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EUROCAT Statistical Monitoring Protocol

Updated methodology

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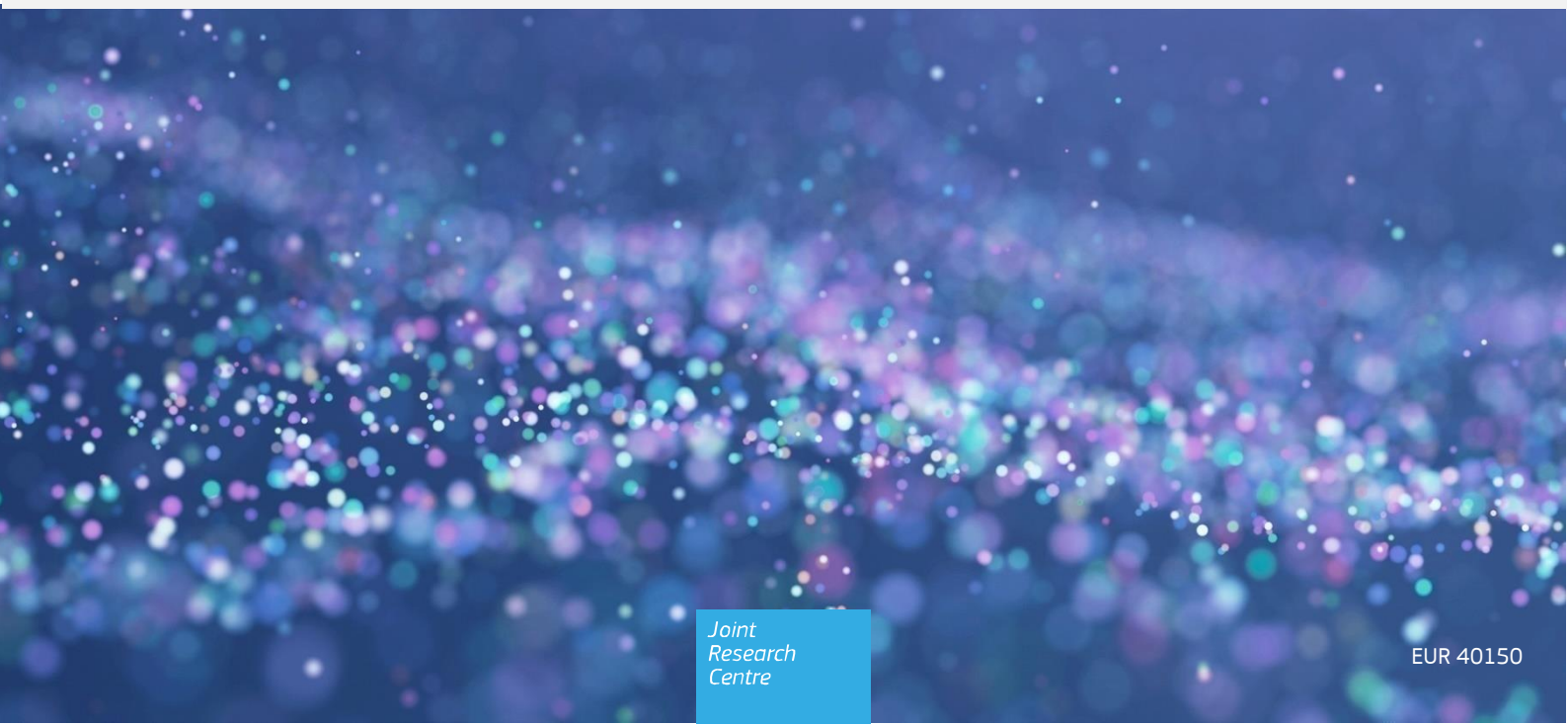

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Contents

Abstract

The European network of population-based registries for the epidemiologic surveillance of congenital anomalies (EUROCAT) was established in 1979. It collects, twice a year, individual cases with congenital anomalies among livebirths, stillbirths and terminations of pregnancy for fetal anomaly from local registries spread all over Europe. Since 2015, the Central Registry of EUROCAT is coordinated by the European Commission Joint Research Centre (JRC), as part of the European Platform on Rare Disease Registration.

Each year, after the first annual submission, the Central Registry runs statistical monitoring analyses as part of EUROCAT surveillance activities. The monitoring mainly contributes to two of EUROCAT objectives: (i) to provide essential epidemiological information on congenital anomalies in Europe and (ii) to facilitate the early warning of teratogenic exposures.

Currently, the statistical monitoring is conducted to detect changes over time within each registry and across all registries as well as unusual aggregations of cases (clusters) within each registry. It enables the data to be regularly and systematically scrutinised and identifies any increases or decreases in frequency that are unlikely to be due to random fluctuations. These identified changes may reflect true changes in the prevalence of the anomalies (perhaps due to potential new teratogenic exposures) or may be due to changes in health care – such as earlier ultrasounds identifying anomalies at earlier gestational ages – or to changes in reporting procedures. Further approaches are then undertaken to confirm the underlying cause(s) of the changes detected, with a particular focus on new teratogens (e.g. drug, environmental exposure) and the effectiveness of primary prevention.

The EUROCAT statistical monitoring protocol describes the statistical methods used for EUROCAT annual statistical surveillance activities. These methods are implemented in the EUROCAT Data Management Software (DMS) provided to member registries for use by non-statisticians. In addition, detailed guidance for non-statisticians is provided to the member registries for the interpretation of DMS outputs and the investigation of the significant trends and clusters. This enables member registries to understand and effectively communicate any relevant results to their public health authorities.

Acknowledgements

Hannah Johnson, Agnieszka Kinsner-Ovaskainen, Joan Morris and Annie Perraud wrote the present protocol. Hannah Johnson developed the R script to perform the individual registries' and the pan-European trends analysis, in consultation with Joan Morris. Fabrizio Zaro and Antonino Brunetto implemented the statistical methods in the Data Management Software (DMS). Annie Perraud, and Monica Lanzoni before her departure, validated the implementation in the DMS.

This protocol documents the recent changes and upgrades in the existing EUROCAT statistical monitoring methods. The existing methods were the work of many people within EUROCAT since the inception of the network.

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1 Introduction

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies. The objectives of EUROCAT are to facilitate the early warning of new teratogenic exposures and to evaluate the effectiveness of primary prevention [1]. The network currently surveys approximately one fourth of the European birth population. The EUROCAT Central Registry is operated by the European Commission's Joint Research Centre, as part of the European Platform on Rare Diseases Registration [2].

EUROCAT was established in 1979 in the wake of the thalidomide epidemic. Each year, EUROCAT conducts the statistical monitoring of congenital anomalies to detect changes in time within each registry and to detect trends across all registries as well as unusual aggregation of cases (clusters) within each registry. Statistical monitoring aims at early detection of any new teratogenic drug, but interest has also widened to other potential teratogens such as environmental chemicals.

Part of the EUROCAT monitoring strategy is the annual statistical monitoring for trends and clusters at central level, 15 months after last date of birth, e.g. year 2022 births included in monitoring in March 2024. The cluster analysis detects unusual aggregation of cases in time within each registry area, which may be a cause of concern (e.g. teratogenic exposures). A pan-European trend analysis enables the monitoring of congenital anomalies that have too few cases to be monitored at individual registry level, as well as presenting an overview of the situation in Europe.

Statistical monitoring is only one part of surveillance of teratogenic exposures, to identify potential cause for concern where there is no specific prior hypothesis about the exposure. It is essentially a screening method to scrutinise data regularly and systematically, to detect any previously unrecognised increases in frequency. Where there are specified hypotheses about new teratogens (e.g. which drug, when, where), other direct approaches for analysis should be undertaken which are not the subject of this protocol.

The elements of the current monitoring strategy are:

- Common user-friendly statistical software for use centrally and locally (DMS).
- Annual statistical monitoring for trends and clusters at central level, 15 months after last date of birth (e.g. year 2022 births are included in monitoring in March 2024).
- More frequent and/or earlier statistical monitoring locally (by member registries).
- Use of EUROCAT communications and special data analyses to respond to news about clusters identified locally or outside the monitoring system.
- A clear system of investigation and reporting of results.
- Use of statistical monitoring additionally as a data quality control system.

The statistical monitoring of pan-European trends and temporal clusters of congenital anomalies is performed using individual case data from full member registries. Cases of congenital anomalies among live births, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly (TOPFA) following prenatal diagnosis at any gestational age are included. The analyses are performed on selected EUROCAT congenital anomaly subgroups. All subgroups are defined in EUROCAT Guide 1.5, chapter 3.3. [3, 4].

Statistical methods have been chosen, which are relatively straightforward for public health authorities to understand and communicate, and which can be supplied to member registries in the EUROCAT Data Management Software (DMS) for use by non-statisticians.

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

The present protocol has been in use for the annual statistical monitoring since 2023 (birth years up to 2021).

2 Timelines of the EUROCAT statistical monitoring

The statistical monitoring analysis is performed usually in the second half of March, using the JRC-EUROCAT Central Database validated after the annual February data transmission deadline (e.g. including data submitted in February 2024 for children born in 2022).

The results of the statistical monitoring performed centrally are reviewed at a Management Committee meeting and reported to local registries in in April/May. These results are the basis for initiating possible further investigations at the local registry level.

The preliminary investigations of the clusters and trends are then discussed at the Registry Leader's Meeting in June. Detailed reports from local registry investigations are sent to the Central Registry by July/August, and are discussed at a Management Committee meeting in September. They are used to prepare the annual EUROCAT surveillance report.

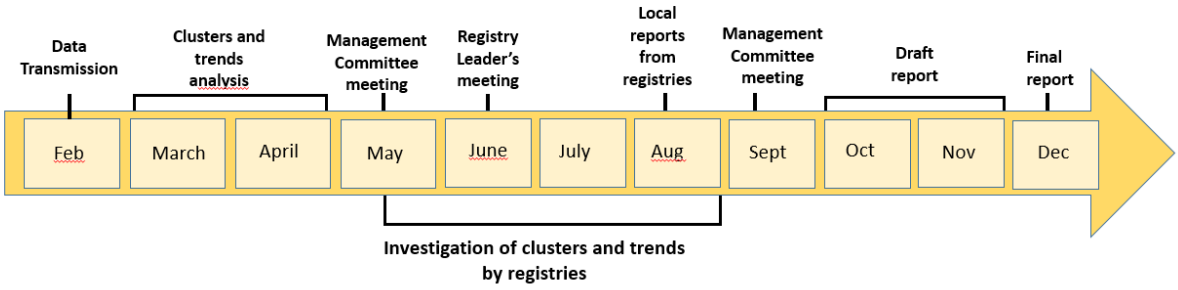
The Central Registry then prepares a draft of the annual report and asks all concerned registries to confirm it. The final Annual Statistical Monitoring Report is published on the EUROCAT website in December.

