eurocat
european surveillance of congenital anomalies

EUROCAT Statistical Monitoring Report – 2009

(Uploaded to EUROCAT website January 2012)

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EUROCAT Joint Action 2011-2013 is funded by the Public Health Programme 2008-2013 of the European Commission

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Acknowledgements

This report was compiled by Nichola McCullough, Maria Loane, Ruth Greenlees and Helen Dolk. Statistical methods were designed by Alan Kelly, Conor Teljeur and Joan Morris. Statistical software was created by BioMedical Computing Ltd (James Densem). Reports of registry investigations were provided by: Antwerp (Vera Nelen), Hainaut (Christine Verellen Dumoulin), Zagreb (Ingeborg Barisic), Odense (Ester Garne), Ile de la Reunion (Hanitra Randrianaivo) , Paris (Babak Khoshnood), Saxony-Anhalt (Anke Rißmann), South East Ireland (Carmel Mullaney), Emilia Romagna (Elisa Calzolari), Tuscany (Fabrizio Bianchi), Malta (Miriam Gatt), Northern Netherlands (Marian Bakker), Wielkopolska, (Ana Latos-Bielenska) Basque Country (Larraitz Arriola), Vaud (Marie-Claude Addor), Ukraine (Wladimir Wertilecki), East Midlands and South Yorkshire (Elizabeth Draper), Northern England (Judith Rankin), Thames Valley (Patricia Boyd), Wales (David Tucker) and Wessex (Diana Wellesley).

EUROCAT 2009 Statistical Monitoring of Congenital Anomalies: Key Findings

Reducing the occurrence of congenital anomalies, a leading cause of fetal death, infant mortality and morbidity in childhood, has been identified as one of the key objectives of the WHO Millennium Development Goal 4. Essential to the success of this objective are surveillance systems that systematically monitor epidemiologic data on the rates of birth defects over time.

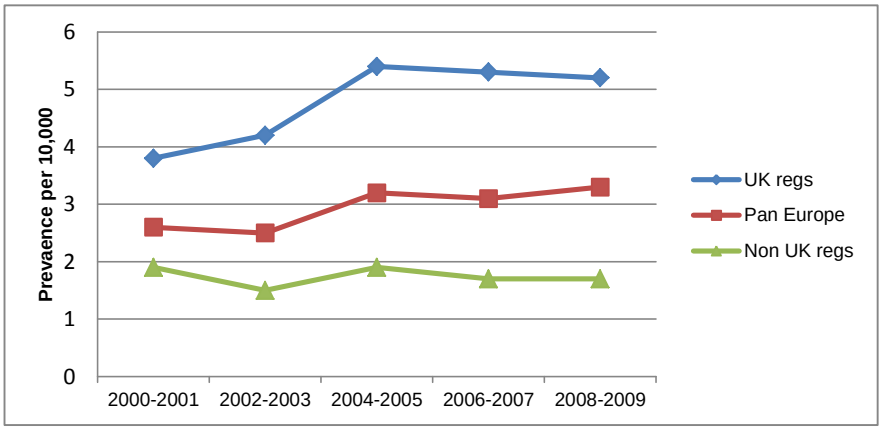
Each year EUROCAT, the European network of population-based registries for the epidemiologic surveillance of congenital anomalies, performs statistical monitoring for both trends and clusters in time in order to detect signals of new or increasing teratogenic exposures and monitor progress in the prevention of congenital anomalies. We monitor total prevalence rates of congenital anomalies, that is, rates which include cases in livebirths, stillbirths, and terminations of pregnancy for fetal anomaly. Before interpreting any increase or decline in total prevalence as a true increase or decline in risk potential diagnostic changes must be considered. In this report 22 EUROCAT regions are included. These regions can find their full results in the main report. Our key findings concentrate on the pan-European analysis, which gives a snapshot of the situation in Europe.

Key findings

Increasing trends

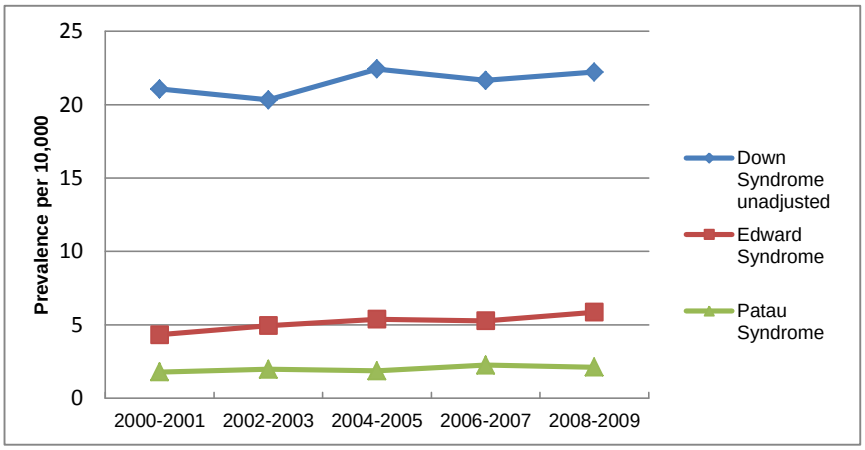
- There has been an increase in the prevalence of **Gastroschisis** by 29%, from 2.56 per 10,000 births in 2000-2001 to 3.30 in 2008-2009.The UK had a higher rate than other countries, increasing in the early part of the decade, and has remained consistently high. Gastroschisis is a rare abdominal defect requiring corrective surgery, associated with factors such as young maternal age, low maternal BMI, maternal smoking and low socioeconomic status.

Prevalence of gastroschisis in pan-Europe analysis



- The prevalence of the three main types of chromosomal trisomy syndromes increased at pan-European level. The prevalence of **Down syndrome/trisomy 21** increased by 5% from 21.07 in 2000-2001 to 22.22 in 2008-2009. Significant increasing trends were also found for **Edward syndrome/trisomy 18**, which increased by 36% from 4.32 per 10,000 in 2000-2001 to 5.86 in 2008-2009 and **Patau syndrome/trisomy 13** which increased by 18% from 1.79 per 10,000 to 2.11 per 10,000 in 2008-2009. Following adjustment for maternal age no increasing trend was found for Down syndrome suggesting that the trend found for this syndrome is associated with increases in the proportion of older mothers. Currently EUROCAT does not adjust for maternal age for Edward and Patau syndrome. In addition to increases in maternal age explanations for increasing trends in these two syndromes could be improvements in prenatal diagnosis.

Prevalence of chromosomal trisomy syndromes in pan-Europe analysis

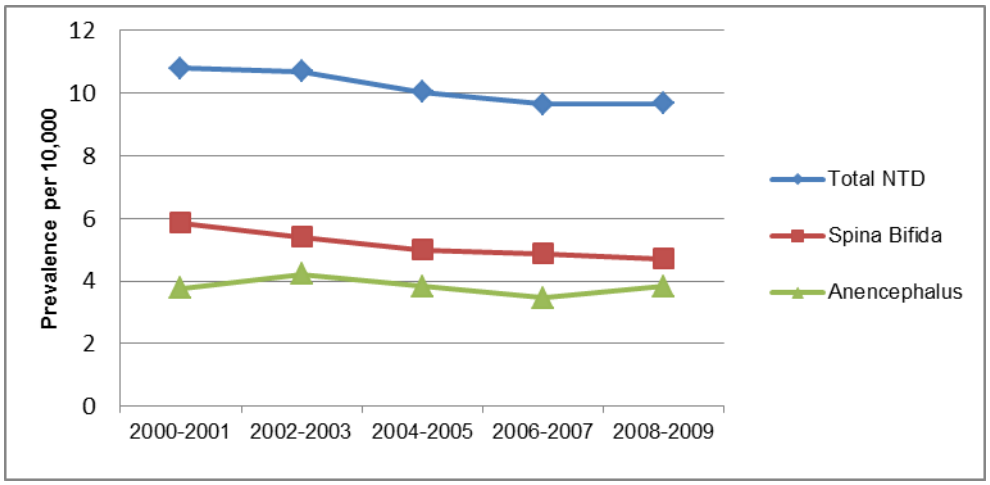


Decreasing trends

Overall, there was a decline in the prevalence of all non-chromosomal anomalies at pan-European level, which included decreasing trends in a range of major anomalies such as neural tube defects and congenital heart defects.

- At pan-European level the prevalence of **neural tube defects** declined by 10% from 10.80 cases per 10,000 in 2000-2001 to 9.67 in 2008-2009. Occurrences of cases with **spina bifida** declined by 19% from 5.86 per 10,000 in 2000-2001 to 4.72 in 2008-2009. There was no significant change in the prevalence of **anencephalus** from 2000-2009. The decreasing trends in neural tube defects and spina bifida suggests that measures to reduce the occurrence of this anomaly, particularly folic acid supplementation and voluntary food fortification, are beginning to have some success. However this decline is relatively small compared to what could be potentially achieved by raising periconceptual folate status for a greater proportion of women.

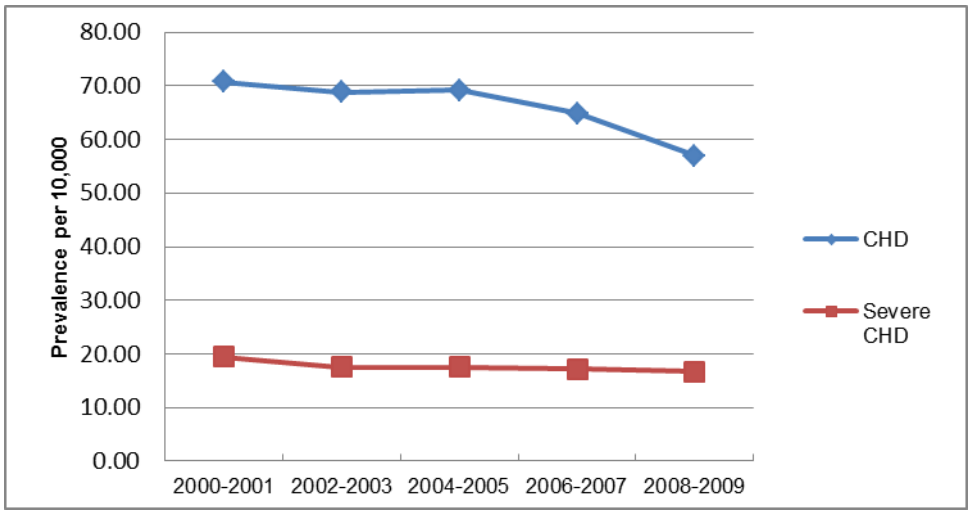
Prevalence of Neural Tube defects in pan-Europe analysis



- Congenital heart defects (CHD) are the most common congenital anomalies, accounting for a third of congenital anomaly cases, and a decline in prevalence is found in the latter part of the decade. The prevalence of **severe CHD** decreased by 14% from 19.49 per 10,000 in 2000-2001 to 16.71 in 2008-2009. Decreasing trends were also observed for specific types of severe CHD as well as ventricular septal

defect and pulmonary valve stenosis. There is growing evidence to suggest that folic acid supplementation may be effective in reducing the risk of CHD. There may also be other explanations such as the improved management of known risk factors such as maternal chronic health conditions e.g. diabetes, and the reduction of health risk behaviours e.g. smoking.

