Congenital Anomalies

Intorduction to population teratology

Antonín Šípek jr.

ÚBLG 1. LF UK a VFN, Praha

National Registry of Congenital Anoamalies

http://www.vrozene-vady.cz/

Outline

1. Congenital anomalies
2. History
3. Population teratology
4. Results
5. International cooperation

Congenital anomalies

Definition

- **Congenital Anomaly (CA)** is an anomaly that affects a body part or physiologic function and is present at birth.

- CA is caused by the abnormal ontogenetic development of the fetus. The process is affected by genetic, environmental or both factors.

- The disturbance of the regulation and development cascades take place on the level of tissue, cell or molecule.

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Definition

- **Malformation** is caused by an abnormal development of the organ / tissue, that is abnormal from the beginning.

- **Disruption** is caused by destructive process, that affects an organ / tissue, that started to develop normally.

- **Deformation** is caused by an abnormal physical force, that damages healthy organ / tissue.

- **Dysplasia** is caused by an abnormal organization of the cells in the organ / tissue.

Definition

- **Isolated anomaly:** an anomaly that is not associated with any other conditions (e.g. isolated polydactyly).

- **Sequence:** multiple anomalies that result from the pathologic cascade caused by a primary insult (e.g. Potter‘s sequence).

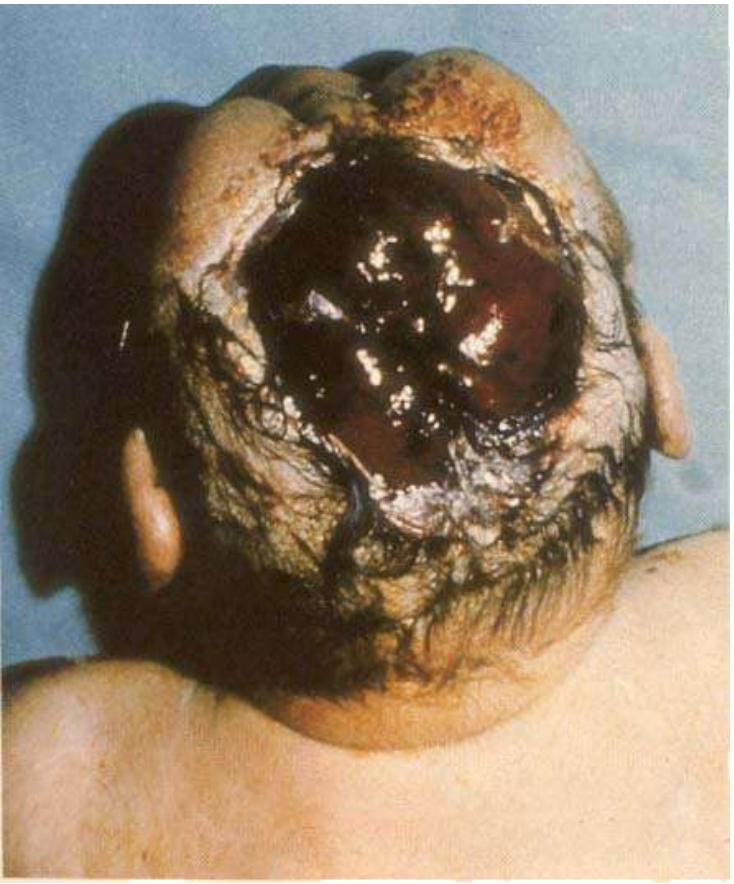
- **Association:** selected congenital anomalies that tend to develop all together – in an association (e.g. VATER association).

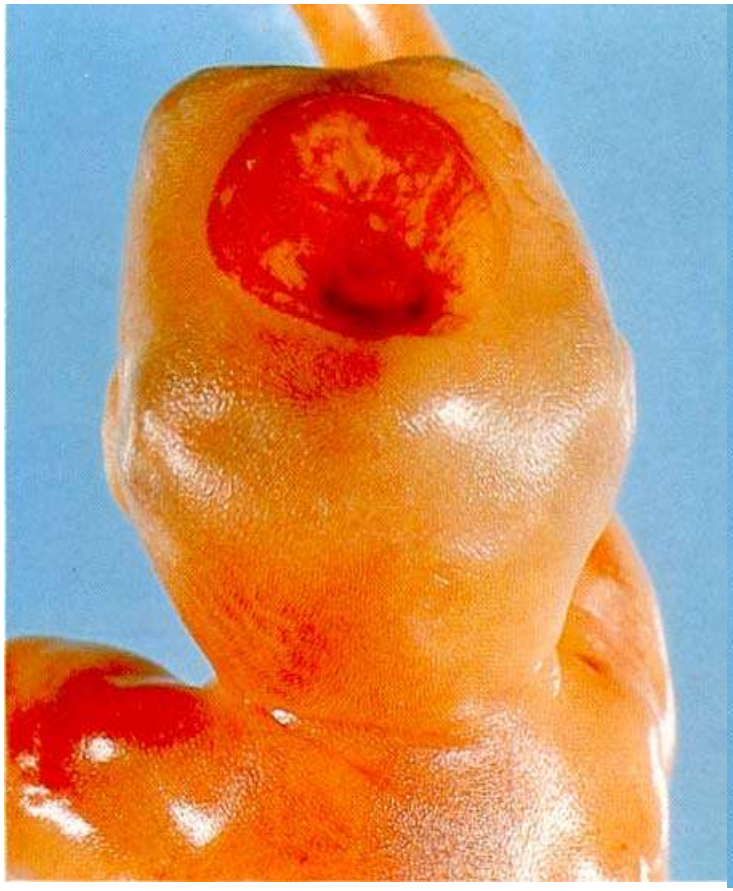
- **Syndrome:** complex of phenotypic traits (anomalies) that are typical for defined clinical diagnosis (e.g. Down syndrome).

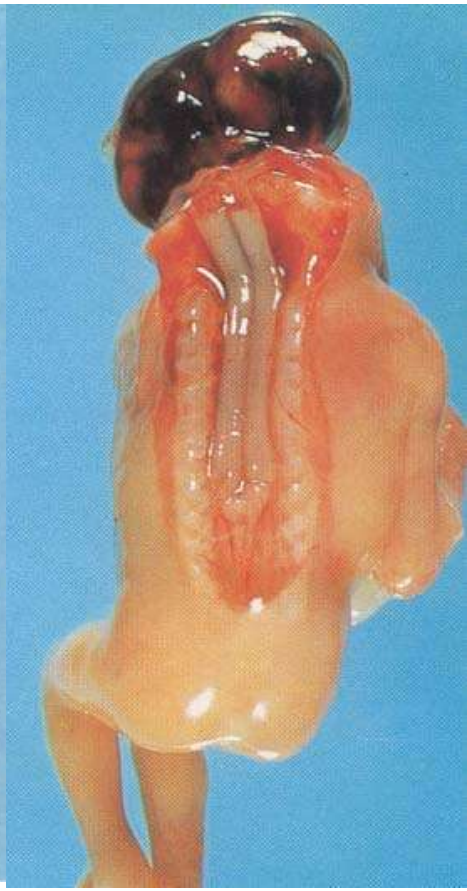
Classification (ICD – 10)

Q00-Q07 Congenital malformations of the nervous system
Q10-Q18 Congenital malformations of eye, ear, face and neck
Q20-Q28 Congenital malformations of the circulatory system
Q30-Q34 Congenital malformations of the respiratory system
Q35-Q37 Cleft lip and cleft palate
Q38-Q45 Other congenital malformations of the digestive system
Q50-Q56 Congenital malformations of genital organs
Q60-Q64 Congenital malformations of the urinary system
Q65-Q79 Congenital malf. and deform. of the musculoskeletal system
Q80-Q89 Other congenital malformations
Q90-Q99 Chromosomal abnormalities, not elsewhere classified