The timeline for the statistical monitoring performed by EUROCAT in 2024 is presented in Figure 1, as an example.

All full member registries who send individual case data and are able to meet the annual February data transmission deadline (e.g. February 2024 for 2022 births) participate in cluster detection monitoring. All full member registries that have data no more than one year behind (e.g. 2021 complete in February 2024) are included in trend analysis. The detailed criteria for inclusion of the registries are presented in section 3.1 and 4.2 of this protocol.

Associate members that provide only aggregate data to EUROCAT can also request to be included in the trend analysis. Associate member registries as well as registries that do not send complete or accurate date of birth are invited to use DMS locally for cluster detection and to report their results to the Central Registry.

Figure 1. Timeline for the annual statistical monitoring performed by EUROCAT.



Source: JRC-EUROCAT Central Registry

3 Statistical methods for the detection of trends

The Central Registry performs for every registry at central level a trend test for the most recent 10 years. Trend tests are performed for 94 anomaly subgroups (see Annex 1). The analysis is based on the number of cases per year of birth and the number of births per year. Data is presented by individual year. Trend tests are not reported if the total number of cases over the time-period is less than 5, or where a chi-squared test of the deviance provides moderate evidence that the model is incorrectly specified ($p<0.05$).

3.1 Registry inclusion criteria

The following criteria are used for the inclusion of the registries in the annual trend analyses conducted at central level:

1. Registries are no more than one year late with data transmission, and have submitted data continuously for at least eight calendar years. For example, if the last year of analysis is 2022, data shall be available for 2013-2022, 2013-2021, 2013-2020, 2014-2022 or 2014-2021;
2. Registries for which the number of submitted cases in the latest year was at least 80% of those submitted in previous calendar years.

3.2 Methodology

Trend tests are not performed if the total number of cases over the time-period is less than 5. The average annual percentage change in prevalence per year is calculated using generalised linear models (GLMs). Poisson models with log-links are used with the outcome number of cases, predictor centred year, and offset log-total number of births in the population. The average percentage change in prevalence, significance level (p-value), and direction (upward or downward) are given in the output.

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

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

The GAM model is sensitive to fluctuations in prevalence. Reports of curved trends with high e.d.f (>4) should be interpreted with caution, as they may indicate inconsistencies with the data collection. Where this is the case, data checking may be warranted.

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

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

3.3 "Pan-European" trend detection

The "Pan-Europe" analysis includes data across all eligible registries. This is particularly useful for rare anomalies which frequently have too few cases per year for analysis in individual registries. Analysis is the same as above but uses generalised linear mixed models (GLMMs), and generalised additive mixed models (GAMMs) with random intercepts and slopes for registries.

All reported Pan-European trends are accompanied by plots with the point prevalence of each registry, along with fitted GLMM and GAMM trend lines (see Annex 2).

Trends are reported and identified as for the registry trends. The GAMM model is sensitive to fluctuations in prevalence. Reports of curved trends with high e.d.f (>4) should be interpreted with caution. If there is no clear explanation for a non-linear response, the GLMM results may be considered more appropriate for interpretation.

4 Statistical methods for the detection of clusters

4.1 Definition of a cluster

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.

The annual statistical monitoring performed at the central level concerns the detection of clusters in time only. The data in the EUROCAT Central Database does not permit geographical evaluations, as precise data on geographic locations of the residence of the mothers is not transmitted to the Central Registry. Cluster investigations, including potentially space investigation, are then conducted by the registry at a local level. The DMS software allows registries locally to detect also temporal clusters within subareas of the area covered by the registry.

4.2 Registry inclusion criteria

The criteria for inclusion of the registry in the annual cluster analyses performed at central level are:

1. Registries must submit individual case data, i.e. must be full EUROCAT members;
2. Registries must have transmitted data for all five years, e.g. for 2017-2021, or 2016-2020;
3. Full individual dataset must include at least full date of birth (day, month, year), outcome of pregnancy (live/still/TOPFA), gestational age, malformation codes and their derived anomaly subgroups.
4. The number of cases submitted by the registry for the last birth year (e.g. 2022) is at least 80% of those submitted in the previous calendar years;
5. Registries must have a stable birth population (annual birth population changes must be less than +/-10% between any two years within the five-year period).

4.3 Methodology for cluster detection

Cluster detection is based on a moving window test described by Nagarwalla [5] (see Annex 3 for statistical details). 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. The method 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 5 cases. A minimum of 7 cases over the study period of interest is needed to run the analysis. All window sizes from a minimum of 5 to a maximum of the total number of cases minus 2 are tested.

Each registry and anomaly subgroup is tested independently and the analysis takes into account the number of tests with different window sizes being performed within each registry/anomaly combination to allocate a likelihood to each cluster. The method gives each cluster identified a scan statistic called “lambda”, from which a p-value for significance is derived (see Annex 3).

Many clusters may overlap in time, the inclusion or exclusion of individual cases changing their significance. All significant clusters are identified ($p<0.05$). The "most significant" cluster (lowest p-value) is then identified. All other significant clusters for which at least 75% of cases overlap with the "most significant" cluster are considered to belong to the same cluster group. The method then looks for the second most significant cluster not already allocated to a cluster group and proceeds similarly identifying the second cluster group. The output identifies the most significant cluster in each cluster group, and the first and last case in time belonging to any cluster within the cluster group.

Following identification of all cluster groups over the time period of analysis, cluster groups overlapping with the last two years of data, and in which the most significant cluster is less than 18 months in length, are chosen for output and investigation. An option is also provided in the software for Central Registry to scan the most significant cluster in all years of data scanned, rather than just the last two years, for research purposes. Similarly, options are available to reset the percentage acceptable for missing gestational age, and cluster lengths greater than 18 months.

Currently Central Registry performs annual cluster analysis using the most recent 5 years of data. More than 5 years may tend to identify trends rather than clusters, and will be computationally slower. Less than 5 years will have less power to detect clusters.

Since it is exposure during early pregnancy (organogenesis) that is relevant, it is preferable to use estimated date of conception[1] rather than date of birth. Thus, cases of different gestational ages (and terminations of pregnancy of low gestational age) are related to a common time when they passed through organogenesis. Cluster detection uses date of conception where gestational age is recorded for more than 90% of cases (for any 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 9 months before the last birth month where data collection is complete. Where full years of data are used for surveillance, this means ending the period of the scan at 31 March (date of conception) of the last year of data collected. After this date, some conceptions may result in births in the next year which are not yet included in the dataset. Similarly, the start of the monitoring period must include a complete cohort of conceptions i.e. to detect clusters by date of conception for cases born (or with estimated date of delivery) in the approximate period e.g. 2021-2022, the scan routine includes cases with date of conception between 1st April 2020 and 31st March 2022 (24 months). The default monitoring period is set to start with estimated dates of conceptions from 1 January of the beginning of the five year period (for simplicity, and to ensure complete coverage of eligible conception outcomes). This means that cluster detection by date of conception is run on 51 months of data (4 complete years: 4 x 12 months = 48 months; and 3 months of the last year included in surveillance). Cluster detection by date of birth is run on 5 complete years of data (60 months).

[1] The EUROCAT date of conception is really the date of LMP (last menstrual period).

The Scan method is based on case counts, and results would not be valid if there is a large underlying change in population (births) size. There are two types of population change: change in geographical area that the registry covers, and large change in birth rate within the same geographical area. When basing cluster detection on conception cohorts, the latter could be easily taken into account by statistical modifications. However, it is the former type of population change that is more frequent, and a decision was therefore made to exclude registries where population (number of births) change is more than 10% between any two years within the five-year period.

Each dataset used for monitoring should be archived, both by Central Registry and by local registries, as the database is dynamic. Registries should archive a copy of the file transmitted to Central Registry in February of the year of monitoring. With this file, registries should be able to reproduce the Central Registry statistical monitoring results using the DMS.

5 Use of the EUROCAT Data Management Software (DMS) at local level

Registries can use the DMS software to perform monitoring earlier at the local level, and may need to consider smaller geographical areas for monitoring. The DMS has been designed to facilitate this.

5.1 Detection of trends

Registries may wish to use the DMS to expand the trend tests run centrally, for example use a different period of years (e.g. since beginning of registry or including a more recent year), or congenital anomaly subgroups outside the selected subgroups for monitoring (such "user defined subgroups" can be defined within the DMS). The procedure to run the tests for trends is explained in the relevant chapter of the DMS User Guide. The output from DMS is presented in Annex 2.

5.2 Detection of clusters

Local monitoring for clusters can be run more frequently using the most recently ascertained data. As a guide, local registries should run the DMS statistical monitoring program at least every 6 months and as early as possible after data collection is complete (apart from late diagnosed cases).

The procedure to run the clusters tests is explained in the relevant chapter of the DMS User Guide. The output from DMS is presented in Annex 4.

Local registries can choose to run cluster monitoring on non-standard anomaly subgroups of interest to them (such "user defined subgroups" can be defined within the DMS).

Local registries can run cluster detection in geographical sub-areas of their registry area. For each sub-area, local registries must create a "user-defined centre" (see chapter IV – Data configuration of the DMS User Guide), and run the cluster analysis separately in each sub-area/centre. Registries must also enter the total births for the user defined registry sub-area.

The time period of the scan is important and may affect the results. The reasons Central Registry has chosen a five-year period are given above. Registries scanning more recent data every 6 months are recommended to add the extra months available to the basic 5 year period. Remember that dates of conception end 9 months before the last birth month available. Which clusters are detected and their statistical significance will depend on the number of years scanned, which is an a priori protocol decision to be made before running the software (i.e. do not make the cluster "disappear" or "appear" by trying many different time periods, as this is statistically invalid).

5.3 Communication to the network of clusters and trends detected locally

Clusters and trends identified locally should be investigated in the same way as those identified by central monitoring (see 136 of this protocol), and reported to EUROCAT at the following Registry Leaders Meeting and in the Annual Statistical Monitoring Report.

Following preliminary investigations, plausible clusters and trends not resulting from data quality errors can be reported to Central Registry for communication to all local registries for further investigation (i.e. are similar clusters and trends occurring elsewhere). In this way the situation across Europe may be monitored for early detection of possible new teratogens.

6 Local investigation of trends and clusters identified by statistical monitoring at central level

After the analysis conducted by the Central Registry, every registry receives a report with trends and clusters for investigation at a local level. The summaries of these investigations are then reported to the Central Registry and used to prepare the EUROCAT annual surveillance report. Hence, the involvement of all the registries in the investigation is key and facilitates interpretation of the findings.

6.1 Guidance for investigation of trends

Registries are asked to investigate the increasing (/),decreasing (\) and curved trends detected at Pan-European level. Investigation templates are provided to make the reporting process consistent between registries (see Annex 5).

