European Commission

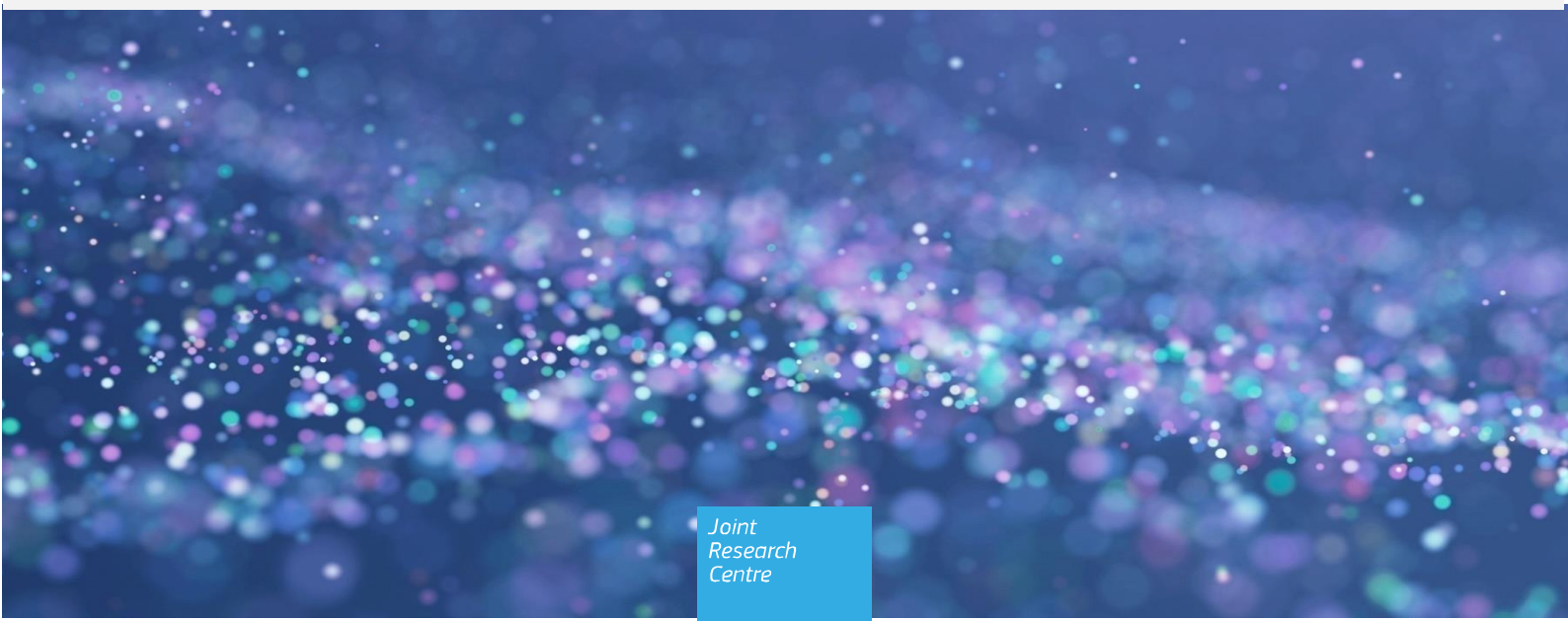
JRC TECHNICAL REPORT

EUROCAT Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2012-2021)

Kinsner-Ovaskainen, A., Perraud, A., Garne, E., Morris, J.

2024



Joint Research Centre

Contact information
Name: Agnieszka Kinsner-Ovaskainen
Address: Via Fermi 2749, 21027, Ispra, Italy
Email: agnieszka.kinsner-ovaskainen@ec.europa.eu
Tel.: +39 0332 78 9246

EU Science Hub
https://joint-research-centre.ec.europa.eu

JRC136083

Ispra: European Commission, 2024

How to cite this report: Kinsner-Ovaskainen, A., Perraud, A., Garne, E. and Morris, J., *EUROCAT Monitoring of Congenital Anomalies*, European Commission, 2024, JRC136083.

Contents

Abstract

Congenital anomalies are a leading cause of infant mortality and morbidity in childhood worldwide.

The European network of population-based registries (EUROCAT) was established to provide essential epidemiologic information on congenital anomalies in Europe, to facilitate the early warning of new teratogenic exposures and to evaluate the effectiveness of primary prevention. The network currently surveys approximately one fourth of the European birth population. The EUROCAT Central Registry is operated by the European Commission's Joint Research Centre, as part of the European Platform on Rare Diseases Registration.

Each year, EUROCAT conducts the statistical monitoring of congenital anomalies to detect changes in time within each registry and to detect trends across all registries. In the present report we describe and comment on the results of the statistical analysis performed centrally on data for the birth years 2012-2021, with a special focus on the investigation of 34 clusters of congenital anomalies detected in 20 registries over the birth years 2016-2020 and 2017-2021. Where available, the outcomes of preliminary investigations conducted by registries are also presented.

Acknowledgements

This report was compiled by Agnieszka Kinsner-Ovaskainen and Annie Perraud. JRC-EUROCAT Central Registry analysis and investigations of the clusters were conducted by Annie Perraud and Agnieszka Kinsner-Ovaskainen, with input from Ester Garne, Joan Morris and Florence Rouget.

Data from the following registries are included in the report: Auvergne (Registry Leader: Isabelle Perthus), Brittany (Florence Rouget), Cork & Kerry (Mary O'Mahony), Emilia Romagna (Amanda Neville), French West Indies (Leïla Frigere), Funen (Ester Garne), Hainaut (Christine Verellen-Dumoulin), Malta (Miriam Gatt), Milan Metropolitan Area (Giampiero Russo), Navarra (Amaia Bengoa Alonso), NCARDRS: Northern England, South West England, Thames Valley and Wessex (Sarah Stevens), Northern Netherlands (Dieuwke Broekstra), Paris (Babak Khoshnood and Nathalie Lelong), Pleven (Katya Kovacheva), Réunion (Lea Bruneau), Saxony Anhalt (Anke Rissmann), Styria (Martin Haeusler), Trento (Riccardo Pertile), Tuscany (Anna Pierini), OMNI-net Ukraine (Natalia Zymak Zakutna), Valencian Region (Clara Cavero-Carbonell), Vaud (Marie-Claude Addor), Wales (David Tucker) and Zagreb (Ljubica Odak).

The report was reviewed and approved by the JRC-EUROCAT Management Committee (Ester Garne, Dieuwke Boekstra, Maria Loane, Joan Morris, Amanda Neville, Florence Rouget, Michele Santoro and David Tucker) and by the registry leaders.

Authors

Agnieszka Kinsner-Ovaskainen, Annie Perraud: European Commission, Joint Research Centre, Ispra, Italy

Ester Garne, Department of Paediatrics and Adolescent Medicine, Lillebaelt Hospital, University Hospital of Southern Denmark, Kolding, Denmark.

Joan Morris, Population Health Research Institute, St George's, University of London, London, UK

1 Introduction

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies, which was established in 1979. Since 2015 the EUROCAT Central Registry is operated by the European Commission's Joint Research Centre (Ispra, Italy), as part of the European Platform on Rare Disease Registration [1, 2, 3].

EUROCAT surveys more than 1.1 million of births per year, approximately one fourth of the European birth population [4]. Registries from 20 European countries transmit yearly to the JRC-EUROCAT Central Registry pseudonymised individual case data (full member registries) or aggregate data (associate members) on congenital anomalies in their region.

Each year, the JRC-EUROCAT Central Registry performs the statistical monitoring of pan-European trends and temporal clusters of congenital anomalies using data submitted by the registries. This analysis is performed on individual case data from full member registries only. Cases of congenital anomalies among live births, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly (TOPFA) following prenatal diagnosis at any gestational age are included.

The results of the statistical monitoring performed centrally are the basis for initiating possible further investigations at the local registry level.

The cluster analysis detects unusual aggregation of cases in time within each registry area, which may be a cause of concern (e.g. teratogenic exposures). After a detailed investigation, registries may decide to inform local public health authorities about the cluster and the findings.

A pan-European trend analysis enables the monitoring of congenital anomalies that have too few cases to be monitored at individual registry level, as well as presenting an overview of the situation in Europe. Annual prevalence rates of 94 subgroups of congenital anomalies, including all three birth outcomes (live births, fetal deaths from 20 weeks gestational age, and TOPFA at any gestational age) are monitored.

The annual statistical monitoring provides timely information on any long-term changes in prevalence or any unusual aggregation of cases in time. Analysis of trends and clusters serves the objective of early warning of potential new teratogenic exposures, and provides evidence for informing public health policies. Monitoring of changes in prevalence of certain anomalies allows also assessing the effectiveness of prevention strategies, or information campaigns, and can help to evaluate screening programmes.

Trends and clusters may occur due to different methods of ascertainment, the introduction of new diagnostic methods that increase the number of cases detected, and other reasons not related to a real increase/decrease of a given anomaly. All trends and clusters identified centrally are investigated at a local level, and summaries of these investigations are reported to the Central Registry and used to prepare the surveillance report. Hence, the involvement of all the registries in the investigation is key and facilitates interpretation of the findings.

The current report covers the birth years between 2012 and 2021. We report here the results of the cluster analyses performed for 91 anomaly subgroups on cases reported for the periods 2016-2020 and 2017-2021 by 20 EUROCAT registries. The pan-European trend analyses were performed on 94 anomaly subgroups on cases reported for the period 2012-2021 by 26 EUROCAT registries but are not described in detail in the report.

2 Clusters

2.1 Cluster detection methodology

EUROCAT defines clusters as an aggregation of cases of congenital anomaly in time and/or space which appears to be unusual.

Each year the JRC-EUROCAT Central Registry performs a temporal cluster analysis using the most recent five years of data. A five-year period is considered optimal for cluster monitoring because the inclusion of more than five years data may detect trends rather than clusters, while less than five years may fail to detect clusters if the most recent years are unusual compared to preceding years [5].

