EUROCAT Statistical Monitoring Report - 2008

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1. Summary

Congenital anomalies are a major cause of fetal death, infant mortality and childhood morbidity. 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.

The aim of this report is to present the results of statistical monitoring for trends and clusters up to birth year 2008. Cases include livebirths and stillbirths with congenital anomalies and terminations of pregnancy for fetal anomaly following prenatal diagnosis of anomalies. 96 standard EUROCAT congenital anomaly subgroups are monitored.

EUROCAT covers 1.7 million births per year, or 31% of the annual EU birth population, but statistical monitoring was done centrally only for full member registries fulfilling inclusion criteria –21 registries covering 413,000 births per year for the detection of trends, of which 16 were also included in cluster detection.

After data transmission to Central Registry in February 2010, statistical monitoring results were communicated to registries in April 2010 for preliminary investigation. Reports of investigations were discussed at the Registry Leaders Meeting in June 2010, followed by written reports.

For monitoring of trends, pan-Europe analysis combining data from all registries is done as well as individual registry monitoring for the ten year period 1999-2008. Pan-Europe analysis found five significant increasing trends, all of which had been previously reported in the 2007 Statistical Monitoring Report:

> An increasing trend in **abdominal wall defects,** particularly **gastroschisis.** Two individual registries, both in the UK, had statistically significant increasing trends of gastroschisis. A UK study investigating the role of environmental, dietary and lifestyle exposures during early pregnancy (first 12 weeks of gestation) in the increasing trend of gastroschisis is in progress.
>
> An increasing trend in **renal dysplasia** prevalence was also found in 4 individual registries. An epidemiologic study of renal dysplasia using EUROCAT data did not find any obvious explanations for the trend. Individual registries indicated ascertainment and diagnostic changes as probable explanations, though a true increasing trend of renal dysplasia could not be completely discounted.
>
> An increasing trend in **hypospadias was** found in 5 individual registries. A more detailed analysis is planned to distinguish true change from change in inclusion criteria for mild cases which was implemented in 2005, particularly as this is an important anomaly to monitor in relation to endocrine disrupting exposures.

An increasing trend in **Edward syndrome/trisomy 18** was found in 4 individual registries. There is an on-going investigation of this increase, with a particular focus on the role of increasing maternal age, and early prenatal detection leading to increasing ascertainment of cases.

The analysis of trends at pan-Europe level provides an important overview of the extent of congenital anomalies at European level. However, the monitoring of specific increasing trends identified in multiple individual registries can provide an opportunity to observe similarities and differences within and between those centres that have increased occurrences of a congenital anomaly and those centres that do not. Such comparative investigations have the potential to identify specific risk factors associated with the anomaly in question. Sixty-eight increasing trends in individual registries were prioritised for preliminary investigation, and reports of investigations were available for 62 of these. The investigations carried out by the registries indicated that nearly 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. This included a number of the registries who had trends in anomalies identified at pan-Europe level (detailed above). As these trends were explained by diagnostic or data quality issues further resources should not be spent on investigating these particular trends. Increasing trends that did require further surveillance and/or investigation (some of which were already signalled in the previous years) were confirmed for the following anomalies: hydrocephaly, anotia, choanal atresia, cystic adenomatous malformation of the lung, cleft lip with or without palate, ano-rectal atresia and stenosis, abdominal wall defects, gastroschisis, urinary anomalies, genital anomalies, hypospadias, and Edward syndrome/trisomy 18. The outcome of these investigations will be reported in subsequent reports.

While this report focuses on evidence of increasing trends, a large number of decreasing trends were also found. Registries will in future be invited to comment and report on decreasing trends, particularly in relation to the success of preventative programmes. See the EUROCAT Special Report on NTD (Special Report: Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe", EUROCAT Central Registry, University of Ulster. http://www.eurocat-network.eu/PREVENTIONAndRISKFACTORS/FolicAcid/) for information on folic acid supplementation and trends in neural tube defects.

A total of sixteen registries were eligible to be included in a cluster analysis based on estimated date of conception identifying time clusters with date of conception from April 2006 to March 2008 (births 2007-2008), covering 0.8 million births in this two year period of time.

Overall 30 clusters were detected, where more cases than would be expected by chance occurred unusually close together in time. There were a number of clusters for specific anomalies found in more than one registry. There were three clusters of neural tube defects, and 3 clusters of Patau syndrome/trisomy 13. There were also two clusters of both renal dysplasia and hypospadias.

Eight of the clusters were identified in the previous statistical monitoring report, and no continuation had been observed into 2008. Of the remaining 22 clusters, nine were explained by diagnostic or data quality issues, and one explained by increasing

prenatal screening and diagnosis. Four clusters were not reported on. A further 8 (across 5 registries) were confirmed as unusual excesses of cases. No explanation was found by preliminary investigation and continued surveillance was recommended, for the 8 anomalies: atrioventricular septal defect, total anomalous pulmonary venous return, bilateral renal agenesis including Potters syndrome, Patau syndrome/trisomy13, neural tube defects, polydactyly, asplenia, and renal dysplasia. As part of the Joint Action 2011-2013 a new committee is being formed, the Taskforce for the Evaluation of Clusters (TEC), with the purpose of forwarding investigations of clusters detected during statistical monitoring.

Only five registries identified a clear protocol for communication of monitoring results to national or regional public health agencies. There continues to be a need for Member states to identify their individual policy and procedure for public health action in response to monitoring results.

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 the increasing trend of 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-2008.pdf).
We report here the results up to birth year 2008. 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 2010, with a complete dataset for the most recent 5 years (2004-2008) are included in cluster detection.

In 2010 we introduced a new subgroup called "Severe Congenital Heart Defects (CHD)", which allows analysis of all the severe congenital heart defects grouped together. We also introduced a new computer generated subgroup whereby we adjusted trends in Down syndrome for the effects of maternal age and survival to 20 weeks gestational age (Down Syndrome Adjusted). This development means that Down syndrome trends explained by changes in maternal age and prenatal screening are not reported.

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 2010 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 2007.

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.

Statistical monitoring is performed on 96 subgroups of congenital anomaly and an additional Central Registry computed subgroup that adjusts Down syndrome trends for the effects of maternal age and survival to 20 weeks gestational age (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 (1999-2008) 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 8 years of data to be included.
- Time period is 1999-2008

At the time of statistical monitoring in Spring 2010, there were 29 full member registries in EUROCAT. Twenty-one full member registries were included in the pan-Europe monitoring 1999-2008. Ukraine and Ile de la Reunion were excluded as they did not have 8 years of data in the time period. Basque Country and Mainz were excluded as data for 2007 was unconfirmed at the time of statistical monitoring. Cork and Kerry, Strasbourg and Norway were excluded as data was more than one year late. Wielkopolska was excluded due to partial transmission of year 2007 data.

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 (1999-2008) 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 96 EUROCAT congenital anomaly subgroups and the computer generated subgroup..
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

The 21 full member registries included in the long-term trend analysis were the same registries included in the pan-Europe analysis. The reasons for excluding 8 registries were the same as for the pan-Europe analysis and are described in section 3.1.1.

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-2008.pdf), scanning all recorded cases in the period 2004-2008.
2. Clusters or deficits occurring in the last 2 years (2007-2008) that are less than 18 months in length are reported.
3. A minimum of 7 cases over the surveillance period (2004-2008) 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 (2008). 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 76 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 2008 data with full date of birth information are included in the cluster monitoring 2004-2008.

- 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 2010, 21 full member registries had transmitted year 2008 data to EUROCAT Central Registry by Feb 15 2010. Cluster analysis was run using 16 registries (Antwerp, Dublin, East Midlands & South Yorkshire, Emilia Romagna, Hainaut, Ile de la Reunion, Malta, Northern England, Northern Netherlands, Odense, Paris, South East Ireland, Styria, Tuscany, Wales, and Wessex). Three registries were excluded from statistical monitoring due to > 10% fluctuations in population (South Portugal, Thames Valley and Zagreb). Saxony-Anhalt was excluded as full date of birth information was unavailable. Ukraine was excluded as the registry has not yet transmitted 5 years of data.

3.2 Statistical software updates from previous report

The output from the trend analysis now only reports significant increasing or decreasing trends where the p-value is <0.05 for the trend component and >0.01 for the non-linear component. Where p<0.05 for trend component and p<0.01 for non-linear component, the results are identified as 'non-linear change'. Where p>0.05 for trend component and <0.05 for non-linear component, the results are identified as 'non-linear change'

4. Results

4.1 Pan-Europe trends (all registries combined)

Pan-Europe trend tests were performed for 96 of the 97 EUROCAT subgroups of congenital anomalies in 21 EUROCAT registries (combined) covering 4.2 million births, 1999-2008.

Significant increasing trends over time were identified in 5 subgroups (Table 1 and Appendix B).

Table 1: Pan-Europe monitoring significant increasing trends

	Significant increasing Chi^2 trend
Abdominal wall defects	P= 0.026
Gastroschisis	P= 0.001
Renal dysplasia	P= 0.013
Hypospadias	P= 0.028
Edward syndrome/trisomy 18	P= 0.014

There were 36 significant decreasing trends over time (Table 2 and Appendix B).

Table 2: Pan-Europe monitoring significant decreasing trends

	Significant decreasing Chi^2 trend
Nervous System	P<0.001
Neural Tube Defects	P=0.001
Anencephalus and similar	P=0.003
Spina Bifida	P<0.001
Eye	P<0.001
Anophthalmos/microphthalmos	P=0.008
Ear, face and neck	P<0.001
Severe congenital heart defects (CHD)	P<0.001
Transposition of great vessels	P=0.009
Single ventricle	P<0.001
Atrioventricular septal defect	P=0.009
Aortic valve atresia/stenosis §	P=0.004
Hypoplastic right heart§	P=0.005
Coarctation of aorta	P=0.006
Respiratory	P<0.001
Cleft Palate	P=0.021
Oesophageal atresia with or without tracheo-oesophageal fistula	P<0.001
Ano-rectal atresia and stenosis	P=0.019
Hirschsprung's disease	P=0.004
Atresia of bile ducts	P=0.001
Diaphragmatic hernia	P=0.01
Urinary	P<0.001
Bilateral renal agenesis incl Potter syndrome	P=0.004
Congenital hydronephrosis	P<0.001
Posterior urethral valve and/or prune belly	P<0.001
Limb	P<0.001
Limb reduction	P<0.001
Upper limb reduction	P=0.039
Lower limb reduction	P=0.002
Hip dislocation and/or dysplasia	P<0.001
Polydactyly	P=0.003
Arthrogryposis multiplex congenita	P=0.01
Asplenia	P=0.03
Disorders of skin	P<0.001
Fetal alcohol syndrome §	P=0.017

Turner's syndrome	P=0.001

Nineteen subgroups (All non-chromosomal anomalies, microcephaly, congenital heart disease, ventricular septal defect, atrial septal defect, tricuspid atresia and stenosis, pulmonary valve stenosis, pulmonary valve atresia, oro-facial clefts, digestive system, genital, syndactyly, musculo-skeletal, other malformations, Valproate syndrome, genetic syndromes and microdeletions, chromosomal, and Down syndrome, (both unadjusted and adjusted) 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 63% of the 96 subgroups.

When data was combined for all registries, Warfarin syndrome was the only subgroup excluded from monitoring due to there being too few cases for statistical analysis (see Methods). In contrast, monitoring of long-term trends in individual registries was not performed on 8 subgroups of congenital anomalies due to there being too few cases (anophthalmos, annular pancreas, complete absence of a limb, Jeunes syndrome, asplenia, conjoined twins, Cri-du-chat syndrome and Wolff-Hirschhorn syndrome).

4.2 Long-term trends in individual registries

Table 3 shows a total of 269 significant long-term trends were reported from surveillance of 97 anomaly subgroups in 21 EUROCAT registries covering 4.1 million births, 1999 - 2008, or the most recent 10-year period of available data. There were 68 increasing trends and 201 decreasing trends. In addition, there were 189 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 1190 chi square tests were performed, with a detection rate of 38% "significant" results, rather than the 5% expected by chance.

Per EUROCAT anomaly subgroup, the number of increasing trends ranged from 0-5, the number of decreasing trends ranged from 0-11, and the number with significant non-linear heterogeneity ranged from 0-11 (Table 3).

Per registry, the number of increasing trends ranged from 0-9, the number of decreasing trends ranged from 0-29, and the number of non-linear heterogeneity ranged from 2-21 (Table 3).

Increasing trends in congenital anomalies

We only further describe increasing trends in this Report.

Significant increasing trends were identified in Paris and Wessex for 9 and 8 subgroups of congenital anomalies respectively. Other registries reported less increasing trends.

Significant increasing trends were identified for 37 subgroups of congenital anomalies. Increasing trends were identified in 7 main organ system subgroups: ear, face & neck anomalies, congenital heart defects, respiratory anomalies, abdominal wall defects, urinary anomalies, genital 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:

- Hypospadias increased in 5 registries – Emilia Romagna, Tuscany, Northern Netherlands, Thames Valley and Northern England
- Ventricular septal defect increased in 4 registries – Paris, Northern Netherlands, Vaud and Zagreb.
- Renal dysplasia increased in 4 registries - Tuscany, Northern Netherlands, Saxony-Anhalt, and East Midlands & South Yorkshire.
- Down syndrome increased in 4 registries - Paris, Vaud, Styria and Wessex (note that maternal-age adjusted Down syndrome did not increase)
- Edward syndrome increased in 4 registries - Paris, Northern Netherlands, Vaud and Wales

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

- Hydrocephalus increased in Hainaut and Paris
- Atrial septal defect increased in Zagreb and Thames Valley
- Pulmonary valve stenosis increased in Paris and Saxony-Anhalt
- Cystic adenomatous malformation of lung increased in Wales and Wessex
- Ano-rectal atresia and stenosis increased in Saxony-Anhalt and Styria
- Gastroschisis increased in Wessex and Northern England
- Congenital hydronephrosis increased in Odense and Zagreb
- Club foot increased in Hainaut and Barcelona

Increasing trends in the following 16 subgroups were detected in a single registry:

- Anotia (Paris)
- Transposition of the great arteries (Hainaut)
- Atrioventricular septal defect (Saxony-Anhalt)
- Tetralogy of fallot (Wales)
- Coarctation of aorta (Saxony-Anhalt)
- Choanal atresia (Paris)
- Cleft lip with or without palate (Wales)
- Indeterminable sex (Wessex)
- Limb reduction (Zagreb)
- Lower limb reduction (Vaud)
- Hip dislocation and /or dysplasia (Styria)
- Polydactyly (Wessex)
- Craniosynostosis (Thames Valley)
- Congenital constriction bands/amniotic band (Northern England)

- Patau syndrome/trisomy 13 (Wessex)
- Klinefelter 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 anomaly

Anomaly	Total trends across all centres			Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony -Anhalt (DE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (SP)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
	/	\	~																						
Years tested (grouped by 2 years)					1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	2000-07	2000-07	1999-08	2001-08	1999-08	1999-08	1999-08
All Non-chromosomal Anomalies	2	8	11	21	~	\	~	/	~	~	\	~	\	\	~	\	~	~	\	\	~	\	~	~	/
Nervous system	0	5	6	11	~	~	~				~	\	\	~	~			\			\			\	
Neural Tube Defects	0	5	3	8		~	~				~	\	\	\				\						\	
Anencephalus and similar	0	1	3	4				*					*		~	*		~			~			\	
Encephalocele	0	0	1	1		*	*	*	*				*		*	*	*	*	*		~		*		
Spina Bifida	0	7	2	9		~		*	\			\	\	\	~			\			\			\	
Hydrocephaly	2	3	3	8			/	*		/	\	\		\	~	*		~			~				
Microcephaly	0	2	6	8	~		~	*	*		~	~		~		*		*	~		\		*	\	
Arhinencephaly/holoprosencephaly	0	0	1	1	*	*	*	*	*		*	*	*		*	*	*	*		*			*	~	
Eye	0	5	3	8		\	\	*	~				*			*	~	\			\			\	~
Anophthalmos/micropthalmos	0	1	1	2	*	*	*	*	*		*	*	*	~		*		*	*	*	\		*		*
Anophthalmos	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	0	1	1	*		*	*		*	*		*	*		*	~	*	*	*			*		*
Congenital glaucoma	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*
Ear, face and neck	1	6	1	8	\			*	*		\		*	\		*	\	~	/	*	\	*	*	\	*
Anotia	1	0	0	1	*	*	*	*	*	/	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital heart disease (CHD)	2	6	9	17	~	~	~	/	~	/	~	~	\	\	\	\		~	\		~	\		~	
Severe CHD §	0	4	1	5		\				\				\				~			\				
Common arterial truncus	0	1	1	2	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	\		*	~	*

Anomaly	Total trends across all centres			Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (SP)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley UK)	Wales (UK)	Wessex (UK)
	/	\	~																						
Years tested (grouped by 2 years)					1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	2000-07	2000-07	1999-08	2001-08	1999-08	1999-08	1999-08
Transposition of great vessels	1	3	0	4			/	*	*				\	\				*		*				\	
Single ventricle	0	1	0	1	*	*	*	*	*	\	*	*	*	*		*	*	*	*	*	*	*	*		*
Ventricular septal defect	4	5	5	14	~			/	~	/				\	\	\	/	~	\	/	~	\		~	
Atrial septal defect	2	8	7	17	~	\	\	/		\	~	~		\	~	\		~	\	~	\	\	/	~	
Atrioventricular septal defect	1	1	1	3				*		~	/		*	\		*		*					*		
Tetralogy of Fallot	1	0	3	4						~			*			*	~				~			/	
Tricuspid atresia and stenosis	0	4	0	4	*	*	*	*	*	\	*	*	*	*	*	*		*	\	*	\	*	*	\	
Ebstein's anomaly	0	0	1	1	*	*	*	*	*	~	*	*	*	*	*	*	*	*	*	*		*	*		*
Pulmonary valve stenosis	2	3	1	6	~			*		/	/		*		\	\			\				*		*
Pulmonary valve atresia	0	1	1	2	*	*	*	*	*	~	*	*	*	\		*	*	*	*	*			*		*
Aortic valve atresia/stenosis §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*				
Hypoplastic left heart	0	1	2	3		\		*	*			~				*		*		*	~				
Hypoplastic right heart §	0	1	0	1	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	\	*	*		
Coarctation of aorta	1	1	2	4			~	*	*		/	~									\				
Total anomalous pulm venous return	0	1	0	1	*	*	*	*	*		*		*	*	*	*	*	*	*	*	\		*		*
Respiratory	1	3	4	8	~				*	~		\	~			*		\			\			~	/
Choanal atresia	1	0	0	1			*	*	*	/	*		*	*		*	*	*		*	*		*		
Cystic adenomatous malf of lung §	2	1	0	3	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X			\	/	/
Oro-facial clefts	0	2	2	4							\	~				~					\				
Cleft lip with or without palate	1	1	2	4		~					\													/	~
Cleft palate	0	1	3	4							~	~				~					\				
Digestive system	0	7	4	11		~			~	\			~	\	\		\				\	\	~	\	

