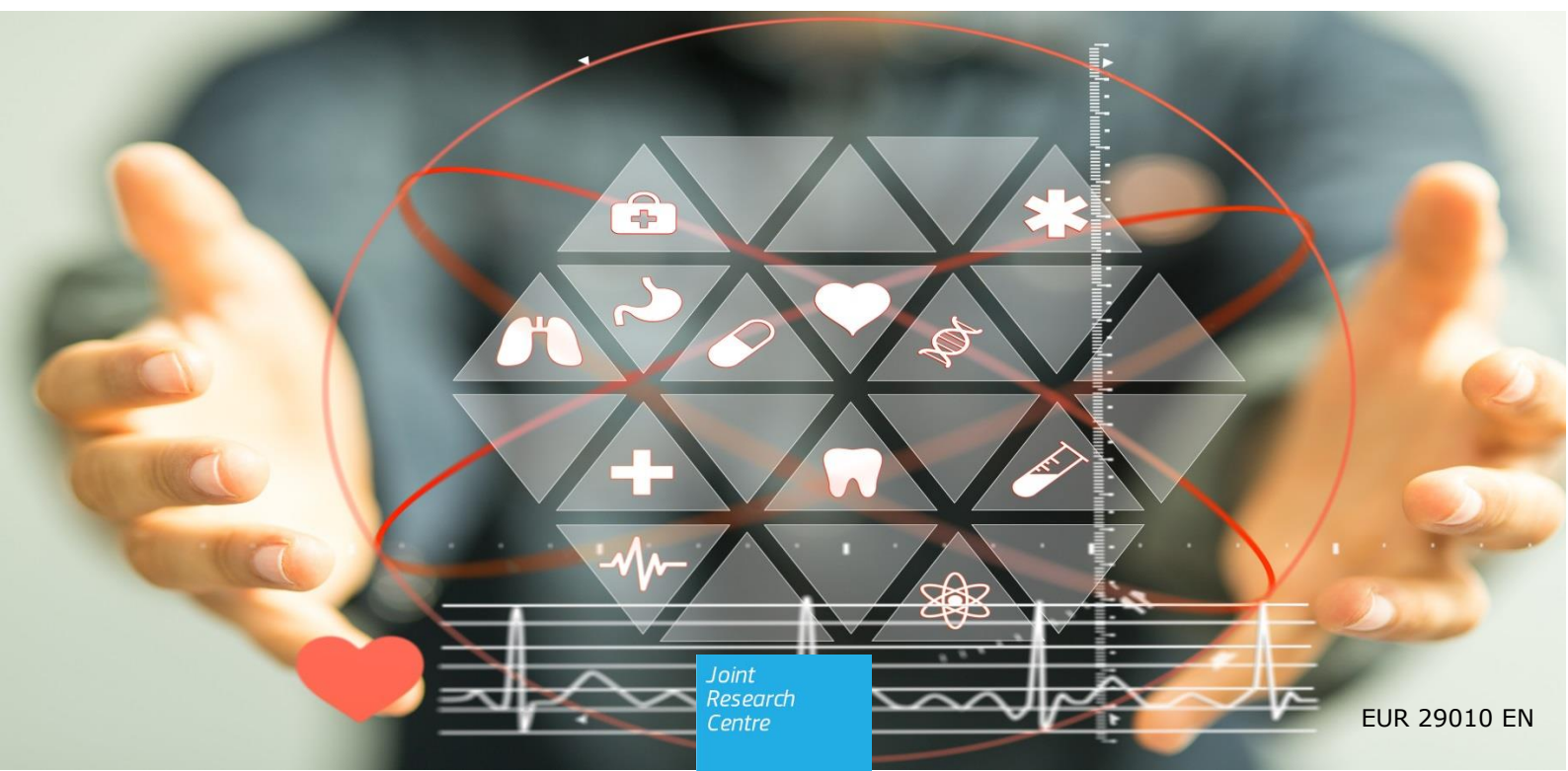# JRC TECHNICAL REPORTS

European Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2006 - 2015)

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European Monitoring of Congenital Anomalies

JRC-EUROCAT Report on Statistical Monitoring of Congenital Anomalies (2006 – 2015)

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Acknowledgements

Abstract

Worldwide, congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood. Of the 5.2 million births in the European Union (EU) each year, approximately 104,000 (2.5%) will be born with congenital anomalies. 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 82 anomaly subgroups. Statistical monitoring relates to two of EUROCAT's objectives: to provide essential epidemiologic information on congenital anomalies in Europe and to co-ordinate the detection of, and response to, clusters and early warning of teratogenic exposures. The results of the statistical monitoring are the basis for possible further investigations at the local registry level.

In 2015 the Central Registry of EUROCAT was transferred from the University of Ulster to the JRC, and became part of the European Platform on Rare Diseases Registration. This is the first time the statistical monitoring has been performed by the JRC-EUROCAT Central registry.

We report here the results of the monitoring performed on data for the birth years 2006-2015. Cases of congenital anomaly among livebirths, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly (TOPFA) at any gestation were included. We report both the statistical results and, where available, the outcome of preliminary investigations conducted by registries. For each anomaly, the trends in prevalence in each registry are shown and in addition the overall pan-European prevalence by single year of birth. Some congenital anomalies take a while to be reported; therefore the prevalence in the latest data is often underreported. Presenting the overall pan-European prevalence by single year allows for the influence of the most recent data (2015) to be evaluated.

Key findings

Trends in Congenital Anomalies excluding genetic conditions

• **Neural tube defects (NTDs)** are largely preventable by consuming sufficient folic acid immediately before pregnancy and in early pregnancy. Many countries outside Europe have introduced the fortification of flour with folic acid and have subsequently observed decreases in the prevalence of NTDs. NTDs have not decreased in prevalence over the last 10 years in Europe. Prevalence rates were 10.10 per 10,000 births in 2006-2007 and 10.27 per 10,000 births in 2014-2015 indicating the current plan of encouraging women to take folic acid supplements before becoming pregnant may not be effective and preventive measures should be strengthened in Europe.

• **Severe Microcephaly** is monitored closely by EUROCAT due to the recent Zika virus outbreaks in South America that started in 2015. The first births in Europe after possible exposure to Zika virus occurred in 2016. The reported prevalence of microcephaly across Europe is so heterogeneous due to the rarity of the anomaly and discrepant diagnostic criteria, that the observed decreasing trend in the 2006-2015 Pan European analysis cannot be interpreted to reflect a true decreasing trend. Furthermore, this heterogeneity means that analyses performed in future years are unlikely to detect any increase in prevalence of microcephaly due to the Zika virus [1].

• A decreasing trend in **anophthalmos/microphthalmos** was detected. Prevalence decreased on average by 5.3% per year from 1.14 per 10,000 births in 2006-2007 to 0.82 per 10,000 births in 2014-2015. In the Ukraine, which has the highest prevalence of anophthalmos/ microphthalmos among all EUROCAT registries, the decrease in prevalence was above 20%, which is a good sign given that this anomaly is known to be sensitive to radiation exposure.

• Increasing trends in both **Tricuspid atresia/stenosis** and **Hypoplastic right heart** were found. Tricuspid atresia/stenosis increased on average by 5.3% per year from 0.54 per 10,000 births in 2006-2007 to 0.84 per 10,000 births in 2014-2015, while Hypoplastic right heart increased on average by 6.8% per year from 0.44 per 10,000 births in 2006-2007 to 0.63 per 10,000 births in 2014-2015. These trends will be followed in the next years.

• A decreasing trend in **Hypoplastic left heart** was found, with a decline in prevalence by 2.3% per year, from 2.74 per 10,000 births in 2006-2007 to 2.43 per 10,000 births in 2014-2015. This is a very severe anomaly with a high termination rate. It is a new decreasing trend not observed in the earlier pan-Europe analyses and will be followed.

• A decreasing trend in **Gastroschisis** was found in the pan-Europe analysis. The prevalence decreased on average by 2.6% per year from 3.11 per 10,000 births in 2006-2007 to 2.75 per 10,000 births in 2014-2015. This anomaly is associated with low maternal age [2, 3]. Over the past 20 years prevalence has increased mainly in UK and some areas outside Europe [4, 5, 6, 7].

• Increasing trends were found for **Congenital hydronephrosis** and **Multicystic renal dysplasia**. For Congenital hydronephrosis prevalence increased on average by 2.8% per year rising from 9.88 per 10,000 births in 2006-2007 to 12.12 per 10,000 births in 2014-2015. Multicystic renal dysplasia increased on average by 1.8% per year rising from 3.85 per 10,000 births in 2006-2007 to 4.37 per 10,000 births in 2014-2015. For both anomalies, the increase might be explained by more frequent use of prenatal ultrasound screening in Europe.

• An increasing pan-European trend in **Club foot (talipes equinovarus)** was detected. The prevalence of club foot increased on average by 3.4% per year, rising from 8.78 per 10,000 births in 2006-2007 to 11.44 per 10,000 births in 2014-2015. The increasing trend has already been reported in the 2011 and 2012 EUROCAT Statistical Monitoring Reports and will be further investigated.

 • Over the last 10 years, there has been an increase in prevalence of the laterality anomalies (on average 2.7% per year), from 1.41 per 10,000 births in 2006-2007 to 1.86 per 10,000 births in 2014-2015. This is the first time EUROCAT have presented this data and the increasing trend will be followed.

• There is a continuous decrease in the prevalence of Valproate syndrome in Europe. The prevalence of this teratogenic syndrome decreased by 27.5% per year, from 0.13 per 10,000 births in 2006-2007 to 0.02 per 10,000 births in 2014-2015.

Clusters

Six clusters in time were detected in individual registry populations which, following preliminary investigations, could not be explained by information held within the registries:

Congenital Cataract in Tuscany (14 cases observed versus six expected); Ventricular Septal Defect (VSD) in Tuscany (five cases observed versus one expected); Ebstein's anomaly in Emilia Romagna (five cases observed versus one expected); Hypoplastic right heart in Isle de Reunion (five cases observed versus one expected); Hypospadias in Tuscany (six cases observed versus one expected); Skeletal dysplasias in Wales (18 cases observed versus seven expected).

The registries involved will continue to monitor these anomalies.

1   Introduction

The EUROCAT network was established in 1979 and from its beginning received European Commission's funding for the central coordinating activities. The EUROCAT Central Registry was based in Brussels from 1979 to 1999 and then moved to London, and from 2000 to 2014 it was hosted by the University of Ulster.

In 2015 the Central Registry was transferred to the European Commission's Joint Research Centre (JRC) in Ispra, Italy to provide a sustainable solution for the continuation of EUROCAT activities, to secure the results of previous work and to keep the network functioning [8]. EUROCAT is now an integral part of the European Platform on Rare Diseases Registration being developed at the JRC in close collaboration with the EC's Directorate for Health and Food Safety (DG SANTE).

The transfer of the EUROCAT Central Registry to the JRC was an intensive and complex process. During this period it was essential to accomplish numerous legal procedures, including the data protection notification, and to create new structures such as secure IT systems for data transfer and data management. Hence, the last two years have been devoted to the transfer of the Central Registry, and the annual statistical monitoring of trends and clusters, which is an important part of EUROCAT's work, was not performed. The new JRC-EUROCAT Central Registry is now fully operational and is ready to effectively continue the surveillance of congenital anomalies in Europe.

In the annual statistical monitoring, both trends and clusters in time are analysed in order to detect signals of new or increasing teratogenic exposures and monitor progress in the prevention of congenital anomalies. Total prevalence rates of 81 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 gestation are monitored and reported. A full protocol is published online, providing details of the rationale and methodology of the statistical monitoring, including changes to methodology and software [9].

A pan-Europe 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. Preliminary investigations of trends and clusters have been performed at local and central registry level, and summaries of these investigations are reported. The last statistical monitoring report was published on the data from birth years 2003-2012 [10]. In this report, we have only been able to report limited comparisons with trends and clusters identified in previous years.

The statistical monitoring provides a methodology for the surveillance of congenital anomalies as well as a tool for the harmonisation of data collection by the EUROCAT registries. 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. Identifying trends and clusters can be spurious 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. The statistical monitoring that involves all the registries in the investigation at the local level of the results found by the Central Registry facilitates this data harmonisation and interpretation.

In 2015, Public Health England's National Congenital Anomaly and Rare Diseases Registration Service (NCARDRS) was established. This new system built on the work of the existing regional congenital anomaly registers which only covered 49% of the population. NCARDRS's aim is to provide a comprehensive registration service for all congenital anomalies and rare diseases diagnosed and treated in England. In the past two years, much has been achieved and national coverage is now in place [11]. However, inevitably during such a significant transition period, ascertainment levels have not yet reached the levels reported to EUROCAT prior to the transition. This must be kept in mind when reviewing the trends and clusters presented in this report from the English registers.

We report here the results of the statistical monitoring performed on births over the ten year period 2006-2015 on data from 22 EUROCAT registries to describe trends, and from 16 EUROCAT registries to detect recent clusters in time. The number of registries included in the analysis is slightly less than in previous years. Two full registries have not signed the JRC-EUROCAT collaboration agreement, which is the legal basis that allows the JRC-EUROCAT Central Registry to collect, manage and analyse the data from each registry member, whilst seven registries are more than one year behind in data transmission and are therefore not eligible to be included in the analysis. This also explains the population coverage decrease from the previous monitoring report, from about 6 million to 4.7 million in the present report.

2 Population and Monitoring Process

2.1 Registries included in the 2006-2015 trend analysis

At the time of statistical monitoring in spring 2017, there were 33 full member registries in EUROCAT (see Appendix A). Twenty-two full member registries met the inclusion criteria for the individual 10-year trend analysis, and 16 met the inclusion criteria for the cluster analysis (see Box 1).

Box 1. Registry inclusion/exclusion criteria for trend analysis

— Registries >1 year late with data transmission excluded from analysis

— Pan-Europe: Registries with 9 or 10 years of continuous data starting from 2006 included (i.e. 2006-2014 or 2006-2015)

— Individual registry analysis: Registries with 8 or 10 years of continuous data included (i.e. 2007-2014 or 2008-2015 or 2006-2015)

Denmark and Hungary did not sign the JRC-EUROCAT collaboration agreement and therefore did not send data to the Central Registry for the years 2013 - 2015. Styria, Auvergne, Paris, Dublin, Norway, Wielkopolska, and East Midlands & South Yorkshire were more than one year behind in data transmission. French West Indies and Brittany were excluded from the trend analysis having less than eight years of data in the monitoring time period.

All the other registries were included in the Pan-European trends analysis (see Appendix A). Considering that the last statistical monitoring report was published three years ago on the data from birth years 2003-2012, and that the number of registries included in the current analysis is slightly less than in previous years, a deviation from the protocol was done for Valencia Region, that had only eight years of continuous data.

2.2 Registries included in the 2015 cluster analysis

EUROCAT defines clusters as: 'An aggregation of cases of congenital anomaly in time and/or space which appears to be unusual'. Registries classified as "early response" i.e. registries that meet the EUROCAT data transmission deadline of the 15th February, with data for the most recent five years (2011-2015) were included in cluster monitoring (see Box 2). Five years is considered an optimal period for cluster monitoring as 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 [9].

Box 2. Registry inclusion criteria for cluster analysis

— Registries must have transmitted data for all years 2011-2015

— Registries must have transmitted full date of birth information

— Registries must have individual case data (i.e. full member registries only)

— Registries must have a stable birth population (annual birth population changes must be less than +/- 10%)

A total of 16 full member registries transmitted year 2015 data to the EUROCAT Central Registry in February 2017 (see Appendix A). All these registries were included in the cluster analysis.

Where registries do not meet the data transmission deadline, monitoring can be run locally to detect clusters and trends using software available in the EDMP. Pan-Europe monitoring can only be conducted centrally as it uses data from all the registries combined.

Registries are encouraged to use the EDMP statistical monitoring function in the periods between annual Statistical Monitoring to look for clusters or trends in more recent data.

2.3   What was monitored?

Cases included livebirths, stillbirths from 20 weeks gestational age and TOPFA at any gestation.

For the 23 registries included in the trend and/or cluster analysis in the period 2006-2015, 79.0% of cases were liveborn, 1.9% were stillborn and 19.1% were TOPFA. Type of birth was unrecorded for a small proportion of cases (0.04%) which are included in the monitoring to avoid missing a potential cluster or trend.

Statistical monitoring is conducted to detect changes in time within individual registries, and also to detect trends across all registries (pan-Europe trends). Seventy-nine EUROCAT congenital anomaly subgroups (non-genetic cases only) plus the three trisomy subgroups adjusted for maternal age and fetal survival to 20 weeks were included in both the pan-Europe and individual registry trend analyses (see Appendix B for the list of anomaly subgroups included). Trend tests were performed for the most recent ten years of data (or eight years if 10 years were unavailable) for every registry and for ten years of data at pan-European level.

Cluster analysis, which detects clusters or deficits occurring in the last two years (2014-2015) that are less than 18 months in length, was run on 75 EUROCAT subgroups of congenital anomalies (see Appendix B for the for the list of anomaly subgroups included and Appendix C for summary of statistical methods).

The following analyses were carried out:

- Analysis of individual registry trends and pan-Europe trends for 22 registries covering 4.71 million births (2006-2015)

- Cluster analysis to detect unusual aggregations of cases in 16 registries covering 0.69 million births (2014-2015)

2.4   Investigation process

The results of the statistical monitoring were reviewed by the JRC-EUROCAT Management Committee (MC) in May 2017. Registries were asked to investigate clusters and 10-year trends detected in the monitoring. The MC selected congenital anomalies with significant increasing or decreasing trends for preliminary investigation using a predefined prioritisation protocol (see Figure 1). The anomalies were selected based on the pattern of the trend identified in the pan-Europe analysis.
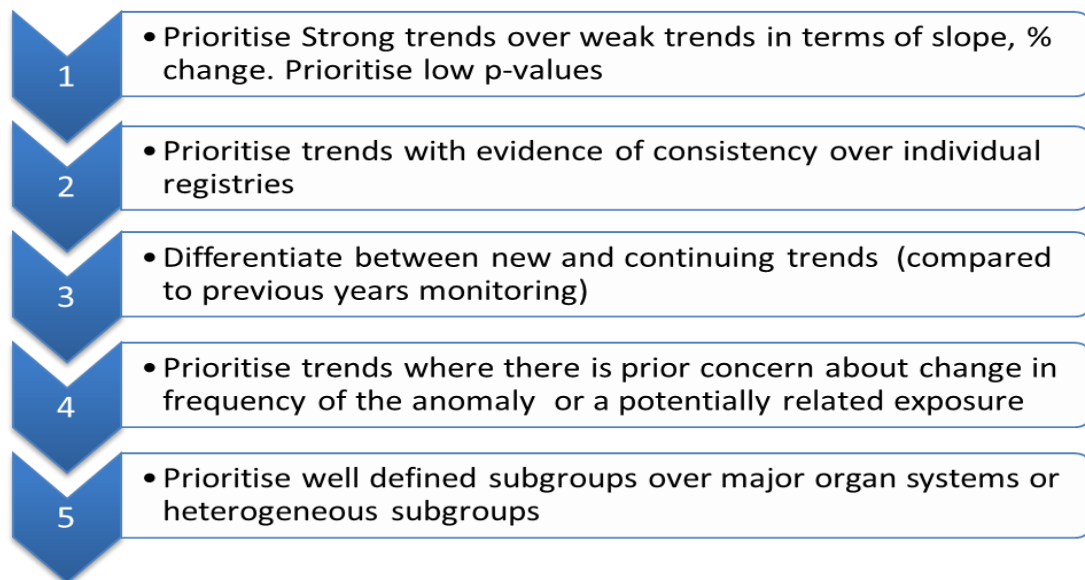

1 • Prioritise Strong trends over weak trends in terms of slope, % change. Prioritise low p-values

2 • Prioritise trends with evidence of consistency over individual registries

3 • Differentiate between new and continuing trends (compared to previous years monitoring)

4 • Prioritise trends where there is prior concern about change in frequency of the anomaly or a potentially related exposure

5 • Prioritise well defined subgroups over major organ systems or heterogeneous subgroups

Fig. 1: Prioritisation criteria for the investigation of ten year trends [4]

Each registry was sent the results of the trends and cluster analysis for their data. Each registry was asked to conduct preliminary investigations using standardised guidelines (see Appendix D). The significant increasing and decreasing trends selected for registry investigation are listed in Appendix E. Registries were also given the option to investigate and report on increasing and decreasing trends detected at local registry level only.

Registries reported their findings to the JRC-EUROCAT Central Registry using standard reporting templates [9]. 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.

Trends not prioritised for investigation are not discussed in this report but will be subject to further monitoring.

The preliminary reports of the trend and cluster investigations were reviewed by the JRC-EUROCAT MC. The individual registry preliminary investigation reports into identified trends and clusters are available on the membership-only section of the EUROCAT website.

2.5 Statistical software updates from the previous report

No changes were made to the software for this year's statistical monitoring. For a full description of statistical software updates in previous years, please see the EUROCAT Statistical Monitoring Protocol 2012 at the EUROCAT website [9].

3 Pan-European Trends

3.1 Overview

The pan-Europe trend analysis was carried out for the time period 2006-2015. The analysis included data from 22 full member registries. Registries that were more than one year late with data transmission were excluded from analysis. Some of the larger registries (e.g. Hungary, East Midlands & South Yorkshire, Paris) were not included this year for various reasons which are outlined in Appendix A.

The trend analysis included 79 subgroups, plus the three trisomy subgroups adjusted for maternal age and fetal survival to 20 weeks. The analysis identified increasing trends for eight congenital anomaly subgroups and decreasing trends for 18 subgroups (Figure 2 and Appendix E).

The **increasing trends** in the pan-Europe analysis were identified for the following subgroups: Ventricular Septal Defect (VSD); Atrial Septal Defect (ASD); Tricuspid atresia and stenosis; Hypoplastic right heart; Multicystic renal dysplasia; Congenital hydronephrosis; Club foot – talipes equinovarus; Laterality Anomalies.

The **decreasing trends** in the pan-Europe analysis were identified for the following anomaly subgroups: Hydrocephaly; Severe microcephaly; Anophthalmos/microphthalmos; Pulmonary valve stenosis; Hypoplastic left heart; Patent ductus arteriosus (PDA); Cleft lip with or without palate; Cleft palate; Gastroschisis; Hypospadias; Syndactyly; Vascular disruption anomalies; Congenital constriction bands; Conjoined twins; Valproate syndrome; Genetic syndromes + microdeletions; Klinefelter syndrome; Down syndrome age adjusted.

