European Commission

EUROCAT Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2013-2022)

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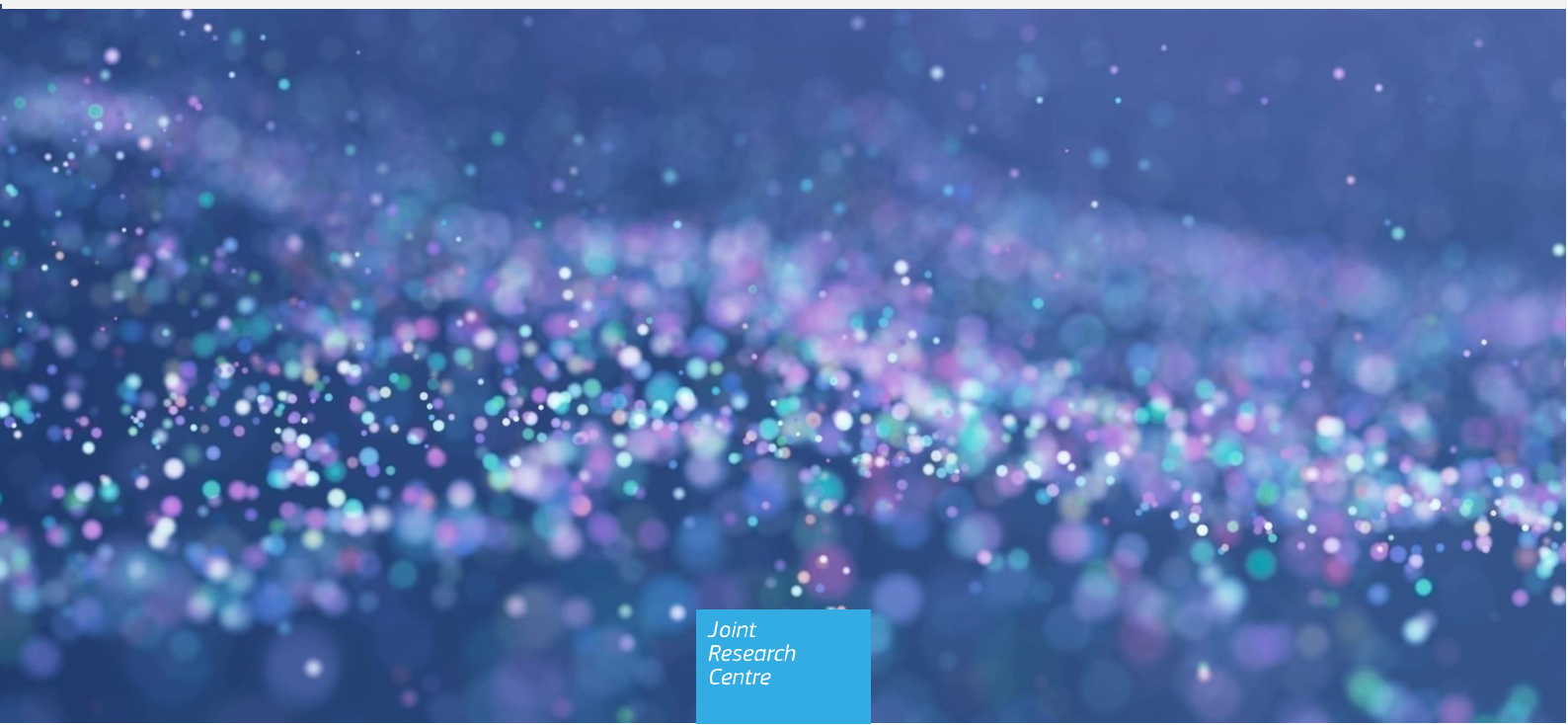
2025



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Contents

Abstract

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

The European network of population-based registries for the surveillance of congenital anomalies (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 trends within and across member registries as well as unusual aggregation of cases in time (clusters). In the present report we describe and comment on the results of the statistical analysis performed centrally on data for the birth years 2013-2022, covering the investigation of both the 32 clusters of congenital anomalies detected in 15 registries over the birth years 2018-2022 and the pan-European trends detected over the birth years 2013-2022. Where available, the outcomes of preliminary investigations conducted by registries are also presented.

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

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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 21 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 groups of congenital anomalies [5, 6, 7] 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. 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 2013 and 2022. We report here the results of the cluster analyses performed for 91 anomaly subgroups on cases reported for the period 2018-2022 by 15 EUROCAT registries. The pan-European trend analyses were performed on 94 anomaly subgroups on cases reported for the period 2013-2022 by 20 EUROCAT registries.

2 Pan-European trends

2.1 Trends methodology

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

Currently, the JRC-EUROCAT Central Registry performs for every registry at central level a trend test for the most recent 10 years, as well as a "Pan-Europe" analysis including data across all eligible registries [8]. The latter is particularly useful for rare anomalies which frequently have too few cases per year for analysis in individual registries.

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. Trend tests are not reported if the total number of cases over the time-period is less than 5, or where a chi-squared test of the deviance provides moderate evidence that the model is incorrectly specified ($p<0.05$).

For individual registries, the average annual percentage change in prevalence per year is calculated using generalised linear models (GLMs). Poisson models with log-links are used with the outcome number of cases, predictor centred year, and offset log-total number of births in the population. The average percentage change in prevalence, significance level (p-value), and direction (upward or downward) are given in the output.

Evidence of a non-linear trend is also assessed using generalised additive models (GAMs). Poisson models with log-links are used with same outcome, predictors and offset as the GLMs. The GAMs additionally use penalised thin-plate splines with a null space dimension of 0.5; the maximum number of knots set to one less than the number of years; and Restricted Maximum Likelihood (REML) estimation. The estimated degrees of freedom (e.d.f) (which is indicative of the complexity of any curvature), significance of the overall trend (p-value), and direction (curve, upward, or downward) are given in the output.

The Pan-European analysis is the same as above but uses generalised linear mixed models (GLMMs), and generalised additive mixed models (GAMMs) with random intercepts and slopes for registries.

Significant trends are identified using the following criteria:

- Where $p<0.05$ for the GAM trend, and e.d.f >1.2 results are identified as a "curved trend".
- Where $p<0.05$ for the GAM trend, and e.d.f <1.2 results are identified as an "increasing or decreasing trend".
- Where $p>0.05$ for the GAM trend, but $p<0.05$ for the GLM average percentage change in prevalence results are identified as an "increasing or decreasing trend".
- Where $p>0.05$ for both GAM and GLM results are interpreted as showing no significant change over time.

All reported trend tests are accompanied by plots of the point percentage and confidence interval of the prevalence each year, along with the fitted GLM and GAM trend lines.

As tests for trend are based on probabilistic statistics, at a significance level of $p<0.05$, 5% of test results will be statistically significant by chance. This should be kept in mind when interpreting these results.

2.2 Registries included in the trends analysis

The pan-European trend analysis was carried out for the time period 2013-2022. The analysis included data from 20 full member registries (see Annex B). The inclusion criteria for the registries were as published in the EUROCAT Statistical monitoring protocol [8]:

1. Registries are no more than one year late with data transmission, and have submitted data continuously for at least eight calendar years;
2. Registries for which the number of submitted cases in the latest year was at least 80% of those submitted in previous calendar years.

The registries included in the trend analysis were: Hainaut (Belgium), Pleven (Bulgaria), Funen (Denmark), Auvergne (France), Brittany (France), French West Indies (France), Paris (France), Réunion (France), Saxony-Anhalt (Germany), Cork & Kerry (Ireland), Emilia-Romagna (Italy), Tuscany (Italy), Trento (Italy), Malta, Northern Netherlands, Wielkopolska (Poland), Vaud (Switzerland), Valencian Region (Spain), Wales (UK), Omni-Net (Ukraine).

The full member registries excluded from the analysis were:

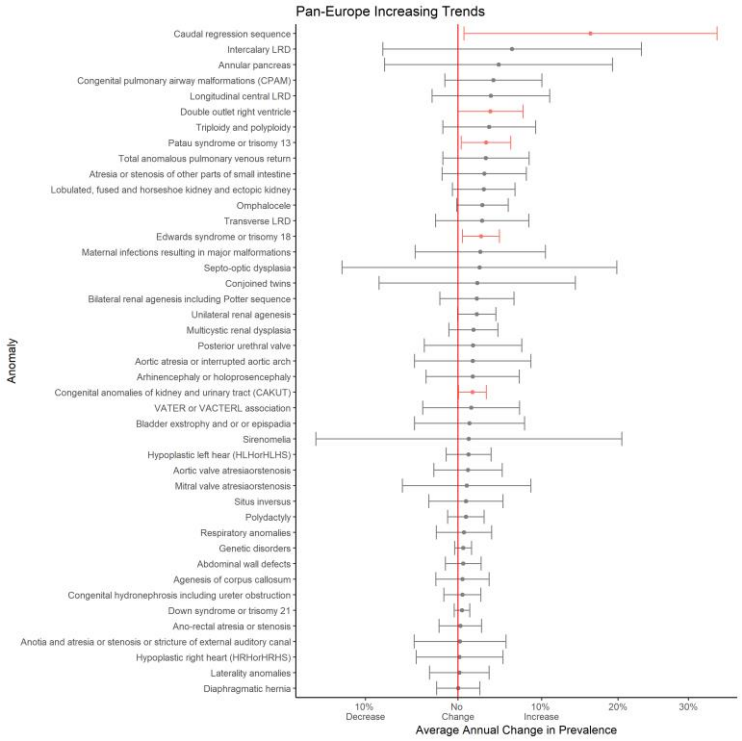
- Styria (Austria), Antwerp (Belgium) and South Portugal, as the data were missing for birth year 2022 and incomplete for 2021;
- Zagreb (Croatia), Milan (Italy), Basque Country (Spain), Navarra (Spain), Northern England (UK), Thames Valley (UK), Wessex (UK) and South West England (UK), as they were more than one year behind in data transmission;
- ATS Valpadana (Italy), Norway, South East Ireland, East Midlands & South Yorkshire (UK), Yorkshire and Humber (UK) and West Midlands (UK), because these registries had less than eight years of data in the Central Database.

2.3 Trends analysis 2013-2022: overview

There were increasing pan-European trends for 5 congenital anomaly subgroups and decreasing pan-European trends for 17 subgroups. These statistically significant trends included four overarching congenital anomaly groups (CAKUT, Nervous system, Oral Facial Clefts and Genital anomalies) which due to their heterogeneity are not included in the detailed trends analysis (Annex A).

The trends include all birth outcomes for each anomaly. Cases with an additional genetic diagnosis are excluded, but the included cases may have additional major anomalies in other organ systems. The estimated percentage change in yearly prevalence for each congenital anomaly subgroup is presented in fig. 1 (increase in prevalence; red lines indicate statistical significance) and fig. 2 (decrease in prevalence; blue lines indicate statistical significance).

Figure 1. Estimated annual percentage change (increase) in the prevalence and 95% CIs (pan-European analysis 2013-2022).

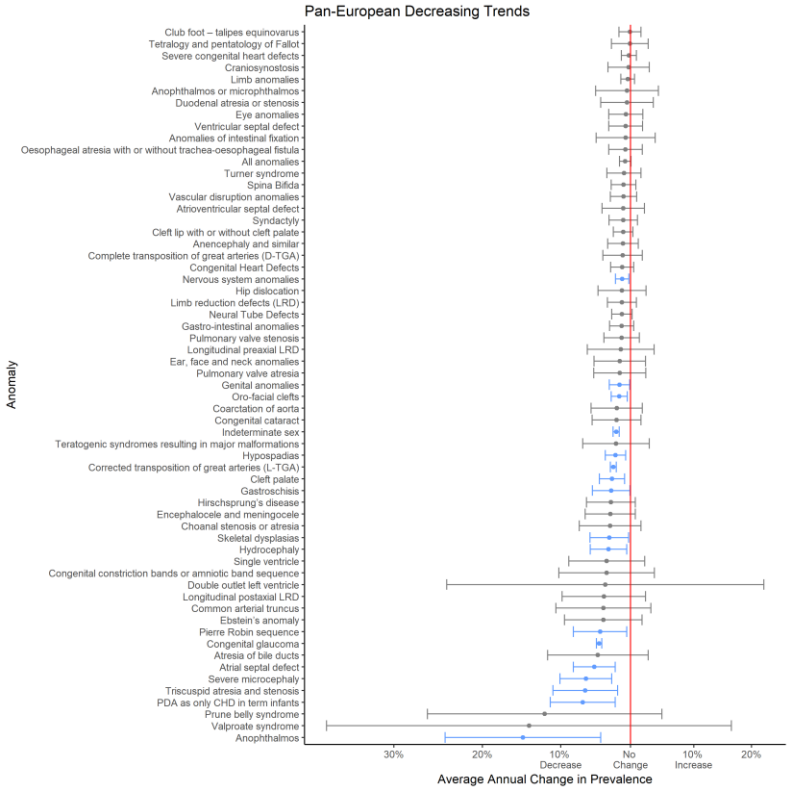


Source: JRC-EUROCAT Central Registry

At the pan-European level, among the subgroups included in the trends analysis (Annex A), the 4 significant increasing trends were: double outlet right ventricle, caudal regression sequence, trisomy 13 and trisomy 18.

All these trends were detected in at least one of the four previous reports [9, 10, 11, 12, 13].

Figure 2. Estimated annual percentage change (decrease) in the prevalence and 95% CIs (pan-European analysis 2013-2022).



Source: JRC-EUROCAT Central Registry

14 significant decreasing trends were detected in the following subgroups, Among the subgroups included in the trends analysis (Annex A): Hydrocephaly, Severe microcephaly, Anophthalmos, Congenital glaucoma, Corrected transposition of great arteries, Atrial septal defect, Tricuspid atresia and stenosis, Patent ductus arteriosus (PDA) as only CHD in term born infants, Cleft palate, Gastrochisis, Hypospadias, Indeterminate sex, Pierre Robin sequence, Skeletal dysplasia.

Table 1 presents the estimated annual percentage change for each of the significant trends detected this year.