Anomaly	Total trends across all centres			Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (SP)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
	/	\	~																						
Years tested (grouped by 2 years)					1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	2000-07	2000-07	1999-08	2001-08	1999-08	1999-08	1999-08
Oesophageal atresia with or without tracheo-oesophageal fistula	0	1	3	4				*					*	~		*	~		~		\				
Duodenal atresia or stenosis	0	0	1	1	*		*	*	*	~	*		*			*	*	*	*	*			*		
Atresia or stenosis of other parts of small intestine	0	2	1	3	*	*	*	*	*			*	*	\	*	*	*	*	*	*	\	~	*		*
Ano-rectal atresia and stenosis	2	4	1	7	/			*			/		*	\	\	*		\		*			~	\	
Hirschsprung's disease	0	1	1	2			*	*	*		*	\	*	*	*			*	*	*		~	*		
Atresia of bile ducts	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*
Annular pancreas	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	2	0	2					*				*	\		*		*	*				\		
Abdominal wall defects	2	1	2	5	/			*		\				~		*					/			~	
Gastroschisis	2	1	1	4				*	*	\			*		*	*				*		/		~	/
Omphalocele	0	1	1	2			*	*					*	~		*	*	*				\			
Urinary	1	6	6	13	~	\	~	/		\	\	~		\				~	~		~		\	\	
Bilateral renal agenesis including Potter syndrome	0	2	0	2	*		*	*	*	\						*		*		*			\		
Renal dysplasia	4	0	3	7		~	~	*			/	~	*		/	*	/				/				
Congenital hydronephrosis	2	6	5	13	~	~	\	/	/	\				\			~	~			~	\	\	\	
Bladder exstrophy and/or epispadia	0	1	0	1	*	*	*	*	*		*		*	*		*	*	*	*	*		*	*	\	*
Posterior urethral valve and/or prune belly	0	1	1	2			*	*	*	~	*	*	*		*	*	\	*	*	*			*		
Genital	4	3	7	14	~			~		\		\		/	/	~	/	~		~	~		/	\	~
Hypospadias	5	2	8	15	~			~		~		\		/	/	~	/	~		~	~	/	/	\	~
Indeterminate sex	1	0	0	1	*	*	*	*	*		*	*	*	*		*	*	*	*	*			*	*	/
Limb	0	6	5	11	~					\	\	~	\		\	\		~			~		~	\	

Anomaly	Total trends across all centres			Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (SP)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
	/	\	~																						
Years tested (grouped by 2 years)					1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	2000-07	2000-07	1999-08	2001-08	1999-08	1999-08	1999-08
Limb reduction	1	2	2	5	~			/					*	~		*		\			\				
Upper limb reduction	0	1	1	2	~			*					*			*		\							
Lower limb reduction	1	1	2	4				*	*	\			*	~		*			*	/	~		*		
Complete absence of a limb	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	2	3	4	9			/					~	~	\	\			~	/		~	*	\		
Hip dislocation and/or dysplasia	1	5	3	9	/	\	\				\	~				*		~	*	\	~	*		\	*
Polydactyly	1	1	5	7	~					~	~	~	*								\		~		/
Syndactyly	0	2	5	7	~		~	*	*	~	~		*	~		*	\				\		*		
Arthrogryposis multiplex congenita	0	1	0	1	*	*		*	*		*	*	*	*	*	*	*	*	*	*	\	*	*		*
Musculo-skeletal	0	6	5	11		~	\			~	~	\	~	\			\	\		~				\	
Thanatophoric dwarfism	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Jeunes syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Achondroplasia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	
Craniosynostosis	1	2	1	4	~			*	*				*			*		*			\	\	/		*
Congenital constriction bands/amniotic band	1	0	0	1	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*		/			
Other malformations	0	7	6	13	~	\				~	\	~	\	~	~		\	~			\		\	\	
Asplenia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	1	0	1	*	*	*	*	*		*	*	*	\	*	*	*	*	*	*			*		*
Conjoined twins	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	0	11	4	15	~	\		*	*	~	\	\	\	\	~	\	\	~	\	\	\		*	\	*
Teratogenic syndromes with malformations §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*				

Anomaly	Total trends across all centres			Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IE)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (SP)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley UK)	Wales (UK)	Wessex (UK)
	/	\	~																						
Years tested (grouped by 2 years)					1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	1999-08	2000-07	2000-07	1999-08	2001-08	1999-08	1999-08	1999-08
Fetal alcohol syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*	*	*		*
Valproate syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*	*	*	*	*
Warfarin syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*	*	*	*	*
Maternal infections resulting in malformations	0	0	0	0	*		*	*	*		*		*		*	*	*	*	*	*	*	*	*		*
Genetic syndromes + microdeletions	0	5	3	8	~			*				~	*	~				\			\		\	\	\
Chromosomal	2	3	3	8					/	/	~		\	~				\			~		\		
Down Syndrome	4	3	1	8	/					/				~				\		/	\		\		/
Down Syndrome Adjusted	0	4	0	4			M						\	\				M			\	M	\		M
Patau syndrome/trisomy 13	1	0	0	1			*	*	*				*			*		*							/
Edward syndrome/trisomy 18	4	0	3	7				*	~	/				~			/	*		/	~			/	
Turner's syndrome	0	3	3	6		\		*	*	~	~		*			*		\		~				\	
Klinefelter syndrome	1	1	1	3		*		*	*			*	*	/		*	*	*	~	\			*		
Cri-du-chat syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolf-Hirschhorn syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Total / trends across registries	68			68	4	0	3	7	2	9	5	0	0	3	3	0	5	0	2	4	2	3	4	4	8
Total \ trends across registries		201		201	1	10	5	0	1	13	10	10	11	23	7	7	7	13	7	4	29	8	11	23	1
Total~ trends across registries			189	189	21	9	9	2	6	15	11	16	4	14	8	4	6	17	4	5	18	2	5	9	4
Total any	68	201	189	458	26	19	17	9	9	37	26	26	15	40	18	11	18	30	13	13	49	13	20	36	13

Key:
/ = significant upward trend **** = significant downward trend **~** = non-linear change over time ***** Too few cases to run analysis

X = Data excluded from analysis. § = Registries must have used ICD10 coding for the whole period 1999-2008 to be included in surveillance of these subgroups

4.3 Detected Clusters

A total of 30 clusters were detected from surveillance of 76 anomaly subgroups in 16 EUROCAT registries, covering approximately 0.8 million births in 2007-2008 (Table 4). 27 of the clusters were detected using date of conception, with 3 detected using date of birth. A total of 766 cluster tests were performed giving a cluster detection rate of 3.9%. By chance alone, we would expect a cluster detection rate of 2.5%. Eight of the 30 clusters (highlighted below) were identified and investigated in the 2007 Report: http://www.eurocat-network.eu/content/Stat-Mon-Report-2007.pdf.

Three clusters of neural tube defects and Patau syndrome/ trisomy13 were detected.

- The neural tube defects clusters were detected in Ile de la Reunion (FR), Wales (UK) and Tuscany (IT). Clusters in Ile de la Reunion and Wales were detected based on date of conception. The cluster in Tuscany was detected based on date of birth.
- The Patau syndrome/trisomy 13 clusters were detected in Styria (AT), Hainaut (BE) and Northern Netherlands (NL). Clusters in Styria and Northern Netherlands were detected based on date of conception. The cluster in Hainaut was detected based on date of birth.

Two clusters of renal dysplasia and hypospadias were detected.

- The renal dysplasia clusters were detected in East Midlands and South Yorkshire (UK) and Emilia Romagna (IT). Both clusters were detected based on date of conception.
- The hypospadias clusters were detected in East Midlands and South Yorkshire and Wessex* (both UK). Both clusters were detected based on date of conception.

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

- Anencephalus (Tuscany, IT)*
- Congenital cataract (Tuscany, IT)*
- Atrioventricular septal defect (Tuscany, IT)
- Tetralogy of Fallot (Wessex, UK)
- Tricuspid atresia and stenosis (Northern Netherlands, NL)
- Aortic valve atresia/stenosis § (Dublin, IE)*
- Total anomalous pulmonary venous return (Wales, UK)
- Choanal atresia (Antwerp, BE)*
- Bilateral renal agenesis including Potter syndrome (Emilia Romagna, IT)
- Congenital hydronephrosis (Dublin, IE)*
- Indeterminate sex (Wales, UK)*
- Limb reduction (Paris)
- Club foot (Wessex)*
- Hip dislocation and /or dysplasia (Styria, AT)
- Polydactyly (Paris, FR)
- Asplenia (Paris, FR)
- Situs inversus (Ile de la Reunion, FR)

- Maternal infections resulting in malformations (Dublin, IE)
- Klinefelter syndrome (Paris, FR)

* Eight clusters were identified and investigated in the Statistical Monitoring Report 2007: http://www.eurocat-network.eu/content/Stat-Mon-Report-2007.pdf.

A further single cluster of coarctation of aorta was detected in East Midlands and South Yorkshire, (UK) based on date of birth.

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 2007-2008

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Ile de la Reunion (FR)	Paris (FR)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	E Mid & S York (UK)	N England (UK)	Wales (UK)	Wessex (UK)
All Anomalies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nervous system	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neural Tube Defects	2	1	3					C					B					C	
Anencephalus and similar	1	0	1										C	*					
Encephalocele	0	0	0	*	*	*	*				*			*	*				
Spina Bifida	0	0	0																
Hydrocephaly	0	0	0								*								
Microcephaly	0	0	0				*				*								
Arhinencephaly/holoprosencephaly	0	0	0	*	*	*	*			*	*			*	*				*
Eye	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anophthalmos/micropthalmos	0	0	0	*		*		*			*			*					*
Anophthalmos	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*
Congenital cataract	1	0	1			*	*	*			*		C	*					*
Congenital glaucoma	0	0	0	*	*	*	*	*	*	*	*	*		*	*	*	*		*
Ear, face and neck	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anotia	0	0	0	*	*	*	*	*		*	*		*	*	*	*		*	*
Congenital heart disease	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Ile de la Reunion (FR)	Paris (FR)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	E Mid & S York (UK)	N England (UK)	Wales (UK)	Wessex (UK)
Severe CHD §	0	0	0																
Common arterial truncus	0	0	0	*	*	*	*		*		*		*	*	*				
Transposition of great vessels	0	0	0								*								
Single ventricle	0	0	0	*		*	*			*	*			*					*
Ventricular septal defect	0	0	0																
Atrial septal defect	0	0	0																
Atrioventricular septal defect	1	0	1								*		C	*					
Tetralogy of Fallot	1	0	1				*							*					C
Tricuspid atresia and stenosis	1	0	1	*	*	*	*	*	*		*	*	*	*	C				
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	0	1	1				*				*			*		B			
Total anomalous pulm venous return	1	0	1	*	*	*	*	*	*		*	*	*	*				C	
Respiratory	X	X	X	X	X	X	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	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Ile de la Reunion (FR)	Paris (FR)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	E Mid & S York (UK)	N 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	X	X	X	X	X	X
Cleft lip with or without palate	0	0	0																
Cleft palate	0	0	0																
Digestive system	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oesophageal atresia with or without tracheo-oesophageal fistula	0	0	0	*							*			*					
Duodenal atresia or stenosis	0	0	0	*		*	*				*		*	*	*				
Atresia or stenosis of other parts of small intestine	0	0	0		*	*	*				*			*					
Ano-rectal atresia and stenosis	0	0	0											*					
Hirschsprung's disease	0	0	0			*	*		*		*	*	*	*					
Atresia of bile ducts	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*		*
Annular pancreas	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	0	0				*				*								
Abdominal wall defects	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gastroschisis	0	0	0				*				*			*					
Omphalocele	0	0	0								*			*	*				
Urinary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Ile de la Reunion (FR)	Paris (FR)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	E Mid & S York (UK)	N England (UK)	Wales (UK)	Wessex (UK)
Bilateral renal agenesis including Potter syndrome	1	0	1				*				*	C		*					
Renal dysplasia	2	0	2								*	C		*		C			
Congenital hydronephrosis	1	0	1					*		C									
Bladder exstrophy and/or epispadia	0	0	0	*	*	*	*	*			*	*	*	*	*			*	*
Posterior urethral valve and/or prune belly	0	0	0			*	*			*	*	*	*	*					
Genital	X	X	X	X	X	X	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	X	X	X	X	X	X
Limb reduction	1	0	1						C		*								
Upper limb reduction	0	0	0								*			*					
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	1	0	1	C							*			*			*		*
Polydactyly	1	0	1						C		*								
Syndactyly	0	0	0								*			*					
Arthrogryposis multiplex congenita	0	0	0				*	*		*	*		*	*	*	*	*		*

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Ile de la Reunion (FR)	Paris (FR)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	E Mid & S York (UK)	N England (UK)	Wales (UK)	Wessex (UK)
Musculo-skeletal	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thanatophoric dwarfism	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Jeunes syndrome	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Achondroplasia	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X
Asplenia	1	0	1	*	*	*	*	*	C	*	*	*	*	*	*	*	*	*	*
Situs inversus	1	0	1	*	*	*	*	C		*	*			*					
Conjoined twins	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*			*	*
Disorders of skin	0	0	0					*			*			*					*
Teratogenic syndromes with malformations §	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	1	0	1	*		*	*	*		C	*		*	*	*	*	*		
Genetic syndromes + microdeletions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Anomaly	Total clusters: date of conception	Total clusters: date of birth	Total clusters: all registries	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Odense (DK)	Ile de la Reunion (FR)	Paris (FR)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	E Mid & S York (UK)	N England (UK)	Wales (UK)	Wessex (UK)
Chromosomal	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Down Syndrome	0	0	0																
Patau syndrome/trisomy 13	2	1	3	C		B					*			*	C				
Edward syndrome/trisomy 18	0	0	0								*			*					
Turner's syndrome	0	0	0								*			*					
Klinefelter syndrome	1	0	1	*	*		*		C		*			*	*				
Cru-du-chat syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolf-Hirschhorn syndrome	0	0	0																
Total clusters: date of conception	27			2	1	0	0	2	4	3	0	2	3	0	2	2	0	3	3
Total clusters: date of birth		3		0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0
Total clusters			30	2	1	1	0	2	4	3	0	2	4	0	2	3	0	3	3

Key:
C = Clusters run by date of conception, -C = Case deficit run by date of conception
B = Clusters run by date of birth, -B = Case deficit run by date of birth
T = Total clusters
X = Data excluded from analysis
* = Too few cases to run analysis (registries must have at least 7 cases over the surveillance period)
§ = Registries must have used ICD10 coding for the whole 5 year period 2004-2008 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 and templates were provided to make the reporting process consistent between registries (http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2008.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 Dublin June 2010 and then a final written report sent to Central Registry.

4.4.1 Local registry investigations into detected clusters

Only the 22 new clusters are investigated and presented below.

Of the new clusters, 11 were considered to be recent clusters whereby they occurred after December 2006. These include atrioventricular septal defect in Tuscany; Tetralogy of Fallot in Wessex; tricuspid atresia and stenosis in Northern Netherlands; total anomalous pulmonary venous return in Wales; bilateral renal agenesis in Emilia Romagna; renal dysplasia and hypospadias both in East Midlands and South Yorkshire; situs inversus in Il de la Reunion; and three separate clusters of Patau syndrome/trisomy 13 clusters were detected in Styria, Hainaut and Northern Netherlands.

11 of the clusters were considered to be fairly old clusters in that they ended by December 2006. Seven of these clusters were not found in last year's statistical monitoring (2007) as the registries in which they occurred were excluded in the

previous statistical monitoring: Emilia Romagna, Ile de la Reunion, Paris and Styria. The remaining four clusters occurred in registries that were included in last year's monitoring, but due to a different time period of analysis, a cluster was not detected last year. These clusters were neural tube defects in Wales and Tuscany; coarctation of aorta in East Midlands and South Yorkshire and maternal infections in Dublin.

Central Registry received reports on preliminary investigations from the following local registries: Dublin, East Midlands and South Yorkshire, Emilia Romagna, Hainaut, Northern Netherlands, Paris, Styria, Tuscany, Wales and Wessex. Of the older clusters Styria did not report on hip dislocation and Tuscany did not report on neural tube defects. Reports were not received from Ile de la Reunion.

No clusters were identified in Odense, Malta, Northern England and South East Ireland.

Table 5a shows the outcomes of the recent cluster investigations, with table 5b the older clusters. Both are classified as follows:

- Apparent cluster with cause for concern, further investigation ongoing
- Excess of cases confirmed, but no further investigation proposed other than further surveillance
- Cluster associated with aetiologic heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence
- Increase in cases, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound detection rates
- Data quality issues found to explain cluster
- No report of preliminary investigations sent to Central Registry

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

Table 5a: Outcomes of local registry preliminary investigations of recently detected clusters 2007-2008

Clusters associated with 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 or late case ascertainment	No detailed report sent to Central Registry
• Tetralogy of Fallot-Wessex	• AVSD-Tuscany	• Patau syndrome/trisomy 13- Hainaut	• Tricuspid atresia-Northern Netherlands	• Situs inversus-Ile de la Reunion
	• TAPVR-Wales		• Renal dysplasia-East Midlands and South Yorkshire	
	• Bilateral renal agenesis-Emilia Romagna		• Hypospadias- East Midlands and South Yorkshire	
	• Patau syndrome/trisomy 13-Northern Netherlands		• Patau syndrome/trisomy 13- Styria	

Table 5b: Outcomes of local registry preliminary investigations of older detected clusters (Ending December 2006)

Clusters associated with 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 or late case ascertainment	No detailed report sent to Central Registry
• Limb reduction-Paris	• Neural tube defects-Wales		• Coarctation of aorta-East Midlands and South Yorkshire	• Neural tube defects-Ile de la Reunion
• Klinefelters syndrome-Paris	• Polydactyly-Paris		• Maternal infections-Dublin	• Neural tube defects-Tuscany
	• Asplenia-Paris			• Hip dislocation-Styria
	• Renal dysplasia-Emilia Romagna			

4.4.2 Local registry investigations into increasing long-term trends

Central Registry received reports on preliminary trend investigations from 14 of 21 local registries with increasing trends (67%): East Midlands and South Yorkshire, Emilia Romagna, Hainaut, Northern England, Northern Netherlands, Odense, Paris, Saxony- Anhalt, Thames Valley, Tuscany, Vaud, Wales, Wessex and Zagreb. No increasing trends were detected in Antwerp, Dublin, Malta, South East Ireland and South Portugal. No reports of investigations were received from Barcelona and Styria.

