JRC TECHNICAL REPORT

European Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2009-2018)

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Joint Research Centre

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Contents

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The report was reviewed and approved by the JRC-EUROCAT Management Committee (Ester Garne, Maria Loane, Simona Martin, Joan Morris, Ciarán Nicholl, Judith Rankin, Florence Rouget, Michele Santoro and David Tucker) and by the registry leaders.

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Abstract

Congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood worldwide. Each year, of the 5.0 million births[1] in the European Union [1], approximately 125,000 fetuses and infants (i.e. 2.5% of all births) have a congenital anomaly according to the EUROCAT estimates.

EUROCAT is a European network of population-based registries whose objectives are 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. Timely surveillance helps to design better strategies for prevention of congenital anomalies and improved care services for children born with these anomalies.

Each year, EUROCAT performs statistical monitoring for pan-European trends and clusters in time on 84 and 75 anomaly subgroups, respectively. Only the trends that are considered of specific public health importance are discussed in the annual report, while all pan-European trends are investigated in depth every two years. The results of the statistical monitoring are the basis for initiating possible further investigations at the local registry level. The last report was published on the data from birth years 2008-2017 [2].

The present report presents the results of the monitoring performed on data for the birth years 2009-2018, with a special focus on the investigation of clusters detected in the periods 2014-2018, 2013-2017 and 2012-2016. Four pan-European trends that were considered of specific interest are also discussed. Cases of congenital anomaly 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 were included. We report both the statistical results performed centrally and, where available, the outcome of the preliminary investigations conducted by registries.

[1] Data for EU28 in 2018. Source EUROSTAT [1].

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 Diseases Registration [3, 4].

EUROCAT surveys more than 1.1 million of births per year, approximately one fifth of the European birth population. Registries from 21 European countries transmit yearly to the JRC-EUROCAT Central Registry individual case data (full member registries) or aggregate data (associate members) on congenital anomalies in their region.

The EUROCAT annual statistical monitoring report includes an analysis of pan-European trends and temporal clusters performed in order to detect signals of new or increasing teratogenic exposures and to monitor progress in the prevention of congenital anomalies [3, 5]. The analysis is done by the JRC-EUROCAT Central Registry and a full statistical monitoring protocol is published online, providing details of the rationale and the methodology [6].

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. Total prevalence rates of 84 subgroups of congenital anomalies, including all cases of live births, fetal deaths from 20 weeks gestational age, and terminations of pregnancy for fetal anomaly (TOPFA) at any gestational age are monitored. The cluster analysis detects unusual aggregation of cases in time, 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.

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. Thus, 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 2009 and 2018, with a special focus on the investigation of clusters. We report here the results of the cluster analyses performed on cases of anomalies reported for the period 2014-2018 by 15 EUROCAT registries. In addition, cluster analyses were performed on data from registries that did not send the most recent birth year to the Central Database. In this case, the following periods were considered: 2013-2017 (seven registries) and 2012-2016 (two registries).

The pan-European trend analyses were performed on all 84 anomaly subgroups but, as agreed by the JRC-EUROCAT Management Committee in 2019, we report here only on trends that were considered of specific interest and of public health importance (*Arhinencephaly/ holoprosencephaly, Bilateral renal agenesis, , Club foot – talipes equinovarus, Laterality anomalies).* A full report on 10-years pan-European trend analyses will be published by EUROCAT next year.

2 Population and Monitoring Process

2.1 Registries included in the 2009-2018 pan-European trend analysis

At the time of statistical monitoring in autumn 2020, there were 37 full member registries in EUROCAT (see Appendix A). Twenty-seven member registries met the inclusion criteria for the individual 10-year trend analysis (see Box 1).

The registries included in the trend analysis were: Styria (Austria), Hainaut (Belgium), Pleven (Bulgaria), Odense (Denmark), Zagreb (Croatia), Auvergne (France), Brittany (France), French West Indies (France), Paris (France), La Réunion (France), Saxony-Anhalt (Germany), Cork & Kerry (Ireland), South-East Ireland (Ireland), Emilia Romagna (Italy), Tuscany (Italy), Malta, Northern Netherlands, Norway, South Portugal, Valencian Region (Spain), Vaud (Switzerland), Ukraine, Northern England (UK), South West England (UK), Thames Valley (UK), Wales (UK), Wessex (UK).

Box 1. Registry inclusion criteria for trend analysis

— *Pan-European and Individual Registry trends*: registries no more than one year late with data transmission, which submitted data continuously for at least eight calendar years counting back from 2017 i.e. for 2009-2018, 2010-2017 or 2011-2018.

— *Pan-European trends*: Registries for which the number of submitted cases in the latest year was at least 80% of those submitted in previous calendar years.

The full member registries excluded from the analysis were:

- Antwerp (Belgium), Mainz (Germany), Dublin (Ireland) and Basque Country (Spain) as they were more than one year behind in data transmission;
- East Midlands & South Yorkshire (UK) – data are available for years 2009-2018 with the exception of the years 2013-2015;
- Wielkopolska (Poland) had large variation in the number of cases between 2015-2017;
- Milan (Italy), Navarra (Spain) and Yorkshire and Humber (UK) were excluded from the trend analyses because these registries had less than eight years of data in the Central Database.

2.2 Registries included in the cluster analysis

EUROCAT defines clusters as: 'An aggregation of cases of congenital anomaly in time and/or space which appears to be unusual'; the annual statistical monitoring performed at the central level concerns the detection of the time clusters only because the data collected does not permit geographical evaluations (precise data on geographic locations of the mothers are not transmitted to the Central Registry). 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 (2014-2018) are included in the monitoring of clusters (see Box 2). 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 [7].

Box 2. Registry inclusion criteria for cluster analysis

— Registries must submit individual case data, i.e. must be full members

— Registries must have transmitted data for all five years, i.e. for 2014-2018

— Registries for which the number of submitted cases for 2018 was at least 80% of those submitted in previous calendar years

— Registries must have transmitted the date of birth (and not week of birth) 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)

A total of 25 full member registries transmitted information for the calendar year 2018 to the EUROCAT Central Registry in October 2020 (see Appendix A); 15 registries were included in the cluster analysis. The registries from England (six registries), Norway and Saxony-Anhalt were excluded 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 was excluded because, for the period 2013-2017, it had a fluctuation of over 10% in the annual birth population. Wielkopolska (Poland) was excluded because it had a large variation in the number of cases between 2015-2017.

This year, we also performed separate analyses for the periods 2013-2017 (seven registries) and 2012-2016 (two registries). Many of these registries had not previously been included in the cluster analyses, since they usually do not submit data to the Central Registry in February but do so in October.

2.3 What was monitored?

For the purpose of monitoring, cases cover live births, fetal deaths from 20 weeks of gestational age onwards, as well as TOPFA at any gestational age. The monitoring included 81 congenital anomaly subgroups, excluding cases with an additional genetic diagnosis as defined by EUROCAT, plus three trisomy subgroups adjusted for maternal age and fetal survival to 20 weeks. Data was analysed as pan-European trends and individual registry trend analyses (see Appendix B).

Trend tests were performed for the most recent 10 years of data, or eight years if 10 years were unavailable (cf. Box 1 and appendix C).

In order to detect clusters or deficits occurring during the last two years (2017-2018), and which lasted for less than 18 months, the EDMP software was used (see Appendix C) and run on 75 EUROCAT subgroups of congenital anomalies (see Appendix B).

In summary, the analyses covered:

- 27 registries with 5.76 million births (2009-2018) for the pan-European trends
- 15 registries with 0.48 million births (2017-2018) for the detection of clusters

2.4 Investigation process

The results of the statistical monitoring reported by the Central Registry were discussed by the JRC-EUROCAT Management Committee (MC) in January and May 2021. The MC selected congenital anomalies with increasing or decreasing trends for preliminary investigation using a predefined prioritisation protocol (see Fig. 1).

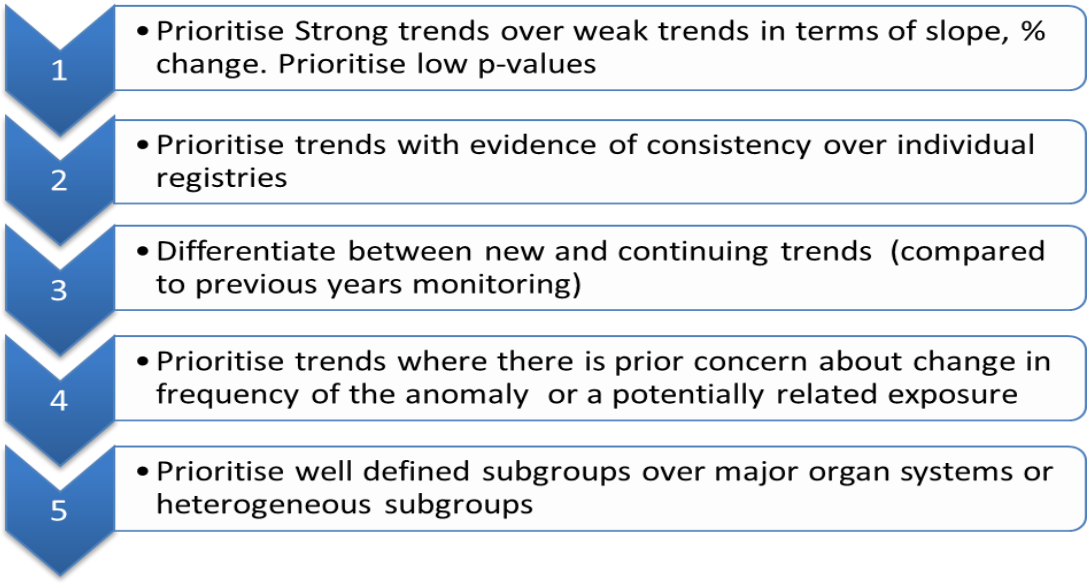

Fig. 1: Prioritisation criteria for the investigation of ten-year trends [5]

3 Pan-European Trends

3.1 Overview

The pan-European trend analysis was carried out for the time period 2009-2018. The analysis included data from 27 full member registries (Box 1 above and Appendix A). The estimated percentage change in yearly prevalence for each congenital anomaly subgroup is presented in Fig. 2a (increase in prevalence) and Fig. 2b (decrease in prevalence). This enables to identify for further analysis the congenital anomaly subgroups with statistically significant increasing or decreasing trends at pan-European level.