Prevalence of congenital heart defects in pan-Europe analysis



Clusters

Cluster analysis did not identify clusters in 2008-9 thought to be of immediate concern.

Conclusions

The EUROCAT network, now a Joint Action between the European Union and Member States, provides essential surveillance information on congenital anomalies in Europe. The high and increasing prevalence of gastroschisis in the UK continues to need attention. The trend towards delayed childbirth in Europe continues to bring with it an increase in the prevalence of Down syndrome and other trisomy syndromes. However we are pleased to report a decline in prevalence of some major anomalies in the last decade, though much work in primary prevention of congenital anomalies remains to be done. Primary prevention of congenital anomalies should be added to National Plans for Rare Diseases currently under development, to make sure that the entire European population has access to appropriate preventive services and policies.

2. Introduction

2.1 Overview of Annual Statistical Monitoring

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-2009.pdf).

We report here the results up to birth year 2009. 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.

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 2011 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.

2.2 Taskforce for the Evaluation of Clusters

EUROCAT defines clusters as 'An aggregation of cases of congenital anomaly in time and/or space which appears to be unusual' (EUROCAT Working Group on the Management of Clusters and Environmental Exposure Incidents, 2003). Each year the statistical monitoring carried out by EUROCAT detects a number of clusters. Registries are asked to investigate and provide preliminary reports on all new clusters identified in their registry during the period of monitoring. In recognising that the investigation and timely response to clusters may present particular challenges a new committee has been formed under Work Package 6 of the EUROCAT Joint Action (WP6: Investigation of Trends, Clusters and New Exposures). The Taskforce for Evaluation of Clusters (TEC) is a permanent committee,

reporting to the EUROCAT Project Management Committee and has the following remit:

- To comment on the output of cluster investigations conducted by EUROCAT, including its presentation and possible uses, at the request of the PMC.
- To serve as a consulting unit in cases of clusters, commissioned by EUROCAT or individual member registries.

It is envisaged that the TEC will liaise with both the individual registries and where required other local health authorities in order to assess the cluster and advise on ad hoc studies aimed at clarification of a cluster. Details of the work of the TEC and any associated investigations will be reported in future reports.

3. Population and Monitoring Process

3.1 Registers included in the trend analysis

At the time of statistical monitoring in Spring 2011, there were 30 full member registries in EUROCAT. Twenty-two full member registries met the required inclusion criteria for the ten year trend analysis (see Box 1) and were included in the pan-Europe and individual registry monitoring 2000-2009. Ukraine, South West England, Cork and Kerry, Strasbourg, Norway and Barcelona were excluded as they did not meet the inclusion criteria for the time period coverage. Mainz and South Portugal were excluded due to data issues and reduction in ascertainment numbers respectively.

Box 1 Registry inclusion criteria for trend analysis

- 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 9 years of data to be included in the pan-Europe analysis (only 8 years are required for individual registry analysis)
- Time period is 2000-2009

3.2 Registers included in the cluster analysis

Registries classified as “early response” i.e. registries that met the EUROCAT data transmission deadline of February 15th 2011, with a complete dataset for the most recent 5 years (2005-2009) are included in cluster detection (see Box 2). 21 full member registries had transmitted year 2009 data to EUROCAT Central Registry by Feb 15 2011. Five of the 21 registries were excluded from the analysis for clusters for the following reasons: Zagreb – population fluctuation; Saxony-Anhalt – not full date of birth information; and Mainz, Emilia Romagna and South Portugal did not submit complete 2009 data.

Box 2 Registry inclusion criteria for cluster analysis

- Only registries that transmitted complete year 2009 data with full date of birth information are included in the cluster monitoring 2005-2009
- 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%)

Where registries do not meet the data transmission deadline monitoring can be run locally to detect clusters and trends using software which is available in the EDMP (EUROCAT Data Management Program). Pan-Europe monitoring can only be conducted centrally as it uses data from all the registries combined.

3.3 What was monitored?

Data from each of the EUROCAT registries was transmitted to central registry in February 2011. Cases include livebirths and stillbirths with congenital anomalies and terminations of pregnancy for fetal anomaly following prenatal diagnosis of anomalies. For ten year trends 96 standard EUROCAT congenital anomaly subgroups are monitored (see Appendix A). Cluster analysis, (which detects clusters or deficits occurring in the last 2 years (2008-2009), and that are less than 18 months in length) is run on 76 EUROCAT subgroups of congenital anomalies. Seventeen major heterogeneous subgroups and a further three subgroups of monogenic origin are excluded (see Appendix A for subgroup inclusion list and Appendix B for summary of statistical methods).

The following analyses were carried out:

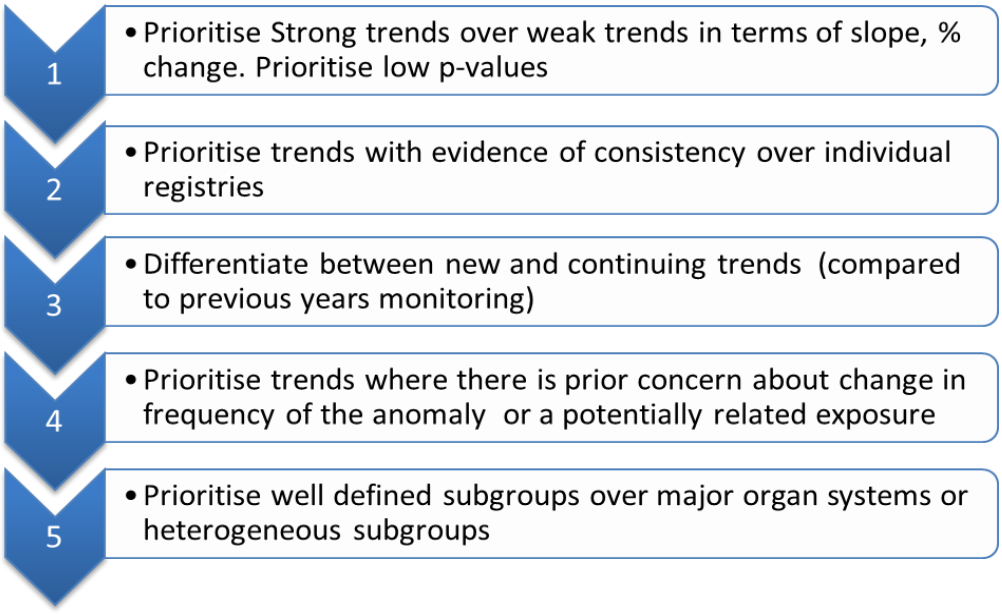
- Analysis of pan-European trends including 22 registries covering 4.5 million births (2000-2009)
- Analysis of individual registry trends for 22 local registries covering 4.5 million births (2000-2009)
- Cluster analysis to detect unusual aggregations of cases in 16 registries covering 0.8 Million births (2005-2009)

3.4 Investigation process

The results of the statistical monitoring were, in the first instance, presented to the Project Management Committee (PMC) in early April 2011. The PMC reviewed the findings for both the ten year trend and cluster analysis. Using a predefined protocol (see Figure1) they identified and prioritised a number of significant ten year trends for preliminary investigation by the individual registries.

A number of statistically significant trends for certain anomalies were not prioritised for investigation. For example lower limb reduction was not investigated as it was not highly statistically significant (p=0.036). Syndactyly was not investigated as it was considered to be too poorly defined in relation to major and minor forms due to ICD10 coding. Hydronephrosis was not investigated as members of the PMC considered that the inclusion criteria for diagnosis of this condition needed to be stricter. Trends that were not prioritised for investigation will not be discussed in this report but will be subject to further monitoring.

Figure 1: Prioritisation criteria for the investigation of ten year trends



Reference: Loane M, Dolk H, Kelly A, Teljeur, C, Greenlees, R, Densem, J and a EUROCAT Working Group, (2011). *Paper 4: EUROCAT Statistical Monitoring: Identification and investigation of ten year trends of congenital anomalies in Europe*. Birth Defects Research (Part A), 91. pp. S31-S43.

The results of the ten year trends and cluster analysis were communicated to the registries. Each registry was asked to conduct preliminary investigations of the following outcomes using standardised guidelines (EUROCAT Statistical Monitoring Protocol http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2009.pdf)

- All significant increasing trends found in their registry
- All significant decreasing trends found in their registry **if** the trends were also found in the pan-Europe analysis
- Registries were also given the option to investigate and report on decreasing trends unique to their registry, if they thought these were of interest to other parties.

Registries reported their findings to Central Registry using standard reporting templates (see EUROCAT Statistical Monitoring Protocol). Registries were asked to provide specific details that included the methods used, results of the investigation and the public health authorities that were to be notified if necessary (see Appendix C for a summary).

Preliminary reports for the ten year trends were received from 20 of the 22 registries. Styria and Antwerp did not send reports. Preliminary reports for cluster investigations were received from all registries found to have newly detected clusters in this year's monitoring (see Table 2 and Appendix G). Twelve registries stated that they would be notifying the results and the findings of their preliminary investigations to public health authorities.

The Reports were discussed at the Registry Leaders Meeting in June 2011, followed by written reports submitted to central registry. Full details of the registry investigations are in a separate Annex in the membership-only section of the EUROCAT website.

3.5 Statistical software updates from previous report

A graph summarising the overall pan-Europe results, both significant and non-significant, is now included (see Figure 3).Trends are plotted (together with their 95% confidence intervals in order to judge statistical significance) if the anomalies have 5 monotonic points i.e. the trend is going in one direction or the P-value for non-linear change is not significant (i.e. P > 0.01).

