4. Prevalence calculation and interpretation

4.1 Calculation of Prevalence and 95% Confidence Intervals

In EUROCAT prevalence calculations, a baby/fetus with several anomalies is counted once within each class of anomaly. The number in different classes cannot be added to reach a total number of babies/fetuses. A baby is counted once only in any given prevalence.

EUROCAT prevalence is always cited as per 10,000 births.

Total prevalence =	$\frac{\text{No. Cases (LB + FD + TOPFA)}}{\text{No. Births (live and still)}} \times 10{,}000$
Live birth prevalence =	$\frac{\text{No. Cases (LB)}}{\text{No. Births (live and still)}} \times 10{,}000$
Fetal death prevalence =	$\frac{\text{No. Cases (FD)}}{\text{No. Births (live and still)}} \times 10{,}000$
TOPFA prevalence =	$\frac{\text{No. Cases (TOPFA)}}{\text{No. Births (live and still)}} \times 10{,}000$

Cases = Cases of congenital anomaly in population

LB = Live birth

FD = Fetal deaths from 20 weeks' gestation

TOPFA = Termination of pregnancy for fetal anomaly after prenatal diagnosis, at any gestational age

Birth (live and still) = All live and still births in the population as declared on official birth registrations. Live births prevalence is also calculated using this denominator, because some registries cannot provide live and still births separately.

Note: Slight discrepancies are present between numerator and denominator as terminations of pregnancy are included in the numerator but not the denominator, but are not great enough to have an important effect on prevalence.

Lower 95% confidence limit =	$\frac{\left(\frac{1.96}{2} - \sqrt{c + 0.02}\right)^2}{b} \times 10{,}000$
Upper 95% confidence limit =	$\frac{\left(\frac{1.96}{2} + \sqrt{c + 0.96}\right)^2}{b} \times 10{,}000$

c = No. cases, b = No. births

Note: The confidence intervals are calculated using the Poisson distribution.

Reference: Bégaud B, Martin K, Abouelfath A, Tubert-Bitter P, Moore N, Moride Y. Any easy to use method to approximate Poisson confidence limits. European Journal of Epidemiology (2005) 20: 213-216.

Differences in total prevalence over time or between regions may reflect one or more of the following factors: genetic differences, environmental differences, differences in diagnostic services, differences in the methods of collecting epidemiological data, and even chance differences (see Interpretation of prevalence).

Differences in live birth or fetal death prevalence over time or between regions may reflect the same factors as above, but also differences in prenatal screening policies and differences in frequency with which prenatal diagnosis is followed by termination of pregnancy.

4.2 Calculation of Proportions and their 95% Confidence Intervals

Live birth proportion =	$\frac{\text{No. Cases (LB)}}{\text{All Cases (LB + FD + TOPFA)}} \times 100$
Fetal death proportion =	$\frac{\text{No. Cases (FD)}}{\text{All Cases (LB + FD + TOPFA)}} \times 100$
TOPFA proportion =	$\frac{\text{No. Cases (TOPFA)}}{\text{All Cases (LB + FD + TOPFA)}} \times 100$

Cases = Cases of congenital anomaly in population

LB = Live birth

FD = Fetal deaths from 20 weeks' gestation

TOPFA = Termination of pregnancy for fetal anomaly after prenatal diagnosis, at any gestational age

Lower 95% confidence limit =	$\frac{\mathrm{p} + \frac{1.96^2}{2\mathrm{a}} - 1.96\sqrt{\frac{\mathrm{p}(1-\mathrm{p})}{\mathrm{a}} + \frac{1.96^2}{4\mathrm{a}^2}}}{1 + \frac{1.96^2}{\mathrm{a}}} \times 100$
Upper 95% confidence limit =	$\frac{\mathrm{p} + \frac{1.96^2}{2\mathrm{a}} + 1.96\sqrt{\frac{\mathrm{p}(1-\mathrm{p})}{a} + \frac{1.96^2}{4\mathrm{a}^2}}}{1 + \frac{1.96^2}{\mathrm{a}}} \times 100$

a = All cases (LB + FD + TOPFA); p = Proportion/100

Note: The confidence intervals are calculated using the Binomial distribution.

Reference: Agresti A, Coull BA. Approximate is Better than "Exact" for Interval Estimation of Binomial Proportions. The American Statistician, Vol. 52, No. 2 (May, 1998), pp. 119-126.