Using these templates and the outputs provided by the Central Registry (see Annex 2), registries are asked to consider the following aspects in their investigation report (consulting with clinicians or others where appropriate):

1. Case verification
    (a) Is the diagnosis confirmed and accurate?
    (b) Are there any duplicates
    (c) Are mothers resident within region? (truly population-based?)
2. Looking at the graph of the yearly prevalence, is the trend gradual or a steep change? When does the trend appear to begin?
3. Has there been a change in definition or diagnosis, or diagnostic methods e.g. increasing use of prenatal or postnatal ultrasound?
4. Have there been changes in how cases are reported to the register?
5. Is the trend found across all reporting hospitals?
6. Is there a similar trend for any other anomalies?
7. Is the trend found in isolated or multiply malformed cases?
8. Have there been changes in register population?
9. Are there any known changes in the risk factors for this anomaly?
10. Have any other registers experienced a similar trend for this anomaly?
11. For upward or curved trends; is the prevalence in your registry at the end of the time period above the EUROCAT average?
12. For downward or curved trends; is the prevalence in your registry at the end of the time period below the EUROCAT average?

Note also that looking at downward trends and heterogeneity over time can help registries with data quality monitoring.

The following codes shall be used by registries to summarise the explanation for each trend and report it to the Central Registry:

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 ongoing

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

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

6.2 Guidance for investigation of clusters

Each year, the Central Registry alerts the registries about any new and continuing clusters. **New clusters** are those that have not been detected previously. **Continuing clusters** are those that were detected in the previous year and have continued in time. These are particularly important to investigate. **Old clusters** are those that were detected and investigated the previous year, but have not continued.

Registries are asked to investigate the clusters. Investigation templates are provided to make the reporting process consistent between registries (see Annex 6). In their investigation they should look at the full 5-year timeline for the congenital anomaly subgroup of interest, as this shows the time distribution of all cases (see Annex 4). Using the templates, registries are asked to include the following in their cluster investigation report:

1. Case verification
    a. Is the diagnosis confirmed and accurate?
    b. Are there any duplicates?
    c. Are mothers resident within region? (truly-population-based?)
2. Diagnostic dimension:
    a. How heterogeneous are the diagnoses? Are cases isolated, multiply malformed, syndromes, is there new evidence of a genetic diagnosis? Any family history recorded?
    b. Do any other anomalies have clusters at the same time?
3. Space dimension:
    a. Are the cases clustered near each other within a geographical area/region?
    b. Do the cases come from a single hospital?
    c. Do other regions have a cluster at a similar time? (use communication via JRC-EUROCAT to query other registries).

    NB. The aim is to describe the cluster in terms of its spatial characteristics, giving clues as to possible causes for further investigation. For example, a new drug on the market

may not show spatial concentration, whereas a local chemical pollution accident would be expected to show spatial concentration.

4. Time dimension:
    a. Is the cluster part of a longer-term trend identified by the trend analysis? (if so, investigate as trend rather than as cluster)
    b. When does the increased risk appear to start and end? Look at other clusters in the cluster group to get an idea of the extent of the cluster.
    c. Look at the timeline graph (found in the Cluster Excel file generated by DMS). Consider evidence that the cluster started earlier than the last 2 years of data, and observe when the greatest number of excess cases occurred.
    d. If cluster is based on date of birth rather than date of conception, is it likely, making assumptions about gestational age of cases within and outside the cluster, that the cluster would also appear if analysed by date of conception?
5. Diagnostic & reporting factors:
    a. Could a change in diagnostic methods, training, personnel or reporting practice have caused the cluster? This might be particularly suspected if only one hospital is involved, and for anomaly subgroups which vary widely in severity.
    b. Does the registry have a lower rate before the cluster compared to other registries? Check the website for the EUROCAT average prevalence of the given anomaly subgroup (https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en).
    c. If there is a very large number of cases in the cluster in a very short time period, it is unlikely to be due to diagnostic factors.
6. Aetiological factors:
    a. Which factors have been investigated? Possible aetiological factors may include: medication during pregnancy, maternal diseases including infections, maternal occupation, BMI, assisted conception and others. The choice of factors to investigate depends on type of anomaly.
    b. Which factors have been looked at within the registry database (list variables) and outside the registry database and do any of these appear to explain the cluster?
    c. Which source of information was used (registry database, further access to medical records or parents etc.).
7. Local context:
    a. Was there local awareness of the cluster before it was found by central statistical monitoring, either by local DMS monitoring or by other means – within the registry or outside in the region (e.g. local community or health professional)?
    b. Are there any local concerns about environmental exposures, which may need investigation?

At the end of the investigation, the registries should explain the basis for the decisions to conduct the investigation in the way they did, and whether they will continue to investigate (if so, how?, if not, why not?).

Registries are asked to conclude from their preliminary investigations if this is a 'true cluster of concern or not' and inform whether and which public health authorities have been or will be notified about the cluster.

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

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

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

If investigation of clusters identifies data errors (e.g. incorrect codes for the diagnoses, incorrect dates of birth, duplicate cases) these errors should be corrected and updated data included in the next data transmission to Central Registry.

The **conclusions** from the cluster investigations shall 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. Clusters to be investigated at local level only.

The investigation reports (separate for each cluster) should be sent to the Central Registry at JRC-EUROCAT@ec.europa.eu.

Recommendations: If it is not already normal practice, registries should go back to original medical records for cluster cases. For clusters of chromosomal anomalies, the exact karyotype should be reported for all cases in the cluster. It is recommended to follow up all cluster cases to their current age for further diagnostic information and family history. When a cluster is confirmed and recommended for continued surveillance, registries should organise to do this surveillance earlier than the centrally performed annual surveillance system.

7 Conclusion

This EUROCAT statistical monitoring protocol describes the statistical methods used for the EUROCAT annual statistical surveillance activities and provides detailed guidance to the member registries for the interpretation of DMS outputs and the investigation of any trends or clusters that are unlikely to have arisen due to chance alone.

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List of abbreviations and definitions

DMS: Data Management Software

e.d.f.: Estimated Degree of Freedom

GLM: Generalized Linear Models

GLMM: Generalized Linear Mixed Models

GAM: Generalized Additive Models

GAMM: Generalized Additive Mixed Models

TOPFA: Termination Of Pregnancy for Fetal Anomaly

List of figures

Annex 1. Congenital anomaly subgroup inclusion list

The EUROCAT congenital anomaly subgroups are defined in EUROCAT Guide 1.5, Chapter 3.3 [3, 4], and are analysed in the following ways:

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

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

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

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

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

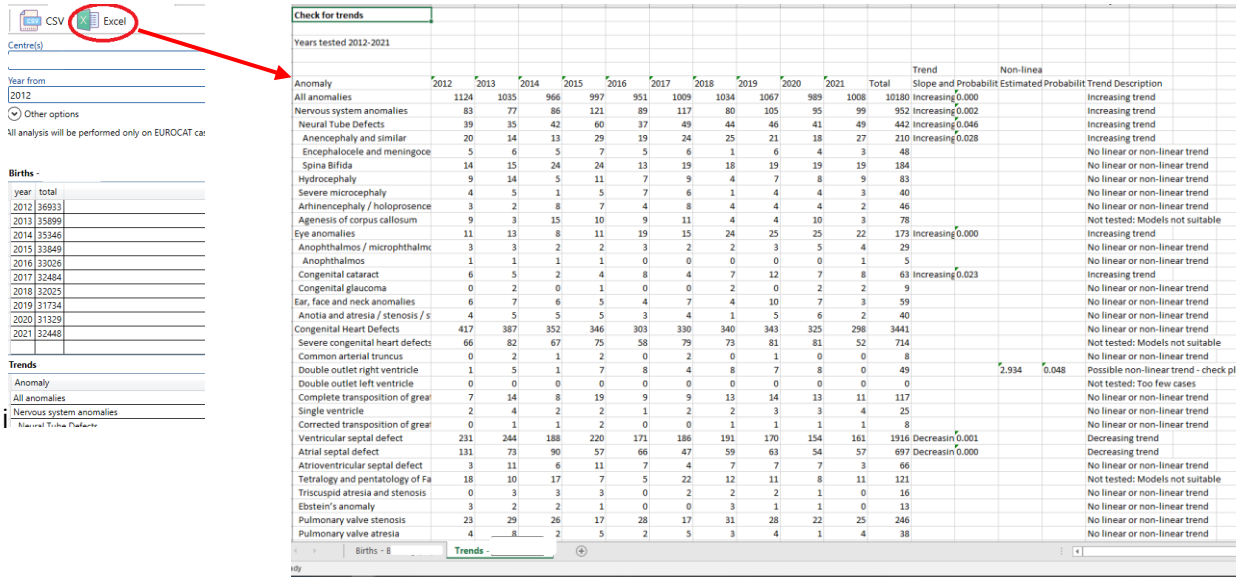
EUROCAT Subgroups	Prevalence by pregnancy outcome, registry, year	Included in monitoring of trends	Included in monitoring of clusters
Longitudinal preaxial LRD	✓	✓	✓
Longitudinal postaxial LRD	✓	✓	✓
Longitudinal central LRD	✓	✓	✓
Intercalary LRD	✓	✓	✓
Clubfoot - talipes equinovarus	✓	✓	✓
Hip dislocation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

Annex 2. Trend analysis - Output from EUROCAT DMS

The procedure to run the clusters tests is explained in the relevant chapter of the DMS User Guide.

1 – One registry selected

The EUROCAT DMS outputs a **summary table**, displayed in the main interface. It can be exported to an Excel file containing a worksheet with the total number of births in the selected registry and a summary of the trends detected in the selected registry.



