Eurocat

European Surveillance of Congenital Anomalies

EUROCAT Statistical Monitoring Report - 2005

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1. Summary

Each year, EUROCAT performs statistical monitoring for both trends and clusters in time in order to detect possible changes in teratogenic exposures which may require public health action. We report here the results up to birth year 2005. Cases of congenital anomaly among livebirths, fetal deaths and terminations of pregnancy following prenatal diagnosis are included. Trends and clusters are subjected to preliminary investigation by registers, which also forms part of data quality monitoring.

30 registries were included in a time trend analysis for their most recent ten years of data (in fifteen registries this was 1996-2005, for the remaining registries the period ended in 2003-4), covering a total population of 5.9 million births. A total of 284 significant trends (87 increasing and 197 decreasing) were reported from surveillance of 95 anomaly subgroups, many more than would be expected by chance. Some of these confirmed known time trends, for example increases in gastroschisis, and in Down Syndrome (the latter due to maternal age increases). Other trends were related to increasing use of prenatal or neonatal screening and diagnosis, or changing inclusion criteria.

Fifteen registries were included in a cluster analysis identifying clusters in 2004-2005, covering approximately 0.5 million births in that two year period. 75 congenital anomaly subgroups were tested, and 14 clusters of low chance probability ($p<0.05$) were found. Preliminary investigations of 11 of these clusters were conducted by registries. One cluster of gastroschisis was considered to be a "real" cluster in the sense that it was likely to be due to a recent excess teratogenic exposure and is being further investigated, two more clusters (spina bifida and cleft lip) were recommended for further surveillance before further investigation. Others were due to diagnostic or data quality issues, or were chance aggregations of heterogeneous conditions. There was no pattern of time clusters in any one congenital anomaly subgroup occurring across Europe.

More resources need to be allocated in Europe to the investigation of trends and clusters in congenital anomalies. Many registries are currently not fully funded for this activity.

2. Introduction

Each year, EUROCAT performs statistical monitoring for both trends and clusters in time. Statistical monitoring relates to two of EUROCAT's objectives:

- to provide essential epidemiologic information on congenital anomalies in Europe
- to co-ordinate the detection of, and response, to clusters and early warning of teratogenic exposures

A full protocol of rationale and methodology is available (EUROCAT Statistical Monitoring Protocol http://www.eurocat.ulster.ac.uk/pubdata/Stat-Mon.html).

We report here the results up to birth year 2005. Cases of congenital anomaly among livebirths, fetal deaths and terminations of pregnancy following prenatal diagnosis are included. We report both the statistical results, and the results of preliminary investigations made by registries.

The statistical analysis of trends and clusters is undertaken annually using the EUROCAT Central Registry database. All registries which have transmitted a new year of data to EUROCAT are included in time trend analysis. Registries classified as "early response" i.e. registries that met the EUROCAT data transmission deadline of February 15th 2007, and having a full dataset for the most recent 5 years (2001-2005) were included in cluster detection.

Registries can also use the common statistical monitoring software to conduct their own monitoring on more recent data, and reports of any such analyses conducted up to June 2007 are also included in this Report. In addition, any trends or clusters detected outside of formal statistical monitoring (e.g. reported to the registry by local clinicians) up to June 2007 are reported here.

Overview of report:

The methodology is described in Section 3. Section 3.1 summarises the statistical methodology. Section 3.2 details changes made to the statistical software since the EUROCAT Statistical Monitoring Report 2004. Section 3.3 lists the registries and anomaly groups included in the current monitoring 2001-2005.

Results are presented in Section 4. Section 4.1 presents the Central Registry monitoring results, using the EUROCAT database. Section 4.2 gives details of member registry investigations into the trends and clusters identified centrally. Section 4.3 describes member registry investigations using the common EDMP software and more recent data held locally. Clusters identified locally by other means are described in Section 4.4.

3. Methodology

3.1 Summary of methods

Software to detect clusters and trends is available in the EDMP (EUROCAT Data Management Program)

3.1.1 Clusters

1. A 'scan' moving window method is used to detect clusters, (See EUROCAT Statistical Monitoring Protocol http://www.eurocat.ulster.ac.uk/pubdata/Stat-Mon.html), scanning all recorded cases in the period 2001-2005.
2. Clusters or deficits occurring in the last 2 years (2004-2005) that are less than 18 months in length are reported.
3. A minimum of 7 cases over the surveillance period (2001-2005) is needed to run the scan analysis.
4. The default scan analysis uses date of conception, which is a program-generated variable calculated from gestational age and date of birth. If gestational age is missing for more than 10% of cases within a registry, the analysis uses date of birth/delivery. Where gestational age is missing for less than 10%, it is estimated based on registry, year of birth, type of birth and anomaly subgroup.
5. Cases with missing or incomplete date of birth/delivery are excluded.
6. When date of conception is used as a basis for cluster detection, the period of surveillance ENDS with dates of conception on 31 March in the last year under surveillance (2005). If date of birth/delivery is used to detect clusters, the last full year (1 January – 31 December) is included in the surveillance.
7. The output of cluster analyses lists all significant clusters which may be over-lapping. All the output data should be examined to determine the full time period over which the excess number of cases is observed. This may be outside the start and end date of the most significant cluster.

3.1.2 Trends

1. Trend detection is based on a chi squared test for trend using the number of cases per year and the number of births per year.
2. Trends during the last 10 years of data (1996-2005) are detected.
3. Trend analysis is always based on date of birth.

3.2 Statistical software updates

Changes to the EDMP software from previous years include:

1. Trend detection is now run using 10 years of data (where available), as opposed to 5 years of data.
2. The output of the trend analysis shows observed cases grouped in 2 year intervals, e.g. 1996-97, 1998-99, 2000-01, 2002-03 and 2004-05. A minimum of 5 EXPECTED cases in each 2 year period is needed to be included in the trend analysis.
3. The cluster output now includes a summary of trend test results run on the same years of the cluster monitoring, 2001-2005, to establish if a cluster is part of an overall trend.

3.3 Inclusion/Exclusion criteria

Registry inclusion criteria

- Registries must have continuous individual case data to be included (i.e. full member registries only).
- Registries must have a stable birth population (annual birth population changes must be less than +/- 10%).
- Only registries that transmitted year 2005 data with full date of birth information are included in the cluster monitoring 2001-2005.
- If a registry does not meet the 15th February deadline for data transmission, then surveillance is carried out locally.