4.3 Interpretation of Prevalence

EUROCAT registries follow a number of principles of organisation and registration to optimise the accuracy of estimation of prevalence and achieve standardisation across regions. The following factors potentially affect the accuracy of estimation of prevalence, as defined in section 4.1.

a) Definition of the population

The definition of the population covered by each registry is given under Member Registries (https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-members/registries_en). The majority of registries of EUROCAT are population-based, which means that they cover residents of a defined geographical area to obtain unbiased rates.

b) Definition and classification of birth defects and diagnostic practice

Epidemiological data are derived from diagnoses made by clinicians working within given health service conditions. Many variations in diagnostic practice may affect the reported prevalence of birth defects. For example, the accurate reporting of chromosomal anomalies (e.g. Trisomy 13 or 18 and Down syndrome) is dependent on karyotyping rates and indications for karyotyping. The autopsy rates for stillbirths and neonatal deaths will determine the likelihood that a birth defect is diagnosed, or the accuracy of the diagnosis, especially for conditions which are not externally visible such as serious congenital heart disease (e.g. hypoplastic left heart syndrome). Renal dysplasia is more likely to be diagnosed early in life if there is ultrasound screening of the kidneys, which leads to variation in prevalence between regions and over time as screening practice changes.

Minor anomalies are those which do not in themselves have serious medical, functional or cosmetic consequences for the child. Cases with only minor anomalies are excluded from EUROCAT (see Guide 1.5, chapter 3.2 for list of minor anomalies). Minor anomalies are included if they appear in association with major anomalies. Some anomalies are present in gradations from minor to major forms and variable prevalence in these anomalies can be due to variable registration of their minor forms and lack of details in the medical notes allowing identification of the minor forms.

Children with syndromes and multiple anomalies present particular classification problems. EUROCAT recommends recording of up to eight malformations, as well as a syndrome if present. Nevertheless, practice may vary as to whether all of the component malformations of a syndrome are recorded. Defects that are seen as consequences of other defects i.e. “sequences” (e.g. hydrocephaly when associated with spina bifida) are counted only under the primary defect in EUROCAT prevalence (see classification of subgroups, Guide 1.5 chapter 3.3).

c) Ascertainment and Coding

Registries work hard to establish and maintain an information pathway which will lead to high case ascertainment (i.e. the proportion of diagnosed cases who are registered), and accurate diagnostic information. EUROCAT registries use version 10 of the International Classification of Disease, using the British Paediatric Association extension to allow more detail to be recorded. The McKusick (OMIM) Classification is used for conditions with Mendelian inheritance.

Registries need to use multiple sources of information. Under-ascertainment of some anomalies can occur if sources of information stop in the early neonatal period, as diagnoses may be made later than this. Specialist services treating children later than the post-neonatal period are also vital for confirmation of diagnostic details.

While EUROCAT recommends registration of fetal deaths from 20 weeks gestation, some registries have difficulties ascertaining fetal deaths outside the official stillbirth definition of their country (which may be 24 or 28 weeks or 500g). As malformed fetuses tend to be born prematurely or stillborn, ascertainment of fetal deaths of 20 weeks to the stillbirth limit can influence prevalence substantially for certain congenital anomalies.

d) Termination of pregnancy for fetal anomaly following prenatal diagnosis

Prenatal screening policies (and the resources for prenatal screening) vary enormously between different countries and between regions and even hospitals within countries. Laws and practices vary between countries as to the upper gestational age limit for termination (see the Registry Descriptions of Member Registries for more detail, and the EUROCAT publications list). How often prenatal diagnosis of a birth defect leads to termination of pregnancy also varies. For example, termination of pregnancy is very widespread for lethal conditions such as anencephaly, but the practice is much more variable for conditions such as spina bifida. Thus, prenatal screening followed by termination of pregnancy introduces considerable geographic and temporal variation in prevalence, and the proportion of terminations must be known or well estimated to assess whether there are real differences in "risk" between populations related to genetic or environmental risk factors.

Ideally for epidemiologic purposes, terminations of pregnancy should be subject to the same rigour of diagnostic verification as live and stillbirths, but this is not always so. For example, autopsies may not be carried out to confirm the diagnosis, and a karyotype may not be performed where multiple malformations have been detected prenatally by ultrasound, to determine whether a chromosomal anomaly is present.

Reporting of terminations of pregnancy can lead to relative "over-ascertainment" of cases. The earlier in pregnancy the termination, the greater the probability that the pregnancy would in other circumstances have ended naturally in a spontaneous abortion. A spontaneous abortion would not necessarily have been examined for malformations or reported to the registry. These probabilities are generally small, but when the numbers of early terminations are high might result in a slight inflation of the total number of cases recorded compared to what would be expected if no terminations had been performed.

Prenatal screening and diagnosis, whether or not followed by termination, can also lead to relative "over-ascertainment" of cases when the average age of detection of a congenital anomaly is brought within the age coverage of the registry. For example children with sex chromosome trisomies are often not diagnosed until puberty. However, some are now detected prenatally due to screening for Down's syndrome.

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