Anomaly	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total	Trend Slope and	Probabilit	Non-linea Estimated	Probabilit	Trend Description
All anomalies	1124	1035	966	997	951	1009	1034	1067	989	1008	10180	Increasing	0.000			Increasing trend
Nervous system anomalies	83	77	86	121	89	117	80	105	95	99	952	Increasing	0.002			Increasing trend
Neural Tube Defects	39	35	42	60	37	49	44	46	41	49	442	Increasing	0.046			Increasing trend
Anencephaly and similar	20	14	13	29	19	24	25	21	18	27	210	Increasing	0.028			Increasing trend
Encephalocele and meningoce	5	6	5	7	5	6	1	6	4	3	48					No linear or non-linear trend
Spina Bifida	14	15	24	24	13	19	18	19	19	19	184					No linear or non-linear trend
Hydrocephaly	9	14	5	11	7	9	4	7	8	9	83					No linear or non-linear trend
Severe microcephaly	4	5	1	5	7	6	1	4	4	3	40					No linear or non-linear trend
Arhinencephaly / holoprosence	3	2	8	7	4	8	4	4	4	2	46					No linear or non-linear trend
Agenesis of corpus callosum	9	3	15	10	9	11	4	4	10	3	78					Not tested: Models not suitable
Eye anomalies	11	13	8	11	19	15	24	25	25	22	173	Increasing	0.000			Increasing trend
Anophthalmos / microphthalmc	3	3	2	2	3	2	2	3	5	4	29					No linear or non-linear trend
Anophthalmos	1	1	1	1	0	0	0	0	0	1	5					No linear or non-linear trend
Congenital cataract	6	5	2	4	8	4	7	12	7	8	63	Increasing	0.023			Increasing trend
Congenital glaucoma	0	2	0	1	0	0	2	0	2	2	9					No linear or non-linear trend
Ear, face and neck anomalies	6	7	6	5	4	7	4	10	7	3	59					No linear or non-linear trend
Anotia and atresia / stenosis / s	4	5	5	5	3	4	1	5	6	2	40					No linear or non-linear trend
Congenital Heart Defects	417	387	352	346	303	330	340	343	325	298	3441					No linear or non-linear trend
Severe congenital heart defects	66	82	67	75	58	79	73	81	81	52	714					Not tested: Models not suitable
Common arterial truncus	0	2	1	2	0	2	0	1	0	0	8					No linear or non-linear trend
Double outlet right ventricle	1	5	1	7	8	4	8	7	8	0	49			2.934	0.048	Possible non-linear trend - check pl
Double outlet left ventricle	0	0	0	0	0	0	0	0	0	0	0					Not tested: Too few cases
Complete transposition of grea	7	14	8	19	9	9	13	14	13	11	117					No linear or non-linear trend
Single ventricle	2	4	2	2	1	2	2	3	3	4	25					No linear or non-linear trend
Corrected transposition of grea	0	1	1	2	0	0	1	1	1	1	8					No linear or non-linear trend
Ventricular septal defect	231	244	188	220	171	186	191	170	154	161	1916	Decreasin	0.001			Decreasing trend
Atrial septal defect	131	73	90	57	66	47	59	63	54	57	697	Decreasin	0.000			Decreasing trend
Atrioventricular septal defect	3	11	6	11	7	4	7	7	7	3	66					No linear or non-linear trend
Tetralogy and pentatology of Fa	18	10	17	7	5	22	12	11	8	11	121					Not tested: Models not suitable
Triscuspid atresia and stenosis	0	3	3	3	0	2	2	2	1	0	16					No linear or non-linear trend
Ebstein's anomaly	3	2	2	1	0	0	3	1	1	0	13					No linear or non-linear trend
Pulmonary valve stenosis	23	29	26	17	28	17	31	28	22	25	246					No linear or non-linear trend
Pulmonary valve atresia	4	8	2	5	2	5	3	4	1	4	38					No linear or non-linear trend

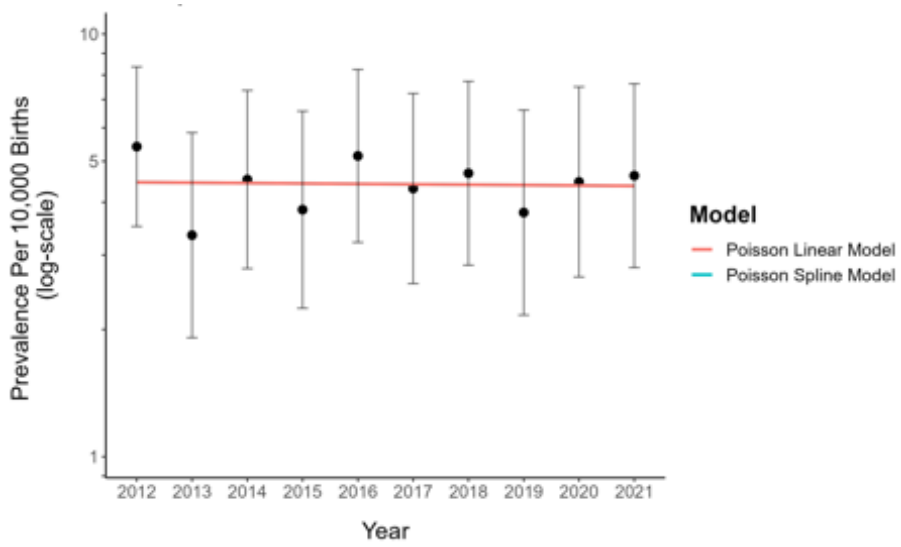
For each anomaly subgroup, the summary of the trends:

- gives the annual and total number of cases;
- flags the increasing (/) or decreasing (\) linear trends with their corresponding P-value;
- identifies the subgroups where a possible non-linear trend has been evidenced with the corresponding estimated degree of freedom and P-value.

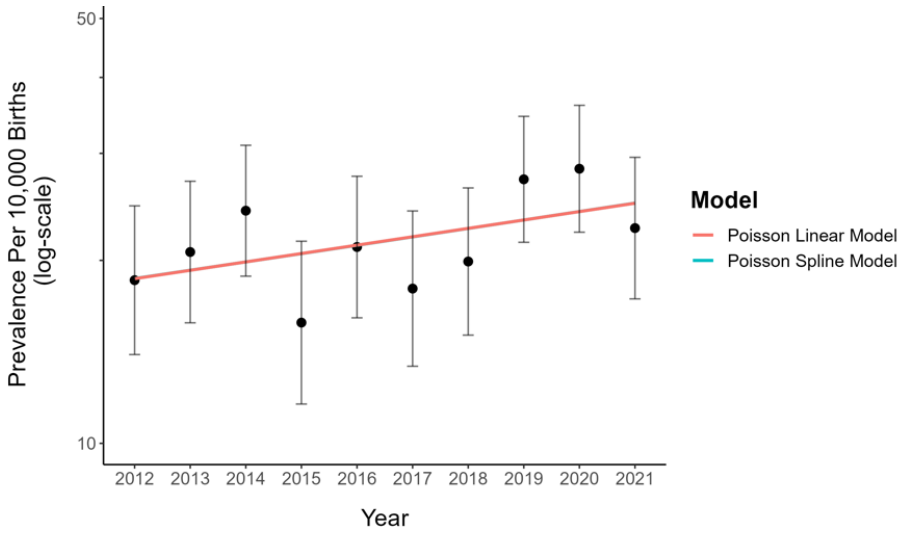
Additionally, the EUROCAT DMS generates **plots** of the data for each anomaly subgroup with the fitted lines for both the linear and the spline models. The linear model provides information on the general trend over the selected period of time. The spline model informs on the trend over shorter periods of time, as well as potentially some information on the data quality.

Different patterns can be seen on these plots: Explain how to interpret the various graphs

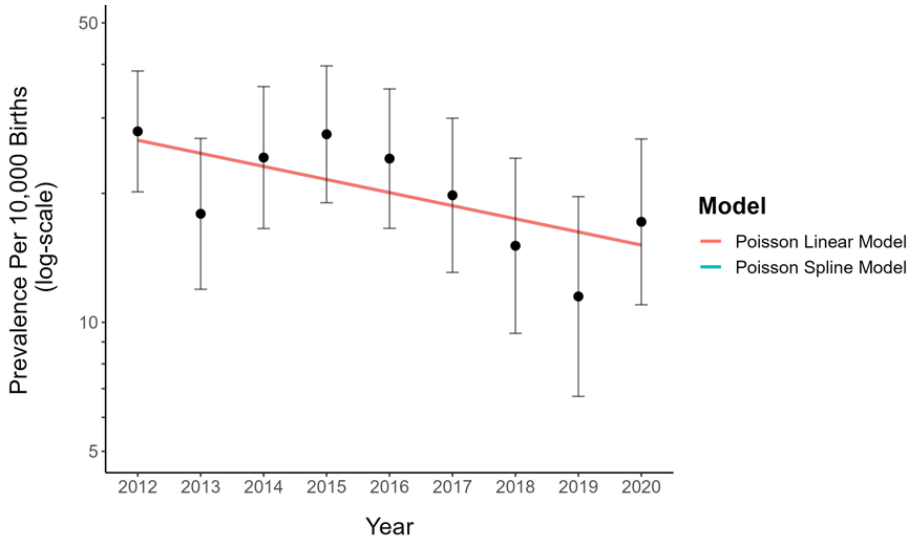
1) **Linear with no trend.** On the plot below only the line for the linear model can be seen. This is because the linear and spline model are the same (the e.d.f. of the spline model is close to 1). The line is horizontal and the p-value for both the GAM and GLM is >0.05. This is interpreted as showing no significant change over time.



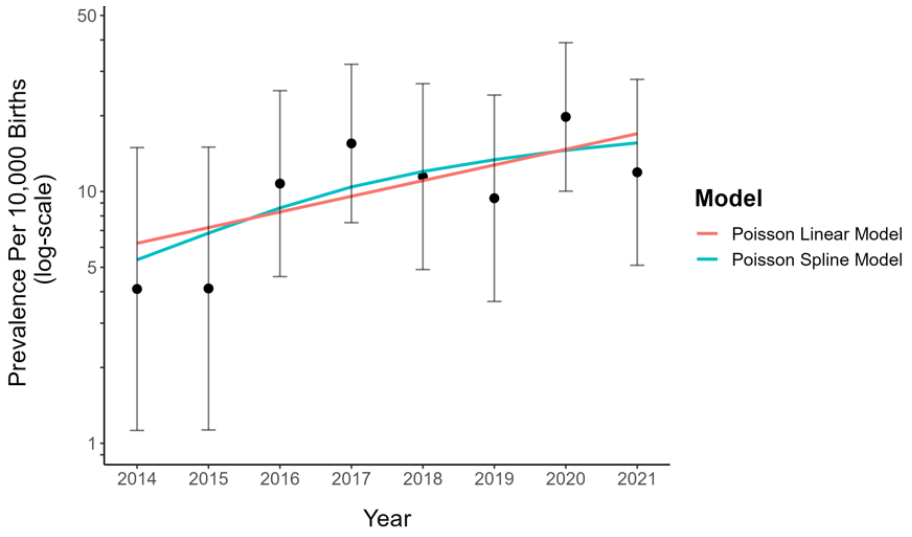
2) **Linear with increasing trend.** On the plot below only the line for the linear model can be seen. This is because the linear and spline model are the same (the e.d.f of the spline model is close to 1). The line is pointing upwards and the p-value for the GAM and GLM is <0.05. This is interpreted as an increasing linear trend.



