of cases present. For small maternity or Pediatric units, registration relies on passive notification. Confirmatory sources: every year a list of abnormal karyotypes is sent by cytogenetics laboratories, and copies of pathology reports are systematically sent to the registry if malformations are present. Ascertainment is not complete because passive notification depends on the goodwill of collaborating doctors. The registry leader has a clinical activity of genetic counseling and stimulates colleagues to notify cases. Constant relationships are maintained with clinicians and also through the Teratology Information Service that is available to them, provided by the doctors working for the registry. Between the years 1980 to 1990 30% of cases are reported by more than one source. Infants up to the age of one are registered, as well as fetuses delivered after medical abortion. A cut-off for notification is applied: for children born in year x, notifications are taken into account until March x+2. There is no follow-up procedure. Children are notified whennoticed by the persons in charge of data collection in hospitals. There is a gap for hypospadias that are notified only by Pediatric surgeons because the children are scarcely operated before the age of 18 months. The following specific anomalies are excluded: balanced chromosomal anomalies, pyloric stenosis, metabolic disorders, minor malformations (small angiomas or naevi, hip subdislocation, small foot deformities, ill-defined facial anomalies, inguinal and umbilical hernias). Aggregated data transmitted to EUROCAT.

Termination of pregnancy: Termination of pregnancy is legal and there is no upper gestational age limit for any cause whatsoever. In the case of termination after diagnosis of a congenital anomaly, agreement is sought from a multidisciplinary committee. Terminations for fetal malformation have been registered since 1985. Notification of terminations of pregnancy is provided by: obstetric units, cytogenetic laboratories and pathology reports.

Stillbirth definition and early fetal deaths: Currently stillbirths of 22 weeks or more gestation are registered. Before 1997, stillbirths were registered at 28weeks or more after the last menstrual period. Stillbirth and infant death certificates are not routinely available as a source. Early fetal deaths/spontaneous abortions are included 22 weeks after the last menstrual period. Again, before 1997, this was 28 weeks or more. Autopsy rates for spontaneous abortions are not registered, stillbirths 90%, induced abortions 90% and early neonatal deaths (0-7 days) 80%. These numbers are only available to the registry as autopsy rates for malformed infants/fetuses. Most autopsies of stillborn babies are performed by a fetal pathologist.

Exposure data availability: Information on maternal and paternal occupation, drug use, diseases, etc. is collected by interviews of the mothers of the malformed infants. This is not transmitted to Central Registry. No controls are interviewed.

Denominators and controls information: Birth statistics are provided by the National Institute of Statistics. The same population definition is used for the birth statistics except for induced abortions. Some background information is also available from the general population statistics. No information on controls is collected.

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Norway
Medical Birth Registry of Norway

History and funding: The programme was started in 1967. The programme is run and funded by the governmental National Institute of Public Health. The registry joined EUROCAT in 1998.

Population coverage: The programme is population-based and covers all mothers delivering within Norway, irrespective of place of residence, approximately 59 000 annual births. Non-resident mothers delivering within the registry area account for approximately 0.2% of all births.

Sources of ascertainment: Reporting is compulsory. The registry is based on the notification of births from the delivery units and since 1999 also from the neonatal units. Congenital anomaly is registered up to 1 year and there is no maximum age for registration of mortality.

Termination of pregnancy: Termination of pregnancy is legal and is the mother's decision up to 12 weeks gestation. After 12 weeks gestation permission is required from the commission and these have been recorded from 1999 onwards. If a congenital anomaly is diagnosed the upper gestational age limit is 18 weeks (with exemptions). On 1st December 1998, registration, by the MBRN, of all abortions induced on the indication of a prenatally diagnosed congenital anomaly was introduced.

Stillbirth definition and early fetal deaths: The official definition of a stillbirth for perinatal mortality purposes is: fetal death before or during labour with a gestational age of >=28 weeks or with a birthweight >=1000g. Early fetal deaths/spontaneous abortions of 16 weeks or more were included between the years 1967 to 2001 inclusive. This has been decreased to a gestational age of 12 weeks or more from 2002 onwards. Autopsy rates were reported as follows: 50% in stillbirths, 50% in induced abortions, 80% in early neonatal deaths (0-7 days), 90% in later deaths 1 week to 1 year and 80% in deaths with congenital anomaly.

Exposure data availability: Some basic information, such as maternal disease and since 1999:smoking and occupation, is collected on all infants, malformed or not.

Denominators and controls information:
All information available for the reported malformed infants is also available for the total population of births.

