Eurocat

European Surveillance of Congenital Anomalies

Special Report:

The Status of Health in the European Union: Congenital Malformations

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Congenital Malformations

Introduction

Collectively, congenital anomalies present an important public health issue in terms of:

- impact on the quality of life of affected children and adults and their families
- contribution to fetal and infant mortality, both in terms of loss of potential years of life and emotional costs to the family
- provision, quality and financial cost of medical, social and educational services to improve the participation and quality of life of affected individuals and their families
- provision, quality and financial cost of prenatal screening in the population and its psychological cost to pregnant women.

Congenital ("present from birth") anomalies which involve structural malformations diagnosed prenatally, at birth or within the first year of life are the focus of epidemiological surveillance through congenital anomaly registers, and the focus of this section. Many registers also include cases diagnosed later in infancy or childhood. "Major" congenital anomalies are those with serious medical or functional consequences and some are lethal. Many affected pregnancies are spontaneously aborted, often in the first trimester, and these are not included in the figures. Many rare genetic disorders are diagnosed later in childhood and these are discussed in the full Report (Chapter 5). Metabolic diseases diagnosed through neonatal screening may be included in congenital anomaly registers, but are not included here. Some behavioural and neurological conditions also have a congenital origin but are not diagnosed or confirmed until after infancy.

The development of the organs occurs in the first trimester of pregnancy (brain development continues later), including the first six weeks before many pregnancies have been recognized. In terms of preventive action regarding environmental risk factors, this places great importance on directing promotion of a healthy environment and protection from adverse exposures to the entire community, or women of childbearing age, rather than pregnant women only, and on developing an effective system of preconceptional care. Moreover, protecting the health of adults and children will not necessarily be enough to protect the health of the foetus, and thus the fetus and pregnant women must have a special status in public health policy.

Within Europe, there are geographic and socioeconomic inequalities in the prevalence of congenital anomalies. These are now of two main types – variation in the prevalence of risk factors affecting total prevalence, and additional variation in prenatal detection and termination of pregnancy rates affecting livebirth prevalence. As well as these inequalities, congenital anomalies are often ignored in the wider public health agenda due to their individual rarity, and thus there are inequalities between congenital anomalies and more common diseases in access to preventive, treatment and rehabilitative research, policy and services.

Data Sources

EUROCAT (European Surveillance of Congenital Anomalies) is the principal source of information on the epidemiology of congenital anomalies in Europe. EUROCAT is a network of population-based congenital anomaly registers, using multiple sources of information to collect high quality data (both in terms of case ascertainment and diagnostic detail). Registries cover affected livebirths, stillbirths and fetal deaths from 20 weeks of gestation, and terminations of pregnancy for fetal anomaly (TOPFA) following prenatal diagnosis (whether before or after 20 weeks gestation). Registries may cover only diagnoses made prenatally and in infancy, or extend registration to new diagnoses made during childhood.

EUROCAT started in 1979. There are currently 38 registries in 20 countries (see Table 1), covering in total 1.4 million birth per year. Annual birth coverage is 23.4% of births of the EU-15 countries, 35.0% of the EU-NMS countries and 25.6% of EU-27. In addition of the EU-27 countries, Norway, Switzerland and Croatia participate in EUROCAT (Table 1), as well as the Ukraine since 2007. The only EU countries with established registers of congenital anomalies not participating in EUROCAT are Czech Republic and Slovak Republic, both of which are working towards full membership in 2009.

Maintaining high quality data usually requires a limit to the total size of the population to be covered by a register, thus the preference in larger nations for regional rather than national registries, networked nationally and at a European level by EUROCAT. The proportion of national births covered by registers in each country is shown in Table 1, ranging among those countries participating from 3% (Germany) to 100% (Norway, Sweden, Finland, Malta and Hungary). Although complete coverage of the European population may be an ideal, this should not replace deeper investment of resources in areas already covered – excellent data from one quarter of Europe will give us more meaningful information than poor data from all of Europe.

Collaboration of registers within a European network has greatly improved data comparability between countries. A standard set of minor or poorly defined anomalies are excluded (EUROCAT, 2005a), although it can be difficult to apply the criteria precisely as there is not always enough information in health service records to distinguish between different severities of the same anomaly. Data quality can also be influenced by health service factors (eg. the proportion of stillbirths with post-mortem carried out, or the proportion of multiply malformed cases where a karyotype has been performed) and registry factors (eg. specificity of coding and completeness of ascertainment of TOPFA or postneonatally diagnosed anomalies among livebirths).

Other sources of epidemiological information about congenital anomalies in Europe include the following:

a) The WHO HFA database contains data on infant mortality due to congenital anomalies. Their data can be seen in Chapter 4.1 (EUGLOREH, 2009). Such infant mortality data from infant death registration is dependent on the quality of death certification, but is particularly useful for countries with no current congenital anomaly registers. The data are limited with regard to type of

congenital anomaly. Differences between countries in infant mortality due to congenital anomaly can reflect one or more of the following factors:

i the risk of pregnancies being affected by a congenital anomaly in that country
ii the level of investigation by autopsy in case of infant death
iii the likelihood that an affected pregnancy will be prenatally diagnosed leading to termination of pregnancy
iv the quality of treatment for congenital anomalies (eg. surgery for congenital heart disease)
v practices regarding registration of a baby as a stillbirth or livebirth where the congenital anomaly is so severe that the baby is not viable.

b) Hospital Episode or Discharge Data (HE/HD). These data are potentially particularly useful for major congenital anomalies where livebirth is the most common outcome, infant survival is high, and surgery is routinely indicated eg. hypospadias, gastroschisis and orofacial clefts. Such data usually do not include terminations of pregnancy following prenatal diagnosis (TOPFA), or still births, and usually do not cover health service episodes on an outpatient basis. In some countries, private hospitals do not make their data available, or hospitals do not use a standard coding system. It can be difficult to link several episodes for the same individual together, particular across years. Many congenital anomaly registers, nevertheless, now use HE/HD data as one of their sources of information.

c) International Clearinghouse for Birth Defects, Surveillance and Research (www.icbdsr.org). Many of the EUROCAT registers belong to ICBDSR also, as well as two EU non-EUROCAT registers in Czech Republic and Slovak Republic.