Table 1. Summary of increasing and decreasing ten-year trends detected in the pan-European analysis (2013-2022)

			95% CI limits	
Group of anomalies	**Trend's direction**	**Annual change**	**lower**	**upper**
Double outlet right ventricle	increasing	+3.8%	+0.0%	+7.7%
Caudal regression sequence	increasing	+16.3%	+0.7%	+34.3%
Patau syndrome – Trisomy 13	increasing	+3.2%	+0.4%	+6.2%
Edward's syndrome – Trisomy 18	increasing	+2.7%	+0.5%	+4.8%
Hydrocephaly	decreasing	-3.3%	-5.9%	-0.6%
Severe microcephaly	decreasing	-6.5%	-10.1%	-2.8%
Anophtalmos	decreasing	-15.0%	-24.4%	-4.4%
Congenital glaucoma	decreasing	-4.6%	-5.0%	-4.2%
Corrected transposition of great arteries (L-TGA)	decreasing	-2.6%	-3.0%	-2.1%
Atrial septal defect	decreasing	-5.3%	-8.2%	-2.3%
Tricuspid atresia and stenosis	decreasing	-6.6%	-11.0%	-1.9%
PDA as only CHD in term infants	decreasing	-6.9%	-11.4%	-2.3%
Cleft palate	decreasing	-2.7%	-4.6%	-0.9%
Gastroschisis	decreasing	-2.9%	-5.6%	-0.1%
Hypospadias	decreasing	-2.2%	-3.7%	-0.7%
Indeterminate sex	decreasing	-2.1%	-2.6%	-1.7%
Pierre Robin sequence	decreasing	-4.5%	-8.2%	-0.6%
Skeletal dysplasia	decreasing	-3.1%	-5.9%	-0.3%

Source: JRC-EUROCAT Central Registry

2.4 Methodology for trends investigations

After the analysis conducted centrally by the Central Registry, registries are asked to investigate the increasing (/),decreasing (\) and curved trends detected at Pan-European level, when a trend is also evidenced at the local registry level. Investigation templates are provided to make the reporting process consistent between registries. [8]

Using these templates and the outputs from the EUROCAT Data Management Software (DMS) [8, 14], investigations cover a variety of aspects: cases confirmation, diagnoses or reporting practices, comparison with EUROCAT average, risk factors, similarity with other registers or anomalies, registry population. [8]

2.5 Details on the trends investigations

This section provides further analysis on increasing and decreasing pan-European trends over 2013-2022, using, when relevant, the results of the investigation from the local registries. Among the 14 decreasing trends identified at pan-European level (see section 2.3), three were not analysed:

- Corrected transposition of great arteries and Patent ductus arteriosus (PDA) as only CHD in term born infants: these anomalies are diagnosed late and the last year available in the central database is under-reported;
- Indeterminate sex: this anomaly group is too heterogeneous and reporting practices vary between the local registries.

Three figures are examined for each congenital anomaly subgroup. Firstly, the pan-European prevalence of the congenital anomaly in each year with its 95% confidence intervals (CIs) is plotted against the year of birth and the estimated annual linear change is shown in red. This enables any sudden changes in prevalence to be identified, which may be due to coding issues rather than an underlying change in prevalence. It also enables to detect the potential under-reporting that may occur in the latest year of data available to be evaluated.

Secondly, the annual change in prevalence and 95% CIs in each registry is plotted, the summary pan-European estimate being given at the top of each graph. This enables the identification of any registries with noticeably

high or low changes in prevalence to be identified. The prevalence within each registry is also given to aid interpretation of the observed trends. For example, a registry with a very low prevalence that experiences a greater increase than the other registries could be interpreted as an improvement in data collection in that registry rather than as a cause for concern. Registries with too few cases are indicated by a cross (see [8] for details of how these are derived).

Thirdly, the prevalence of the congenital anomaly subgroup in each registry over the whole time period is plotted. This is to illustrate the heterogeneity of reporting of the congenital anomaly between registries and to identify registries potentially under- or over-reporting. Such information is of use when interpreting any trends. If an anomaly is consistently reported across registries, the underlying trend will more likely reflect a true increase or decrease in prevalence. However, if there is great heterogeneity in the prevalence of an anomaly in registries, more caution should be taken in interpreting an observed trend as reflecting a true increase or decrease in prevalence.

2.5.1 Increasing trends identified at pan-European level

2.5.1.1 Double outlet right ventricle

Double outlet right ventricle is a severe cardiac anomaly where both the aorta and the pulmonary artery originate from the right ventricle of the heart. The new born baby may be asymptomatic, but symptoms usually appear within the first weeks after birth. Corrective surgery is performed in infancy.

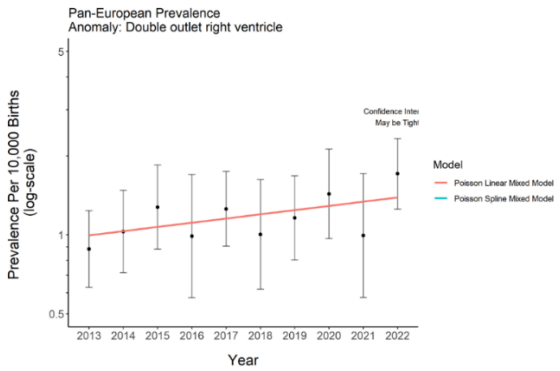
The prevalence of double outlet right ventricle is estimated to have increased each year by +3.8% (95% CIs: +0.0%; +7.7%) at the pan-European level (fig. 3). The increasing trend at the pan-European level was detected already in two previous reports [9, 11].

There is considerable heterogeneity of the prevalence over the 10-year period in the registries with a minimum value in Vaud (0.35 per 10,000 births) and a maximum value in Ukraine (2.24 per 10,000 births) (fig. 5).

The significant increasing trend in prevalence was found in three individual registries during the same period (Saxony-Anhalt, Emilia Romagna and Tuscany) (fig. 4). Saxony-Anhalt's investigation report underlined that double outlet right ventricles have been increasingly diagnosed since 2017 and may have been categorised as Fallot before. The registry will continue its investigations.

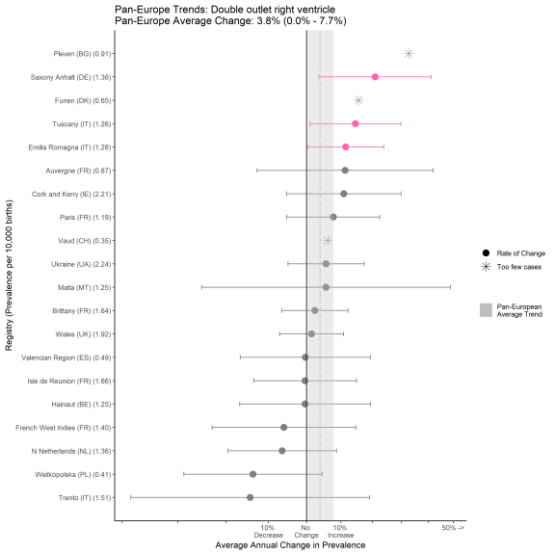
Conclusion: the increasing pan-European trend, also found in previous reports, may be explained by a change in coding by the hospitals in the EUROCAT registry areas as this specific code did not exist in ICD9. This is relevant for Emilia Romagna and Tuscany where the hospitals billing systems still use ICD9. Further, there is also more clinical focus on the difference between double outlet right ventricle and Tetralogy of Fallot. Double outlet right ventricle is defined as an overriding aorta with more than 50% while Tetralogy of Fallot is defined as less than 50% overriding of the aorta.

Figure 3. Double outlet right ventricle - Prevalence and 95% CIs for the birth years 2013-2022



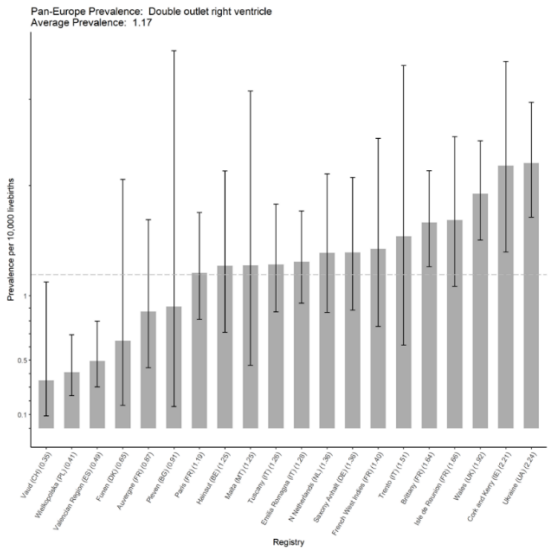
Source: JRC-EUROCAT Central Registry

Figure 4. Double outlet right ventricle - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 5. Double outlet right ventricle – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.1.2 Caudal regression sequence

Caudal regression sequence is a severe and very rare congenital anomaly with aplasia or hypoplasia of the sacrum and lumbar spine and variable involvement of the lower limbs, gastrointestinal and urogenital tract and the nervous system. The anomaly is highly associated to maternal pre-gestational diabetes with high level of HbA1c at the time of conception (poor diabetic control before and just after conception) [15].

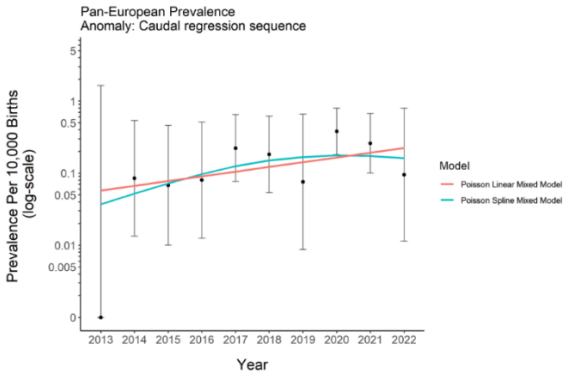
The prevalence of caudal regression sequence is estimated to have increased each year by +16.3% (95% CIs: +0.7%; +34.3%) at the pan-European level (fig. 6). The increasing trend at the pan-European level was detected already in two previous reports [12, 13].

No registry has a significant increasing trend in prevalence (fig. 7) and many have too few cases for running the trends analysis. Therefore, only the pan-European trend can be analysed. Caudal regression sequence is

indeed a very rare anomaly. It is heterogeneously reported by the registries: caudal regression sequence is more often reported when there is a post mortem examination by a foetopathologist, and autopsy rates vary across regsitries. A case is only included in the subgroup if it is coded using a 4-digit ICD10-BPA code. The average prevalence over the 10-year period in the registries varies from 0 in Funen, Hainaut, Malta, Pleven, Trento, Tuscany and Wielkopolska to 0.77 in Saxony-Anhalt (fig. 8).

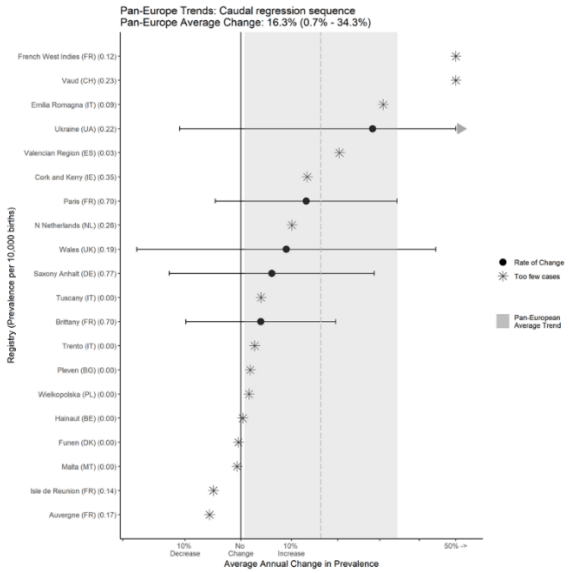
Conclusion: This pan-European increasing trend is of concern. A more detailed analysis of this anomaly is initiated and is expected to be published within 1-2 years. The increase in obesity and maternal diabetes among pregnant women may explain the increasing trend.

Figure 6. Caudal regression sequence - Prevalence and 95% CIs for the birth years 2013-2022



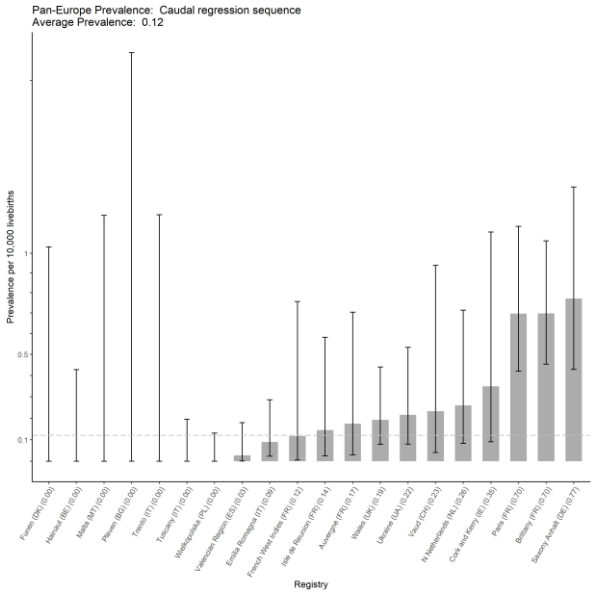
Source: JRC-EUROCAT Central Registry

Figure 7. Caudal regression sequence - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 8. Caudal regression sequence – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

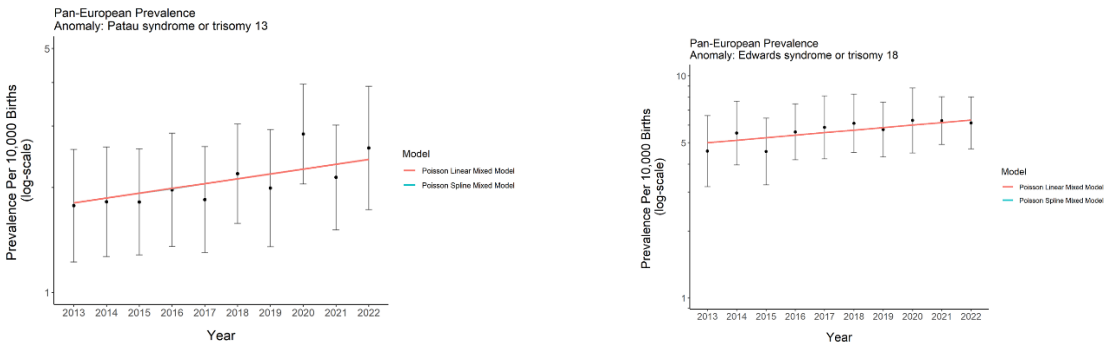
2.5.1.3 Patau syndrome (trisomy 13) and Edward's syndrome (trisomy 18)

Patau syndrome (trisomy 13) and Edward's syndrome (trisomy 18) are rare chromosomal anomalies with an additional copy of chromosome 13 and chromosome 18 respectively. These anomalies are associated with severe intellectual disability and are lethal in infancy. There are often associated major congenital anomalies.