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ECEMC (Spain)
Spanish Collaborative Study of Congenital Malformations

History and funding: The programme started in 1976 as a hospital-based case-control study and surveillance system. It is a research programme with voluntary participation of hospitals, and is financed mainly by the Spanish Administration and, partially, by non-governmental organisations. Since 2002, the ECEMC is integrated into the CIAC (Research Center on Congenital Anomalies). The main objectives are: active surveillance of congenital defects, investigation of causes, education and information to the population (through informative sessions and two teratology information services by telephone). The Registry joined EUROCAT as an associate member in 1998.

Population coverage: The registry is hospital based and includes all mothers delivering in selected hospitals, irrespective of place of residence. Reports are obtained from hospitals (84 at present) distributed all over Spain. The annual number of births now surpasses 100,000, representing more than 27% of all Spanish births. Almost 100% of births take place in hospitals in the registry region.

Sources of ascertainment: The detection period is the first 3 days of life, including major and/or minor/mild defects. In some special cases, a longer follow-up is performed. Reports come from delivery units and Pediatric departments of the participating hospitals. Mothers are interviewed directly to fill in the ECEMC standard protocols, which include more than 300 data items for each child (family history, demographic and obstetrical data, prenatal exposures, etc), whether case or control. In many instances, photographs, imaging studies, high-resolution bands karyotypes and molecular analysis when needed, and other complementary studies are available.

Termination of pregnancy: Up to 1985 termination of pregnancy was illegal in Madrid. From 1985 onwards, induced abortions have been legal but they are not registered by ECEMC. It should be noted that they *are* registered by the other Spanish registers, which results in a lower total prevalence rate for ECEMC compared with other Spanish registers. The upper gestational age limit for termination is 22 weeks in cases of congenital anomaly or 12 weeks in cases of violation.

Stillbirth definition and early fetal deaths: The official definition of stillbirth in Spain registry is: 24 weeks or later or weighing at least 500g. Stillbirths have been included since 1980. Autopsy rates in the year 2000 were: 31% for stillbirths and 38% for deaths with a congenital anomaly. Other autopsy rates were not available.

Exposure data availability: The mother of each reported infant (case or control) is interviewed on various exposures (parental occupation, maternal acute or chronic diseases, drug usage, exposure to other chemical or physical factors) within the first three days after delivery.

Denominators and controls information: Total number of births by sex and number of twin pairs in each participating hospital is gathered. Other background information (including maternal age) is obtained from the control material. Controls are defined as the next non-malformed infant born at the same hospital as the case with the same sex as the malformed infant.

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Preventing neural tube defects in Europe: A missed opportunity

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Abstract

Each year, more than 4500 pregnancies in the European Union are affected by neural tube defects (NTD). Unambiguous evidence of the effectiveness of periconceptional folic acid in preventing the majority of neural tube defects has been available since 1991. We report on trends in the total prevalence of neural tube defects up to 2002, in the context of a survey in 18 European countries of periconceptional folic acid supplementation (PFAS) policies and their implementation. EUROCAT is a network of population-based registries in Europe collaborating in the epidemiological surveillance of congenital anomalies. Representatives from 18 participating countries provided information about policy, health education campaigns and surveys of PFAS uptake. The yearly total prevalence of neural tube defects including livebirths, stillbirths and terminations of pregnancy was calculated from 1980 to 2002 for 34 registries, with UK and Ireland estimated separately from the rest of Europe. A meta-analysis of changes in NTD total prevalence between 1989–1991 and 2000–2002 according to PFAS policy was undertaken for 24 registries. By 2005, 13 countries had a government recommendation that women planning a pregnancy should take 0.4 mg folic acid supplement daily, accompanied in 7 countries by government-led health education initiatives. In the UK and Ireland, countries with PFAS policy, there was a 30% decline in NTD total prevalence (95% CI 16–42%) but it was difficult to distinguish this from the pre-existing strong decline. In other European countries with PFAS policy, there was virtually no decline in NTD total prevalence whether a policy was in place by 1999 (2%, 95% CI 28% reduction to 32% increase) or not (8%, 95% CI 26% reduction to 16% increase). 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 result in large-scale prevention of NTDs.

Keywords: Neural tube defects; Folic acid supplementation; Folic acid supplementation policy; Folate; Surveillance of congenital anomalies; EUROCAT

1. Introduction

Each year, more than 4500 pregnancies in the European Union are affected by neural tube defects (NTD). Many are prenatally diagnosed, often leading to termination of a wanted pregnancy, and each diagnosis of a neural tube defect is a tragedy for the parents. Evidence of a possible association between folic acid and neural tube defects has been described in the scientific literature for more than three decades [1]. The first unambiguous evidence of the effectiveness of periconceptional folic acid came in 1991 on the publication of the results of the Medical Research Council Vitamin Study [2], on the basis of which it was estimated that improving folate status sufficiently could result in the prevention of the majority of all NTD. However, translating this knowledge into effective public health strategies has proved to be a challenge [3–5]. This paper examines trends in NTD total prevalence in Europe up to 2002, in the context of a survey in 18 European countries of periconceptional folic acid policies and their implementation.

