

eurocat
european surveillance of
congenital anomalies
EUROCAT Annual Surveillance Report

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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](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 conditions¹

- **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.

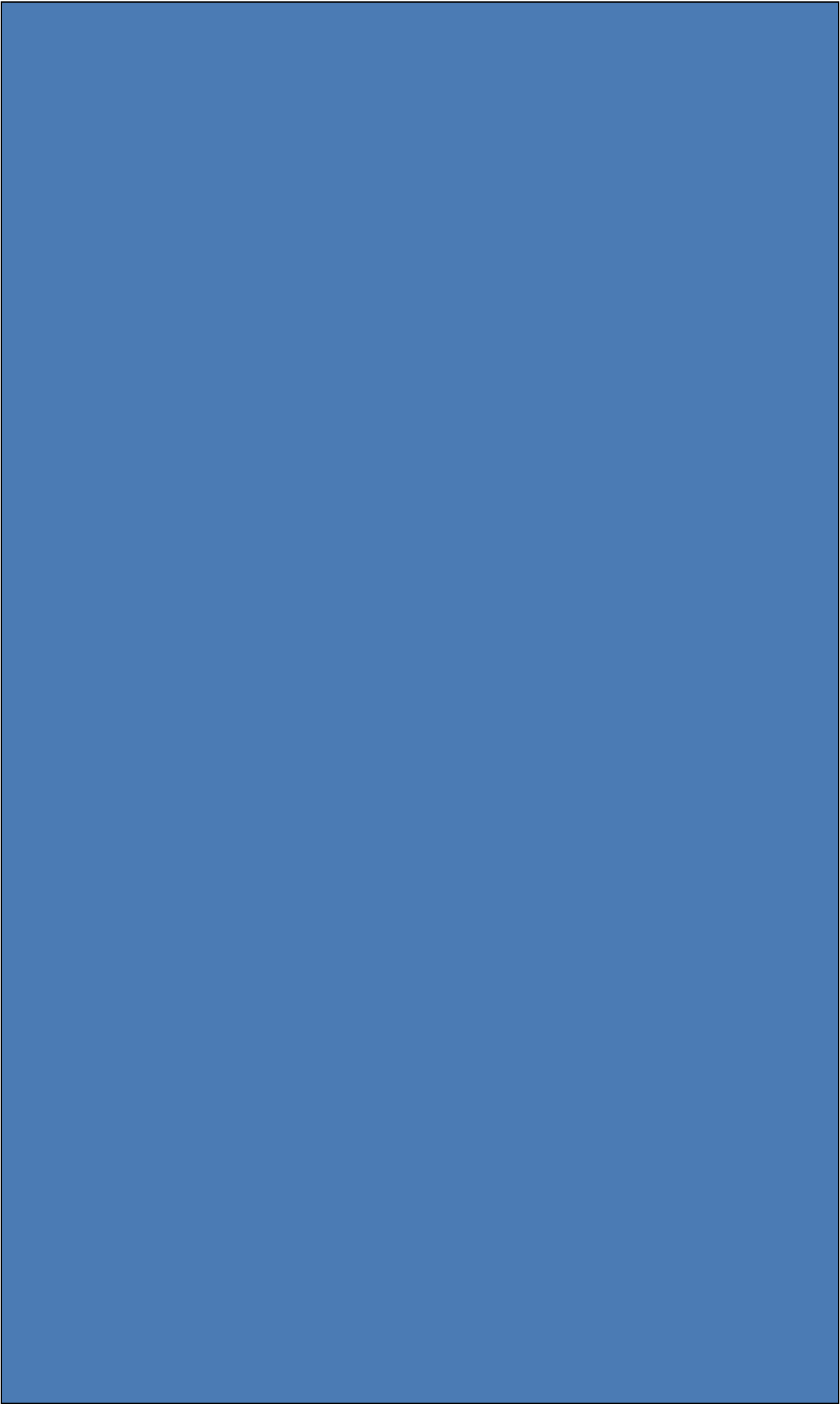
Clusters

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

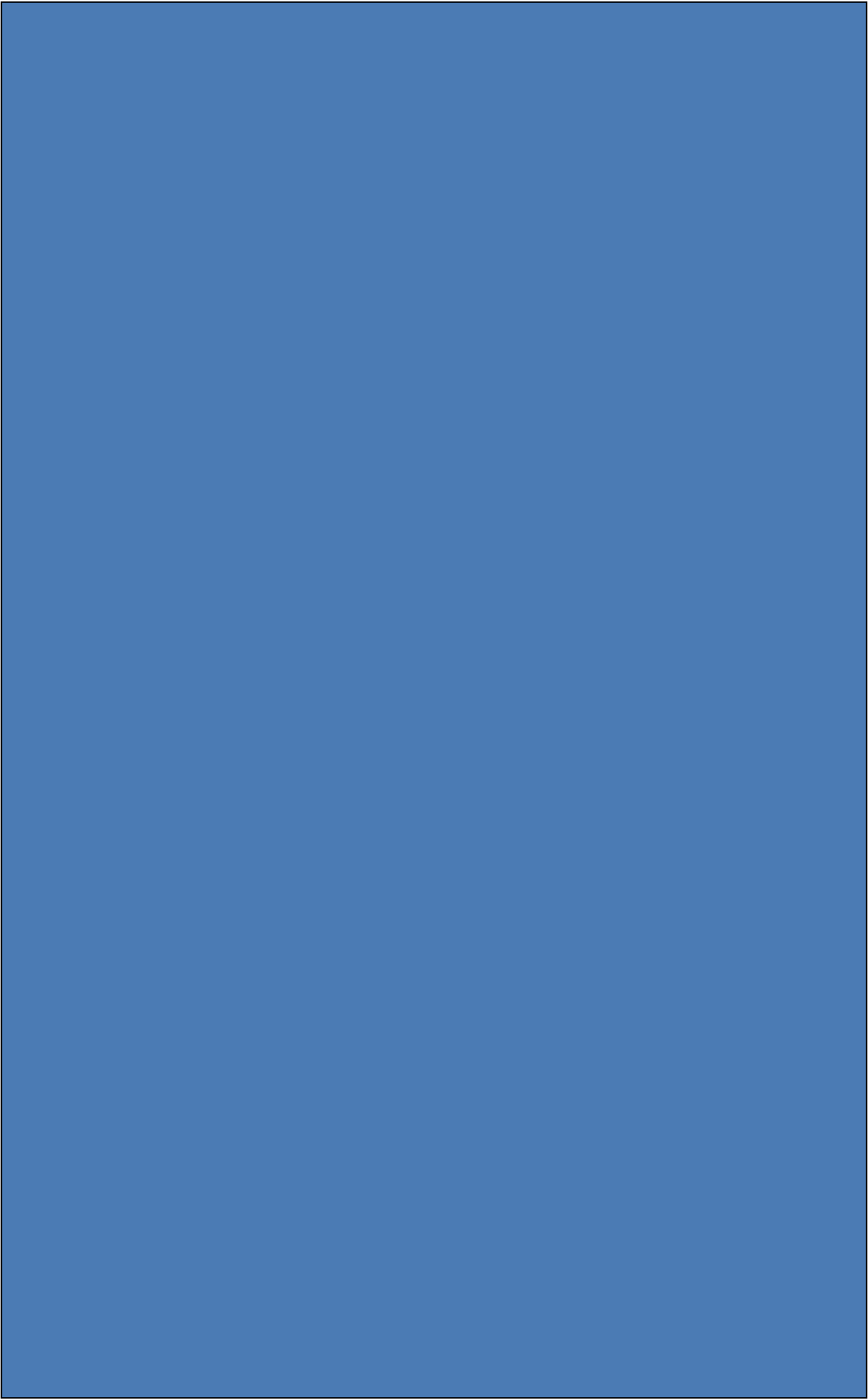
The average total prevalence of the category of anomalies typically requiring surgery is over 5 per 1,000 births. Most (by definition) are livebirths. Eight registries have data on surgery, which show that the average prevalence of babies requiring surgery one or more times is nearly 10 per 1,000 births 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
<i>EFTA countries in EUROCAT</i>						
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

Anomaly	LB N	FD N	TOPFA N	LB+FD+TOPFA N	LB+FD+TOPFA Rate	Excluding Genetic Conditions	
						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 malformation 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)

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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+TOPF A 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+TOPF A 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 A 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)

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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, hypoplastic left heart, 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.