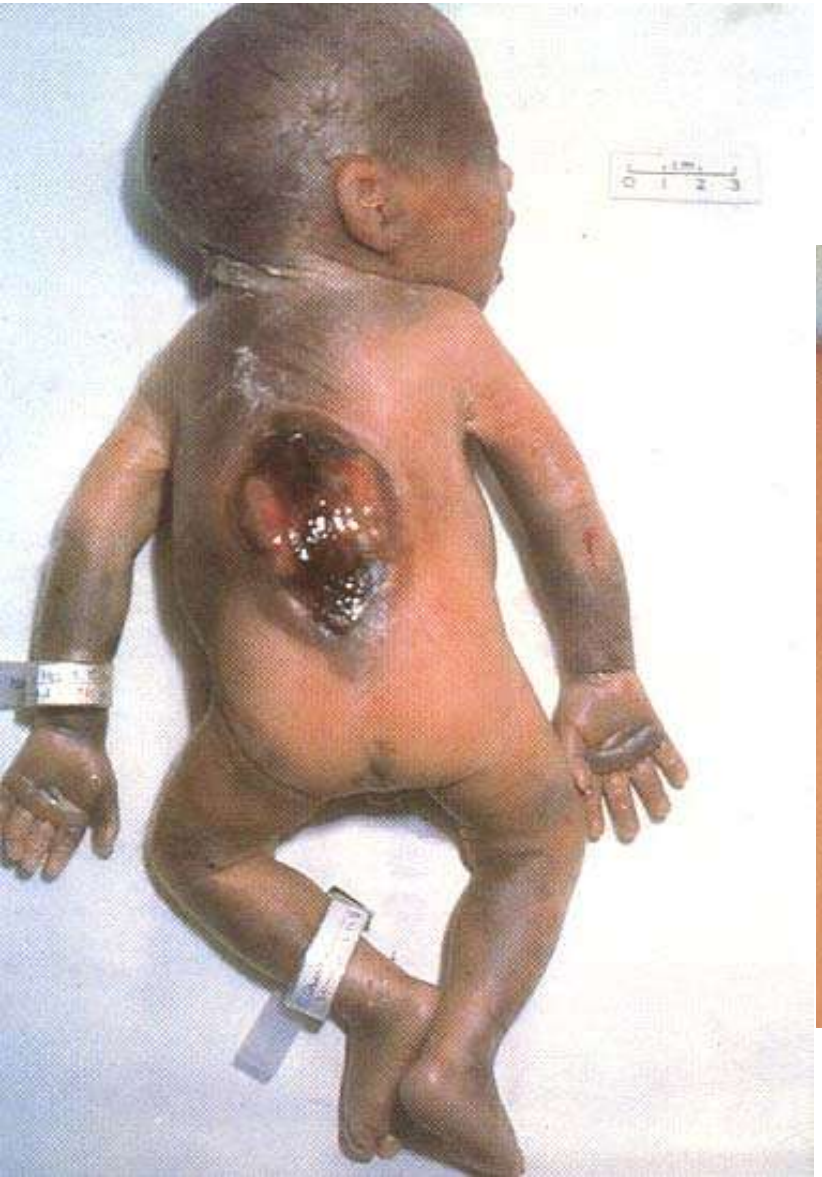
Anencephaly

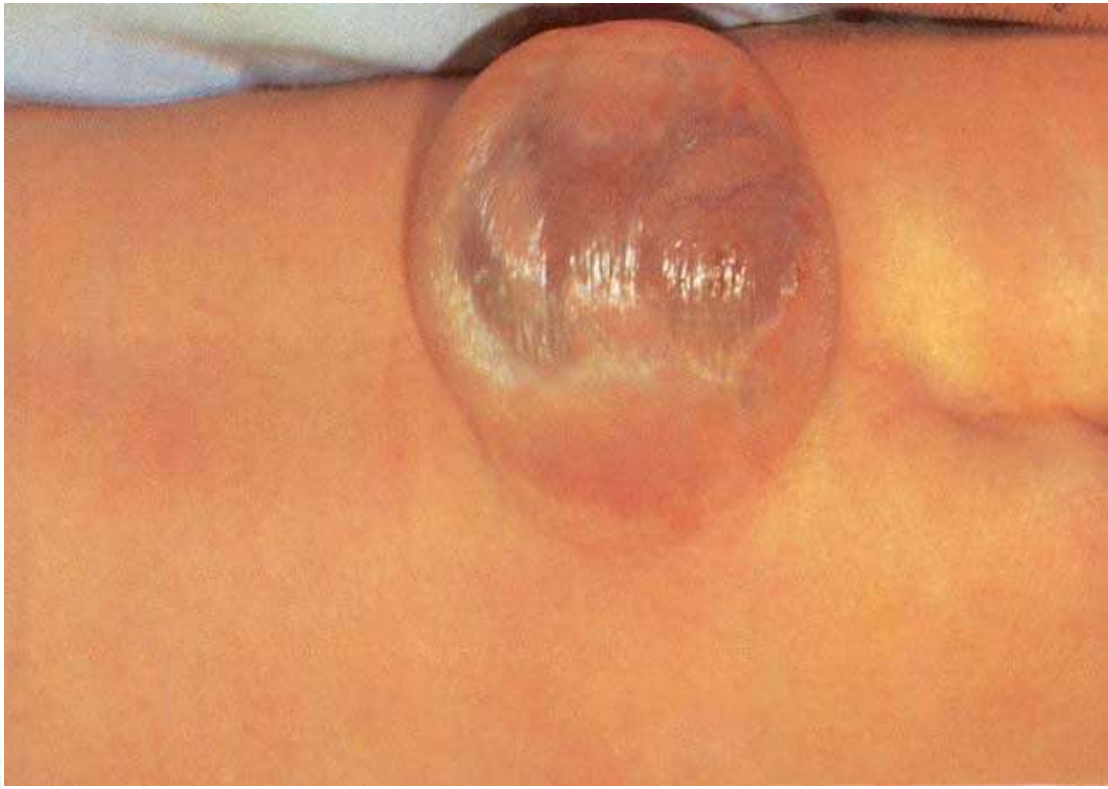




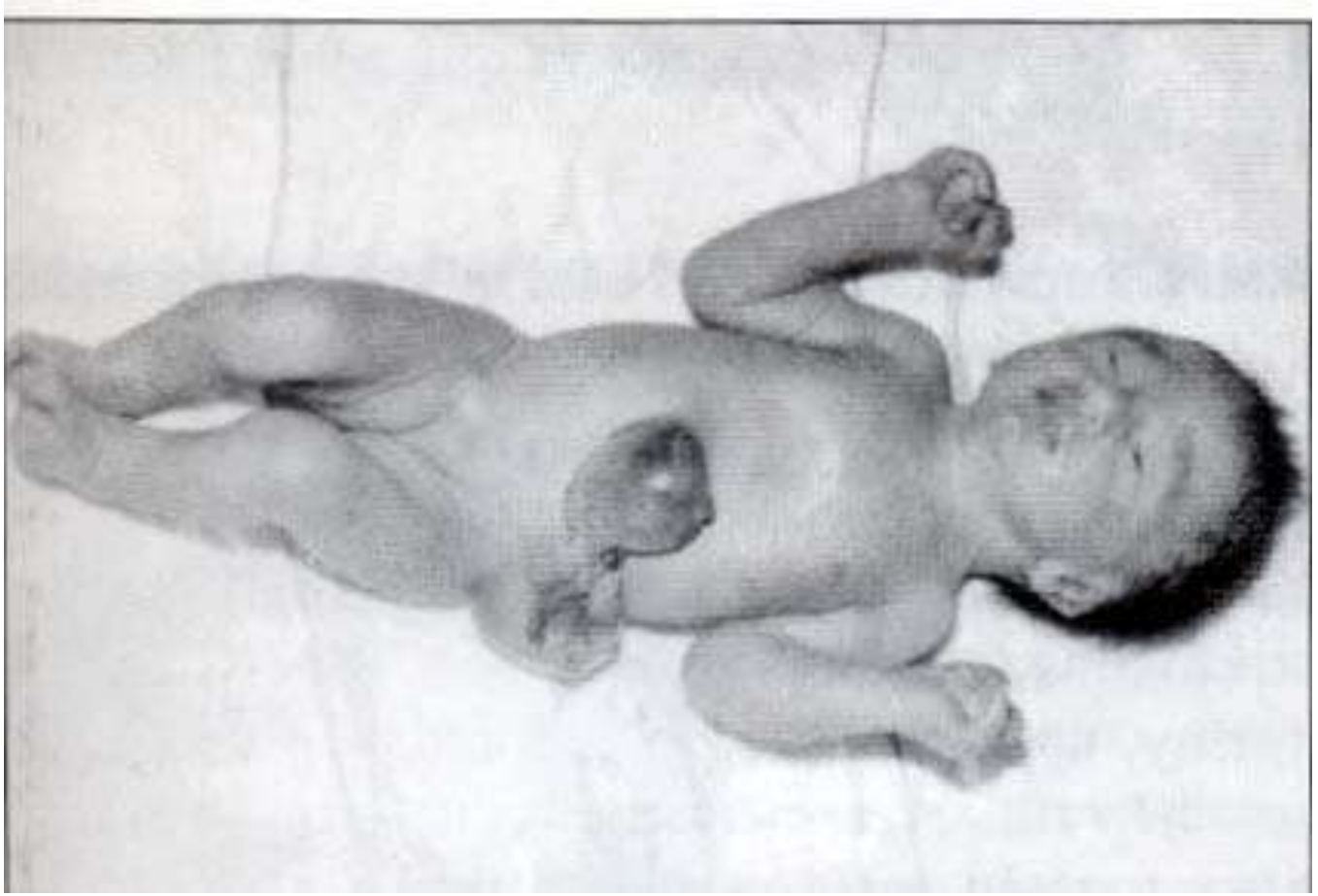


Spina bifida

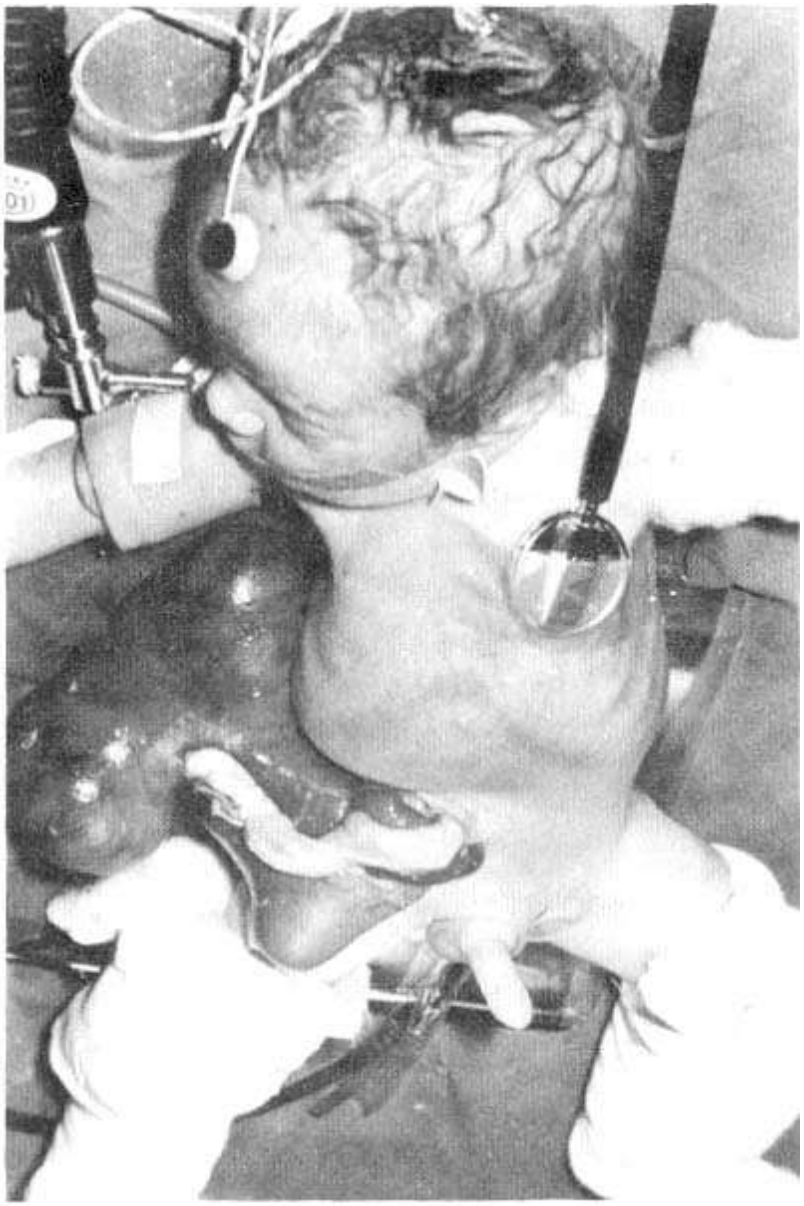




