Eurocat

European Surveillance of Congenital Anomalies

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EUROCAT Statistical Monitoring Report - 2004

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Appendices

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1. Summary

2. Overview

This Report presents the results of EUROCAT statistical monitoring 2000-2004 and the investigations carried out by member registries into identified trends and clusters.

The statistical analysis of trends and clusters is undertaken annually using the EUROCAT Central Registry database. Registries classified as early response i.e. registries that meet the EUROCAT data transmission deadline of February 15th each year, and having a full dataset for the most recent 5 years (2000-2004) were included in statistical monitoring.

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 test monitoring exercise 1998-2002. Section 3.3 lists the registries and anomaly groups included in the current monitoring 2000-2004. Section 3.4 details methodological issues which have arisen from the current surveillance exercise and how these were resolved. The methods section should be read in conjunction with the EUROCAT Protocol for Statistical Monitoring and Investigation of Trends and Clusters (www.eurocat.ulster.ac.uk/) which gives more detailed information about the statistical methodology and the statistical monitoring system.

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

3. Methodology

3.1 Summary of methods

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

3.1.1 Clusters

1. A 'scan' moving window method is used to detect clusters, (See EUROCAT Protocol for Statistical Monitoring and Investigation of Trends and Clusters www.eurocat.ulster.ac.uk), scanning all recorded cases in the period 2000-2004.
2. Clusters or deficits occurring in the last 2 years (2003-2004) that are less than 18 months in length are reported.
3. A minimum of 7 cases over the surveillance period (2000-2004) is needed to run the scan analysis.
4. The default scan analysis uses date of conception, which is a program-generated variable calculated from gestational age and date of birth. If gestational age is missing for more than 10% of cases within a registry, the analysis uses date of birth/delivery. Where gestational age is missing for less than 10%, it is estimated based on registry, year of birth, type of birth and anomaly subgroup.
5. Cases with missing or incomplete date of birth/delivery are excluded.
6. When date of conception is used as a basis for cluster detection, the period of surveillance ENDS with dates of conception on 31 March in the last year under surveillance (2004). If date of birth/delivery is used to detect clusters, the last full year (1 January – 31 December) is included in the surveillance.
7. The output of cluster analyses lists all significant clusters which may be over-lapping. All the output data should be examined to determine the full time period over which the excess number of cases is observed. This may be outside the start and end date of the most significant cluster.

3.1.2 Trends

1. Trend detection is based on a chi squared test for trend using the number of cases per year and the number of births per year.
2. Trends during the last 5 years of data (2000-2004) are detected.
3. Trend analysis is always based on date of birth.

3.2 Statistical software updates

Changes to the EDMP software from previous years include:

1. Chromosomal anomalies are excluded from the statistical monitoring of non-chromosomal subgroups
2. Cluster detection is run by estimated date of conception, instead of date of birth/delivery, unless date of conception is unavailable. See EUROCAT Protocol for Statistical Monitoring and Investigation of Trends and Clusters for details of calculation of date of conception (www.eurocat.ulster.ac.uk).
3. Output now shows all significant clusters in each anomaly subgroup, which may overlap in time.

4. Users can print information on all significant clusters within the registry, as well as a timeline showing the occurrence of all cases within the anomaly subgroup over the time period.
5. A further option allows users to print graphs depicting trends within the registry.

3.3 Inclusion/Exclusion criteria

Registry inclusion criteria

- Registries must have 5 years continuous individual case data (full member registries only).
- Registries must have recent data i.e. include year 2004, 2003 or 2002 as the last year.
- Registries must have stable birth population (annual changes must be less than +/- 10%).

Statistical monitoring was run using 27 EUROCAT registries (Appendix A). Six Associate member registries were excluded as they do not transmit individual case data to EUROCAT (Finland, Central East France, Madrid, Norway, Poland, and Sweden). A further 3 registries were excluded due to > 10% fluctuations in population (Oxford, Trent, and Emilia Romagna). Four registries were excluded as EUROCAT has received no recent data (Galway, Glasgow, Strasbourg, and Styria). Auvergne was excluded as the registry has not yet transmitted 5 years of data.

Cluster analysis was run on 75 EUROCAT subgroups of congenital anomalies (Appendix A). Sixteen major hetero-geneous subgroups (e.g. Nervous system, Eye, Congenital heart disease etc) were excluded from cluster analysis (see Appendix A). A further 3 subgroups (Thanatophoric dwarfism, Jeunes syndrome, and Achondroplasia) were excluded from cluster analysis. Finally the hypospadias subgroup was excluded from both cluster and trend surveillance due to a minor program error (since rectified).

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

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

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

3.4 Issues arising from statistical monitoring

- Large registries incorporating more than one geographical region suggested that the EDMP monitoring function would be improved if it allowed analysis to be run on specific regions within the registry. James Densem will address this issue in the next edition of the software.

- Checking of lower limit of number of cases for trend test is needed.

- Local registries are still unsure how to recognise a cluster of concern. This is, of course, a central issue without an adequate answer. Registries and others are referred to the Cluster Advice Service (http://www.eurocat.ulster.ac.uk/clusteradservice.html). This will be modified to provide further guidance.

4. Results

4.1 Central Registry statistical monitoring results

4.1.1 Detected Clusters

A total of 56 clusters were detected from surveillance of 75 anomaly subgroups in 27 EUROCAT registries, covering 1.4 million births in the last 2 years of the monitoring period (Table 1). A total of 1067 cluster tests were performed. Forty-two clusters were detected using date of conception as surveillance method, while 14 were detected based on date of birth/delivery. The number of detected clusters per EUROCAT anomaly subgroup ranged from 0 to 5, while the number of detected clusters per registry ranged from 0 to 9 (Table 1).

Five clusters of "Club foot – talipes equinovarus" were identified. Three were detected based on date of conception in Paris (France), Tuscany and Campania (Italy). Two were detected based on date of birth in Saxony-Anhalt (Germany) and Wales (UK).

Four clusters of "Ano-rectal atresia and stenosis" were identified. Two were detected based on date of conception in Tuscany (Italy) and North West Thames (UK), and two were detected in Saxony-Anhalt (Germany) and Campania (Italy) based on date of birth.

Three clusters of "Atrial septal defect (ASD)", "Gastroschisis", "Congenital hydronephrosis" and "Hip dislocation and/or dysplasia" were detected.

- The ASD clusters were detected in Saxony-Anhalt (Germany) based on date of conception, and in Sicily and Wales (UK) based on date of birth.
- The Gastroschisis clusters were detected using date of conception in South Portugal, Wales (UK) and Northern regions (UK).
- The Congenital hydronephrosis clusters were detected in South Portugal and Asturias (Spain) based on date of conception, and in Sicily based on date of birth.
- The Hip dislocation and/or dysplasia clusters were detected in Dublin and Cork & Kerry (Ireland) based on date of conception, and in Sicily based on date of birth.

Two clusters of Spina Bifida, Microcephaly, Pulmonary valve stenosis, Omphalocele, Cystic kidney disease, Posterior urethral valve, Limb reduction, and Edward syndrome were detected.

- The Spina Bifida clusters were detected in North West Thames (UK) and Wielkopolska (Poland) based on date of conception.
- The Microcephaly clusters were detected in Hainaut (Belgium) based on date of conception, and in Saxony-Anhalt (Germany) based on date of birth.
- The Pulmonary valve stenosis clusters were detected in Saxony-Anhalt (Germany) and Hungary based on date of conception.
- The Omphalocele clusters were detected in Emilia Romagna (Italy) and Saxony-Anhalt (Germany) based on date of conception.
- The Cystic kidney disease clusters were detected in Barcelona (Spain) based on date of conception, and in Saxony-Anhalt (Germany) based on date of birth.

- The Posterior urethral valve clusters were detected in Dublin (Ireland) and Basque Country (Spain) based on date of conception.
- The Limb reduction clusters were detected in South Portugal based on date of conception, and in Saxony-Anhalt (Germany) based on date of birth.
- The Edward syndrome clusters were detected in Odense (Denmark) and Barcelona (Spain) based on date of conception.