Data Description and Analysis

Prevalence of Congenital Anomalies

EUROCAT records a total prevalence of major congenital anomalies of 23.8 per 1,000 births for 2000-2004 (Table 2). Total prevalence includes livebirths, stillbirths, and terminations of pregnancy for fetal anomaly (TOPFA) following prenatal diagnosis. The livebirth prevalence is 19.9 per 1,000 births.

The average prevalence of different subgroups in Europe is shown in Table 2. The prevalence of chromosomal anomalies is 3.4 per 1,000 births. In the data shown in Table 2, these cases have been excluded from other subgroups (i.e. a child with an abdominal wall defect and a chromosomal anomaly is recorded only under chromosomal anomalies). Congenital heart disease is the most common subgroup, at 6.4 per 1,000 births, followed by limb defects (3.6 per 1,000), urinary system (2.8 per 1,000) and nervous system defects (2.0 per 1,000). EUROCAT updates each year prevalence figures on 95 subgroups of congenital anomaly, available on its website (EUROCAT, 2007). Those with a total prevalence above 0.1 per 1,000 births are shown in Table 2.

There has been a slight increase in recent years in the overall prevalence of congenital anomalies (followed by the usual dip in the most recent years due to late case registration). This increase is seen to be in part due to an increase in the prevalence of congenital heart disease (Figure 1), but an overall improvement in data quality and increases in risk factors are other possible partial explanations. Despite the steady rise in the overall prevalence of terminations of pregnancy for Fetal anomaly (TOPFA), the livebirth prevalence has increased.

Perinatal Mortality and Termination of Pregnancy

Congenital anomalies are an important contributor to perinatal mortality. The overall recorded rate of stillbirths with congenital anomaly is 0.43 per 1,000 births, and deaths in the first week 0.55 per 1,000 births, giving a total perinatal mortality rate associated with congenital anomaly of 0.99 per 1,000 births (Table 3). The main congenital anomaly subgroups contributing to perinatal mortality are congenital heart disease (23% of perinatal deaths with anomaly), nervous system anomalies (19% of perinatal deaths with anomaly), and chromosomal anomalies (21%) (Table 3).

Chromosomal anomalies contribute more to stillbirths than first week deaths, while congenital heart disease contributes more to first week deaths than stillbirths. Nervous system defects contribute equally in both categories.

Perinatal mortality due to congenital anomaly varies by country (Table 4). The lowest rates are recorded in Italy (0.2 per 1,000) but there is a known problem with recording of cause of death for stillbirths and neonatal deaths so this figure is probably considerably underascertained. The highest rates of perinatal mortality associated with congenital anomaly are recorded in Ireland (2.4 per 1,000) and Malta (2.3 per 1,000). These are both countries where TOPFA is illegal, and thus the perinatal mortality rate includes affected foetuses with a lethal or high mortality anomaly which would have been prenatally diagnosed in other countries leading to termination of pregnancy (and exclusion from mortality statistics).

The ratio of TOPFA to births varies from 0 (Ireland and Malta) to 11.4 (France) per 1,000 births. Differing prenatal screening policies and practices, differences in uptake of screening and diagnosis due to cultural and organisational factors, and differences in TOPFA laws, influence the rate of TOPFA in the population, as discussed in detail elsewhere (EUROCAT, 2005b). In Poland, TOPFA is not encouraged, and done only in case of lethal anomaly. Some countries allow TOPFA at any gestational age (Austria, Belgium, Croatia, England & Wales, France, Germany). Others have an upper gestational age limit (Finland, Italy, Spain, Sweden, Switzerland, Czech Republic), and yet others have an upper gestational age limit but allow TOPFA for lethal anomalies beyond this limit (Netherlands, Norway, Portugal, Denmark).

Table 4 shows TOPFA before and after 20 weeks gestation. The highest TOPFA ratio both before and after 20 weeks gestation is recorded in France (5.6 and 5.8 per 1,000 births respectively). Comparison between countries is complicated by different laws and practices regarding the recording of late terminations. Late TOPFA, where legal, may be recorded as stillbirth or as livebirth with neonatal death in some countries, and practice may also vary within countries.

TOPFA in most countries far outnumber stillbirths and neonatal deaths with congenital anomaly (Table 4). Up to 0.8% (Switzerland) of foetuses die due to the presence of a congenital anomaly, whether as a TOPFA, stillbirth or neonatal death (but excluding spontaneous abortions), and 5 countries record a rate above 0.5% (Table 4). The differences in total mortality (TOPFA + perinatal) between countries probably mainly reflects the frequency with which TOPFA is carried out for non-lethal anomalies, but is also influenced by differences between countries in the prevalence of anomalies such as neural tube defects and Down syndrome and, as previously mentioned, the completeness of ascertainment of stillbirths, neonatal deaths, and TOPFA.

Despite the important mortality consequences of congenital anomaly, the vast majority of cases of congenital anomaly across Europe are liveborn children who survive infancy, but who may have important medical, social or educational needs.

Congenital Heart Disease

The live birth prevalence of congenital heart disease is 6.1 per 1,000 births (Table 2), the largest group of congenital anomalies. This average figure is almost certainly under-ascertained, as registries collecting data on diagnoses after the neonatal period, and with full access to echography data report a prevalence of 8-10 per 1,000. The reported prevalence of congenital heart disease has been increasing (Figure 1), probably associated with greater referral of babies with a heart murmur for early echography. Severe heart defects are quite commonly prenatally diagnosed e.g. 39% of transposition of great vessels, and 73% of hypoplastic left heart (EUROCAT, 2007). TOPFA is not common for congenital heart disease, unless the heart defect is associated with other congenital anomalies or is lethal.

Down Syndrome

Risk of Down Syndrome is strongly associated with advanced maternal age. The increase in average maternal age in Europe is documented in Chapter 8 of the EUGLOREH Report, 2009. Figure 2 shows the resulting increase in the total

prevalence of Down Syndrome across Europe, to 2.2 per 1,000 births. Geographical variation in total prevalence corresponds to differences in maternal age profile between countries (Dolk et al, 2005a). For example, the registries in France and Switzerland, where the proportion of births to mothers over 35 is high, recorded a total prevalence (including LB, SB and TOPFA) of 3.4 per 1,000.