This section provides details of the result, and the investigations and the interpretation of pan-Europe trends for specific anomaly subgroups (for the summary of significant 10-year increasing and decreasing trends detected in the pan-Europe analysis 2015 see also Appendix E).

For each congenital anomaly subgroup, the trends in prevalence in each registry are shown and the overall pan-European prevalence by single year of birth. This enables the influence of the most recent data (2015) to be evaluated as some anomalies are reported late, which can result in the prevalence in the latest data being underreported.
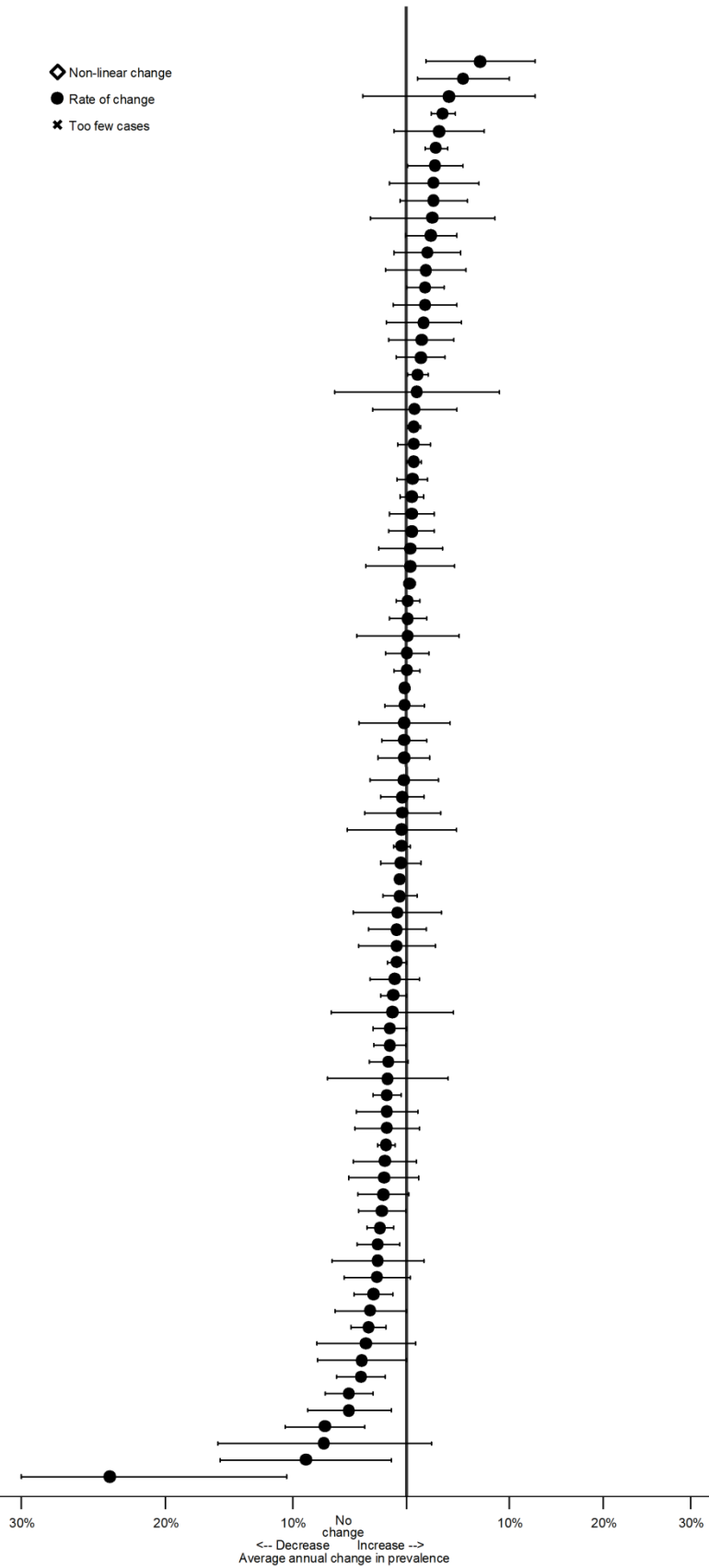
Fig. 2: Estimated average percentage change in the prevalence and 95% confidence intervals (pan-Europe analysis 2006-2015)

3.2   Increasing trends identified at the pan-Europe level

Ventricular septal defect (VSD)

VSD is a defect in the ventricular septum of the heart. The size of the opening can vary from a few millimetres to large holes leaving most of the ventricular septum absent, creating one common ventricle. VSD usually does not cause symptoms at birth and often manifests a couple of weeks after birth. The defect may be associated with Down syndrome and other genetic syndromes, but most infants with VSD have no associated anomalies.

The pan-Europe analysis showed that the prevalence of VSD is increasing on average 0.7% per year (Fig. 3a). Six registries (Basque Country, Zagreb, Antwerp, Isle de Reunion, Ukraine and Tuscany) had statistically significant increasing trends and five registries had significantly decreasing trends (South Portugal, Northern England, Wales, Vaud and Cork and Kerry). Figure 3b shows the annual prevalence and indicates that the increase in prevalence may be an underestimate, because the prevalence in 2015 is likely to be underreported.

VSD is diagnosed by a murmur and confirmed on an echocardiography. In regions with routine paediatric examinations of all newborns and with easy access to echocardiography, the number of infants diagnosed with small defects will be high. It is expected that all VSDs requiring surgery will be diagnosed in all areas. Therefore, the observed increasing trend may not be a true increase but due to the heterogeneity of the diagnosis.
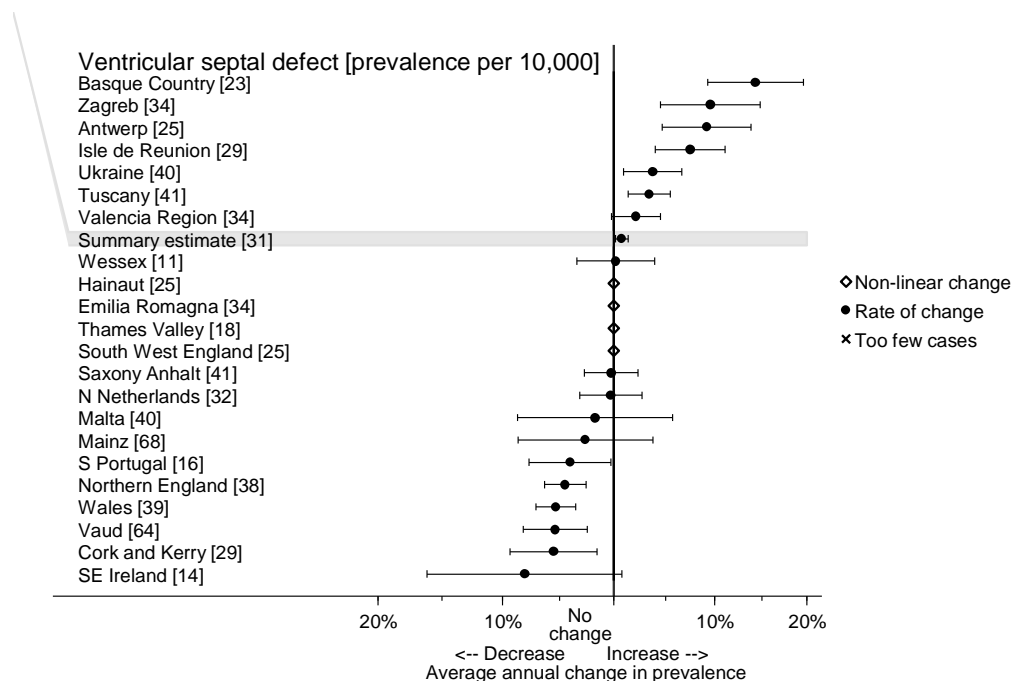

Fig. 3a: Ventricular Septal Defect (VSD) - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Fig. 3b: Ventricular Septal Defect (VSD) - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Atrial septal defect (ASD)

ASD is a defect in the atrial septum, causing a flow of blood between the left and right atrium. ASD may not produce noticeable signs or symptoms in infancy or childhood and may therefore be diagnosed late, especially if the defect is small. In fetal life there is a natural flow of blood from the right to the left atrium. After birth this defect will close, but sometimes remain open for weeks or months as a persistent foramen ovale. EUROCAT recommends reporting only defects in the atrial septum where six months after birth there is flow across the defect.

The pan-Europe analysis showed that the prevalence of ASD is increasing on average 1.0% per year (Fig. 4a). Three registries had statistically significant increasing trends (South Portugal, Saxony-Anhalt and Tuscany), and three registries had significantly decreasing trends (Valencia Region, Northern England and Wales). The overall increasing trend appears to be influenced by the increases up until 2011 (Fig. 4b).

Fig. 4a: Atrial septal defect (ASD) - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
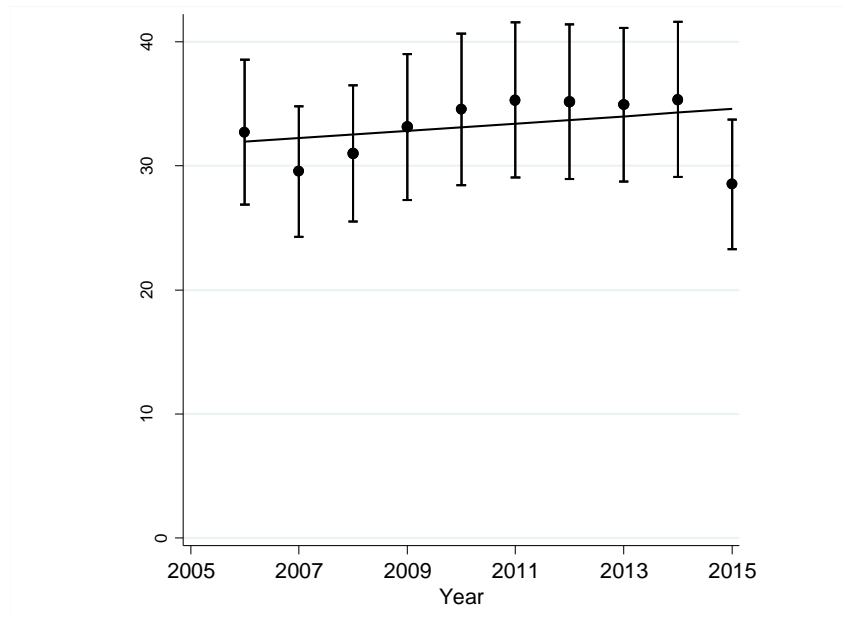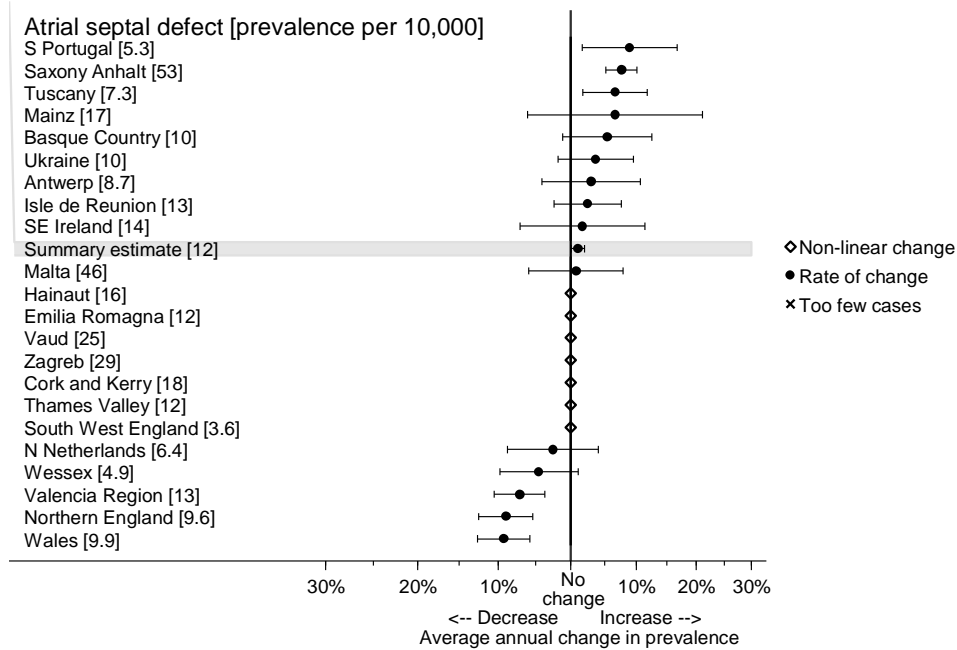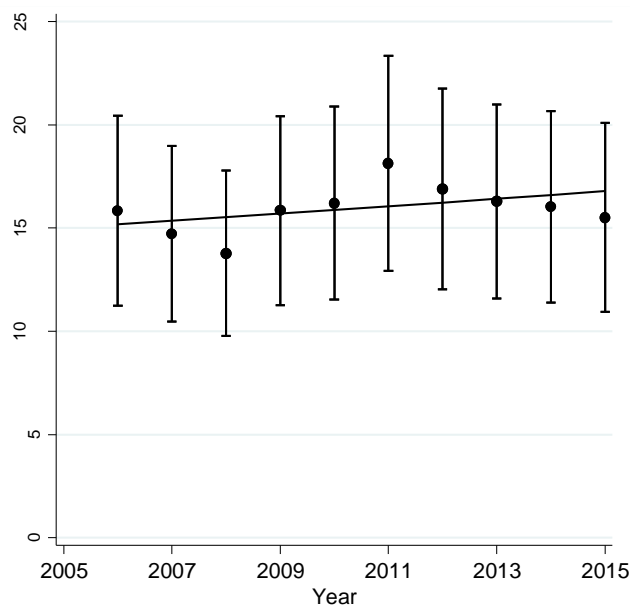

Fig. 4b: Atrial septal defect (ASD) - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

It is difficult, even using echocardiography, to discriminate between persistent foramen ovale and ASD. The growing use of echocardiography in neonatal intensive care may explain the rise in number of ASDs reported to EUROCAT. Due to the extreme heterogeneity in ascertainment of ASD between the registries, the changes in prevalence over the years should not be interpreted as a true trend. In the future, an additional analysis of the pan-European trend on cases with ASD that require surgery could be performed in order to be more consistent in the identification of a true trend. However, this will reduce the sample size as some registries do not report the surgery variable and some children may have surgery very late. Most surgeries are performed before the age of five years, but may also be performed later.

Tricuspid atresia and stenosis

Tricuspid atresia and stenosis is a severe congenital heart defect. It is usually associated with the underdevelopment of the right ventricle. The anomaly is so rare that only the pan-Europe trend can provide any information.

The pan-Europe analysis showed that the prevalence of Tricuspid atresia and stenosis is increasing on average 5.3% per year (Fig. 5). However, no significantly increasing trends were identified for any of the registries included in the pan-European trend analysis. Figure 5b indicates that the true increase in prevalence may be greater as the prevalence in 2015 is likely to be underreported. We do not know at present if the observed increase is due to a real increase in prevalence or because the reporting of this anomaly has increased due to the coding tips written by the Coding Committee in 2013 focusing on this anomaly. The trend will be followed and investigated in more detail.

Fig. 5a: Tricuspid atresia and stenosis - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

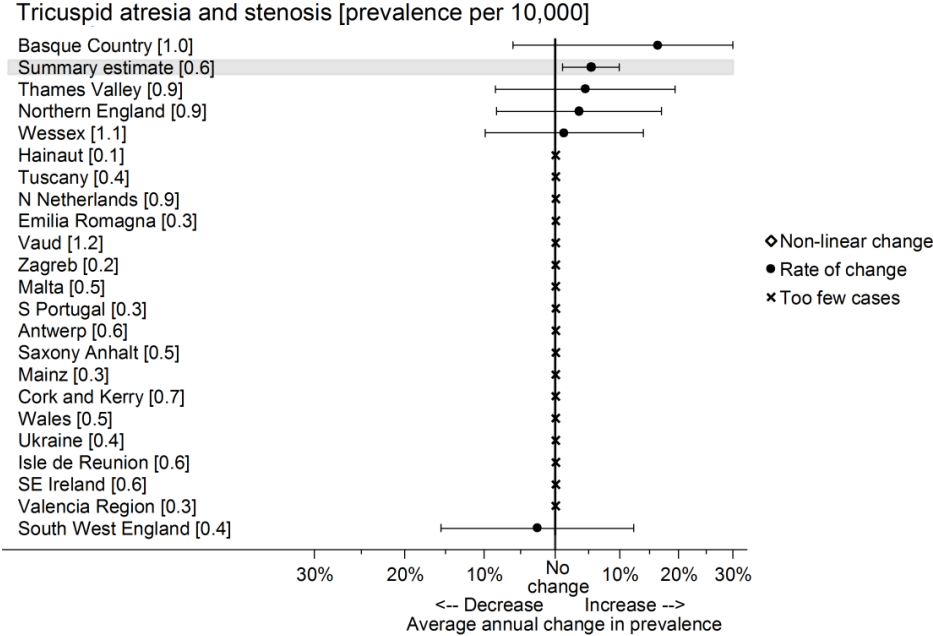

Fig. 5a: Tricuspid atresia and stenosis - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
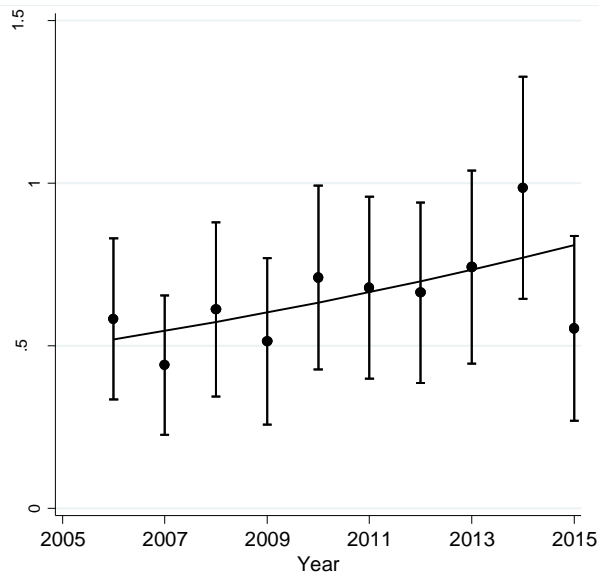
Fig. 5b: Tricuspid atresia and stenosis - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

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. The anomaly is so rare that only the pan-Europe trend can provide any information. The overall pan-European trend is increasing (on average 6.8% per year) and is significant (Fig. 6a and 6b), whilst no significantly increasing trends were identified for any of the registries. We do not know at present if the observed increase is due a real increase in prevalence or because the reporting of this anomaly has increased due to the coding tips written by the Coding Committee in 2013 focusing on this anomaly. The trend will be followed and investigated in more detail.
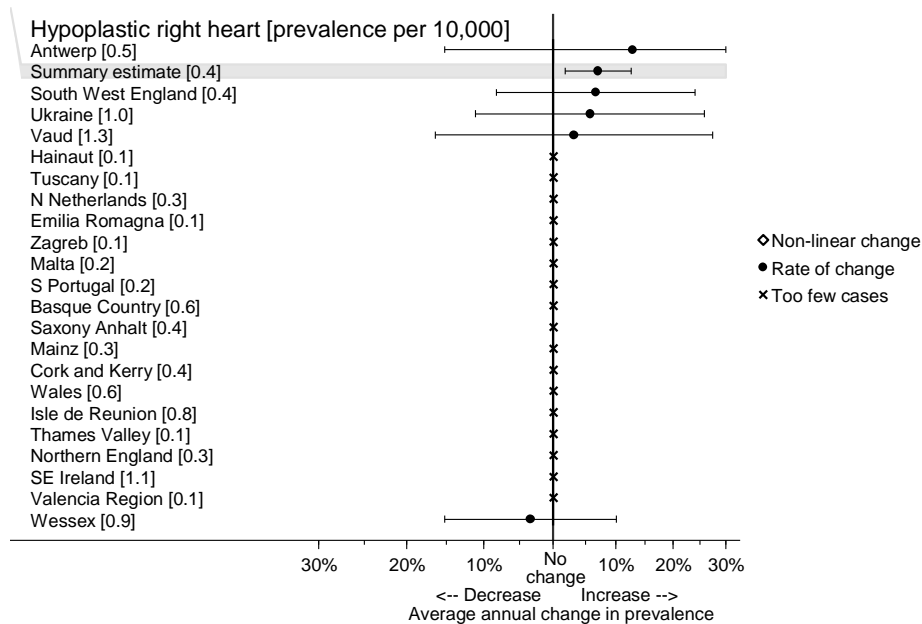

Fig. 6a: Hypoplastic right heart - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
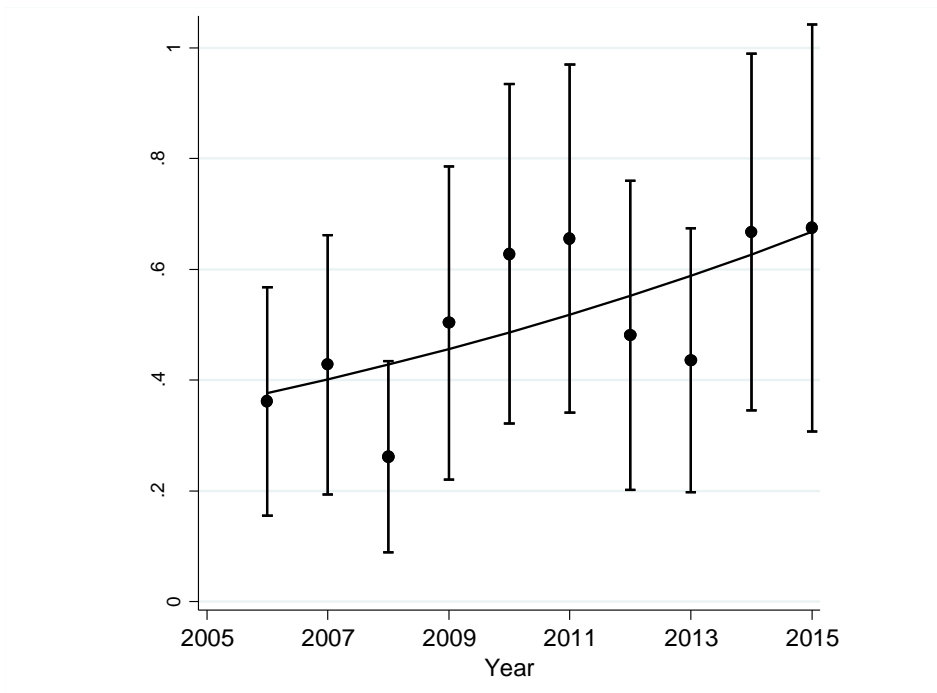
Fig. 6b: Hypoplastic right heart - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

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 renal pelvis is ≥ 10 mm after birth should be reported to EUROCAT. Hydronephrosis caused by vesico-ureteral reflux should not be reported to EUROCAT.