Omphalocoele



Gastroschisis



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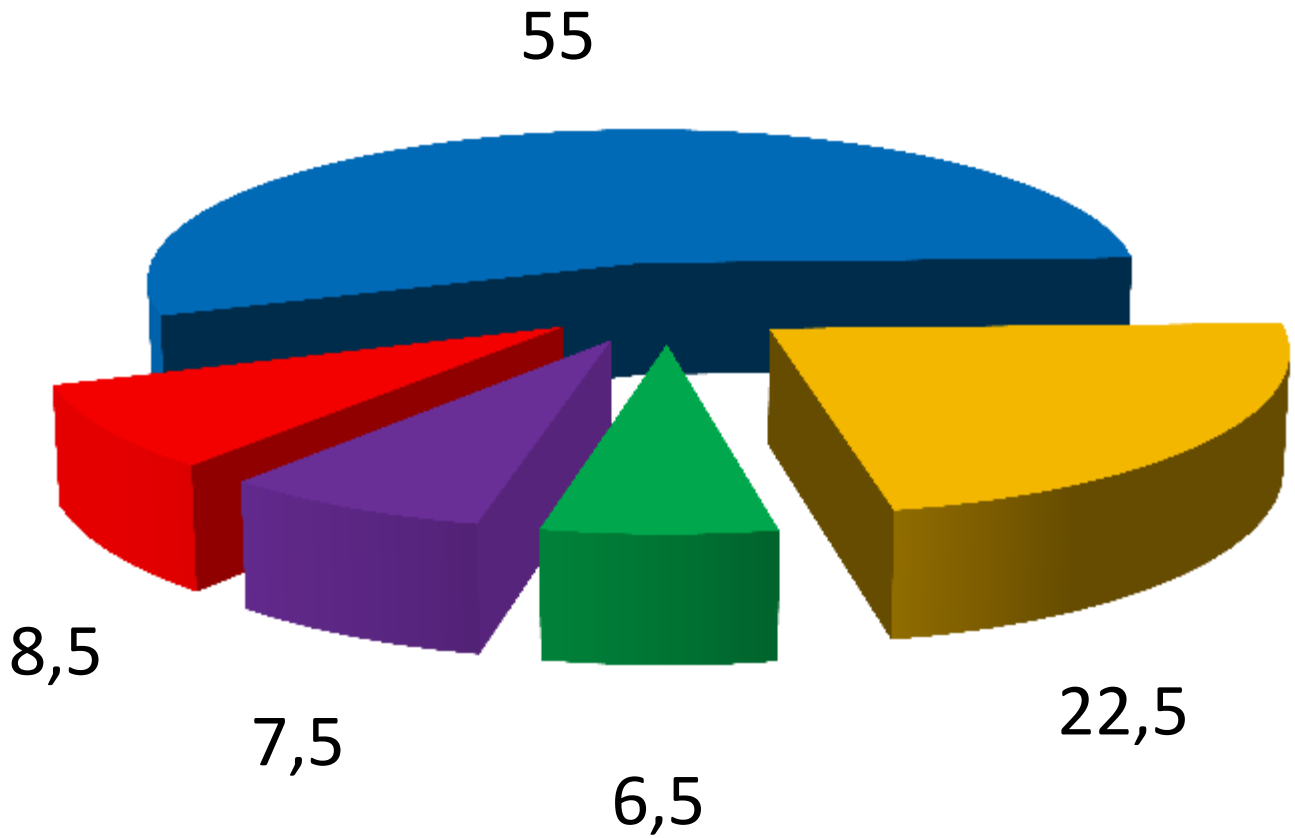
Causes of Congenital Anomalies