There were increasing trends for 12 congenital anomaly subgroups and decreasing trends for 11 subgroups (Appendix E). In the present report, trends not prioritised for investigation are not discussed, but will be monitored in subsequent analysis and presented in next year's report.

The following sections provide further analysis on selected significant increasing pan-European trends. The anomalies in question are:

- *Arhinencephaly / holoprosencephaly,*
- *Bilateral renal agenesis,*
- *Club foot – talipes equinovarus,*
- *Laterality anomalies.*

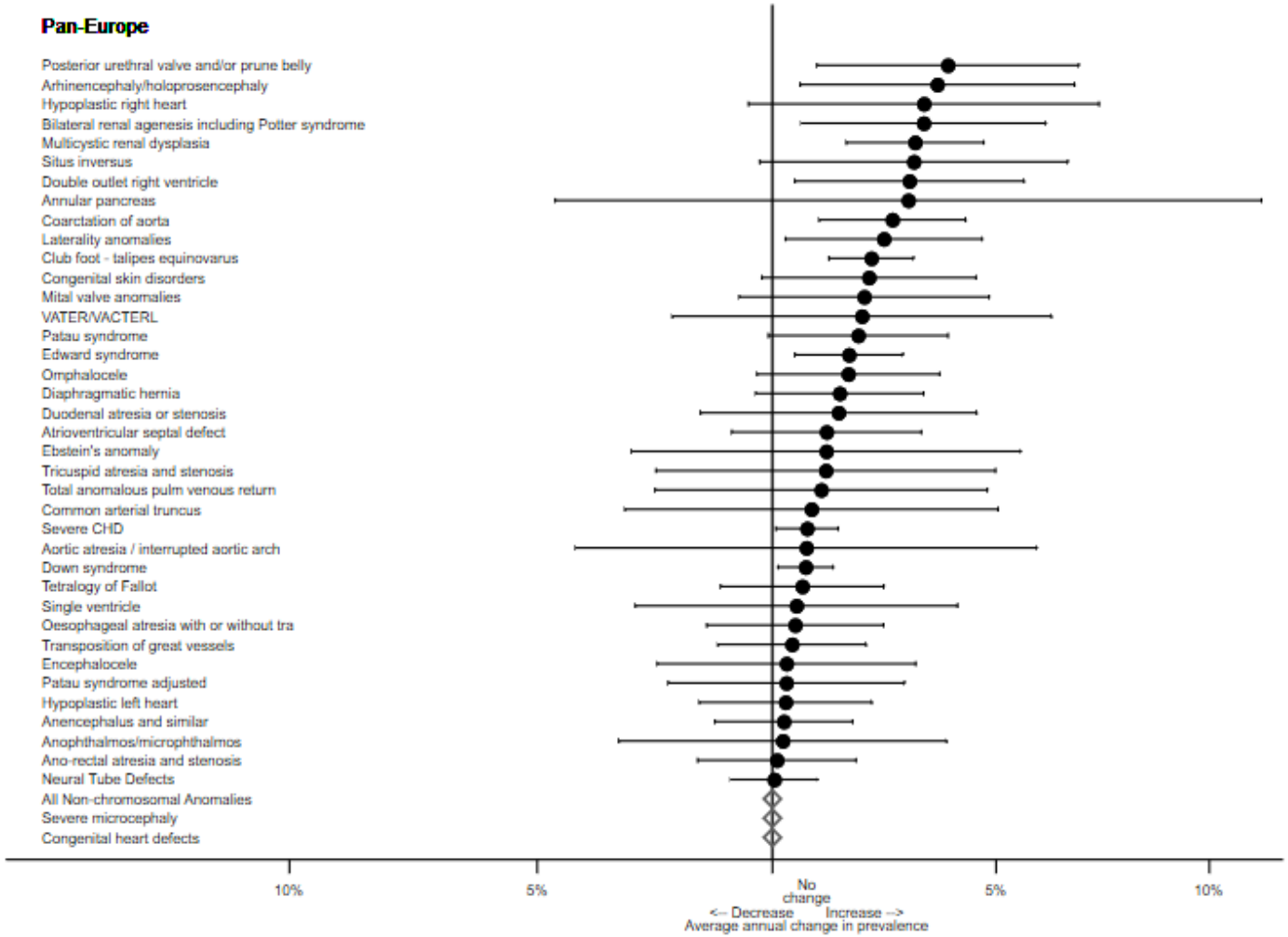

Fig. 2a: Estimated annual percentage change (increase) in the prevalence and 95% CIs (pan-European analysis 2009-2018).

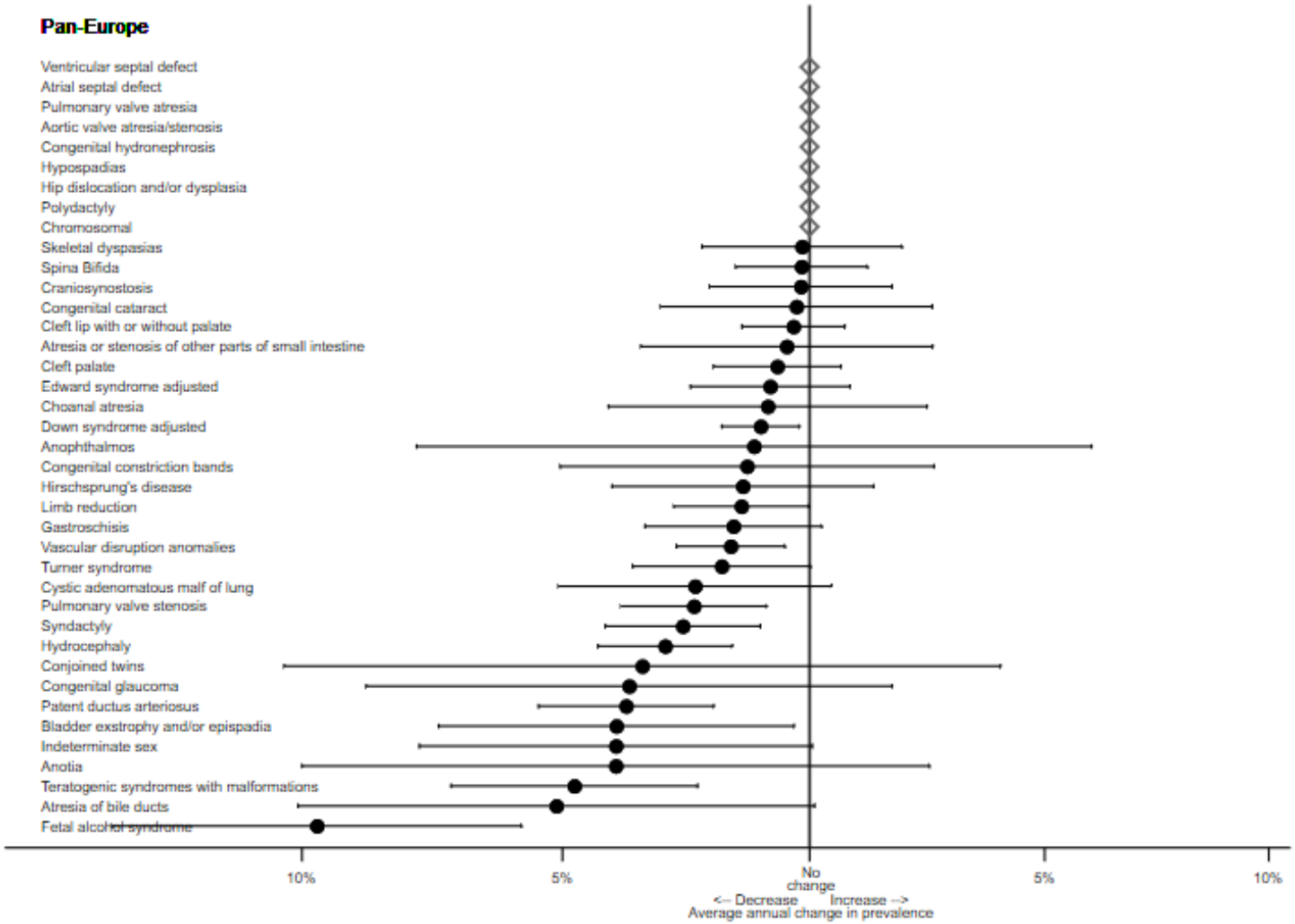

Fig. 2b: Estimated annual percentage change (decrease) in the prevalence and 95% CIs (pan-European analysis 2009-2018).

3.2 Selected pan-European trends

Arhinencephaly/holoprosencephaly

Arhinencephaly/holoprosencephaly are rare and severe cerebral anomalies with a combined prevalence around 1 per 10,000 births. In the EUROCAT registry areas, the majority of cases are diagnosed by prenatal ultrasound examinations/screening and approximately 80% of all cases are TOPFA.

When taking into account the information from all registries between 2009-2018, the prevalence of arhinencephaly/holoprosencephaly is estimated to have increased each year by 3.6% (95% CIs: 0.6%; 6.8%) on the pan-European level (Fig. 3a). This congenital anomaly subgroup shows an increasing trend for the first time at the pan-European level. However, the only significant increasing trend is for one English registry - South West England (Fig. 3b).