The pan-Europe analysis showed that the prevalence of congenital hydronephrosis is increasing on average by 2.8% per year (Fig. 7a). Twelve registries had increasing trends, six of them were significantly increasing: Antwerp, Basque Country, Emilia Romagna, Mainz, Thames Valley and Valencia Region, and Wales was significantly decreasing. Figure 7b indicates that the true increase in prevalence may be greater as the prevalence in 2015 is likely to be underreported. The increase might be explained by more frequent use of prenatal ultrasound screening in Europe.
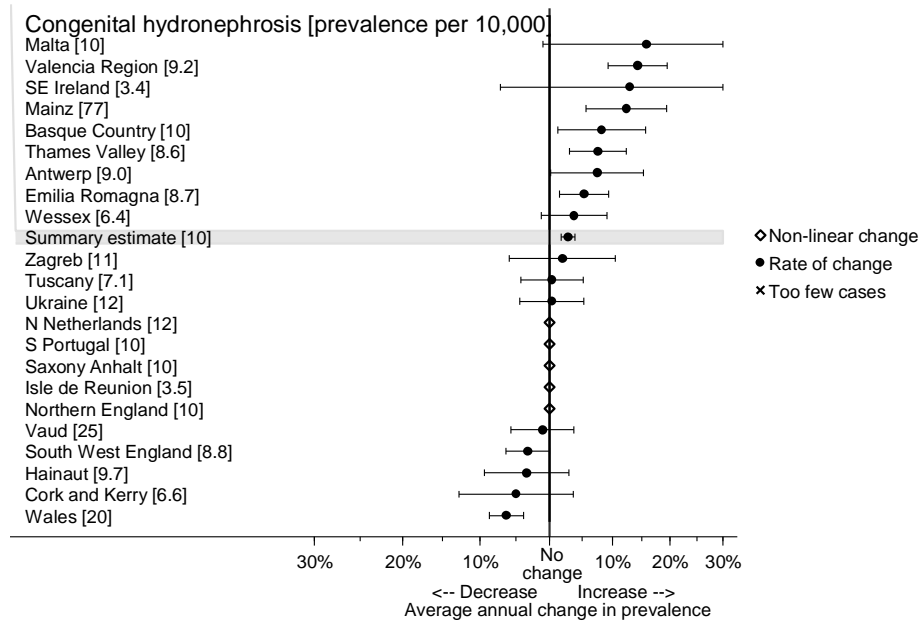
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Fig. 7a: Congenital hydronephrosis - Estimated average percentage change in the prevalence ad 95% confidence intervals for the registries included in the pan-Europe trend analysis.
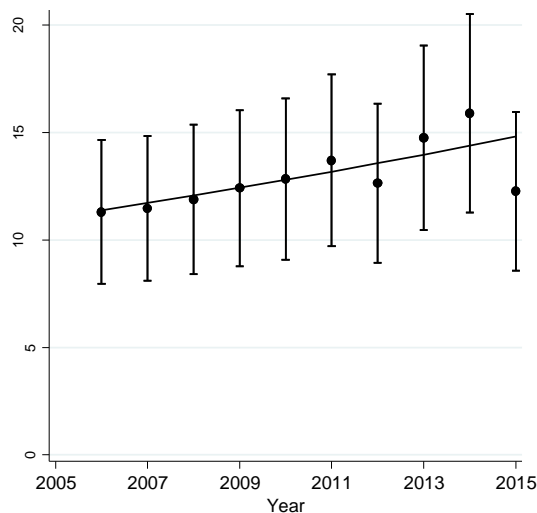

Fig. 7b: Congenital hydronephrosis - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Multicystic renal dysplasia

Bilateral multicystic renal dysplasia is usually lethal shortly after birth. Unilateral multicystic renal dysplasia is much more common, is asymptomatic and 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. The pan-Europe analysis showed that the prevalence of multicystic renal dysplasia is increasing on average by 1.8% per year (Fig. 8a and 8b). Seven registries had increasing trends of which only two (North Netherlands and Thames Valley) were significantly increasing, and three were significantly

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decreasing (Wessex, Saxony Anhalt, Hainaut). The increased pan-Europe trend might be explained by more frequent use of prenatal ultrasound screening in Europe.
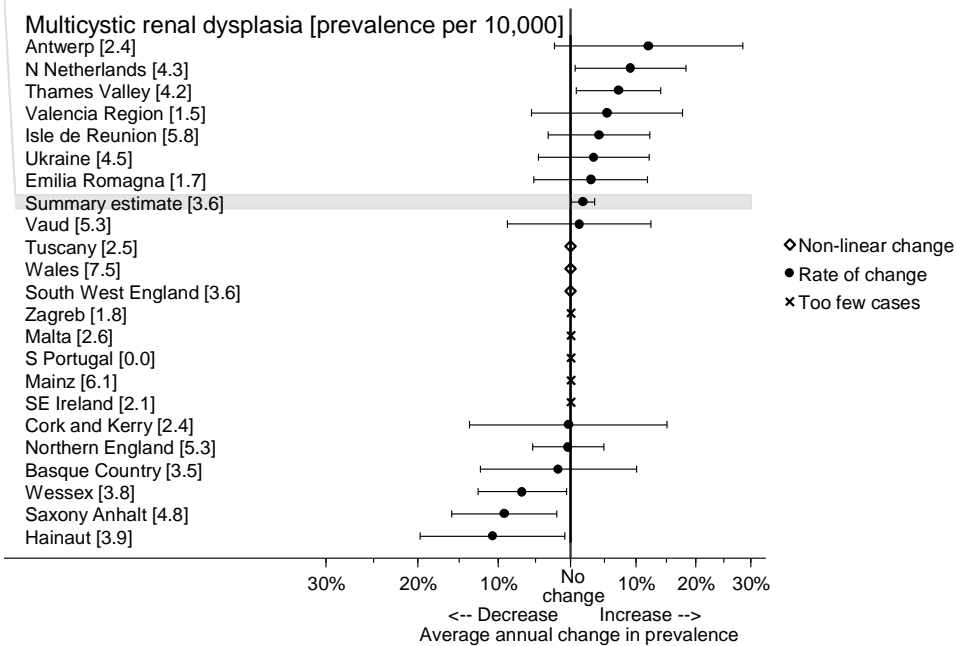

Fig. 8a: Multicystic renal dysplasia - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
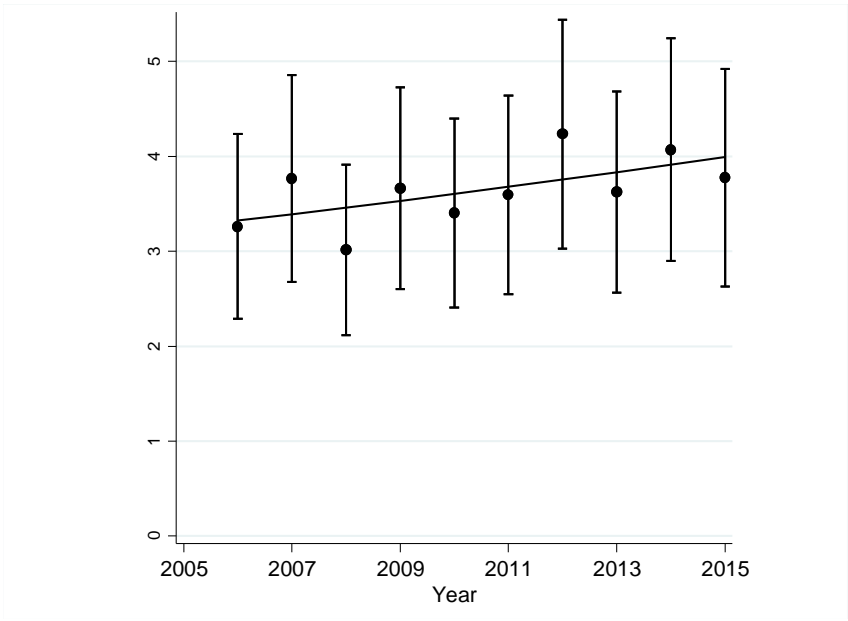

Fig. 8b: Multicystic renal dysplasia - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

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Club foot – talipes equinovarus

Club foot can be unilateral or bilateral and has a familial pattern of inheritance. Club foot cases requiring surgery or Ponseti treatment [12] should be reported to EUROCAT as a major congenital anomaly. If the club foot is of postural origin and not receiving treatment as mentioned, the anomaly should be classified as a minor anomaly.

The pan-Europe analysis showed that the prevalence of club foot is increasing on average by 3.4% per year. Six registries (Antwerp, Northern England, North Netherlands, Ukraine, Valencia Region, Vaud) had significantly increasing and three registries had significantly decreasing trends (South Portugal, Tuscany, Wales). (Fig. 9a) The significant increasing trend remains after the data from Northern England is removed. The increase in Northern England was due to a change in coding practice, however, there is no explanation of the increased trend in other registries for this anomaly. This increasing trend (Fig. 9b) has already been reported in the 2012 EUROCAT Statistical Monitoring Reports [10] and is being investigated.
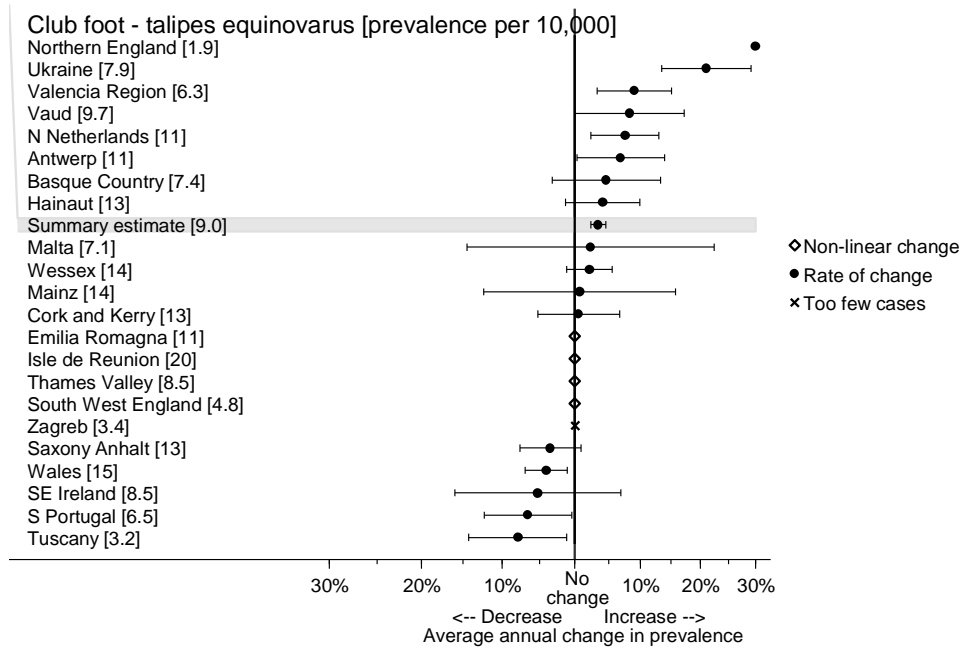

Fig. 9a: Club foot – talipes equinovarus - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
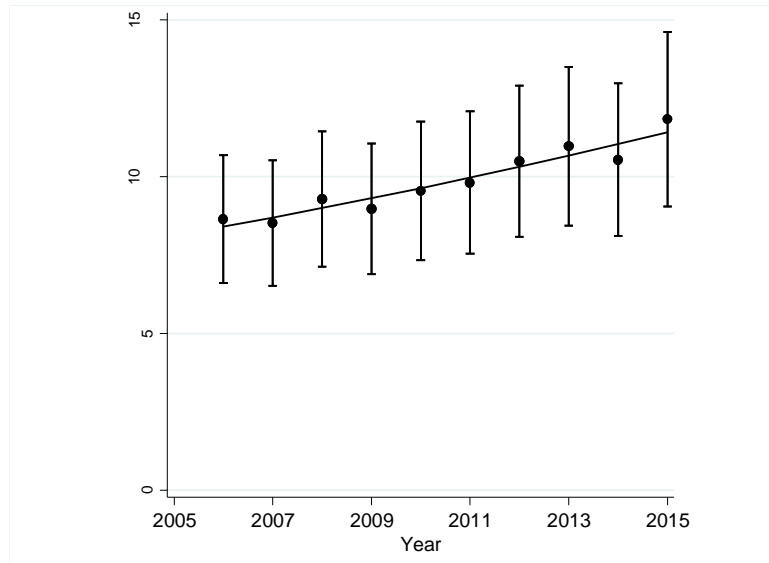
Fig. 9b: Club foot – talipes equinovarus - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Laterality Anomalies

This is a new subgroup of anomalies which includes atrial isomerisms, dextrocardia, bronchopulmonary isomerism, situs inversus and anomalies of spleen. The pan-Europe analysis showed that the prevalence of laterality anomalies is increasing on average by 2.7% per year. The increasing trend is significant only at the pan-Europe level, but 13 registries show not significant increasing trends (Fig. 10a). Figure 10b indicates that the true increase in prevalence may be greater as the prevalence in 2015 is likely to be underreported. The increasing trend will be followed as it is of interest because a potential association with maternal diabetes [13].
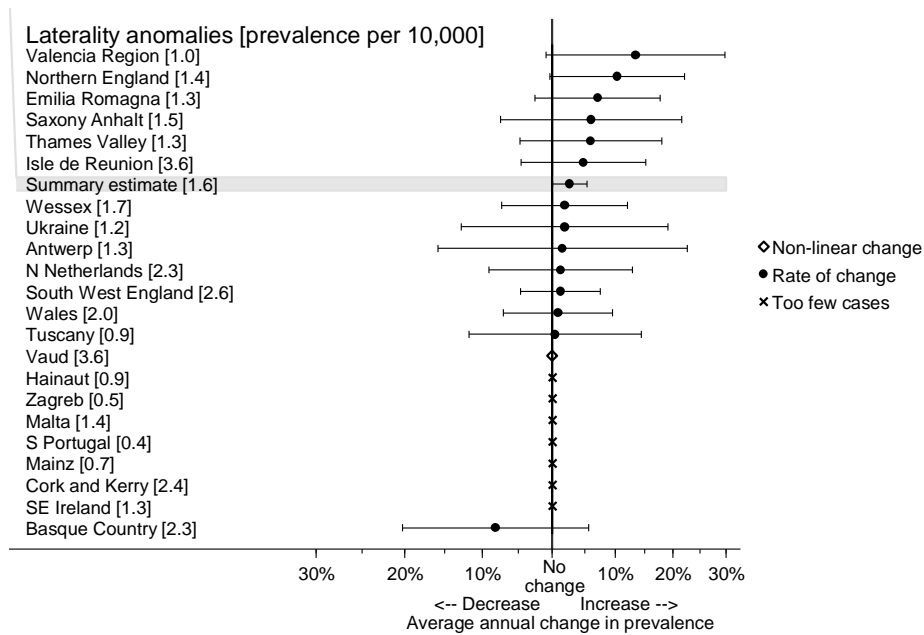

Fig. 10a: Laterality Anomalies – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
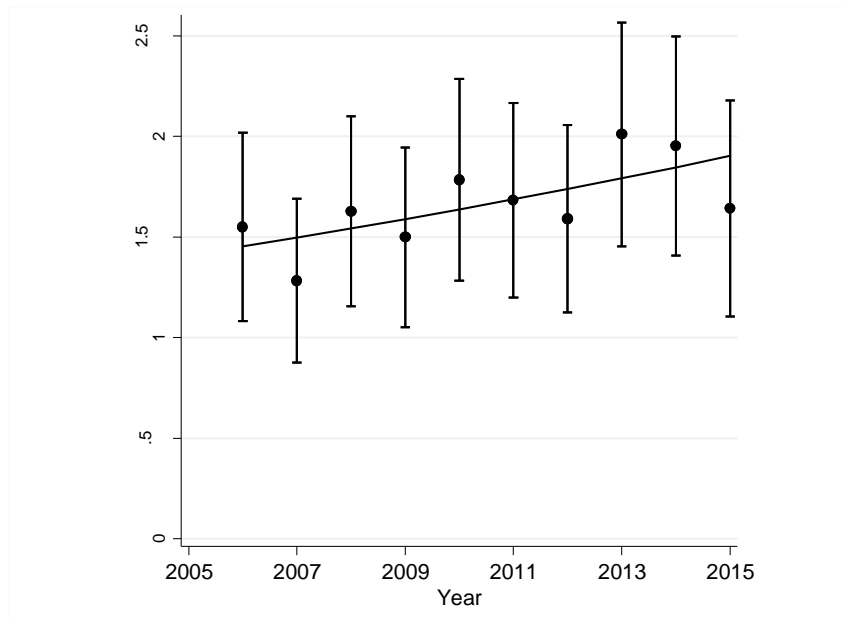
Fig. 10b: Laterality Anomalies – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

3.3 Decreasing trends identified at the pan-Europe level

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.

The pan-Europe analysis showed that the prevalence of hydrocephaly is decreasing on average by 1.6% per year. A decreasing trend is reported in 13 registries (Basque Country, Wessex, Emilia-Romagna, Valencia Region, South West England, Tuscany, North Netherlands, Northern England, Ukraine, Wales, Hainaut, Cork & Kerry) but only at the pan-Europe level and in Wales it is statistically significant (Fig. 11a). The decreasing trend in this anomaly was not observed earlier and not reported in the 2012 Statistical Monitoring Report [10].
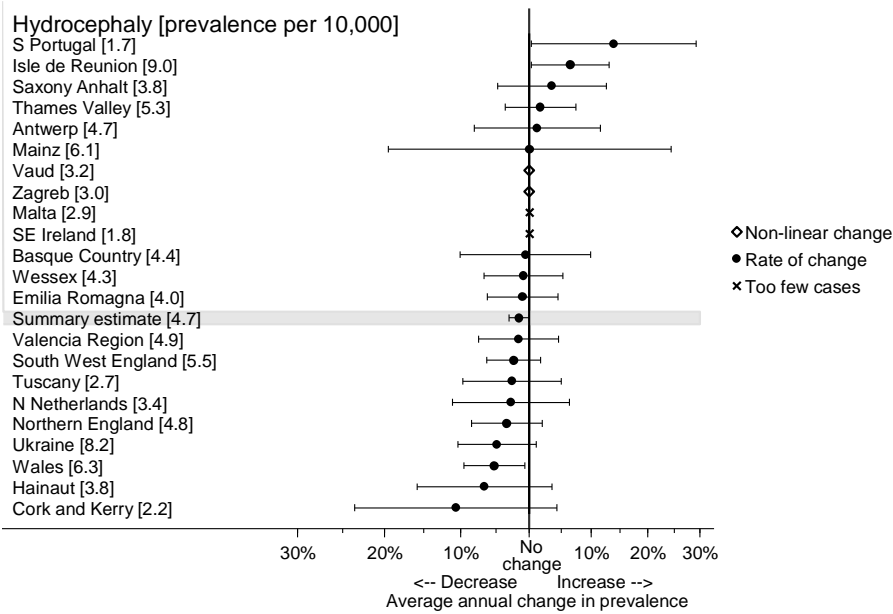

Fig. 11a: Hydrocephaly – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
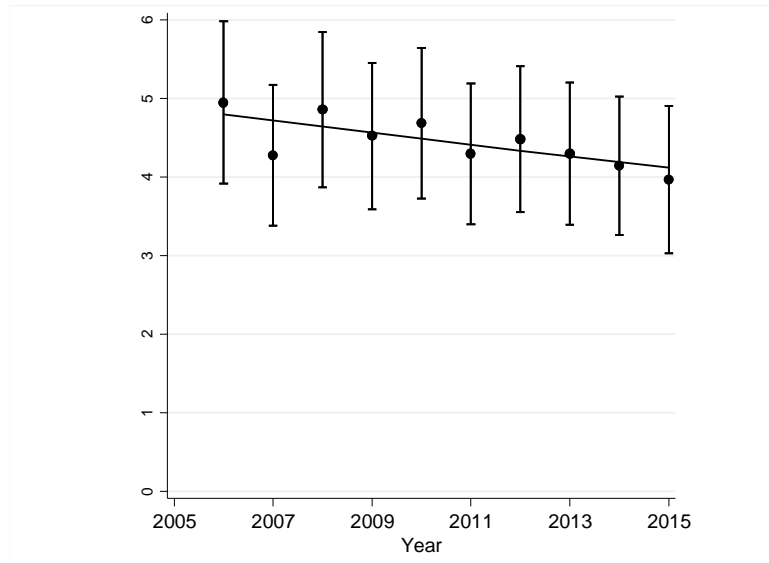
Fig. 11b: Hydrocephaly – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Severe microcephaly

Severe microcephaly should be reported if 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.