4. Trends

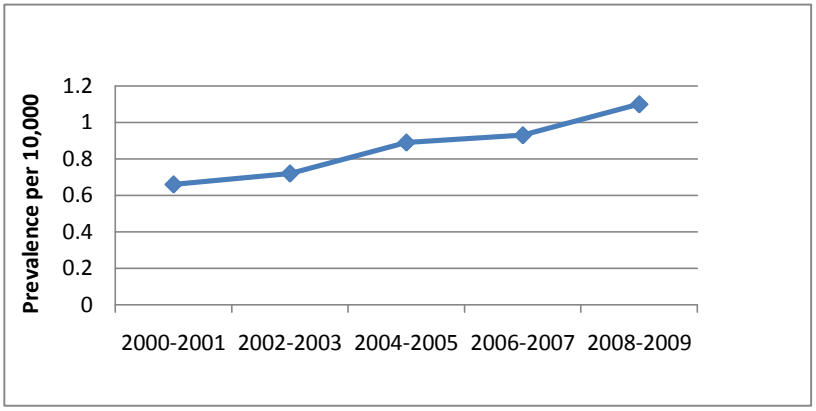
4.1 Overview

Overall there was a decline in the prevalence of all non-chromosomal anomalies at pan-European level. The analysis identified increasing trends for six subgroups of anomalies, decreasing trends for 30 subgroups and non-linear change for 14 subgroups (see Figure 8 and Appendix D). A number of the trends had previously been identified in the 2008 report (see appendix D for details). For ten year trends in individual registries a total of 1302 chi squared tests were performed with 31% being statistically significant compared with the 5% expected by chance. The analysis identified a total of 83 increasing trends, 162 decreasing trends and 154 non-linear changes (see Table 1). This section provides details of the results investigation and interpretation of specific anomaly subgroups that were prioritised for further investigation by the PMC (see section 3.3)

4.2 Increasing trends

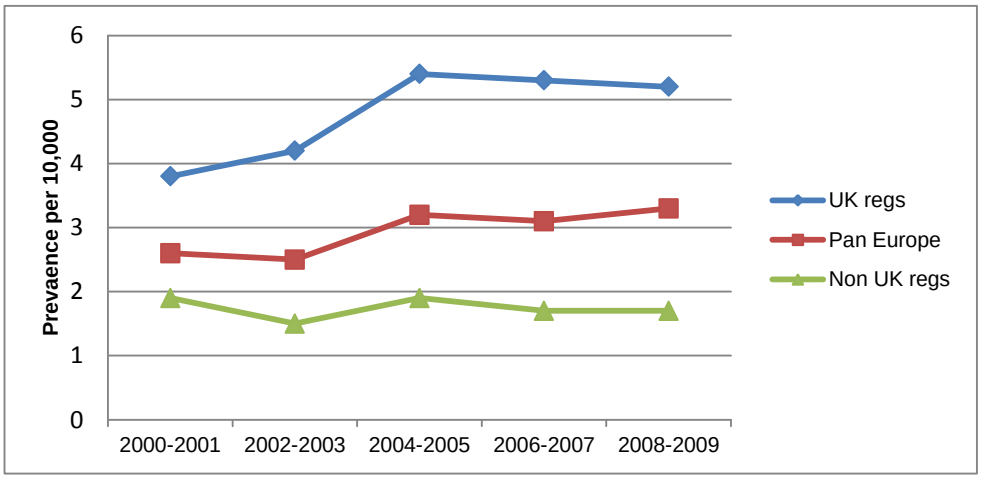
Cystic adenomatous malformation of the lung (CCAM) is a rare condition in which a benign mass of abnormal lung tissue is present on a section of the lung. In the pan-Europe analysis this anomaly increased in prevalence from 0.66 per 10,000 in 2000-2001 to 1.10 in 2008-2009, a 10% increase per year (see Figures 2 & 8). A statistically significant increasing trend was detected in two UK registries, Wessex and Wales, though notably 8 registries did not have enough data for individual registry analysis, with a further 9 registries also excluded from the individual analysis as they had not used the ICD10 coding for the whole period 2000-2009 (see Table 1). Almost all cases were diagnosed prenatally. Following preliminary investigation the Wessex registry suggested that improved ultrasound scanning technology may account for the increase however, the prevalence of CCAM has varied widely year by year over this period and further surveillance is required. Wales confirmed that the prevalence of cases was increasing and that further surveillance was to be undertaken before any further investigation (Appendix E1). Currently, the causes of this anomaly are not well understood.

Figure 2: Prevalence of Cystic adenomatous malformation of the lung in pan-Europe analysis



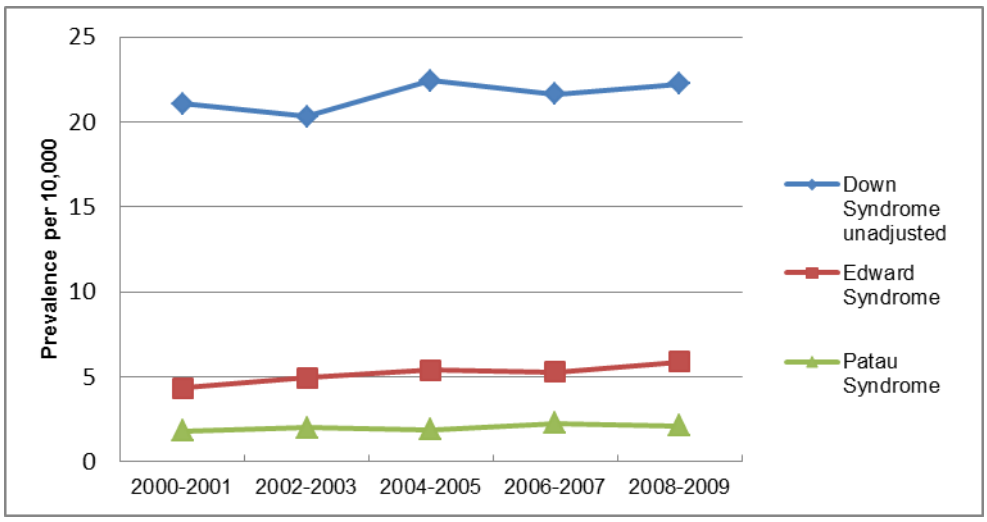
The abdominal wall defect **gastroschisis** is characterised by a hole in the abdomen through which some of the intestine then protrudes. Requiring corrective surgery, it is associated with factors such as young maternal age, maternal smoking, low maternal BMI and socioeconomic status. Pan-Europe analysis revealed that the prevalence of this anomaly has risen by 4% per year from 2.56 per 10,000 in 2000-2001 to 3.30 in 2008-2009. The increase in the proportion of cases was mainly in the UK in the early part of the decade (see Figures 3 & 8) and has remained consistently high since. In individual registries statistically significant increasing trends were found in one UK registry, Northern England and also in the Ile de la Reunion registry (see Table1). Following preliminary investigations the Ile de la Reunion registry confirmed there had not been an increase in the proportion of younger mothers giving birth in the registry area. They reported that they would continue with surveillance before conducting a more detailed investigation (see Appendix E1). A UK study is currently investigating environmental, dietary and lifestyle exposures during early pregnancy (first 12 weeks of gestation) as possible causes for this defect.

Figure 3: Prevalence of gastroschisis in pan-Europe analysis



Trisomy syndromes are genetic disorders that occur due to the addition of all or part of a specific chromosome. Pan-Europe analysis detected increasing trends for three trisomy syndromes (see Figures 4 & 8). **Down syndrome/trisomy 21**, which occurs due to the addition of all or part of an extra 21st chromosome, increased by 1 % per year from 21.07 per 10,000 in 2000-2001 to 22.22 in 2008-2009. The main risk factor for this anomaly is older maternal age. Average maternal age has been increasing across Europe. Following statistical adjustment for maternal age an increasing trend was no longer observed (see Figure 3). In individual registries statistically significant increasing trends were also observed in Paris, Tuscany and Vaud (see Table 1). Paris and Vaud reported an increase in the proportion of older mothers in their registry. Vaud also reported that they considered improvements in prenatal screening techniques as a possible explanation (see Appendix E1). Tuscany plan to conduct further surveillance, and note that their ascertainment of Down syndrome had been incomplete according to EUROCAT Data Quality Indicators (http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators)

Figure 4: Prevalence of trisomy syndromes in pan-Europe analysis



Patau syndrome, which occurs due to the addition of an extra 13th chromosome, increased by 2% per year from 1.79 per 10,000 in 2000-2001 to 2.11 in 2008-2009. This is a rare chromosomal anomaly in comparison to Down syndrome, and no increasing trends were detected in individual registries. **Edward syndrome/trisomy 18**, which occurs due to the addition of all or part of an extra 18th chromosome, increased by 3% per year from 4.32 per 10,000 in 2000-2001 to 5.86 in 2008-2009. Statistically significant increasing trends were also observed in four individual registries, Paris, Tuscany, Northern Netherlands and Vaud. Both the Paris and Vaud registries provided explanations similar to that given for the increase in Down syndrome. Northern Netherlands reported that changes in diagnostic methods could explain the increasing trend in their registry (see Appendix E1). Currently, EUROCAT does not adjust for maternal age for the analysis of trends in Edward and Patau syndrome, though this is being developed. Additional explanations for increasing trends in these two syndromes could be improvements in prenatal/postnatal diagnostics. A EUROCAT study investigating time trends of the 3 major trisomies in relation to maternal age and prenatal screening is currently nearing completion.

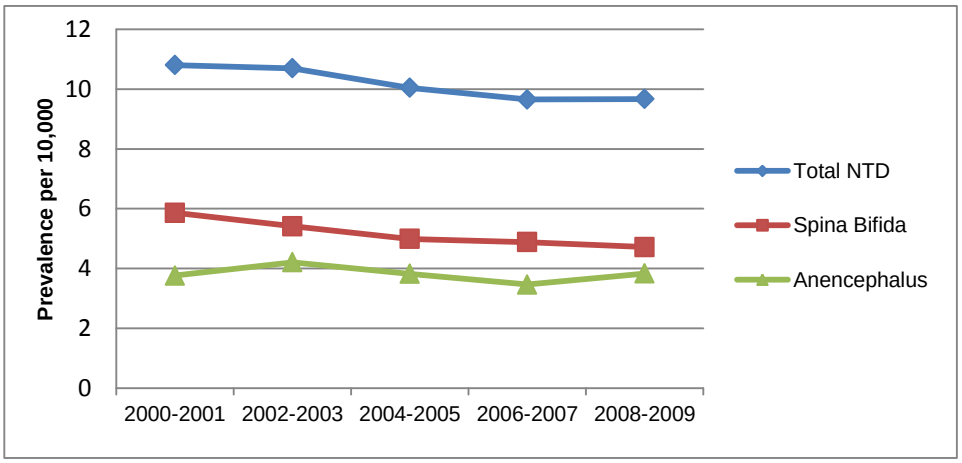
Apart from the increasing trends in congenital anomaly subgroups that are significant at pan-Europe level and are presented above, some additional statistically significant increasing trends in other congenital anomaly were found in individual registries (see Table 1) which were confirmed as requiring further monitoring or investigation (see Appendix E1).