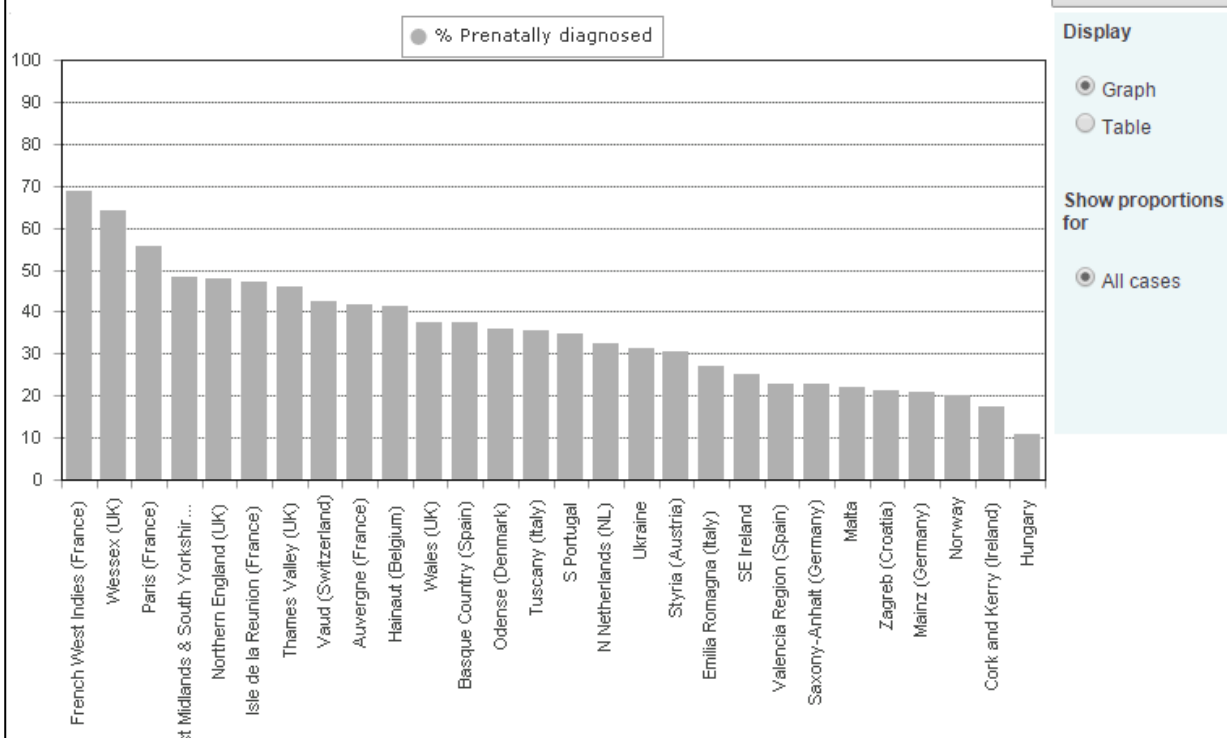
EUROCAT Prenatal Detection Rates

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



Prenatal Detection Rates - All Anomalies (Excluding genetic conditions)

