EUROCAT Statistical Monitoring Report - 2007

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1. Summary

One of EUROCAT's objectives is "to co-ordinate the detection of, and response, to clusters and early warning of teratogenic exposures". Each year, EUROCAT Central Registry 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.

This report presents the results including 2007 data transmitted to EUROCAT Central Registry by February 2009. Cases include livebirths and stillbirths with congenital anomaly, and terminations of pregnancy for fetal anomaly following prenatal diagnosis. 95 standard EUROCAT congenital anomaly subgroups are monitored.

Whereas EUROCAT covers 1.5 million births per year, or 28% of the annual EU birth population, statistical monitoring is done centrally only for full member registries fulfilling criteria in terms of data recency. Thus, detection of trends over time included 22 registries covering 400,000 births per year, and detection of clusters included 10 registries covering 270,000 births per year. No reports were received from other registries as to the results of their monitoring activities. Member States should review their congenital anomaly monitoring activities, and where possible contribute to the co-ordinated EUROCAT system, whether through transmission of data or sharing of reports.

After data transmission to Central Registry in February 2009, statistical monitoring results were communicated to registries in April 2009 for preliminary investigation. Reports of investigations were discussed at the Registry Leaders Meeting in June 2009, followed by written reports. Only five registries identified a clear protocol for communication of monitoring results to national or regional public health agencies. Responsibility for public health action in response to monitoring results needs to be more clearly defined by Member States.

1264 statistical analyses were performed to detect change over time in the most recent decade. 28% of tests showed evidence of significant increasing, decreasing, or non-linear change over time. The **eighty-nine increasing trends** were prioritised for preliminary investigation, and reports of investigations were available for 60 of these. Almost two-thirds of the ten-year trends were explained by diagnostic or data quality issues such as changes in case ascertainment, definition and inclusion criteria, or diagnostic methods. Increasing trends requiring further surveillance and/or investigation (some of which were already signalled in previous years) were confirmed for the following anomalies: respiratory (1 registry), cleft palate (1), gastroschisis (3), renal dysplasia (1), upper limb reduction (1), polydactyly (1), syndactyly (1), Down syndrome (2), Edward syndrome (3) and Klinefelter syndrome (1).

For the first time this year, a "pan-Europe" analysis combined data from all registries to consider overall evidence of trend in Europe, and to consider evidence for trend in the rarer of the 95 subgroups which cannot be effectively examined in individual registries. Taken together with the results for the individual registries, the following trends are of note:

While generally, the prevalence of **Congenital Heart Defects (CHD)** is found to be declining, the prevalence of **Hypoplastic Left Heart** (HLH) and **Total Anomalous Pulmonary Venous Return** (TAPVR) specifically was found to be increasing. A full analysis of trends in CHD and its component subgroups is ongoing,

The prevalence of the abdominal wall anomaly **gastroschisis** continues to increase, particularly in the United Kingdom. This has not yet been explained by known risk factors. A UK study investigating possible environmental, dietary and lifestyle exposures during early pregnancy (first 12 weeks of gestation) as possible causes for this defect is in progress. ***More concerted research in Europe is necessary to tackle this ongoing public health concern***.

An increasing trend in **renal dysplasia** prevalence was found. A study of potential explanations using EUROCAT data is ongoing.

Hypospadias increased in prevalence but a more detailed analysis is planned to distinguish true change from change in inclusion criteria for mild cases which was implemented in 2005,

There was more evidence of an increase in **Edward syndrome/trisomy 18** than Down syndrome. While increasing maternal age can be expected to lead to an increase in both these conditions, the greater increase in Edward syndrome is under investigation, particularly as to the role of early prenatal detection in increasing ascertainment of cases.

While this report focuses on evidence of increasing trends, many decreasing trends were found, of which a decline in neural tube defects is of particular interest, and is fully reported in a EUROCAT Special Report on neural tube defects http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-I.pdf.

Ten registries were included in a cluster analysis based on estimated date of conception identifying time clusters with date of conception from April 2005 to March 2007 (births 2006-2007), covering 0.5 million births per year. 23 clusters were detected where cases were unusually close together in time, more clusters than would be expected by chance. There was no pattern of time clusters in any one congenital anomaly subgroup occurring across Europe. Five of the clusters were identified in the previous statistical monitoring report, and no continuation of the cluster had been observed into 2007. Of the remaining 18 clusters, diagnostic or data quality issues were thought to explain nine and 3 were not reported on. A further 6 (across 5 registries) were confirmed, no explanation was found by preliminary investigation and continued surveillance was recommended (choanal atresia, Edward syndrome, anencephalus, coarctation of aorta, bladder exstrophy, cleft palate).

EUROCAT provides integrated statistical monitoring for congenital anomalies in Europe for response by regional/ national public health authorities. Further investment is needed in many European countries to extend the geographical coverage of EUROCAT statistical monitoring. We continue to identify gastroschisis as the main cause for concern.

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 detailing rationale and methodology is available (EUROCAT Statistical Monitoring Protocol http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2007.pdf)..
We report here the results up to birth year 2007. Cases of congenital anomaly among livebirths, fetal deaths and terminations of pregnancy for fetal anomaly are included. We report both the statistical results, and the outcome of preliminary investigations conducted 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 2009, with a complete dataset for the most recent 5 years (2003-2007) are included in cluster detection.

This year, we introduced a new development in the monitoring surveillance process whereby we conducted a trend analysis for all registries combined ("pan-Europe"). This is useful for monitoring the rarer anomalies with too few cases to allow analysis of trend for each registry separately. This analysis allows a wider overview of whether a trend is unique to a registry or is more commonly experienced in Europe.

Registries can also use the statistical monitoring software to conduct their own monitoring on more recent data, and reports of any such analyses conducted up to June 2009 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 reported.

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 2006.

Results are presented in Section 4. Section 4.1 presents the pan-Europe trend results, while section 4.2 presents the long term trend results for individual registries. The cluster results are documented in section 4.3. Details of local registry preliminary investigations into the trends and clusters identified centrally are detailed in section 4.4. Sections 4.5 and 4.6 describe updates on previous local registry investigations and local registry monitoring using the EDMP software and more recent data not yet transmitted to Central Registry. Clusters identified locally by other means are described in Section 4.7.

3. Methodology

3.1 Summary of methods

Statistical methods are described in the EUROCAT Statistical Monitoring Protocol.. Software to detect clusters and trends locally is available in the EDMP (EUROCAT Data Management Program) and where registries do not meet data transmission deadlines, all analyses can be run locally.

The 95 EUROCAT congenital anomaly subgroups for which monitoring is performed are shown in Appendix A. Chromosomal cases are excluded from monitoring except for monitoring of chromosomal subgroups.

3.1.1 Pan-Europe trends

The pan-Europe monitoring can only be conducted centrally as it uses data from all the registries combined. The methodology used for pan-Europe monitoring is the same as for the long-term trend monitoring (described below) with the exception that it is run only on the last 10 years of data (1998-2007) or data within this period.

Registry inclusion criteria:

- All full member registries who have submitted new data since the previous Statistical Monitoring Report are included in pan-Europe monitoring.
- Registries must have a minimum 5 years of data to be included.
- Time period is 1998-2007

At the time of statistical monitoring in Spring 2009, there were 32 full member registries in EUROCAT. Twenty-two full member registries were included in the pan-Europe monitoring 1998-2007. Ukraine was excluded as it had less than 5 years of data. Paris, Malta, South Portugal, Mainz, Styria, NW Thames, Campania, Sicily, and Norway were excluded as data was unchanged from previous report (See http://www.eurocat-network.eu/content/Stat-Mon-Report-2006.pdf).

3.1.2 Long term trends in individual registries

1. A chi square test for trend and for non-linear change based on number of cases and number of births per year is performed.
2. Long-term trend tests are run using the last 10 years of data (1998-2007) or data for the most recent 10 year period for the registry
3. Trend analysis groups data by 2 year intervals.
4. Trend analysis is always based on year of birth/delivery.
5. A trend test is performed if the average expected number of cases per 2 year interval is 5 or more, **OR** if the observed number of cases per 2 year interval is 2 or more
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.

Registry inclusion criteria:

- All full member registries who have submitted new data since the previous Statistical Monitoring Report.
- Registries must have a minimum 8 years of data

Twenty-one full member registries were included in the long-term trend analysis. Ile de la Reunion and Ukraine were excluded as they had less than 8 years of data at the time of monitoring. Paris, Malta, South Portugal, Mainz, Styria, NW Thames, Campania, Sicily, and Norway were excluded as data was unchanged from previous report (See http://www.eurocat-network.eu/content/Stat-Mon-Report-2006.pdf).

3.1.3 Clusters

1. A 'scan' moving window method is used to detect clusters, (See EUROCAT Statistical Monitoring Protocol http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2007.pdf), scanning all recorded cases in the period 2003-2007.
2. Clusters or deficits occurring in the last 2 years (2006-2007) that are less than 18 months in length are reported.
3. A minimum of 7 cases over the surveillance period (2003-2007) is needed to run the scan analysis.
4. The default scan analysis uses estimated date of conception, If date of conception cannot be estimated for more than 10% of cases, then cluster analysis uses date of birth.
5. 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 (2007). If date of birth/delivery is used to detect clusters, the last full year (1 January – 31 December) is included in the surveillance.
6. 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.
7. 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.
8. Cluster test results are presented alongside 5-year trend (chi square) results, to help assess whether the cluster could be described as a short term trend.

Registry inclusion criteria

- Only registries that transmitted year 2007 data with full date of birth information are included in the cluster monitoring 2003-2007.
- Registries must have 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%).

At the time of statistical monitoring in Spring 2009, 17 full member registries had transmitted year 2007 data to EUROCAT Central Registry by Feb 15 2009. Cluster analysis was run using 10 registries (Antwerp, Dublin, East Midlands & South Yorkshire, Northern England, Northern Netherlands, Odense, Tuscany, Vaud, Wales, and Wessex). Two registries were excluded from statistical monitoring due to > 10% fluctuations in population (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. Emilia Romagna, Hainaut and South East Ireland were excluded as their 2007 data transmission was incomplete or unconfirmed.

3.2 Statistical software updates from previous report

In addition to the expected number of cases criterion (i.e. at least an average of 5 per subgroup/ per 2-year interval), trend analysis is now run if the observed number of cases per subgroup/ per 2 year interval is at least 2.

The output now shows both the test for trend and the test for non-linearity (Chi square). All significant results are shown ($p < 0.05$).

4. Results

4.1 Pan-Europe trends (all registries combined)

Pan-Europe trend tests were performed for 94 of the 95 EUROCAT subgroups of congenital anomalies in 22 EUROCAT registries (combined) covering 4.0 million births, 1998-2007.

Significant increasing trends over time were identified in 9 subgroups (Table 1 and Appendix B). A further subgroup (atresia/stenosis other parts of small intestine) significantly increased over time but also showed significant non-linear change i.e. although an increasing trend was identified, the increase was not linear over the time period and it is not statistically appropriate to consider this a trend.

Table 1: Pan-Europe monitoring significant increasing trends

	Significant increasing Chi^2 trend	Significant non-linear change
Hypoplastic left heart	p=0.004	
Total anomalous pulm venous return	p= 0.032	
Cystic adenomatous malf of lung	p< 0.001	
Atresia/stenosis other parts of small intestine	p=0.035	p=0.006
Abdominal wall defects	p< 0.001	
Gastroschisis	p< 0.001	
Omphalocele	p=0.035	
Renal dysplasia	p< 0.001	
Hypospadias	p< 0.001	
Edward syndrome/trisomy 18	p< 0.001	

There were 26 significant decreasing trends over time, 10 of which also showed significant non-linear change i.e. the decrease was not linear over the time period (Table 2 and Appendix B).

Table 2: Pan-Europe monitoring significant decreasing trends

	Significant decreasing Chi^2 trend	Significant non-linear change
All Non-chromosomal Anomalies	<0.001	<0.001
Neural Tube Defects	0.002	
Spina Bifida	0.003	
Eye	<0.001	
Congenital cataract	0.036	0.006
Ear, face and neck	<0.001	
Congenital heart disease	<0.001	<0.001
Transposition of great vessels	0.019	
Ventricular septal defect	<0.001	<0.001
Atrial septal defect	<0.001	<0.001
Atrioventricular septal defect	0.026	
Tricuspid atresia and stenosis	<0.001	
Aortic valve atresia/stenosis §	0.011	
Coarctation of aorta	0.042	0.043
Respiratory	<0.001	
Digestive system	<0.001	0.005
Urinary	<0.001	0.004
Bilateral renal agenesis incl Potter syndrome	0.001	
Congenital hydronephrosis	<0.001	
Limb	<0.001	
Hip dislocation and/or dysplasia	<0.001	
Syndactyly	<0.001	
Arthrogryposis multiplex congenita	0.039	
Musculo-skeletal	<0.001	0.025
Other malformations	<0.001	
Disorders of skin	<0.001	<0.001

Eight subgroups (congenital glaucoma, anotia, ano-rectal atresia and stenosis, conjoined twins, teratogenic syndromes with malformations, fetal alcohol syndrome, chromosomal and Down syndrome) showed significant non-linear change over time, but no overall increasing or decreasing trend.

In total, significant trends/non-linear change over time were detected in 47% of the 94 subgroups.

When data was combined for all registries, Warfarin syndrome was the only subgroup excluded from monitoring due to too there being few cases for statistical analysis (see Methods). In contrast, monitoring of long-term trends in individual registries was not performed on 9 subgroups of congenital anomalies due to there being too few cases (anophthalmos/ micropthalmos, annular pancreas, jeunes syndrome, asplenia, conjoined twins, fetal alcohol syndrome, valproate syndrome, warfarin syndrome and cri-du-chat syndrome).