Prenatal screening for Down Syndrome has resulted in the prenatal detection of an increasing proportion of cases, among both older and younger mothers. This is associated with an increasing number of TOPFA. Overall in Europe, as represented by EUROCAT registers, the live birth prevalence of Down Syndrome has slightly declined (Figure 2) to 1.0 per 1,000 births as the increase in TOPFA has outweighed the increase in maternal age. In 2000-2004, differences in policy and practice regarding prenatal screening and TOPFA, as well as maternal age differences, resulted in an over four-fold variation in live birth prevalence of Down Syndrome in Europe, ranging from 0.4 per 1,000 to 2.0 per 1,000 (the high rates being in Ireland and Malta).

Neural Tube Defects

In 1991, results of a randomised trial of peri-conceptional folic acid supplementation (MRC, 1991) established that raising folic acid status could be an effective measure to prevent neural tube defects (MRC, 1991), potentially more than halving the prevalence in Europe. The prevalence of NTD in Europe has, however, not declined over the subsequent decade (Figure 3), representing a failure in preventive policy.

During the 1980s and previously, a strong decline in rates of neural tube defects occurred in the British Isles, where rates have traditionally been high (Busby et al, 2005a; Busby et al, 2005b; EUROCAT, 1991). During the 1990s, a shallow further decline was experienced in the British Isles (Busby et al, 2005a; Busby et al, 2005b). In the period 2000-2004, total prevalence in the British Isles was not higher than many continental European areas, and the geographic differences which are most apparent are the lower prevalence experienced by Southern European countries, particularly Italy. Diet and/or genetic factors may explain this low prevalence.

In many countries, the majority of cases of neural tube defects are prenatally diagnosed leading to TOPFA, while in others TOPFA is rare (see above). This has resulted in a very wide variation in livebirth prevalence rates, from 0.1 per 1,000 in France and Spain to 1.0 per 1,000 in Poland (Table 5).

Orofacial Clefts

Cleft palate and cleft lip occur in 1.3 per 1,000 births in Europe (Table 2). Cleft lip with or without palate is aetiologically different from cleft palate and accounts for nearly two thirds of cases. Geographic variation within Europe has consistently been shown for cleft lip with or without palate (EUROCAT, 2002a; EUROCAT, 2002b). Some Northern European countries have higher rates, for example Germany, Netherlands and Denmark had rates between 1.3 and 1.6 per 1,000 for 2000-2004 (EUROCAT, 2007), while rates of 0.6 per 1,000 or below were recorded in Italy, Spain and Ireland.

Gastroschisis

Gastroschisis is an anomaly of the abdominal wall, with an average prevalence of 0.2 per 1,000 births in 2000-2004 (Table 2). It is associated with low socioeconomic status and young maternal age (less than 20 years). A strong increase in gastroschisis prevalence has occurred both in Europe (Loane et al, 2007) and elsewhere in the world. Particularly high rates and increases have been experienced in Britain, only part of which is associated with high rates of teenage pregnancy (Loane et al, 2007). In Italy however, rates are lower and an increase in prevalence has not been experienced (Loane et al, 2007). The great majority of cases of gastroschisis are prenatally diagnosed (EUROCAT, 2007), but TOPFA is rare as the prognosis is good with surgery.

Hypospadias

Hypospadias, where the urethral opening in boys is misplaced, has a prevalence of a minimum of 1.3 per 1,000 births (Table 2). Individual registries report prevalence rates up to 2.5 per 1,000 in the period 2000-2004, and two areas report higher prevalences – Sicily at 3.0 per 1,000, and Malta at 4.2 per 1,000. It is difficult to produce a valid prevalence estimate unless data regarding surgery in the first three years of life are accessed (Dolk et al, 2004). Criteria may vary over the diagnosis of milder cases. Hypospadias is of particular current interest in relation to the possibility that it can be caused by exposure to endocrine disrupting chemicals. The high rate of hypospadias in Sicily is under investigation in relation to industrial and agricultural chemical exposures (Bianchi et al, 2006).

Risk Factors

In the majority of individual cases of congenital anomaly, the cause of the condition is unknown, but suspected to be an interaction of multiple environmental and genetic factors. For about 15% of cases, there is an identifiable chromosomal abnormality. Under 5% of cases can be attributed to a known single gene mutation, and under 5% to exposure to a single environmental teratogen (such as a drug taken during early pregnancy).

Congenital anomalies are usually grouped under "medical genetics", but the study of socioeconomic differences emphasises the importance of environmental factors as causes, and these are at present the most amenable to prevention. Genetic susceptibility to environmental exposures is likely to vary importantly in the population.

Low folic acid status in the periconceptional period is an established risk factor for neural tube defects (MRC 91) and probably a range of other anomalies (Botto et al, 2006). Other nutrients are most probably also important, particular attention having been paid to vitamin B12, but generally a healthy diet is to be promoted for the prevention of congenital anomalies. Some dietary elements in excess, such as vitamin A, are teratogenic and high dose dietary supplements should not be promoted.

Some women are at higher risk of congenital anomaly due to chronic disease status. Diabetes and epilepsy are both associated with higher congenital anomaly risk (EUROCAT 2004, Macintosh et al 2006), and there is increasing evidence that obesity is also associated with a higher risk (Waller 2007, EUROCAT 2004). In the case of epilepsy and diabetes, appropriate clinical care can reduce the risk, and there is still much to do in European countries to ensure that all women with these conditions receive the highest standard of care (Macintosh et al 2006). Prevention of obesity is discussed elsewhere in the EUGLOREH Report 2009. The rising prevalence of obesity and diabetes are of concern in relation to the burden of congenital anomalies in the population.

Rubella vaccination programmes for babies and/or young girls are an essential continuing measure to prevent congenital rubella syndrome, associated with deafness, eye defects and congenital heart disease. Monitoring of vaccination uptake rate, as well as attention to vaccination status of immigrants, is needed. Additional information systems are needed to capture all cases of congenital rubella syndrome, as some do not present with structural malformations diagnosed at birth.

The thalidomide (softenon) tragedy turned the world's attention to the potential dangers of therapeutic drugs taken during early pregnancy. A number of drugs are now known to be teratogenic (Schaefer et al 2001). Some of these are to be avoided during pregnancy, others are necessary (such as antiepileptic drugs) but a careful selection of the type of drug is needed to balance risks and benefits. Pharmacovigilance or postmarketing surveillance of drugs taken during pregnancy is not systematic, and it is possible that there are more drugs currently on the market which carry a risk of congenital anomaly when taken during pregnancy.