A decreasing trend is reported in nine registries but only at the pan-Europe level (-4.2% per year), South West England and in Wales it is statistically significant (Fig. 12a). The reported prevalence of microcephaly across Europe (Fig. 12a) is so heterogeneous due to the rarity of the anomaly and discrepant diagnostic criteria that the decreasing trend observed in the 2006-2015 Pan European analysis (Fig. 12b) cannot be interpreted to reflect a true decrease in prevalence. Furthermore, this heterogeneity means that analyses performed in future years are unlikely to detect any increase in prevalence of microcephaly due to the Zika virus [1].
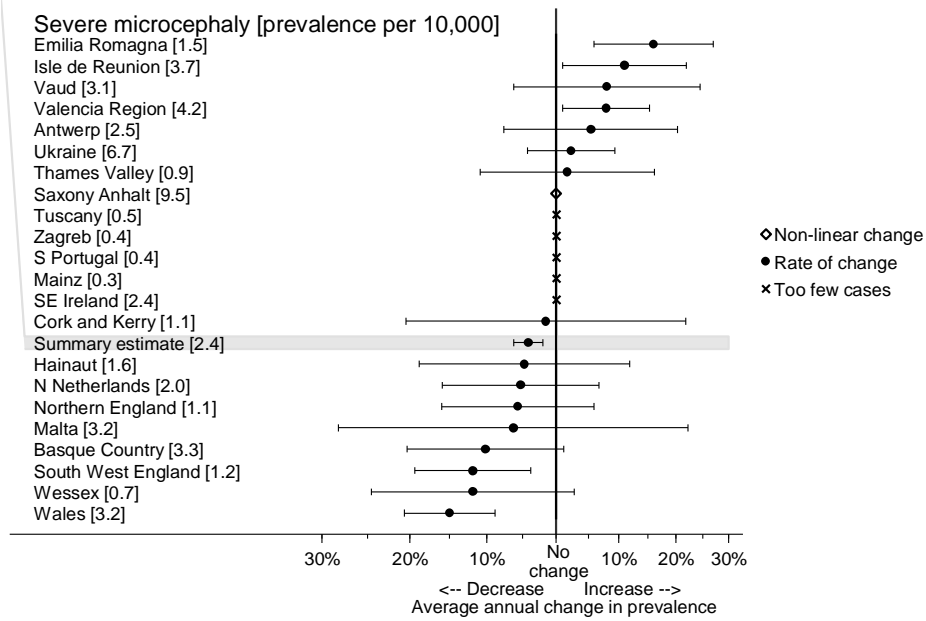
Fig. 12a: Severe microcephaly – Estimated average percentage change in the prevalence ad 95% confidence intervals for the registries Included in the pan-Europe trend analysis.
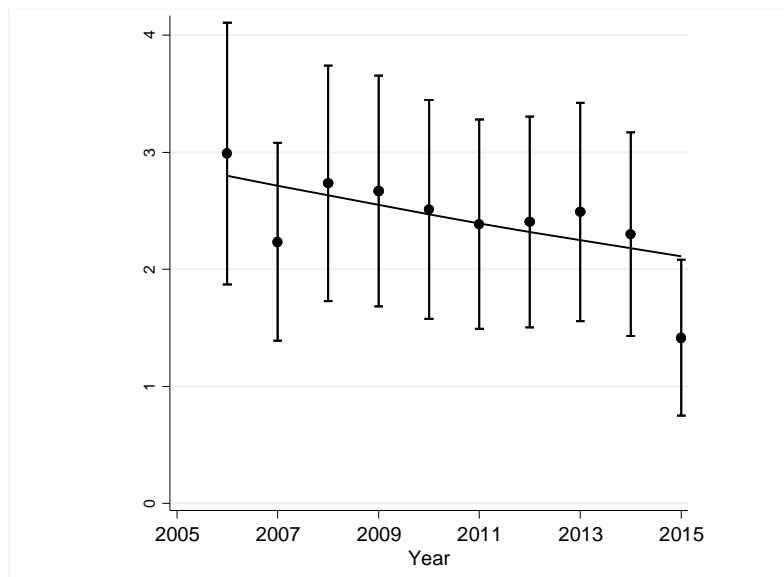

Fig. 12b: Severe microcephaly - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Anophthalmos/microphthalmos

Anophthalmos is a unilateral or bilateral absence of the eye tissue. Microphthalmos is defined as small eye/eyes with smaller than normal axial length.

The pan-Europe analysis showed that the prevalence of anophthalmos/microphthalmus is decreasing on average by 5.3% per year. Only the large decrease in Ukraine (-20% per year) is statistically significant. This decrease will continue to be monitored.
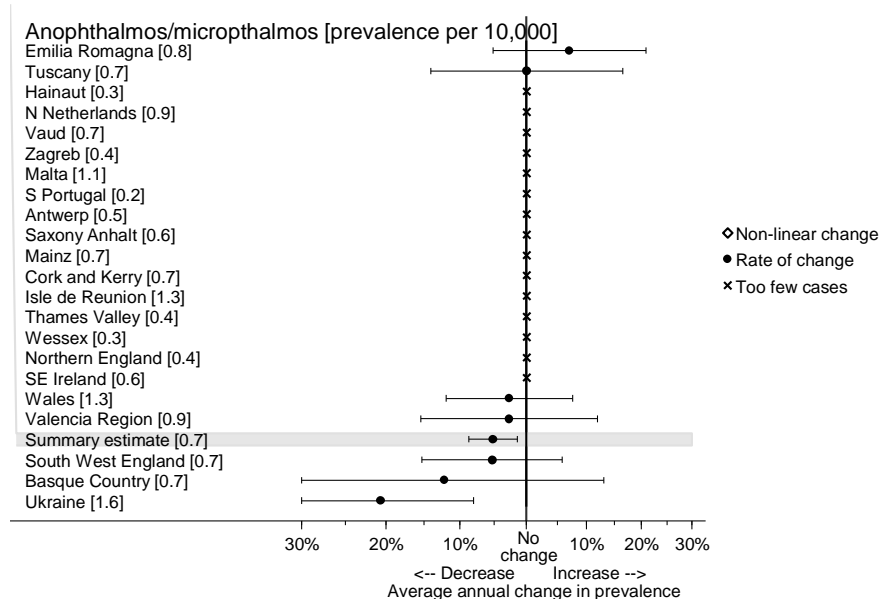

Fig. 13a: Anophthalmos/microphthalmos - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Fig. 13b: Anophthalmus/microphthalmus - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

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. There is a significant decreasing pan-Europe trend (-3.5%) for this anomaly, maybe due to less reporting of small gradients (less severe cases). Due to the heterogeneity of the prevalence between the registries, this decreasing pan-Europe trend has to be interpreted with caution.

Fig. 14a: Pulmonary valve stenosis – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
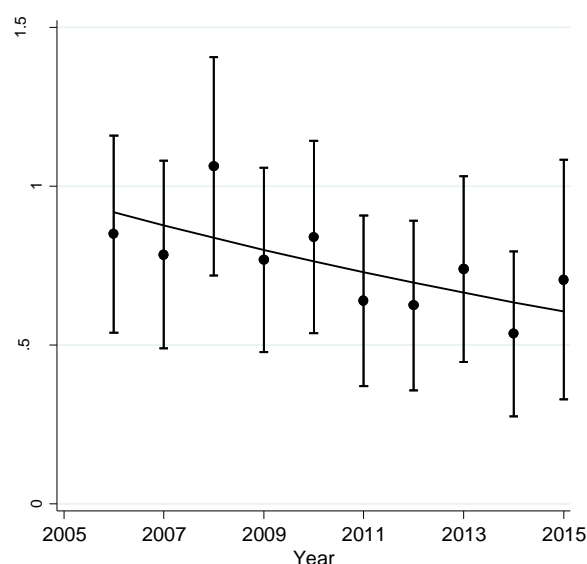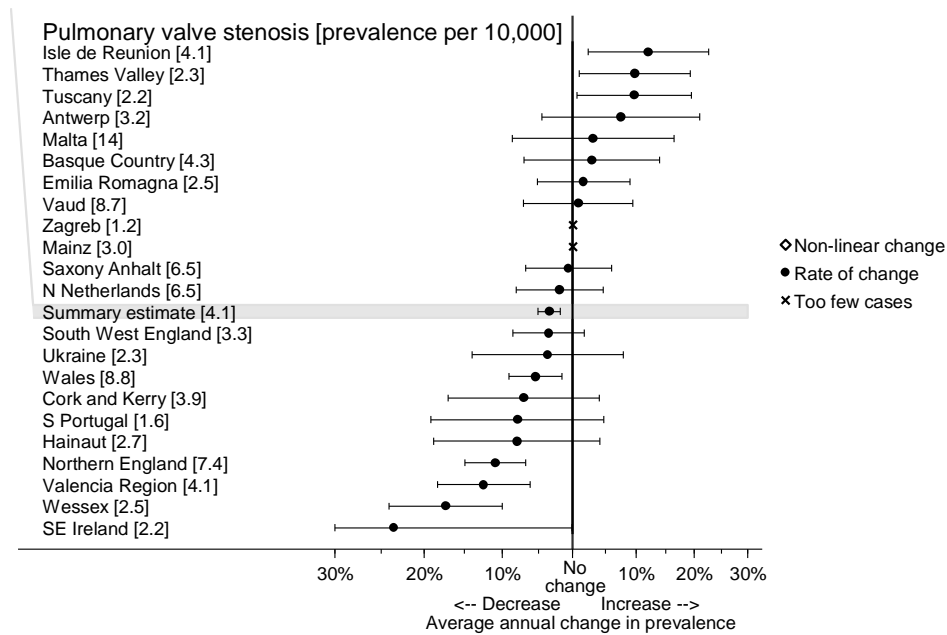

Fig. 14b: Pulmonary valve stenosis – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

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Hypoplastic left heart

Hypoplastic left heart is a spectrum of cardiac defects characterized by severe underdevelopment of the left side of the heart. The definition includes atresia or marked hypoplasia of aortic orifice or valve with hypoplasia of ascending aorta and defective development of left ventricle (with or without mitral valve stenosis/atresia). This is a very severe anomaly with a high termination rate.

A decreasing trend is reported in 12 registries but only at the pan-Europe level (-2.3% per year) and in Wessex it is statistically significant (Fig. 15a). It is a new decreasing trend that will be followed.

Fig. 15a: Hypoplastic left heart - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
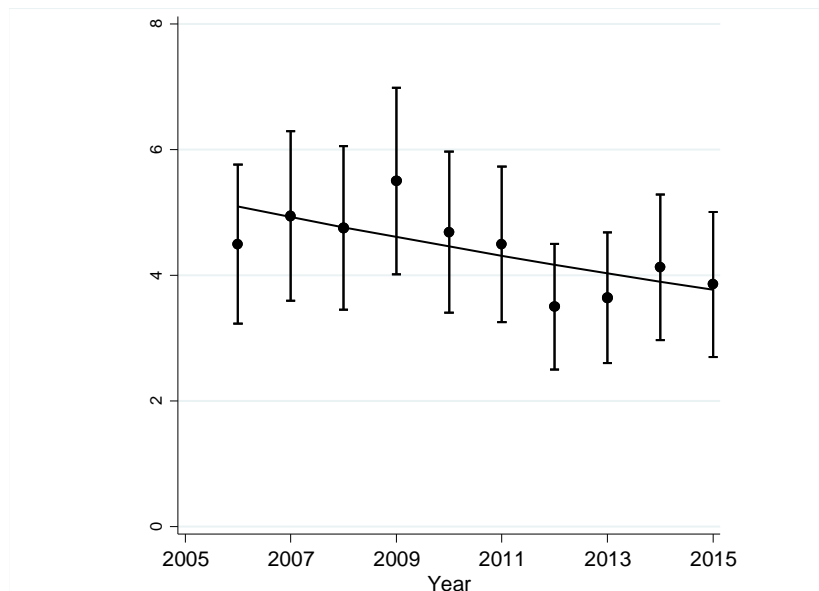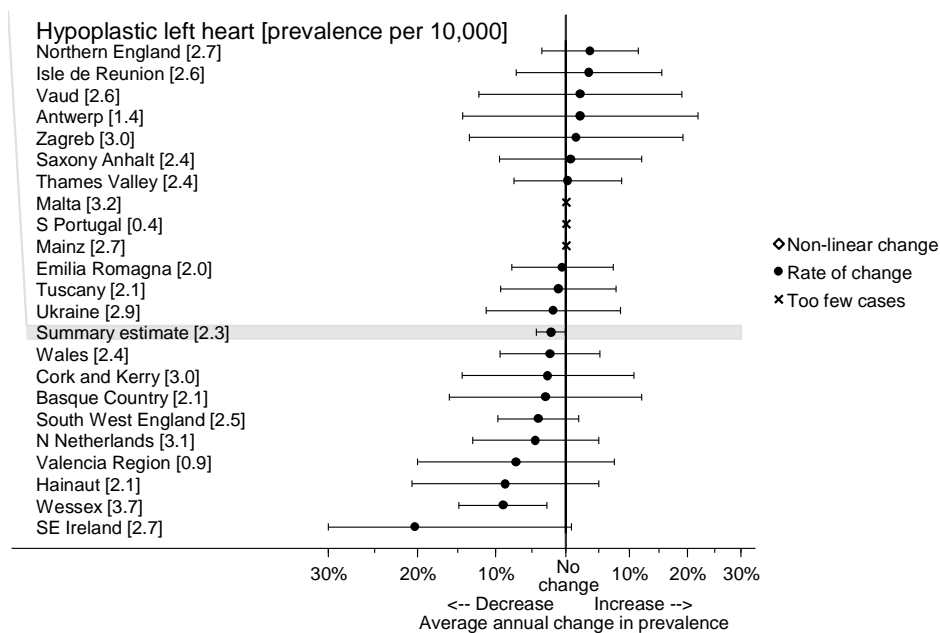

Fig. 15b: Hypoplastic left heart - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Patent ductus arteriosus (PDA)

Patent ductus arteriosus 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 with spontaneous closure. These babies should not be reported to EUROCAT. The pan-Europe analysis showed that the prevalence of PDA is decreasing on average by 5.3% per year (Fig. 16a). The decreasing trend in prevalence may be less as the prevalence in 2015 is likely to be underreported and has inflated the estimated decrease (Fig. 16b). The pan-Europe trend is decreasing most probably due to more restrictive reporting.

Fig. 16a: Patent ductus arteriosus (PDA) - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
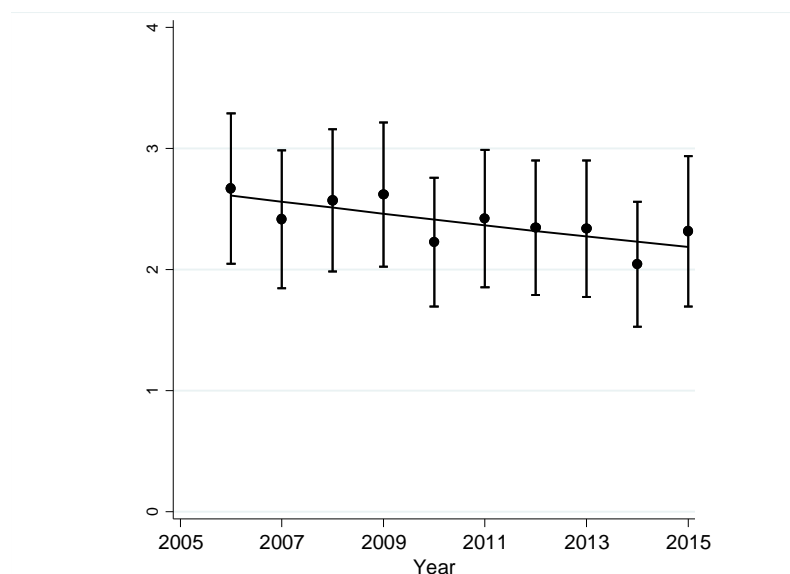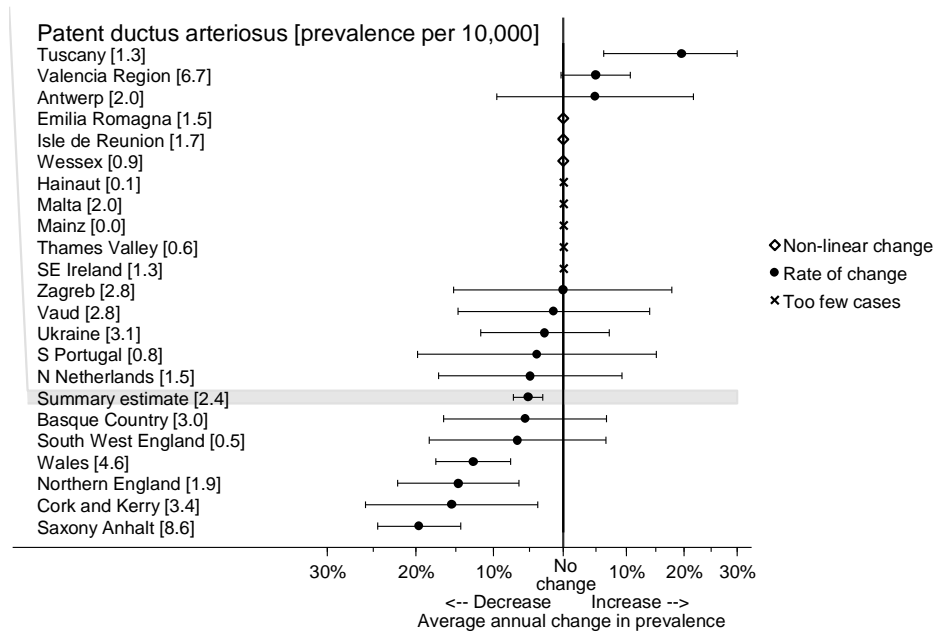

Fig. 16b: Patent ductus arteriosus (PDA) – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Cleft lip with or without palate

This is an anomaly where clefting of the upper lip occurs with or without clefting of the maxillary alveolar process and hard and soft palate. This anomaly is visible at birth and should have a high ascertainment rate. There is a known geographical difference in prevalence throughout Europe. The pan-Europe analysis showed that the prevalence of cleft lip is decreasing on average by 1.2% per year. This decrease is likely to be a chance finding, because the statistical significance is borderline. No single registry shows a significant rate of change despite the high number of cases (Fig. 17a) and the pan-European prevalence has fluctuated greatly over the past 10 years (Fig. 17b).

Fig. 17a: Cleft lip with or without palate - Estimated average percentage change in the prevalence ad 95% confidence intervals for the registries Included in the pan-Europe trend analysis.
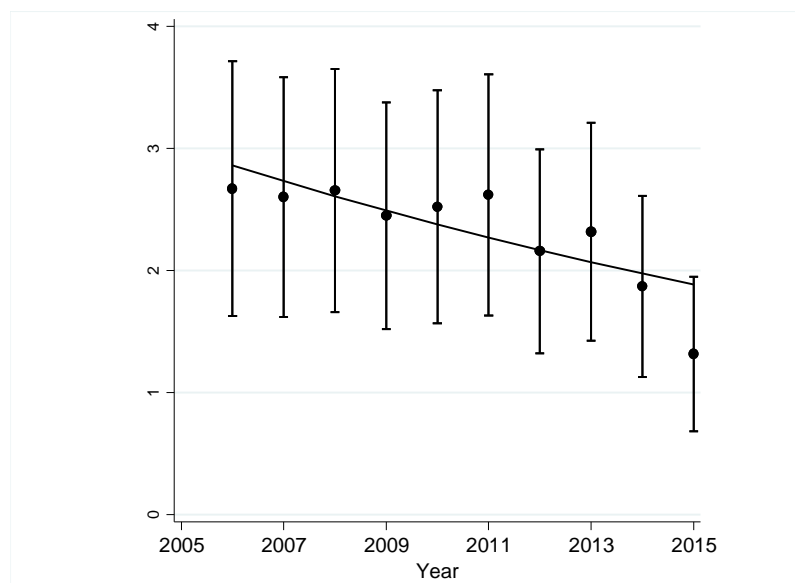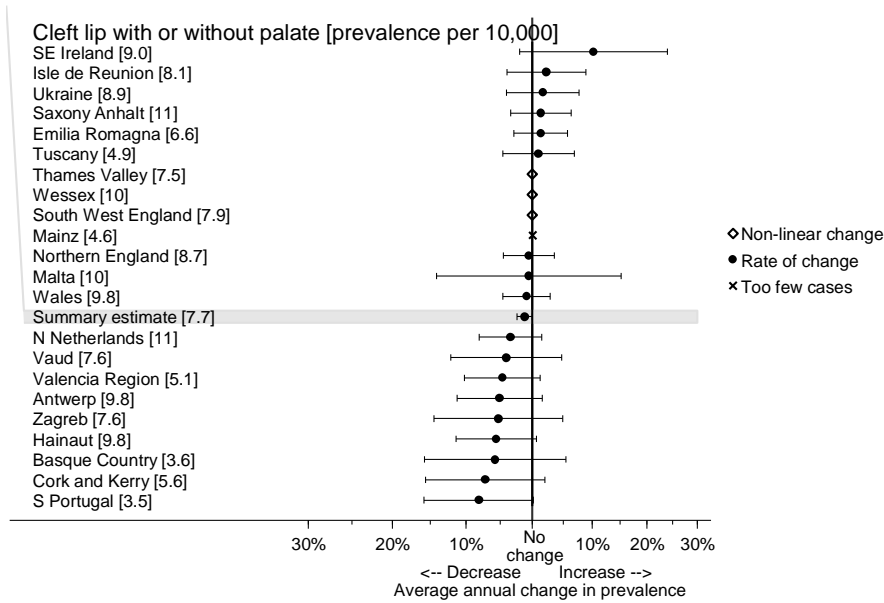

Fig. 17b: Cleft lip with or without palate - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Cleft palate

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

The pan-Europe analysis showed that the prevalence of cleft palate is decreasing on average by 1.6% per year. The significant overall decreasing trend (-1.6% per year) also occurred in Wessex, north Netherlands, Zagreb and Malta. Northern England was the only registry with a significantly increasing trend (Fig. 18a). The decreasing trend in prevalence may not be `true' as the prevalence in 2015 is likely to be underreported (Fig. 18b) which will inflate the estimated decrease and the pan-European prevalence has fluctuated greatly over the past 10 years.