Single clusters of the following subgroups were detected:

- Hydrocephaly (Paris, France)
- Common arterial truncus (Northern regions, UK)
- Ventricular septal defect (Hungary)
- Atrioventricular septal defect (S Portugal)
- Tetralogy of Fallot (Campania, Italy)
- Coarctation of aorta (Asturias, Spain)
- Choanal atresia (Dublin, Ireland)
- Cystic adenomatous malformation of lung (NW Thames, UK)
- Cleft lip with/without palate (Emilia Romagna, Italy)
- Abdominal wall defects (Wales, UK)
- Bilateral renal agenesis (Saxony-Anhalt, Germany)
- Syndactyly (S Portugal)
- Amniotic band (Wales, UK)
- Situs inversus (Tuscany, Italy)
- Conjoined twins (NW Thames, UK)
- Disorders of skin (Wielkopolska, Poland)
- Down syndrome (NW Thames, UK)
- Turner's syndrome (Hungary)
- Klinefelter's syndrome (Barcelona, Spain)

Full statistical details of each cluster are found in Appendix B. Details include name of registry, congenital anomaly subgroup, the type of cluster (identified using either date of birth/delivery or date of conception), the start and end date of the cluster, the expected number of cases, the probability of the cluster occurring, the number of valid cases included in surveillance (i.e. must have valid date of birth/delivery), the % of cases with estimated gestational age, and whether the finding shows an excess of cases (i.e. cluster) or a deficit of cases within the time period of the cluster.

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

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

Anomaly Subgroup	Total clusters across all registries			Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
				2000-2004	2000-2004	1999-2003	2000-2004	2000-2004	1999-2003	2000-2004	1998-2002	1998-2002	2000-2004	1999-2003	2000-2004	1999-2003	1998-2002	2000-2004	2000-2004	2000-2004	2000-2004	1999-2003	1999-2003	1999-2003	1999-2003	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004
	C	B	T		1	2	3	4	5	5	6	7	7	8	8	8	8	8	9	10	11	12	13	13	13	14	15	15	15	15
All Anomalies	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X
Neural Tube Defects	0	0	0																											
Anencephalus and similar	0	0	0			*			*								*		*											
Encephalocele	0	0	0	*	*	*	*		*			*					*	*	*	*		*	*	*	*					
Spina Bifida	2	0	2			*															C		*					C		
Hydrocephaly	1	0	1			*		C											*											
Microcephaly	1	1	2		C	*	*		X	B		*				X			*							*				
Arhinencephaly/holoprosencephaly	0	0	0	*	*	*	*		*	*		*	*			X	*	*	*		*	*	*	*		*				
Eye	X	X	X	X	X	X	X	X	X	X	X	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	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	X	X	X	X	X	X	X	X	X	X	X
Common arterial truncus	1	0	1	*	*	*	*		*	*		*	*	*		X		*	*	*	*	*	*	*		*	C			*
Transposition of great vessels	0	0	0		*		*		*							X						*				*				
Single ventricle	0	0	0	*	*	*	*		*	*		*		*	*	*	*		*	*	*	*		*	*	*				*
Ventricular septal defect	0	1	1								B																			
Atrial septal defect	1	2	3							C							B												B	

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Atrioventricular septal defect	1	0	1	*		*	*		*			*							*			C	*							
Tetralogy of Fallot	0	1	1											B					*											
Tricuspid atresia and stenosis	0	0	0	*	*	*	*		*	*		*	*	*		*	*		*		*	*			*	*				*
Ebstein's anomaly	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	
Pulmonary valve stenosis	2	0	2			*			*	C	C	*																		*
Pulmonary valve atresia	0	0	0		*	*	*		*	*	*	*				*	*	*	*		*	*	*	*		*				*
Aortic valve atresia/stenosis §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X		X	X	X		X				
Hypoplastic left heart	0	0	0		*	*			*			*					*					*				*				
Hypoplastic right heart §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	*	X	*		*	*
Coarctation of aorta	1	0	1			*																	C							
Total anomalous pulm venous return	0	0	0	*	*	*	*		*	*		*		*	*	*	*	*	*	*	*	*	*	*	*	*				*
Respiratory	X	X	X	X	X	X	X	X	X	X	X	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		*				*	*		*		*		*				*
Cystic adenomatous malf of lung §	1	0	1	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	X	X	*	X	X	X	*	X		C		*
Oro-facial clefts	X	X	X	X	X	X	X	X	X	X	X	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	1	0	1												C		X													
Cleft palate	0	0	0														X													
Digestive system	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oesophageal atresia with/ without tracheo-oesophageal fistula	0	0	0			*	*		*			*					*		*					*						
Duodenal atresia or stenosis	0	0	0	*	*	*	*		*	*		*	*			X	*	*	*	*	*	*	*	*	*		*				
Atresia or stenosis of other parts of small intestine	0	0	0	*	*	*	*		*	*	*	*		*		X	*	*	*	*	*	*	*	*	*	*	*	*	*		
Ano-rectal atresia and stenosis	2	2	4			*				B				B				C					*			*		C		
Hirschsprung's disease	0	0	0		*	*	*		*	*		*			*	*	*	*	*		*	*	*	*		*		*		
Atresia of bile ducts	0	0	0	*	*	*	*	*	*	*		*	*	*	*	*	*		*		*	*	*	*		*	*	*		*
Annular pancreas	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	0	0			*	*		*			*				X					*	*								
Abdominal wall defects	1	0	1			*													*										C	
Gastroschisis	3	0	3			*	*											*	*			C			*		C		C	

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Omphalocele	2	0	2		*	*				C		*			C		*		*			*								
Urinary	X	X	X	X	X	X	X	X	X	X	X	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	1	0	1		*	*	*		*	C							X		*							*				
Cystic kidney disease	1	1	2			*				B						X			*					C						
Congenital hydronephrosis	2	1	3									*					B		*			C	C							
Bladder exstrophy and/or epispadia	0	0	0	*	*	*	*		*	*		*		*	*			*	*	*	*	*	*	*	*	*	*			
Posterior urethral valve and/or prune belly	2	0	2	*	*	*	*		*	*	*	*	C	*		*	*	*	*		*	*	*	*	C	*		*		*
Genital	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypospadias	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indeterminate sex	0	0	0	*		*	*		*	*		*	*		*	X	*	*	*	*		*	*	*	*	*		*	*	
Limb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limb reduction	1	1	2			*				B												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	3	2	5					C		B				C		*	*	C						*			*		B	
Hip dislocation and/or dysplasia	2	1	3									C	C			*	B		*					*	*		*	*		*
Polydactyly	0	0	0																									X		
Syndactyly	1	0	1				*															C						X		
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	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	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	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	X	X	X	X	X	X	X	X	X	X	X	X
Craniosynostosis	0	0	0			*	*		*		*	*			*	*		*		*	*						*			*
Congenital constriction bands/amniotic band	1	0	1	*	*	*	*		*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	C	*
Other malformations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Asplenia	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	1	0	1	*	*	*	*		*	*		*	*				*	C	*	*	*	*	*	*	*	*	*				*
Conjoined twins	1	0	1	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	C	*	*
Disorders of skin	1	0	1				*		*			*									C							*		*
Teratogenic syndromes with malformations §	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fetal alcohol syndrome §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	*	X	*	*	*	*
Valproate syndrome §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	*	X	*	*	*	*
Warfarin syndrome §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	*	X	*	*	*	*
Maternal infections resulting in malformations	0	0	0	*	*	*	*		*	*	*	*		*	*		*	*	*	*	*	*	*	*	*	*	*	*	*		
Genetic syndromes + microdeletions	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X
Down Syndrome	1	0	1																									C		
Patau syndrome/trisomy 13	0	0	0		*	*	*		*	*						X	*		*		*		*						
Edward syndrome/trisomy 18	2	0	2			*	C									X	*							C						
Turner's syndrome	0	1	1			*	*		*		B	*					*		*				*	*						
Klinefelter's syndrome	1	0	1	*	*	*	*		*			*	*				*		*	*	*	*		C						
Cru-du-chat syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*
Total clusters: Date of conception	42			0	1	0	1	2	0	4	1	1	3	1	2	0	0	3	0	0	2	5	2	3	1	0	2	5	3	0
Total clusters: Date of birth		14		0	0	0	0	0	0	5	2	0	0	2	0	0	3	0	0	0	0	0	0	0	0	0	0	0	2	0
Total clusters: All			56	0	1	0	1	2	0	9	3	1	3	3	2	0	3	3	0	0	2	5	2	3	1	0	2	5	5	0

Key:

C = Clusters run by Date of conception, B = Clusters run by Date of birth, T = Total clusters
x Data excluded from analysis
* Too few cases to run analysis (registries must have at least 7 cases over the surveillance period)

4.1.2 Detected trends

A total of 414 trends were reported from surveillance of 94 anomaly subgroups in 27 EUROCAT registries covering 3.4 million births, 2000-2004 (Table 2). A total of 2,419 trend tests were performed. Results of the chi square test for trend showed 75 significant increasing trends, 156 significant decreasing trends, and 183 with significant non-linear heterogeneity (or significant change from year to year, but no overall trend). By chance alone, we would expect the chi square trend test to detect approximately 121 significant trends at the 5% significance probability level.