The annual statistical monitoring performed at the central level concerns the detection of the time clusters only. The data does not permit geographical evaluations, as precise data on geographic locations of the residence of the mothers is not transmitted to the Central Registry. Cluster investigations, including potentially space investigation, are then conducted by the registry at a local level.

For the purpose of monitoring, cases cover all live births, fetal deaths from 20 weeks of gestational age onwards, as well as terminations of pregnancy for fetal anomalies (TOPFA) at any gestational age. As the surveillance is conducted for identifying new teratogens, cases with an associated genetic diagnosis are excluded.

Cluster detection is based on a 'scan' moving window test. It detects whether the given number of cases has occurred in a shorter time than would be expected by chance. A minimum of seven cases over the study period of interest is needed to run the analysis. Each registry and anomaly subgroup is tested independently. Clusters are reported when they are within or overlapping the last two years (in this report 2019-2020 or 2020-2021) and are of less than 18 months in length.

In order to detect clusters or deficits occurring during the last two years, and which lasted for less than 18 months, the EUROCAT Data Management Software (DMS) [6] is used and run on 91 EUROCAT subgroups of congenital anomalies (see Annex A). Excluded from the analysis are the major heterogeneous subgroups listed in Annex A (e.g. nervous system anomalies, congenital heart defects).

Since the exposure during early pregnancy, i.e. when organogenesis occurs, is pertinent, it is preferable to use the estimated date of conception rather than the date of birth. Cluster detection uses date of conception where gestational age is recorded for more than 90% of cases (for any one anomaly subgroup and registry) allowing its estimation. 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, i.e. 2021 or 2020 in the current analysis.

Where gestational age is missing, it is estimated on the basis of the average gestational age in the registry, by year, anomaly subgroup, and outcome of pregnancy. Gestational age is not estimated if it is missing for more than 10% of cases for the registry and anomaly subgroup, in which case cluster detection is based on date of birth. If date of birth/delivery is used to detect clusters, the last full year (1 January – 31 December) is included in the surveillance.

After the analysis conducted by the Central Registry, every registry receives a report with its clusters for investigation. In the report, the clusters are visually identified over the time period. If the investigation of clusters identifies data errors (e.g. incorrect diagnoses, incorrect dates of birth) these errors should be corrected and the updated data shall be included in the next data transmission to the Central Registry.

2.2 Registries included in the cluster analysis

Usually, only registries classified as "early responders", i.e. registries that meet the EUROCAT data transmission deadline of the 15th February, and with data for the most recent five years (2017-2021) should be included in the monitoring of clusters. For this report, however, only 12 registries sent data on the 15th February 2023 for birth year 2021, due to disruptions in data collection and delays in reporting, largely related to backlogs from the Covid-19 pandemic. Hence, data from all registries that submitted the cases to the Central Registry for birth years 2016-2020 were considered, as this period was not covered by the previous analysis which was run up to birth year 2019 [7].

The registry inclusion criteria for cluster analysis were the following:

- registries must submit individual case data, i.e. must be full EUROCAT members;
- registries must have transmitted data for all five years, i.e. for 2017-2021, or 2016-2020;
- the number of cases submitted by the registry for 2021 (or 2020) was at least 80% of those submitted in previous calendar years;
- registries must have transmitted the full date of birth/date of termination for all cases;
- registries must have a stable birth population (annual birth population changes must be less than +/-10% between any two years within the five-year period).

At the time of statistical monitoring in May 2023, there were 36 full member registries in EUROCAT (see Annex B). Twenty registries were included in the cluster analysis. Eleven registries satisfied the criteria to be included in the cluster analysis on the period 2017-2020. For nine registries that did not submit the data for the last birth year (2021) exceptionally the analysis was run for the period 2016-2020.

The registries with data for 2017-2021 were: Funen (Denmark), Paris (France), Tuscany (Italy), Northern Netherlands, Emilia Romagna (Italy), Vaud (Switzerland), Cork & Kerry (Ireland), Wales (UK), French West Indies (France), Brittany (France), and Trento (Italy).

The registries with data for 2016-2020 were: Styria (Austria), Hainaut (Belgium), Malta, Auvergne (France), Réunion (France), Valencian Region (Spain), Pleven (Bulgaria), Navarra (Spain), and Milan Metropolitan Area (Italy).

The full member registries excluded from the analysis were:

- the registries from England (seven registries), Norway and Saxony-Anhalt because the date of birth transmitted to the Central Registry is not the exact date (for privacy reasons). The analysis done by the Central Registry cannot detect clusters unless an accurate date of birth is provided. Hence, in this situation registries are advised to perform the cluster analysis locally using accurate dates of birth;
- the registry in Zagreb as for the period 2016-2020, it had a fluctuation of over 10% in the annual birth population;
- the registries in South Portugal and OMNI-net (Ukraine), as the data for birth year 2020 were incomplete;
- Wielkopolska (Poland) had a large variation in the number of cases between 2016-2020;
- Antwerp (Belgium), Basque country (Spain), South-East Ireland were excluded from the cluster analyses because for the period 2016-2020 these registries had less than five years of data in the Central Database.

2.3 Cluster analysis 2017-2021 and 2016-2020

The analysis of clusters was conducted by the Central Registry in May 2023. The results were discussed by the JRC-EUROCAT Management Committee in June and September 2023.

The following number of potential clusters were detected in the analysis:

- 2017-2021: 11 registries included, 25 clusters detected in 10 registries. No clusters were detected in Paris.
- 2016-2020: 9 registries included, 9 clusters detected in 6 registries. No clusters were detected in Hainaut, Milan, and Navarra.

The clusters are presented in Table 1 and Table 2. All the detected clusters were sent to the registries with a request for a local investigation. In addition, four clusters were detected based on the date of birth (DoB). The Management Committee agreed that clusters detected by DoB will not be investigated further. Indeed, a similar DoB does not necessarily imply a similar date of conception, hence it is less accurate.

Table 1. Clusters detected by date of conception in 11 EUROCAT registries over the birth years 2017-2021.

Anomaly subgroup	Brittany	Cork & Kerry	Emilia Romagna	Funen	French West Indies	Northern Netherlands	Trento	Tuscany	Vaud	Wales
Spina Bifida						C				
Hydrocephaly						C				
Severe CHD			C							
Atrial septal defect		C								
Atrioventricular septal defect					C					
Pulmonary valve stenosis						C				
Aortic valve atresia or stenosis								C		
Hypoplastic right heart			C							
Congenital pulmonary airway malformations (CPAM)	C									
Oesophageal atresia with or without trachea-oesophageal fistula								C		
Diaphragmatic hernia				C					C	
Unilateral renal agenesis			C							
Congenital hydronephrosis including ureter obstruction	C							C		
Hypospadias			C							

Anomaly subgroup	**Brittany**	**Cork & Kerry**	**Emilia Romagna**	**Funen**	**French West Indies**	**Northern Netherlands**	**Trento**	**Tuscany**	**Vaud**	**Wales**
Limb reduction defects (LRD)		C								
Club foot – talipes equinovarus						C				
Polydactyly							C			
Syndactyly										C
Laterality anomalies			C							
Vascular disruption anomalies	C									
Maternal infections resulting in major malformations	C									
Patau syndrome/trisomy 13							C			
Triploidy and polyploidy	C									

Table 2. Clusters detected by date of conception in 9 EUROCAT registries over the birth years 2016-2020.

Anomaly subgroup	**Auvergne**	**Malta**	**Pleven**	**Réunion**	**Styria**	**Valencian Region**
Atrial septal defect	C					
Ventricular septal defect		C*				
Diaphragmatic hernia				C		
Gastroschisis						C*
Multicystic renal dysplasia		C				
Congenital hydronephrosis including ureter obstruction			C*		C	
Posterior urethral valves	C	C				

*Cluster detected in last year's analysis [7].

2.4 Methodology for cluster investigations

Investigation templates are provided to make the reporting process consistent between registries (see Annex C). Using the templates, registries were asked to include the following in their cluster investigation report:

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 (medication during pregnancy, maternal diseases including infections, maternal occupation, BMI, assisted conception and others), and which source of information was used (registry database, further access to medical records or parents etc.).
3. Geographical distribution of the cases within the registry area.
4. Any local concerns about exposures and how they came to registry's attention.
5. Whether anyone in the region (e.g. local community or health professional) had previously been aware of the cluster.
6. The basis for registry's decisions to conduct the investigation in the way they did, and whether they will continue to investigate (if so, how? if not, why not?).
7. Which public health authorities have been or will be notified about the cluster?
8. Registries are asked to conclude from their preliminary investigations if this is a 'true cluster of concern or not'.

The detailed review of the cluster cases helps not only to detect potential teratogenic exposures, but also to identify some issues with quality or with coding, and subsequently improve the quality of the data in the local and Central databases.

The most common reasons for a cluster not being confirmed at local level are:

- Issues with coding of cases (cluster disappears after correction of code)
- Genetic cases: late diagnosis of the genetic anomaly or coding issues (cluster disappears after exclusion of genetic cases)
- Duplicate cases
- Changes in case ascertainment / new data sources
- Clusters by date of conception with cases occurring within 1 or 2 days. As the date of conception is not as accurate, this could be a statistical artefact.

The following section discusses in detail only those clusters, which were investigated by the registries and where the excess of cases was confirmed.

The conclusions from the cluster investigations are summarised in Table 3 and were classified as follows:

- Apparent cluster with cause for concern, further investigation on-going.
- Cluster associated with etiologic 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. Clusters to be investigated at local level only.

The cluster investigations are presented below and summarised in Table 3.

2.5 Details on the cluster investigations

2.5.1 Spina bifida

The cluster was detected in Northern Netherlands. There were five cases over 27 days (expected number of cases = 0.5). The registry confirmed the excess of cases, but the cluster could not be explained by the local investigation. The registry considers that there are no reasons for concern. The cluster will require a further period of surveillance.