Zdroj: Moore K. L., Persaud T. V. N.; The Developing Human: Clinically Oriented Embryology, 6th Edition; 1998

Exogenous factors

There are many environmental factors that cause congenital anomalies, or are able to cause them in specific situations.

Those factors are commonly known as **teratogens**.
However - the effect of teratogens is dependent on the genetics. The genotype can modify the teratogenic effect.

There are three main groups of teratogens:

- **Physical**
- **Chemical**
- **Biological**

Physical teratogens

- **X-rays** (common diagnostic doses are not dangerous)
- **Ionizing radiation** (e.g. gamma radiation)
- **High temperature** (sauna, fever)
- **Mechanical factors** (amniotic bands, oligohydramnion)

Ultrasonography and electromagnetic field seem to be safe.

Chemické teratogeny

- **chemical substances** used in industry or agriculture (organic solvents, paints, polychlorinated biphenyls, heavy metals)

- **alcohol** (cause Fetal alcohol syndrome)

- **products of cigarette smoking** (teratogenic effect of marihuana smoking was also proved)
- **other drugs** (e.g. cocaine), **doping** (steroids)

- **cytostatics** and some other groups of medicaments (antiepileptics, antibiotics, warfarine, ACE-inhibitors)

Drugs

The four main groups of drugs according to teratogenic effect:

1. **Teratogenic effect proved** (cytostatics, methotrexat and aminopterin, warfarine, high doses of vitamin A, alcohol, cocaine).
2. **Teratogenic effect presumable** (antiepileptics, lithium).
3. **Teratogenic effect possible** (hormones, amphetamin, diazepam, enzyme inhibitors, d-penicilamin).
4. **Teratogenic effect cannot be excluded**.

Prooved teratogens

Alcohol (facial dysmorphy, brain growth retardation, congenital anomalies of the heart)

Warfarine (chondrodysplasia punctata, risk of abortion)

Retinoids (anomalies like Di-George syndrome, anomalies of CNS, anomalies of the internal ear)

Aminopterine + Methotrexate (anomalies of cranium and skeleton, anencephaly)

Thalidomide (abnormal development of long bones, phocomelia, polydactyly, syndactyly, oligodactyly and other malformations)

Presumable teratogens

Fenytoine (congenital anomalies of the heart, failure of th CNS closure, cleft palate)

Trimetadione (anomalies of the heart, anomalies of the urogenital system, mental retardation)

Valproate (facial dysmorphy, defects of CNS)

Lithium (anomalies of the heart, Ebstain‘s anomaly)

Possible Teratogens

Amfetamine (congenital anomalies of the heart, exencephaly, atresia of bile ducts)

Diazepame (cleft lip and cleft palate)

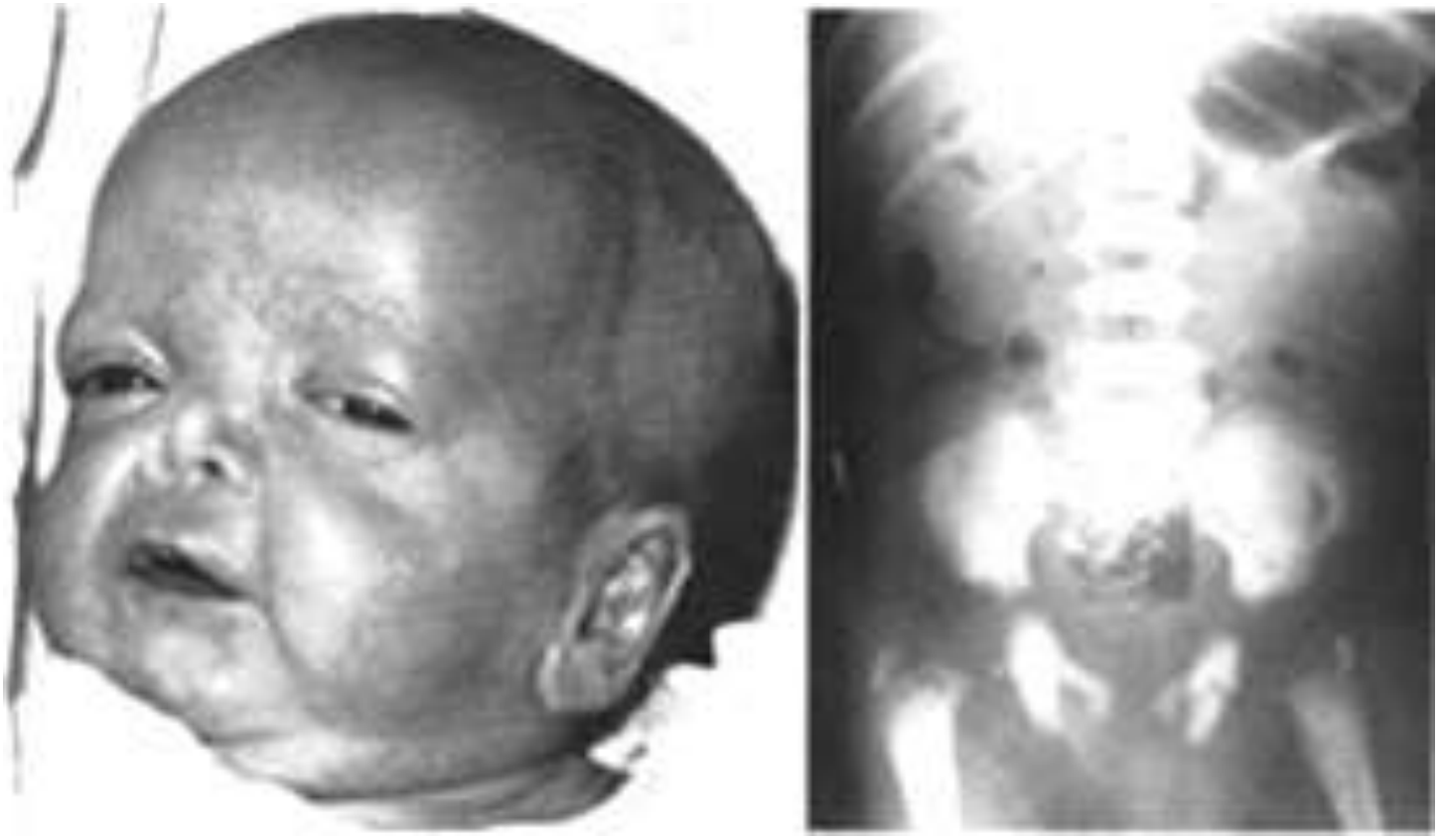
ACE-Inhibitors (hypoplasia of the skull, renal dysgenesis)

Corticosteroids (cleft palate, renal atrophy)

Androgens (masculinization of the external genitalia)