The number of increasing trends per EUROCAT anomaly subgroup ranged from 0-4, the number of decreasing trends per EUROCAT anomaly subgroup ranged from 0-8, and the number with significant non-linear heterogeneity per EUROCAT anomaly subgroup ranged from 0-11 (Table 2). The "All Anomalies" subgroup showed significant non-linear heterogeneity for 26 of the 27 registries.

The number of increasing trends per registry ranged from 0-13, the number of decreasing trends per registry ranged from 1-17, and the number of non-linear heterogeneity per registry ranged from 0-28 (Table 2). Due to the large number of reported trends, we only describe registries with 9 or more trends in any direction. Hungary and Saxony-Anhalt reported significant increasing trends in 9 or more subgroups. Five registries (Campania, North East Italy, Northern Netherlands, South Portugal and Wales) reported significant decreasing trends in 9 or more subgroups. Six registries (Hungary, North East Italy, Paris, Saxony-Anhalt, Sicily and Wielkopolska) reported significant non-linear heterogeneity in 9 or more subgroups.

Increasing trends in congenital anomalies

Surveillance showed significant increasing trends in 4 registries for the following congenital anomaly subgroups:

- Atrial septal defect increased in Northern regions (UK), Saxony-Anhalt (Germany), Vaud (Switzerland) and Zagreb (Croatia).
- Total anomalous pulmonary venous return increased in Emilia Romagna (Italy), Hungary, Northern regions (UK) and Saxony-Anhalt (Germany).
- Oesophageal atresia increased in Campania (Italy), Hungary, Northern Netherlands and Tuscany (Italy).
- Edward syndrome increased in Hungary, Odense (Denmark), Paris (France) and Saxony-Anhalt (Germany).

Surveillance showed significant increasing trends in 3 registries for the following congenital anomaly subgroups:

- Ear, face & neck anomalies increased in Barcelona (Spain), Hungary and Sicily.
- Coarctation of aorta increased in Dublin (Ireland), Hungary and Mainz (Germany).
- Abdominal wall defects increased in Saxony-Anhalt (Germany), Northern regions (UK) and Wales (UK).
- Gastroschisis increased in Saxony-Anhalt (Germany), Northern regions (UK) and Wales (UK).
- Urinary anomalies increased in Basque Country (Spain), Sicily and South Portugal.

Decreasing trends in congenital anomalies

Significant decreasing trends were reported for "Other malformations" in 8 registries (Asturias, Campania, Mainz, N W Thames, N Netherlands, S Portugal and Wales).

Significant decreasing trends were reported for "Limb malformations" in 7 registries (Antwerp, Asturias, Barcelona, Campania, N Netherlands, S Portugal, Tuscany and Wales).

Significant decreasing trends were reported for "Digestive system anomalies" in 6 registries (Campania, NorCAS, N Netherlands, Paris, Wales and Wielkopolska).

Significant decreasing trends were reported for "Disorders of skin" in 6 registries (Asturias, Campania, Emilia Romagna, N Netherlands, Vaud and Wales).

Significant decreasing trends in Congenital Heart Disease were reported in 5 registries (Barcelona, Hainaut, Malta, N Netherlands and S Portugal). Three of these registries (Malta, N Netherlands and S Portugal) along with Campania and Emilia Romagna reported significant decreasing trends in Ventricular septal defects.

Significant decreasing trends in Club foot – talipes equinovarus were reported in 5 registries (Basque Country, Mainz, NW Thames, S Portugal and Wielkopolska).

Significant decreasing trends in Musculo-skeletal anomalies were reported in 5 registries (Dublin, Odense, Tuscany, Vaud and Wales).

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

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

Anomaly subgroup	Total trends across all registries			Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
	/	\	~	2000-2004	2000-2004	1999-2003	1999-2003	2000-2004	1999-2003	2000-2004	1998-2002	1998-2002	2000-2004	1999-2003	2000-2004	1999-2003	1998-2002	2000-2004	2000-2004	2000-2004	2000-2004	1999-2003	1999-2003	1999-2003	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004
All anomalies	0	0	26	~	~		~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Nervous system	1	4	4	\	~			/	\		~				~	\												~	\	
Neural Tube Defects	0	1	4	\	~						~					~	~													
Anencephalus and similar	0	2	1								~					\		\												
Encephalocele	0	3	0									\					\					\								
Spina Bifida	0	0	2								~						~													
Hydrocephaly	0	3	2								~					\		~				\					\			
Microcephaly	1	0	2		~					/		~																		
Arhinencephaly/holoprosencephaly	2	0	1							/	~						/													
Eye	1	3	2		\			~			~									\		\								/
Anophthalmos/microphthalmos	1	2	1								\				/										~				\	
Anophthalmos	0	1	0																			\								
Congenital cataract	0	0	1								~																			
Congenital glaucoma	1	0	1								~							/												
Ear, face and neck	3	2	3					~			/		\				/			\		~	~	/						
Anotia	0	0	0																											
Congenital heart disease	0	5	11		\			~		~	~			~		~	~	~	\	\	~	\		\			~	~	~	
Common arterial truncus	1	0	0														/													
Transposition of great vessels	0	1	2								~														~	\				
Single ventricle	0	2	0				\													\										
Ventricular septal defect	2	5	4					~			/			\	\	~	/		\	\	~	\				~				
Atrial septal defect	4	3	8		\	/				/	~	~	~			~	~		\		~	\			/	/		~	~	
Atrioventricular septal defect	0	2	0											\		\														

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Tetralogy of Fallot	0	1	1									~			\															
Tricuspid atresia and stenosis	1	3	0	\														\				\						/		
Ebstein's anomaly	0	1	1							~																	\			
Pulmonary valve stenosis	2	3	2		\					/	/					\				\						~	~			
Pulmonary valve atresia	0	2	1									\										~		\						
Aortic valve atresia/stenosis §	0	0	0																											
Hypoplastic left heart	2	3	1			\				\														/	/			\	~	
Hypoplastic right heart §	0	0	0																											
Coarctation of aorta	3	1	2						/		/		/	\		~										~				
Total anomalous pulmonary venous return	4	0	0							/	/				/												/			
Respiratory	0	2	4							~	~		\			~	~			\										
Choanal atresia	0	0	2								~						~													
Cystic adenomatous malf of lung §	1	0	0																									/		
Oro-facial clefts	0	3	3					\					~	\		\	~													~
Cleft lip with or without palate	1	3	1	/									~	\				\												\
Cleft palate	0	2	0					\								\														
Digestive system	0	6	6	~				\		~	~			\		~	~			\	\						\	~	\	
Oesophageal atresia with/ without tracheo-oesophageal fistula	4	2	1								/			/	~			/		/	\						\			
Duodenal atresia or stenosis	0	2	0																	\										\
Atresia or stenosis of other parts of small intestine	1	3	2							/				\			~				~			\						\
Ano-rectal atresia and stenosis	0	2	3								~			~		\												~	\	
Hirschsprung's disease	1	0	0											/																
Atresia of bile ducts	1	1	0		/																									\
Annular pancreas	2	0	0		/															/										
Diaphragmatic hernia	0	2	1																~							\	\			
Abdominal wall defects	3	2	1					\		/	~																/	\	/	
Gastroschisis	3	0	2							/	~											~					/		/	
Omphalocele	2	0	0								/												/							