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

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Display

☐ Graph
☒ Table

Show proportions for

☒ All cases

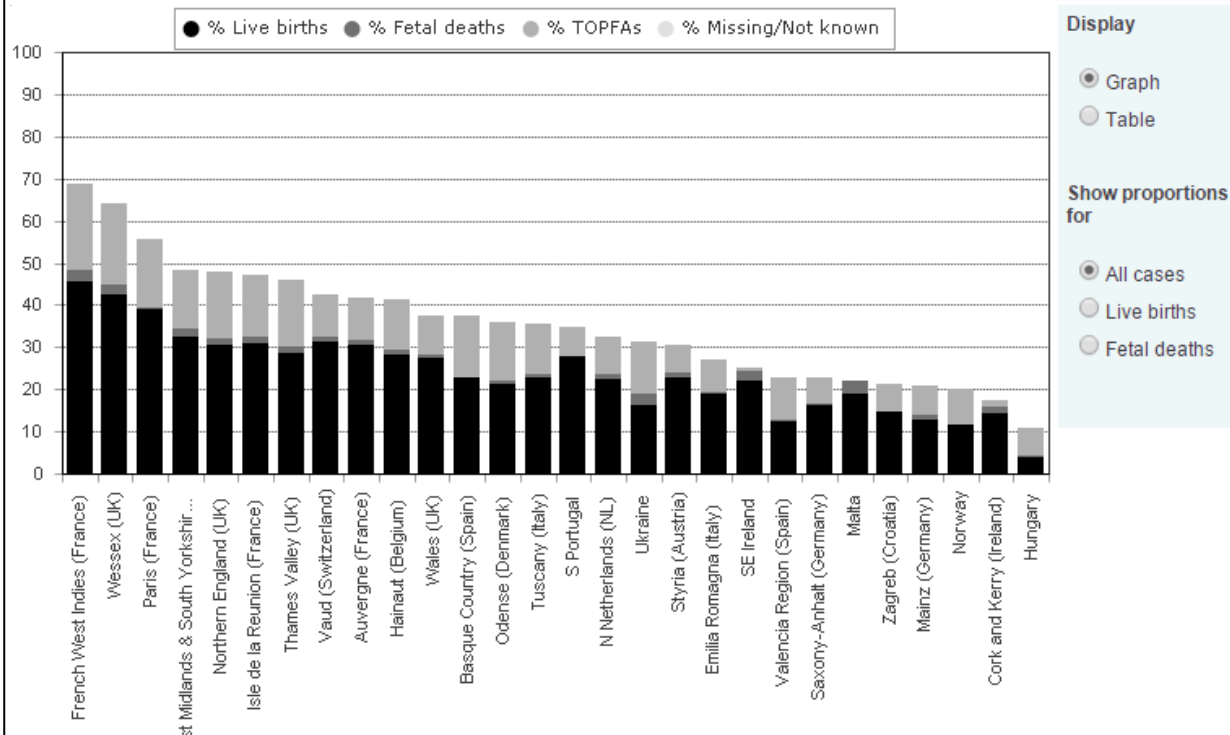
Registry	Total number of cases	Number prenatally diagnosed	Percentage of all cases (95% CI)
French West Indies (France)	608	419	68.9 (65.1 - 72.5)
Wessex (UK)	2,200	1,413	64.2 (62.2 - 66.2)
Paris (France)	3,244	1,799	55.5 (53.7 - 57.2)
East Midlands & South Yorkshire (UK)	6,269	3,023	48.2 (47.0 - 49.5)
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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Proportion of All Anomalies (Excluding genetic conditions) cases prenatally diagnosed by outcome, 2008-2012

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Registry	Live births		Fetal deaths		TOPFAs		Missing/Not known	
	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)	*	*	*	*

[Back to selection](#)