4.2 Long-term trends in individual registries

Table 3 shows a total of 259 significant long-term trends were reported from surveillance of 95 anomaly subgroups in 21 EUROCAT registries covering 4.1 million births, 1998-2007, or the most recent 10-year period of available data. There were 61 increasing trends and a further 28 increasing trends with significant non-linear change (n=89). There were 115 decreasing trends and a further 55 decreasing trends with significant non-linear change (n=170). In addition, there were 91 subgroups with significant non-linear change (i.e significant change from year to year, but no overall trend). Rare anomalies with less than 25 expected cases or < 10 observed cases over the 10 year period have not been tested, particularly in the smaller registries (see Table 3). A total of 1264 chi square tests were performed, with a detection rate of 28% "significant" results, rather than the 5% expected by chance.

Per EUROCAT anomaly subgroup, the number of increasing trends ranged from 0-8, the number of decreasing trends ranged from 0-12, and the number with significant non-linear heterogeneity ranged from 0-5 (Table 3).

Per registry, the number of increasing trends ranged from 0-12, the number of decreasing trends ranged from 0-17, and the number of non-linear heterogeneity ranged from 0-12 (Table 3).

Increasing trends in congenital anomalies

Due to the large number of identified trends, and the primary role of monitoring in identifying increases requiring public health action, we only further describe increasing trends in this Report.

Significant increasing trends were identified in Wielkopolska and Wessex for 10-12 subgroups of congenital anomalies. Other registries reported less increasing trends.

Significant increasing trends were identified for 39 subgroups of congenital anomalies. Increasing trends were identified in 11 main organ system subgroups: nervous system anomalies, ear, face & neck anomalies, congenital heart defects, respiratory anomalies, orofacial clefts, digestive system anomalies, abdominal wall defects, urinary anomalies, genital anomalies, limb anomalies 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 3). Only trends in a specific subgroup are described below.

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

- Renal dysplasia increased in 8 registries - Tuscany, Dublin, Northern Netherlands, Antwerp, Saxony-Anhalt, Barcelona, Wielkopolska and East Midlands & South Yorkshire.
- Hypospadias increased in 7 registries – Emilia Romagna, Tuscany, N Netherlands, Zagreb, Barcelona, Thames Valley and Wessex
- Gastroschisis increased in 5 registries, 4 of which are located in UK –Tuscany, East Midlands & South Yorkshire, Northern England, Wales and Wessex
- Edward syndrome increased in 4 registries - Northern Netherlands, Emilia Romagna, Strasbourg and Wales

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

- Hypoplastic left heart increased in Dublin, Basque Country and East Midlands & South Yorkshire.
- Polydactyly increased in Emilia Romagna, Barcelona and Wessex.
- Down syndrome increased in Odense, Vaud and Wessex.

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

- Hydrocephalus increased in Zagreb and East Midlands & South Yorkshire
- Ventricular septal defect increased in Vaud and Zagreb.
- Atrial septal defect increased in Zagreb and Wielkopolska
- Cystic adenomatous malformation of lung increased in Wales and East Midlands & South Yorkshire
- Congenital hydronephrosis increased in Odense and Wielkopolska
- Posterior urethral valve increased in Basque Country and Wales
- Club foot increased in Barcelona and East Midlands & South Yorkshire
- Syndactyly increased in Emilia Romagna and Wessex
- Turner's syndrome increased in Barcelona and Thames Valley

Increasing trends in the following 10 subgroups were detected in a single registry:

- Anencephalus (East Midlands & South Yorkshire)
- Microcephaly (Saxony-Anhalt)
- Pulmonary valve stenosis (Saxony-Anhalt)
- Total anomalous venous return (Northern England)
- Cleft palate (Wessex)
- Diaphragmatic hernia (Wielkopolska)
- Upper limb reduction (Emilia Romagna)
- Lower limb reduction (Vaud)
- Craniosynostosis (Wielkopolska)
- Klinefelters syndrome (Emilia Romagna)

The outcomes of the individual registry preliminary investigations into the identified trends are shown in Section 4.4.2.

Table 3: Central Registry Statistical Monitoring Results: Table of reported ten year trends by registry and by anomaly

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Years tested (grouped by 2 years)					1998-07	1997-06	1998-07	1998-07	1995-04	1998-07	1997-04	1998-07	1997-06	1997-06	1998-07	1998-07	1999-06	1997-06	1997-06	1998-07	1998-07	2000-07	1998-07	1998-07	1998-07
All Non-chromosomal Anomalies	3	12	2	17	\	\	/			\		\	\		\	\	/	\	~	\	~	\	\	\	/
Nervous system	1	3	3	7		~				/			\				~	~						\	\
Neural Tube Defects	0	2	1	3		~						\												\	
Anencephalus and similar	1	1	0	2			*						*								/			\	
Encephalocele	0	0	0	0	*	*	*	*			*		*		*	*		*	*	*			*		
Spina Bifida	0	2	0	2			*					\													\
Hydrocephaly	2	0	2	4		~	/										~				/				
Microcephaly	1	2	2	5		\	*	*	*	/							~				\		*	~	
Arhinencephaly/holoprosencephaly	0	0	0	0	*	*	*	*	*	*	*	*	*		*	*	*	*		*			*		
Eye	0	4	2	6	~	\	*		\							\					\		*		~
Anophthalmos/ micropthalmos	0	1	1	2		*	*		*	*	*		*	~	*	*		*	*	*	\		*		*
Anophthalmos	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	2	0	2		*	*	*		*	*		*	*		\	*	*	*	*		\	*		*
Congenital glaucoma	0	0	0	0	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*		*
Ear, face and neck	1	9	0	10			*	*	\	\	*	\	*	\	\	\		/	\	\	\		*		*
Anotia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*		*	*	*
Congenital heart defects	3	7	2	12	~		/			/			\	\	\		/	\			~	\	\	\	
Common arterial truncus	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*			*		*

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Transposition of great vessels	0	1	0	1		*				\										*					
Single ventricle	0	1	0	1	*	*	*	*	*	*	*	*	*	\	*	*		*	*	*	*	*	*		*
Ventricular septal defect	2	4	5	11	~		/							\	\		~	\	~	/	~	\		~	
Atrial septal defect	2	6	4	12	~		/	\		~		~		\	\		/	\			\	~		\	
Atrioventricular septal defect	0	1	0	1			*	*		*			*				\						*		
Tetralogy of Fallot	0	0	1	1			*						*				~								
Tricuspid atresia and stenosis	0	2	0	2	*	*	*	*		*	*		*	\	*		*	\	*	*		*	*		*
Ebstein's anomaly	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*		*
Pulmonary valve stenosis	1	1	1	3			*			/			*		\							~	*		*
Pulmonary valve atresia	0	0	1	1	*	*	*	*	*	*	*		*				*	*	~	*			*		
Aortic valve atresia/stenosis	0	0	0	0	X	X	X	X	X	X		X	X	X	X	X		X	X	X					
Hypoplastic left heart	3	1	0	4	\	*	*	*				/						*	/	*	/				
Hypoplastic right heart	0	0	0	0	X	X	X	X	X	X	*	X	X	X	X	X	*	X	X	X		*	*		
Coarctation of aorta	0	2	1	3		\	*	*					*				\				~				
Total anomalous pulmonary venous return	1	1	0	2	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	\	/	*		*
Respiratory	1	5	1	7	~			*				\	\			\					\			\	/
Choanal atresia	0	0	0	0		*	*	*	*		*		*	*	*	*	*			*			*		*
Cystic adenomatous malf of lung	2	0	0	2	X	X	X	X	X	X	*	X	X	X	X	X	*	X	X	X	/			/	
Oro-facial clefts	1	1	1	3									~								\				/
Cleft lip with or without palate	0	2	1	3	~			\							\										
Cleft palate	1	1	0	2																	\				/
Digestive system	1	7	3	11	\				~				\	~	\	\	/	\			~	\		\	

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Oesophageal atresia with/without tracheo-oesophagal fistula	0	1	2	3			*				*		*		~	~					\		*		
Duodenal atresia or stenosis	0	0	1	1	*	*	*	*	*	*	*		*		*	*		*	*	*			*		~
Atresia or stenosis of other parts of small intestine	0	0	1	1		*	*	*	*	*	*	*	*		*	*	*	*	*	*			*		~
Ano-rectal atresia and stenosis	0	1	3	4			*		\				*		~		~		~	*					
Hirschsprung's disease	0	0	0	0		*	*	*	*	*	*		*	*	*		*	*	*	*			*		
Atresia of bile ducts	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*		*
Annular pancreas	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	1	2	1	4			*	*	~		*		*				/	\				\			
Abdominal wall defects	5	1	2	8						~	/			~		\					/	/		/	/
Gastroschisis	5	0	1	6			*	*		~	*		*		/			*		*	/	/		/	/
Omphalocele	0	0	1	1		*	*				*		*	~											
Urinary	2	7	2	11	\	\				\		~					/		~	\	/	\	\	\	
Bilateral renal agenesis including Potter syndrome	0	2	0	2	\	*	*	*					*						\	*					
Renal dysplasia	8	0	1	9	/		*			/		/	*	~	/	/	/	/			/				
Congenital hydronephrosis	2	7	5	14	~	\		/				~		\	~	~	/		\		~	\	\	\	\
Bladder exstrophy and/or epispadia	0	0	0	0	*	*	*	*	*	*	*		*	*		*	*	*	*	*		*	*	*	*
Posterior urethral valve and/or prune belly	2	1	1	4		*	*	*		*	*		*	*	*	\	*	*	/	*			*	/	~
Genital	6	1	4	11			/			~		\		/	/	/	~			~			/	~	/
Hypospadias	7	1	4	12			/			~		\		/	/	/	~	/		~			/	~	/
Indeterminate sex	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*			*	*	*
Limb	1	10	2	13	\		\			\		\	\		\	\	~		\		~		\	\	/

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Limb reduction	1	0	0	1									*				/								
Upper limb reduction	1	0	2	3		~	*						*	/					~						
Lower limb reduction	1	1	0	2			*	*					*			\				/			*		
Complete absence of a limb	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Club foot - talipes equinovarus	2	6	1	9					~			\		\	\	\		/	\		/	*	\		
Hip dislocation and/or dysplasia	0	7	0	7	\					\		\	\					*	*	\	\	*	*	\	*
Polydactyly	3	0	0	3									*	/				/							/
Syndactyly	2	3	1	6		~		*		\			*	/		\					\		*		/
Arthrogryposis multiplex congenita	0	2	0	2			*	*	*	*	*	*	*	*	*	*	*	\	*	*	\	*	*		*
Musculo-skeletal	0	6	4	10	~	\				\		\	\			\	~		~	~				\	
Thanatophoric dwarfism	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Jeunes syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Achondroplasia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*		*
Craniosynostosis	1	2	2	5			*			\	*		*				/		~		\	~	*		*
Congenital constriction bands/amniotic band	0	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*		
Other malformations	0	11	2	13	\				\	\		~	\	~	\	\			\	\	\		\	\	
Asplenia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	0	0	0	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*		*	*		*
Conjoined twins	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	0	12	1	13	\		*	*	\	\	*	\		\	\	\	~	\	\	\	\		*	\	*
Teratogenic syndromes with malformations	0	0	0	0	X	X	X	X	X	X	*	X	X	X	X	X	*	X	X	X	*	*			

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Fetal alcohol syndrome	0	0	0	0	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	*	*	*	*	*
Warfarin syndrome	0	0	0	0	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	0	3	1	4			*														\		\	~	\
Chromosomal	2	0	4	6				/						/			~	~			~			~	
Down Syndrome	3	1	3	7				/										~	~	/	~		\		/
Patau syndrome/trisomy 13	0	0	0	0		*	*			*			*												
Edward syndrome/trisomy 18	4	0	1	5			*		/					/		/				~				/	
Turner's syndrome	2	0	2	4			*	*			*		*		~			/		~			/		
Klinefelters syndrome	1	1	1	3	*		*	*			*	*	*	/		*	*	~					*	\	
Cri-du-chat syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Total / trends across registries	89			89	1	0	7	3	1	5	1	2	0	8	4	4	10	6	2	3	9	3	3	5	12
Total \ trends across registries		170		170	9	7	1	2	5	11	0	12	9	9	12	15	2	9	7	6	17	8	9	16	4
Total ~ trends across registries			91	91	8	5	0	0	3	5	0	5	1	6	4	2	12	4	9	5	9	3	0	6	4
Total any	89	170	91	350	18	12	8	5	9	21	1	19	10	23	20	21	24	19	18	14	35	14	12	27	20

Key:
/ = significant upward trend \ = significant downward trend ~ = non-linear change over time
X = Data excluded from analysis. Registries must have used ICD10 coding for the whole period 1998-2007 to be included in surveillance of these subgroups
***** Too few cases to run analysis.

4.3 Detected Clusters

A total of 23 clusters based on date of conception were detected from surveillance of 75 anomaly subgroups in 10 EUROCAT registries, covering approximately 0.5 million births in 2006-2007 (Table 4). A total of 487 cluster tests were performed giving a cluster detection rate of 4.7%. By chance alone, we would expect a cluster detection rate of 2.5%. Five of the 23 clusters (highlighted below) were identified and investigated in the 2006 Report: http://www.eurocat-network.eu/content/Stat-Mon-Report-2006.pdf.

Two clusters of congenital hydronephrosis and hypospadias were detected.

- The hydronephrosis clusters were detected in Dublin (Ireland) and Northern England (UK). The hydronephrosis cluster in Dublin* was identified in the 2006 Report. The cluster in Northern England was detected in the context of a decreasing 5 year trend (See Appendix C).
- The hypospadias clusters were detected in Dublin (Ireland) and Wessex (UK). The cluster in Dublin was detected in the context of an increasing 5 year trend with significant non-linear change, while the cluster in Wessex was detected in the context of a decreasing 5 year trend (See Appendix C).