North Netherlands (NL)

Anomaly subgroup:	**Spina Bifida**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2017 and 31/03/2021

Most significant cluster

Number of cases:	5	Expected number of cases:	0.451	p value:	0.038
Start date:	17/10/2019				
End date:	13/11/2019				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

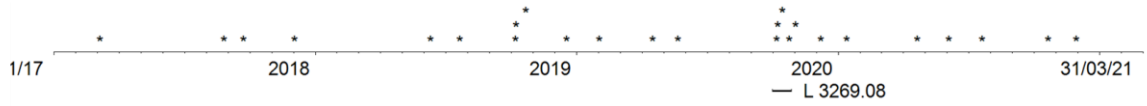


Figure 1. Cluster of Spina bifida detected in Northern Netherlands

2.5.2 Hydrocephaly

The cluster was detected in Northern Netherlands. There were 11 cases over 15 months (expected number of cases = 3.8). Five cases had isolated brain anomalies, five were cases of multiple congenital anomalies and one case had hydrocephaly due to a toxoplasmosis infection. The last case was not considered further in the investigations. Based on the detailed local investigation the registry concluded that the cluster will require a longer period of surveillance.

North Netherlands (NL)

Anomaly subgroup:	**Hydrocephaly**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2017 and 31/03/2021

Most significant cluster

Number of cases:	11	Expected number of cases:	3.847	p value:	0.014
Start date:	06/08/2018				
End date:	07/11/2019				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

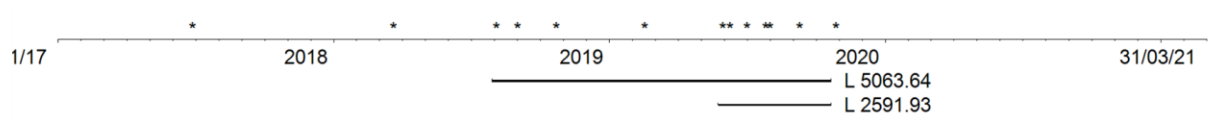


Figure 2. Cluster of hydrocephaly detected in Northern Netherlands

2.5.3 **Atrial septal defect (ASD)**

The cluster was detected in Cork & Kerry. There were 18 cases over 108 days (expected number of cases = 4.5). The cluster could be explained by a data quality issue. The registry records any case of ASD with a neonatal echography, without a follow up to confirm if the case has a true ASD or just an open foramen ovale in the neonatal period. Thus, many ASDs present in the central database were not confirmed 6 months after birth, which is the EUROCAT recommendation for diagnosing ASD.

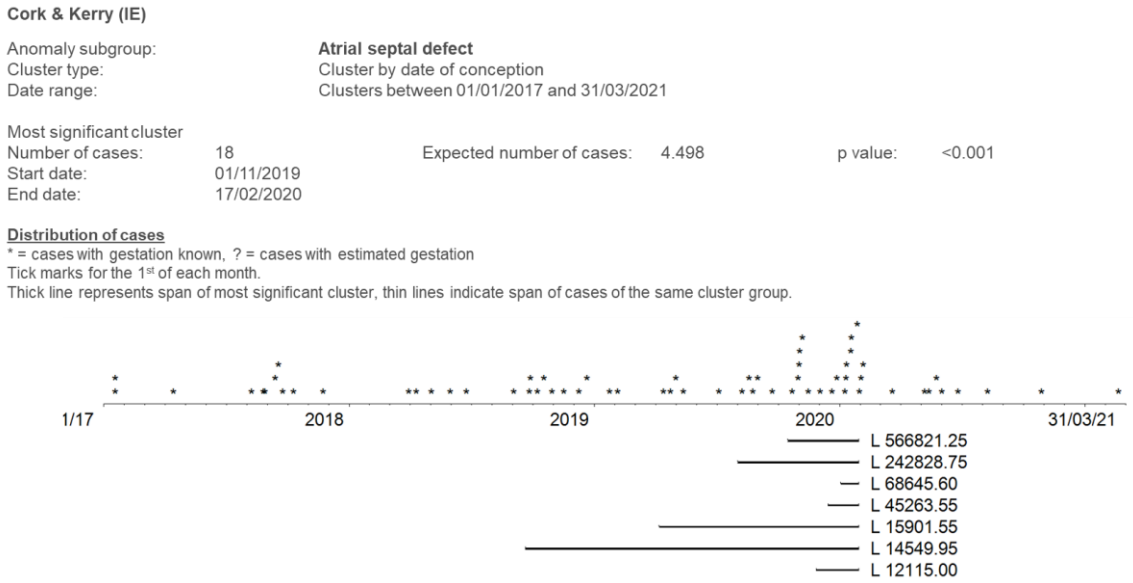


Figure 3. Cluster of Atrial septal defect detected in Cork and Kerry.

2.5.4 **Atrioventricular septal defect**

The cluster was detected in French West Indies. There were five cases over 54 days (expected number of cases = 0.4). The cluster could be explained by a data quality issue. The local investigation found that two cases had incorrect coding. After exclusion of these cases, there was not more cluster.

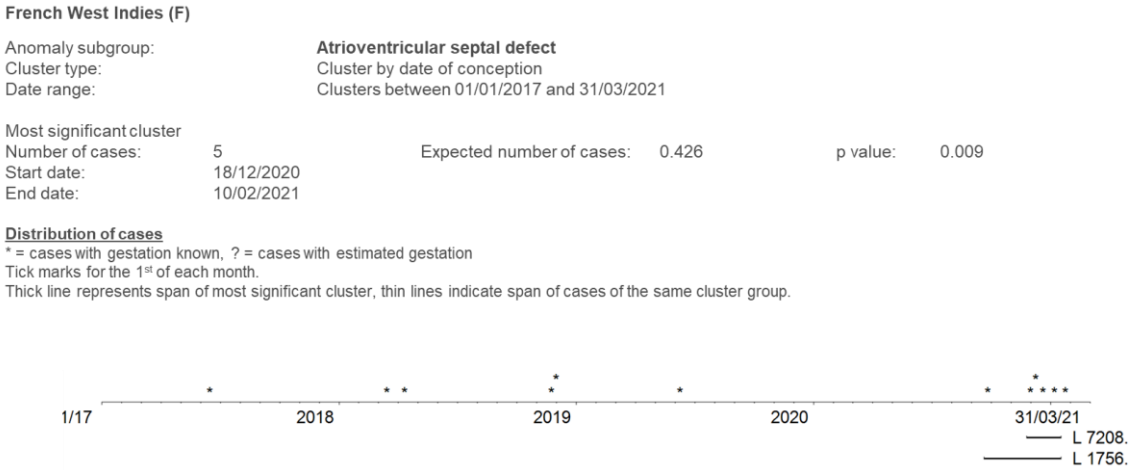


Figure 4. Cluster of Atrioventricular septal defect detected in French West Indies

2.5.5 **Pulmonary valve stenosis**

The cluster was detected in Northern Netherlands. There were 12 cases over 95 days (expected number of cases = 3.0). The local investigation has found that one case had a genetic diagnosis that was not yet reported to the Central Database. After exclusion of the case, the cluster is no longer significant.

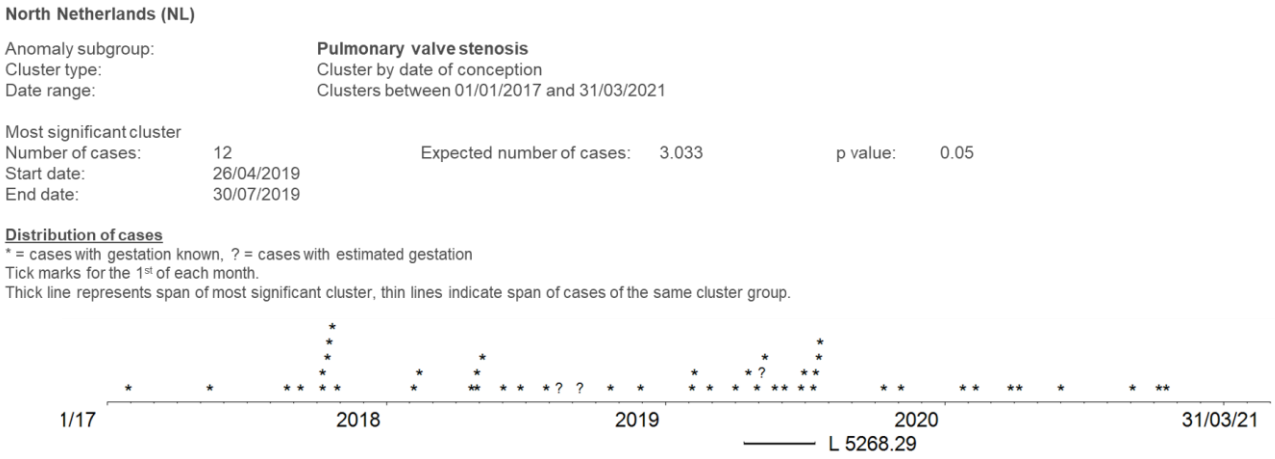


Figure 5. Cluster of pulmonary valve stenosis detected in Northern Netherlands

2.5.6 **Aortic valve atresia / stenosis**

The cluster was detected in Tuscany. There were five cases over 182 days (expected number of cases = 0.9). The registry confirmed the excess of cases, but the cluster could not be explained by the local investigation. The cluster will require a further period of surveillance.