Zagreb reported that they are investigating an increasing trend in cleft palate. Ile de la Reunion reported that they are currently monitoring increasing trends for atrial septal defect and hypospadias. Paris reported that they are currently monitoring increasing trends for hydrocephaly, choanal atresia, bladder exstrophy and/or epispadia and also hip dislocation and/or dysplasia. Saxony-Anhalt reported that they are investigating an increasing trend for ano-rectal atresia. Wales reported that they are currently monitoring an increasing trend for cleft lip with or without palate.

4.3 Decreasing trends

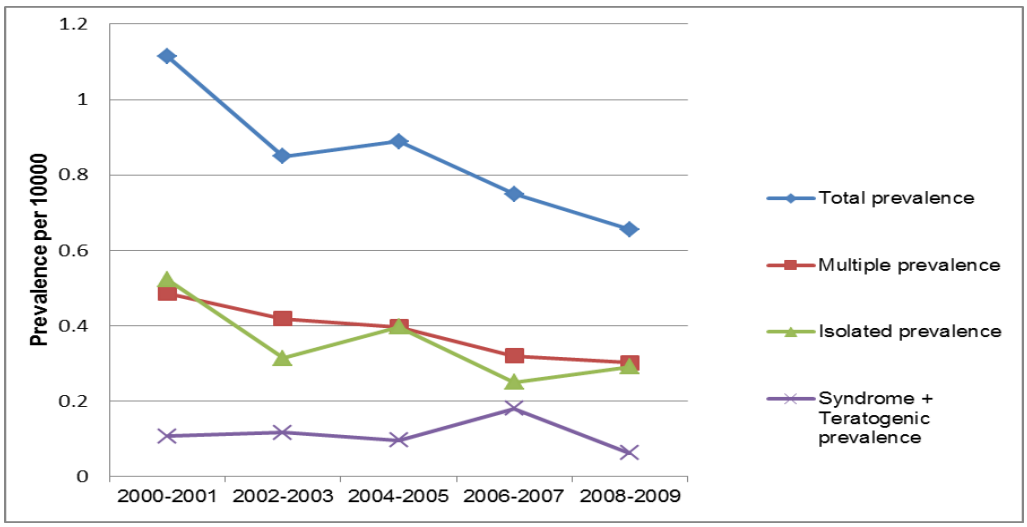
Neural Tube Defects (NTD) occur as a consequence of the neural tube failing to close completely in the very early stages of development. Pan-Europe analysis showed that the prevalence of this anomaly declined from 10.80 per 10,000 in 2000-2001 to 9.67 in 2008-2009, a decrease of 1.6% per year (see Figures 5 & 8) A specific type of neural tube defects is **spina bifida** which declined in prevalence from 5.86 per 10,000 in 2000-2001 to 4.72 in 2008-2009 (2.7%). The significant decrease in spina bifida was observed in four individual registries, Odense, Dublin, Emilia Romagna and Wales (see Table 1). Preliminary investigations by Odense and Wales confirmed that the prevalence of cases with spina bifida was decreasing in their registries. Dublin reported that the decrease observed in their registry was likely to be a consequence of changes in case ascertainment (see Appendix E2). There was no significant change in the prevalence of **Anencephalus**, also a specific type of neural tube defect. The decreasing trends in NTD and spina bifida suggest that measures to reduce the occurrence of this anomaly, particularly folic acid supplementation and voluntary food fortification, are beginning to have some success. However this decline is relatively small compared to what could be potentially achieved by raising folate status for a greater proportion of women periconceptionally. The EUROCAT Special Report (http://www.eurocat-network.eu/preventionandriskfactors/folicacid/folicacidspecialreports) reviews policy on periconceptional folic acid supplementation in EUROCAT countries and the proportion of women who take it periconceptionally. As part of the Joint Action (2011-2013) a more detailed investigation of the decreasing trends in neural tube defects is being conducted.

Figure 5: Prevalence of Neural Tube Defects in pan-Europe analysis



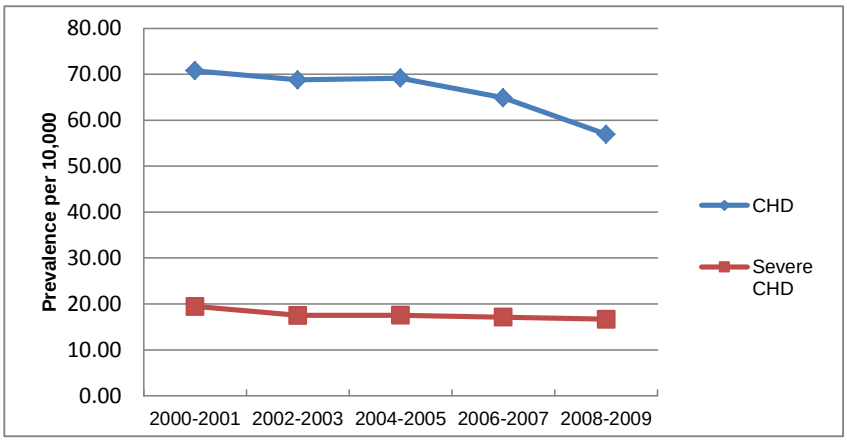
Anophthalmos/microphthalmos is a rare condition in which the normal development of the eye is disrupted. Anophthalmos is the complete absence of the tissue which forms the eye, whereas microphthalmos is characterised by the eye being abnormally small (one or both). The pan-Europe analysis showed that the prevalence of this anomaly reduced by 5% per year from 1.11 per 10,000 in 2000-2001 to 0.69 in 2008-2009 (see Figures 6 & 8). The majority of cases were categorised as microphthalmos. Decreasing trends were also observed in 3 individual registries, Paris, Wielkopolska and East Midlands and South Yorkshire (see Table1). Preliminary investigations by these registries indicated that the decreasing trend was a consequence of either changes in case ascertainment or changes in local or central registry methods such as definition or inclusion criteria (see Appendix E2).

Figure 6: Prevalence of Anophthalmos/Microphthalmos by multiple, isolated and syndrome/teratogenic classifications



Congenital heart defects (CHD) are the most common subgroup of congenital anomaly. Known risk factors for CHD include maternal chronic health conditions and maternal health risk behaviours. The pan-Europe analysis showed that the prevalence of **severe CHD** decreased by 2% per year from 19.49 per 10,000 in 2000-2001 to 16.71 in 2008-2009 (see Figures 7 & 8). Decreasing trends in severe CHD were identified in two individual registries, Paris and Wielkopolska (see Table 1). The preliminary investigation by Paris confirmed that the prevalence of cases with severe CHD was declining, and that they planned to carry out further surveillance before conducting a more detailed investigation. Wielkopolska reported that initially they considered the decline in their registry to be a consequence of changes in case ascertainment, however they would continue to monitor the trend (see Appendix E2). Some decreasing trends in specific types of severe CHD in individual registries were also reported and confirmed: coarctation of aorta in Hainaut, and atrioventricular septal defect in Northern England (see Table 1). There is growing evidence to suggest that folic acid supplementation may be effective in reducing the risk of CHD, but improved management of known maternal risk factors may also have a significant impact. It is also possible that less severe types of CHD are not yet reported in the most recent data as CHD may be diagnosed late in infancy. A EUROCAT paper describing trends in CHD has been submitted for publication.

Figure 7: Prevalence of congenital heart defects in pan-Europe analysis



Additional decreasing trends found in the pan-Europe analysis include **Atresia of bile ducts** a condition which is characterised by the congenital absence of the lumen of the extrahepatic bile ducts (see Figure 8). This rare anomaly decreased in prevalence by 10%

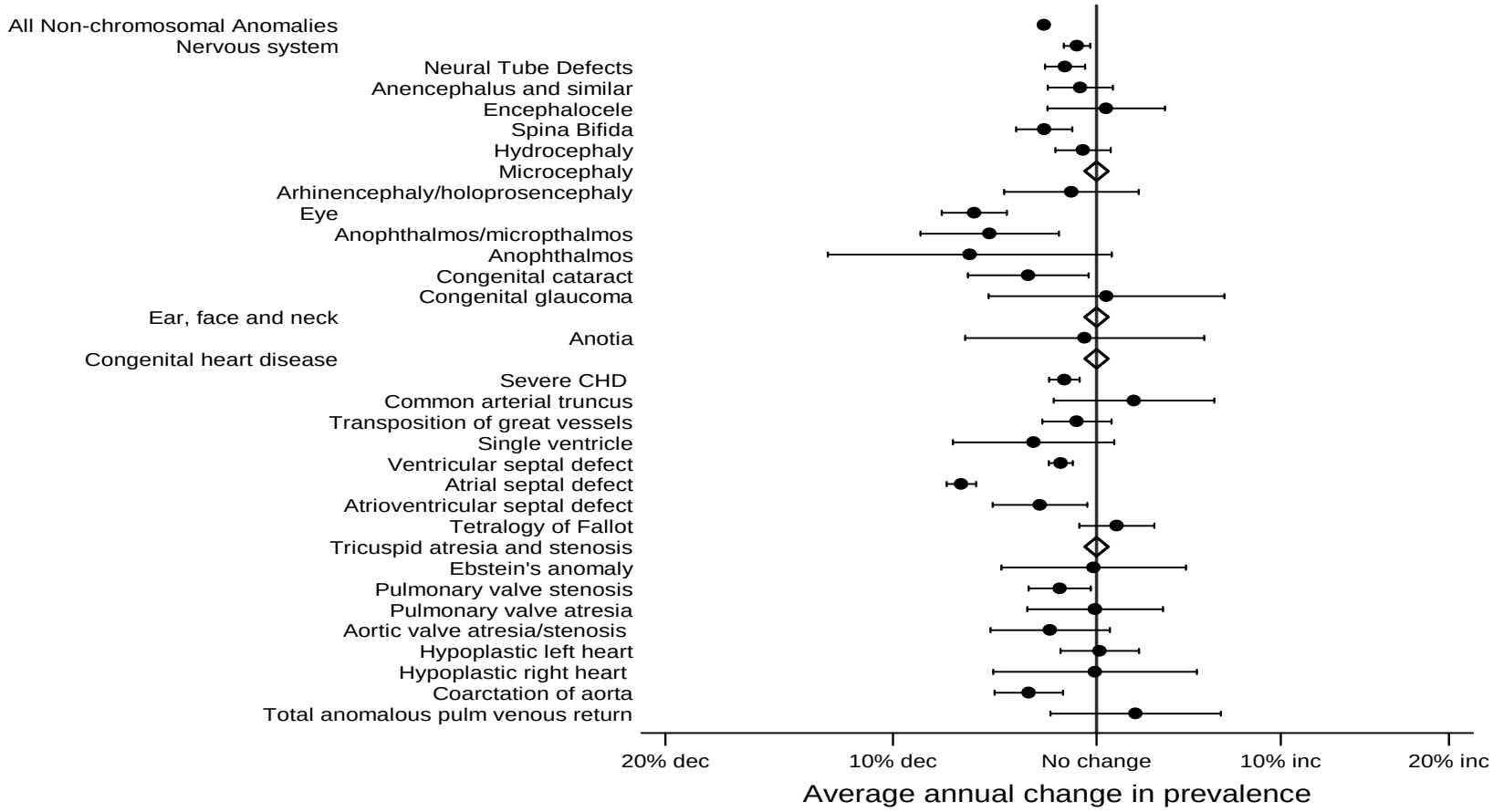
per year from 0.40 per 10,000 in 2000-2001 to 0.16 in 2008-2009 with no decreasing trends observed in individual registries (see Table 1). An investigation of the pan-European trend is being planned.

