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European Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2008 - 2017)

Agnieszka Kinsner-Ovaskainen, Joan Morris, Ester Garne, Maria Loane, Monica Lanzoni

2020

Joint Research Centre

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The report was reviewed and approved by the JRC-EUROCAT Management Committee (Ester Garne, Maria Loane, Simona Martin, Joan Morris, Amanda Neville, Ciarán Nicholl, Judith Rankin, Anke Rissmann, Florence Rouget and David Tucker) and by the 26 registry leaders.

Background

Worldwide, congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood. According to the EUROCAT estimates, of the 5.1 million births in the European Union (EU) each year [1] approximately 127,000 (2.5%) have a congenital anomaly.

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.

Each year, EUROCAT performs statistical monitoring for both trends and clusters in time on 84 anomaly subgroups. The results of the statistical monitoring are the basis for instigating possible further investigations at the local registry level.

The present report shows the results of the monitoring performed on data for the birth years 2008-2017 by the JRC-EUROCAT Central Registry. Cases of congenital anomaly among livebirths, 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 and, where available, the outcome of the preliminary investigations conducted by registries.

1 Key findings

Pan-European Trends in Congenital Anomalies (excluding genetic conditions)

- **Hypoplastic right heart**: Hypoplastic right heart is one of the univentricular cardiac anomalies with underdevelopment of the right ventricle. Its prevalence increased each year by 8.1% over the 10-years period (2008-2017). Most cases also have tricuspid atresia or pulmonary atresia with intact ventricular septum. Cases of hypoplastic right heart are so rare that only the pan-European trend is informative. It is important to monitor this trend in the coming years and to follow-up on correct coding of cases.
- **Laterality anomalies and situs inversus**: The subgroup of laterality anomalies includes atrial isomerisms, dextrocardia, bronchopulmonary isomerism, situs inversus and anomalies of spleen. Another name for these anomalies is heterotaxy anomalies. Between 2007 and 2016, the prevalence of laterality anomalies is estimated to have increased by 3.1% each year on the pan-European level, confirming the results found for the first time in the previous report. In the same period, also the prevalence of situs inversus is estimated to have increased by 3.8% each year. These increasing trends will be monitored closely by EUROCAT and a study to investigate in detail the anomalies included in this subgroup is ongoing.
- **Clubfoot**: the pan-European trend remains significantly increasing with an annual increase of 1.7%. This trend excludes Northern England, as the registry did not collect this condition at the start of the monitoring period.
- The increasing pan-European trends that were detected in last year's report (2007-2016) [2] and are **no longer present** in the current analysis of data from 2008-2017 are: Double outlet right ventricle, Bilateral renal agenesis (including Potter syndrome), Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD) and Tricuspid atresia and stenosis and Polydactyly.
- The decreasing pan-European trends that were detected in last year's report (2007-2016) [2] and are **no longer present** in the current analysis of data from 2008-2017 are: Anophtalmos/microphtalmos, Cleft lip, Cleft palate, Klinefelter syndrome.

Analysing 10-year trends every year results in very little change each year for many anomalies as only 10% of new data is added. Therefore, in 2020 EUROCAT decided to perform the 10-years pan-European trends analysis every year but to only report all trends every two years. Annual reporting will be restricted to only those trends that are of specific interest. Therefore, the next report will investigate the clusters and will report any new trends of importance. Trends in clubfoot, laterality anomalies and hypoplastic right heart will continue to be monitored.

Clusters

Sixteen clusters were identified in 11 out of 14 registries included in the analysis. Registries informed that two clusters will be followed (Ano-rectal atresia in Brittany and Turner syndrome in Emilia Romagna).

A cluster of microcephaly was detected in French West Indies. The excess of cases in this area was noted already by the clinicians and presented at the EUROCAT Registry Leader's Meeting in Baveno in June 2017. The present analysis of registry's data confirmed the occurrence of a statistically significant cluster. The cluster may be associated with the Zika virus infection in the French West Indies.

Six clusters were not of concern and/or could be explained by data quality issues (changes in diagnostics, case ascertainment) or methodological issues. For the remaining clusters the registry investigations were not available at the time of preparation of this report.

Surveillance of multiple anomalies

Surveillance of multiple congenital anomaly cases is considered to be more sensitive for detecting new teratogens than surveillance of all or isolated congenital anomaly cases. As multiple congenital anomalies are rare and specific combinations of anomalies are very rare, the surveillance needs to be done using the pan-European data and not individual EUROCAT registry data.

The first step in the surveillance is correct case classification. EUROCAT developed a multiple congenital anomaly computer algorithm to classify congenital anomaly cases into defined aetiological groups: approximately 90% of all EUROCAT cases are assigned into one classification group. The remaining 10% of cases are potential multiple cases and were reviewed by three EUROCAT geneticists to reach agreement for classification as true multiple congenital anomaly cases. The multiple congenital anomaly cases are then subject to statistical analysis to identify potential associations.

The analysis presented in Chapter 6 of the present report includes data from 32 full member registries for the years from 2008-2016. Most associations found by the statistical analysis were known associations described in the literature. There were six potential new associations. The individual cases in these associations will be reviewed in detail together with the local registries and these associations will be followed in the coming years.

2 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 1.2 million of births per year, which is about one quarter of the European birth population. Registries from 20 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. Total prevalence rates of 84 subgroups of congenital anomalies, including all cases of livebirths, stillbirths/late fetal deaths from 20 weeks gestational age, and terminations of pregnancy for fetal anomaly (TOPFA) at any gestational age are monitored and reported. A full protocol is published online, providing details of the rationale and the methodology of the statistical monitoring, including changes to methodology and software [5, 6].

The EUROCAT annual statistical monitoring report includes the analysis of trends and clusters in time performed in order to detect signals of new or increasing teratogenic exposures and to monitor progress in the prevention of congenital anomalies. The analysis is done by the JRC-EUROCAT Central Registry on the data collected from EUROCAT registries, updated and validated annually [5]. The number of variables collected and the way these variables are coded are in continuous development in order to adapt to and represent correctly the evolving knowledge on the topic. The last statistical monitoring reports were published on the data from birth years 2006-2015 [7] and 2007-2016 [2].

A pan-European trend analysis enables the monitoring of rare 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. The statistical monitoring contributes to the harmonisation of data collected by the EUROCAT registries. Identified trends and clusters are most likely to be 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 pathology. Preliminary investigations of trends and clusters are performed at local and central registry level, and summaries of these investigations are reported. The involvement of all the registries in these investigations by the Central Registry facilitates data harmonisation and interpretation.

We report here the results of the statistical monitoring performed on births over the ten-year period (2008-2017) using data from 25 EUROCAT registries to describe trends and from 14 EUROCAT registries to detect recent clusters in time.

3 Population and Monitoring Process

3.1 Registries included in the 2008-2017 trend analysis

At the time of statistical monitoring in spring 2019, there were 34 full member registries in EUROCAT (see Appendix A). Twenty five full member registries met the inclusion criteria for the individual 10-year trend analysis (see Box 1).

The following registries were included also in last year's report: Antwerp (Belgium), Hainaut (Belgium), Zagreb (Croatia), Ile de la Reunion (France), Paris (France), Saxony-Anhalt (Germany), Cork & Kerry (Ireland), Emilia Romagna (Italy), Tuscany (Italy), Malta, Northern Netherlands, South Portugal, Valencian Region (Spain), Vaud (Switzerland), Ukraine, Northern England (UK), South West England (UK), Thames Valley (UK), Wales (UK), Wessex (UK).

In addition, five registries were included in this year's analysis: French West Indies (France), South East Ireland (Ireland), Norway, Wielkopolska (Poland) and Basque Country (Spain).

The inclusion/exclusion particularly of large registries may affect the detection of certain trends and explain differences between results from previous years.

Box 1. Registry inclusion criteria for trend analysis

— *Pan-European and Individual Registry trends*: Registries that signed the JRC-EUROCAT collaboration agreement

— *Pan-European trends*: Registries no more than one year late with data transmission

— *Pan-European trends*: Registries that submitted data continuously for at least nine calendar years starting from 2008, i.e. for 2008-2016 or 2008-2017

— *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

— *Individual registry trends*: registries no more than one year late with data transmission that submitted data continuously for at least eight calendar years counting back from 2016 i.e. for 2008-2017, 2009-2016 or 2010-2017.

The registries excluded from the analysis were:

- Hungary was not in a position to sign the JRC-EUROCAT collaboration agreement and therefore the registry did not send data to the Central Registry;
- Navarra is a new full member registry and was still in the process of finalising the collaboration agreement;
- Auvergne (France), Basque Country (Spain), Dublin (Ireland), Mainz (Germany), Odense (Denmark), Styria (Austria) were more than one year behind in data transmission;
- East Midlands & South Yorkshire (UK) - cases were submitted for 2016 but not for the years 2013-2015;
- Brittany (France) was not included in the trend analyses because it started collecting data in 2011 and hence has less than eight years of data in the Central Database.

3.2 Registries included in the 2013-2017 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. 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 (2013-2017) were 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 [8].

Box 2. Registry inclusion criteria for cluster analysis in individual registries

— Registries that signed the collaboration agreement

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

— Registries that transmitted data for all five years, i.e. for 2013-2017

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

— Registries that transmitted information on the date of birth for all cases

— Registries with 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 19 full member registries transmitted information for birth year 2017 to the EUROCAT Central Registry in February 2019 (see Appendix A). Fourteen registries were included in the cluster analysis. Four registries from England were excluded because the date of birth transmitted by Public Health England to the Central Registry is not the exact date (for privacy reasons). Zagreb was excluded due to significant changes in the annual birth population.

The analysis done by the Central Registry cannot detect clusters unless an accurate date of birth is provided. In this situation the cluster analysis can only be performed by the local registry. Registries are encouraged to use the statistical monitoring function in the EUROCAT Data Management Programme (EDMP) to check for clusters or trends for their registry for time periods not covered by the annual statistical monitoring.

3.3 What was monitored?

For the purpose of monitoring, cases cover livebirths, stillbirths or late fetal deaths from 20 weeks of gestational age onwards, as well as TOPFA at any gestational age.

As the aim is to detect changes over time within individual registries, as well as across all registries (pan-European trends), 81 congenital anomaly subgroups, i.e. non-genetic ones defined by EUROCAT, plus three trisomy subgroups adjusted for maternal age and fetal survival to 20 weeks were included in both, the pan-European 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, for every individual registry (see Box 1), and for 10 calendar years to establish the pan-European trends.

In order to detect clusters occurring during the last two years (2016-2017), and which lasted for less than 18 months, the ECD/EDMP software was used (see Appendix C) and run on 75 EUROCAT subgroups of congenital anomalies (see Appendix B).

In summary, the analyses covered:

- 25 registries with 5.95 million births (2008-2017) for the pan-European trends
- 14 registries with 0.59 million births (2016-2017) for the detection of clusters

3.4 Investigation process

The results of the statistical monitoring reported by the Central Registry were reviewed by the JRC-EUROCAT Management Committee (MC) in May 2019. The MC selected congenital anomalies with increasing or decreasing trends for preliminary investigation using a predefined prioritisation protocol (see Fig. 1).

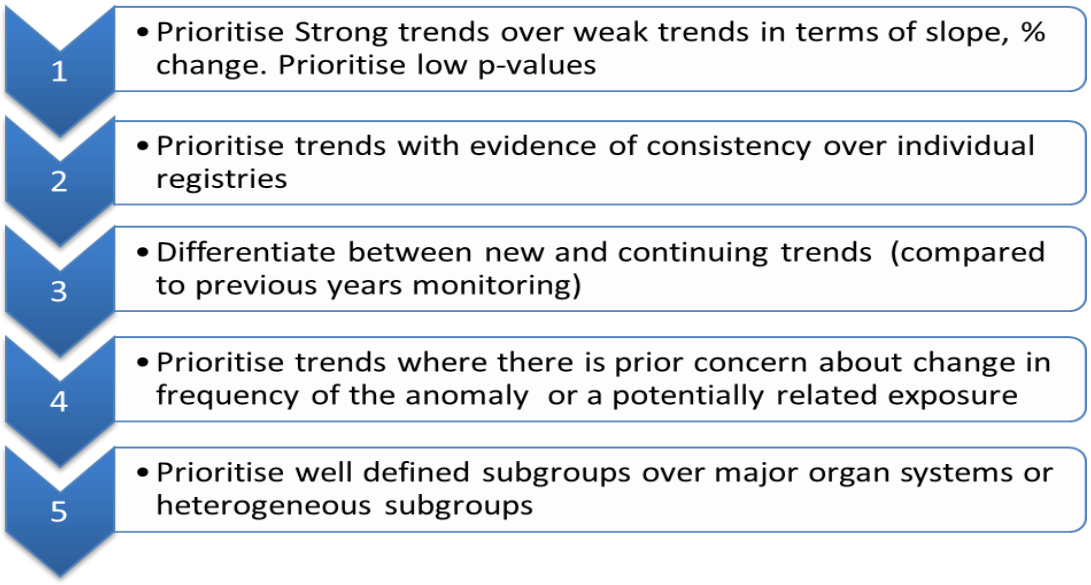

Fig. 1: Prioritisation criteria for the investigation of ten-year trends [6]

In April 2019 the Central Registry sent the results of the trends' and clusters' review to the individual registries in order to allow them to conduct preliminary investigations into the results for their registry.

These preliminary investigations were carried out according to a standardised protocol (see Appendix D). The increasing and decreasing trends selected for registry investigation are listed in Appendix E. In addition, registries were sent a list of their own increasing or decreasing trends detected in the individual trend analysis. Reporting of these trends was optional.

Once the preliminary investigations were carried out by the individual registries, they reported their findings to the JRC-EUROCAT Central Registry using standard reporting templates [8]. In these reports, they were asked to provide specific details, including the investigation methods, the results of the preliminary investigation and the public health authorities that were notified. Thereafter, the preliminary reports of the trends' and clusters' investigations were reviewed by the JRC-EUROCAT MC.

In the present annual report, trends not prioritised for investigation are not discussed but will be monitored further.

3.5 Statistical software updates from the previous report

No changes were made to the software used to identify clusters and trends within each registry for this year's statistical monitoring. Updates were made in the investigation of the pan-European trends using Poisson regression. For a full description of the methodology please refer to the EUROCAT Statistical Monitoring Protocol available on the EUROCAT website [8].

4 Pan-European Trends

4.1 Overview

The pan-European trend analysis was carried out for the time period 2008-2017. The analysis included data from 25 full member registries (Box 1 above and Appendix A).

The trend analysis included 81 subgroups, and the three trisomy subgroups adjusted for maternal age and fetal survival to 20 weeks. Figure 2 plots the estimated percentage change in yearly prevalence for each congenital anomaly subgroup. This enables congenital anomaly groups with statistically significant increasing or decreasing trends to be identified for further analysis. There were significant increasing trends for seven congenital anomaly subgroups and decreasing trends for 16 subgroups (Fig. 2 and Appendix E).

On the pan-European level, **new increasing trends**, i.e. increasing trends that were not mentioned as increasing in last year's report, were identified in two subgroups: *Coarctation of aorta and Situs inversus*.

Pan-European trends that were already seen to increase in last year's report, i.e. during the period 2007-2016, and are continuing to increase during the period covered by the present report, were: *Hypoplastic right heart; Multicystic renal dysplasia; Congenital hydronephrosis; Clubfoot – talipes equinovarus,* and *Laterality Anomalies*.

Eight **new decreasing trends** on the pan-European level were observed for *All non-chromosomal anomalies, Aortic valve atresia/stenosis, Congenital heart defects, Fetal alcohol syndrome, Hip dislocation and /or dysplasia, Hypospadias.*

Pan-European decreasing trends identified for the period covered by the present report that were also identified as decreasing in last year's report were the following: *Hydrocephaly; Severe microcephaly; Pulmonary valve stenosis; Patent ductus arteriosus (PDA) in term infants (gestational age+37 weeks); Gastroschisis; Syndactyly; Vascular disruption anomalies; Genetic syndromes + microdeletions; Teratogenic syndromes with malformations; Down syndrome (age adjusted)*.

The following subgroups were not considered further in this report. The subgroup *'Teratogenic syndromes with malformations*' and '*Hip dislocation'* are very heterogeneous and the data collected from EUROCAT registries are not consistently reported and many are underreported or overreported. Therefore, the results of the trends analysis could be misleading. The data on *'Genetic syndromes and microdeletions'* for the last birth year collected are incomplete at the time of analysis, because of late reporting from the registries. *"Fetal alcohol syndrome"* is underreported by many registries and the results of trend analysis could be misleading.

Due to increases both in prenatal diagnoses and subsequent termination of Down syndrome fetuses and also in maternal age across Europe, the prevalence of Down syndrome is adjusted for both fetal loss (a large proportion of early terminations would not survive to term) and maternal age (older mothers have a higher risk of Down syndrome). It is expected that this adjusted prevalence would remain stable over time. However, there appears to be increases in this adjusted prevalence, which are likely to reflect the fact that the adjustments for fetal loss are not correct. These adjustments will be investigated in 2020. Thus, the trend in *Down syndrome (age adjusted)* is not discussed further in this report.

The following sections provide further analysis on the significant increasing and decreasing pan-European trends, the preliminary investigations into them and their interpretation (Appendix E).

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 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 together with the summary pan-European estimate. 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 in which the change in prevalence is considered non-linear are indicated by a diamond and those with too few cases 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 those 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.