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Urinary	3	4	7		~			~	\		~			\	~	~	/	~		\		/			/	~			\	
Bilateral renal agenesis including Potter syndrome	0	1	1								~				\															
Cystic kidney disease	0	0	2																				~	~						
Congenital hydronephrosis	2	2	5					~	~		/			~		~	/			\			~						\	
Bladder exstrophy and/or epispadia	0	0	0																											
Posterior urethral valve and/or prune belly	2	1	3	\									/					~				~			/				~	
Genital	2	4	6								~	\	\		\	~	/	~				\	~			/			~	~
Hypospadias																														
Indeterminate sex	0	0	0																											
Limb	2	7	5						\		~		~	\	/	~	/	~		\	~	\	\					\	\	
Limb reduction	0	1	0																					\						
Upper limb reduction	0	0	1								~																			
Lower limb reduction	0	1	0																					\						
Complete absence of a limb	0	2	0								\											\								
Club foot - talipes equinovarus	1	5	6						\		~		~	~	~			/			\	\		~	\			\	~	
Hip dislocation and/or dysplasia	0	2	4							~	~		~				~			\									\	
Polydactyly	0	1	3							~													\	~						~
Syndactyly	0	3	1		\			~								\				\										
Arthrogryposis multiplex congenita	0	1	0											\																
Musculo-skeletal	1	5	5				\						\	~		~	~	\			~		~		/	\			\	
Thanatophoric dwarfism	0	0	0																											
Jeunes syndrome	0	0	0																											
Achondroplasia	0	1	0																						\					
Craniosynostosis	2	1	0														/								/				\	
Congenital constriction bands/amniotic band	0	3	0		\			\												\										
Other malformations	0	8	3	\										\		~	~	\		\	~	\	\	\					\	
Asplenia	1	0	0													/														
Situs inversus	0	3	0						\						\					\										

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Conjoined twins	0	2	0													\					\									
Disorders of skin	1	6	5					~		~	/			\	\			~		\	~	~	\			\			\	
Teratogenic syndromes with malformations §	0	0	0																											
Fetal alcohol syndrome §	0	0	0																											
Valproate syndrome §	0	0	0																											
Warfarin syndrome §	0	0	0																											
Maternal infections resulting in malformations	0	1	1		~																		\							
Genetic syndromes + microdeletions	1	1	4						~		/			~		\	~							~						
Chromosomal	0	2	6					~		~	~		\		~				~			\							~	
Down Syndrome	0	2	3								~		\		~				~					\						
Patau syndrome/trisomy 13	1	1	0										\											/						
Edward syndrome/trisomy 18	4	0	0				/	/		/	/																			
Turner's syndrome	1	1	2								/					\		~					~							
Klinefelter's syndrome	2	0	1				~				/													/						
Cru-du-chat syndrome	1	0	0					/																						
Wolff-Hirschorn syndrome	0	1	0																										\	
Total /	75			1	2	1	1	3	1	9	13	0	2	2	3	1	8	4	0	2	0	1	1	3	6	2	4	2	2	1
Total \		156		5	6	1	2	5	5	1	2	3	7	12	5	13	1	5	3	17	5	14	4	8	2	5	4	4	13	4
Total ~			183	2	6	0	2	10	3	9	28	4	7	7	7	13	15	8	5	1	9	6	6	5	4	4	4	5	8	5
Total any				8	14	2	5	18	9	19	43	7	16	21	15	27	24	17	8	20	14	21	11	16	12	11	12	11	23	10

Key:
/ = significant upward trend
\ = significant downward trend
~ = non-linear trends indicating significant heterogeneity

4.2 Local registry investigations of clusters/trends identified centrally

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

Clusters

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

Trends

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

4.2.1 Local registry preliminary investigations into detected clusters

Central Registry received reports on preliminary cluster investigations from 15 of 27 (56%) local registries: Antwerp, Barcelona, Basque Country, Dublin, Emilia Romagna, Malta, N Netherlands, NorCAS, NW Thames, Odense, Paris, Tuscany, Vaud, Wales and Wessex. The level of investigation varied between registries, with some registries such as NorCAS doing extensive checking and cross-referencing registry data with hospital records. Outcomes of the preliminary investigations were classified as follows:

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

Table 3 shows the outcomes of 27 (48%) of the 56 detected clusters. Three of the detected clusters are cause for concern and further, fuller investigations are underway. Six of the detected clusters were due to changes in diagnosis, aetiologic heterogeneity and familial/twin recurrence. No explanations were found for 6 identified clusters, and further investigation is not proposed other than surveillance. A further 4 clusters were perceived to be caused by changes and improvements in prenatal detection techniques. Seven detected clusters were caused by data quality issues. Full details

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

Table 3: Outcomes of local registry preliminary investigations of detected clusters

Anomaly Subgroup	Total clusters across all registries			Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Vaud (CH)	Basque Country (ES)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
	C	B	T	2000-2004	2000-2004	1999-2003	2000-2004	2000-2004	1999-2003	2000-2004	1998-2002	1998-2002	2000-2004	1999-2003	2000-2004	1999-2003	1998-2002	2000-2004	2000-2004	2000-2004	2000-2004	1999-2003	1999-2003	1999-2003	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004
All Anomalies	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X
Neural Tube Defects	0	0	0																											
Anencephalus and similar	0	0	0			*			*								*		*											
Encephalocele	0	0	0	*	*	*	*		*			*					*	*	*	*		*	*	*		*				
Spina Bifida	2	0	2			*															N		*					C		
Hydrocephaly	1	0	1			*		C											*											
Microcephaly	1	1	2		N	*	*		X	N		*				X			*						*					
Arhinencephaly/holoprosencephaly	0	0	0	*	*	*	*		*	*		*	*			X	*	*	*		*	*	*	*	*					
Eye	X	X	X	X	X	X	X	X	X	X	X	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	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	X	X	X	X	X	X	X	X	X	X	X
Common arterial truncus	1	0	1	*	*	*	*		*	*		*	*	*		X		*	*	*	*	*	*	*		B				*
Transposition of great vessels	0	0	0		*		*		*							X						*		*						
Single ventricle	0	0	0	*	*	*	*		*	*		*		*	*	*	*		*	*	*	*		*	*					*
Ventricular septal defect	0	1	1								N																			
Atrial septal defect	1	2	3							N							N												C	

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Vaud (CH)	Basque Country (ES)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Atrioventricular septal defect	1	0	1	*		*	*		*			*							*			N	*								
Tetralogy of Fallot	0	1	1											N					*												
Tricuspid atresia and stenosis	0	0	0	*	*	*	*		*	*		*	*	*		*	*		*		*	*			*	*				*
Ebstein's anomaly	0	0	0	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	
Pulmonary valve stenosis	2	0	2			*			*	N	N	*																			*
Pulmonary valve atresia	0	0	0		*	*	*		*	*	*	*				*	*	*	*		*	*	*	*	*						*
Aortic valve atresia/stenosis §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X		X	X	X	X						
Hypoplastic left heart	0	0	0		*	*			*			*					*						*		*					
Hypoplastic right heart §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	X	*	*		*	*
Coarctation of aorta	1	0	1			*																	N								
Total anomalous pulm venous	0	0	0	*	*	*	*		*	*		*		*	*	*	*	*	*	*	*	*	*	*	*	*					*
Respiratory	X	X	X	X	X	X	X	X	X	X	X	X	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		*					*	*			*	*						*
Cystic adenomatous malf of lung §	1	0	1	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	X	*		E			*
Oro-facial clefts	X	X	X	X	X	X	X	X	X	X	X	X	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	1	0	1												B		X														
Cleft palate	0	0	0														X														
Digestive system	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oesophageal atresia with/ without tracheo-oesophageal fistula	0	0	0			*	*		*			*					*		*					*							
Duodenal atresia or stenosis	0	0	0	*	*	*	*		*	*		*	*			X	*	*	*	*	*	*	*	*	*	*					
Atresia or stenosis of other parts of small intestine	0	0	0	*	*	*	*		*	*	*	*		*		X	*	*	*	*	*	*	*	*	*	*	*	*	*		
Ano-rectal atresia and stenosis	2	2	4			*				N				N				E					*		*			C		
Hirschsprung's disease	0	0	0		*	*	*		*	*		*			*	*	*	*	*		*	*	*	*	*			*		
Atresia of bile ducts	0	0	0	*	*	*	*	*	*	*		*	*	*	*	*	*		*		*	*	*	*	*		*	*		*
Annular pancreas	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Diaphragmatic hernia	0	0	0			*	*		*			*				X					*	*								
Abdominal wall defects	1	0	1			*													*										A	
Gastroschisis	3	0	3			*	*											*	*			N					*	A		A	