The anomaly **Cleft Palate** decreased in prevalence by 2% per year from 6.66 per 10,000 in 2000-2001 to 5.56 in 2008-2009 (see Figure 8). Preliminary investigations by Dublin have confirmed this trend in their registry, and that they are currently monitoring it before proceeding with a fuller investigation (see Appendix E2). The inconsistent trend in this anomaly across Europe requires investigation (see Figure 8 & Table 1).

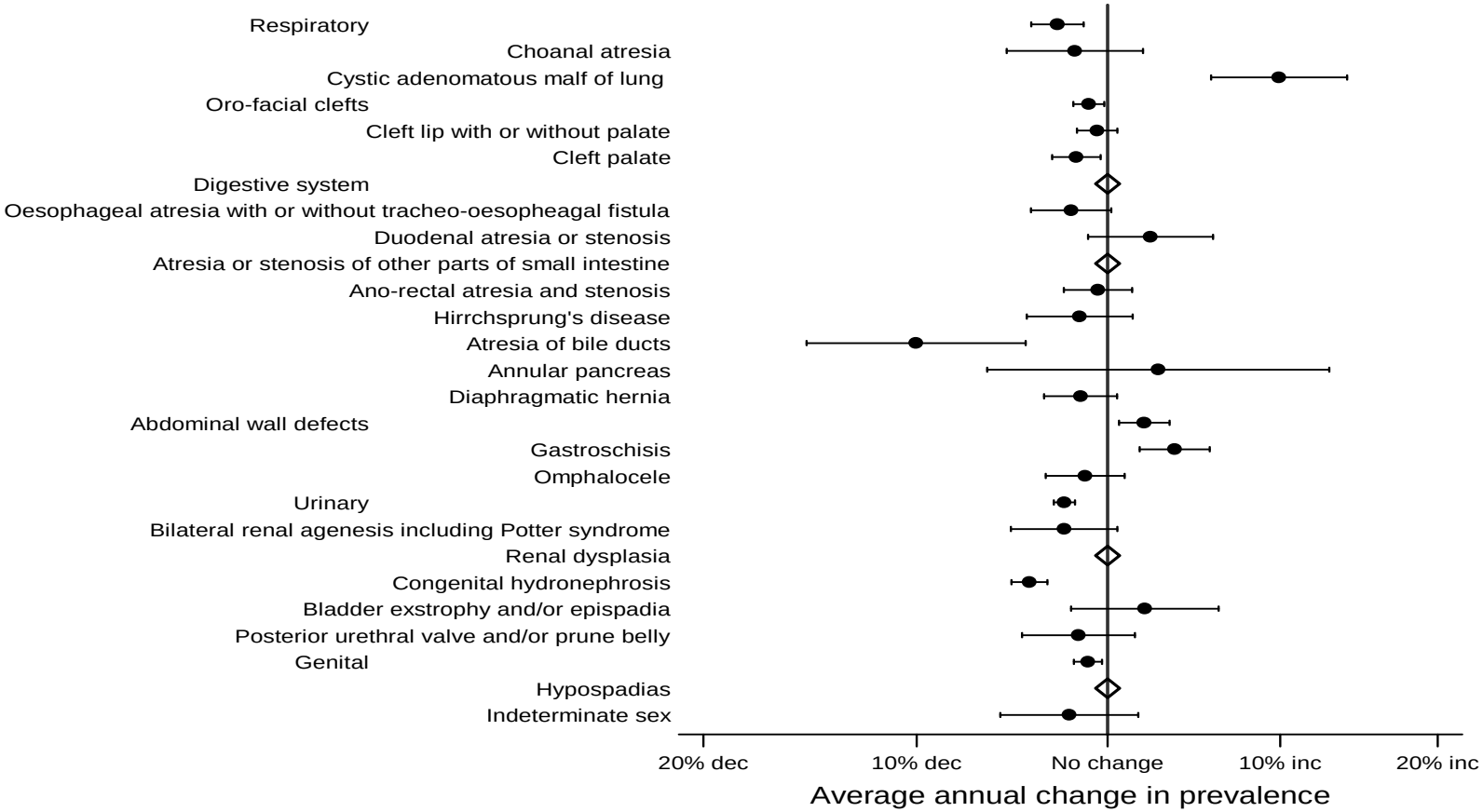
The prevalence of **Turner's syndrome,** a chromosomal anomaly also decreased by 3% per year in the pan-Europe analysis from 3.19 per 10,000 in 2001-2002 to 2.66 in 2008-2009 (see Figure 8) This decreasing trend is also currently under investigation. One registry, Wales, did confirm this trend and that they are currently monitoring it before proceeding with a fuller investigation (see Appendix E2).

Apart from the decreasing trends in congenital anomaly subgroups that are significant at pan-Europe level and are presented above, some statistically significant decreasing trends in other congenital anomaly subgroups were found in individual registries (Table 1) which were confirmed as requiring further monitoring or investigation (see Appendix E2). Hainaut reported that they are currently monitoring a decreasing trend for limb reduction before proceeding with a detailed investigation. Saxony-Anhalt is currently monitoring a decreasing trend for syndactyly before proceeding with a detailed investigation.

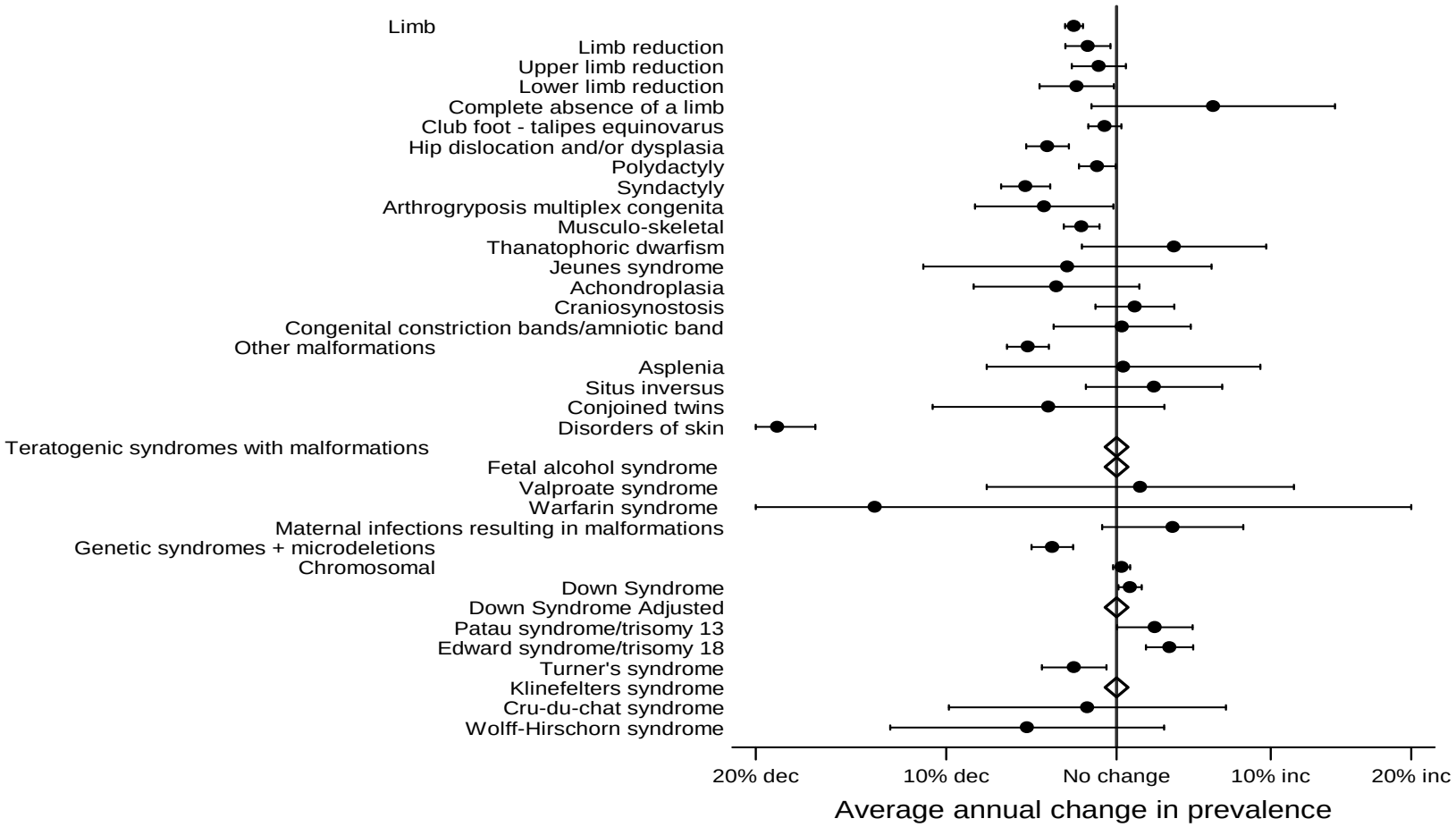
Figure 8: Outcome of pan-Europe ten year trends analysis, all congenital anomalies



Key: ◇ Non-linear change



Key: ◇ Non-linear change



Key: ◇ Non-linear change

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Table 1: Central Registry Statistical Monitoring Results: Reported ten year trends by registry and anomaly