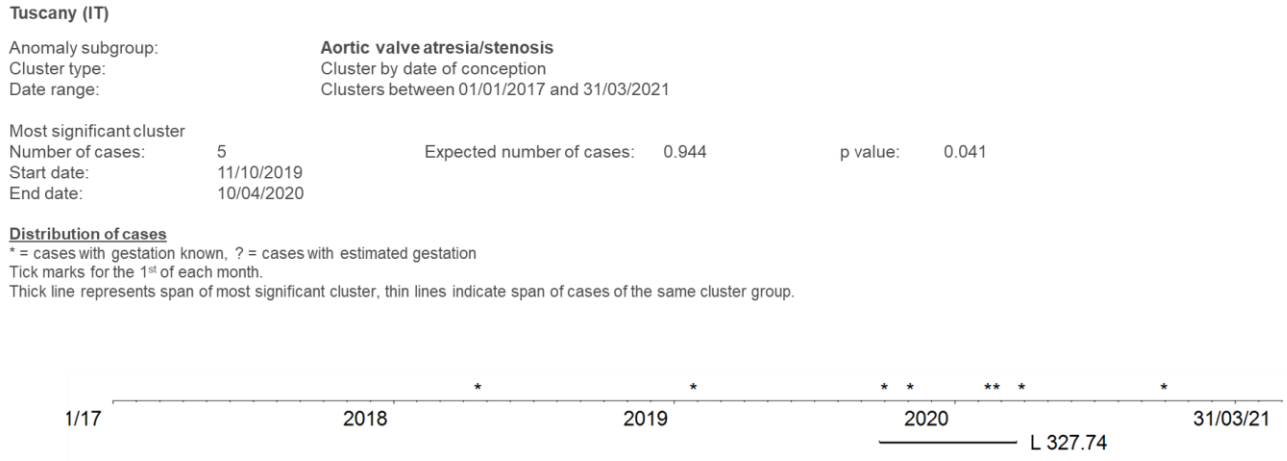


Figure 6. Cluster of aortic valve atresia / stenosis detected in Tuscany

2.5.7 **Hypoplastic right heart (HRH / HRHS)**

The cluster was detected in Emilia Romagna. There were six cases over 206 days (expected number of cases = 1.1). The investigation has found that one case was a duplicate. No additional investigation was proposed other than further surveillance.

Emilia Romagna (IT)

Anomaly subgroup: **Hypoplastic right heart (HRH/HRHS)**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2017 and 31/03/2021

Most significant cluster
Number of cases: 6 Expected number of cases: 1.068 p value: 0.009
Start date: 22/11/2019
End date: 15/06/2020

Distribution of cases
* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

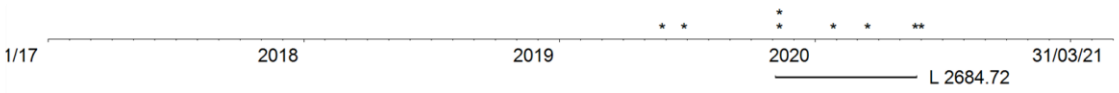


Figure 7. Cluster of HRH/HRHS detected in Emilia Romagna.

2.5.8 **Congenital pulmonary airway malformations (CPAM)**

The cluster was detected in Brittany. There were five cases over 35 days (expected number of cases = 0.5).

The excess of cases was confirmed by the registry. The registry also informed that a cluster of these anomalies was notified in 2019 by clinicians and led to increased surveillance of this subgroup and the detection of a significant Standardized Incidence Ratio (SIR) in one county. It was notified to Santé Publique France (French Public Health) and the Regional Health Agency. In May 2023 significant SIR in another county of Brittany for the 2021 births was found (3 cases overlap with the temporal cluster). The update on this subgroups has been notified to the Regional Health Agency by the registry.

Brittany (FR)

Anomaly subgroup: **Congenital pulmonary airway malformations (CPAM)**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2017 and 31/03/2021

Most significant cluster
Number of cases: 5 Expected number of cases: 0.487 p value: 0.039
Start date: 11/08/2020
End date: 15/09/2020

Distribution of cases
* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

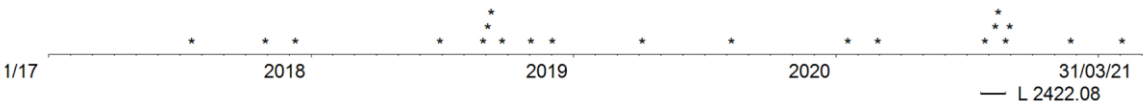


Figure 8. Cluster of CPAM detected in Brittany.

2.5.9 **Oesophageal atresia with or without trachea-oesophageal fistula**

The cluster was detected in Tuscany. There were seven cases over 78 days (expected number of cases = 1.2). The registry confirmed the excess of cases, but the cluster could not be explained by the local investigation. The cluster will require a further period of surveillance.

Tuscany (IT)

Anomaly subgroup:	**Oesophageal atresia with or without trachea-oesophageal fistula**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2017 and 31/03/2021

Most significant cluster

Number of cases:	7	Expected number of cases:	1.172	p value:	0.049
Start date:	09/11/2019				
End date:	26/01/2020				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

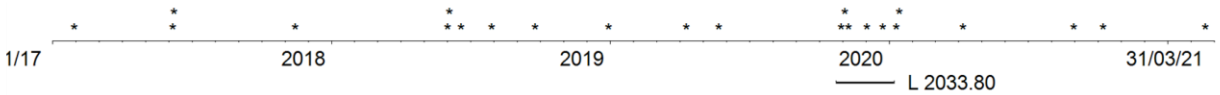


Figure 9. Cluster of oesophageal atresia with or without trachea-oesophageal fistula detected in Tuscany

2.5.10 **Diaphragmatic hernia**

The clusters were detected in Funen and Vaud.

In Funen there were five cases over 6.5 months (expected number of cases = 0.9).

Funen (DK)

Anomaly subgroup:	**Diaphragmatic hernia**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2017 and 31/03/2021

Most significant cluster

Number of cases:	5	Expected number of cases:	0.898	p value:	0.018
Start date:	22/02/2019				
End date:	08/09/2019				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

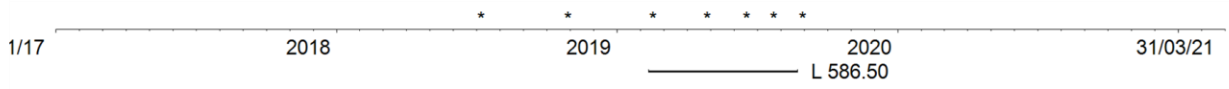


Figure 10. Cluster of diaphragmatic hernia detected in Funen

In Vaud there were five cases over 8.5 months (expected number of cases = 1.1).

Vaud (CH)

Anomaly subgroup:	**Diaphragmatic Hernia**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2017 and 31/03/2021

Most significant cluster

Number of cases:	5	Expected number of cases:	1.146	p value:	0.042
Start date:	10/07/2019				
End date:	19/03/2020				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

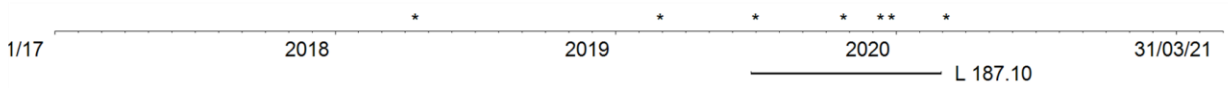


Figure 11. Cluster of diaphragmatic hernia detected in Vaud

In both registries that performed the investigation (Funen and Vaud) the excess of cases was confirmed, but the clusters could not be explained by the local investigations. A longer period of surveillance is required as the clusters were over a long period and there are no cases in the year before and the year after.

A third cluster of diaphragmatic hernia was also detected in Reunion, but it was not further investigated locally, thus it is not presented in detail here.

2.5.11 **Gastroschisis**

The cluster was detected in Valencian Region. A cluster of gastroschisis was detected also in last year's analysis but over a shorter period of time [7]. In the current cluster, there were 11 cases over 6 months (expected number of cases = 2.7). The registry confirmed the excess of cases. The investigation found that the mean maternal age in the 11 cases (24.8) was lower than the mean age of all mothers of children with CA in the registry. There were no difference in for the other factors investigated (type of birth, residence, GA). No further local investigation was proposed other than further surveillance.

Valencian Region (ES)

Anomaly subgroup:	**Gastroschisis**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2016 and 31/03/2020

Most significant cluster

Number of cases:	11	Expected number of cases:	2.653	p value:	0.014
Start date:	09/10/2018				
End date:	05/04/2019				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

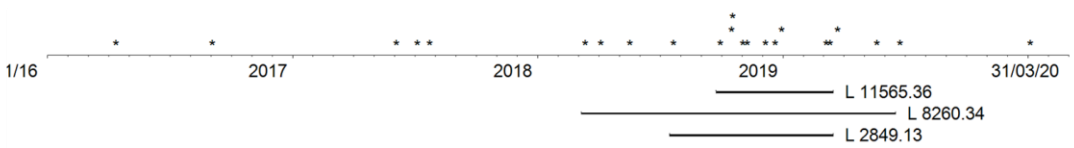


Figure 12. Cluster of gastroschisis in detected Valencian Region

2.5.12 **Unilateral renal agenesis**

The cluster was detected in Emilia Romagna. There were 14 cases over 59 days (expected number of cases = 3.1). The investigation found two duplicate cases. The increase in the number of cases may be due to the variability in prenatal diagnosis. If the renal agenesis is not known prenatally, it may not be diagnosed in infancy or within the upper age limit for registering cases in the registry. No further investigation was proposed other than continued surveillance.

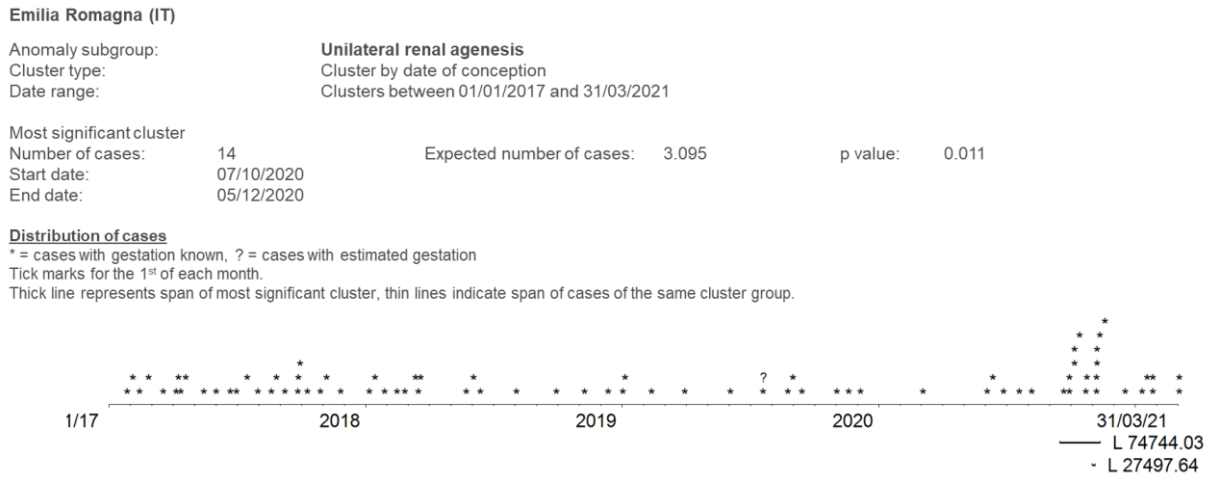


Figure 13. Cluster of Unilateral renal agenesis detected in Emilia Romagna

2.5.13 **Congenital hydronephrosis**

The cluster was detected in Tuscany and Pleven.