Progesteron (virilization, anomalies of the hearth, anomalies of the CNS, defects of the extremities, esophageal atresia)

Warfarine syndrome



Hypoplastic nose, flat face, altered bone calcification

Fetal alcohol syndrome

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Further information

State Institute for Drug Control (CZE) (SÚKL)
http://www.sukl.cz/

European Medicines Agency (EMEA)
http://www.emea.europa.eu/

U S Food and Drug Administration (FDA)
http://www.fda.gov/

Czech Teratology Information Service (CZTIS)
http://old.lf3.cuni.cz/histologie/english/33.htm

European Network Teratology Information Services (ENTIS)
http://www.entis-org.com/

Organization of Teratology Information Specialists (OTIS)
http://www.otispregnancy.org/

Biologic teratogens

- **Infectious agents**
  - **TORCH** (acronym for most important teratologic agents)
    - **T**oxoplasma
    - **O**ther
    - **R**ubivirus
    - **C**ytomegalovirus
    - **H**erpesvirus
- **Diseases of the mother**
  - Diabetes mellitus (DM)
  - Phenylketonuria (PKU)

Infections

- **Rubivirus** (cataract, deafness, anomalies of the heart, microcephaly, mental retardation)
- **Cytomegalovirus** (microcephaly, chorioretinitis, deafness, hepatosplenomegaly)
- **Varicella-Zoster virus** (microcephaly, chorioretinitis, defects of the extremities, mental retardation, cataract)
- **Parvovirus B-19** (hydrops fetalis, anemy, malformation of the heart)
- **Influenzavirus** (failure of the CNS closure)
- **Coxsackie virus** (fetal pancreatitis and fetal meningoencephalitis)
- **HIV (**immunodeficiency, dysmorphy)
- **Treponema pallidum** (failure of teeth development, IUGR, hydrops fetalis)
- **Toxoplasma gondii (**hydrocephaly, microcephaly, chorioretinitis, blindness)

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History

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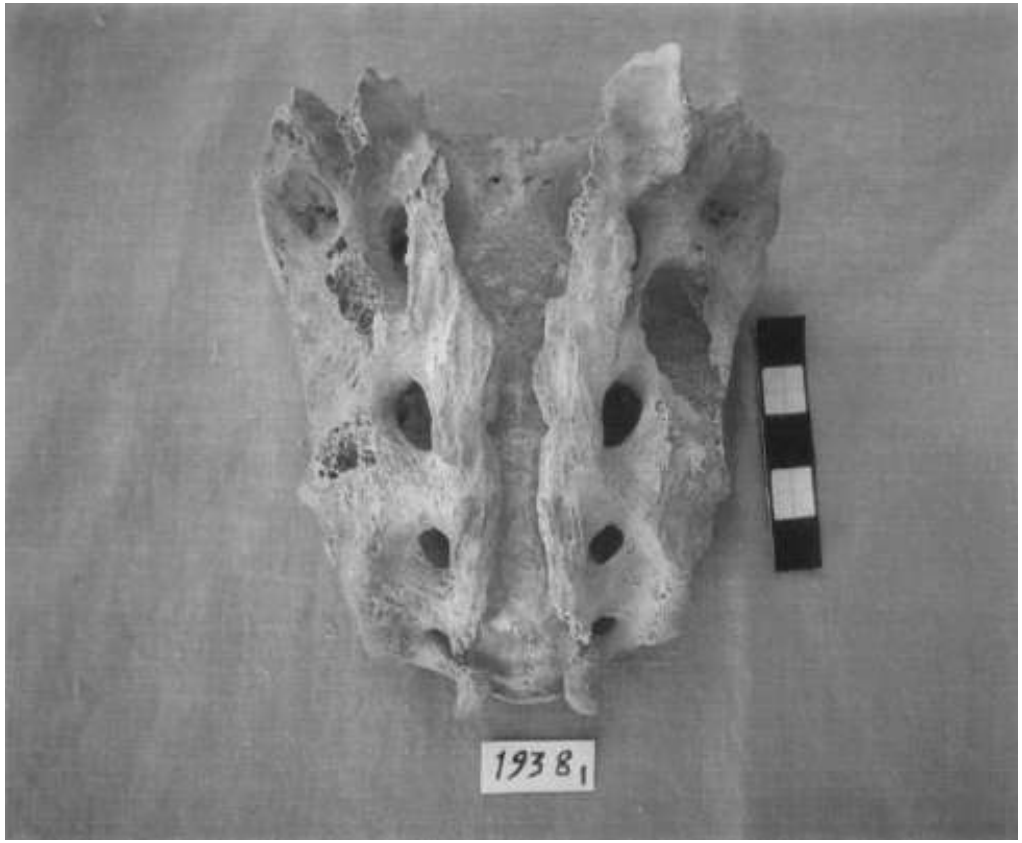
Congenital anomalies in history



Spina bifida (S1-S5), man 45-50years, oblast Gisa, Egypt (2630-2180 BC)

Sarry El-Din AM, El Banna, RA ES. (2006) Congenital anomalies of the vertebral column: a case study on ancient and modern Egypt. International Journal of Osteoarchaeology, 16: 200–207.

Congenital anomalies in history

Münchener Neue Pinakothek.
Fig. 45. Flugblatt vom Jahre 1566.

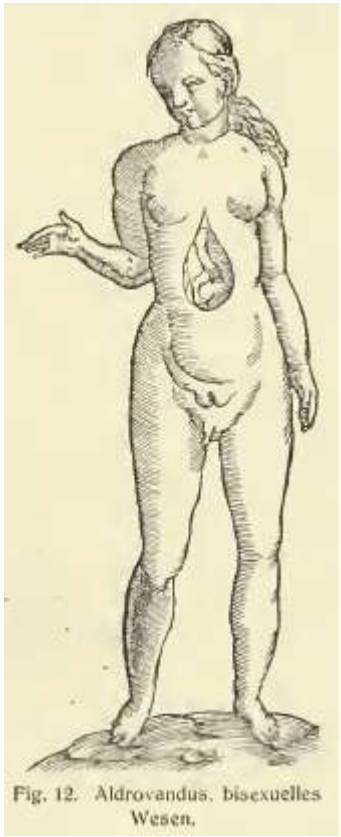


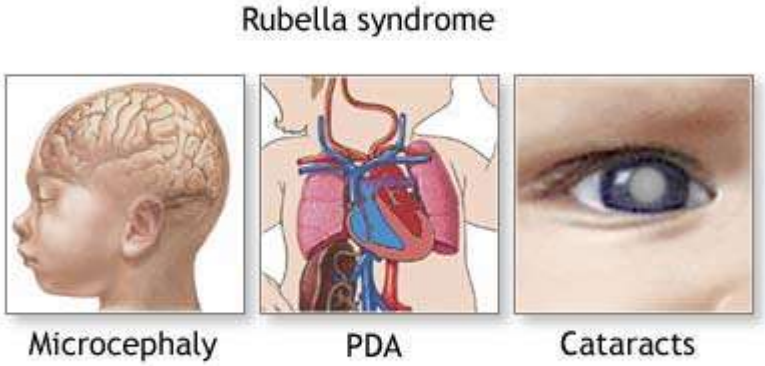
Fig. 12. Aldrovandus. bisexuelles Wesen.

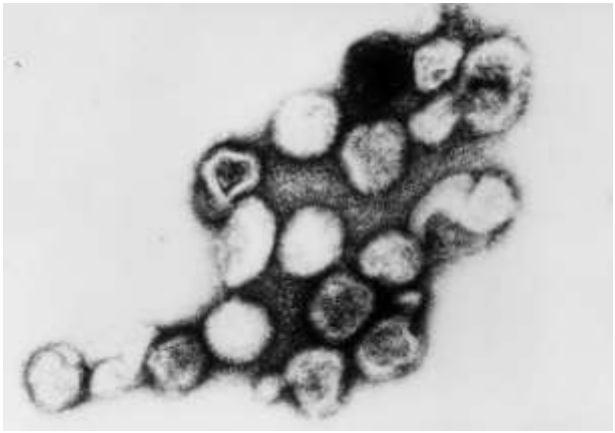
Fig. 81. Flugblatt von Aubry.