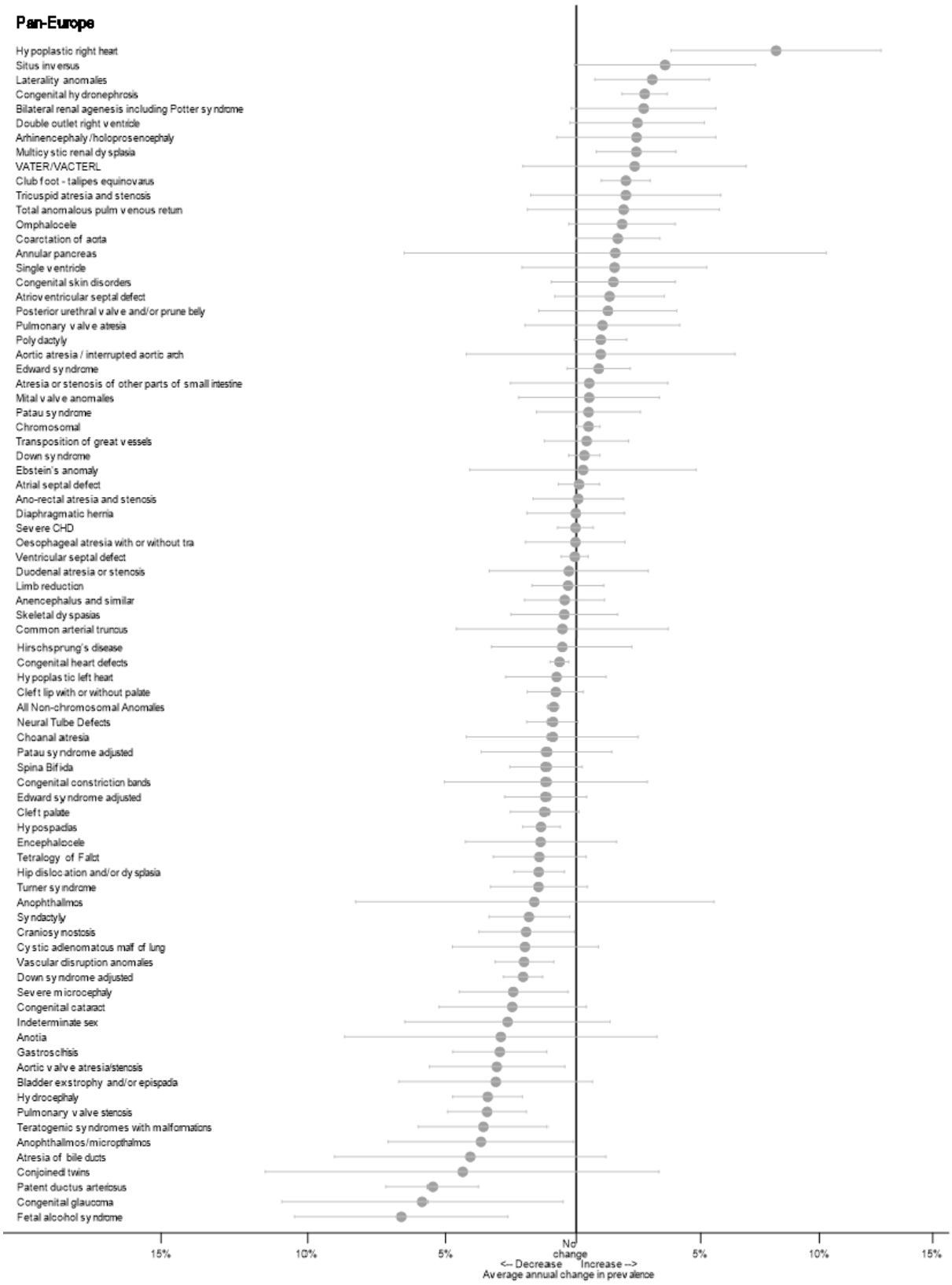

Fig. 2: Estimated annual percentage change in the prevalence and 95% CIs for the 84 congenital anomalies subgroups (pan-Europe analysis 2008-2017).

4.2 Increasing trends identified at the pan-European level

Hypoplastic right heart

Hypoplastic right heart is one of the univentricular cardiac anomalies with underdevelopment of the right ventricle. Most cases also have tricuspid atresia or pulmonary atresia with intact ventricular septum (see analysis presented in [2]). Prenatal detection rate is usually high and in many countries there is a high rate of TOPFA due to the severity. The anomaly is so rare that only the pan-Europe trend can be informative.

The prevalence of hypoplastic right heart is estimated to have increased each year by 8.1% (95% CI: 3.8%; 12.7%) at the pan-European level (Fig. 3a).

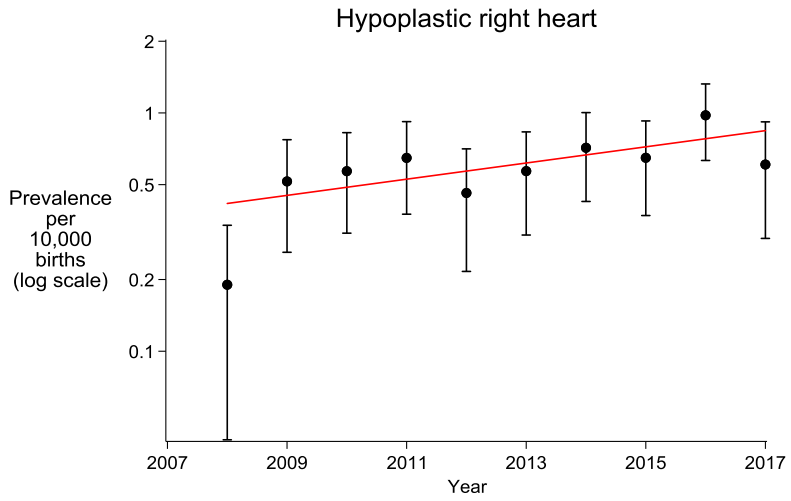

Fig. 3a: Hypoplastic right heart - Prevalence and 95% CIs (2008-2017).

The increasing trend in hypoplastic right heart at the pan-European level had been observed in last year's report [2]. The only statistically significant increasing trend was identified in Isle de Reunion (Fig. 3b). Isle de Reunion suggested that they will monitor the increasing trend by further surveillance.

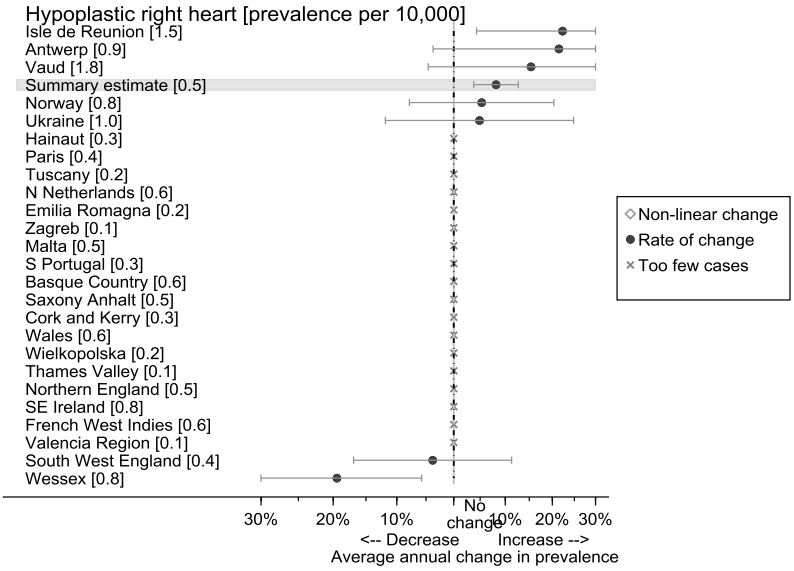

Fig. 3b: Hypoplastic right heart - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

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 Vaud (1.8 per 10,000) (Fig. 3c).

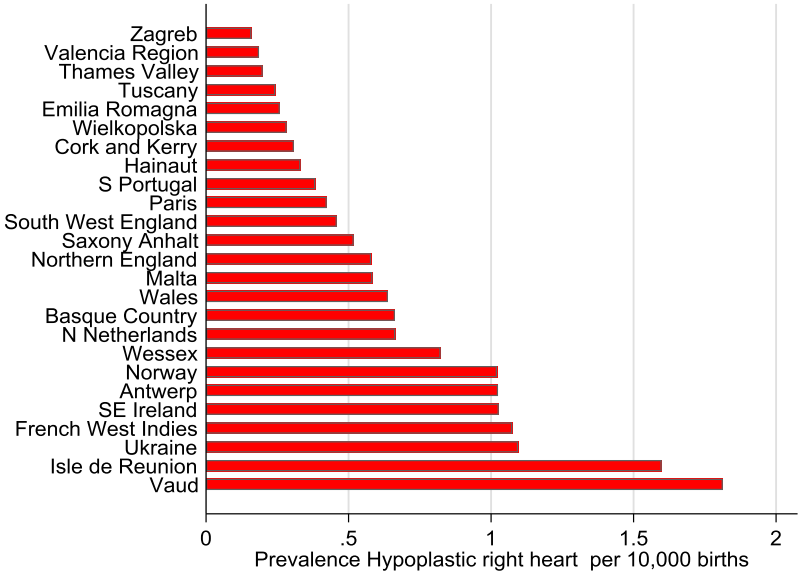

Fig. 3c: Hypoplastic right heart – Ten-year prevalence (2008-2017).

In conclusion, the trend will be monitored but there are no major concerns.

Coarctation of aorta

Coarctation of aorta is a constriction in the region of aorta where the ductus joins aorta. It is classified as a congenital heart defect. If the stenosis is proximal to the ductus (preductal), the baby will be critically ill when the duct closes within the first week after birth. If the stenosis is distal to the duct, the anomaly may be diagnosed later in infancy or childhood. It is possible to diagnose coarctation of aorta by prenatal ultrasound, but such diagnoses related to the fetal aorta are challenging.

The prevalence of coarctation of aorta is estimated to have increased each year by 1.8% (95% CI: 0.2%; 3.6%) at the pan-European level (Fig. 4a).

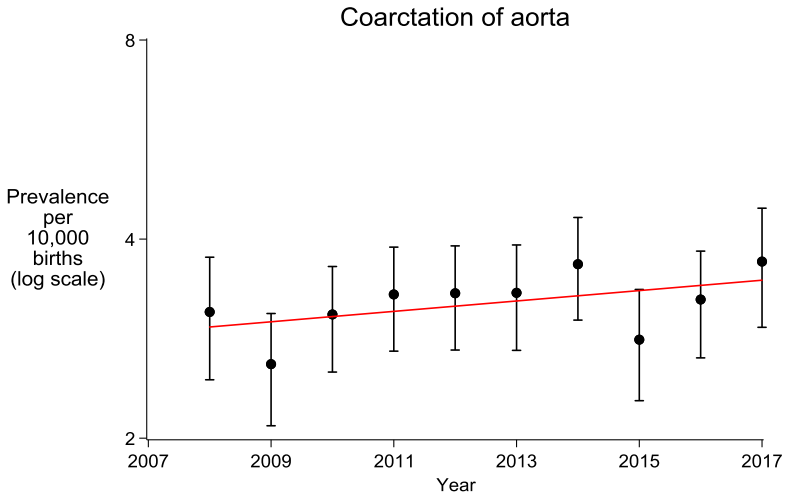

Fig. 4a: Coarctation of aorta - Prevalence and 95% CIs (2008-2017).

Coarctation of aorta shows an increasing trend for the first time at the pan-European level. The statistically significant increasing trends were found in Tuscany and Norway (Fig. 4b). The prevalence of coarctation of aorta was lower in Tuscany (2.2 per 10,000 births) compared to the EUROCAT average (3.3 per 10,000 births). Tuscany suggested that the changes in case ascertainment could explain the increasing trends.

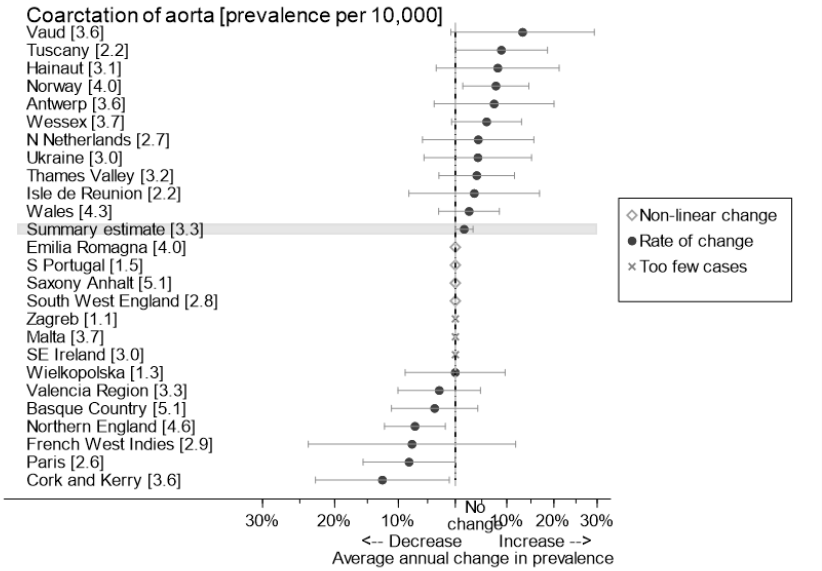

Fig. 4b: Coarctation of aorta - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

The prevalence of coarctation of aorta ranged between 1.1 and 5.1 per 10,000 births (Fig. 4c).

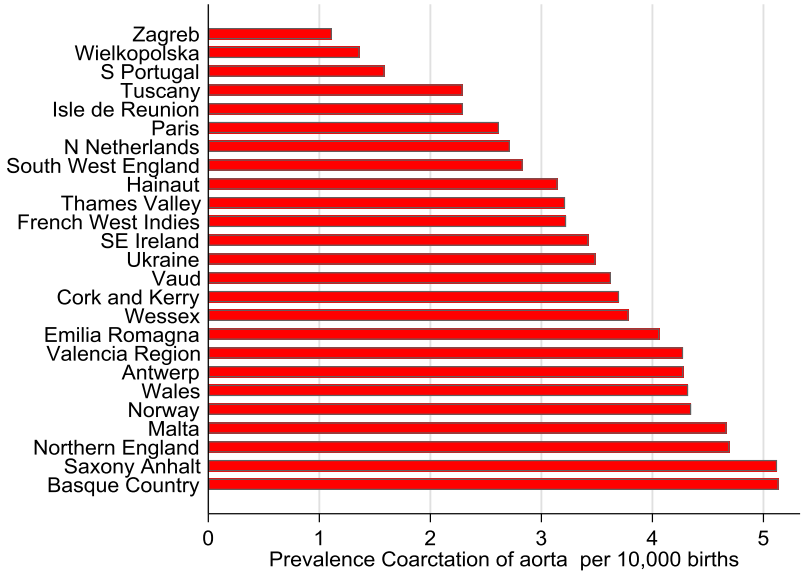

Fig. 4c: Coarctation of aorta - Ten-year prevalence (2008-2017).

In conclusion, the trend will be monitored but there are no major concerns.

Multicystic renal dysplasia

Bilateral multicystic renal dysplasia is usually lethal shortly after birth. Unilateral multicystic renal dysplasia is much more common, is asymptomatic and is usually diagnosed prenatally. Kidneys with multicystic renal dysplasia usually undergo atrophy within the first year after birth. If diagnosed later in life, the diagnosis will be renal agenesis.

As in the previous reports on the period 2006-2015 [7] and 2007-2016 [2], the prevalence of multicystic renal dysplasia is increasing at the pan-European level. Between 2008 and 2017 the prevalence of multicystic renal dysplasia is estimated to have increased each year by 2.3% (95% CI: 0.7%; 3.9%) (Fig. 5a).

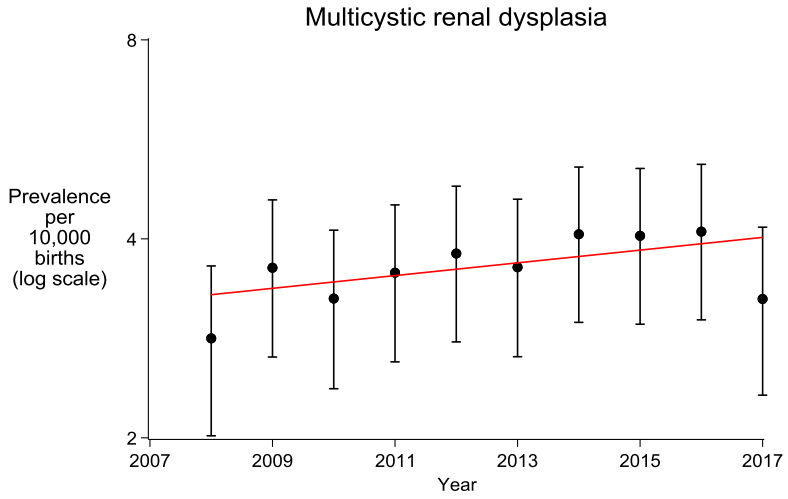

Fig. 5a: Multicystic renal dysplasia - Prevalence and 95% CIs (2008-2017).

The prevalence increased significantly during the same period in four individual registries (Norway, South West England, Ukraine and Reunion, Fig 5b). The prevalence of multicystic renal dysplasia was considerably lower in Norway (0.7 per 10,000 births) compared to the EUROCAT average (3.5 per 10,000 births), 2008-2017. The prevalence in South West England is similar to the EUROCAT average (3.7 per 10,000 births), but prevalence is higher than the EUROCAT average for Ukraine (5.0 per 10,000 births) and Reunion (5.9 per 10,000 births).

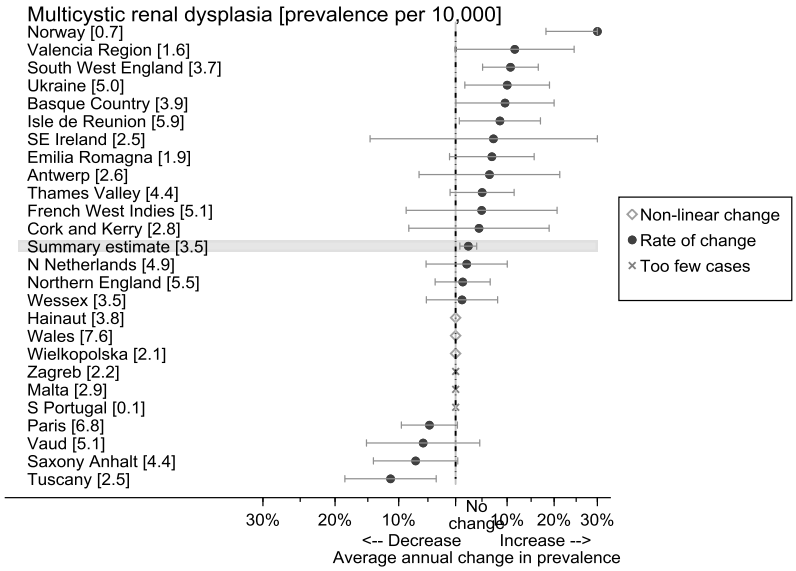

Fig. 5b: Multicystic renal dysplasia - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

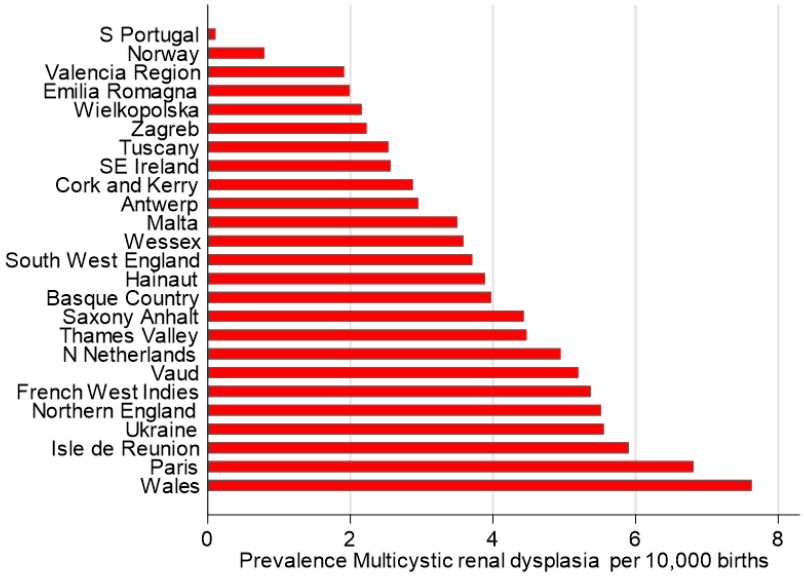

Fig. 5c: Multicystic renal dysplasia – Ten-years prevalence (2008-2017).