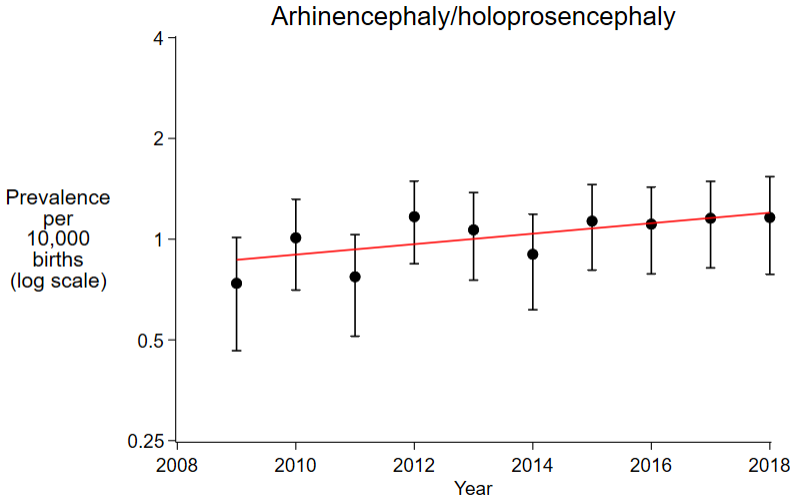

Fig. 3a Arhinencephaly/holoprosencephaly - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

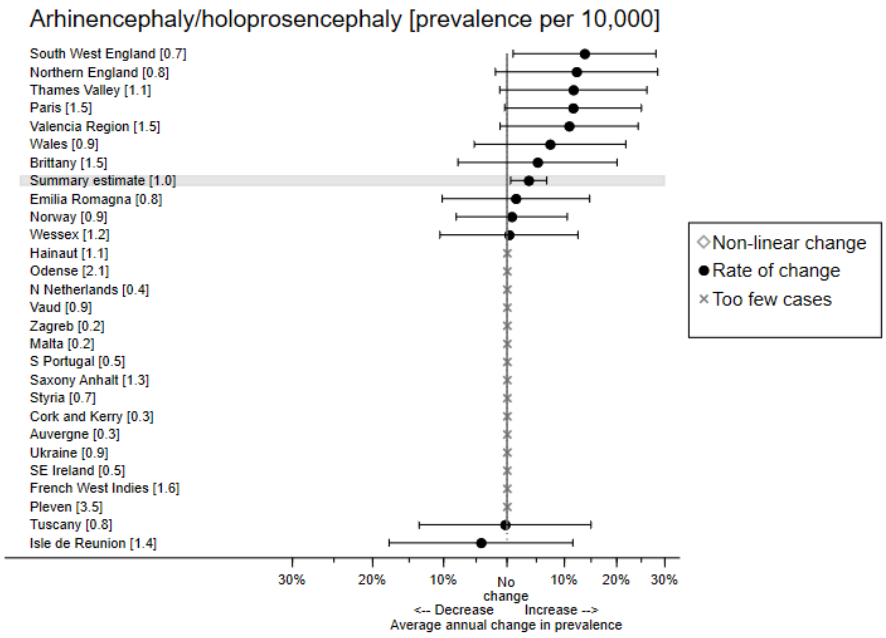

Fig. 3b: Arhinencephaly/holoprosencephaly - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

There is considerable heterogeneity of the prevalence over the 10-year period in the registries with a minimum value in Zagreb (0.2 per 10,000 births) and a maximum in Pleven (3.5 per 10,000) (Fig. 3c).

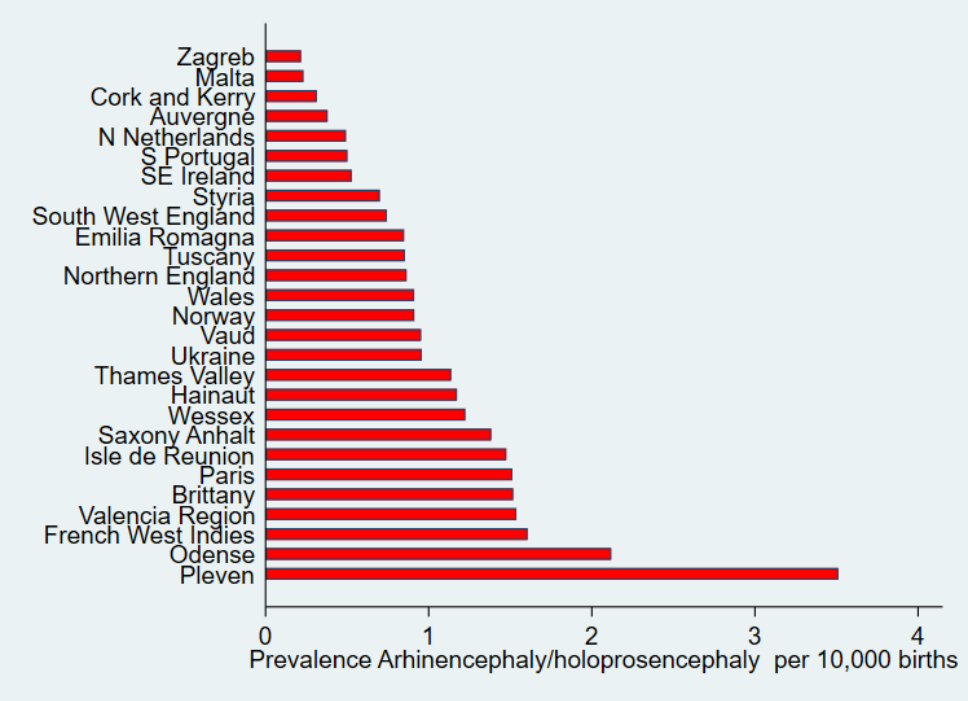

Fig. 3c: Arhinencephaly/holoprosencehaly - Estimated 10 years prevalence for the registries included in the pan-European trend analysis (2009-2018).

In conclusion, the pan-European trend will be monitored but there are no major concerns. The registry in South West England will be recommended to investigate their significantly increasing trend of this anomaly.

Bilateral renal agenesis (including Potter syndrome)

Bilateral renal agenesis is usually associated with oligohydramnios and is lethal shortly after birth because of lung hypoplasia and no function of the kidneys. Potter syndrome is the clinical phenotype of a newborn baby without kidneys or with very limited renal function in fetal life. Prenatal detection rate is high and most pregnancies result in a TOPFA [8].

Between 2009 and 2018, the prevalence of a bilateral renal agenesis (including Potter syndrome) is estimated to have increased each year by 3.3% (95% CI: 0.6%; 6.1%) on the pan-European level (Fig. 4a).

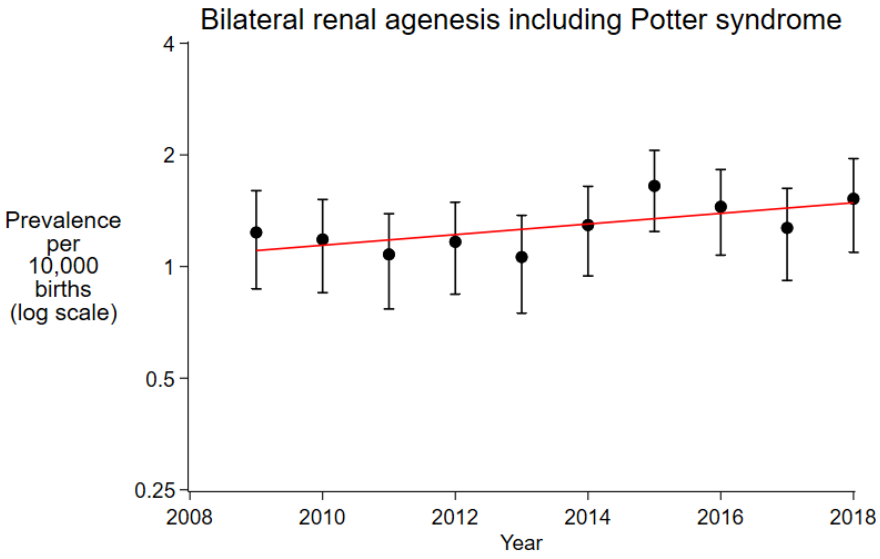

Fig. 4a Bilateral renal agenesis (including Potter syndrome) - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

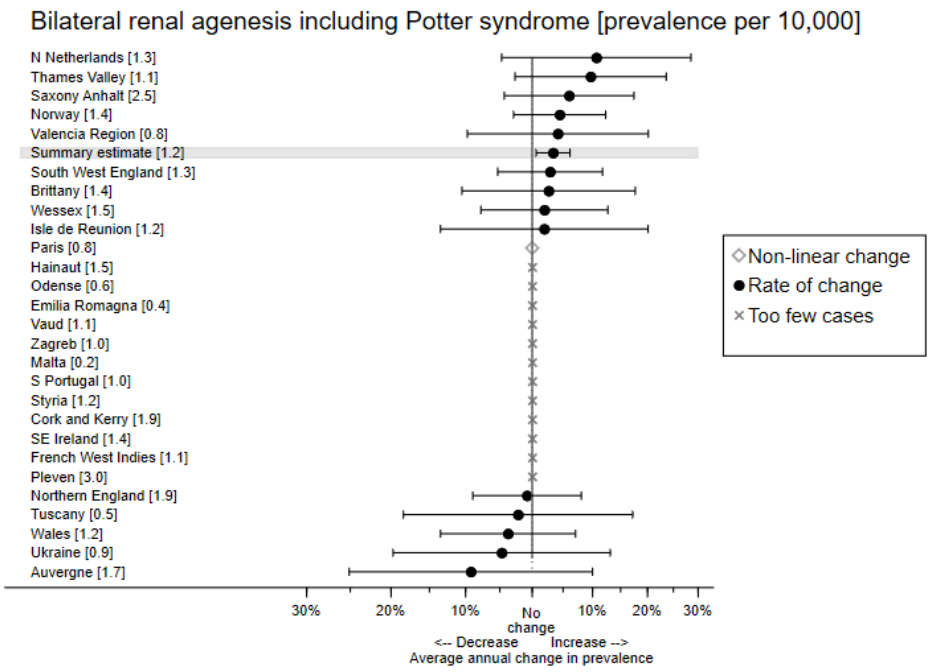

Fig. 4b: Bilateral renal agenesis (including Potter syndrome) - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

The trend is not significant in any of the individual registries (Fig. 4b).

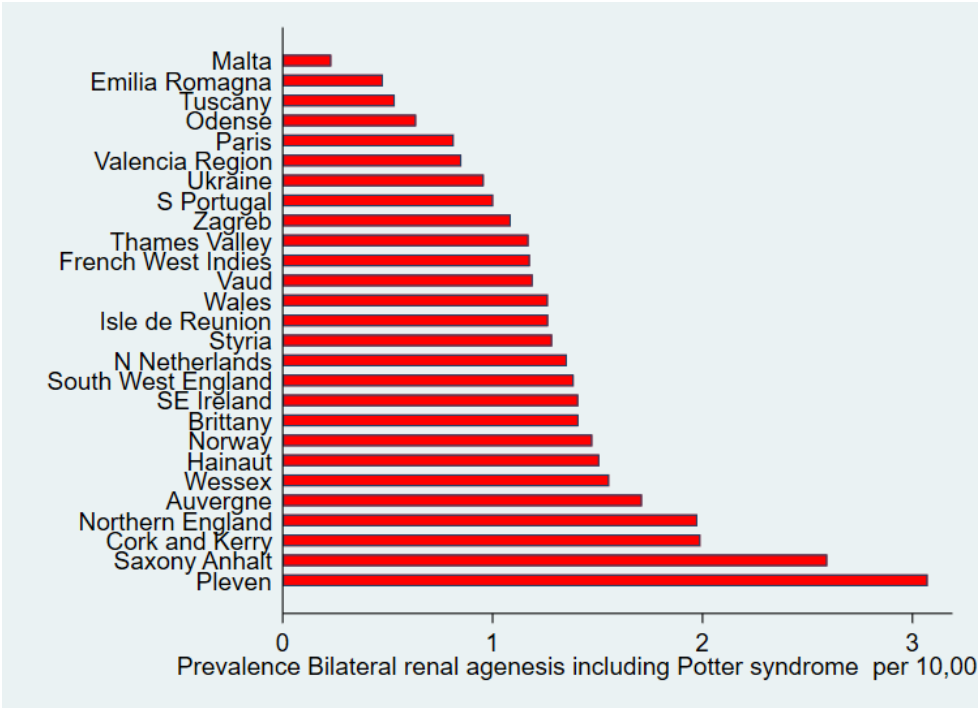

Fig. 4c: Bilateral renal agenesis (including Potter syndrome) - Estimated prevalence for the registries included in the pan-European trend analysis (2009-2018).

