# EUROCAT Annual Surveillance Report

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WHO Collaborating Centre for the Surveillance of Congenital Anomalies

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# 1. Introduction

EUROCAT has thirty years of experience of epidemiologic surveillance of congenital anomalies. The scope of work includes:

- providing essential epidemiologic information on congenital anomalies in Europe
- facilitating the early warning of new teratogenic exposures
- evaluating the effectiveness of primary prevention
- assessing the impact of developments in prenatal screening
- acting as an information and resource centre for the population, health professionals and managers regarding clusters or exposures or risk factors of concern
- providing a ready collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children
- acting as a catalyst for the setting up of registries throughout Europe collecting comparable, standardised data

For the first time in 2014, EUROCAT under CHAEFA Operating Grant Number 2013 3307 has produced this Annual Surveillance Report bringing together the different areas of surveillance conducted in 2014. The report includes Executive Summaries of the various reports produced, as well as a selection of epidemiologic data that can be found in the interactive tables on the EUROCAT website, updated in 2014 to birth year 2012. It also summarises the progress of research projects using EUROCAT data.

# 2. Statistical Monitoring

Annual Statistical Monitoring Reports are available on the EUROCAT website. The most recent "EUROCAT Statistical Monitoring Report – 2012" is available under the Clusters & Trends section:
http://www.eurocat-network.eu/content/Stat-Mon-Report-2012.pdf

The protocols are revised in line with changes in the monitoring methodology. The latest protocol (revised in 2014) is available under the Clusters and Trends section:
http://www.eurocat-network.eu/content/Stat-Mon-Protocol-(Jan-2015)-2012.pdf

The EUROCAT 2012 Statistical Monitoring of Congenital Anomalies Executive Summary is shown below.

## EUROCAT 2012 Statistical Monitoring of Congenital Anomalies: Executive Summary

Worldwide, congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood. Of the 5.2 million births in the EU each year, approximately 104,000 (2%) will be born with congenital anomalies. EUROCAT is a European network of population-based registries whose objectives are to provide essential epidemiologic information on congenital anomalies in Europe, to facilitate the early warning of new teratogenic exposures and to evaluate the effectiveness of primary prevention.

To meet these objectives, EUROCAT annually performs statistical monitoring for both trends and clusters in time in order to detect signals of new or increasing teratogenic exposures and monitor progress in the prevention of congenital anomalies. Total prevalence rates of 81 subgroups of congenital anomalies, including all cases of livebirths, stillbirths/ late fetal deaths from 20 weeks gestational age, and terminations of pregnancy for fetal anomaly are monitored and reported. We report here on births over the ten year period 2003-2012, and include data from 25 EUROCAT registries to describe trends, and 18 EUROCAT registries to detect recent clusters in time. A pan-Europe trend and country cluster analyses enable monitoring of rare congenital anomalies that have too few cases to be monitored at individual registry level, as well as presenting an overview of the situation in Europe. Preliminary investigations of trends and clusters have been performed at local and central registry level, and summaries of these investigations are included.

### Key findings

### Congenital anomalies excluding genetic conditions[1]

- **Neural tube defects (NTDs),** which are largely preventable by raising periconceptional folate status, have *not* decreased in prevalence over the last 10 years. Prevalence was 9.47 per 10,000 births in 2003-2004 and 9.10 per 10,000 births in 2011-2012 indicating preventive measures should be reinforced.

[1] Includes genetic syndromes/microdeletions, skeletal dysplasias, chromosomal anomalies

• In this year's pan-Europe analysis, an *increasing* trend was again found for **Severe congenital heart defects (CHD)** which increased on average by 1.4% per year from 16.44 per 10,000 births in 2003-2004 to 17.92 per 10,000 births in 2011-2012. For the third consecutive year, increasing trends were found for **Single ventricle** and **Tetralogy of Fallot**. **Single ventricle** increased by 4.7% per year from 0.46 per 10,000 births in 2003-2004 to 0.65 per 10,000 births in 2011-2012, while **Tetralogy of Fallot** increased on average by 4.1% per year from 2.36 per 10,000 births in 2003-2004 to 3.21 per 10,000 births in 2011-2012. **Atrioventricular Septal Defect (AVSD)** increased by 3.5% per year from 1.57 per 10,000 births in 2003-2004 to 2.12 per 10,000 births in 2011-2012. Further monitoring and investigation of these trends is required as they are unlikely to be explained by diagnostic factors.

• *Increasing* trends were found for some gastrointestinal anomalies. A new increasing trend was found for **Oesophageal atresia with or without trachea-oesophageal fistula (OA)** which increased on average by 2.3% per year from 2.00 per 10,000 births in 2003-2004 to 2.24 per 10,000 births in 2011-2012. For the third consecutive year, an increasing trend was detected for **Duodenal atresia and stenosis** (N.B. pan-Europe trends exclude cases with chromosomal anomalies such as Down syndrome) which rose by 3.4% from 0.79 per 10,000 births in 2003-2004 to 1.02 per 10,000 births in 2011-2012. For the second consecutive year, an increasing trend was found for **Ano-rectal atresia and stenosis** which increased by 2.0% per year from 2.65 per 10,000 births in 2003-2004 to 2.80 per 10,000 births in 2011-2012.

• For the third consecutive year a significantly *increasing* trend was detected for the skeletal anomaly **Craniosynostosis**, which increased on average by 4.7% per year rising from 1.41 per 10,000 births in 2003-2004 to 2.09 per 10,000 births in 2011-2012.

• For the fourth consecutive year, an *increasing* pan-Europe trend was detected for **Cystic adenomatous malformation of the lung (CCAM)** which increased on average by 6.7% per year with prevalence rising from 0.62 per 10,000 births in 2003-2004 to 1.26 per 10,000 births in 2011-2012. Prevalence of CCAM is higher in the UK possibly due to better antenatal detection.

• A new *increasing* trend was found for **Maternal infections resulting in malformations** which includes Rubella, Cytomegalovirus (CMV) and Toxoplasmosis exposed cases. The pan-Europe analysis showed that the prevalence of Maternal infections increased on average by 3.9% per year from 0.51 per 10,000 births in 2003-2004 to 0.79 per 10,000 births in 2011-2012. The majority of cases in the panEurope monitoring had CMV which is associated with young maternal age. More neonatal screening and awareness of CMV infection in recent years may explain some of the increase.

• For the third consecutive year, *decreasing* trends were found for **Upper limb reduction defects**. Prevalence decreased by an average of 3.4% per year from 3.41 per 10,000 births in 2003-2004 to 2.57 per 10,000 births in 2011-2012.

## Chromosomal anomalies

• *Increasing trends* were again detected in **Chromosomal anomalies**, due to the increasing trends in **Down syndrome and Edward syndrome**. These trends are due to rising maternal age across Europe.

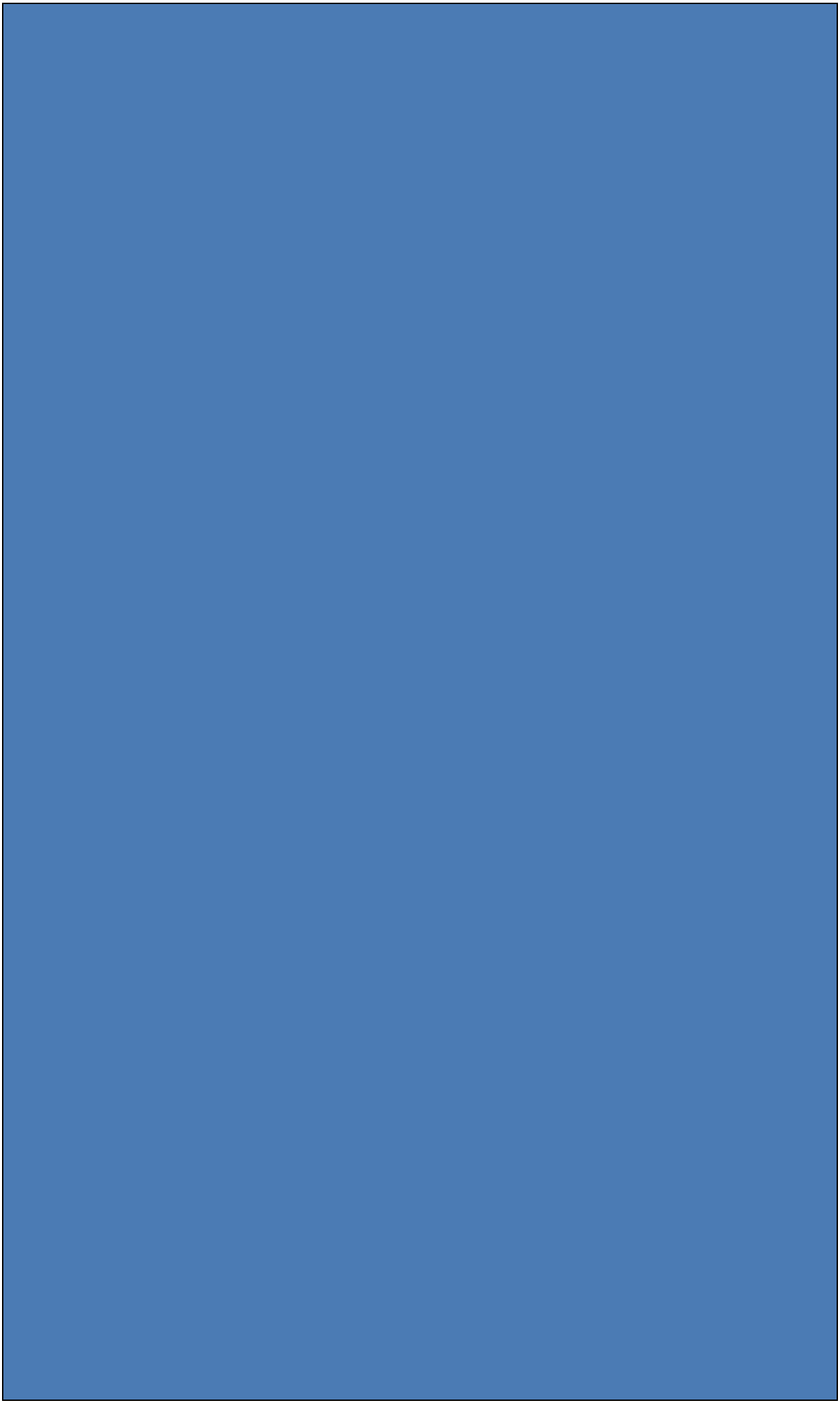
## Clusters

Thirteen new clusters in time were detected in individual registry populations which, following preliminary investigations, could not be explained by information held within the registries. The registries involved will continue to monitor these anomalies: **Arhinencephaly/holoprosencephaly** in Emilia Romagna (9 cases observed versus 2 expected); **Atrioventricular septal defect** in Antwerp (7 cases observed versus 1 expected); **Pulmonary valve stenosis** in Antwerp (17 cases observed versus 7 expected); **Pulmonary valve atresia** in Thames Valley (8 cases observed versus 2 expected); **Aortic valve atresia/stenosis** in Wales (8 cases observed versus 1 expected); **Coarctation of Aorta** in Emilia Romagna (5 cases observed versus 1 expected); **Cystic adenomatous malformation of lung** in Emilia Romagna (12 cases observed versus 4 expected); **Cleft lip with or without palate** in SE Ireland (5 cases observed versus 1 expected); **Bilateral renal agenesis including Potter syndrome** in Thames Valley (5 cases observed versus 1 expected); **Renal dysplasia** in Wessex (13 cases observed versus 3 expected); **Syndactyly** in Paris (15 cases observed versus 4 expected); **Congenital constriction bands/amniotic band** in N Netherlands (5 cases observed versus 1 expected); and **Turner syndrome** in Vaud (10 cases observed versus 3 expected).

At country level, no explanation was found for the **Duodenal atresia and stenosis** cluster detected in Belgium (5 cases observed versus 1 expected). The two Belgian registries will continue to monitor this anomaly.

## Conclusion

The statistical monitoring of trends and clusters is fundamental to the primary prevention of congenital anomalies, providing timely information on the stability or changes in the prevalence of anomalies. Primary prevention of congenital anomalies continues to be a key objective of the EUROCAT network.



# 3. EUROCAT Special Report:
Geographic Inequalities in Public Health Indicators related to Congenital Anomalies. 2014

## Executive Summary

EUROCAT first introduced a set of "public health indicators" for congenital anomalies in 2011. A public health indicator generally refers to a quantitative summary which can guide public health policy and indicate the effect of policy interventions. It is particularly useful for EUROCAT to use a small set of public health indicators as a summary of the vast amount of epidemiological information that EUROCAT publishes on an annual basis regarding prevalence, pregnancy outcome, perinatal mortality, and prenatal diagnosis of 91 congenital anomaly subgroups. A small set of summary indicators is more focused to the needs of policymakers. Indicators can be used to make geographical comparisons, or to track change over time. This report builds on the previous work, analysing the most recent 5 years of data (2008-2012) for 31 full member registries and particularly focussing on geographical comparisons.

## Key Findings

**Perinatal mortality due to congenital anomaly**
The average perinatal mortality due to congenital anomaly across EUROCAT registries is 0.9 per 1,000 births. The perinatal mortality due to CA indicator should be interpreted alongside the TOPFA indicator – for example where TOPFA are illegal (Malta, Ireland), perinatal mortality is expected to be higher. Malta has high perinatal mortality, particularly first week deaths, due to CA, at over 3 per 1,000 births. The Irish registries have the second highest perinatal mortality at 2 per 1,000, and Ukraine also has a relatively high perinatal mortality of 1.5 per 1,000 or above.

**Congenital anomaly prenatal diagnosis prevalence**
The EUROCAT average for prenatally diagnosed CA is 9.5 per 1,000 births, of which approximately one third are chromosomal and two thirds non-chromosomal cases. The prevalence of prenatally diagnosed congenital anomaly cases varies from less than 5 per 1,000 births in some countries up to 18 per 1,000 in Switzerland and France

**Termination of pregnancy for fetal anomaly (TOPFA)**
The overall prevalence of TOPFA across EUROCAT is 4.4 per 1,000. The prevalence of TOPFA varies from zero in countries where this is illegal (Ireland, Malta) to around 8 per 1,000 in France and Switzerland. Paris has the highest TOPFA prevalence – over 10 per 1,000 births, Compared to prenatally diagnosed cases, the prevalence of TOPFA is approximately half i.e. half of prenatal diagnoses on average in Europe result in TOPFA.

**Down syndrome prevalence**
The average total prevalence of Down Syndrome in EUROCAT is 2.3 per 1,000 births, of which 44.6% are livebirths, 2.5% late fetal deaths/stillbirths, and 52.9% TOPFA. The total prevalence varies by country and this variation has been shown in separate analyses to be due to variation in maternal age at delivery.
Total Down Syndrome prevalence has increased over time, also shown in separate analyses to be due to rising maternal age across Europe. The livebirth prevalence has remained stable over the last five years due to the increasing rate of TOPFA.

**Neural tube defects (NTD) total prevalence**
The average total prevalence of neural tube defects is 0.9 per 1,000 births, of which nearly one quarter are livebirths. The highest total prevalence of NTD is in Ukraine

with 1.8 per 1,000 births. The NTD prevalence has not changed in Europe, despite the fact that it is known that periconceptional folic acid supplementation can prevent neural tube defects, and that levels of supplementation in the European population are low and therefore reinforced efforts at implementing preventive strategies are needed.