Prevalence of multicystic renal dysplasia ranged from 0.1 to 7.6 per 10.000 births.

As shown in last years' report [2, 7], this trend is mainly based on unilateral multicystic renal dysplasia (84% of cases) diagnosed because of increasing use of prenatal ultrasound screening in Europe.

Congenital hydronephrosis

Congenital hydronephrosis is mainly diagnosed prenatally. Cases have to be followed-up as some intrauterine diagnoses are not confirmed after birth. Only cases where the renal pelvis is ≥ 10 mm after birth should be reported to EUROCAT. Hydronephrosis caused by vesico-ureteral reflux should not be reported to EUROCAT.

As in the previous reports on the period 2006-2015 [7] and 2007-2016 [2], the prevalence of congenital hydronephrosis is increasing. Between 2008 and 2017, its prevalence is estimated to have increased each year by 2.6% (95% CI: 1.7%; 3.5%) at the pan-European level (Fig. 6a).

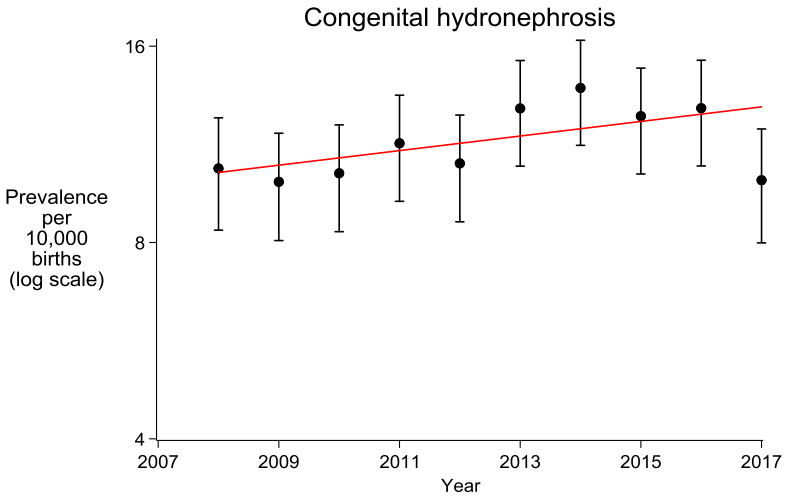

Fig. 6a: Congenital hydronephrosis - Prevalence and 95% CIs (2008-2017).

The prevalence increased significantly during the same period in five individual registries (French West Indies, Valencian Region, Antwerp, Basque Country and Zagreb, Fig 6b). The prevalence rate in French West Indies, Antwerp, and Basque Country are similar to the EUROCAT average of 11 per 10,000 births, while the prevalence rates are higher in Zagreb (14 per 10,000 births) and Valencian Region (17 per 10,000 births).

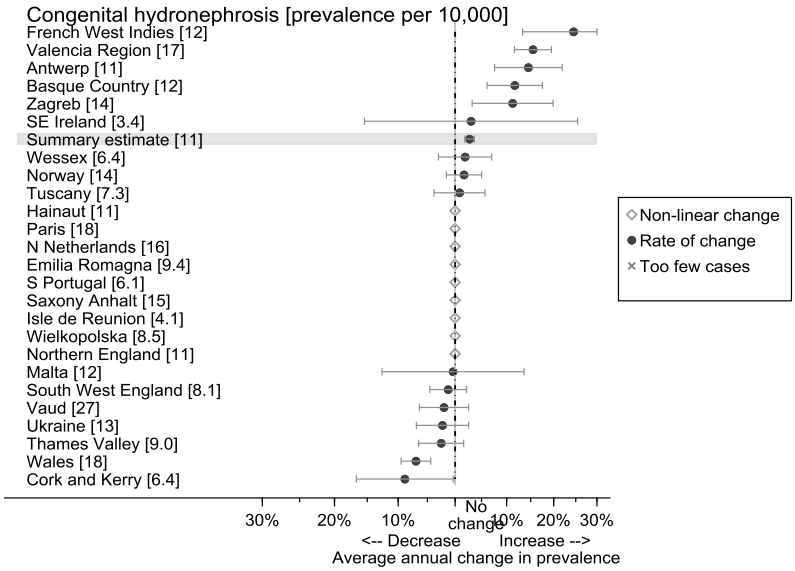

Fig. 6b: Congenital hydronephrosis - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

Prevalence of congenital hydronephrosis ranged from 3.4 per 10,000 births in South East Ireland to 27 per 10,000 births in Vaud (Fig. 6c). The prevalence in Vaud is more than twice the EUROCAT average (11 per 10,000).

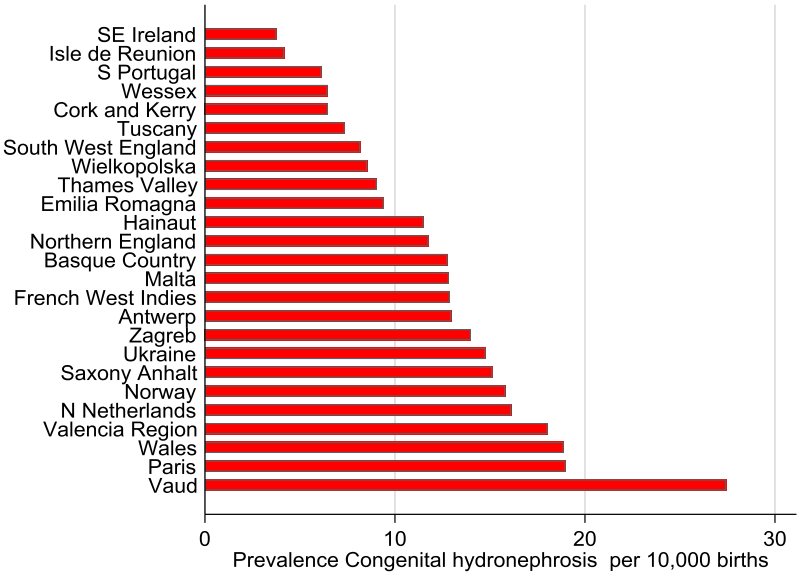

Fig. 6c: Congenital hydronephrosis – Ten-years prevalence (2008-2017).

In conclusion, the increasing pan-European trend is likely to reflect increases in prenatal ultrasound screening over the last 10 years.

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.
A recently published study on data from 18 EUROCAT registries found a decrease in prevalence of clubfoot in earlier years (1995-2011) [9], mainly after 2002 due to new coding recommendations.

The prevalence of clubfoot is now increasing, as documented in the previous reports on the period 2006-2015 [7] and 2007-2016 [2]. Between 2008 and 2017, its prevalence is estimated to have increased each year by 2.0% (95% CI: 1.0%; 3.0%) at the pan-European level (Fig. 7a).

The prevalence of clubfoot increased dramatically (+59.2%) for Northern England, because clubfoot was not reported at the beginning of the 10 year period. Performing the trend analysis excluding the Northern England registry the pan-European trend remains significantly increasing with an annual increase of 1.7% (95% CI: 1.2%; 3.4%).

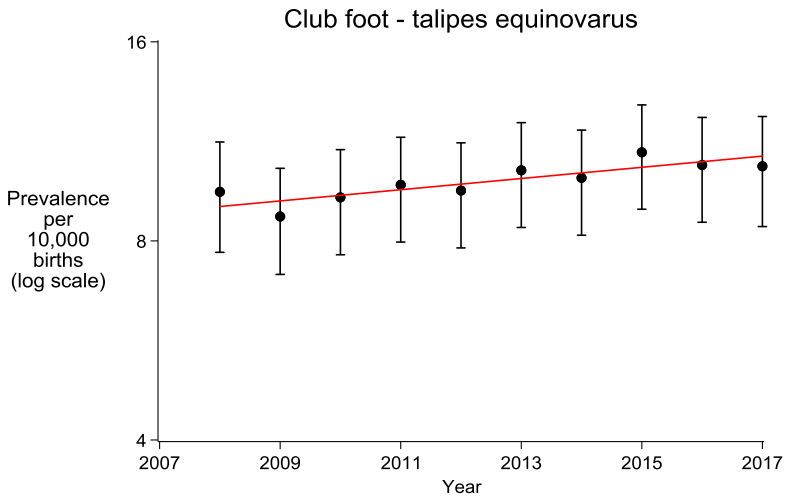

Fig. 7a: Clubfoot - Prevalence and 95% CIs (2008-2017).

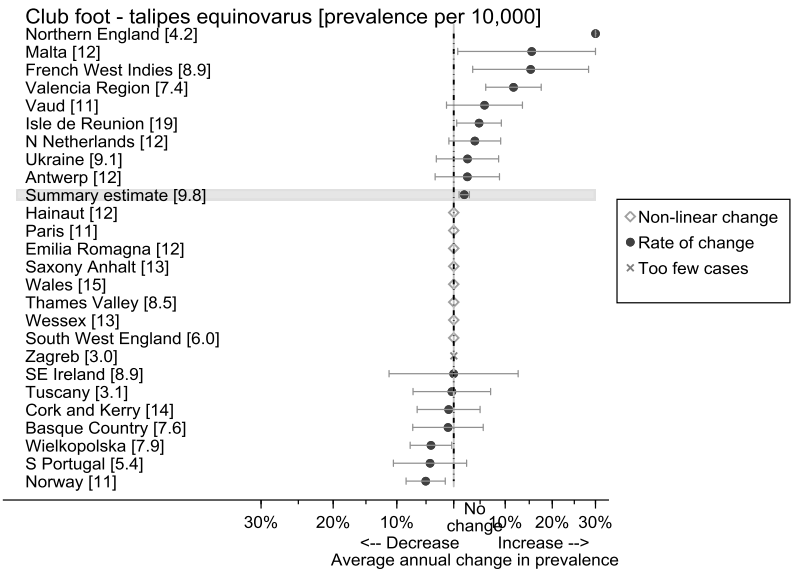

Fig. 7b: Clubfoot - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

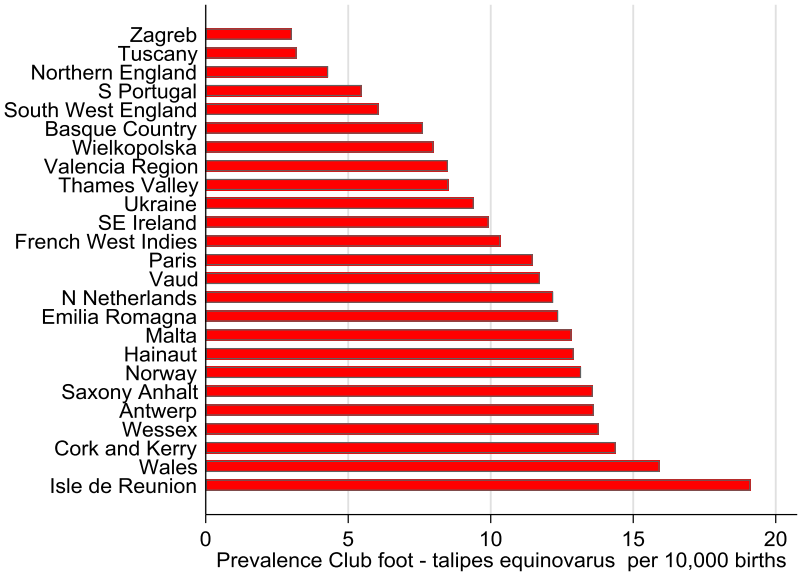

Fig. 7c: Clubfoot – Ten-years prevalence (2008-2017).

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 followed.

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 report on the period 2006-2015 [7] and 2007-2016 [2] the prevalence of laterality anomalies is increasing. Between 2007 and 2016, its prevalence is estimated to have increased by 3.1% (95% CI: 0.8%; 5.5%) each year at the pan-European level (Fig. 8a). Laterality anomalies have been associated to maternal pre-gestational diabetes [12]. For the cases with laterality anomalies 4% reported maternal diabetes before or during pregnancy compared to 2% of all cases in the same EUROCAT registries over the same period, but there is considerable heterogeneity in reporting of diabetes between registries.

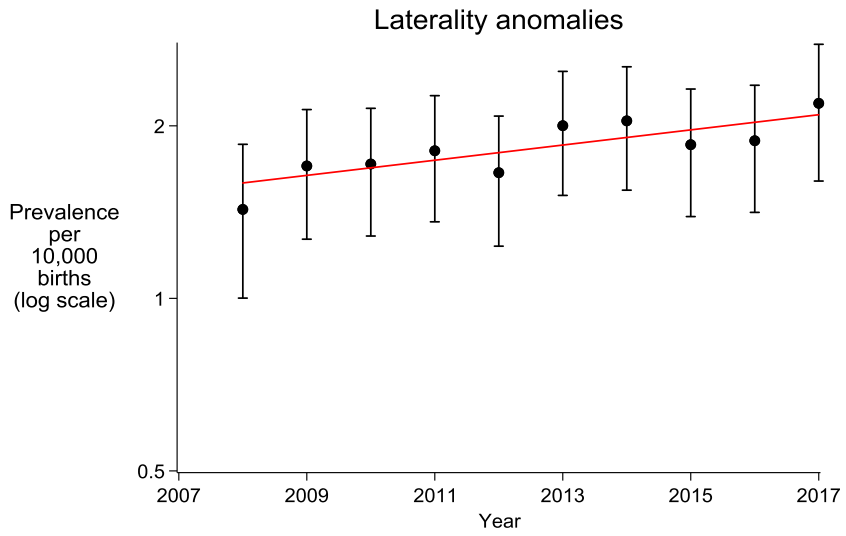

Fig. 8a: Laterality anomalies - Prevalence and 95% CIs (2008-2017).

In the Ukraine and Thames Valley registries prevalence increased significantly during this period (Fig. 8b).

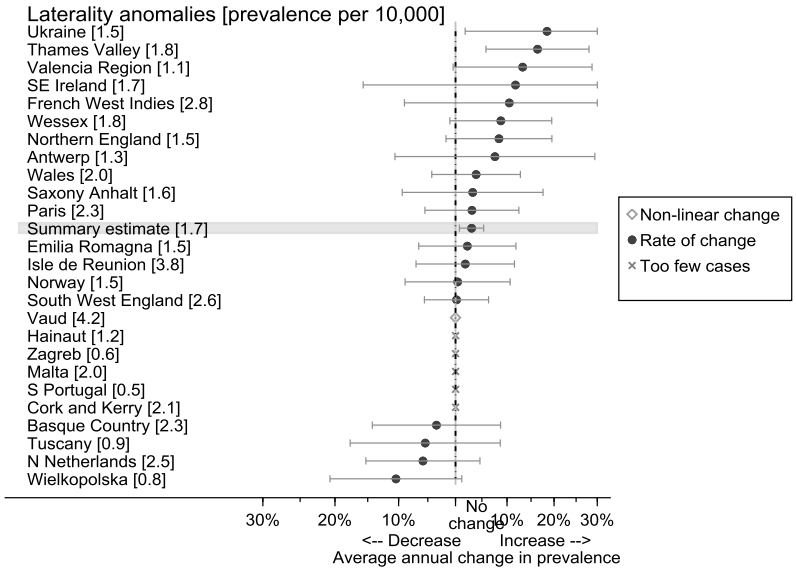

Fig. 8b: Laterality anomalies - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

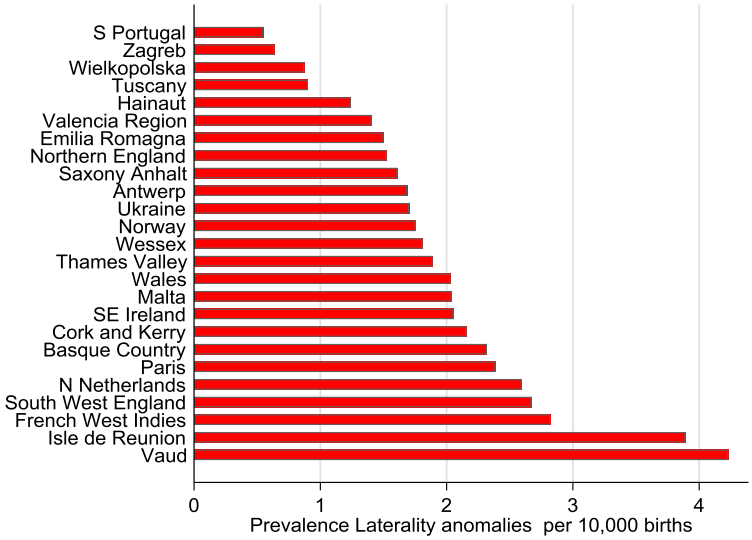

Fig. 8c: Laterality anomalies – Ten-years prevalence (2008-2017).

In conclusion, the increasing trends in both laterality anomalies and situs inversus will be investigated in more detail in 2020 with focus on the association to maternal diabetes.

Situs inversus

Situs inversus is a congenital anomaly where all visceral organs or those in the chest or in the abdomen are reversed from their normal positions. Most infants with situs inversus have no symptoms or complications, but there is an increased risk of congenital heart defects. With the increasing use of prenatal ultrasound examinations more cases are expected to be diagnosed. Between 2008 and 2017, the prevalence of situs inversus is estimated to have increased each year by 3.8% (95% CI: 0.1%; 7.5%) at the pan-European level (Fig. 9a). As for laterality anomalies, also for situs inversus 4% of the cases reported maternal diabetes before or during pregnancy compared to 2% of all cases in the same EUROCAT registries over the same period.