A detailed analysis of the cases included in the trend performed two years ago [8] showed that the large majority of cases were very severe as the TOPFA rate was high and there were few survivors after one week. The coding of the diagnosis was correct and valid. In conclusion, the pan-European trend is most likely correct and will be monitored closely over the next years with focus on risk factors and possible explanations for the trend.

Clubfoot – talipes equinovarus

Clubfoot can be unilateral or bilateral and has a familial pattern of inheritance. Clubfoot cases requiring surgery or Ponseti treatment should be reported to EUROCAT as a major congenital anomaly. If the clubfoot is of postural origin and not receiving treatment as mentioned, the anomaly should be classified as a minor anomaly.

The prevalence of clubfoot is now increasing at pan-European level, as documented in four consecutive EUROCAT reports on the periods 2006-2015 [9], 2007-2016 [8], 2008-2017 [2]. Between 2009 and 2018, clubfoot prevalence is estimated to have increased each year by 2.2% (95% CI: 1.2%; 3.1%) on the pan-European level. (Fig. 5a).

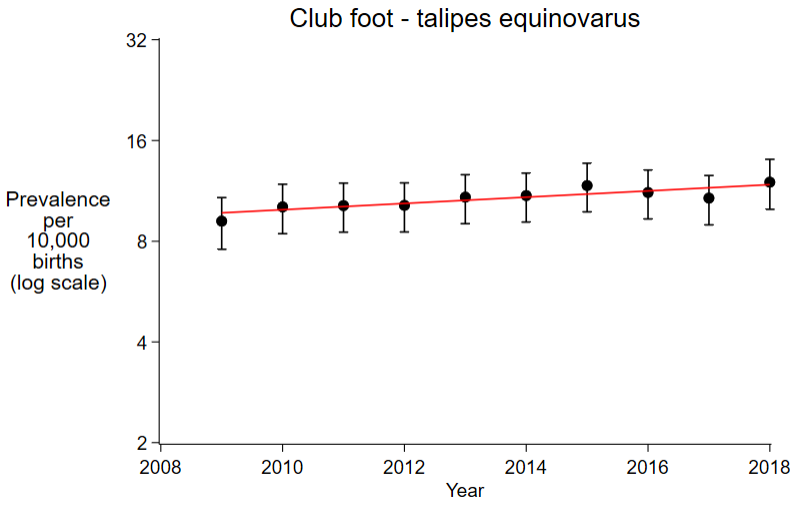

Fig. 5a Clubfoot - talipes equinovarus : Prevalence and 95% CIs for the years included in the pan-European trend analysis.

The prevalence increased for Northern England, due to significant changes in ascertainment from the start of the 10 year period when there was under-reporting (as reported previously in [2]). In the same period, the trend increased significantly also in other three registries (French West Indies, Wales and Valencian Region, Fig 5b). The prevalence increased dramatically for Northern England, due to significant changes in ascertainment from the start of the 10 year period when there was under-reporting (Fig. 5b). When performing the trend analysis excluding the Northern England registry, the pan-European trend remains significantly increasing with an annual increase of 1.2% (95% CI: 0.2%; 2.1%). The trend is significant (annual increase of 1.5%) also when only isolated club foot was considered.

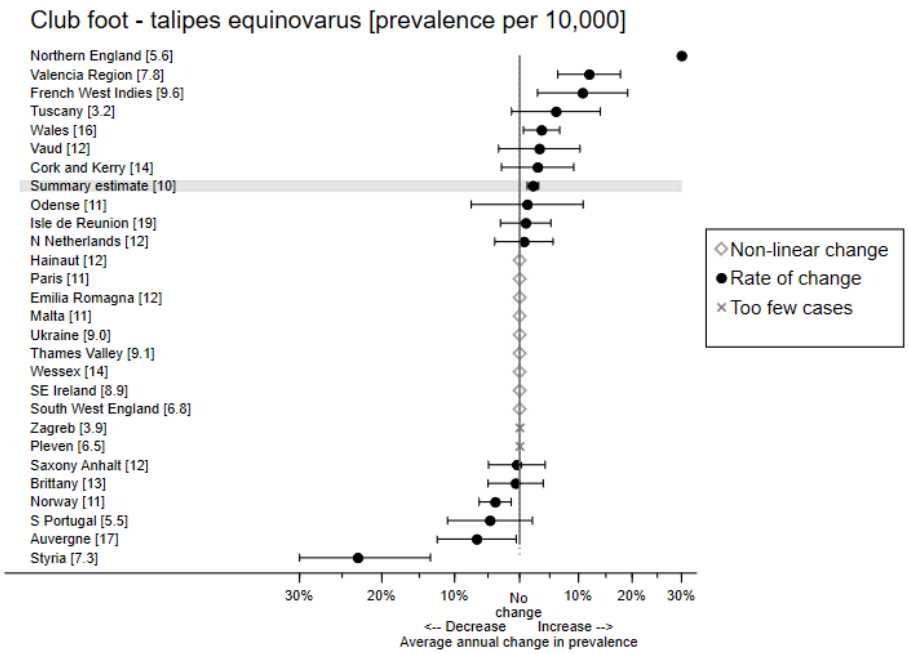

Fig. 5b: Clubfoot – talipes equinovarus: Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

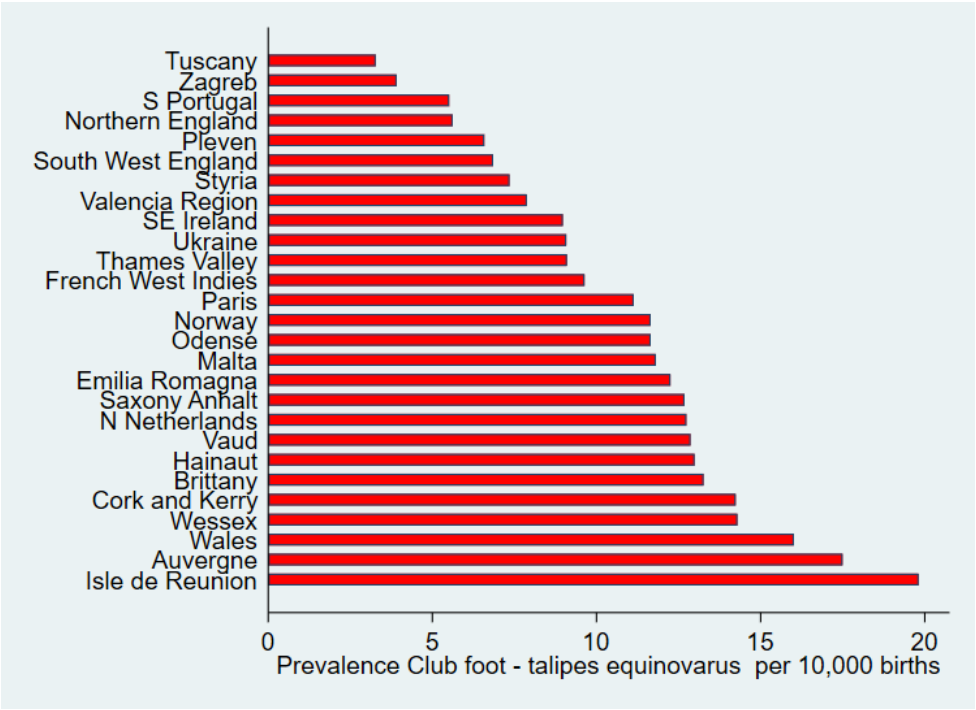

Fig. 5c: Clubfoot - Estimated prevalence for the registries included in the pan-European trend analysis.

Maternal diabetes and smoking are risk factors for clubfoot [10, 11]. The proportion of pregnant women in Europe with diabetes and of pregnant women with obesity is increasing. Therefore, the observed increasing trend might be of concern and will be further investigated by EUROCAT.

Laterality Anomalies

This subgroup of laterality anomalies includes atrial isomerism, dextrocardia, bronchopulmonary isomerism, situs inversus and anomalies of spleen. Another name for these anomalies is heterotaxy anomalies.

As in the previous three consecutive reports [2, 8, 9], the prevalence of laterality anomalies is increasing. Between 2009 and 2018, its prevalence is estimated to have increased by 2.4% (95% CI: 0.3%; 4.7%) each year on the pan-European level (Fig. 6a). Laterality anomalies have been associated with maternal pre-gestational diabetes. In the report from last year, it was planned to investigate this in more detail in the EUROCAT database, but due to the COVID-19 pandemic this has not been done. A plan for this will be written later in 2021.

