Eurocat

European Surveillance of Congenital Anomalies

Supported by the EU-Commission Public Health Directorate, Public Health Programme
WHO Collaborating Centre for the Epidemiologic Surveillance of Congenital Anomalies

EUROCAT Statistical Monitoring Report - 2006

(Uploaded to EUROCAT website April 2009)

EUROCAT Central Registry
University of Ulster
Newtownabbey, Co Antrim
Northern Ireland, BT37 0QB

Tel: +44 28 9036 6639
Fax: +44 28 9036 8341
Email: eurocat@ulster.ac.uk
Web: www.eurocat.ulster.ac.uk

Table of Contents

Appendices

Appendix A: Congenital Anomaly Subgroup inclusion list

Appendix B: Clusters by anomaly and registry – statistical details

Appendix C: Trends by anomaly and registry – website details

Acknowledgements

This report was compiled by Maria Loane and Helen Dolk. Statistical methods were designed by Alan Kelly and Conor Teljeur. Statistical software was created by BioMedical Computing Ltd (James Densem) and operated by Ruth Greenlees. Reports of registry investigations were provided by: Antwerp, Basque Country, Dublin, East Midlands & South Yorkshire, Emilia Romagna, Northern England, Northern Netherlands, Norway, Paris, Saxony-Anhalt, Thames Valley, Tuscany, Vaud, Wales, Wessex, Wielkopolska and Zagreb.

1. Summary

Each year, EUROCAT performs statistical monitoring for both trends and clusters in time in order to detect signals of new or increasing teratogenic exposures which may require public health action.

We report here the results up to birth year 2006. Cases of congenital anomaly among livebirths, fetal deaths and terminations of pregnancy following prenatal diagnosis are included. Monitoring was conducted for 25 Full Member EUROCAT registries which fulfilled monitoring data criteria, covering approximately 500,000 births per year in Europe. Trends and clusters were subjected to preliminary investigation by registers. These investigations also form part of data quality monitoring.

A total of 89 increasing trends in prevalence over the most recent ten year period were reported from surveillance of 95 EUROCAT anomaly subgroups in the 25 registry areas, many more than would be expected by chance. Twenty-two registries reported results of local investigations, with varying levels of detail. **Down syndrome** increased significantly in 5 regions and Trisomy 18 in 3 regions, most likely due to increasing maternal age but further investigation is ongoing. Further investigation of an increase in **Gastroschisis** in UK (2 regions) is ongoing, and follows an increase in most EUROCAT regions in previous years which remains unexplained but almost certainly due to environmental exposures. Congenital heart defects (CHD) increased in 4 regions and various specific CHD subgroups accounted for 18 increasing trends. Most of these increases were thought to be likely to be due to changes in screening and diagnosis or case ascertainment, but there are also other potential causes such as an increase in maternal diabetes or other environmental factors requiring further investigation. Increases in **Hypoplastic Left Heart**, a very severe type of CHD, in three regions, requires further surveillance and investigation. Increasing trends in **upper limb reduction** in 2 regions are also recommended for further surveillance and investigation. Other increasing trends were thought possibly or likely to be due to changing diagnostic or ascertainment methods (renal dysplasia (5), congenital hydronephrosis (5), hypospadias (5), clubfoot (3), cleft palate (2)). An epidemiological analysis of renal dysplasia in EUROCAT registries is ongoing. The rarer congenital anomaly subgroups were not included in trend analysis where there were less than an average of 2.5 cases per year in a region – next year's Statistical Monitoring Report will consider these in more detail.

Eleven registries which had transmitted full data for 2006 by Feb 15 2008 were included in a cluster analysis identifying time clusters based on estimated date of conception from April 2004 to March 2006 (births 2005-2006), covering approximately 225,000 births per year. 75 congenital anomaly subgroups were tested. 17 clusters were detected where cases were unusually close together in time. This number was within what might be expected by chance. There was no pattern of time clusters in any one congenital anomaly subgroup occurring across Europe. Registry data were examined to determine whether there was cause for immediate concern. Seven clusters were due to diagnostic or data quality issues. An excess of cases was confirmed for 10 of the 17 clusters, involving 9 anomaly subgroups. For all ten of these clusters, registries concluded that close further monitoring was necessary, but no immediate public health action was needed. Two of these clusters had already been

detected in the 2005 statistical monitoring, and no continuation of the cluster had been observed into 2006.

EUROCAT registries covers approximately 25% of EU births but not all of the registries fulfil the criteria for inclusion in Statistical Monitoring. For the detection of clusters in particular, most of Europe is not covered by any systematic monitoring. Moreover, even when included in statistical monitoring, the registries generally have insufficient resources to investigate trends and clusters, and further clarification is needed of the pathways by which issues of potential public health concern are identified and acted upon.

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 2006. 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 2008, and having a full dataset for the most recent 5 years (2002-2006) 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 2008 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) are also 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 2005. Section 3.3 lists the registries and anomaly groups included in the current monitoring 2002-2006.

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 monitoring 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 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. Trend tests are run using the last 10 years of data (1997-2006) or data for the most recent 10 year period, if available.
3. Trend analysis groups data by 2 year intervals.
4. Trend analysis is always based on date of birth.
5. A trend test is performed if the average expected number of cases per 2 year interval is at least 5
6. Trend analysis is conducted on all 95 EUROCAT congenital anomaly subgroups.
7. Registries must have used ICD10 coding for the whole 10 year period tested to be included in surveillance of the following 7 subgroups that have 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.

3.1.2 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 2002-2006.
2. Clusters or deficits occurring in the last 2 years (2005-2006) that are less than 18 months in length are reported.
3. A minimum of 7 cases over the surveillance period (2002-2006) 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 (2006). 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.
8. Cluster analysis is run on 75 EUROCAT subgroups of congenital anomalies (Appendix A). Seventeen major heterogeneous subgroups (e.g. Nervous system, Eye, Congenital heart disease etc) are excluded from analysis. A further 3 subgroups of monogenic origin (Thanatophoric dwarfism, Jeunes syndrome, and Achondroplasia) are also excluded.