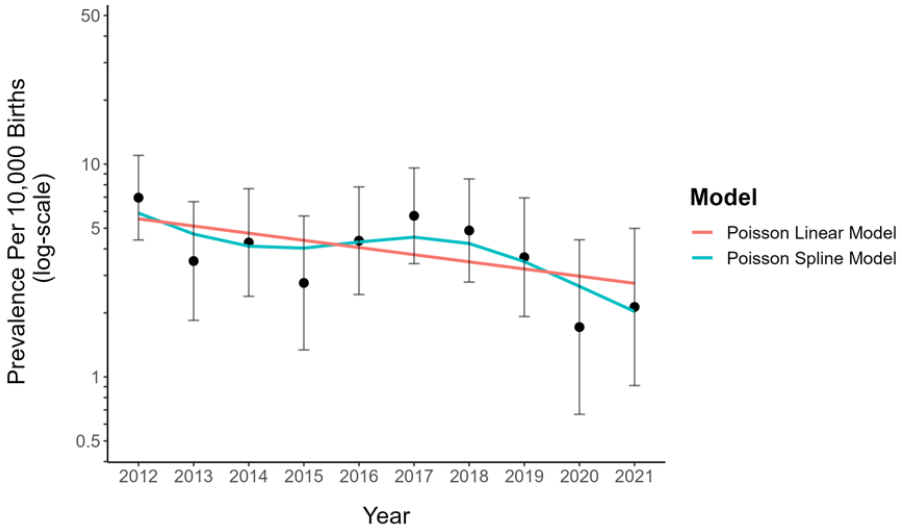
3) **Linear with decreasing trend.** On the plot below only the line for the linear model can be seen. This is because the linear and spline model are the same (the e.d.f. of the spline model is close to 1). The line is pointing downwards and the p-value for the GAM and GLM is <0.05. This is interpreted as a decreasing linear trend.



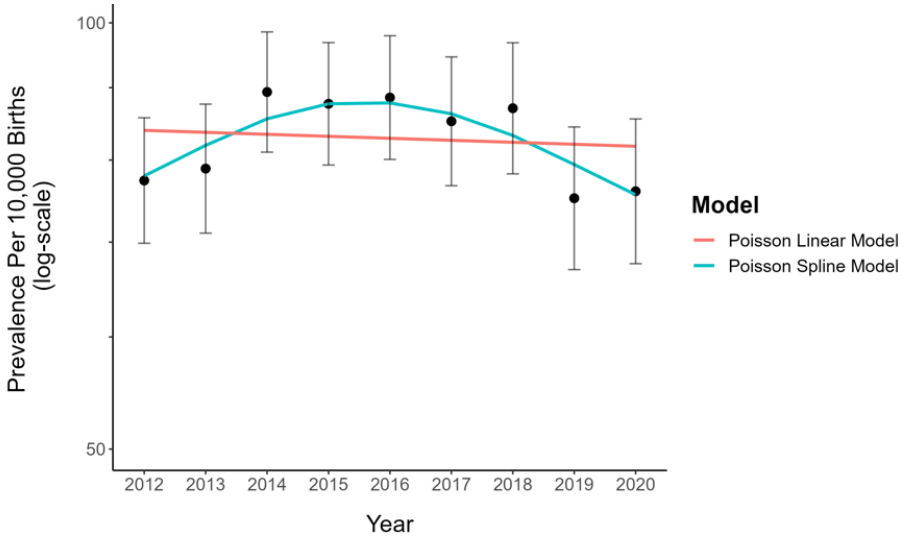
4) **Increasing trend.** On the plot below two lines can be seen, one linear and one spline model. This is because the linear and spline model are not the same (the e.d.f. of the spline model here is close to 1.5). The line for the linear model is pointing upwards and the p-value for the GLM is <0.05. The p-value for the GAM spline is >0.05. This is interpreted as an increasing trend.



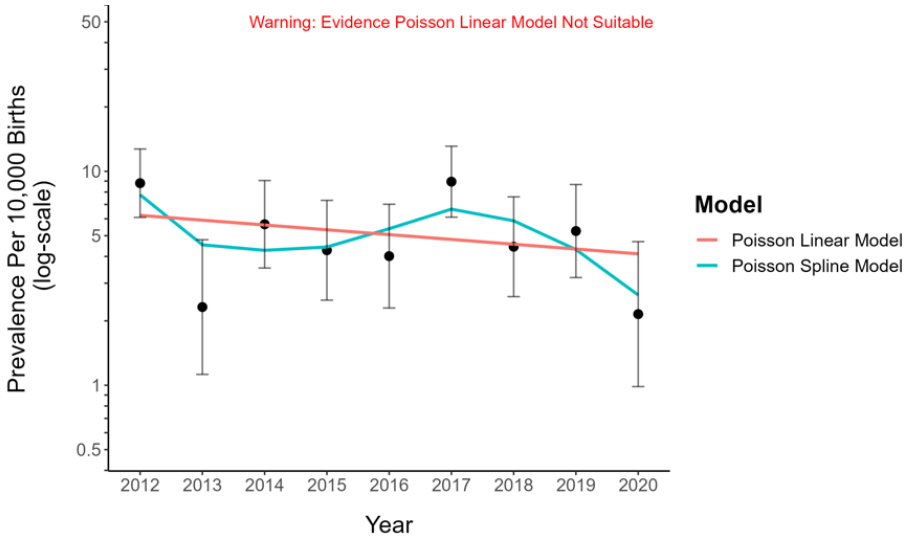
5) **Decreasing trend.** On the plot below two lines can be seen, one linear and one spline model. This is because the linear and spline model are not the same (the e.d.f. of the spline model here is close to 3). The line for the linear model is pointing downwards and the p-value for the GLM is <0.05. The p-value for the GAM spline is >0.05. This is interpreted as a decreasing trend.



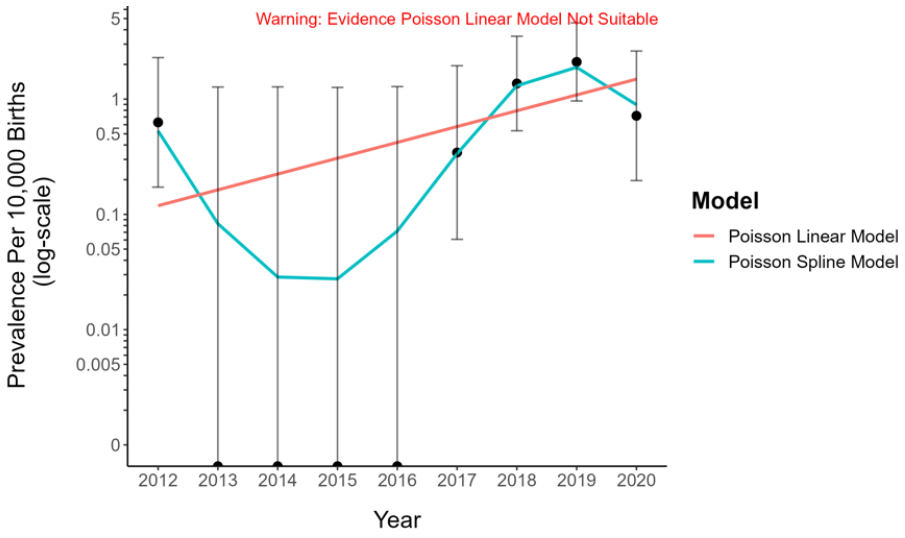
6) **Curved trend without warning message.** On the plot below two lines can be seen, one linear and one spline model. This is because the linear and spline model are not the same (the e.d.f. here is close to 2). The line for the linear model is horizontal and the p-value for the GLM is >0.05. The line for the spline is curved and the p-value for the GAM spline <0.05. This is interpreted as a curved trend. The deviations from the straight line may be due to under-ascertainment in the first years or the latter years



7) **Curved trend with warning message and high prevalence.** On the plot below two lines can be seen, one linear and one spline model. This is because the linear and spline model are not the same (the e.d.f. here is close to 4). Reports of curved trends with high e.d.f (>4) should be interpreted with caution, as they may indicate inconsistencies with the data collection. The p-value for GAM spline is <0.05, while the p-value for the GLM is >0.05. This is interpreted as a curved trend. There is a warning that the Poisson linear model is not suitable. This pattern may be due to extra-Poisson variability indicative of inconsistencies with the data collection / reporting, shown by several confidence intervals quite close together not overlapping.



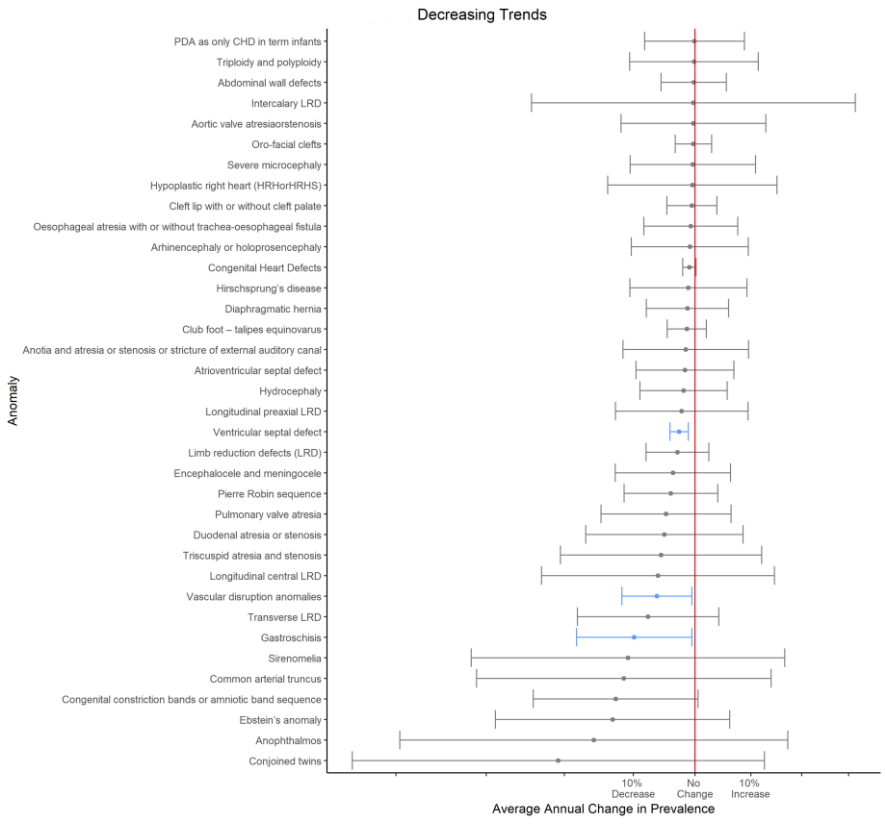
8) **Curved trend with warning message and low prevalence.** On the plot below two lines can be seen, one linear and one spline model. This is because the linear and spline models are not the same (the e.d.f here is close to 3). The p-value for both the GLM and GAM is >0.05. This is interpreted as a curved trend. There is a warning that the Poisson linear model is not suitable. This pattern is due to several years with zero cases, which may be expected for rarer anomalies.