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=24)
- 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=6)
- F: Trend confirmed, further surveillance proposed before more detailed investigation (n=5)
- G: Not real trend when additional years added, or heterogeneous subgroup (n=5)

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.

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

- Hydrocephaly in Paris
- Anotia in Paris
- Transposition of great vessels in Hainaut
- Choanal atresia in Paris
- Cystic adenomatous malformation of the lung in Wales
- Cleft lip with or without palate in Wales
- Ano-rectal atresia and stenosis in Saxony- Anhalt
- Abdominal wall defects in East Midlands & South Yorkshire
- Gastroschisis in Wessex
- Genital and hypospadias in Emilia Romagna

Five registries (Antwerp, East Midlands and South Yorkshire, Northern England, Northern Netherlands and Odense,) 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	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Years tested (grouped by 2 years)					1999-2008	1999-2008	**1999-2008**	**1999-2008**	**1999-2008**	**1999-2008**	**1999-2008**	1999-2008	1999-2008	**1999-2008**	**1999-2008**	1999-2008	**1999-2008**	1999-2008	2000-2007	**2000-2007**	**1999-2008**	**2001-2008**	**1999-2008**	**1999-2008**	**1999-2008**
All Non-chromosomal Anomalies	2	8	11	21	≈	\	≈	**A B C**	≈	≈	\	≈	\	\	≈	\	≈	≈	\	\	≈	\	≈	≈	**A**
Nervous system	0	5	6	11	≈	≈	≈				≈	\	\	≈	≈			\			\			\	
Neural Tube Defects	0	5	3	8		≈	≈				≈	\	\	\				\						\	
Anencephalus and similar	0	1	3	4				*					*		≈	*		≈			≈			\	
Encephalocele	0	0	1	1		*	*	*	*				*		*	*	*	*	*		≈		*		
Spina Bifida	0	7	2	9		≈		*	\			\	\	\	≈			\			\			\	
Hydrocephaly	2	3	3	8			**A**	*		**F**	\	\		\	≈	*		≈			≈				
Microcephaly	0	2	6	8	≈		≈	*	*		≈	≈		≈		*		*	≈		\		*	\	
Arhinencephaly/holoprosencephaly	0	0	1	1	*	*	*	*	*		*	*	*		*	*	*	*		*			*	≈	
Eye	0	5	3	8		\	\	*	≈				*			*	≈	\			\			\	≈
Anophthalmos/micropthalmos	0	1	1	2	*	*	*	*	*		*	*	*	≈		*		*	*	*	\		*		*
Anophthalmos	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	0	1	1	*		*	*		*	*		*	*		*	≈	*	*	*			*		*
Congenital glaucoma	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*
Ear, face and neck	1	6	1	8	\			*	*		\		*	\		*	\	≈	/	*	\	*	*	\	*

	Total /	Total \	Total ~	Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Anotia	1	0	0	1	*	*	*****	*****	*****	**F**	*****	*	*	*****	*****	*	*****	*	*	*****	*****	*****	*****	*****	*****
Congenital heart disease	2	6	9	17	~	~	~	**A B C**	~	**B**	~	~	\	\	\	\		~	\		~	\		~	
Severe CHD §	0	4	1	5		\				\				\				~			\				
Common arterial truncus	0	1	1	2	*	*	*****	*****	*****	*****	*****		*	*****	*****	*	*****	*	*	*****	\		*****	~	*****
Transposition of great vessels	1	3	0	4			**F**	*****	*****				\	\				*		*****				\	
Single ventricle	0	1	0	1	*	*	*****	*****	*****	\	*****	*	*	*****		*	*****	*	*	*****	*****	*****	*****		*****
Ventricular septal defect	4	5	5	14	~			**A B C**	~	**B**				\	\	\	**A**	~	\	**C**	~	\		~	
Atrial septal defect	2	8	7	17	~	\	\	**A B C**		\	~	~		\	~	\		~	\	~	\	\	**A**	~	
Atrioventricular septal defect	1	1	1	3				*****		~	**C**		*	\		*		*					*****		
Tetralogy of Fallot	1	0	3	4						~			*			*	~				~			**A**	
Tricuspid atresia and stenosis	0	4	0	4	*	*	*****	*****	*****	\	*****	*	*	*****	*****	*		*	\	*****	\	*****	*****	\	
Ebstein's anomaly	0	0	1	1	*	*	*****	*****	*****	~	*****	*	*	*****	*****	*	*****	*	*	*****		*****	*****		*****
Pulmonary valve stenosis	2	3	1	6	~			*****		**B**	**C**		*		\	\			\				*****		*****
Pulmonary valve atresia	0	1	1	2	*	*	*****	*****	*****	~	*****	*	*	\		*	*****	*	*	*****			*****		*****
Aortic valve atresia/stenosis §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*				
Hypoplastic left heart	0	1	2	3		\		*	*			~				*		*		*	~				
Hypoplastic right heart §	0	1	0	1	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	\	*****	*****		
Coarctation of aorta	1	1	2	4			~	*****	*****		**C**	~									\				
Total anomalous pulm venous return	0	1	0	1	*	*	*****	*****	*****		*****		*	*****	*****	*	*****	*	*	*****	\		*****		*****

	Total /	Total \	Total ~	Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Respiratory	1	3	4	8	~				*	~		\	~			*		\			\			~	A
Choanal atresia	1	0	0	1			*	*	*	F	*		*	*		*	*	*		*	*		*		
Cystic adenomatous malf of lung §	2	1	0	3	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X			\	F E	A
Oro-facial clefts	0	2	2	4							\	~				~					\				
Cleft lip with or without palate	1	1	2	4		~					\													E	~
Cleft palate	0	1	3	4							~	~				~					\				
Digestive system	0	7	4	11		~			~	\			~	\	\		\				\	\	~	\	
Oesophageal atresia with or without tracheo-oesophageal fistula	0	1	3	4				*					*	~		*	~		~		\				
Duodenal atresia or stenosis	0	0	1	1	*		*	*	*	~	*		*			*	*	*	*	*			*		
Atresia or stenosis of other parts of small intestine	0	2	1	3	*	*	*	*	*			*	*	\	*	*	*	*	*	*	\	~	*		*
Ano-rectal atresia and stenosis	2	4	1	7	/			*			E F		*	\	\	*		\		*			~	\	
Hirschsprung's disease	0	1	1	2			*	*	*		*	\	*	*	*			*	*	*		~	*		
Atresia of bile ducts	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*
Annular pancreas	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	2	0	2					*				*	\		*		*	*				\		
Abdominal wall defects	2	1	2	5	/			*		\				~		*					E			~	
Gastroschisis	2	1	1	4				*	*	\			*		*	*				*		D		~	E
Omphalocele	0	1	1	2			*	*					*	~		*	*	*				\			
Urinary	1	6	6	13	~	\	~	A E		\	\	~		\				~	~		~		\	\	
Bilateral renal agenesis including Potter syndrome	0	2	0	2	*		*	*	*	\						*		*		*			\		

	Total /	Total \	Total ~	Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Renal dysplasia	4	0	3	7		~	~	*			C	~	*		B	*	A				G				
Congenital hydronephrosis	2	6	5	13	~	~	\	A	C	\				\			~	~			~	\	\	\	
Bladder exstrophy and/or epispadia	0	1	0	1	*	*	*	*	*		*		*	*		*	*	*	*	*		*	*	\	*
Posterior urethral valve and/or prune belly	0	1	1	2			*	*	*	~	*	*	*		*	*	\	*	*	*			*		
Genital	4	3	7	14	~			~		\		\		E	B	~	G	~		~	~		A	\	~
Hypospadias	5	2	8	15	~			~		~		\		E	B	~	G	~		~	~	B	A	\	~
Indeterminate sex	1	0	0	1	*	*	*	*	*		*	*	*	*		*	*	*	*	*			*	*	G
Limb	0	6	5	11	~					\	\	~	\		\	\		~			~		~	\	
Limb reduction	1	2	2	5	~			A					*	~		*		\			\				
Upper limb reduction	0	1	1	2	~			*					*			*		\							
Lower limb reduction	1	1	2	4				*	*	\			*	~		*			*	A	~		*		
Complete absence of a limb	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	2	3	4	9			A					~	~	\	\			~	/		~	*	\		
Hip dislocation and/or dysplasia	1	5	3	9	/	\	\				\	~				*		~	*	\	~	*		\	*
Polydactyly	1	1	5	7	~					~	~	~	*								\		~		G
Syndactyly	0	2	5	7	~		~	*	*	~	~		*	~		*	\				\		*		
Arthrogryposis multiplex congenita	0	1	0	1	*	*		*	*		*	*	*	*	*	*	*	*	*	*	\	*	*		*
Musculo-skeletal	0	6	5	11		~	\			~	~	\	~	\			\	\		~				\	
Thanatophoric dwarfism	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Jeunes syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Achondroplasia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	

	Total /	Total \	Total ~	Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Craniosynostosis	1	2	1	4	~			*	*				*			*		*			\	\	A		*
Congenital constriction bands/amniotic band	1	0	0	1	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*		A			
Other malformations	0	7	6	13	~	\				~	\	~	\	~	~		\	~			\		\	\	
Asplenia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	1	0	1	*	*	*	*	*		*	*	*	\	*	*	*	*	*	*			*		*
Conjoined twins	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	0	11	4	15	~	\		*	*	~	\	\	\	\	~	\	\	~	\	\	\		*	\	*
Teratogenic syndromes with malformations §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*				
Fetal alcohol syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*	*	*		*
Valproate syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*	*	*	*	*
Warfarin syndrome §	0	0	0	0	X	X	X	X	X	X	X	X	X	X	X	*	X	X	X	X	*	*	*	*	*
Maternal infections resulting in malformations	0	0	0	0	*		*	*	*		*		*		*	*	*	*	*	*	*	*	*		*
Genetic syndromes + microdeletions	0	5	3	8	~			*				~	*	~				\			\		\	\	\
Chromosomal	2	3	3	8					C	D	~		\	~				\			~		\		
Down Syndrome	4	3	1	8	/					D				~				\		D	\		\		A
Down Syndrome Adjusted	0	4	0	4			M						\	\				M			\	M	\		M
Patau syndrome/trisomy 13	1	0	0	1			*	*	*				*			*		*							A
Edward syndrome/trisomy 18	4	0	3	7				*	~	D				~			A	*		C F	~			D	
Turner's syndrome	0	3	3	6		\		*	*	~	~		*			*		\		~				\	
Klinefelter syndrome	1	1	1	3		*		*	*			*	*	D		*	*	*	~	\			*		
Cru-du-chat syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolf-Hirschhorn syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

	Total /	Total \	Total ~	Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	S Portugal (PT)	Barcelona (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Total / trends across registries	68			68	4	0	3	7	2	9	5	0	0	3	3	0	5	0	2	4	2	3	4	4	8
Total \ trends across registries		201		201	1	10	5	0	1	13	10	10	11	23	7	7	7	13	7	4	29	8	11	23	1
Total ~ trends across registries			189	189	21	9	9	2	6	15	11	16	4	14	8	4	6	17	4	5	18	2	5	9	4
Total any	68	201	189	458	26	19	17	9	9	37	26	26	15	40	18	11	18	30	13	13	49	13	20	36	13

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 1999-2008 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

The 5 increasing trends identified in the 2007 Report were again found to be increasing: http://www.eurocat-network.eu/content/Stat-Mon-Report-2007.pdf..

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, gastroschisis continues to increase - prevalence increased from 2.6 per 10,000 births in 1999-2000 to 3.0 in 2007-2008. Increases were found in 2 out of 5 UK registry areas. No increases were observed in non-UK registries 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.

Prevalence of renal dysplasia also continues to increase, with prevalence increasing from 3.8 per 10,000 births in 1999-2000 to 4.4 in 2007-2008. Significant increasing trends were identified in 4 registries. Following registry investigations, 1 was explained by changes in diagnostic methods, 1 by changes in case ascertainment, 1 by changes to coding classification and 1 was thought to be due to lower reporting in earlier years. In April 2008, the previous EUROCAT polycystic kidney subgroup was restricted to renal dysplasia, so this is the second 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 completed.

Prevalence of hypospadias increased from 12.7 per 10,000 births in 1999-2000 to 13.8 in 2007-2008. 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. Five individual registries reported increasing trends. Three of the registries reported that the increasing trend was mainly due to changing inclusion criteria and/or ascertainment. One registry confirmed the trend was present and undergoing further investigations, whilst one registry found that no real trend existed following preliminary investigations. Increasing trends of hypospadias were identified in previous annual statistical monitoring reports. A more detailed investigation of hypospadias trends is in the planning stages, as it is currently difficult to detect any real changes against a background of inclusion criteria changes, yet this anomaly is of importance in relation to changes in endocrine disrupting exposures.

Prevalence of Edward syndrome/trisomy 18 increased from 4.5 per 10,000 births in 1999- 2000 to 5.0 in 2007-2008. Significantly increasing trends were identified in four individual registries. Preliminary investigations showed that one registry considered the increased trend to be mainly due to changes in case ascertainment. A further registry reported that whilst the increased trend was due to changes in diagnostic methods, they would continue to carry out surveillance. The remaining two registries considered it likely to be due to demographic change. Increasing trends of Edward syndrome/ trisomy 18 were already identified in the Statistical Monitoring

2004, 2005 and 2007 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 nearing completion. The pan-Europe monitoring statistical methodology is currently being developed to allow adjustment for maternal age for Trisomy 18 and 13.

(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.

Whilst the main focus of this report is on increasing trends, we note a continuation of decreasing trends in congenital heart disease (CHD) and a range of CHD subgroups that were reported in last year's report: http://www.eurocat-network.eu/content/Stat-Mon-Report-2007.pdf. A EUROCAT paper describing these trends is due to be published. The new subgroup Severe CHD was also found to be decreasing.

We note also that neural tube defects and arthrogryposis multiplex congenita (AMC) continue to decrease. These were identified as decreasing in last year's report: http://www.eurocat-network.eu/content/Stat-Mon-Report-2007.pdf. A more detailed investigation of decreasing trends in NTD is currently being conducted as part of the EUROCAT Joint Action 2011-2013.

The EUROCAT network does not have the resources to investigate all trends fully. The Steering Committee determines the areas of priority based on the EUROCAT Statistical Monitoring prioritisation strategy (Loane et al 2011). 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.

Loane M, Dolk H, Kelly A, Teljeur C, Greenlees R, Densem J and a EUROCAT Working Group (2011). EUROCAT Statistical Monitoring: identification and investigation of ten year trends of congenital anomalies in Europe. Birth Defects Res Part A Clin Mol Teratol Suppl 91: S31-S43

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-2007.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. As part of the Joint Action 2011-2013 a new committee is being formed, the Taskforce for the Evaluation of Clusters (TEC), with the purpose of advancing investigation of clusters detected during statistical monitoring. The TEC, when requested by EUROCAT or individual registry leaders, will serve as consulting unit for clusters identified through routine surveillance activities. Further information on the function of the TEC and its members will be made available on the EUROCAT website (http://www.eurocat-network.eu/CLUSTERSAndTRENDS/ClusterAdvisoryService/Introduction)

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
Severe CHD	X	X
Common arterial truncus	X	X
Transposition of great vessels	X	X
Single ventricle	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-oesophageal 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 exstrophy 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
Down's syndrome adjusted		X
Patau syndrome/ trisomy 13	X	X
Edward syndrome/ trisomy 18	X	X
Turner's syndrome	X	X
Klinefelter syndrome	X	X
Cri-du-chat syndrome	X	X
Wolf-Hirschhorn 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 1999 and 2008

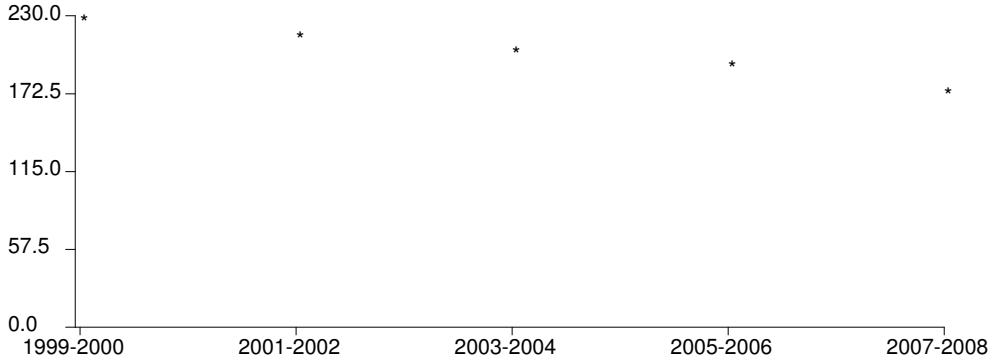
Anomaly Subgroup: **All Non-chromosomal Anomalies**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	707.227	(1 df)	Chi2	13.547	(3 df)
p value	<0.001		p value	0.004	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	17424	763393	228.24
2001 - 2002	16635	771536	215.61
2003 - 2004	16790	820463	204.64
2005 - 2006	17639	906634	194.55
2007 - 2008	16041	919991	174.36