3.2 Statistical software updates

No changes to the EDMP software from last year.

3.3 Inclusion/Exclusion criteria

3.3.1 Trends

Registry inclusion criteria

- All full member registries who have submitted new data since the previous Statistical Monitoring Report are included in trend analysis.
- Registries must have a minimum 5 years of data to be included in trend analysis.
- If a registry does not meet the 15th February deadline for data transmission, then trend surveillance is carried out locally.

At the time of statistical monitoring in Spring 2008, there were 34 full member registries in EUROCAT. Twenty-five full member registries were included in the trend analysis 1997-2006. Auvergne and Ukraine were excluded from trend analysis as they had only 1 year of data at the time of monitoring. Barcelona, Campania, Cork & Kerry, Hainaut, Hungary, NE Italy, NW Thames were excluded as data was unchanged from previous report (See http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Statistical-Monitoring-Report-2005-(April-2008).pdf).

3.3.2 Clusters

Registry inclusion criteria

- Only registries that transmitted year 2006 data with full date of birth information are included in the cluster monitoring 2002-2006.
- 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%).
- If a registry does not meet the 15th February deadline for data transmission, then cluster surveillance is carried out locally.

At the time of statistical monitoring in Spring 2008, 20 full member registries had transmitted year 2006 data to EUROCAT Central Registry. Cluster analysis was run

using 11 registries (Antwerp, Dublin, Malta, Northern England, Northern Netherlands, Odense, Paris, Tuscany, Vaud, Wales, and Wessex). Five registries were excluded from statistical monitoring due to > 10% fluctuations in population (East Midlands & South Yorkshire, Emilia Romagna, South Portugal, Thames Valley, and Zagreb). Saxony-Anhalt was excluded as full date of birth information was unavailable. Ukraine was excluded as the registry has not yet transmitted 5 years of data. Mainz and South East Ireland were excluded as their 2006 data transmission was incomplete or unconfirmed.

4. Results

4.1 Central Registry statistical monitoring results

4.1.1 Detected Clusters

A total of 17 clusters based on date of conception were detected from surveillance of 75 anomaly subgroups in 11 EUROCAT registries, covering approximately 0.5 million births in 2005-2006 (Table 1). A total of 500 cluster tests were performed giving a cluster detection rate of 3.4%. By chance alone, we would expect a cluster detection rate of 2.5%. 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 4 (Table 1).

Two clusters of ventricular septal defect (VSD), and hip dislocation and/or dysplasia were detected.

- The VSD clusters were detected in Paris (France) and Dublin (Ireland). The VSD cluster in Paris showed significant non-linear heterogeneity over the preceding 5 years, while the VSD cluster in Dublin was detected in the context of a decreasing 5 year trend (See Appendix B).
- The hip dislocation and/or dysplasia clusters were detected in Paris (France) and Vaud (Switzerland). Again, the cluster in Paris showed significant non-linear heterogeneity over the preceding 5 years, while the cluster in Vaud was detected in the context of a decreasing 5 year trend (See Appendix B).

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

- Congenital cataract (Tuscany, Italy)
- Single ventricle (Northern England, UK)
- Hypoplastic right heart (Wales, UK)
- Cleft lip with/without palate (Antwerp, Belgium)
- Diaphragmatic hernia (Vaud, Switzerland)
- Congenital hydronephrosis (Dublin, Ireland)
- Posterior urethra valve and/or prune belly (Wales, UK)
- Hypospadias (Tuscany, Italy)
- Polydactyly (Dublin, Ireland)
- Congenital constriction bands/amniotic band (Wessex, UK)
- Asplenia (Paris, France)
- Patau syndrome/ trisomy 13 (Tuscany, Italy)
- Klinefelter's syndrome (Paris, France)

The hypoplastic right heart cluster detected in Wales and the cleft lip with or without palate (CLWWP) cluster detected in Antwerp were identified in the previous report (See http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Statistical-Monitoring-Report-2005-(April-2008).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 by registry and by anomaly 2005-2006

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Antwerp (BE)	Odense (DK)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Northern England (GB)	Wales (GB)	Wessex (GB)
All Anomalies	X	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	X
Neural Tube Defects	0	0	**0**											
Anencephalus and similar	0	0	**0**						*					
Encephalocele	0	0	**0**	*	*			*	*	*				
Spina Bifida	0	0	**0**											
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	X
Anophthalmos/ micropthalmos	0	0	**0**		*				*		*			*
Anophthalmos	0	0	**0**	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	1	0	**1**		*			C	*		*			
Congenital glaucoma	0	0	**0**	*	*	*		*	*	*	*	*		*
Ear, face and neck	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X
Anotia	0	0	**0**	*	*		*	*	*	*	*		*	*
Congenital heart defects	X	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	1	0	**1**	*	*		*		*	*	*	C		*
Ventricular septal defect	2	0	**2**			C	C							
Atrial septal defect	0	0	**0**											
Atrioventricular septal defect	0	0	**0**						*					
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**	*	*	*		*	*					
Hypoplastic left heart	0	0	**0**						*					
Hypoplastic right heart §	1	0	**1**	*	*	*	*	*	*	*	*	*	C	
Coarctation of aorta	0	0	**0**		*				*					
Total anomalous pulmonary venous return	0	0	**0**	*	*			*	*		*			*
Respiratory	X	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**		*		*	*	*	*	*			
Oro-facial clefts	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X
Cleft lip with or without palate	1	0	**1**	C										