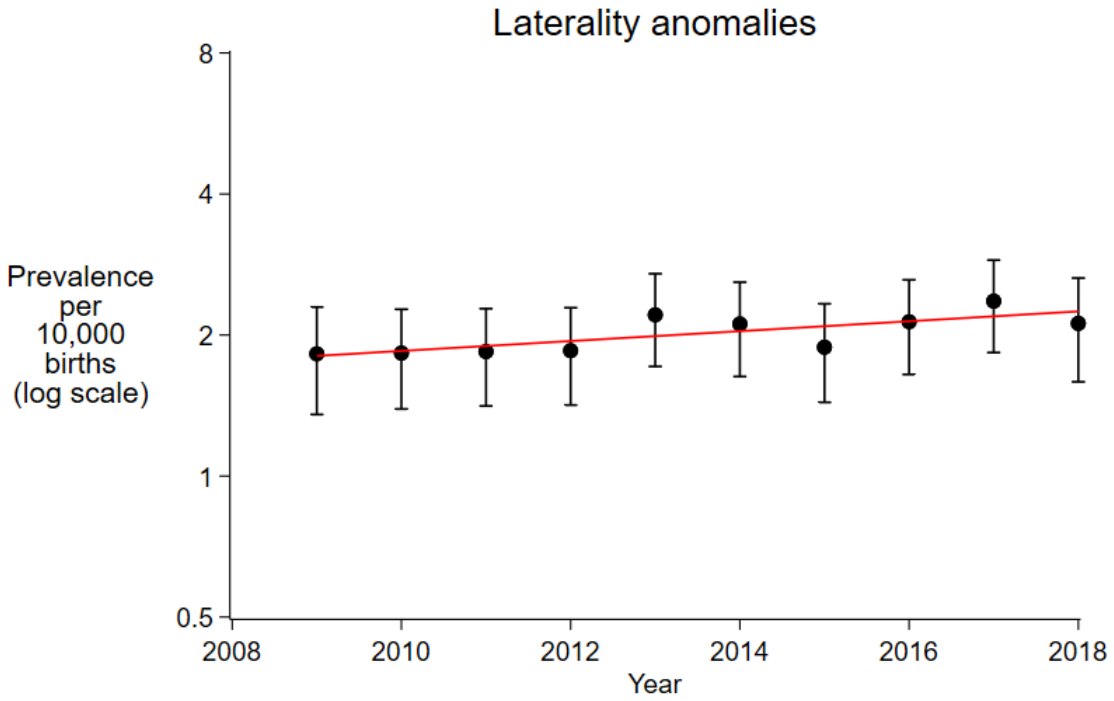

Fig. 6a Laterality anomalies - Prevalence and 95% CIs for the years included in the pan-European trend analysis.

The significant increasing trend in prevalence was found in three individual registries during the same period (Valencian Region, Thames Valley and Northern England) (Fig 6b).

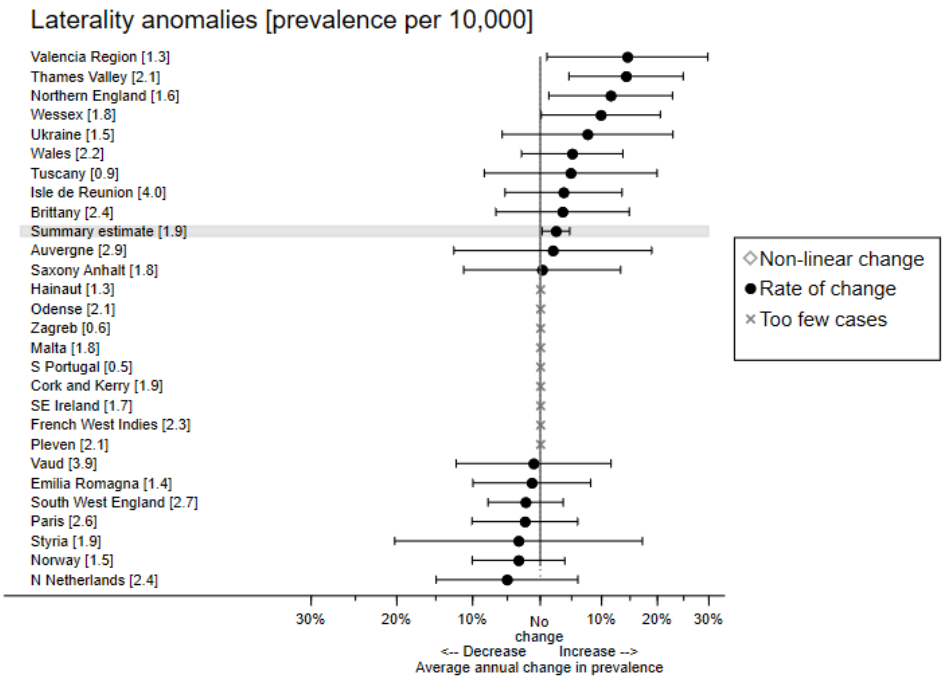

Fig. 6b: Laterality anomalies - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

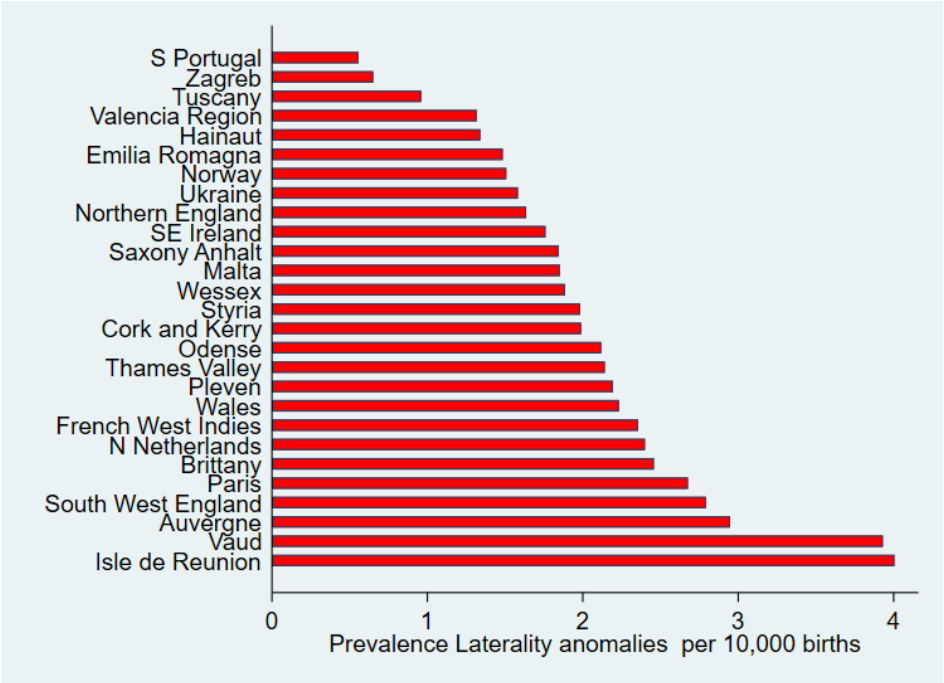

Fig. 6c: Laterality anomalies - Estimated prevalence for the registries included in the pan-European trend analysis.

In conclusion, the increasing pan-European trend in the laterality subgroup is continuing. Maternal diabetes is a risk factor for laterality anomalies [12]. The proportion of pregnant women in Europe with diabetes and of pregnant women with obesity is increasing. Therefore, the increasing trend of laterality anomalies will be monitored closely by EUROCAT.

4 Clusters

4.1 Overview

EUROCAT defines a cluster as an aggregation of cases of congenital anomaly in time and/or space, which appears to be unusual. Currently, the statistical monitoring at the Central Registry detects only temporal clusters within each registry area and the investigation, including potentially space investigation, is then conducted by the registry at a local level.

Currently, the JRC-EUROCAT Central Registry performs annual cluster analysis using the most recent five years of data.

Cluster detection is based on a 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.

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.

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.

Central Registry produces a report of all clusters detected in each registry. Every registry then 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 updated data included in the next data transmission to the Central Registry.

4.2 Cluster analysis 2014-2018, 2013-2017 and 2012-2016

Fifteen registries satisfied the criteria to be included in the cluster analysis on the period 2014-2018 (see Appendix A). For registries that did not submit the data for the last birth year (2018, seven registries) or last two birth years collected (2017 and 2018, two registries), exceptionally the analysis was run for the periods 2013-2017 and 2012-2016, respectively.

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

- 2014 – 2018: 15 registries, 23 clusters
- 2013 – 2017: 7 registries, 15 clusters
- 2012 – 2016: 2 registries, 4 clusters

The details on these clusters are presented in Table 1 on page 28-29.

All registries were asked to report on the investigation into their clusters. The conclusions from these investigations are summarised in Table 1.

Review of the clusters 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 (cluster disappears after exclusion of genetic cases)
- Duplicate cases
- Changes in case ascertainment
- 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.

4.3 Cluster investigations

Anencephalus

The cluster was detected in Odense. There were six cases over 187 days (expected number of cases = 1.1). The registry confirmed the excess of cases, but no further investigation was proposed other than further surveillance. The Danish Patient Safety Authority will be informed about this cluster.

Anomaly Subgroup:	**Anencephalus and similar**				
Cluster type:	Cluster by date of conception				
Date range:	Clusters between 01/01/2014 and 31/03/2018				
Most significant cluster					
Number of cases:	6	Expected number of cases:	1.091	p value:	0.017
Start date:	30/03/2016				
End date:	03/10/2016				

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.

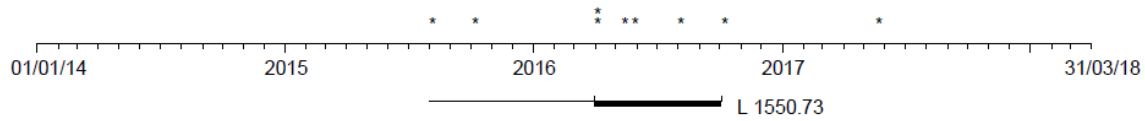

Fig. 7: Cluster of Anencephalus detected in Odense.

Tetralogy of Fallot

The cluster was detected in Vaud. There were five cases over 107 days (expected number of cases = 0.48).

The registry confirmed the excess of cases, but no further investigation was proposed other than further surveillance, as this could be a random aggregation of cases.

Anomaly Subgroup:	**Tetralogy of Fallot**				
Cluster type:	Cluster by date of conception				
Date range:	Clusters between 01/01/2014 and 31/03/2018				
Most significant cluster					
Number of cases:	5	Expected number of cases:	0.478	p value:	<0.001
Start date:	28/01/2017				
End date:	13/05/2017				

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.

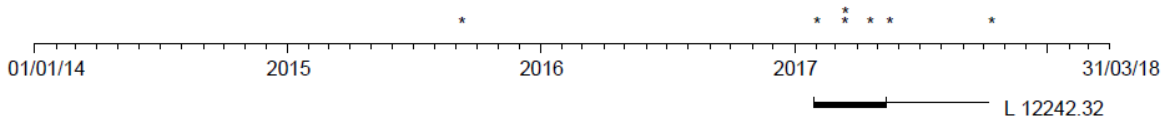

Fig. 8: Cluster of Tetralogy of Fallot detected in Vaud.

Hypoplastic left heart

The cluster was detected in Valencia. There were five cases over 51 days (expected number of cases = 0.57).

The registry confirmed the excess of cases, but no further investigation was proposed other than further surveillance, as this could be a random aggregation of cases.