Fig. 18a: Cleft palate – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
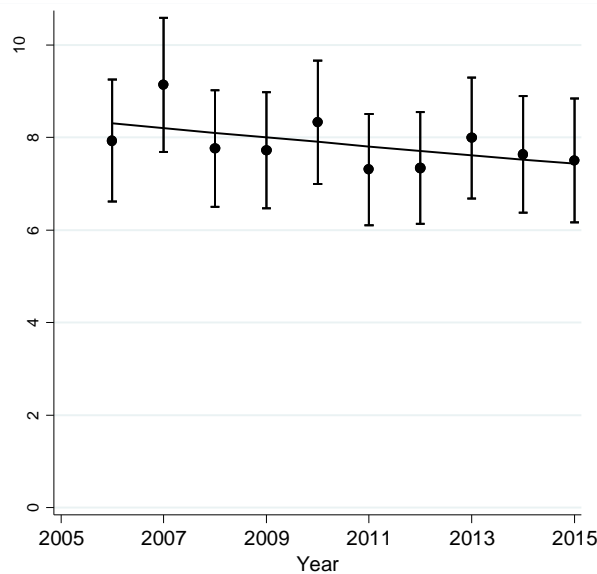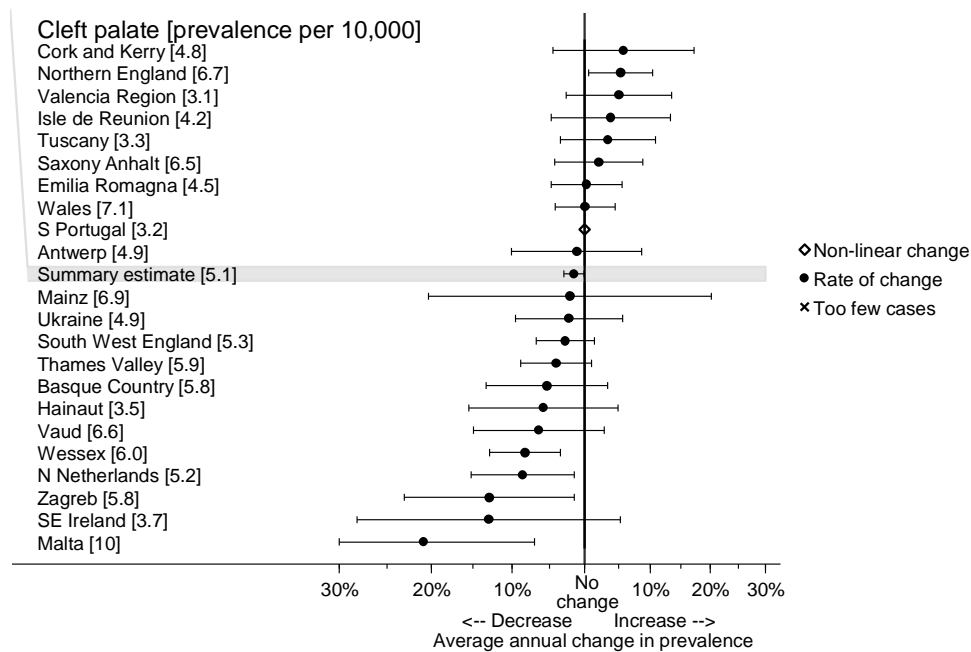
Fig. 18b: Cleft palate – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Gastroschisis

Gastroschisis is defined as protrusion of abdominal contents through an abdominal wall defect lateral to an intact umbilical cord and not covered by a membrane. It is associated with low maternal age. Over the past 20 years prevalence has increased mainly in UK and also described in other areas outside Europe [4, 5, 6, 7]. The pan-Europe decrease (-2.6% per year) involves many UK registries (South West England, Wessex, Thames Valley, Northern England, Wales) as well as Isle de Reunion, Hainaut and Ukraine (Fig. 19). The decreasing trend appears to be mainly due to a step change in prevalence from 2010 to 2011 (Fig. 19b). Since this anomaly is associated with low maternal age [2, 3], the decreasing trend will be investigated in more detail to investigate whether the decrease can be explained by a decrease in the number of teenage pregnancies.

Fig. 19a: Gastroschisis – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
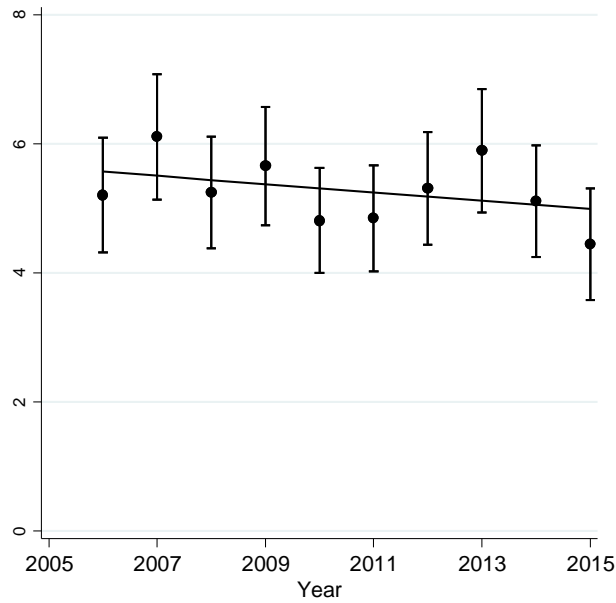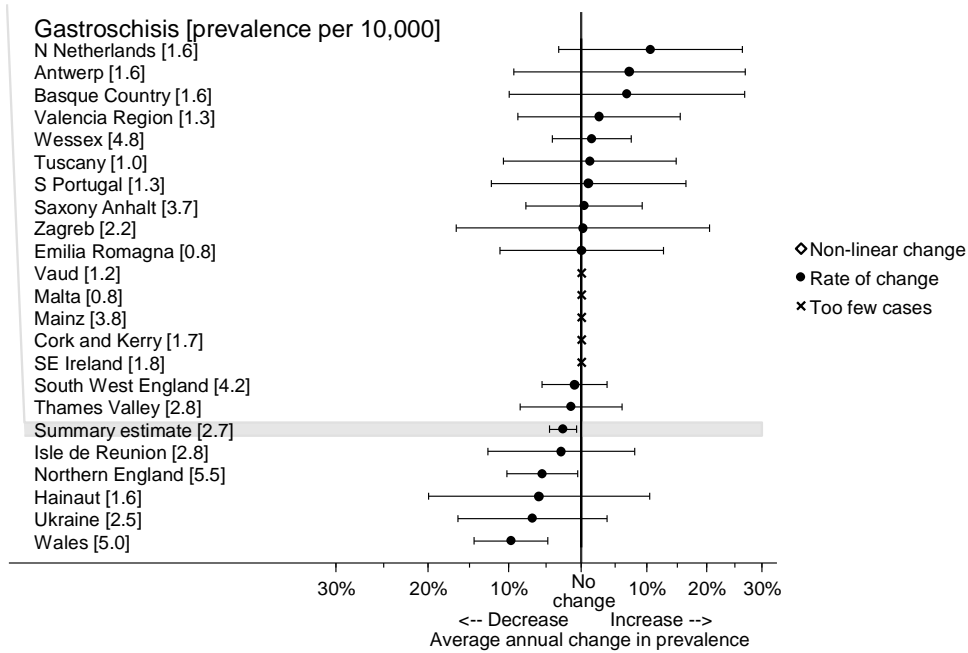

Fig. 19b: Gastroschisis – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Hypospadias

In hypospadias the urethral meatus is abnormally located and is displaced proximally on the ventral surface of the penis. There are many reports of increasing trends over the last 20 years and an association to endocrine disrupters has been proposed. This is the first time a pan-Europe decrease is observed (-1.9% per year, Fig. 20a). Figure 20b indicates that the decreasing trend is likely to be highly influenced by the low prevalence in 2015. Follow up of this trend is not needed but this anomaly will continue to be monitored.

Fig. 20a: Hypospadias - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
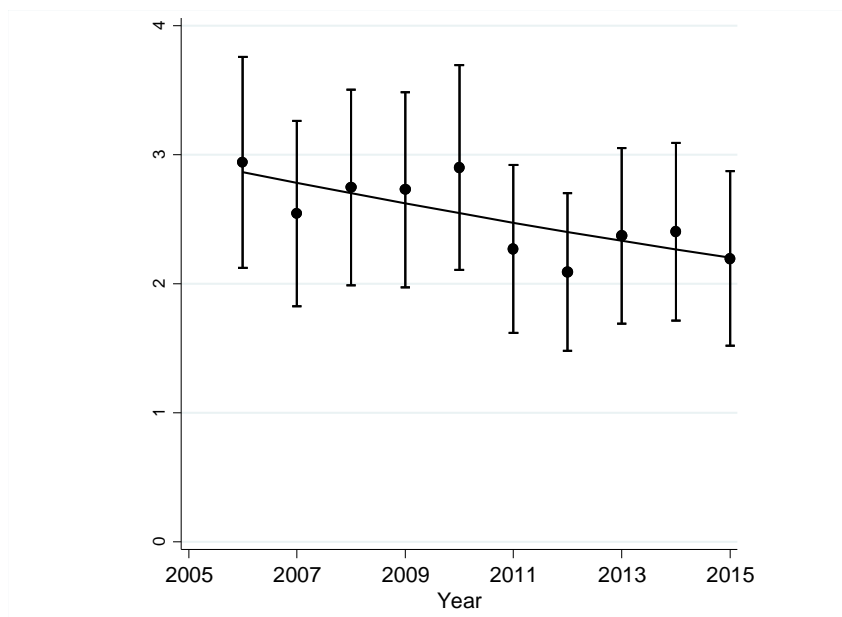

Fig. 20b: Hypospadias - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

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Syndactyly

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

The overall pan-Europe decrease in prevalence of syndactyly is of -3.1% per year (Fig. 21a). Fig 21b indicates that the decreasing trend is likely to be due to the low prevalence in 2015.

Fig. 21: Syndactyly – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Fig. 21b: Syndactyly – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Congenital constriction bands

This rare anomaly is part of the vascular disruption subgroup. There is an overall decrease in prevalence of -4.1% per year with borderline significance (Fig. 22). The decrease is likely to be highly influenced by the high prevalence in 2006 (Fig. 22b).

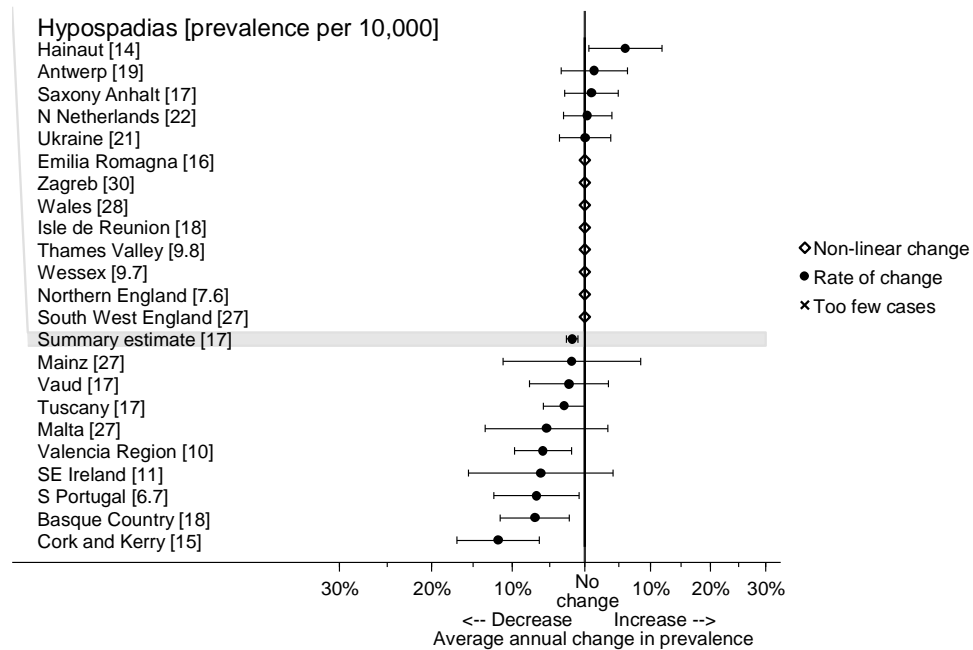**Fig. 22a:** Congenital constriction bands – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis
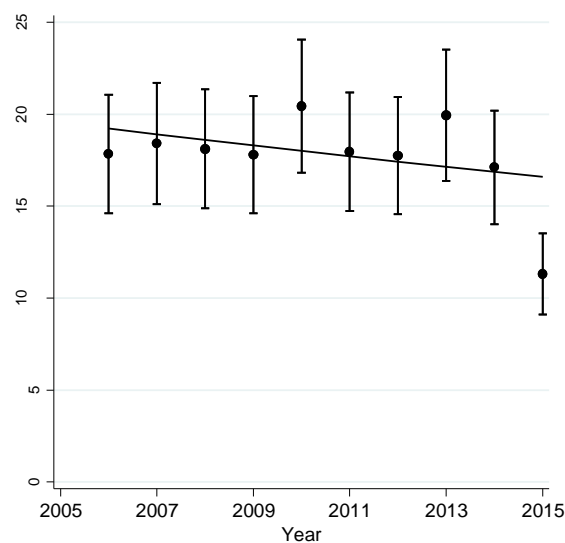

Fig. 22b: Congenital constriction bands – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Conjoined twins

The occurrence of conjoined twins is very rare, with a pan-Europe prevalence of 0.1 per 10,000 births. No significant trends were reported previously for this anomaly, while there was a significant decrease of -9.4% per year in this year's investigation (Fig. 23a). The condition is so rare that only biennial pan-European prevalence estimates can be reliably estimated and no individual registry has enough cases to investigate trends (Fig. 23b).

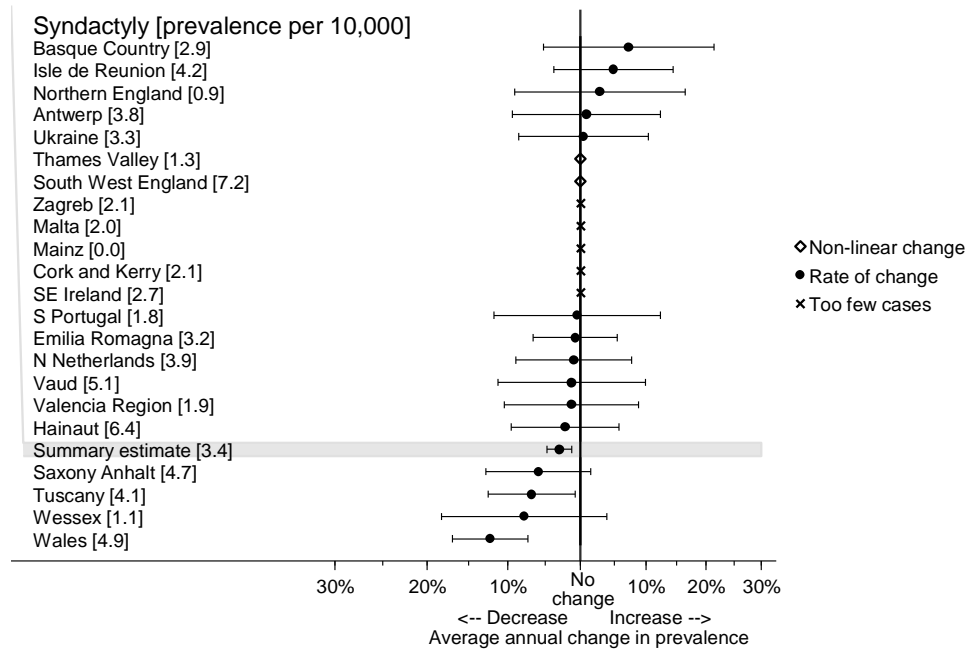**Fig. 23a:** Conjoined twins – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
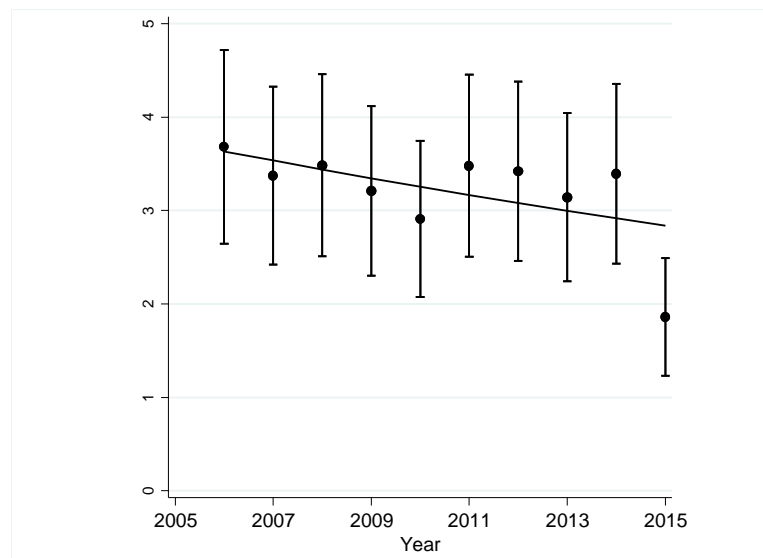

Fig. 23b: Conjoined twins – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Valproate syndrome

Valproate syndrome is a teratogenic syndrome. There is a significant annual decrease (-27.5%, Fig. 24) in this syndrome. The numbers of cases are extremely small; 12 in 2006-7; seven in 2008-9; four in 2010-11; one in 2012-13 and two in 2014-15. No yearly prevalence is presented.

In Europe, the therapy prescribed to pregnant women with epilepsy or bipolar disorder has changed as recommended by the European Medicines Agency (EMA) [14].

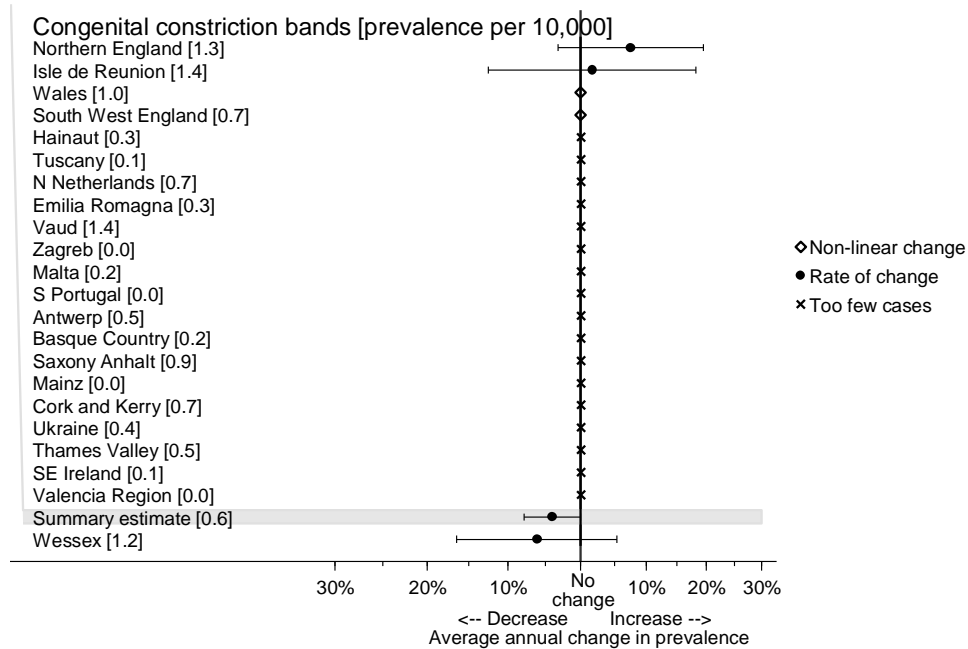**Fig. 24:** Valproate syndrome – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

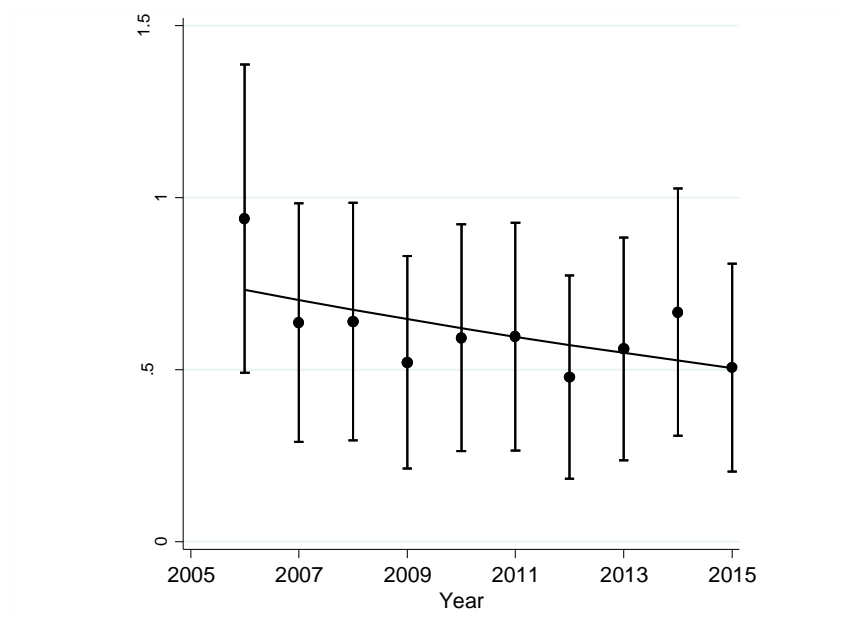## Genetic syndromes and microdeletions

With the increasing number of genetic tests an increase in the reporting of genetic syndromes is to be expected. Conversely, clinical diagnosis might have overestimated the real number of cases in previous years. The decreasing trend (-1.8% per year, Fig. 25) is probably due to a high prevalence in 2005 and a low prevalence in 2015 possibly due to late confirmations of diagnosis based on genetic testing.