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Antwerp (BE)	Odense (DK)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Northern England (GB)	Wales (GB)	Wessex (GB)
Cleft palate	0	0	**0**											
Digestive system	X	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	1	0	**1**		*				*		C			
Abdominal wall defects	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X
Gastroschisis	0	0	**0**		*				*		*			
Omphalocele	0	0	**0**						*					
Urinary	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X
Bilateral renal agenesis including Potter syndrome	0	0	**0**	*	*				*		*			
Renal dysplasia	0	0	**0**						*					
Congenital hydronephrosis	1	0	**1**				C							
Bladder exstrophy and/or epispadia	0	0	**0**	*	*			*	*	*	*	*	*	*
Posterior urethral valve and/or prune belly	1	0	**1**		*				*		*		C	
Genital	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X
Hypospadias	1	0	**1**					C						
Indeterminate sex	0	0	**0**	*	*		*		*	*	*			
Limb	X	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	0	**0**						*					
Complete absence of a limb	0	0	**0**	*	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	0	0	**0**									*		
Hip dislocation and/or dysplasia	2	0	**2**			C			*		C	*		*
Polydactyly	1	0	**1**				C							
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	X
Thanatophoric dwarfism	X	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	X
Achondroplasia	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X
Craniosynostosis	0	0	**0**						*					*
Congenital constriction bands/amniotic band	1	0	**1**	*	*	*	*	*	*	*				C
Other malformations	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Antwerp (BE)	Odense (DK)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Northern England (GB)	Wales (GB)	Wessex (GB)
Asplenia	1	0	**1**	*	*	C	*	*	*	*	*	*	*	*
Situs inversus	0	0	**0**	*	*		*		*	*	*	*		*
Conjoined twins	0	0	**0**	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	0	0	**0**		*									*
Teratogenic syndromes with malformations §	X	X	**X**	X	X	X	X	X	X	X	X	X	X	X
Fetal alcohol syndrome §	0	0	**0**	*	*	*	*	*	*	*	*	*	*	*
Valproate syndrome §	0	0	**0**	*	*	*	*	*	*	*	*	*	*	*
Warfarin syndrome §	0	0	**0**	*	*	*	*	*	*	*	*	*	*	*
Maternal infections resulting in malformations	0	0	**0**		*			*	*	*	*	*		*
Genetic syndromes + microdeletions	X	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	X
Down Syndrome	0	0	**0**											
Patau syndrome/trisomy 13	1	0	**1**					C	*					
Edward syndrome/trisomy 18	0	0	**0**											
Turner's syndrome	0	0	**0**		*				*					
Klinefelters syndrome	1	0	**1**	*	*	C	*		*	*				
Cru-du-chat syndrome	0	0	**0**	*	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	**0**	*	*	*	*	*	*	*	*	*	*	*
Total clusters: date of conception	17	0	17	1	0	4	3	3	0	0	2	1	2	1
Total clusters: date of birth	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total clusters			17	1	0	4	3	3	0	0	2	1	2	1

Key:
C = Clusters run by date of conception
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 2002-2006 in order to be included in surveillance of these subgroups

4.1.2 Detected trends

A total of 266 significant trends (89 increasing and 177 decreasing) were reported from surveillance of 95 anomaly subgroups in 25 EUROCAT registries covering 4.6 million births, 1997-2006 (Table 2). In addition, there were 183 with significant non-linear heterogeneity (or significant change from year to year, but no overall trend). A total of 1235 chi square tests were performed. Rare anomalies with less than 25 cases over the 10 year period have not been tested (see Table 2). 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 analysis yielded a detection rate of 36%.

Per EUROCAT anomaly subgroup, the number of increasing trends ranged from 0-5, the number of decreasing trends ranged from 0-13, and the number with significant non-linear heterogeneity ranged from 1-25 (Table 2). The "All Anomalies" subgroup showed significant non-linear heterogeneity for all 25 registries.

Per registry, the number of increasing trends ranged from 0-14, the number of decreasing trends ranged from 1-23, and the number of non-linear heterogeneity ranged from 2-17 (Table 2).

Due to the large number of identified trends, we only describe increasing trends in this Report. Significant increasing trends for 11-14 subgroups of congenital anomalies were identified in Wessex, Styria and Norway.

Increasing trends in congenital anomalies

Significant increasing trends were identified for 41 subgroups of congenital anomalies. Increasing trends were identified in 10 main organ system subgroups: nervous system anomalies, eye anomalies, congenital heart defects, respiratory anomalies, abdominal wall defects, urinary anomalies, genital anomalies, limb anomalies, genetic syndromes & microdeletions and chromosomal anomalies. Increasing trends in the main organ subgroups are generally explained by an increasing trend in a specific congenital anomaly within the main subgroup (See Table 2). Only trends in a specific subgroup are described below.

Significant increasing trends were identified in 5 registries for the following congenital anomaly subgroups:

- Renal dysplasia increased in Styria, Dublin, Tuscany, N Netherlands and East Midlands & South Yorkshire
- Congenital hydronephrosis increased in Antwerp, Zagreb, Saxony-Anhalt, Norway and Wielkopolska
- Hypospadias increased in Mainz, Tuscany, N Netherlands, Thames Valley and Wessex
- Down syndrome increased in Paris, Mainz, Norway, Vaud and Wessex

Significant increasing trends in atrial septal defect were identified in 4 registries - Zagreb, Mainz, Norway and Wessex.

Significant increasing trends were identified in 3 registries for the following congenital anomaly subgroups:

- Ventricular septal defect increased in the German registries (Mainz and Saxony-Anhalt) and Basque Country.
- Hypoplastic left heart increased in Styria, Dublin and East Midlands & South Yorkshire.
- Club foot - talipes equinovarus increased in Styria, East Midlands & South Yorkshire and Wessex.
- Edward syndrome /trisomy 18 increased in the French registries (Paris and Strasbourg) and N Netherlands.