In Tuscany there were 10 cases over 15 days (expected number of cases = 1.3). The registry confirmed the excess of cases but the cluster could not be explained by the local investigation. The registry considers that there are no reasons for concern. Moreover, the registry does not have information on the exact dimension of pyelectasis or hydronephrosis (the diameter of the pelvis), therefore cannot evaluate fully whether the anomalies in all cases have to be considered major according to EUROCAT criteria (10 mm or more after birth). No further surveillance is planned.

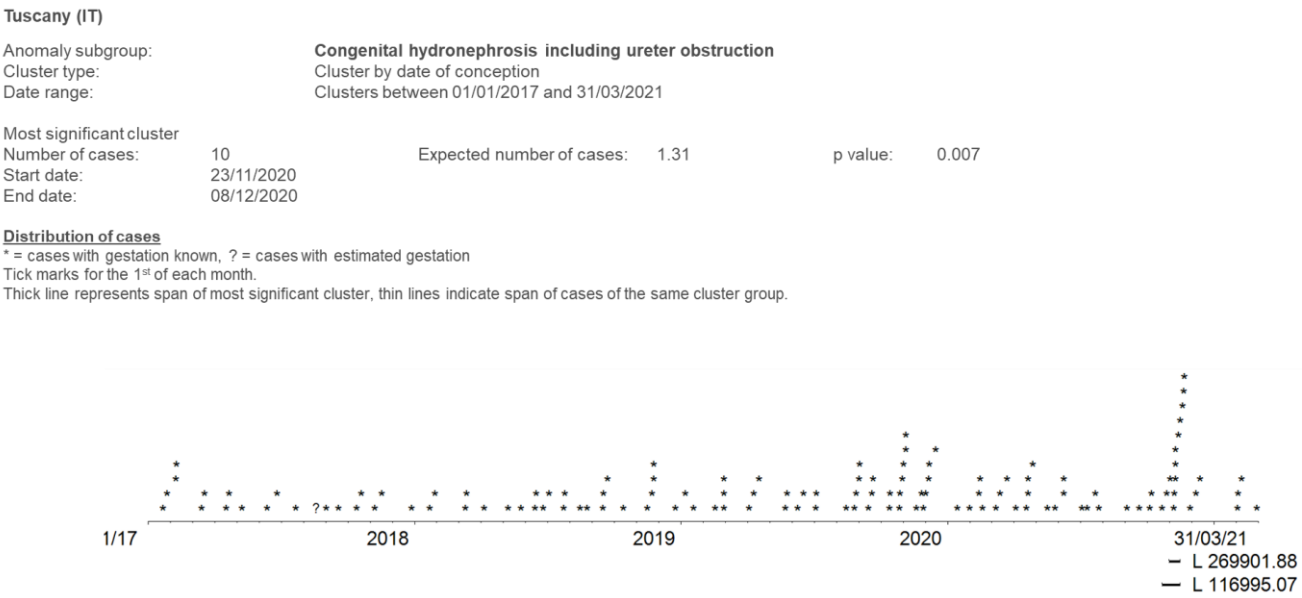


Figure 14. Cluster of congenital hydronephrosis detected in Tuscany

In Pleven there were 5 cases over 8.5 months (expected number of cases = 1.2). The registry confirmed the excess of cases, but no further local investigation was proposed other than further surveillance. The registry considers that there are no reasons for concern. There is no information on the exact dimension of pyelectasis or hydronephrosis of the registered cases, which makes it difficult to accurately consider the anomaly as major.

Pleven (BG)

Anomaly subgroup: **Congenital hydronephrosis including ureter obstruction**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2016 and 31/03/2020

Most significant cluster
Number of cases: 5 Expected number of cases: 1.186 p value: 0.047
Start date: 09/06/2018
End date: 26/02/2019

Distribution of cases
* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

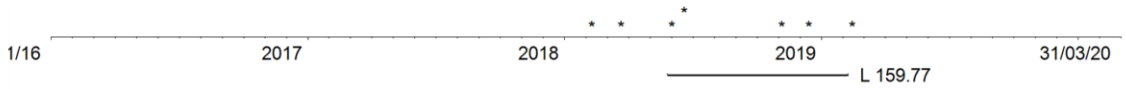


Figure 15. Cluster of congenital hydronephrosis detected in Pleven

2.5.14 **Posterior urethral valves**

The cluster was detected in Auvergne. There were five cases over 121 days (expected number of cases = 0.8). The cluster was explained by data quality issues, as two cases were not correctly coded. In two cases with lower urinary tract obstruction, posterior urethral valves diagnosis was a hypothesis at ultrasound examinations in early pregnancy, but not confirmed by autopsy (possible atresia or stenosis of urethra), and one was also a possible syndromic case. After change of the ICD-10 codes from Q6420 to Q643 for two cases, there was no more cluster.

Auvergne (FR)

Anomaly subgroup: **Posterior urethral valve**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2016 and 31/03/2020

Most significant cluster
Number of cases: 5 Expected number of cases: 0.786 p value: 0.046
Start date: 08/05/2019
End date: 06/09/2019

Distribution of cases
* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

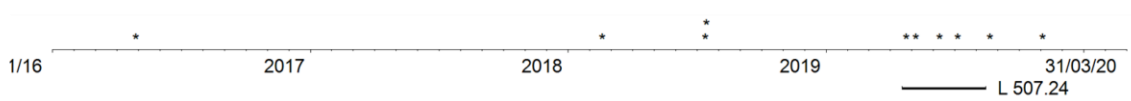


Figure 16. Cluster of posterior urethral valves detected in Auvergne

2.5.15 **Limb reduction defects (LRD)**

The cluster was detected in Cork and Kerry. There were eight cases over 11 months (expected number of cases = 2.2). The excess of cases was confirmed, but it was concluded that the eight cases are not homogeneous, have different diagnoses and different types of LRD. One etiological factor cannot explain the occurrence of these eight cases within a short time span and it could be a random aggregation of cases. The registry considers that there are no reasons for concern. The cluster will require a further period of surveillance.

Cork & Kerry (IE)

Anomaly subgroup:	**Limb reduction defects (LRD)**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2017 and 31/03/2021

Most significant cluster

Number of cases:	8	Expected number of cases:	2.166	p value:	0.016
Start date:	26/12/2018				
End date:	26/11/2019				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

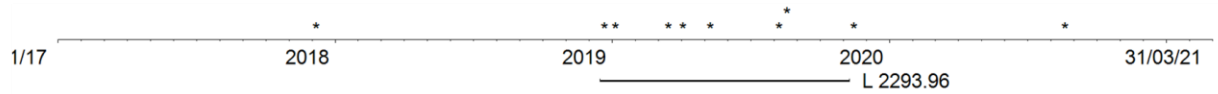


Figure 17. Cluster of Limb reduction defects detected in Cork and Kerry.

2.5.16 **Club foot – talipes equinovarus**

The cluster was detected in Northern Netherlands. There were 10 cases over 35 days (expected number of cases = 1.8). The registry confirmed the excess of cases, but the cluster could not be explained by the extensive local investigation. The cluster will require a further period of surveillance.

North Netherlands (NL)

Anomaly subgroup:	**Club foot – talipes equinovarus**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2017 and 31/03/2021

Most significant cluster

Number of cases:	10	Expected number of cases:	1.81	p value:	0.036
Start date:	29/05/2020				
End date:	03/07/2020				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation
Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

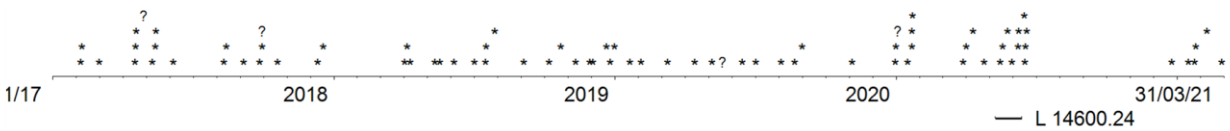


Figure 18. Cluster of Club foot – talipes equinovarus detected in Northern Netherlands

2.5.17 **Polydactyly**

The cluster was detected in Trento. There were 11 cases over 15.5 months (expected number of cases = 4.2). The registry reported that 6 out of 11 cases were born to mothers from specific ethnic groups. Ethnicity is a known risk factor for this anomaly, and polydactyly is one of the most common congenital malformations in Africa [8, 9]. The registry considers that the cluster is explained by ethnicity and there are no reasons for concern. The cluster will require a further period of surveillance.