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Vaud (CH)	Basque Country (ES)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Omphalocele	2	0	2		*	*				N		*			A		*		*			*								
Urinary	X	X	X	X	X	X	X	X	X	X	X	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	1	0	1		*	*	*		*	N							X		*							*				
Cystic kidney disease	1	1	2			*				N						X			*					D						
Congenital hydronephrosis	2	1	3									*					N		*			N	N							
Bladder exstrophy and/or epispadia	0	0	0	*	*	*	*		*	*		*		*	*			*	*	*	*	*	*	*	*	*	*			
Posterior urethral valve and/or prune belly	2	0	2	*	*	*	*		*	*	*	*	B	*		*	*	*	*		*	*	*	*	*	D		*		*
Genital	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypospadias	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indeterminate sex	0	0	0	*		*	*		*	*		*	*		*	X	*	*	*	*		*	*	*	*	*		*	*	
Limb	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Limb reduction	1	1	2			*				N												N								
Upper limb reduction	0	0	0			*																								
Lower limb reduction	0	0	0		*	*	*		*			*					*		*			*								
Complete absence of a limb	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Club foot - talipes equinovarus	3	2	5					B		N				N		*	*	E						*			*		E	
Hip dislocation and/or dysplasia	2	1	3									N	B			*	N		*					*		*	*	*		*
Polydactyly	0	0	0																									X		
Syndactyly	1	0	1				*															N						X		
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	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	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	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	X	X	X	X	X	X	X	X	X	X	X	X
Craniosynostosis	0	0	0			*	*		*		*	*			*	*		*		*	*							*		*
Congenital constriction bands/amniotic band	1	0	1	*	*	*	*		*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	C	*
Other malformations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Vaud (CH)	Basque Country (ES)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Asplenia	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Situs inversus	1	0	1	*	*	*	*		*	*		*	*				*	E	*	*	*	*	*	*	*	*	*	*			*
Conjoined twins	1	0	1	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	E	*	*
Disorders of skin	1	0	1				*		*			*								N								*		*
Teratogenic syndromes with	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fetal alcohol syndrome §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	X	*	*	*	*	*
Valproate syndrome §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	X	*	*	*	*	*
Warfarin syndrome §	0	0	0	X	X	X	*	X	X	*	X	*	X	X	X	X	X	X	*	X	*	X	X	X	X	*	*	*	*	*
Maternal infections resulting in	0	0	0	*	*	*	*		*	*	*	*		*	*		*	*	*	*	*	*	*	*	*	*	*	*	*		
Genetic syndromes +	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X	X
Down Syndrome	1	0	1																									E		
Patau syndrome/trisomy 13	0	0	0		*	*	*		*	*						X	*		*		*		*							
Edward syndrome/trisomy 18	2	0	2			*	B									X	*							D						
Turner's syndrome	0	1	1			*	*		*		N	*					*		*				*	*						
Klinefelter's syndrome	1	0	1	*	*	*	*		*			*	*				*		*	*	*	*		D						
Cru-du-chat syndrome	0	0	0	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Wolff-Hirschorn syndrome	0	0	0	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*			*	*
Total clusters: Date of conception	42			0	1	0	1	2	0	4	1	1	3	1	2	0	0	3	0	0	2	5	2	3	0	1	2	5	3	0
Total clusters: Date of birth		14		0	0	0	0	0	0	5	2	0	0	2	0	0	3	0	0	0	0	0	0	0	0	0	0	0	2	0
Total clusters: All			56	0	1	0	1	2	0	9	3	1	3	3	2	0	3	3	0	0	2	5	2	3	0	1	2	5	5	0

Key
A: Apparent cluster with cause for concern, further investigation ongoing
B: Not true cluster as caused by aetiologic heterogeneity, changes in diagnosis, familial or twin recurrence.
C: Excess of cases, but no further investigation proposed other than further surveillance
D: Increase in cases, due to increasing use of invasive prenatal diagnostic procedures or improvements in prenatal ultrasound detection rates
E: Data quality errors
N: No report of preliminary investigations sent to Central Registry
X: Data excluded from surveillance; * No surveillance, as too few cases

4.2.2 Local registry preliminary investigations into detected trends

Central Registry received reports on preliminary trend investigations from 8 of 27 local registries (30%): Antwerp, Barcelona, Dublin, Malta, NorCAS, NW Thames, Paris and Vaud. The level of investigation varied between registries. Outcomes of the preliminary investigations were classified as follows:

- A: Increase in ascertainment of cases
- B: Increase in use of prenatal diagnostic techniques, including invasive tests, echocardiography
- C: Trend not apparent when analysed over a longer time period, or when surveillance included year 2005 data
- D: Data quality issues, including changes in reporting practices
- E: Too few cases or incomplete data collection
- F: Large heterogeneous subgroups – investigation not meaningful
- G: Reduction in ascertainment possibly due to prenatal diagnosis and subsequent referral to private TOP clinics
- H: Apparent trend, continued surveillance necessary
- N: No explanation provided to Central Registry

The results of the investigations carried out by each registry are summarised in Table 4. Increasing trends are highlighted in yellow, decreasing trends are highlighted in blue.

Analysis of trends detected in the major Hetero-geneous subgroups such as congenital heart disease, digestive system, limb defects etc is of little significance, as the groups are too Hetero-geneous. They are included in the table for descriptive purposes only.

Results of preliminary investigations of significant non-linear heterogeneity in the remaining subgroups are not included in the table.

Outcomes of 58 (25%) of the 231 significant increasing / decreasing detected trend investigations are described. One significant trend was due to an increase in case ascertainment. Three trends were as a result of increasing prenatal diagnostic techniques, including the use of echocardiography which increased diagnosis of mild cardiac conditions. A further 4 trends disappeared when trend investigations considered the whole time period of the registry or included year 2005 data, as opposed to concentrating on the 2000-2004 period. Eleven trends were caused by data quality errors or changes in reporting practices of certain cardiac malformations such as small septal defects which close in early life and are therefore no longer registered. A further 11 trends were identified in subgroups with too few cases, therefore these are unlikely to be real trends. Major Hetero-geneous subgroups accounted for 18 detected trends. Surveillance showed 2 significant trends which require continued monitoring. A decrease in ascertainment as a result of increasing prenatal diagnosis and subsequent referral to private TOP clinics of cases were likely causes of a further 3 trends. Finally, no explanation was sent to Central Registry for 5 detected trends.

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

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

Anomaly subgroup	Total trends across all registries			Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
	/	\	~	2000-2004	2000-2004	1999-2003	1999-2003	2000-2004	1999-2003	2000-2004	1998-2002	1998-2002	2000-2004	1999-2003	2000-2004	1999-2003	1998-2002	2000-2004	2000-2004	2000-2004	2000-2004	1999-2003	1999-2003	1999-2003	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004	2000-2004
All anomalies	0	0	26	~	~		~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~
Nervous system	1	4	4	F	~			F	\		~				~	\											~	\	
Neural Tube Defects	0	1	4	H	~						~					~	~													
Anencephalus and similar	0	2	1								~					\		\												
Encephalocele	0	3	0									\					\					\							
Spina Bifida	0	0	2								~						~													
Hydrocephaly	0	3	2								~					\		~				\					D			
Microcephaly	1	0	2		~					/		~																		
Arhinencephaly/holoprosencephaly	2	0	1							/	~						/													
Eye	1	3	2		\			~			~									\		\								/
Anophthalmos/microphthalmos	1	2	1								\				/										~				\	
Anophthalmos	0	1	0																			\								
Congenital cataract	0	0	1								~																			
Congenital glaucoma	1	0	1								~							/												
Ear, face and neck	3	2	3					~			/		F				/			\		~	~	F						
Anotia	0	0	0																											
Congenital heart disease	0	5	11		\			~		~	~			~		~	~	~	D	\	~	\		F			~	~	~	
Common arterial truncus	1	0	0														/													
Transposition of great vessels	0	1	2								~														~	E				
Single ventricle	0	2	0				\													\										
Ventricular septal defect	2	5	4					~			/			\	\	~	/		D	\	~	\					~			
Atrial septal defect	4	3	8		\	/				/	~	~	~			~	~		D		~	\			N	D		~	~
Atrioventricular septal defect	0	2	0											\		\														