Surveillance showed significant increasing trends in 2 registries for the following anomaly subgroups:

- Atrioventricular septal defect increased in Styria and Norway.
- Pulmonary valve atresia increased in Norway and Northern England.
- Cleft palate increased in Norway and Wessex
- Gastroschisis increased in the UK registries – Wales and Wessex
- Limb reduction anomalies increased in Wielkopolska and Wessex
- Upper limb reduction anomalies increased in Emilia Romagna and Wielkopolska
- Syndactyly increased in Emilia Romagna and Wessex

Increasing trends in the following 15 subgroups were detected in a single registry:

- Anencephalus (East Midlands & South Yorkshire)
- Spina Bifida (Styria)
- Arhinencephaly/holoprosencephaly (Norway)
- Anotia (Paris)
- Common arterial truncus (Sicily)
- Pulmonary valve stenosis (Styria)
- Aortic valve atresia/stenosis (Norway)
- Coarctation of aorta (Styria)
- Cystic adenomatous malformation of lung (East Midlands & South Yorkshire)
- Lower limb reduction (Wessex)
- Hip dislocation and/or dysplasia (Norway)
- Disorders of skin (Styria)
- Patau syndrome/trisomy 13 (Northern England)
- Turner's syndrome (Basque Country)
- Klinefelters syndrome (Emilia Romagna)

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	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Years tested (grouped by 2 years)					1996-2005	1997-2006	1997-2006	1997-2006	1997-2006	1994-2003	1997-2006	1997-2006	1997-2006	1997-2006	1997-2006	1995-2004	1997-2006	1997-2006	1997-2006	2000-2005	2000-2005	1997-2006	1996-2005	1997-2006	2001-2006	1997-2006	1999-2006	1999-2006	1997-2006
All Anomalies	0	0	25	25	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Nervous system	2	5	4	11	/				~		\	/		\	~		~		\		\	~						\	
Neural Tube Defects	0	4	1	5							\		\								\	~						\	
Anencephalus and similar	1	1	1	3			*	*			*			*		*		*	\			~		*			/		
Encephalocele	0	1	1	2	*	*	*	*			*		\	*	*	*	*	*	*			*	*	*		*	~		
Spina Bifida	1	3	0	4	/		*				\		\					*									\		
Hydrocephaly	0	3	1	4			*			\	\							*				\					~		
Microcephaly	0	5	2	7	~	\	*	*		*	X	~		*			*	*	\	*		\		*		*	\	\	*
Arhinencephaly/holoprosencephaly	1	0	0	1	*	*	*	*		*	*	*	*	*		*	*	*	*	/	*	*	*	*		*		*	*
Eye	1	4	4	9	~		*	~		~	*		\	*		/		*	\			\				*	\		~
Anophthalmos/ micropthalmos	0	1	0	1	*	*	*	*		*	*	*		*		*	*	*	*	*		*	*	*		*	\		*
Anophthalmos	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	1	1	2	*	*	*	*		~	*	*		*	*	*		*	\		*	*	*	*		*			*
Congenital glaucoma	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Ear, face and neck	0	8	5	13	~		*	*	\	~	*	\	~	*	\	~	\	*	\			~	\	\	*	*	\		*
Anotia	1	0	0	1	*	*	*	*	/	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital heart defects	4	2	15	21	~		/		~	~	/	~		\	~	~	~	~		~	~	~	/	~	~	\	~	~	/
Common arterial truncus	1	0	1	2	*	*	*	*		*	*	*	*	*	*	/	*	*	*		*	*	*	*		*		~	*
Transposition of great vessels	0	3	2	5			*	*	~		*			*		\		*				*	~	*			\	\	
Single ventricle	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Ventricular septal defect	3	2	10	15	~				~		/	/	\		~	~	~	\		~	~	~	/	~			~		
Atrial septal defect	4	4	12	20	~	~	/	\		~	/	~	~	\	~	~	~	\		/	~	~		~			\	~	/
Atrioventricular septal defect	2	3	1	6	/	*	*	*		*	*	*		*	\	*	~	*		/	\	*				*	\		
Tetralogy of Fallot	0	1	2	3			*	*			*			*		\		*	~					*		*	~		
Tricuspid atresia and stenosis	0	4	0	4	*	\	*	*	\	*	*	*	*	*	\	*	*	*			*	*	*	*	*	*		\	*
Ebstein's anomaly	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*
Pulmonary valve stenosis	1	4	2	7	/		*			\	*	~	\	*			\					*		~		*	\		*
Pulmonary valve atresia	2	1	0	3	*	*	*	*	\	*	*	*	*	*	*	*	*	*	*	/	*	*		*	/	*			*
Aortic valve atresia/stenosis §	1	0	0	1	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	/		X	X	X		*	*		
Hypoplastic left heart	3	0	1	4	/		*	*			*		/	*		*		*				~		*			/		
Hypoplastic right heart §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X		*	X	X	X	*	*		*	*
Coarctation of aorta	1	2	1	4	/		*	*			*		~	*				*				\					\		
Total anomalous pulmonary venous return	0	1	0	1	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*		*	\		*
Respiratory	2	5	4	11	/		*	*			~	\	\	~		~		*	\			\					\	~	/
Choanal atresia	0	0	1	1	*	*	*	*		*	*	*		*	*	~	*	*	*		*	*	*	*		*	*	*	*
Cystic adenomatous malf of lung §	1	0	0	1	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X		*	/		
Oro-facial clefts	0	2	5	7									~	~		\		~				\	~				~		
Cleft lip with or without palate	0	1	2	3		~					~	\		*		X													
Cleft palate	2	2	1	5			*									X				/		\	~				\		/
Digestive system	0	9	5	14	\	~	\				\		\	~	~	\	~		\			\				~	\	\	
Oesophageal atresia with/without tracheo-oesophagal fistula	0	1	0	1	*		*				*			*		*		*				*		*		*	\		
Duodenal atresia or stenosis	0	0	0	0	*	*	*	*		*	*	*	*	*		*	*	*	*		*	*	*	*		*			
Atresia or stenosis of other parts of small intestine	0	2	0	2	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*		*	\		\
Ano-rectal atresia and stenosis	0	1	2	3			*	*		~	*			*			~	*						*		*		\	