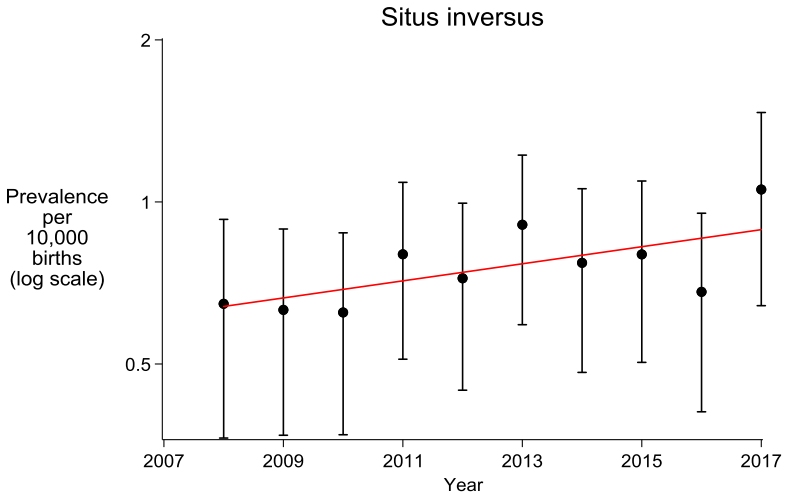

Fig. 9a: Situs inversus - Prevalence and 95% CIs (2008-2017).

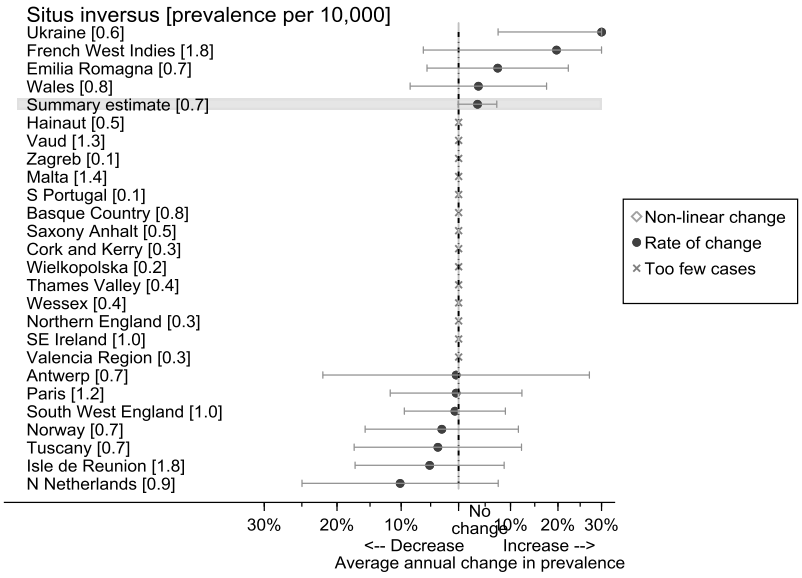

Fig. 9b: Situs inversus - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

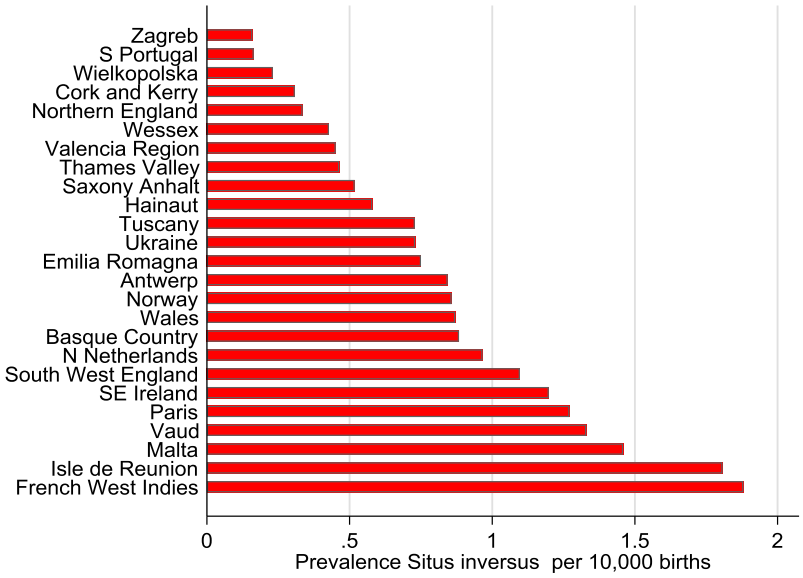

Fig. 9c: Situs inversus – Ten-years prevalence (2008-2017).

In conclusion, the increasing trends in laterality anomalies, including situs inversus, will be investigated in more detail in 2020.

4.3 Decreasing trends identified at the pan-European level

All non-chromosomal anomalies

The prevalence of all non-chromosomal congenital anomalies is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -0.9% (95% CI: -1.1%; -0.7%) each year at the pan-European level (Fig. 10a).

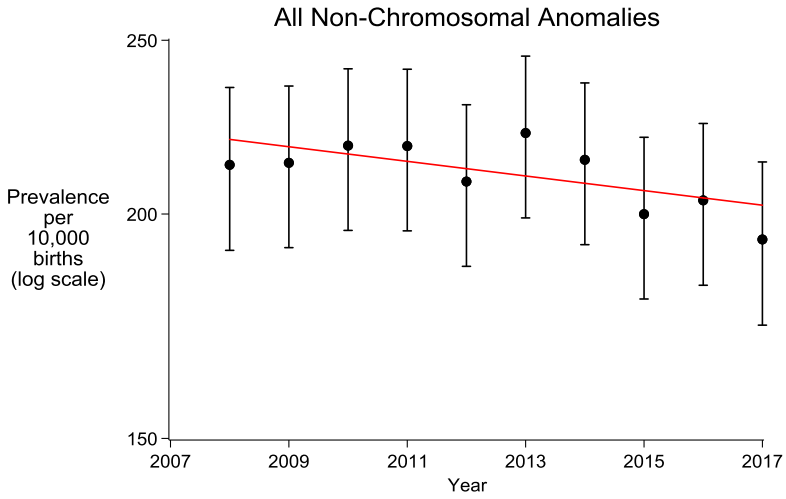

Fig. 10a: All non-chromosomal anomalies - Prevalence and 95% CIs (2008-2017).

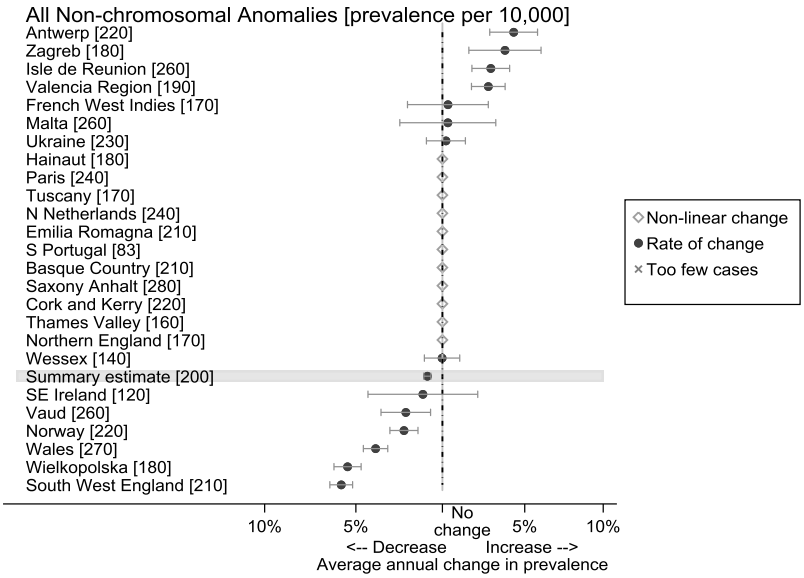

Fig. 10b: All non-chromosomal anomalies - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

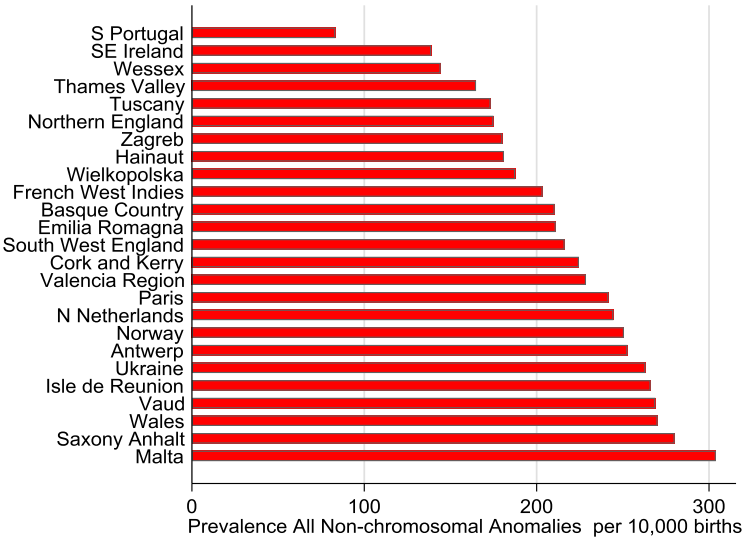

Fig. 10c: All non-chromosomal anomalies – Ten-years prevalence (2008-2017).

In conclusion, the prevalence of all anomalies appears to be decreasing. This could reflect the fact that several registries are improving the coding and more minor anomalies are excluded.

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 previous reports on the period 2006-2015 [7] and 2007-2016 [2], the prevalence of hydrocephaly is decreasing. Between 2007 and 2016, its prevalence is estimated to decrease by -3.4% (95% CI: -4.8%; -2.1%) each year on the pan-European level (Fig. 11a).

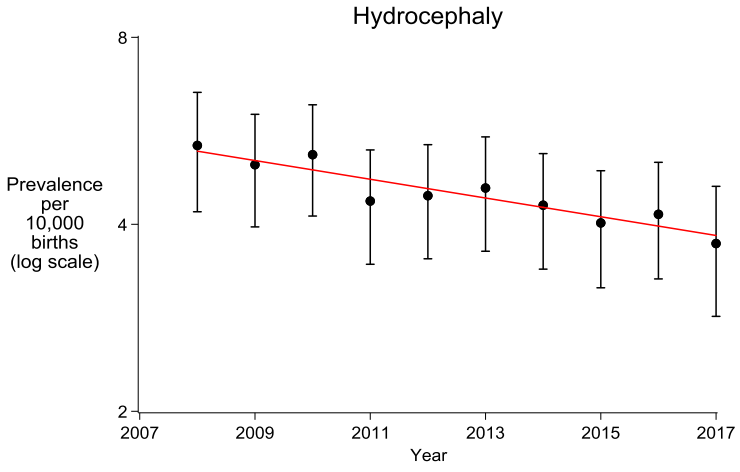

Fig. 11a: Hydrocephaly - Prevalence and 95% CIs (2008-2017).

In four individual registries, the prevalence decreased significantly during the same period (Paris, Norway, Wielkopolska and South West England, Fig 11b).

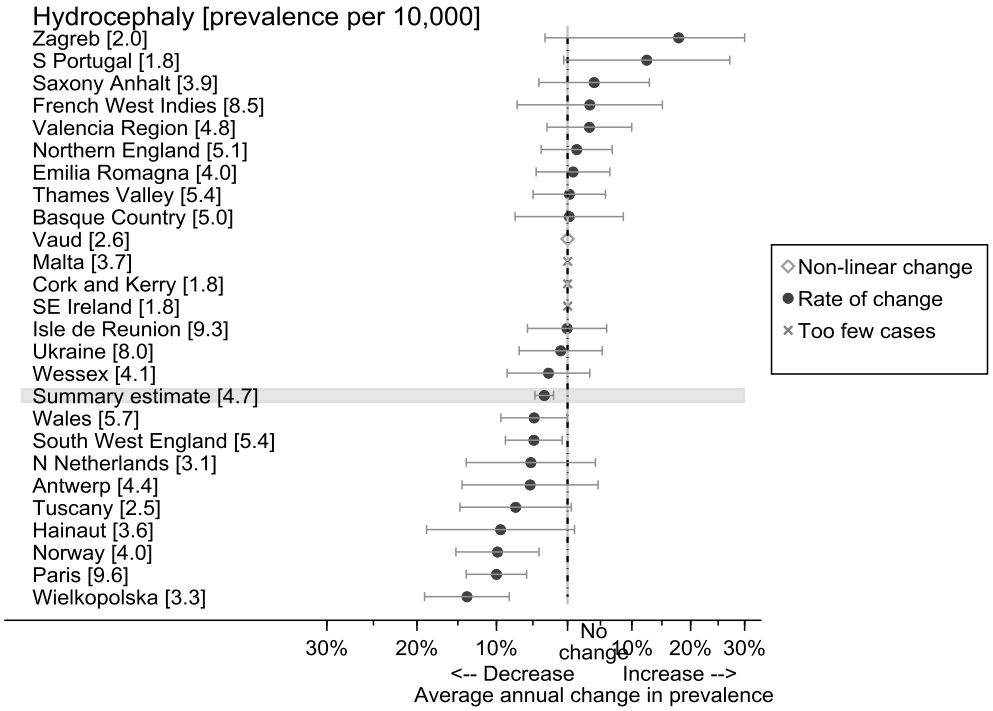

Fig. 11b: Hydrocephaly - Estimated annual percentage change in the prevalence and 95% CIs for the registries included in the pan-European trend analysis.

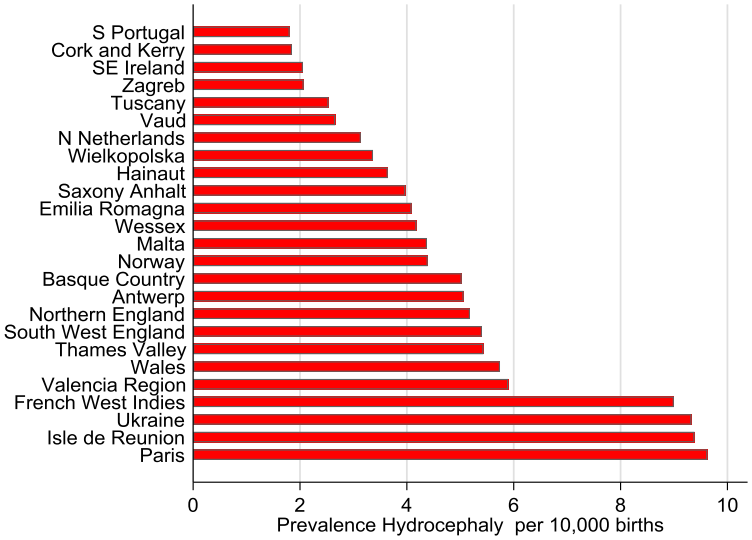

Fig. 11c: Hydrocephaly - Ten-years prevalence (2008-2017).

In conclusion, hydrocephaly is decreasing in general in Europe. This decreasing trend will be followed.

Severe microcephaly

Severe microcephaly should be reported if the head circumference (occipito-frontal) is less than -3 SD for sex and GA. This anomaly will be followed closely due to the recent Zika virus outbreaks that started in 2015 in South America. The first births in Europe after possible exposure to Zika virus occurred in 2016. The reporting of cases with microcephaly may be delayed as the head circumference must be followed in infancy for a final diagnosis.

Between 2007 and 2016, its prevalence is estimated to have decreased by -2.3% (95% CI: -4.4%; -0.2%) each year on the pan-European level (Fig. 12a).

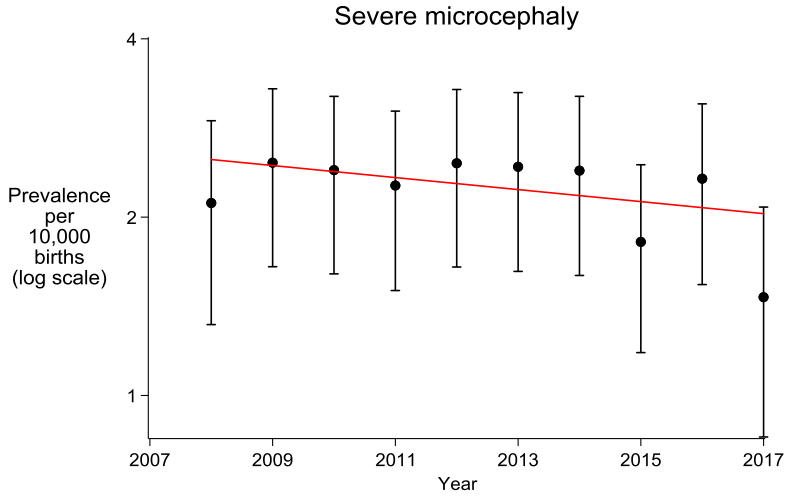

Fig. 12a: Severe microcephaly - Prevalence and 95% CIs (2008-2017).

In three individual registries, the prevalence decreased significantly during the same period (Saxony-Anhalt, South-West England and Wales, Fig 12b).

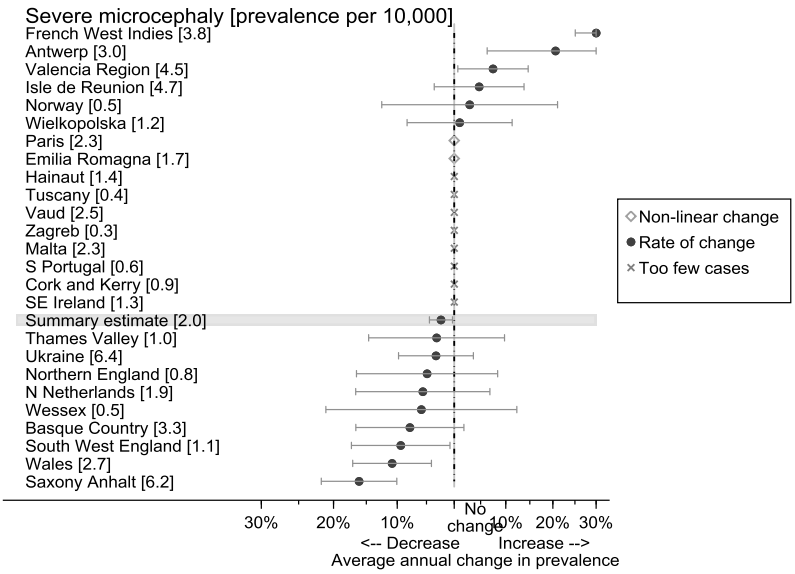

Fig. 12b: Severe microcephaly - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

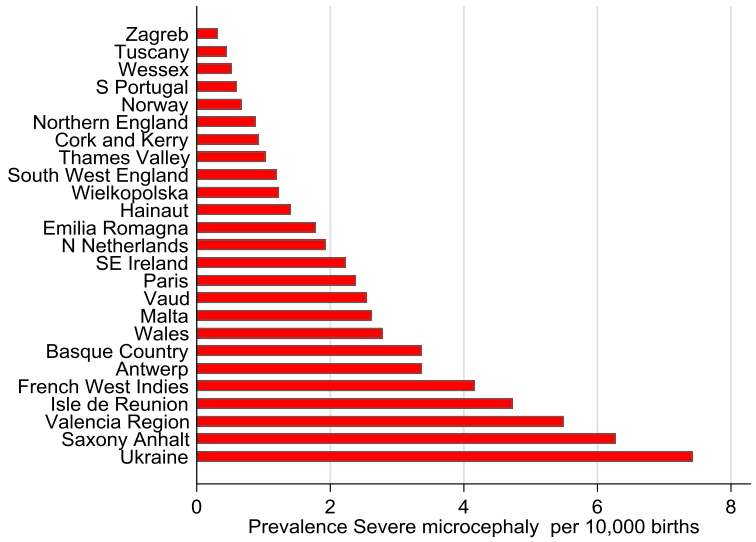

Fig. 12c: Severe microcephaly – Ten-years prevalence (2008-2017).

