Special Report: Congenital Anomalies are a Major Group of Mainly Rare Diseases

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What is EUROCAT (European Surveillance of Congenital Anomalies)?

- A European **network of population-based registries** for epidemiologic surveillance of congenital anomalies. Started in 1979.
- Over 1.7 million births surveyed per year in Europe. 38 registries in 21 countries. 31% of EU birth population covered.
- High quality multiple source registries ascertain still births/fetal deaths, terminations of pregnancy following prenatal diagnosis of congenital anomaly and live births.
- This enables provision of prevalence, prenatal diagnosis and perinatal mortality data.
- Member registries send anonymised individual case data (full members) or summary data (associate members) to the EUROCAT Central Registry database.
- WHO Collaborating Centre for the Surveillance of Congenital Anomalies
- Currently funded as a Joint Action of the EU and Member States through the DG Sanco Public Health Programme (2008-2013), relating to European Action on Rare Diseases.

The EU Definition of Rare Diseases

Rare diseases are diseases with a particularly low prevalence; the European Union considers diseases to be rare when they **affect not more than 5 per 10,000** persons in the EU. Rare diseases include genetic diseases, congenital anomalies, rare cancers, auto-immune diseases, toxic and infectious diseases... It is estimated that between 5,000 and 8,000 distinct rare diseases exist, affecting between 6% and 8% of the population in the course of their lives [1]. In other words, although rare diseases are characterised individually by low prevalence [2], the total number of people affected by rare diseases in the EU is between 27 and 36 million. Most of them suffer from less frequently occurring diseases affecting one in 100,000 people or less. The definition of a rare disease as having a prevalence of 5 per 10,000 first appeared in EU legislation in Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products [3]. The Community action programme on rare diseases including genetic diseases for the period 1 January 1999 to 31 December 2003 then applied this definition to the field of public health.

The Contribution of Congenital Anomalies to Rare Diseases

EUROCAT prevalence of congenital anomalies is the proportion of births affected by a congenital anomaly:

EUROCAT **Live birth prevalence** = (No. Cases (live birth)/No. Births (live birth)) x 10,000

The "actual" current EU population prevalence depends on past live birth prevalence and past survival to adulthood and is therefore unknown. EUROCAT live birth prevalence provides the future maximum EU population prevalence. It is a maximum because survival to adulthood of babies born with congenital anomalies is on average lower than survival of babies in the general population.

EUROCAT mainly registers cases of congenital anomaly diagnosed prenatally or in infancy. For some genetic conditions, including chromosomal disorders such as Klinefelter and Turner Syndrome, most cases are diagnosed later in life, and thus live birth prevalence does not represent EU population prevalence.

Congenital anomalies are structural anomalies (congenital malformations, deformations, disruptions and dysplasias), chromosomal anomalies, syndromes and other hereditary conditions associated with structural anomalies, presenting prenatally or postnatally. Congenital anomalies are also sometimes called "birth defects".
EUROCAT defines a **syndrome** as a recognizable pattern of anomalies which are known or thought to be causally related. The causes may be a single gene defect, a chromosomal anomaly or an environmental teratogen. Isolated malformations may also be given a syndrome diagnosis when they have a single known cause [4].
EUROCAT only collects major congenital anomalies that require surgical treatment (medical), have serious adverse effects on health or development (functional), or have significant cosmetic impact (cosmetic).

Congenital anomalies are coded in the Q chapter of the International Classification of

Disease version 10 [5] with British Paediatric Association one digit extension. EUROCAT uses these codes to create 89 "subgroups" of congenital anomaly [6] for surveillance. Some of these subgroups are a combination of many different congenital anomalies

The live birth prevalence of all EUROCAT anomalies in 2010 was 176.27. Of these, **69 EUROCAT subgroups were rare** (< 5 per 10,000) by EU definition (see grey lines in Table 1) with a total live birth prevalence of 96.23 per 10,000, which equates to approximately 4.7M affected persons in the EU (or over 50,000 affected live births in the EU per year (27 countries) [7]. Thus, 12-15% of the currently estimated total persons affected by Rare Diseases in Europe have rare congenital anomalies. Congenital anomalies are particularly important because they are **potentially preventable**.

Many genetic syndromes are amongst the "rarest" of the congenital anomalies. When congenital anomalies are so rare EUROCAT pools data across registries to show prevalence. The total prevalence (including live births, fetal deaths from 20 weeks of gestation and terminations of pregnancy for fetal anomaly) of selected **monogenic syndromes in Europe** with unique ICD10-BPA codes can be seen in Table 2.

Survival and Burden of Disease

The most recent Global Burden of Disease Project estimated that congenital anomalies in 2010 accounted for 732,000 Disability Adjusted Life Years Lost (DALYs) in Western Europe, 274,000 in Central Europe and 898,000 in Eastern Europe[8]. Thus, like other Rare Diseases, congenital anomalies are individually rare but collectively a significant public health issue.