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

- Anencephalus (Tuscany, Italy)
- Hydrocephaly (East Midlands & South Yorkshire, UK)
- Congenital cataract (Tuscany, Italy) *
- Common arterial truncus (East Midlands & South Yorkshire, UK)
- Transposition of great vessels (East Midlands & South Yorkshire, UK)
- Ventricular septal defect (East Midlands & South Yorkshire, UK)
- Aortic valve atresia/stenosis (Dublin, Ireland)
- Coarctation of aorta (Vaud, Switzerland)
- Choanal atresia (Antwerp, Belgium)
- Cleft palate (East Midlands & South Yorkshire, UK)
- Bladder exstrophy (Northern England, UK)
- Diaphragmatic hernia (Vaud, Switzerland) *
- Posterior urethra valve and/or prune belly (Wales, UK) *
- Indeterminate sex (Wales, UK)
- Upper limb reduction (Dublin, Ireland)
- Club foot (Wessex, UK)
- Polydactyly (Wessex, UK)
- Patau syndrome/ trisomy 13 (Tuscany, Italy) *
- Edward syndrome (Antwerp, Belgium)

* Clusters identified and investigated in the Statistical Monitoring Report 2006.

Full details of each cluster are found in Appendix C.

The outcomes of the individual registry preliminary investigations into the detected clusters are shown in Section 4.4.1.

Table 4: Central Registry Statistical Monitoring Results: Table of detected clusters by registry and by anomaly 2006-2007

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Antwerp (BE)	Odense (DK)	Dublin (IE)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Wales (UK)	Wessex (UK)
All Non-chromosomal 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	1	0	1				**C**						
Encephalocele	0	0	0		*		*	*					
Spina Bifida	0	0	0										
Hydrocephaly	1	0	1							**C**			
Microcephaly	0	0	0		*								
Arhinencephaly/holoprosencephaly	0	0	0	*	*	*		*	*				*
Eye	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
Anotia	0	0	0	*	*	*	*	*	*	*		*	*
Congenital heart defects	X	X	X	X	X	X	X	X	X	X	X	X	X
Common arterial truncus	1	0	1	*	*		*	*	*	**C**			
Transposition of great vessels	1	0	1		*					**C**			
Single ventricle	0	0	0	*	*	*		*	*		*		*
Ventricular septal defect	1	0	1							**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 §	1	0	1	*	*	**C**	*						
Hypoplastic left heart	0	0	0										
Hypoplastic right heart §	0	0	0	*	*	*	*	*	*		*		
Coarctation of aorta	1	0	1		*				**C**				
Total anomalous pulmonary venous return	0	0	0	*	*		*		*				
Respiratory	X	X	X	X	X	X	X	X	X	X	X	X	X
Choanal atresia	1	0	1	**C**	*		*	*	*				

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Antwerp (BE)	Odense (DK)	Dublin (IE)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Wales (UK)	Wessex (UK)
Cystic adenomatous malf of lung §	0	0	0	*	*	*	*	*	*				
Oro-facial clefts	X	X	X	X	X	X	X	X	X	X	X	X	X
Cleft lip with or without palate	0	0	0										
Cleft palate	1	0	1							**C**			
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	1	0	1		*				**C**				
Abdominal wall defects	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
Bilateral renal agenesis including Potter syndrome	0	0	0		*		*		*				
Renal dysplasia	0	0	0										
Congenital hydronephrosis	2	0	2			**C**					**C**		
Bladder exstrophy and/or epispadia	1	0	1	*	*			*	*		**C**	*	*
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
Hypospadias	2	0	2			**C**							**C**
Indeterminate sex	1	0	1	*	*	*	*	*	*			**C**	
Limb	X	X	X	X	X	X	X	X	X	X	X	X	X
Limb reduction	0	0	0										
Upper limb reduction	1	0	1			**C**							
Lower limb reduction	0	0	0										
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	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
Thanatophoric dwarfism	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)	Dublin (IE)	Tuscany (IT)	N Netherlands (NL)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Wales (UK)	Wessex (UK)
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										*
Teratogenic syndromes with malformations §	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
Chromosomal	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	1	0	1	**C**									
Turner's syndrome	0	0	0		*								
Klinefelters syndrome	0	0	0	*	*	*		*					
Cri-du-chat syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*
Total clusters: date of conception	23			2	0	4	3	0	2	5	2	2	3
Total clusters: date of birth		0		0	0	0	0	0	0	0	0	0	0
Total clusters			23	2	0	4	3	0	2	5	2	2	3

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 2003-2007 in order to be included in surveillance of these subgroups

4.4 Local registry preliminary investigations of clusters/trends identified centrally

Investigation protocols are described in the EUROCAT Statistical Monitoring Protocol (http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2007.pdf).

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 methods, training, personnel or reporting practice 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. 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?);
6. which public health authorities have been or will be notified about the cluster?

Increasing long-term 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. Which public health authority will the result be reported to?

Local investigation reports were initially discussed at RLM in Bilbao June 2009 and then a final written report sent to Central Registry.

4.4.1 Local registry investigations into detected clusters

Only the 18 new clusters are investigated and presented below. Central Registry received reports on preliminary investigations from the following local registries: Antwerp, Tuscany, Vaud, E Midlands & S Yorkshire, N England, Wales and Wessex. Dublin indicated difficulties investigating clusters due to data protection and confidentiality issues. No clusters were identified in Odense or the Northern Netherlands. Reports were not received from Dublin.

Table 5 shows the outcomes of the cluster investigations, classified as follows:

- Apparent cluster with cause for concern, further investigation ongoing (n=0)
- Cluster associated with aetiologic heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence (n=2)
- Excess of cases confirmed, but no further investigation proposed other than further surveillance (n=6)
- Increase in cases, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound detection rates (n=2)
- Data quality issues found to explain cluster (n=5)

- No report of preliminary investigations sent to Central Registry (n=3).

Full details of the registry investigations are found in a separate Annex in the membership-only section of the EUROCAT website http://www.eurocat-network.eu/

Table 5: Outcomes of local registry preliminary investigations of detected clusters 2006-2007

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	Increase in cases/ascertainment, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound rates	Clusters due to data quality errors	No detailed report sent to Central Registry
• Hydronephrosis - Northern England • Polydactyly – Wessex	• Choanal atresia - Antwerp • Edward syndrome - Antwerp • Anencephalus - Tuscany • Coarctation of aorta - Vaud • Bladder exstrophy – N England • Cleft palate - E Mid & S York (UK)	• Hypospadias - Wessex • Club foot - Wessex	• Hydrocephalus – E Mid & S York (UK) • Common arterial truncus - E Mid & S York (UK) • Transposition great vessels – E Mid & S York (UK) • Ventricular septal defect - E Mid & S York (UK) • Indeterminate sex - Wales	• Aortic valve – Dublin • Upper limb reduction – Dublin • Hypospadias – Dublin

4.4.2 Local registry investigations into increasing long-term trends

Central Registry received reports on preliminary trend investigations from 12 of 19 local registries with increasing trends (63%): Barcelona, East Midlands & South Yorkshire, Emilia Romagna, N Netherlands, Northern England, Odense, Saxony-Anhalt, Strasbourg, Tuscany, Vaud, Wessex and Zagreb. No increasing trends were detected in Hainaut or SE Ireland. No reports of investigations were received from Antwerp, Basque Country, Cork & Kerry, Dublin, Thames Valley, Wales or Wielkopolska.

The results of the investigations into the significant increasing trends are described in Table 6, classified as follows:

- A: Changes in case ascertainment (data quality) (n=22)
- B: Changes in local or central registry methods e.g. definitions and inclusion criteria (n=7)
- C: Changes in diagnostic methods (n=8)
- D: Trend confirmed, due to known demographic changes (n=7)
- E: Trend confirmed, investigation ongoing (n=9)
- F: Trend confirmed, further surveillance proposed before more detailed investigation (n=5)
- G: Not real trend when additional years added, or heterogeneous subgroup (n=2)
- H: No report or clear interpretation of preliminary investigations sent to Central Registry (n=29)

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.

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

- Respiratory anomalies in Wessex
- Cleft palate in Wessex
- Renal dysplasia in N Netherlands
- Gastroschisis in 3 regions of UK (E Midlands & S Yorkshire, N England and Wessex)
- Upper limb reduction in Emilia Romagna
- Down syndrome in Odense
- Edward syndrome in N Netherlands

Five registries (Emilia Romagna, Odense, Saxony-Anhalt, Wessex and Zagreb) indicated that their findings would be reported to the local health authorities in their region.

Full details of the registry investigations are found in a separate Annex in the membership-only section of the EUROCAT website http://www.eurocat-network.eu/

Table 6: Outcomes of local registry preliminary investigations into increasing long-term trends

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Years tested (grouped by 2 years)					1998-2007	1997-2006	1998-2007	1998-2007	1995-2004	1998-2007	1997-2004	1998-2007	1997-2006	1997-2006	1998-2007	1998-2007	1999-2006	1997-2006	1997-2006	1998-2007	1998-2007	2000-2007	1998-2007	1998-2007	1998-2007
All Non-chromosomal Anomalies	3	12	2	17	\	\	**A/ B**			\		\	\		\	\	**H**	\	~	\	~	\	\	\	**A**
Nervous system	1	3	3	7		~				**A/ B**			\				~	~						\	\
Neural Tube Defects	0	2	1	3		~						\												\	
Anencephalus and similar	1	1	0	2			*						*								**H**			\	
Encephalocele	0	0	0	0	*	*	*	*			*		*		*	*		*	*	*			*		
Spina Bifida	0	2	0	2			*					\													\
Hydrocephaly	2	0	2	4		~	**A/ E**										~				**A**				
Microcephaly	1	2	2	5		\	*	*	*	**A/ B**							~				\		*	~	
Arhinencephaly/holoprosencephaly	0	0	0	0	*	*	*	*	*	*	*	*	*		*	*	*	*		*			*		
Eye	0	4	2	6	~	\	*		\							\					\		*		~
Anophthalmos/ micropthalmos	0	1	1	2		*	*		*	*	*		*	~	*	*		*	*	*	\		*		*
Anophthalmos	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	2	0	2		*	*	*		*	*		*	*		\	*	*	*	*		\	*		*
Congenital glaucoma	0	0	0	0	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*		*
Ear, face and neck	1	9	0	10			*	*	\	\	*	\	*	\	\	\		**A**	\	\	\		*		*
Anotia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*		*	*	*
Congenital heart defects	3	7	2	12	~		**A/ B/ C**			**C**			\	\	\		**H**	\			~	\	\	\	
Common arterial truncus	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*			*		*

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Transposition of great vessels	0	1	0	1		*				\										*					
Single ventricle	0	1	0	1	*	*	*	*	*	*	*	*	*	\	*	*		*	*	*	*	*	*		*
Ventricular septal defect	2	4	5	11	~		A/ B/ C							\	\		~	\	~	C	~	\		~	
Atrial septal defect	2	6	4	12	~		A/ B/ C	\		~		~		\	\		H	\			\	~		\	
Atrioventricular septal defect	0	1	0	1			*	*		*			*				\						*		
Tetralogy of Fallot	0	0	1	1			*						*				~								
Tricuspid atresia and stenosis	0	2	0	2	*	*	*	*		*	*		*	\	*		*	\	*	*		*	*		*
Ebstein's anomaly	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*		*
Pulmonary valve stenosis	1	1	1	3			*			C			*		\							~	*		*
Pulmonary valve atresia	0	0	1	1	*	*	*	*	*	*	*		*				*	*	~	*			*		
Aortic valve atresia/stenosis	0	0	0	0	X	X	X	X	X	X		X	X	X	X	X		X	X	X					
Hypoplastic left heart	3	1	0	4	\	*	*	*				H						*	H	*	A				
Hypoplastic right heart	0	0	0	0	X	X	X	X	X	X	*	X	X	X	X	X	*	X	X	X		*	*		
Coarctation of aorta	0	2	1	3		\	*	*					*				\				~				
Total anomalous pulmonary venous return	1	1	0	2	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	\	G	*		*
Respiratory	1	5	1	7	~			*				\	\			\					\			\	F
Choanal atresia	0	0	0	0		*	*	*	*		*		*	*	*	*	*			*			*		*
Cystic adenomatous malf of lung	2	0	0	2	X	X	X	X	X	X	*	X	X	X	X	X	*	X	X	X	A			H	
Oro-facial clefts	1	1	1	3									~								\				F
Cleft lip with or without palate	0	2	1	3	~			\							\										
Cleft palate	1	1	0	2																	\				F
Digestive system	1	7	3	11	\				~				\	~	\	\	H	\			~	\		\	
Oesophageal atresia with/without	0	1	2	3			*				*		*		~	~					\		*		

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
tracheo-oesophagal fistula																									
Duodenal atresia or stenosis	0	0	1	1	*	*	*	*	*	*	*		*		*	*		*	*	*			*		~
Atresia or stenosis of other parts of small intestine	0	0	1	1		*	*	*	*	*	*	*	*		*	*	*	*	*	*			*		~
Ano-rectal atresia and stenosis	0	1	3	4			*		\				*		~		~		~	*					
Hirschsprung's disease	0	0	0	0		*	*	*	*	*	*		*	*	*		*	*	*	*			*		
Atresia of bile ducts	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*		*
Annular pancreas	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	1	2	1	4			*	*	~		*		*				**H**	\				\			
Abdominal wall defects	5	1	2	8						~	**H**			~		\					**E**	**E**		**H**	**E**
Gastroschisis	5	0	1	6			*	*		~	*		*		**H**			*		*	**E**	**E**		**H**	**E**
Omphalocele	0	0	1	1		*	*				*		*	~											
Urinary	2	7	2	11	\	\				\		~					**H**		~	\	**A**	\	\	\	
Bilateral renal agenesis including Potter syndrome	0	2	0	2	\	*	*	*					*						\	*					
Renal dysplasia	8	0	1	9	**H**		*			**C**		**H**	*	~	**H**	**F**	**H**	**C**			**A**				
Congenital hydronephrosis	2	7	5	14	~	\		**C**				~		\	~	~	**H**		\		~	\	\	\	\
Bladder exstrophy and/or epispadia	0	0	0	0	*	*	*	*	*	*	*		*	*		*	*	*	*	*		*	*	*	*
Posterior urethral valve and/or prune belly	2	1	1	4		*	*	*		*	*		*	*	*	\	*	*	**H**	*			*	**H**	~
Genital	6	1	4	11			**A/ B**			~		\		**B**	**B**	**B**	~			~			**H**	~	**A**
Hypospadias	7	1	4	12			**A/ B**			~		\		**B**	**B**	**B**	~	**B**		~			**H**	~	**A**
Indeterminate sex	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*			*	*	*
Limb	1	10	2	13	\		\			\		\	\		\	\	~		\		~		\	\	**C**
Limb reduction	1	0	0	1									*				**H**								
Upper limb reduction	1	0	2	3		~	*						*	**E**					~						