For the fourth time in the past six years, [11, 12, 13], the prevalence of Patau syndrome and Edward's syndrome are estimated to have increased each year by +3.2% (95% CIs: +0.4%; +6.2%) and +2.7% (95% CIs: +0.5%; +4.8%) respectively at the pan-European level (fig. 9).

Conclusion: The increasing trends in these 2 anomalies may be due to the wider use of non-invasive first trimester prenatal testing for chromosomal anomalies, including analysis of fetal DNA in maternal blood, that provide earlier diagnoses. Indeed, in the 20 registries included in the trends analysis 2013-2022, the gestational age at discovery has decreased from 16.3 weeks in 2013 to 13.9 weeks in 2022 for Patau syndrome and from 16.5 weeks in 2013 to 14.1 weeks in 2022 for Edward's syndrome. There are extremely high fetal loss rates in these two anomalies, which would account for a lower prevalence in earlier years due to the later prenatal diagnoses missing many fetuses that had already been lost. The trends will be monitored, but there are no major concerns.

Figure 9. Patau syndrome (trisomy 13) and Edward's syndrome (trisomy 18) - Prevalence and 95% CIs for the birth years 2013-2022



Source: JRC-EUROCAT Central Registry

2.5.2 **Decreasing trends identified at pan-European level**

2.5.2.1 Hydrocephaly

The definition of hydrocephaly is dilatation of the ventricular system with impaired circulation and absorption of the cerebrospinal fluid. The dilatation should not be due to primary atrophy of the brain, with or without enlargement of the skull.

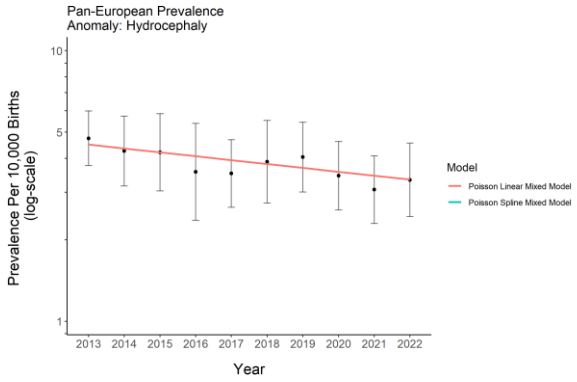
As in the five previous reports [9, 10, 11, 12, 13], the prevalence of hydrocephaly is estimated to have decreased each year by -3.3% (95% CIs: -5.9%; -0.6%) at the pan-European level (fig.10).

The anomaly was found significantly decreasing in prevalence in four individual registries during the same period (Paris, Réunion, Emilia Romagna and Wielkopolska) (fig.11).

Heterogeneity of the prevalence over the 10-year period is observed in the registries with a minimum value in Cork & Kerry (1.40 per 10,000 births) and a maximum value in Pleven (13.70 per 10,000 births) (fig. 12).

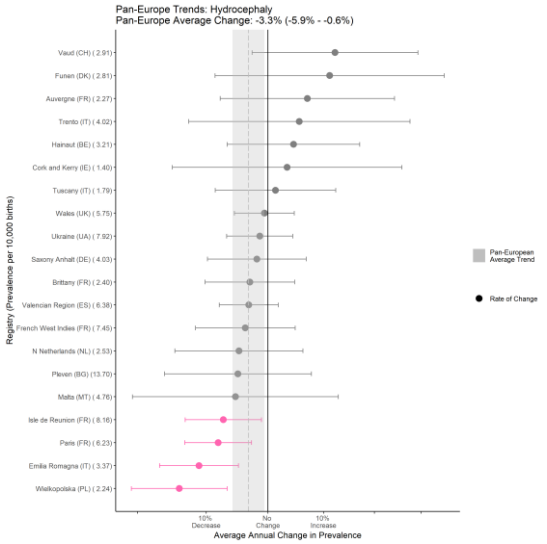
Conclusion: The prevalence of congenital hydrocephaly is decreasing in Europe. This may be explained by improved maternal health and less infections during pregnancy, as well as by better diagnosis of other cerebral anomalies with prenatal ultrasound screening. A more detailed analysis of this anomaly is initiated and is expected to be published within 1-2 years.

Figure 10. Hydrocephaly - Prevalence and 95% CIs for the birth years 2013-2022



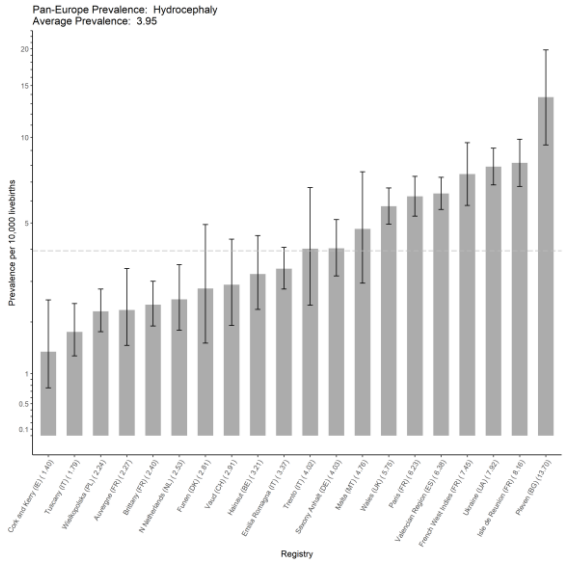
Source: JRC-EUROCAT Central Registry

Figure11. Hydrocephaly - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure12. Hydrocephaly – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.2 Severe microcephaly

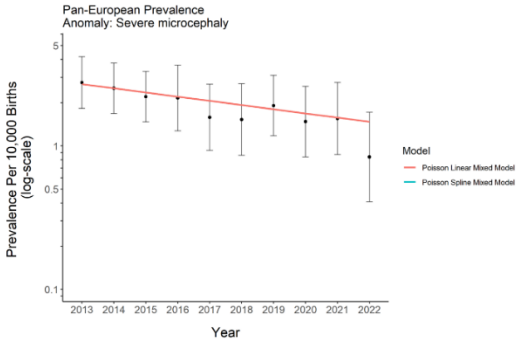
Severe microcephaly should be reported if the head circumference (occipito-frontal) is less than -3 SD for sex and GA.

As in the previous reports [9, 10, 11, 12, 13], the prevalence of severe microcephaly is decreasing. Between 2013 and 2022, its prevalence is estimated to have decreased by -6.5% (95% CI: -10.1%; -2.8%) (fig.13).

The anomaly was found significantly decreasing in prevalence in two individual registries during the same period (Ukraine and Emilia Romagna) (fig.14).

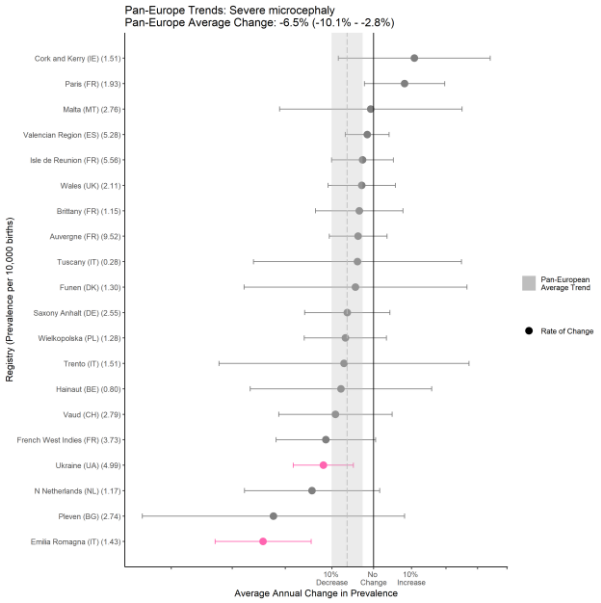
Conclusion: The decreasing trend may be explained by less overreporting: in June 2016, the EUROCAT Coding and Classification Committee published a new coding tip on microcephaly [16]. The prevalence from 2017 to 2021 appears to have stabilised, with a very large decrease in 2022 perhaps due to late reporting of microcephaly cases.

Figure 13. Severe microcephaly - Prevalence and 95% CIs for the birth years 2013-2022



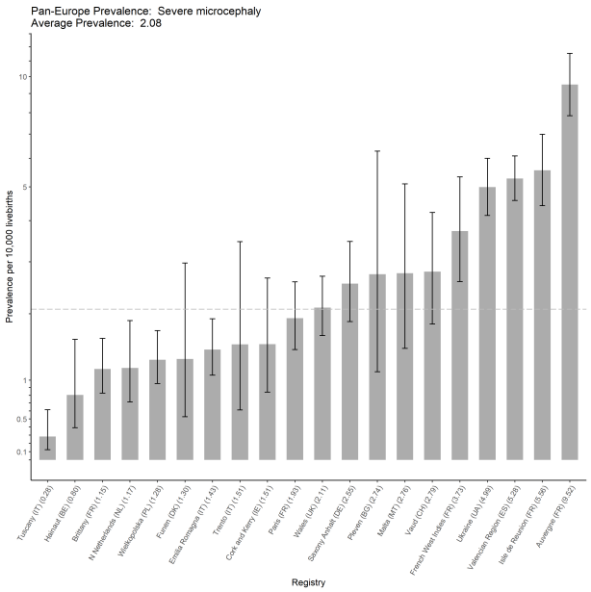
Source: JRC-EUROCAT Central Registry

Figure 14. Severe microcephaly - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 15. Severe microcephaly – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.3 Anophthalmos

Anophthalmos is a unilateral or bilateral absence of the eye tissue.

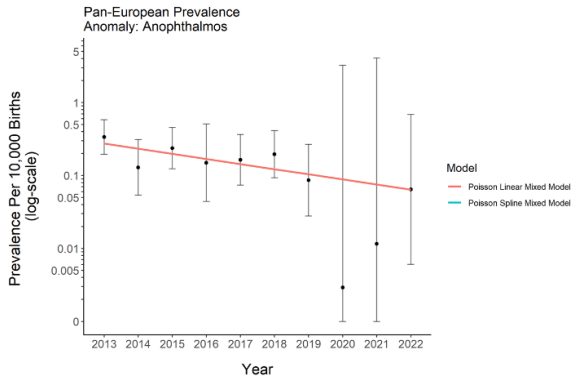
As in the previous report [13], the prevalence of anophthalmos is decreasing. Between 2013 and 2022, its prevalence is estimated to have decreased by -15% (95% CI: -24.4%; -4.4%) (fig.16). The prevalence of anophthalmos was extremely low in 2020 and 2021, but the wide confidence intervals indicate that all these estimates are based on very small numbers.

No registry has a significant decreasing trend in prevalence (fig. 17) and many have too few cases for running the trends analysis. Anophthalmos is indeed a very rare anomaly (fig.18).

The average prevalence over the 10-year period in the registries varies from 0 in Funen, Hainaut, Malta, Pleven and Trento to 0.47 in Saxony-Anhalt.

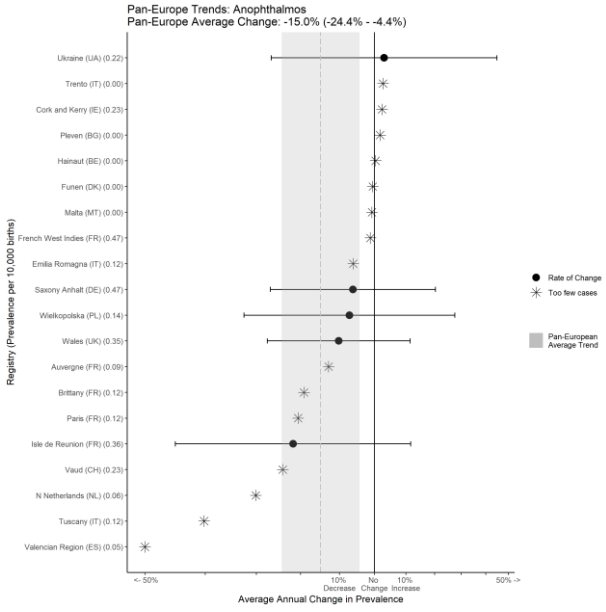
Conclusion: We have no explanation of this decreasing pan-European trend that is based on very small numbers. It requires further surveillance.

Figure 16. Anophthalmos - Prevalence and 95% CIs for the birth years 2013-2022



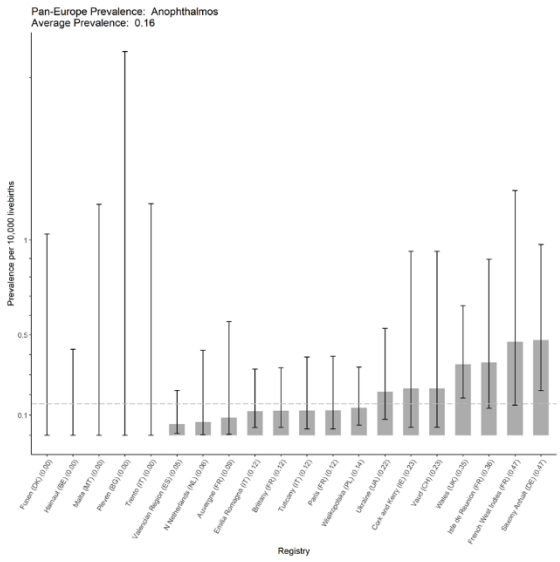
Source: JRC-EUROCAT Central Registry

Figure17. Anophthalmos - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 18. Anophthalmos – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.4 Congenital glaucoma

Congenital glaucoma is a large ocular globe as a result of increased ocular pressure in fetal life. It may be associated with blindness or poor vision.

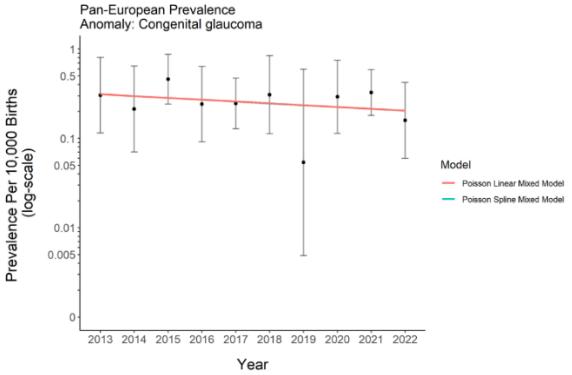
As in the previous report [13], the prevalence of congenital glaucoma is decreasing. Between 2013 and 2022, its prevalence is estimated to have decreased by -4.6% (95% CI: -5.0%; -4.2%) (fig.19).