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Tetralogy of Fallot	0	1	1									~			\															
Tricuspid atresia and stenosis	1	3	0	E														\				\					A			
Ebstein's anomaly	0	1	1							~																EI				
Pulmonary valve stenosis	2	3	2		\					/	/					\				\						~	~			
Pulmonary valve atresia	0	2	1									\										~		E						
Aortic valve atresia/stenosis §	0	0	0																											
Hypoplastic left heart	2	3	1			\				\														B	/			D	~	
Hypoplastic right heart §	0	0	0																											
Coarctation of aorta	3	1	2						/		/		C	\		~										~				
Total anomalous pulmonary venous return	4	0	0							/	/				/												C			
Respiratory	0	2	4							~	~		F			~	~				\									
Choanal atresia	0	0	2								~						~													
Cystic adenomatous malf of lung §	1	0	0																								D			
Oro-facial clefts	0	3	3					F					~	\		\	~													~
Cleft lip with or without palate	1	3	1	C									~	\				\												\
Cleft palate	0	2	0					N								\														
Digestive system	0	6	6	~				F		~	~			\		~	~			\	\						F	~	\	
Oesophageal atresia with/ without tracheo-oesophageal fistula	4	2	1								/			/	~			/		/	\						C			
Duodenal atresia or stenosis	0	2	0																	\										\
Atresia or stenosis of other parts of small intestine	1	3	2							/				\			~				~			E						\
Ano-rectal atresia and stenosis	0	2	3								~			~		\												~	\	
Hirschsprung's disease	1	0	0											/																
Atresia of bile ducts	1	1	0		/																									\
Annular pancreas	2	0	0		/															/										
Diaphragmatic hernia	0	2	1																~								EI	D		
Abdominal wall defects	3	2	1					F		/	~																F	F	/	
Gastroschisis	3	0	2							/	~											~					H		/	
Omphalocele	2	0	0								/												/							

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Urinary	3	4	7		~			~	\		~			\	~	~	/	~		\		/			/	~			\	
Bilateral renal agenesis including Potter syndrome	0	1	1								~				\															
Cystic kidney disease	0	0	2																				~	~						
Congenital hydronephrosis	2	2	5					~	~		/			~		~	/			\			~						\	
Bladder exstrophy and/or epispadia	0	0	0																											
Posterior urethral valve and/or prune belly	2	1	3	E									N					~				~			/				~	
Genital	2	4	6								~	\	F		\	~	/	~				\	~			F			~	~
Hypospadias																														
Indeterminate sex	0	0	0																											
Limb	2	7	5						\		~		~	\	/	~	/	~		\	~	\	\					D	\	
Limb reduction	0	1	0																					E						
Upper limb reduction	0	0	1								~																			
Lower limb reduction	0	1	0																					E						
Complete absence of a limb	0	2	0								\										\									
Club foot - talipes equinovarus	1	5	6						\		~		~	~	~			/			\	\		~	\			D	~	
Hip dislocation and/or dysplasia	0	2	4							~	~		~				~			\									\	
Polydactyly	0	1	3							~													\	~						~
Syndactyly	0	3	1		\			~								\				\										
Arthrogryposis multiplex congenita	0	1	0											\																
Musculo-skeletal	1	5	5				\						F	~		~	~	\			~		~		/	F			\	
Thanatophoric dwarfism	0	0	0																											
Jeunes syndrome	0	0	0																											
Achondroplasia	0	1	0																						\					
Craniosynostosis	2	1	0														/								/				\	
Congenital constriction bands/amniotic band	0	3	0		\			N												\										
Other malformations	0	8	3	N										\		~	~	\		\	~	\	\	F					\	
Asplenia	1	0	0													/														
Situs inversus	0	3	0						\						\					\										

				Antwerp (BE)	Hainaut (BE)	Zagreb (HR)	Odense (DK)	Paris (FR)	Mainz (DE)	Saxony Anhalt (DE)	Hungary (HU)	Cork and Kerry (IE)	Dublin (IE)	Campania (IT)	Emilia Romagna (IT)	North East Italy (IT)	Sicily (IT)	Tuscany (IT)	Malta (MT)	N Netherlands (NL)	Wielkopolska (PL)	S Portugal (PT)	Asturias (ES)	Barcelona (ES)	Basque Country (ES)	Vaud (CH)	NorCAS (UK)	North Thames (UK)	Wales (UK)	Wessex (UK)
Conjoined twins	0	2	0													\					\									
Disorders of skin	1	6	5					~		~	/			\	\			~		\	~	~	\			D			\	
Teratogenic syndromes with malformations §	0	0	0																											
Fetal alcohol syndrome §	0	0	0																											
Valproate syndrome §	0	0	0																											
Warfarin syndrome §	0	0	0																											
Maternal infections resulting in malformations	0	1	1		~																		E							
Genetic syndromes + microdeletions	1	1	4						~		/			~		\	~							~						
Chromosomal	0	2	6					~		~	~		F		~				~			\							~	
Down Syndrome	0	2	3								~		G		~				~					G						
Patau syndrome/trisomy 13	1	1	0										G											/						
Edward syndrome/trisomy 18	4	0	0				/	B		/	/																			
Turner's syndrome	1	1	2								/					\		~					~							
Klinefelter's syndrome	2	0	1				~				/												B							
Cru-du-chat syndrome	1	0	0					E																						
Wolff-Hirschorn syndrome	0	1	0																										\	
Total /	75			1	2	1	1	3	1	9	13	0	2	2	3	1	8	4	0	2	0	1	1	3	6	2	4	2	2	1
Total \		156		5	6	1	2	5	5	1	2	3	7	12	5	13	1	5	3	17	5	14	4	8	2	5	4	4	13	4
Total ~			183	2	6	0	2	10	3	9	28	4	7	7	7	13	15	8	5	1	9	6	6	5	4	4	4	5	8	5
Total any				8	14	2	5	18	9	19	43	7	16	21	15	27	24	17	8	20	14	21	11	16	12	11	12	11	23	10

Key (Increasing trends highlighted in yellow, decreasing trends highlighted in blue):

- A: Increase in ascertainment of cases
- B: Increase in use of invasive prenatal diagnostic techniques
- C: Trend not apparent when analysed over a longer time period
- D: Data quality
- E: Increase in use of echocardiography leading to increase in diagnosis of mild cardiac conditions
- F: Major Hetero-geneous subgroups
- G: Surveillance including year 2005 data ended the trend
- H: Apparent trend, fuller investigation ongoing
- I: Too few cases
- J: Reduction in ascertainment possibly due to prenatal diagnosis and subsequent referral to private TOP clinics
- N: No report of preliminary investigations sent to Central Registry

4.3 Local registry surveillance using EDMP

The detection of significant trends may be dependent on the time period under surveillance. The current report focuses on the time period 2000-2004. Three registries, Antwerp (Belgium), Dublin (Ireland) and NorCAS (UK) used EDMP to investigate the trend results obtained by Central Registry. By running the trend tests over the longer time period of the registry's existence, the 3 registries found that the Central Registry reported significant trends for 2000-2004 were not clear trends in the light of a longer period.

Central Registry received no results of local cluster investigations using more recently ascertained data.

4.4 Clusters identified by other means

4.4.1 Report on the investigation of a cluster of gastroschisis in Bridgend County, Wales, UK

(http://www.wales.nhs.uk/sites3/docmetadata.cfm?orgid=368&id=37887&pid=6008)

Why this investigation took place

Concerns were raised by the Welsh Congenital Anomaly Register (CARIS) about a rise in notifications of antenatally detected gastroschisis in late 2003. There had been no change in reporting practice to the register. In spring 2004, clinicians at the tertiary referral centre also raised concerns that they were seeing increased numbers of babies with gastroschisis. Analysis by the register showed an unusual number of cases in Bridgend County. An investigation team was formed including clinical and academic staff from the University of Wales College of Medicine, The National Public Health Service, The Welsh Assembly Government and CARIS.

Evidence

Expected numbers of gastroschisis for Bridgend County range between 0-3 in any one year. A list of cases was compiled using data from the CARIS database and the University Hospital of Wales, Cardiff. Seven cases of gastroschisis could be identified where the mother was normally resident in Bridgend County and where expected date of delivery was in 2004. Of the seven cases, 6 were live born.

Five liveborn cases were linked in time as they all had an expected date of delivery (EDD) within a month of each other. The other 2 cases had EDDs within a few weeks of this time period. Literature suggests that the embryo is most vulnerable to gastroschisis between the 4^{th} and 6^{th} weeks after conception. Therefore, the summer of 2003 was the most sensitive period for environmental exposures.

It was agreed that the occurrence of these seven cases during 2004 may not have arisen by chance and that further investigation of this event was warranted.

Methods

For the purpose of this investigation, it was agreed that cases in the potential cluster should be defined as:

Babies / fetuses with gastroschisis whose mothers were normally resident in Bridgend County and who had an expected date of delivery during 2004

The Investigation Group considered possible causes for the cluster. Risk factors were chosen on the basis of data availability or previous investigations reported, accepting that the exact cause is unknown.