Congenital anomalies are a leading cause of **perinatal mortality** (late fetal death and up to 1 week after birth). The 2009 EUROCAT data for the "All Anomalies" subgroup indicate a prevalence of 4.7 fetal deaths per 10,000 births, 4.7 first week deaths per 10,000 births and a perinatal mortality prevalence of 9.4 per 10,000 births.

A recent UK population-based study investigated the 20-year survival of children born with congenital anomalies between 1985 and 2003 [9]. The 20-year survival varied between congenital anomaly subgroups, ranging from 66.2% for nervous system anomalies to 97.6% for orofacial clefts. The overall 20-year survival in individuals born with at least one congenital anomaly was 85.5%.

In 2010, there were also 49.16 per 10,000 births recorded as terminations of pregnancy following prenatal diagnosis of congenital anomaly in EUROCAT data.

Genetic and environmental causes of Rare Diseases

Congenital anomalies can be caused by genetic or environmental factors or an interaction of both. The precise cause of congenital anomalies is not known for the majority. In EUROCAT data, 1.85% of congenital anomaly cases are recorded as monogenic syndromes, 13% as chromosomal anomalies, and 0.65% as teratogenic syndromes caused by maternal infections, drugs or alcohol. Most congenital anomalies are probably caused by an interaction of environmental and genetic factors. Although genetic factors play an important role, it is by changing environmental exposures that we can prevent congenital anomalies.

Table 1: Live birth (LB) Prevalence (per 10,000 births) of Congenital Anomalies*

Anomaly	LB Prev	Anomaly	LB Prev
All Anomalies	176.3	Ano-rectal atresia or stenosis	2.39
Nervous system	11.00	Hirschsprung's disease	1.43
Neural Tube Defects	2.20	Atresia of bile ducts	0.20
Anencephalus and similar	0.22	Annular pancreas	0.14
Encephalocele	0.33	Diaphragmatic hernia	2.00
Spina bifida	1.65	**Abdominal wall defects**	4.55
Hydrocephalus	3.16	Gastroschisis	3.14
Microcephaly	1.91	Omphalocele	1.22
Arhinencephaly/holoprosencephaly	0.16	**Urinary**	24.5
Eye	2.86	Bilateral renal agenesis including Potter syndrome	0.18
Anophthalmos/micropthalmos	0.51	Renal dysplasia	4.12
Anophthalmos	0.14	Congenital hydronephrosis	8.80
Congenital cataract	0.98	Bladder exstrophy and/or epispadia	0.39
Congenital glaucoma	0.25	Posterior urethral valve and/or prune belly	0.78
Ear, face and neck	1.57	**Genital**	18.8
Anotia	0.31	Hypospadias	15.7
Congenital heart defects	55.4	Indeterminate sex	0.53
Severe CHD	16.8	**Limb**	30.1
Common arterial truncus	0.43	Limb reduction	3.37
Transposition of great vessels	3.31	Upper limb reduction	2.29
Single ventricle	0.43	Lower limb reduction	1.31
Ventricular septal defect	26.5	Complete absence of limb	0.04
Atrial septal defect	10.7	Club foot – talipes equinovarus	8.39
Atrioventricular septal defect	2.74	Hip dislocation and/or dysplasia	6.08
Tetralogy of Fallot	3.29	Polydactyly	7.61
Tricuspid atresia and stenosis	0.49	Syndactyly	3.57
Ebstein's anomaly	0.29	**Other anomalies/syndromes**	
Pulmonary valve stenosis	3.31	Skeletal dysplasias	0.92
Pulmonary valve atresia	0.63	Craniosynostosis	2.43
Aortic valve atresia/stenosis	1.08	Cong. constriction/amniotic bands	0.27
Hypoplastic left heart	1.29	Situs inversus	0.45
Hypoplastic right heart	0.41	Conjoined twins	0.00
Coarctation of aorta	3.31	Congenital skin disorders	1.16
Total anomalous pulm venous return	0.67	Teratogenic syndromes with malf.	0.73
PDA as only CHD in term infants (≥37 wk)	1.65	Fetal alcohol syndrome	0.16
Respiratory	4.96	Valproate syndrome	0.04
Choanal atresia	0.78	Maternal infection resulting in malf.	0.37
Cystic adenomatous malf of lung	1.18	Genetic syndromes / microdeletions	3.51
Oro-facial clefts	13.3	Sequences	1.29
Cleft lip with or without palate	8.04	**Chromosomal**	13.6
Cleft palate	5.21	Down syndrome	8.82
Digestive system	14.6	Patau syndrome/trisomy 13	0.37
Oesophageal atresia with or without trachea-oesophageal fistula	2.43	Edwards syndrome/trisomy 18	0.86
Duodenal atresia or stenosis	1.18	Turner syndrome**	0.63
Atresia or stenosis of other parts of small intestine	0.96	Klinefelter syndrome**	0.37