**Congenital anomaly pediatric surgery**

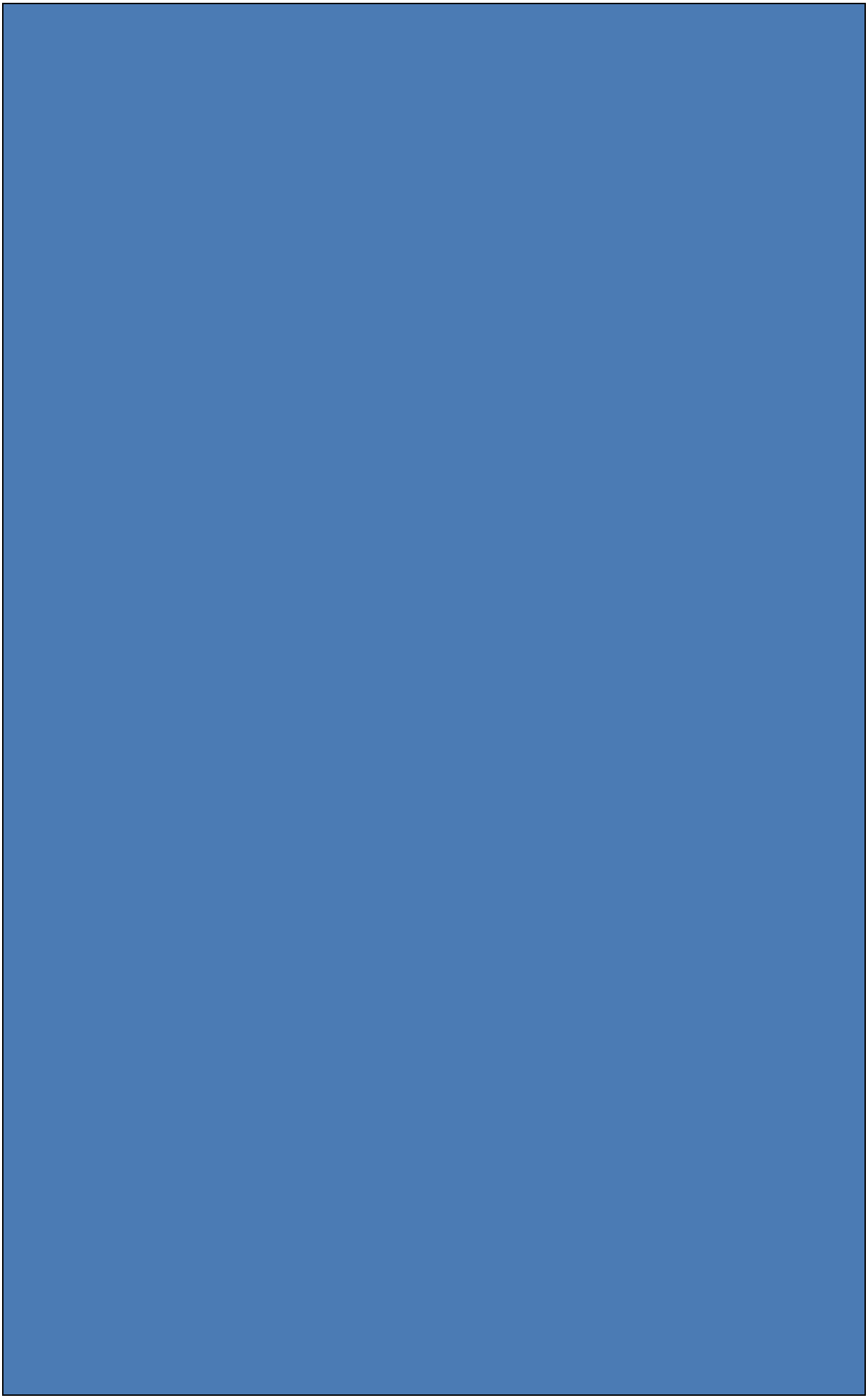
The average total prevalence of the category of anomalies typically requiring surgery is over 5 per 1,000 births. Most (by definition) are livebirths. Eight registries have data on surgery, which show that the average prevalence of babies requiring surgery one or more times is nearly 10 per 1,000 births and that just under half of these are “anomalies typically requiring surgery”.

## Conclusion

It was found that there are huge geographic inequalities in public health indicators relating to congenital anomalies. The reasons for any inequalities cannot be ascertained from the indicators alone and require further investigation within and between countries. Some differences may reflect the social and cultural diversity of Europe.

A comparison with the previously published indicators for 2004-2008 show that there has been very little change, either in the average situation, or in the inequalities between countries. This suggests that the last decade has seen little progress towards improving public health indicators for congenital anomalies, or addressing within or between country inequities where they exist.

The report concludes with a series of questions that member registries may wish to present to the Public Health Authorities in their respective countries to address some of the inequalities highlighted.



# 4. Website Tables

EUROCAT has 33 years of congenital anomaly data available on the website (1980-2012). The range of information available:

- Percentage of the European population covered by the EUROCAT registries
  Information is available for years 2010, 2011 and 2012 and can be found on the EUROCAT website under the 'Member Registries' section
  http://www.eurocat-network.eu/content/EUROCAT-Population-Table-I.pdf
  http://www.eurocat-network.eu/content/EUROCAT-Population-Table-I-Year2011.pdf
  http://www.eurocat-network.eu/content/EUROCAT-Population-Table-I-Year2012.pdf

- For user convenience some *preformatted* tables are available.
  There is a table showing cases and prevalence of Down Syndrome in Europe. This provides the number of livebirths, the number of fetal deaths, the number of TOPFAs and prevalence rates for each full and associate EUROCAT member over the most recent 5 year period
  http://www.eurocat-network.eu/newprevdata/showPDF.aspx?winx=1256&winy=884&file=downs.aspx

  There is a table showing the number of cases and prevalence of 91 EUROCAT congenital anomaly subgroups for all full members combined over the most recent 5 year period. This can be accessed from the 'Prevalence Tables' section of the website
  http://www.eurocat-network.eu/newprevdata/showPDF.aspx?winx=1256&winy=884&file=allsubgroups.aspx

  The prevalence of selected monogenic syndromes in Europe is provided. This currently covers an 8 year period 2005-2012. Registries with good genetic syndrome prevalence (5+ per 10, 000 births) and use of ICD10/BPA extended codes (5+ per 10,000 births) as determined by data quality indicators[#], are included in the figures.
  Monogenic syndrome information can be accessed from the 'Prevalence Tables' section of the website
  http://www.eurocat-network.eu/newprevdata/showPDF.aspx?winx=1256&winy=884&file=Prevalence%20of%20monogenic%20syndromes%20in%20Europe.pdf

- [#]Data quality indicators can be found under Data Collection\Data Quality section of the website. DQI reports cover 5 year periods. The first report is for years 1999-2003 and the most recent covers years 2007-2011. They serve to highlight the strengths and weaknesses of the data. The DQIs help to focus the attention of registries on areas needing improvement, and they are useful to data users for the interpretation of data.
  http://www.eurocat-network.eu/content/DQI-2014-v2.pdf

- Users can obtain tailored prevalence information by creating their own reports. They can select all registries, individual registries or select analysis by country; they can select any number of congenital anomaly subgroups; include all cases or exclude cases with a genetic condition; select any time period of interest between years 1980-2012; and there are many output options. These interactive tables can be found on the 'Prevalence Tables' section of the website
  http://www.eurocat-network.eu/AccessPrevalenceData/PrevalenceTables

- Prenatal detection rates are available for 18 selected congenital anomaly subgroups for the most recent 5 year period. Only registries with 80% known

for the “when discovered” variable and 4 or more years of data in the latest time period are included in the figures. Interactive graphs and tables are available and the user has a number of choices in the way the data can be displayed, for example by gestation, or by outcome etc. Prenatal detection rates are available on the ‘Prenatal Screening & Diagnosis’ section of the website
http://www.eurocat-network.eu/PrenatalScreeningAndDiagnosis/PrenatalDetectionRates

- Information on perinatal mortality is available under the ‘Key Public Health Indicators’ section of the website
http://www.eurocat-network.eu/accessprevalencedata/keypublichealthindicators

  Only full member registries with good recording of the variable ‘survival’ are included in the analyses.

  Table 1 shows perinatal mortality associated with CAs in EUROCAT full member registries, for the most recent 5 year period, by type of anomaly.
  http://www.eurocat-network.eu/content/EUROCAT-Perinatal-Mortality-Table-1v.pdf

  Table 2 shows fetal death, early neonatal death & perinatal mortality associated with CAs in EUROCAT full member registries, per country, for the most recent 5 year period.
  http://www.eurocat-network.eu/content/EUROCAT-Perinatal-Mortality-Table-2.pdf

  Table 3 shows rate of terminations of pregnancy for fetal anomaly following prenatal diagnosis (TOPFA) and rates of perinatal deaths per 1,000 births by country, for the most recent 5 year period, for EUROCAT full member registries.
  http://www.eurocat-network.eu/content/EUROCAT-Perinatal-Mortality-Table-3.pdf

Please follow the links above to avail of the full range of reports. The website tables displayed in the remainder of this section of the Annual Surveillance Report are just a small sample of those available online.

# 4.1 EUROCAT Population Statistics

- **Years of EUROCAT Data from Member Registries, Full and Associate**
- **Coverage of the European Population, Birth Year 2012**

| Country | EUROCAT Registry | Years of EUROCAT data in central database | | Annual Births 2012, Registry | Annual Births 2012, Country[1] | % Country Covered (2012) |
|---|---|---|---|---|---|---|
| **EU** | | | | | | |
| EU (Present EU Member States) | | | | 1,509,534 | 5,232,583 | 28.8 |
| Belgium | Antwerp | 1990-2012 | | 21,316 | | |
| | Hainaut | 1980-2012 | | 12,901 | | |
| | **Total** | | | **34,217** | **127,591** | **26.8** |
| Bulgaria | | | | | 69,609 | 0.0 |
| Croatia | Zagreb | 1983-2012 | | 8,288 | 41,905 | 19.8 |
| Czech Republic | Czech Republic[2] | 2000-2010 | | 108,206[4] | 108,206 | 100.0 |
| Denmark | Odense | 1980-2012 | | 4,605 | 58,037 | 7.9 |
| Germany | Mainz | 1990-2012 | | 3,246 | | |
| | Saxony-Anhalt | 1987-2012 | | 16,951 | | |
| | **Total** | | | **20,197** | **674,754** | **3.0** |
| Estonia | | | | | 14,047 | 0.0 |
| Ireland | Cork & Kerry | 1996-2012 | | 9,994 | | |
| | Dublin | 1980-2012 | | 27,767* | | |
| | South East | 1997-2012 | | 7,461 | | |
| | **Total** | | | **45,222** | **71,948** | **62.9** |
| Greece | | | | | 100,107 | 0.0 |
| Spain | Basque Country | 1990-2011 | | 21,257* | | |
| | Spain Hospital Network [2] | 1980-2012 | | 84,235 | | |
| | Valencia Region | 2007-2012 | | 47,296 | | |
| | **Total** | | | **152,788** | **454,137** | **33.6** |
| France | French West Indies | 2009-2012 | | 9,845 | | |
| | Isle de la Reunion | 2002-2012 | | 14,288 | | |
| | Paris | 1981-2012 | | 25,869 | | |
| | Rhone-Alpes [2] | 2006-2012 | | 59,123 | | |
| | **Total** | | | **109,125** | **822,627** | **13.3** |
| Italy | Emilia Romagna | 1981-2012 | | 39,415 | | |
| | Tuscany | 1980-2012 | | 30,015 | | |
| | **Total** | | | **69,430** | **534,548** | **13.0** |
| Cyprus | | | | | 10,172 | 0.0 |
| Latvia | | | | | 20,039 | 0.0 |
| Lithuania | | | | | 30,637 | 0.0 |
| Luxembourg | | | | | 5,931 | 0.0 |
| Hungary | Hungary | 1998-2012 | | 90,269 | 90,269 [3] | 100.0 |
| Malta | Malta | 1986-2012 | | 4,258 | 4,258[3] | 100.0 |

| Country | EUROCAT Registry | Years of EUROCAT data in central database | | Annual Births 2012, Registry | Annual Births 2012, Country [1] | % Country Covered (2012) |
|---|---|---|---|---|---|---|
| Netherlands | Northern | 1981-2012 | | 16,582 | 175,669 | 9.4 |
| Austria | Styria | 1985-2012 | | 10,385 | 79,036 | 13.1 |
| Poland | Wielkopolska | 1999-2010 | | 37,787 * | | |
| | Rest of Poland [2] | 1999-2010 | | 347,597 * | | |
| | **Total** | | | **385,384** [4] | **385,384** | **100.0** |
| Portugal | South | 1990-2012 | | 16,948 | 89,610 | 18.9 |
| Romania | | | | | 200,960 | 0.0 |
| Slovenia | | | | | 21,994 | 0.0 |
| Slovakia | | | | | 55,665 | 0.0 |
| Finland | Finland [2] | 1993-2011 | | 59,857 | 59,857 [3] | 100.0 |
| Sweden | Sweden [2] | 2001-2011 | | 112,846 [4] | 112,846 | 100.0 |
| UK | E Mid & S York | 1998-2012 | | 76,439 | | |
| | Northern England | 2000-2012 | | 33,831 | | |
| | South West England | 2005-2012 | | 52,246 | | |
| | Thames Valley | 1991-2012 | | 31,179 | | |
| | Wales | 1998-2012 | | 35,419 | | |
| | Wessex | 1994-2012 | | 31,813 | | |
| | **Total** | | | **260,927** | **812,740** | **32.1** |
| **Non EU** | | | | | | |
| Ukraine | Ukraine | 2005-2012 | | 32,736 | 520,705 [5] | 6.3 |
| *EFTA countries in EUROCAT* | | | | | | |
| Norway | Norway | 1980-2012 | | 61,550 | 61,550 [3] | 100.0 |
| Switzerland | Vaud | 1989-2012 | | 8,241 | 81,933 | 10.1 |

[1] Source: EUROSTAT crude birth rate (accessed 25/09/2014)
http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&language=en&pcode=tps00112&plugin=1
[2] Associate EUROCAT Registries (transmit aggregate data)
[3] Source of annual births in country provided by registry rather than by EUROSTAT
[4] Source of annual births in registry provided by EUROSTAT rather than by registry
[5] Source http://www.ukrstat.gov.ua (accessed 01/10/2014)
*Estimated provisional figures

## 4.2 Congenital Anomaly Prevalence

### 4.2.1….Cases and Prevalence 2012

In March 2014, data relating to cases born in 2012 were new to the EUROCAT website. Below is an example of a prevalence report for year 2012, for all full member registries who had supplied data in the year 2014 (n=30). It shows the number of livebirths, the number of fetal deaths and the number of TOPFAs per CA subgroup. The prevalence rate per 10,000 births is calculated for all cases and also all cases excluding 'genetic conditions' per CA subgroup. 'Genetic conditions' are defined as chromosomal, skeletal dysplasias and genetic syndromes + microdeletions.

**A1 - cases and prevalence (per 10,000 births) for the following registries: Styria (Austria), Antwerp (Belgium), Hainaut (Belgium), Zagreb (Croatia), Odense (Denmark), Auvergne (France), French West Indies (France), Isle de la Reunion (France), Paris (France), Mainz (Germany), Saxony-Anhalt (Germany), Hungary, Cork and Kerry (Ireland), Dublin (Ireland), SE Ireland, Emilia Romagna (Italy), Tuscany (Italy), Malta, N Netherlands (NL), Norway, S Portugal, Valencia Region (Spain), Vaud (Switzerland), East Midlands & South Yorkshire (UK), Northern England (UK), South West England (UK), Thames Valley (UK), Wales (UK), Wessex (UK), Ukraine, from 2012 - 2012**

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| **All Anomalies** | 15867 | 364 | 3660 | 19891 | 250.14 | 16362 | 205.76 |
| **Nervous system** | 1017 | 77 | 904 | 1998 | 25.13 | 1735 | 21.82 |
| Neural Tube Defects | 193 | 32 | 523 | 748 | 9.41 | 701 | 8.82 |
| Anencephalus and similar | 30 | 20 | 235 | 285 | 3.58 | 276 | 3.47 |
| Encephalocele | 27 | 1 | 49 | 77 | 0.97 | 66 | 0.83 |
| Spina Bifida | 136 | 11 | 239 | 386 | 4.85 | 359 | 4.51 |
| Hydrocephalus | 253 | 23 | 158 | 434 | 5.46 | 371 | 4.67 |
| Microcephaly | 233 | 8 | 24 | 265 | 3.35 | 231 | 2.92 |
| Arhinencephaly/holoprosencephaly | 18 | 2 | 105 | 125 | 1.57 | 77 | 0.97 |
| **Eye** | 253 | 3 | 11 | 267 | 3.36 | 222 | 2.79 |
| Anophthalmos/micropthalmos | 48 | 2 | 9 | 59 | 0.74 | 44 | 0.55 |
| Anophthalmos | 12 | 0 | 4 | 16 | 0.2 | 14 | 0.18 |
| Congenital cataract | 80 | 1 | 0 | 81 | 1.02 | 66 | 0.83 |
| Congenital glaucoma | 25 | 0 | 0 | 25 | 0.31 | 24 | 0.3 |
| **Ear, face and neck** | 149 | 6 | 16 | 171 | 2.15 | 152 | 1.91 |

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| Anotia | 21 | 0 | 0 | 21 | 0.26 | 19 | 0.24 |
| **Congenital heart defects** | 5561 | 83 | 620 | 6264 | 78.77 | 5504 | 69.22 |
| Severe CHD § | 1406 | 45 | 335 | 1786 | 22.46 | 1461 | 18.37 |
| Common arterial truncus | 27 | 1 | 16 | 44 | 0.55 | 35 | 0.44 |
| Double outlet right ventricle § | 58 | 2 | 21 | 81 | 1.4 | 74 | 1.28 |
| Transposition of great vessels | 213 | 3 | 24 | 240 | 3.02 | 231 | 2.9 |
| Single ventricle | 46 | 2 | 26 | 74 | 0.93 | 65 | 0.82 |
| Ventricular septal defect | 2544 | 29 | 164 | 2737 | 34.42 | 2450 | 30.81 |
| Atrial septal defect | 1507 | 5 | 61 | 1573 | 19.78 | 1413 | 17.77 |
| Atrioventricular septal defect | 251 | 12 | 78 | 341 | 4.29 | 183 | 2.3 |
| Tetralogy of Fallot | 263 | 4 | 32 | 299 | 3.76 | 252 | 3.17 |
| Tricuspid atresia and stenosis | 29 | 3 | 12 | 44 | 0.55 | 40 | 0.5 |
| Ebstein's anomaly | 31 | 2 | 5 | 38 | 0.48 | 37 | 0.47 |
| Pulmonary valve stenosis | 277 | 0 | 16 | 293 | 3.68 | 262 | 3.29 |
| Pulmonary valve atresia | 47 | 1 | 13 | 61 | 0.77 | 57 | 0.72 |
| Aortic valve atresia/stenosis § | 81 | 3 | 16 | 100 | 1.26 | 89 | 1.12 |
| Mitral valve anomalies | 64 | 2 | 17 | 83 | 1.44 | 79 | 1.37 |
| Hypoplastic left heart | 124 | 11 | 100 | 235 | 2.96 | 199 | 2.5 |
| Hypoplastic right heart § | 22 | 2 | 14 | 38 | 0.48 | 34 | 0.43 |
| Coarctation of aorta | 274 | 5 | 15 | 294 | 3.7 | 263 | 3.31 |
| Aortic atresia/interrupted aortic arch | 19 | 1 | 6 | 26 | 0.45 | 20 | 0.35 |
| Total anomalous pulm venous return | 53 | 0 | 3 | 56 | 0.7 | 51 | 0.64 |
| PDA as only CHD in term infants (>=37 weeks) | 211 | 0 | 0 | 211 | 2.65 | 187 | 2.35 |
| **Respiratory** | 262 | 12 | 54 | 328 | 4.12 | 303 | 3.81 |
| Choanal atresia | 69 | 2 | 3 | 74 | 0.93 | 66 | 0.83 |