Cluster monitoring is run using year 2001-2005 data while trend analysis is run using 1996-2005 data or data for the most recent 10 year period, if available. Registries must have a minimum 5 years of data to be included in trend analysis.

At the time of annual statistical monitoring in Spring 2007, 15 registries had transmitted year 2005 data to EUROCAT Central Registry. Cluster analysis was run using 10 registries (Antwerp, Dublin, Hainaut, Northern Region, Northern Netherlands, Paris, Tuscany, Vaud, Wales, and Wessex). Two registries were excluded due to > 10% fluctuations in population (Thames Valley and Emilia Romagna). Norway and Ukraine were excluded as these registries had not transmitted 5 years of data at time of annual monitoring, and Saxony-Anhalt was excluded as the full date of birth information was unavailable.

Cluster analysis was run on 75 EUROCAT subgroups of congenital anomalies (Appendix A). Seventeen major heterogeneous subgroups (e.g. Nervous system, Eye, Congenital heart disease etc) were excluded from cluster analysis. A further 3 subgroups (Thanatophoric dwarfism, Jeunes syndrome, and Achondroplasia) were also excluded.

Seven EUROCAT congenital anomaly subgroups have a specific ICD10 code with no equivalent ICD9 code:

- Aortic valve atresia/stenosis
- Hypoplastic right heart
- Cystic adenomatous malformation of lung
- Teratogenic syndromes with malformations
- Fetal alcohol syndrome
- Valproate syndrome
- Warfarin syndrome.

Registries must have used ICD10 coding for the whole 5 year period 2001-2005 in order to be included in surveillance of these 7 specified subgroups.

Thirty full member registries were included in the trend analysis covering the last 10 years of the registry's existence (if available). Norway, Auvergne and Ukraine were excluded from trend analysis as they had only 1 year of data at the time of monitoring. Hungary was excluded as data was unchanged from previous report (See http://www.eurocat.ulster.ac.uk/pdf/Statistical-Monitoring-Report-2004.pdf).

4. Results

4.1 Central Registry statistical monitoring results

4.1.1 Detected Clusters

A total of 14 clusters were detected from surveillance of 75 anomaly subgroups in 10 EUROCAT registries, with a total population of 469,000 births in 2004-2005 (Table 1). A total of 482 cluster tests were performed giving a cluster detection rate of almost 3%. Thirteen clusters were detected using date of conception as surveillance method, while 1 was detected based on date of birth/delivery. The number of detected clusters per EUROCAT anomaly subgroup ranged from 0 to 2, while the number of detected clusters per registry ranged from 0 to 3 (Table 1).

Two clusters of Congenital cataract, Cleft lip with or without palate, and Posterior urethral valve and/or prune belly were detected based on date of conception.

- The Congenital cataract clusters were detected in Paris (France) and Tuscany (Italy).
- The Cleft lip with or without palate (CLWWP) clusters were detected in Belgium in Antwerp and Hainaut. In Hainaut, the CLWWP cluster was part of an increasing trend (See Appendix B).
- The Posterior urethral valve and/or prune belly clusters were detected in Dublin (Ireland) and Wales (UK).

Single clusters of the following subgroups were detected based on date of conception:

- Spina Bifida (Wessex, UK)
- Atrial septal defect (Vaud, Switzerland)
- Atrioventricular septal defect (Wessex, UK)
- Hypoplastic right heart (Wales, UK)
- Gastroschisis (Northern Region, UK)
- Cystic kidney disease (Northern Region, UK)
- Club foot – talipes equinovarus (Wales, UK)

A single cluster of Lower limb reduction was identified in Hainaut (Belgium) based on date of birth.

The Posterior urethral valve and/or prune belly cluster detected in Dublin and Gastroschisis cluster detected in Northern Region, UK were identified in the previous report (See http://www.eurocat.ulster.ac.uk/pdf/Statistical-Monitoring-Report-2004.pdf).

Full details of each cluster are found in Appendix B.

The outcomes of the individual registry preliminary investigations into the detected clusters are shown in Section 4.2.1.

Table 1: Central Registry Statistical Monitoring Results: Table of detected clusters (highlighted), by registry and by anomaly

Anomaly Subgroup	Total clusters across all registries			Antwerp (BE)	Hainaut (BE)	Paris (FR)	Dublin (IE)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	Northern Region (UK)	Wales (UK)	Wessex (UK)
				2001-2005	2001-2005	2001-2005	2001-2005	2001-2005	2001-2005	2001-2005	20012005	2001-2005	2001-2005
	C	B	T										
All Anomalies	X	X	X	X	X	X	X	X	X	X	X	X	X
Nervous system	X	X	X	X	X	X	X	X	X	X	X	X	X
Neural Tube Defects	0	0	0										
Anencephalus and similar	0	0	0										
Encephalocele	0	0	0	*	*			*	*				
Spina Bifida	1	0	1										C
Hydrocephaly	0	0	0										
Microcephaly	0	0	0						*	*			
Arhinencephaly/holoprosencephaly	0	0	0	*	*		*			*			
Eye	X	X	X	X	X	X	X	X	X	X	X	X	X
Anophthalmos/microphthalmos	0	0	0		*				*	*			*
Anophthalmos	0	0	0	*	*		*	*	*	*	*	*	*
Congenital cataract	2	0	2		*	C		C		*			
Congenital glaucoma	0	0	0	*	*	*	*	*	*	*	*		*
Ear, face and neck	X	X	X	X	X	X	X	X	X	X	X	X	X
Anotia	0	0	0	*	*		*	*	*	*		*	*
Congenital heart disease	X	X	X	X	X	X	X	X	X	X	X	X	X
Common arterial truncus	0	0	0	*	*		*	*	*	*			
Transposition of great vessels	0	0	0		*					*			
Single ventricle	0	0	0	*	*			*	*	*			*
Ventricular septal defect	0	0	0										
Atrial septal defect	1	0	1							C			
Atrioventricular septal defect	1	0	1	*									C
Tetralogy of Fallot	0	0	0										
Tricuspid atresia and stenosis	0	0	0	*	*			*		*			*
Ebstein's anomaly	0	0	0	*	*		*	*	*	*	*		
Pulmonary valve stenosis	0	0	0						*				*
Pulmonary valve atresia	0	0	0	*	*			*		*			*
Aortic valve atresia/stenosis §	0	0	0	*	X			X	X				
Hypoplastic left heart	0	0	0		*								
Hypoplastic right heart §	1	0	1	*	X	*	*	X	X	*	*	C	
Coarctation of aorta	0	0	0										
Total anomalous pulm venous return	0	0	0	*	*			*		*			*
Respiratory	X	X	X	X	X	X	X	X	X	X	X	X	X
Choanal atresia	0	0	0					*		*			
Cystic adenomatous malf of lung §	0	0	0	*	X		*	X	X	*			*
Oro-facial clefts	X	X	X	X	X	X	X	X	X	X	X	X	X
Cleft lip with or without palate	2	0	2	C	C								