Two registries (Réunion and Emilia Romagna) have a significant decreasing trend in prevalence (fig. 20). Many registries have too few cases for running the trends analysis.

The average prevalence over the 10-year period in the registries varies from 0 in Cork & Kerry, Malta, Pleven and Vaud to 1.52 in Réunion. The significant decreasing trend in Réunion may indicate improved registration in this centre with less overreporting, more consistent with the other registries (fig 21).

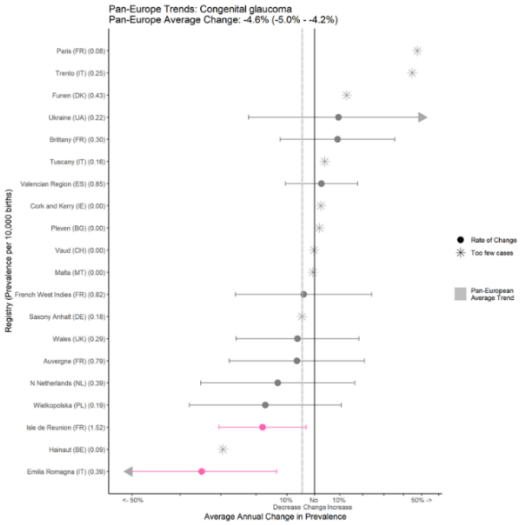
Conclusion: We have no explanation of this decreasing pan-European trend.

Figure19. Congenital glaucoma - Prevalence and 95% CIs for the birth years 2013-2022



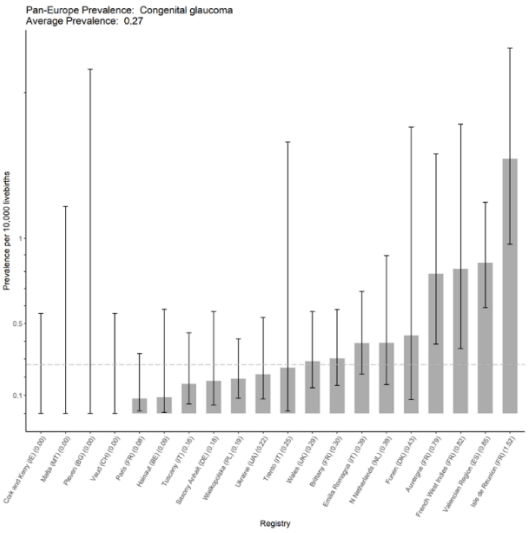
Source: JRC-EUROCAT Central Registry

Figure 20. Congenital glaucoma - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure21. Congenital glaucoma – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.5 Atrial Septal Defect (ASD)

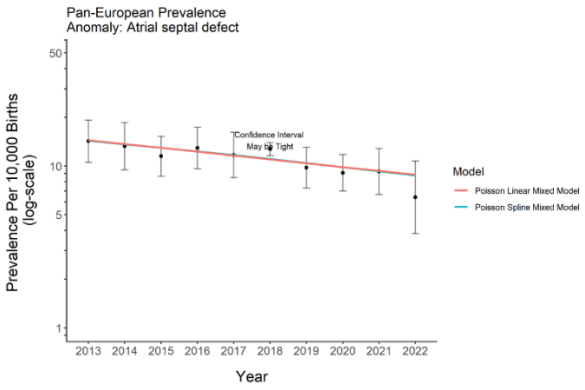
ASD is a defect in the atrial septum allowing blood to flow between the left and the right side of the heart. In fetal life the atrial septum is open (foramen ovale) and will close at birth or within the first months after birth. There is no international consensus on the discrimination between ASD and a persistent foramen ovale from fetal life [17]. EUROCAT recommends only to report cases with flow across the atrial septum confirmed by echocardiography after 6 months of age after correction for gestational age in preterm births. ASD requiring surgery may be diagnosed after the first year of life.

The prevalence of ASD is estimated to have significantly decreased by -5.3% (95% CI: -8.2%; -2.3%) between 2013 and 2022 (fig.22). This trend is detected for the first time in the past 6 years. Eight registries have a significant decreasing trend in prevalence (fig. 23).

The reporting of ASD is roughly homogeneous over the registries. The average prevalence over the 10-year period in the 20 registries varies between 7.22 to 18.17 per 10,000 births, except for Paris (3.48), Saxony-Anhalt (39.29) and Malta (46.88) (fig. 24).

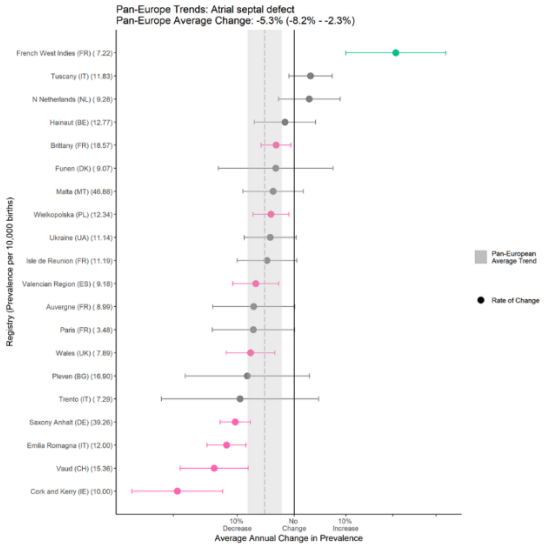
Conclusion: The pan-European decreasing trend is most likely explained by less reporting of diagnosis of ASD/persistent foramen ovale in the neonatal period without follow up within the first year.

Figure 22. Atrial septal defect - Prevalence and 95% CIs for the birth years 2013-2022



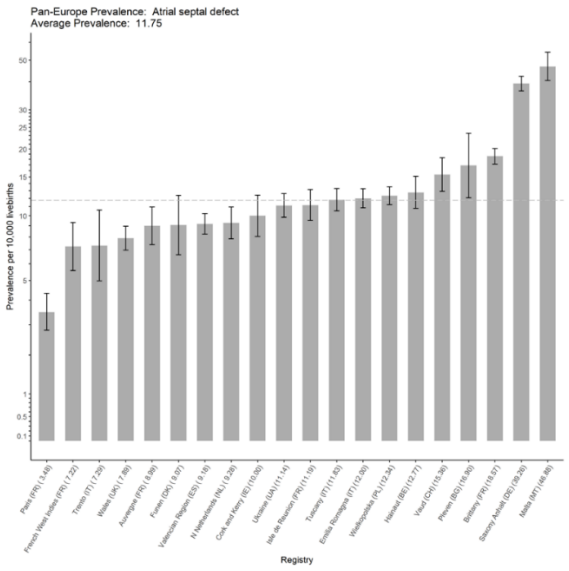
Source: JRC-EUROCAT Central Registry

Figure 23. Atrial septal defect - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure24. Atrial septal defect – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.6 Tricuspid atresia and stenosis

Tricuspid atresia is a severe congenital heart defect with obstruction of the tricuspid valve and associated hypoplasia of the right ventricle. Tricuspid stenosis is a less severe congenital heart defect, but included in the same subgroup as tricuspid atresia as the ICD10 code covers both anomalies. Aetiology of tricuspid atresia is unknown and expected to be multifactorial.

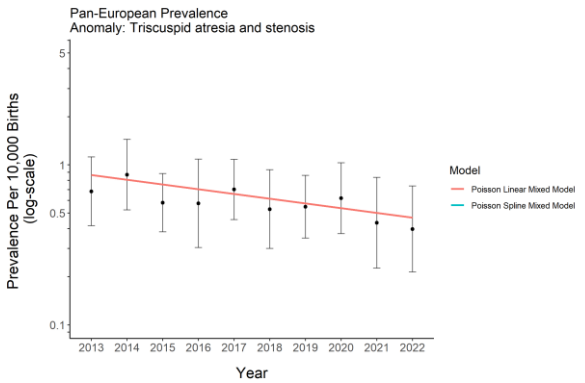
The prevalence of tricuspid atresia and stenosis is estimated to have decreased by -6.6% (95% CI: -11.0%; -1.9%) between 2013 and 2022 at the pan-European level (fig.25). None of the five previous reports identified this trend.

The anomaly is found significantly decreasing in prevalence in one local registry only (Paris) (fig. 26).

The reporting of tricuspid atresia and stenosis is roughly homogeneous over the registries (fig. 27).

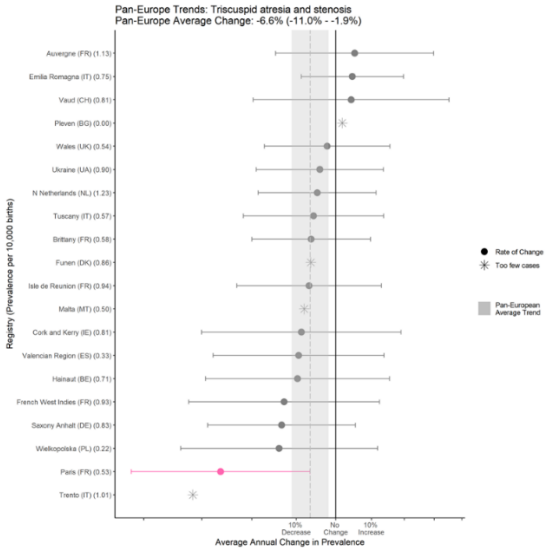
Conclusion: There is no clear explanation for the decreasing trend of tricuspid atresia and stenosis. It may be related to coding changes in the registries. There was a decrease in the number of cases coded with both tricuspid atresia and hypoplastic right heart. The proportion of TOPFA cases increased over the 10-year period. Registries may have chosen to code only the hypoplastic right heart for these TOPFA cases. However, changes in exposures and unknown risk factors for tricuspid atresia and stenosis may also explain the decreasing trend.

Figure 25. Tricuspid atresia and stenosis- Prevalence and 95% CIs for the birth years 2013-2022



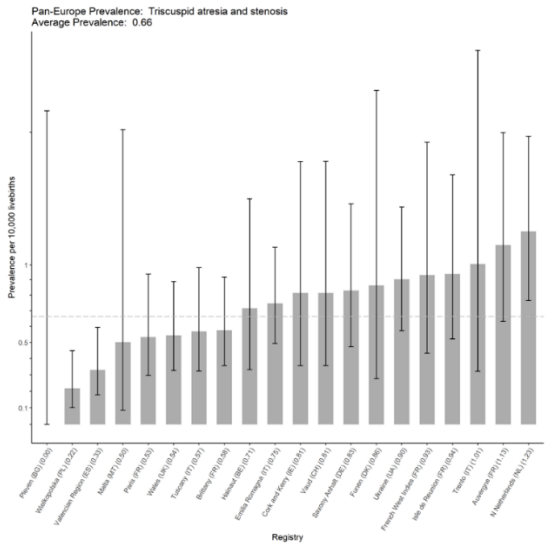
Source: JRC-EUROCAT Central Registry

Figure 26. Tricuspid atresia and stenosis - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 27. Tricuspid atresia and stenosis – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.7 Cleft palate

The subgroup "Cleft palate" is defined as fissure defect of the soft and/or hard palate(s) or submucous cleft and without having a cleft lip. The anomaly may be diagnosed days or weeks after birth. It is often associated with other severe anomalies that may have a high termination rate, in which case this specific anomaly might not be reported.

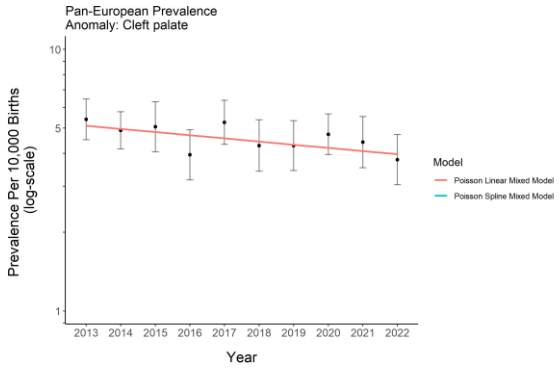
As in the two of the five previous reports [9, 13], the prevalence of cleft palate between 2013 and 2022 is estimated to have decreased by -2.7% (95% CI: -4.6%; -0.9%) each year on the pan-European level (fig. 28).

The prevalence decreased significantly in one of the individual registries during the same period (Wales, fig. 29).

The prevalence of cleft palate is roughly consistent among the 20 local registries included in this year's monitoring (fig. 30).

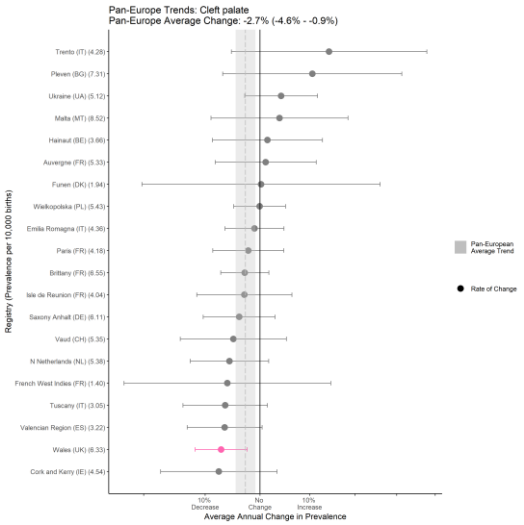
Conclusion: There may be a true decrease in the prevalence of non-genetic cleft palate in Europe. The decrease may also be explained by an increase in the proportion of fetuses and liveborn children with an associated genetic diagnosis. This will be investigated in more detail within the next year.

Figure 28. Cleft palate - Prevalence and 95% CIs for the birth years 2013-2022



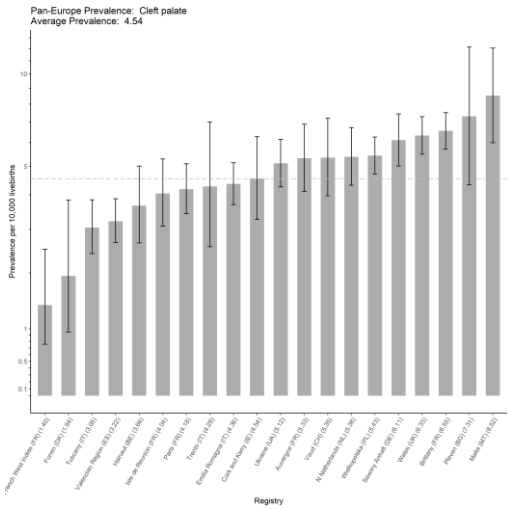
Source: JRC-EUROCAT Central Registry

Figure 29. Cleft palate - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 30. Cleft palate – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.8 Gastroschisis

Gastroschisis is defined as a protrusion of the abdominal contents not covered by a membrane, through an abdominal wall defect lateral to an intact umbilical cord. Gastroschisis is strongly associated with low maternal age.