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| Cystic adenomatous malf of lung § | 76 | 2 | 11 | 89 | 1.12 | 84 | 1.06 |
| **Oro-facial clefts** | 960 | 19 | 95 | 1074 | 13.51 | 966 | 12.15 |
| Cleft lip with or without palate | 560 | 15 | 60 | 635 | 7.99 | 586 | 7.37 |
| Cleft palate | 400 | 4 | 35 | 439 | 5.52 | 380 | 4.78 |
| **Digestive system** | 1248 | 28 | 186 | 1462 | 18.39 | 1305 | 16.41 |
| Oesophageal atresia with or without tracheo-oesophageal fistula | 177 | 6 | 8 | 191 | 2.4 | 171 | 2.15 |
| Duodenal atresia or stenosis | 109 | 4 | 6 | 119 | 1.5 | 82 | 1.03 |
| Atresia or stenosis of other parts of small intestine | 80 | 3 | 0 | 83 | 1.04 | 81 | 1.02 |
| Ano-rectal atresia and stenosis | 183 | 4 | 44 | 231 | 2.9 | 210 | 2.64 |
| Hirschsprung's disease | 113 | 0 | 1 | 114 | 1.43 | 103 | 1.3 |
| Atresia of bile ducts | 18 | 0 | 0 | 18 | 0.23 | 17 | 0.21 |
| Annular pancreas | 7 | 0 | 1 | 8 | 0.1 | 8 | 0.1 |
| Diaphragmatic hernia | 166 | 8 | 45 | 219 | 2.75 | 196 | 2.46 |
| **Abdominal wall defects** | 284 | 23 | 216 | 523 | 6.58 | 398 | 5.01 |
| Gastroschisis | 162 | 8 | 31 | 201 | 2.53 | 192 | 2.41 |
| Omphalocele | 108 | 12 | 154 | 274 | 3.45 | 167 | 2.1 |
| **Urinary** | 2338 | 41 | 349 | 2728 | 34.31 | 2584 | 32.5 |
| Bilateral renal agenesis including Potter syndrome | 28 | 1 | 57 | 86 | 1.08 | 81 | 1.02 |
| Multicystic renal dysplasia | 219 | 8 | 59 | 286 | 3.6 | 265 | 3.33 |
| Congenital hydronephrosis | 712 | 5 | 36 | 753 | 9.47 | 722 | 9.08 |
| Bladder exstrophy and/or epispadia | 31 | 0 | 12 | 43 | 0.54 | 40 | 0.5 |
| Posterior urethral valve and/or prune belly | 32 | 3 | 10 | 45 | 0.57 | 45 | 0.57 |
| **Genital** | 1528 | 11 | 86 | 1625 | 20.44 | 1560 | 19.62 |

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| Hypospadias | 1280 | 2 | 38 | 1320 | 16.6 | 1288 | 16.2 |
| Indeterminate sex | 27 | 1 | 18 | 46 | 0.58 | 37 | 0.47 |
| **Limb** | 2801 | 53 | 335 | 3189 | 40.1 | 2938 | 36.95 |
| Limb reduction defects | 278 | 14 | 117 | 409 | 5.14 | 343 | 4.31 |
| Club foot - talipes equinovarus | 739 | 19 | 106 | 864 | 10.87 | 806 | 10.14 |
| Hip dislocation and/or dysplasia | 605 | 1 | 7 | 613 | 7.71 | 601 | 7.56 |
| Polydactyly | 629 | 8 | 33 | 670 | 8.43 | 626 | 7.87 |
| Syndactyly | 338 | 7 | 36 | 381 | 4.79 | 330 | 4.15 |
| Skeletal dysplasias § | 51 | 1 | 64 | 116 | 1.46 | 0 | 0 |
| Craniosynostosis | 183 | 5 | 14 | 202 | 2.54 | 176 | 2.21 |
| Congenital constriction bands/amniotic band | 12 | 8 | 16 | 36 | 0.45 | 31 | 0.39 |
| Situs inversus | 43 | 0 | 13 | 56 | 0.7 | 54 | 0.68 |
| Conjoined twins | 3 | 3 | 16 | 22 | 0.28 | 20 | 0.25 |
| Congenital skin disorders | 182 | 1 | 12 | 195 | 2.45 | 190 | 2.39 |
| VATER/VACTERL | 21 | 0 | 6 | 27 | 0.55 | 26 | 0.53 |
| Vascular disruption anomalies § | 267 | 18 | 72 | 357 | 6.56 | 326 | 5.99 |
| Lateral anomalies § | 83 | 3 | 30 | 116 | 2.01 | 112 | 1.94 |
| Teratogenic syndromes with malformations § | 94 | 5 | 16 | 115 | 1.45 | 112 | 1.41 |
| Fetal alcohol syndrome | 43 | 0 | 0 | 43 | 0.54 | 43 | 0.54 |
| Valproate syndrome § | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Maternal infections resulting in malformations | 47 | 5 | 15 | 67 | 0.84 | 65 | 0.82 |
| Genetic syndromes + microdeletions | 277 | 6 | 63 | 346 | 4.35 | 0 | 0 |

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| **Chromosomal** | 1165 | 139 | 1780 | 3084 | 38.78 | 0 | 0 |
| Down Syndrome | 787 | 36 | 1001 | 1824 | 22.94 | 0 | 0 |
| Patau syndrome/trisomy 13 | 28 | 13 | 118 | 159 | 2 | 0 | 0 |
| Edward syndrome/trisomy 18 | 62 | 48 | 334 | 444 | 5.58 | 0 | 0 |
| Turner syndrome | 47 | 17 | 122 | 186 | 2.34 | 0 | 0 |
| Klinefelter syndrome | 28 | 1 | 21 | 50 | 0.63 | 0 | 0 |

LB = Live Births

FD = Fetal Deaths / Still Births from 20 weeks gestation

TOPFA = Termination of pregnancy for fetal anomaly following prenatal diagnosis

- = Data not available

§ = Incomplete or missing specification of ICD 9 codes

**Source:** EUROCAT Website Database: http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables (data uploaded 06/01/2015)

## 4.2.2….Cases and Prevalence for most recent 5 year period, 2008-2012

Data for all years are updated twice yearly on the EUROCAT website. Below is an example of the preformatted prevalence report for the most recent 5 year period, 2008-2012, for all full member registries who have some years of data in the central database within this time period (n=32). (See population table at section 4.1 for registries/years). It shows the number of livebirths, the number of fetal deaths and the number of TOPFAs per CA subgroup. The prevalence rate per 10,000 births is calculated for all cases and also all cases excluding 'genetic conditions' per CA subgroup. 'Genetic conditions' are defined as chromosomal, skeletal dysplasias and genetic syndromes + microdeletions.

**A1 - cases and prevalence (per 10,000 births) for the following registries: Styria (Austria), Antwerp (Belgium), Hainaut (Belgium), Zagreb (Croatia), Odense (Denmark), Auvergne (France), French West Indies (France), Isle de la Reunion (France), Paris (France), Mainz (Germany), Saxony-Anhalt (Germany), Hungary, Cork and Kerry (Ireland), Dublin (Ireland), SE Ireland, Emilia Romagna (Italy), Tuscany (Italy), Malta, N Netherlands (NL), Norway, Wielkopolska (Poland), S Portugal, Basque Country (Spain), Valencia Region (Spain), Vaud (Switzerland), East Midlands & South Yorkshire (UK), Northern England (UK), South West England (UK), Thames Valley (UK), Wales (UK), Wessex (UK), Ukraine, from 2008 - 2012**

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| **All Anomalies** | 89514 | 1970 | 19060 | 110544 | 261.45 | 91132 | 215.54 |
| **Nervous system** | 5375 | 400 | 4947 | 10722 | 25.36 | 9395 | 22.22 |
| Neural Tube Defects | 1032 | 158 | 2906 | 4096 | 9.69 | 3872 | 9.16 |
| Anencephalus and similar | 118 | 101 | 1339 | 1558 | 3.68 | 1505 | 3.56 |
| Encephalocele | 138 | 19 | 319 | 476 | 1.13 | 421 | 1 |
| Spina Bifida | 776 | 38 | 1248 | 2062 | 4.88 | 1946 | 4.6 |
| Hydrocephalus | 1415 | 99 | 953 | 2467 | 5.83 | 2153 | 5.09 |
| Microcephaly | 1056 | 52 | 93 | 1201 | 2.85 | 1014 | 2.41 |
| Arhinencephaly/holoprosencephaly | 124 | 28 | 433 | 585 | 1.38 | 369 | 0.87 |
| **Eye** | 1652 | 14 | 94 | 1760 | 4.16 | 1518 | 3.59 |
| Anophthalmos/micropthalmos | 338 | 8 | 61 | 407 | 0.96 | 318 | 0.75 |
| Anophthalmos | 65 | 3 | 24 | 92 | 0.22 | 79 | 0.19 |
| Congenital cataract | 524 | 2 | 1 | 527 | 1.25 | 471 | 1.11 |
| Congenital glaucoma | 154 | 0 | 1 | 155 | 0.37 | 149 | 0.35 |
| **Ear, face and neck** | 734 | 24 | 106 | 864 | 2.04 | 721 | 1.71 |
| Anotia | 112 | 1 | 10 | 123 | 0.29 | 106 | 0.25 |

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| **Congenital heart defects** | 31347 | 493 | 2899 | 34739 | 82.16 | 30393 | 71.88 |
| Severe CHD § | 7955 | 255 | 1644 | 9854 | 23.31 | 8048 | 19.03 |
| Common arterial truncus | 213 | 17 | 87 | 317 | 0.75 | 247 | 0.58 |
| Double outlet right ventricle § | 271 | 13 | 90 | 374 | 1.27 | 323 | 1.1 |
| Transposition of great vessels | 1291 | 13 | 154 | 1458 | 3.45 | 1409 | 3.33 |
| Single ventricle | 215 | 12 | 123 | 350 | 0.83 | 322 | 0.76 |
| Ventricular septal defect | 13852 | 155 | 769 | 14776 | 34.95 | 13114 | 31.02 |
| Atrial septal defect | 9026 | 35 | 202 | 9263 | 21.91 | 8201 | 19.4 |
| Atrioventricular septal defect | 1323 | 75 | 378 | 1776 | 4.2 | 817 | 1.93 |
| Tetralogy of Fallot | 1343 | 27 | 160 | 1530 | 3.62 | 1295 | 3.06 |
| Tricuspid atresia and stenosis | 195 | 11 | 59 | 265 | 0.63 | 248 | 0.59 |
| Ebstein's anomaly | 159 | 12 | 23 | 194 | 0.46 | 187 | 0.44 |
| Pulmonary valve stenosis | 1717 | 5 | 65 | 1787 | 4.23 | 1639 | 3.88 |
| Pulmonary valve atresia | 336 | 6 | 93 | 435 | 1.03 | 395 | 0.93 |
| Aortic valve atresia/stenosis § | 542 | 12 | 60 | 614 | 1.45 | 569 | 1.35 |
| Mitral valve anomalies | 383 | 8 | 54 | 445 | 1.51 | 386 | 1.31 |
| Hypoplastic left heart | 643 | 48 | 474 | 1165 | 2.76 | 1048 | 2.48 |
| Hypoplastic right heart § | 148 | 9 | 74 | 231 | 0.55 | 218 | 0.52 |
| Coarctation of aorta | 1515 | 23 | 75 | 1613 | 3.81 | 1432 | 3.39 |
| Aortic atresia/interrupted aortic arch | 102 | 1 | 29 | 132 | 0.45 | 103 | 0.35 |
| Total anomalous pulm venous return | 264 | 1 | 16 | 281 | 0.66 | 266 | 0.63 |
| PDA as only CHD in term infants (>=37 weeks) | 1593 | 0 | 0 | 1593 | 3.77 | 1446 | 3.42 |
| **Respiratory** | 1425 | 56 | 266 | 1747 | 4.13 | 1585 | 3.75 |
| Choanal atresia | 379 | 8 | 5 | 392 | 0.93 | 340 | 0.8 |
| Cystic adenomatous malf of lung § | 392 | 8 | 45 | 445 | 1.05 | 432 | 1.02 |
| **Oro-facial clefts** | 5431 | 86 | 533 | 6050 | 14.31 | 5376 | 12.71 |
| Cleft lip with or without palate | 3169 | 67 | 381 | 3617 | 8.55 | 3292 | 7.79 |

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| Cleft palate | 2262 | 19 | 152 | 2433 | 5.75 | 2084 | 4.93 |
| **Digestive system** | 6776 | 175 | 935 | 7886 | 18.65 | 7036 | 16.64 |
| Oesophageal atresia with or without tracheo-oesophageal fistula | 991 | 31 | 57 | 1079 | 2.55 | 985 | 2.33 |
| Duodenal atresia or stenosis | 531 | 23 | 37 | 591 | 1.4 | 421 | 1 |
| Atresia or stenosis of other parts of small intestine | 370 | 8 | 9 | 387 | 0.92 | 375 | 0.89 |
| Ano-rectal atresia and stenosis | 1072 | 26 | 254 | 1352 | 3.2 | 1226 | 2.9 |
| Hirschsprung's disease | 546 | 0 | 1 | 547 | 1.29 | 499 | 1.18 |
| Atresia of bile ducts | 128 | 1 | 2 | 131 | 0.31 | 121 | 0.29 |
| Annular pancreas | 64 | 0 | 4 | 68 | 0.16 | 55 | 0.13 |
| Diaphragmatic hernia | 895 | 40 | 253 | 1188 | 2.81 | 1063 | 2.51 |
| **Abdominal wall defects** | 1546 | 128 | 1093 | 2767 | 6.54 | 2233 | 5.28 |
| Gastroschisis | 954 | 44 | 185 | 1183 | 2.8 | 1152 | 2.72 |
| Omphalocele | 503 | 73 | 747 | 1323 | 3.13 | 846 | 2 |
| **Urinary** | 12603 | 231 | 1885 | 14719 | 34.81 | 13823 | 32.69 |
| Bilateral renal agenesis including Potter syndrome | 117 | 35 | 336 | 488 | 1.15 | 464 | 1.1 |
| Multicystic renal dysplasia | 1079 | 31 | 264 | 1374 | 3.25 | 1284 | 3.04 |
| Congenital hydronephrosis | 4213 | 35 | 223 | 4471 | 10.57 | 4261 | 10.08 |
| Bladder exstrophy and/or epispadia | 242 | 2 | 57 | 301 | 0.71 | 289 | 0.68 |
| Posterior urethral valve and/or prune belly | 289 | 7 | 81 | 377 | 0.89 | 368 | 0.87 |
| **Genital** | 9085 | 60 | 315 | 9460 | 22.37 | 9124 | 21.58 |
| Hypospadias | 7622 | 17 | 69 | 7708 | 18.23 | 7561 | 17.88 |
| Indeterminate sex | 197 | 15 | 72 | 284 | 0.67 | 226 | 0.53 |

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| **Limb** | 15482 | 265 | 1609 | 17356 | 41.05 | 16014 | 37.88 |
| Limb reduction defects | 1448 | 66 | 612 | 2126 | 5.03 | 1817 | 4.3 |
| Club foot - talipes equinovarus | 4043 | 92 | 494 | 4629 | 10.95 | 4316 | 10.21 |
| Hip dislocation and/or dysplasia | 3433 | 5 | 8 | 3446 | 8.15 | 3376 | 7.98 |
| Polydactyly | 3475 | 43 | 221 | 3739 | 8.84 | 3438 | 8.13 |
| Syndactyly | 1977 | 28 | 131 | 2136 | 5.05 | 1915 | 4.53 |
| Skeletal dysplasias § | 366 | 19 | 395 | 780 | 1.84 | 0 | 0 |
| Craniosynostosis | 1023 | 14 | 44 | 1081 | 2.56 | 967 | 2.29 |
| Congenital constriction bands/amniotic band | 100 | 28 | 86 | 214 | 0.51 | 205 | 0.48 |
| Situs inversus | 225 | 5 | 58 | 288 | 0.68 | 274 | 0.65 |
| Conjoined twins | 8 | 6 | 64 | 78 | 0.18 | 76 | 0.18 |
| Congenital skin disorders | 794 | 9 | 32 | 835 | 1.97 | 797 | 1.89 |
| VATER/VACTERL | 98 | 2 | 29 | 129 | 0.52 | 126 | 0.51 |
| Vascular disruption anomalies § | 1422 | 66 | 431 | 1919 | 6.91 | 1806 | 6.5 |
| Lateral anomalies § | 403 | 22 | 124 | 549 | 1.86 | 504 | 1.71 |
| Teratogenic syndromes with malformations § | 460 | 28 | 89 | 577 | 1.36 | 558 | 1.32 |
| Fetal alcohol syndrome | 203 | 3 | 7 | 213 | 0.5 | 210 | 0.5 |
| Valproate syndrome § | 16 | 0 | 4 | 20 | 0.05 | 19 | 0.04 |
| Maternal infections resulting in malformations | 200 | 21 | 68 | 289 | 0.68 | 282 | 0.67 |
| Genetic syndromes + microdeletions | 1736 | 46 | 326 | 2108 | 4.99 | 0 | 0 |

| | | | | | | Excluding Genetic Conditions | |
|---|---|---|---|---|---|---|---|
| **Anomaly** | **LB N** | **FD N** | **TOPFA N** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** | **LB+FD+TOPFA N** | **LB+FD+TOPFA Rate** |
| **Chromosomal** | 6546 | 668 | 9422 | 16636 | 39.35 | 0 | 0 |
| Down Syndrome | 4288 | 231 | 5215 | 9734 | 23.02 | 0 | 0 |
| Patau syndrome/trisomy 13 | 157 | 45 | 666 | 868 | 2.05 | 0 | 0 |
| Edward syndrome/trisomy 18 | 344 | 196 | 1753 | 2293 | 5.42 | 0 | 0 |
| Turner syndrome | 259 | 70 | 661 | 990 | 2.34 | 0 | 0 |
| Klinefelter syndrome | 167 | 6 | 122 | 295 | 0.7 | 0 | 0 |

LB = Live Births

FD = Fetal Deaths / Still Births from 20 weeks gestation

TOPFA = Termination of pregnancy for fetal anomaly following prenatal diagnosis

- = Data not available

§ = Incomplete or missing specification of ICD 9 codes

**Source:** EUROCAT Website Database: http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables (data uploaded 06/01/2015)

## 4.3 Prenatal Detection Rates

Prenatal detection rates are available for 18 selected congenital anomaly subgroups (All anomalies, anencephalus and similar, spina bifida, hydrocephalus, transposition of great vessels, hypolplastic left hart, cleft lip with or without palate, diaphragmatic hernia, gastroschisis, omphalocele, bilateral renal agenesis including Potter syndrome, posterior urethral valve and/or prune belly, limb reduction defects, club foot, chromosomal, Down syndrome, Patau syndrome, Edwards syndrome) for the most recent 5 year period.