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Lower limb reduction	1	1	0	2			*	*					*			\				A			*		
Complete absence of a limb	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Club foot - talipes equinovarus	2	6	1	9					~			\		\	\	\		A	\		H	*	\		
Hip dislocation and/or dysplasia	0	7	0	7	\					\		\	\					*	*	\	\	*	*	\	*
Polydactyly	3	0	0	3									*	D				H							A
Syndactyly	2	3	1	6		~		*		\			*	D		\					\		*		G
Arthrogryposis multiplex congenita	0	2	0	2			*	*	*	*	*	*	*	*	*	*	*	\	*	*	\	*	*		*
Musculo-skeletal	0	6	4	10	~	\				\		\	\			\	~		~	~				\	
Thanatophoric dwarfism	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Jeunes syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Achondroplasia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*		*
Craniosynostosis	1	2	2	5			*			\	*		*				H		~		\	~	*		*
Congenital constriction bands/amniotic band	0	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*		
Other malformations	0	11	2	13	\				\	\		~	\	~	\	\			\	\	\		\	\	
Asplenia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	0	0	0	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*		*	*		*
Conjoined twins	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	0	12	1	13	\		*	*	\	\	*	\		\	\	\	~	\	\	\	\		*	\	*
Teratogenic syndromes with malformations	0	0	0	0	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	*	*	*	*	*
Valproate syndrome	0	0	0	0	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	*	*	*	*	*
Maternal infections resulting in malformations	0	0	1	1	*	*	*	*	*	*	*	~	*		*	*	*	*	*	*	*	*	*		*
Genetic syndromes + microdeletions	0	3	1	4			*														\		\	~	\

Anomaly	Total /	Total \	Total ~	Total any	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Strasbourg (FR)	Saxony Anhalt (DE)	Cork and Kerry (IE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	N Netherlands (NL)	Wielkopolska (PL)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	Northern England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Chromosomal	2	0	4	6				**E**						**D**			~	~			~			~	
Down Syndrome	3	1	3	7				**E**										~	~	**D**	~		\		**C**
Patau syndrome/trisomy 13	0	0	0	0		*	*			*			*												
Edward syndrome/trisomy 18	4	0	1	5			*		**D**					**D**		**F**				~				**H**	
Turner's syndrome	2	0	2	4			*	*			*		*		~			**A**		~			**H**		
Klinefelters syndrome	1	1	1	3	*		*	*			*	*	*	**D**		*	*	~					*	\	
Cri-du-chat syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Total / trends across registries	89			89	1	0	7	3	1	5	1	2	0	8	4	4	10	6	2	3	9	3	3	5	12
Total \ trends across registries		170		170	9	7	1	2	5	11	0	12	9	9	12	15	2	9	7	6	17	8	9	16	4
Total ~ trends across registries			91	91	8	5	0	0	3	5	0	5	1	6	4	2	12	4	9	5	9	3	0	6	4
Total any	89	170	91	350	18	12	8	5	9	21	1	19	10	23	20	21	24	19	18	14	35	14	12	27	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: Not real trend when additional years added or heterogeneous
- H: 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 1998-2007 in order to be included in surveillance of this subgroup
- * No surveillance, as too few cases

4.4.3 Interpretation of pan-Europe increasing trends

Prevalence of Hypoplastic Left Heart (HLH) increased from 2.1 per 10,000 births in 1998-1999 to 2.9 in 2006-2007. Three individual registries reported statistically significant increasing trends, 12 had no significant trend, 5 had too few cases for analysis, and one had a decreasing trend. Increasing trends in individual registries had already been reported in two previous annual monitoring reports (2004, 2005). Two of those with an increasing trend reported that it was likely to be due to known changes in data quality over the period. The increase in HLH comes within a context of an overall decreasing rate of CHD. A full analysis of CHD trends is currently ongoing.

Total anomalous pulmonary venous return (TAPVR) increased from 0.48 per 10,000 births 1998-9 to 0.68 per 10,000 births 2006-7. TAPVR was too rare to analyse separately in all but four individual registries. One reported a downward trend, two reported no trends, and the other found no evidence of trend when considered in the context of the entire history of the registry (23 years). TAPVR will be further considered within the general analysis of CHD trends.

The prevalence of cystic adenomatous malformation of the lung significantly increased from 0.2 per 10,000 births in 1998-1999 to 0.9 in 2006-2007. However, this EUROCAT subgroup is coded using the British Paediatric Association (BPA) extension code, and the increase in cases was thought to be a data quality issue as some registries only used the extension code in recent years. Furthermore, most registries were excluded from surveillance due to use of ICD9 in early years. No further investigation is recommended.

The prevalence of atresia and/or stenosis other parts of small intestine significantly increased over time but also showed significant non-linear change (i.e. prevalence varied from year to year). Prevalence was 0.84 in 1998-1999, 0.80 in 2000-2001, 0.58 in 2002-2003, 0.83 in 2004-2005, and finally 1.16 in 2006-2007. This trend was not detected in the individual registry long-term trend monitoring (15 of the 21 registries were excluded from long-term trend monitoring as they had too few cases). Further analysis of the individual diagnoses included and coding issues needs to be undertaken.

The increasing trend of the abdominal wall defect gastroschisis has been well documented (Loane et al). Up to 2002, the upward trend was occurring in all areas of Europe except Italy, and in all age groups although young mothers were consistently at particularly high risk. In pan-Europe monitoring, prevalence increased from 2.2 per 10,000 births in 1998-1999 to 3.6 in 2006-2007. Increases were found in 4 out of 5 UK registry areas, but only one (Tuscany, Italy) of the 10 non-UK registry areas individually monitored for this anomaly. A UK study is currently investigating possible environmental, dietary and lifestyle exposures during early pregnancy (first 12 weeks of gestation) as possible causes for this defect.

An increasing trend was also identified for the abdominal wall defect omphalocele. Omphalocele is commonly associated with chromosomal syndromes but these cases were excluded from analysis according to protocol. Prevalence increased from 1.8 per 10,000 births in 1998-1999 to 2.4 in 2006-2007. This trend was not detected in

the individual registry long-term trend monitoring. Further analysis to be conducted if still evident in next year's surveillance results.

Prevalence of renal dysplasia increased from 2.9 per 10,000 births in 1998-1999 to 4.4 in 2006-2007. Eight individual registries reported significantly increasing trends. Two considered this due to changes in diagnostic methods, one to change in case ascertainment, one confirmed the trend and proposes further surveillance before further investigation, and four did not report any investigation. In April 2008, the previous EUROCAT polycystic kidney subgroup was restricted to renal dysplasia, so this is the first time monitoring has been conducted on this specific subgroup. Improvement in general ascertainment and changes in diagnostic methods were thought to explain the increase in cases. A EUROCAT study investigating trends in relation to prenatal screening and terminations of pregnancy for fetal anomaly is currently being conducted. Results will be published in due course.

Prevalence of hypospadias increased from 12.1 per 10,000 births in 1998-1999 to 14.5 in 2006-2007. A change in exclusion criteria was implemented from 2005 births on. Before 2005, cases of isolated glanular (or 1st degree) hypospadias were excluded as a minor anomaly. After 2005, glanular hypospadias is included, but registries are recommended to record whether there was surgery (performed or planned) and the severity of hypospadias. Seven individual registries reported increasing trends. The six who investigated considered that this was due to changing inclusion criteria and/or ascertainment. Increasing trends of hypospadias were identified in previous annual statistical monitoring reports. A more detailed investigation of hypospadias trends is in planning stages, as it is currently difficult to detect any real changes against a background of inclusion criteria changes.

Prevalence of Edward Syndrome/trisomy 18 increased from 4.2 per 10,000 births in 1998-1999 to 4.9 in 2006-2007. Significantly increasing trends were identified in four individual registries. Of the three who investigated, two considered it likely to be due to demographic change, and one proposed further surveillance. Increasing trends of Edward syndrome/ trisomy 13 were already identified in the Statistical Monitoring 2004 and 2005 reports. Increasing maternal age seems not to be the only explanation, as no increasing trend was found for the other trisomies which are also associated with increasing maternal age. Earlier prenatal detection may be leading to an increased counting of cases which would otherwise not have survived to birth. A study investigating time trends of all trisomies in relation to maternal age and prenatal screening is currently underway by EUROCAT. The pan-Europe monitoring statistical methodology is currently being developed to allow adjustment for maternal age.

(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)

4.4.4. Interpretation of pan-Europe decreasing trends.

It is not the purpose of this report to report further on decreasing trends. We note however that decreases are found in congenital heart disease and a range of CHD subgroups. CHD trends are under investigation.

We note also that there is recent evidence of a decrease in neural tube defects, which is fully described in the latest EUROCAT Special Report on the prevention of neural tube defects by folic acid (http://www.eurocat-network.eu/content/Special-Report-NTD-3rdEd-Part-I.pdf).

Finally, we note a decreasing trend in arthrogryposis multiplex congenital (AMC). Further surveillance of this anomaly is necessary.

The EUROCAT network does not have the resources to investigate all trends fully. The Steering Committee determines the areas of priority. A guide to changes in coding and diagnosis for each of the subgroups is to be compiled, to aid interpretation. The types of explanation that need to be examined include changing exclusion criteria for minor anomalies (changes implemented for 2005 births onwards), changing coding precision, changing diagnostic methods including prenatal diagnosis.

4.5 Updates on previous local registry investigations into clusters and trends

No further investigations were required following local registry investigations into the clusters identified in last year's Report: http://www.eurocat-network.eu/content/Stat-Mon-Report-2006.pdf .

4.6 Local registry surveillance using EDMP

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

4.7 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 subgroup inclusion list

Congenital anomaly subgroups included in statistical monitoring (see Guide 1.3 chapter 3.3 for definition of subgroups http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. Chromosomal cases are excluded from the analysis of non-chromosomal subgroups.

	Included in cluster analysis	Included in trend analysis
All Non-chromosomal 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: Pan-Europe analysis: congenital anomaly subgroups showing significant upward or downward trend, or evidence of non-linear change

Significant trends found between 1998 and 2007

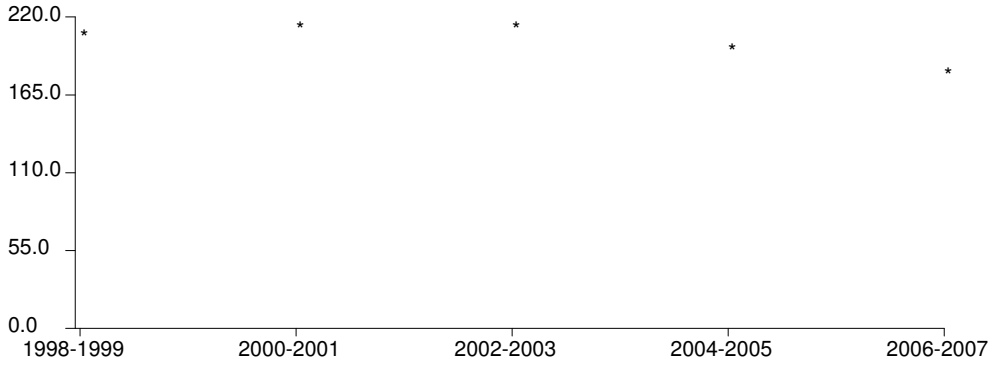
Anomaly Subgroup: **All Anomalies**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	187.952	(1 df)	Chi2	103.402	(3 df)
p value	<0.001		p value	<0.001	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	14370	689143	208.52
2000 - 2001	17144	801394	213.93
2002 - 2003	18117	846806	213.95
2004 - 2005	17935	901639	198.92
2006 - 2007	14415	791866	182.04

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



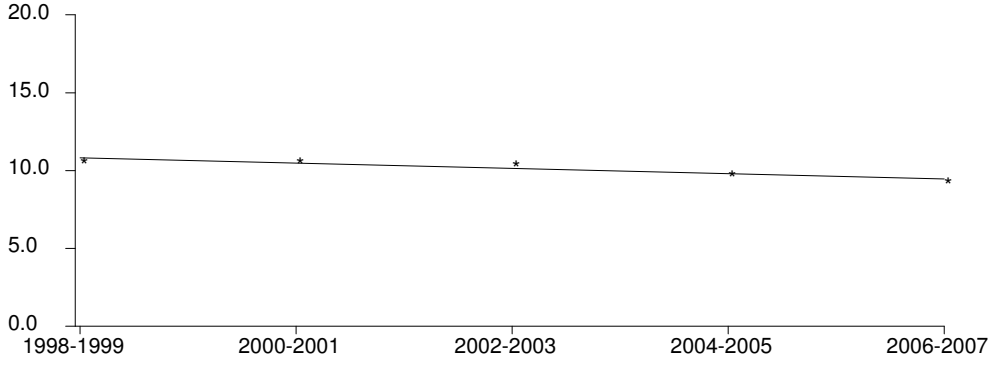
Anomaly Subgroup: **Neural Tube Defects**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	9.153	(1 df)	Not significant
p value	0.002		
Slope	Decreasing		
Rate of change	-0.279	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	729	689143	10.58
2000 - 2001	851	801394	10.62
2002 - 2003	882	846806	10.42
2004 - 2005	877	901639	9.73
2006 - 2007	738	791866	9.32