2. Methods

EUROCAT is a network of population-based congenital anomaly registries in Europe collaborating in the epidemiological surveillance of congenital anomalies (http://www.eurocat.ulster.ac.uk). Data on all congenital anomalies are collected by active case ascertainment and are transmitted by each registry, using a standard data format [6], to a central database. A full description of each registry can be found elsewhere (http://www.eurocat.ulst.ac.uk/memberreg/memberreg.html).

Neural tube defect cases (livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis) were extracted from the EUROCAT Central Registry database for 1980–2002. Neural tube defects include anencephaly, encephalocele, spina bifida and iniencephaly (as defined in EUROCAT Guide 1.2 [6]). (In Finland, encephaloceles are excluded from the analysis as this anomaly has not been validated in Finnish data prior to 1993.)

Terminations of pregnancy were included in order to be absolutely sure that variation in the rate of selective termination of affected pregnancies was not a cause of differences in observed NTD rates. Years and registries with known deficiencies in the ascertainment of terminations of pregnancy were excluded [5]. The final dataset included 34 registries in 17 countries (Table 1). Total prevalence was calculated as livebirths, stillbirths and terminations of pregnancy divided by all live and stillbirths, birth prevalence was calculated as livebirths and stillbirths (excluding terminations of pregnancy) divided by all live and stillbirths.

The analysis of NTD prevalence rates for the UK and Ireland (UKI) was undertaken separately from that of the other countries of Europe (Europe-exclUKI) 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 [7].

Representatives from 18 countries participating in EUROCAT provided information about policy, health education campaigns and surveys of knowledge about and uptake of folic acid supplementation in their country up to January 1st, 2005. Each country was classified as having one of the following by 1999:

A: government policy of periconceptional folic acid supplementation (PFAS) plus a government-led health education campaign.
B1: government policy of PFAS without a health education campaign.

Table 1
EUROCAT population surveyed and national folic acid policies

Country	Registry	No. of births/year	Years of data in the analysis	Year govt policy introduced	Year government-led HE[a] campaign started	Details on recommendations (all recommendations are government policy, and recommend supplementation, unless otherwise stated)[b]
Austria	Styria	11000	1985–2001	–	–	Austrian Pediatric Society/Austrian Society of Prenatal and Perinatal Medicine (1998): 0.4 mg FA[c] supplement daily before conception → 12 weeks of gestation
Belgium	Antwerp	12000	1990–2002	–	–	'Unofficial policy' (no further information on source of recommendation): 0.4 mg FA supplement daily from 2 to 3 weeks pre conception → 3 months after
	Hainaut	12000	1980–2002			
Croatia	Zagreb	6000	1983–2002	–	–	Most gynaecologists/paediatricians recommend 0.4 mg FA daily at least 4 weeks preconception → 12th week of pregnancy. Many media initiatives and antenatal groups informing women of the importance of FA supplementation. No dates as unofficial only
Denmark	Odense	5500	1980–2002	1997	1997, 1999, 2001	0.4 mg daily pre conception → 3 months gestation. HE campaign includes press releases, distribution of folders with information to clinicians, pharmacies, GP, hospitals, etc.
Finland	Finland	57000	1986–2002	1995[d]	–	Adequate amount of dietary folate (equivalent to 0.4 mg FA daily), or supplements if diet unlikely to be sufficient. For some specified situations (e.g. women with folate insufficiency) 0.4 mg supplement daily from at least 4 weeks pre conception → end 12th week. HE information is given at schools/maternity and child health clinics/women's magazines
France	Auvergne	13000	2002	2000	2000, 2004	French Pediatric Society (1995), National College of Obstetrics and Gynaecology (1997) recommendations: 0.2 mg FA supplement daily during the periconceptional period. Government recommendations (2000): 0.4 mg FA preconception → 12 weeks. HE via an illustrated leaflet on nutrition emphasising importance of FAS, plus in 2004 a leaflet by National Spina Bifida Association distributed via physicians and family planning clinics
	Central East France	100000	1986–2002			
	Paris	39000	1981–2002			
	Strasbourg	14000	1982–2001			
Germany	Mainz	3000	1990–2002	–	–	German Nutrition Society (1991): 0.3 mg folate equivalent daily; Five National Clinical bodies (1994/5) recommended 0.4 mg FA daily from 1 month pre conception → 3 months. Local HE initiatives but in the registry areas
	Saxony-Anhalt	14000	1987–2002			
Ireland	Dublin	21000	1980–2002	1993	1993 and ongoing	0.4 mg daily pre conception → 12 weeks of pregnancy. HE includes television/radio/newspaper advertising plus promotion via public health departments
	Cork and Kerry	7600	1996–2002			
Italy	Campania	50000	1996–2002	–		Italian Network for the Promotion of Folic Acid for the Prevention of Congenital Defects (supported by 120 organisations) recommendations 2004: 0.4 mg per day from 1 month before to end of 1st trimester. This draft recommendation has been published by the Ministry of Health in a Drugs Bulletin. A Prevention of Spina Bifida Week 2004 included primary prevention leaflet distributed at family planning clinics and supermarkets, media advertising
	Emilia Romagna	25000	1996–2002			
	North East Italy	55000	1989–2002			
	Tuscany	26000	1980–2002			
Malta	Malta	4000	1986–2002	1994[d]	–	1) Achieve a diet of 0.4 mg per day of folate/folic acid prior to conception and during the first 12 weeks of pregnancy. 2) Women planning a pregnancy should eat more folate rich foods and avoid overcooking them. 3) Increase intake of wholemeal breads and fortified breakfast cereals
Netherlands	Northern Netherlands	20000	1981–2002	1993	1995	0.5 mg daily for all women wishing to become pregnant. HE aimed at all women but with special emphasis on reaching those of low socioeconomic status. Pilot campaign to distribute information on folic acid via pharmacists will now be extended to whole country [54]