Registry	Total /	Total \	Total ~	Total any	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Ile de Reunion (FR)	Paris (FR)	Saxony-Anhalt (DE)	Dublin (IRL)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	Basque Country (ES)	Vaud (CH)	E Mid & S York (GB)	N England (GB)	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Years tested (grouped by 2 years)					2000-2009	2000-2009	2001-2008	2000-2009	2000-2009	2002-2009	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009
Anomaly																										
All Non-chromosomal Anomalies	2	7	10	19	~	~	\	~			~	~	\	\		\	\	~	~	/	\	~	\	/	~	~
Nervous system	2	5	1	8	\		~				/			\	\					/		\			\	
Neural Tube Defects	0	2	0	2									\												\	
Anencephalus and similar	0	1	0	1				*						*			*		\							
Encephalocele	0	0	1	1	*	*	*	*	*		~			*		*	*	*		*				*		
Spina Bifida	0	4	0	4				*	\				\		\										\	
Hydrocephaly	1	6	2	9	\			~			/	\	\	\	\		*		\			~				
Microcephaly	1	2	3	6			~	*	*			~					*		~	/		\		*	\	
Arhinencephaly/holoprosencephaly	0	0	0	0	*	*	*	*	*				*	*		*	*	*	*		*			*		
Eye	0	6	1	7		\	\	*									*	\				\	\		\	~
Anophthalmos/microphthalmos	1	3	1	5	*	*	*	*		/	\	*		*	~		*	*	\	*	*	\		*		
Anophthalmos	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	2	0	2			*	*	*		*	*		*	*		*	\	*		*		\	*		*
Congenital glaucoma	0	0	0	0	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*		*
Ear, face and neck	0	3	4	7	\			*	*		~	~		*	\		*	~		~	*	\		*		*
Anotia	0	0	0	0	*	*	*	*	*			*	*	*	*	*	*	*		*	*	*	*	*	*	*

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Years tested (grouped by 2 years)					2000-2009	2000-2009	2001-2008	2000-2009	2000-2009	2002-2009	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009
Anomaly																										
Congenital heart disease	1	2	12	15	~	~	\	~			~	~	~			\	~		~			~	~	/	~	~
Severe CHD §	0	2	2	4							\						~		\			~				
Common arterial truncus	0	0	0	0	*	*	*	*	*		*	*	*	*		*	*	*			*			*		
Transposition of great vessels	1	0	0	1			/	*									*				*					
Single ventricle	0	0	0	0	*	*	*	*	*			*	*	*	*	*	*	*	*	*	*		*	*		*
Ventricular septal defect	3	4	6	13	~	~		/			~					\	\		\		/	~	\	/	~	~
Atrial septal defect	2	4	9	15	~		\	~		/	\	~	~			\	~		~		\	~	~	/	~	
Atrioventricular septal defect	0	3	1	4				*	*				~	*	\		*		\				\	*		
Tetralogy of Fallot	1	0	0	1				*						*			*								/	
Tricuspid atresia and stenosis	0	0	0	0	*	*	*	*	*	*	*	*		*	*	*	*		*	*	*		*	*		*
Ebstein's anomaly	0	0	1	1	*	*	*	*	*		~	*	*	*	*	*	*	*	*	*	*		*	*		
Pulmonary valve stenosis	2	4	2	8	~			*	\		/	/					\		\	\			~	*		*
Pulmonary valve atresia	0	0	1	1	*	*	*	*	*	*		*	*	*			*		*	~	*			*		
Aortic valve atresia/stenosis §	0	1	0	1	X	X	X	*	*	*	X		X	*	X	X	*	X	\		X					
Hypoplastic left heart	0	1	1	2			*	*	*								*		\		*	~				
Hypoplastic right heart §	0	0	0	0	X	X	X	*	*	*	X	*	X	*	X	X	*	X	*	*	X		*	*		
Coarctation of aorta	1	2	1	4			\	*	*								*			/	~	\				

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Years tested (grouped by 2 years)					2000-2009	2000-2009	2001-2008	2000-2009	2000-2009	2002-2009	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009
Anomaly																										
Respiratory	1	3	2	6		~			*					~			*		\	/		\			\	
Choanal atresia	1	0	0	1			*	*	*		/			*	*	*	*	*			*			*		*
Cystic adenomatous malf of lung §	2	0	0	2	X	X	X	*	*	*	X	*	X	*	X	X	*	X	*	*	X				/	/
Oro-facial clefts	1	2	2	5	~			/				\										\				~
Cleft lip with or without palate	2	1	1	4		~						\		/											/	
Cleft palate	3	2	0	5				/					\				/			/		\				
Digestive system	2	5	3	10		~					\				~	~		\	/		/	\	\		\	
Oesophageal atresia with or without tracheo-oesophageal fistula	1	1	2	4				*						*	~	~	*	\	/							
Duodenal atresia or stenosis	1	0	1	2	*	*	*	*	*			*		*		*	*	*		*	*			*	/	~
Atresia or stenosis of other parts of small intestine	0	0	1	1	*		*	*	*			*	~	*		*	*	*	*		*			*		*
Ano-rectal atresia and stenosis	2	1	1	4				*				/							/		*	\			~	
Hirschsprung's disease	1	0	1	2			*	*	*			*		*	*	*	*		/		*		~	*		
Atresia of bile ducts	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*		*
Annular pancreas	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	1	1	2				*	*								*		~					\		
Abdominal wall defects	1	0	3	4						/	~	~			~		*									
Gastroschisis	2	0	2	4				*	*	/	~	~		*			*				*		/			

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Years tested (grouped by 2 years)					2000-2009	2000-2009	2001-2008	2000-2009	2000-2009	2002-2009	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009
Anomaly																										
Omphalocele	0	1	1	2		\	*	*						*	~		*									
Urinary	2	5	7	14	\	~	\		/		~		~					/	~	~	\	~	\	~	\	
Bilateral renal agenesis including Potter syndrome	0	1	1	2	*		*	*	*						~		*			*	*			\		
Renal dysplasia	5	0	4	9	~	~	~	*				/	~	*		/	*	/		/		/				
Congenital hydronephrosis	3	4	9	16	~	~	\		/	~	\		~		~	~	*		~	/	/	~	\	~	\	
Bladder exstrophy and/or epispadia	1	0	0	1	*	*	*	*	*	*	/	*	*	*	*		*	*		*	*		*	*	*	
Posterior urethral valve and/or prune belly	0	2	1	3			*	*	*			*	*	*		*	*	\	*	~	*	\		*		
Genital	3	6	6	15	\			~		/			\		/	~	\	~	\	~	~	\		/	\	~
Hypospadias	4	5	7	16	~			~		/			\		/	~	\	~	\	~	~	\	/	/	\	~
Indeterminate sex	0	0	0	0	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*			*		
Limb	0	6	2	8							\		\	\		\			\	~		\			~	
Limb reduction	0	3	1	4	\		\							*	~							\				
Upper limb reduction	0	2	0	2	\		\	*						*			*									
Lower limb reduction	0	0	2	2				*					~	*	~		*							*		
Complete absence of a limb	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	1	3	4	8			/						~	\	~	\				~		~	*	\		
Hip dislocation and/or dysplasia	3	5	4	12	~	\	\	\			/	~	\				*	~		/		~	*	/	\	*

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Years tested (grouped by 2 years)					2000-2009	2000-2009	2001-2008	2000-2009	2000-2009	2002-2009	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009
Anomaly																										
Polydactyly	4	2	1	7		/					\			*					~		/	\		/		/
Syndactyly	0	4	1	5					*		\	\		*	~		*	\				\		*		
Arthrogryposis multiplex congenita	0	1	0	1	*	*		*	*	*			*	*		*	*	*	*	*	*	\	*	*	*	*
Musculo-skeletal	2	5	3	10	\	~	\	~					\	~					\	/				/	\	
Thanatophoric dwarfism	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*		*
Jeunes syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Achondroplasia	0	0	0	0	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*		*
Craniosynostosis	2	2	2	6	~			*						*			*		~	/		\	\	/		*
Congenital constriction bands/amniotic band	0	0	1	1	*	*	*	*	*		*		*	*	*	*	*	*	*	*	*		*		~	
Other malformations	3	5	2	10	\						/	\			/	~		~		/	\	\			\	
Asplenia	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	0	1	1	*	*	*	*	*	*	~	*	*	*	*		*	*	*	*	*		*	*		*
Conjoined twins	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Disorders of skin	0	9	2	11	~	\		*	*	*		\		\		~	*	\	\	\	\	\		*	\	*
Teratogenic syndromes with malformations §	0	0	1	1	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	*	*	*		*
Valproate syndrome §	0	0	0	0	X	X	X	*	*		X	*	X	*	X	X	*	X	*	*	X	*	*	*	*	*

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Years tested (grouped by 2 years)					2000-2009	2000-2009	2001-2008	2000-2009	2000-2009	2002-2009	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2001-2008	2001-2008	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009	2000-2009
Anomaly																										
Warfarin syndrome §	0	0	0	0	X	X	X	*	*	*	X	*	X	*	X	X	*	X	*	*	X	*	*	*	*	*
Maternal infections resulting in malformations	0	0	1	1	*	~	*	*	*	*		*		*		*	*	*	*	*	*	*	*	*		
Genetic syndromes + microdeletions	0	4	2	6	\			*							~							\	~	\	\	
Chromosomal	3	1	3	7					/		/				~					~		\			~	/
Down's Syndrome	4	1	2	7	/				~		/					/				~	/	\				
Down's Syndrome Adjusted	0	1	1	2			M		M	M										~		\	M		M	
Patau syndrome/trisomy 13	0	1	0	1			*	*				*	\	*			*									
Edward syndrome/trisomy 18	4	0	0	4				*			/					/	*	/			/					
Turner's syndrome	1	2	3	6				*	*		~			*		~	*	/			\			~	\	
Klinefelter's syndrome	0	0	0	0	*	*		*	*	*			*	*			*	*	*		*			*		
Cri-du-chat syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolf-Hirschhorn syndrome	0	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Total / in registries	83				1	1	2	3	3	6	10	3	0	1	3	3	1	4	4	12	6	1	2	10	4	3
Total \ in registries		162			10	4	11	1	2	0	8	6	11	6	5	6	5	7	15	2	6	27	9	4	17	0
Total ~ in registries			154		12	11	3	7	1	2	11	8	9	2	13	8	3	6	9	11	3	11	5	3	8	8
Total any in registries				399	23	16	16	11	6	8	29	17	20	9	21	17	9	17	28	25	15	39	16	17	29	11

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5. Clusters

For clusters a total of 805 tests were performed with 2.5% being statistically significant, which is the proportion we would expect by chance (see Appendix F). Twenty clusters were identified, four of which had been reported in the previous Statistical Monitoring Report (http://www.eurocat-network.eu/content/Stat-Mon-Report-2008.pdf) (also see Appendix G). Preliminary investigations by registries into the clusters detected in the analysis indicated that 14 of the 16 new detected clusters were not 'true' clusters as defined by the EUROCAT definition, and could be explained as a consequence of other factors within the registries (see Table 2). Preliminary investigations of the remaining two clusters for **hydrocephaly** and **Down syndrome** in the Tuscany registry confirmed that they could not find an explanation for the aggregation of these cases within the registry data.