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



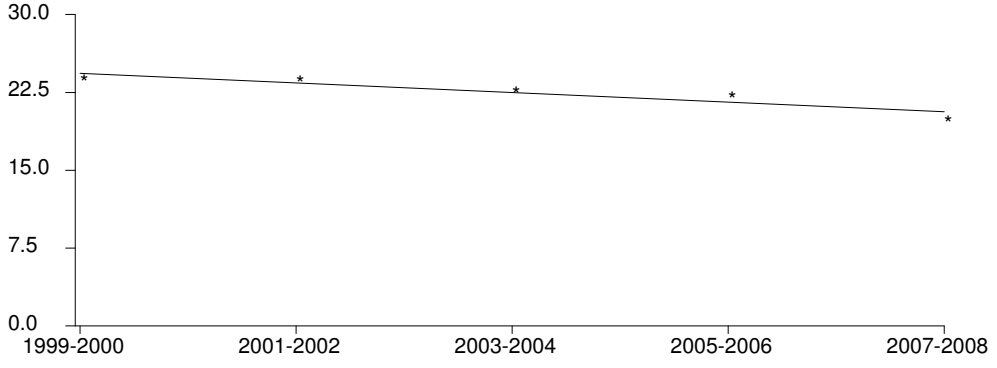
Anomaly Subgroup: **Nervous system**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	33.281	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.754	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	1819	763393	23.83
2001 - 2002	1831	771536	23.73
2003 - 2004	1862	820463	22.69
2005 - 2006	2014	906634	22.21
2007 - 2008	1835	919991	19.95

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



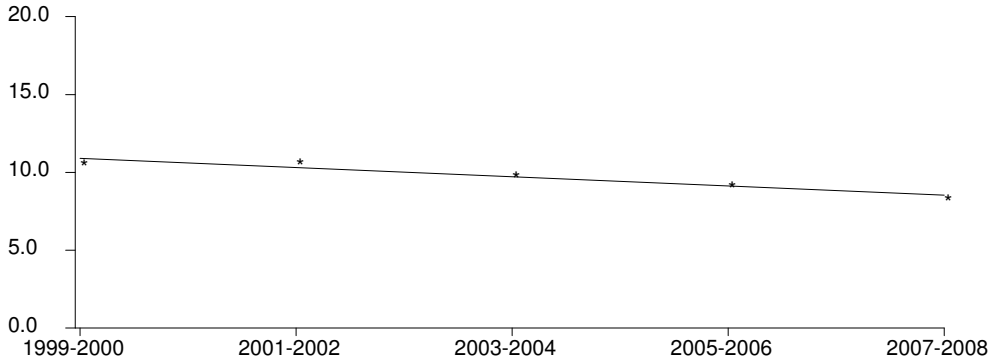
Anomaly Subgroup: **Neural Tube Defects**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	31.077	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.479	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	808	763393	10.58
2001 - 2002	822	771536	10.65
2003 - 2004	804	820463	9.80
2005 - 2006	832	906634	9.18
2007 - 2008	769	919991	8.36

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



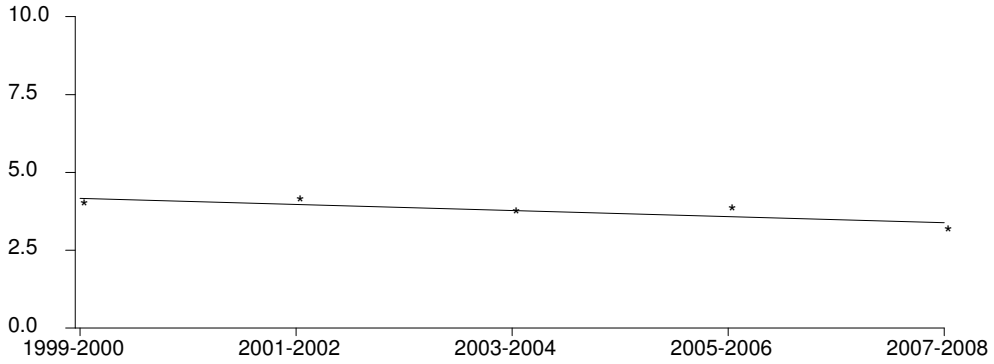
Anomaly Subgroup: **Anencephalus and similar**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	8.811	(1 df)	Not significant
p value	0.003		
Slope	Decreasing		
Rate of change	-0.159	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	306	763393	4.01
2001 - 2002	318	771536	4.12
2003 - 2004	306	820463	3.73
2005 - 2006	348	906634	3.84
2007 - 2008	292	919991	3.17

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



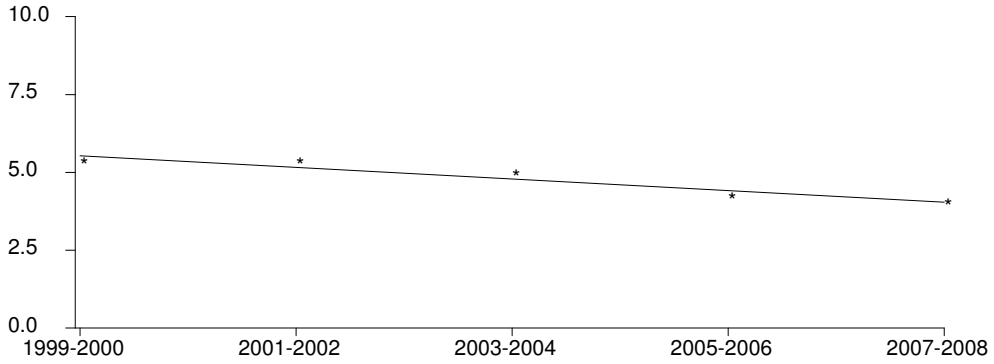
Anomaly Subgroup: **Spina Bifida**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	25.122	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.302	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	408	763393	5.34
2001 - 2002	413	771536	5.35
2003 - 2004	408	820463	4.97
2005 - 2006	382	906634	4.21
2007 - 2008	372	919991	4.04

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



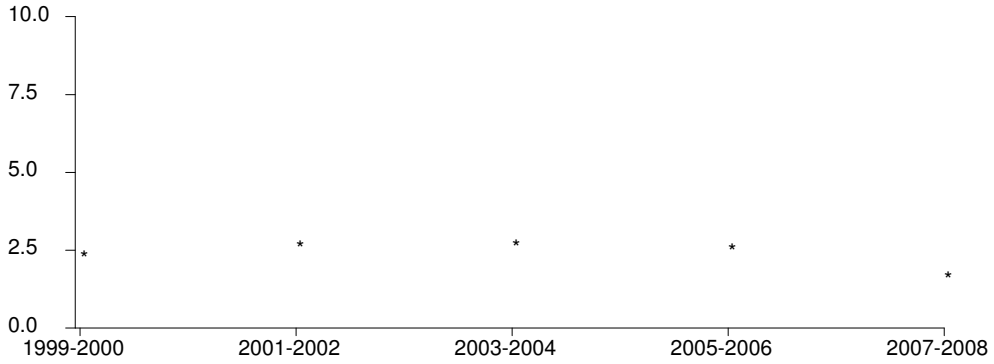
Anomaly Subgroup: **Microcephaly**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	8.609	(1 df)	Chi2	19.321	(3 df)
p value	0.003		p value	<0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	180	763393	2.36
2001 - 2002	208	771536	2.70
2003 - 2004	222	820463	2.71
2005 - 2006	236	906634	2.60
2007 - 2008	154	919991	1.67

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



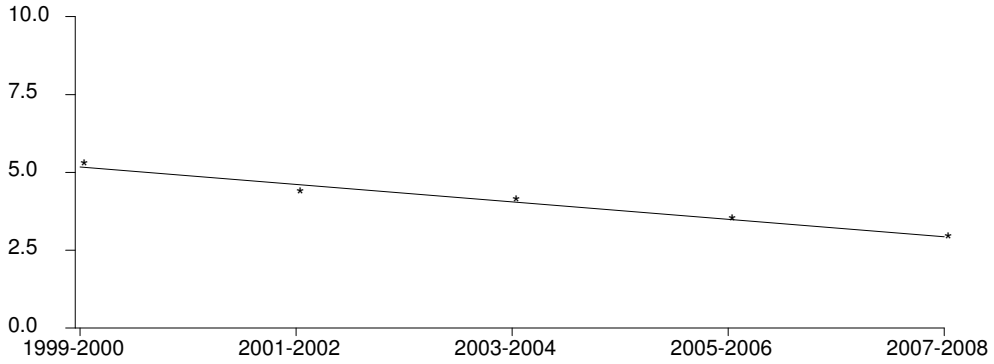
Anomaly Subgroup: **Eye**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	65.339	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.447	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	404	763393	5.29
2001 - 2002	338	771536	4.38
2003 - 2004	339	820463	4.13
2005 - 2006	318	906634	3.51
2007 - 2008	270	919991	2.93

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



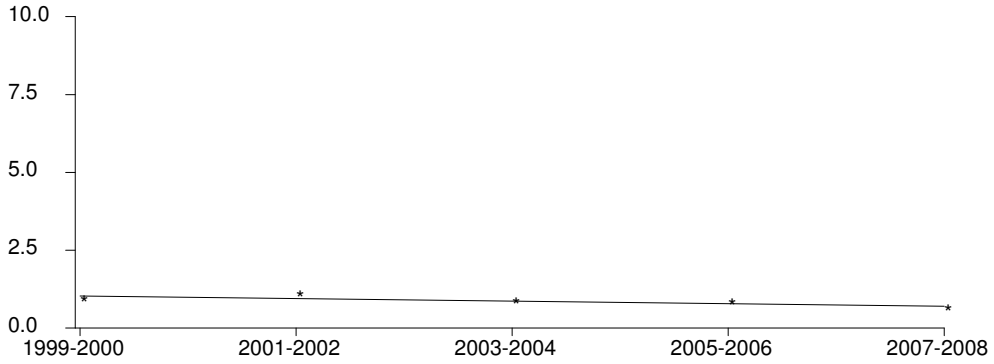
Anomaly Subgroup: **Anophthalmos/micropthalmos**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	7.115	(1 df)	Not significant
p value	0.008		
Slope	Decreasing		
Rate of change	-0.068	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	70	763393	0.92
2001 - 2002	84	771536	1.09
2003 - 2004	70	820463	0.85
2005 - 2006	75	906634	0.83
2007 - 2008	58	919991	0.63

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



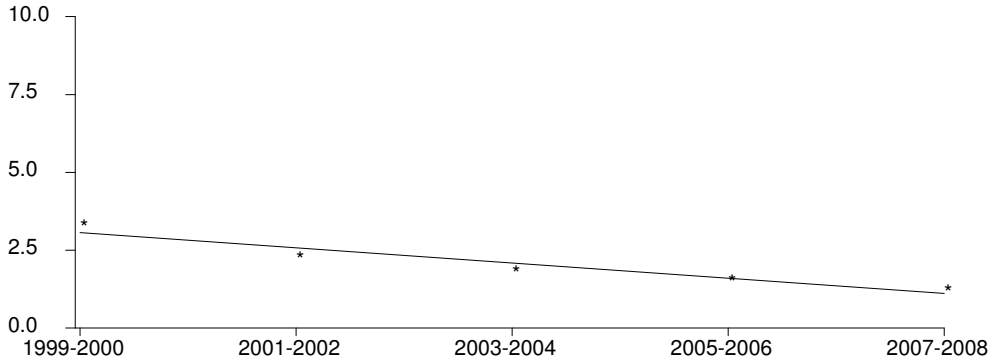
Anomaly Subgroup: **Ear, face and neck**

Decreasing trend

Test for Trend			Test for non-linear change		
Chi2	95.965	(1 df)	Chi2	8.211	(3 df)
p value	<0.001		p value	0.042	
Slope	Decreasing				
Rate of change	-0.387	(Cases per 10,000 births per year)			

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	256	763393	3.35
2001 - 2002	179	771536	2.32
2003 - 2004	155	820463	1.89
2005 - 2006	146	906634	1.61
2007 - 2008	116	919991	1.26

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



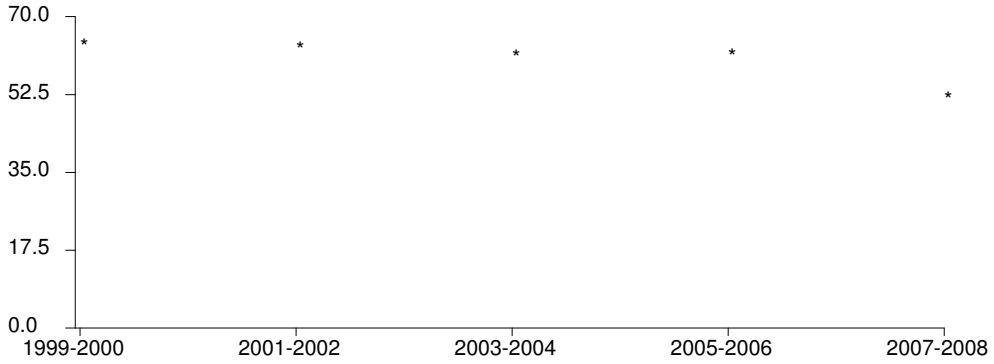
Anomaly Subgroup: **Congenital heart disease**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	92.992	(1 df)	Chi2	40.680	(3 df)
p value	<0.001		p value	<0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	4904	763393	64.24
2001 - 2002	4905	771536	63.57
2003 - 2004	5062	820463	61.70
2005 - 2006	5611	906634	61.89
2007 - 2008	4826	919991	52.46

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



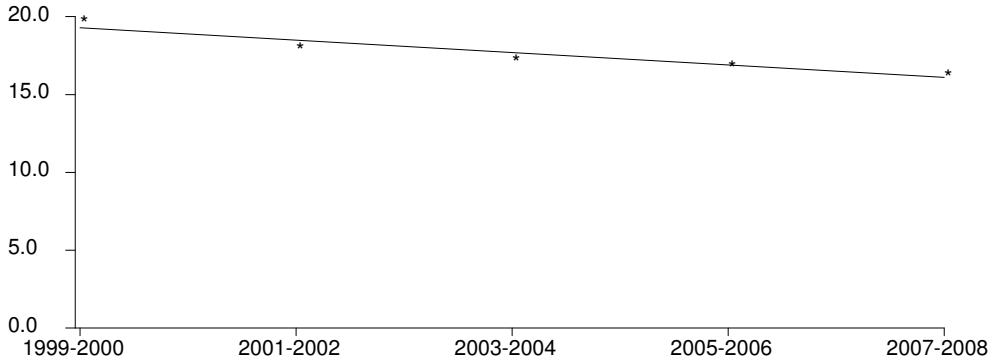
Anomaly Subgroup: **Severe CHD §**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	29.513	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.630	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	1512	763393	19.81
2001 - 2002	1393	771536	18.05
2003 - 2004	1422	820463	17.33
2005 - 2006	1536	906634	16.94
2007 - 2008	1506	919991	16.37

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



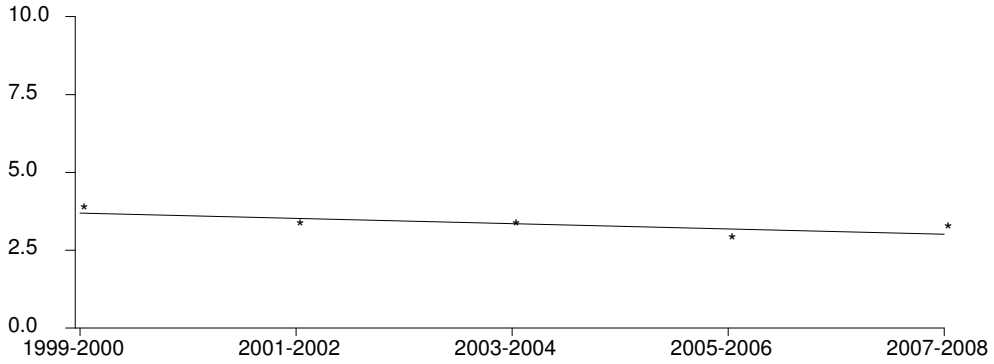
Anomaly Subgroup: **Transposition of great vessels**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	6.777	(1 df)	Not significant
p value	0.009		
Slope	Decreasing		
Rate of change	-0.131	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	296	763393	3.88
2001 - 2002	259	771536	3.36
2003 - 2004	275	820463	3.35
2005 - 2006	265	906634	2.92
2007 - 2008	299	919991	3.25

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



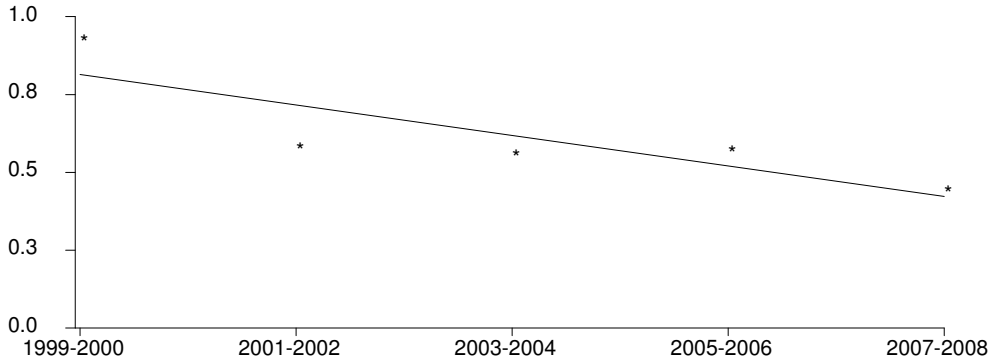
Anomaly Subgroup: **Single ventricle**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	12.656	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.077	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	71	763393	0.93
2001 - 2002	45	771536	0.58
2003 - 2004	46	820463	0.56
2005 - 2006	52	906634	0.57
2007 - 2008	41	919991	0.45

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



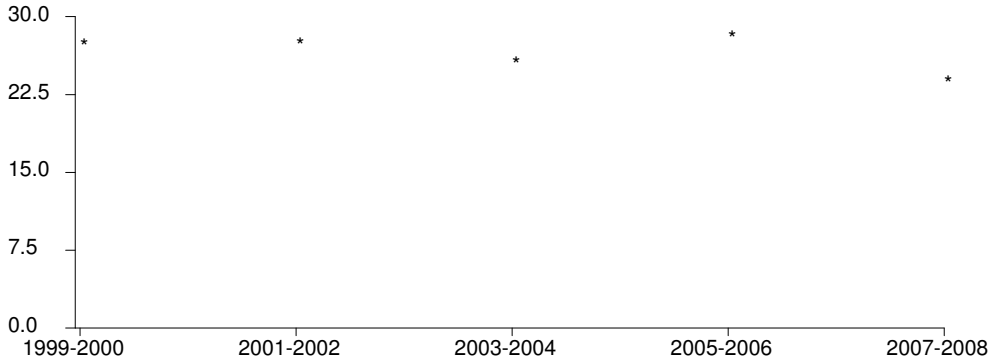
Anomaly Subgroup: **Ventricular septal defect**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	13.201	(1 df)	Chi2	27.708	(3 df)
p value	<0.001		p value	<0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	2098	763393	27.48
2001 - 2002	2128	771536	27.58
2003 - 2004	2114	820463	25.77
2005 - 2006	2564	906634	28.28
2007 - 2008	2205	919991	23.97