Table 1 (*Continued*)

Country	Registry	No. of births/year	Years of data in the analysis	Year govt policy introduced	Year government-led HE[a] campaign started	Details on recommendations (all recommendations are government policy, and recommend supplementation, unless otherwise stated)[b]
Norway	Norway	60000	1980–2002	1998	1998, 1999, ongoing to lesser extent	0.4 mg daily pre conception → first 2–3 months of pregnancy. HE via public website; leaflets distributed by healthcare professionals/centres, pharmacies, posters and advertisements in women's magazines
Poland	Wielkoploska	33000	No data[e]	1997	1997	Nationwide government programme including health education. A pilot food fortification programme is planned in one province
Portugal	Southern Portugal	18000	1990–2002	1998	–	Health care professionals should inform the childbearing population about the importance of folic acid
Spain	Asturias	6000	1990–2002	2001	–	raggedright 0.4 mg from 1 month pre conception → 3 months gestation. 4 mg per day for women with previously affected pregnancy
	Barcelona	12000	1992–2002			
	Basque Country	17000	1990–2001			
Sweden	Sweden	100000	2001–2002	1996	–	Government recommendation is for 0.4 mg per day from 1 month before to 3 months after conception, or 4–5 mg per day for women with previously affected pregnancy
Switzerland	Vaud	7500	1989–2001	1996	–	0.4 mg folic acid daily from 4 weeks pre conception → 12 weeks after. HE initiative in preparation
UK	Glasgow	10000	1980–2002	1992	1995	raggedright 0.4 mg folic acid daily when planning a pregnancy. HE campaign included advertising on television and in newspapers, magazines and professional journals
	Mersey	27000	1995–1999			
	North West Thames	47000	1991–2002			
	Wales	32000	1998–2002			
	Oxford	8000	1991–2002			
	Trent	62000	1998–2002			
	Wessex	26000	1994–2002			

[a] HE, health education campaign in the year stated (if ongoing or repeated campaigns, additional years are indicated).
[b] Detailed information on policy can be found at http://www.eurocat.ulst.ac.uk/pubdata/folic%20acid.html.
[c] FA, folic acid.
[d] Dietary only.
[e] Polish data are not included because of lack of information on terminations.

B2: government policy of improving dietary folate (with or without a health education campaign).
C: no government policy.

2.1. Statistical analysis

To avoid bias in graphs of total prevalence of NTD by year (1980–2002) pooled across registries, we adjusted for differences in years over which registers were contributing data (Table 1). Technically, this was by including year and register effects in a negative binomial regression model and subtracting out the "registry" effects. All registries and years listed in Table 1 were included.

Comparisons of changes in total prevalence between 2000–2002 and 1989–1991 according to policy were made in a two-step analysis, in order to reflect the two-level (individual and registry) structure of the data. Simpler analyses ignoring variations across registries in changes over time would have given spuriously narrow confidence intervals. Specifically, this involved:

Step 1. Estimating, for each registry, the ratio of total prevalence in 2000–2002 to that in 1989–1991.

Step 2. Obtaining the mean of such ratios (on the log scale) over all registries in countries with similar policy types, using standard random affects meta-analysis techniques [8]. Significance of differences between the means, thus calculated was assessed using random effects meta-regression [8].

This process was then repeated replacing Step 1 by estimating registry-specific linear trends in total prevalence over the period 1989–2002. Both analyses first looked at the effect of any government policy (A, B1 or B2 versus C) on the decline in NTD total prevalence, before disaggregating the policy types to investigate any differences between them.