				Antwerp (BE)	Hainaut (BE)	Paris (FR)	Dublin (IE)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	Northern Region (UK)	Wales (UK)	Wessex (UK)
Cleft palate	0	0	0										
Digestive system	X	X	X	X	X	X	X	X	X	X	X	X	X
Oesophageal atresia with/ without tracheo-oesophageal fistula	0	0	0										
Duodenal atresia or stenosis	0	0	0	*	*			*	*	*			
Atresia or stenosis of other parts of small intestine	0	0	0	*	*				*	*			*
Ano-rectal atresia and stenosis	0	0	0							*			
Hirschsprung's disease	0	0	0		*			*		*			
Atresia of bile ducts	0	0	0	*	*	*	*			*			*
Annular pancreas	0	0	0	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	0	0							*			
Abdominal wall defects	X	X	X	X	X	X	X	X	X	X	X	X	X
Gastroschisis	1	0	1					*		*	C		
Omphalocele	0	0	0		*								
Urinary	X	X	X	X	X	X	X	X	X	X	X	X	X
Bilateral renal agenesis including Potter syndrome	0	0	0							*			
Cystic kidney disease	1	0	1								C		
Congenital hydronephrosis	0	0	0										
Bladder exstrophy and/or epispadia	0	0	0	*	*			*	*	*	*		*
Posterior urethral valve and/or prune belly	2	0	2	*	*		C			*		C	*
Genital	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypospadias	0	0	0										
Indeterminate sex	0	0	0	*			*	*	*	*			
Limb	X	X	X	X	X	X	X	X	X	X	X	X	X
Limb reduction	0	0	0										
Upper limb reduction	0	0	0										
Lower limb reduction	0	1	1		B								
Complete absence of a limb	0	0	0	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	1	0	1								*	C	
Hip dislocation and/or dysplasia	0	0	0								*		*
Polydactyly	0	0	0										
Syndactyly	0	0	0										
Arthrogryposis multiplex congenita	0	0	0	*			*		*	*	*	*	*
Musculo-skeletal	X	X	X	X	X	X	X	X	X	X	X	X	X
Thanatophoric dwarfism	X	X	X	X	X	X	X	X	X	X	X	X	X
Jeunes syndrome	X	X	X	X	X	X	X	X	X	X	X	X	X
Achondroplasia	X	X	X	X	X	X	X	X	X	X	X	X	X
Craniosynostosis	0	0	0										*
Congenital constriction bands/amniotic band	0	0	0	*	*	*	*	*	*	*			*
Other malformations	X	X	X	X	X	X	X	X	X	X	X	X	X
Asplenia	0	0	0	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	0	0		*		*	*	*	*			*
Conjoined twins	0	0	0	*	*		*	*	*	*	*	*	*
Disorders of skin	0	0	0										*

				Antwerp (BE)	Hainaut (BE)	Paris (FR)	Dublin (IE)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	Northern Region (UK)	Wales (UK)	Wessex (UK)
Teratogenic syndromes with malformations §	X	X	X	X	X	X	X	X	X	X	X	X	X
Fetal alcohol syndrome §	0	0	0	*	X	*	*	X	X	*	*	*	*
Valproate syndrome §	0	0	0	*	X	*	*	X	X	*	*	*	*
Warfarin syndrome §	0	0	0	*	X	*	*	X	X	*	*	*	*
Maternal infections resulting in malformations	0	0	0		*			*	*	*	*		
Genetic syndromes + microdeletions	X	X	X	X	X	X	X	X	X	X	X	X	X
Chromosomal	X	X	X	X	X	X	X	X	X	X	X	X	X
Down Syndrome	0	0	0										
Patau syndrome/trisomy 13	0	0	0	*	*								
Edward syndrome/trisomy 18	0	0	0										
Turner's syndrome	0	0	0										
Klinefelter's syndrome	0	0	0	*			*		*			*	
Cru-du-chat syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*
Total clusters: Date of conception	13			1	1	1	1	1	0	1	2	3	2
Total clusters: Date of birth		1		0	1	0	0	0	0	0	0	0	0
Total clusters: All			14	1	2	1	1	1	0	1	2	3	2

Key:

C = Clusters run by Date of conception, B = Clusters run by Date of birth, T = Total clusters
X = Data excluded from analysis
* Too few cases to run analysis (registries must have at least 7 cases over the surveillance period)
§ Registries must have used ICD10 coding for the whole 5 year period 2001-2005 in order to be included in surveillance of these subgroups

4.1.2 Detected trends

A total of 284 significant trends (87 increasing and 197 decreasing) were reported from surveillance of 95 anomaly subgroups in 30 EUROCAT registries covering 5.9 million births, 1996-2005 (Table 2). In addition, there were 218 with significant non-linear heterogeneity (or significant change from year to year, but no overall trend). A total of 1419 chi square tests for trend were performed. By chance alone, we would expect the chi square trend test to detect significant trends/non-linear heterogeneity in approximately 5% of tests. The current trend analysis yielded a detection rate of 35%.

Per EUROCAT anomaly subgroup, the number of increasing trends ranged from 0-6, the number of decreasing trends ranged from 0-16, and the number with significant non-linear heterogeneity ranged from 1-30 (Table 2). The "All Anomalies" subgroup showed significant non-linear heterogeneity for all 30 registries.

Per registry, the number of increasing trends ranged from 0-13, the number of decreasing trends ranged from 1-20, and the number of non-linear heterogeneity ranged from 1-16 (Table 2). Due to the large number of reported trends, we only describe registries with 9 or more trends in any direction. Only Wessex reported significant increasing trends in 9 or more subgroups. Eight registries (Dublin, Campania, North East Italy, Tuscany, Northern Netherlands, South Portugal, Thames Valley and Trent) reported significant decreasing trends in 9 or more subgroups. Nine registries (Styria, Paris, Saxony-Anhalt, Campania, Sicily, South Portugal, Basque Country, Trent and Wales) reported significant non-linear heterogeneity in 9 or more subgroups.