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Hirschsprung's disease	0	0	0	0	*		*	*		*	*	*		*	*	*	*	*			*	*		*		*			
Atresia of bile ducts	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Annular pancreas	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	1	1	2			*	*			*			*				*	\		~	*							
Abdominal wall defects	2	0	2	4			*		~					*	~	*		*										/	/
Gastroschisis	2	0	2	4		*	*	*	~	*	*			*		*	*	*	*			*	*	*	~			/	/
Omphalocele	0	0	1	1	*		*	*		*	*			*	~	*		*				*		*					
Urinary	2	4	8	14	~				~		~				\	~				/	/	~	~	\		\	~	~	\
Bilateral renal agenesis including Potter syndrome	0	3	1	4	*	\	*	*	\		*			*	*	X		*	~			*	\	*	*	*			
Renal dysplasia	5	1	1	7	/		*				*		/	*	\	*	/	*	/		*	~					/		
Congenital hydronephrosis	5	4	10	19	~	/	/		~		~	/			~	~		*	\	/	/	~	~	~	\	\	~	\	~
Bladder exstrophy and/or epispadia	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*		*		*	*
Posterior urethral valve and/or prune belly	0	0	0	0	*		*	*		*	*	*	*	*	*	*	*	*		*	*	*	*	*		*			
Genital	4	4	9	17	~		~				/	~	\		~	~	/	~		~	\	\		~		/	~	\	/
Hypospadias	5	4	9	18	~		~		~		/	~	\		~	~	/	~	/			\	\	~		/	~	\	/
Indeterminate sex	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*		*	*
Limb	2	8	9	19	/	~	\		~		~	\	\	\		~	~	\	~	~		\	\			\	~	~	/
Limb reduction	2	2	1	5			*					~		*				*			/	\					\		/
Upper limb reduction	2	1	2	5	~		*			~	*			*	/			*			/	\				*			
Lower limb reduction	1	0	0	1	*		*	*			*			*		*		*				*				*			/
Complete absence of a limb	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	3	4	3	10	/								~		~	*			\			\	\		*	\	/	~	/
Hip dislocation and/or dysplasia	1	4	4	9	*				~				\	*		~		*	\	/		~	*	\	*	*	~	\	*
Polydactyly	0	1	1	2								~		*														\	

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Syndactyly	2	3	2	7			*	*	~		*	~		*	/			\	\			\				*			/
Arthrogryposis multiplex congenita	0	1	0	1	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	\	*	*
Musculo-skeletal	0	8	7	15		~			\		~	\	\	~	\	~			\		~	\	~	~			\	\	
Thanatophoric dwarfism	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*		*	*
Jeunes syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Achondroplasia	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Craniosynostosis	0	3	1	4			*	*			*			*		*	*	*	*		*	*	~		\	*	\	\	*
Congenital constriction bands/amniotic band	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		
Other malformations	0	12	3	15	~	\	\			\			~	\		~	\		\		\	\		\		\	\	\	
Asplenia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*			*
Conjoined twins	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	1	13	3	17	/	\	\	*	~	~	*	\	\	\	\		\	\	\	\	~	*		\		*	\	\	*
Teratogenic syndromes with malformations §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X	*	*	*		
Fetal alcohol syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X	*	*	*	*	*
Valproate syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X	*	*	*	*	*
Warfarin syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X	*	*	*	*	*
Maternal infections resulting in malformations	0	0	1	1	*	*	*	*	~	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*		*
Genetic syndromes + microdeletions	1	5	2	8	/		*		\	~								~				\				\	\	\	
Chromosomal	4	1	5	10	/				~		/	~			~		\			/		~		/					~
Down Syndrome	5	2	1	8					/		/				~	\				/		\		/					/
Patau syndrome/trisomy 13	1	0	1	2		*	*	*			*	*		*		*		*	*		*	*	~	*	/				
Edward syndrome/trisomy 18	3	0	3	6			*	~	/	/	*			*	~	*		*	/			*						~	
Turner's syndrome	1	2	3	6			*	*	~		*	~		*		*	\	*			*	~	/					\	

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Klinefelters syndrome	1	0	0	1	*	*	*	*		*	*	*	*	*	/	*		*	*	*	*	*		*		*			
Cru-du-chat syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Total / trends across registries	89				13	1	3	0	3	1	7	3	2	0	3	2	3	0	3	11	4	0	3	2	2	2	5	2	14
Total \ trends across registries		177			1	5	4	1	6	3	5	6	14	6	7	5	6	5	16	1	5	19	5	5	2	7	23	18	2
Total ~ trends across registries			183		12	5	2	2	16	9	6	11	6	4	14	14	8	5	3	4	6	14	8	9	2	1	13	7	3
Total all trends				449	26	11	9	3	25	13	18	20	22	10	24	21	17	10	22	16	15	33	16	15	6	10	41	27	19

Key:
/ = significant upward trend
\ = significant downward trend
~ = non-linear trends indicating significant heterogeneity
X = Data excluded from analysis
* Too few cases to run analysis.
§ Registries must have used ICD10 coding for the whole period 1997-2006 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?).

Local investigation reports were initially discussed at RLM in Helsinki June 2008 and then a final written report sent to Central Registry.

4.2.1 Local registry preliminary investigations into detected clusters

No clusters were identified in Odense, Malta or the Northern Netherlands. Central Registry received reports on preliminary cluster investigations from all local registries with detected clusters: Antwerp, Paris, Dublin, Tuscany, Vaud, Northern England, Wales and Wessex. The level of investigation varied between registries, with some registries such as Northern England doing extensive checking and cross-referencing registry data with hospital records.

Table 3 shows the outcomes of the cluster investigations, classified as follows:

- Apparent cluster with cause for concern, further investigation ongoing (n=0)
- Not 'true' cluster as associated with aetiologic heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence (n=3)
- Excess of cases confirmed, but no further investigation proposed other than further surveillance (n=10)
- Increase in cases, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound detection rates (n=0)
- Data quality issues found to explain cluster (n=4)
- No report of preliminary investigations sent to Central Registry (n=0).