Only registries with 80% known for the “when discovered” variable and 4 or more years of data in the latest time period are included in the figures. The figures are updated twice yearly.

Interactive graphs and tables are available and the user has a number of choices in the way the data can be displayed, for example by gestation, or by outcome etc. The following tables and graphs are for All anomalies, but the website user can access the same graphic representations for the other 17 CA subgroups listed above.

## EUROCAT Prenatal Detection Rates

**Prenatal diagnosis of 18 selected congenital anomaly subgroups for the following registries: Styria (Austria), Hainaut (Belgium), Zagreb (Croatia), Odense (Denmark), Auvergne (France), French West Indies (France), Isle de la Reunion (France), Paris (France), Mainz (Germany), Saxony-Anhalt (Germany), Hungary, Cork and Kerry (Ireland), SE Ireland, Emilia Romagna (Italy), Tuscany (Italy), Malta, N Netherlands (NL), Norway, S Portugal, Basque Country (Spain), Valencia Region (Spain), Vaud (Switzerland), East Midlands & South Yorkshire (UK), Northern England (UK), Thames Valley (UK), Wales (UK), Wessex (UK), Ukraine, from 2008 - 2012**

| Malformation | Total Cases | Cases Prenatally Diagnosed (% of Total Cases) |
|---|---|---|
| **Non-chromosomal** | | |
| All Anomalies (Excluding genetic conditions) | 79067 | 24520 (31.0%) |
| Anencephalus and similar (Excluding genetic conditions) | 1332 | 1287 (96.6%) |
| Spina Bifida (Excluding genetic conditions) | 1679 | 1385 (82.5%) |
| Hydrocephalus (Excluding genetic conditions) | 1872 | 1374 (73.4%) |
| Transposition of great vessels (Excluding genetic conditions) | 1214 | 544 (44.8%) |
| Hypoplastic left heart (Excluding genetic conditions) | 923 | 681 (73.8%) |
| Cleft lip with or without palate (Excluding genetic conditions) | 2821 | 1485 (52.6%) |
| Diaphragmatic hernia (Excluding genetic conditions) | 931 | 553 (59.4%) |
| Gastroschisis (Excluding genetic conditions) | 972 | 884 (90.9%) |
| Omphalocele (Excluding genetic conditions) | 745 | 622 (83.5%) |
| Bilateral renal agenesis including Potter syndrome (Excluding genetic conditions) | 390 | 348 (89.2%) |
| Posterior urethral valve and/or prune belly (Excluding genetic conditions) | 283 | 223 (78.8%) |
| Limb reduction defects (Excluding genetic conditions) | 1551 | 765 (49.3%) |
| Club foot - talipes equinovarus (Excluding genetic conditions) | 3905 | 1611 (41.3%) |
| **Chromosomal** | | |
| Chromosomal | 14133 | 10150 (71.8%) |
| Down Syndrome | 8289 | 5397 (65.1%) |
| Patau syndrome/trisomy 13 | 737 | 678 (92.0%) |
| Edward syndrome/trisomy 18 | 1972 | 1789 (90.7%) |

## Prenatal Detection Rates - All Anomalies (Excluding genetic conditions)

Proportion of All Anomalies (Excluding genetic conditions) cases prenatally diagnosed, 2008-2012

Back to selection

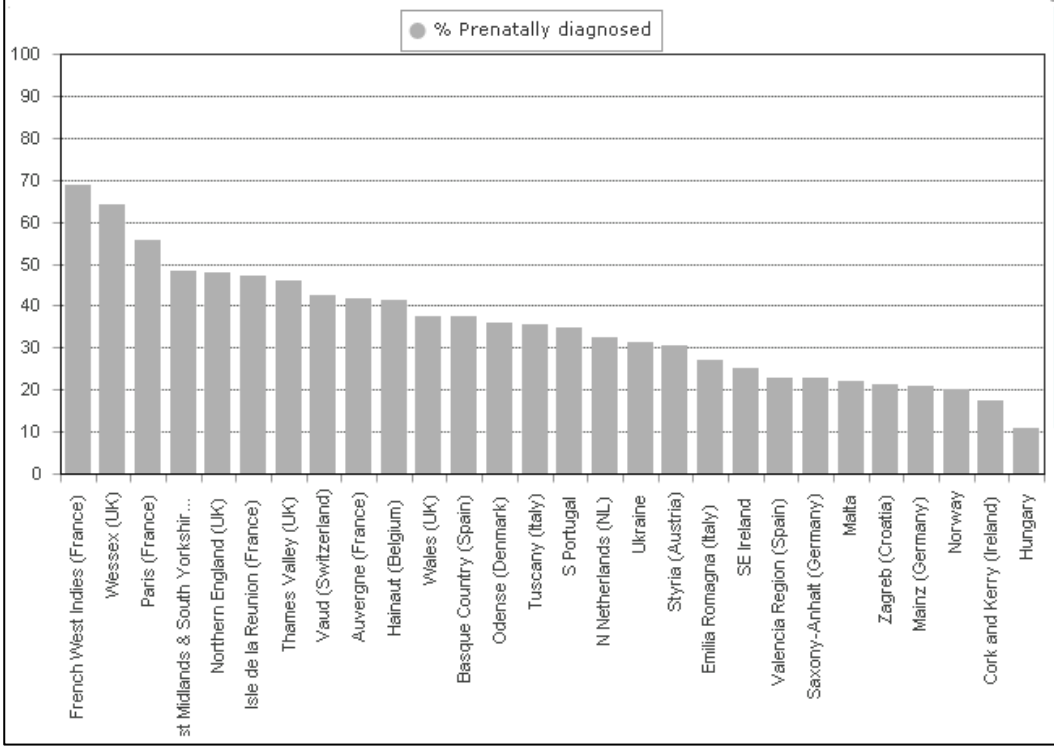
Display

Graph

Table

Show proportions for

All cases




## Prenatal Detection Rates - All Anomalies (Excluding genetic conditions)

Proportion of All Anomalies (Excluding genetic conditions) cases prenatally diagnosed, 2008-2012

Back to selection

Display

Graph

Table

Show proportions for

All cases

| Registry | Total number of cases | Number prenatally diagnosed | Percentage of all cases (95% CI) |
|---|---|---|---|
| French West Indies (France) | 608 | 419 | 68.9 (65.1 - 72.5) |
| Wessex (UK) | 2,200 | 1,413 | 64.2 (62.2 - 66.2) |
| Paris (France) | 3,244 | 1,799 | 55.5 (53.7 - 57.2) |
| East Midlands & South Yorkshire (UK) | 6,269 | 3,023 | 48.2 (47.0 - 49.5) |
| Northern England (UK) | 3,008 | 1,445 | 48.0 (46.3 - 49.8) |
| Isle de la Reunion (France) | 1,735 | 818 | 47.1 (44.8 - 49.5) |
| Thames Valley (UK) | 2,484 | 1,141 | 45.9 (44.0 - 47.9) |
| Vaud (Switzerland) | 1,116 | 475 | 42.6 (39.7 - 45.5) |
| Auvergne (France) | 1,966 | 818 | 41.6 (39.4 - 43.8) |
| Hainaut (Belgium) | 1,179 | 487 | 41.3 (38.5 - 44.1) |
| Wales (UK) | 5,157 | 1,929 | 37.4 (36.1 - 38.7) |
| Basque Country (Spain) | 1,797 | 672 | 37.4 (35.2 - 39.7) |
| Odense (Denmark) | 580 | 208 | 35.9 (32.1 - 39.8) |
| Tuscany (Italy) | 2,579 | 913 | 35.4 (33.6 - 37.3) |
| S Portugal | 778 | 271 | 34.8 (31.6 - 38.2) |
| N Netherlands (NL) | 1,876 | 611 | 32.6 (30.5 - 34.7) |
| Ukraine | 3,624 | 1,135 | 31.3 (29.8 - 32.8) |
| Styria (Austria) | 1,105 | 336 | 30.4 (27.8 - 33.2) |
| Emilia Romagna (Italy) | 3,972 | 1,080 | 27.2 (25.8 - 28.6) |
| SE Ireland | 448 | 112 | 25.0 (21.2 - 29.2) |
| Valencia Region (Spain) | 4,950 | 1,126 | 22.7 (21.6 - 23.9) |
| Saxony-Anhalt (Germany) | 2,419 | 547 | 22.6 (21.0 - 24.3) |
| Malta | 416 | 92 | 22.1 (18.4 - 26.3) |
| Zagreb (Croatia) | 686 | 146 | 21.3 (18.4 - 24.5) |
| Mainz (Germany) | 632 | 132 | 20.9 (17.9 - 24.2) |
| Norway | 7,094 | 1,429 | 20.1 (19.2 - 21.1) |
| Cork and Kerry (Ireland) | 1,044 | 181 | 17.3 (15.2 - 19.8) |
| Hungary | 16,101 | 1,747 | 10.9 (10.4 - 11.3) |
| **Total** | **79,067** | **24,505** | **31.0 (30.7 - 31.3)** |

* = Data suppressed to protect the confidentiality of individuals

## Prenatal Detection Rates - All Anomalies (Excluding genetic conditions)

Proportion of All Anomalies (Excluding genetic conditions) cases prenatally diagnosed by outcome, 2008-2012

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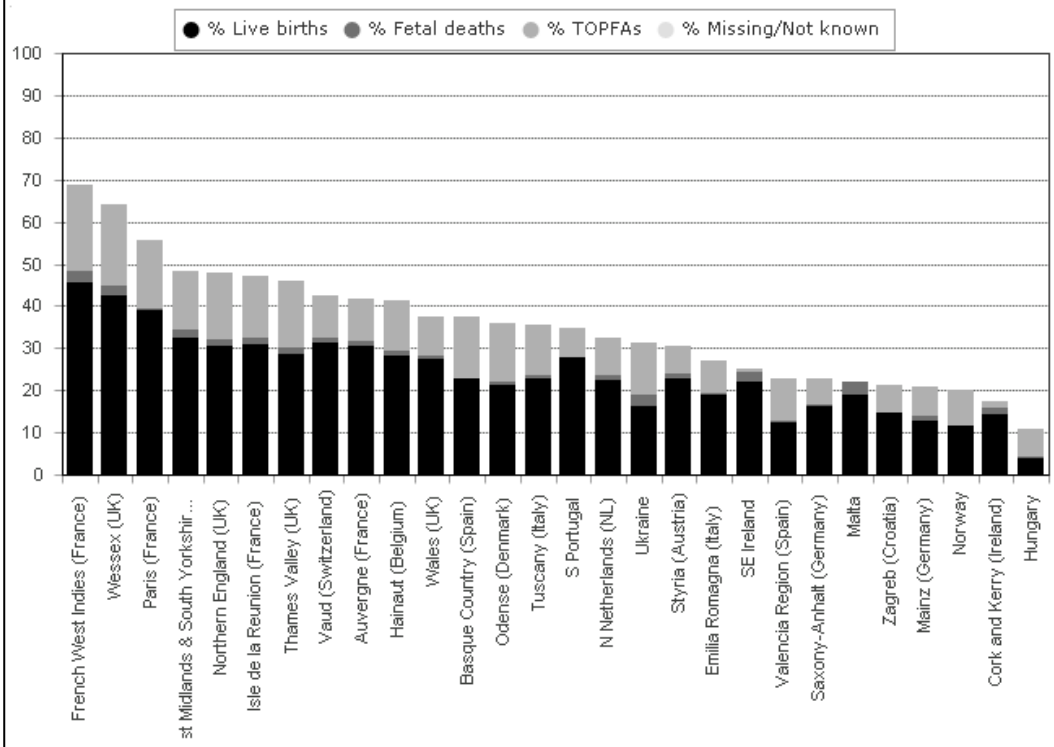



Display

- (•) Graph
- ( ) Table

Show proportions for

- (•) All cases
- ( ) Live births
- ( ) Fetal deaths

The number of cases in this congenital anomaly subgroup is NOT the number of isolated cases. In particular the outcome, such as fetal deaths (FD) or terminations (TOPFA), for seemingly less severe anomalies may have occurred as the case had other more severe major anomalies.

Proportion of All Anomalies (Excluding genetic conditions) cases prenatally diagnosed by outcome, 2008-2012