Display: ☐ Graph ☒ Table

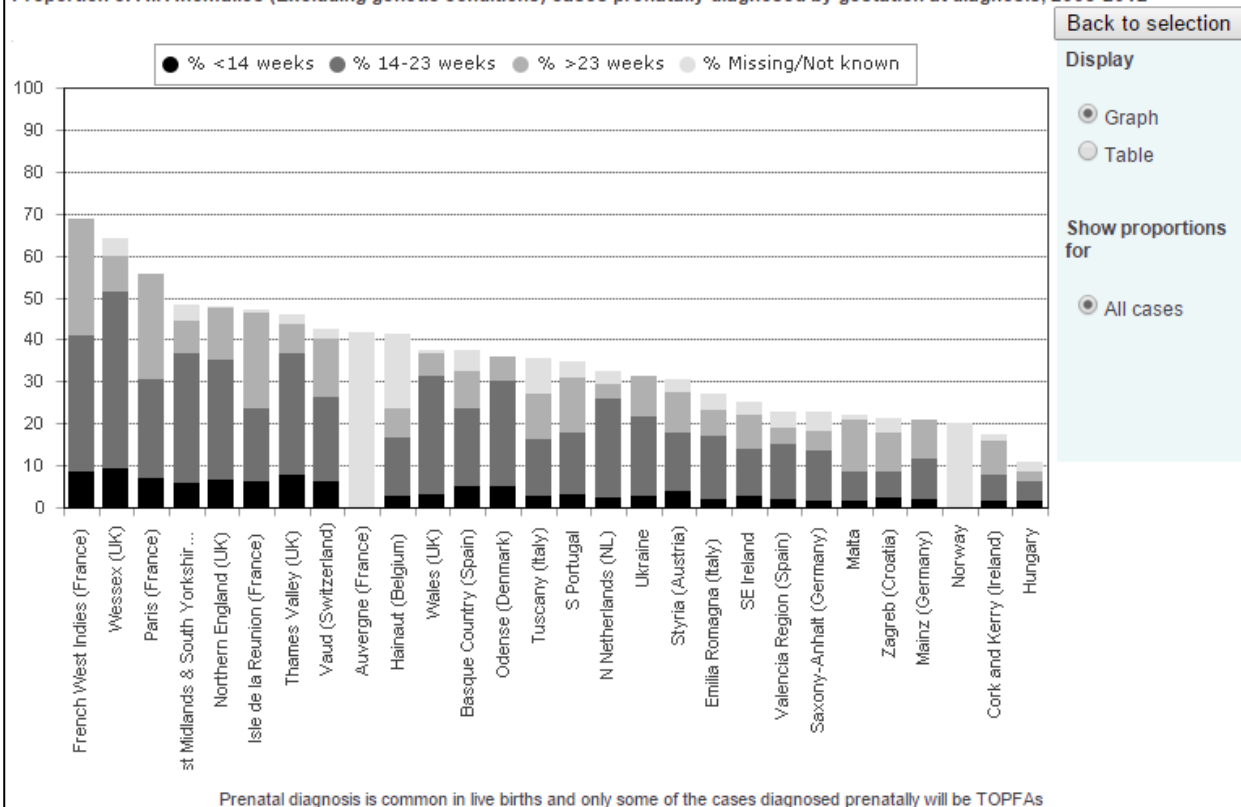
Show proportions for: ☒ All cases ☐ Live births ☐ Fetal deaths

* = 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



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		14-23 weeks		>23 weeks		Missing/Not known	
	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)	*	*	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 $\geq 5\%$ of all fetal deaths, or $\geq 5\%$ 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 indicators¹ 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 registries²

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.