Assisted reproductive technology (ART) is being used with increasing frequency with

new techniques being developed over time (eg. intracytoplasmic sperm injection) to add to the range already available. Currently, there is controversy about the level of risk of congenital anomaly associated with ART (Hansen et al 200%). Particularly stringent data confidentially in relation to ART makes this area particularly difficult to research.

Smoking, alcohol and many recreational drugs can be harmful to the fetus if used in early pregnancy (EUROCAT 2004). The most extensive evidence relates to alcohol. Fetal alcohol syndrome or spectrum is discussed in the EUGLOREH Report 2009. There is a typical constellation of facial features and developmental delay and learning disability, and diagnosis is often made in early childhood rather than the first year of life. Special surveys are therefore needed to supplement congenital anomaly registers to determine numbers. Trends regarding alcohol drinking among young women in some countries, especially binge drinking, are of great concern. The effects of binge drinking on the fetus are largely unknown. Other recreational drugs such as cocaine and solvent abuse also carry teratogenic risks. These are particularly difficult to study, as the drug use may be illegal and there are often many coexisting risk factors such as smoking, alcohol, poor nutrition and other risk factors associated with deprivation.

Older maternal age is a risk factor for chromosomal anomalies such as Down syndrome. Trends towards older age at childbearing are a complex phenomenon, but are associated with poorer reproductive outcomes.

Our knowledge of the risks of exposure to chemicals, in the occupational, domestic and community environment is very incomplete (Cordier 1992, Dolk and Vrijheid 2003, EUROCAT 2004). To protect the fetus, we need to adopt a precautionary approach in reducing exposure particularly to byproducts of chlorination in drinking water, releases from waste disposal sites, endocrine disrupting chemicals, pesticides and solvents.

Control Tools and Policies

Primary Prevention

Primary prevention of congenital anomalies has not been an area of overall improvement in Europe, as evidenced by the lack of decline in prevalence since 1992.

Very little data is available about socioeconomic differences in congenital anomaly risk at a European level, but the evidence to date generally suggests a substantial socioeconomic gradient (Vrijheid et al, 2000). Socio-economic deprivation may be associated with a number of environmental risk factors for congenital anomaly such as maternal nutrition, maternal infection, maternal drug exposure, occupational exposures and environmental pollution. Minority ethnic groups may experience higher risks due to deprivation, as well as some specific risks due to genetic or cultural factors. Measures to alleviate family poverty should help to reduce congenital anomaly risk, as well as specific measures to reduce known risk factors.

The potential to prevent neural tube defects, and possibly other anomalies also (Botto et al, 2006) by raising the folate status of women preconceptionally has not been fulfilled (Busby et al, 2005a; Busby et al, 2005b; Abramsky et al, 2007; EUROCAT, 2005) and is the major primary prevention opportunity. Experience has shown that peri-conceptional folic acid supplementation (i.e. recommending that women start taking supplements from before conception to the first trimester) is an unsuccessful population prevention strategy, since it is difficult to reach women preconceptionally, particularly if they do not plan their pregnancy. Socio-economic inequalities in neural tube defect prevalence are likely to be widening because of the uneven uptake of supplementation (De Walle and de Jong van den Berg, 2007). Some European countries are considering folic acid fortification of a staple food, such as flour, following the example of countries in North and South America, where such a strategy has been demonstrated to be successful in preventing neural tube defects (De Wals et al, 2007). For example, this has recently been recommended by the British Food Standards Agency. Research has suggested a role for folic acid in protecting against cardiovascular disease, an additional argument for food fortification.

Secondary Prevention

Developments in surgical treatments and neonatal intensive care have improved outcome in terms of survival and long-term morbidity, for example for congenital heart defects, diaphragmatic hernia, and gastroschisis. Developments have concerned both surgical procedures, and organization of services within centres of excellence treating a sufficient volume of cases. However, information on improvement of outcomes over time tends to come from individual specialized clinics, rather than from populations experiencing the full range of care (Garne et al, 1999)

Prenatal diagnosis can help in the preparation for postnatal surgery, and there is suggestive evidence for example that survival of babies with Transposition of Great Arteries is improved if diagnosis is prenatal (Garne et al, 2007). This is a potentially important area for future development.

Prenatal Screening and Diagnosis

The two main types of prenatal screening are biochemical screening, and ultrasound scanning for structural malformations and “soft markers”. For Down Syndrome, a

combined approach is increasingly used, but screening developments have diffused unevenly across Europe (EUROCAT, 2005). Screening policies vary between European countries (EUROCAT, 2005), and even countries with similar policy may vary considerably in its implementation (EUROCAT, 2005).

An increasing proportion (Figure 4.2.1) of affected pregnancies are prenatally diagnosed, and prenatal diagnosis rates are particularly high for some anomalies. Comparisons of the proportion of cases prenatally diagnosed, the average gestational age at diagnosis, diagnostic methods used and the proportion of cases resulting in termination of pregnancy have shown enormous variation between and within countries (Garne et al, 2004; Garne et al, 2005). Such variation may result from cultural differences underlying policy or individual uptake, from differing interpretations of the scientific evidence in the design and implementation of screening, or from differences in organization, resources and systems in place to effect change in the health services.

However, prenatal screening also presents the health care system significant challenges in terms of increasing "medicalisation" of pregnancy, ethical questions, and giving women fully informed choices during pregnancy (Green et al, 2004). The option of termination of pregnancy necessitates decisions on which anomalies justify this, and how late in pregnancy. The pregnant woman needs to be given full information on the likely outcome for the anomaly which has been diagnosed, information which is only partially available for many rare anomalies. Inevitably, screening involves both false positives and false negatives, either of which can cause distress (Green et al, 2004).

Public Health Initiatives and Policies

Congenital anomalies straddle different public health agendas – rare diseases, peri-natal and child health, environmental health and major health determinants. Funding for EUROCAT network co-ordination currently comes from the European Commission's Directorate General for Health and Consumer Protection, under its Public Health Programme, as a component of the European information system for rare diseases. The added value of European collaboration is particularly great for congenital anomalies, coming from the opportunity to pool data on rare anomalies and/or exposures, to compare data between regions and countries, to give a common response to European public health questions, and to share expertise and resources, including computing tools in an area which is generally under-resourced. Nevertheless, there are currently no plans for a sustainable European information system – decisions on funding are short-term. Moreover, national and regional funding for registers is insufficient and short-term. In 2005, approximately 4 million euro was being spent on congenital anomaly registers by European Union countries. This equates to approximately 3 euro per birth in a registry area, or 1 euro per birth in the European Union.