Medieval Europe

Holländer E. (1921) ***Wunder, Wundergeburt und Wundergestalt in Einblattdrucken des fünfzehnten bis achtzehnten Jahrhunderts,*** *Stuttgart, 373 s.*

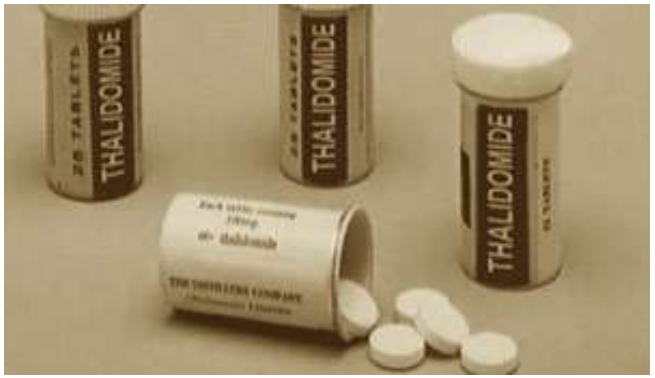
Measles



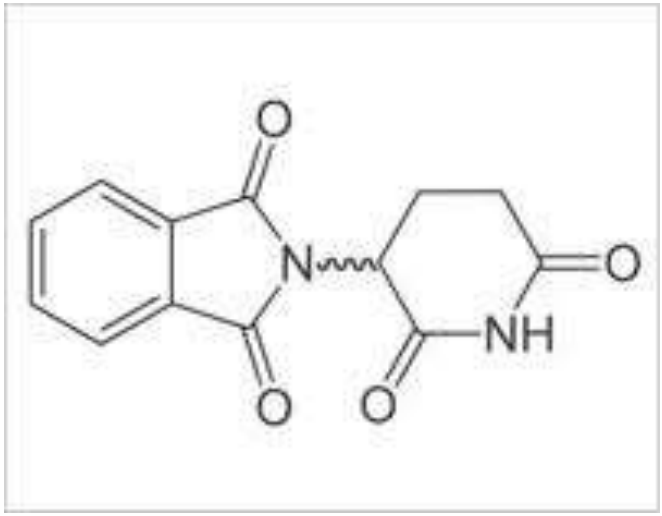


N. MCALISTER GREGG (1942) ***Congenital cataract following german measles in the mother.*** *Trans Ophthalmol Soc Austr 3, 35–46.*

Thalidomide



Country	Brand Name
Canada	Talimol, Kevadon
Great Britain	Asmaval, Distaval, Distaval Forte, Tensival, Valgis, Valgraine
United States	Kevadon
West Germany	Algosediv, Contergan, Contergan Forte, Contergan Saft, Contergan-Suppositorium, Grippex, Pantosediv, Peracon-Expectorans, Prednisev, Softenon, Softenon Forte



Thalidomide

THALIDOMIDE AND CONGENITAL ABNORMALITIES [22]

SIR: Dr. McBride (December 16) describes congenital abnormalities in babies delivered of women who have taken thalidomide. I have seen 52 malformed infants whose mothers had taken Contergan in early pregnancy, and I understand that Contergan is a synonym of thalidomide, others being Distaval, Softenon, Neurosedyn, Isomin, Kedavon, Telargan, and Sedalis.

Since I discussed the possible etiological role of Contergan in human malformations at a conference on November 18, 1961, I have received letters from many places in the German Federal Republic, as well as from Belgium, England, and Sweden, reporting 115 additional cases in which this drug was thought to be the cause.

Though these malformations are variable, they are of a rather specific nature. It is usually possible to infer from the type of the abnormalities alone whether Contergan has been taken. Typical of a Contergan history are defects of the arms (amelia, atypical phocomelia with absence of the thumbs and sometimes of other fingers as well, aplasia of the radius, defects of the long bones of the legs, especially the femora and tibiae, absence of the auricles, hemangiomata of the nose and the upper lip (wine-spot variety), atresia of the esophagus, the duodenum, or the anus, cardiac anomalies, and aplasia of the gallbladder and of the appendix.

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Thalidomide

Effect of Drugs Upon the Fetus and the Infant

It is a basic premise of pediatrics that physical size is not the most important difference between children and adults. There is increasing awareness that it is also necessary to make more than a quantitative distinction between infants and children. The fetus and the newborn infant often behave so differently as to warrant consideration as separate categories of the human species. This necessitates reevaluation of the effects of drugs independently in each category of the human so that they may be used safely.

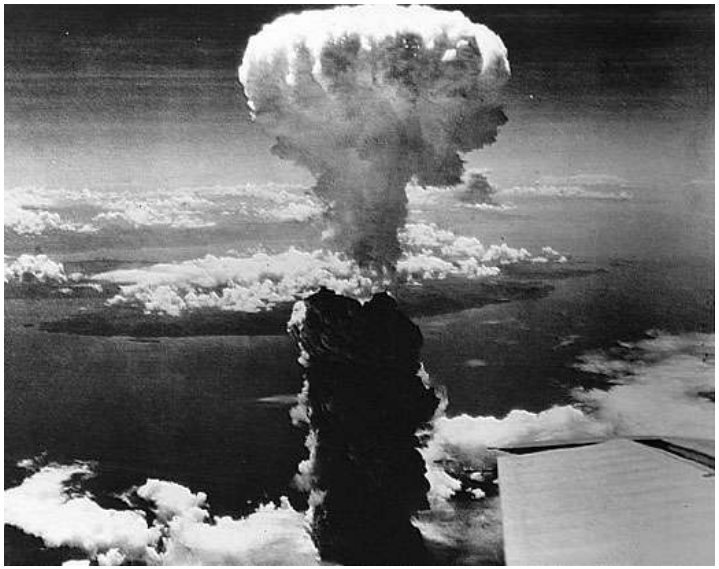
Existing drugs and agents that are developed in the future for use in the fetus and in infants must be subjected to more extensive preclinical investigation than is being carried out at the present time.[17] The pharmacologic responses of the immature human may differ greatly both quantitatively and qualitatively from those of the adult. As a result, data obtained from tests in mature animals and human adults or older children cannot be accepted as a satisfactory basis for recommendations concerning the fetus and infant.

The pharmacologic properties of drugs should be studied in vitro and in vivo in the fetus and newborn animal and compared with those in the adult of the same animal species. Of particular importance would be a knowledge of the LD_{50}, dose response, metabolism, and distribution and disposition of the drug. These determinations should be performed in two or more animal species (a rodent and nonrodent species). Pharmacodynamic actions and clinical effects of drugs in humans should be assessed in clinical situations in which they may be useful.

In order to pursue these principles, it is recommended that drug labels should specifically indicate the extent of existing information concerning the use of the agent in the fetus and the infant.[18] When there have been no pharmacologic studies of a drug in immature subjects, an explicit statement of this fact should be indicated on the drug label or in a readily available package leaflet. Physicians who administer drugs to the fetus and the infant must be alert to unusual effects in this subdivision of the human species.