Only the 24 registries with data covering at least 1 year in each of the comparison periods (1989–1991 and 2000–2002) were included in these statistical analyses. Policy was classified as the policy current in 1999 in order that all births in the 2000–2002 comparison period should be potentially affected by the introduction of policy in the country.

3. Results

3.1. Periconceptional folic acid supplementation policy

At the time of the survey 13 countries had government folic acid supplementation policies (Table 1). The first governments to formulate a policy concerning folic acid supplementation were the UK (1992), Ireland (1993) and Netherlands (1993). Ten more countries had introduced government PFAS policy by 2002, two (France and Spain) as late as 2000–2001. Malta and Finland recommended raising folate status by dietary means only. Austria, Belgium, Croatia, Germany and Italy had no government policy by 2005, although in all these countries professional bodies have issued guidelines or recommendations. Seven countries launched some type of government-led health education campaign (Table 1) so that the information about the protective effect of folic acid could reach women directly rather than uniquely through health professionals. Detailed information for each country is available in the EUROCAT Special Report on Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe [5].

3.2. Prevalence of neural tube defects in Europe (1980–2002) in 34 registries

A total of 11,256,856 births were surveyed by 34 registries 1980–2002, including 10,932 babies/fetuses with neural tube defects (4071 livebirths, 1107 stillbirths and 5983 terminations of pregnancy). The graph of yearly total prevalence of NTD for UK and Ireland (UKI, Fig. 1) shows the well-documented dramatic decline in neural tube defects (predating any PFAS policy initiatives) from 49 per 10,000 births in 1980 to 12–16 per 10,000 in the 1990s. This is an average across Ireland (where terminations are illegal) and the UK (where terminations are legal) (full data can be found on http://www.eurocat.ulst.ac.uk/pubdata/). In contrast, in Europe excluding UK and Ireland (exclUKI) (Fig. 2) the total prevalence rate during the 1980s, and thereafter was close to 10 per 10,000 births. Figs. 1 and 2 also show the birth prevalence of NTD over time excluding the increasing number of terminations.

3.3. Analysis of changes over time (1989–2002) in 24 registries

In the UK and Ireland, with PFAS policies and health education initiatives, registers combined show a significant 30% (95% CI 16–42%) overall mean reduction in NTD total prevalence in 2000–2002 compared with 1989–1991 (see Table 2 for prevalance data and Fig. 3 for meta-analysis results).

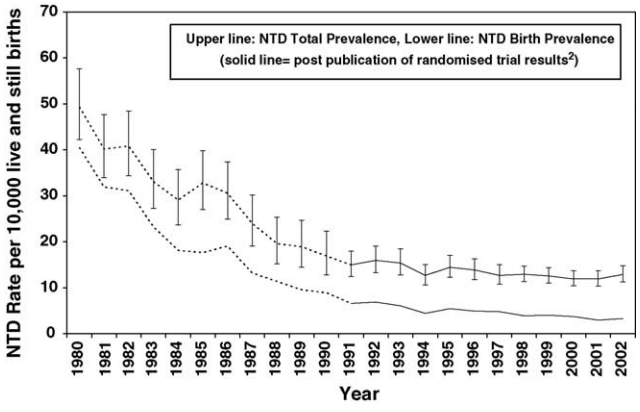

Fig. 1. Total prevalence rate per 10,000 births and birth prevalence rate (excluding terminations) of neural tube defects in UK and Ireland (UKI), 1980–2002, adjusted for registry.

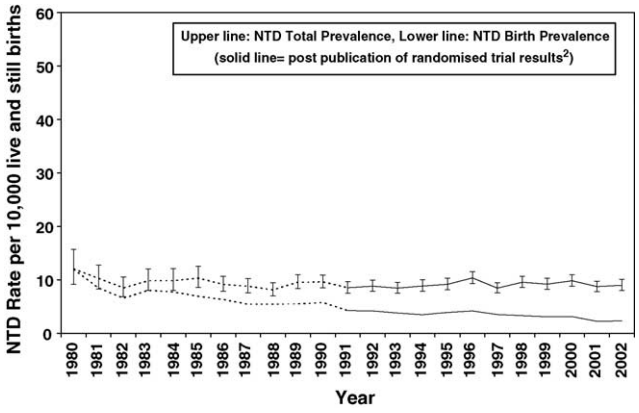

Fig. 2. Total prevalence rate per 10,000 births and birth prevalence rate (excluding terminations) of neural tube defects in Europe-exclUKI, 1980–2002, adjusted for registry.