Anomaly Subgroup:	**Hypoplastic left heart**				
Cluster type:	Cluster by date of conception				
Date range:	Clusters between 01/01/2013 and 31/03/2017				
Most significant cluster					
Number of cases:	5	Expected number of cases:	0.57	p value:	0.048
Start date:	21/01/2016				
End date:	12/03/2016				

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.

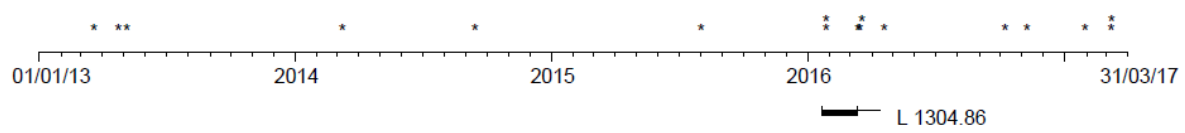

Fig. 9: Cluster of Hypoplastic left heart detected in Valencia.

Hirschsprung's disease

The cluster was detected in Vaud. There were five cases over 165 days (expected number of cases = 0.75). The registry investigation concluded that there were two familial cases, which could explain the cluster. The cluster will require a further period of surveillance.

Anomaly Subgroup: **Hirschsprung's disease**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2014 and 31/03/2018
Most significant cluster
Number of cases: 5 Expected number of cases: 0.749 p value: 0.010
Start date: 14/09/2016
End date: 26/02/2017

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.

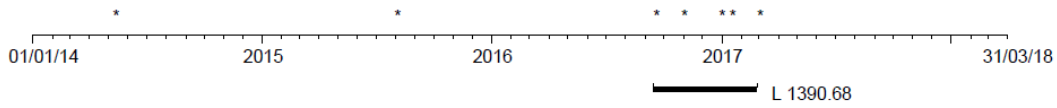

Fig. 10: Cluster of Hirschsprung's disease detected in Vaud.

Diaphragmatic hernia

The clusters were detected in La Réunion and Auvergne.

In La Réunion there were seven cases over 116 days (expected number of cases = 1.28). The registry reported that the cluster of diaphragmatic hernia is heterogeneous and only two cases were isolated cases. The others cases were cases with multiple malformations.. In the literature, the causes of congenital diaphragmatic hernia are largely unknown; abnormal embryogenesis due to retinoid signalling dysfunction is likely involved as are mutations of ZFPM2 and GATA6 in some cases. Most cases are sporadic and appear to be multifactorial, two thirds are male. Recurrence in siblings is 2%.

In La Réunion and in the Indian Ocean, there is a specific risk factor. Fryns syndrome (SF) is an autosomal recessive, rare, lethal syndrome. The main symptom of this syndrome is congenital diaphragmatic hernia (HDC). The PIGN gene is the gene of interest whose recurrent deletion of exons 5 to 7 suggests a founder effect in the Indian Ocean (OI). The registry will investigate with the genetics department to find out if these children have been tested for the PIGN gene after their first year.

Further surveillance will be done on this anomaly, especially focusing on non-isolated cases of diaphragmatic hernia. Public health authorities, both local and national, will be informed.

Anomaly Subgroup: **Diaphragmatic hernia**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2014 and 31/03/2018
Most significant cluster
Number of cases: 7 Expected number of cases: 1.282 p value: 0.041
Start date: 07/11/2017
End date: 03/03/2018

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.

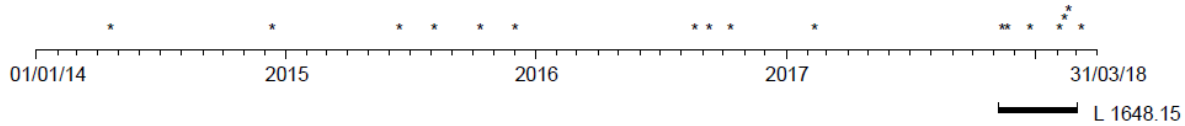

Fig. 11: Cluster of Diaphragmatic hernia detected in La Réunion.

In Auvergne, there were eight cases over 324 days (expected number of cases = 2.3). The registry confirmed the excess of cases, but no further investigation was proposed other than further surveillance. Santé Publique France has been informed about this cluster.

Anomaly Subgroup: **Diaphragmatic hernia**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2013 and 31/03/2017
Most significant cluster
Number of cases: 8 Expected number of cases: 2.305 p value: 0.036
Start date: 12/10/2015
End date: 31/08/2016

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.

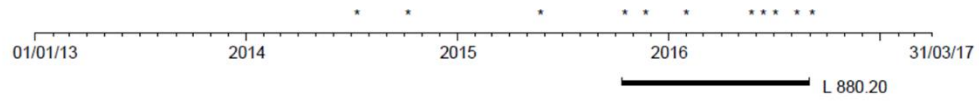

Fig. 12: Cluster of Diaphragmatic hernia detected in Auvergne.

Duodenal atresia or stenosis

The cluster was detected in Antwerp. There were 11 cases over 18 months (expected number of cases = 4.5). The registry investigation did not identify any exposures that could explain the cluster or did not lead to a common cause. However, the majority of cases were born to mothers living in the city of Antwerp. In order to determine whether this could be a geographical cluster, this anomaly will be further monitored in the future.

Anomaly Subgroup:	**Duodenal atresia or stenosis**				
Cluster type:	Cluster by date of conception				
Date range:	Clusters between 01/01/2012 and 31/03/2016				
Most significant cluster					
Number of cases:	11	Expected number of cases:	4.515	p value:	0.042
Start date:	01/01/2013				
End date:	23/06/2014				

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.

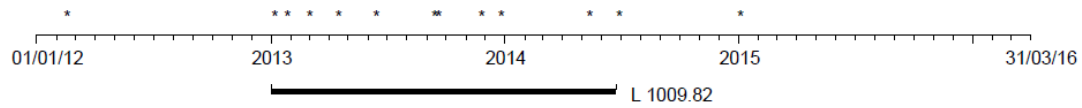

Fig. 13: Cluster of Duodenal atresia or stenosis detected in Antwerp.

Multicystic renal dysplasia

The cluster was detected in La Réunion. There were 6 cases over 21 days (expected number of cases = 0.54). An increasing trend in the prevalence of this anomaly subgroup was observed both at registry and at pan-European level. The cluster will require a further period of surveillance to understand whether it is not part of an increasing trend.

Anomaly Subgroup:	**Multicystic renal dysplasia**				
Cluster type:	Cluster by date of conception				
Date range:	Clusters between 01/01/2014 and 31/03/2018				
Most significant cluster					
Number of cases:	6	Expected number of cases:	0.539	p value:	0.018
Start date:	12/07/2017				
End date:	02/08/2017				

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.

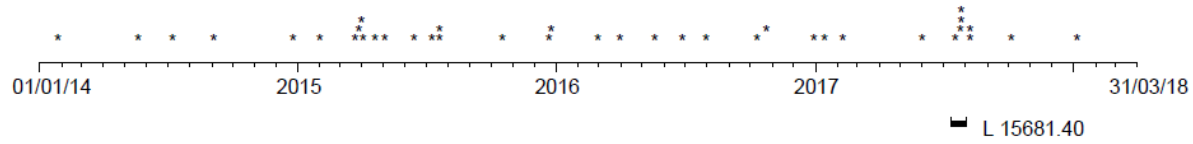

Fig. 14: Cluster of Multicystic renal dysplasia detected in La Réunion.

Posterior urethral valve and/or prune belly

The cluster was detected in Emilia Romagna. There were 5 cases over 229 days (expected number of cases = 1.04). The registry reported that they need a further period of surveillance. It could be a random cluster or an ongoing increasing trend.

Anomaly Subgroup:	**Posterior urethral valve and/or prune belly**				
Cluster type:	Cluster by date of conception				
Date range:	Clusters between 01/01/2014 and 31/03/2018				
Most significant cluster					
Number of cases:	5	Expected number of cases:	1.038	p value:	0.030
Start date:	01/11/2016				
End date:	18/06/2017				

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.

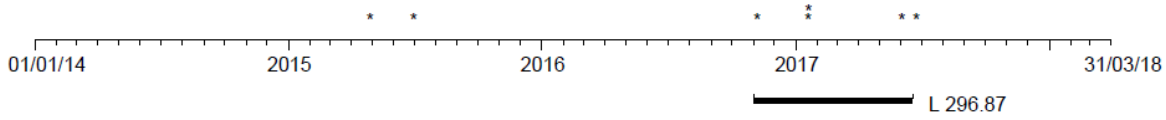

Fig. 15: Cluster of Posterior urethral valve and/or prune belly detected in Emilia Romagna.

Syndactyly

The cluster was detected in Cork and Kerry. There were five cases over 76 days (expected number of cases = 0.55). The registry confirmed the excess of cases confirmed, but no further investigation was proposed other than further surveillance. All syndactyly cases were non-isolated cases, and the findings in each of the cases differ suggesting aetiological heterogeneity. Additional malformations in other body systems were found in two cases, while other two cases were associated with limb reduction defects. One case is associated with polydactyly.

Anomaly Subgroup: **Syndactyly**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2014 and 31/03/2018
Most significant cluster
Number of cases: 5 Expected number of cases: 0.546 p value: 0.018
Start date: 30/03/2016
End date: 14/06/2016

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.

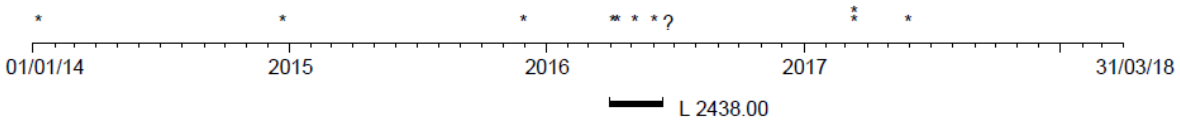

Fig. 16: Cluster of Syndactyly detected in Cork and Kerry.

Situs inversus

The cluster was detected in La Réunion. There were five cases over 76 days (expected number of cases = 0.55). The registry confirmed the excess of cases, but no further investigation was proposed other than further surveillance, as this could be a random aggregation of cases.

Anomaly Subgroup:	**Situs inversus**				
Cluster type:	Cluster by date of conception				
Date range:	Clusters between 01/01/2014 and 31/03/2018				
Most significant cluster					
Number of cases:	5	Expected number of cases:	0.745	p value:	0.010
Start date:	21/02/2016				
End date:	03/08/2016				

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.