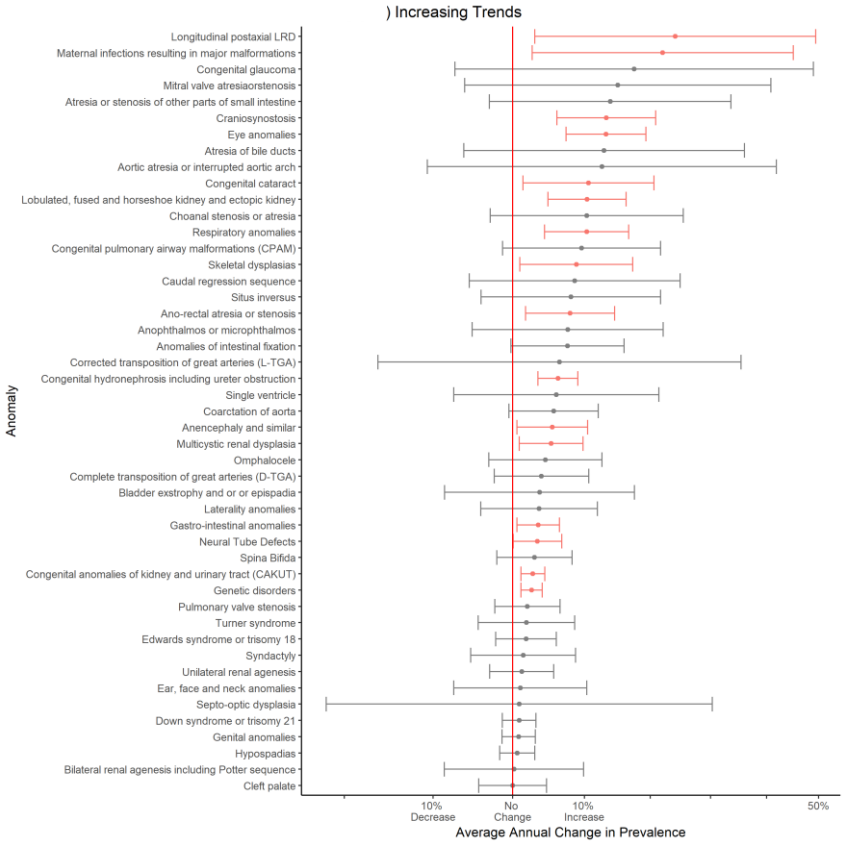


3

9) **Small numbers.** No data is plotted where there are less than 5 cases over the time-period.

Finally, the EUROCAT DMS provides **forest plots**, based on the linear models, to visualise the anomalies that have an increasing (/) or decreasing trend (\). The significant trends are indicated in blue (decreasing) or red (increasing).

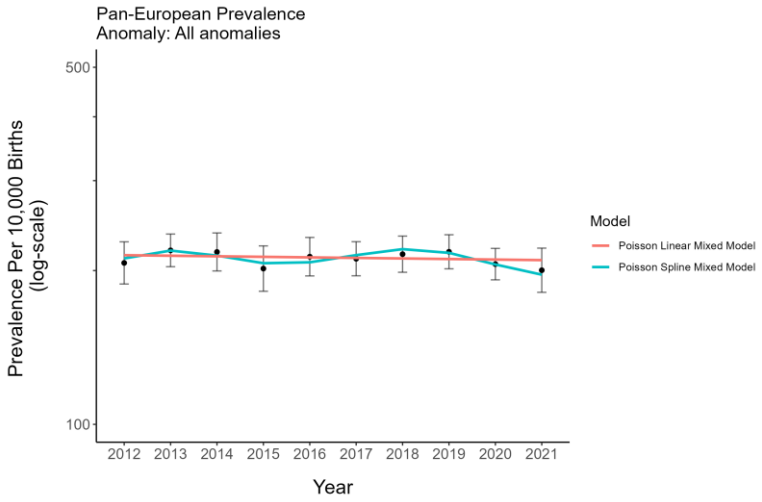




2 – Two or more registries selected

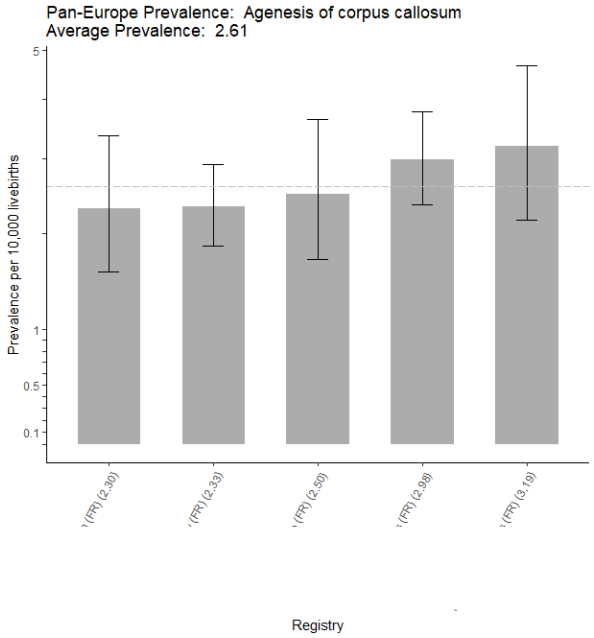
This concerns multi-centre registries like the JRC-EUROCAT Central Registry or NCARDRS. In addition to the outputs generated for one registry (see previous section), the DMS provides **pan-centre plots** of trends for each anomaly. These can be interpreted the same as those for individual registries although the modelling is slightly different[2].

[2] Mixture models are used at pan-centre level to take into account the different sizes of each registry in the multi-centre group.

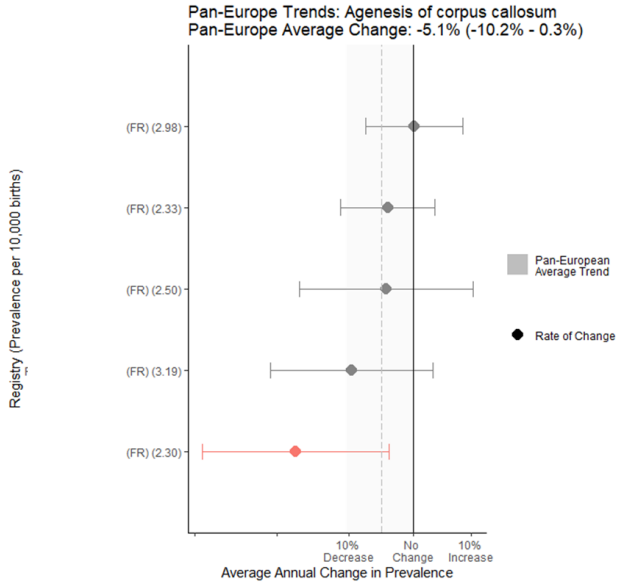


The EUROCAT DMS also generates **plots comparing the registries** included in the analysis.

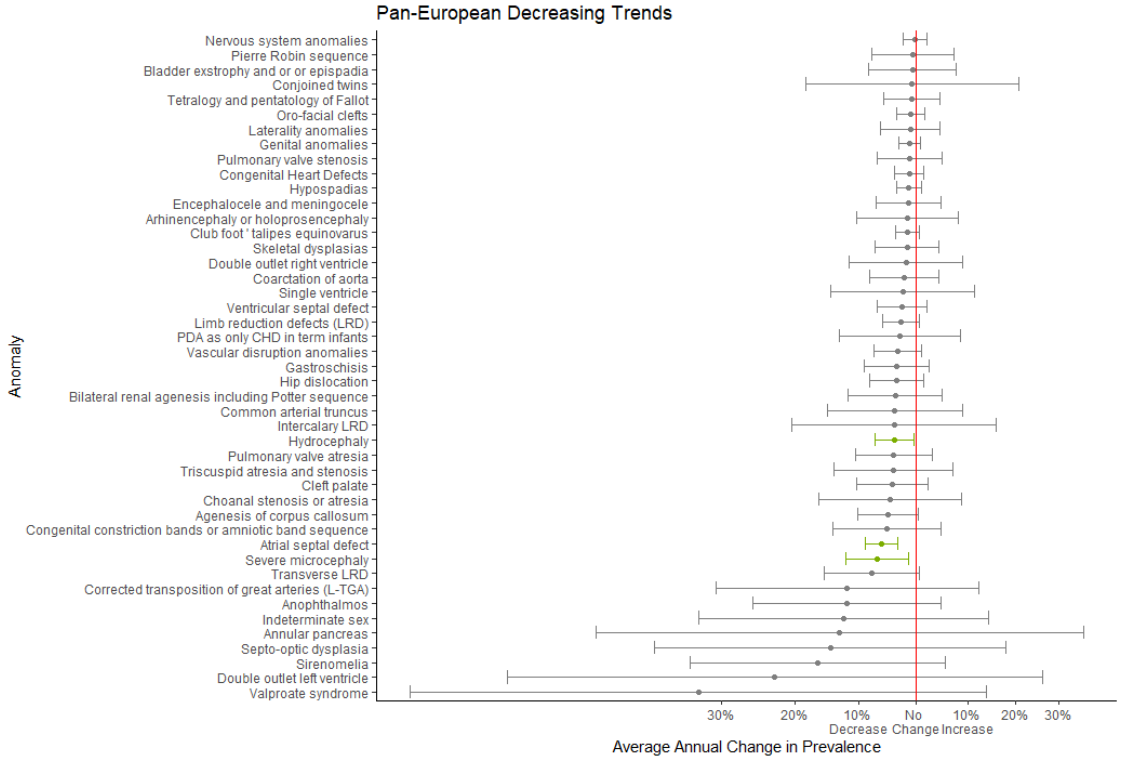
- **Prevalence** by registry with corresponding 95% confidence intervals

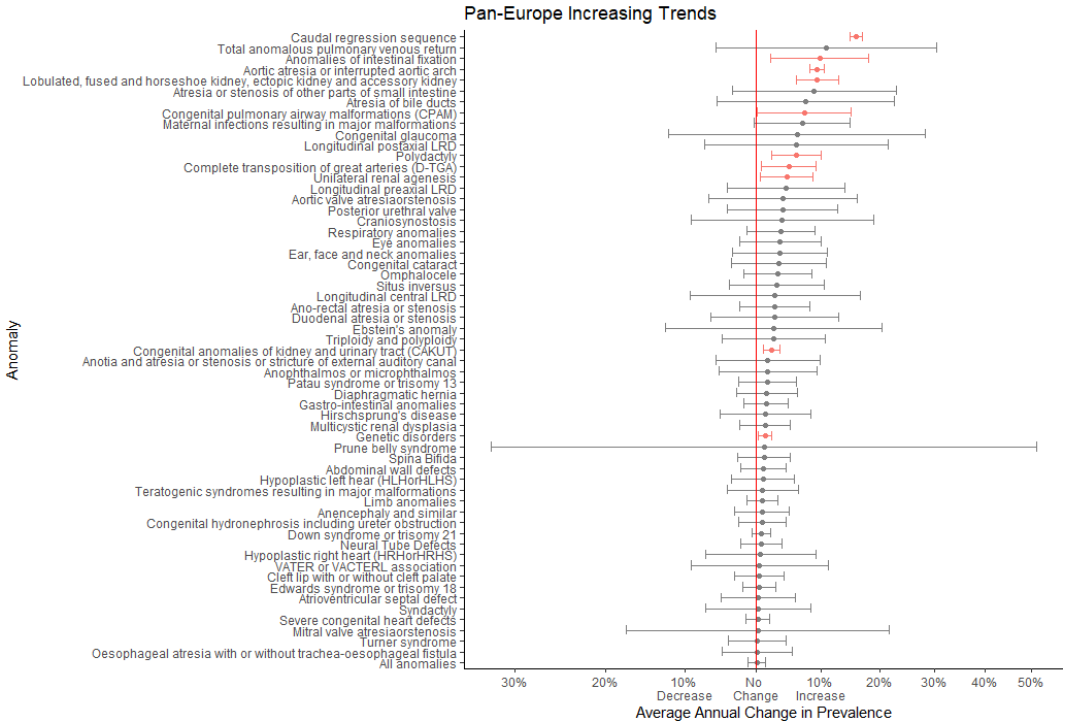


- **linear trends** by registry with corresponding 95% confidence intervals



Finally, the EUROCAT DMS provides **forest plots**, based on the linear models, to visualise the anomalies that have an increasing (/) or decreasing trend (\) across all the centres. The significant trends are indicated in green (decreasing) or red (increasing).