In the previous reports on the period 2006-2015 [7] and 2007-2016 [2], the prevalence of *severe* microcephaly was also reported as decreasing. However, due to the late reporting of cases when the trend analysis was re-run this year for the period 2007-2016, the decrease was no longer significant.

In conclusion, the observed decreasing trend is probably due to late reporting of cases to the registries, a delay caused by the fact that the head circumference must be followed in infancy for a final diagnosis. The trend will be followed.

Congenital heart defects

Congenital heart defects (CHD) are the most frequent group of congenital anomalies. The spectrum range from complex cardiac anomalies with high mortality to small innocent septal defects. Prevalence of non-genetic cardiac defects is around 7 per 1,000 births [13].

When taking into account the information from all European registries between 2008-2017, the prevalence of congenital heart defects is estimated to have decreased each year by -0.7% (95% CI: -1.0%; -0.3%) on the pan-European level (Fig. 13a). One large registry experienced a non-linear decrease of over 50% in the prevalence of congenital heart defects and when they were excluded from the analysis there was no significant decrease.

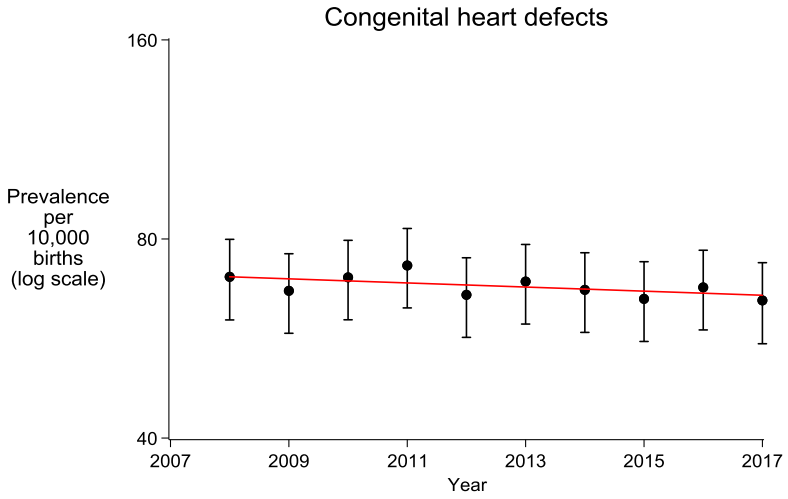

Fig. 13a: Congenital heart defects - Prevalence and 95% CIs (2008-2017).

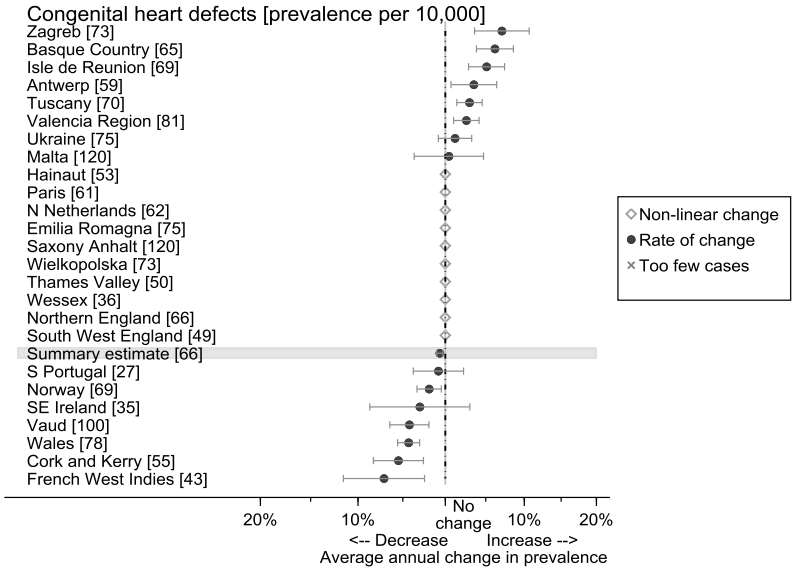

Fig. 13b: Congenital heart defects - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

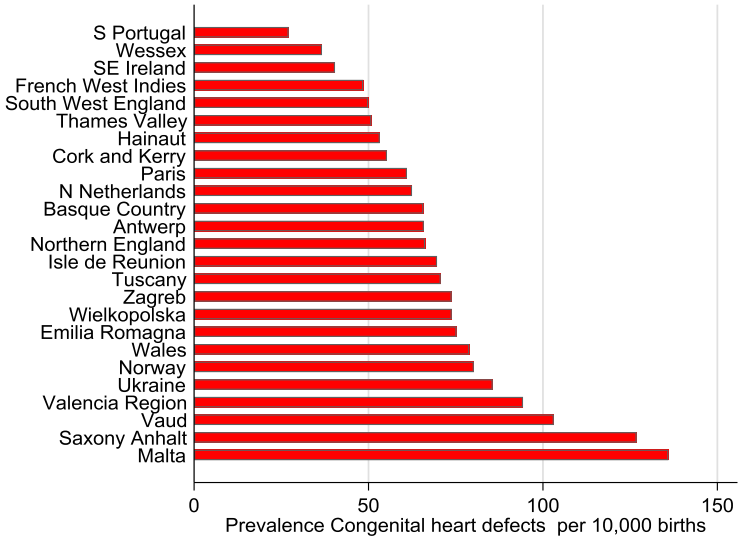

Fig. 13c: Congenital heart defects - Ten-years prevalence (2008-2017).

In conclusion, the apparent decrease was due to extreme decrease in prevalence in one large registry.

Pulmonary valve stenosis

Pulmonary valve stenosis is defined as obstruction or narrowing of the pulmonary valves, which may impair blood flow through the valves. The anomaly covers all spectra of severity - from small stenosis to critical pulmonary valve stenosis in severely ill neonates.

As in the previous reports on the period 2006-2015 [7] and 2007-2016 [2], the prevalence of pulmonary valve stenosis is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -3.5% (95% CI: -5.0%; -2.0%) each year on the pan-European level (Fig. 14a).

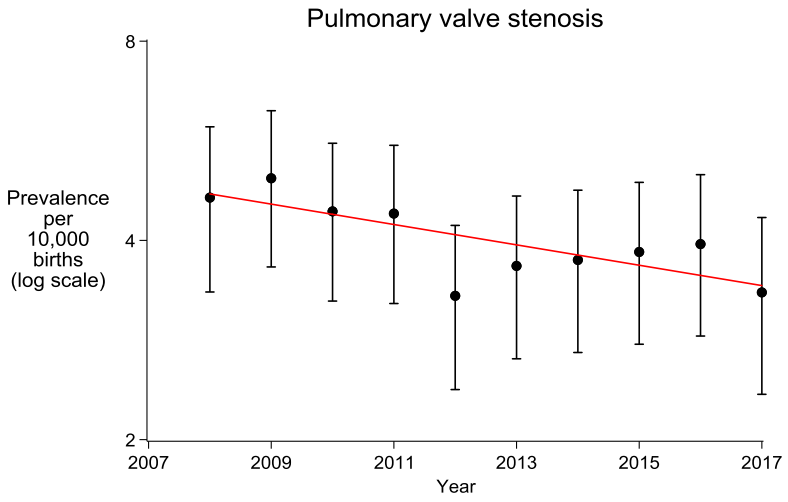

Fig. 14a: Pulmonary valve stenosis - Prevalence and 95% CIs (2008-2017).

In five individual registries, the prevalence decreased significantly during the same period (Northern Netherlands, Northern England, Vaud, Wielkopolska, Paris, South Portugal and Wales Fig 14b).

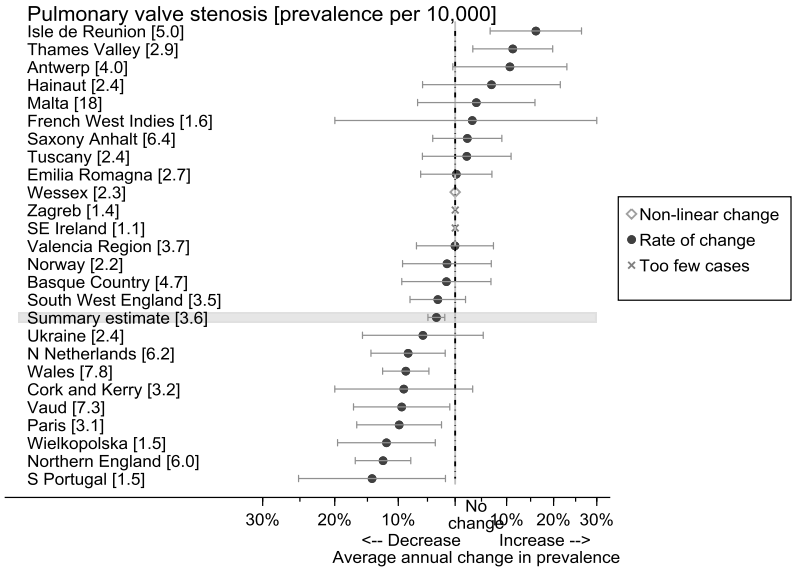

Fig. 14b: Pulmonary valve stenosis - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

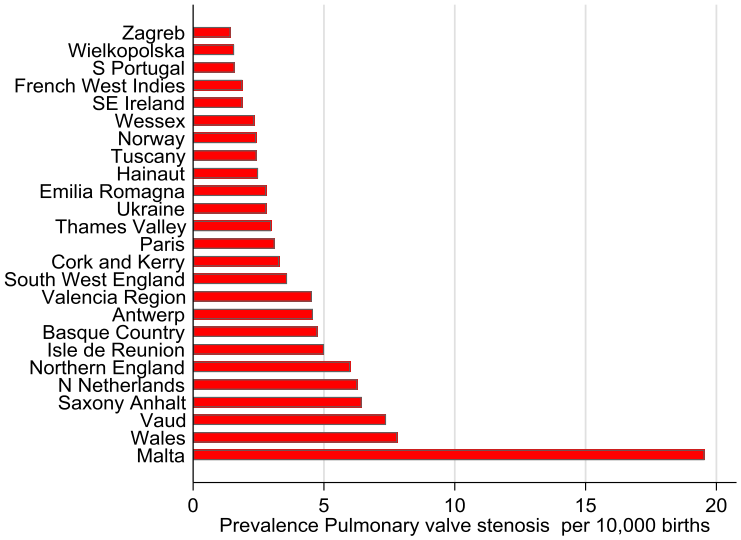

Fig. 14c: Pulmonary valve stenosis - Ten-years prevalence (2008-2017).

There is considerable heterogeneity in the pan European prevalence of pulmonary valve stenosis over time (Fig. 14c), with decreases appearing to occur between 2011 and 2012 and potentially the prevalence has been increasing since then (Fig. 14a). The high prevalence in Malta has been described previously [14].

In conclusion, the decreasing trend should be interpreted with caution.

Aortic valve atresia/stenosis

Aortic valve atresia/stenosis: This anomaly is occlusion of the aortic valve or stenosis of varying degree, often associated with bicuspid valves. Aortic valve atresia and severe stenosis are diagnosed in the neonatal period. Less severe aortic stenosis is usually asymptomatic and may be diagnosed later in childhood.

The prevalence of aortic valve atresia/stenosis is estimated to have decreased each year by -2.8% (95% CI: -5.4%; -0.2%) at the pan-European level (Fig. 15a). This is a new decreasing trend.

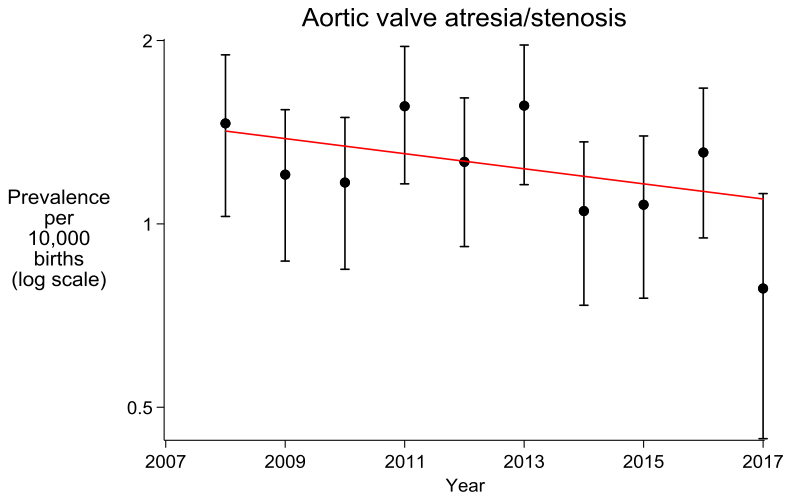

Fig. 15a: Aortic valve atresia/stenosis - Prevalence and 95% CIs (2008-2017).

In two individual registries, the prevalence decreased significantly during the same period (Northern England and Wales, Fig. 15b).

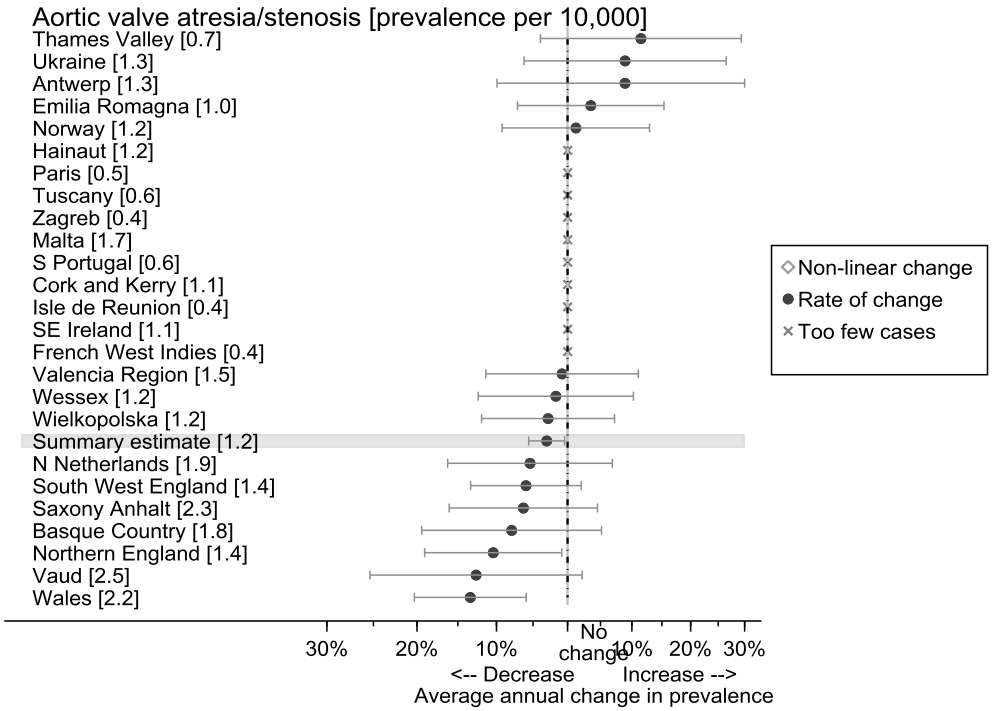

Fig. 15b: Aortic valve atresia/stenosis - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

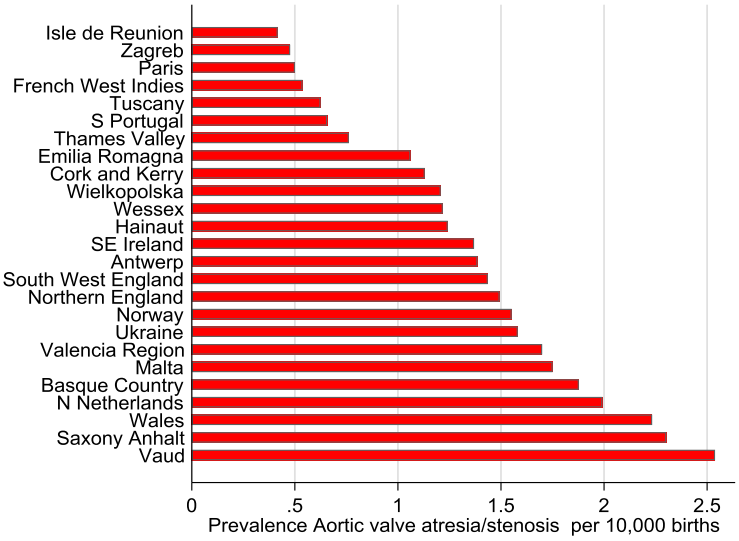

Fig. 15c: Aortic valve atresia/stenosis - Ten-years prevalence (2008-2017).

In conclusion, there is considerable heterogeneity in the prevalence of aortic valve atresia/stenosis over the past 10 years, with the very low prevalence in 2017 probably due to late reporting of diagnosis after the neonatal period, which is likely to influence the statistical significance of the decreasing trend. The trend should therefore be interpreted with caution.

Patent ductus arteriosus

Patent ductus arteriosus (PDA) is considered a major anomaly only if it occurs in term born babies (GA ≥ 37 weeks). Cases should be reported only if the PDA is still present six months after birth or if surgery/catheter closure is required. Many critically ill neonates have an open PDA for days or weeks after birth with later spontaneous closure. These babies should not be reported to EUROCAT.

As in the previous reports on the period 2006-2015 [7] and 2007-2016 [2], the prevalence of patent ductus arteriosus is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -5.5% (95% CI: -7.2%; -3.7%) each year at the pan-European level (Fig. 16a).