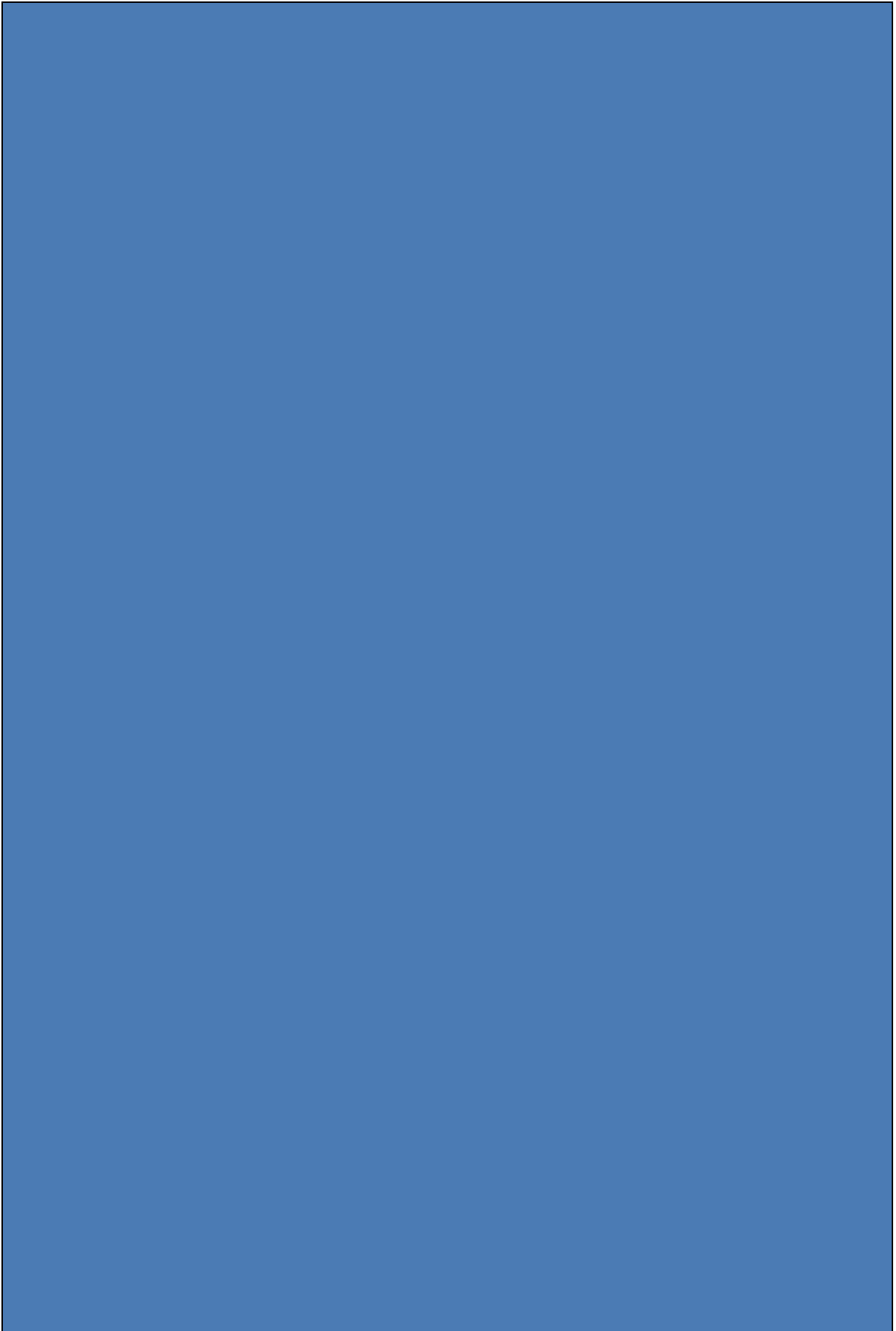
Genetic syndromes	ICD10-BPA	Number of cases	Prevalence per 10,000 births
Aarskog syndrome	Q8710	11	0.05
Acrocephalopolysyndactyly (all types)	Q8700	5	0.02
Alagille syndrome	Q4471	20	0.08
Angelman syndrome	Q8785	32	0.13
Apert's syndrome (acrocephalosyndactyly type I and II)	Q8701	34	0.14
Bardet-Biedl 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 dysplasia	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)