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



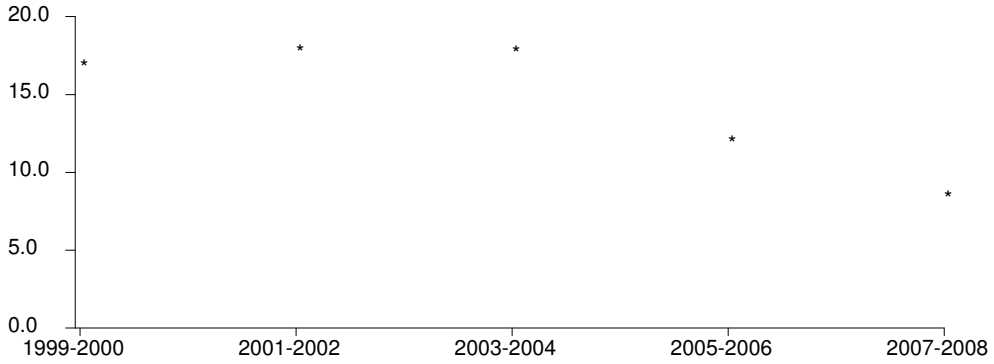
Anomaly Subgroup: **Atrial septal defect**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	316.349	(1 df)	Chi2	106.076	(3 df)
p value	<0.001		p value	<0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	1299	763393	17.02
2001 - 2002	1385	771536	17.95
2003 - 2004	1469	820463	17.90
2005 - 2006	1099	906634	12.12
2007 - 2008	789	919991	8.58

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



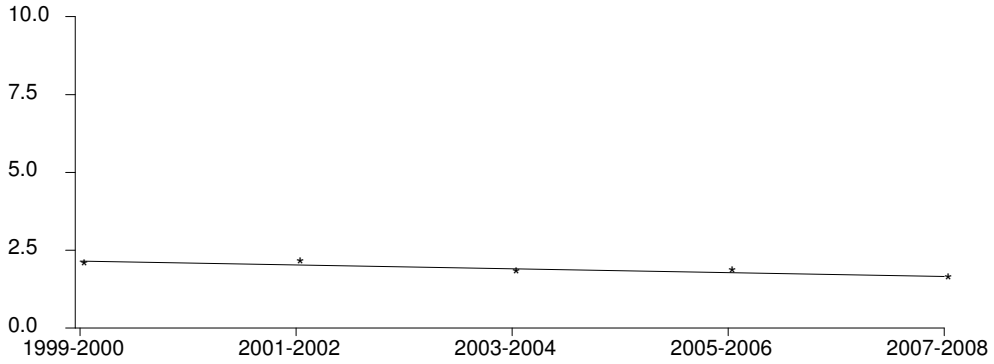
Anomaly Subgroup: **Atrioventricular septal defect**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	6.806	(1 df)	Not significant
p value	0.009		
Slope	Decreasing		
Rate of change	-0.099	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	159	763393	2.08
2001 - 2002	166	771536	2.15
2003 - 2004	149	820463	1.82
2005 - 2006	167	906634	1.84
2007 - 2008	149	919991	1.62

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



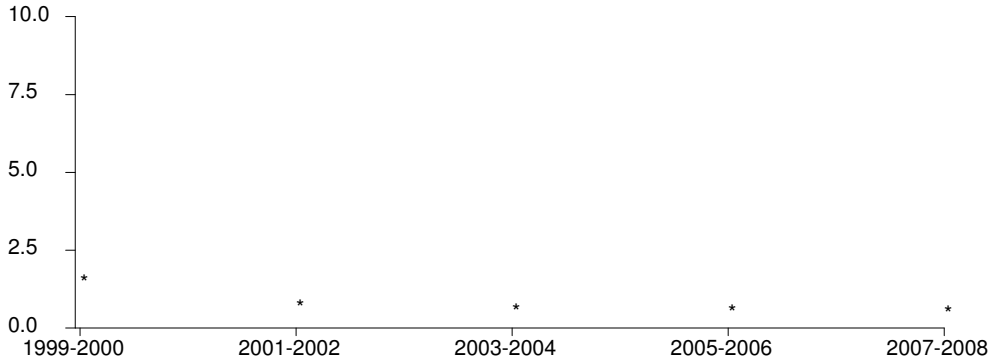
Anomaly Subgroup: **Tricuspid atresia and stenosis**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	45.761	(1 df)	Chi2	23.068	(3 df)
p value	<0.001		p value	<0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	122	763393	1.60
2001 - 2002	61	771536	0.79
2003 - 2004	54	820463	0.66
2005 - 2006	56	906634	0.62
2007 - 2008	54	919991	0.59

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



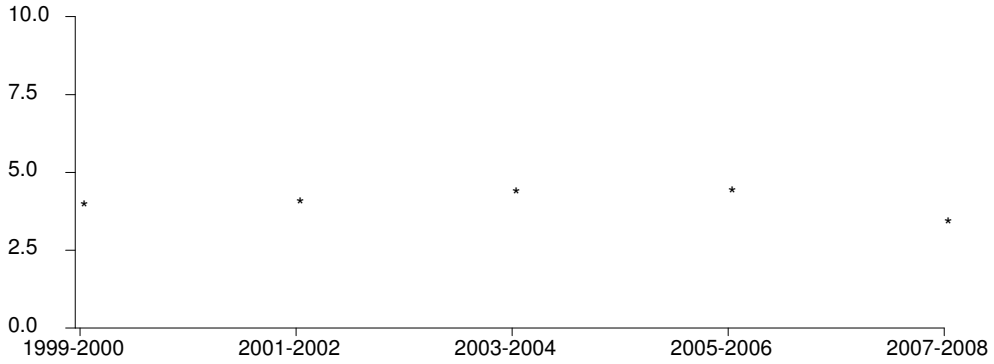
Anomaly Subgroup: **Pulmonary valve stenosis**

Non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	13.086	(3 df)
	p value	0.004	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	304	763393	3.98
2001 - 2002	314	771536	4.07
2003 - 2004	360	820463	4.39
2005 - 2006	402	906634	4.43
2007 - 2008	315	919991	3.42

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



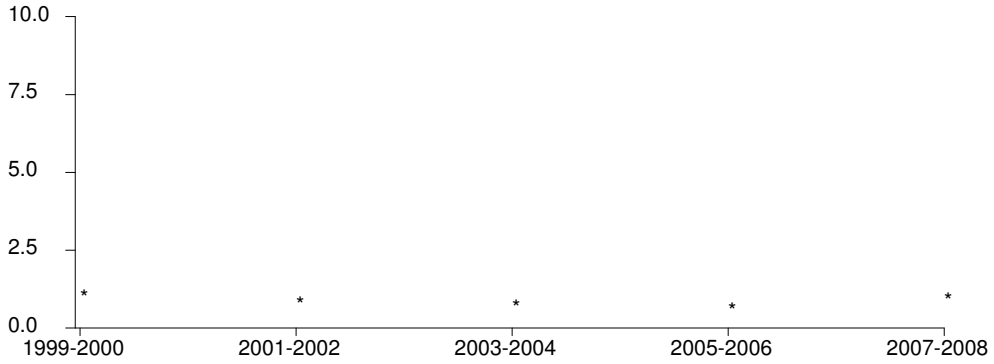
Anomaly Subgroup: **Pulmonary valve atresia**

Non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	8.861	(3 df)
	p value	0.031	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	85	763393	1.11
2001 - 2002	69	771536	0.89
2003 - 2004	65	820463	0.79
2005 - 2006	63	906634	0.69
2007 - 2008	92	919991	1.00

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



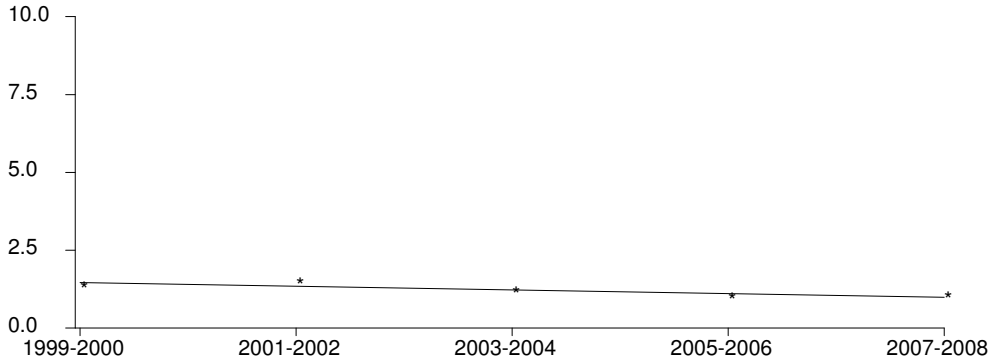
Anomaly Subgroup: **Aortic valve atresia/stenosis §**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	8.257	(1 df)	Not significant
p value	0.004		
Slope	Decreasing		
Rate of change	-0.102	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	45	328032	1.37
2001 - 2002	98	652206	1.50
2003 - 2004	96	806121	1.19
2005 - 2006	91	906634	1.00
2007 - 2008	95	919991	1.03

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



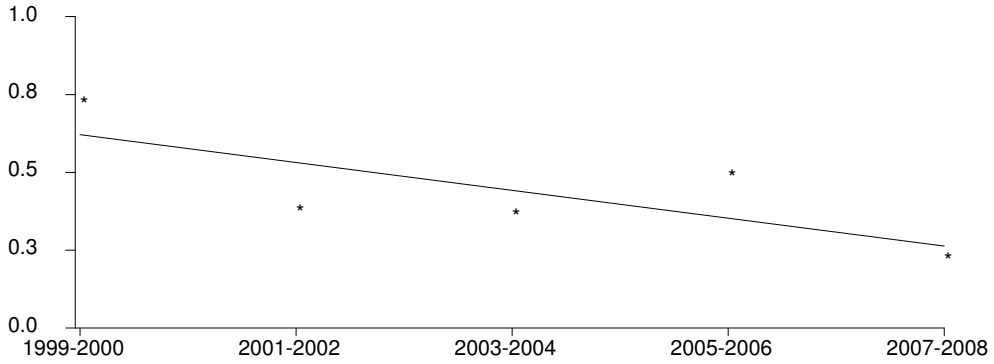
Anomaly Subgroup: **Hypoplastic right heart §**

Decreasing trend

Test for Trend			Test for non-linear change		
Chi2	7.969	(1 df)	Chi2	10.079	(3 df)
p value	0.005		p value	0.018	
Slope	Decreasing				
Rate of change	-0.059	(Cases per 10,000 births per year)			

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	24	328032	0.73
2001 - 2002	25	652206	0.38
2003 - 2004	30	806121	0.37
2005 - 2006	45	906634	0.50
2007 - 2008	21	919991	0.23

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



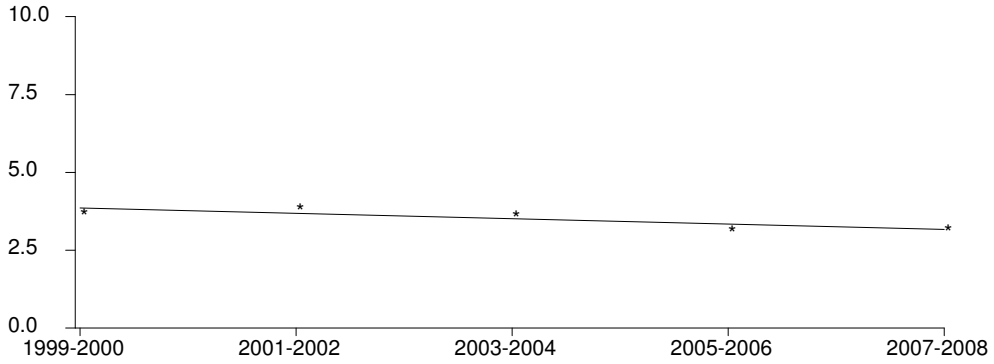
Anomaly Subgroup: **Coarctation of aorta**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	7.550	(1 df)	Not significant
p value	0.006		
Slope	Decreasing		
Rate of change	-0.142	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	283	763393	3.71
2001 - 2002	298	771536	3.86
2003 - 2004	299	820463	3.64
2005 - 2006	286	906634	3.15
2007 - 2008	293	919991	3.18

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



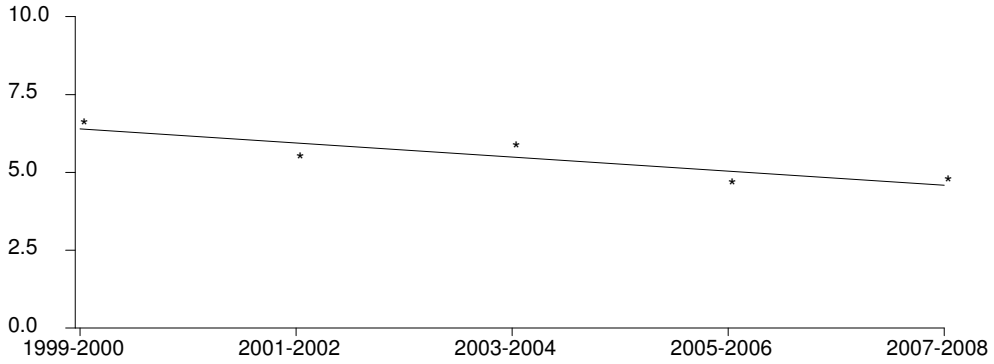
Anomaly Subgroup: **Respiratory**

Decreasing trend

Test for Trend			Test for non-linear change		
Chi2	31.234	(1 df)	Chi2	8.349	(3 df)
p value	<0.001		p value	0.039	
Slope	Decreasing				
Rate of change	-0.360	(Cases per 10,000 births per year)			

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	505	763393	6.62
2001 - 2002	425	771536	5.51
2003 - 2004	482	820463	5.87
2005 - 2006	424	906634	4.68
2007 - 2008	439	919991	4.77

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



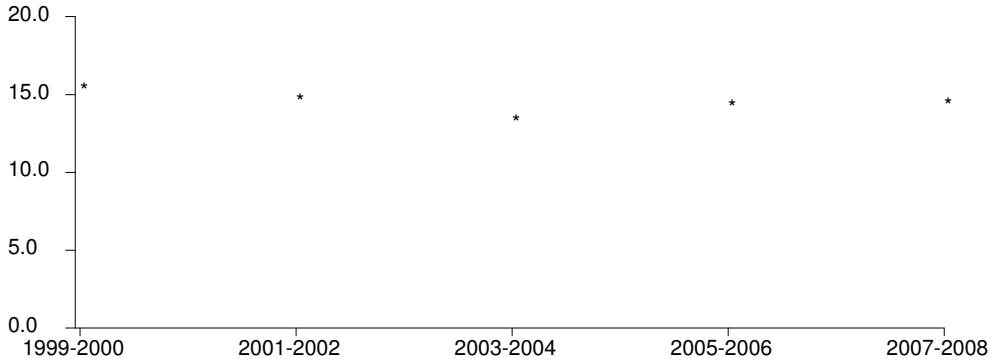
Anomaly Subgroup: **Oro-facial clefts**

Non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	9.964	(3 df)
	p value	0.019	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	1188	763393	15.56
2001 - 2002	1142	771536	14.80
2003 - 2004	1104	820463	13.46
2005 - 2006	1307	906634	14.42
2007 - 2008	1342	919991	14.59

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



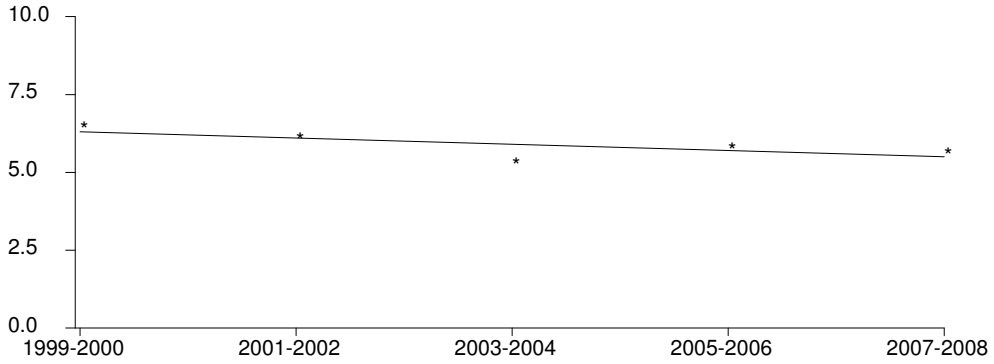
Anomaly Subgroup: **Cleft palate**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	5.313	(1 df)	Not significant
p value	0.021		
Slope	Decreasing		
Rate of change	-0.155	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	497	763393	6.51
2001 - 2002	474	771536	6.14
2003 - 2004	439	820463	5.35
2005 - 2006	528	906634	5.82
2007 - 2008	521	919991	5.66

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



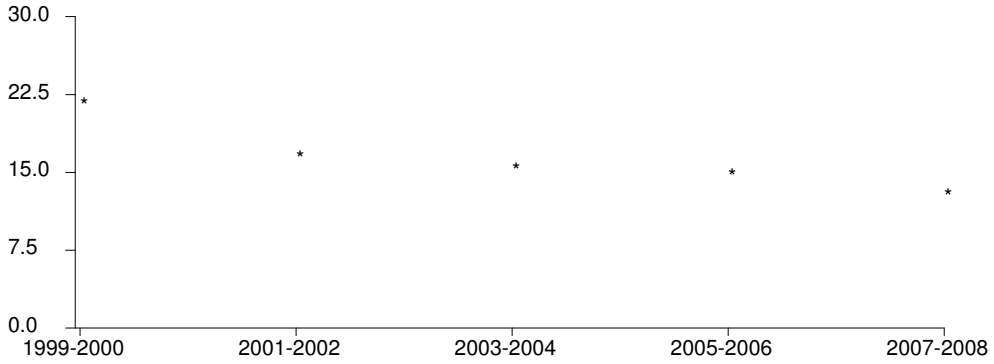
Anomaly Subgroup: **Digestive system**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	189.237	(1 df)	Chi2	29.748	(3 df)
p value	<0.001		p value	<0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	1669	763393	21.86
2001 - 2002	1293	771536	16.76
2003 - 2004	1281	820463	15.61
2005 - 2006	1361	906634	15.01
2007 - 2008	1198	919991	13.02