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



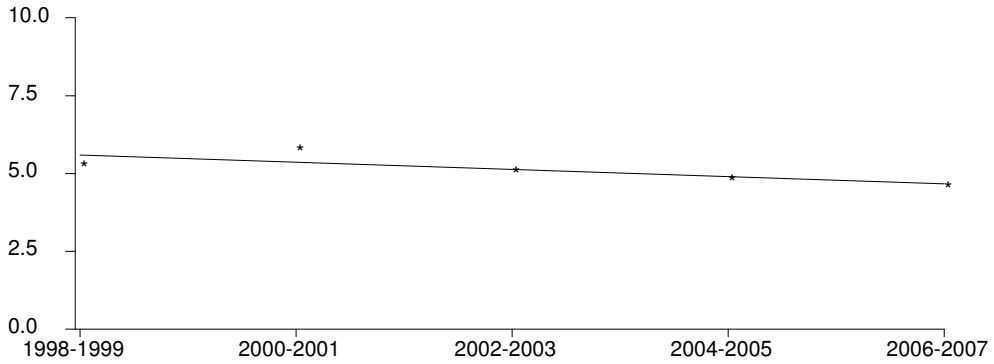
Anomaly Subgroup: **Spina Bifida**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	8.561	(1 df)	Not significant
p value	0.003		
Slope	Decreasing		
Rate of change	-0.192	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	364	689143	5.28
2000 - 2001	465	801394	5.80
2002 - 2003	433	846806	5.11
2004 - 2005	437	901639	4.85
2006 - 2007	365	791866	4.61

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Eye**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	38.920	(1 df)	Chi2	10.158	(3 df)
p value	<0.001		p value	0.017	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	321	689143	4.66
2000 - 2001	407	801394	5.08
2002 - 2003	337	846806	3.98
2004 - 2005	354	901639	3.93
2006 - 2007	236	791866	2.98

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

Anomaly Subgroup: **Congenital cataract**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	4.406	(1 df)	Chi2	12.540	(3 df)
p value	0.036		p value	0.006	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	69	689143	1.00
2000 - 2001	121	801394	1.51
2002 - 2003	102	846806	1.20
2004 - 2005	90	901639	1.00
2006 - 2007	71	791866	0.90

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

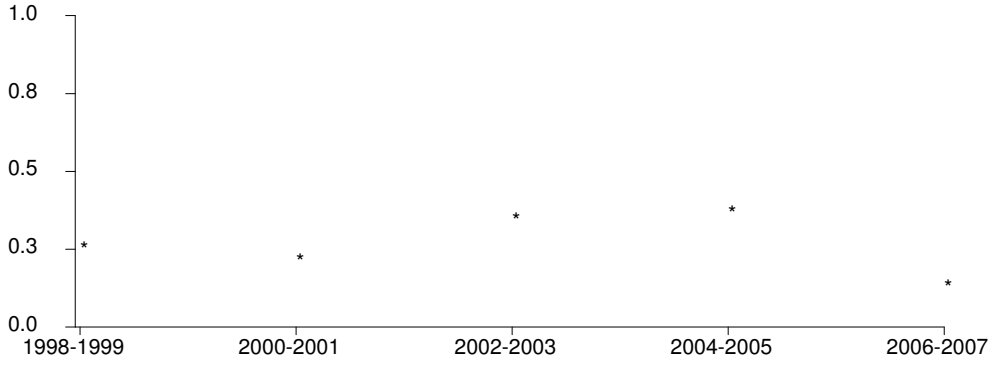
Anomaly Subgroup: **Congenital glaucoma**

Significant non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	11.261	(3 df)
	p value	0.010	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	18	689143	0.26
2000 - 2001	18	801394	0.22
2002 - 2003	30	846806	0.35
2004 - 2005	34	901639	0.38
2006 - 2007	11	791866	0.14

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



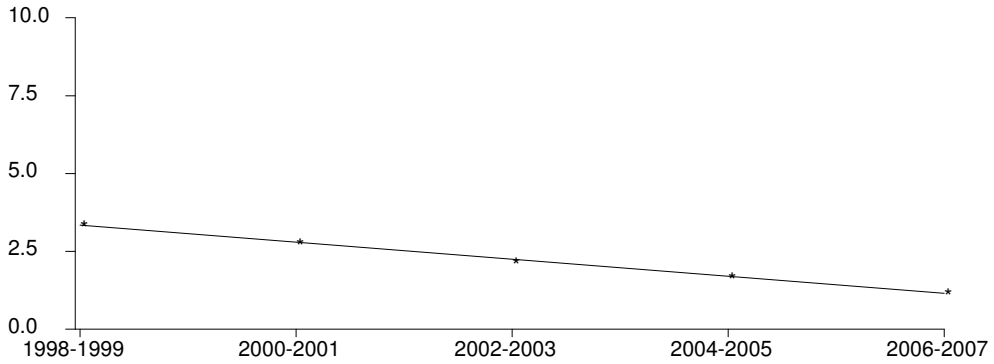
Anomaly Subgroup: **Ear, face and neck**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	102.588	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.436	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	232	689143	3.37
2000 - 2001	223	801394	2.78
2002 - 2003	185	846806	2.18
2004 - 2005	154	901639	1.71
2006 - 2007	93	791866	1.17

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



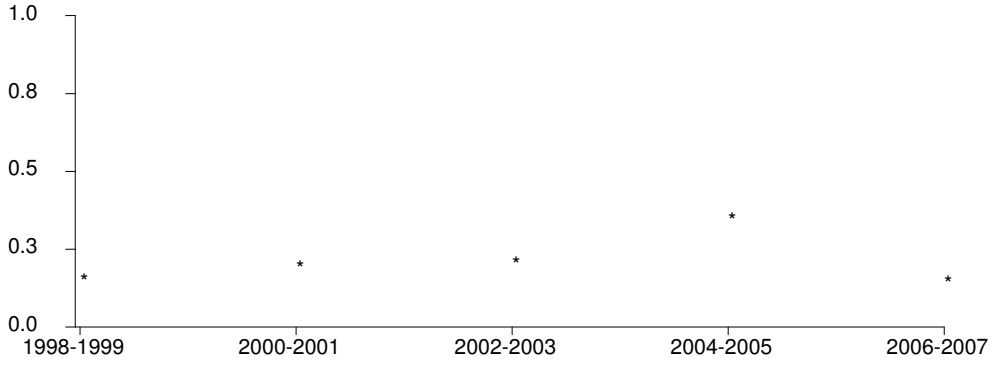
Anomaly Subgroup: **Anotia**

Significant non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	9.668	(3 df)
	p value	0.022	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	11	689143	0.16
2000 - 2001	16	801394	0.20
2002 - 2003	18	846806	0.21
2004 - 2005	32	901639	0.35
2006 - 2007	12	791866	0.15

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Congenital heart disease**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	12.035	(1 df)	Chi2	64.849	(3 df)
p value	<0.001		p value	<0.001	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	4171	689143	60.52
2000 - 2001	5170	801394	64.51
2002 - 2003	5587	846806	65.98
2004 - 2005	5745	901639	63.72
2006 - 2007	4460	791866	56.32

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

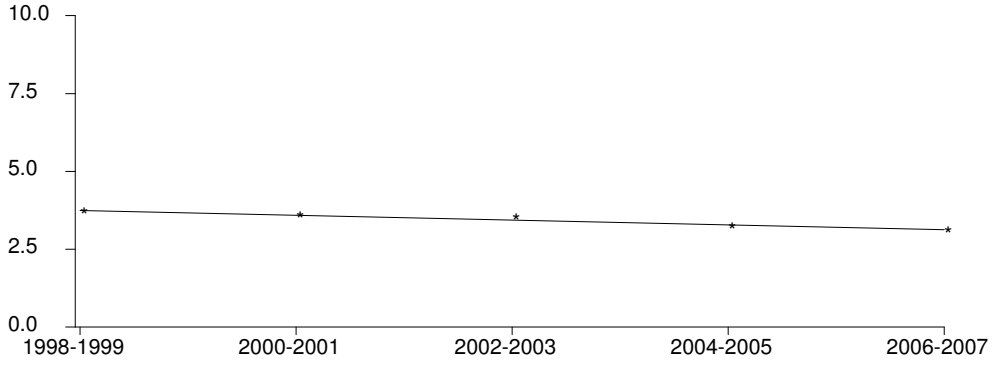
Anomaly Subgroup: **Transposition of great vessels**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	5.502	(1 df)	Not significant
p value	0.019		
Slope	Decreasing		
Rate of change	-0.126	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	256	689143	3.71
2000 - 2001	288	801394	3.59
2002 - 2003	298	846806	3.52
2004 - 2005	291	901639	3.23
2006 - 2007	247	791866	3.12

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Ventricular septal defect**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	14.383	(1 df)	Chi2	28.820	(3 df)
p value	<0.001		p value	<0.001	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	1832	689143	26.58
2000 - 2001	2327	801394	29.04
2002 - 2003	2454	846806	28.98
2004 - 2005	2393	901639	26.54
2006 - 2007	1942	791866	24.52

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

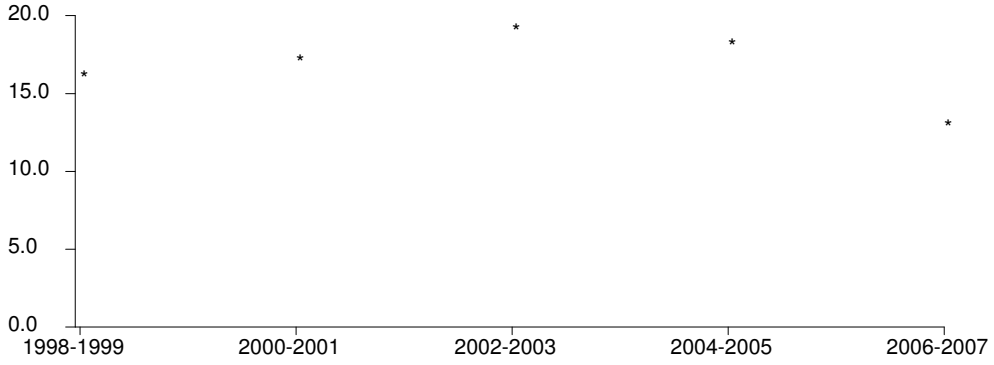
Anomaly Subgroup: **Atrial septal defect**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	13.871	(1 df)	Chi2	95.823	(3 df)
p value	<0.001		p value	<0.001	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	1120	689143	16.25
2000 - 2001	1383	801394	17.26
2002 - 2003	1630	846806	19.25
2004 - 2005	1650	901639	18.30
2006 - 2007	1034	791866	13.06

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



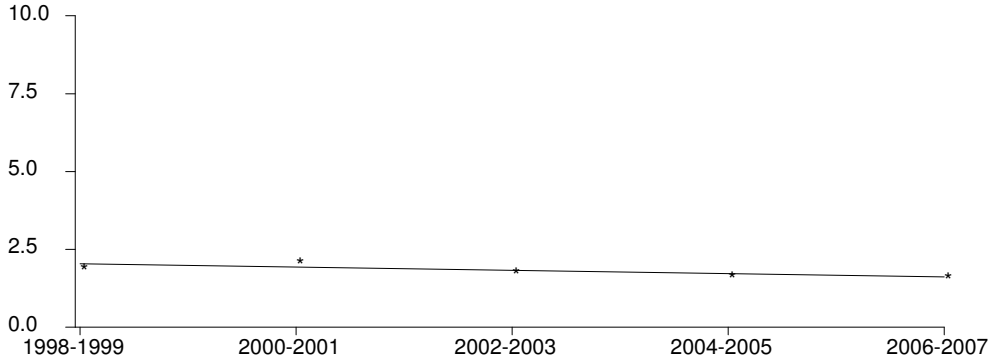
Anomaly Subgroup: **Atrioventricular septal defect**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	4.931	(1 df)	Not significant
p value	0.026		
Slope	Decreasing		
Rate of change	-0.087	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	132	689143	1.92
2000 - 2001	170	801394	2.12
2002 - 2003	152	846806	1.79
2004 - 2005	149	901639	1.65
2006 - 2007	129	791866	1.63

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



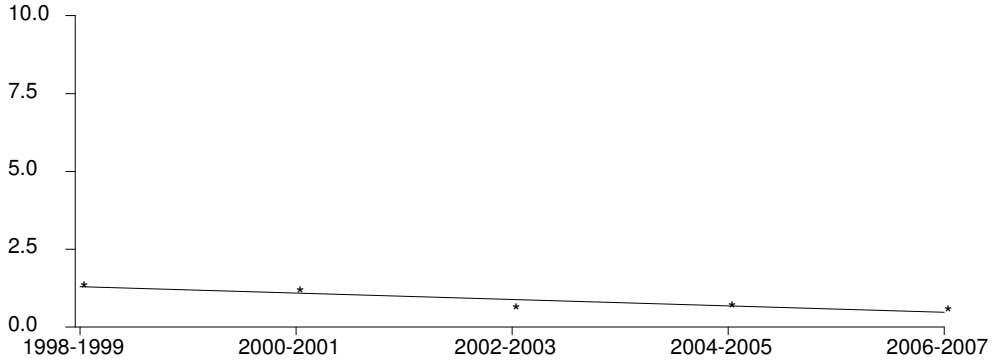
Anomaly Subgroup: **Tricuspid atresia and stenosis**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	36.855	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.163	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	92	689143	1.33
2000 - 2001	95	801394	1.19
2002 - 2003	54	846806	0.64
2004 - 2005	62	901639	0.69
2006 - 2007	44	791866	0.56

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



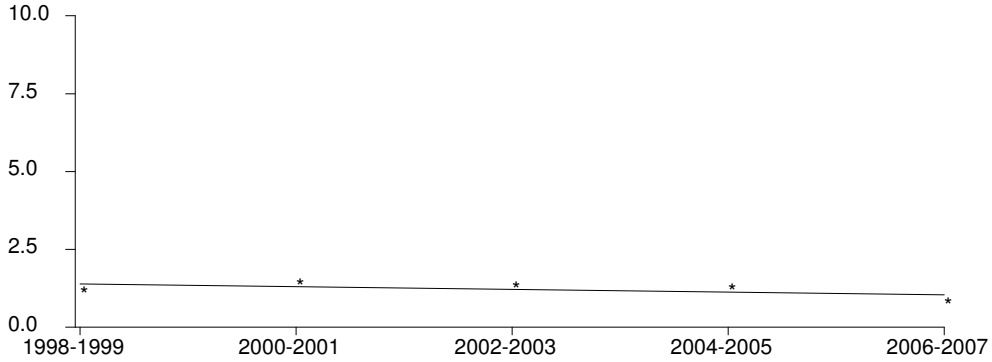
Anomaly Subgroup: **Aortic valve atresia/stenosis §**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	6.526	(1 df)	Not significant
p value	0.011		
Slope	Decreasing		
Rate of change	-0.097	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	37	313638	1.18
2000 - 2001	76	529102	1.44
2002 - 2003	110	819430	1.34
2004 - 2005	115	901639	1.28
2006 - 2007	65	791866	0.82