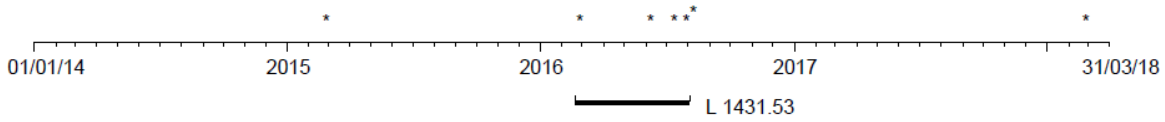

Fig. 17: Cluster of Situs inversus detected in La Réunion.

Table 1: Details of the clusters detected and outcomes of local registry preliminary investigations.

Anomaly	Registry	Classification of Explanations	No of cases in cluster	Expected cases	Valid cases	Length of cluster (days)	p-value
2014 – 2018							
Neural Tube defects	Hainaut (BE)	No report	6	0.50	30	25	0.01
Anencephalus	Odense (DK)	Excess of cases confirmed	6	1.09	9	187	0.017
Severe microcephaly	Emilia Romagna (IT)	Data quality issue	5	0.24	31	11	<0.001
	French West Indies	Discussed in previous report [2]	15	2.4	22	168	<0.001
Ventricular Septal Defect	Malta	No report	14	3.34	57	90	0.013
Atrial Septal Defect	Tuscany (IT)	Discussed in previous report [2]	66	30.07	157	296	<0.001
	Malta	No report	9	1.23	100	18	0.017
Tetralogy of Fallot	Vaud (CH)	Excess of cases confirmed	5	0.48	7	105	<0.001
Aortic valve atresia/stenosis	Paris (FR)	Data quality issue	5	0.57	7	125	<0.001
Mitral valve anomalies	Brittany (FR)	Data quality issue	5	0.6	14	66	0.042
Coarctation of aorta	Cork and Kerry (IE)	Data quality issue	5	0.57	9	98	0.012
	French West Indies (ES)	No report	5	0.87	8	167	0.031
Cystic adenomatous malformation of lung	Paris (FR)	Data quality issue	5	0.45	17	40	0.022
Hirschsprung's disease	Vaud (CH)	Excess of cases confirmed	5	0.75	7	165	0.01
Diaphragmatic hernia	La Réunion (FR)	Excess of cases confirmed	7	1.28	17	116	0.041
Multicystic renal dysplasia	La Réunion (FR)	Excess of cases confirmed	6	0.54	38	21	0.018
Congenital hydronephrosis	Brittany (FR)	Discussed in previous report [2]	103	63.35	203	483	<0.001
Posterior urethral valve and/or prune belly	Emilia Romagna (IT)	Excess of cases confirmed	5	1.04	7	229	0.03
Limb reduction defects	Cork and Kerry (IE)	Data quality issue	9	2.57	15	265	0.05
Syndactyly	Cork and Kerry (IE)	Excess of cases confirmed	5	0.55	11	76	0.018
Situs inversus	La Réunion (FR)	Excess of cases confirmed	5	0.74	7	164	0.01
Vascular disruption anomalies	Wales (UK)	Heterogeneity of subgroup	69	44.38	127	541	0.042
Laterality anomalies	French West Indies	No report	7	1.5	9	258	0.01
2013 – 2017							
Hydrocephalus	Auvergne (FR)	Data quality issue	15	5.02	20	388	<0.001
	Valencian Region (ES)	Methodology	5	0.33	102	4	0.032
Severe microcephaly	Valencian Region (ES)	Data quality issue	63	37.95	109	539	0.009
Arhinencephaly/holoprosencephaly	Milan (IT)	Data quality issue	5	1.17	7	258	0.045
Atrial Septal Defect	Milan (IT)	Data quality issue	67	35.68	155	356	<0.001

Anomaly	Registry	Classification of Explanations	No of cases in cluster	Expected cases	Valid cases	Length of cluster (days)	p-value
Aortic valve atresia/stenosis	Styria	Data quality issue	5	0.47	7	100	<0.001
Mitral valve anomalies	Milan (IT)	Data quality issue	8	0.88	17	79	<0.001
Hypoplastic left heart	Valencian Region (ES)	Excess of cases confirmed	5	0.57	17	51	0.048
Oesophageal atresia	Auvergne (FR)	Data quality issue	11	4.01	15	414	0.045
Ano-rectal atresia or stenosis	Auvergne (FR)	Data quality issue	5	0.54	11	75	0.017
Hirschsprung's disease	Milan (IT)	Data quality issue	5	0.44	26	30	0.037
Diaphragmatic hernia	Auvergne (FR)	Excess of cases confirmed	8	2.3	11	324	0.036
Posterior urethral valve and/or prune belly	Auvergne (FR)	Data quality issue	8	2.45	10	379	0.03
Craniosynostosis	Milan (IT)	Data quality issue	19	5.06	33	279	<0.001
Turner syndrome	Milan (IT)	Data quality issue	10	2.33	20	180	0.017
2012 – 2016							
Mitral valve anomalies	Basque country (ES)	No report	10	2.12	16	205	<0.001
Duodenal atresia or stenosis	Antwerp (BE)	Excess of cases confirmed	11	4.51	13	538	0.042
Bilateral renal agenesis incl. Potter syndrome	Basque country (ES)	No report	6	0.99	11	138	0.023
Congenital hydronephrosis	Basque country (ES)	No report	6	0.43	132	4	0.013

***** Data quality issues: changes in diagnostics, case ascertainment.

****** Methodology: EUROCAT records gestational age in completed weeks and the estimated date of conception may vary up to 6 days. If a cluster occurs in a one- or two-day period, the detection of the cluster may be an artefact of the methodology.

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List of boxes

List of figures

List of tables

Annex 1: EUROCAT full member registries inclusion list

	Pan-Europe trends		Cluster monitoring	
	Included in analysis	**Investigation report**	**Included in analysis**	**Investigation report**
Austria, Styria	✓	---	✓ (2013-2017)	✓
Belgium, Antwerp	No, data transmission late > 1 year		✓ (2012-2016)	✓
Belgium, Hainaut	✓	---	✓ (2014-2018)	**X**
Bulgaria, Pleven	✓	---	✓ (2014-2018)	---
Croatia, Zagreb	✓	---	variation in birth population >10%	
Denmark, Odense	✓	---	✓ (2014-2018)	✓
France, Auvergne	✓	---	✓ (2013-2017)	**X**
France, Brittany	✓	---	✓ (2014-2018)	✓
France, French West Indies	✓	---	✓ (2014-2018)	**X**
France, Paris	✓	---	✓ (2014-2018)	✓
France, La Réunion	✓	---	✓ (2014-2018)	✓
Germany, Saxony Anhalt	✓	---	Analysis not done (see chapter 2.2)	
Germany, Mainz	No, data missing for >3 years			
Ireland, Cork & Kerry	✓	---	✓ (2014-2018)	✓
Ireland, Dublin	No, data missing for >3 years			
Ireland, South East	✓	---	✓ (2013-2017)	---
Italy, Emilia Romagna	✓	---	✓ (2014-2018)	✓
Italy, Milan Metropolitan Area	No, as data for 6 years only		✓ (2013-2017)	✓
Italy, Tuscany	✓	---	✓ (2014-2018)	✓
Malta	✓	---	✓ (2014-2018)	**X**
Netherlands, Northern	✓	---	✓ (2014-2018)	---
Norway	✓	---	Analysis not done (see chapter 2.2)	
Poland, Wielkopolska	Large variation in number of cases for 2015-2017			
Portugal, South	✓	---	✓ (2014-2018)	---
Spain, Basque Country	No, data transmission late > 1 year		✓ (2012-2016)	**X**
Spain, Valencian Region	✓	---	✓ (2013-2017)	✓

Spain, Navarra	No, as data for 5 years only		✓ (2013-2017)	---
Switzerland, Vaud	✓		✓ (2014-2018)	✓
Ukraine	✓	---	✓ (2013-2017)	---
UK, E Midlands & S Yorkshire	No, data missing for >1 year			
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	✓	---	✓ (2014-2018)	**X**
UK, Wessex	✓	---	Analysis not done (see chapter 2.2)	
UK, Yorkshire and Humber	No, as data for 3 years only			

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

Annex 2: Congenital anomaly subgroup inclusion list

The EUROCAT congenital anomaly subgroups are defined in EUROCAT Guide 1.4, Chapter 3.3 [13], and are analysed in the following ways:

- Prevalence by outcome of pregnancy, by registry and year. *All cases* and *All cases excluding genetic conditions*[2] are included in the analysis and the results are published in the prevalence tables available on the EUROCAT website[3]. It is possible to perform dynamic prevalence calculations for combined registries/years on the website.
- Analysis of trends, all outcomes of pregnancy are jointly considered. Genetic conditions are excluded from the statistical monitoring of all other subgroups.

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	✓	**NO**	**NO**
Neural Tube Defects	✓	✓	✓
Anencephalus and similar	✓	✓	✓
Encephalocele	✓	✓	✓
Spina Bifida	✓	✓	✓
Hydrocephalus	✓	✓	✓
Severe microcephaly	✓	✓	✓
Arhinencephaly / holoprosencephaly	✓	✓	✓
Eye	✓	**NO**	**NO**
Anophthalmos / microphthalmos	✓	✓	✓
Anophthalmos	✓	✓	✓
Congenital cataract	✓	✓	✓
Congenital glaucoma	✓	✓	✓
Ear, face and neck	✓	**NO**	**NO**
Anotia	✓	✓	✓
Congenital heart defects (CHD)	✓	✓	**NO**
Severe CHD	✓	✓	✓
Common arterial truncus	✓	✓	✓
Double outlet right ventricle	✓	✓	✓