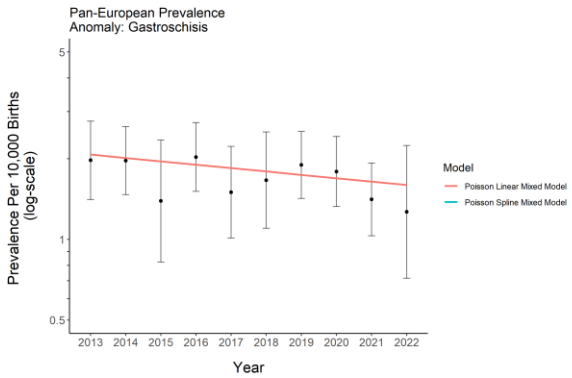
The prevalence of gastroschisis between 2013 and 2022 is estimated to have decreased by -2.9% (95% CI: -5.6%; -0.1%) each year on the pan-European level (fig. 31), for the fifth time in the past six years [9, 10, 12, 13].

The prevalence decreased in many of the registries included in this year's monitoring but significantly in only one individual registry (Brittany, fig. 32).

There is some variation in the prevalence of gastroschisis across registries with a lower prevalence in Southern Europe (fig 33). This is in line with previous publications from EUROCAT [18].

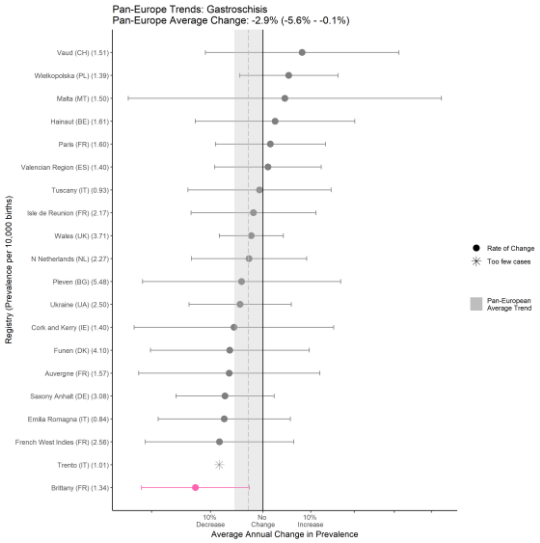
Conclusion: In the four previous reports the decrease in the pan-European trend was explained by a decrease in number of teenage pregnancies in UK. In this year's report only data from Wales are included as the English registries did not submit their recent data. It seems as if the decreasing trend is also present in continental Europe. This will be followed in the coming years.

Figure 31. Gastroschisis - Prevalence and 95% CIs for the birth years 2013-2022



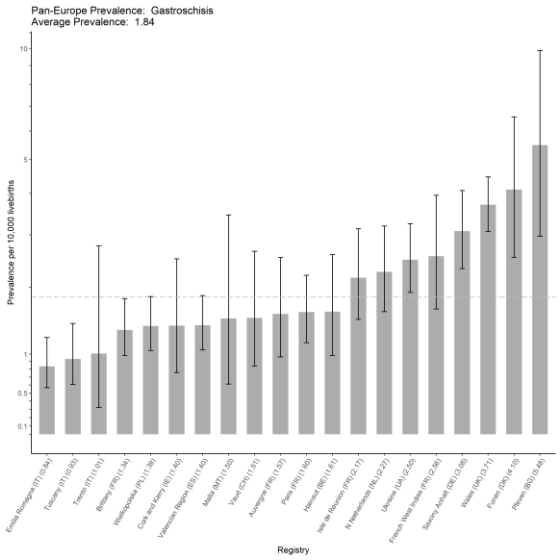
Source: JRC-EUROCAT Central Registry

Figure 32. Gastroschisis - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 33. Gastroschisis – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.9 Hypospadias

Hypospadias is a congenital anomaly affecting boys, where the urethral meatus is abnormally located and is displaced proximally on the ventral surface of the penis. There are many reports of increasing prevalence of hypospadias in studies from the 1960s to the 1980s. From 1980 to 1999 there were no consistent trends across EUROCAT registries [19]. The prevalence was stable from 2001 to 2010 among EUROCAT registries [20]. The origin of hypospadias is probably multifactorial, involving notably genetic and possibly environmental factors.. In particular there are some hypothesis about an association between hypospadias and fetal exposure to endocrine disrupting chemicals [21, 22, 23].

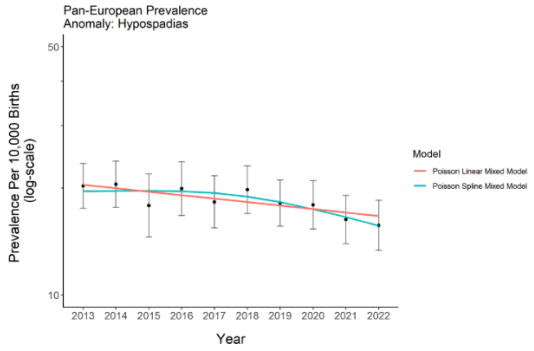
The prevalence of hypospadias between 2013 and 2022 is estimated to have decreased by -2.2% (95% CI: -3.7%; -0.7%) each year on the pan-European level (fig. 34). It is the second time the trend is found decreasing in the past six years [10].

The prevalence decreased in more than half of the local registries included in this year's monitoring and significantly in five of them (Emilia Romagna, Paris, Pleven, Tuscany, Wales, fig. 35).

The prevalence among local registries is quite homogeneous (fig. 36).

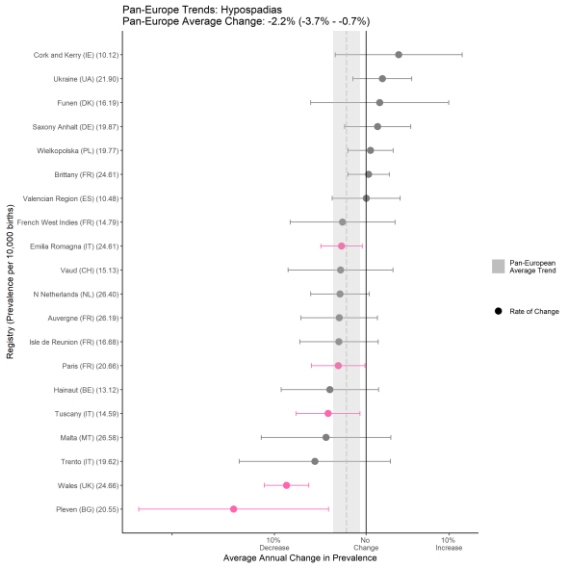
Conclusion: It is re-assuring that the previous increases in prevalence of hypospadias reported from many places in the eighties and nineties has levelled out and now seems to decrease. The evolution of hypospadias will however require further surveillance. Hypospadias might be underreported in the last birth years covered by the present monitoring, especially for late diagnoses (e.g.: balanic subtypes).

Figure 34. Hypospadias - Prevalence and 95% CIs for the birth years 2013-2022



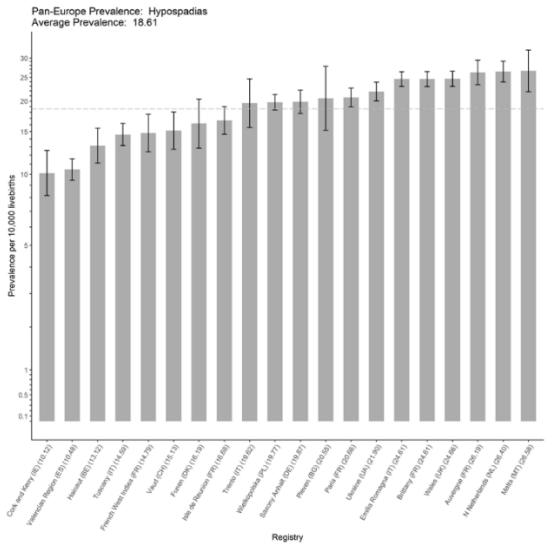
Source: JRC-EUROCAT Central Registry

Figure 35. Hypospadias - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 36. Hypospadias – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.10 Pierre Robin Sequence

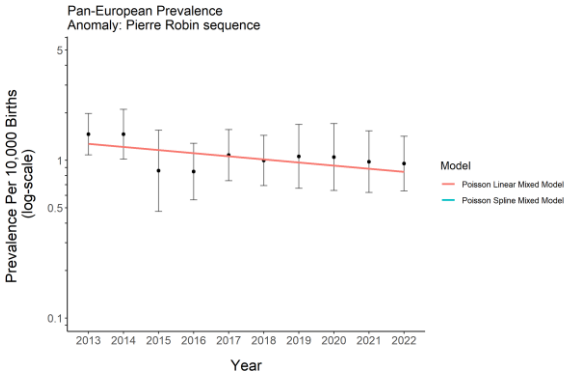
Pierre Robin sequence is defined by the presence of micrognathia, glossoptosis and airway obstruction. A posterior median cleft palate may also be present. The prevalence of Pierre Robin sequence between 2013 and 2022 is estimated to have decreased by -4.5% (95% CI: -8.2%; -0.6%) each year on the pan-European level (fig. 37).

The prevalence decreased significantly in two individual registries (Brittany, Saxony-Anhalt, fig. 38).

The prevalence among local registries varies almost tenfold between the lowest and the highest registry with the highest prevalence in the French registries (fig. 39).

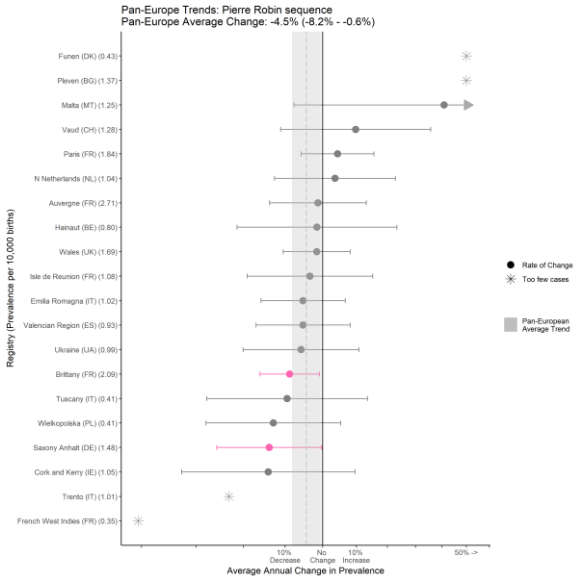
Conclusion: The decreasing pan-European trend may be explained by less reporting of cases with Pierre Robin from registries with a previous very high prevalence [24].

Figure 37. Pierre Robin sequence - Prevalence and 95% CIs for the birth years 2013-2022



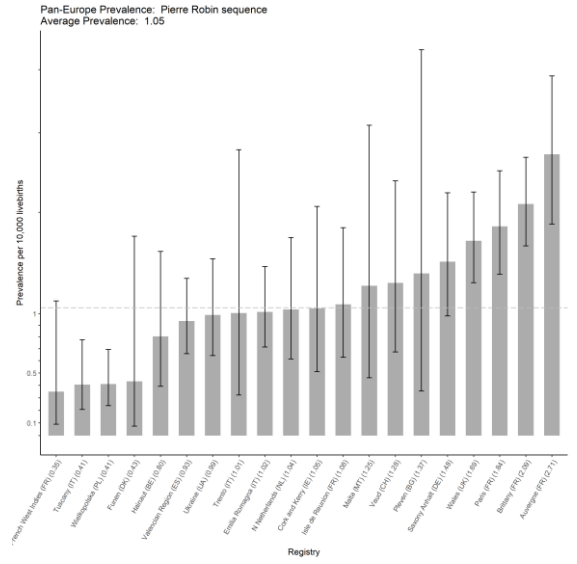
Source: JRC-EUROCAT Central Registry

Figure 38. Pierre Robin sequence - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 39. Pierre Robin sequence – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

2.5.2.11 Skeletal dysplasias

Skeletal dysplasias are a group of genetic diseases with developmental disorders of chondro-osseous tissue. Some of these anomalies are lethal while others may be diagnosed after infancy.

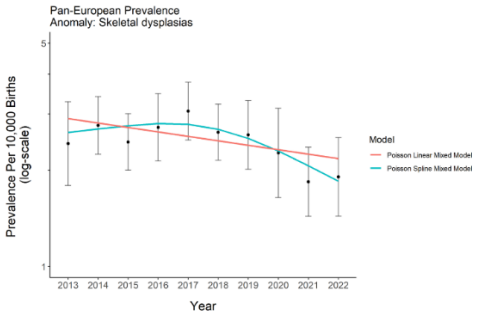
The prevalence of skeletal dysplasias between 2013 and 2022 is estimated to have decreased by -3.1% (95% CI: -5.9%; -0.3%) each year on the pan-European level (fig. 40).

The prevalence decreased significantly in two individual registries (Paris, Vaud, fig. 41).

The prevalence differs across registries ranging from 1.42 per 10,000 births (Tuscany) to 4.30 per 10.000 births (Cork and Kerry) with no clear North-South or East-West gradients (fig. 42).

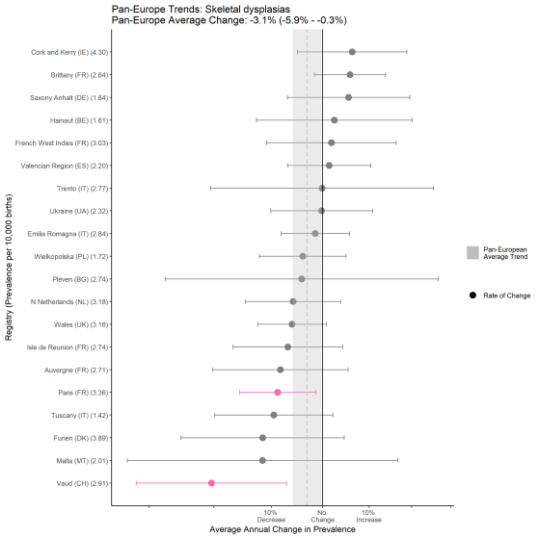
Conclusion: We have no explanation for the decreasing trend or European differences in the prevalence of skeletal dysplasias. As these anomalies are genetic, the occurrence is not related to fetal exposures.