Hydrocephaly is a condition characterised by the dilation of the ventricular system, not due to primary atrophy of the brain, with or without enlargement of the skull. This cluster started at the end of November 2008 and ended mid December 2008. In 20 days 5 cases were found when only an average of 0.04 cases would normally occur ($p<0.05$). Two of the cases were livebirths (see Appendix G). The preliminary investigation by the registry confirmed the diagnosis of hydrocephaly, though they noted that for 3 of the cases ventriculomegaly, the enlargement of the lateral ventricles, had not been measured. Of the five cases one had multiple malformations. The cases were from the entire region with four municipalities involved, with each case being born in different hospitals in different areas. The registry stated that they did not find any associations with aetiological factors that were recorded in the database, including medications. It was observed that prior to the cluster the registry had a lower prevalence rate when compared to most of the EUROCAT registries. The registry concluded that although the cases come from different areas of residence, a re-evaluation would be carried out the next year.

The second cluster detected in this registry was for **Down syndrome**. Starting on 31st December 2008 there were five cases discovered over a period of two days, when only an average of 0.15 cases would have usually occurred ($P=0.01$) (see Appendix G). The preliminary investigation by the registry confirmed the diagnosis of Down syndrome and that two cases also had ventricular septal defect and one case had cleft palate with cleft lip. An examination of the spatial dimension established that the cases were not clustered near each other having come from four municipalities, though the origin of one case was

Table 2: Outcomes of local registry preliminary investigations of detected clusters

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
Encephalocele- Tuscany	**Hydrocephaly-** Tuscany	**Arhinencephaly/holoprosencephaly-** Ukraine	**Atrial septal defect-** Antwerp
Duodenal atresia or stenosis- Northern England	**Down syndrome-** Tuscany	**Severe CHD-** Ukraine	**Congenital hydronephrosis-** Ile de la Reunion
Ano-rectal atresia- Odense		**Ventricular septal defect-** Ukraine	
Syndactyly- Thames Valley		**Tetralogy of Fallot-** Ukraine	
Maternal infection- Vaud		**Pulmonary valve stenosis-** Ukraine	
		Polydactyly- Thames Valley	
		Turners syndrome- Paris	

unknown. All cases were born in separate hospitals, with two hospitals in the same urban area. The registry reported that they had examined the distribution of maternal age, a known risk factor for Down syndrome. Four of the cases were conceived by mothers who were aged between 36 and 39 years of age. No other aetiological factors were reported as being examined. As with the cluster of hydrocephaly identified in the registry, Down syndrome had a lower prevalence rate prior to the detection of the cluster when compared to most of the EUROCAT registries. The registry concluded that as a significant increased trend of Down syndrome was found and Tuscany had, prior to the cluster, a lower than EUROCAT average Down syndrome rate a further period of surveillance was considered suitable.

The TEC reviewed the registry reports for the two clusters and agreed with the registry conclusion that no immediate action is necessary especially as the prevalence of the anomalies concerned had been lower than the EUROCAT average prior to the clusters.

6. Conclusion

The EUROCAT network, now a Joint Action between the European Union and Member States, provides essential surveillance information on congenital anomalies in Europe. The EUROCAT Central Registry monitored for trends and clusters in 96 anomalies across 22 registries in 14 countries, including at pan-European level. Our key findings concern pan-European analysis, but full results are available for all individual registries. The high and increasing prevalence of gastroschisis in the UK continues to need attention. The trend towards delayed childbirth in Europe continues to bring with it an increase in the prevalence of Down syndrome and other trisomy syndromes. However we are pleased to report a decline in prevalence of some major anomalies in the last decade, though much work in primary prevention of congenital anomalies remains to be done. Primary prevention of congenital anomalies should be added to National Plans for Rare Diseases currently under development, to make sure that the entire European population has access to appropriate preventive services and policies.

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/ microphthalmos	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: Summary of statistical methods

Ten year 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 (Box 1) with the exception that it is run using the last 10 years of data (2000-2009) or using 9 years of data within the 10 year period (2000-2009).

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 at least eight years of data within the 10 year period (2000-2009). Data before the year 2000 cannot be included.
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. Only significant increasing or decreasing trends where the p-value is <0.05 for the trend component and >0.01 for the non-linear component are reported.
   - 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 p>0.05 for non-linear component, the results are interpreted as showing no significant change over time.
7. Trend analysis is conducted on all 96 EUROCAT congenital anomaly subgroups and the computer generated subgroup for Down syndrome adjusted for maternal age.
8. 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.

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-2009.pdf), scanning all recorded cases in the period 2005-2009.

2. Clusters or deficits occurring in the last 2 years (2008-2009) that are less than 18 months in length are reported.

3. A minimum of 7 cases over the surveillance period (2005-2009) 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 (2009). 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.

   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.

7. 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.

Appendix C: Summary of local registry preliminary investigation protocols for identified ten year trends and clusters.

Investigation protocols and templates provided to make the reporting process consistent between registries are described in full in the EUROCAT Statistical Monitoring Protocol (http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2009.pdf). Using the templates registries were asked to include the following in their investigation report:

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?

Investigations into significant decreasing trends are classified as follows:

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 on-going

F: Trend confirmed, further surveillance proposed before more detailed investigation

G: Not real trend when additional years added, or heterogeneous subgroup

H: No report or clear interpretation of preliminary investigations sent

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.

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?

7. Registries are asked to conclude from their preliminary investigations if this is a 'true cluster of concern or not'

Cluster investigations can be classified as follows:

- Apparent cluster with cause for concern, further investigation on-going
- Cluster associated with aetiologic heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence
- Excess of cases confirmed, but no further investigation proposed other than further surveillance
- 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

Appendix D: Summary of significant ten year increasing and decreasing trends detected in the pan-Europe analysis*

Anomaly	Direction	Signalled in 2008 report	P	% Change
Nervous system	Decreasing	Yes	=0.004	-8.36
Neural Tube defects	Decreasing	Yes	=0.002	-2.40
Spina bifida	Decreasing	Yes	<0.001	-3.80
Eye	Deceasing	Yes	<0.001	-7.74
Anophthalmos/Microphthalmos	Decreasing	Yes	=0.002	-6.75
Congenital cataract	Decreasing	No	=0.027	-4.84
Severe CHD	Decreasing	Yes	<0.001	-2.40
Ventricular septal defect	Decreasing	No	<0.001	-2.78
Atrioventricular septal defect	Decreasing	Yes	=0.019	-3.95
Pulmonary valve stenosis	Decreasing	No	=0.02	-3.07
Aortic valve atresia/ stenosis	Decreasing	Yes	<0.001	-7.68
Coarctation of aorta	Decreasing	Yes	<0.001	-4.72
Respiratory	Decreasing	Yes	<0.001	-3.79
Cystic adenomatous malf of lung	Increasing	No	<0.001	+13.48
Oro-facial clefts	Decreasing	No	=0.018	-1.53
Cleft palate	Decreasing	Yes	=0.012	-2.47
Atresia of bile ducts	Decreasing	Yes	<0.001	-12.75
Abdominal wall defects	Increasing	Yes	=0.004	+3.41
Gastroschisis	Increasing	Yes	<0.001	+6.79
Urinary	Decreasing	Yes	<0.001	-3.52
Congenital hydronephrosis	Decreasing	Yes	<0.001	-5.85
Genital	Decreasing	No	=0.007	-1.71
Limb	Decreasing	Yes	<0.001	-3.80
Limb reduction	Decreasing	Yes	=0.013	-2.76
Lower limb reduction	Decreasing	Yes	=0.036	-3.78
Hip dislocation and/or dysplasia	Decreasing	Yes	<0.001	-5.78
Polydactyly	Decreasing	Yes	=0.041	-1.82
Syndactyly	Decreasing	No	<0.001	-7.67
Arthrogryposis multiplex congenita	Decreasing	Yes	=0.04	-6.51
Musculo-skeletal	Decreasing	No	<0.001	-3.23
Other malformations	Decreasing	No	<0.001	-6.72
Genetic syndromes + microdeletions	Decreasing	No	<0.001	-5.68
Down syndrome/triosomy 21	Increasing	No	=0.021	+1.36
Patau syndrome/trisomy 13	Increasing	No	=0.046	+4.28
Edward syndrome/trisomy 18	Increasing	Yes	<0.001	+6.25
Turner syndrome	Decreasing	Yes	=0.01	-3.57

Note: Main organ subgroups are in bold; *Significant non-linear change not included in this table

Appendix E Outcomes of local registries preliminary investigations into ten year trends

Table E1: Increasing ten year trends

	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Ile de la Reunion	Paris (FR)	Saxony- Anhalt (DE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (Pol)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Hydrocephaly							F														
Microcephaly															A						
Anophthalmos/microphthalmos																					
Congenital heart disease																			A		
Transposition of great vessels			A																		
Ventricular septal defect				C												C			A		
Atrial septal defect						F													A		
Tetralogy of Fallot																				F	
Pulmonary valve stenosis							B	A													
Coarctation of aorta															A/B						
Choanal atresia							F														
Cystic adenomatous malf of lung																				F	G
Cleft lip with or without palate									A											F/A	
Cleft palate				E								G			A/B						
Oesophageal atresia with or without tracheo-oesophageal fistula														A							

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	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Ile de la Reunion	Paris (FR)	Saxony- Anhalt (DE)	SE Ireland (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (Pol)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Thames Valley (UK)	Wales (UK)	Wessex (UK)
Duodenal atresia or stenosis																				A	
Ano-rectal atresia and stenosis								E						A							
Hirschsprung's disease														A							
Gastroschisis						F												E			
Renal dysplasia								B			B		A		A/B		A				
Congenital hydronephrosis					C										A/B	C					
Bladder exstrophy and/or epispadia							F														
Hypospadias						F				B								A	A		
Club foot - talipes equinovarus			B/G																		
Hip dislocation and/or dysplasia							F								A/B				A		
Polydactyly		H														C			A		G
Craniosynostosis															A/B				A		
Down's Syndrome	H						D				F					E					
Edward syndrome/trisomy 18							D				A		C			E					
Turner's syndrome													C								

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 on-going F: Trend confirmed, further surveillance proposed before more detailed investigation G: Not real trend when additional years added, or heterogeneous subgroup H : No report or clear interpretation of preliminary investigations sent

Table E2: Decreasing ten year trends

	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (Pol)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Wales (UK)
Neural Tube Defects								A										F
Spina Bifida					E			A	H									F
Anophthalmos/micropthalmos						B							A			A		
Congenital cataract												A					A	
Severe CHD §						F							A/F					
Ventricular septal defect										H	A		A/F				G	
Atrioventricular septal defect									H				A				F	
Pulmonary valve stenosis					G						A		A/F	A/B				
Aortic valve atresia/stenosis §													A/F					
Coarctation of aorta			F													G		
Cleft palate								F								G		
Congenital hydronephrosis			C			B											C	B/A
Limb reduction	H		F													G		
Hip dislocation and/or dysplasia		H	C	B/F				A										A

	Styria (AT)	Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Saxony- Anhalt (DE)	Dublin (IRL)	Emilia Romagna (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (Pol)	Basque Country (ES)	Vaud (CH)	E Mid & S York (UK)	N England (UK)	Wales (UK)
Polydactyly						B										G		
Syndactyly						B	F					A				A		
Arthrogryposis multiplex congenita																G		
Turner's syndrome															G			F

Note: Pan Europe decreasing trends were also found for atresia of bile ducts and lower limb reduction but decreasing trends were not observed in individual registries.