*** 2010: All Full Registries ** prevalence refers only to cases diagnosed prenatally or in infancy**

Table 2: Prevalence of selected monogenic syndromes in Europe, 2005 – 2009*

Genetic syndromes	Total Prevalence per 10,000 births	% Live Birth	% Fetal Death	% Termination of pregnancy for fetal anomaly
Aarskog syndrome	0.04	100	0	0
Acrocephalopolysyndactyly (all types)	0.02	100	0	0
Alagille syndrome	0.04	100	0	0
Angelman syndrome	0.11	100	0	0
Apert's syndrome (acrocephalosyndactyly type I and II)	0.12	88	8	4
Bardet-Biedl syndrome	0.02	100	0	0
Beckwith-Wiedemann syndrome (EMG syndrome)	0.25	93	4	4
Cleidocranial dysplasia	0.04	89	0	11
Cornelia de Lange syndrome (de Lange syndrome)	0.12	81	4	15
Crouzon's disease (craniofacial dysostosis type 1)	0.09	95	0	5
Di George syndrome	0.65	86	1	13
Dubowitz syndrome	0.02	100	0	0
Ehlers-Danlos syndrome	0.05	100	0	0
Holt-Oram syndrome (heart-hand syndrome)	0.05	70	0	30
Incontinentia pigmenti	0.09	80	0	20
Klippel-Feil syndrome	0.06	100	0	0
Klippel-Trenaunay (-Weber) syndrome (angioosteohypertrophy)	0.08	100	0	0
Larsen's syndrome	0.05	73	0	27
Meckel Gruber	0.19	10	13	78
Noonan's syndrome	0.23	96	2	2
Pena-Shokeir syndrome (fetal akinesia)	0.13	44	15	41
Prader-Willi syndrome	0.29	97	2	2
Rubinstein-Taybi syndrome	0.06	100	0	0
Russell-Silver syndrome/Silver syndrome	0.08	100	0	0
Smith-Lemli-Opitz syndrome	0.06	69	8	23
Sotos syndrome	0.03	100	0	0
Stickler syndrome	0.05	100	0	0
TAR syndrome	0.03	57	14	29
Williams	0.18	100	0	0
Skeletal dysplasias				
Diastrophic dysplasia	0.04	22	0	78
Ellis-van Creveld syndrome	0.05	55	9	36
Jeune's syndrome (asphyxiating thoracic dystrophy)	0.14	41	3	55
Osteogenesis imperfect Type II (neonatal lethal form)	0.22	33	2	65
Thanatophoric dysplasia	0.36	14	5	81
Associations and other developmental anomalies				
Goldenhar	0.29	98	2	0
Poland's anomaly (syndrome)	0.11	100	0	0
Sturge-Weber syndrome	0.04	100	0	0
VATER	0.46	75	3	22

***prevalence refers only to cases diagnosed prenatally or in infancy**

Prevention of Congenital Anomalies

Primary Prevention:

- pre disease (attacking basic cause(s) of disease, altering environment)
- organogenesis is early in pregnancy often before pregnancy is confirmed
- needs to start preconceptionally

Secondary Prevention:

- disease has started but symptoms have not appeared (detecting/treating early to prevent disease development) e.g. better cardiac surgery outcomes after prenatal diagnosis

Tertiary Prevention:

Disease has become symptomatic (curing, controlling or preventing complications) e.g. paediatric surgery

In relation to congenital anomalies that can be prenatally diagnosed, primary prevention DOES NOT INCLUDE termination of pregnancy. Termination of pregnancy should **not** be a substitute for primary prevention.

Examples of Primary Preventive Measures

- Appropriate clinical care (particularly in the periconceptional period) of high risk women with chronic disease status (diabetes and epilepsy) who need special attention to appropriate medication in order to reduce the congenital anomaly risk
- Maternal infection control – e.g. continuation of the rubella vaccination programme
- Avoidance of known teratogenic agents
- Cessation of maternal smoking, alcohol consumption and recreational drugs
- Pre-marketing drug testing, post-marketing pharmacovigilance of drugs taken during pregnancy (of unknown teratogenicity), health technology surveillance (e.g. assisted reproductive technologies).
- Maternal nutritional considerations (periconceptional folate status, vitamin B12 status, excess of vitamin A, general healthy diet, deprivation-related poor diet)
- Reduction of exposure to environmental pollutants (precautionary where necessary and envirovigilance)
- Genetic counselling for high risk families

Investment in aetiologic research and in congenital anomaly surveillance is an important part of any primary prevention strategy.