- Information was gathered about individual cases from patient notes and interviews conducted by clinicians directly involved.
- general information relating to the environment was sought.

The group considered the possibility that a common environmental exposure might be responsible for the cluster. It was noted that the summer of 2003 was a particularly hot and dry period. The group considered the possibility that this affected the mothers' exposure to environmental factors, either through changing patterns of behaviour or changing the behaviour of substances in the physical environment. Data was supplied by a number of different agencies relating to aspects of the physical environment during the summer of 2003, including Bridgend County Borough Council, the Environment Agency and Dŵr Cymru (Welsh Water).
In particular:

- the pollution inventories of all regulated industry
- questioning site inspectors
- UK based web sources of data e.g. the emissions inventory
- Details of water supply

Result
No specific factors were identified from the interviews that connected the individuals or that could have explained the cluster. There were, however, features evident among some of the cases that have previously been described as having an association with gastroschisis:

- Lower maternal body mass-index / poor diet
- Smoking
- Cold / flu-like symptoms or taking cold remedies / pain killers.

The only abnormal industrial problem reported was that one major plant had been idle for the period.

There are data suggesting that a UK wide peak in airborne particulates occurred during the time period. There is no evidence to date that the situation in Bridgend County Borough was different to the general UK picture.

Information from Dŵr Cymru confirmed that the area in which most of the cases had occurred shared a common water supply with a very large, unaffected population, and individual cases did not share local reservoirs with each other.

Conclusion
Despite detailed clinical interviews and review of environmental data, the Investigation Group has not identified either

- an obvious cause for the cluster in Bridgend County Borough, or
- any plausible suggestions to explain the cluster that could be investigated in a formal study in that locality.

Public Health Action
As no factor was identified that may have caused the cluster, no specific action was possible to reduce risks and prevent further cases arising. However, issuing general advice on reducing risk for congenital anomalies was considered appropriate.

Concerns remain about the recent trend in Wales and close monitoring continues. Further studies into the causes of gastroschisis are underway.

4.4.2 Investigation of a higher risk of congenital anomalies aboard a Norwegian missile torpedo boat (Occupational and Environmental Medicine 2006; 63: 92-97)

Background: In the 1990s, congenital anomalies were reported among children whose fathers had served aboard a Norwegian missile torpedo boat (MTB). The Royal Norwegian Navy asked the University of Bergen to look into this problem as one part of a general health and work environment surveillance.
Aims: To estimate any increased risk of having children with congenital anomalies and having stillborn children among the offspring of workers that had served aboard the MTB and to investigate possible differences in exposure and other risk factors between these groups.
Methods: Data from a cross-sectional study among all current employees of the Norwegian Navy (n = 2265, response rate 58%) were analysed.
Results: The prevalence ratio of having a child with congenital malformations associated with working on the ship was 4.0 (95% CI 1.9 to 8.6). The prevalence ratio of having a child who was stillborn or died within one week was 4.1 (95% CI 1.7 to 9.9).
Conclusion: Service aboard the MTB was associated with an increased risk of having children with congenital birth defects and having children that were stillborn. The causes of these findings are unknown.

Appendix A:

27 EUROCAT registries and time period included in surveillance

1. Antwerp (BE), 2000-2004
2. Asturias (ES), 1999-2003
3. Barcelona (ES), 1999-2003
4. Basque Country (ES), 2000-2004
5. Campania (IT), 1999-2003
6. Cork and Kerry (IE), 1998-2002
7. Dublin (IE), 2000-2004
8. Emilia Romagna (IT), 2000-2004
9. Hainaut (BE), 2000-2004
10. Hungary (HU), 1998-2002
11. Mainz (DE), 1999-2003
12. Malta (MT), 2000-2004
13. NorCAS (UK), 2000-2004
14. North East Italy (IT), 1999-2003
15. North West Thames (UK), 2000-2004
16. Northern Netherlands (NL), 2000-2004
17. Odense (DK), 2000-2004
18. Paris (FR), 2000-2004
19. S Portugal (PT), 1999-2003
20. Saxony Anhalt (DE), 2000-2004
21. Sicily (IT), 1998-2002
22. Tuscany (IT), 2000-2004
23. Vaud (CH), 2000-2004
24. Wales (UK), 2000-2004
25. Wessex (UK), 2000-2004
26. Wielkopolska (PL), 2000-2004
27. Zagreb (HR), 1999-2003

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

	Included in cluster analysis	Included in trend analysis
All anomalies		X
Nervous system		X
Neural Tube Defects	X	X
Anencephalus and similar	X	X
Encephalocele	X	X
Spina Bifida	X	X
Hydrocephaly	X	X
Microcephaly	X	X
Arhinencephaly/ holoprosencephaly	X	X
Eye		X
Anophthalmos/ micropthalmos	X	X
Anophthalmos	X	X
Congenital cataract	X	X

Congenital glaucoma	X	X
Ear, face and neck		X
Anotia	X	X
Congenital heart disease		X
Common arterial truncus	X	X
Transposition of great vessels	X	X
Single ventrical	X	X
Ventricular septal defect (VSD)	X	X
Atrial septal defect (ASD)	X	X
Atrioventricular septal defect (AVSD)	X	X
Tetralogy of Fallot	X	X
Tricuspid atresia and stenosis	X	X
Ebstein's anomaly	X	X
Pulmonary valve stenosis	X	X
Pulmonary valve atresia	X	X
Aortic valve atresia/stenosis	X	X
Hypoplastic left heart	X	X
Hypoplastic right heart	X	X
Coarctation of aorta	X	X
Total anomalous pulm venous return	X	X
Respiratory		X
Choanal atresia	X	X
Cystic adenomatous malf of lung	X	X
Oro-facial clefts		X
Cleft lip with or without palate	X	X
Cleft palate	X	X
Digestive system		X
Oesophageal atresia with or without tracheo-oesophagal fistula	X	X
Duodenal atresia or stenosis	X	X
Atresia or stenosis of other parts of small intestine	X	X
Ano-rectal atresia and stenosis	X	X
Hirschsprung's disease	X	X
Atresia of bile ducts	X	X
Annular pancreas	X	X
Diaphragmatic hernia	X	X
Abdominal wall defects	X	X
Gastroschisis	X	X
Omphalocele	X	X
Urinary		X
Bilateral renal agenesis including Potter syndrome	X	X
Cystic kidney disease	X	X
Congenital hydronephrosis	X	X
Bladder extrophy and/or epispadia	X	X
Posterior urethral valve and/or prune belly	X	X
Genital		X
Hypospadias		
Indeterminate sex	X	X
Limb		X
Limb reduction	X	X
Upper limb reduction	X	X
Lower limb reduction	X	X
Complete absence of a limb	X	X
Club foot - talipes equinovarus	X	X
Hip dislocation and/or dysplasia	X	X
Polydactyly	X	X
Syndactyly	X	X

Arthrogryposis multiplex congenita	X	X
Musculo-skeletal		X
Thanatophoric dwarfism		X
Jeunes syndrome		X
Achondroplasia		X
Craniosynostosis	X	X
Congenital constriction bands/amniotic band	X	X
Other malformations		X
Asplenia	X	X
Situs inversus	X	X
Conjoined twins	X	X
Disorders of skin	X	X
Teratogenic syndromes with malformations		X
Fetal alcohol syndrome	X	X
Valproate syndrome	X	X
Warfarin syndrome	X	X
Maternal infections resulting in malformations	X	X
Genetic syndromes & microdeletions		X
Chromosomal		X
Down's syndrome	X	X
Patau syndrome/ trisomy 13	X	X
Edward syndrome/ trisomy 18	X	X
Turner's syndrome	X	X
Klinefelter's syndrome	X	X
Cri-du-chat syndrome	X	X
Wolff-Hirschorn syndrome	X	X