Pan-Europe Increasing Trends
Anomaly
Caudal regression sequence
Total anomalous pulmonary venous return
Anomalies of intestinal fixation
Aortic atresia or interrupted aortic arch
Lobulated, fused and horseshoe kidney, ectopic kidney and accessory kidney
Atresia or stenosis of other parts of small intestine
Atresia of bile ducts
Congenital pulmonary airway malformations (CPAM)
Maternal infections resulting in major malformations
Congenital glaucoma
Longitudinal postaxial LRD
Polydactyly
Complete transposition of great arteries (D-TGA)
Unilateral renal agenesis
Longitudinal preaxial LRD
Aortic valve atresiaorstenosis
Posterior urethral valve
Craniosynostosis
Respiratory anomalies
Eye anomalies
Ear, face and neck anomalies
Congenital cataract
Omphalocele
Situs inversus
Longitudinal central LRD
Ano-rectal atresia or stenosis
Duodenal atresia or stenosis
Ebstein's anomaly
Triploidy and polyploidy
Congenital anomalies of kidney and urinary tract (CAKUT)
Anotia and atresia or stenosis or stricture of external auditory canal
Anophthalmos or microphthalmos
Patau syndrome or trisomy 13
Diaphragmatic hernia
Gastro-intestinal anomalies
Hirschsprung's disease
Multicystic renal dysplasia
Genetic disorders
Prune belly syndrome
Spina Bifida
Abdominal wall defects
Hypoplastic left hear (HLHorHLHS)
Teratogenic syndromes resulting in major malformations
Limb anomalies
Anencephaly and similar
Congenital hydronephrosis including ureter obstruction
Down syndrome or trisomy 21
Neural Tube Defects
Hypoplastic right heart (HRHorHRHS)
VATER or VACTERL association
Cleft lip with or without cleft palate
Edwards syndrome or trisomy 18
Atrioventricular septal defect
Syndactyly
Severe congenital heart defects
Mitral valve atresiaorstenosis
Turner syndrome
Oesophageal atresia with or without trachea-oesophageal fistula
All anomalies
30%
20%
10%
Decrease
No
Change
10%
Increase
20%
30%
40%
50%
Average Annual Change in Prevalence

Annex 3. Scan statistics - procedure for calculation

Scan statistic formula based on the formula defined by Nagarwalla (1996).

Data

The date for each case is provided. A start and end date are specified and each case date is represented as a fraction of the period of interest.

$$fraction_{case} = \frac{date_{case} - date_{start}}{date_{end} - date_{start}}$$

Methods

Calculation of lambda

For a given subset of cases, it is possible to calculate the test statistic lambda as follows:

$$\lambda = \left(\frac{n}{r}\right)^n \left(\frac{r-n}{r}\right)^{r-n} \left(\frac{1}{d}\right)^n \left(\frac{1}{1-d}\right)^{r-n}$$

Where r is the total number of cases, n is the number of cases in the subset, also called the scanning window, and d is the date fraction spanned by the subset of cases. Typically a minimum scanning window of 5 is used. Lambda is calculated for every possible subset of n consecutive cases for n = 5,..., r-2.

The first step is to generate simulated datasets with random numbers. For each simulation, the lambda for each subset is calculated and the largest lambda is recorded. After, for example, 999 iterations the lambdas are ordered by size from smallest to largest and the 95th percentile is noted as λsig. In order to save computing time, and to give accurate p-values based on sufficient iterations, a look-up table was created for all r between 7 and 700 cases, using 100,000 iterations for r under 200 cases and 50,000 iterations for r over 200 cases. For r of more than 700 cases, Monte Carlo simulations (999 iterations) are used to create an array of lambdas.

For the real dataset, the lambda for each subset of cases is calculated. If the lambda is greater than or equal to λsig then the cases are designated as a significant cluster and the details of the cluster, such as start date and duration, are recorded. The p-value is recorded as the position of lambda within the simulated lambdas.

As a first step, a 'quick' check is performed to test whether the most significant cluster is significant at p<=0.1. If no significant cluster, then move on to next anomaly subgroup. If significant cluster is found then a full check is performed for all clusters with a p-value less than 0.06.

Group allocation

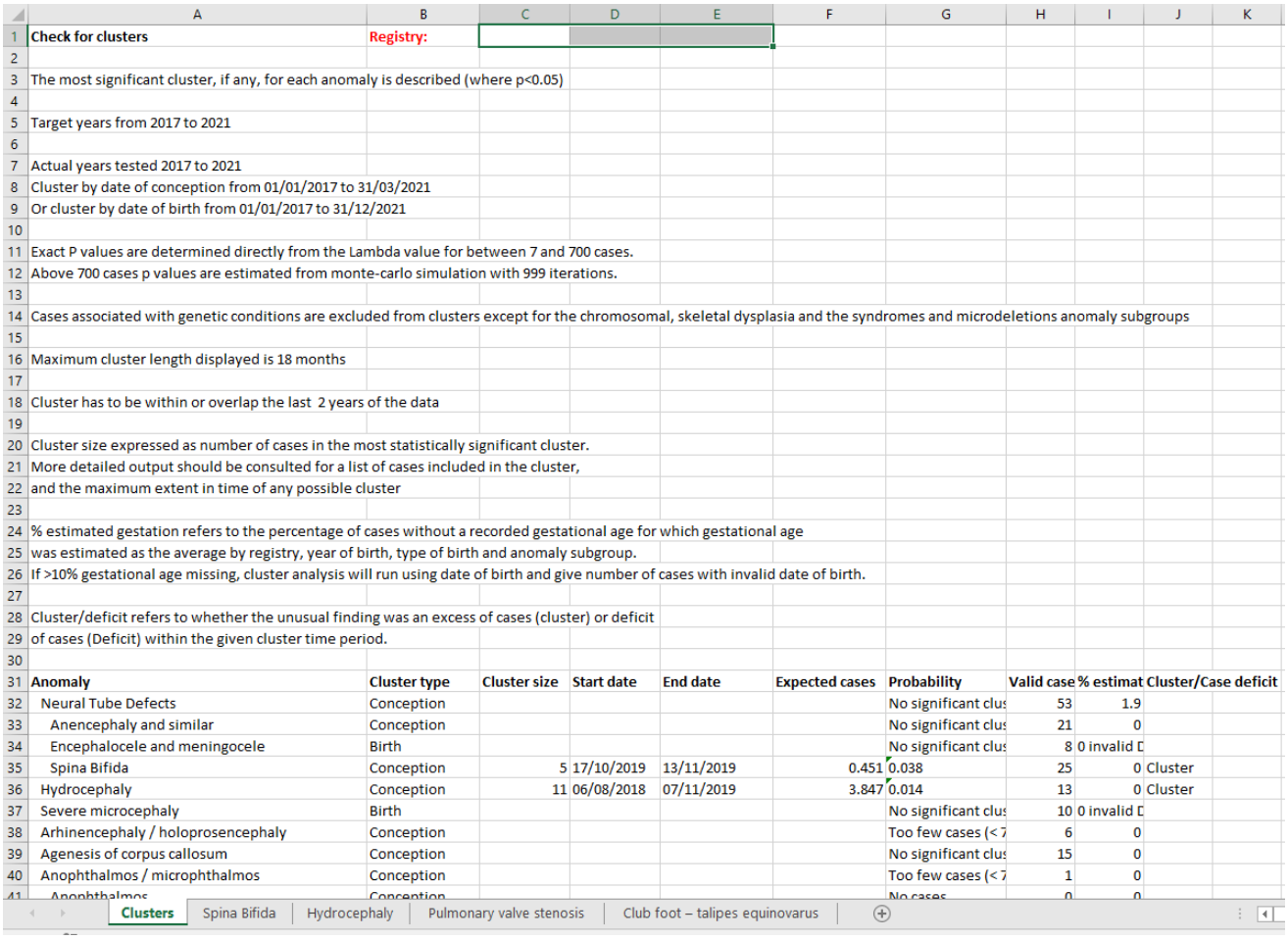
The final step is to allocate clusters to groups based on their overlap. The cluster with the largest lambda is identified and is allocated to the first group. Each ungrouped cluster is then tested for overlap with the first cluster. Overlap is calculated as the number of cases appearing in both clusters divided by the number of cases appearing in either cluster. If the overlap is greater than or equal to 0.75 then both are given the same group label. If any clusters remain ungrouped then the cluster with the largest lambda is identified and given a new group label and the procedure is repeated until all clusters are grouped.

Annex 4. Cluster analysis - Output from EUROCAT DMS

For each registry, the results are output in one Excel file containing a summary worksheet and separate worksheets for each subgroup where a cluster was detected.