Figure 40. Skeletal dysplasias - Prevalence and 95% CIs for the birth years 2013-2022



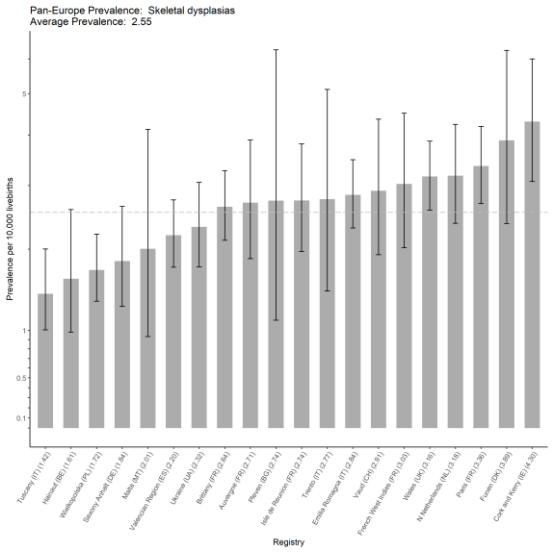
Source: JRC-EUROCAT Central Registry

Figure 41. Skeletal dysplasias - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis



Source: JRC-EUROCAT Central Registry

Figure 42. Skeletal dysplasias – Annual average prevalence for the registries included in the pan-European trend analysis (2013-2022)



Source: JRC-EUROCAT Central Registry

3 Clusters

3.1 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 [8].

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 occurring during the last two years, and which lasted for less than 18 months, the EUROCAT Data Management Software (DMS) [14] 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. 2022 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 local 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.

The clusters methodology, the use of the EUROCAT Data Management Software and the template for the local investigation report are detailed in the EUROCAT Statistical monitoring protocol [8].

3.2 Registries included in the cluster analysis

The registries that met the EUROCAT data transmission deadline of the 15th February were considered for the monitoring of clusters and scrutinised according to the following inclusion criteria:

- 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 2018-2022;

- the number of cases submitted by the registry for 2022 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 April 2024, there were 37 full member registries in EUROCAT (see Annex B). Fifteen registries were included in the cluster analysis: Hainaut (Belgium), Pleven (Bulgaria), Funen (Denmark), Brittany (France), French West Indies (France), Paris (France), Réunion (France), Cork & Kerry (Ireland), Emilia Romagna (Italy), Trento (Italy), Tuscany (Italy), Wielkopolska (Poland), Northern Netherlands, Vaud (Switzerland) and Wales (UK).

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;
- Zagreb (Croatia), Malta, South Portugal, Antwerp (Belgium), Basque country (Spain), Styria (Austria), Auvergne (France), OMNI-net (Ukraine), South-East Ireland, Valencian Region (Spain), Navarra (Spain), ATS Valpadana (Italy) and Milan Metropolitain area (Italy) were excluded from the cluster analyses because they had less than five years of data in the Central Database for the period 2018-2022.

3.3 Cluster analysis 2018-2022: overview

The analysis of clusters was conducted by the Central Registry in April 2024. The results were discussed by the JRC-EUROCAT Management Committee in May and October 2024.

No clusters were identified in Paris, Pleven and Trento. 32 potential clusters were detected in 12 registries: 29 by date of conception (DoC) and 3 by date of birth (DoB). The clusters are presented in Table 2. 23 clusters were sent to the registries with a request for a local investigation. The others did not lead to local investigation as, e.g., they occurred on less than 5 days[1] or they were already investigated the previous years.

[1] The methodology used to estimate the date of conception cannot guarantee that level of precision.

Table 2. Clusters detected in 12 EUROCAT registries over the birth years 2018-2022

Anomaly subgroup	**Brittany**	**Cork & Kerry**	**Emilia Romagna**	**Funen**	**French West Indies**	**Hainaut**	**Northern Netherlands**	**Réunion**	**Tuscany**	**Vaud**	**Wales**	**Wielkopolska**
Neural Tube Defects	C											B
Agenesis of corpus callosum												C
Double outlet right ventricle									C			
Ventricular septal defect			C									
Atrial septal defect					C							
Atrioventricular septal defect											C	
Tetralogy and pentalogy of Fallot			B*									
Hypoplastic left heart (HLH/HLHS)		C										
Hypoplastic right heart (HRH/HRHS)			C*									
Choanal stenosis or atresia											C	
Cleft palate			C									
Oesophageal atresia with or without trachea-oesophageal fistula		C										
Ano-rectal atresia or stenosis			C									C
Omphalocele								C				
Unilateral renal agenesis			C*									

Anomaly subgroup	Brittany	Cork & Kerry	Emilia Romagna	Funen	French West Indies	Hainaut	Northern Netherlands	Réunion	Tuscany	Vaud	Wales	Wielkopolska
Multicystic renal dysplasia										C		
Congenital hydronephrosis including ureter obstruction									C*			B
Hypospadias			C*									
Limb Reduction Defects (LRD)			C	C		C						
Club foot – talipes equinovarus							C*					
Hip dislocation		C										
Polydactyly			C	C								
Syndactyly											C*	
Maternal infections resulting in major malformations	C*											
Down syndrome / trisomy 21									C			
Edwards syndrome / trisomy 18								C				

Source: JRC-EUROCAT Central Registry

C: Cluster by date of conception; B: Cluster by date of birth; : Not sent for investigation

*Cluster detected in last year's analysis [13].

3.4 Methodology for cluster investigations

Investigation templates are provided to make the reporting process consistent between registries [8]. 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 less than 5 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 changes in clinical and reporting practices (e.g. increasing use of invasive prenatal diagnostic procedures, improvements in prenatal ultrasound detection rates, change in reporting practices).
- Data quality issues found to explain cluster.
- No report of preliminary investigations sent to Central Registry. Clusters to be investigated at local level only.

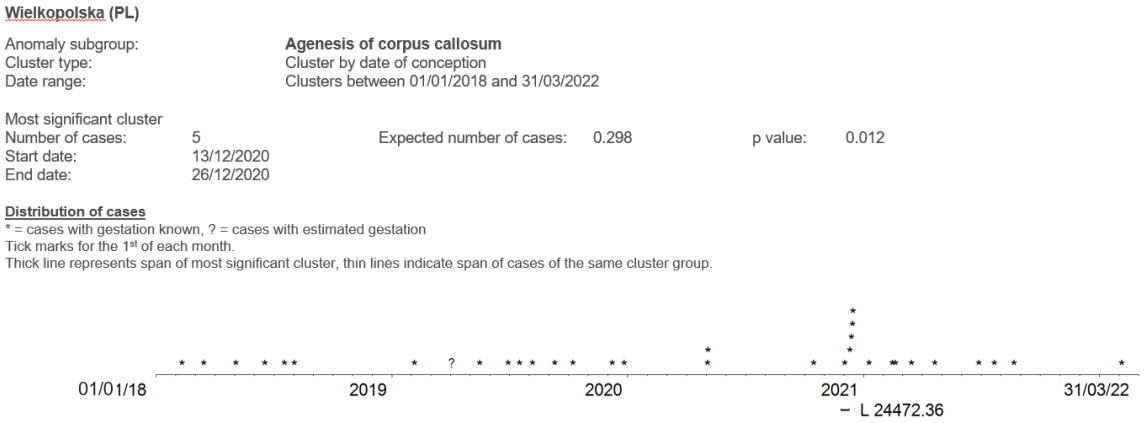
The cluster investigations are presented below and summarised in Table 3. Clusters for which no investigation report was received from the local registries are not presented.

3.5 Details on the cluster investigations

3.5.1 Agenesis of corpus callosum

The cluster was detected in Wielkopolska. There were 5 cases over 13 days (expected number of cases = 0.298). The registry confirmed the excess of cases. One case had dysmorphic features, but genetic tests were not available. If this case is excluded there is no cluster. Two of the five mothers had covid late in the first trimester which is within the critical period for this anomaly. This signal for covid exposure will be analysed in more detail in the central EUROCAT database before the next statistical monitoring report is written.

Figure 43. Cluster of agenesis of corpus callosum detected in Wielkopolska

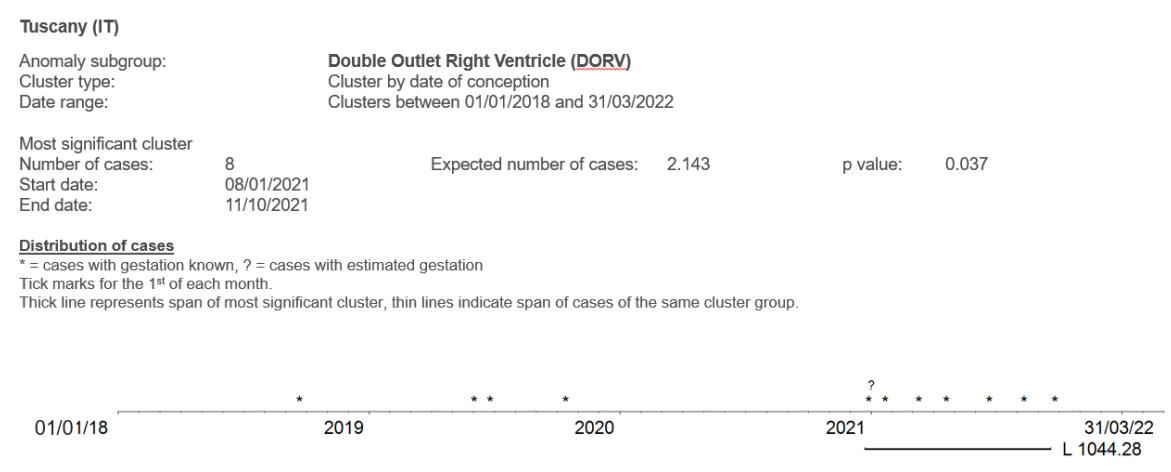


Source: JRC-EUROCAT Central Registry

3.5.2 Double Outlet Right Ventricle (DORV)

The cluster was detected in Tuscany. There were 8 cases over a long period of 276 days (expected number of cases = 2.143). The registry confirmed the excess of cases, but the cluster could not be explained by the local investigation. A significant increasing trend was also detected over 2013-2022 in the registry. There was no ICD9 code – still in use in the Italian national coding system – for this anomaly. The cluster and increasing trend of this severe cardiac anomaly may be explained by a change of coding habits by the paediatric cardiologists in the region. The anomaly will require a further period of surveillance to be sure that the cluster and the trend can be explained by changes in the coding of complex CHD cases.

Figure 44. Cluster of double outlet right ventricle detected in Tuscany

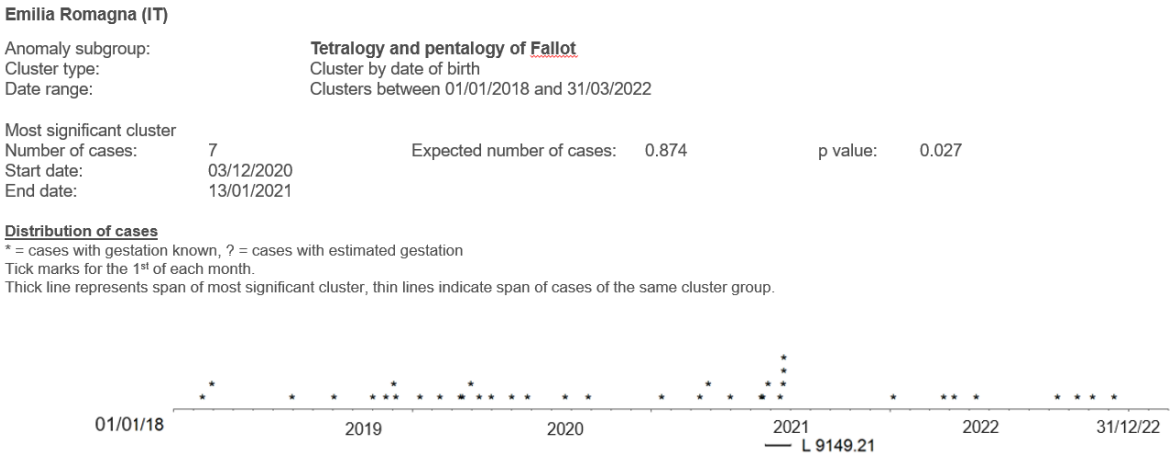


Source: JRC-EUROCAT Central Registry

3.5.3 **Tetralogy and pentalogy of Fallot**

The cluster was detected in Emilia Romagna. There were 7 cases over 41 days (expected number of cases = 0.874). One TOPFA case was excluded because the analysis was run by date of birth and one duplicate case was removed. After removing those cases, the cluster disappeared.

Figure 45. Cluster of tetralogy and pentalogy of Fallot detected in Emilia Romagna

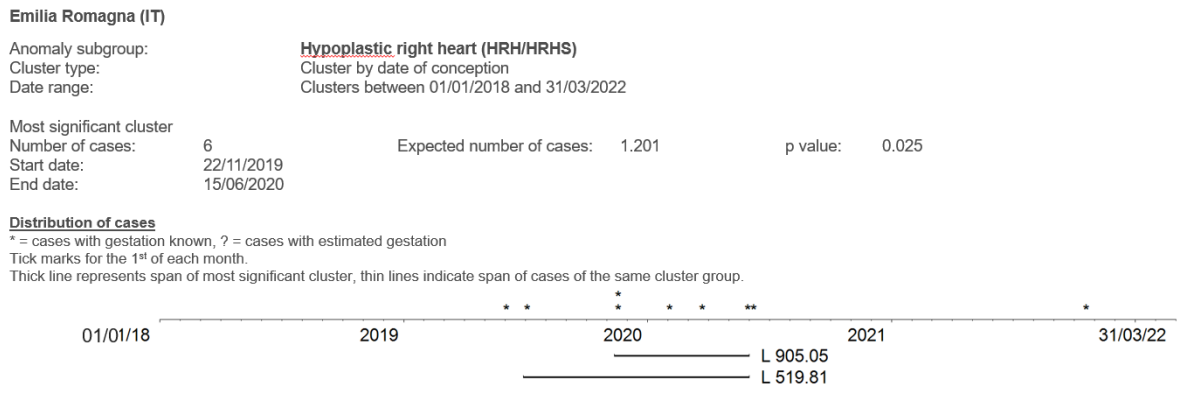


Source: JRC-EUROCAT Central Registry

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

The cluster was detected in Emilia Romagna. There were 6 cases over 206 days (expected number of cases = 1.201). The investigation found one duplicate case. After removing this case, the cluster disappeared.