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 2005-2006

Clusters due to data quality errors	Clusters due to aetiologic heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence	Excess of cases confirmed with no explanation in registry data; no further action other than continued surveillance
• Single ventricle - Northern England • Hypoplastic right heart – Wales • Posterior urethral valve/prune belly - Wales • Hip dislocation and/or dysplasia – Vaud	• Congenital hydronephrosis - Dublin • Hypospadias - Tuscany • Polydactyly – Dublin	• Congenital cataract – Tuscany • Ventricular septal defect – Paris, Dublin • Cleft lip with/without palate – Antwerp • Diaphragmatic hernia – Vaud • Hip dislocation and/or dysplasia - Paris • Congenital constriction bands – Wessex • Asplenia – Paris • Patau syndrome (Trisomy 13) – Tuscany • Klinefelters syndrome – Paris

4.2.2 Local registry preliminary investigations into increasing trends detected by statistical monitoring

In April 2008, the EUROCAT Project Management Committee agreed that registries should only investigate increasing trends.

No increasing trends were detected in Malta, Odense, SE Ireland and S Portugal. Central Registry received reports on preliminary trend investigations from 18 of 21 local registries with increasing trends (86%): Antwerp, Basque Country, Dublin, East Midlands & South Yorkshire, Emilia Romagna, N Netherlands, Northern England, Norway, Paris, Saxony-Anhalt, Styria, Thames Valley, Tuscany, Vaud, Wales, Wessex, Wielkopolska and Zagreb. This is a marked improvement from last year. The level of investigation varied between registries. The results of the investigations into the significant increasing trends are described in Table 4, classified as follows:

- A: Changes in case ascertainment (data quality) (n=41)
- B: Changes in local or central registry methods e.g. definitions and inclusion criteria (n=7)
- C: Changes in diagnostic methods (n=5)
- D: Trend confirmed, due to known demographic changes (n=10)
- E: Trend confirmed, investigation ongoing (n=4)
- F: Trend confirmed, further surveillance proposed before more detailed investigation (n=9)
- G: No report or clear interpretation of preliminary investigations sent to Central Registry (n=13)

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

Seven of the reported increasing trends require further local surveillance and/or investigation to determine if they are "true" increasing trends. These are:

- Hypoplastic left heart in Dublin and in East Midlands & South Yorkshire
- Gastroschisis in Wessex
- Congenital hydronephrosis in Zagreb
- Upper limb reduction in Emilia Romagna and Wielkopolska
- Turners syndrome in Basque Country.

The reported increasing trends in chromosomal anomalies are explained by changes in maternal age and prenatal screening.

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/).

The recommendations of the EUROCAT PMC concerning increasing trends are:

- Ongoing analysis of Down Syndrome and other Trisomies by Central Registry should determine whether changes in maternal age explain all of the increases in prevalence found

- Previous analysis by Central Registry has shown a steady increase in prevalence of gastroschisis since 1980 in many parts of Europe (except Italy), a higher risk among young mothers, especially mothers less than 20 years of age, an increase in prevalence since 1980 in all maternal age groups, and a higher prevalence in UK (Loane et al). The continuing evidence of increasing trends in two UK regions up to 2007 emphasises the need for aetiologic research within UK and across Europe (including Italy), further investigating known associations with low socioeconomic status, smoking and recreational drugs.
- An investigation of hypoplastic left heart prevalence by EUROCAT Central Registry, building on a recent EUROCAT Special Report on Congenital Heart Defects, should be prioritised within the work programme.
- A study of limb reduction prevalence in Europe is needed, and proposals should be invited in the first instance from EUROCAT member registries for such a study using the central database.

(Reference: Loane M, Dolk H, Bradbury I, and a EUROCAT Working Group. Increasing prevalence of gastroschisis in Europe 1980-2002: a phenomenon restricted to younger mothers? Paediatric & Perinatal Epidemiology 2007; 21 (4): 363-369)