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



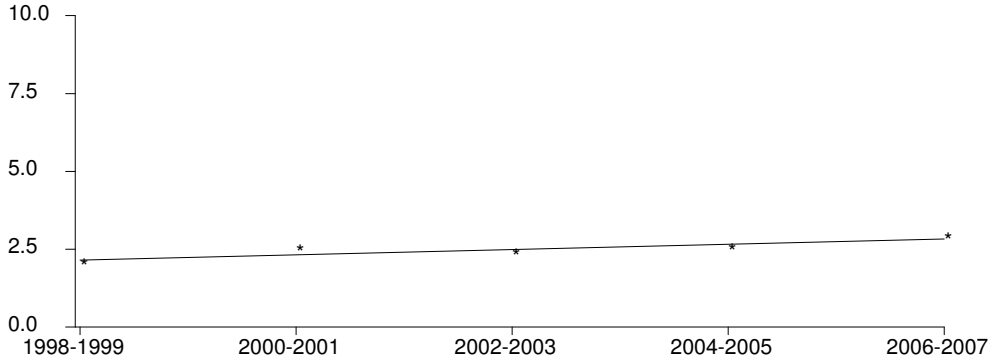
Anomaly Subgroup: **Hypoplastic left heart**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	8.347	(1 df)	Not significant
p value	0.004		
Slope	Increasing		
Rate of change	0.132	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	143	689143	2.08
2000 - 2001	201	801394	2.51
2002 - 2003	202	846806	2.39
2004 - 2005	229	901639	2.54
2006 - 2007	230	791866	2.90

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Coarctation of aorta**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	4.138	(1 df)	Chi2	8.173	(3 df)
p value	0.042		p value	0.043	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	227	689143	3.29
2000 - 2001	314	801394	3.92
2002 - 2003	307	846806	3.63
2004 - 2005	301	901639	3.34
2006 - 2007	234	791866	2.96

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

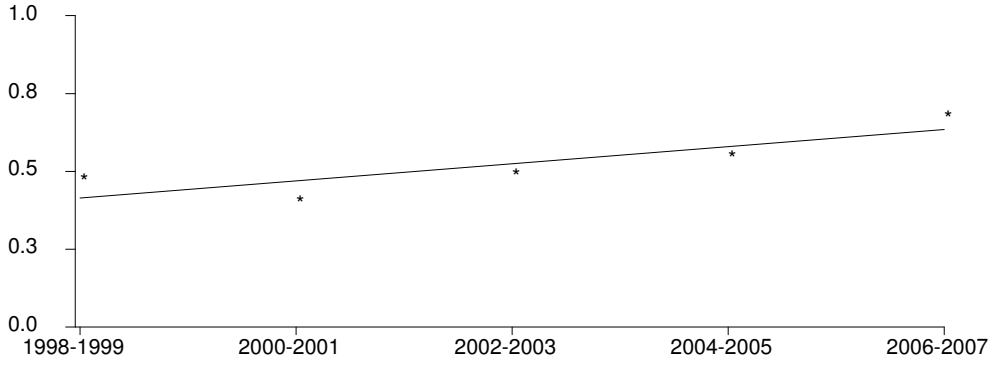
Anomaly Subgroup: **Total anomalous pulm venous return**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	4.607	(1 df)	Not significant
p value	0.032		
Slope	Increasing		
Rate of change	0.045	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	33	689143	0.48
2000 - 2001	33	801394	0.41
2002 - 2003	42	846806	0.50
2004 - 2005	50	901639	0.55
2006 - 2007	54	791866	0.68

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



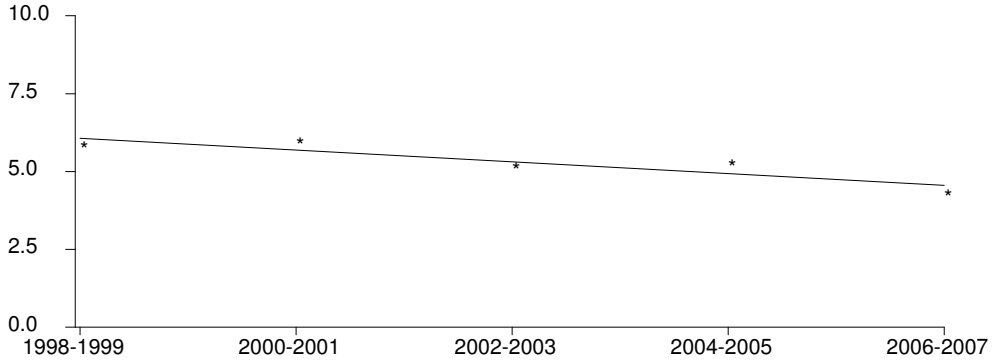
Anomaly Subgroup: **Respiratory**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	20.879	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.305	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	403	689143	5.85
2000 - 2001	479	801394	5.98
2002 - 2003	436	846806	5.15
2004 - 2005	475	901639	5.27
2006 - 2007	341	791866	4.31

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



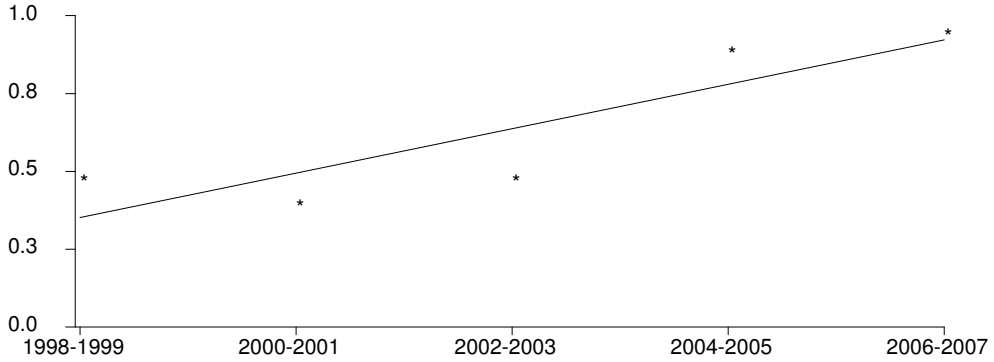
Anomaly Subgroup: **Cystic adenomatous malf of lung §**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	21.170	(1 df)	Not significant
p value	<0.001		
Slope	Increasing		
Rate of change	0.132	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	15	313638	0.48
2000 - 2001	21	529102	0.40
2002 - 2003	39	819430	0.48
2004 - 2005	80	901639	0.89
2006 - 2007	75	791866	0.95

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Digestive system**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	98.533	(1 df)	Chi2	12.930	(3 df)
p value	<0.001		p value	0.005	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	1368	689143	19.85
2000 - 2001	1501	801394	18.73
2002 - 2003	1307	846806	15.43
2004 - 2005	1442	901639	15.99
2006 - 2007	1094	791866	13.82

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

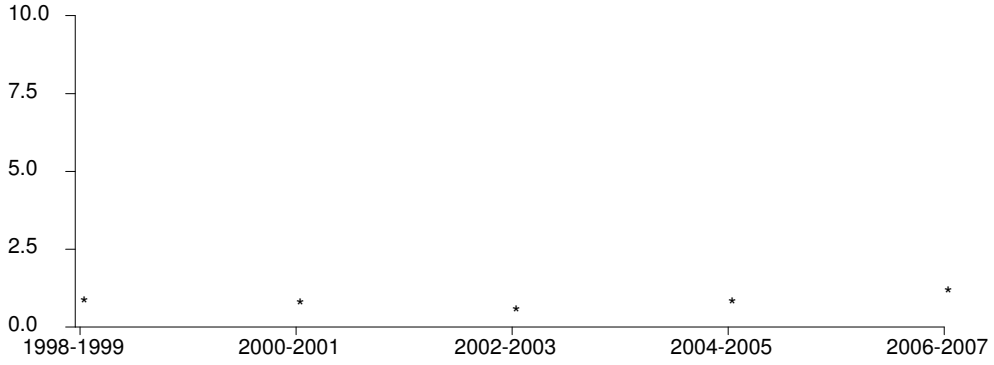
Anomaly Subgroup: **Atresia or stenosis of other parts of small intestine**

Significant upward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	4.467	(1 df)	Chi2	12.382	(3 df)
p value	0.035		p value	0.006	
Slope	Increasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	58	689143	0.84
2000 - 2001	64	801394	0.80
2002 - 2003	49	846806	0.58
2004 - 2005	75	901639	0.83
2006 - 2007	92	791866	1.16

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Ano-rectal atresia and stenosis**

Significant non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	8.399	(3 df)
	p value	0.038	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	173	689143	2.51
2000 - 2001	261	801394	3.26
2002 - 2003	247	846806	2.92
2004 - 2005	251	901639	2.78
2006 - 2007	212	791866	2.68

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

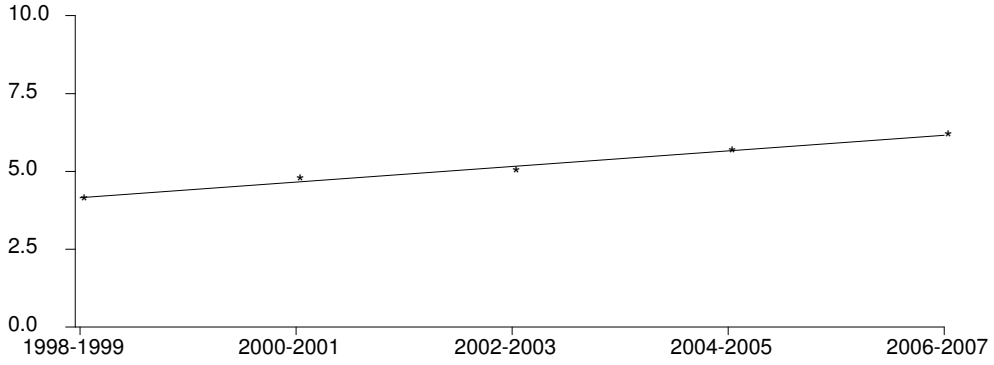
Anomaly Subgroup: **Abdominal wall defects**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	36.837	(1 df)	Not significant
p value	<0.001		
Slope	Increasing		
Rate of change	0.401	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	284	689143	4.12
2000 - 2001	382	801394	4.77
2002 - 2003	427	846806	5.04
2004 - 2005	510	901639	5.66
2006 - 2007	490	791866	6.19

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



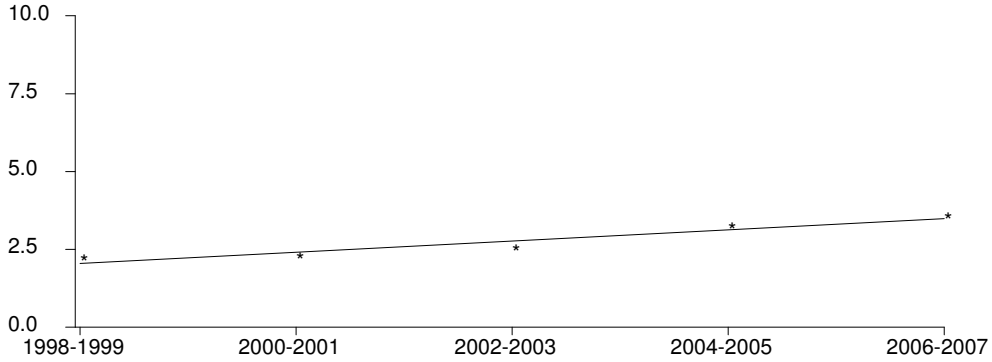
Anomaly Subgroup: **Gastroschisis**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	36.975	(1 df)	Not significant
p value	<0.001		
Slope	Increasing		
Rate of change	0.294	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	153	689143	2.22
2000 - 2001	183	801394	2.28
2002 - 2003	215	846806	2.54
2004 - 2005	290	901639	3.22
2006 - 2007	282	791866	3.56

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



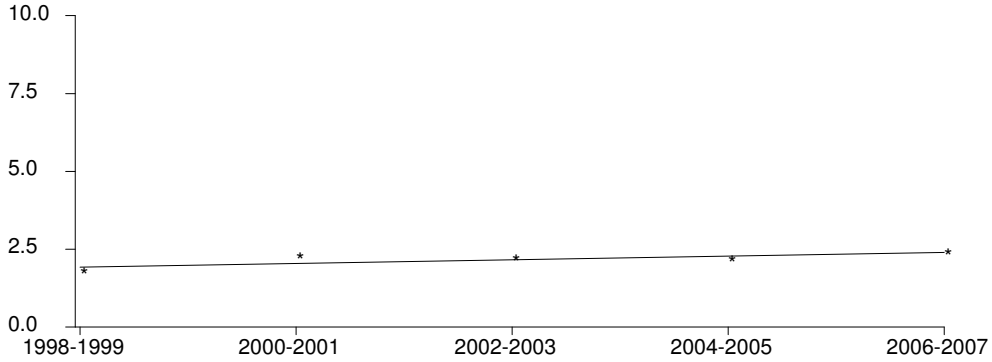
Anomaly Subgroup: **Omphalocele**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	4.432	(1 df)	Not significant
p value	0.035		
Slope	Increasing		
Rate of change	0.090	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	122	689143	1.77
2000 - 2001	181	801394	2.26
2002 - 2003	187	846806	2.21
2004 - 2005	195	901639	2.16
2006 - 2007	191	791866	2.41