Figure 46. Cluster of hypoplastic right heart detected in Emilia Romagna



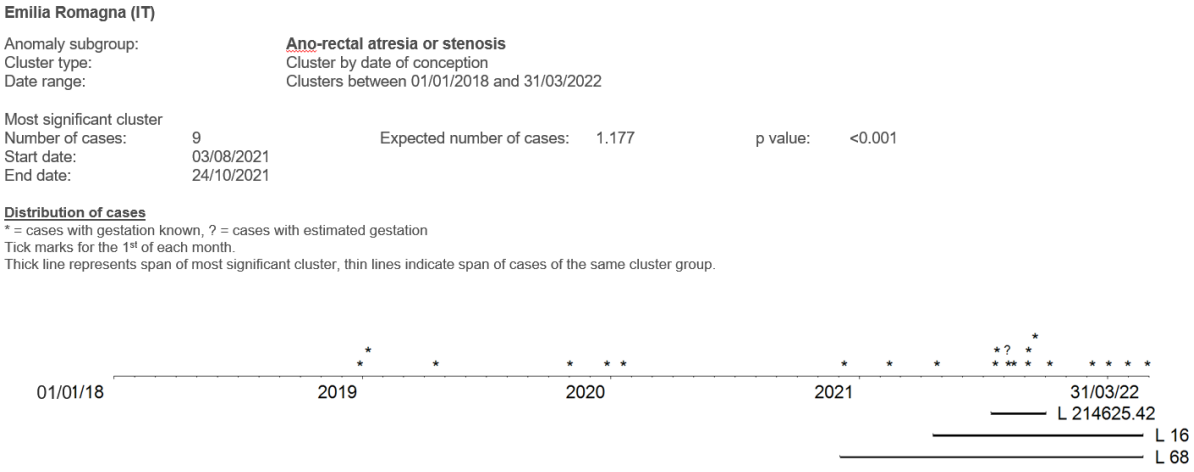
Source: JRC-EUROCAT Central Registry

3.5.5 **Anorectal atresia or stenosis**

The clusters were detected in Emilia Romagna and Wielkopolska.

In Emilia Romagna, there were 9 cases over 82 days (expected number of cases = 1.177), with one duplicate case and apparent data quality issues with 5 other cases.

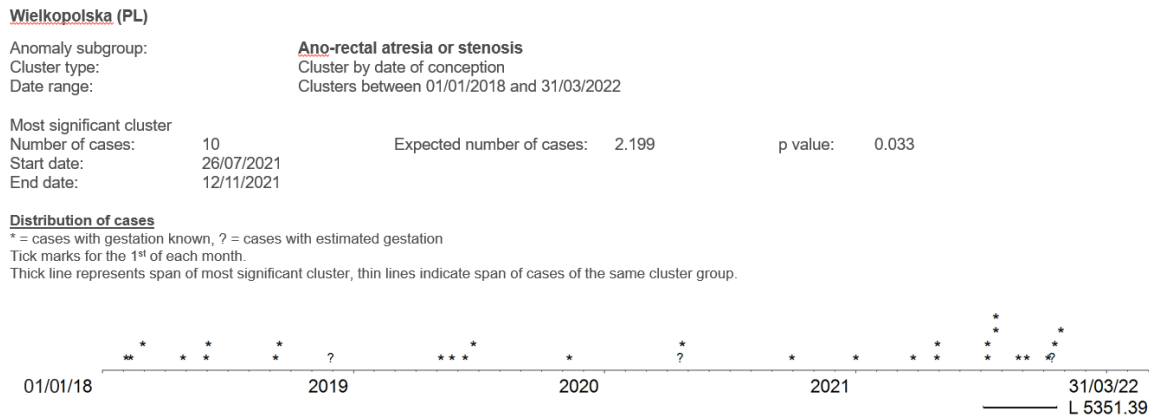
Figure 47. Cluster of anorectal atresia or stenosis detected in Emilia Romagna



Source: JRC-EUROCAT Central Registry

In Wielkopolska, there were 10 cases over 109 days (expected number of cases = 2.199). The registry confirmed the excess of cases, but the local investigation on spatial dimension, diagnosis, mother characteristics and exposure could not explain the cluster. For one case the reported anal stenosis was secondary to Hirschsprung's anomaly. After excluding this case the cluster disappeared.

Figure 48. Cluster of anorectal atresia or stenosis detected in Wielkopolska

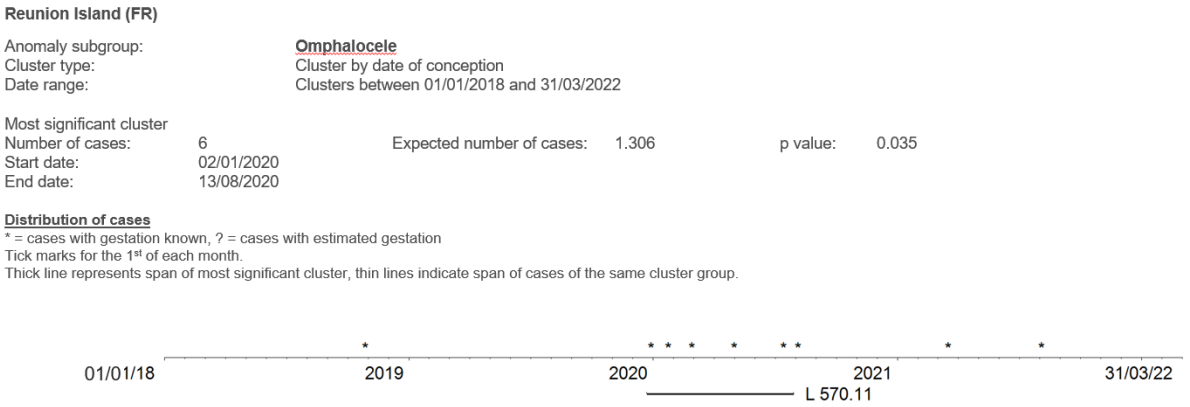


Source: JRC-EUROCAT Central Registry

3.5.6 **Omphalocele**

The cluster was detected in Réunion. There were 6 cases over 224 days (expected number of cases = 1.306). The investigation confirmed the diagnosis. Five cases were early TOPFA with associated severe anomalies. Associations observed were with spina bifida, limb anomalies, cardiac anomalies, Cantrell's pentalogy and OEIS complex and aetiology seems to be different across cases. No mother was more than 35 years old. The registry confirmed the excess of cases, but the cluster could not be explained by the local investigation. The registry concludes that there are no reasons for concern.

Figure 49. Cluster of omphalocele detected in Réunion

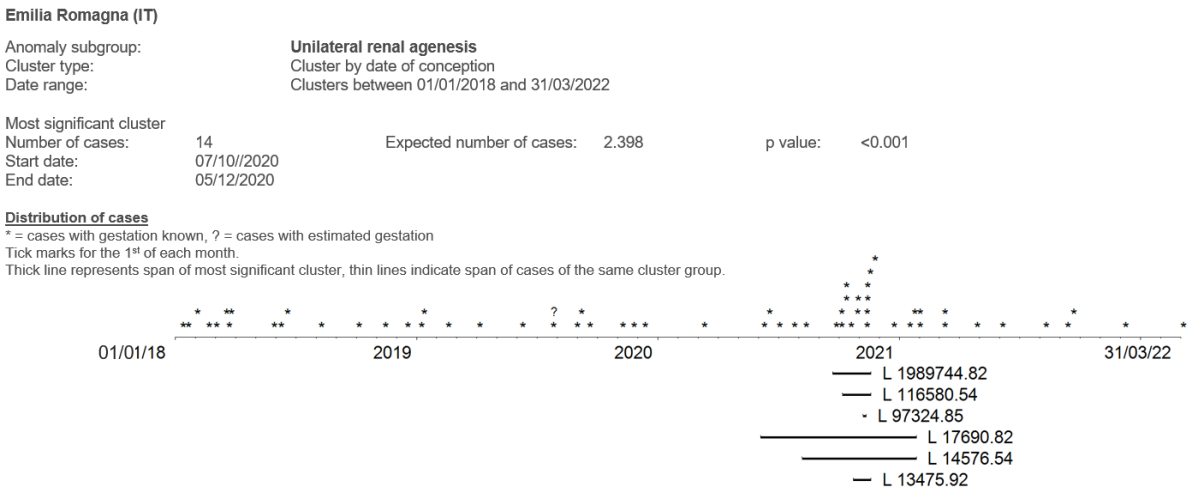


Source: JRC-EUROCAT Central Registry

3.5.7 **Unilateral renal agenesis**

The cluster was detected in Emilia Romagna. There were 14 cases over 59 days (expected number of cases = 2.398). The investigation found 2 pairs of duplicate cases: A case with caudal regression sequence was also excluded as aetiology is considered different. 11 cases remained in the cluster. The registry confirmed the excess of cases, but the cluster could not be explained by the local investigation on spatial dimension, diagnosis, mother characteristics and exposure.

Figure 50. Cluster of unilateral renal agenesis detected in Emilia Romagna

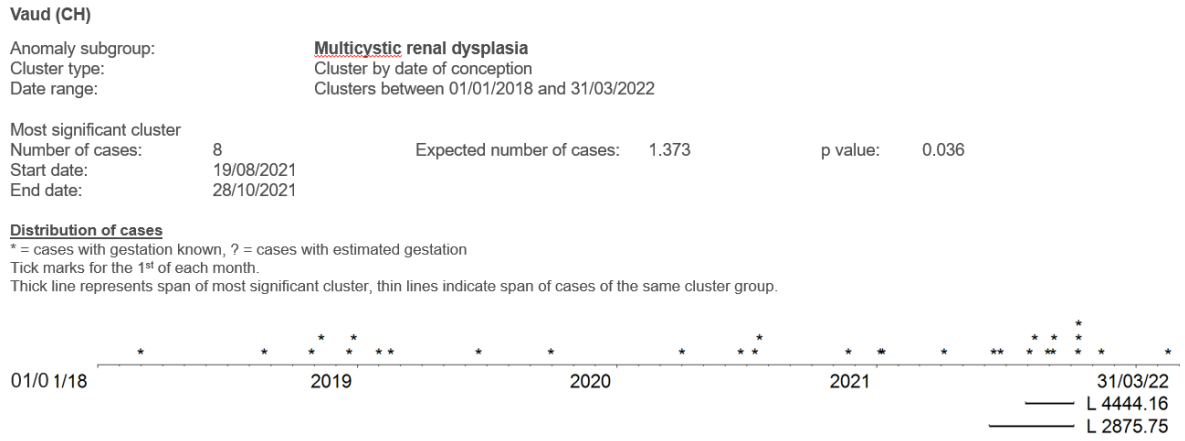


Source: JRC-EUROCAT Central Registry

3.5.8 **Multicystic renal dysplasia**

The cluster was detected in Vaud. There were 8 cases over 70 days (expected number of cases = 1.373). One case was diagnosed with posterior urethral valves and had secondary renal dysplasia. After exclusion of this case the cluster disappeared.

Figure 51. Cluster of multicystic renal dysplasia detected in Vaud



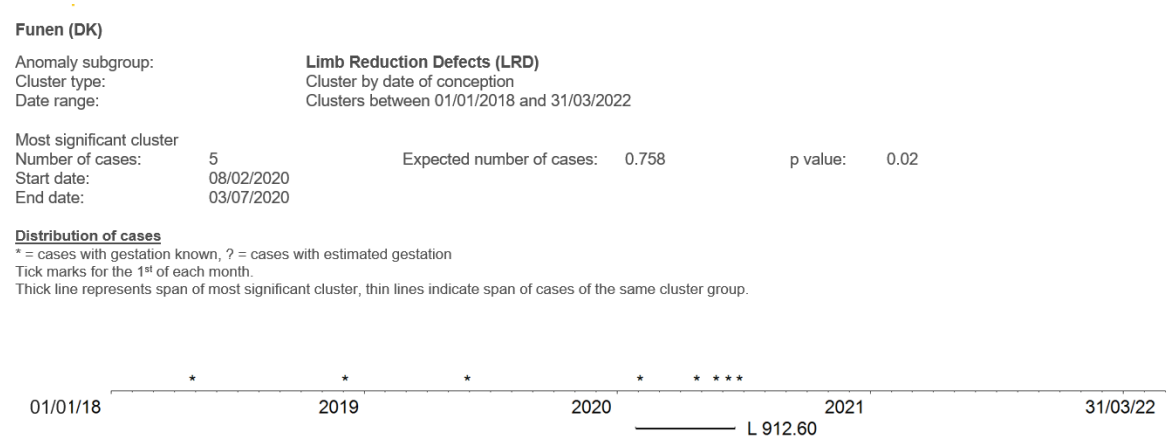
Source: JRC-EUROCAT Central Registry

3.5.9 **Limb Reduction defects (LRD)**

The clusters were detected in Funen, Emilia Romagna and Hainaut.

In Funen, there were 5 cases over 146 days (expected number of cases = 0.758). The local investigation confirmed the excess of cases, but could not explain the cluster. The cases presented diverse LRDs (missing hand, missing toe, split hand); there were no evident spatial correlations and no common exposure.

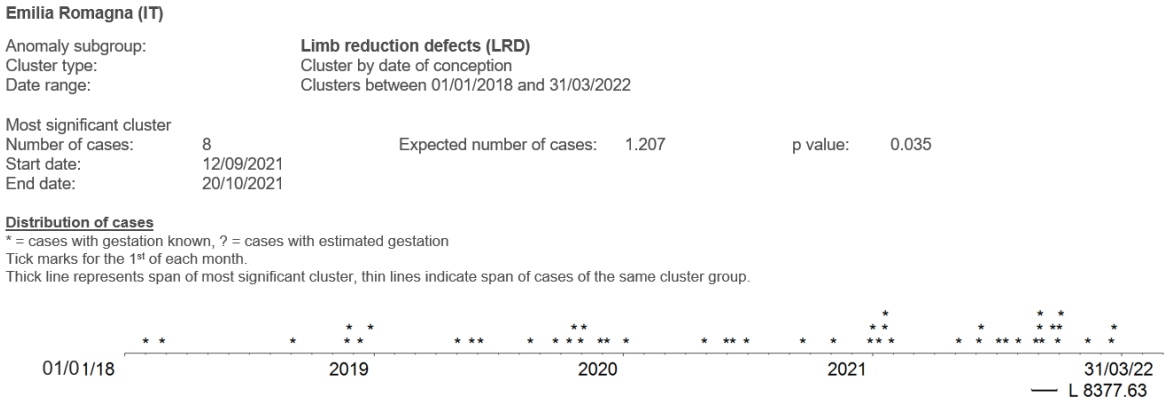
Figure 52. Cluster of limb reduction defect detected in Funen



Source: JRC-EUROCAT Central Registry

In Emilia Romagna, there were 8 cases over 38 days (expected number of cases = 1.207). The local investigation found one case with Moebius syndrome. The cluster disappeared when the case was removed.