FDA

Radiation



1945

Only one type of congenital anomaly (**microcephaly**) was found in elevated numbers in Japan after nuke attack on Hiroshima and Nagasaki.
(Plummer, 1952; Yamazaki et al., 1954; Sutow a West, 1955)

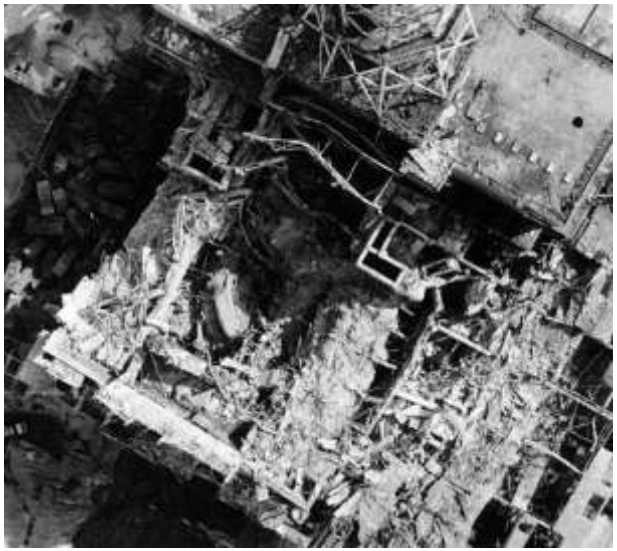
Radiation

1979

No changes in incidences of congenital anomalies were found after the incident at Three Mile Island.

(Upton, 1981; Kalter, 2003)

Radiation



1986

Higher incidence of thyroid cancer was reported in the Chernobyl area. However no association with congenital anomalies numbers increase was proved.
(Kotz, 1995; Castronovo, 1999; Hoffmann 2001; Kalter, 2003)

Radiation

2011

No increase of incidences of congenital anomalies was found in Japan after Fukushima disaster
(Hirahara, 2011 and 2012)

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Population teratology

Congenital Anomalies Registries

1963 – Finland
1964 – ČSSR (unofficial from1961)
1966 – Canada, Israel
1967 – Atlanta (USA), Norway, South Africa
1968 – Denmark
1970 – Northern Ireland (Belfast from1957)

Population teratology

Population teratology analyses the mean incidences of congenital anomalies (CAs) in selected population. Long, consensual monitoring is necessary in order to find any trends that may appear in the incidence of some congenital anomalies (either increase or decrease).

Other findings may be accumulation of CAs, clustering of CAs, cyclic changes in the incidence of CAs, or so called nesting.

Surveillance in the Czech Republic

History of Congenital Anomalies Monitoring Program of Czech Republic is very long. The regular monitoring started in **1964.** The registration itself undergo many changes during almost 50 years of existence.

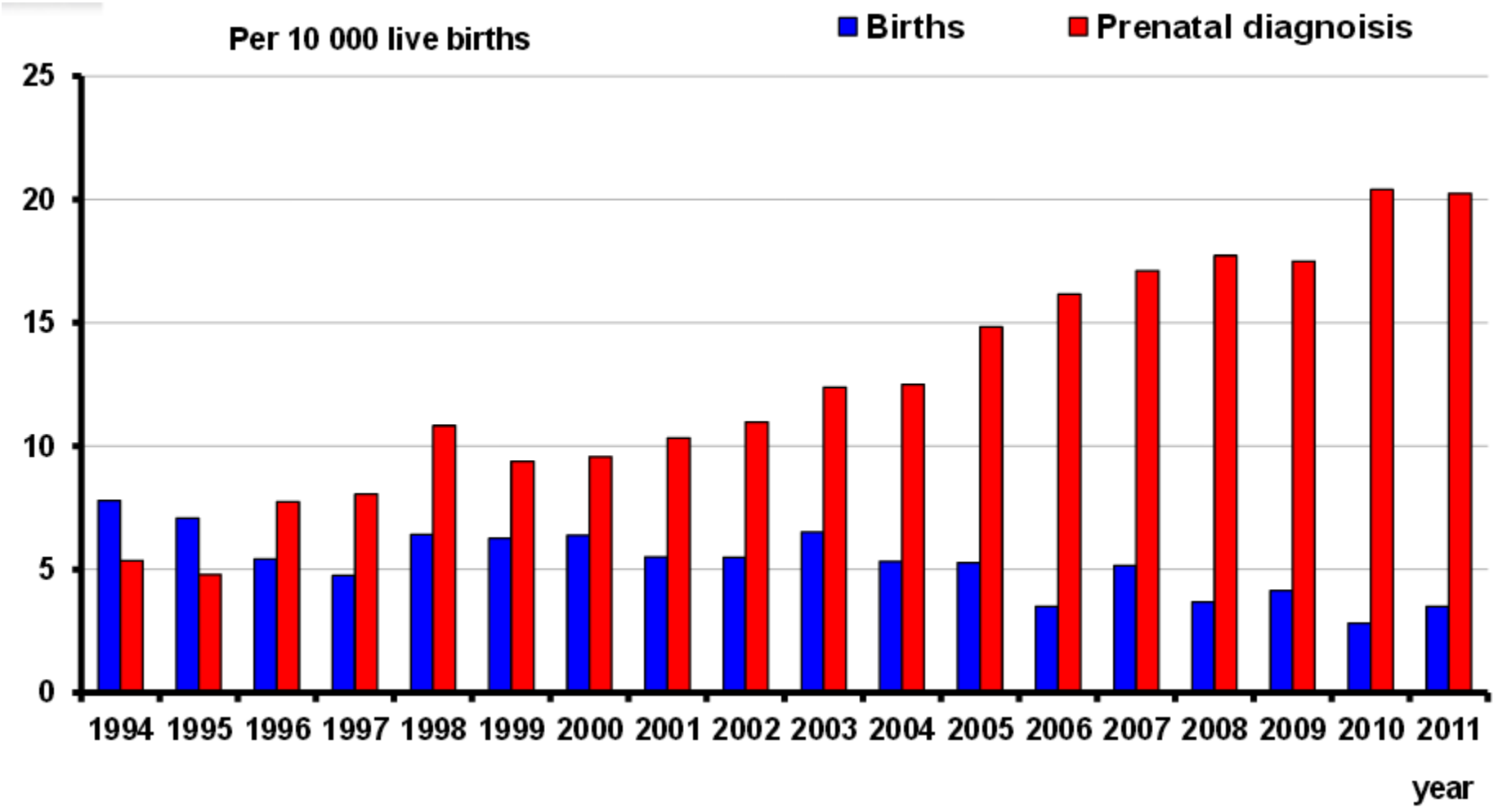
Currently we register any diagnosis from ICD-X Q00-Q99 group, that was diagnosed prenatally or postnatally until (finished) 15th year of live.

The data for the registry are collected in the Institute of Health Information and Statistics of the Czech Republic (**ÚZIS ČR**).

The Czech Registry was one of founding members of ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research) international organization.