Appendix B: Clusters by anomaly and registry – statistical details

Anomaly subgroup	Country	Registry	Cluster type	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA* (invalid DOB)	Cluster/ case deficit
Spina Bifida	Poland	Wielkopolska	Conception	51	26/06/01	06/12/02	30.62	0.039	90	2.2	Cluster
Spina Bifida	UK	NW Thames	Conception	46	14/01/02	14/05/03	26.25	0.027	84	0	Cluster
Hydrocephaly	France	Paris	Conception	5	10/07/02	11/07/02	0.14	0.008	216	0	Cluster
Microcephaly	Belgium	Hainaut	Conception	12	02/08/01	22/04/02	2.88	0.003	17	5.9	Cluster
Microcephaly	Germany	Saxony-Anhalt	Birth	6	07/02/03	07/02/03	0	0.001	78	11 invalid DoB	Cluster
Common arterial truncus	UK	NorCAS	Conception	8	10/07/01	15/08/02	2.58	0.033	10	0	Cluster
Ventricular septal defect	Hungary	Hungary	Birth	6	11/06/01	11/06/01	0	0.014	1620	2 invalid DoB	Cluster
Atrial septal defect	Germany	Saxony-Anhalt	Conception	5	31/08/02	31/08/02	0	0.001	332	8.1	Cluster
Atrial septal defect	Italy	Sicily	Birth	25	06/01/02	11/03/02	7.57	0.004	216	56 invalid DoB	Cluster
Atrial septal defect	UK	Wales	Birth	15	01/01/03	11/01/03	3.09	0.05	564	No invalid DoB	Cluster
Atrioventricular septal defect	Portugal	South Portugal	Conception	6	10/07/01	20/11/01	0.94	0.019	11	0	Cluster
Tetralogy of Fallot	Italy	Campania	Birth	6	25/03/03	11/04/03	0.55	0.035	59	No invalid DoB	Cluster
Pulmonary valve stenosis (PVS)	Germany	Saxony-Anhalt	Conception	16	24/01/03	29/01/04	5.96	0.02	25	4	Cluster
Pulmonary valve stenosis (PVS)	Hungary	Hungary	Conception	6	06/06/01	12/06/01	0.24	0.002	62	9.7	Cluster

Anomaly subgroup	Country	Registry	Cluster type	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA* (invalid DOB)	Cluster/ case deficit
Coarctation of aorta	Spain	Asturias	Conception	6	27/11/00	04/05/01	0.81	0.005	8	0	Cluster
Choanal atresia	Ireland	Dublin	Conception	6	06/06/01	07/04/02	1.57	0.05	8	0	Cluster
Cystic adenomatous malf of lung §	UK	NW Thames	Conception	10	17/06/03	16/12/03	1.52	0.001	13	0	Cluster
Cleft lip with or without palate	Italy	Emilia Romagna	Conception	14	31/01/03	01/05/03	3.65	0.032	63	3.2	Cluster
Ano-rectal atresia and stenosis	Germany	Saxony-Anhalt	Birth	13	07/08/01	07/02/03	4.81	0.01	16	4 invalid DoB	Cluster
Ano-rectal atresia and stenosis	Italy	Campania	Birth	18	08/01/02	25/03/03	7.49	0.038	31	No invalid DoB	Cluster
Ano-rectal atresia and stenosis	Italy	Tuscany	Conception	6	27/12/03	29/01/04	0.66	0.028	31	6.5	Cluster
Ano-rectal atresia and stenosis	UK	NW Thames	Conception	5	18/01/03	27/01/03	0.34	0.043	59	0	Cluster
Abdominal wall defects	UK	Wales	Conception	21	16/05/03	14/08/03	6.96	0.043	120	0.8	Cluster
Gastroschisis	Portugal	South Portugal	Conception	8	28/08/00	05/06/01	2.17	0.026	12	0	Cluster
Gastroschisis	UK	NorCAS	Conception	9	28/01/04	29/02/04	1.34	0.019	65	0	Cluster
Gastroschisis	UK	Wales	Conception	14	04/06/03	14/08/03	3.52	0.029	77	1.3	Cluster
Omphalocele	Germany	Saxony-Anhalt	Conception	6	16/06/02	31/08/02	0.73	0.021	15	0	Cluster
Omphalocele	Italy	Emilia Romagna	Conception	15	21/10/02	23/07/03	5.14	0.027	29	6.9	Cluster
Bilateral renal agenesis	Germany	Saxony-Anhalt	Conception	10	18/03/02	13/03/03	3.02	0.022	13	0	Cluster

Anomaly subgroup	Country	Registry	Cluster type	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA* (invalid DOB)	Cluster/ case deficit
Cystic kidney disease	Germany	Saxony-Anhalt	Birth	8	08/03/04	08/04/04	0.93	0.014	55	17 invalid DoB	Cluster
Cystic kidney disease	Spain	Barcelona	Conception	15	14/05/00	10/06/01	5.81	0.03	23	4.3	Cluster
Congenital hydronephrosis	Italy	Sicily	Birth	34	02/01/02	08/11/02	13.58	0.001	80	8 invalid DoB	Cluster
Congenital hydronephrosis	Portugal	South Portugal	Conception	14	25/04/02	15/08/02	3.68	0.024	51	0	Cluster
Congenital hydronephrosis	Spain	Asturias	Conception	5	11/07/01	24/07/01	0.29	0.013	35	0	Cluster
Posterior urethral valve and/or prune belly	Ireland	Dublin	Conception	5	09/08/03	17/12/03	0.67	0.011	8	0	Cluster
Posterior urethral valve and/or prune belly	Spain	Basque Country	Conception	7	02/02/03	14/11/03	1.65	0.019	9	0	Cluster
Limb reduction	Germany	Saxony-Anhalt	Birth	5	07/11/03	07/11/03	0	0.001	50	15 invalid DoB	Cluster
Limb reduction	Portugal	South Portugal	Conception	6	05/02/02	16/04/02	0.81	0.026	18	0	Cluster
Club foot - talipes equinovarus	France	Paris	Conception	5	22/05/02	23/05/02	0.1	0.003	156	0	Cluster
Club foot - talipes equinovarus	Germany	Saxony-Anhalt	Birth	5	07/08/04	07/08/04	0	0.001	118	31 invalid DoB	Cluster
Club foot - talipes equinovarus	Italy	Campania	Conception	49	23/07/01	10/01/03	19.35	0.001	56	8.9	Cluster
Club foot - talipes equinovarus	Italy	Tuscany	Conception	31	08/05/02	05/09/03	15.63	0.02	50	2	Cluster
Club foot - talipes equinovarus	UK	Wales	Birth	5	07/02/04	09/02/04	0.22	0.038	205	No invalid DoB	Cluster

Anomaly subgroup	Country	Registry	Cluster type	No of cases in cluster	Cluster start date	Cluster end date	Expected cases	Probability	Valid cases	% estimated GA* (invalid DOB)	Cluster/ case deficit
Hip dislocation and/or dysplasia	Ireland	Cork & Kerry	Conception	39	08/11/00	21/04/02	21.81	0.034	64	0	Cluster
Hip dislocation and/or dysplasia	Ireland	Dublin	Conception	7	15/11/02	19/11/02	0.43	0.007	167	0	Cluster
Hip dislocation and/or dysplasia	Italy	Sicily	Birth	23	05/11/99	29/04/01	10.67	0.016	36	4 invalid DoB	Cluster
Syndactyly	Portugal	South Portugal	Conception	5	22/10/01	20/11/01	0.39	0.018	21	0	Cluster
Congenital constriction band /amniotic band	UK	Wales	Conception	11	23/12/01	17/10/02	3.46	0.031	18	5.6	Cluster
Situs inversus	Italy	Tuscany	Conception	5	12/09/02	01/01/03	0.57	0.008	8	0	Cluster
Conjoined twins	UK	NW Thames	Conception	6	31/10/02	14/05/03	1.26	0.046	10	10	Cluster
Disorders of skin	Poland	Wielkopolska	Conception	11	03/04/01	23/04/02	3.72	0.03	15	0	Cluster
Down Syndrome	UK	NW Thames	Conception	6	04/12/03	05/12/03	0.3	0.024	462	0.4	Cluster
Edward syndrome/ trisomy 18	Denmark	Odense	Conception	6	03/09/02	11/02/03	1.14	0.033	11	0	Cluster
Edward syndrome/ trisomy 18	Spain	Barcelona	Conception	14	10/08/01	19/03/02	3.99	0.011	28	7.1	Cluster
Turner's syndrome	Hungary	Hungary	Birth	20	18/03/01	23/06/02	7.59	0.004	30	2 invalid DoB	Cluster
Klinefelter's syndrome	Spain	Barcelona	Conception	7	09/07/01	07/01/02	1.29	0.014	11	9.1	Cluster

* GA: Gestational age; DOB: Date of birth;

§: ICD10 codes with no equivalent ICD9 codes

Appendix C: Trends by anomaly and registry– statistical details

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