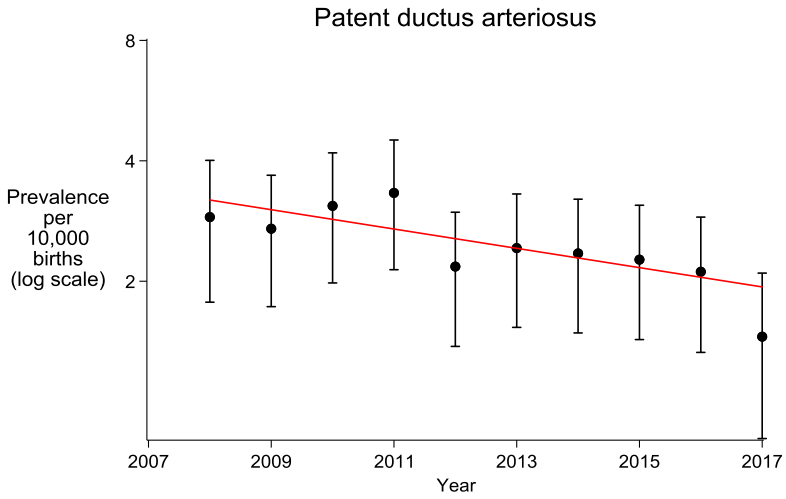

Fig. 16a: Patent ductus arteriosus - Prevalence and 95% CIs (2008-2017).

In three individual registries, the prevalence of PDA decreased significantly during the same period (Ukraine, Saxony-Anhalt and Wales, Fig. 16b).

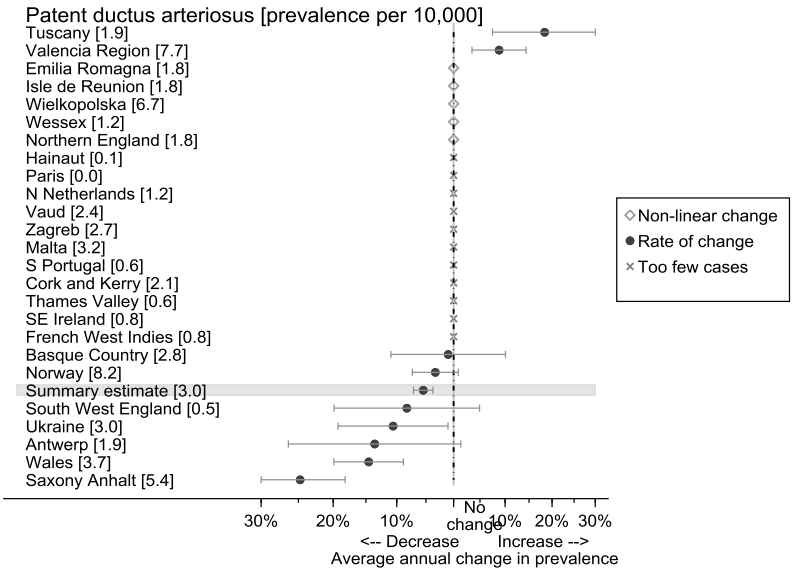

Fig. 16b: Patent ductus arteriosus - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

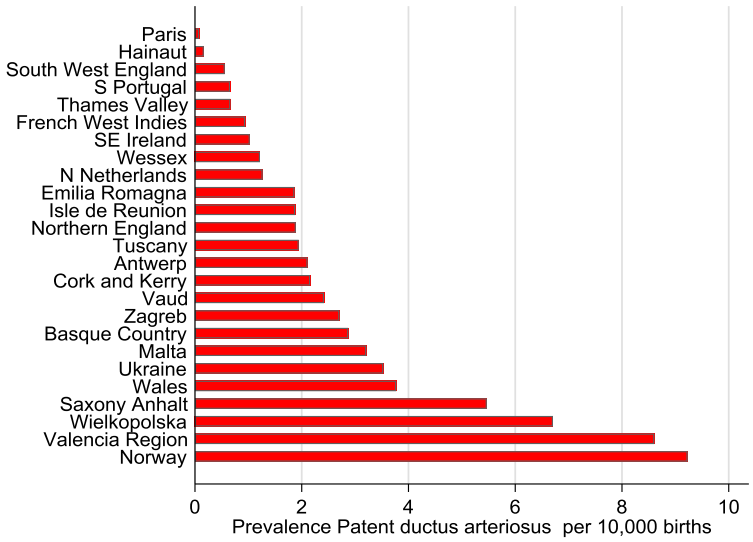

Fig. 16c: Patent ductus arteriosus - Ten-years prevalence (2008-2017).

In 2016, the EUROCAT Coding and Classification Committee issued a coding tip for this anomaly:

"*Infants with patent ductus will be included as a major anomaly for term born babies only (GA ≥ 37 weeks). To be reported only if the PDA is still present six months after birth or if surgery/catheter closure is required. Many critically ill neonates have an open PDA for days or weeks with spontaneous closure. These babies should not be reported to EUROCAT. Do not code the PDA if part of a ductus dependent CHD such as transposition of great arteries (Q203), hypoplastic left heart (Q234) and coarctation of aorta (Q2510)*" [15].

The large amount of heterogeneity in the prevalence in the different registries and in the changes in prevalence over the ten-year period indicates that there are clear issues with reporting of this anomaly. The coding tip will hopefully result in more homogeneous reporting. Until then any observed trends are most probably due to corrections in reporting and should not be interpreted as indicating underlying real changes in prevalence.

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 associated with low maternal age. From the 1990s increases in prevalence have been observed in the UK and other areas outside Europe for 20 years [16, 17, 18]. However, between 2008 and 2017 the prevalence of gastroschisis is now decreasing in the EUROCAT registries (as reported in the previous EUROCAT reports on the period 2006-2015 and 2007-2016 [2, 7]. Prevalence is estimated to have decreased by -3.0% (95% CI: -4.8%; -1.1%) each year at the pan-European level (Fig. 17a)

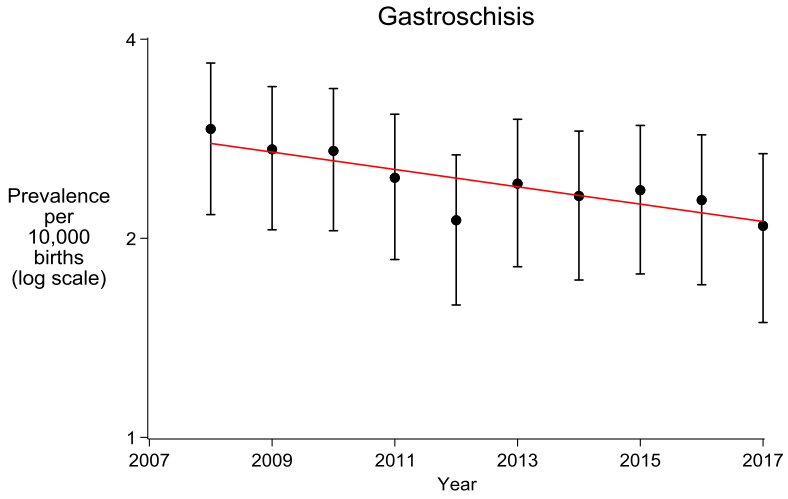

Fig. 17a: Gastroschisis - Prevalence and 95% CIs (2008-2017).

In one individual registry, Thames Valley, the prevalence also decreased significantly during the same period (Fig 17b).

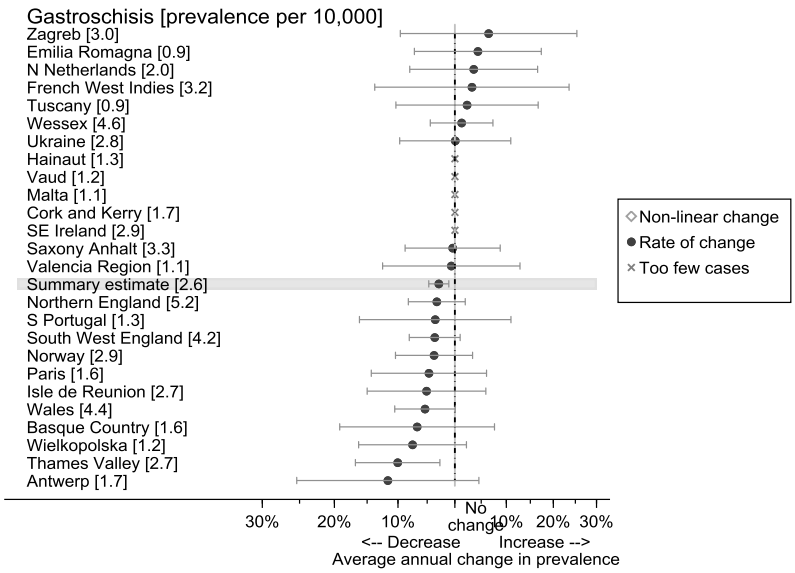

Fig. 17b: Gastroschisis - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

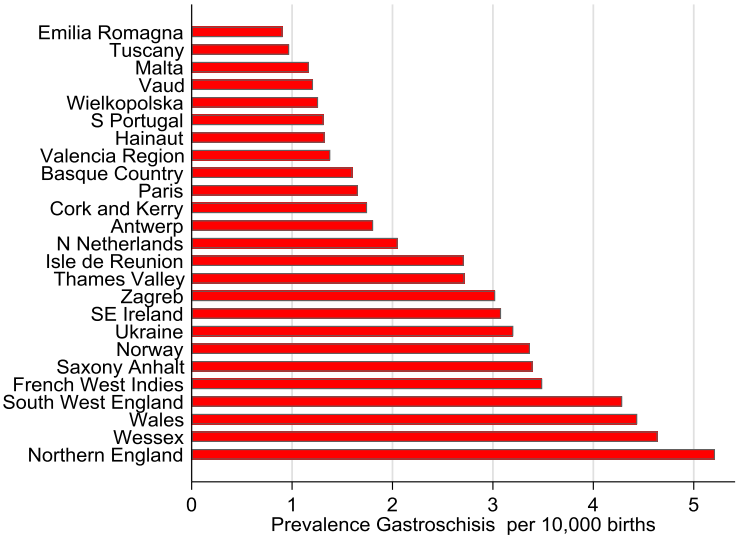

Fig. 17c: Gastroschisis – Ten-years prevalence (2008-2017).

This decreasing trend was presented in the last two consecutive EUROCAT reports [2, 7]. A more in depth analysis was conducted and presented in last year's report, and the conclusion was that the decreasing pan-European trend seems to be explained by less teenage pregnancies in the UK.

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 was no consistent trends across EUROCAT registries [19]. There is some evidence about an association between hypospadias and fetal exposure to endocrine disrupting chemicals [20].

The prevalence of hypospadias is estimated to have decreased each year by -1.3% (95% CI: -2.1%; -0.6%) at the pan-European level (Fig. 18a).

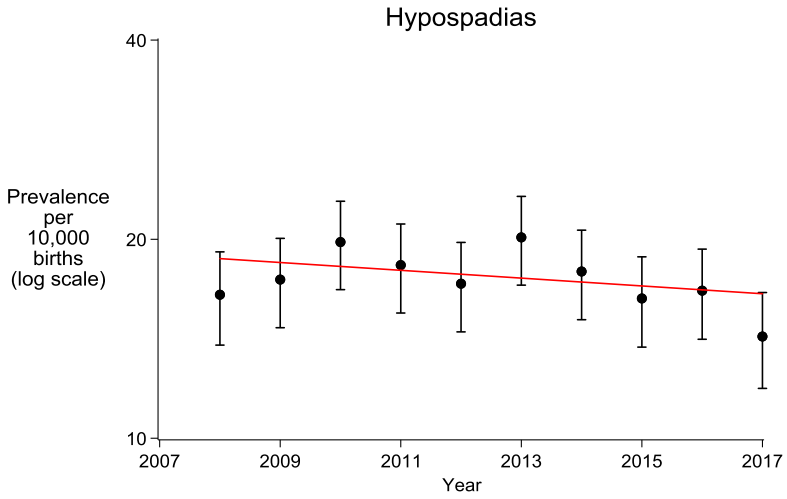

Fig. 18a: Hypospadias - Prevalence and 95% CIs (2008-2017).

In four individual registries, the prevalence also decreased significantly during the same period (Basque Country, Wales, Vaud and Cork and Kerry, Fig 18b).

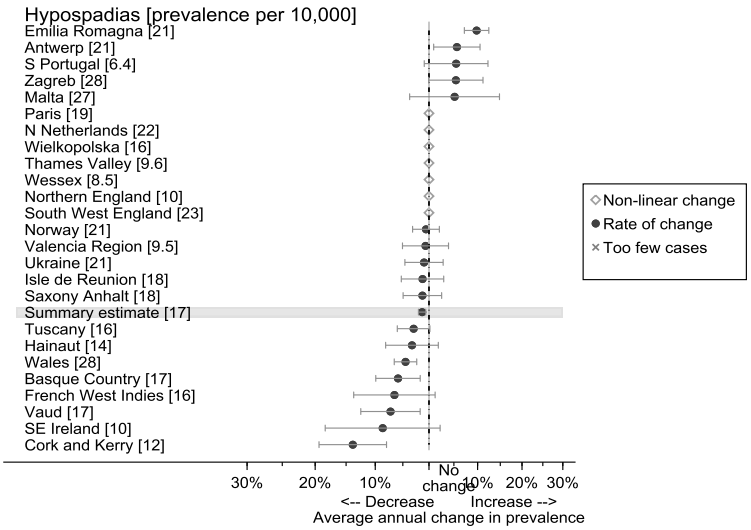

Fig. 18b: Hypospadias - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

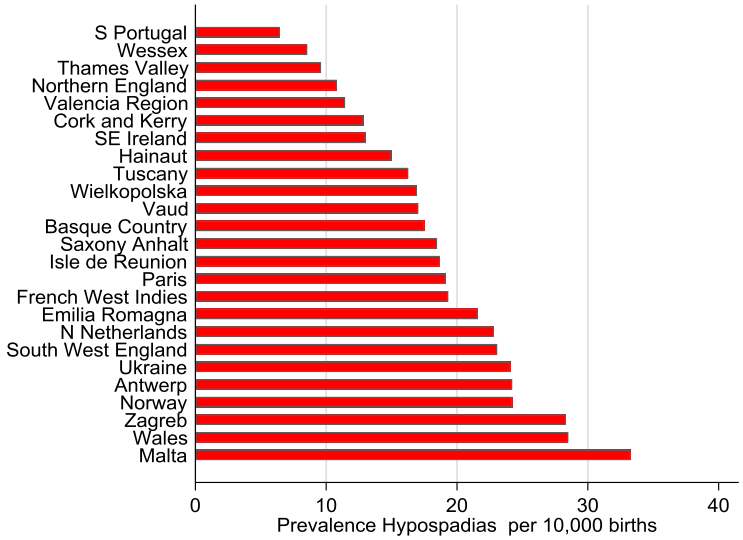

Fig. 18c: Hypospadias –Ten-years prevalence (2008-2017).

There is large amount of heterogeneity in the prevalence in the different registries and this decreasing trend should be interpreted with caution, but will be followed.

Syndactyly

Syndactyly is defined as partial or total webbing between two or more digits, with the exclusion of syndactyly between 2nd and 3rd toes.

As in the previous reports on the period 2006-2015 and 2007-2016 [2, 7], the prevalence of syndactyly is decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -1.9% (95% CI: -3.4%; -0.3%) each year at the pan-European level (Fig. 19a).

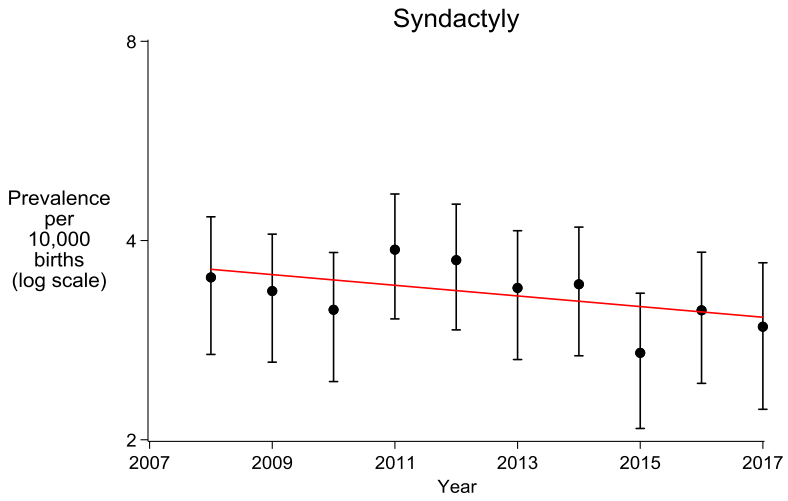

Fig. 19a Syndactyly - Prevalence and 95% CIs (2008-2017).

In one individual registry, the prevalence also decreased significantly during the same period (Wales, Fig 19b).

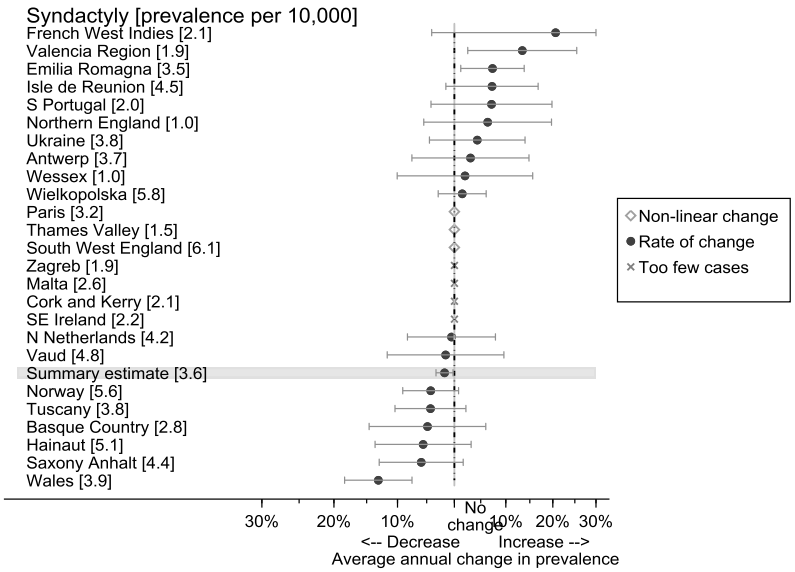

Fig. 19b: Syndactyly - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

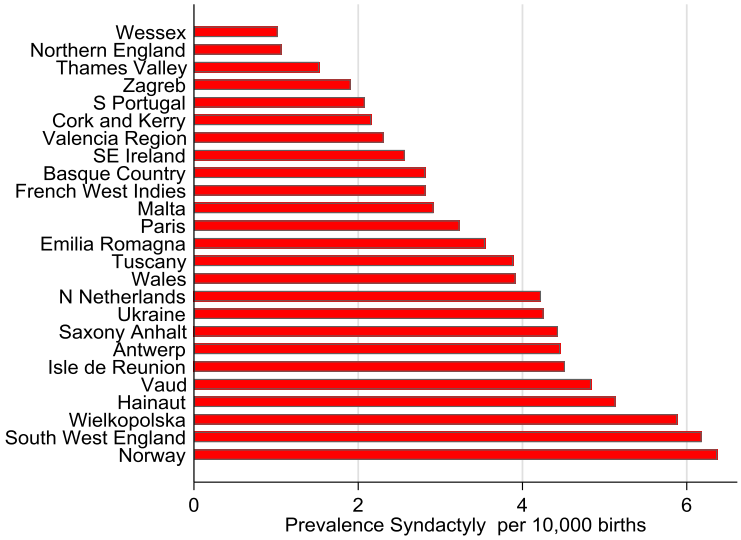

Fig. 19c: Syndactyly – Ten-years prevalence (2008-2017).