The majority of congenital anomalies are rare (as defined by prevalence less than 5 per 10 000 in the EU), depending on how one delimits the clinical or disease entities. The majority of rare diseases (see Chapter 5) are congenital. The rare disease public health agenda, however, is mainly oriented toward genetic diseases and toward developing drug treatments for genetic diseases. Full attention should in addition be

paid to reducing environmental risk factors for congenital anomalies, and to further development of non-drug treatments e.g. improved shunts for hydrocephalus.

Registries provide syntheses across a variety of data sources generated by the health system. There are many areas therefore where improvement in underlying health information systems across Europe will improve the quality or efficiency of registries: a) full coding of cause of death on stillbirth and infant death certificates b) the potential to link registry cases to death notifications in order to ascertain survival c) greater accuracy and accessibility of hospital episode data d) electronic access to birth registrations and medical records for diagnostic detail and core risk factor information e) full information on terminations of pregnancy following prenatal diagnosis f) linkage between different health information systems using unique patient identifiers. EUROCAT is working with EURO-PERISTAT towards better peri-natal information across Europe. Each registry follows national practice in relation to data confidentiality (Busby et al, 2005c). Registers in some countries are currently in a difficult position because of national interpretations of the European directive regarding patient consent. Although a reasonable requirement in theory, experience shows that while parental refusals are very rare, obtaining informed parental consent for registration is logistically difficult and requires resources much greater than those made available. The issue of consent and confidentiality is central to the creation of European public health information.

Little information is currently available on long term outcome for the child and family in terms of survival, morbidity, quality of life and participation. Longitudinal and retrospective follow-up studies of children with congenital anomalies need support. There has been no recent economic evaluation of the “burden” of congenital anomalies in Europe. Such an evaluation is needed to help give them their place in the public health agenda.

Risk factors for congenital anomalies amenable to primary prevention have been presented in Table 9.1a (EUGLOREH 2007 (2009), "The Status of Health in the European Union: Towards a Healthier Europe", *EU Public Health Programme Project, Global Report on the Health Status in the European Union* [http://www.eugloreh.it/ActionPagina_993.do].

a) Many major “lifestyle” determinants of ill health in the population, such as alcohol, recreational drugs, smoking, and obesity, are also risk factors for congenital anomalies. Any strategy to tackle these health determinants should pay special attention to women of childbearing age, remembering that the harm is often done before the pregnancy is recognized, and that the foetus may have special susceptibility.

b) Policies aimed at ensuring “healthy pregnancy” can pay attention to congenital anomalies as part of a range of outcomes including birth weight and neuro-developmental outcomes. However, for congenital anomalies a system of pre-conceptional care is needed, as reduction of risk factors needs to start very early in or before pregnancy.

c) Folic acid fortification of a staple food is the single most promising preventive strategy, and may have other health benefits.

d) Public health measures should have regard to the “precautionary principle” as well as “evidence-based practice”, protecting the foetus despite scientific uncertainty, particularly with regard to complex exposures such as environmental pollution.

e) Public health measures aimed at migrants between European countries, or immigrants from non-European countries should pay special attention to women of childbearing age, for example in relation to poverty, rubella vaccination and specific genetic risks.

f) The phenomenon of older maternal age at childbirth and its reproductive risks needs to be understood at a social level, in order to create an appropriate policy response.

g) Much greater investment is needed in systematic follow-up of medicinal drugs and assisted reproduction technologies, in relation to their potential to affect the foetus. The recent initiation of the EnCePP pharmacovigilance network by the European Medicines Agency is an important step forward. It should be a priority to ensure safe use of medicine during pregnancy.

h) More research should be funded into the environmental causes of congenital anomalies.

Future Developments

The last few decades have not seen increasing success in congenital anomaly prevention, as evidenced by the lack of decline in prevalence. Implementation of current knowledge with effective policies, as well as research into causes of congenital anomalies, have the potential to change this situation with political will.

Prenatal screening and diagnosis have seen rapid development. The near future will bring less invasive technologies for the detection of chromosomal anomalies, and greater sensitivity and specificity of diagnosis of anomalies. Variation in the quality of screening services within Europe need examination. The challenge for European countries is also to reduce the number of women having to consider termination of pregnancy as an option by achieving effective primary prevention, and improving the outcome of affected children and their families in terms of health, quality of life and participation.

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Acronyms

TOPFA Terminations of Pregnancy for Fetal Anomaly

Table 1 Coverage of the European Population by EUROCAT Full or Associate Member Registries

Country	EUROCAT Registry	Year Started EUROCAT Data Transmission	Annual Births 2005, registry	Annual Births 2005, Country[1]	% Country Covered
EU					
EU (Present EU Member States)				5,123,500	25.6
EU-15 (EU Member countries since before 2004				4,114,700[2]	23.4
EU-NMS (Countries acceded in2004-2007)				1,007,700[2]	35.0
Belgium	Antwerp	1990	19,200		
	Hainaut	1980	12,500		
	TOTAL		31,170	117,400	27.0
Bulgaria				71,300	
Czech*				102,100	
Denmark	Odense	1980	5,300	64,200	8.2
Germany	Mainz	1990	3,100		
	Saxony-Anhalt	1987	17,200		
	TOTAL		20,400	686,100	3.0
Estonia				14,400	
Ireland	Cork & Kerry	1996	8,500		
	Dublin	1980	23,400		
	South East	1997	6,300		
	TOTAL			60,300	63.4
Greece				107,300	
Spain	Barcelona	1992	14,700		
	Basque Country	1990	19,800		
	Madrid[3]	1980	106,700		
	TOTAL		141,200	462,500	30.5
France	Auvergne	2002	13,600		
	Ile de la Reunion[3]	2001	14,500		
	Paris	1981	39,300		
	Strasbourg	1982	12,900		
	TOTAL		80,400	804,700	10.0
Italy	Campania	1996	59,900		
	Emilia Romagna	1981	37,600		
	North East	1981	60,200		
	Sicily	1991	16,000		
	Tuscany	1980	29,400		
	TOTAL		203,200	552,600	36.8
Cyprus				8,200	
Latvia				21,600	