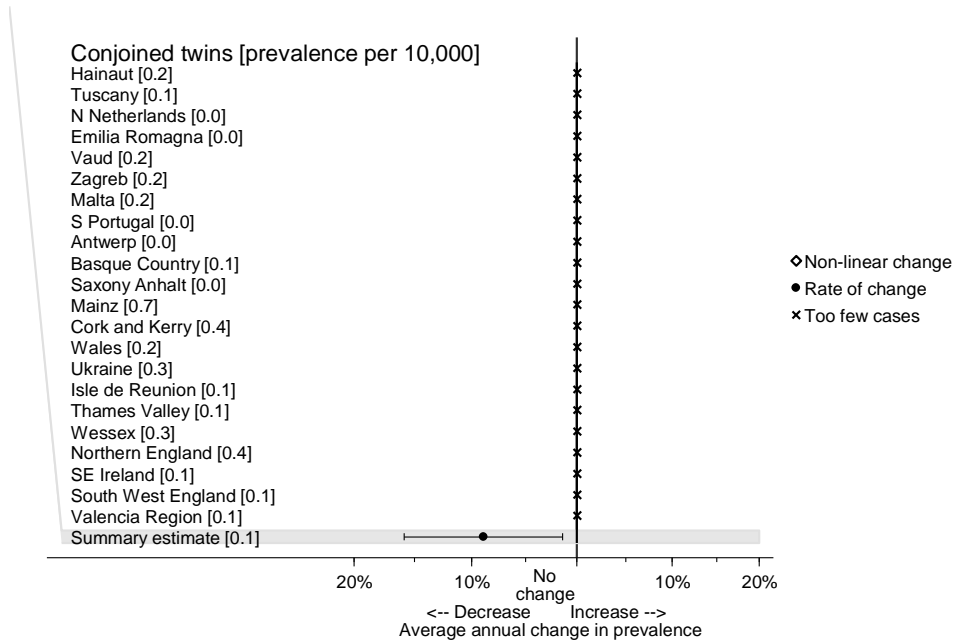**Fig. 25a:** Genetic syndromes and microdeletions – Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
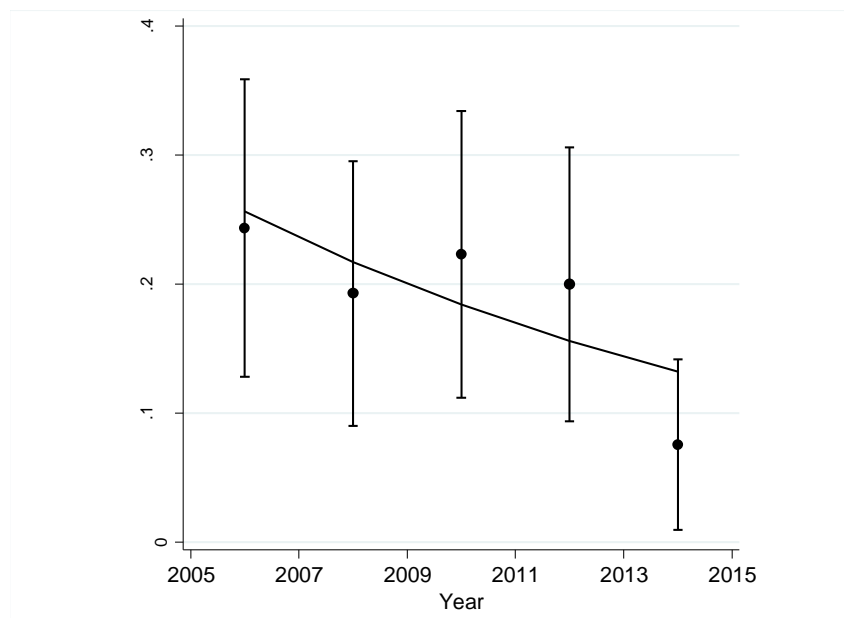

Fig. 25b: Genetic syndromes and microdeletions – Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Klinefelter syndrome

Klinefelter syndrome (XXY karyotype) is frequently detected due to the prenatal diagnostics used to diagnose Down syndrome. The decreasing trend (-7.6% per year, Fig. 26) in Klinefelter syndrome observed prior to 2012 reflects the change in clinical practice in the UK of not performing full prenatal karyotyping. Four of the registries with decreasing trends are in the UK.
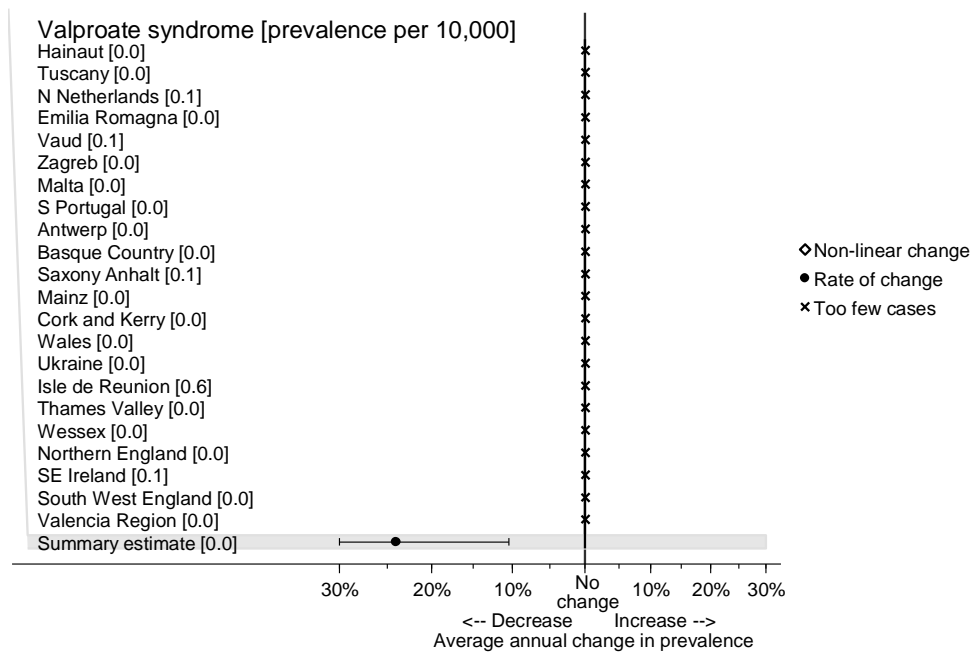

Fig.26a: Klinefelter syndrome - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Fig.26b: Klinefelter syndrome - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

Down syndrome age adjusted

Down syndrome is due to an additional chromosome 21. The risk of a Down syndrome pregnancy is highly associated with increasing maternal age. Therefore, any increasing or decreasing trends should be investigated only once maternal age is adjusted for. This is only possible for the 11 registries that report the number of unaffected pregnancies in their population by five year maternal age groups (Fig 27a). Any observed trends are unlikely to be true changes in prevalence, but are likely to be due to changes in reporting. The decreasing trend for age adjusted Down syndrome appears to be highly influenced by the low prevalence in 2015. Only one registry had a significantly decreasing trend (Vaud) and one a significantly increasing trend (S. Portugal). It is the first time the trend for the age adjusted Down syndrome has decreased. The decreasing trend in prevalence may be negligible as the prevalence in 2015 is likely to be underreported and this has inflated the estimated decrease.
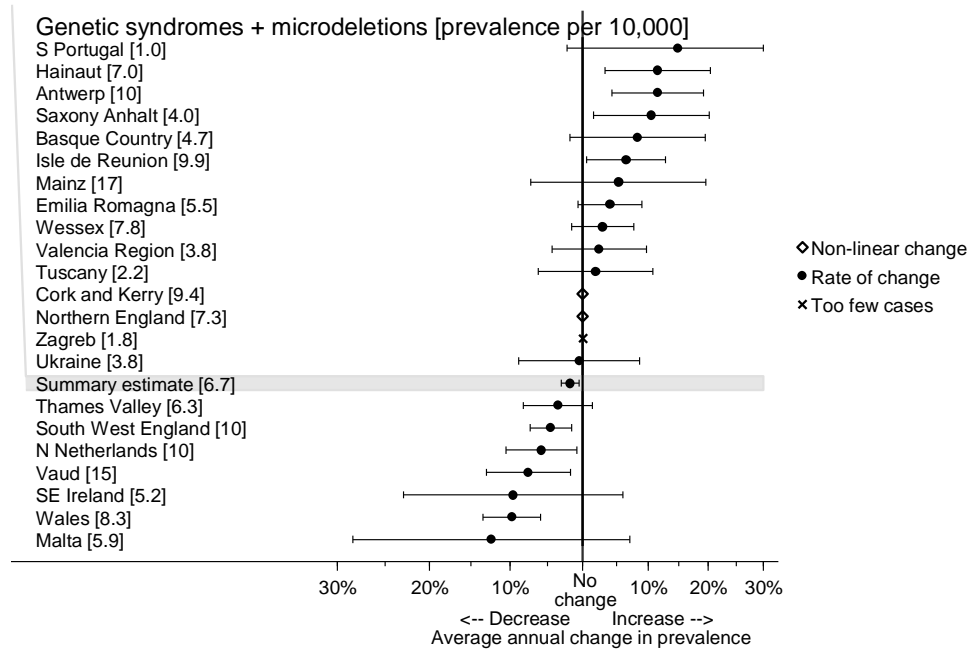

Fig. 27a: Down syndrome age adjusted - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
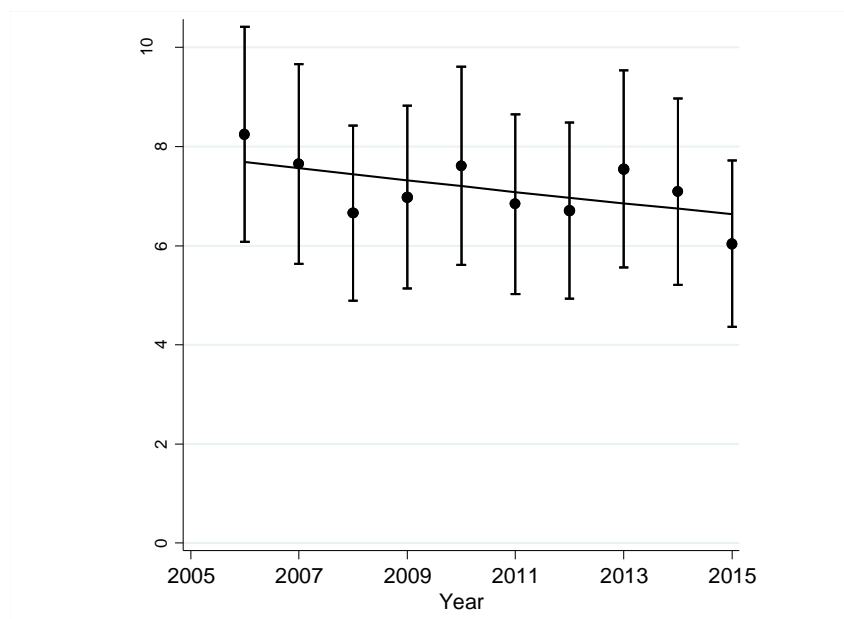

Fig. 27b: Down syndrome age adjusted - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

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Vascular disruption anomalies

It's a new subgroup including all anomalies where the aetiology is thought to be vascular disruption. Anomalies included are small intestinal atresia, gastroschisis, limb reduction defects, amniotic bands, hydranencephaly, Moebius syndrome. The pan-Europe trend is decreasing (-7.5% per year; Fig. 28a) and will be followed. The individual subgroups are also decreasing, although only gastroschisis was statistically significant. The decreasing trend in prevalence may be less as the prevalence in 2015 is likely to be underreported and has inflated the estimated decrease (Fig. 28b).

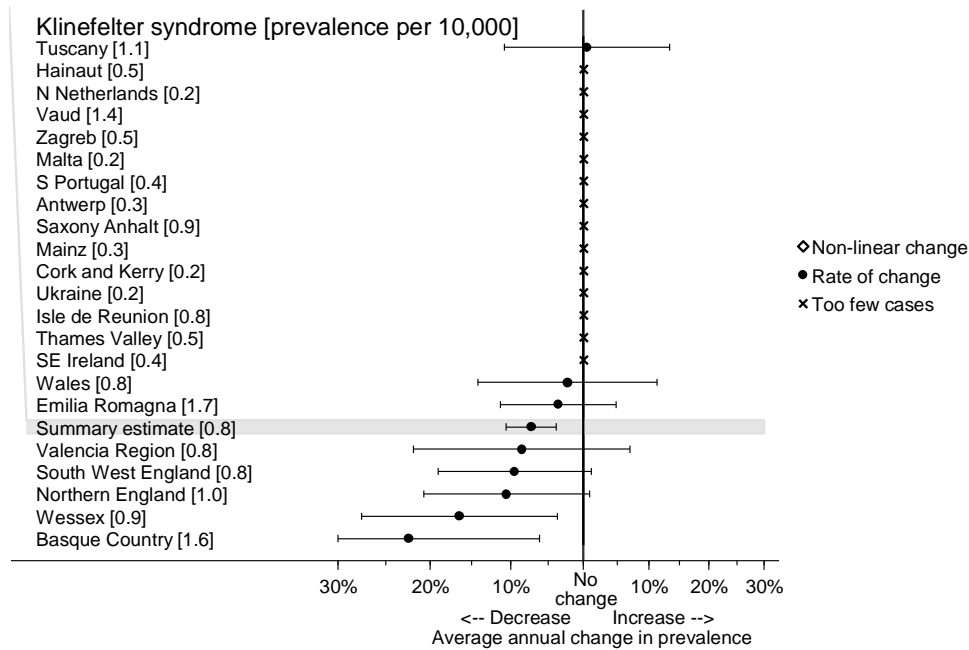**Fig. 28a:** Vascular disruption anomalies - Estimated average percentage change in the prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.
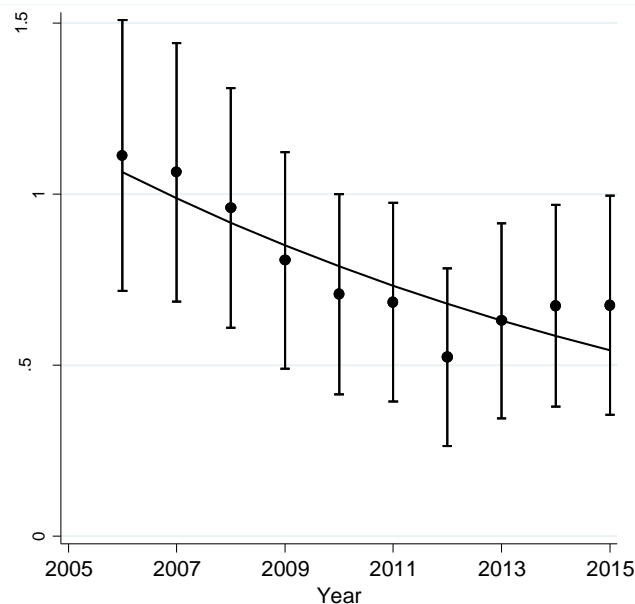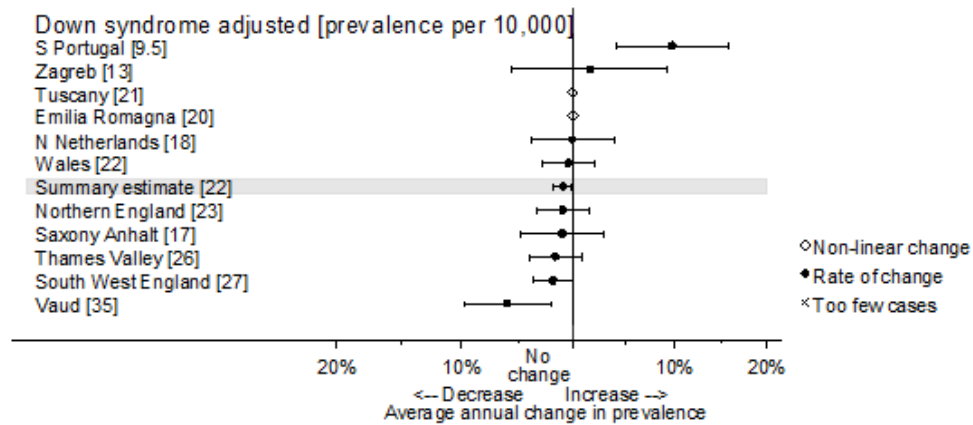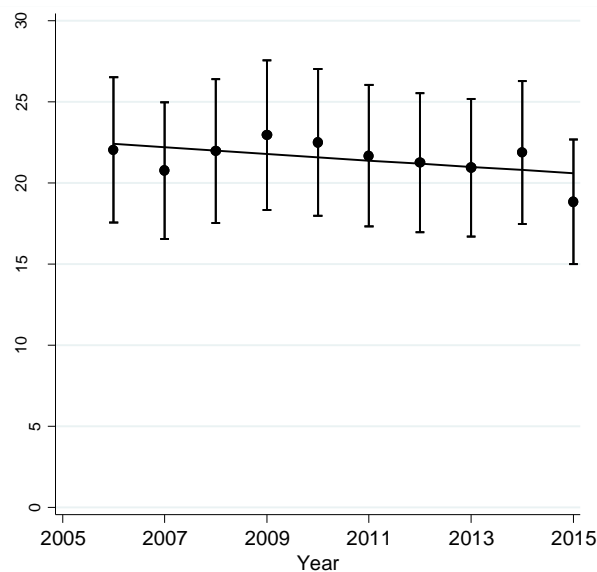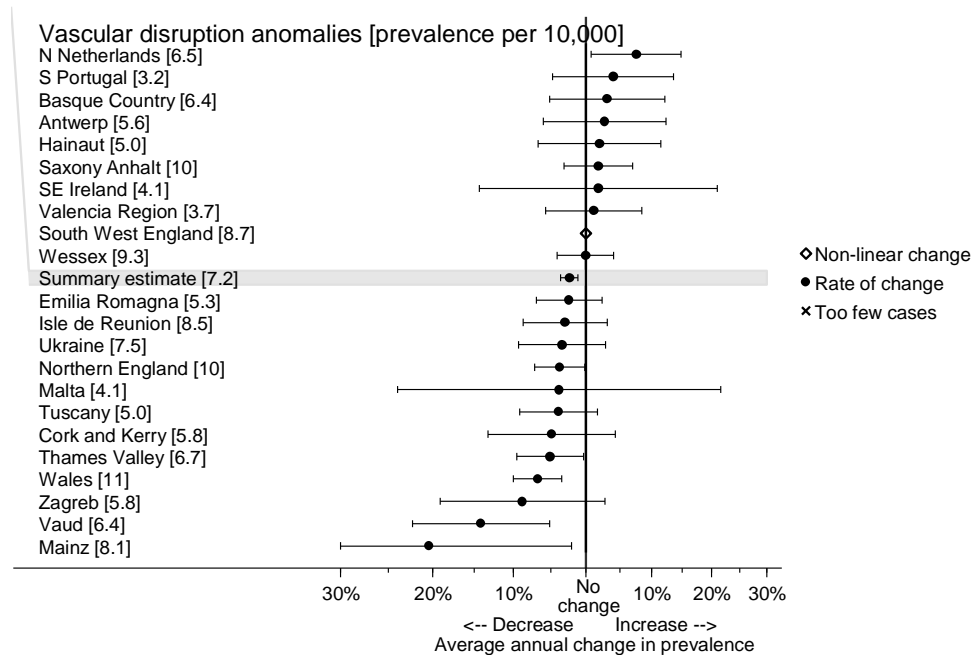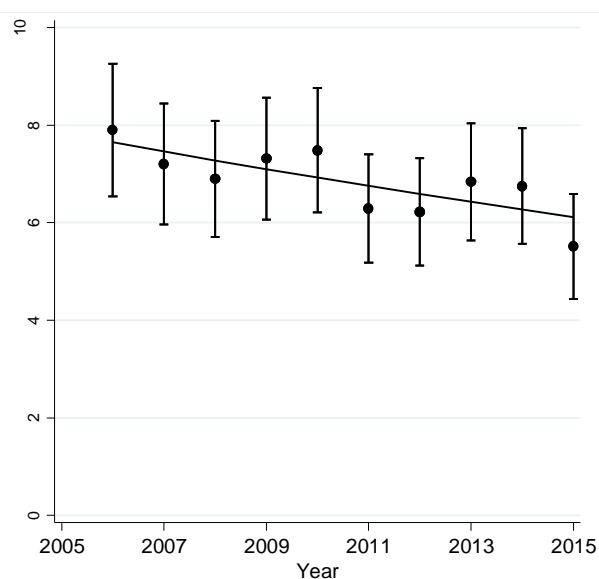

Fig. 28b: Vascular disruption anomalies - Prevalence and 95% confidence intervals for the registries included in the pan-Europe trend analysis.

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4 Clusters

4.1 Overview

EUROCAT defines a cluster as: "An aggregation of cases of congenital anomaly in time and/or space which appears to be unusual". This definition includes space as defined by a common activity such as a place of work/ education/ recreation etc. and not just space as defined by residence. Currently, the statistical monitoring at the Central Registry detects temporal clusters within each registry area while the space investigation is conducted by the registry at a local level.

Currently, the JRC-EUROCAT Central Registry performs annual cluster analysis using the most recent five years of data. More than five years may tend to identify trends rather than clusters, and will be computationally slower. Less than five years may fail to detect if the most recent years are unusual compared to preceding years.

Cluster detection is based on a moving window test; the method uses a moving window of a given number of cases (window size), measuring the length of time between the first and last case. It detects whether the given number of cases has occurred in a shorter time than would be expected by chance. The method is not robust with a window size of less than five cases, hence a minimum of seven cases over the study period of interest is needed to run the analysis. All window sizes from a minimum of five to a maximum of the total number of cases minus 2 are tested. Each registry and anomaly subgroup is tested independently.

Many clusters may overlap in time, the inclusion or exclusion of individual cases changing their significance. In a first step, all significant clusters are identified. Then, the "most significant" cluster (lowest p-value) is selected. All other significant clusters (p<0.05) for which at least 75% of cases overlap with the "most significant" cluster are considered to belong to the same cluster group.

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.

Where date of conception is used as a basis for cluster detection, the conception period for statistical monitoring must end nine months before the last birth month where data collection is complete. The scan routine used here (see also Appendix C) includes cases with date of conception between 1st April 2013 and 31st March 2015 (24 months).

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. Each case is represented by an asterisk and the cluster identified by the segment under the timeline. These figures are also used in the present report. Registries are also provided with the ID codes that anonymise the cases included in each cluster. If the investigation of clusters identifies data errors (e.g. incorrect diagnoses, incorrect dates of birth) these errors should be corrected and updated data included in the next data transmission to the Central Registry.

4.2   Cluster analysis 2011–2015

Sixteen registries satisfied the criteria to be included in the cluster analysis reported here (see Appendix A). A total of 25 clusters were identified in nine registries (see Table 1).

Reports on preliminary investigations were received from 8 out of 9 registries. The reports by registries into the 25 clusters detected in the monitoring indicated that 16 were not 'true' clusters as defined by EUROCAT, and were explained by data quality issues/changes in case ascertainment. No preliminary report was available for three clusters (see Table 1).

For the following six clusters, the excess of cases was not explained, the significance was uncertain and future monitoring at the registry level is recommended: **Ebstein's anomaly** (Emilia Romagna), **Hypoplastic right heart** (Isle de Reunion), **Congenital cataract** (Tuscany), **VSD** (Tuscany), **Hypospadias** (Tuscany), **Skeletal dysplasia** (Wales).

4.3   Preliminary investigations of specific clusters by registries

Ebstein's anomaly

The cluster was detected in Emilia Romagna, Italy. It was a small cluster of five cases. As the number of total reported cases is very stable in recent years and high quality multisource ascertainment is in place for this anomaly, the registry considers this a chance occurrence. This cluster will be followed.

Anomaly Subgroup: **Ebstein's anomaly**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015

Most significant cluster

Number of cases: 5   Expected number of cases: 0.848   p value: 0.015
Start date: 22/10/2012
End date: 27/04/2013

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.

Hypoplastic right heart

The cluster was detected in Isle de Reunion. It is a small cluster, to be followed to verify if this is a 'true' cluster or a random fluctuation of cases.