Increasing trends in congenital anomalies

Surveillance showed significant increasing trends in Hypospadias in 6 registries (Paris, Saxony-Anhalt, Tuscany, Malta, Northern Netherlands and Vaud).

Significant increasing trends were identified in 4 registries for the following congenital anomaly subgroups:

- Ventricular septal defect increased in Paris (France), Saxony-Anhalt (Germany), Mainz (Germany) and North Thames (UK).
- Congenital hydronephrosis increased in Antwerp (Belgium), Saxony-Anhalt (Germany), Tuscany (Italy) and Barcelona (Spain).
- Genital anomalies increased in Saxony-Anhalt (Germany), Tuscany (Italy), Malta and Vaud (Switzerland).
- Chromosomal anomalies increased in Styria (Austria), Mainz (Germany), Barcelona (Spain) and Vaud (Switzerland).
- Down syndrome increased in Paris (France), Mainz (Germany), Barcelona (Spain) and Wessex (UK).

Decreasing trends in congenital anomalies

Significant decreasing trends were reported for 5 main organ system subgroups (Digestive system anomalies, Urinary anomalies, Limb anomalies, Musculo-skeletal anomalies and Other malformations). Only the "Other malformations" subgroup had

a specific subgroup within it showing significant decreasing trends ("Disorders of skin").

"Other malformations" decreased in 16 registries (Paris, Tuscany, Dublin, N Netherlands, Emilia Romagna, Strasbourg, Vaud, S Portugal, Antwerp, Basque Country, N Thames, Cork & Kerry, Campania, Wales, Thames Valley and Trent). "Disorders of skin" decreased in 9 registries (Paris, Dublin, N Netherlands, Emilia Romagna, Vaud, S Portugal, Antwerp Saxony-Anhalt and Trent).

"Digestive system anomalies" decreased in 11 registries (Paris, Tuscany, Dublin, N Netherlands, Vaud, Zagreb, S Portugal, Basque Country, Campania, Wielkopolska and S E Ireland).

Urinary anomlaies decreased in 9 registries (Dublin, N Netherlands Emilia Romagna, Vaud, Malta, Cork & Kerry, Campania, Wessex and Northern Region).

Limb anomalies decreased in 9 registries (Tuscany, Emilia Romagna, Vaud, Zagreb, S Portugal, Basque Country, North Thames, Thames Valley and S E Ireland).

Musculo-skeletal malformations decreased in 10 registries (Paris, Tuscany, Dublin, N Netherlands, Zagreb, S Portugal, Styria, Wales, Thames Valley and Trent).

The outcomes of the individual registry preliminary investigations into the identified trends are shown in Section 4.2.2.

Table 2: Central Registry Statistical Monitoring Results: Table of reported ten year trends by registry and by anomaly

Anomaly subgroup	Total trends across all centres /	\	~	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	Northern Region (UK)	North Thames (UK)	Thames Valley (UK)	Trent (UK)	Wales (UK)	Wessex (UK)
	Years tested			1995-2004	1996-2005	1996-2005	1995-2004	1995-2004	1996-2005	1993-2002	1995-2004	1996-2005	1997-2004	1996-2005	1998-2003	1997-2004	1996-2005	1994-2003	1993-2002	1996-2005	1995-2004	1996-2005	1999-2004	1995-2004	1994-2003	1995-2004	1996-2005	2000-2005	1995-2004	1996-2005	1999-2004	1998-2005	1996-2005
All Anomalies	0	0	30	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Nervous system	1	3	2	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Neural Tube Defects	0	4	0						~			/		\								\									~	\	
Anencephalus and similar	0	2	2															\				\							\			\	
Encephalocele	0	0	1	*			*	*			*	~			*			\	*		*	\		~									
Spina Bifida	0	1	0	*	*	*	*	*		*	*		*		*		*		*	*	*	*		*	*	*	*			*	~		
Hydrocephaly	0	4	1				*				\																						
Microcephaly	1	1	1				*			\			\								*			~			\				\		
Arhinencephaly/holoprosencephaly	0	0	1				*	*		*	X	/		~				X		*	*	\			*		*			*			*
Eye	1	7	2	*	*	*	*	*		*	*	*	*	*	*			X	*	*	*	*	*	*	*	*	*			*	~	*	*
Anophthalmos/microphthalmos	0	2	2	\			*		~	~	*			\							*	\		\	\			\		*	\		/
Anophthalmos	0	0	0	*	*	*	*	*	~		*	*	*	\	*			\	*	*	*	*	*	*	*	*	*	*	*	*		~	*
Congenital cataract	0	1	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital glaucoma	0	0	0	*	*	*	*	*			*	*	*		*	*	*		*		*		*	*	*	*	*	\	*	*			*
Ear, face and neck	1	7	5	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Anotia	0	0	0	\			*	*	\		*	~	*	~	*			\	/	\	*	~		\	~	~	\	*		*	\		*
Congenital heart disease	3	3	17	~			/		~	~	/	~	~			~	~	X	~	~	~	\	~	~	\		~	~	/	\	~	~	~
Common arterial truncus	1	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	X	/	*	*	*	*	*	*	*	*	*	*	*	*			*

				Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	Northern Region (UK)	North Thames (UK)	Thames Valley (UK)	Trent (UK)	Wales (UK)	Wessex (UK)
Transposition of great vessels	2	3	0			*	*	*	/		*					\		X			*		\	*		/	*			*	\		
Single ventricle	0	1	0	*	*	*	*	*		*	*	*	*	*	*	\	*	X	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Ventricular septal defect	4	6	5	~					/		/	/				\	\	X	~	\	\	\		~				~	/	\	~		
Atrial septal defect	3	5	9	~			/	\				~	~	\			\	X	/		~	\	~	~	~			~	~		*		\	/
Atrioventricular septal defect	1	1	0		*		*	*	/	*	*	*	*		*			X	*		*			*	*		*			*		\	
Tetralogy of Fallot	1	0	2				*	*			*		*		*			X	~		*						*			/	*	~		
Tricuspid atresia and stenosis	0	4	1	*	\	*	*	*		*	*	*	*	*	*	*	\	X	*	~	*		*	*	\	*	*	*		*		\	*
Ebstein's anomaly	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	X	*	*	*	*	*	*	*	*	*	*	*		*	*	*
Pulmonary valve stenosis	3	5	2	/		~	*			\	*	~		\	*	\		X	/	\		\		*				/		*			*
Pulmonary valve atresia	1	0	0	*	*	*	*	*		*	*	*	*	*	*	*		X	*	*	*	*	*	*	*		*		/	*			*
Aortic valve atresia/stenosis §	1	0	0	X	X	X	X	X	X	X	X	X	*	X	X	X	X	X	X	X	*	X		X	X	X	X			*	*		/
Hypoplastic left heart	2	0	2	/		*	*	*	/		*		*		*			X	*		*			~	*		*		~	*			
Hypoplastic right heart §	1	1	0	X	X	X	X	X	X	X	X	X	*	X	X	X	X	X	X	X	*	X	*	X	X	X	X	*	/	*	\	*	*
Coarctation of aorta	1	2	0				*	*			*				*	\		X			*								/	*	\		
Total anomalous pulm venous return	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	X	*	*	*	*	*	*	*	*	*		*	*			*
Respiratory	1	5	3				*	*				~		\	\	~			~		*	\							\		\		/
Choanal atresia	0	0	2	*	*	*	*	*		*	*	~	*		*	*	*		~	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Cystic adenomatous malf of lung §	0	0	0	X	X	X	X	X	X	X	X	X	*	X	X	X	X	X	X	X	*	X	*	X	X	X	X		*	*	*		*
Oro-facial clefts	0	3	1													\	~		\												\		
Cleft lip with or without palate	1	2	1			/					~				*				X											\			\
Cleft palate	0	2	0																X		\										\		
Digestive system	2	11	6	~	~		\		\			~		\	\	\		/	~	\		\	\	\	\		\	\		~			~	/

				Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	Northern Region (UK)	North Thames (UK)	Thames Valley (UK)	Trent (UK)	Wales (UK)	Wessex (UK)
Oesophageal atresia with or without tracheo-oesophagal fistula	3	2	1		/	/	*	*			*		*		*	/		\	*		*	~	\		*		*			*		
Duodenal atresia or stenosis	0	0	1	*	*	*	*	*		*	*	*	*	*	*			X	*	*	*	*	*	*	*	*			*			~
Atresia or stenosis of other parts of small intestine	0	2	0	*	*	*	*	*		*	*	*	*	*	*	*		X	*	*	*	*	*	*	*	*		*	*	\		\
Ano-rectal atresia and stenosis	1	0	2	~			*	*		~			*		*	/					*				*		*					
Hirchspung's disease	0	0	0	*		*	*	*		*	*	*	*		*	*	*	*	*	*	*		*	*	*	*		*	*			
Atresia of bile ducts	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Annular pancreas	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	1	1				*	*			*	*	*		*			X			*	\	*	~			*					
Abdomnal wall defects	2	1	2				*		~			~			*		/	\			*											/
Gastroschisis	1	0	2		*	*	*	*	~	*	*	~	*		*		*	*	*	*	*	*		*	*	*	*						/
Omphalocele	0	1	2	*		*	*	*	~	*	*	~	*		*				*		*	\		*			*						
Urinary	1	9	13	~		~			~	~	~	~	\	\		\	\	~	~	~	\	\		/		~	\	\		~	~	~	\
Bilateral renal agenesis including Potter syndrome	0	2	2	*	\	*	*	*	~		*		*		*				X	\	*			*		~	*			*			
Cystic kidney disease	2	2	0				*	/							\			X	/		*								\				
Congenital hydronephrosis	4	6	11	~	/	~			~		~	/	\			~	\	~	~	/		\			/	~	~	\		~	~	\	\
Bladder extrophy and/or epispadia	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*
Posterior urethral valve and/or prune belly	0	0	1	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*		*	*	*	~	*
Genital	4	4	10	~						~		/	\	\	\	~	~	~	~	/	/			~			/		\		~	~	~
Hypospadias	6	5	9	~					/	~		/	\	\	\	~		~	~	/	/	/		~	\	\	/		X	*	~	~	~
Indeterminate sex	0	0	0	*	*	*	*	*		*	*	*	*	*	*		*	X	*	*	*	*	*	*	*	*	*		*	*		*	*
Limb	3	9	12		~	~	\		~	/	~	~	~	~	\	~	\	~	/	\		~		\		\	\		\	\	~	~	/
Limb reduction	1	3	0				*						\		*			\			*			\			\						/
Upper limb reduction	1	3	0				*				*				*	\	/	\			*			\									
Lower limb reduction	2	1	0	*		*	*	*			*		*		*	/			*		*			*	*	*				*	\		/

				Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	Northern Region (UK)	North Thames (UK)	Thames Valley (UK)	Trent (UK)	Wales (UK)	Wessex (UK)
Complete absence of a limb	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	3	5	4								\			~		/	~	*	*			\		\	*	~		*	\	\	/	~	/
Hip dislocation and/or dysplasia	1	1	9	*		~			\	/		~		~	*	~		*	~		*	~		~	*	*		*	*	*	~	~	*
Polydactyly	0	1	0													\													X				
Syndactyly	1	2	2				*	*	~		*							\				~			*		\		X	*			/
Arthrogryposis multiplex congenita	0	3	0	*	*	*	*	*		*	*	*	*	*	*	\	*	*	*	*	*	*	*		*	*	*	*	\	*	\	*	*
Musculo-skeletal	0	10	7	\	~		\		\		~	~		\	~			~	~	\		\		\		~				\	\	\	
Thanatophoric dwarfism	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Jeunes syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Achondroplasia	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Craniosynostosis	0	2	3	~			*	*			*		*	\	*			*	*	*	*	*	*		~		~	*	*	\			*
Congenital constriction bands/amniotic band	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*			*
Other malformations	2	16	1		\				\	\			\	\		\	\	/	/	\		\		\	~	\	\		\	\	\	\	
Asplenia	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	1	0	*	*	*	*	*	\	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*				*
Conjoined twins	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	0	9	6	~	\			*	\	~	*	\	*	\		~	\			~		\		\	~		\		*	*	\	~	*
Teratogenic syndromes with malformations §	0	0	0	X	X	X	X	X	X	X	X	X	*	X	X	X	X	X	X	X	*	X	*	X	X	X	X	*	*	*	*		
Fetal alcohol syndrome §	0	0	0	X	X	X	X	X	X	X	X	X	*	X	X	X	X	X	X	X	*	X	*	X	X	X	X	*	*	*	*	*	*
Valproate syndrome §	0	0	0	X	X	X	X	X	X	X	X	X	*	X	X	X	X	X	X	X	*	X	*	X	X	X	X	*	*	*	*	*	*
Warfarin syndrome §	0	0	0	X	X	X	X	X	X	X	X	X	*	X	X	X	X	X	X	X	*	X	*	X	X	X	X	*	*	*	*	*	*
Maternal infections resulting in malformations	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*			*
Genetic syndromes + microdeletions	3	4	2	/		\	*				~				*			\		/						/			~	\			\

				Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	Northern Region (UK)	North Thames (UK)	Thames Valley (UK)	Trent (UK)	Wales (UK)	Wessex (UK)
Chromosomal	4	2	8	/	~				~		/					~	~			\				~	/	~	/		~	\		~	
Down Syndrome	4	1	5		~	~		~	/		/								\					~	/	~							/
Patau syndrome/trisomy 13	1	0	0	/	*	*	*	*		*	*	*	*		*			X	*		*	*	*	*			*						
Edward syndrome/trisomy 18	3	0	2				*		/			/	*		*			X	*		*		~					/			~		
Turner's syndrome	2	3	2			*	*	*		/	*		*		*	\			*	\	*	\	*	~	*	/			~	*			
Klinefelters syndrome	0	0	0	*	*		*	*		*	*	*	*	*	*				*		*	*	*	*			*	*		*			
Cru-du-chat syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Total /	87			5	2	2	2	1	7	3	4	7	0	0	0	4	2	2	7	4	2	1	0	1	3	2	4	2	6	0	1	0	13
Total \		197		3	4	1	3	1	7	3	2	1	7	14	6	13	8	10	2	10	3	20	3	10	4	4	8	4	7	9	17	8	5
Total ~			218	12	6	7	1	2	14	8	7	16	4	6	2	10	6	7	13	5	3	6	4	14	5	10	4	5	5	4	14	13	5
Total any				20	12	10	6	4	28	14	13	24	11	20	8	27	16	19	22	19	8	27	7	25	12	16	16	11	18	13	32	21	23

Key: / = significant upward trend
\ = significant downward trend
~ = non-linear trends indicating significant heterogeneity
* Too few cases to run analysis.
§ Registries must have used ICD10 coding for the whole 5 year period 2001-2005 in order to be included in surveillance of these subgroups

4.2 Local registry investigations of clusters/trends identified centrally

Registries were asked to include the following in their investigation report:

Clusters

1. the methods and results of investigations as to whether changes in diagnostic or reporting practice might have contributed to the cluster;
2. the methods and results of any investigation into aetiological factors, including which aetiological factors were investigated and which source of information was used (registry database, further access to medical records or parents etc).
3. an account of any local concerns about exposures and how they came to your attention
4. whether anyone in your region (e.g. local community or health professional) had previously been aware of the cluster;
5. the basis for your decisions to conduct the investigation in the way you did, and whether you will continue to investigate (if so, how? if not, why not?).

Trends

1. Are there changes in diagnosis, in reporting, in coding, or in population definition that explain the trend?
2. Are there any known reasons why this might be a "real" trend in frequency of the anomaly?
3. Will the investigation continue (if so, how? if not, why not?).

4.2.1 Local registry preliminary investigations into detected clusters

No clusters were identified in Northern Netherlands. Central Registry received reports on preliminary cluster investigations from 7 of the remaining 9 (78%) local registries: Antwerp, Dublin, Paris, Northern Region, Tuscany, Wales and Wessex. The level of investigation varied between registries, with some registries such as Northern Region doing extensive checking and cross-referencing registry data with hospital records.

Of the 14 clusters detected from surveillance, 11 (79%) were investigated by the local registries. Table 3 shows the outcomes of the cluster investigations, classified as follows:

- A: Apparent cluster with cause for concern, further investigation ongoing (n=1)
- B: Not 'true' cluster as associated with aetiologic heterogeneity, changes in diagnosis, familial or twin recurrence (n=5)
- C: Excess of cases confirmed, but no further investigation proposed other than further surveillance (n=2)
- D: Increase in cases, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound detection rates (n=0)
- E: Data quality issues found to explain cluster (n=3)
- N: No report of preliminary investigations sent to Central Registry (n=3).

A possible cluster of gastroschisis cases was identified in Northern Region, UK, which is being monitored by the registry.

Full details of the registry investigations are found in a separate Annex in the membership-only section of the EUROCAT website (http://www.eurocat.ulster.ac.uk/).

Table 3: Outcomes of local registry preliminary investigations of detected clusters 2001-2005

Anomaly subgroups	Antwerp BE)	Hainaut (BE)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Vaud (CH)	Northern Region (UK)	Wales ((UK)	Wessex (UK)
Spina Bifida									C
Congenital cataract			B		B				
Atrial septal defect						N			
Atrioventricular septal defect									B
Hypoplastic right heart §			*	*	X		*	E	
Cleft lip with or without palate	C	N							
Gastroschisis					*		A		
Cystic kidney disease							B		
Posterior urethral valve and/or prune belly				B				E	*
Lower limb reduction		N							
Club foot - talipes equinovarus							*	E	

Key
A: Apparent cluster with cause for concern, further investigation ongoing
B: Not true cluster as caused by aetiologic heterogeneity, changes in diagnosis, familial or twin recurrence.
C: Excess of cases, but no further investigation proposed other than further surveillance
D: Increase in cases, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound detection rates
E: Data quality errors
N: No report of preliminary investigations sent to Central Registry
X: Data excluded from surveillance as Registries must have used ICD10 coding for the whole 5 year period 2001-2005 in order to be included in surveillance of this subgroup
* No surveillance, as too few cases

4.2.2 Local registry preliminary investigations into detected trends

Due to the shorter time interval between Central Monitoring and the RLM 2007, registries were asked to concentrate on cluster rather than trend investigations, thus the number of trend investigation reports is low. Central Registry received reports on preliminary trend investigations from 7 of 30 local registries (23%): Barcelona, Basque Country, Dublin, S E Ireland, Tuscany, Wessex and Odense. The level of investigation varied between registries. The results of the investigations into 23 of the 87 significant increasing trends (26%), and 45 of the 197 significant decreasing detected trends (23%) are described in Table 4, classified as follows:

- A: Changes in case ascertainment and/or coding (n=16)
- B: Changes in prenatal detection (n=1)
- C: Changes in referral to clinics/areas not covered by registry(n=0)
- D: Changes in definition or inclusion criteria(n=1)
- E: Changes in use of postnatal echocardiography or ultrasound (n=3)
- F: Heterogeneous subgroups (n=6)
- G: Most recent years lower prevalence due to non-inclusion of late diagnosed or late notified cases (n=3)
- H: Apparent trend, further investigation ongoing, or further surveillance indicated (n=2)
- I: Continuing trend previously detected and investigated/under investigation (n=4)
- J: Trend not apparent when more recent years included (n=0)
- N: No report of preliminary investigations sent to Central Registry (n=32)

Some trends can be explained by a combination of the classification categories e.g. B/E. The first classification category is considered the principal one, so trends classified as B/E will be counted in the B category.