Registries in Europe excluding UK and Ireland (Europe-exclUKI) from the eight countries with PFAS policy by 1999 show a slight, non-significant 2% reduction in NTD total prevalence (95% CI 28% reduction to 32% increase), comparable with registries from countries with no policy which show a slight and non-significant reduction of 8% (95% CI 26% reduction to 16% increase) (Table 2 and Fig. 3). Registries from Europe-exclUKI with a health education campaign as well as government policy (policy type A; Fig. 3) represented by Netherlands, Norway and Denmark also show little reduction in total prevalence (4%, 95% CI 41% reduction to 80% increase) which is not markedly different from registries from countries with government policy but no health education campaign (policy type B1; Fig. 3). In northern Netherlands, however, where policy was introduced considerably earlier than other European countries (introduced in 1993 compared with 1997, 1998 in other countries), there is a 43% (95% CI 15–61%) reduction in total prevalence from 11.44 per 10,000 in 1989–1991 to 6.52 per 10,000 in 2000–2002.

The analyses of linear trend gave broadly similar results and are thus not presented here.

4. Discussion

These results show little or no progress in Europe over the last decade towards prevention of NTDs. Reductions have fallen short of the potential for prevention of half to two

Table 2
Number of cases of NTD and total prevalence rate per 10,000 births in 24 EUROCAT registries for time periods 1989–1991, 1992–1995, 1996–1999 and 2000–2002

	1989–1991			1992–1995			1996–1999			2000–2002		
	Cases	Births	Prevalence	Cases	Births	Prevalence	Cases	Births	Prevalence	Cases	Births	Prevalence
UK and Ireland (all have policy in 1999)												
Dublin-Ireland	86	58107	14.80	101	74386	13.58	79	81239	9.72	57	66324	8.59
Glasgow-UK	69	37591	18.36	83	46856	17.71	82	41933	19.56	34	28825	11.80
North Thames (West), UK	68	47330	14.37	253	189105	13.38	226	189102	11.95	156	137856	11.32
Oxford, UK	7	5895	11.87	35	23029	15.20	27	22513	11.99	24	19284	12.45
Total	230	148923	15.44	472	333376	14.16	414	334787	12.37	271	252289	10.74
Europe-exclUKI with policy in 1999												
Odense, Denmark	23	16699	13.77	21	23982	8.76	24	22859	10.50	23	16191	14.21
N Netherlands	67	58581	11.44	73	77106	9.47	77	78538	9.80	40	61380	6.52
Norway	126	182621	6.90	197	241596	8.15	186	239420	7.77	174	173570	10.03
Southern Portugal	11	11015	9.99	20	36502	5.48	37	65091	5.68	35	56553	6.19
Vaud, Switzerland	20	23120	8.65	32	31156	10.27	29	30195	9.60	28	21691	12.91
Malta	14	16345	8.57	26	20171	12.89	25	18692	13.38	11	11981	9.18
Finland	155	195191	7.94	175	260967	6.71	198	235661	8.40	119	169134	7.04
Total	416	503572	8.26	544	691480	7.87	576	690456	8.34	430	510500	8.42
Europe-exclUKI without policy in 1999												
Styria, Austria	34	40304	8.44	44	52403	8.40	34	46059	7.38	15	20769	7.22
Hainaut, Belgium	49	40677	12.05	49	50117	9.78	53	48871	10.85	38	37330	10.18
Antwerp, Belgium	16	8428	18.98	31	35598	8.71	50	64976	7.70	48	52444	9.15
Zagreb, Croatia	14	21280	6.58	12	25428	4.72	12	24975	4.81	10	17090	5.85
Central East France	137	313835	4.37	256	405556	6.31	251	410995	6.11	188	281089	6.69
Paris, France	152	111709	13.61	184	145090	12.68	187	151504	12.34	160	116364	13.75
Strasbourg, France	38	40970	9.28	58	53062	10.93	70	53845	13.00	38	27644	13.75
Mainz, Germany	7	8016	8.73	24	15290	15.70	42	14310	29.35	25	9256	27.01
Saxony-Anhalt, Germany	47	39090	12.02	15	29757	5.04	50	40254	12.42	52	54635	9.52
Tuscany, Italy	26	25964	10.01	61	99181	6.15	67	100668	6.66	42	79590	5.28
North East Italy	105	150813	6.96	126	201004	6.27	145	222080	6.53	78	162328	4.81
Asturias, Spain	23	15415	14.92	35	27665	12.65	32	25817	12.40	20	20261	9.87
Basque Country, Spain	36	32729	11.00	67	62961	10.64	76	65485	11.61	61	53336	11.44
Total	684	849230	8.05	962	1203112	8.00	1069	1269839	8.42	775	932136	8.31