Anomaly Subgroup: **Hypoplastic right heart §**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015

Most significant cluster

Number of cases: 5   Expected number of cases: 1.110   p value: 0.038
Start date: 01/10/2013
End date: 03/06/2014

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation

Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

Congenital cataract (Tuscany),

A cluster of congenital cataract was detected in Tuscany, Italy. The 14 cases in the cluster were all isolated cases with confirmed diagnosis. There were no changes in the diagnostic or reporting practice. Since the prevalence of the anomaly observed in the last period in Tuscany is similar to the EUROCAT average, the registry does not consider the need for immediate action. The anomaly will be monitored at the local level.
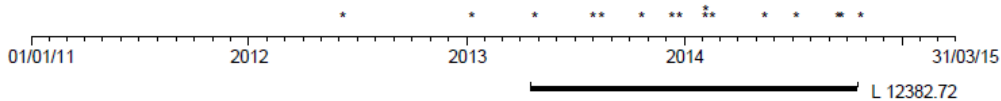
Anomaly Subgroup:	**Congenital cataract**	
Cluster type:	Cluster by date of conception	
Date range:	Clusters between 01/01/2011 and 31/03/2015	

Most significant cluster

Number of cases:	14	Expected number of cases:	5.653	p value:	0.009

Start date: 19/04/2013
End date: 18/10/2014

Distribution of cases

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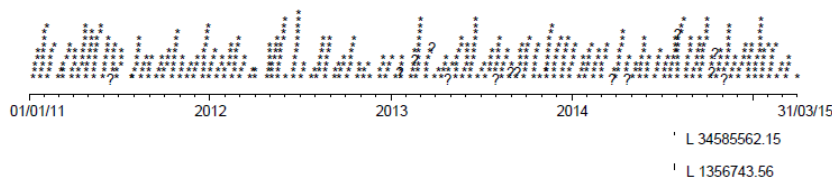

Ventricular Septal Defect (VSD)

The cluster was detected in Tuscany, Italy. Five cases born on the same day were included in the cluster. All were isolated cases, distributed throughout the region. There were no changes in the diagnostic or reporting practice. Since the prevalence of the anomaly observed in the last period in Tuscany is similar to the EUROCAT average, the registry does not consider the need for immediate action. The registry concluded that these cluster requires follow-up of the cases to confirm the diagnosis and the surgery performed.

Anomaly Subgroup:	**Ventricular septal defect**	
Cluster type:	Cluster by date of conception	
Date range:	Clusters between 01/01/2011 and 31/03/2015	

Most significant cluster

Number of cases:	5	Expected number of cases:	0.348	p value:	<0.001

Start date: 27/07/2014
End date: 27/07/2014

Distribution of cases

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

Hypospadias

A cluster of hypospadias cases was detected in Tuscany. Out of the six cases in the cluster (duration four days) four were isolated cases, and two cases were from a twin pregnancy. There were no changes in the diagnostic or reporting practice. The registry does not consider the need for immediate action. The anomaly will be monitored at the local level.
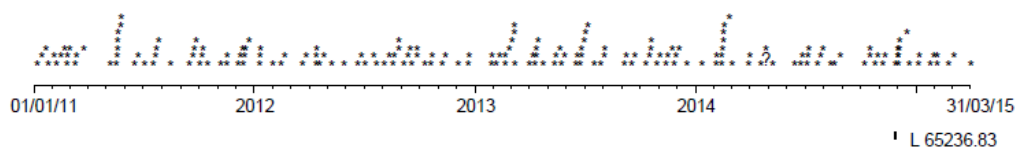
Anomaly Subgroup: **Hypospadias**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015

Most significant cluster

Number of cases: 6   Expected number of cases: 0.500   p value: 0.027
Start date: 26/11/2014
End date: 29/11/2014

Distribution of cases

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

01/01/11   2012   2013   2014   31/03/15

L 65236.83

Skeletal dysplasias

The cluster was detected in Wales. Skeletal dysplasias are a very heterogeneous group of conditions (many of which are genetic). This appears to be a cluster in time but the heterogeneous diagnoses and geography suggest it is more apparent than real, and it is difficult to judge if the cluster merits further investigation. However, the numbers involved in this time frame are very unusual and the registry will follow the cluster in next year's analysis.

Anomaly Subgroup: **Skeletal dysplasias §**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015

Most significant cluster

Number of cases: 18   Expected number of cases: 6.654   p value: 0.035
Start date: 10/09/2012
End date: 25/05/2013

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.

01/01/11   2012   2013   2014   31/03/15

L 6670.36

51

4.4 Clusters that were considered being not 'true' clusters after registries' investigations

Arhinencephaly / holoprosencephaly

The cluster was detected in South West England. The cluster disappeared after removing a genetic case. <u>It is not considered a 'true' cluster</u>.

Anomaly Subgroup: Arhinencephaly/holoprosencephaly
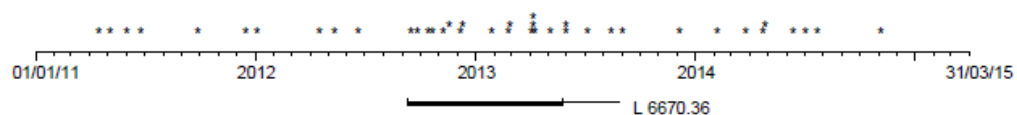Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 6   Expected number of cases: 0.704   p value: 0.025
Start date: 03/07/2014
End date: 23/08/2014

Distribution of cases

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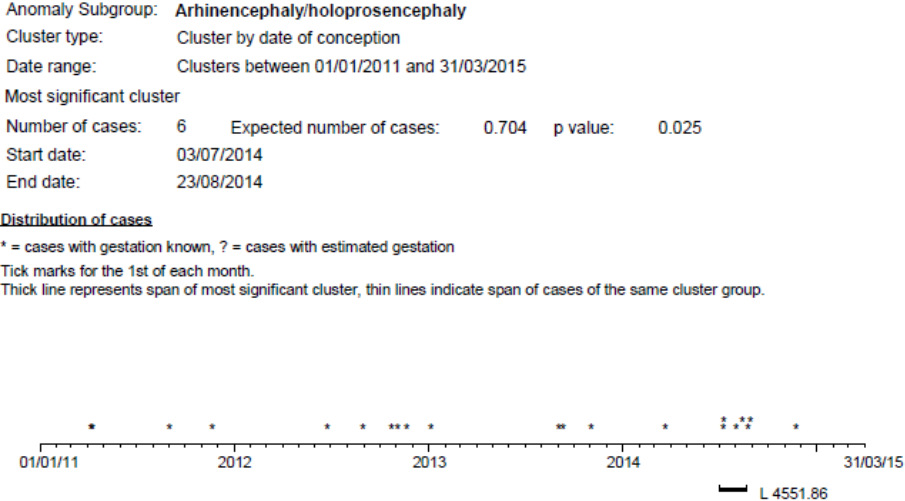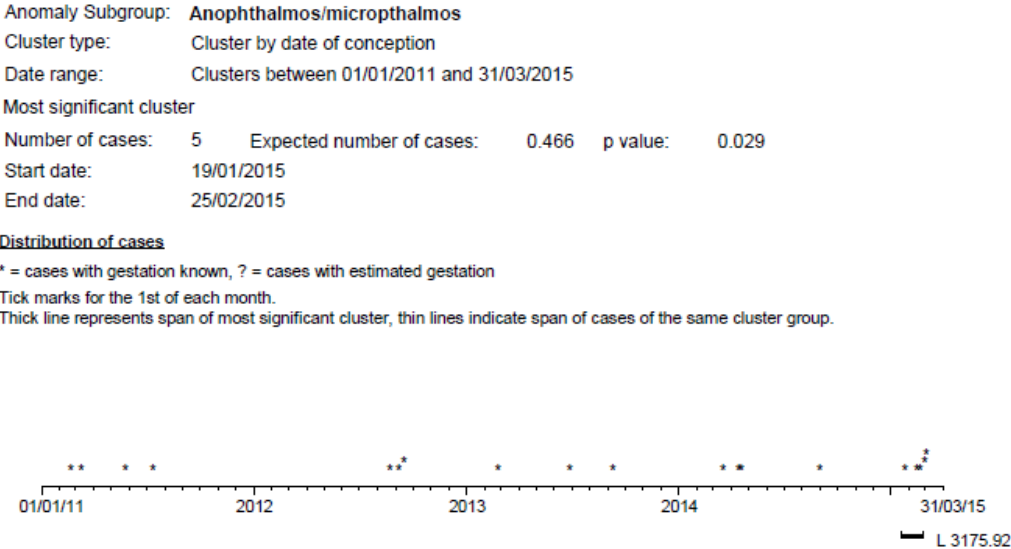Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

01/01/11   2012   2013   2014   31/03/15

L 4551.86

Anophtalmos / Microphtalmos

The cluster was detected in Wales. All cases in the cluster were geographically separated. There were only five cases in the cluster and taking into account the timeline, three cases in this time period would not be unusual. The cluster is considered small and will not be further investigated.

Anomaly Subgroup: Anophthalmos/micropthalmos
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 5   Expected number of cases: 0.466   p value: 0.029
Start date: 19/01/2015
End date: 25/02/2015

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.

01/01/11   2012   2013   2014   31/03/15

L 3175.92

Congenital cataract

The single cluster across one year identified in the Northern England registry appears to be due to the increased ascertainment of eye anomalies following a new source of notification. The expectation is that congenital cataracts will continue to be reported at this higher rate in the next year's data.
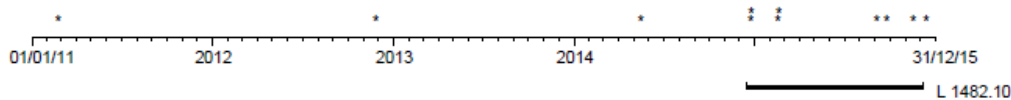
Anomaly Subgroup:	**Congenital cataract**
Cluster type:	Cluster by date of birth
Date range:	Clusters between 01/01/2011 and 31/12/2015

Most significant cluster

Number of cases:	8	Expected number of cases:	2.145	p value:	0.025
Start date:	17/12/2014				
End date:	07/12/2015				

Distribution of cases

* = cases with valid date of birth

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.

Atrial Septal Defect (ASD)

The cluster was detected in South West England. When errors in dates of conception were corrected, a cluster was no longer detected. The registry concluded that this is not a 'true' cluster.
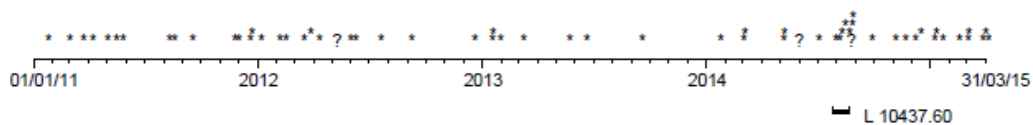
Anomaly Subgroup:	**Atrial septal defect**
Cluster type:	Cluster by date of conception
Date range:	Clusters between 01/01/2011 and 31/03/2015

Most significant cluster

Number of cases:	8	Expected number of cases:	1.159	p value:	0.037
Start date:	25/07/2014				
End date:	22/08/2014				

Distribution of cases

* = cases with gestation known, ? = cases with estimated gestation

Tick marks for the 1st of each month.
Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

PDA as only CHD in term infants

The cluster was detected in Thames Valley, England. The gestational age for some of the cases in the cluster had been incorrectly reported and hence these were not cases of PDA in term infants. Once these cases were removed, a cluster was no longer detected.
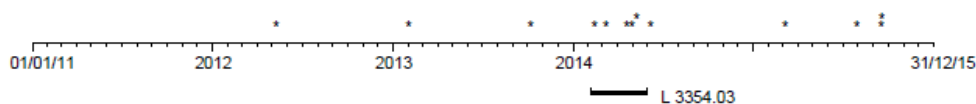
Anomaly Subgroup: PDA as only CHD in term infants (>=37 weeks)
Cluster type: Cluster by date of birth
Date range: Clusters between 01/01/2011 and 31/12/2015

Most significant cluster
Number of cases: 6   Expected number of cases: 0.819   p value: 0.018
Start date: 06/02/2014
End date: 31/05/2014

Distribution of cases
* = cases with valid date of birth
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.

01/01/11   2012   2013   2014   31/12/15
L 3354.03

Hirschsprung's Disease

The cluster was detected in Thames Valley, England. The transition from the CAROBB (Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire) into the NCARDRS[1] is thought to have affected the reporting of this anomaly. This was not judged a `true' cluster.
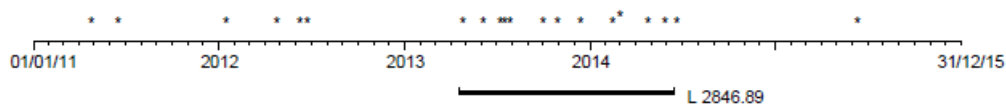
Anomaly Subgroup: Hirschsprung's disease
Cluster type: Cluster by date of birth
Date range: Clusters between 01/01/2011 and 31/12/2015

Most significant cluster
Number of cases: 13   Expected number of cases: 4.622   p value: 0.033
Start date: 19/04/2013
End date: 14/06/2014

Distribution of cases
* = cases with valid date of birth
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.

01/01/11   2012   2013   2014   31/12/15
L 2846.89

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[1] Public Health England (PHE) has expanded congenital anomaly and rare disease registration to cover the whole population of England. The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) records congenital anomalies and rare diseases cases across England. The geographical areas previously covered by the regional congenital anomalies registries in England are now covered by NCARDRS.

Diaphragmatic hernia

The cluster was detected in Cork and Kerry, Ireland. The report on this cluster investigation was not provided.
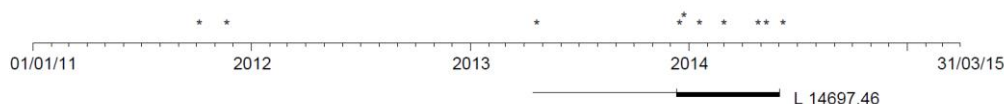
Anomaly Subgroup: **Diaphragmatic hernia**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 7   Expected number of cases: 1.122   p value: <0.001
Start date: 11/12/2013
End date: 02/06/2014

Distribution of cases

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

Congenital hydronephrosis

A cluster of congenital hydronephrosis was detected in Northern Netherlands. The registry reported that the majority of cases in the cluster are 'minor anomalies' that were sent to the Central Registry with the text "Hydronephrosis (due to UPJ stenosis)". A congenital hydronephrosis is only considered a major anomaly if the diameter is greater than 10 mm; cases with a diameter $\geq$10 mm are a minority in the registry's database. Congenital hydronephrosis is detected in ultrasound screening which occurs more frequently now and therefore it is reported more nowadays. This is not a 'true' cluster.
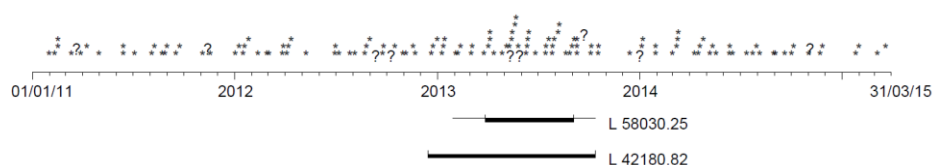
Anomaly Subgroup: **Congenital hydronephrosis**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 34   Expected number of cases: 14.64   p value: 0.022
Start date: 28/03/2013
End date: 04/09/2013

Distribution of cases

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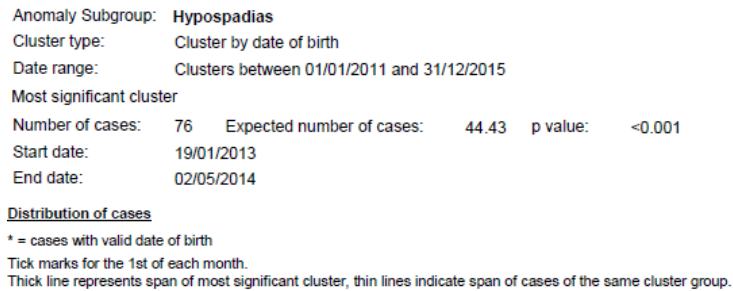Tick marks for the 1st of each month.
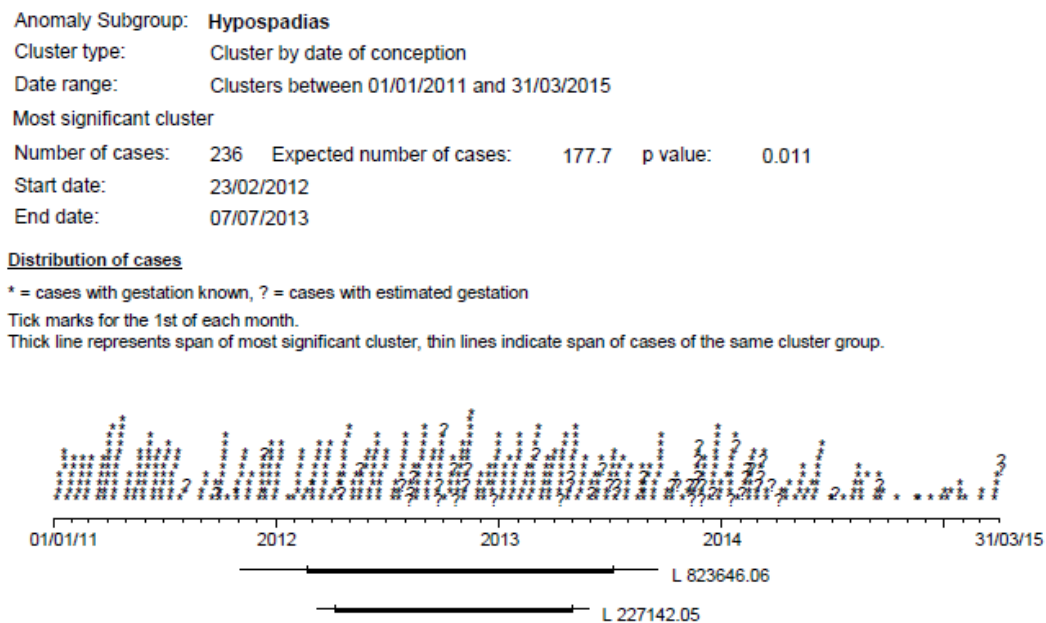Thick line represents span of most significant cluster, thin lines indicate span of cases of the same cluster group.

Hypospadias

Clusters of hypospadias were detected in Northern England and South West England.

In Northern England, isolated cases of hypospadias have only been recorded since 2013. This has given rise to a marked increase in the prevalence rate from 2013 onwards. Therefore, this is not a 'true' cluster.

Anomaly Subgroup: **Hypospadias**
Cluster type: Cluster by date of birth
Date range: Clusters between 01/01/2011 and 31/12/2015
Most significant cluster
Number of cases: 76   Expected number of cases: 44.43   p value: <0.001
Start date: 19/01/2013
End date: 02/05/2014

Distribution of cases

* = cases with valid date of birth
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.

In South West England, the cluster was not detected once errors in dates of conception were corrected. South West England concluded that this is not a 'true' cluster.

Anomaly Subgroup: **Hypospadias**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 236   Expected number of cases: 177.7   p value: 0.011
Start date: 23/02/2012
End date: 07/07/2013

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.

Polydactyly

The cluster was detected in Thames Valley, UK and Isle de Reunion, France.

In the Thames Valley registry, the notification of orthopaedic anomalies was reduced during the transition to NCARDRS. Only six cases were recorded in 2015 compared with 22 in 2014. Thames Valley reported that this is probably not a 'true' cluster.
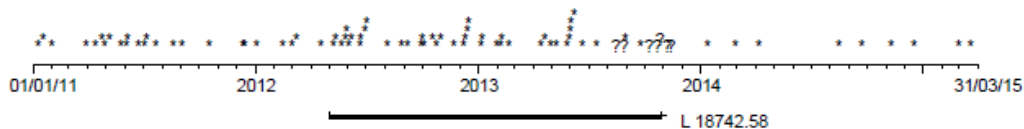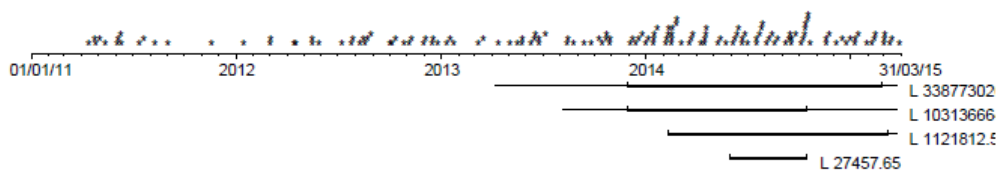
Anomaly Subgroup: **Polydactyly**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster

Number of cases: 50   Expected number of cases: 29.92   p value: 0.032
Start date: 02/05/2012
End date: 29/10/2013

Distribution of cases

* = cases with valid date of birth
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.

Regarding the cluster detected in the Isle de Reunion registry, the registry reported that it had added information from the consultation of infant surgery planning to their information sources from 2013. Also, hospital coding has improved for this anomaly. Before 2013, the cases were probably underestimated. The registry will follow closely this anomaly to understand if the increase is due to better ascertainment or as a result of other factor(s) (hereditary, high level of population of African origin, etc.).

Anomaly Subgroup: **Polydactyly**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster

Number of cases: 82   Expected number of cases: 44.88   p value: <0.001
Start date: 28/11/2013
End date: 25/02/2015

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.

Club Foot

Clusters of club foot were detected in South West England and Northern England.

Northern England reported that the change in registering club foot is highly likely to have contributed to the detection of clusters and to the increased prevalence of this anomaly in 2014 and 2015. It is likely that clusters are artefacts and will not be detected in the context of 5 years data at the increased prevalence level.
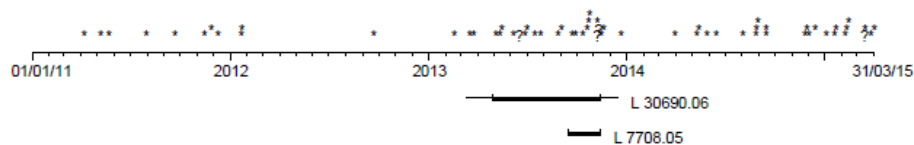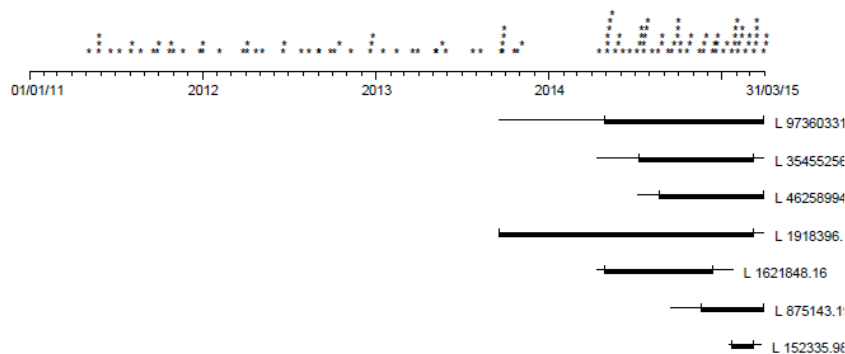
Anomaly Subgroup: Club foot - talipes equinovarus
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 22   Expected number of cases: 7.995   p value: 0.017
Start date: 29/04/2013
End date: 14/11/2013

Distribution of cases

* = cases with valid date of birth
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.