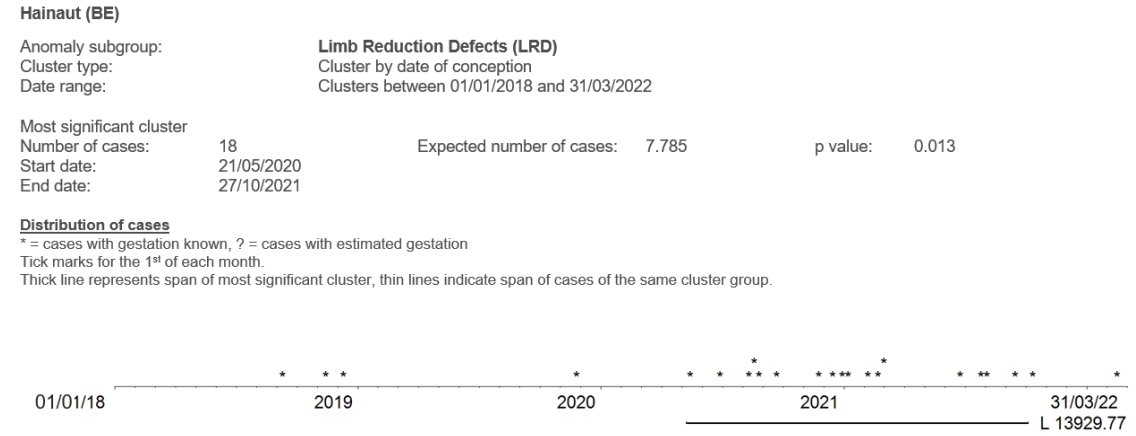
Figure 53. Cluster of limb reduction defect detected in Emilia Romagna



Source: JRC-EUROCAT Central Registry

In Hainaut, there were 18 cases over 524 days (expected number of cases = 7.785). The local investigation did not confirm the diagnosis for 2 cases and found 4 cases with a genetic cause or family history and 4 cases with another major anomaly as underlying cause (amniotic bands syndrome or vascular disruption). The cluster remains after these cases were removed. However, the reduction defects of the remaining cases are still anatomically heterogeneous.

Figure 54. Cluster of limb reduction defect detected in Hainaut



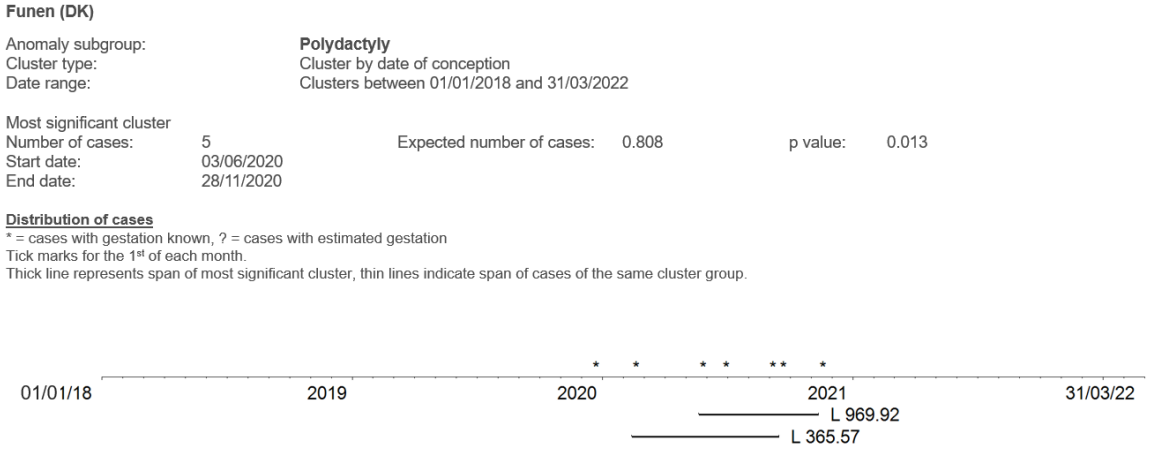
Source: JRC-EUROCAT Central Registry

3.5.10 **Polydactyly**

The clusters were detected in Funen and Emilia Romagna.

In Funen, there were 5 cases over 178 days (expected number of cases = 0.808). The local investigation confirmed the excess of cases, and explained the cluster by a change in methodology with a new data source and a change in indication for surgery.

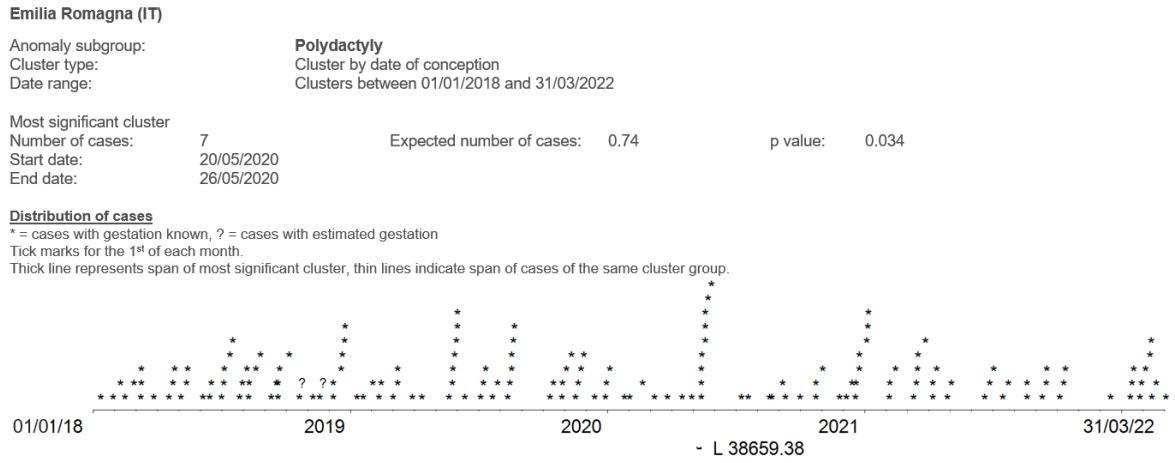
Figure 55. Cluster of polydactyly detected in Funen



Source: JRC-EUROCAT Central Registry

In Emilia Romagna, there were 7 cases over 6 days (expected number of cases = 0.74). The local investigation confirmed the excess of cases, but could not explain the cluster. The registry has previously explained cluster and trends of polydactyly in the region by a change in the distribution of ethnic groups. This cannot explain the current cluster because none of these mothers were from Africa. The registry considers there are no reasons for concern as the reductions affecting the cases are heterogeneous.

Figure 56. Cluster of polydactyly detected in Emilia Romagna



Source: JRC-EUROCAT Central Registry

3.5.11 **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
Hainaut	Limb Reduction Defects (LRD)	18	7.785	0.013	23	524	Excess of cases confirmed
Funen	Limb Reduction Defects (LRD)	5	0.758	0.02	8	146	Etiologic heterogeneity
	Polydactyly	5	0.808	0.013	7	178	Change in reporting and clinical practices
Tuscany	Double Outlet Right Ventricule (DORV)	8	2.143	0.037	12	276	Changes in clinical and reporting practices
	Congenital hydronephrosis including ureter obstruction	9	1.362	0.04	132	15	Investigated last year
	Down syndrome / trisomy 21	5	0.33	0.015	256	1	Cluster on less than 5 days
Northern Netherlands	Club foot – talipes equinovarus	10	1.787	0.033	77	35	Investigated last year
Emilia Romagna	Ventricular septal defect (VSD)	8	1.8	<0.001	698	3	Cluster on less than 5 days
	Tetralogy and pentalogy of Fallot	7	0.874	0.027	38	41	Data quality
	Hypoplastic right heart (HRH/HRHS)	6	1.201	0.025	9	206	Data quality
	Cleft palate	5	0.348	0.03	54	9	Data quality

Registry	Anomaly	No of cases in cluster	Expected cases	p-value	Valid cases	Length of cluster (days)	Classification of explanation
	Ano-rectal atresia or stenosis	9	1.177	<0.001	22	82	Data quality
	Unilateral renal agenesis	14	2.398	<0.001	62	59	Excess of cases confirmed
	Hypospadias	5	0.355	0.02	275	1	Cluster on less than 5 days
	Limb Reduction Defects (LRD)	8	1.207	0.035	48	38	Data quality
	Polydactyly	7	0.74	0.034	164	6	Excess of cases confirmed
Vaud	Multicystic renal dysplasia	8	1.373	0.036	30	70	Data quality
Cork & Kerry	Hypoplastic left heart (HLH/HLHS)	7	1.546	0.028	11	217	No report received
	Oesophageal atresia with or without trachea-oesophageal fistula	5	0.535	0.013	10	82	No report received
	Hip dislocation	35	17.306	0.017	69	388	No report received
Wales	Atrioventricular septal defect	5	0.383	0.029	33	17	No report received
	Choanal stenosis or atresia	11	4.61	0.049	13	549	No report received
	Syndactyly	10	1.679	0.01	42	61	No report received
Réunion	Omphalocele	6	1.306	0.035	9	224	Etiologic heterogeneity
	Edward's syndrome / Trisomy 18	8	1.193	0.024	37	49	No report required

Registry	Anomaly	No of cases in cluster	Expected cases	p-value	Valid cases	Length of cluster (days)	Classification of explanation
Wielkopolska	Neural Tube Defects	8	1.002	0.017	59	30	No report required
	Agenesis of corpus callosum	5	0.298	0.012	33	13	Etiologic heterogeneity
	Ano-rectal atresia or stenosis	10	2.199	0.033	31	109	Data quality
	Congenital hydronephrosis including ureter obstruction	97	61.241	0.021	286	390	No report required
French West Indies	Atrial septal defect	20	6.99	0.006	39	277	No report received
Brittany	Neural Tube Defects	5	0.36	0.041	186	2	Cluster on less than 5 days
	Maternal infections resulting in major malformations	7	1.683	0.028	10	260	Investigated last year

Source: JRC-EUROCAT Central Registry

3.6 Retrospective analysis of clusters

For many years, EUROCAT has conducted annual analyses to detect unusual aggregation of cases in time. However, comparing clusters over time and across geographical areas has not been done. Therefore, it was decided to analyse clusters detected over the last 10 years to see which anomalies most frequently occurred in clusters, to see how many clusters disappeared after cleaning and updating the data and to summarize the conclusions of the clusters over this 10-year period.

There was a gap in the annual statistical monitoring for 2 years when the EUROCAT central registry moved from University of Ulster in Northern Ireland to Joint Research Centre in Italy and during the COVID pandemic. These years will be analysed for the first time.

Originally, we detected 114 clusters. Using data from November 2023 (which will include the years that have missing reports), 166 clusters are detected.

A more detailed investigation of these clusters is being undertaken, in collaboration with the local registries. Some registries have been contacted in October 2024 with questions on their cluster cases for the anomalies most frequently occurring in clusters.

4 Conclusions

The present report describes the results of the statistical analysis performed centrally on data for the birth years 2013-2022. Where available, the outcome of the preliminary investigations conducted by registries are also presented.

The pan-European trend analysis detected increasing trends for 4 congenital anomaly subgroups and decreasing trends for 14 subgroups. Several studies are on-going to further investigate some of our findings.

The cluster analysis detected 32 clusters in 15 registries. Following the registry investigations, most clusters were considered of no concern. Some registries will report (or have reported) the findings to their local public health authorities. Five 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 being prepared at the central level.

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List of abbreviations and definitions

ASD	Atrial Septal Defect
CHD	Congenital Heart Defects
CI	Confidence Interval
DNA	Desoxyribose Nucleic Acid
DORV	Double Outlet Right Ventricle
GA	Gestational Age
HRH	Hypoplastic Right Heart
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

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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[2], 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 2018-2022. 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	✓	✓	✓

[2] 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 ureter 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	No, data incomplete for 2021 and no data for 2022		
Belgium, Antwerp	No, data incomplete for 2021 and no data for 2022		
Belgium, Hainaut	✓	✓	✓
Bulgaria, Pleven	✓	✓	no cluster
Croatia, Zagreb	No, data transmission late > 1 year		
Denmark, Funen	✓	✓	✓
France, Auvergne	✓	No, less than 5 years of complete data	
France, Brittany	✓	✓	not requested
France, French West Indies	✓	✓	**X**
France, Paris	✓	✓	no cluster
France, Réunion	✓	✓	✓
Germany, Saxony Anhalt	✓	Analysis not done (see chapter 2.2)	
Ireland, Cork & Kerry	✓	✓	**X**
Ireland, South East	No, data transmission late > 1 year		
Italy, Emilia Romagna	✓	✓	✓
Italy, Milan Metropolitan Area	No, data transmission late > 1 year		
Italy, Trento	✓	✓	no cluster
Italy, Tuscany	✓	✓	✓
Italy, Valpadana	No, data transmission late > 1 year		
Malta	✓	No, less than 5 years of complete data	
Netherlands, Northern	✓	✓	not requested
Norway	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	
Poland, Wielkopolska	✓	✓	✓
Portugal, South	No, data incomplete for 2020 and 2021, no data for 2022		
Spain, Basque Country	No, data transmission late > 1 year		
Spain, Valencian Region	✓	No, less than 5 years of complete data	

Spain, Navarra	No, data transmission late > 1 year		
Switzerland, Vaud	✓	✓	✓
Ukraine	✓	No, less than 5 years of complete data	
UK, E Midlands & S Yorkshire	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	
UK, Northern England	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	
UK, South West England	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	
UK, Thames Valley	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	
UK, Wales	✓	✓	**X**
UK, Wessex	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	
UK, West Midlands	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	
UK, Yorkshire and Humber	No, data transmission late > 1 year	Analysis not done (see chapter 2.2)	

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

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