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 on-going F: Trend confirmed, further surveillance proposed before more detailed investigation G: Not real trend when additional years added, or heterogeneous subgroup H : No report or clear interpretation of preliminary investigations sent

Appendix F: Central Registry Statistical Monitoring Results: Table of detected clusters by registry and by anomaly 2008-2009

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Styria (AT)	Antwerp (BE)	Odense (DK)	Ile de Reunion (FR)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Ukraine (UA)	E Mid & S York (GB)	N England (GB)	Thames Valley (GB)	Wales (GB)	Wessex (GB)
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	0	0	0																
Anencephalus and similar	0	0	0								*								
Encephalocele	0	1	1	*		*				**B**	*	*	*						
Spina Bifida	0	0	0																
Hydrocephaly	1	0	1							**C**	*								
Microcephaly	0	0	0			*					*		*						
Arhinencephaly/holoprosencephaly	1	0	1	*	*	*					*	*	*	**C**					
Eye	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anophthalmos/microphthalmos	0	0	0	*	*						*		*						
Anophthalmos	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Congenital cataract	0	0	0		*	*					*		*				*		*
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	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Styria (AT)	Antwerp (BE)	Odense (DK)	Ile de Reunion (FR)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Ukraine (UA)	E Mid & S York (GB)	N England (GB)	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Congenital heart disease	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Severe CHD §	1	0	1											C					
Common arterial truncus	0	0	0	*	*	*		*		*	*	*	*				*		
Transposition of great vessels	0	0	0																
Single ventricle	0	0	0	*		*			*		*		*				*		*
Ventricular septal defect	1	0	1											C					
Atrial septal defect	0	1	1		B														
Atrioventricular septal defect	0	0	0								*								
Tetralogy of Fallot	1	0	1											C					
Tricuspid atresia and stenosis	1	0	1	*	*	*	*	*		*	*	C	*	*					
Ebstein's anomaly	0	0	0	*	*	*		*		*	*	*	*			*	*		
Pulmonary valve stenosis	1	0	1											C					
Pulmonary valve atresia	0	0	0	*	*	*	*				*		*	*			*		
Aortic valve atresia/stenosis §	0	0	0		*	*	*	*		*	*								
Hypoplastic left heart	0	0	0			*													
Hypoplastic right heart §	0	0	0	*	*	*	*	*	*	*	*	*	*			*	*		
Coarctation of aorta	0	0	0			*					*								
Total anomalous pulm venous return	0	0	0	*		*	*	*		*	*	*	*	*					

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Styria (AT)	Antwerp (BE)	Odense (DK)	Ile de Reunion (FR)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Ukraine (UA)	E Mid & S York (GB)	N England (GB)	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Respiratory	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Choanal atresia	0	1	1		**B**	*	*				*	*	*	*					
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	1	0	1	*		*				*	*	*	*			**C**			
Atresia or stenosis of other parts of small intestine	0	0	0		*	*					*		*						
Ano-rectal atresia and stenosis	1	0	1			**C**					*								
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								*								

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Styria (AT)	Antwerp (BE)	Odense (DK)	Ile de Reunion (FR)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Ukraine (UA)	E Mid & S York (GB)	N England (GB)	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Urinary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bilateral renal agenesis including Potter syndrome	0	0	0			*					*		*						
Renal dysplasia	0	0	0								*								
Congenital hydronephrosis	1	0	1				C												
Bladder exstrophy and/or epispadia	0	0	0	*		*	*		*		*		*						
Posterior urethral valve and/or prune belly	0	0	0			*			*		*	*	*	*					
Genital	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypospadias	1	0	1												C				
Indeterminate sex	0	0	0	*	*	*	*		*		*	*	*	*					
Limb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limb reduction	0	0	0																
Upper limb reduction	0	0	0								*								
Lower limb reduction	0	0	0			*					*								
Complete absence of a limb	0	0	0	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*
Club foot - talipes equinovarus	0	0	0													*			
Hip dislocation and/or dysplasia	0	0	0								*					*			*
Polydactyly	1	0	1														C		
Syndactyly	0	1	1								*						B		

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Styria (AT)	Antwerp (BE)	Odense (DK)	Ile de Reunion (FR)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Ukraine (UA)	E Mid & S York (GB)	N England (GB)	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Arthrogryposis multiplex congenita	0	0	0		*	*	*	*	*	*	*	*	*		*	*			*
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	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*
Situs inversus	0	0	0	*		*			*	*	*		*	*			*		*
Conjoined twins	0	0	0	*	*	*	*	*	*	*	*	*	*	*			*	*	*
Disorders of skin	0	0	0			*	*			*	*		*				*		*
Teratogenic syndromes with malformations §	X	X	X	X	X	X	X	X	X	X	X	X	X	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**	*	*				

Anomaly	Total clusters: Date of conception	Total clusters : Date of birth	Total clusters: All registries	Styria (AT)	Antwerp (BE)	Odense (DK)	Ile de Reunion (FR)	Paris (FR)	Dublin (IE)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Vaud (CH)	Ukraine (UA)	E Mid & S York (GB)	N England (GB)	Thames Valley (GB)	Wales (GB)	Wessex (GB)
Genetic syndromes + microdeletions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chromosomal	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Down's Syndrome	1	0	1							C									
Patau syndrome/trisomy 13	2	0	2	C							*	C							
Edward syndrome/trisomy 18	0	0	0								*								
Turner's syndrome	1	0	1					C			*			*					
Klinefelter's syndrome	0	0	0	*	*	*					*	*	*	*					
Cri-du-chat syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolf-Hirschhorn syndrome	0	0	0																
Total clusters: Date of conception	17			1	0	1	1	1	0	2	0	2	1	5	1	1	1	0	0
Total clusters: Date of birth		4		0	2	0	0	0	0	1	0	0	0	0	0	0	1	0	0
Total clusters			21	1	2	1	1	1	0	3	0	2	1	5	1	1	2	0	0

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

Appendix: G Clusters identified in the cluster analysis

Anomaly subgroup (Outcome of local registry preliminary investigations)	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
Encephalocele(A)	Italy	Tuscany	5	08/11/2007	02/01/2008	0.39	0.009	13	0	Cluster	*
Hydrocephaly (B)	Italy	Tuscany	5	29/11/2008	18/12/2008	0.04	0.042	33	0	Cluster	No sig. change
Arhinencephaly/ Holoprosencephaly (C)	Ukraine	Ukraine	7	23/04/2008	27/05/2008	0.77	0.015	35	0	Cluster	Inc. trend
Severe CHD § (C)	Ukraine	Ukraine	88	07/10/2007	04/09/2008	54.1	0.018	252	1.2	Cluster	Inc. trend
Ventricular septal defect (C)	Ukraine	Ukraine	167	18/01/2008	27/01/2009	116.05	0.04	480	0.4	Cluster	Non-linear change
Atrial septal defect (D)	Belgium	Antwerp	21	14/12/2007	06/06/2008	7.28	0.026	76	0	Cluster	Non-linear change
Tetralogy of Fallot (C)	Ukraine	Ukraine	18	23/02/2008	17/09/2008	6.01	0.019	45	0	Cluster	Inc. trend
Tricuspid atresia and stenosis (D)#	NL	N Netherlands	5	04/08/2007	16/09/200	0.33	<0.001	12	0	Cluster	*
Pulmonary valve stenosis (C)	Ukraine	Ukraine	9	01/10/2008	25/12/2008	1.7	0.03	31	3.2	Cluster	Inc. trend
Duodenal atresia or stenosis (A)	UK	N England	13	27/11/2006	11/01/2008	4.16	0.025	18	0	Cluster	*
Ano-rectal atresia and stenosis (A)	Denmark	Odense	10	16/08/2007	28/12/2008	3.87	0.044	12	0	Cluster	*

Anomaly subgroup (Outcome of local registry preliminary investigations)	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
Congenital hydronephrosis (D)	France	Isle de la Reunion	21	17/04/2008	24/03/2009	5.06	<0.001	23	0	Cluster	*
Hypospadias (D)#	UK	E Mid & S York	7	03/01/2008	04/01/2008	0.31	<0.001	478	0	Cluster	Dec. trend
Polydactyly (C)	UK	Thames Valley	38	11/10/2007	23/12/2008	19.53	0.014	69	8.7	Cluster	Inc. trend
Syndactyly (A)	UK	Thames Valley	5	27/05/2008	28/09/2008	0.61	0.015	9	0	Cluster	*
Maternal infection (A)	CH	Vaud	6	31/03/2008	28/07/2008	0.69	<0.001	9	0	Cluster	*
Down's Syndrome (B)	Italy	Tuscany	5	31/12/2008	01/01/2009	0.15	0.01	233	5.6	Cluster	Inc. Trend
Patau syndrome/ trisomy 13 (D)#	Austria	Styria	5	27/12/2007	25/04/2008	0.77	0.045	10	10	Cluster	*
Patau syndrome/ trisomy 13 (B)#	NL	N Netherlands	9	25/11/2006	24/07/2007	2.02	0.008	13	0	Cluster	*
Turner's syndrome (C)	France	Paris	24	03/09/2007	09/05/2008	9.95	0.04	62	0	Cluster	Inc. Trend

Key: GA: Gestational age; DOB: Date of Birth; * Too few cases to run the analysis; §; incomplete or misspecification of ICD 9 codes; # Cluster identified and reported on in 2008 Report

Key for Outcome of local registry preliminary investigations of detected clusters

A: Clusters associated with aetiologic heterogeneity, changes in inclusion criteria, diagnosis, familial or twin recurrence
B: Excess of cases confirmed with no explanation in registry data; no further action other than continued surveillance
C: Increase in cases/ascertainment, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound rates
D: Clusters due to data quality errors or late case ascertainment

Appendix H: 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.eurocatnetwork.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.