Similarly, for South West England, there was an increase in cases reported in 2015. This is known to be due to a change in coding practice as result of standardisation within the new NCARDRS service, which resulted in more cases being coded/confirmed than was the previous practice within the South West Congenital Anomaly Register (SWCAR).

Anomaly Subgroup: Club foot - talipes equinovarus
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 66   Expected number of cases: 26.73   p value: <0.001
Start date: 28/04/2014
End date: 30/03/2015

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.

Hip dislocation and/or dysplasia

The cluster was detected in Thames Valley and Cork and Kerry.

Due to a problem with data quality during transition from CAROBB to NCARDRS, there was a marked drop in the notification of hip dysplasia in 2015. Only one case was recorded in 2015 compared with 61 in 2014. Thames Valley considers that this is not a 'true' cluster.
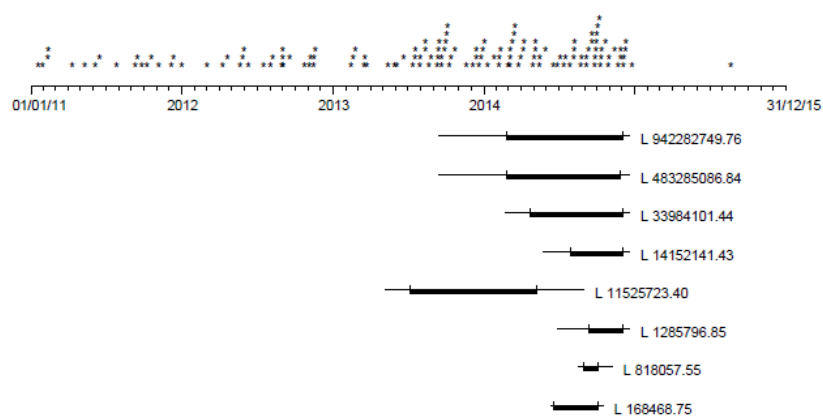
Anomaly Subgroup: **Hip dislocation and/or dysplasia**
Cluster type: Cluster by date of birth
Date range: Clusters between 01/01/2011 and 31/12/2015
Most significant cluster

Number of cases:	53	Expected number of cases:	21.7	p value:	<0.001

Start date: 26/02/2014
End date: 03/12/2014

Distribution of cases

* = cases with valid date of birth
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.

The investigation report is not available for the cluster detected in Cork and Kerry.

Anomaly Subgroup: **Hip dislocation and/or dysplasia**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster

Number of cases:	5	Expected number of cases:	0.308	p value:	<0.001

Start date: 26/03/2014
End date: 26/03/2014

Distribution of cases

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

Down syndrome

Clusters of Down syndrome cases were detected in Emilia Romagna and Tuscany.

In Emilia Romagna, the cluster was explained by quality issues: this cluster is a clear case of previous underreporting which the registry had identified, and also as a result of TOPFAs being reported late in the region.
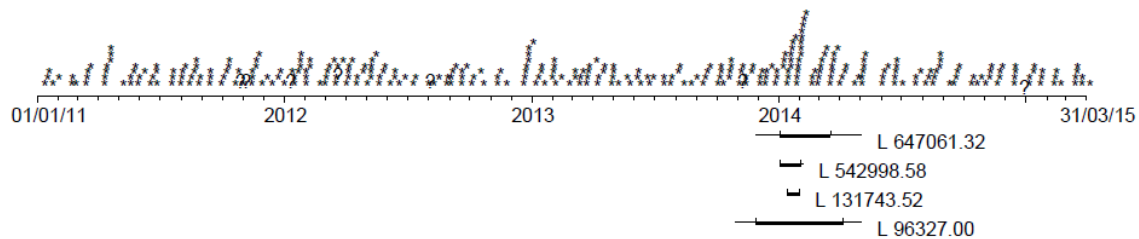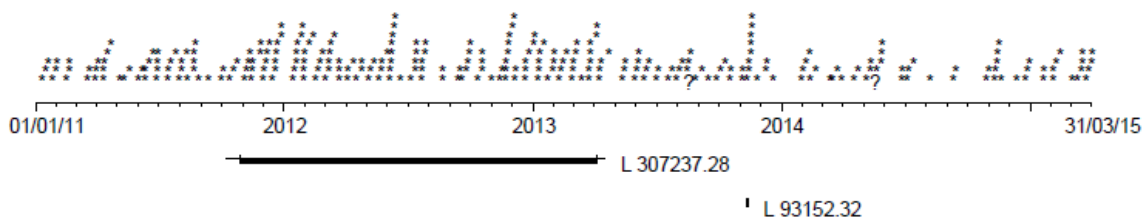
Anomaly Subgroup: **Down Syndrome**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 41   Expected number of cases: 16.95   p value: 0.009
Start date: 02/01/2014
End date: 18/03/2014

Distribution of cases

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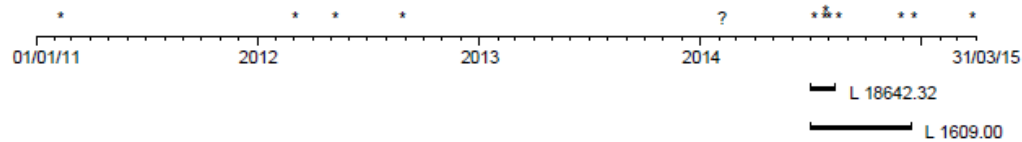

01/01/11   2012   2013   2014   31/03/15

L 647061.32
L 542998.58
L 131743.52
L 96327.00

In Tuscany, the investigation was not performed because the cluster's dimension is too large to be explored.

Anomaly Subgroup: **Down Syndrome**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 140   Expected number of cases: 98.50   p value: 0.013
Start date: 29/10/2011
End date: 05/04/2013

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.

01/01/11   2012   2013   2014   31/03/15

L 307237.28
L 93152.32

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Klinefelter syndrome

A cluster of Klinefelter syndrome was detected in South West England. The cluster included two cases from monozygotic twins. When they were evaluated as a single case, the cluster disappeared. This is not a 'true' cluster.

Anomaly Subgroup: **Klinefelter syndrome**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2011 and 31/03/2015
Most significant cluster
Number of cases: 5   Expected number of cases: 0.344   p value: <0.001
Start date: 02/07/2014
End date: 11/08/2014

Distribution of cases

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

Table 1: Details of the 25 clusters detected in the 2011-2015 monitoring and outcomes of local registry preliminary investigations.

Anomaly	Registry	EUROCAT Classification of Explanation	No of cases in cluster	Expected cases	Valid cases	Length of cluster (days)	P value
Arhinencephaly / holoprosencephaly	South West England (UK)	**Data quality issues found to explain cluster** – cluster disappeared after exclusion of one genetic case	6	0.7	21	51	0.025
Anophtalmos / Microphtalmos	Wales (UK)	The number of cases in cluster is too small to warrant further investigation.	5	0.47	19	37	0.029
Congenital cataract	North England (UK)	**Data reporting found to explain cluster:** increased ascertainment due to a new data source	8	2.14	11	355	0.025
	Tuscany (Italy)	**Excess of cases – to be followed**	14	5.65	16	547	0.009
Ventricular Septal Defect	Tuscany (Italy)	**Excess of cases – to be followed**	5	0.35	540	-----	<0.001
Atrial Septal Defect	South West England (UK)	**Data quality issues found to explain cluster**	8	1.16	62	28	0.037
Ebstein's anomaly	Emilia Romagna (Italy)	**Excess of cases – to be followed**	5	0.85	7	187	0.015
Hypoplastic right heart	Isle de Reunion (France)	**Excess of cases – to be followed**	5	1.11	7	245	0.038
PDA as only CHD in term infants	Thames Valley (UK)	**Data quality issues found to explain cluster**	6	0.82	13	114	0.018
HirschsprungDisease	Thames Valley (UK)	**Data quality issues found to explain cluster**	13	4.62	20	421	0.033
Diaphragmatic hernia	Cork and Kerry (Ireland)	No report	7	1.12	10	173	<0.001
Congenital hydronephrosis	North Netherlands (NL)	**Data reporting found to explain cluster:** most cases are minor anomalies, detected in US screening	34	14.64	141	160	0.022
Hypospadias	North England (UK)	**Data reporting found to explain cluster:** change in registering club food, reported as isolated anomaly from 2013.	76	44.43	173	468	<0.001
	South West England (UK)	**Data quality issues found to explain cluster**	236	177.66	550	500	0.011
	Tuscany (Italy)	**Excess of cases – to be followed**	6	0.5	194	3	0.027
Club Foot	North England (UK)	**Data reporting found to explain cluster:** change in registering club food, reported as isolated anomaly from 2014.	22	7.99	62	199	0.017
	South West England (UK)	**Data quality issues found to explain cluster:** changes in coding practice.	66	26.73	123	336	<0.001

Anomaly	Registry	EUROCAT Classification of Explanation	No of cases in cluster	Expected cases	Valid cases	Length of cluster (days)	P value
Hip dislocation and/or dysplasia	Thames Valley (UK)	**Data quality issues found to explain cluster**	53	21.7	141	280	<0.001
	Cork and Kerry (Ireland)	No report	5	0.31	477	-----	<0.001
Polydactyly	Isle de Reunion (France)	**Data quality issues found to explain cluster**	82	44.88	153	454	<0.001
	Thames Valley (UK)	**Data quality issues found to explain cluster**	50	29.92	85	545	0.032
Skeletal dysplasias	Wales (UK)	**Excess of cases – to be followed**	18	6.65	40	257	0.035
Down syndrome	Emilia Romagna (Italy)	**Data quality issues found to explain cluster:** timing of data reporting	41	16.95	346	75	0.009
	Tuscany (Italy)	No report	140	98.5	291	542	0.013
Klinefelter syndrome	South West England (UK)	**Data quality issues found to explain cluster –** when monozygotic twin are evaluated as one case, the cluster disappears	5	0.34	13	40	<0.001

Appendix A: EUROCAT full member registries inclusion list

	Pan-Europe trends		Cluster monitoring	
	Included in analysis	Investigation reports	Included in analysis	Investigation reports
Austria, Styria	No, as data transmission >1 year late			
Belgium, Antwerp	✓	—	No data for 2015	
Belgium, Hainaut	✓	—	✓	—
Croatia, Zagreb	✓	x	✓	—
Denmark, Odense	Collaboration agreement not signed			
France, Auvergne	No, as data transmission >1 year late			
France, Brittany	No, as data for 4 years only			
France, French West Indies	No, as data for 7 years only		✓	—
France, Paris	No, as data transmission >1 year late			
France, Reunion	✓	x	✓	✓
Germany, Mainz	✓	—	No data for 2015	
Germany, Saxony Anhalt	✓	x	✓	—
Hungary	Collaboration agreement not signed			
Ireland, Cork & Kerry	✓	x	✓	x
Ireland, Dublin	No, as data transmission >1 year late			
Ireland, South East	✓	—	No data for 2015	
Italy, Emilia Romagna	✓	✓	✓	✓
Italy, Tuscany	✓	x	✓	✓
Malta	✓	—	No data for 2015	
Netherlands, Northern	✓	✓	✓	✓
Norway	No, as data transmission >1 year late			
Poland, Wielkopolska	No, as data transmission >1 year late			
Portugal, South	✓	x	✓	—
Spain, Basque Country	✓	—	No data for 2015	
Spain, Valencia Region	✓	—	No data for 2015	
Switzerland, Vaud	✓	✓	✓	—
Ukraine	✓	—	No data for 2015	
UK, E Midlands & S Yorkshire	No, as data transmission >1 year late			
UK, Northern England	✓	✓	✓	✓
UK, South West England	✓	✓	✓	✓
UK, Thames Valley	✓	✓	✓	✓
UK, Wales	✓	x	✓	✓
UK, Wessex	✓	✓	✓	—

✓ Investigation report received

X No Investigation report received

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

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Appendix B: Congenital anomaly subgroup inclusion list

The EUROCAT congenital anomaly subgroups are defined in EUROCAT Guide 1.4, Chapter 3.3 (http://www.eurocat-network.eu/content/Section%203.3-%2027_Oct2016.pdf), and are analysed in the following ways:

- Prevalence by outcome of pregnancy, by registry and year. All cases and All cases excluding genetic conditions[2] are included in the analysis and the results are published in the prevalence tables available on the EUROCAT website (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.

- Detection of clusters, 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

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[2] 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
Anotia	✔	✔	✔
Congenital heart defects (CHD)	✔	✔	**NO**
Severe CHD	✔	✔	✔
Common arterial truncus	✔	✔	✔
Double outlet right ventricle	✔	✔	✔
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	✔	✔	✔

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Atresia of bile ducts	✓	✓	✓
Annular pancreas	✓	✓	✓
Diaphragmatic hernia	✓	✓	✓
Abdominal wall defects	✓	**NO**	**NO**
Gastroschisis	✓	✓	**NO**
Omphalocele	✓	✓	✓
Urinary	✓	**NO**	**NO**
Bilateral renal agenesis including Potter syndrome	✓	✓	✓
Multicystic renal dysplasia	✓	✓	✓
Congenital hydronephrosis	✓	✓	✓
Bladder exstrophy and/or epispadia	✓	✓	✓
Posterior urethral valve and/or prune belly	✓	✓	✓
Genital	✓	**NO**	**NO**
Hypospadias	✓	✓	✓
Indeterminate sex	✓	✓	✓
Limb	✓	**NO**	**NO**
Limb reduction	✓	✓	✓
Club foot – talipes equinovarus	✓	✓	✓
Hip dislocation and/or dysplasia	✓	✓	✓
Polydactyly	✓	✓	✓
Syndactyly	✓	✓	✓
Other anomalies/ syndromes			
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	✓	✓	✓

EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Genetic syndromes + microdeletions	✔	✔	NO
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: Summary of statistical methods

Trends

The pan-Europe monitoring can only be conducted centrally as it uses data from all the registries combined. The methodology used for pan-Europe monitoring is the same as for the ten year trend monitoring (Box 1) with the exception that it is run using the last 10 years of data (2006-2015) or using nine years of data within the 10 year period (2006-2015) and adjusts for the effect of registry by fitting a multi-level Poisson regression model.

Statistical methods:

1. A chi square test for trend and for non-linear change based on number of cases and number of births per year is performed.

2. Ten year trend tests are run using eight or 10 years of data within the 10 year period (2006-2015).

3. Trend analysis is presented by individual year unless there are too few cases, when data is then grouped by two year intervals.

4. Trend analysis is always based on year of birth/delivery.

5. A trend test is performed if the average expected number of cases per two year interval is 5 or more, OR if the observed number of cases per two year interval is 2 or more

6. Significant increasing or decreasing monotonic (going in one direction) trends are reported.

    – Where $p<0.05$ for trend component and $p>0.01$ for non-linear component, the results are identified as 'increasing or decreasing trend'

    – Where $p<0.05$ for trend component and $p<0.01$ for non-linear component and the prevalence trend is monotonic, the results are identified as 'increasing or decreasing trend '

    – Where $p<0.05$ for trend component and $p<0.01$ 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.

    – The significance level (p-value) for both chi squared tests, direction (upward or downward) are given in the output.

7. Trend analysis is conducted on 79 EUROCAT congenital anomaly subgroups and the following computer generated subgroups adjusted for maternal age and in utero survival: Down syndrome, Patau syndrome and Edward syndrome.

Clusters

A 'scan' moving window method is used to detect clusters, (See EUROCAT Statistical Monitoring Protocol http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2012.pdf), scanning all recorded cases in the period 2011-2015.

1. Clusters or deficits occurring in the last two years (2014-2015) that are less than 18 months in length are reported.

2. A minimum of seven cases over the surveillance period (2011-2015) is needed to run the scan analysis.

3. The default scan analysis uses estimated date of conception, if date of conception is cannot be estimated for > 10% of cases, then cluster analysis uses 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 (2015). If date of birth/delivery is used to detect clusters, the last full year (1 January – 31 December) is included in the surveillance.

5. The output of cluster analyses lists all significant clusters which may be over-lapping. All the output data should be examined to determine the full time period over which the excess number of cases is observed. This may be outside the start and end date of the most significant cluster. Cluster analysis is run on 75 EUROCAT subgroups of congenital anomalies (Appendix B). Seventeen major heterogeneous subgroups (e.g. nervous system, eye, congenital heart defects etc.) are excluded from analysis.

6. Cluster test results are presented alongside 5-year trend (chi square) results, to help assess whether the cluster could be described as a short term trend.

Appendix D: Summary of registry preliminary investigation protocols 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 (http://www.eurocat-network.eu/content/EUROCAT-Statistical-Monitoring-Protocol-2012.pdf). 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 significant ten-year increasing and decreasing trends detected in the pan-Europe analysis 2015

Anomaly Subgroup	Direction	Annual % change		
		% change	Lower CI	Upper CI
Hydrocephaly	Decreasing	-1.6	-3.1	0.0
Severe microcephaly	Decreasing	-4.2	-6.5	-2.0
Anophtalmos/microphtalmos	Decreasing	-5.3	-9.2	-1.5
Ventricular septal defect	Increasing	0.7	0.1	1.3
Atrial septal defect	Increasing	1.0	0.1	2.0
Tricuspid atresia and stenosis	Increasing	5.3	1.0	9.5
Pulmonary valve stenosis	Decreasing	-3.5	-5.2	-1.9
Hypoplastic right heart	Increasing	6.8	1.8	11.9
Hypoplastic left heart	Decreasing	-2.3	-4.5	-0.1
PDA as only	Decreasing	-5.3	-7.5	-3.1
Cleft lip with or without palate	Decreasing	-1.2	-2.4	0.0
Cleft palate	Decreasing	-1.6	-3.0	-0.1
Gastroschisis	Decreasing	-2.6	-4.6	-0.7
Multicystic renal dysplasia	Increasing	1.8	0.0	3.5
Congenital hydronephrosis	Increasing	2.8	1.7	3.8
Hypospadias	Decreasing	-1.9	-2.7	-1.1
Club foot – talipes equinovarus	Increasing	3.4	2.3	4.5
Syndactyly	Decreasing	-3.1	-4.9	-1.3
Vascular disruption anomalies	Decreasing	-2.4	-3.7	-1.2
Congenital constriction bands	Decreasing	-4.1	-8.3	0.0
Conjoined twins	Decreasing	-9.4	-17.3	-1.4
Laterality anomalies	Increasing	2.7	0.1	5.2
Valproate syndrome	Decreasing	-27.5	-43.9	-11.1
Genetic syndromes and microdeletions	Decreasing	-1.8	-3.1	-0.5
Klinefelter syndrome	Decreasing	-7.6	-11.2	-3.9
Down Syndrome age adjusted	Decreasing	-0.9	-1.8	-0.1

*Note: *Significant non-linear change is not included in this table*

References

1. Morris JK, Rankin J, Garne E, Loane M, Greenlees R, Addor MC, Arriola L, Barisic I, Bergman JE, Csaky-Szunyogh M, Dias C, Draper ES, Gatt M, Khoshnood B, Klungsoyr K, Kurinczuk JJ15, Lynch C16, McDonnell R, Nelen V, Neville AJ, O'Mahony MT, Pierini A, Randrianaivo H, Rissmann A, Tucker D, Verellen-Dumoulin C, de Walle HE, Wellesley D, Wiesel A, Dolk H. (2016) Prevalence of microcephaly in Europe: population based study. BMJ 13; 354: i472.

2. Loane M, Dolk H, Bradbury I. (2007) Increasing prevalence of gastroschisis in Europe 1980-2002: a phenomenon restricted to younger mothers? Paediatric and Perinatal Epidemiology 21: 363–369.

3. Rittler M, Campana H, Ermini ML, Gili JA, Poletta FA, Pawluk MA, Giménez LG, Cosentino VR, Castilla EE, López-Camelo JS (2015) Gastroschisis and young mothers: what makes them different from other mothers of the same age? Birth Defects Research Part A: Clinical and Molecular Teratology 103: 536–543.

4. Loane M, Dolk H, Kelly A, Teljeur C, Greenlees R, Densem J. (2011) Paper 4: EUROCAT statistical monitoring: identification and investigation of ten year trends of congenital anomalies in Europe. Birth Defects Research Part A: Clinical and Molecular Teratology 91(Suppl 1): S31–S43.

5. Whitehall JS, Kandasamy Y, Stalewski H, Gill A. (2010) Perinatal demography of gastroschisis in North Queensland. J Paediatr Child Health. 46(12): 749-53.

6. Benjamin BG, Ethen MK, Van Hook CL, Myers CA, Canfield MA. (2010) Gastroschisis prevalence in Texas 1999-2003. Birth Defects Res A Clin Mol Teratol. 88(3):178-85.

7. Fillingham A, Rankin J. (2008) Prevalence, prenatal diagnosis and survival of gastroschisis. Prenat Diagn. 28(13):1232-7.

8. Martin S, de la Cruz J, Lanzoni M, Nicholl C. (2016) Transfer of the Central Database and coordinating activities of EUROCAT to the JRC, EUR 28225 EN, doi:10.2788/973472

9. EUROCAT Statistical Monitoring Protocol, http://www.eurocat-network.eu/content/Stat-Mon-Protocol-(Jan-2015)-2012.pdf

10. 2012 EUROCAT Statistical Monitoring Report, http://www.eurocat-network.eu/content/Stat-Mon-Report-2012.pdf

11. Stevens S, Miller N, Rashbass J. (2017) Development and progress of the National Congenital Anomaly and Rare Disease Registration Service. Arch Dis Child pii: archdischild-2017-312833.

12. Švehlík M, Floh U, Steinwender G, Sperl M, Novak M, Kraus T. (2017) Ponseti method is superior to surgical treatment in clubfoot - Long-term, randomized, prospective trial. Gait Posture 58:346-351.

13. Frías JL, Frías JP, Frías PA, Martínez-Frías ML (2007) Infrequently studied congenital anomalies as clues to the diagnosis of maternal diabetes mellitus. Am J Med Genet A. 143A (24):2904-9.

14. EMA Recommendation (2014)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f (accessed 12/12/2017)

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