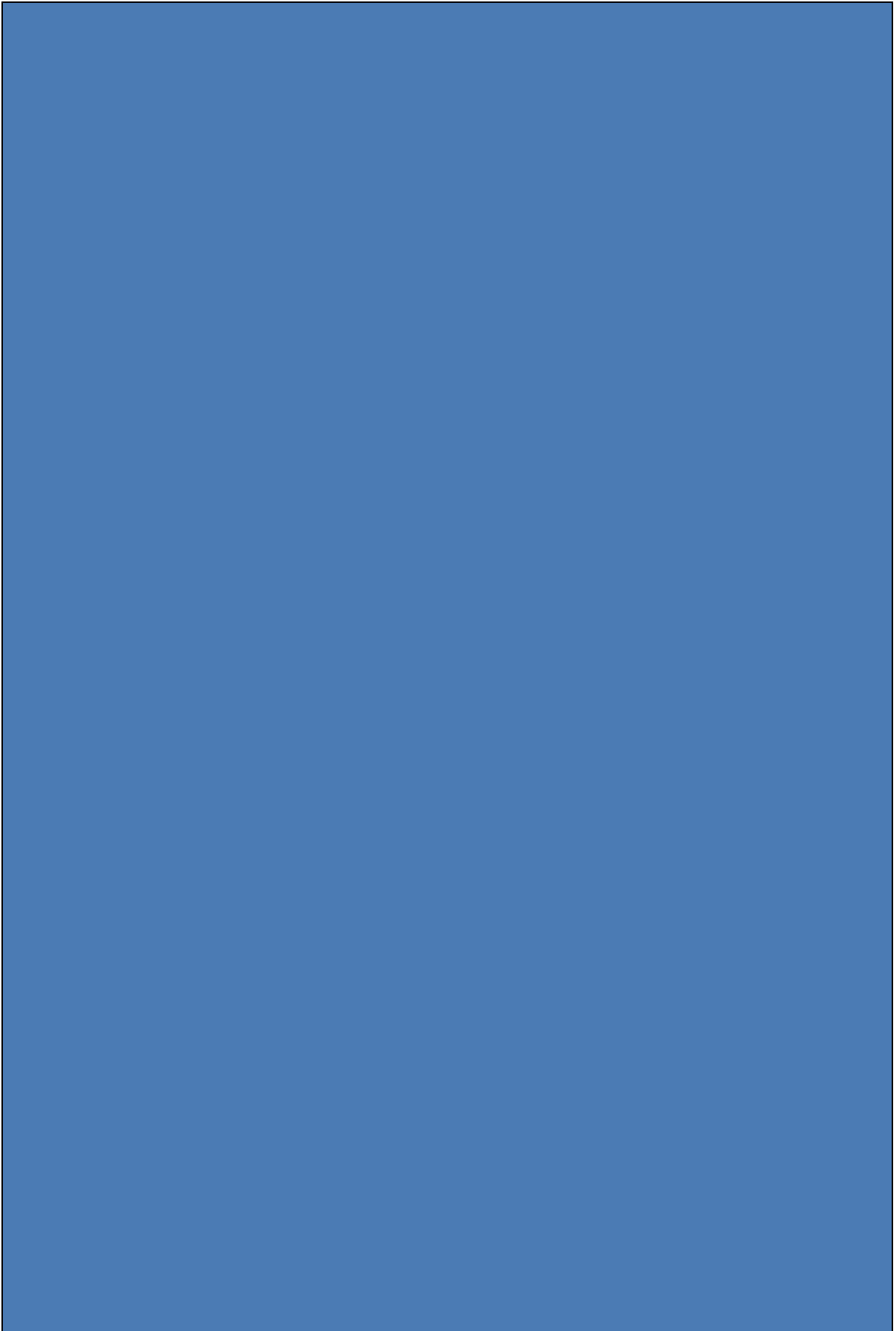
Antwerp (BE), Cork & Kerry (IE), French West Indies (FR), Isle de la Reunion (FR), , Mainz (DE), Malta (MT), N England (GB), N Netherlands (NL), Odense (DK), Paris (FR), SE Ireland (IE), SW England (GB), Thames Valley (GB), Vaud (CH), Wales (GB), Wessex (GB).



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.