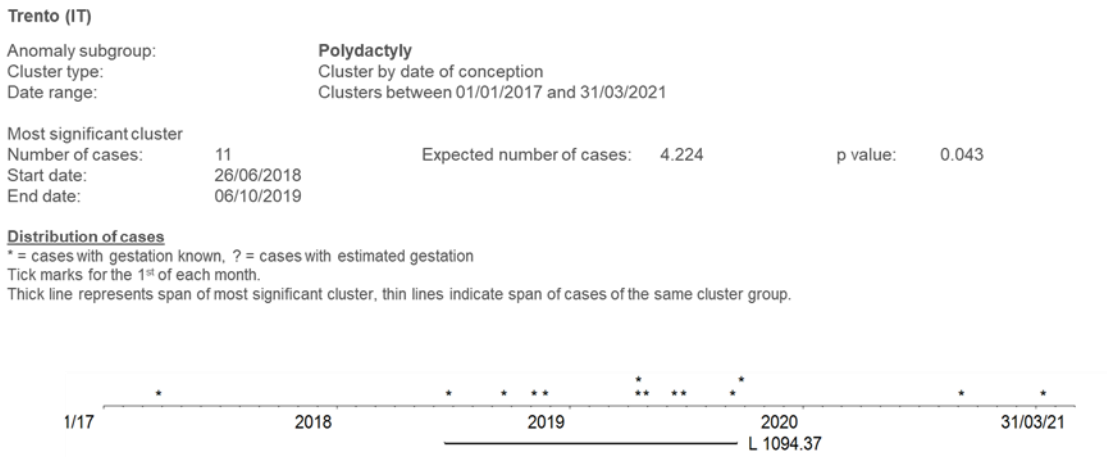


Figure 19. Cluster of polydactyly detected in Trento

2.5.18 **Laterality anomalies**

The cluster was detected in Emilia Romagna. There were 16 cases over 15.5 months (expected number of cases = 6.7). One case was not considered further in the investigations (a case of mesocardia in VACTER). No additional local investigation was proposed other than further surveillance. The registry also noticed a heterogeneity in the reported cases, suggesting a need for improvement in clinical competence and reporting.

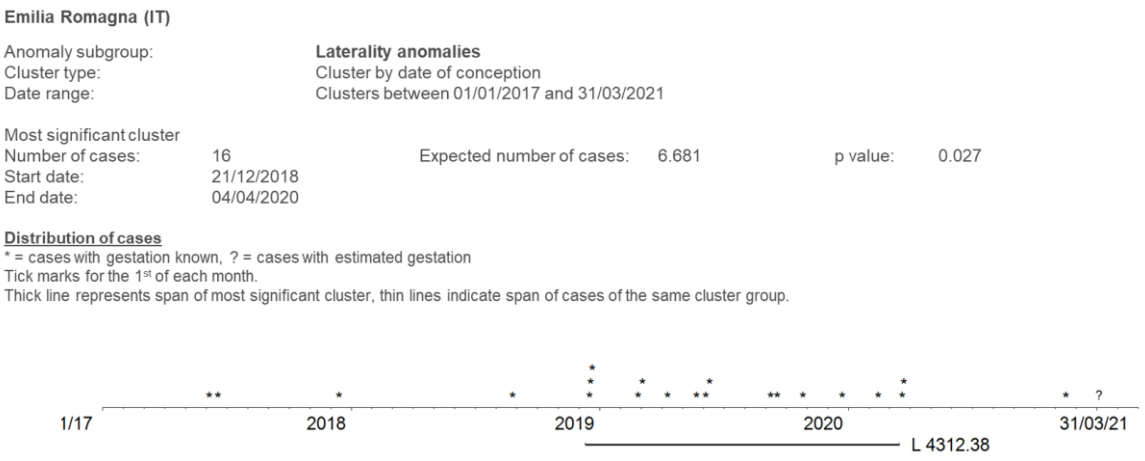


Figure 20. Cluster of laterality anomalies detected in Emilia Romagna

2.5.19 **Vascular disruption anomalies**

The cluster was detected in Brittany. There were six cases over 23 days (expected number of cases = 0.6).

The cluster was explained by data quality issues, as one case was not correctly coded (initially coded Q418 instead of Q410). After correction of the code, there was no more cluster.

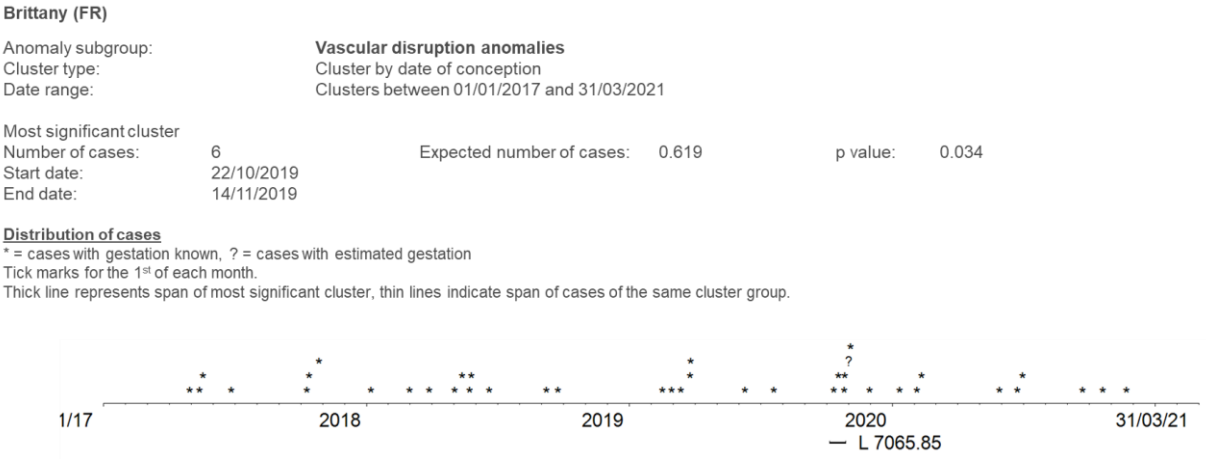


Figure 21. Cluster of Vascular disruption anomalies detected in Brittany.

2.5.20 **Maternal infections resulting in major malformations**

The cluster was detected in Brittany. There were seven cases over 260 days (expected number of cases = 1.7). Six out of the 7 cases had congenital cytomegalovirus (CMV). The registry considered that there may be a link with maternal occupation/age, which caused increased exposure to the virus, as most mothers were exposed to children or potential infected people through their occupation (I.e. teacher, healthcare personnel) or their young age (teenagers). No further investigation was proposed other than continued surveillance.

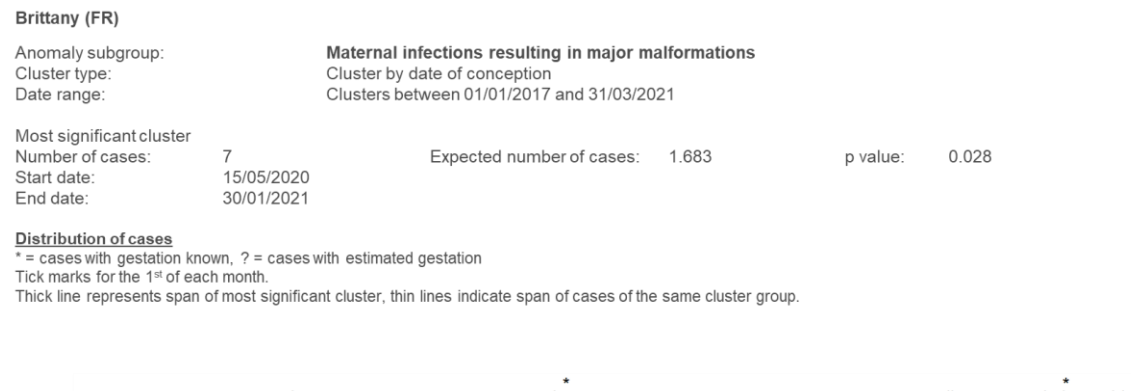


Figure 22. Cluster of Maternal infections resulting in major malformations detected in Brittany.

In Brittany there was also a cluster of teratogenic syndromes resulting in malformations but it overlapped with the cluster of maternal infections: 7 out of 8 cases were the same, hence it was not investigated further.

2.5.21 **Summary of cluster investigations**

Table 3. Details of the clusters detected and outcomes of local registry preliminary investigations.

Registry	Anomaly	No of cases in cluster	Expected cases	p-value	Valid cases	Length of cluster (days)	Classification of explanation
Auvergne	Atrial septal defect	6	0.7	0.048	43	23	Investigation not requested.
	Posterior urethral valves	5	0.8	0.046	10	121	Data quality issues found to explain cluster (two cases with inaccurate coding, no more cluster after correction).
Brittany	Congenital pulmonary airway malformations (CPAM)	5	0.5	0.039	21	35	Apparent cluster with cause for concern. The registry has informed the regional health authority.
	Congenital hydronephrosis including ureter obstruction	5	0.4	0.039	317	1	All cases in the clusters occurred within a one-day period. Since the estimated date of conception may vary up to 6 days, the detection of the cluster may be an artefact of the methodology.
	Vascular disruption anomalies	6	0.6	0.034	40	23	Data quality issues found to explain cluster (one case with inaccurate coding, no more cluster after correction).
	Maternal infections resulting in major malformations	7	1.7	0.028	10	260	Excess of cases confirmed, but no further investigation proposed other than further surveillance.
	Triploidy and polyploidy	6	1.0	0.035	13	115	Investigation not requested.
Cork & Kerry	Atrial septal defect	18	4.5	<0.001	64	108	Data quality issues found to explain cluster.
	Limb reduction anomalies	8	2.2	0.016	10	335	Excess of cases confirmed, but no further investigation proposed other than further surveillance.
Emilia Romagna	Severe CHD	5	0.4	0.029	296	1	All cases in the clusters occurred within a one-day period. Since the estimated date of conception may vary up to 6 days, the detection of the cluster may be an artefact of the methodology.