The Contribution of EUROCAT to European Action on Rare Diseases

The Council Recommendation of 8th June 2009 on an action in the field of Rare Diseases, and the Communication from the Commission on Rare Diseases: Europe's Challenges of November 2008, recognise the need for registries and databases co-ordinated at European level (such as EUROCAT), for:

- Pooling and sharing of data and expertise
- Improving the coding and classification of Rare Diseases
- Comparable epidemiological data at EU level
- Identifying and evaluating primary preventive measures
- Joint approach to European public health questions

EUROCAT have developed recommendations on policies to be considered for the primary prevention of congenital anomalies in **National Plans (and Strategies) on Rare Diseases.** In the field of:

- Medicinal drugs
- Food/nutrition and lifestyle
- Health Services
- Environmental pollution including the workplace

EUROPLAN (European Project for Rare Diseases National Plan Development) part of the EUCERD (European Union Committee of Experts on Rare Diseases) Joint Action, will support and facilitate EU Member States to incorporate the recommendations in their National Plans, and will facilitate exchange of experience among Member States, in collaboration with EUROCAT.

Classification and coding is problematic for Rare Disease. Specific codes do not exist for many Rare Diseases, in particular for many

syndromes. The EUROCAT Coding and Classification Committee are working with the WHO, Orphanet and EUCERD to revise the Developmental Anomalies chapter for the new ICD11 in order to improve the coding of congenital anomalies and other Rare Diseases.

EUROCAT representatives work with the European Platform for Rare Disease Registries (EPIRARE) to share their long experience of registry networks and pooled databases in Europe with other rare disease registries. What distinguishes EUROCAT registries from many other Rare Disease Registries is their population base (i.e. they register **all** cases in a **defined geographical area**), and that their main function is surveillance underpinning primary prevention.

EUROCAT has been working with the International Federation for Spina Bifida and Hydrocephalus to monitor Neural Tube Defect rates and public health policies aimed at raising the periconceptional folate status.

"The potential for preventing Neural Tube Defects by periconceptual folic acid supplementation is still far from being fulfilled in Europe. In order to achieve a reduction in Neural Tube Defect prevalence, new efforts are needed in all countries to implement a combined strategy to increase folate status by dietary means, increase uptake of folic acid supplements periconceptionally, and to increase availability and identification of fortified foods." *[10]*

The importance of population-based congenital anomaly registries and of epidemiological surveillance (in the context of rare disease policy)

- Population-based registries, which refer to a geographically defined population, aim to register <u>all</u> cases in that population and provide essential epidemiologic information on congenital anomalies in Europe. Population-based registries allow the calculation of population prevalence without the biases inherent in hospital or clinic-based registries which have selective case referrals. They also allow the gathering of data on congenital anomalies in the entire population, rather than those selectively reaching centres of excellence.
- The main function of congenital anomaly registries is epidemiologic surveillance. Epidemiological surveillance data is important to support rare disease policy decisions on prevention, health and other service requirements,
- Congenital anomaly surveillance began in the wake of the thalidomide epidemic, to ensure that any new widespread new teratogenic exposure, whether a medication or an environmental pollutant, should be detected early allowing effective public health action.
- Due to the rarity of cases, for research purposes, very large study populations (often achieved by combining population-based registry data) are often needed to obtain enough affected individuals.
- Population-based studies can demonstrate the effectiveness of interventions.
- All EUROCAT registries collect the same standard dataset, and this means that comparisons between countries can be made

Thus, an established collaborative network of population-based registries performing surveillance, such as EUROCAT can;

- provide an infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children
- facilitate the early warning of new teratogenic exposures
- assess the impact of developments in prenatal screening
- act as an information and resource center for the population, health professionals and managers regarding clusters or exposures or risk factors of concern
- act as a catalyst for the setting up of new registries throughout Europe collecting comparable, standardised data

What epidemiological information can be found on the EUROCAT website?

Interactive Website Prevalence Tables can be accessed at any time at http://www.eurocat-network.eu/accessprevalencedata/prevalencetables.

The prevalence of selected **monogenic syndromes in Europe** can also be accessed via the Interactive Website Prevalence Tables.

The latest EUROCAT **Perinatal Mortality** data can be viewed on the **Key Public Health Indicator** section of the EUROCAT website http://www.eurocat-network.eu/accessprevalencedata/keypublichealthindicators.

Prenatal Detection Rates for the latest 5 year period created from surveillance data collected by EUROCAT member registries can be accessed via http://www.eurocat-network.eu/prenatalscreeninganddiagnosis/prenataldetectionrates

EUROCAT performs annual **Statistical Monitoring** for both trends and clusters in time in order to detect signals of new or increasing teratogenic exposures which may require public health action.

- to provide essential epidemiologic information on congenital anomalies in Europe
- to co-ordinate the detection of, and response, to clusters and early warning of teratogenic exposures

View the latest Statistical Monitoring protocols and reports at: http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoringintroduction

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