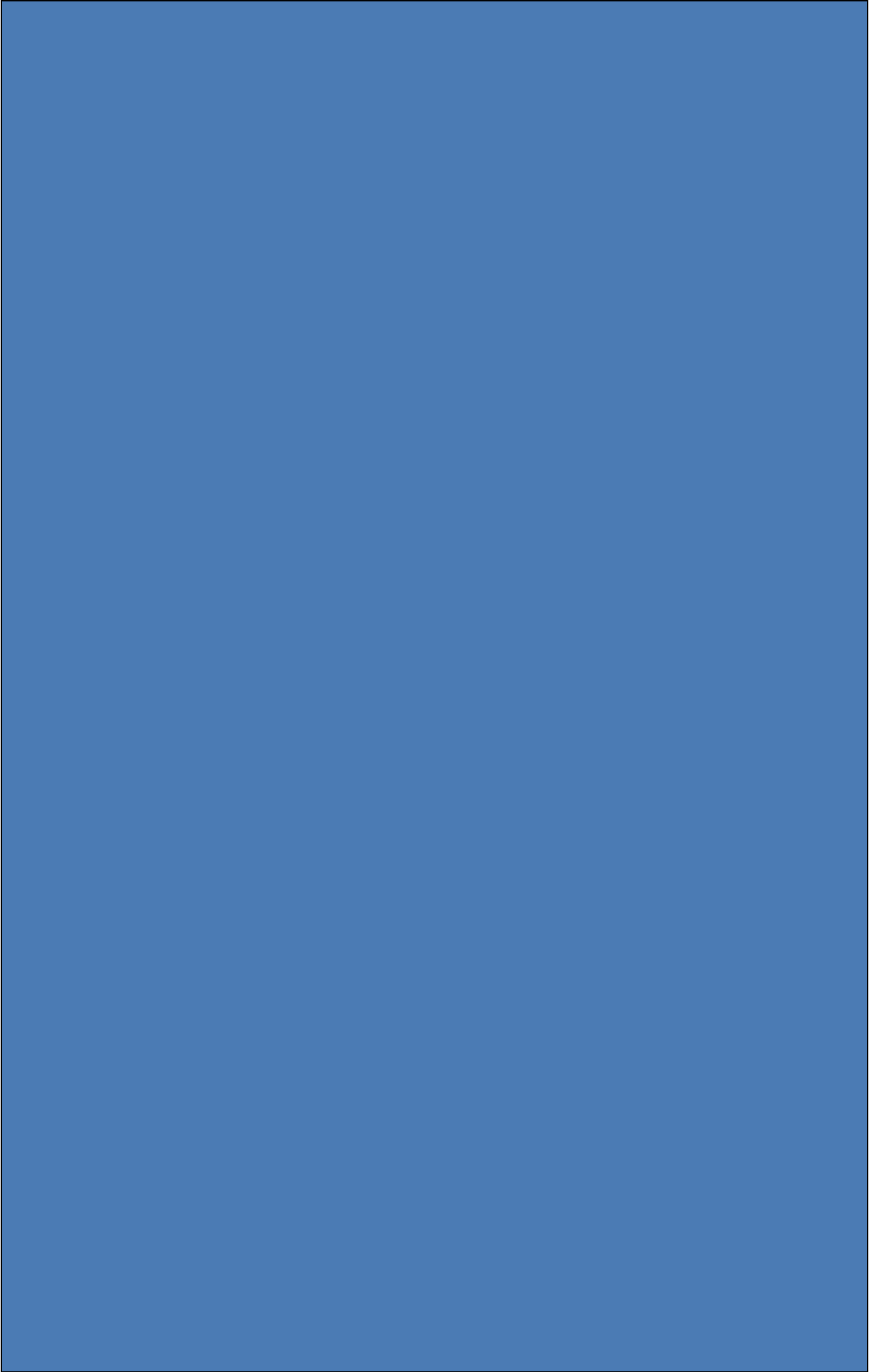


6. Current Projects and Papers

	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

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@kbcsn.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

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@kbcsn.hr)	34
	Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum	Ingeborg Barisic (ingeborg.barisic@kbcsn.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 monotherapy¹. 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.

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; ²University of Ulster, Belfast, United Kingdom; ³Region Syddanmark, Odense, Denmark; ⁴Queen Mary University of London, London, United Kingdom; ⁵Provinciaal Instituut voor Hygiene, Antwerp, Belgium; ⁶Institut National de la Sante et de la Recherche Medicale, Paris, France; ⁷Otto-von-Guericke Universitat Megdeburg, Magdeburg, Germany; ⁸Johannes Gutenberg Universitat, Mainz, Germany; ⁹St Finbarr's Hospital, Cork, Ireland; ¹⁰CNR Institute of Clinical Physiology, Pisa, Italy; ¹¹Azienda Ospedaliero Universitaria di Ferrara, Ferrara, Italy; ¹²G'mangia Gill, Malta, Malta; ¹³University Medical Centre Groningen, Groningen, Netherlands; ¹⁴Registre Vaudois des Malformations, Lausanne, Switzerland; ¹⁵Singleton Hospital, Swansea, United Kingdom; ¹⁶Medical Birth Registry of Norway, Bergen, Norway; ¹⁷Polish Registry of Congenital Malformations, Poznan, Poland; ¹⁸Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu, Poland, Poland; ¹⁹Swedish National Board of Health and Welfare and University of Lund, Lund, Sweden; ²⁰Klinika z a Djecje Bolesti Zagreb, Zagreb, Croatia; ²¹Centre de Génétique Humaine Institut de Pathologie et de Génétique, Charleroi, Belgium; ²²Registre des Malformations Congenitales D'Alsace, France; ²³Registro Anomalias Congénitas CAPV, Vitoria-Gasteiz, Spain; ²⁴Princess 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.

**British Isles Network of Congenital Anomaly Registers
Biennial Scientific Meeting
Congenital Anomaly Registers: maximizing a valuable resource**

**Tuesday 7th October 2014
Dylan Thomas Centre, Swansea SA1 1RR**



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 study¹ 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.

¹Dolk 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

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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

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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%CI 1.08-10.8, $n=3$). Nine EA cases were exposed to maternal mental health conditions/medications were adjOR 2.68 (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.