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Urinary**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	20.397	(1 df)	Chi2	13.374	(3 df)
p value	<0.001		p value	0.004	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	2060	689143	29.89
2000 - 2001	2377	801394	29.66
2002 - 2003	2592	846806	30.61
2004 - 2005	2573	901639	28.54
2006 - 2007	2070	791866	26.14

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

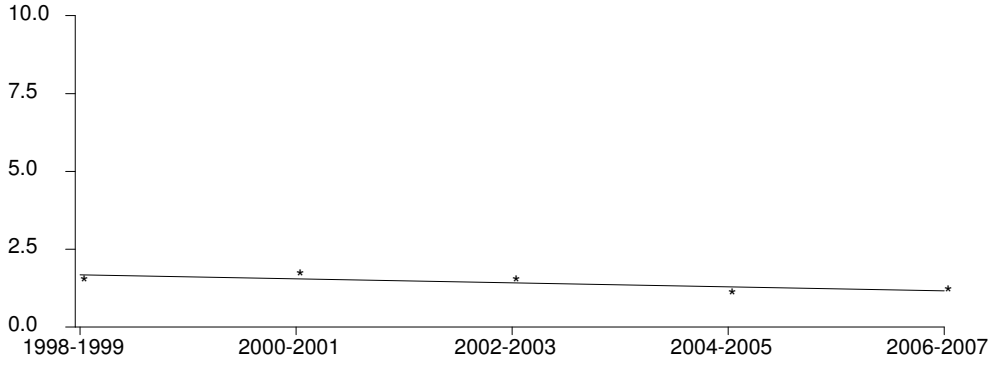
Anomaly Subgroup: **Bilateral renal agenesis including Potter syndrome**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	10.114	(1 df)	Not significant
p value	0.001		
Slope	Decreasing		
Rate of change	-0.109	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	106	689143	1.54
2000 - 2001	137	801394	1.71
2002 - 2003	130	846806	1.54
2004 - 2005	100	901639	1.11
2006 - 2007	94	791866	1.19

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



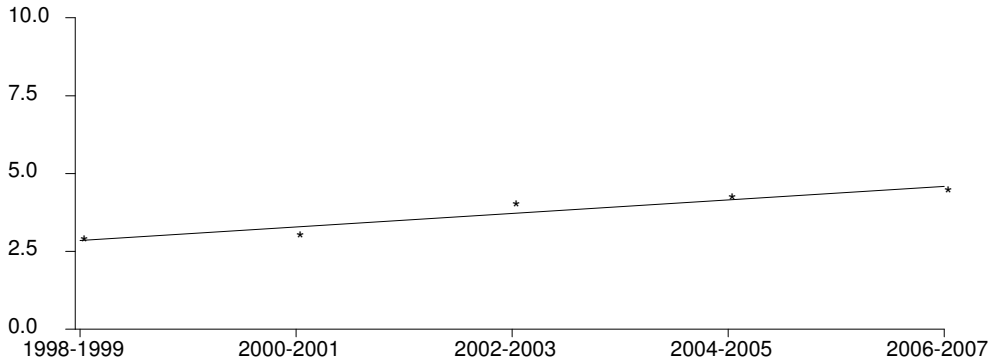
Anomaly Subgroup: **Renal dysplasia**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	38.926	(1 df)	Not significant
p value	<0.001		
Slope	Increasing		
Rate of change	0.351	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	198	689143	2.87
2000 - 2001	241	801394	3.01
2002 - 2003	341	846806	4.03
2004 - 2005	381	901639	4.23
2006 - 2007	352	791866	4.45

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



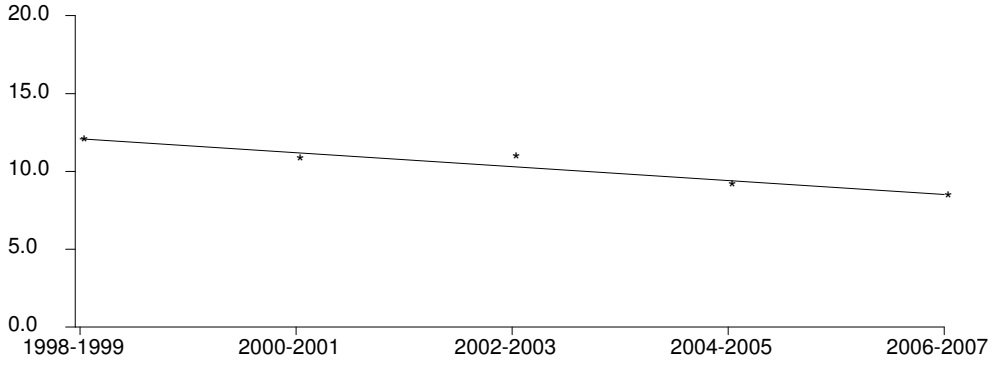
Anomaly Subgroup: **Congenital hydronephrosis**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	59.631	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.716	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	832	689143	12.07
2000 - 2001	867	801394	10.82
2002 - 2003	930	846806	10.98
2004 - 2005	827	901639	9.17
2006 - 2007	668	791866	8.44

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



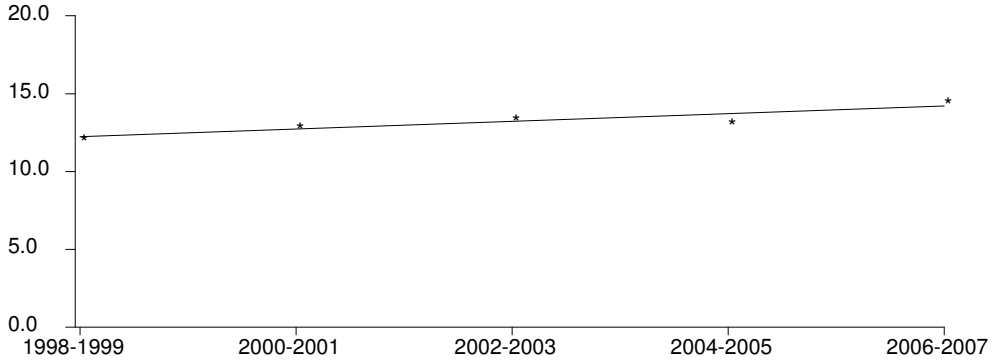
Anomaly Subgroup: **Hypospadias**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	13.602	(1 df)	Not significant
p value	<0.001		
Slope	Increasing		
Rate of change	0.389	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	836	689143	12.13
2000 - 2001	1035	801394	12.91
2002 - 2003	1137	846806	13.43
2004 - 2005	1184	901639	13.13
2006 - 2007	1149	791866	14.51

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



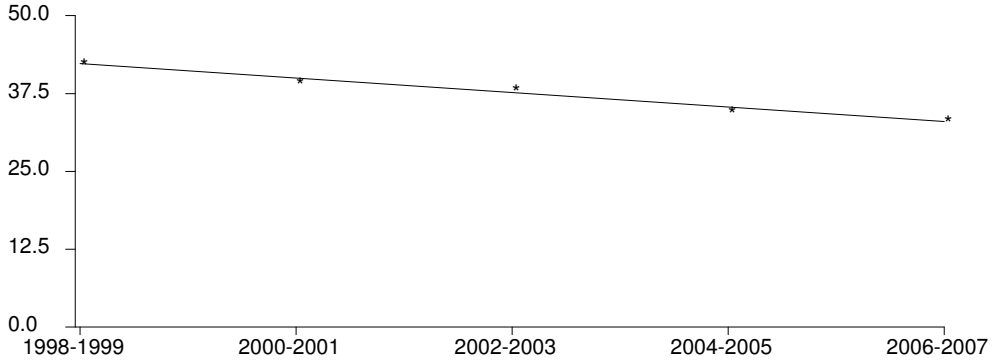
Anomaly Subgroup: **Limb**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	110.167	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-1.860	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	2930	689143	42.52
2000 - 2001	3165	801394	39.49
2002 - 2003	3239	846806	38.25
2004 - 2005	3130	901639	34.71
2006 - 2007	2636	791866	33.29

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



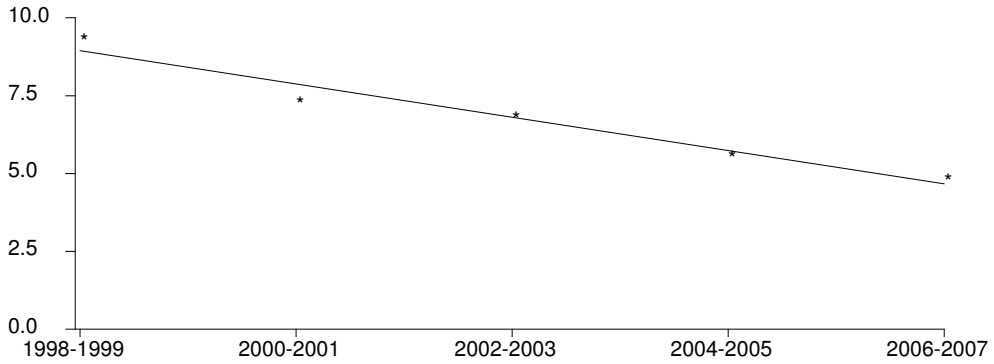
Anomaly Subgroup: **Hip dislocation and/or dysplasia**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	127.394	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.848	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	645	689143	9.36
2000 - 2001	588	801394	7.34
2002 - 2003	582	846806	6.87
2004 - 2005	507	901639	5.62
2006 - 2007	385	791866	4.86

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



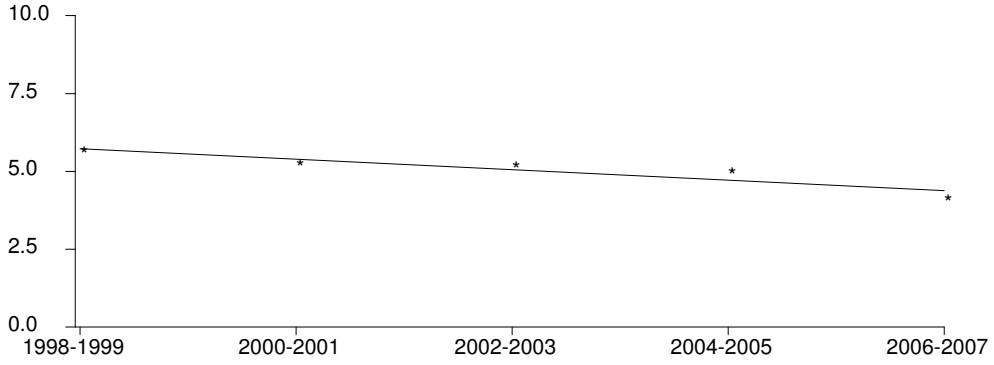
Anomaly Subgroup: **Syndactyly**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	16.719	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.266	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	391	689143	5.67
2000 - 2001	422	801394	5.27
2002 - 2003	440	846806	5.20
2004 - 2005	451	901639	5.00
2006 - 2007	327	791866	4.13

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



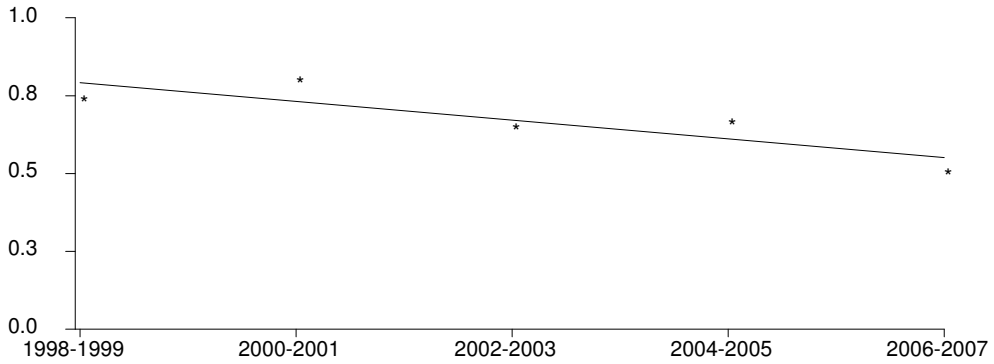
Anomaly Subgroup: **Arthrogryposis multiplex congenita**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	4.241	(1 df)	Not significant
p value	0.039		
Slope	Decreasing		
Rate of change	-0.049	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	51	689143	0.74
2000 - 2001	64	801394	0.80
2002 - 2003	55	846806	0.65
2004 - 2005	60	901639	0.67
2006 - 2007	40	791866	0.51

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



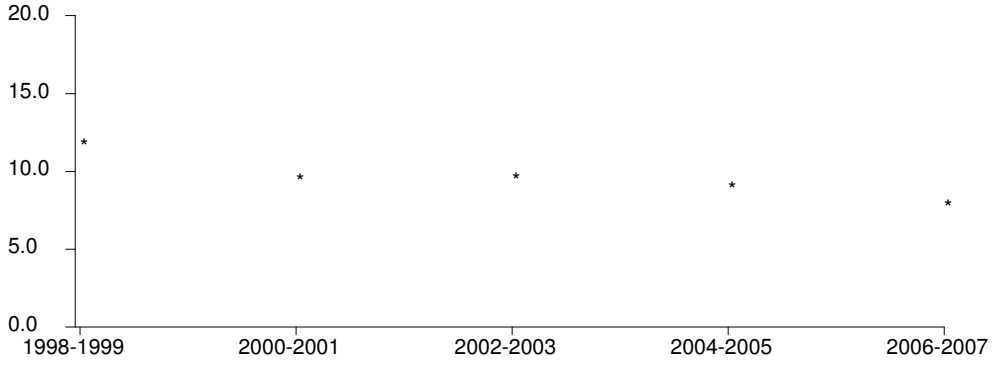
Anomaly Subgroup: **Musculo-skeletal**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	52.968	(1 df)	Chi2	9.318	(3 df)
p value	<0.001		p value	0.025	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	819	689143	11.88
2000 - 2001	771	801394	9.62
2002 - 2003	817	846806	9.65
2004 - 2005	821	901639	9.11
2006 - 2007	630	791866	7.96