Lithuania				30,600	
Luxembourg				5,300	
Hungary	Hungary	1998	97,600	97,600	100.0
Malta	Malta	1986	3,900	3,900	100.0
Netherlands	Northern	1981	18,400	187,700	9.8
Austria	Styria	1985	10,500	77,900	13.4
Poland	Wielkopolska Rest of Poland[3] TOTAL	1999 1999	33,600 217,900 251,500	364,400	69.0
Portugal	South	1990	18,000	109,200	16.6
Romania				221,300	
Slovenia				18,100	
Slovakia				54,400	
Finland[3]	Finland	1993	57,600	57,600	100.0
Sweden[3]	Sweden	2001	101,100	101,100	100.0
UK	Northern Region North West Thames Thames Valley Trent Wales Wessex TOTAL	2000 1991 1991 1998 1998 1994	31,600 48,500 27,300 67,300 32,800 27,000 234,600	720,500	32.6
Non EU Candidate Countries in EUROCAT					
Croatia		1983	5,900	42,500	14.0
EFTA Countries in EUROCAT					
Norway		1980	56,500	56,500	100.0
Switzerland	Vaud	1989	7,200	72,700	9.9

[1] Source: Crude birth rate (accessed 29-08-08)
http://ec.europa.eu/health/ph_information/dissemination/echi/echi_02_em.pdf
http://epp.eurostat.ec.europa.eu/portal/page?_pageid=1996,45323734&_dad=portal&_schema=PORT
[2] Calculations used year 2005 EU-15 and EU-NMS annual births/total population *1,000
[3] Associate EUROCAT Registries (transmit aggregate data only)
* National non-EUROCAT congenital anomaly register

Table 2: Prevalence per 1,000 Births of EUROCAT Congenital Anomaly Subgroups 2000-2004

Anomaly Subgroup	LB (prevalence)[#]	LB+FD+TOPFA (prevalence)
All Anomalies	19.93	23.82
All Anomalies Excluding Chromosomals	18.45	20.46
Nervous system **	0.97	2.04
Neural Tube Defects	0.27	0.94
Anencephalus and similar	0.04	0.37
Encephalocele	0.03	0.10
Spina Bifida	0.20	0.47
Hydrocephaly	0.25	0.49
Microcephaly	0.16	0.18
Eye	0.31	0.33
Ear, face and neck	0.20	0.23
Congenital heart disease **	6.05	6.39
Transposition of great vessels	0.28	0.30
Ventricular septal defect	2.64	2.70
Atrial septal defect	1.95	1.96
Atrioventricular septal defect	0.11	0.15
Tetralogy of Fallot	0.24	0.26
Pulmonary valve stenosis	0.32	0.32
Hypoplastic left heart	0.13	0.23
Coarctation of aorta	0.30	0.31
Respiratory	0.35	0.48
Oro-facial clefts	1.26	1.34
Cleft lip with or without palate **	0.77	0.82
Cleft palate **	0.50	0.52
Digestive system	1.24	1.42
Oesophageal atresia with or without tracheo-oesophagal fistula	0.19	0.20
Ano-rectal atresia and stenosis	0.23	0.28
Diaphragmatic hernia	0.20	0.24
Abdominal wall defects	0.31	0.46
Gastroschisis **	0.19	0.22
Omphalocele	0.12	0.21
Urinary	2.44	2.80
Bilateral renal agenesis including Potter syndrome	0.03	0.12
Renal dysplasia	0.21	0.29
Congenital hydronephrosis	0.96	0.98

Genital	1.64	1.67
Hypospadias	1.34	1.32
Limb **	3.33	3.59
Limb reduction	0.39	0.51
Upper limb reduction	0.28	0.36
Lower limb reduction	0.12	0.18
Club foot - talipes equinovarus	0.79	0.87
Hip dislocation and/or dysplasia	0.61	0.60
Polydactyly	0.73	0.75
Syndactyly	0.50	0.52
Musculo-skeletal	0.53	0.77
Craniosynostosis	0.12	0.12
Other malformations	0.69	0.84
Disorders of skin	0.44	0.45
Genetic syndromes + microdeletions	0.38	0.47
Chromosomal **	1.48	3.36
Down Syndrome	0.96	1.92
Patau syndrome/trisomy 13	0.04	0.17
Edward syndrome/trisomy 18	0.09	0.42
Turner's syndrome	0.06	0.22

LB – Live Births
FD – Fetal Deaths / Stillbirths from 20 weeks gestation
TOPFA – Terminationa of Pregnancy for Fetal Anomaly following prenatal diagnosis

* Subgroups with total prevalence of at least 0.1 per 1,000 births are shown. For the full list of 96 subgroups see http://www.eurocat.ulster.ac.uk/pubdata/tables.html, (accessed 22nd January 2008)
** For Czech Republic the numbers per 1,000 births are: heart disease 2.14 (years unspecified); cleft lip with/without palate 1.4 (year 2005); cleft palate 1.0 (year 2005); gastroschisis livebirth prevalence 0.12, total prevalence 0.34 (year 2005); limb defect 9.81 per 1,000 births (years unspecified); chromosomal abnormalities 1.09 (years unspecified) and defects of CNS 1.05 (years unspecified). Information supplied by non-EUROCAT Czech Republic registry.
[#] LB denominators unavailable for Antwerp (Belgium), SE Ireland, NE Italy and Sicily, therefore total births were used for these 4 registries

Table 3: Perinatal Mortality Due to Congenital Anomalies, 2000-2004* (Source: EUROCAT Full Member Registries Combined)

Anomaly Subgroup **	% of 1st week LB deaths (all anomalies)	% of SB (all anomalies)	Prevalence of non-surviving LB per 1,000 births	Prevalence of SB per 1,000 births	Perinatal mortality per 1,000 births #
All Anomalies	100	100	0.55	0.43	0.99
All Anomalies Excluding Chromosomals	81	71	0.45	0.31	0.75
Nervous system	19	19	0.1	0.08	0.19
Neural Tube Defects	10	11	0.06	0.05	0.1
Anencephalus and similar	6	7	0.03	0.03	0.06
Hydrocephaly	3	5	0.02	0.02	0.04
Congenital heart disease	28	17	0.15	0.07	0.23
Hypoplastic left heart	7	1	0.04	0.01	0.04
Respiratory	12	9	0.07	0.04	0.1
Oro-facial clefts	5	5	0.03	0.02	0.05
Digestive system	16	9	0.09	0.04	0.13
Diaphragmatic hernia	8	1	0.04	0.01	0.05
Abdominal wall defects	3	6	0.02	0.03	0.04
Urinary	17	13	0.09	0.06	0.15
Bilateral renal agenesis including Potter syndrome	5	3	0.03	0.01	0.04
Limb	10	14	0.06	0.06	0.12
Limb reduction	3	5	0.01	0.02	0.03
Club foot - talipes equinovarus	3	5	0.02	0.02	0.04
Musculo-skeletal	8	9	0.04	0.04	0.08
Other malformations	5	6	0.03	0.02	0.05
Chromosomal	15	29	0.08	0.13	0.21
Down Syndrome	2	9	0.01	0.04	0.05
Edward Syndrome/trisomy 18	6	8	0.03	0.04	0.07