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



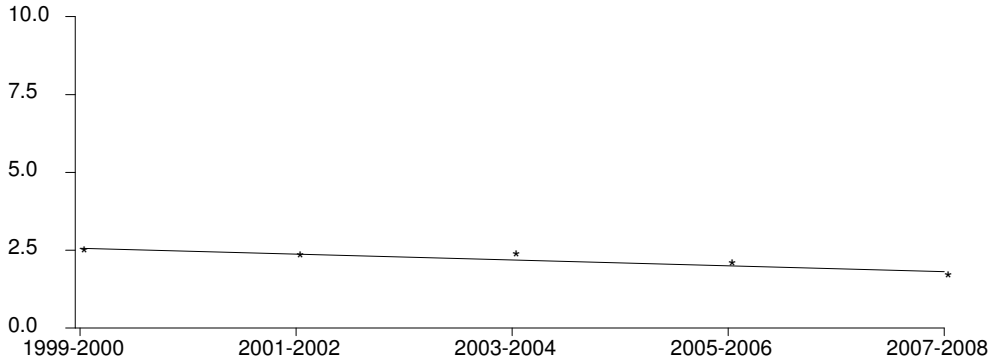
Anomaly Subgroup: **Oesophageal atresia with or without tracheo-oesopheagal fistula**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	13.977	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.152	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	190	763393	2.49
2001 - 2002	180	771536	2.33
2003 - 2004	193	820463	2.35
2005 - 2006	188	906634	2.07
2007 - 2008	155	919991	1.68

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



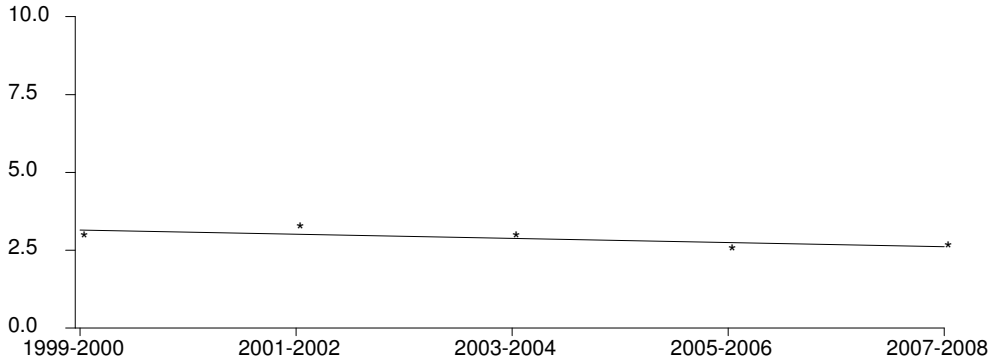
Anomaly Subgroup: **Ano-rectal atresia and stenosis**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	5.460	(1 df)	Not significant
p value	0.019		
Slope	Decreasing		
Rate of change	-0.109	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	226	763393	2.96
2001 - 2002	252	771536	3.27
2003 - 2004	244	820463	2.97
2005 - 2006	232	906634	2.56
2007 - 2008	243	919991	2.64

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



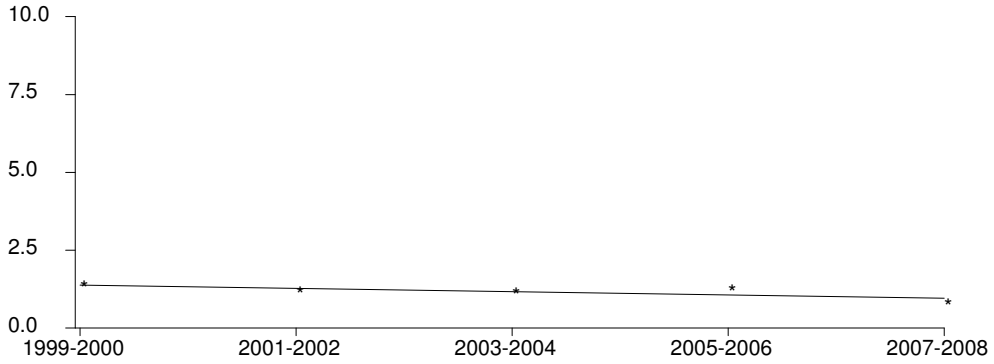
Anomaly Subgroup: **Hirrchsprung's disease**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	8.347	(1 df)	Not significant
p value	0.004		
Slope	Decreasing		
Rate of change	-0.086	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	106	763393	1.39
2001 - 2002	92	771536	1.19
2003 - 2004	95	820463	1.16
2005 - 2006	116	906634	1.28
2007 - 2008	75	919991	0.82

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



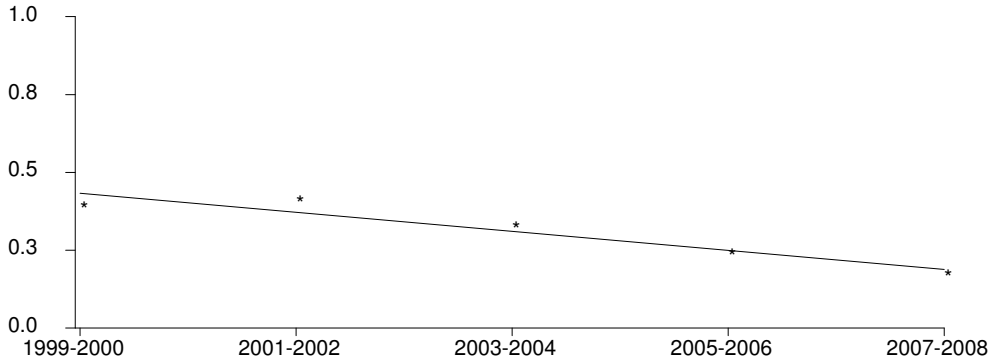
Anomaly Subgroup: **Atresia of bile ducts**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	10.489	(1 df)	Not significant
p value	0.001		
Slope	Decreasing		
Rate of change	-0.049	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	30	763393	0.39
2001 - 2002	32	771536	0.41
2003 - 2004	27	820463	0.33
2005 - 2006	22	906634	0.24
2007 - 2008	16	919991	0.17

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



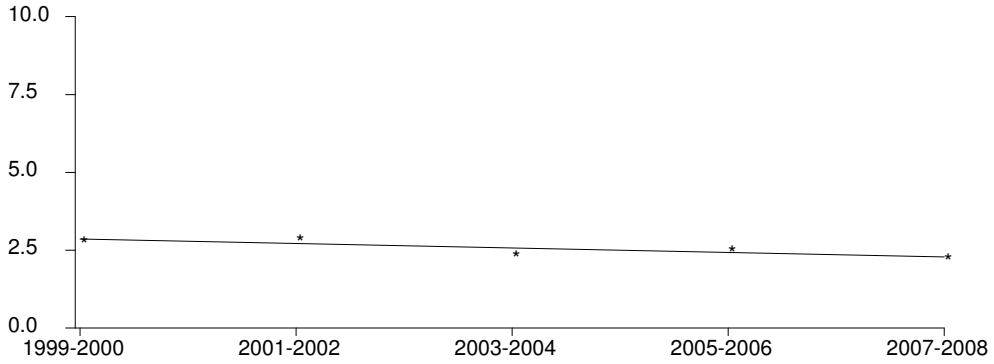
Anomaly Subgroup: **Diaphragmatic hernia**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	6.680	(1 df)	Not significant
p value	0.010		
Slope	Decreasing		
Rate of change	-0.114	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	214	763393	2.80
2001 - 2002	222	771536	2.88
2003 - 2004	194	820463	2.36
2005 - 2006	229	906634	2.53
2007 - 2008	208	919991	2.26

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



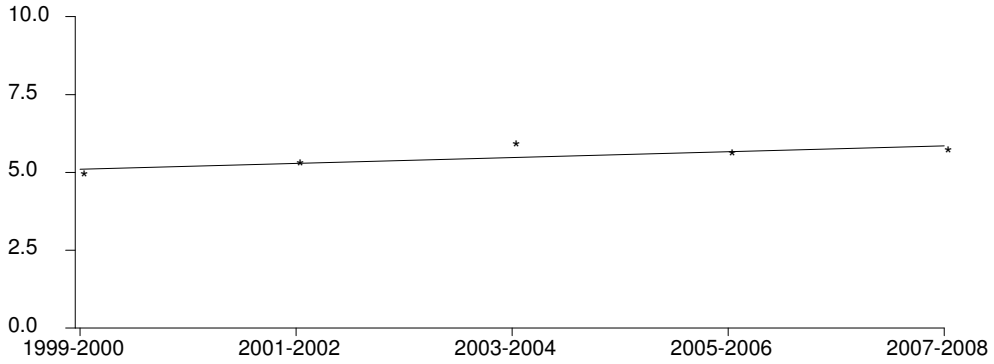
Anomaly Subgroup: **Abdominal wall defects**

Increasing trend

Test for Trend			Test for non-linear change
Chi2	4.942	(1 df)	Not significant
p value	0.026		
Slope	Increasing		
Rate of change	0.144	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	376	763393	4.93
2001 - 2002	407	771536	5.28
2003 - 2004	483	820463	5.89
2005 - 2006	508	906634	5.60
2007 - 2008	524	919991	5.70

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



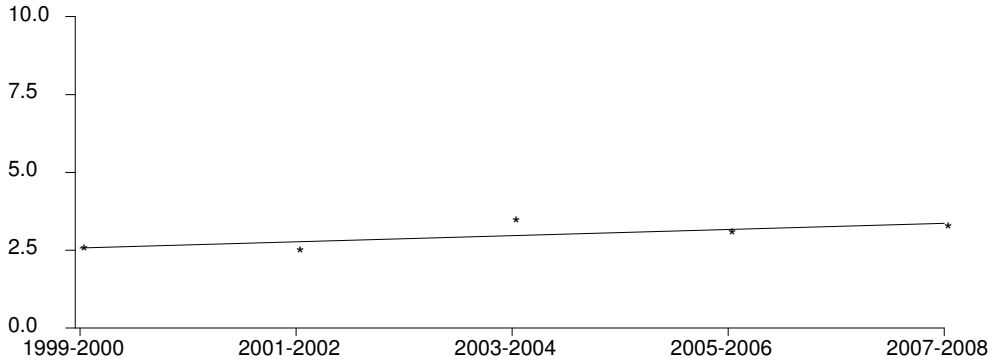
Anomaly Subgroup: **Gastroschisis**

Increasing trend

Test for Trend			Test for non-linear change		
Chi2	10.417	(1 df)	Chi2	9.055	(3 df)
p value	0.001		p value	0.029	
Slope	Increasing				
Rate of change	0.154	(Cases per 10,000 births per year)			

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	195	763393	2.55
2001 - 2002	192	771536	2.49
2003 - 2004	283	820463	3.45
2005 - 2006	279	906634	3.08
2007 - 2008	299	919991	3.25

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



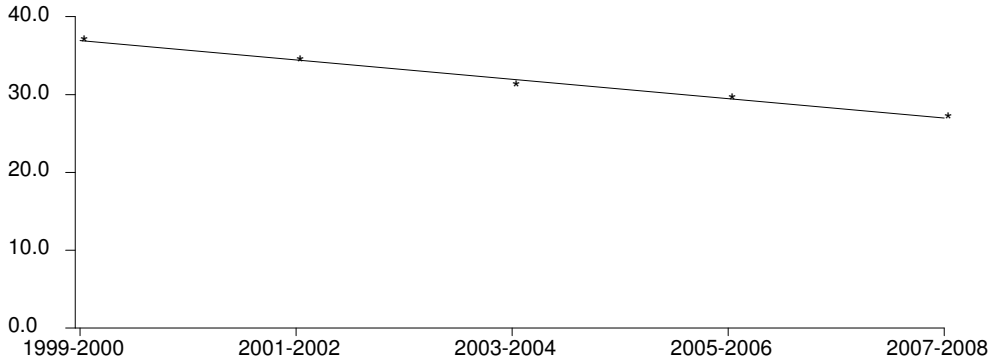
Anomaly Subgroup: **Urinary**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	162.588	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-1.982	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	2834	763393	37.12
2001 - 2002	2663	771536	34.52
2003 - 2004	2572	820463	31.35
2005 - 2006	2685	906634	29.62
2007 - 2008	2497	919991	27.14

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



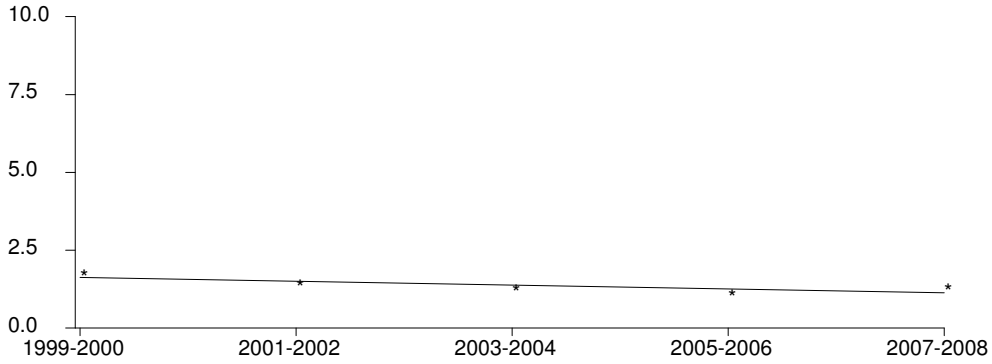
Anomaly Subgroup: **Bilateral renal agenesis including Potter syndrome**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	8.444	(1 df)	Not significant
p value	0.004		
Slope	Decreasing		
Rate of change	-0.094	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	134	763393	1.76
2001 - 2002	111	771536	1.44
2003 - 2004	104	820463	1.27
2005 - 2006	100	906634	1.10
2007 - 2008	121	919991	1.32

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



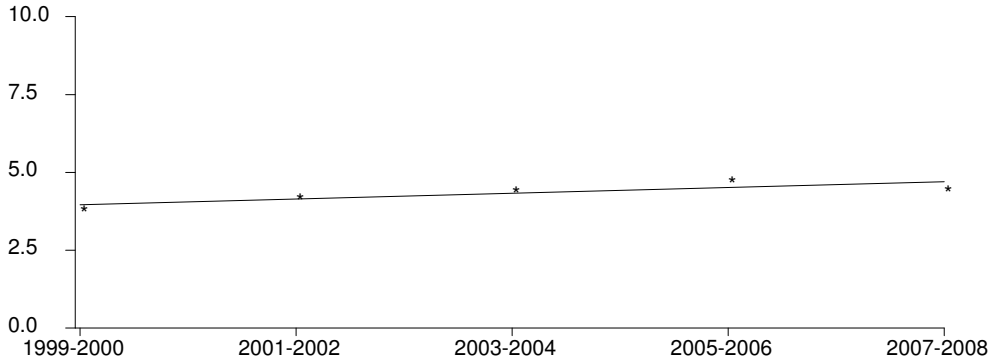
Anomaly Subgroup: **Renal dysplasia**

Increasing trend

Test for Trend			Test for non-linear change
Chi2	6.176	(1 df)	Not significant
p value	0.013		
Slope	Increasing		
Rate of change	0.143	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	291	763393	3.81
2001 - 2002	324	771536	4.20
2003 - 2004	364	820463	4.44
2005 - 2006	431	906634	4.75
2007 - 2008	410	919991	4.46

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



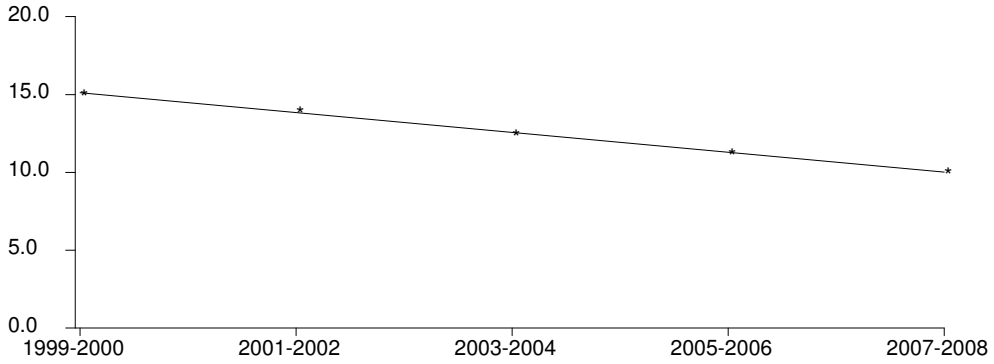
Anomaly Subgroup: **Congenital hydronephrosis**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	110.107	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-1.023	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	1150	763393	15.06
2001 - 2002	1080	771536	14.00
2003 - 2004	1024	820463	12.48
2005 - 2006	1020	906634	11.25
2007 - 2008	924	919991	10.04

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



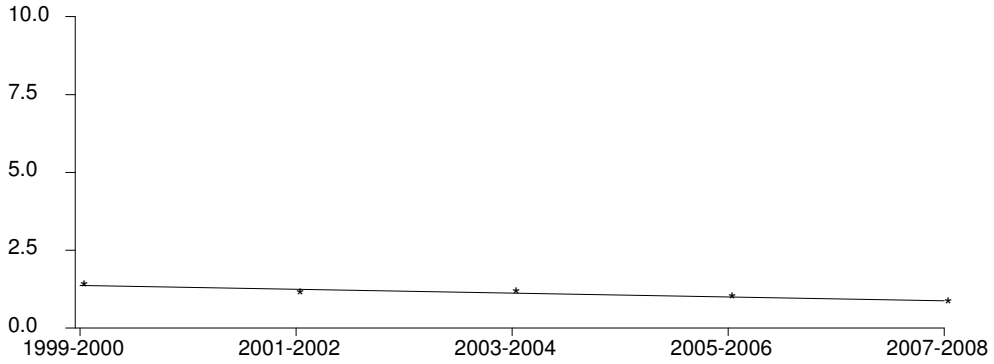
Anomaly Subgroup: **Posterior urethral valve and/or prune belly**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	11.602	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.099	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	107	763393	1.40
2001 - 2002	89	771536	1.15
2003 - 2004	95	820463	1.16
2005 - 2006	91	906634	1.00
2007 - 2008	79	919991	0.86