The table only includes registries that sent a report on at least one trend to Central Registry. Results of preliminary investigations of significant non-linear heterogeneity in the remaining subgroups are included in the table for descriptive purposes.

An increasing trend of Transposition of great vessels was identified in Basque Country and a decreasing trend in the Digestive system anomalies was identified in S E Ireland. These new trends are being monitored by the registries.

Four known trends were identified in four subgroups (Nervous system, Gastroschisis, Chromosomal anomalies and Down syndrome). A decreasing trend of Nervous system anomalies was identified in Dublin while an increasing trend of gastroschisis cases was identified in Wessex. Chromosomal anomalies and Down syndrome showed increasing trends in the Barcelona registry.

No report on 16 identified increasing trends and 16 identified decreasing trends was sent to Central Registry.

Full details of the registry investigations are found in a separate Annex in the membership-only section of the EUROCAT website (http://www.eurocat.ulster.ac.uk/).

Table 4: Outcomes of local registry preliminary investigations of detected trends*

	Odense (DK)	Dublin (IE)	SE Ireland (IE)	Tuscany (IT)	Barcelona (ES)	Basque Country (ES)	Wessex (UK)
	1995-2004	1996-2005	1998-2003	1996-2005	1994-2003	1995-2004	1996-2005
Anomaly subgroup							
All Anomalies	G	N	N	N	N	A	N
Nervous system		I/C					
Microcephaly		N					
Eye		A/H			F		N
Anophthalmos/micropthalmos		A/H					
Ear, face and neck		A		N	F	A	
Congenital heart disease				N	E		N
Transposition of great vessels						H/A	
Ventricular septal defect				N			
Atrial septal defect	G/D	N			D		N
Tricuspid atresia and stenosis				N	E		
Pulmonary valve stenosis		N		N			
Aortic valve atresia/stenosis §							N
Respiratory		F/A	A				N
Cleft lip with or without palate							N
Digestive system		F/A	H	N		A	N
Duodenal atresia or stenosis							N
Atresia or stenosis of other parts of small intestine							N
Abdomnal wall defects							N
Gastroschisis							I
Urinary		F/A		N		A/D	N
Bilateral renal agenesis including Potter syndrome				N		H	
Cystic kidney disease	B/E		A				
Congenital hydronephrosis				N	E	A	N
Genital		G	A	N			A
Hypospadias		G	A	D	A	A	A
Limb		A	A	N		A	N
Limb reduction							N
Lower limb reduction							N
Club foot - talipes equinovarus		A				A	N
Hip dislocation and/or dysplasia		A					
Syndactyly							N
Musculo-skeletal		A	A	N		A	
Craniosynostosis		A				A	
Other malformations		F/A		N	F/A	A	
Disorders of skin		F/A		N	A		
Genetic syndromes + microdeletions				N			N
Chromosomal				A	I/B	I/B/C	
Down Syndrome	I				I/B	I/B/C	N
Turner's syndrome				N		N	

Key (Increasing trends highlighted in yellow, decreasing trends highlighted in blue, significant heterogeneity not highlighted):

* Only registries that sent a report to Central Registry are shown

- A: Changes in case ascertainment and/or coding
- B: Changes in prenatal detection
- C: Changes in referral to clinics/areas not covered by registry
- D: Change in definition or inclusion criteria
- E: Change in use of post-natal echocardiography or ultrasound
- F: Hetero-geneous subgroups
- G: Most recent year(s) lower prevalence due to non-inclusion of late diagnosed or late notified cases
- H: Apparent trend, further investigation ongoing, or further surveillance indicated
- I: Continuing trend previously detected and investigated/under investigation
- J: Trend not apparent when more recent year(s) included
- N: No report of preliminary investigations sent to Central Registry

4.2.3 Updates on previous local registry investigations into clusters and trends

Two of the clusters detected in the current statistical monitoring exercise were also identified in last year's Report (Posterior urethral valve/Prune Belly in Dublin and gastroschisis in Northern Region). Dublin has re-iterated that the Posterior urethral valve is not a "true" cluster. The Northern Region carried out further investigations of gastroschisis cases following the Statistical Monitoring Report 2004, but the excess of gastroschisis cases remain. Result of a trend test 2001-2005 showed that there was a significant non-linear heterogeneous trend (p=0.018) for gastroschisis in the Northern Region.

4.3 Local registry surveillance using EDMP

Central Registry received no results of local cluster or trend investigations using more recently ascertained data in EDMP.

4.4 Clusters and trends identified by other means

4.4.1 Limb reduction anomalies (hand) in Vaud, Switzerland

Local clinicians in Vaud were concerned about a possible cluster of limb reduction anomalies following the birth of 3 babies with limb reduction anomalies involving the left hand between September and October 2006. The expected number of cases was 1.05 for a 2 month period. A simple statistical test showed that this was not a statistically significant unusual cluster (P=0.09). Nevertheless, this information was circulated to other registries, to see if an excess of limb reduction anomalies was reported in other areas. Two registries (Northern Region, UK and Hainaut-Namur in Belgium) reported a single case of upper limb reduction defects.

4.4.2 Gastroschisis case-control study (UK)

Cardiff University (Wales) and partners have received funding from the Birth defects Foundation Newlife to carry out a case-control study to investigate the lifestyle, dietary and environmental risk factors associated with gastroschisis. Recruitment has started in Wales since April 2007. Newcastle, Southampton, East Midlands and South Yorkshire and Scotland hope to start recruiting cases, subject to getting the necessary approvals from the individual Research & Development departments. The study will run over two years and the aim is to recruit 100 cases and 300 controls.