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

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Years tested (grouped by 2 years)					1996-2005	1997-2006	1997-2006	1997-2006	1997-2006	1994-2003	1997-2006	1997-2006	1997-2006	1997-2006	1997-2006	1995-2004	1997-2006	1997-2006	1997-2006	2000-2005	2000-2005	1997-2006	1996-2005	1997-2006	2001-2006	1997-2006	1999-2006	1999-2006	1997-2006
All Anomalies	0	0	25	25	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Nervous system	2	5	4	11	A				~		\	C		\	~		~		\		\	~						\	
Neural Tube Defects	0	4	1	5							\		\								\	~						\	
Anencephalus and similar	1	1	1	3			*	*			*			*		*		*	\			~		*			C		
Encephalocele	0	1	1	2	*	*	*	*			*		\	*	*	*	*	*	*			*	*	*		*	~		
Spina Bifida	1	3	0	4	A		*				\		\					*									\		
Hydrocephaly	0	3	1	4			*			\	\							*				\					~		
Microcephaly	0	5	2	7	~	\	*	*		*	X	~		*			*	*	\	*		\		*		*	\	\	*
Arhinencephaly/holoprosencephaly	1	0	0	1	*	*	*	*		*	*	*	*	*		*	*	*	*	A/ C	*	*	*	*		*		*	*
Eye	1	4	4	9	~		*	~		~	*		\	*		G		*	\			\				*	\		~
Anophthalmos/ micropthalmos	0	1	0	1	*	*	*	*		*	*	*		*		*	*	*	*	*		*	*	*		*	\		*
Anophthalmos	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	1	1	2	*	*	*	*		~	*	*		*	*	*		*	\		*	*	*	*		*			*
Congenital glaucoma	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Ear, face and neck	0	8	5	13	~		*	*	\	~	*	\	~	*	\	~	\	*	\			~	\	\	*	*	\		*
Anotia	1	0	0	1	*	*	*	*	A	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital heart defects	4	2	15	21	~		B		~	~	G	~		\	~	~	~	~		~	~	~	A	~	~	\	~	~	A
Common arterial truncus	1	0	1	2	*	*	*	*		*	*	*	*	*	*	G	*	*	*		*	*	*	*		*		~	*
Transposition of great vessels	0	3	2	5			*	*	~		*			*		\		*				*	~	*			\	\	
Single ventricle	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Ventricular septal defect	3	2	10	15	~				~		G	C	\		~	~	~	\		~	~	~	A	~			~		
Atrial septal defect	4	4	12	20	~	~	B	\		~	G	~	~	\	~	~	~	\		A	~	~		~			\	~	A
Atrioventricular septal defect	2	3	1	6	A	*	*	*		*	*	*		*	\	*	~	*		A	\	*				*	\		
Tetralogy of Fallot	0	1	2	3			*	*			*			*		\		*	~					*		*	~		
Tricuspid atresia and stenosis	0	4	0	4	*	\	*	*	\	*	*	*	*	*	\	*	*	*			*	*	*	*	*	*		\	*
Ebstein's anomaly	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*
Pulmonary valve stenosis	1	4	2	7	A		*			\	*	~	\	*			\					*		~		*	\		*
Pulmonary valve atresia	2	1	0	3	*	*	*	*	\	*	*	*	*	*	*	*	*	*	*	A	*	*		*	A	*			*
Aortic valve atresia/stenosis §	1	0	0	1	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	A		X	X	X		*	*		
Hypoplastic left heart	3	0	1	4	A		*	*			*		F	*		*		*				~		*			F		
Hypoplastic right heart §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X		*	X	X	X	*	*		*	*
Coarctation of aorta	1	2	1	4	A		*	*			*		~	*				*				\					\		
Total anomalous pulm venous return	0	1	0	1	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*		*	\		*
Respiratory	2	5	4	11	A		*	*			~	\	\	~		~		*	\			\					\	~	G
Choanal atresia	0	0	1	1	*	*	*	*		*	*	*		*	*	~	*	*	*		*	*	*	*		*	*	*	*
Cystic adenomatous malf of lung §	1	0	0	1	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X		*	A		
Oro-facial clefts	0	2	5	7									~	~		\		~				\	~				~		
Cleft lip with or without palate	0	1	2	3		~					~	\		*		X													
Cleft palate	2	2	1	5			*									X				A		\	~				\		A
Digestive system	0	9	5	14	\	~	\				\		\	~	~	\	~		\			\				~	\	\	
Oesophageal atresia with/without tracheo-oesophagal fistula	0	1	0	1	*		*				*			*		*		*				*		*		*	\		
Duodenal atresia or stenosis	0	0	0	0	*	*	*	*		*	*	*	*	*		*	*	*	*		*	*	*	*		*			
Atresia or stenosis of other parts of small intestine	0	2	0	2	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*		*	\		\
Ano-rectal atresia and stenosis	0	1	2	3			*	*		~	*			*			~	*						*		*		\	

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Hirschsprung's disease	0	0	0	0	*		*	*		*	*	*		*	*	*	*	*			*	*		*		*			
Atresia of bile ducts	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Annular pancreas	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	1	1	2			*	*			*			*				*	\		~	*							
Abdominal wall defects	2	0	2	4			*		~					*	~	*		*										E	E
Gastroschisis	2	0	2	4		*	*	*	~	*	*			*		*	*	*	*			*	*	*	~			E	E
Omphalocele	0	0	1	1	*		*	*		*	*			*	~	*		*				*		*					
Urinary	2	4	8	14	~				~		~				\	~				A	A/ C	~	~	\		\	~	~	\
Bilateral renal agenesis inclg Potter syndrome	0	3	1	4	*	\	*	*	\		*			*	*	X		*	~			*	\	*	*	*			
Renal dysplasia	5	1	1	7	A		*				*		A	*	\	*	G	*	F		*	~					A		
Congenital hydronephrosis	5	4	10	19	~	B/ C	F		~		~	C			~	~		*	\	A/ C	A/ C	~	~	~	\	\	~	\	~
Bladder exstrophy and/or epispadia	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*		*		*	*
Posterior urethral valve and/or prune belly	0	0	0	0	*		*	*		*	*	*	*	*	*	*	*	*		*	*	*	*	*		*			
Genital	4	4	9	17	~		~				G	~	\		~	~	B	~		~	\	\		~		A	~	\	A
Hypospadias	5	4	9	18	~		~		~		G	~	\		~	~	B	~	B			\	\	~		A	~	\	A
Indeterminate sex	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*		*	*
Limb	2	8	9	19	A	~	\		~		~	\	\	\		~	~	\	~	~		\	\			\	~	~	A
Limb reduction	2	2	1	5			*					~		*				*			F	\					\		A
Upper limb reduction	2	1	2	5	~		*			~	*			*	F			*			F	\				*			
Lower limb reduction	1	0	0	1	*		*	*			*			*		*		*				*				*			A
Complete absence of a limb	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	3	4	3	10	A								~		~	*			\			\	\		*	\	B	~	C
Hip dislocation and/or dysplasia	1	4	4	9	*				~				\	*		~		*	\	A/ C		~	*	\	*	*	~	\	*
Polydactyly	0	1	1	2								~		*														\	