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



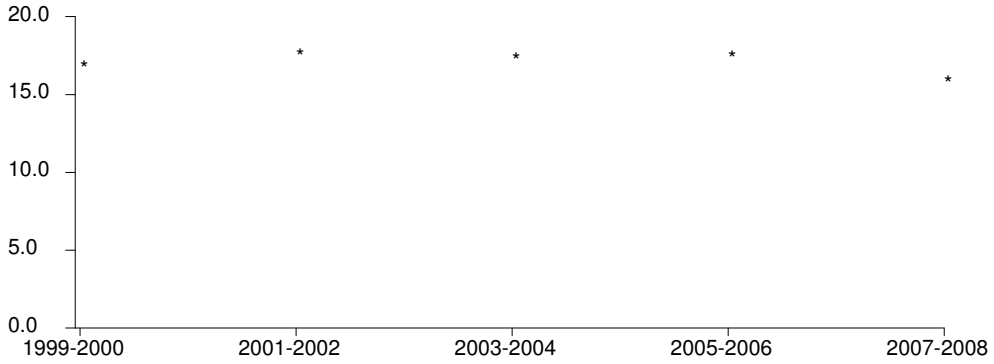
Anomaly Subgroup: **Genital**

Non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	8.622	(3 df)
	p value	0.035	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	1291	763393	16.91
2001 - 2002	1367	771536	17.72
2003 - 2004	1433	820463	17.47
2005 - 2006	1597	906634	17.61
2007 - 2008	1468	919991	15.96

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



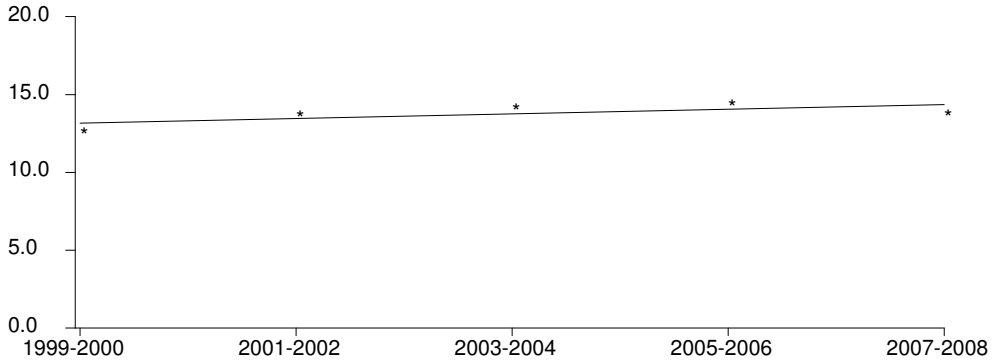
Anomaly Subgroup: **Hypospadias**

Increasing trend

Test for Trend			Test for non-linear change
Chi2	4.849	(1 df)	Not significant
p value	0.028		
Slope	Increasing		
Rate of change	0.226	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	966	763393	12.65
2001 - 2002	1058	771536	13.71
2003 - 2004	1161	820463	14.15
2005 - 2006	1312	906634	14.47
2007 - 2008	1266	919991	13.76

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



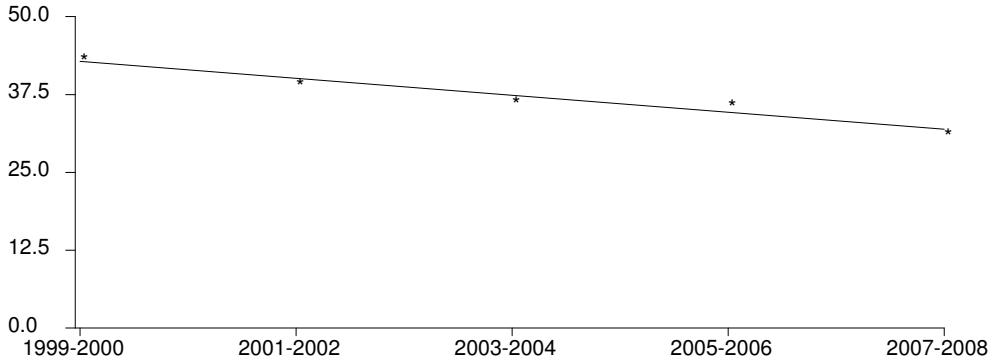
Anomaly Subgroup: **Limb**

Decreasing trend

Test for Trend			Test for non-linear change		
Chi2	167.793	(1 df)	Chi2	8.350	(3 df)
p value	<0.001		p value	0.039	
Slope	Decreasing				
Rate of change	-2.179	(Cases per 10,000 births per year)			

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	3314	763393	43.41
2001 - 2002	3046	771536	39.48
2003 - 2004	3001	820463	36.58
2005 - 2006	3270	906634	36.07
2007 - 2008	2895	919991	31.47

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



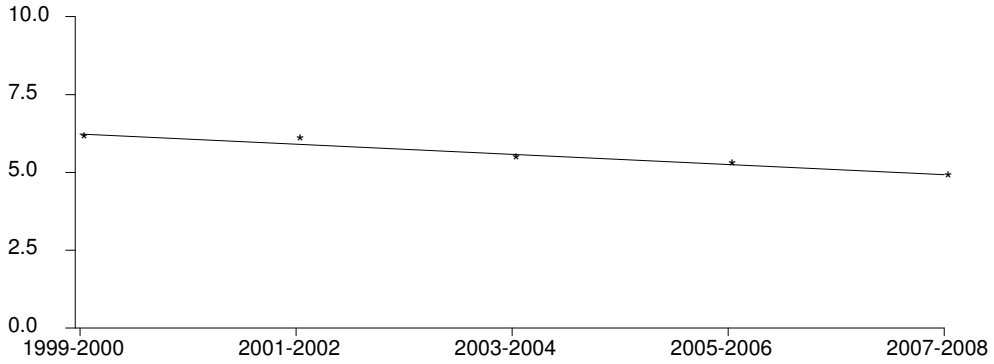
Anomaly Subgroup: **Limb reduction**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	16.148	(1 df)	Not significant
p value	<0.001		
Slope	Decreasing		
Rate of change	-0.262	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	469	763393	6.14
2001 - 2002	469	771536	6.08
2003 - 2004	450	820463	5.48
2005 - 2006	480	906634	5.29
2007 - 2008	451	919991	4.90

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



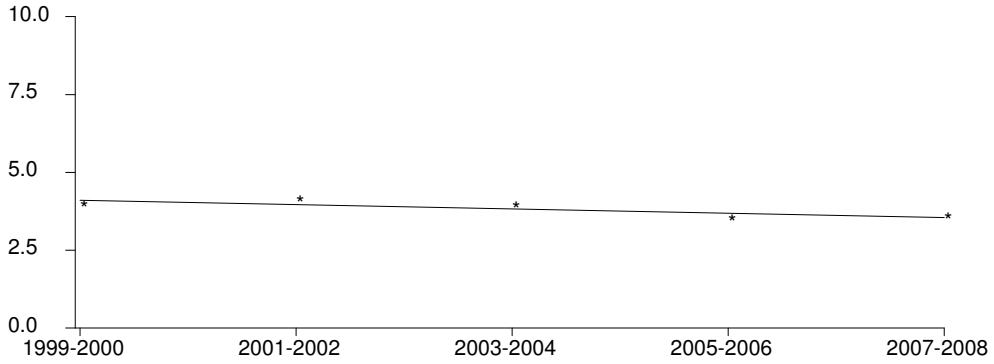
Anomaly Subgroup: **Upper limb reduction**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	4.281	(1 df)	Not significant
p value	0.039		
Slope	Decreasing		
Rate of change	-0.112	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	302	763393	3.96
2001 - 2002	319	771536	4.13
2003 - 2004	324	820463	3.95
2005 - 2006	319	906634	3.52
2007 - 2008	329	919991	3.58

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



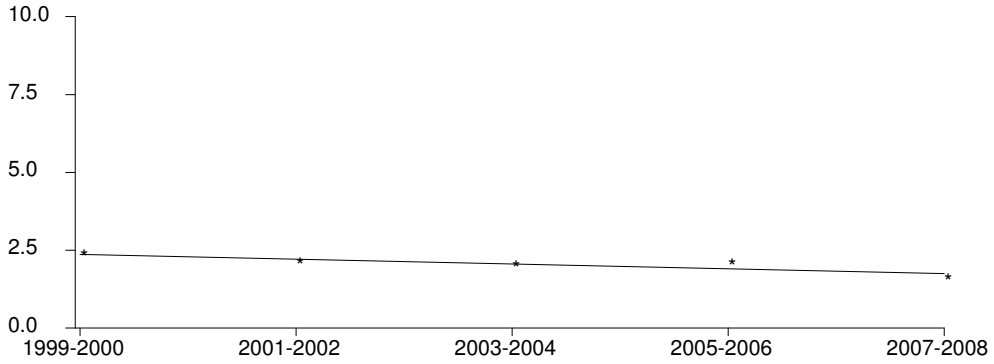
Anomaly Subgroup: **Lower limb reduction**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	9.837	(1 df)	Not significant
p value	0.002		
Slope	Decreasing		
Rate of change	-0.124	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	182	763393	2.38
2001 - 2002	166	771536	2.15
2003 - 2004	166	820463	2.02
2005 - 2006	192	906634	2.12
2007 - 2008	150	919991	1.63

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



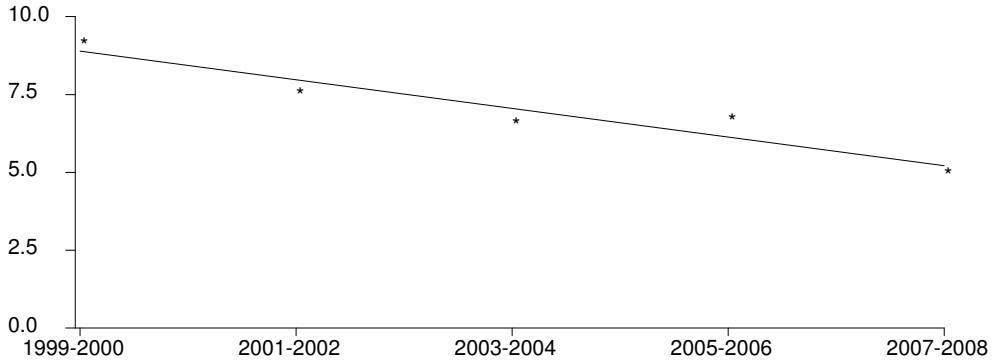
Anomaly Subgroup: **Hip dislocation and/or dysplasia**

Decreasing trend

Test for Trend			Test for non-linear change		
Chi2	100.600	(1 df)	Chi2	10.271	(3 df)
p value	<0.001		p value	0.016	
Slope	Decreasing				
Rate of change	-0.732	(Cases per 10,000 births per year)			

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	704	763393	9.22
2001 - 2002	586	771536	7.60
2003 - 2004	545	820463	6.64
2005 - 2006	613	906634	6.76
2007 - 2008	464	919991	5.04

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



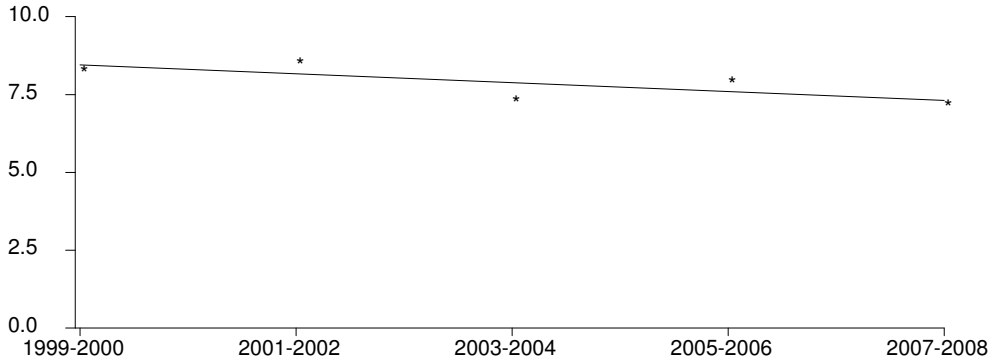
Anomaly Subgroup: **Polydactyly**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	8.556	(1 df)	Not significant
p value	0.003		
Slope	Decreasing		
Rate of change	-0.227	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	635	763393	8.32
2001 - 2002	661	771536	8.57
2003 - 2004	603	820463	7.35
2005 - 2006	722	906634	7.96
2007 - 2008	662	919991	7.20

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



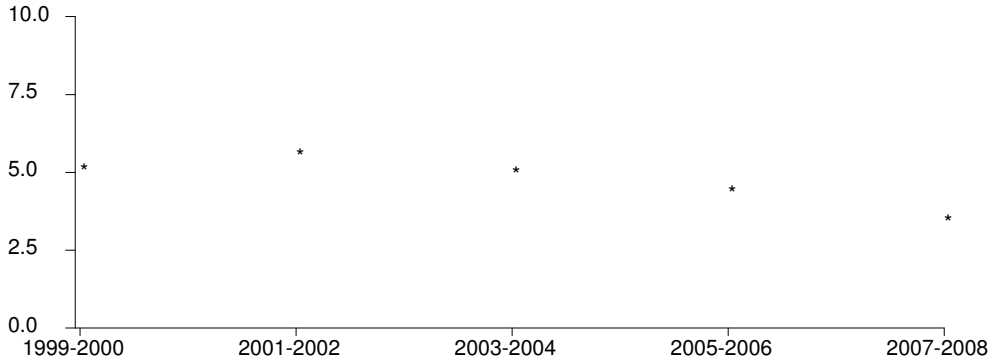
Anomaly Subgroup: **Syndactyly**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	37.290	(1 df)	Chi2	11.383	(3 df)
p value	<0.001		p value	0.010	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	394	763393	5.16
2001 - 2002	436	771536	5.65
2003 - 2004	415	820463	5.06
2005 - 2006	404	906634	4.46
2007 - 2008	324	919991	3.52

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



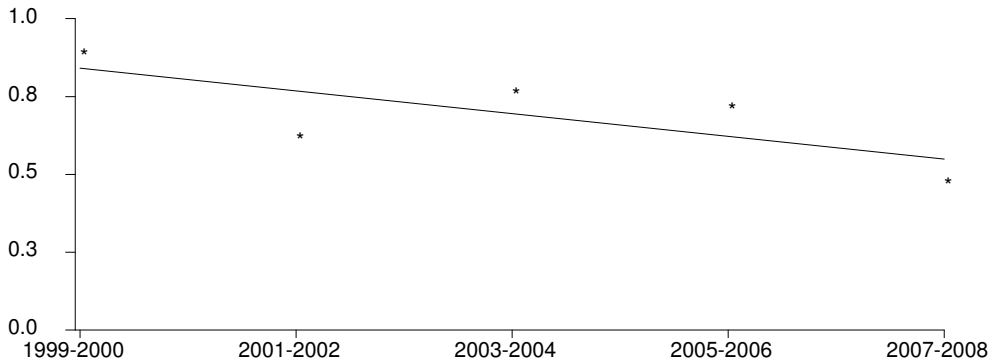
Anomaly Subgroup: **Arthrogryposis multiplex congenita**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	6.647	(1 df)	Not significant
p value	0.010		
Slope	Decreasing		
Rate of change	-0.059	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	68	763393	0.89
2001 - 2002	48	771536	0.62
2003 - 2004	63	820463	0.77
2005 - 2006	65	906634	0.72
2007 - 2008	44	919991	0.48

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



Anomaly Subgroup: **Musculo-skeletal**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	74.762	(1 df)	Chi2	24.551	(3 df)
p value	<0.001		p value	<0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	947	763393	12.41
2001 - 2002	711	771536	9.22
2003 - 2004	739	820463	9.01
2005 - 2006	788	906634	8.69
2007 - 2008	736	919991	8.00

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

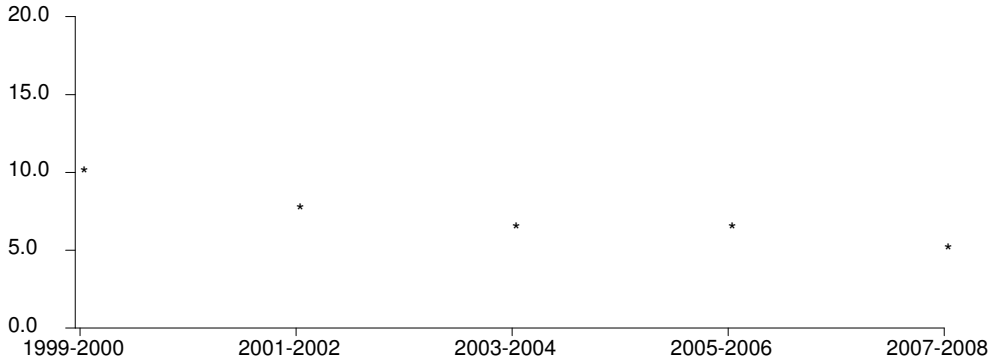
Anomaly Subgroup: **Other malformations**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	140.845	(1 df)	Chi2	16.784	(3 df)
p value	<0.001		p value	<0.001	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	771	763393	10.10
2001 - 2002	598	771536	7.75
2003 - 2004	534	820463	6.51
2005 - 2006	592	906634	6.53
2007 - 2008	476	919991	5.17