LB - Live Births, SB - Fetal deaths / Still Births from 20 weeks gestation
* Perinatal Mortality rates associated with congenital malformations as reported in EUROCAT database
** Subgroups contributing to at least 5% of first week deaths or SB are shown.
# In Czech Republic, nervous system defects contribute more to stillbirth (18.98%) than to first week deaths (8.13%).Chromosomal anomalies and congenital heart disease have the same distribution. Information supplied by non-EUROCAT Czech Republic registry.

Table 4: Ratio of Termination of Pregnancy for Fetal Anomaly following Prenatal Diagnosis (TOPFA) to all Births, and Perinatal Mortality per 1,000 Births*, by Country, 2000-2004 (Source: EUROCAT)

Country[1]	TOPFA < 20 weeks	TOPFA 20+ weeks	Total TOPFA**	Perinatal Mortality***	Perinatal Mortality + TOPFA#
Austria	2.15	0.98	3.14	0.84	3.99
Belgium	1.64	1.34	3.18	1.19	4.36
Croatia	0.54	0.43	0.96	0.54	1.5
Denmark	2.43	0.86	3.29	1.57	4.86
France	5.62	5.77	11.39	1.14	12.53
Germany	2.34	1.71	4.08	0.99	5.08
Hungary[2]	1.12	0.69	2.01	-	-
Ireland3	-	-	-	2.43	2.43
Italy	1.41	1.73	3.31	0.25	3.56
Malta[3]	-	-	-	2.32	2.32
Netherlands	0.82	0.43	1.26	1.75	3.01
Norway[4]	-	-	2.67	-	-
Poland[5]	-	-	-	1.4	1.4
Portugal	1.02	1.21	2.26	0.55	2.81
Spain	3.54	2.02	5.98	0.74	6.72
Switzerland	5.47	1.68	7.24	1.01	8.25
UK	3.51	3.06	6.90	1.65	8.55
Total	2.24	1.99	4.64	1.08	5.63

[1] EUROCAT Full Member registries only
[2] No information on survival of livebirth cases
[3] Termination of pregnancy illegal
[4] No information available on gestational age at TOPFA or survival
[5] TOPFA known to be under-ascertained
* Perinatal Deaths associated with congenital malformations as reported in EUROCAT database
** Total TOPFA includes cases with gestational age not known
# Perinatal Mortality + TOPFA refers to all TOPFA
*** Czech Republic: TOPFA rate is 6.49 per 1,000 births in 2005; Perinatal mortality in is 0.5 per 1,000 births during 2005-2006. Information supplied by non-EUROCAT Czech Republic registry.

Table 5: Total and LB Prevalence per 1,000 Births of Neural Tube Defects and Down Syndrome by Country, Average 2000-2004 (Source: EUROCAT)

	Neural Tube Defects (NTD)		**Down Syndrome**	
Country*	**Live Birth Prevalence ****	**Total Prevalence**	**Live Birth Prevalence ****	**Total Prevalence**
Belgium	0.22	0.87	0.76	1.64
Denmark	0.56	1.31	0.75	1.65
Germany	0.41	1.34	0.94	1.93
Ireland	0.75	0.97	2.04	2.13
Spain	0.12	1.05	0.71	2.73
France	0.14	1.40	0.60	3.41
Italy	0.16	0.59	0.65	1.56
Hungary	0.26	0.69	0.96	1.32
Malta	0.66	0.86	1.93	1.92
Netherlands	0.39	0.65	1.10	1.57
Austria	0.42	1.00	0.79	1.67
Poland	0.99	1.08	1.60	1.59
Portugal	0.18	0.68	0.38	0.87
United Kingdom	0.19	1.28	1.02	2.18
Croatia	0.29	0.54	0.97	1.25
Norway	0.36	1.05	1.30	1.72
Switzerland	0.25	1.32	0.45	2.92
TOTAL	**0.28**	**0.98**	**0.96**	**1.93**

Figure 1: **Trends in the Total and Livebirth Prevalence per 1,000 Births of All Anomalies and Cardiac Anomalies, 1992-2004**
(Source: EUROCAT)