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Syndactyly	2	3	2	7			*	*	~		*	~		*	D			\	\			\				*			G
Arthrogryposis multiplex congenita	0	1	0	1	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	\	*	*
Musculo-skeletal	0	8	7	15		~			\		~	\	\	~	\	~			\		~	\	~	~			\	\	
Thanatophoric dwarfism	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*		*	*
Jeunes syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Achondroplasia	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Craniosynostosis	0	3	1	4			*	*			*			*		*	*	*	*		*	*	~		\	*	\	\	*
Congenital constriction bands/amniotic band	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		
Other malformations	0	12	3	15	~	\	\			\			~	\		~	\		\		\	\		\		\	\	\	
Asplenia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*			*
Conjoined twins	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	1	13	3	17	A	\	\	*	~	~	*	\	\	\	\		\	\	\	\	~	*		\		*	\	\	*
Teratogenic syndromes with malformations §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X	*	*	*		
Fetal alcohol syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X	*	*	*	*	*
Valproate syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X	*	*	*	*	*
Warfarin syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	X	X	*	X	*	*	X	X	X	*	*	*	*	*
Maternal infections resulting in malformations	0	0	1	1	*	*	*	*	~	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*		*
Genetic syndromes + microdeletions	1	5	2	8	A		*		\	~								~				\				\	\	\	
Chromosomal	4	1	5	10	A				~		G	~			~		\			D		~		D					~
Down Syndrome	5	2	1	8					D		G				~	\				D		\		D					D
Patau syndrome/trisomy 13	1	0	1	2		*	*	*			*	*		*		*		*	*		*	*	~	*	D				
Edward syndrome/trisomy 18	3	0	3	6			*	~	D	G	*			*	~	*		*	F			*					~		
Turner's syndrome	1	2	3	6			*	*	~		*	~		*		*	\	*			*	~	F					\	

Anomaly	Total /	Total \	Total ~	Total trends	Styria (AT)	Antwerp (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Strasbourg (FR)	Mainz (DE)	Saxony Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Norway (NO)	Wielkopolska (PL)	S Portugal (PT)	Basque Country (ES)	Vaud (CH)	Northern England (GB)	Thames Valley (GB)	E Mid & S York (GB)	Wales (GB)	Wessex (GB)
Klinefelters syndrome	1	0	0	1	*	*	*	*		*	*	*	*	*	D	*		*	*	*	*	*		*		*			
Cru-du-chat syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Total / trends across registries	89				13	1	3	0	3	1	7	3	2	0	3	2	3	0	3	11	4	0	3	2	2	2	5	2	14
Total \ trends across registries		177			1	5	4	1	6	3	5	6	14	6	7	5	6	5	16	1	5	19	5	5	2	7	23	18	2
Total ~ trends across registries			208		13	6	3	3	17	10	7	12	7	5	15	15	9	6	4	5	7	15	9	9	3	2	14	8	4
Total all trends				474	27	12	10	4	26	14	19	21	23	11	25	22	18	11	23	17	16	34	17	16	7	11	42	28	20

Key:

- A: Changes in case ascertainment (data quality)
- B: Changes in local or central registry methods e.g. definitions and inclusion criteria
- C: Changes in diagnostic methods
- D: Trend confirmed, due to known demographic changes
- E: Trend confirmed, investigation ongoing
- F: Trend confirmed, further surveillance proposed before more detailed investigation
- G: No report or clear interpretation of preliminary investigations sent to Central Registry

- X: Data excluded from surveillance as Registries must have used ICD10 coding for the whole 1997-2006 in order to be included in surveillance of this subgroup
- *No surveillance, as too few cases

4.2.3 Updates on previous local registry investigations into clusters and trends

Two clusters detected in the current statistical monitoring exercise were also identified in last year's Report (Hypoplastic right heart in Wales and Cleft lip with/without palate in Antwerp) http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Statistical-Monitoring-Report-2005-(April-2008).pdf . Both registries have re-iterated that these are unusual aggregation of cases, but not of concern in relation to teratogenic exposures.

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 Local registry investigations/results identified by other means

Central Registry received no information on clusters and trends in Europe identified using other means.

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 defects		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
Congenital cataract	Italy	Tuscany	Conception	6	04/02/06	04/03/06	0.43	<0.001	24	4.2	Cluster	
Single ventricle	UK	Northern Region	Conception	5	07/05/05	07/08/05	0.59	0.019	10	0	Cluster	
Ventricular septal defect	France	Paris	Conception	6	06/03/06	07/03/06	0.32	0.045	502	0.2	Cluster	Significant non-linear change (p=0.011)
Ventricular septal defect	Ireland	Dublin	Conception	18	06/07/04	26/08/04	4.6	0.012	140	0	Cluster	Significant decreasing trend (p=0.016)
Hypoplastic right heart §	UK	Wales	Conception	6	12/05/04	04/09/04	0.89	0.021	12	0	Cluster	
Cleft lip with or without palate	Belgium	Antwerp	Conception	59	20/01/03	15/07/04	35.29	0.011	101	5.9	Cluster	Significant non-linear change (p=0.023)
Diaphragmatic hernia	Switzerland	Vaud	Conception	7	27/05/05	23/11/05	1.39	0.024	12	0	Cluster	
Congenital hydronephrosis	Ireland	Dublin	Conception	10	04/07/05	08/12/05	2.33	0.025	23	0	Cluster	
Posterior urethral valve and/or prune belly	UK	Wales	Conception	9	12/08/05	27/10/05	1.42	0.01	29	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
Hypospadias	Italy	Tuscany	Conception	43	06/08/05	02/02/06	21.01	0.043	181	1.1	Cluster	Significant increasing trend (p<0.001)
Hip dislocation and/or dysplasia	France	Paris	Conception	7	04/04/05	11/04/05	0.68	0.044	151	0	Cluster	Significant non-linear change (p<0.001)
Hip dislocation and/or dysplasia	Switzerland	Vaud	Conception	9	14/07/04	21/02/05	2.15	0.019	15	0	Cluster	Significant decreasing trend (p=0.023)
Polydactyly	Ireland	Dublin	Conception	13	21/05/04	20/07/04	2.98	0.03	77	0	Cluster	
Congenital constriction bands/amniotic band	UK	Wessex	Conception	5	28/07/04	26/08/04	0.43	0.036	23	0	Cluster	
Asplenia	France	Paris	Conception	7	05/06/05	17/01/06	1.6	0.037	11	0	Cluster	
Patau syndrome/trisomy 13	Italy	Tuscany	Conception	7	20/01/06	14/03/06	0.72	<0.001	21	0	Cluster	
Klinefelters syndrome	France	Paris	Conception	17	18/03/03	23/06/04	6.87	0.013	23	0	Cluster	

* 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.