Back to selection

| | Live births | | Fetal deaths | | TOPFAs | | Missing/Not known | |
|---|---|---|---|---|---|---|---|---|
| Registry | N | % of all cases (95% CI) | N | % of all cases (95% CI) | N | % of all cases (95% CI) | N | % of all cases (95% CI) |
| French West Indies (France) | 278 | 45.7 (41.8 - 49.7) | 15 | 2.5 (1.5 - 4.0) | 126 | 20.7 (17.7 - 24.1) | 0 | 0.0 |
| Wessex (UK) | 937 | 42.6 (40.5 - 44.7) | 45 | 2.0 (1.5 - 2.7) | 431 | 19.6 (18.0 - 21.3) | 0 | 0.0 |
| Paris (France) | 1,264 | 39.0 (37.3 - 40.7) | 19 | 0.6 (0.4 - 0.9) | 516 | 15.9 (14.7 - 17.2) | 0 | 0.0 |
| East Midlands & South Yorkshire (UK) | 2,036 | 32.5 (31.3 - 33.6) | 108 | 1.7 (1.4 - 2.1) | 879 | 14.0 (13.2 - 14.9) | 0 | 0.0 |
| Northern England (UK) | 922 | 30.7 (29.0 - 32.3) | 46 | 1.5 (1.1 - 2.0) | 477 | 15.9 (14.6 - 17.2) | 0 | 0.0 |
| Isle de la Reunion (France) | 537 | 31.0 (28.8 - 33.2) | 27 | 1.6 (1.1 - 2.3) | 254 | 14.6 (13.1 - 16.4) | 0 | 0.0 |
| Thames Valley (UK) | 710 | 28.6 (26.8 - 30.4) | 42 | 1.7 (1.3 - 2.3) | 389 | 15.7 (14.3 - 17.1) | 0 | 0.0 |
| Vaud (Switzerland) | 350 | 31.4 (28.7 - 34.1) | 12 | 1.1 (0.6 - 1.9) | 113 | 10.1 (8.5 - 12.0) | 0 | 0.0 |
| Auvergne (France) | 600 | 30.5 (28.5 - 32.6) | 20 | 1.0 (0.7 - 1.6) | 198 | 10.1 (8.8 - 11.5) | 0 | 0.0 |
| Hainaut (Belgium) | 332 | 28.2 (25.7 - 30.8) | 12 | 1.0 (0.6 - 1.8) | 143 | 12.1 (10.4 - 14.1) | 0 | 0.0 |
| Wales (UK) | 1,411 | 27.4 (26.2 - 28.6) | 44 | 0.9 (0.6 - 1.1) | 474 | 9.2 (8.4 - 10.0) | 0 | 0.0 |
| Basque Country (Spain) | 408 | 22.7 (20.8 - 24.7) | * | * | 260 | 14.5 (12.9 - 16.2) | * | * |
| Odense (Denmark) | 124 | 21.4 (18.2 - 24.9) | * | * | 81 | 14.0 (11.4 - 17.0) | * | * |
| Tuscany (Italy) | 588 | 22.8 (21.2 - 24.5) | 23 | 0.9 (0.6 - 1.3) | 302 | 11.7 (10.5 - 13.0) | 0 | 0.0 |
| S Portugal | 215 | 27.6 (24.6 - 30.9) | * | * | 55 | 7.1 (5.5 - 9.1) | * | * |
| N Netherlands (NL) | 421 | 22.4 (20.6 - 24.4) | 23 | 1.2 (0.8 - 1.8) | 167 | 8.9 (7.7 - 10.3) | 0 | 0.0 |
| Ukraine | 594 | 16.4 (15.2 - 17.6) | 87 | 2.4 (2.0 - 3.0) | 454 | 12.5 (11.5 - 13.6) | 0 | 0.0 |
| Styria (Austria) | 252 | 22.8 (20.4 - 25.4) | 12 | 1.1 (0.6 - 1.9) | 72 | 6.5 (5.2 - 8.1) | 0 | 0.0 |
| Emilia Romagna (Italy) | 755 | 19.0 (17.8 - 20.3) | 5 | 0.1 (0.1 - 0.3) | 320 | 8.1 (7.2 - 8.9) | 0 | 0.0 |
| SE Ireland | 98 | 21.9 (18.3 - 25.9) | 11 | 2.5 (1.4 - 4.3) | * | * | * | * |
| Valencia Region (Spain) | 609 | 12.3 (11.4 - 13.2) | 17 | 0.3 (0.2 - 0.5) | 500 | 10.1 (9.3 - 11.0) | 0 | 0.0 |
| Saxony-Anhalt (Germany) | 395 | 16.3 (14.9 - 17.9) | 11 | 0.5 (0.3 - 0.8) | 141 | 5.8 (5.0 - 6.8) | 0 | 0.0 |
| Malta | 79 | 19.0 (15.5 - 23.0) | 13 | 3.1 (1.8 - 5.3) | 0 | 0.0 | 0 | 0.0 |
| Zagreb (Croatia) | 100 | 14.6 (12.1 - 17.4) | * | * | 45 | 6.6 (4.9 - 8.7) | * | * |
| Mainz (Germany) | 80 | 12.7 (10.3 - 15.5) | 8 | 1.3 (0.6 - 2.5) | 44 | 7.0 (5.2 - 9.2) | 0 | 0.0 |
| Norway | 809 | 11.4 (10.7 - 12.2) | 0 | 0.0 | 620 | 8.7 (8.1 - 9.4) | 0 | 0.0 |
| Cork and Kerry (Ireland) | 148 | 14.2 (12.2 - 16.4) | 18 | 1.7 (1.1 - 2.7) | 15 | 1.4 (0.9 - 2.4) | 0 | 0.0 |
| Hungary | 645 | 4.0 (3.7 - 4.3) | 9 | 0.1 (0.0 - 0.1) | 1,093 | 6.8 (6.4 - 7.2) | 0 | 0.0 |
| **Total** | **15,697** | **19.9 (19.6 - 20.1)** | **636** | **0.8 (0.7 - 0.9)** | * | * | * | * |

Display

- ( ) Graph
- (•) Table

Show proportions for

- (•) All cases
- ( ) Live births
- ( ) Fetal deaths

* = Data suppressed to protect the confidentiality of individuals

The number of cases in this congenital anomaly subgroup is NOT the number of isolated cases. In particular the outcome, such as fetal deaths (FD) or terminations (TOPFA), for seemingly less severe anomalies may have occurred as the case had other more severe major anomalies.

## Prenatal Detection Rates - All Anomalies (Excluding genetic conditions)

Proportion of All Anomalies (Excluding genetic conditions) cases prenatally diagnosed by gestation at diagnosis, 2008-2012

Back to selection

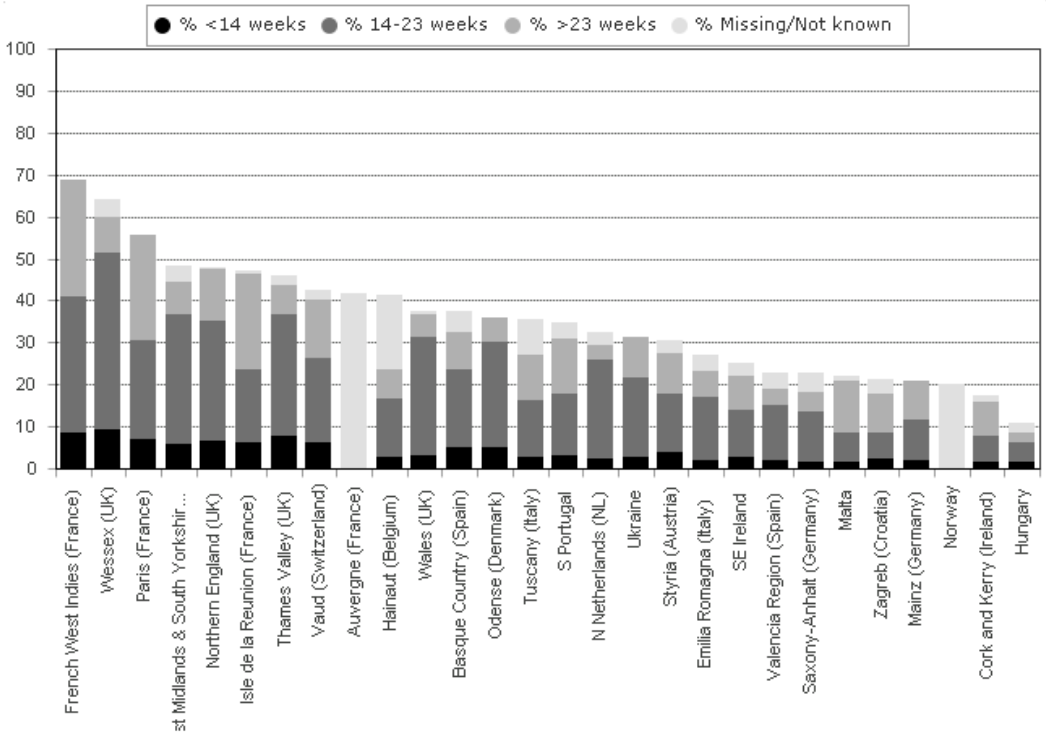
Display

Graph

Table

Show proportions for

All cases




Prenatal diagnosis is common in live births and only some of the cases diagnosed prenatally will be TOPFAs

Proportion of All Anomalies (Excluding genetic conditions) cases prenatally diagnosed by gestation at diagnosis, 2008-2012

Back to selection

Display

Graph

Table

Show proportions for

All cases

| Registry | <14 weeks N | <14 weeks % of all cases (95% CI) | 14-23 weeks N | 14-23 weeks % of all cases (95% CI) | >23 weeks N | >23 weeks % of all cases (95% CI) | Missing/Not known N | Missing/Not known % of all cases (95% CI) |
|---|---|---|---|---|---|---|---|---|
| French West Indies (France) | * | * | 198 | 32.6 (29.0 - 36.4) | 167 | 27.5 (24.1 - 31.1) | * | * |
| Wessex (UK) | 202 | 9.2 (8.0 - 10.5) | 928 | 42.2 (40.1 - 44.3) | 184 | 8.4 (7.3 - 9.6) | 99 | 4.5 (3.7 - 5.4) |
| Paris (France) | 229 | 7.1 (6.2 - 8.0) | 756 | 23.3 (21.9 - 24.8) | 814 | 25.1 (23.6 - 26.6) | 0 | 0.0 |
| East Midlands & South Yorkshire (UK) | 365 | 5.8 (5.3 - 6.4) | 1,926 | 30.7 (29.6 - 31.9) | 483 | 7.7 (7.1 - 8.4) | 249 | 4.0 (3.5 - 4.5) |
| Northern England (UK) | 203 | 6.7 (5.9 - 7.7) | 858 | 28.5 (26.9 - 30.2) | 368 | 12.2 (11.1 - 13.5) | 16 | 0.5 (0.3 - 0.9) |
| Isle de la Reunion (France) | 109 | 6.3 (5.2 - 7.5) | 298 | 17.2 (15.5 - 19.0) | 400 | 23.1 (21.1 - 25.1) | 11 | 0.6 (0.4 - 1.1) |
| Thames Valley (UK) | 192 | 7.7 (6.7 - 8.8) | 723 | 29.1 (27.4 - 30.9) | 170 | 6.8 (5.9 - 7.9) | 56 | 2.3 (1.7 - 2.9) |
| Vaud (Switzerland) | 71 | 6.4 (5.1 - 7.9) | 220 | 19.7 (17.5 - 22.1) | 155 | 13.9 (12.0 - 16.0) | 29 | 2.6 (1.8 - 3.7) |
| Auvergne (France) | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 818 | 41.6 (39.4 - 43.8) |
| Hainaut (Belgium) | 32 | 2.7 (1.9 - 3.8) | 163 | 13.8 (12.0 - 15.9) | 81 | 6.9 (5.6 - 8.5) | 211 | 17.9 (15.8 - 20.2) |
| Wales (UK) | 168 | 3.3 (2.8 - 3.8) | 1,436 | 27.8 (26.6 - 29.1) | 286 | 5.5 (5.0 - 6.2) | 39 | 0.8 (0.6 - 1.0) |
| Basque Country (Spain) | 91 | 5.1 (4.1 - 6.2) | 335 | 18.6 (16.9 - 20.5) | 154 | 8.6 (7.4 - 10.0) | 92 | 5.1 (4.2 - 6.2) |
| Odense (Denmark) | 30 | 5.2 (3.6 - 7.3) | 145 | 25.0 (21.6 - 28.7) | 33 | 5.7 (4.1 - 7.9) | 0 | 0.0 |
| Tuscany (Italy) | 74 | 2.9 (2.3 - 3.6) | 346 | 13.4 (12.2 - 14.8) | 278 | 10.8 (9.6 - 12.0) | 215 | 8.3 (7.3 - 9.5) |
| S Portugal | 25 | 3.2 (2.2 - 4.7) | 112 | 14.4 (12.1 - 17.0) | 102 | 13.1 (10.9 - 15.7) | 32 | 4.1 (2.9 - 5.7) |
| N Netherlands (NL) | 43 | 2.3 (1.7 - 3.1) | 440 | 23.5 (21.6 - 25.4) | 66 | 3.5 (2.8 - 4.5) | 62 | 3.3 (2.6 - 4.2) |
| Ukraine | 104 | 2.9 (2.4 - 3.5) | 675 | 18.6 (17.4 - 19.9) | 348 | 9.6 (8.7 - 10.6) | 8 | 0.2 (0.1 - 0.4) |
| Styria (Austria) | 41 | 3.7 (2.7 - 5.0) | 155 | 14.0 (12.1 - 16.2) | 107 | 9.7 (8.1 - 11.6) | 33 | 3.0 (2.1 - 4.2) |
| Emilia Romagna (Italy) | 83 | 2.1 (1.7 - 2.6) | 587 | 14.8 (13.7 - 15.9) | 251 | 6.3 (5.6 - 7.1) | 159 | 4.0 (3.4 - 4.7) |
| SE Ireland | 12 | 2.7 (1.5 - 4.6) | 51 | 11.4 (8.8 - 14.7) | 36 | 8.0 (5.9 - 10.9) | 13 | 2.9 (1.7 - 4.9) |
| Valencia Region (Spain) | 93 | 1.9 (1.5 - 2.3) | 643 | 13.0 (12.1 - 14.0) | 206 | 4.2 (3.6 - 4.8) | 184 | 3.7 (3.2 - 4.3) |
| Saxony-Anhalt (Germany) | 41 | 1.7 (1.3 - 2.3) | 285 | 11.8 (10.6 - 13.1) | 111 | 4.6 (3.8 - 5.5) | 110 | 4.5 (3.8 - 5.5) |
| Malta | 7 | 1.7 (0.8 - 3.4) | 29 | 7.0 (4.9 - 9.8) | 50 | 12.0 (9.2 - 15.5) | 6 | 1.4 (0.7 - 3.1) |
| Zagreb (Croatia) | 15 | 2.2 (1.3 - 3.6) | 44 | 6.4 (4.8 - 8.5) | 62 | 9.0 (7.1 - 11.4) | 25 | 3.6 (2.5 - 5.3) |
| Mainz (Germany) | * | * | 62 | 9.8 (7.7 - 12.4) | 58 | 9.2 (7.2 - 11.7) | * | * |
| Norway | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1,429 | 20.1 (19.2 - 21.1) |
| Cork and Kerry (Ireland) | 15 | 1.4 (0.9 - 2.4) | 67 | 6.4 (5.1 - 8.1) | 84 | 8.0 (6.5 - 9.9) | 15 | 1.4 (0.9 - 2.4) |
| Hungary | 233 | 1.4 (1.3 - 1.6) | 743 | 4.6 (4.3 - 4.9) | 408 | 2.5 (2.3 - 2.8) | 363 | 2.3 (2.0 - 2.5) |
| **Total** | **2,541** | **3.2 (3.1 - 3.3)** | **12,225** | **15.5 (15.2 - 15.7)** | **5,462** | **6.9 (6.7 - 7.1)** | **4,277** | **5.4 (5.3 - 5.6)** |

* = Data suppressed to protect the confidentiality of individuals

Prenatal diagnosis is common in live births and only some of the cases diagnosed prenatally will be TOPFAs

## 4.4 Perinatal Mortality

Information on perinatal mortality due to congenital anomaly is available for the most recent 5 year period and is updated twice yearly.
Only full member registries with good recording of the variable 'survival' are included in the analyses.
CA subgroups that contribute either to >=5% of all fetal deaths, or >=5% of all early neonatal deaths are included. The current CA subgroups matching these selection criteria are:

- All anomalies
- All anomalies (excluding chromosomal anomalies)
- Nervous system
- NTDs
- Anencephalus and similar
- Congenital heart defects
- Severe CHD
- Ventricular septal defect
- Hypoplastic left heart
- Respiratory
- Digestive system
- Diaphragmatic hernia
- Urinary
- Limb
- Chromosomal
- Down syndrome
- Edwards syndrome

Three tables of information are provided: perinatal mortality by type of anomaly subgroup; fetal death, early neonatal death & perinatal mortality per country; and rates of TOPFA and rates of perinatal deaths by country. These tables can be seen below:

**Perinatal Mortality Associated with Congenital Anomalies in EUROCAT Full Member Registries (n=29^), 2008-2012, by Type of Anomaly**

| Description** | Breakdown by anomaly subgroup (as a % of all FDs) | Breakdown by anomaly subgroup (as a % of all Early Neonatal Deaths) | Prevalence of FD per 1,000 births | Prevalence of Early Neonatal Deaths per 1,000 births | *Perinatal Mortality per 1,000 births |
|---|---|---|---|---|---|
| All Anomalies | 100 | 100 | 0.45 | 0.47 | 0.92 |
| | | | | | |
| All Anomalies Excluding Chromosomal Anomalies | 66.9 | 85.0 | 0.30 | 0.40 | 0.70 |
| Nervous system | 18.3 | 15.6 | 0.08 | 0.07 | 0.16 |
| Neural Tube Defects | 7.9 | 7.2 | 0.04 | 0.03 | 0.07 |
| Anencephalus and similar | 5.4 | 4.8 | 0.02 | 0.02 | 0.05 |
| Congenital heart defects | 16.6 | 30.6 | 0.07 | 0.14 | 0.22 |
| Severe CHD § | 8.2 | 17.4 | 0.04 | 0.08 | 0.12 |
| Ventricular septal defect | 4.6 | 7.7 | 0.02 | 0.04 | 0.06 |
| Hypoplastic left heart | 2.0 | 6.6 | 0.01 | 0.03 | 0.04 |
| Respiratory | 5.4 | 13.0 | 0.02 | 0.06 | 0.09 |
| Digestive system | 6.6 | 16.5 | 0.03 | 0.08 | 0.11 |
| Diaphragmatic hernia | 1.8 | 8.5 | 0.01 | 0.04 | 0.05 |
| Urinary | 10.1 | 18.3 | 0.05 | 0.09 | 0.13 |
| Limb | 10.2 | 9.5 | 0.05 | 0.04 | 0.09 |
| | | | | | |
| Chromosomal | 33.1 | 15.0 | 0.15 | 0.07 | 0.22 |
| Down Syndrome | 11.1 | 2.6 | 0.05 | 0.01 | 0.06 |
| Edward syndrome/trisomy 18 | 10.4 | 5.8 | 0.05 | 0.03 | 0.07 |

FD=Fetal deaths from 20 weeks; early neonatal deaths=liveborns that died within the 1st week

*Perinatal mortality is sum of FD + early neonatal deaths. All figures rounded to 2 decimal places.