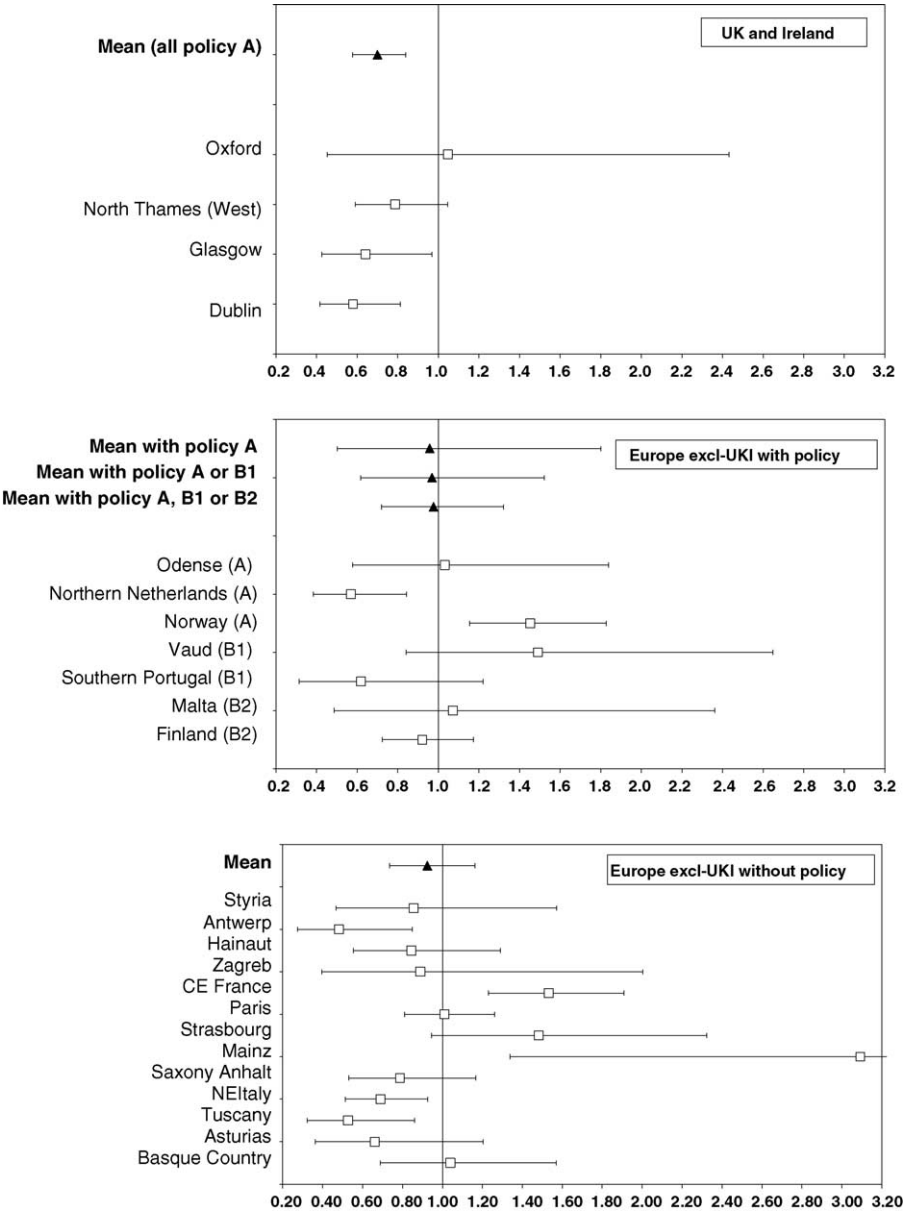

Fig. 3. Ratio of NTD total prevalence (rate per 10,000 live and stillbirths) 2000–2002 vs. 1989–1991 by registry and meta-analysis mean estimates of rate ratio in each policy group (NB upper confidence interval for Mainz, 7.15).

thirds of NTD cases in Europe [1]. In the UK and Ireland, it is difficult to establish how much of the 30% decline in NTD, since 1989 is due to folic acid supplementation in response to government policy/health education rather than to a continuation of the pre-existing decline. The earlier decline may itself be mediated, at least in part, by improved folate status as a result of improvements in diet [9]. While uptake of folic acid supplementation in UK and Ireland has improved during the 1990s, none of the varying estimates of uptake during the entire recommended periconceptional period from local surveys exceed 45% [10,11]. By 2000–2002, the total prevalence of NTD in UK and Ireland was still higher than that in the rest of Europe, though the difference had lessened considerably.

In other European countries the very small decline in NTD total prevalence (2% in countries with folic acid policy and 8% in countries with no policy) is compatible with either chance variation over time or a small average uptake of supplements. It is notable that the only country showing a significant decline in total prevalence was northern Netherlands (43%) where policy and education interventions were introduced relatively early and folic acid uptake rose to 36% of pregnant women by 1999 [12]. On the other hand, in Norway where supplementation intake was reported to rise considerably [5] between 1998 and 2002, there was no apparent effect on reducing NTD total prevalence rates (although there may have been ascertainment changes as described below). In addition, surveys have shown supplement

uptake rates of as little as 5% periconceptionally in some countries [5].