Registry	Anomaly	No of cases in cluster	Expected cases	p-value	Valid cases	Length of cluster (days)	Classification of explanation
	Hypoplastic right heart (HRH/HRHS)	6	1.1	0.009	8	206	No further investigation proposed other than further surveillance.
	Unilateral renal agenesis	14	3.1	0.011	80	59	No further investigation proposed other than further surveillance.
	Hypospadias	5	0.4	0.034	307	1	All cases in the clusters occurred within a one-day period. Since the estimated date of conception may vary up to 6 days, the detection of the cluster may be an artefact of the methodology.
	Laterality anomalies	16	6.7	0.027	21	470	No further investigation proposed other than further surveillance.
Funen	Diaphragmatic hernia	5	0.9	0.018	7	198	Excess of cases confirmed, but no further investigation proposed other than further surveillance
French West Indies	Atrioventricular septal defect	5	0.4	0.009	12	54	Data quality issues found to explain cluster (two cases with inaccurate coding, no more cluster after correction).
Malta	Ventricular septal defect	8	0.6	< 0.001	89	9	The cluster was detected and investigated already last year [7].
	Multicystic renal dysplasia	6	0.5	<0.001	9	76	No report received.
	Posterior urethral valves	9	3.2	0.039	11	81	No report received.
Northern Netherlands	Spina bifida	5	0.5	0.038	25	27	Excess of cases confirmed, but no further investigation proposed other than further surveillance.
	Hydrocephaly	11	3.9	0.014	13	458	Excess of cases confirmed, but no further investigation proposed other than further surveillance.
	Pulmonary valve stenosis	12	3.0	0.05	49	95	Data quality issues found to explain cluster (one case had a genetic diagnosis).
	Club foot	10	1.8	0.036	78	35	Excess of cases confirmed, but no further investigation proposed other than further surveillance.

Registry	Anomaly	No of cases in cluster	Expected cases	p-value	Valid cases	Length of cluster (days)	Classification of explanation
Pleven	Congenital hydronephrosis including ureter obstruction	5	1.2	0.047	7	262	Excess of cases confirmed, but no further investigation proposed other than further surveillance.
Réunion	Diaphragmatic hernia	15	5.5	0.009	20	423	No report received.
Styria	Congenital hydronephrosis including ureter obstruction	24	8.7	0.006	61	219	Investigation not requested.
Trento	Polydactyly	11	4.2	0.043	14	467	Excess of cases confirmed. Maternal ethnicity was found to explain the cluster.
	Trisomy 13 / Patau syndrome	5	0.6	0.037	12	82	Investigation not requested.
Tuscany	Aortic valve atresia or stenosis	5	0.9	0.041	8	182	Excess of cases confirmed, but no further investigation proposed other than further surveillance.
	Oesophageal atresia with or without tracheo-oesophageal fistula	7	1.2	0.049	23	78	Excess of cases confirmed, but no further investigation proposed other than further surveillance.
	Congenital hydronephrosis including ureter obstruction	10	1.3	0.007	127	15	Excess of cases confirmed, but no further investigation proposed other than further surveillance.
Valencian Region	Gastroschisis	11	2.7	0.014	23	178	Excess of cases confirmed, but no further investigation proposed other than further surveillance The cluster was detected and investigated already last year, although on a shorter period of time [7].
Vaud	Diaphragmatic hernia	5	1.1	0.042	7	253	Excess of cases confirmed, but no further investigation proposed other than further surveillance
Wales	Syndactyly	10	1.9	0.024	47	61	No report received.

3 Pan-European trends

Each year, EUROCAT performs statistical monitoring for pan-European trends on 94 anomaly subgroups (see Annex A).

The pan-European trend analysis was carried out for the time period 2012-2021. The analysis included data from 26 full member registries (see Annex B). The inclusion criteria for the registries were as published before [7].

There were increasing trends for 8 congenital anomaly subgroups and decreasing trends for 9 subgroups.

The significant increasing trends were:
- Caudal regression sequence*
- Lobulated, fused and horseshoe kidney, ectopic kidney*
- *Pulmonary valve atresia*
- Agenesis of corpus callosum*
- Patau syndrome (trisomy 13)*
- Edwards syndrome (trisomy 18)*
- Unilateral renal agenesis*
- *Genetic disorders*

Nine significant decreasing trends were detected:
- *Anophtalmos*
- *PDA as only CHD in term infants*
- Severe microcephaly*
- Hydrocephaly*
- Gastroschisis*
- Limb reduction defects*
- *Cleft palate*
- Vascular disruption anomalies*
- *Oro-facial clefts*

The trends indicated with an asterisk* had already been detected in the 2022 monitoring and presented in last years' report [7]. Trends in i*talic* are new increasing or decreasing trends.

All pan-European trends are investigated in depth every two years. In the present report, the new pan-European trends are not discussed. They will be further monitored in the subsequent analysis and (if still present) will be investigated in detail in next year's report.

4 Conclusions

The present report describes the results of the statistical analysis performed centrally on data for the birth years 2012-2021. Where available, the outcome of the preliminary investigations conducted by registries are also presented.

The cluster analysis detected 34 clusters in 16 registries. Following the registries investigations most clusters were considered of no concern. Some registries will report (or have reported) the findings to their local public health authorities. For 14 clusters a longer period of surveillance will be required before final conclusions can be made. Three clusters were explained by data quality issues (e.g. coding), demonstrating that the review of the clusters cases helps not only to detect potential teratogenic exposures, but also to improve the quality of the data in the local registries and the Central Database.

A more detailed follow-up of all clusters that were detected in previous analyses, covering the birth years between 2010-2022, is planned for next year at the central level.

The pan-European trend analysis detected increasing trends for 8 congenital anomaly subgroups and decreasing trends for 9 subgroups. Eleven of these trends were previously found and discussed in last year's report [7]. Indeed, analysing 10-year trends every year results in very little change each year for many anomalies as only 10% of new data is added. Therefore, in 2020, EUROCAT decided not to perform the 10-year pan-European trends analysis every year but to conduct a detailed investigation of all trends only every two years. All the trends detected in the current analysis will be further monitored next year and (if still present) will be investigated in detail in the subsequent report.

References

1. Kinsner-Ovaskainen, A. et al., *A sustainable solution for the activities of the European network for surveillance of congenital anomalies: EUROCAT as part of the European Platform on Rare Diseases Registration.* European Journal of Medical Genetics. 2018. Vol. 61, pp. 513-517, doi: 10.1016/j.ejmg.2018.03.008
2. Martin, S. et al. *Transfer of the Central Database and coordinating activities of EUROCAT to the JRC*, 2016, Luxembourg : Publications Office of the European Union, 2016. EUR 28225 EN.
3. Tucker, D., et al., *EUROCAT: an update on its functions and activities.* J Community Genet. 2018, Vol. 9, pp. 407-410. doi: 10.1007/s12687-018-0367-3
4. EUROCAT. *Coverage of the European live births, Birth year 2018.* [Online] Available at: https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/EUROCAT-Population-2018.pdf [accessed on 27.11.2023]
5. EUROCAT. *Statistical Monitoring Protocol. 2015.* [Online] Available at: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/statistical-monitoring_en [accessed on 27.11.2023]
6. EUROCAT. *Data Management Software (DMS).* [Online] Available at: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/data-management-program_en [accessed on 27.11.2023]
7. Kinsner-Ovaskainen, A., Perraud, A., Morris, J. and Garne, E., *European Monitoring of Congenital Anomalies: JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2010 - 2019),* European Commission, Ispra, 2023, JRC132424. Available at: https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/2023_EUROCAT_Statistical_Monitoring_Report.pdf. [accessed on 27.11.2023].
8. Sunday-Adeoye, I., Okonta, P.I., Egwuatu V.E. *Congenital malformations in singleton and twin births in rural Nigeria.* Nigerian Postgraduate Medical Journal. 2007 14(4), pp. 277-80.
9. Sevene E, Bardají A, Mariano A, Machevo S, Ayala E, Sigaúque B, Aponte JJ, Carné X, Alonso PL, Menendez C. *Drug exposure and pregnancy outcome in Mozambique.* Paediatric Drugs. 2012 14(1), pp. 43-9. doi: 10.2165/11591270-000000000-00000.
10. EUROCAT Guide 1.5: Instruction for the registration of congenital anomalies. Section 3.3. "EUROCAT Subgroups of Congenital Anomalies" (version 23.10.23). [Online] Available at: https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_3.3.pdf [accessed on 27.11.2023].

List of abbreviations and definitions

ASD	Atrial Septal Defect
AVSD	Atrio-Ventricular Septal Defect
CHD	Congenital Heart Defects
GA	Gestational Age
ICD10	International Classification of Disease, 10th Revision
ICD10-BPA	ICD10 – British Paediatric Association (*Paediatric Adaptation of ICD-10*)
LRD	Limb Reduction Defects
PDA	Patent Ductus Arteriosus
TOPFA	Termination of Pregnancy for Fetal Anomaly
VSD	Ventricular Septal Defect

List of figures

List of tables

Annex A: Congenital anomaly subgroup inclusion list

The EUROCAT congenital anomaly subgroups are defined in EUROCAT Guide 1.5, Chapter 3.3 [10], and are analysed in the following ways:

- Prevalence: in the tables available on the EUROCAT website[1], prevalence is available by outcome of pregnancy, by registry and year (not presented in the current report). Prevalence for *All cases* and *Cases excluding genetic conditions* is calculated separately.
- Trend analysis: all pregnancy outcomes are jointly considered. Genetic conditions are excluded from the statistical monitoring (for all subgroups except Skeletal dysplasias, Triploidy and polyploidy, Trisomy 21/Down syndrome, Trisomy 13/Patau syndrome, Trisomy 18/Edward syndrome and Turner syndrome).
- Cluster analysis: for a given subgroup all cases that occurred in the period 2017-2021 (or 2016-2020) are included in the analyses. Genetic conditions are excluded from the analysis (for all subgroups except Skeletal dysplasias, Triploidy and polyploidy, Trisomy 21/Down syndrome, Trisomy 13/Patau syndrome, Trisomy 18/Edward syndrome and Turner syndrome).

The following table lists the subgroups that are included in the EUROCAT prevalence tables, trends analysis and cluster analysis.