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



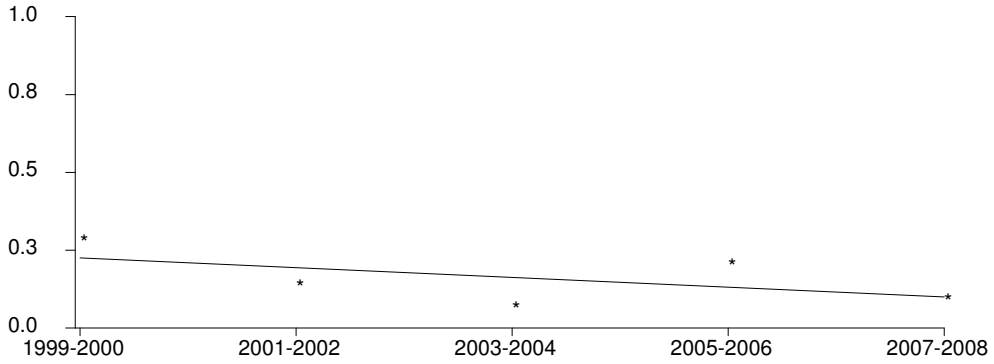
Anomaly Subgroup: **Asplenia**

Decreasing trend

Test for Trend			Test for non-linear change		
Chi2	4.733	(1 df)	Chi2	10.718	(3 df)
p value	0.030		p value	0.013	
Slope	Decreasing				
Rate of change	-0.024	(Cases per 10,000 births per year)			

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	22	763393	0.29
2001 - 2002	11	771536	0.14
2003 - 2004	6	820463	0.07
2005 - 2006	19	906634	0.21
2007 - 2008	9	919991	0.10

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



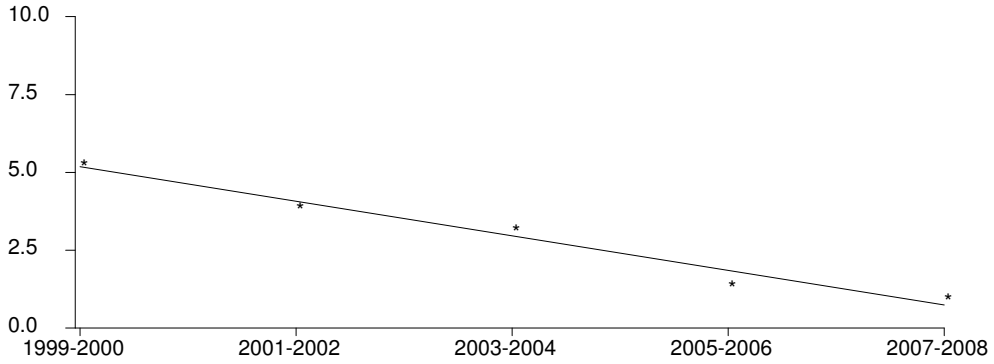
Anomaly Subgroup: **Disorders of skin**

Decreasing trend

Test for Trend			Test for non-linear change		
Chi2	361.502	(1 df)	Chi2	10.999	(3 df)
p value	<0.001		p value	0.012	
Slope	Decreasing				
Rate of change	-0.886	(Cases per 10,000 births per year)			

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	404	763393	5.29
2001 - 2002	301	771536	3.90
2003 - 2004	263	820463	3.21
2005 - 2006	128	906634	1.41
2007 - 2008	91	919991	0.99

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



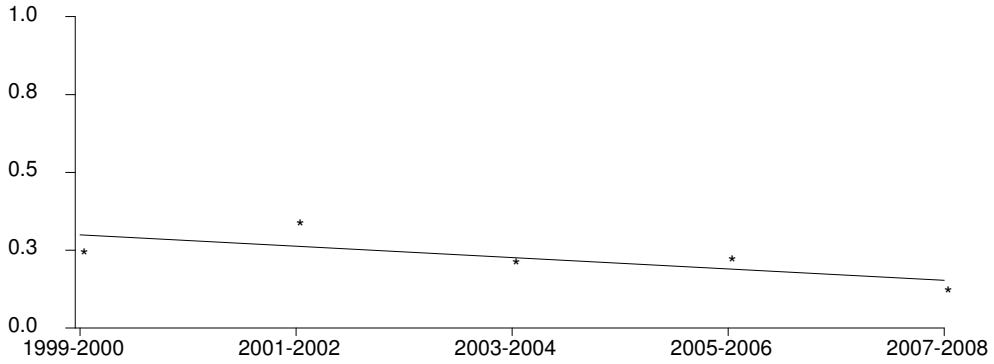
Anomaly Subgroup: **Fetal alcohol syndrome §**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	5.670	(1 df)	Not significant
p value	0.017		
Slope	Decreasing		
Rate of change	-0.036	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	8	328032	0.24
2001 - 2002	22	652206	0.34
2003 - 2004	17	806121	0.21
2005 - 2006	20	906634	0.22
2007 - 2008	11	919991	0.12

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



Anomaly Subgroup: **Valproate syndrome §**

Non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	8.010	(3 df)
	p value	0.046	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	7	328032	0.21
2001 - 2002	4	652206	0.06
2003 - 2004	3	806121	0.04
2005 - 2006	7	906634	0.08
2007 - 2008	5	919991	0.05

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

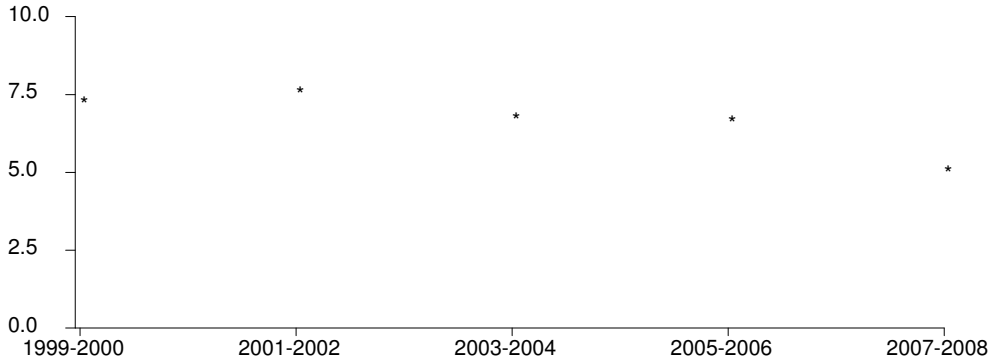
Anomaly Subgroup: **Genetic syndromes + microdeletions**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	38.259	(1 df)	Chi2	12.307	(3 df)
p value	<0.001		p value	0.006	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	559	763393	7.32
2001 - 2002	589	771536	7.63
2003 - 2004	558	820463	6.80
2005 - 2006	608	906634	6.71
2007 - 2008	468	919991	5.09

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



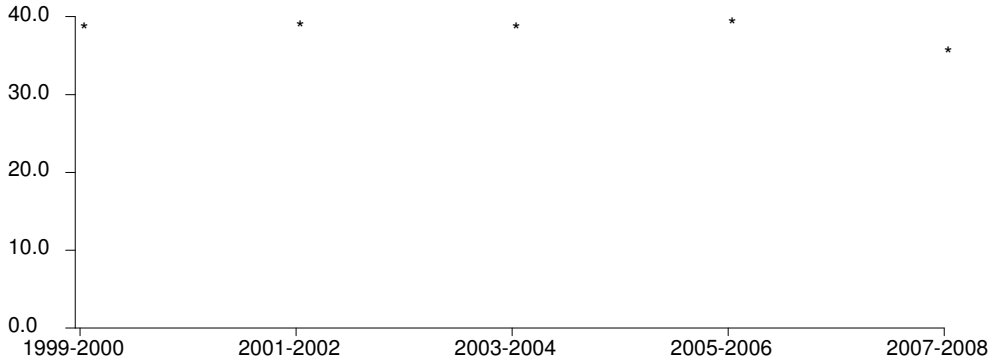
Anomaly Subgroup: **Chromosomal**

Non-linear change

Test for Trend			Test for non-linear change		
Chi2	8.251	(1 df)	Chi2	14.203	(3 df)
p value	0.004		p value	0.003	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	2960	763393	38.77
2001 - 2002	3012	771536	39.04
2003 - 2004	3179	820463	38.75
2005 - 2006	3579	906634	39.48
2007 - 2008	3278	919991	35.63

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



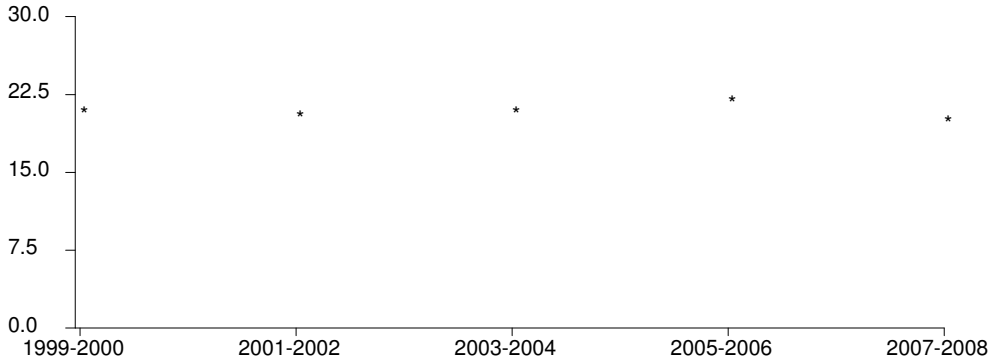
Anomaly Subgroup: **Down Syndrome**

Non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	8.586	(3 df)
	p value	0.035	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	1602	763393	20.99
2001 - 2002	1587	771536	20.57
2003 - 2004	1719	820463	20.95
2005 - 2006	1996	906634	22.02
2007 - 2008	1849	919991	20.10

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



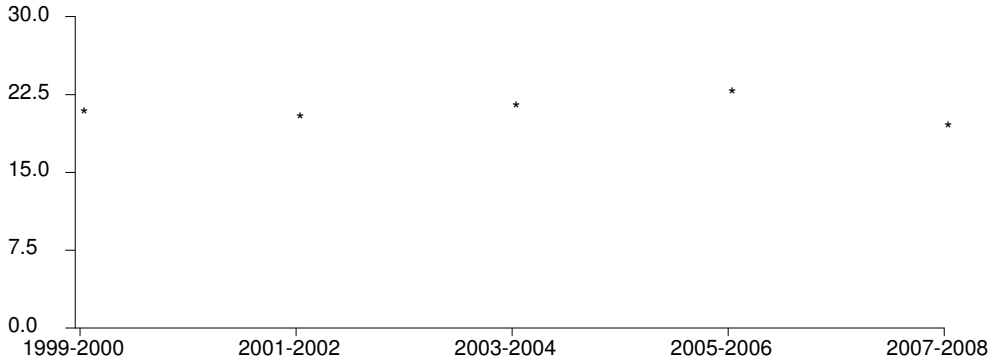
Anomaly Subgroup: **Down Syndrome Adjusted**

Non-linear change

Test for Trend	Test for non-linear change		
Not significant	Chi2	23.569	(3 df)
	p value	<0.001	

Year groups:	Adjusted cases:	Adjusted total births:	Adjusted rate (per 10,000 births):
1999 - 2000	1539	738473	20.84
2001 - 2002	1547	759434	20.37
2003 - 2004	1631	759977	21.46
2005 - 2006	1907	835967	22.81
2007 - 2008	1626	831265	19.56

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



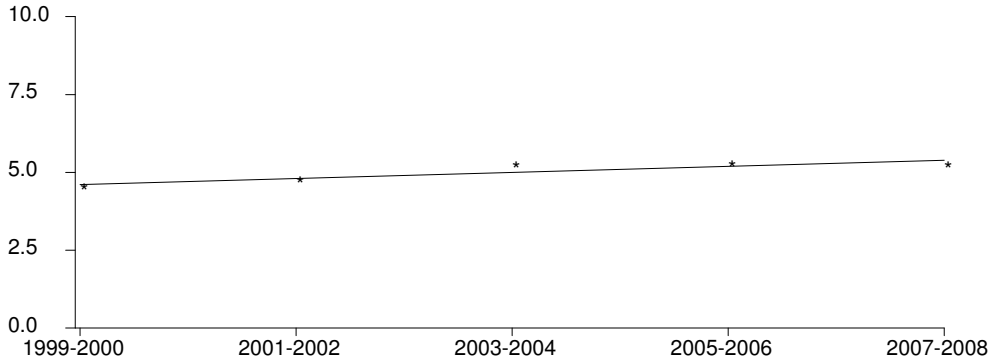
Anomaly Subgroup: **Edward syndrome/trisomy 18**

Increasing trend

Test for Trend			Test for non-linear change
Chi2	6.101	(1 df)	Not significant
p value	0.014		
Slope	Increasing		
Rate of change	0.153	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	345	763393	4.52
2001 - 2002	366	771536	4.74
2003 - 2004	429	820463	5.23
2005 - 2006	477	906634	5.26
2007 - 2008	482	919991	5.24

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



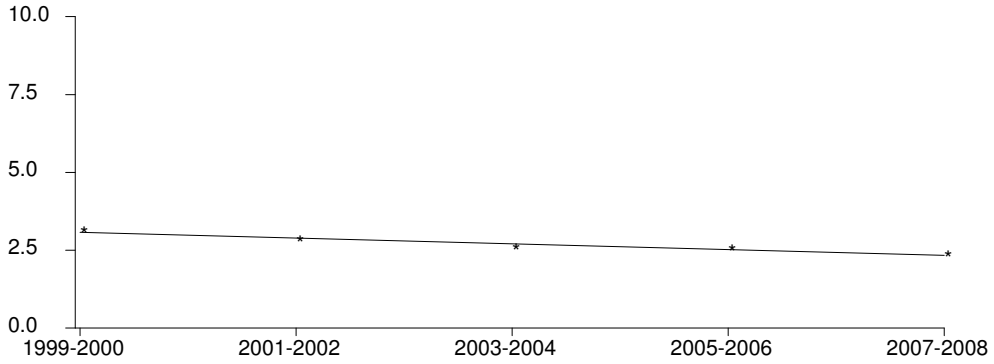
Anomaly Subgroup: **Turner's syndrome**

Decreasing trend

Test for Trend			Test for non-linear change
Chi2	10.342	(1 df)	Not significant
p value	0.001		
Slope	Decreasing		
Rate of change	-0.146	(Cases per 10,000 births per year)	

Year groups:	Cases:	Total births:	Rate (per 10,000 births):
1999 - 2000	240	763393	3.14
2001 - 2002	220	771536	2.85
2003 - 2004	214	820463	2.61
2005 - 2006	230	906634	2.54
2007 - 2008	219	919991	2.38

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
Neural Tube defects	France	Ile de la Reunion	14	27/09/2006	14/11/2006	3.12	0.019	101	0	Cluster	
Neural Tube defects	UK	Wales	5	15/12/2006	17/12/2006	0.25	0.048	193	0.5	Cluster	
Neural Tube defects~	Italy	Tuscany	5	06/10/2006	13/10/2006	0.3	0.039	78	2	Cluster	
Anencephalus and similaræ	Italy	Tuscany	5	05/07/2006	26/07/2006	0.3	0.009	22	9.1	Cluster	Non-linear change
Congenital cataract æ	Italy	Tuscany	7	04/02/2006	03/04/2006	0.93	0.022	25	8	Cluster	Non-linear change
Atrioventricular septal defect	Italy	Tuscany	5	30/08/2007	02/11/2007	0.58	0.039	14	0	Cluster	*
Tetralogy of Fallot	UK	Wessex	5	03/01/2007	15/01/2007	0.31	0.021	40	5	Cluster	
Tricuspid atresia and stenosis	Netherlands	N Netherlands	5	04/08/2007	16/09/2007	0.47	0.028	17	0	Cluster	
Aortic valve atresia/stenosis §æ	Ireland	Dublin	5	17/09/2006	27/02/2007	0.74	0.01	7	0	Cluster	*
Coarctation of aorta~	UK	E Mid & S York	5	29/04/2006	06/05/2006	0.28	0.03	74	0	Cluster	
Total anomalous pulm venous return	UK	Wales	5	25/12/2006	22/03/2007	0.62	0.028	11	0	Cluster	*
Choanal atresia æ	Belgium	Antwerp	6	14/08/2006	07/12/2006	0.82	0.012	11	9.1	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
Bilateral renal agenesis including Potter syndrome	Italy	Emilia Romagna	8	12/04/2006	17/04/2007	2.38	0.027	10	0	Cluster	*
Renal dysplasia	UK	E Mid & S York	18	04/10/2007	25/11/2007	4.79	0.018	143	0	Cluster	
Renal dysplasia	Italy	Emilia Romagna	7	16/08/2006	13/09/2006	0.78	0.02	43	4.7	Cluster	Non-linear change
Congenital hydronephrosis æ	Ireland	Dublin	22	04/07/2005	04/01/2007	10.26	0.012	29	0	Cluster	Non-linear change
Hypospadias	UK	E Mid & S York	7	03/01/2008	04/01/2008	0.31	<0.001	488	0	Cluster	Decreasing trend
Hypospadias æ	UK	Wessex	72	08/01/2005	12/05/2006	34.34	<0.001	109	1.8	Cluster	Non-linear change
Indeterminate sex æ	UK	Wales	9	18/06/2005	29/08/2006	3.1	0.038	11	9.1	Cluster	*
Limb reduction	France	Paris	7	27/04/2006	13/05/2006	0.72	0.026	70	0	Cluster	
Club foot - talipes equinovarus æ	UK	Wessex	11	29/12/2006	17/01/2007	1.95	0.042	159	0	Cluster	
Hip dislocation and/or dysplasia	Austria	Styria	20	23/02/2005	01/05/2006	8.35	0.014	30	6.7	Cluster	Non-linear change
Polydactyly	France	Paris	54	23/10/2004	15/04/2006	30.56	<0.001	88	0	Cluster	Decreasing trend
Asplenia	France	Paris	11	05/06/2005	02/09/2006	3.8	0.013	13	0	Cluster	*
Situs inversus	France	Ile de la Reunion	10	09/06/2006	07/09/2007	3.52	0.024	12	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
Maternal infections resulting in malformations	Ireland	Dublin	9	25/04/2005	21/04/2006	2.79	0.036	12	0	Cluster	*
Patau syndrome/trisomy 13	Austria	Styria	5	27/12/2007	19/03/2008	0.59	0.024	11	9.1	Cluster	*
Patau syndrome/trisomy 13~	Belgium	Hainaut	8	05/07/2007	21/02/2008	1.64	0.013	13	0	Cluster	*
Patau syndrome/trisomy 13	Netherlands	N Netherlands	9	25/11/2006	24/07/2007	2.33	0.029	15	0	Cluster	*
Klinefelters syndrome	France	Paris	6	14/04/2006	26/07/2006	0.93	0.038	14	0	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
- ~ Cluster detected by Date of Birth
- æ Clusters identified in the Statistical Monitoring Report 2007

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.