^ Antwerp, Basque Country, Cork & Kerry, Dublin, E Mid & S York, Emilia Romagna, French West Indies, Hainaut, Hungary, Isle de la Reunion, Mainz, Malta, N England, N Netherlands, Norway, Odense, Paris, Saxony Anhalt, SE Ireland, S Portugal, Styria, Thames Valley, Tuscany, Ukraine, Valencia Region, Vaud, Wales, Wessex, Zagreb

**Only subgroups contributing to at least 5% of early neonatal deaths or FD are shown

**Fetal Death, Early Neonatal Death & Perinatal Mortality Associated with Congenital Anomalies per Country, 2008-2012, EUROCAT Full Member Registries (n=29)**

| Country | Prevalence of FD per 1,000 births | Prevalence of Early Neonatal Deaths per 1,000 births | *Perinatal Mortality per 1,000 births |
|---|---|---|---|
| Austria (Styria) | 0.41 | 0.41 | 0.81 |
| Belgium (Antwerp, Hainaut) | 0.36 | 0.55 | 0.90 |
| Croatia (Zagreb) | 0.07 | 0.39 | 0.47 |
| Denmark (Odense) | 0.44 | 0.20 | 0.64 |
| France (Paris, Isle de Reunion, French West Indies) | 0.55 | 0.65 | 1.20 |
| Germany (Saxony Anhalt, Mainz) | 0.75 | 0.24 | 1.00 |
| Hungary (Hungary) | 0.09 | 0.50 | 0.59 |
| Ireland (Dublin, SE Ireland, Cork and Kerry) | 1.09 | 1.07 | 2.16 |
| Italy (Tuscany, Emilia Romagna) | 0.15 | 0.16 | 0.31 |
| Malta (Malta) | 1.19 | 1.95 | 3.14 |
| Netherlands (N Netherlands) | 0.59 | 0.45 | 1.04 |
| Norway (Norway) | 0.35 | 0.38 | 0.74 |
| Portugal (S Portugal) | 0.11 | 0.20 | 0.31 |
| Spain (Basque Country, Valencia Region) | 0.17 | 0.31 | 0.48 |
| Switzerland (Vaud) | 0.52 | 0.35 | 0.87 |
| Ukraine (Ukraine) | 0.69 | 0.83 | 1.52 |
| UK (N England, Thames Valley, E Mid & S York, Wales, Wessex) | 0.65 | 0.44 | 1.09 |
| EUROCAT total | 0.45 | 0.47 | 0.92 |

FD=Fetal deaths from 20 weeks; early neonatal deaths=liveborns that died within the 1st week

*Perinatal mortality is sum of FD + early neonatal deaths. All figures rounded to 2 decimal places.

**Rate of Terminations of Pregnancy for Fetal Anomaly Following Prenatal Diagnosis (TOPFA) and Rates of Perinatal Deaths per 1,000 Births by Country, 2008-2012, EUROCAT Full Member Registries (n=29)**

| Country | Prevalence TOPFA <20 Weeks per 1,000 Births | Prevalence TOPFA 20+ Weeks per 1,000 Births | Total Prevalence TOPFA per 1,000 Births | *Perinatal Mortality per 1,000 births | ^Perinatal Mortality + TOPFA per 1,000 births |
|---|---|---|---|---|---|
| Austria (Styria) | 2.79 | 1.01 | 3.82 | 0.81 | 4.63 |
| Belgium (Antwerp, Hainaut) | 2.39 | 1.30 | 3.96 | 0.90 | 4.86 |
| Croatia (Zagreb) | 1.28 | 0.52 | 1.82 | 0.47 | 2.28 |
| Denmark (Odense) | 4.78 | 2.07 | 6.85 | 0.64 | 7.49 |
| France (Paris, Isle de Reunion, French West Indies) | 4.87 | 3.81 | 8.69 | 1.20 | 9.89 |
| Germany (Saxony Anhalt, Mainz) | 2.66 | 1.33 | 4.02 | 1.00 | 5.02 |
| Hungary (Hungary) | 2.52 | 1.39 | 4.25 | 0.59 | 4.84 |
| Ireland (Dublin, SE Ireland, Cork and Kerry) | 0.02 | 0.03 | 0.18 | 2.16 | 2.34 |
| Italy (Tuscany, Emilia Romagna) | 2.97 | 1.31 | 4.40 | 0.31 | 4.71 |
| Malta (Malta) | 0.00 | 0.00 | 0.00 | 3.14 | 3.14 |
| Netherlands (N Netherlands) | 2.15 | 2.16 | 4.35 | 1.04 | 5.39 |
| Norway (Norway) | 1.92 | 1.06 | 3.82 | 0.74 | 4.56 |
| Portugal (S Portugal) | 0.68 | 0.36 | 1.15 | 0.31 | 1.46 |
| Spain (Basque Country, Valencia Region) | 3.20 | 1.95 | 5.23 | 0.48 | 5.71 |
| Switzerland (Vaud) | 5.72 | 2.10 | 7.82 | 0.87 | 8.69 |
| Ukraine (Ukraine) | 1.42 | 1.97 | 3.41 | 1.52 | 4.93 |
| UK (N England, Thames Valley, E Mid & S York, Wales, Wessex) | 3.24 | 2.00 | 5.28 | 1.09 | 6.37 |
| EUROCAT total | 2.70 | 1.65 | 4.52 | 0.92 | 5.44 |

*Perinatal mortality is sum of FD + early neonatal deaths.

^Perinatal mortality+TOPFA is sum of previous 2 columns. All figures rounded to 2 decimal places.

## 4.5 Prevalence of selected monogenic syndromes in Europe

Data were extracted from the EUROCAT central database in November 2014:
The list includes syndromes with a specified ICD10/BPA code and with more than five cases reported from the 16 registries
Criteria for inclusion of registries: Data quality indicators[1] for genetic syndrome prevalence minimum 5.0 per 10, 000 births (EUROCAT average) and use of ICD10/BPA extended codes minimum 5 per 10,000 births
16 EUROCAT registries[2]
Years of birth: 2005-2012
Total number of births covered 2 401 473
Total prevalence is shown, including livebirths, fetal deaths from 20 weeks of gestation and terminations of pregnancy for fetal anomaly

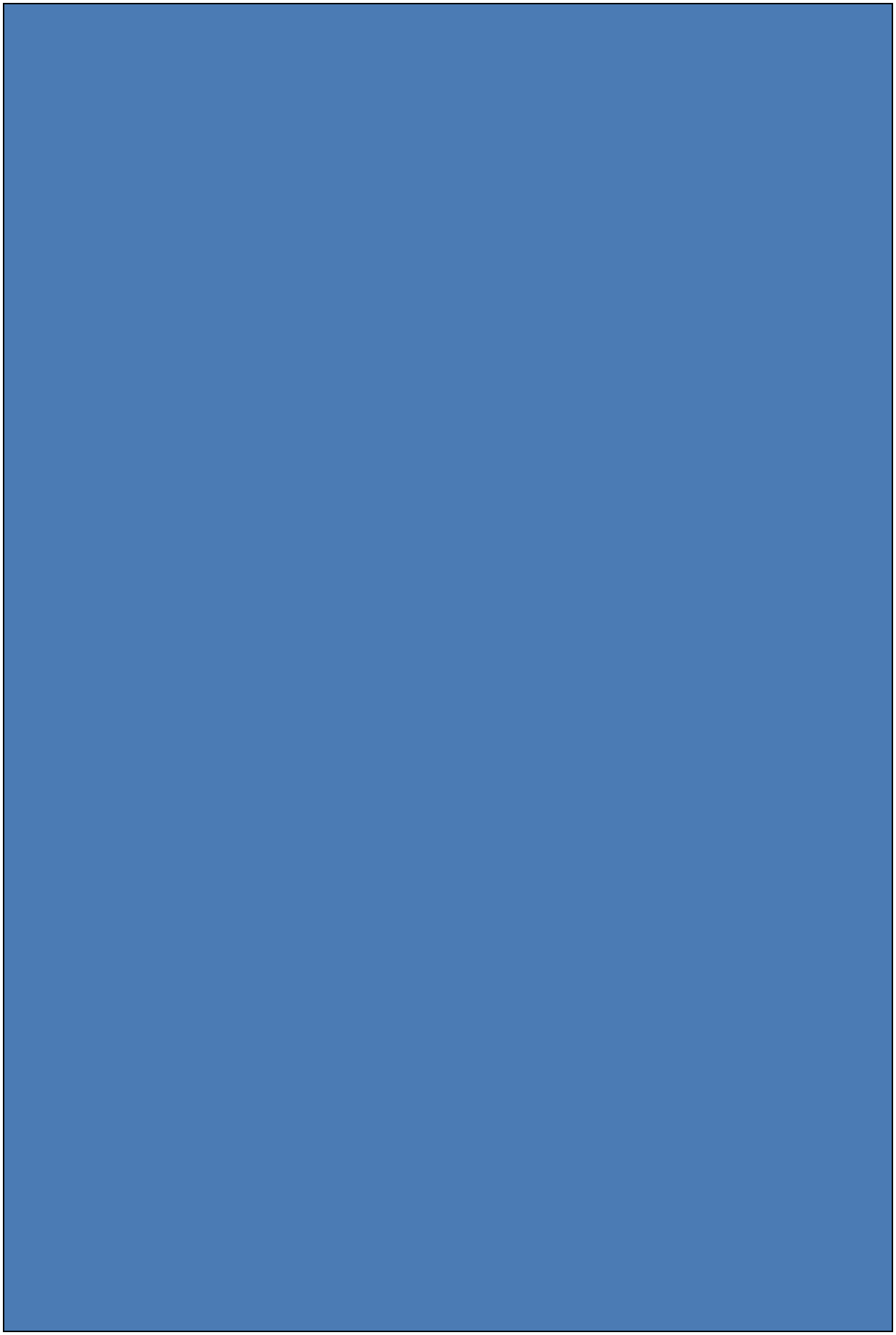
The prevalences are minimum values, as there may be some under-reporting due to coding problems at local level. Furthermore, EUROCAT mainly registers cases of congenital anomalies diagnosed prenatally or in infancy. For some of the monogenic syndromes listed here, cases may be diagnosed later in life and therefore not included in the EUROCAT prevalence.

| Genetic syndromes | ICD10-BPA | Number of cases | Prevalence per 10,000 births |
|---|---|---|---|
| Aarskog syndrome | Q8710 | 11 | 0.05 |
| Acrocephalopolysyndactyly (all types) | Q8700 | 5 | 0.02 |
| Alagille syndrome | Q4471 | 20 | 0.08 |
| Angelman syndrome | Q8785 | 32 | 0.13 |
| Apert's syndrome (acrocephalosyndactyly type I and II) | Q8701 | 34 | 0.14 |
| Bardet-Biedl syndrome | Q8781 | 12 | 0.05 |
| Beckwith-Wiedemann syndrome (EMG syndrome) | Q8730 | 83 | 0.35 |
| Cleidocranial dysplasia | Q7402 | 10 | 0.04 |
| Cockayne's syndrome | Q8711 | 5 | 0.02 |
| Cornelia de Lange syndrome (de Lange syndrome) | Q8712 | 31 | 0.13 |
| Crouzon's disease (craniofacial dysostosis type I) | Q751 | 21 | 0.09 |
| Di George syndrome | D821 | 231 | 0.96 |
| Ehlers-Danlos syndrome | Q796 | 22 | 0.09 |
| Fragile X syndrome | Q992 | 57 | 0.24 |
| Frontonasal dysplaisa | Q7581 | 17 | 0.07 |
| Holt-Oram syndrome (heart-hand syndrome) | Q8720 | 11 | 0.05 |
| Incontinentia pigmenti | Q823 | 29 | 0.12 |
| Kartageners' syndrome | Q8934 | 7 | 0.03 |
| Klippel-Feil syndrome | Q761 | 10 | 0.04 |

| Genetic syndromes | ICD10-BPA | Number of cases | Prevalence per 10,000 births |
|---|---|---|---|
| Klippel-Trenaunay (-Weber) syndrome (angioosteohypertrophy) | Q8721 | 13 | 0.05 |
| Larsen's syndrome | Q7484 | 9 | 0.04 |
| Meckel Gruber | Q6190 | 55 | 0.23 |
| Nail patella syndrome (onychoosteodysplasia) | Q8722 | 5 | 0.02 |
| Noonan's syndrome | Q8714 | 95 | 0.40 |
| Oro-facial-digital syndrome (all types inc. Papillon-Leage and Psaume) | Q8707 | 5 | 0.02 |
| Pena-Shokeir syndrome (fetal akinesia) | Q870E | 35 | 0.15 |
| Prader-Willi syndrome | Q8715 | 75 | 0.31 |
| Rubinstein-Taybi syndrome | Q8723 | 17 | 0.07 |
| Russell-Silver syndrome/Silver's syndrome | Q8717 | 16 | 0.07 |
| Seckel's syndrome | Q8718 | 5 | 0.02 |
| Smith-Lemli-Opitz syndrome | Q8719 | 25 | 0.10 |
| Sotos syndrome | Q8731 | 13 | 0.05 |
| Stickler syndrome | Q8709 | 23 | 0.10 |
| TAR syndrome | Q8725 | 11 | 0.05 |
| Williams | Q8784 | 78 | 0.32 |
| | | | |
| **Skeletal dysplasias** | | | |
| Albers-Schonberg syndrome (osteopetrosis) | Q782 | 5 | 0.02 |
| Diastrophic dysplasia | Q775 | 8 | 0.03 |
| Ellis-van Creveld syndrome | Q776 | 10 | 0.04 |
| Jeune’s syndrome (asphyxiating thoracic dystrophy) | Q772 | 33 | 0.14 |
| Metatropic dwarfism | Q7780 | 6 | 0.02 |
| Osteogenesis imperfecta Type II (neonatal lethal form) | Q7800 | 96 | 0.40 |
| | | | |
| **Associations and other developmental anomalies** | | | |
| Goldenhar | Q8704 | 70 | 0.29 |
| Poland's anomaly (syndrome) | Q7982 | 35 | 0.15 |
| Sturge-Weber syndrome | Q8581 | 19 | 0.08 |
| VATER | Q8726 | 153 | 0.64 |

[1] http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators

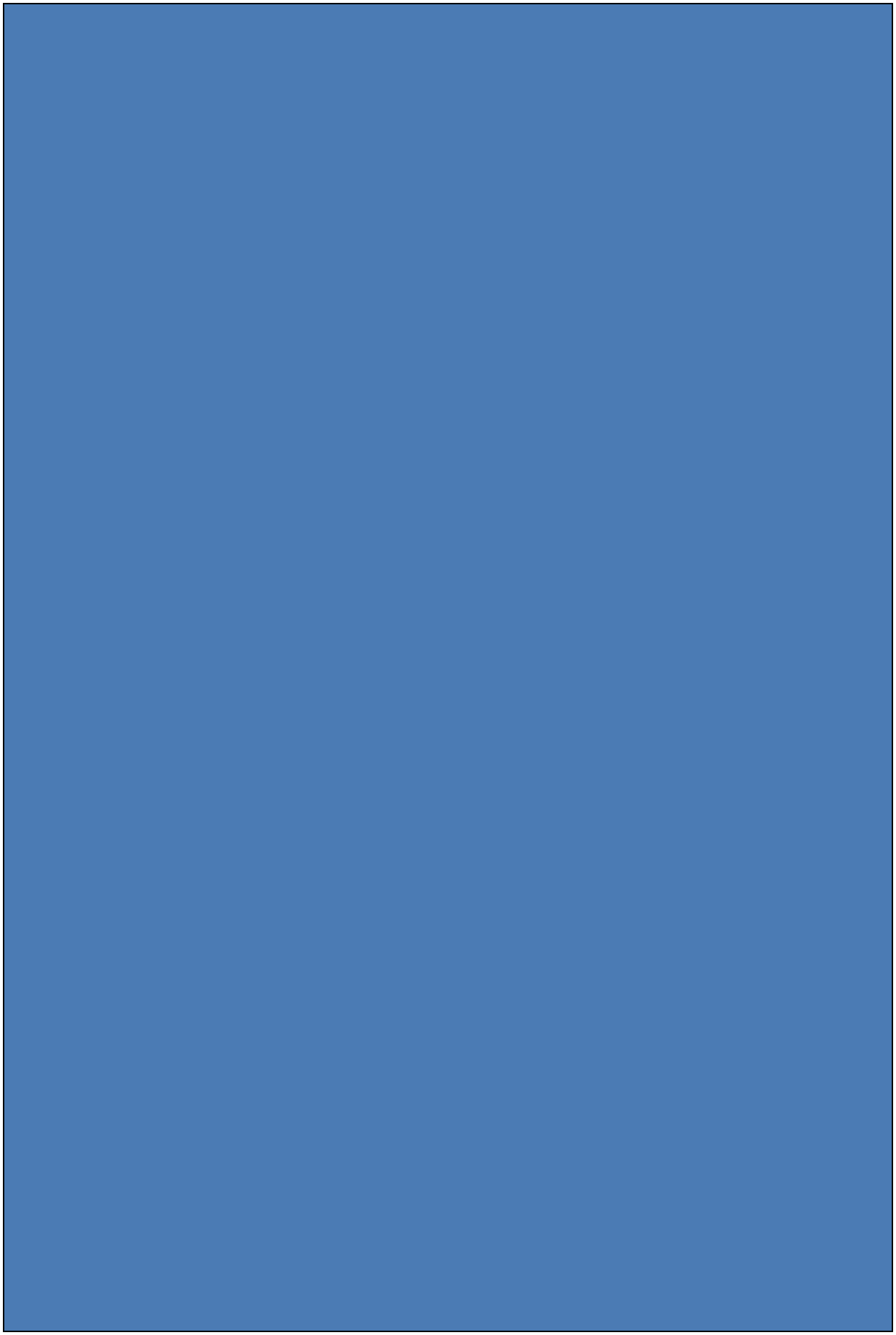
[2] (name of the 16 registries)
Antwerp (BE), Cork & Kerry (IE), French West Indies (FR), Isle de la Reunion (FR), ), Mainz (DE), Malta (MT), N England (GB), N Netherlands (NL), Odense (DK), Paris (FR), SE Ireland (IE), SW England (GB), Thames Valley (GB), Vaud (CH), Wales (GB), Wessex (GB).