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
All anomalies	✓	**NO**	**NO**
All anomalies excluding genetic conditions	✓	✓	**NO**
Nervous system anomalies	✓	**NO**	**NO**
Neural Tube Defects	✓	✓	✓
Anencephaly and similar	✓	✓	✓
Encephalocele and meningocele	✓	✓	✓
Spina Bifida	✓	✓	✓
Hydrocephaly	✓	✓	✓
Severe microcephaly	✓	✓	✓
Arhinencephaly / holoprosencephaly	✓	✓	✓
Agenesis of corpus callosum	✓	✓	✓
Eye	✓	**NO**	**NO**
Anophthalmos / microphthalmos	✓	✓	✓
Anophthalmos	✓	✓	✓
Congenital cataract	✓	✓	✓
Congenital glaucoma	✓	✓	✓

[1] https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Ear, face and neck	✓	**NO**	**NO**
Anotia and atresia / stenosis /stricture of external auditory canal	✓	✓	✓
Congenital heart defects	✓	✓	**NO**
Severe Congenital Heart Defects	✓	✓	✓
Common arterial truncus	✓	✓	✓
Double outlet right ventricle	✓	✓	✓
Double outlet left ventricle	✓	✓	✓
Complete transposition of great arteries	✓	✓	✓
Single ventricle	✓	✓	✓
Corrected transposition of great arteries	✓	✓	✓
VSD	✓	✓	✓
ASD	✓	✓	✓
AVSD	✓	✓	✓
Tetralogy and pentalogy of Fallot	✓	✓	✓
Tricuspid atresia and stenosis	✓	✓	✓
Ebstein's anomaly	✓	✓	✓
Pulmonary valve stenosis	✓	✓	✓
Pulmonary valve atresia	✓	✓	✓
Aortic valve atresia/stenosis	✓	✓	✓
Mitral valve atresia/stenosis	✓	✓	✓
Hypoplastic left heart	✓	✓	✓
Hypoplastic right heart	✓	✓	✓
Coarctation of aorta	✓	✓	✓
Aortic atresia / interrupted aortic arch	✓	✓	✓
Total anomalous pulmonary venous return	✓	✓	✓
PDA as only CHD in term infants (GA 37+ weeks)	✓	✓	✓
Respiratory anomalies	✓	**NO**	**NO**
Choanal stenosis or atresia	✓	✓	✓
Congenital pulmonary airway malformations	✓	✓	✓
Oro-facial clefts	✓	**NO**	**NO**
Cleft lip with or without cleft palate	✓	✓	✓
Cleft palate	✓	✓	✓

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Gastro-intestinal anomalies	✓	**NO**	**NO**
Oesophageal atresia with or without tracheo-oesophageal fistula	✓	✓	✓
Duodenal atresia or stenosis	✓	✓	✓
Atresia or stenosis of other parts of small intestine	✓	✓	✓
Ano-rectal atresia or stenosis	✓	✓	✓
Hirschsprung's disease	✓	✓	✓
Atresia of bile ducts	✓	✓	✓
Annular pancreas	✓	✓	✓
Anomalies of intestinal fixation		✓	✓
Diaphragmatic hernia	✓	✓	✓
Abdominal wall defects	✓	**NO**	**NO**
Gastroschisis	✓	✓	✓
Omphalocele	✓	✓	✓
Congenital anomalies of kidney and urinary tract	✓	**NO**	**NO**
Unilateral renal agenesis	✓	✓	✓
Bilateral renal agenesis including Potter sequence	✓	✓	✓
Multicystic renal dysplasia	✓	✓	✓
Congenital hydronephrosis including urether obstruction	✓	✓	✓
Lobulated, fused and horseshoe and ectopic kidney	✓	✓	✓
Bladder exstrophy and/or epispadias	✓	✓	✓
Posterior urethral valves	✓	✓	✓
Prune belly syndrome	✓	✓	✓
Genital anomalies	✓	**NO**	**NO**
Hypospadias	✓	✓	✓
Indeterminate sex	✓	✓	✓
Limb anomalies	✓	**NO**	**NO**
Limb reduction defects (LRD)	✓	✓	✓
Transverse LRD	✓	✓	✓
Longitudinal preaxial LRD	✓	✓	✓
Longitudinal postaxial LRD	✓	✓	✓
Longitudinal central LRD	✓	✓	✓

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Intercalary LRD	✓	✓	✓
Clubfoot - talipes equinovarus	✓	✓	✓
Hip dislocation	✓	✓	✓
Polydactyly	✓	✓	✓
Syndactyly	✓	✓	✓
Other anomalies/ syndromes	**NO**	**NO**	**NO**
Craniosynostosis	✓	✓	✓
Congenital constriction bands /amniotic band sequence resulting in major malformations	✓	✓	✓
Situs inversus	✓	✓	✓
Conjoined twins	✓	✓	✓
VATER/VACTERL association	✓	✓	✓
Pierre-Robin sequence	✓	✓	✓
Caudal regression sequence	✓	✓	✓
Sirenomelia	✓	✓	✓
Septo-optic dysplasia	✓	✓	✓
Vascular disruption anomalies	✓	✓	✓
Laterality anomalies	✓	✓	✓
Teratogenic syndromes resulting in major malformations	✓	✓	✓
Valproate syndrome	✓	✓	✓
Maternal infections resulting in major malformations	✓	✓	✓
Genetic disorders	✓	✓	**NO**
Skeletal dysplasias	✓	✓	✓
Down syndrome /trisomy 21	✓	✓	✓
Patau syndrome/trisomy 13	✓	✓	✓
Edward syndrome/trisomy 18	✓	✓	✓
Turner syndrome	✓	✓	✓
Triploidy and polyploidy	✓	✓	✓

Annex B: EUROCAT full member registries inclusion list

	Pan-Europe trends	Cluster monitoring	
	Included in analysis	Included in analysis	Investigation report
Austria, Styria	✓	✓	not requested
Belgium, Antwerp	No, data transmission late > 1 year		
Belgium, Hainaut	✓	✓	not requested
Bulgaria, Pleven	✓	✓	✓
Croatia, Zagreb	✓	Variation in birth population >10%	
Denmark, Funen	✓	✓	✓
France, Auvergne	✓	✓	✓
France, Brittany	✓	✓	✓
France, French West Indies	✓	✓	✓
France, Paris	✓	✓	not requested
France, Réunion	✓	✓	✓
Germany, Saxony Anhalt	✓	Analysis not done (see chapter 2.2)	
Ireland, Cork & Kerry	✓	✓	✓
Ireland, South East	No, data transmission late > 1 year		
Italy, Emilia Romagna	✓	✓	✓
Italy, Milan Metropolitan Area	✓	✓	not requested
Italy, Trento	✓	✓	✓
Italy, Tuscany	✓	✓	✓
Malta	✓	✓	**X**
Netherlands, Northern	✓	✓	✓
Norway	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	
Poland, Wielkopolska	No, data incomplete for 2020 and no data for 2021		
Portugal, South	No, data incomplete for 2020 and no data for 2021		
Spain, Basque Country	No, data transmission late > 1 year		
Spain, Valencian Region	✓	✓	✓
Spain, Navarra	No, less than 8 years of data in the Central Database for 2012-2021	✓	not requested

Switzerland, Vaud	✓	✓	✓
Ukraine	✓	No, less than 5 years of complete data in the Central Database for 2016-2020	
UK, E Midlands & S Yorkshire	No, data missing for 2013-2015	Analysis not done (see chapter 2.2)	
UK, Northern England	✓	Analysis not done (see chapter 2.2)	
UK, South West England	✓	Analysis not done (see chapter 2.2)	
UK, Thames Valley	✓	Analysis not done (see chapter 2.2)	
UK, Wales	✓	✓	**X**
UK, Wessex	✓	Analysis not done (see chapter 2.2)	
UK, West Midlands	No, less than 8 years of data in the Central Database for 2012-2021	Analysis not done (see chapter 2.2)	
UK, Yorkshire and Humber	No, less than 8 years of data in the Central Database for 2012-2021	Analysis not done (see chapter 2.2)	

✓ Investigation report received, **X** Investigation report not received

Annex C: Template for the investigation of clusters provided to the registries

Name of the anomaly for which the cluster was detected	
Methods and results of case verification	
Dimensions	
- Diagnostic dimension:	
- Spatial dimension:	
- Time dimension:	
Methods and results of any investigations as to whether changes in diagnostic or reporting practices might have contributed to the cluster	
Aetiological factors examined and result. Please include the following information:	
- Which factors have been investigated?	
- Which of these factors are recorded within the registry database (please list variables)?	
Which of these factors are NOT recorded within the registry database (please list variables)?	
- Do any of these appear to explain the cluster?	
Local context	
Conclusions	
Do you consider the cluster 'explained' by your preliminary investigation? Yes / No.	

If yes, give a summary of your explanation.	
If no, - Does the cluster require a further period of surveillance before a decision is made to investigate further? Why?	
OR If no, - Is there going to be further aetiological/other investigation? Please give details.	
Which public health authorities have been or will be notified about this cluster? Please give details.	

GETTING IN TOUCH WITH THE EU

In person

All over the European Union there are hundreds of Europe Direct centres. You can find the address of the centre nearest you online (european-union.europa.eu/contact-eu/meet-us_en).

On the phone or in writing

Europe Direct is a service that answers your questions about the European Union. You can contact this service:

— by freephone: 00 800 6 7 8 9 10 11 (certain operators may charge for these calls),

— at the following standard number: +32 22999696,

— via the following form: european-union.europa.eu/contact-eu/write-us_en.

FINDING INFORMATION ABOUT THE EU

Online

Information about the European Union in all the official languages of the EU is available on the Europa website (european-union.europa.eu).

EU publications

You can view or order EU publications at op.europa.eu/en/publications. Multiple copies of free publications can be obtained by contacting Europe Direct or your local documentation centre (european-union.europa.eu/contact-eu/meet-us_en).

EU law and related documents

For access to legal information from the EU, including all EU law since 1951 in all the official language versions, go to EUR-Lex (eur-lex.europa.eu).

Open data from the EU

The portal data.europa.eu provides access to open datasets from the EU institutions, bodies and agencies. These can be downloaded and reused for free, for both commercial and non-commercial purposes. The portal also provides access to a wealth of datasets from European countries.

Science for policy

The Joint Research Centre (JRC) provides independent, evidence-based knowledge and science, supporting EU policies to positively impact society

EU Science Hub
joint-research-centre.ec.europa.eu

@EU_ScienceHub

EU Science Hub - Joint Research Centre

EU Science, Research and Innovation

EU Science Hub

@eu_science