The **summary worksheet *"clusters"*** contains information about:

- type of cluster analysis run (date of conception or date of birth),
- the number of cases in the most significant cluster,
- the start and end date of most significant cluster,
- the number of expected cases in the time period of the most significant cluster,
- total number of valid cases within the subgroup (i.e. must have valid date of birth
- the proportion of cases with missing gestational age
- the level of statistical significance (p-value and lamda)

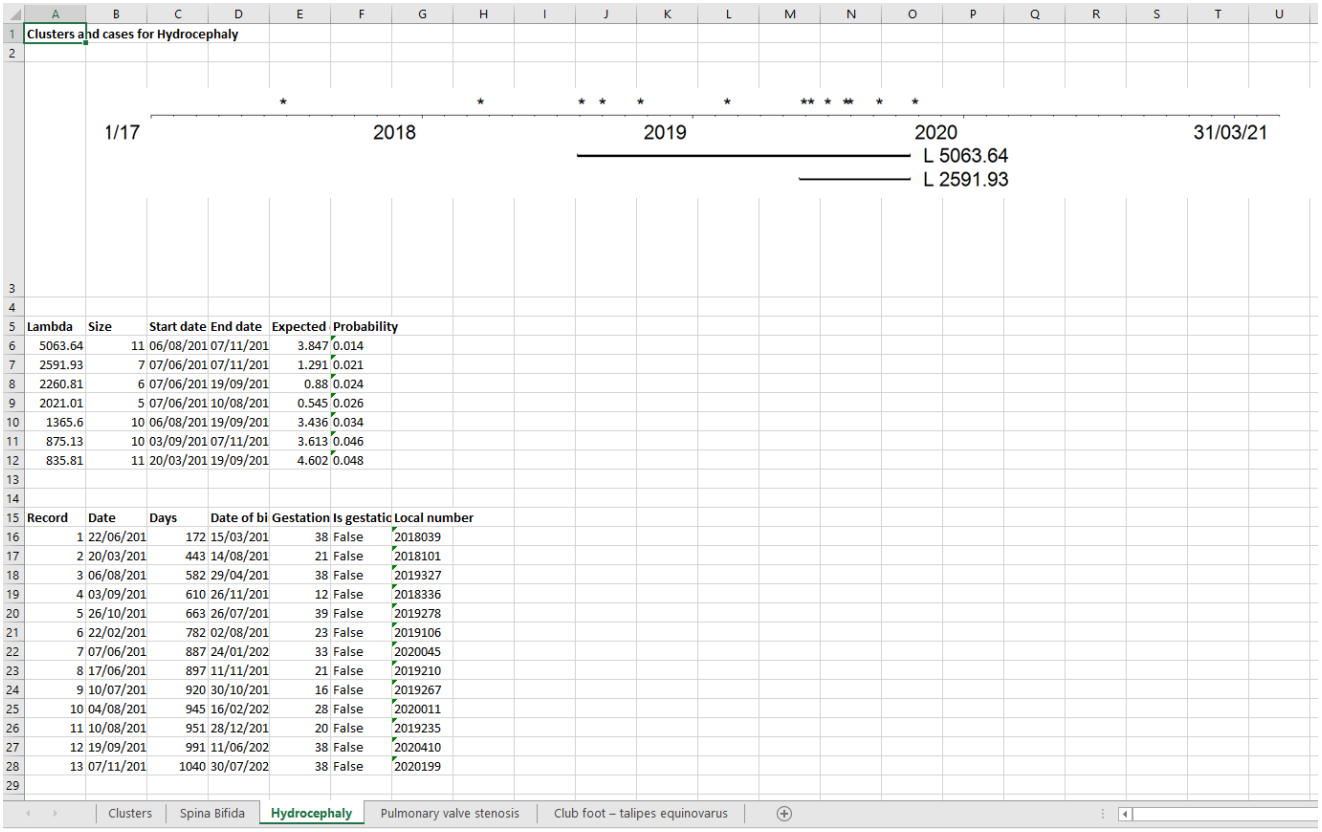


	A	B	C	D	E	F	G	H	I	J	K
1	**Check for clusters**	**Registry:**									
2											
3	The most significant cluster, if any, for each anomaly is described (where p<0.05)										
4											
5	Target years from 2017 to 2021										
6											
7	Actual years tested 2017 to 2021										
8	Cluster by date of conception from 01/01/2017 to 31/03/2021										
9	Or cluster by date of birth from 01/01/2017 to 31/12/2021										
10											
11	Exact P values are determined directly from the Lambda value for between 7 and 700 cases.										
12	Above 700 cases p values are estimated from monte-carlo simulation with 999 iterations.										
13											
14	Cases associated with genetic conditions are excluded from clusters except for the chromosomal, skeletal dysplasia and the syndromes and microdeletions anomaly subgroups										
15											
16	Maximum cluster length displayed is 18 months										
17											
18	Cluster has to be within or overlap the last 2 years of the data										
19											
20	Cluster size expressed as number of cases in the most statistically significant cluster.										
21	More detailed output should be consulted for a list of cases included in the cluster,										
22	and the maximum extent in time of any possible cluster										
23											
24	% estimated gestation refers to the percentage of cases without a recorded gestational age for which gestational age										
25	was estimated as the average by registry, year of birth, type of birth and anomaly subgroup.										
26	If >10% gestational age missing, cluster analysis will run using date of birth and give number of cases with invalid date of birth.										
27											
28	Cluster/deficit refers to whether the unusual finding was an excess of cases (cluster) or deficit										
29	of cases (Deficit) within the given cluster time period.										
30											
31	**Anomaly**	**Cluster type**	**Cluster size**	**Start date**	**End date**	**Expected cases**	**Probability**	**Valid case**	**% estimat**	**Cluster/Case deficit**	
32	Neural Tube Defects	Conception					No significant clus	53	1.9		
33	Anencephaly and similar	Conception					No significant clus	21	0		
34	Encephalocele and meningocele	Birth					No significant clus	8	0 invalid D		
35	Spina Bifida	Conception	5	17/10/2019	13/11/2019	0.451	0.038	25	0	Cluster	
36	Hydrocephaly	Conception	11	06/08/2018	07/11/2019	3.847	0.014	13	0	Cluster	
37	Severe microcephaly	Birth					No significant clus	10	0 invalid D		
38	Arhinencephaly / holoprosencephaly	Conception					Too few cases (< 7	6	0		
39	Agenesis of corpus callosum	Conception					No significant clus	15	0		
40	Anophthalmos / microphthalmos	Conception					Too few cases (< 7	1	0		
41	Anophthalmos	Conception					No cases	0	0		

Clusters | Spina Bifida | Hydrocephaly | Pulmonary valve stenosis | Club foot – talipes equinovarus

The **worksheets "*congenital anomaly subgroup name*"** give more details on all significant clusters. There is one worksheet per each subgroup where a cluster was identified. It contains:

- A timeline that shows the occurrence of all cases within the anomaly subgroup over the time period. It is important to remember that if a cluster is detected using date of conception, the timeline represents the date of conception of those cases.
- Lambda values for the most significant cluster are listed, along with the lambda values for all possible overlapping clusters. The highest lambda value indicates the most unusual cluster. Many clusters may overlap in time, with the inclusion or exclusion of individual cases changing their significance. The "most" significant cluster (highest "lambda" value) is listed first, followed by all significant clusters, with "cluster group" showing groups of highly overlapping clusters.
- The list of ALL cases in the anomaly subgroup both within and outside cluster, with date of conception, date of birth, gestational age (GA), estimated GA, and local ID number.



Clusters and cases for Hydrocephaly

Lambda	Size	Start date	End date	Expected	Probability
5063.64	11	06/08/201	07/11/201	3.847	0.014
2591.93	7	07/06/201	07/11/201	1.291	0.021
2260.81	6	07/06/201	19/09/201	0.88	0.024
2021.01	5	07/06/201	10/08/201	0.545	0.026
1365.6	10	06/08/201	19/09/201	3.436	0.034
875.13	10	03/09/201	07/11/201	3.613	0.046
835.81	11	20/03/201	19/09/201	4.602	0.048

Record	Date	Days	Date of bi	Gestation	Is gestatic	Local number
1	22/06/201	172	15/03/201	38	False	2018039
2	20/03/201	443	14/08/201	21	False	2018101
3	06/08/201	582	29/04/201	38	False	2019327
4	03/09/201	610	26/11/201	12	False	2018336
5	26/10/201	663	26/07/201	39	False	2019278
6	22/02/201	782	02/08/201	23	False	2019106
7	07/06/201	887	24/01/202	33	False	2020045
8	17/06/201	897	11/11/201	21	False	2019210
9	10/07/201	920	30/10/201	16	False	2019267
10	04/08/201	945	16/02/202	28	False	2020011
11	10/08/201	951	28/12/201	20	False	2019235
12	19/09/201	991	11/06/202	38	False	2020410
13	07/11/201	1040	30/07/202	38	False	2020199

Clusters | Spina Bifida | Hydrocephaly | Pulmonary valve stenosis | Club foot – talipes equinovarus

Annex 5. Template for the local investigation of trends

Name and # of Registry:	

1a. Increasing trends shown at pan-European level

Whilst these may not show in your individual output as a significant increasing trend, a significant increase has been shown at Pan European level.

Please investigate the trends that are statistically significant in your registry as indicated in column 2 of the table.

Pan-European increasing trends		**To be completed by registry**	
Anomaly	**Significant increasing trend in your registry**	**Code[3]: A,B,C,D, E,F,G**	**Summary Explanation (Please attach full report)**

1b. To which Public Health authority will the results of increasing trends be reported. (Please give details of how you will be reporting these results regionally and/or nationally)

[3] **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 ongoing; **F:** Trend confirmed, further surveillance proposed before more detailed investigation: **G:** Not real trend when additional years added or heterogeneous subgroup.

2a. Decreasing trends shown at Pan European level

Whilst these may not show in your individual output as a significant decreasing trend, a significant decrease has been shown at Pan European level.

Please investigate the trends that are statistically significant in your registry as indicated in column 2 of the table.

Pan-European increasing trends		**To be completed by registry**	
Anomaly	**Significant increasing trend in your registry**	**Code[3]: A,B,C,D, E,F,G,**	**Summary Explanation (Please attach full report)**

2b. To which Public Health authority will the results of decreasing trends be reported. (Please give details of how you will be reporting these results regionally and/or nationally)

3a. <u>Increasing</u> trends at individual registry level (but not significant increasing trends at the Pan European level)

Please note that for some anomalies there can be significant decreasing trends at Pan European level, while increasing in your registry (see Table 2a).

	To be completed by registry	
Anomaly	**Code[3]: A,B,C,D, E,F,G,**	**Summary Explanation (Please attach full report)**

3b. To which Public Health authority will the results of increasing trends be reported. (Please give details of how you will be reporting these results regionally and/or nationally)

4.a. <u>Decreasing</u> trends at individual registry level (but not significant decreasing trends at the Pan European level)

Please note that for some anomalies there can be significant increasing trends at Pan European level, while decreasing in your registry (see Table 1a).

	To be completed by registry	
Anomaly	**Code[3]: A,B,C,D, E,F,G,**	**Summary Explanation (Please attach full report)**

4b. To which Public Health authority will the results of decreasing trends be reported. (Please give details of how you will be reporting these results regionally and/or nationally)

Annex 6. Template for the local investigation of clusters

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

before a decision is made to investigate further? Why?	
OR If no, - Is there going to be further aetiological/other investigation? Please give details.	
Which public health authorities have been or will be notified about this cluster? Please give details.	
Has your registry used the DMS statistical monitoring function in the last year to look for clusters or trends in more recent data, or for different anomaly subgroups, or any other purpose? **If yes, provide details.**	

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