[2] Genetic syndromes/ microdeletions, skeletal dysplasias, chromosomal anomalies
[3] 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
Transposition of great vessels	✓	✓	✓
Single ventricle	✓	✓	✓
VSD	✓	✓	✓
ASD	✓	✓	✓
AVSD	✓	✓	✓
Tetralogy of Fallot	✓	✓	✓
Tricuspid atresia and stenosis	✓	✓	✓
Ebstein's anomaly	✓	✓	✓
Pulmonary valve stenosis	✓	✓	✓
Pulmonary valve atresia	✓	✓	✓
Aortic valve atresia/stenosis	✓	✓	✓
Mitral valve anomalies	✓	✓	✓
Hypoplastic left heart	✓	✓	✓
Hypoplastic right heart	✓	✓	✓
Coarctation of aorta	✓	✓	✓
Aortic atresia/interrupted aortic arch	✓	✓	✓
Total anomalous pulm venous return	✓	✓	✓
PDA as only CHD in term infants (GA 37+ weeks)	✓	✓	✓
Respiratory	✓	**NO**	**NO**
Choanal atresia	✓	✓	✓
Cystic adenomatous malf of lung	✓	✓	✓
Oro-facial clefts	✓	**NO**	**NO**
Cleft lip with or without cleft palate	✓	✓	✓
Cleft palate	✓	✓	✓
Digestive system	✓	**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 and stenosis	✓	✓	✓
Hirschsprung's disease	✓	✓	✓
Atresia of bile ducts	✓	✓	✓
Annular pancreas	✓	✓	✓
Diaphragmatic hernia	✓	✓	✓

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Abdominal wall defects	✓	**NO**	**NO**
Gastroschisis	✓	✓	**NO**
Omphalocele	✓	✓	✓
Urinary	✓	**NO**	**NO**
Bilateral renal agenesis including Potter syndrome	✓	✓	✓
Multicystic renal dysplasia	✓	✓	✓
Congenital hydronephrosis	✓	✓	✓
Bladder exstrophy and/or epispadia	✓	✓	✓
Posterior urethral valve and/or prune belly	✓	✓	✓
Genital	✓	**NO**	**NO**
Hypospadias	✓	✓	✓
Indeterminate sex	✓	✓	✓
Limb	✓	**NO**	**NO**
Limb reduction	✓	✓	✓
Clubfoot - talipes equinovarus	✓	✓	✓
Hip dislocation and/or dysplasia	✓	✓	✓
Polydactyly	✓	✓	✓
Syndactyly	✓	✓	✓
Other anomalies/ syndromes	**NO**	**NO**	**NO**
Skeletal dysplasias	✓	✓	✓
Craniosynostosis	✓	✓	✓
Congenital constriction bands/amniotic band	✓	✓	✓
Situs inversus	✓	✓	✓
Conjoined twins	✓	✓	✓
Congenital skin disorders	✓	✓	✓
VATER/VACTERL	✓	✓	✓
Vascular disruption anomalies	✓	✓	✓
Laterality anomalies	✓	✓	✓
Teratogenic syndromes with malformations	✓	✓	**NO**
Fetal alcohol syndrome	✓	✓	✓
Valproate syndrome	✓	✓	✓
Maternal infections resulting in malformations	✓	✓	✓
Genetic syndromes +	✓	✓	**NO**

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
microdeletions			
Chromosomal	✓	✓	**NO**
Down syndrome	✓	✓	✓
Patau syndrome/trisomy 13	✓	✓	✓
Edward syndrome/trisomy 18	✓	✓	✓
Turner syndrome	✓	✓	✓
Klinefelter syndrome	✓	✓	✓
Down syndrome Adjusted	**NO**	✓	**NO**
Patau syndrome Adjusted	**NO**	✓	**NO**
Edward syndrome Adjusted	**NO**	✓	**NO**

Annex 3: Statistical methods used by EUROCAT

Part of the current monitoring strategy is the annual statistical monitoring for trends and clusters at central level, 15 months after last date of birth, e.g. year 2016 births included in monitoring in March 2018. More details on the statistical methods for monitoring given here can be found in the EUROCAT Statistical Monitoring Protocol [7].

Statistical methods for the detection of trends in every registry

Trend tests are performed for 81 anomaly subgroups (see Appendix B) for each registry, and for an additional 3 subgroups adjusting for maternal age and in utero survival for registries with maternal age denominators.

Currently, Central Registry performs a trend test for the most recent five years of data, as well as a trend test for the most recent 10 years (or 8 years if 10 years are not available). The analysis is based on the number of cases per year of birth and the number of births per year. Data is presented by individual year or grouped by two year intervals if there are too few cases to meet the criterion for testing by single year. A trend test is not performed if the expected number of cases per year (or 2 year interval) is less than 5 and if the observed number of cases in any one year (or 2 year interval) is less than 2.

Change over time is tested with a chi square test for heterogeneity, divided into the trend component ("chi square test for trend") and the non-linear component ("chi square test for non-linear change"). The average annual percentage change in prevalence per year is calculated from a logistic regression. The Chi square test for trend identifies evidence of an increasing or decreasing trend in prevalence. The Chi square test for non-linear change identifies evidence of significant change over time (i.e. the prevalence changes from year to year).

Monotonicity of the prevalence in five two yearly intervals is recorded. Monotonicity exists if for each point in turn the prevalence is greater than the previous point OR each point in turn the prevalence is less than the previous point. The significance level (p-value) for both chi squared tests, direction (upward or downward) and average annual percentage change in prevalence per year (with 95% confidence intervals) are given in the output.

- Where $p<0.05$ for trend component and $p>0.01$ for non-linear component, the results are identified as an "increasing or decreasing trend". Since overall directional trend is of most concern for investigation, a chi square for trend p-value less than 0.05 is interpreted as a trend even where the p-value for non-linear change is weakly significant also (between 0.05 and 0.01).
- Where $p<0.05$ for trend component, $p<0.01$ for non-linear component and the prevalence trend is monotonic, the results are also identified as 'increasing or decreasing trend'.
- Where $p<0.05$ for trend component, $p<0.01$ for non-linear component and the prevalence trend is not monotonic, the results are identified as "non-linear change".
- Where $p>0.05$ for trend component and $p<0.05$ for non-linear component, the results are identified as "non-linear change".
- Where $p>0.05$ for trend component and $p>0.05$ for non-linear component, the results are interpreted as showing no significant change over time.

Since the Chi squared test is based on conventional probabilistic statistics, at a significance level of $p<0.05$, 5% of the test results will be statistically significant by chance. This should be kept in mind in interpretation (see protocol for investigation).

"Pan-Europe" trend detection.

The "Pan-Europe" analysis repeats the procedures above to present data from individual registries. In order to calculate the overall trend across Europe and include data across all eligible registries, Poisson random effects regression models with the registries as strata are fitted. These models can include data from registries with too few cases for the chi-squared analyses and they also allow for heterogeneity between registries. To be consistent with the registry analyses the Poisson model only includes 8 years of data for those registries in whom 10 years were not available. Tests for pan-European monotonicity are not performed.

Clusters

A 'scan' moving window method is used to detect clusters, based on the cases who occurred in the period 2014-2018 (or 2013-2017, or 2012-2016). The analysis for detecting clusters is run on 75 EUROCAT subgroups of congenital anomalies (see Appendix B). Excluded from the analysis are 16 major heterogeneous subgroups listed in Appendix B (e.g. nervous system, eye, congenital heart defects).

1. To run the scan analysis for cluster detection, a minimum of seven cases over the surveillance period (2012-2016 or 2013-2017 or 2014-2018) is needed.
2. Clusters are reported when they are within or overlapping the last two years (2015-2016, or 2016-2017, or 2017-2018) and are of less than 18 months in length.
3. The default scan analysis uses estimated dates of conception. If date of conception is missing for > 10% of cases, then the analysis is based on the date of birth.
4. 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. 2016 (or 2017, or 2018, depending on the overall period investigated).

   If date of birth/delivery is used to detect clusters, the last full year (1 January – 31 December) is included in the surveillance.

Annex 4: Summary of a registry's preliminary investigation protocol for identified clusters

Investigation protocols and templates, provided to make the reporting process consistent between registries, are described in full in the EUROCAT Statistical Monitoring Protocol [7]. Using the templates, registries were asked to include the following in their investigation report:

Clusters:

1. The methods and results of investigations as to whether changes in diagnostic methods, training, personnel or reporting practice contributed to the cluster.
2. The methods and results of any investigation into aetiological factors, including which aetiological factors were investigated and which source of information was used (registry database, further access to medical records or parents etc.).
3. Any local concerns about exposures and how they came to your attention.
4. Whether anyone in your region (e.g. local community or health professional) had previously been aware of the cluster.
5. The basis for your decisions to conduct the investigation in the way you did, and whether you will continue to investigate (if so, how? if not, why not?).
6. Which public health authorities have been or will be notified about the cluster?
7. Registries are asked to conclude from their preliminary investigations if this is a 'true cluster of concern or not'

Cluster investigations can be classified as follows:

- Apparent cluster with cause for concern, further investigation on-going
- Cluster associated with 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

Annex 5: Summary of increasing and decreasing ten-year trends detected in the pan-European analysis (2009-2018)

			95% CI limits	
Group of anomalies	**Trend's direction**	**Annual change**	**lower**	**upper**
Posterior urethral valve and/or prune belly	increasing	+3.8%	+1.0%	+6.9%
Arhinencephaly/holoprosencephaly	increasing	+3.6%	+0.6%	+6.8%
Bilateral renal agenesis including Potter syndrome	increasing	+3.3%	+0.6%	+6.1%
Multicystic renal dysplasia	increasing	+3.1%	+1.6%	+4.7%
Double outlet right ventricle	increasing	+3.0%	+0.5%	+5.6%
Coarctation of aorta	increasing	+2.6%	+1.0%	+4.3%
Laterality anomalies	increasing	+2.4%	+0.3%	+4.7%
Club foot - talipes equinovarus	increasing	+2.2%	+1.2%	+3.1%
Patau syndrome	increasing	+1.9%	-0.1%	+3.9%
Edward syndrome	increasing	+1.7%	+0.5%	+2.9%
Severe CHD	increasing	+0.8%	+0.1%	+1.4%
Down syndrome	increasing	+0.7%	+0.1%	+1.3%
Fetal alcohol syndrome	decreasing	-10.2%	-13.5%	-5.8%
Atresia of bile ducts	decreasing	-5.3%	-10.1%	+0.1%
Teratogenic syndromes with malformations	decreasing	-4.9%	-7.2%	-2.3%
Indeterminate sex	decreasing	-4.0%	-7.8%	+0.1%
Bladder exstrophy and/or epispadia	decreasing	-4.0%	-7.4%	-0.3%
Patent ductus arteriosus	decreasing	-3.8%	-5.5%	-2.0%
Hydrocephaly	decreasing	-3.0%	-4.3%	-1.6%
Syndactyly	decreasing	-2.6%	-4.2%	-1.0%
Pulmonary valve stenosis	decreasing	-2.4%	-3.8%	-0.9%
Vascular disruption anomalies	decreasing	-1.6%	-2.7%	-0.5%
Down syndrome adjusted	decreasing	-1.0%	-1.8%	-0.2%

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