It has been suggested that there may be under ascertainment of terminations prior to 1998 in Norway [13]. If Norway data are excluded the results show a reduction in NTD for European countries with folic acid supplementation policy (group A) of around 15% but confidence intervals are wide (47% reduction to 35% increase) and the meta-analysis indicates that this reduction is not significantly different from the reduction seen in countries without policy.

Our results indicate the overall extent to which government policy in European countries has ensured, by 2002, that all women have the opportunity to prevent an affected pregnancy. We recognize that government policy, as classified in our survey, is not necessarily a good indicator of supplementation uptake. For example, in Finland and Malta where government policy largely recommends dietary modifications (Finnish policy recommends supplements for specific groups, see Table 1), surveys of supplementation suggested 19% uptake in Finland in 2000 [14] and 15% uptake in Malta in 1999 [15], comparable with many countries with governments recommending supplementation. Local initiatives promoting supplementation may exist without the existence of central government policy (for example in Mainz, Saxony and Croatia, Table 1). The quality of health education campaigns may differ widely. In the Netherlands, the highest level of folic acid supplementation uptake was achieved 3 years after a health education campaign (and 5 years after the introduction of official government policy) [12,16,17] so it is possible that some countries with recent policy introduction have yet to show an impact.

Furthermore, regional or national differences in the impact of policy implementation and health education are necessarily obscured by the need to combine neural tube defect data from different regions in order to estimate the extent of any decline with acceptable precision. This is an intractable problem with neural tube defect surveillance, and suggests that accompanying surveillance of supplement uptake rates and/or red cell or serum folate is needed in order to evaluate local initiatives. A further difficulty with surveillance is the possibility of changes in registry ascertainment masking or exaggerating the impact of preventive measures. We have no reason to believe, however, that a uniform improvement in ascertainment could have occurred across Europe to mask a supplementation-related decline in total prevalence.

The reasons for the low uptake of supplements, even in the presence of government policy and health education campaigns are complex. Surveys suggest that in most countries less than half of all pregnancies are said to be “planned” [5], thus preventing women from starting supplementation periconceptionally.

Even when pregnancies are “planned” many women may not receive or respond to health promotion messages, or may remain unaware that dietary modifications are unlikely to achieve sufficient folate intake [12,18–22]. Uptake of folic acid supplements is lower amongst women of lower socio-economic status, potentially further widening socio-economic inequalities in NTD prevalence [16,23,24]. More research is needed on the evidence base for the effectiveness of different methods of delivering health education to women before conception.

Many non-European countries have implemented mandatory fortification of staple foods with folic acid. In the USA and Canada, the introduction of fortification of all cereal grain products was followed by a lowering of NTD rates [25,26–28].

In Europe, reluctance to proceed to mandatory food fortification may reflect a lack of recognition of the public health importance of NTD. Termination of pregnancy has made NTD a relatively “hidden” problem in many countries. However, we believe that it is unacceptable to continue to rely mainly on a prenatal screening and termination strategy where primary prevention is possible. Moreover, there is growing evidence that fortification may have additional health benefits, both for other congenital anomalies [29–36] and in prevention of cardiovascular disease [37] and certain cancers [38–41]. Discussion of potential harm of fortification [42] has centred on the possible problem of masking the presentation of pernicious anaemia among the elderly [43,44], and the possibility of increased twinning associated with raised folate status [45–47], but consideration of all available evidence, including now the experience in countries with fortification, does not support continuing concern that these problems could outweigh the advantages of fortification [1,48–53].

EUROCAT data suggest that the considerable potential for folic acid to reduce neural tube defect prevalence in Europe is so far largely unfulfilled. The EUROCAT Working Group has issued the recommendations shown in Box 1, [5].

5. Funding

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6. Ethics approval

All registries have the ethics approval appropriate to their national and local ethics guidelines.

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Box 1: Recommendations of the EUROCAT Folic Acid Working Group

(1) Countries should review their policies regarding folic acid fortification and supplementation.
(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 socioeconomic 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.

Francannet, Ester Garne, Lorentz Irgens, David Lillis, Maria-Luisa Martinez-Frias, Carmen Mosquera-Tenreiro, Vera Nelen, Mary O'Mahoney, Annette Queisser-Luft, Joaquin Salvador, Claude Stoll, David Stone, Romano Tenconi, Dave Tucker, Diana Wellesley. Maria Loane extracted NTD cases and births from the EUROCAT Central Registry Database.

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