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



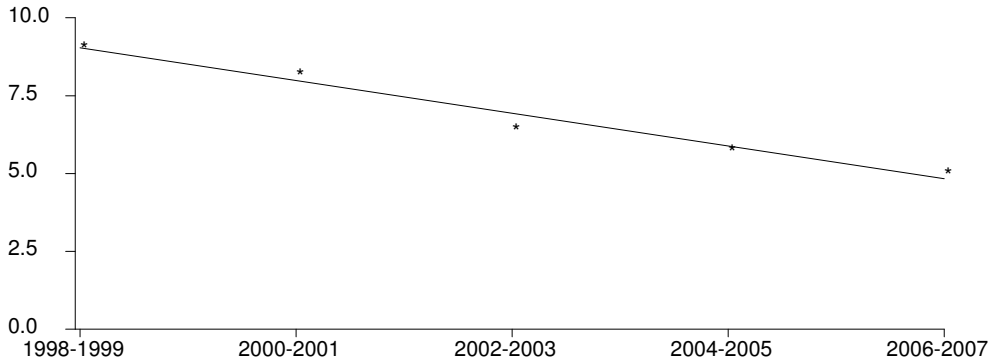
Anomaly Subgroup: **Other malformations**

Significant downward trend

Test for Trend			Test for non-linear change
Chi2	122.467	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.840	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	627	689143	9.10
2000 - 2001	660	801394	8.24
2002 - 2003	550	846806	6.49
2004 - 2005	523	901639	5.80
2006 - 2007	401	791866	5.06

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



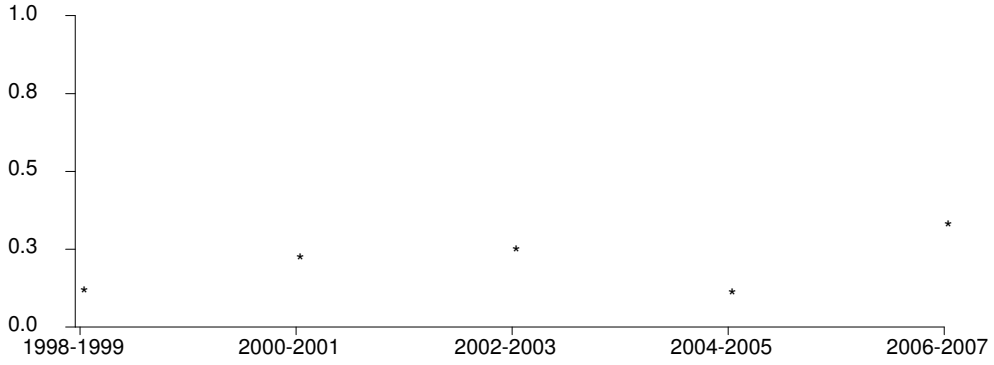
Anomaly Subgroup: **Conjoined twins**

Significant non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	10.272	(3 df)
	p value	0.016	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	8	689143	0.12
2000 - 2001	18	801394	0.22
2002 - 2003	21	846806	0.25
2004 - 2005	10	901639	0.11
2006 - 2007	26	791866	0.33

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Disorders of skin**

Significant downward trend with significant non-linear change

Test for Trend			Test for non-linear change		
Chi2	257.956	(1 df)	Chi2	24.216	(3 df)
p value	<0.001		p value	<0.001	
Slope	Decreasing				

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	302	689143	4.38
2000 - 2001	373	801394	4.65
2002 - 2003	236	846806	2.79
2004 - 2005	155	901639	1.72
2006 - 2007	81	791866	1.02

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

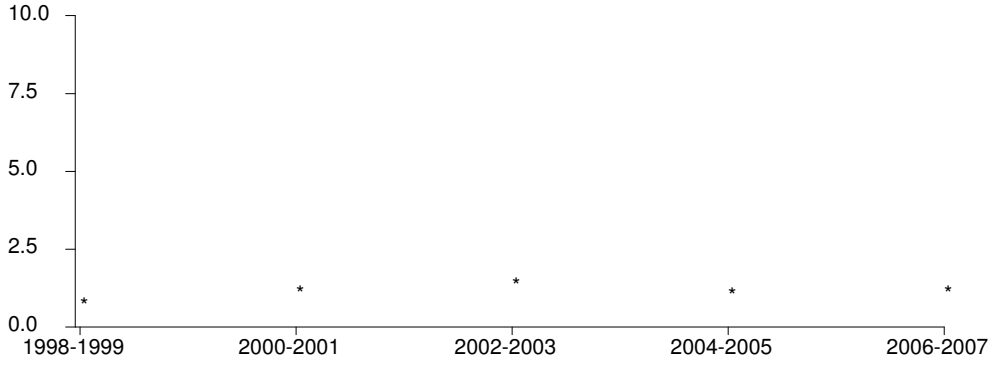
Anomaly Subgroup: **Teratogenic syndromes with malformations §**

Significant non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	8.255	(3 df)
	p value	0.041	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	26	313638	0.83
2000 - 2001	64	529102	1.21
2002 - 2003	120	819430	1.46
2004 - 2005	102	901639	1.13
2006 - 2007	95	791866	1.20

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



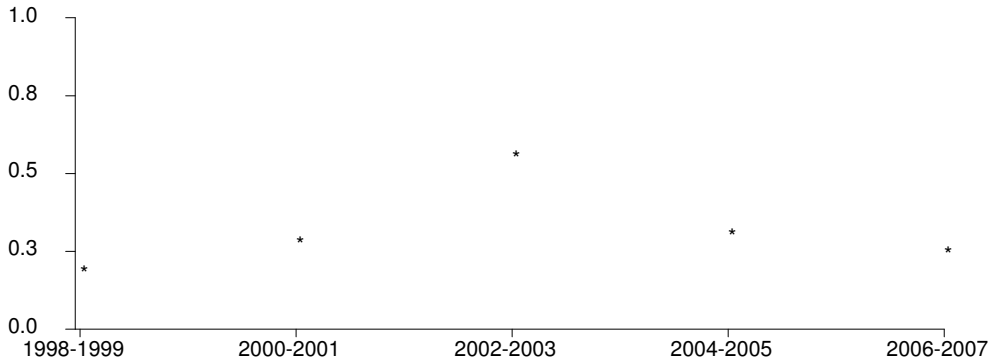
Anomaly Subgroup: **Fetal alcohol syndrome §**

Significant non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	16.108	(3 df)
	p value	0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	6	313638	0.19
2000 - 2001	15	529102	0.28
2002 - 2003	46	819430	0.56
2004 - 2005	28	901639	0.31
2006 - 2007	20	791866	0.25

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



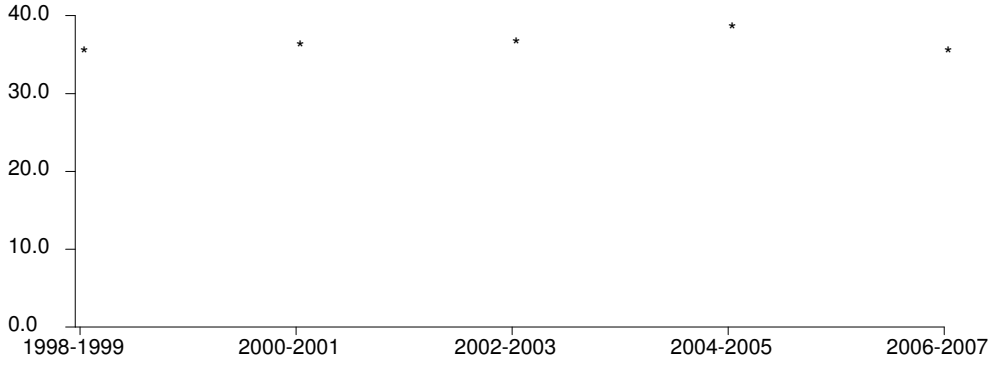
Anomaly Subgroup: **Chromosomal**

Significant non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	13.333	(3 df)
	p value	0.004	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	2452	689143	35.58
2000 - 2001	2916	801394	36.39
2002 - 2003	3109	846806	36.71
2004 - 2005	3478	901639	38.57
2006 - 2007	2812	791866	35.51

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Anomaly Subgroup: **Down Syndrome**

Significant non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	10.742	(3 df)
	p value	0.013	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	1356	689143	19.68
2000 - 2001	1615	801394	20.15
2002 - 2003	1646	846806	19.44
2004 - 2005	1955	901639	21.68
2006 - 2007	1592	791866	20.10

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth

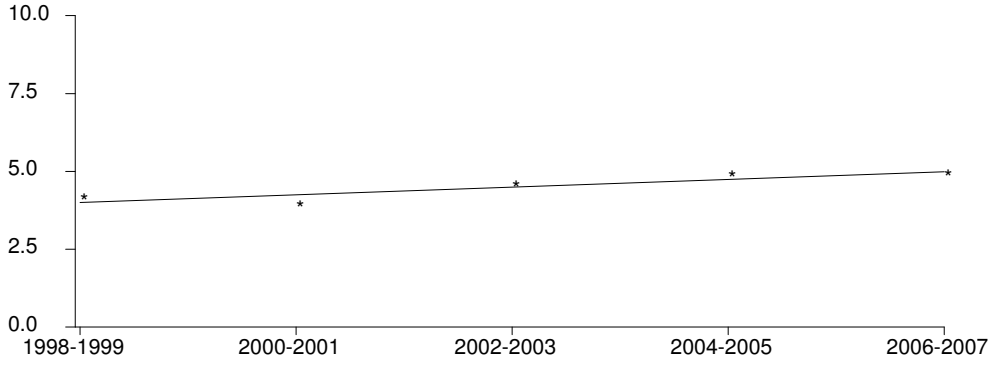
Anomaly Subgroup: **Edward syndrome/trisomy 18**

Significant upward trend

Test for Trend			Test for non-linear change
Chi2	10.964	(1 df)	Not significant
p value	<0.001		
Slope	Increasing		
Rate of change	0.204	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1998 - 1999	287	689143	4.16
2000 - 2001	315	801394	3.93
2002 - 2003	387	846806	4.57
2004 - 2005	441	901639	4.89
2006 - 2007	390	791866	4.93

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



Appendix C: Clusters by date of conception, by anomaly and registry – statistical details

Anomaly subgroup	Country	Registry	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
Anencephalus and similar	Italy	Tuscany	5	05/07/2006	26/07/2006	0.27	0.005	20	10	Cluster	Significant non-linear change
Hydrocephaly	UK	E Mid & S York	32	14/09/2006	26/01/2007	13.3	0.03	154	0	Cluster	Significant upward trend with significant non-linear change
Congenital cataract	Italy	Tuscany	6	04/02/2006	04/03/2006	0.42	<0.001	23	4.3	Cluster	Significant non-linear change
Common arterial truncus	UK	E Mid & S York	8	28/08/2005	10/01/2006	1.48	0.018	17	0	Cluster	*
Transposition of great vessels	UK	E Mid & S York	8	19/01/2006	08/02/2006	0.93	0.017	72	8.3	Cluster	
Ventricular septal defect	UK	E Mid & S York	141	15/12/2005	25/01/2007	96.07	0.011	367	6.3	Cluster	Significant upward trend with significant non-linear change
Aortic valve atresia/stenosis §	Ireland	Dublin	5	17/09/2006	27/02/2007	0.84	0.029	8	0	Cluster	*
Coarctation of aorta	Switzerland	Vaud	9	25/05/2005	28/01/2006	2.08	0.009	13	0	Cluster	*

Anomaly subgroup	Country	Registry	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
Choanal atresia	Belgium	Antwerp	6	14/08/2006	07/12/2006	0.89	0.021	12	8.3	Cluster	*
Cleft palate	UK	E Mid & S York	5	21/05/2005	23/05/2005	0.16	0.007	125	0	Cluster	
Diaphragmatic hernia	Switzerland	Vaud	7	27/05/2005	23/11/2005	1.04	<0.001	9	0	Cluster	*
Congenital hydronephrosis	UK	N England	8	03/01/2006	20/01/2006	1	0.037	91	0	Cluster	Significant downward trend
Congenital hydronephrosis	Ireland	Dublin	14	04/07/2005	22/12/2005	3.31	<0.001	30	0	Cluster	Significant upward trend with significant non-linear change
Bladder exstrophy and/or epispadia	UK	N England	5	13/05/2005	07/11/2005	0.92	0.039	8	0	Cluster	*
Posterior urethral valve and/or prune belly	UK	Wales	9	12/08/2005	27/10/2005	1.67	0.036	34	0	Cluster	Significant non-linear change
Hypospadias	UK	Wessex	72	08/01/2005	12/05/2006	36.57	<0.001	116	1.7	Cluster	Significant non-linear change
Hypospadias	Ireland	Dublin	5	22/07/2005	26/07/2005	0.28	0.04	107	0	Cluster	

Anomaly subgroup	Country	Registry	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
Indeterminate sex	UK	Wales	10	03/06/2005	04/07/2006	3.06	0.01	12	0	Cluster	*
Upper limb reduction	Ireland	Dublin	6	24/12/2005	24/02/2006	0.8	0.04	20	0	Cluster	Significant downward trend with significant non-linear change
Club foot - talipes equinovarus	UK	Wessex	5	15/01/2007	17/01/2007	0.21	0.023	164	0	Cluster	
Polydactyly	UK	Wessex	5	18/08/2006	09/09/2006	0.4	0.036	28	0	Cluster	
Patau syndrome/trisomy 13	Italy	Tuscany	6	20/01/2006	14/03/2006	0.75	0.039	22	4.5	Cluster	*
Edward syndrome/trisomy 18	Belgium	Antwerp	9	28/03/2005	24/06/2005	1.76	0.039	31	6.5	Cluster	

GA: Gestational age
DOB: Date of birth

- Too few cases to run analysis
- § Registries must have used ICD10 coding for the whole period 2003-2007 in order to be included in surveillance of these subgroups

Appendix D: Trends by anomaly and registry– website 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-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables
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.