# 5. European Centre for Disease Prevention and Control: Congenital Rubella Syndrome in Europe

Summary

Rubella and congenital rubella are diseases due for elimination from the European region by 2015. Congenital rubella is among the 52 diseases and health issues under surveillance in the EU covered by a Commission Decision for epidemiological surveillance (Commission Decision No 2119/98/EC). Cases of rubella infections in pregnant women are currently reported to the European Centre for Disease Control (ECDC) through the rubella case-based monthly reporting scheme. However, reporting of the outcome of pregnancy and potential complications to the newborn is not actively followed-up by ECDC. The reporting of CRS data from EU Member States to WHO-EURO is established and operational through the annual WHO/UNICEF Joint Reporting Form. ECDC would like to further support EU Member States in their attempt to identify CRS cases and estimate the prevalence of CRS. Data on CRS cases is registered by the EUROCAT network and this source of information could constitute an additional source of data in the EU to document the burden of CRS. A study was therefore performed which covered the CRS cases {livebirths, stillbirths or terminations of pregnancy following prenatal diagnosis (TOPFA)} reported to EUROCAT with a date of delivery during the period 2000 to 2012. In the period 2000 to 2012, 19 cases classified by EUROCAT registry leaders as Congenital Rubella Syndrome were reported from 9 registries out of 34 registries participating in the study. Seventeen cases were livebirths, the others TOPFA. EUROCAT registries reported some cases that were not known to national authorities, but a complete comparison was not possible. Thirteen cases were born to mothers who had a previous pregnancy, suggesting that an opportunity to establish non-immune status during care of the mother for her previous pregnancy had been lost, and possibly reflecting the increased risk of contracting rubella by contact with small children. The report recommends better links between EUROCAT registries and national authorities responsible for CRS surveillance. The Full Report will be made available early in 2015 pending ECDC approval, and a draft paper for publication is in preparation.



## 6. Current Projects and Papers

| | Name of Project | Key Contact | Number of Participating Registries |
|---|---|---|---|
| Data Analysis | Hierarchical models in the analysis of congenital anomaly data | Joan Morris (j.k.morris@qmul.ac.uk) | 18 |
| | Association between maternal use of antibiotics in the first trimester and risk of congenital anomaly | Aminkeng Z Leke(Leke-a@email.ulster.ac.uk) | 17 |
| | A European case-malformed control study of Gastroschisis with special emphasis on medication exposure | Given, Joanne (Given-J@email.ulster.ac.uk) | 18 |
| | Neuraminidase Inhibitors | Luteijn, Johannes <jm.luteijn@ulster.ac.uk> | 8 |
| | The epidemiology of Tetralogy of Fallot with special emphasis on medication exposure | Breidge Boyle (b.boyle1@ulster.ac.uk) | 20 |
| | Perinatal mortality burden associated with congenital anomalies, an European perspective with special emphasis on the Dutch situation | Henk Groen (h.groen01@umcg.nl) | 13 |
| | Do occupational exposures in pregnancy increase risk of specific major congenital malformations relative to other malformations | Sylvainne Cordier | 15 |
| | Rare syndromes in Europe | Ingeborg Barisic (ingeborg.barisic@kbcsm.hr) | 34 |
| Write Up | The epidemiology of Ebstein's anomaly with special emphasis on medication exposure | Breidge Boyle (b.boyle1@ulster.ac.uk) | 20 |
| | Methodological Issues in Estimating Mortality due to Congenital Anomaly | Breidge Boyle (b.boyle1@ulster.ac.uk) | 27 |
| | Pierre Robin Sequence and Methadone Exposure in Pregnancy | Brian Cleary | 20 |
| | The prevalence of additional anomalies in babies with trisomy 13 or trisomy 18 | Joan Morris (j.k.morris@qmul.ac.uk) | 25 |

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|---|---|---|---|
| Write Up | Trends in the prevalence of Neural Tube Defects in Europe, 1991-2011: A tale of (continuing) missed opportunities for prevention of a largely preventable congenital anomaly | Babak Khoshnood (babak.khoshnood@inserm.fr) | 28 |
| | Antidepressant use in pregnancy | Helen Dolk (h.dolk@ulster.ac.uk) | 12 |
| | Congenital Rubella Syndrome | Tarik Derrough <Tarik.Derrough@ecdc.europa.eu> | 10 |
| | NTD in Teenage mothers | Maria Loane (ma.loane@ulster.ac.uk) | 25 |
| Accepted for Publication | Trends in hypospadias in Europe in the period 2001-2010 | Jorieke van Kammen-Bergman (j.e.h.van.kammen@umcg.nl) | 24 |
| | Detection and investigation of temporal clusters of congenital anomaly in Europe: seven years of experience of the EUROCAT surveillance system | Helen Dolk (h.dolk@ulster.ac.uk) | 20 |
| | Using scan statistics for congenital anomalies surveillance – the EUROCAT experience | Conor Teljeur | - |
| Published in 2014 | Major congenital anomalies in babies born with Down syndrome: a EUROCAT population-based registry study | Joan Morris (j.k.morris@gmul.ac.uk) | 29 |
| | Prenatal Diagnosis and Epidemiology of Multicystic Kidney Dysplasia in Europe | Louise Winding | 14 |
| | Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study | Judith Rankin (j.m.rankin@newcastle.ac.uk) | 31 |
| | Holt Oram syndrome: a registry-based study in Europe | Ingeborg Barisic (ingeborg.barisic@kbcsm.hr) | 34 |
| | Prevalence and risk of Down syndrome in monozygotic and dizygotic multiple pregnancies in Europe: implications for prenatal screening | Breidge Boyle (b.boyle1@ulster.ac.uk) | 9 |

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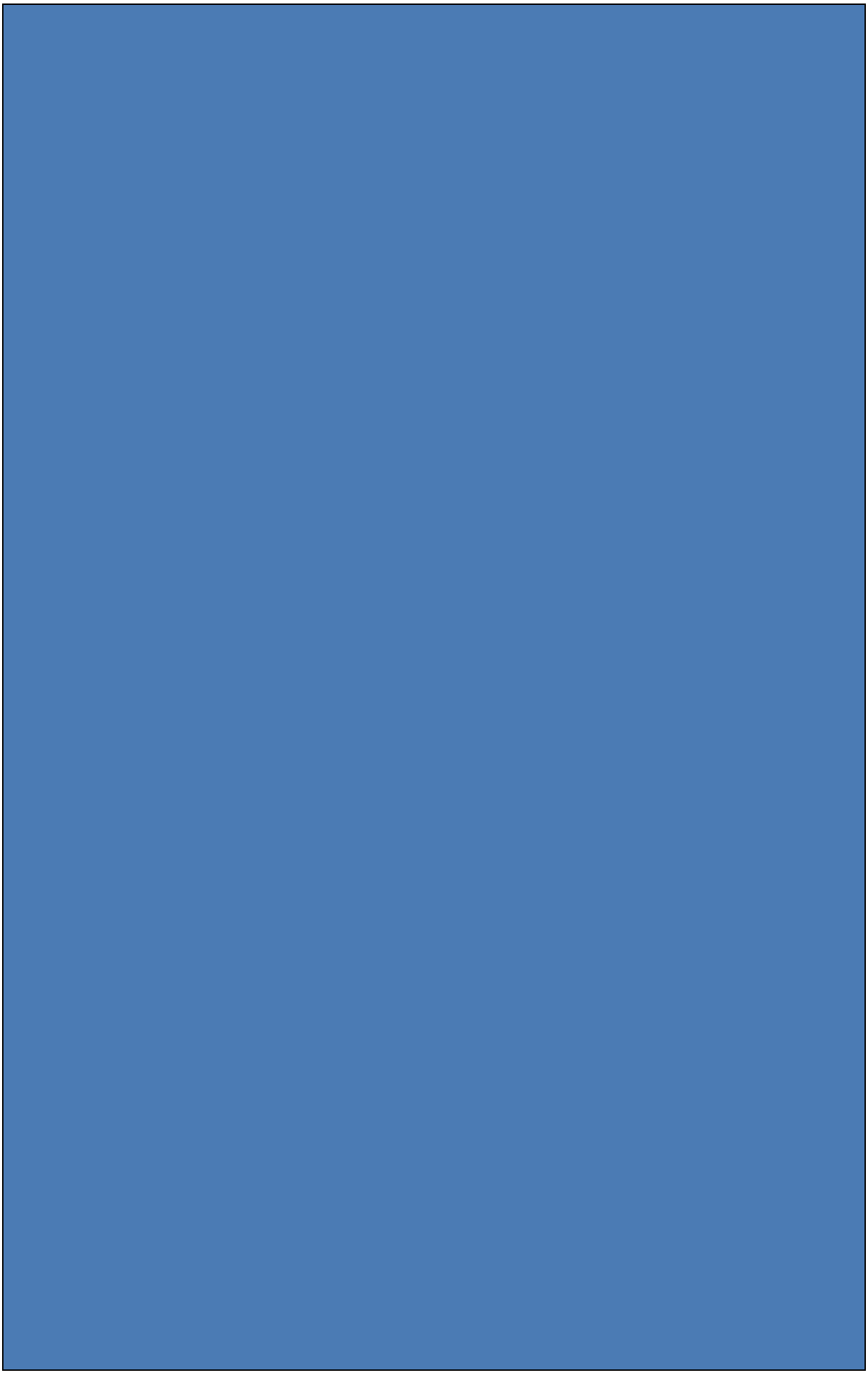
|---|---|---|---|
| Published in 2014 | Surveillance of multiple congenital anomalies: implementation of a computer algorithm in European registers for classification of cases | Ester Garne (EGarne@dadlnet.dk) | 24 |
| | Seasonality of Congenital Anomalies in Europe | Michiel Luteijn (jm.luteijn@ulster.ac.uk) | 20 |
| | Epidemiology of Multiple Congenital Anomalies in Europe: A EUROCAT Population-Based Registry Study | Elisa Calzolari (cls@unife.it) | - |
| | Epidemiology of Hirschsprung's disease in Europe: a register-based study | Judith Rankin (j.m.rankin@newcastle.ac.uk) | 30 |
| | Meckel-Gruber syndrome: a population-based study on prevalence, prenatal diagnosis, clinical features, and survival in Europe | Ingeborg Barisic (ingeborg.barisic@kbcsm.hr) | 34 |
| | Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum | Ingeborg Barisic (ingeborg.barisic@kbcsm.hr) | 34 |



# 7. EUROCAT Pharmacovigilance Report 2014

EUROCAT pharmacovigilance activities remain distinct from the activities conducted by the FP7 funded EUROmediCAT project on medication safety in pregnancy. EUROCAT continues to be registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website as a research resource http://www.encepp.eu/encepp/resourcesDatabase.jsp. In the 2014 EUROCAT Data Quality Indicators (DQI), 23 out of 31 full member EUROCAT registries recorded medication exposures using ATC codes, which was one more compared to the previous year, and 82% of the ATC codes had 7 digits and were in the correct format which was the same as reported in 2013 (http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators).

In 2014, EUROCAT pharmacovigilance included risk assessment studies of specific medications and specific congenital anomalies and epidemiological studies investigating maternal risk factors associated with specific congenital heart defects (CHD). These studies required verification of the anomaly and medication exposures, and following liaison with local registries, the corrections have been implemented in the EUROCAT central database. The studies were:

1. Lamotrigine use in Pregnancy and Risk of Orofacial Clefts
2. Methadone use in pregnancy and risk of Pierre Robin Sequence
3. Ebstein's anomaly (a severe congenital heart defect) and mental health related exposures

### 1. Lamotrigine use in Pregnancy and Risk of Orofacial Clefts

The original EUROCAT lamotrigine case-malformed control study, commissioned by GlaxoSmithKline in 2007 to investigate an alert from the US Federal Drugs Agency, found no evidence of an increased risk of isolated orofacial clefts or isolated cleft palate relative to other malformations due to first trimester exposure to lamotrigine monotherapy[1]. However, due to the small number of cases exposed to lamotrigine in the database at that time, GSK commissioned a follow-up study to include five annual updates up to birth year 2011 in order to estimate the risk more precisely. The final update study doubled the population included in the original study from 4 million births in 19 EUROCAT registries, 1995-2005, to over 10 million births in 21 registries, 1995-2011. There were 1,364 congenital anomaly registrations with maternal first trimester antiepileptic drug (AED) exposure, of which 157 had lamotrigine monotherapy exposure. Again, no evidence of an increased risk of orofacial clefts relative to other malformations associated with lamotrigine exposure in the first trimester was found. The maternal age adjusted odds ratios (ORs) for lamotrigine monotherapy vs non-AED use were 1.26 (95% CI: 0.71 - 2.23) for all orofacial clefts, and 1.40 (95% CI: 0.77 - 2.53) for isolated orofacial clefts**.** The adjusted OR were 1.52 (95% CI 0.67-3.45) for all cleft palate and 1.61 (95%CI 0.46-3.94) for isolated cleft palate. The Report from the fifth and final update study was submitted to GlaxoSmithKline in March 2014 who have submitted it to the Regulatory Authorities. A paper is being prepared for submission to journal publication.

The findings of the fourth update study were presented at the 30th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, October

[1] Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LTW and EUROCAT Antiepileptic Drug Working Group **(2008),** "Does Lamotrigine Use in Pregnancy Increase Orofacial Cleft Risk Relative to Other Malformations?", *Neurology,* Vol 71, pp 714-722

24–27, 2014 in Taiwan (Pharmacoepidemiology and Drug Safety 2014, 23, S1, pages 1–497 (see Annex 1). The findings of the fifth and final update study were presented at the British Isles British Isles Network of Congenital Anomaly Registers Biennial Scientific Meeting in Wales October 7, 2014 (Abstract in Annex 1).

Both the original study (Lamotrigine use in Pregnancy and Risk of Orofacial Clefts) and the update study (Lamotrigine use in Pregnancy and Risk of Orofacial Clefts II) are listed on the ENCePP register.

**2. Methadone in Pregnancy and Pierre Robin Sequence**

Methadone is an essential public health intervention for opioid-dependent pregnant women. It has been shown to improve engagement with antenatal care and lead to better pregnancy outcomes relative to ongoing heroin use. Two independent reports signalled a potential association between maternal methadone exposure and Pierre Robin sequence (PRS). Following an external enquiry, EUROCAT conducted a population-based case malformed-control study in 2014 to investigate whether maternal first trimester exposure to methadone is associated with risk of PRS. There were 127 methadone exposed registrations in 12 EUROCAT registries, covering almost 4 million births, 1995-2011. The study confirmed the *a priori* hypothesis that early pregnancy methadone exposure is associated with PRS. There was a strong association between methadone-only exposure and all PRS (adjusted OR 14.19; 95% CI 3.75-38.17 and isolated PRS (adjusted OR 17.48; 95% CI 4.61-47.13). These findings were presented at the European Conference on Safety of Medication use in Pregnancy**,** February 2-4, 2015 in Poznan, Poland (Abstract – see Annex 1). A paper is currently being circulated for registry approval before being submitted to a journal for publication.

**3. Ebstein's anomaly and medication exposure** (BB has not analysed ToF in relation to drugs)

A PhD study completed in 2013 using EUROCAT data from 12 registries covering 3.3 million births found significant associations between the congenital heart defects (CHD) Tetralogy of Fallot and Ebstein's anomaly and SSRI exposure in pregnancy. These findings were presented at two international conferences in 2014: International Marcé Society Biennial Conference on Perinatal Mental Health 10-12 September 2014 in Swansea, Wales; and the 30th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, October 24–27, 2014 in Taiwan (Pharmacoepidemiology and Drug Safety 2014, 23, S1, pages 1–497 see Annex 1).

In 2014, an epidemiological study was conducted to assess risk factors including maternal medication exposures associated with Ebstein's anomaly. This study included data from 15 EUROCAT registries covering a population of 3.7 million births 1995-2011. Of the 173 cases with Ebstein's anomaly, 9 were exposed to either antidepressants or psycholeptic medications. An association was found between maternal mental health conditions/ medication use and Ebstein's anomaly. Odds ratios (OR) adjusted for time and country were OR 2.68 (95%CI 1.36-5.28). Overall, cases were more likely to have been exposed to psycholeptic medications (OR 4.26; 95%CI 1.56-11.7), antidepressants in general (OR 5.74; 95%CI 2.64-12.4) and SSRIs (OR 5.02; 95%CI 1.80-13.3). These findings were presented at the European Conference on Safety of Medication use in Pregnancy**,** February 2-4, 2015 in Poznan, Poland (Abstract – see Annex 1). A paper is currently being circulated for registry approval before being submitted to a journal for publication.

A further epidemiological study investigated the association between Tetralogy of Fallot and maternal risk factors including medication exposures. The exposure information has been verified by the registries and the data are currently being analysed. A report is expected to be circulated to the participating registries for approval soon.