In conclusion, the decreasing trend is probably due to reduced over-reporting of minor anomaly cases in registries with previously high prevalence.

Vascular disruption anomalies

This subgroup includes all anomalies where the aetiology is thought to be vascular disruption. Anomalies included are small intestinal atresia, gastroschisis, limb reduction defects, amniotic bands, hydranencephaly and Moebius syndrome.

As in the previous reports on the period 2006-2015 [7] and 2007-2016 [2], the prevalence of vascular disruption anomalies is still decreasing. Between 2007 and 2016, its prevalence is estimated to have decreased by -2.1% (95% CI: -3.2%; -0.9%) on the pan-European level (Fig. 20a)

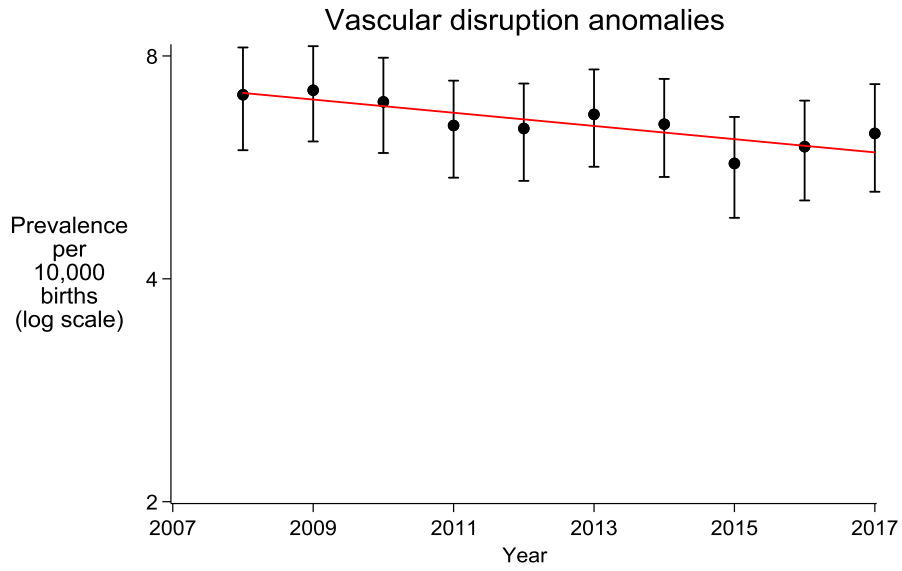

Fig. 20a: Vascular disruption anomalies - Prevalence and 95% CIs (2008-2017).

In four individual registries, the prevalence also decreased significantly during the same period (Northern England, Thames Valley and Wielkopolska and Antwerp)

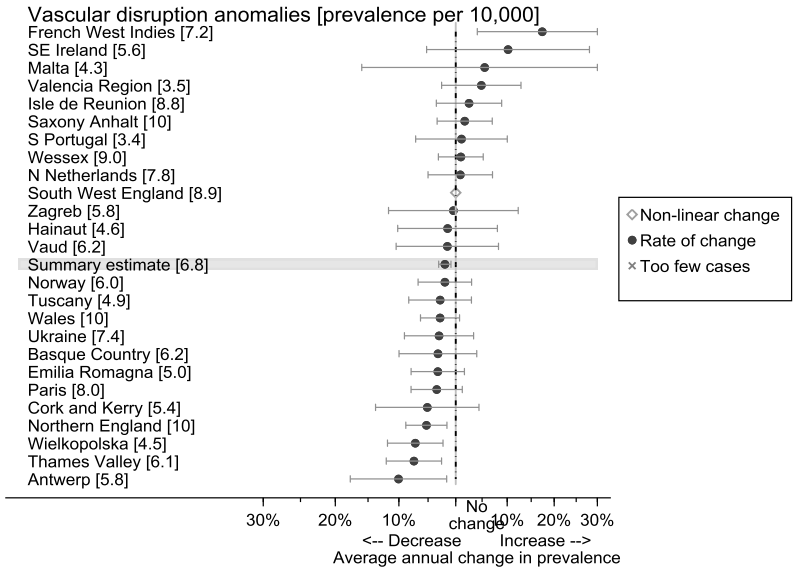

Fig. 20b: Vascular disruption anomalies - Estimated annual percentage change in the prevalence and 95% CIs (2008-2017).

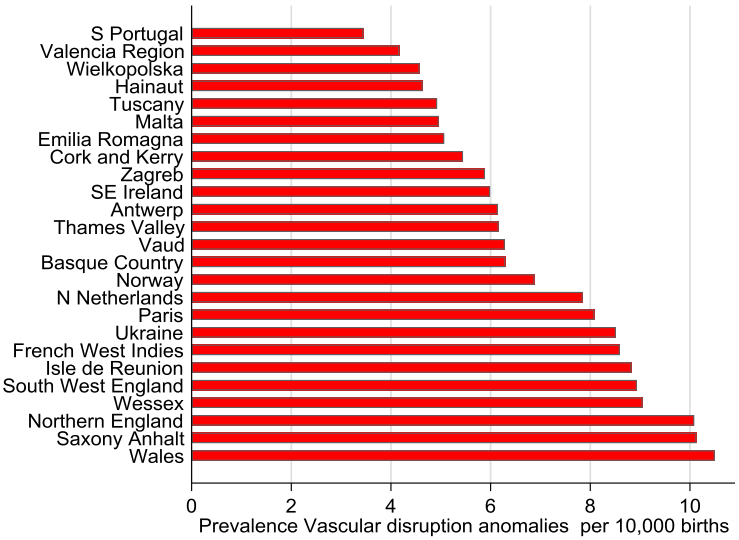

Fig. 20c: Vascular disruption anomalies – Ten-years prevalence (2008-2017).

In conclusion, the decreasing trend in gastroschisis described above might contribute to the observed decrease in prevalence of the vascular disruption anomalies subgroup. There is an ongoing EUROCAT study investigating this group of anomalies in depth.

5 Clusters

5.1 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.

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 occurring 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.

5.2 Cluster analysis 2013-2017

Fourteen registries fulfilled the criteria to be included in the cluster analysis reported here (see Appendix A). A total of 16 clusters were identified in 11 registries (see Table 1 on page 57). The English registries and the Zagreb registry were not included, as explained in Section 3.2 of this report.

Reports on the investigation into the clusters were received from six registries. Only the conclusions on the thirteen clusters investigated are detailed in the following section.

5.3 Investigations into specific clusters by the registries

Encephalocele

The cluster in Brittany covers conceptions between May and June 2015, and was described already in last year's report [2]. As stated previously, the five cases are not clustered near each other within the region. They come from five different hospitals, located in four remote cities in four different departments. Among the five cases, no common factor was identified from the registry database and no local context can explain the cluster. There was no local awareness of the cluster before it was found by central statistical monitoring. No further etiological investigation is planned at present as there is no hypothesis and it is not a continuing nor spatialized cluster so far. Sante Publique France was notified about this cluster.

Anomaly Subgroup: **Encephalocele**
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: 0.309 p value: 0.008
Start date: 23/05/2015
End date: 15/06/2015

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.

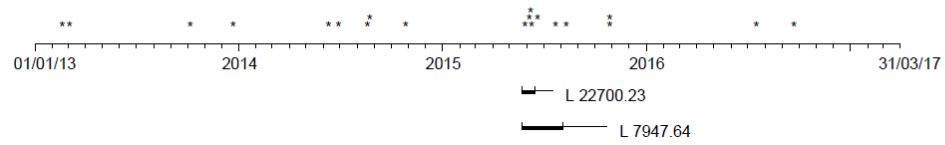

Fig. 21: Cluster of Encephalocele detected in Brittany.

Severe microcephaly

The cluster of severe microcephaly was detected in French West Indies. The cluster is likely to be associated with the occurrence of Zika virus in 2016. Seven out of the 15 cases of microcephaly included in the cluster had also lissencephaly, which is also associated with Zika virus exposure in utero.

Anomaly Subgroup: **Microcephaly**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2013 and 31/03/2017
Most significant cluster
Number of cases: 15 Expected number of cases: 2.833 p value: <0.001
Start date: 07/01/2016
End date: 23/06/2016

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.

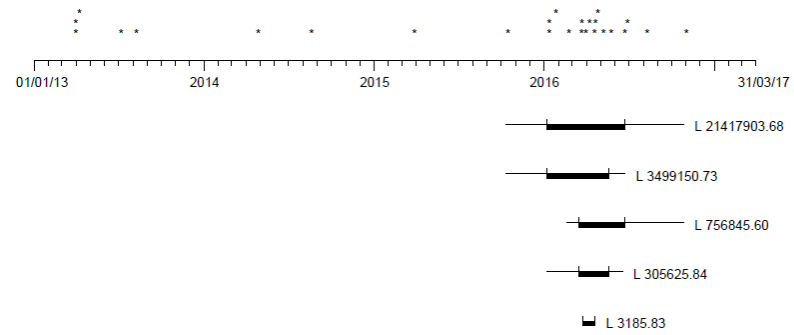

Fig. 22: Cluster of Microcephaly detected in French West Indies.

Ventricular septal defect (VSD)

The cluster was detected in Wales, UK. VSD may be an isolated cardiac defect or reported and coded together with more severe cardiac defects. After exclusion of cases of severe CHD, the cluster disappeared. This means that there was no cluster of isolated VSD in Wales.

Anomaly Subgroup: **Ventricular septal defect**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2013 and 31/03/2017
Most significant cluster
Number of cases: 28 Expected number of cases: 10.06 p value: 0.042
Start date: 11/08/2015
End date: 14/09/2015

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.

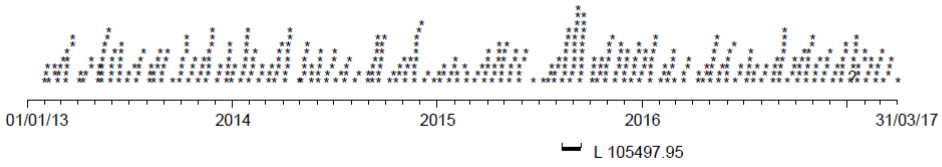

Fig. 23: Cluster of VSD detected in Wales.

Atrial Septal Defect (ASD)

The cluster was detected in Tuscany, Italy. The registry confirmed the cases, but it considers that the increase in the number of cases is explained by a change in ascertainment that occurred over time due to the appointment of a new paediatrician in one of the reporting units. No action is necessary.

Anomaly Subgroup: **Atrial septal defect**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2013 and 31/03/2017
Most significant cluster
Number of cases: 54 Expected number of cases: 22.27 p value: <0.001
Start date: 13/07/2016
End date: 04/03/2017

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.

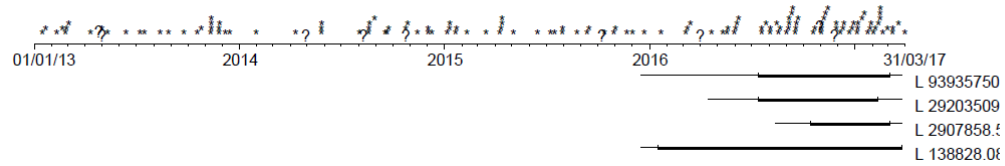

Fig. 24: Cluster of ASD detected in Tuscany.

Ano-rectal atresia and stenosis

The clusters were detected in the registries of Brittany, France and South Portugal.

In Brittany all 8 cases included in the largest cluster were confirmed. The registry did not identify any common factor in the available variables in the database. Sante Publique France was notified about this cluster.

Anomaly Subgroup: **Ano-rectal atresia and stenosis**
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: 0.271 p value: 0.013
Start date: 16/08/2016
End date: 22/08/2016

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.

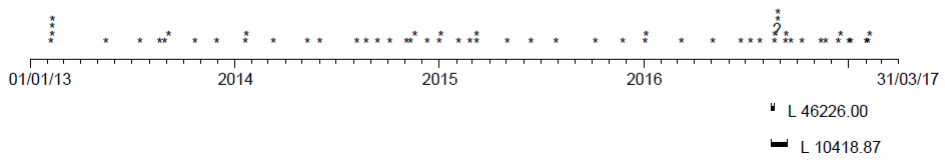

Fig. 25: Cluster of Ano-rectal atresia and stenosis detected in Brittany.

Congenital hydronephrosis

The cluster was detected in the registry of Brittany. The registry explained that a change in coding practice after 2016 might explain the very large cluster in time observed in 2017. Further surveillance will help to confirm this hypothesis.

Anomaly Subgroup: **Congenital hydronephrosis**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2013 and 31/03/2017
Most significant cluster
Number of cases: 50 Expected number of cases: 22.88 p value: <0.001
Start date: 27/06/2016
End date: 07/02/2017

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.

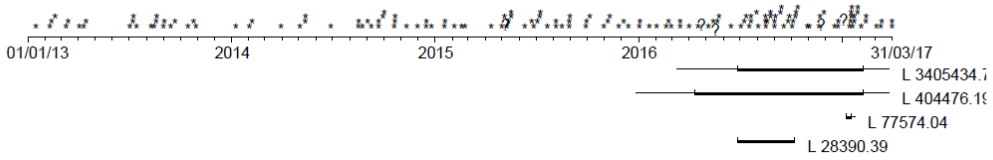

Fig. 26: Cluster of congenital hydronephrosis detected in Brittany.

Bladder exstrophy and / or epispadias

The cluster was detected in the registry of Wales, UK. The cluster was described already in last year's report. According to the registry this cluster of five cases can be explained: When the cluster is broken down, there is one complex case, two cases of isolated bladder exstrophy and two cases of epispadia. The registry notes that there is no spatial relationship and that bladder exstrophy is a very different anomaly to epispadias. Therefore, the registry plans no further action.

Anomaly Subgroup: **Bladder exstrophy and/or epispadia**
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: 0.348 p value: 0.010
Start date: 25/12/2015
End date: 23/01/2016

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.

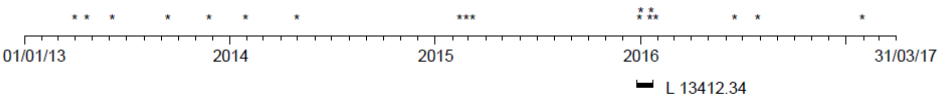

Fig. 27: Cluster of Bladder exstrophy and / or epispadias detected in Wales.

Hypospadias

Two clusters were detected in the registry of Northern Netherlands, and Wielkopolska.

In the registry of Northern Netherlands the cluster occurred in a two-day period. EUROCAT records gestational age in completed weeks, therefore the estimated date of conception may vary up to 6 days, so the detection of the cluster may be an artefact of the methodology.

Anomaly Subgroup: **Hypospadias**
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: 0.193 p value: <0.001
Start date: 09/03/2016
End date: 10/03/2016

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.

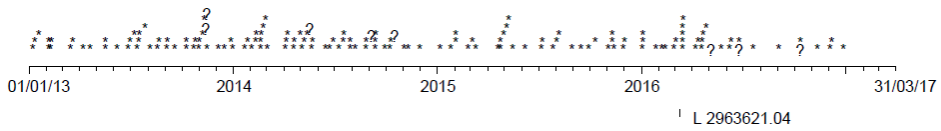

Fig. 28: Cluster of Hypospadias detected in Northern Netherlands

Similarly, in Wielkopolska the cluster cases were confirmed, but they all occurred on the same day, so the detection of the cluster may be an artefact of the methodology.

Anomaly Subgroup: **Hypospadias**
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: 0.179 p value: <0.001
Start date: 07/08/2015
End date: 07/08/2015

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.

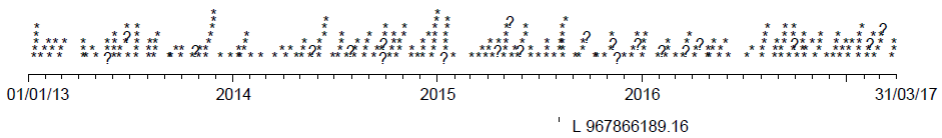

Fig. 29: Cluster of Hypospadias detected in Wielkopolska.

Turner syndrome

The cluster was detected in the registry of Emilia Romagna, Italy. The increase in cases with Turner syndrome could be due to increased prenatal diagnosis of Turner syndrome in more recent years. The cluster requires a further period of surveillance before a decision is made to investigate further.

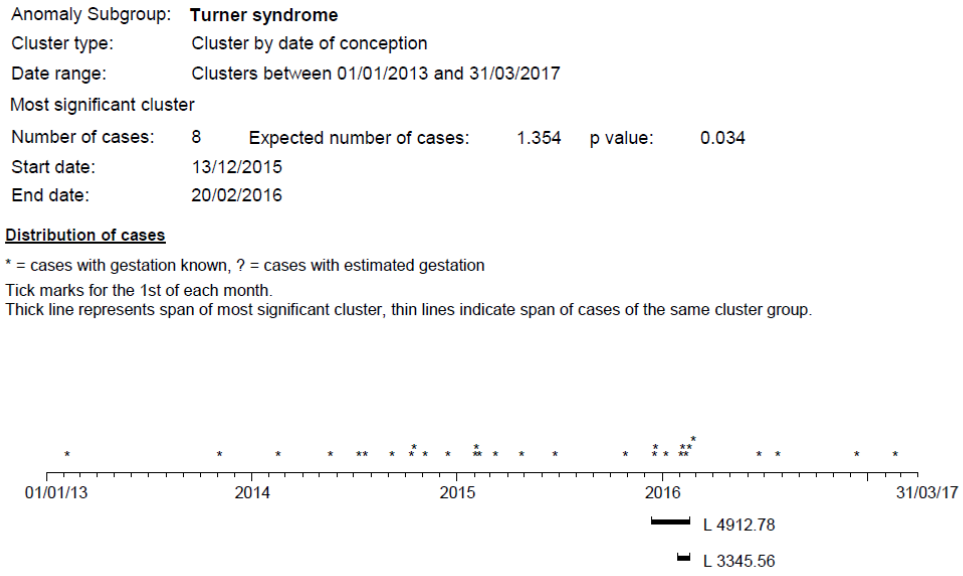

Fig. 30: Cluster of Turner syndrome detected in Emilia Romagna.