Appendix A

Congenital anomaly subgroups included in statistical monitoring (see Guide 1.3 chapter 3.3 for definition of subgroups http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Guide-1.3.pdf)

	Included in cluster analysis	Included in trend analysis
All anomalies		X
Nervous system		X
Neural Tube Defects	X	X
Anencephalus and similar	X	X
Encephalocele	X	X
Spina Bifida	X	X
Hydrocephaly	X	X
Microcephaly	X	X
Arhinencephaly/ holoprosencephaly	X	X
Eye		X
Anophthalmos/ micropthalmos	X	X
Anophthalmos	X	X
Congenital cataract	X	X
Congenital glaucoma	X	X
Ear, face and neck		X
Anotia	X	X
Congenital heart disease		X
Common arterial truncus	X	X
Transposition of great vessels	X	X
Single ventrical	X	X
Ventricular septal defect (VSD)	X	X
Atrial septal defect (ASD)	X	X
Atrioventricular septal defect (AVSD)	X	X
Tetralogy of Fallot	X	X
Tricuspid atresia and stenosis	X	X
Ebstein's anomaly	X	X
Pulmonary valve stenosis	X	X
Pulmonary valve atresia	X	X
Aortic valve atresia/stenosis	X	X
Hypoplastic left heart	X	X
Hypoplastic right heart	X	X
Coarctation of aorta	X	X
Total anomalous pulm venous return	X	X
Respiratory		X
Choanal atresia	X	X
Cystic adenomatous malf of lung	X	X
Oro-facial clefts		X
Cleft lip with or without palate	X	X
Cleft palate	X	X
Digestive system		X
Oesophageal atresia with or without tracheo-oesophagal fistula	X	X
Duodenal atresia or stenosis	X	X
Atresia or stenosis of other parts of small intestine	X	X
Ano-rectal atresia and stenosis	X	X
Hirschsprung's disease	X	X
Atresia of bile ducts	X	X
Annular pancreas	X	X

Diaphragmatic hernia	X	X
Abdominal wall defects		X
Gastroschisis	X	X
Omphalocele	X	X
Urinary		X
Bilateral renal agenesis including Potter syndrome	X	X
Cystic kidney disease	X	X
Congenital hydronephrosis	X	X
Bladder extrophy and/or epispadia	X	X
Posterior urethral valve and/or prune belly	X	X
Genital		X
Hypospadias	X	X
Indeterminate sex	X	X
Limb		X
Limb reduction	X	X
Upper limb reduction	X	X
Lower limb reduction	X	X
Complete absence of a limb	X	X
Club foot - talipes equinovarus	X	X
Hip dislocation and/or dysplasia	X	X
Polydactyly	X	X
Syndactyly	X	X
Arthrogryposis multiplex congenita	X	X
Musculo-skeletal		X
Thanatophoric dwarfism		X
Jeunes syndrome		X
Achondroplasia		X
Craniosynostosis	X	X
Congenital constriction bands/amniotic band	X	X
Other malformations		X
Asplenia	X	X
Situs inversus	X	X
Conjoined twins	X	X
Disorders of skin	X	X
Teratogenic syndromes with malformations		X
Fetal alcohol syndrome	X	X
Valproate syndrome	X	X
Warfarin syndrome	X	X
Maternal infections resulting in malformations	X	X
Genetic syndromes & microdeletions		X
Chromosomal		X
Down's syndrome	X	X
Patau syndrome/ trisomy 13	X	X
Edward syndrome/ trisomy 18	X	X
Turner's syndrome	X	X
Klinefelter's syndrome	X	X
Cri-du-chat syndrome	X	X
Wolff-Hirschorn syndrome	X	X

Appendix B: Clusters by anomaly and registry – statistical details

Anomaly subgroup	Country	Registry	Cluster type	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA* (invalid DOB)	Cluster/ case deficit	Trend Summary
Spina Bifida	UK	Wessex	Conception	5	30/05/03	09/06/03	0.38	0.049	59	0	Cluster	
Congenital cataract	France	Paris	Conception	5	16/08/04	14/12/04	0.54	0.002	7	0	Cluster	
Congenital cataract	Italy	Tuscany	Conception	11	20/03/02	27/05/03	3.91	0.025	14	0	Cluster	
Atrial septal defect	Switzerland	Vaud	Conception	56	04/12/03	22/12/04	32.93	0.049	133	1.5	Cluster	
Atrioventricular septal defect	UK	Wessex	Conception	5	15/01/05	17/02/05	0.43	0.023	20	0	Cluster	
Hypoplastic right heart	UK	Wales	Conception	6	12/05/04	04/09/04	0.82	0.01	11	9.1	Cluster	
Cleft lip with or without palate	Belgium	Antwerp	Conception	57	20/01/03	15/07/04	33.55	0.01	96	9.4	Cluster	
Cleft lip with or without palate	Belgium	Hainaut	Conception	8	05/04/04	10/05/04	1.24	0.041	55	7.3	Cluster	Significant increasing trend (p=0.024)
Gastroschisis	UK	Northern Region	Conception	9	28/01/04	29/02/04	1.32	0.015	64	0	Cluster	Significant non-linear heterogeneous trend (p=0.018)
Cystic kidney disease	UK	Northern Region	Conception	8	03/10/03	15/10/03	0.67	0.006	87	0	Cluster	
Posterior urethral valve and/or prune			Conception	5	09/08/03	17/12/03	0.67	0.015	8	0	Cluster	

Anomaly subgroup	Country	Registry	Cluster type	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA* (invalid DOB)	Cluster/ case deficit	Trend Summary
belly	Ireland	Dublin										
Posterior urethral valve and/or prune belly	UK	Wales	Conception	12	28/05/03	20/06/04	4.01	0.014	16	6.2	Cluster	
Lower limb reduction	Belgium	Hainaut	Birth	5	27/10/04	08/04/05	0.71	0.014	8	No invalid DoB	Cluster	
Club foot - talipes equinovarus	UK	Wales	Conception	84	05/03/03	30/08/04	55.77	0.03	159	9.4	Cluster	Significant non-linear heterogeneous trend ($p<0.001$)

* GA: Gestational age
DOB: Date of birth

Appendix C: Trends by anomaly and registry– statistical details

Information on the number of cases in each anomaly subgroup, by registry and time period are available on the EUROCAT website: http://www.eurocat.ulster.ac.uk/pubdata/tables.html
To access this information, click on the link above, select an A5 table to output the number of cases for each year in the specified time period. The A5 table outputs the number of cases by type of birth (livebirth, stillbirth, termination of pregnancy and total cases) and the total prevalence of the anomaly subgroup for each of the specified years, as well as the total for all years combined.