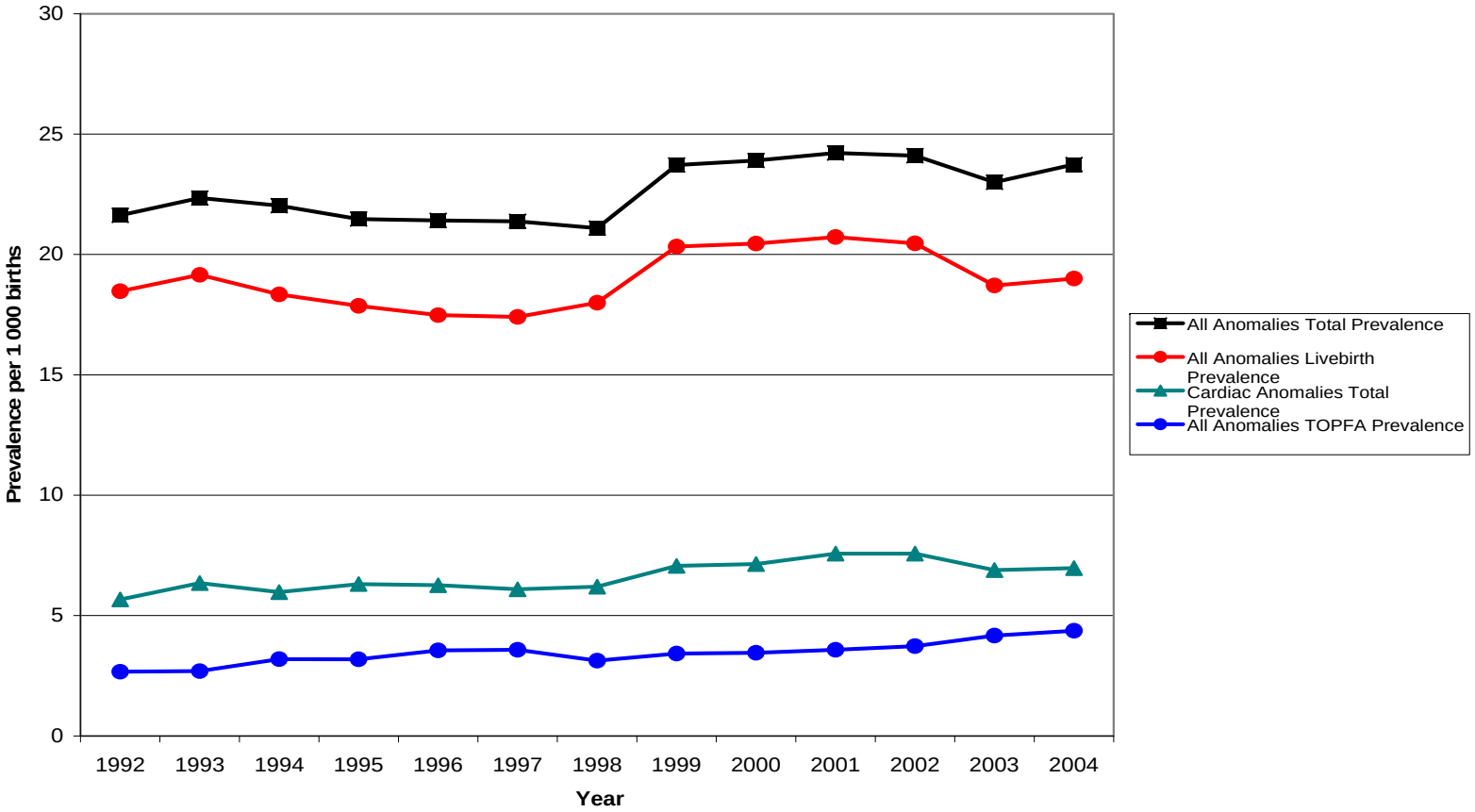

Figure 2: Trends in the Total and Livebirth Prevalence per 1,000 Births of Down Syndrome, 1992-2004 (Source: EUROCAT)

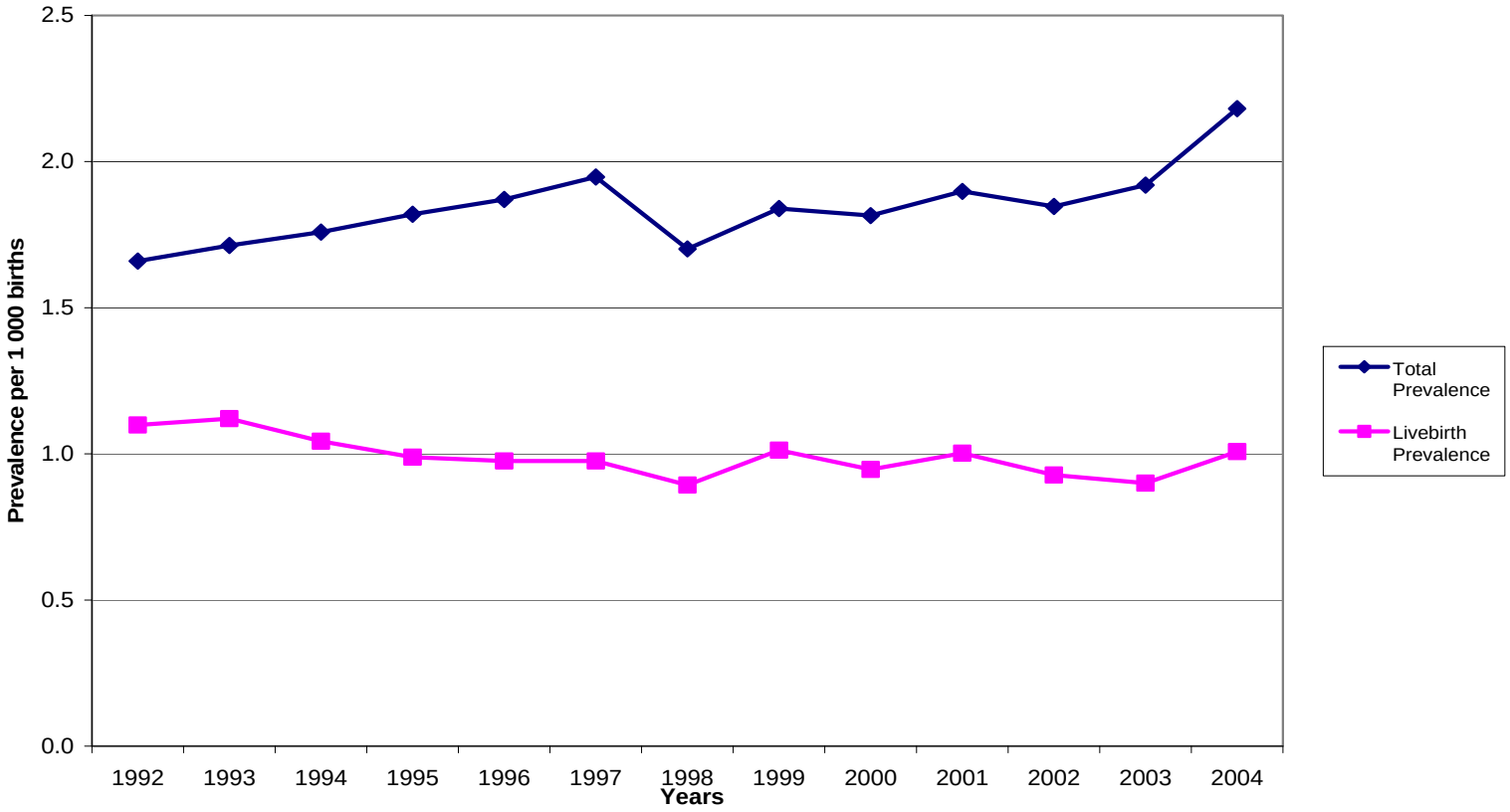

Figure 3: Trends in the Total and Livebirth Prevalence per 1,000 Births of Neural Tube Defects, 1992-2004 (Source: EUROCAT)