**Report on Sources of Information on Medication Use in Pregnancy**

This Report was updated in 2014 to include sources of medication data for the Ukraine registry as these data have been used in some studies. The Report also now includes a table listing registries that transmit medication data restricted to first trimester only and registries that transmit medication data for the whole of pregnancy. Knowledge of the availability of different sources of medication information and whether these data are transmitted for first trimester or all of pregnancy is essential for interpreting differences in prevalence of medication exposure between registries: http://www.eurocat-network.eu/content/Special-Report-Medication-Use-In-Pregnancy.pdf

**External enquiries**

There were no external enquiries from the pharmaceutical industry relating to medication exposures recorded in the central database in the period January to December 2014.

Annex 1

## Lamotrigine Use in Pregnancy and Risk of Orofacial Cleft, an Update of EUROCAT Lamotrigine Study **30th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, October 24–27, 2014 in Taiwan**

Hao Wang,[1] Maria Loane,[2] Ester Garne,[3] Joan Morris,[4] Vera Nelen,[5] Babak Khoshnood,[6] Anke Rißmann,[7] Awi Wiesel,[8] Mary O'Mahony,[9] Anna Pierini,[10] Elisa Calzolari,[11] Miriam Gatt,[12] Marian Bakker,[13] Marie-Claude Addor,[14] David Tucker,[15] Kari Klungsoyr,[16] Anna Latos-Bielenska,[17] Jan P Mejnartowicz,[18] Karin Kallen,[19] Ingeborg Barisic,[20] Christine Verellen-Dumoulin,[21] Bérénice Doray,[22]Larraitz Arriola,[23] Diana Wellesley,[24] Amanda Neville,[11] Lolkje TW de Jong-van den Berg,[1] Helen Dolk.[21]*University of Groningen, Groningen, Netherlands; [2]University of Ulster, Belfast, United Kingdom; [3]Region Syddanmark, Odense, Denmark; [4]Queen Mary University of London, London, United Kingdom; [5]Provinciaal Instituut voor Hygiene, Antwerp, Belgium; [6]Institut National de la Sante et de la Recherche Medicale, Paris, France; [7]Otto-von-Guericke Universitat Megdeburg, Magdeburg, Germany; [8]Johannes Gutenberg Universitat, Mainz, Germany; [9]St Finbarr's Hospital, Cork, Ireland; [10]CNR Institute of Clinical Physiology, Pisa, Italy;[11]Azienda Ospedaliero Universitaria di Ferrara, Ferrara, Italy; [12]G'mangia Gill, Malta, Malta; [13]University Medical Centre Groningen, Groningen, Netherlands; [14]Registre Vaudois des Malformations, Lausanne, Switzerland; [15]Singleton Hospital, Swansea, United Kingdom; [16]Medical Birth Registry of Norway, Bergen, Norway; [17]Polish Registry of Congenital Malformations, Poznan, Poland; [18]Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu, Poland, Poland; [19]Swedish National Board of Health and Welfare and University of Lund, Lund, Sweden; [20]Klinika z a Djecje Bolesti Zagreb, Zagreb, Croatia; [21]Centre de Génétique Humaine Institut de Pathologie et de Génétique, Charleroi, Belgium; [22]Registre des Malformations Congenitales D'Alsace, France; [23]Registro Anomalias Congénitas CAPV, Vitoria-Gasteiz, Spain; [24]Princess Anne Hospital, Southampton, United Kingdom.*

**Background:** Lamotrigine (LTG) is increasingly used during pregnancy. A FDA warning was issued for an association of LTG exposure and increased risk of orofacial clefts (OCs), based on data from the North American Antiepileptic Drug Pregnancy Registry (Holmes, 2006; Holmes et al., 2008). The signal was examined in the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database (Dolk, 2008). No significantly increased risk of OCs was found relative to other malformations, either for isolated orofacial clefts or for isolated cleft palate. There has been no independent confirmation of increased risk of OCs in relation to LTG from all studies in the literature combined (Dolk et al., 2012).
**Objectives:** To investigate whether first trimester exposure to LTG monotherapy is specifically associated with an increased risk of OCs, using the EUROCAT antiepileptic-study database including birth years up to 2010.
**Methods:** A population-based case-control study with malformed controls was performed. The updated EUROCAT antiepileptic-study dataset included 226,806 live births, stillbirths, or terminations with malformations among 7.6 million births in 20 European countries from 1995 to 2010, more than twice the population of the original study. Cases were 10,523 nonsyndromic OC registrations, of whom 8,771 were isolated, and 3,789 cleft palate (CP) of whom 2,984 were isolated. Controls were 144,914 non-chromosomal, non-OC registrations. We compared first trimester LTG vs no antiepileptics (non-AED use), for mono and polytherapy.

**Results:** There were 181 LTG exposed (109 mono- and 72 polytherapy) registrations. The maternal age adjusted odds ratios (ORs) for LTG monotherapy vs non-AED use were 0.84 (95% CI 0.37-1.92) for OC relative to other malformations, 1.01 (95% CI 0.44-2.30) for isolated OC; 1.18 (95% CI 0.38-3.72) for CP, and 1.49 (95% CI 0.47-4.72) for isolated CP.
**Conclusions:** This update does not change the conclusion of the original study: we found no evidence of an increased risk of isolated orofacial clefts relative to other malformations for LTG monotherapy exposure in the first trimester, nor any evidence of an increased risk for isolated cleft palate.

**TITLE:** Maternal first trimester lamotrigine exposure and risk of orofacial clefts: analysis using data from EUROCAT congenital anomaly registries

**AUTHOR LIST:** Maria Loane, Hao Wang, Helen Dolk, Lolkje de Jon van den Berg, Joan Morris and the EUROCAT Antiepileptic Drug Working Group

**INSTITUTION LIST FOR FIRST AUTHOR:** WHO Collaborating Centre for the Surveillance of Congenital Anomalies and EUROCAT Central Registry, University of Ulster

**(Max 300 words)**

**BACKGROUND:**

As many women with chronic conditions take medications in pregnancy, post marketing surveillance evaluating the safety of these medications is essential. EUROCAT and its sister project EUROmediCAT have successfully conducted pharmacovigilance studies using data from congenital anomaly (CA) registries. We present results from an EUROCAT update study assessing whether first trimester exposure to lamotrigine (LTG) is associated with an increased risk of orofacial clefts (OC) relative to other malformations. This update doubles the population included in an initial study[1] investigating an alert from the US Federal Drugs Agency in 2006.

**METHODS:**

A population-based case-control study with malformed controls was performed using data from 21 EUROCAT registries covering over 10 million births, 1995-2011. Cases were 14,027 non-syndromic OC registrations, of whom 11,632 were isolated; and 5,398 cleft palate (CP) of whom 4,240 were isolated CP. Controls were 183,921 non-chromosomal, non-OC registrations. We compared first trimester LTG exposure versus non-AED exposure.

**RESULTS:**

There were 1,364 CA registrations with first trimester AED exposure, of which 157 have LMT monotherapy exposure. The maternal age adjusted odds ratios (ORs) for LTG monotherapy vs non-AED use were 1.26 (95% CI: 0.71 - 2.23) for all OC, and 1.40 (95% CI: 0.77 - 2.53) for isolated OC**.** The adjusted OR were 1.52 (95% CI 0.67-3.45) for all CP and 1.61 (95%CI 0.46-3.94) for isolated CP.

**CONCLUSIONS:**

We found no evidence of an increased risk of OC relative to other malformations associated with LMT monotherapy exposure in the first trimester, or any evidence of an increased risk for isolated CP. This study highlights the importance of CA registries in a post-marketing surveillance system as signals can be tested in an independent large dataset. CA registries can uniquely provide the large population coverage needed to achieve sufficient statistical power to detect associations between rare medication exposures and rare CA.

[1]Dolk H, Jentink J, **Loane M**, Morris J, de Jong-van den Berg LTW and EUROCAT Antiepileptic Drug Working Group (2008). Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology 71: 714-722

**Methadone Maintenance Treatment in Pregnancy and Pierre Robin Sequence: a Case-control Study**

**European Conference on Safety of Medication use in Pregnancy, February 2-4, 2015 in Poznan, Poland**

Cleary BJ, Loane MA and Dolk H for EUROCAT.

**Background**

Methadone is a treatment of choice for opioid-dependent pregnant women. It improves engagement with antenatal care and perinatal outcomes. Two previous reports suggested an association between methadone exposure and Pierre Robin Sequence (PRS). This study tested the hypothesis that first trimester methadone exposure is associated with PRS.

**Methods**

A case-control study was performed using EUROCAT population-based congenital anomaly registries. Cases were defined as all live births, fetal deaths from 20 weeks' gestation and terminations of pregnancy with a diagnosis of PRS. A case-malformed control analysis was carried out comparing the odds of methadone exposure among cases with that of controls with malformations other than PRS (genetic syndromes and chromosomal anomalies excluded).

**Results**

Twelve registries in eleven countries participate in this study. The dataset included 101,873 registrations between 1995 and 2011 from a total of 3,978,229 births. Of the 336 PRS cases, 272 were classified as isolated (81%), 59 were classified as multiple, and 5 were teratogenic syndromes (4 fetal alcohol syndrome and 1 valproate syndrome). There were 7 methadone-exposed cases among 336 PRS registrations. The odds ratio for the association between methadone exposure and PRS was 15.52 (95% Confidence Interval 6.06-33.31). After excluding a case which was included in the original reported signal, the odds ratio was 13.1 (95% CI 5.73-29.95). Adjustment for maternal age or registry did not alter the results. In absolute terms this association reflects an increase in the risk of PRS from 0.84 cases per 10,000 to approximately 13 cases per 10,000.

**Conclusions**

This study supports the hypothesis that first trimester exposure to methadone is associated with PRS. This study had limited data on potential confounding factors and cannot determine causation. The small increased risk does not alter the risk-benefit balance for methadone use in pregnancy.

## 576 Selective Serotonin Reuptake Inhibitor Use in First Trimester Pregnancy and Risk of Congenital Anomalies: A Register-Based Study in 12 European Countries.

**30th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, October 24–27, 2014 in Taiwan**

Anthony Wemakor,[1,2] Karen Casson,[1] Ester Garne,[3] Mariam Bakker,[4] David Tucker,[5] Babak Khoshnood,[6] Vera Nelen,[7] Mary O'Mahoney,[8] Anna Pierini,[9] Kari Klungsoyr,[10] Mariam Gatt,[11] Marie-Claude Addor,[12] Anke Rissmann,[13] Larraitz Arriola,[14] Lolkje de Jong-van Berg,[15] Helen Dolk.[1] *[1]Institute of Nursing and Health Research, University of Ulster, Jordanstown, Co Antrim, United Kingdom; [2]School of Medicine and Health Sciences, University for Development Studies, Tamale, Ghana; [3]Hospital Lillebaelt, Kolding, Denmark; [4]Eurocat Northern Netherlands, Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [5]Public Health Wales, Swansea, United Kingdom; [6]Paris Registry of Congenital Malformations, INSERM, Paris, France; [7]Provinciaal Instituut voor Hygiene, Antwerp, Belgium; [8]Department of Public Health, Cork, Ireland; [9]CNR Institute of Clinical Physiology, Pisa, Italy; [10]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway;[11]Malta Congenital Anomalies Registry, G'mangia, Malta; [12]Service of Medical Genetics, Lausanne, Switzerland; [13]Malformation Monitoring Centre, Medical Faculty Otto-von-Guericke-University, Magdeburg, Germany; [14]Registro Anomalias Congenitas, Vitoria-Gasteiz, Spain; [15]Groningen University, Groningen, Netherlands.*

**Background:** The Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants are widely prescribed in pregnancy, but there is evidence that they may cause congenital anomalies, particularly congenital heart defects (CHD).
**Objectives:** To determine the specificity of association between first trimester pregnancy exposure to individual SSRIs and specific congenital anomalies (CAs).
**Methods:** Population-based case-malformed control study covering 3.3 million births from 12 EUROCAT registries 1995-2009. CAs included non-syndromic livebirths, fetal deaths and terminations of pregnancy for fetal anomaly (n = 42,839). Three groups of CA were studied: CHD (n = 12,828), non-CHD “signals” derived from the literature (n = 12,460), and other subgroups of CA not previously associated with SSRIs (controls, n = 17,046). First trimester SSRI exposure was compared to no SSRI use. Odds ratios (OR) and 95% confidence intervals (CI) were calculated adjusting for registry, maternal age and birth year.
**Results:** SSRI use in first trimester pregnancy was associated with CHD overall (OR 1.38, 95% CI 1.05-1.82, n = 109); and with severe CHDs (OR 1.56, 95% CI 1.03-2.38, n = 29). Specific associations between SSRI and Tetralogy of Fallot (OR 3.36, 95% CI 1.67-6.75, n = 9), and Ebstein's anomaly (OR 8.23, 95% CI 2.91-23.28, n = 4) were detected. Statistically significant associations between SSRI and four non-CHD signals (anorectal atresia and stenosis, gastroschisis, renal dysplasia, clubfoot) were supported. In all the statistically significant associations identified there was little evidence of SSRI type specificity.
**Conclusions:** These data support the previously reported association between SSRIs and CHDs and a number of other CAs but do not suggest specificity of action in relation to SSRI type. This may indicate confounding or a common mechanism of teratogenic effect among SSRIs. Preconceptional and pregnancy care for women should include weighing the benefits of SSRIs against the growing evidence of risk when assessing treatment options.

**The epidemiology of Ebstein's anomaly in Europe: a registry-based study with special emphasis on medication exposure.**

**European Conference on Safety of Medication use in Pregnancy, February 2-4, 2015 in Poznan, Poland**

Breidge Boyle[1], Ester Garne[2], Maria Loane[1], Marie-Claude Addor[3], Larraitz Arriola[4], Clara Cavero-Carbonell,[5], Hermien EK deWall[6], Miriam Gatt[7], Nathalie Lelong[8], Catherine Lynch[9], Vera Nelen[10], Amanda J Neville[11], Mary O'Mahony[12], Anna Pierini[13], Anke Rissmann[14], David Tucker[16], Natalia Zymak-Zakutnia[16] and Helen Dolk[1]. [1]Institute of Nursing and Health Research, Ulster University, Belfast, United Kingdom; [2]Paediatrics Department, Hospital Lillebaelt, Kolding, Denmark; [3]Division of Medical Genetics, CHUV, Lausanne, Swaziland; [4]Registro Anomalías Congénitas, CAV Subdirección de Salud Pública, San Sebastian, Spain; [5]Centro Superior de Investigación, Salud, Valencia, Spain; [6]Department of Genetics,, University of Groningen, Groningen, Netherlands; [7]Department of Health Information and Research, Guardamangia, Malta; [8]Paris Registry of Congenital Malformations, INSERM, Paris, France; [9]Health Service Executive, Kilkenny, Ireland; [10]PIH, Bepartment of the Enviroment, Antwerp, Belgium; [11]Emila Romagna Registry of Birth Defects, Universitaria di FerraraCorso Giovecca, Ferrara, Italy; [12]Health Service Executive, , Cork, Ireland; [13]CNR, Institute of Clinical Physiology, Pisa, Italy; [14]Malformation Monitoring Centre, Saxony-Anhalt, Medical Faculty Otto-von-Guericke university, Magdeburg, Germany; [15]Congenital Anomaly Register and Information Service for Wales (CARIS), Public Health Wales, Swansea, United Kingdom and [16]OMNI-Net Ukraine Birth Defects Program, Khmelnytsky, Ukraine.

**Background:** Ebstein's anomaly (EA) is a rare congenital malformation of the tricuspid valve and right ventricle of the heart. It has been associated with lithium and benzodiazepine exposure in pregnancy.
**Objectives:** to describe the epidemiology of Ebstein's anomaly in Europe with reference to geographic and temporal variation in prevalence, associated malformations and syndromes, and risk factors including maternal age, parity, medical history and medication exposure during pregnancy.
**Methods:** Descriptive epidemiologic analysis of data from 15 EUROCAT Congenital Anomaly Registries in 12 European countries covering a population of 5.6 million births 1982-2011. EA cases included livebirths, fetal deaths from 20 weeks gestation, and terminations of pregnancy for fetal anomaly (TOPFA). Prevalence rate per 10,000 births was calculated. Odds ratios (OR) for exposure to maternal illnesses and medications in the first trimester of pregnancy were calculated using logistic regression; by comparing EA cases to non-EA and non-cardiac controls, excluding genetic syndromes. OR are adjusted for time period and country.
**Results:** The prevalence of EA was 0.47 (95%CI 0.41-0.53) per 10,000 births. Prevalence rose from 0.29 (95%CI 0.20-0.41) in the decade 1982-1991 to 0.55 (95%CI 0.46-0.67) in the decade 1992-2001 ($p<0.01$). Cases were more likely to be exposed to maternal beta thalassemia adjOR 12.3(95%CI 3.69-40.9, n=3), haemorrhage in early pregnancy adjOR 1.74 (95%CI 0.91-3.33, n=11), and insulin adjOR 3.41 (95%CI1.08-10.8, n=3). Nine EA cases were exposed to maternal mental health conditions/medications were adjOR2.68 (95%CI 1.36-5.28), including 7 who took antidepressants and 4 who took psycholeptics.
**Conclusions:** There is no evidence that EA is becoming more prevalent. Our data support previous literature concerning an association with mental health-related exposures. We find some new associations requiring confirmation.