Table 1: Details of the 21 clusters detected in the 2013-2017 monitoring 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
Neural tube defects	Hainaut (BE)	No report received	5	0.47	28	25	0.049
Encephalocele	Brittany (FR)	Excess of cases confirmed	5	0.31	20	23	0.008
Severe microcephaly	French West Indies (FR)	Excess of cases confirmed	15	2.83	26	168	< 0.001
Ventricular septal defect (VSD)	Wales (UK)	No report received	28	10.06	446	34	0.042
Atrial septal defect (ASD)	Tuscany (Italy)	Data quality issues*	54	22.27	147	234	< 0.001
Tetralogy of Fallot	Hainaut (BE)	No report received	7	1.77	9	304	0.021
Total anomalous pulm. ven. return	Wales (UK)	No report received	5	0.56	14	61	0.032
Cystic adenomatous malf. Of the lung	Paris (France)	No report received	5	0.45	17	40	0.022
Ano-rectal atresia and stenosis	Brittany (FR)	Excess of cases confirmed	5	0.27	60	6	0.013
	South Portugal	No report received	5	0.27	13	31	< 0.001
Congenital hydronephrosis	Brittany (France)	Data quality issues*	50	22.88	157	225	< 0.001
Bladder exstrophy	Wales (UK)	Data quality issues*	5	0.35	18	29	0.01
Hypospadias	Northern Netherlands	Methodology**	5	0.19	150	2	< 0.001
	Wielkopolska (Poland)	Methodology**	5	0.18	277	1	< 0.001
Syndactyly	Cork and Kerry (Ireland)	No report received	5	0.57	10	90	0.016
Turner syndrome	Emilia Romagna (Italy)	Excess of cases confirmed	8	1.35	30	69	0.034

*****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.

6 Surveillance of multiple congenital anomalies

6.1 Introduction

Surveillance of multiple congenital anomaly (MCA) cases is considered to be more sensitive for detecting new teratogens than surveillance of all or isolated CA cases since many known human teratogens are associated with a spectrum of birth defects rather than single defects [21, 22, 23, 24, 25]. As multiple congenital anomalies are rare and specific combinations of anomalies are very rare, the surveillance needs to be done using the pan-European data and not individual EUROCAT registry data. The main aim is to detect new associations/combinations of anomalies, detect increasing trends of overall or specific combinations of multiple anomalies and detect other changes in the overall multiple congenital anomaly population.

The first step in the surveillance is correct case classification. The EUROCAT multiple congenital anomaly algorithm has been developed in collaboration between EUROCAT Central Registry and the Coding and Classification Committee and continuously improved since 2004. The aim of the algorithm is to classify congenital anomaly cases into aetiological groups: chromosomal anomalies, genetic syndromes, teratogenic syndromes, isolated anomalies and potential multiple congenital anomalies. Papers published in 2011 and 2014 describe the methodology and results of the first 2 years of data [26, 27].

The computer algorithm allocates 90% of all EUROCAT cases into a classification group. Approx. 10% of cases are potential multiple cases and these cases are reviewed by three EUROCAT geneticists to reach agreement for classification as true multiple congenital anomaly cases or allocation to another group. A web-based system for review of cases has been developed, which allows easy and fast review of many cases and transfer of the final decision back to the central database. If two geneticists agree on a case classification, this will be the final decision. If all three geneticists disagree or one of them classify the case for query, the moderator takes the final decision.

In 2019, cases from 2008-2016 from 32 full member registries covering 6,599,765 births have been reported and were ready for analysis. The total number of cases included were 123,566 cases (one or more major congenital anomalies).

6.2 Statistical methodology

Sixty-one anomaly subgroups were used in the analysis (Appendix F); 58 specific congenital anomalies and three more general congenital anomaly subgroups (Neural Tube Defects (NTD), All CHD and Severe CHD). From the data set of 8805 cases with a multiple anomaly for each pair of anomalies considered, the following table (Table 2) was calculated.

Table 2. Illustrative table of the categorisation of cases according to anomalies

	Number of Cases with Anomaly A	**Number of Cases without Anomaly A**
Number of Cases with Anomaly B	Nab	Nob
Number of Cases without Anomaly B	Nao	Noo

The odds of a case having anomaly B given that it had anomaly A relative to the odds of a case having anomaly B given that it did not have anomaly A was calculated for each anomaly pair and the associated P value calculated using a two-sided Fisher's exact test. (note that the OR for anomaly A given anomaly B is identical to the OR for anomaly B given anomaly A – so only one test was performed for each anomaly pair).

Anomalies that were part of a sequence (secondary anomalies) were excluded (examples: club foot is a known sequalae of spina bifida, lung hypoplasia is secondary to diaphragmatic hernia [23]). Anomalies included in the larger group of same organ system anomalies were also excluded (for instance VSD and any other cardiac anomaly). Known associations (e.g. VACTERL, OEIS) were included in the multiple anomaly group.

Multiple testing procedures were carried out using the Benjamini-Hochberg procedure to control the false discovery rate (FDR). This gave a corrected overall p-value to determine statistical significance and thus adjusted p-values were calculated. Pairs of anomalies with adjusted p-values < 0.05 were examined further. Cases with missing or indeterminate sex were excluded and the analysis was repeated for males and females separately.

The whole analysis was then repeated on the population of all anomaly cases (n=123,566) not just those with multiple anomalies. This meant in practice that Nab (in figure 1) remained the same, but all other numbers were much greater due to the inclusion of cases with only one anomaly. The estimated relative odds were therefore inflated, the p values reduced and hence only pairs of anomalies with adjusted p-values < 0.01 were examined further.

Similar analyses were carried out for cases with three anomalies (three-way comparisons) using logistic regression models. Each anomaly in turn was regressed on two other anomalies and the interaction term provided an estimate of the odds ratio for all three anomalies given any of the other two anomalies. As before, sets of anomalies known to be related were excluded, and identical multiple testing procedures were carried out on the p-values to obtain adjusted p-values.

6.3 Results

There were 8,804 cases with two or more anomalies, 9 cases for Malta (birth year 2011) were excluded. This left 8,795 cases with multiple anomalies (4920 males, 3353 females, 33 indeterminate sex and 489 with missing sex). The population controls dataset comprised 123,021 cases (69,098 males, 49,378 females and 4,545 with indeterminate sex or missing). After excluding those combinations of anomalies known to be related there were 1386 possible combinations of two anomalies and 18,427 combinations of three anomalies.

There were no combinations of three anomaly subgroups that were statistically significantly more likely to occur than any of the combinations of two anomalies.

A total of 26 statistically significant positive associations between two EUROCAT subgroups were found. The list was reviewed by the Coding Committee in June and the conclusions are presented in Table 3. Sixteen associations were selected for literature reviews and tasks were distributed to Coding Committee members.

Table 3. Conclusion reached by the Coding Committee in June 2019

Conclusion	Number of significant associations
Known association	5
Sequence	3
Coding issues	1
Overlap of subgroups	1
Literature review	16

6.4 Results of the literature reviews

The 16 literature reviews were done by the EUROCAT Coding and Classification Committee members over the summer 2019 and 13 discussed in detail at the coding meeting in October. One was not done and two had overlap with other subgroups. Seven associations were previously described in the literature and for six associations there were no or very limited published data.

Four associations with anal atresia:

- *Anal atresia – posterior urethral valves*
- *Anal atresia – bilateral renal agenesis*
- *Anal atresia – multicystic renal dysplasia*
- *Anal atresia – limb reduction defects*

The cases with anal atresia and posterior urethral valves were mainly Prune-Belly sequence (11 of 14 cases). The aetiology of Prune-Belly is unknown. The three other associations were part of the VACTERL association, which is well described in the literature.

Three associations with bladder exstrophy/epispadias

- *Omphalocele – bladder exstrophy/epispadias*
- *Anal atresia – bladder exstrophy/epispadias*
- *Spina bifida – bladder exstrophy/epispadias*

These three associations were all part of the OEIS complex (omphalocele-exstrophy-imperforate anus-spinal defects), so the associations found are expected. The subgroup for bladder exstrophy/epispadias (ICD10 Q640 and Q641) also includes cases with cloacal exstrophy, ICD/BPA code Q6410. Table 4 describes the number of cases reported with cloacal exstrophy in combination with the other anomalies included in OEIS complex.

Table 4: Numbers of cases with any of omphalocele, bladder exstrophy/epispadias, anal atresia or spina bifida subgroups and number with Q6410 (Cloacal exstrophy of urinary bladder)

	Anomalies	Total number of cases	Number of cases with Q6410
All 4 anomalies	Omphalocele & Bladder exstrophy & Anal atresia & Spina bifida	11	6
3 Anomalies only	Omphalocele & Bladder exstrophy & Anal atresia	15	1
	Omphalocele & Bladder exstrophy & Spina bifida	4	0
	Omphalocele & Anal atresia & Spina bifida	3	0
	Bladder exstrophy & Anal atresia & Spina bifida	2	1
2 Anomalies only	Omphalocele & Spina bifida	27	0
	Omphalocele & Anal atresia	24	0
	Anal atresia & Spina bifida	17	0
	Bladder exstrophy & Anal atresia	15	5
	Omphalocele & Bladder exstrophy	13	4
	Bladder exstrophy & Spina bifida	7	2

Potential new associations

There were six associations of anomalies that seemed not to be described in the literature or only published as isolated case reports. These associations will be investigated in more detail over the next year in collaboration with the local registries. The registries will be asked to check for the most recent genetic testing, that may have been performed after the case was notified to the registry.

6.5 Discussion

The method of analysis differs significantly from the CODA approach recommended by Benjamin et al [28] to analyse clustering of birth defects. The CODA approach is based on a modified observed-to-expected (O/E) ratio of co-occurring birth defects that was originally proposed by Khoury, James, and Erickson [29]. The method adjusts for the tendency of birth defects to cluster with other major malformations. The data analysed in this study firstly only compared the occurrence of a pair of anomalies within cases that had at least two anomalies and therefore the tendency to cluster did not need to be adjusted for in the first set of analyses. The second analyses did compare pairs of anomalies to cases with only one anomaly and as expected the odds ratios were higher. However, when adjusted p values were calculated a similar set of anomalies were statistically significant at $p<0.01$.

A second important difference between the method adopted by Benjamin et al [28], was that in this analysis we excluded any cases with known chromosome or genetic anomalies. We wanted to identify any new anomaly clusters – we were not interested in identifying known syndromes or associations.

6.6 Conclusions

Most associations found by the statistical analysis were known associations described in the literature. There were six potential new associations. The individual cases in these associations will be reviewed in detail together with the local registries and these associations will be followed in the coming years.

Appendix A: EUROCAT full member registries inclusion list

	Pan-Europe trends		Cluster monitoring	
	Included in analysis	**Investigation report**	**Included in analysis**	**Investigation report**
Austria, Styria	No, as data transmission >1 year late			
Belgium, Antwerp	✓	✓	No data for 2017	
Belgium, Hainaut	✓	X	✓	X
Croatia, Zagreb	✓	X	Annual birth population changes	
Denmark, Odense	No, as data transmission >1 year late			
France, Auvergne	No, as data transmission >1 year late			
France, Brittany	No, as data for 7 years only		✓	✓
France, French West Indies	✓	X	✓	X
France, Paris	✓	X	✓	X
France, Reunion	✓	✓	✓	—
Germany, Mainz	No, as data transmission >1 year late			
Germany, Saxony Anhalt	✓	✓	✓	—
Hungary	No, as collaboration agreement not signed			
Ireland, Cork & Kerry	✓	X	✓	—
Ireland, Dublin	No, as data transmission >1 year late			
Ireland, South East	✓	✓	No data for 2017	
Italy, Emilia Romagna	✓	✓	✓	✓
Italy, Tuscany	✓	✓	✓	✓
Malta	✓	X	No data for 2017	
Netherlands, Northern	✓	✓	✓	✓
Norway	✓	X	No data for 2017	
Poland, Wielkopolska	✓	✓	✓	✓
Portugal, South	✓	X	✓	X
Spain, Basque Country	✓	✓	No data for 2017	
Spain, Navarra	No, as collaboration agreement not signed			
Spain, Valencian Region	✓	✓	No data for 2017	
Switzerland, Vaud	✓	✓	✓	—
Ukraine	✓	✓	No data for 2017	
UK, E Midlands & S Yorkshire	No, data missing for >1 year			
UK, Northern England	✓	✓	Analysis not done (see chapter 3.2)	
UK, South West England	✓	✓	Analysis not done (see chapter 3.2)	
UK, Thames Valley	✓	✓	Analysis not done (see chapter 3.2)	
UK, Wales	✓	—	✓	—
UK, Wessex	✓	✓	Analysis not done (see chapter 3.2)	

✓ Investigation report received

X No Investigation report received

— Investigation report not required as no pan-Europe trends or clusters detected in registry

Appendix B: Congenital anomaly subgroup inclusion list

The EUROCAT congenital anomaly subgroups are defined in EUROCAT Guide 1.4, Chapter 3.3 [30], and are analysed in the following ways:

- Prevalence by outcome of pregnancy, by registry and year. *All cases* and *All cases excluding genetic conditions*[1] are included in the analysis and the results are published in the prevalence tables available on the EUROCAT website (http://www.eurocat-network.eu/accessprevalencedata/prevalencetables). 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	✓	✓	✓

[1] Genetic syndromes/ microdeletions, skeletal dysplasias chromosomal anomalies

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	✓	✓	✓
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**

Appendix C: 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 2017 births included in monitoring in March 2019. More details on the statistical methods for monitoring given here can be found in the EUROCAT Statistical Monitoring Protocol [8].

Statistical methods for the detection of trends within each 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 two-year interval) is less than 5 and if the observed number of cases in any one year (or two-year interval) is less than 2.

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

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 squared 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 2013-2017 [8]. The analysis for detecting clusters is run on 75 EUROCAT subgroups of congenital anomalies (see Appendix B). Excluded from the analysis are 17 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 (2013-2017) is needed.
2. Clusters are reported when they are within or overlapping the last two years (2016-2017) 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. 2017.

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

Appendix D: Summary of a registry's preliminary investigation protocol for identified ten-year trends and clusters

Investigation protocols and templates, provided to make the reporting process consistent between registries, are described in full in the EUROCAT Statistical Monitoring Protocol [8]. Using the templates, registries were asked to include the following in their investigation report:

Ten-year trends:

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

Investigations into significant increasing trends are classified as follows:

A: Changes in case ascertainment (data quality)

B: Changes in local or central registry methods e.g. definitions and inclusion criteria

C: Changes in diagnostic methods

D: Trend confirmed, due to known demographic changes

E: Trend confirmed, investigation on-going

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

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

H: No report or clear interpretation of preliminary investigations sent

Some trends can be explained by a combination of the classification categories e.g. A/B. The first classification category is considered the principal one, so trends classified as A/B are counted in the A category.

Clusters:

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

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

Cluster investigations can be classified as follows:

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

Appendix E: Summary of increasing and decreasing ten-year trends detected in the pan-European analysis

			95% CI limits	
Group of anomalies	**Trend's direction**	**Annual % change**	**lower**	**upper**
Hypoplastic right heart	increasing	8.1	3.8	12.7
Coarctation of aorta	increasing	1.8	0.2	3.6
Multicystic renal dysplasia	increasing	2.3	0.7	3.9
Congenital hydronephrosis	increasing	2.6	1.7	3.5
Clubfoot - talipes equinovarus	increasing	2.0	1.0	3.0
Laterality anomalies	increasing	3.1	0.8	5.5
Situs inversus	increasing	3.8	0.1	7.5
All non-chromosomal anomalies	decreasing	-0.9	-1.1	-0.7
Hydrocephaly	decreasing	-3.4	-4.8	-2.1
Severe microcephaly	decreasing	-2.3	-4.4	-0.2
Congenital heart defects	decreasing	-0.7	-1.1	-0.3
Pulmonary valve stenosis	decreasing	-3.5	-5.0	-2.0
Aortic valve atresia/stenosis	decreasing	-2.8	-5.4	-0.2
Patent ductus arteriosus	decreasing	-5.5	-7.2	-3.7
Gastroschisis	decreasing	-3.0	-4.8	-1.1
Hypospadias	decreasing	-1.3	-2.1	-0.6
Syndactyly	decreasing	-1.9	-3.4	-0.3
Vascular disruption anomalies	decreasing	-2.1	-3.2	-0.9

Appendix F: Anomaly subgroups included in the surveillance of multiple anomalies

Subgroups and diagnoses within sub-group	EUROCAT al codes included in analysis
Nervous system	
Neural Tube Defects	al3
Anencephalus and similar	al4
Encephalocele	al5
Spina Bifida	al6
Hydrocephalus	al7
Microcephaly	al8
Arhinencephaly/holoprosencephaly	al9
Eye	
Anophthalmos/micropthalmos	al11
Congenital cataract	al13
Congenital glaucoma	al14
Ear, face and neck	
Anotia	al16
Congenitalheart defects	
Congenital heart defects	al17
Severe CHD	al97
Common arterial truncus	al18
Transposition of great vessels	al19
Single ventricle	al20
Ventricular septal defect	al21
Atrial septal defect	al22
Atrioventricular septal defect	al23
Tetralogy of Fallot	al24
Tricuspid atresia and stenosis	al25
Ebstein's anomaly	al26
Pulmonary valve stenosis	al27
Pulmonary valve atresia	al28
Aortic valve atresia/stenosis	al29
Hypoplastic left heart	al30
Hypoplastic right heart	al31
Coarctation of aorta	al32
Total anomalous pulm venous return	al33
PDA as only CHD in term infants (GA≥37 wks)	al100
Respiratory	
Choanal atresia	al35
Cystic adenomatous malf of lung	al36

Oro-facialclefts	
Cleft lip with or without palate	al102
Cleft palate	al103
Digestive system	
Oesophageal atresia with or without tracheo-oesophageal fistula	al41
Duodenal atresia or stenosis	al42
Atresia or stenosis of other parts of small intestine	al43
Ano-rectal atresia and stenosis	al44
Hirschsprung's disease	al45
Atresia of bile ducts	al46
Annular pancreas	al47
Diaphragmatic hernia	al48
Abdominalwall defects	
Gastroschisis	al50
Omphalocele	al51
Urinary	
Bilateral renal agenesis including Potter syndrome	al53
Renal dysplasia	al54
Congenital hydronephrosis	al55
Bladder exstrophy and/or epispadia	al56
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Genital	
Hypospadias	al59
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Limb reduction	al62
Club foot - talipes equinovarus	al66
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Syndactyly	al69
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