Results

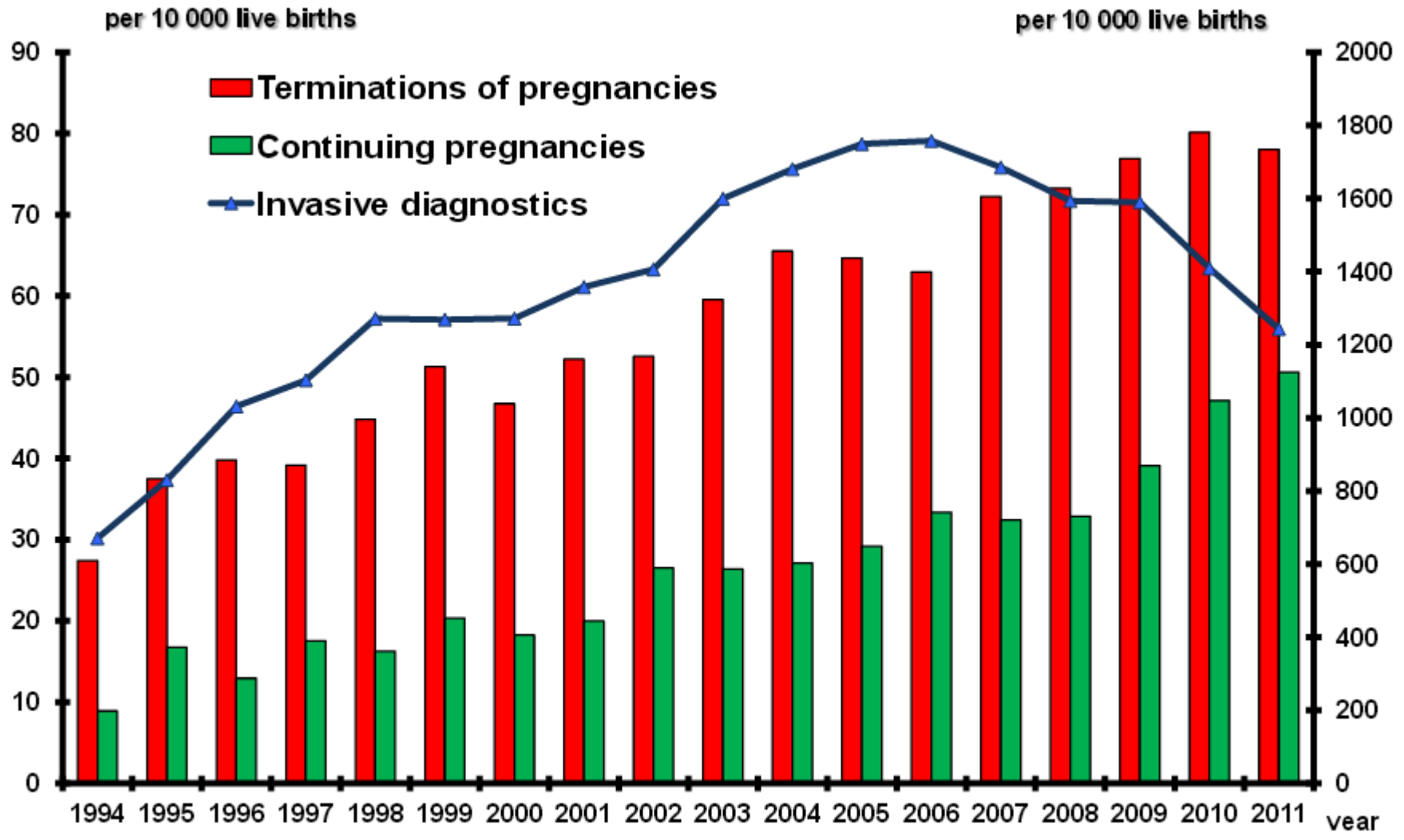
Down Syndrome, Czech Republic, 1994 - 2011



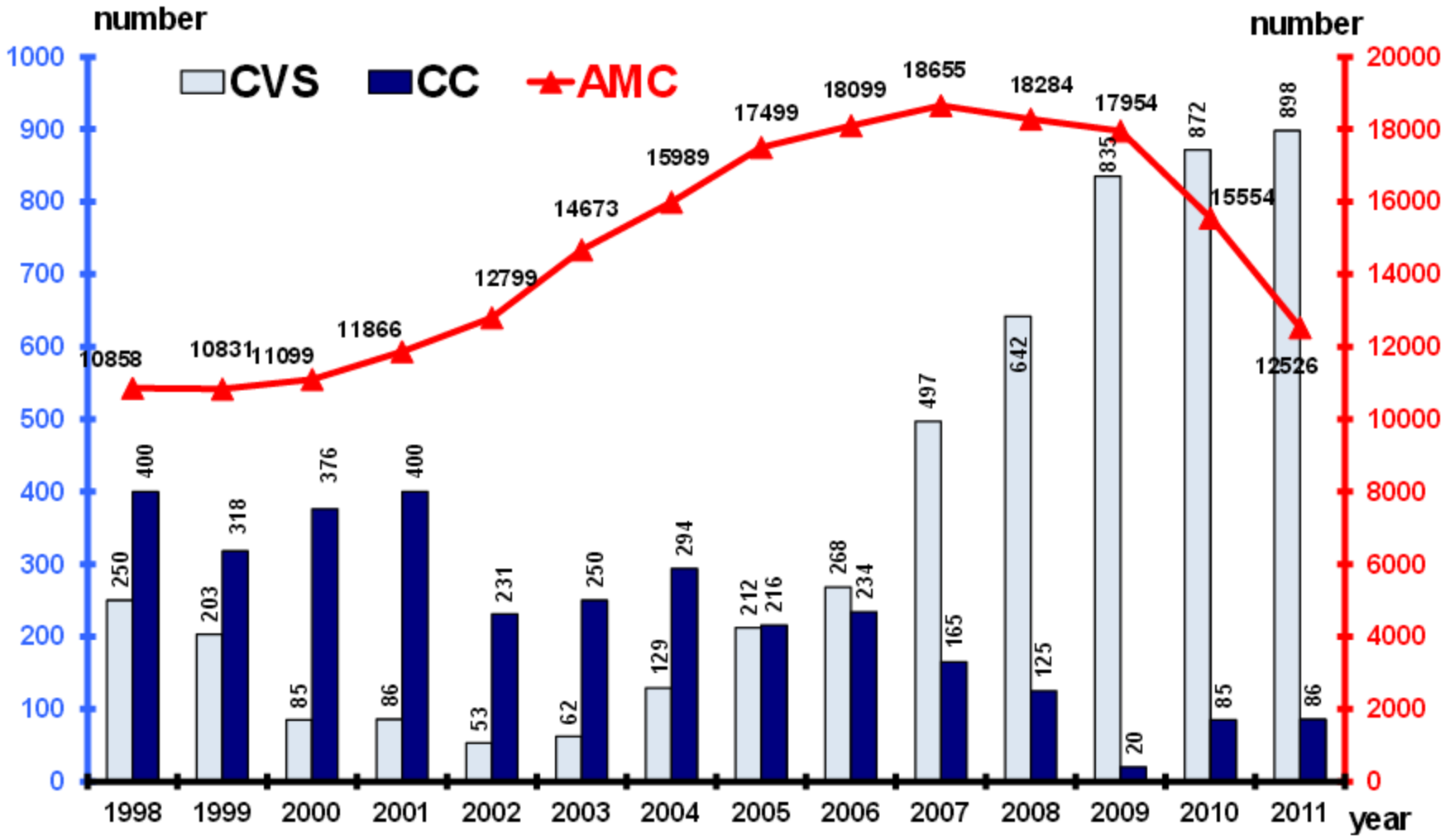
Down Syndrome, Czech Republic, 1994 - 2011

Year	Absolute numbers				Relative numbers (per 10 000)		
	DS - Births	DS - Prenatal diagnosis	DS - Total	Total births in the CZE	DS - Births	DS - Prenatal diagnosis	DS - Total
1994	83	57	140	106 579	7,79	5,35	13,14
1995	68	46	114	96 097	7,08	4,79	11,86
1996	49	70	119	90 446	5,42	7,74	13,16
1997	43	73	116	90 657	4,74	8,05	12,80
1998	58	98	156	90 535	6,41	10,82	17,23
1999	56	84	140	89 471	6,26	9,39	15,65
2000	58	87	145	90 910	6,38	9,57	15,95
2001	50	94	144	90 978	5,50	10,33	15,83
2002	51	102	153	93 047	5,48	10,96	16,44
2003	61	116	177	93 685	6,51	12,38	18,89
2004	52	122	174	97 664	5,32	12,49	17,82
2005	54	152	206	102 498	5,27	14,83	20,10
2006	37	171	208	105 831	3,50	16,16	19,65
2007	59	196	255	114 642	5,15	17,10	22,24
2008	44	212	256	119 570	3,68	17,73	21,41
2009	49	207	256	118 348	4,14	17,49	21,63
2010	33	239	272	117 153	2,82	20,40	23,22
2011	38	220	258	108 673	3,50	20,24	23,74
Total	**943**	**2346**	**3289**	**1 816 784**	**5,08**	**11,42**	**16,50**

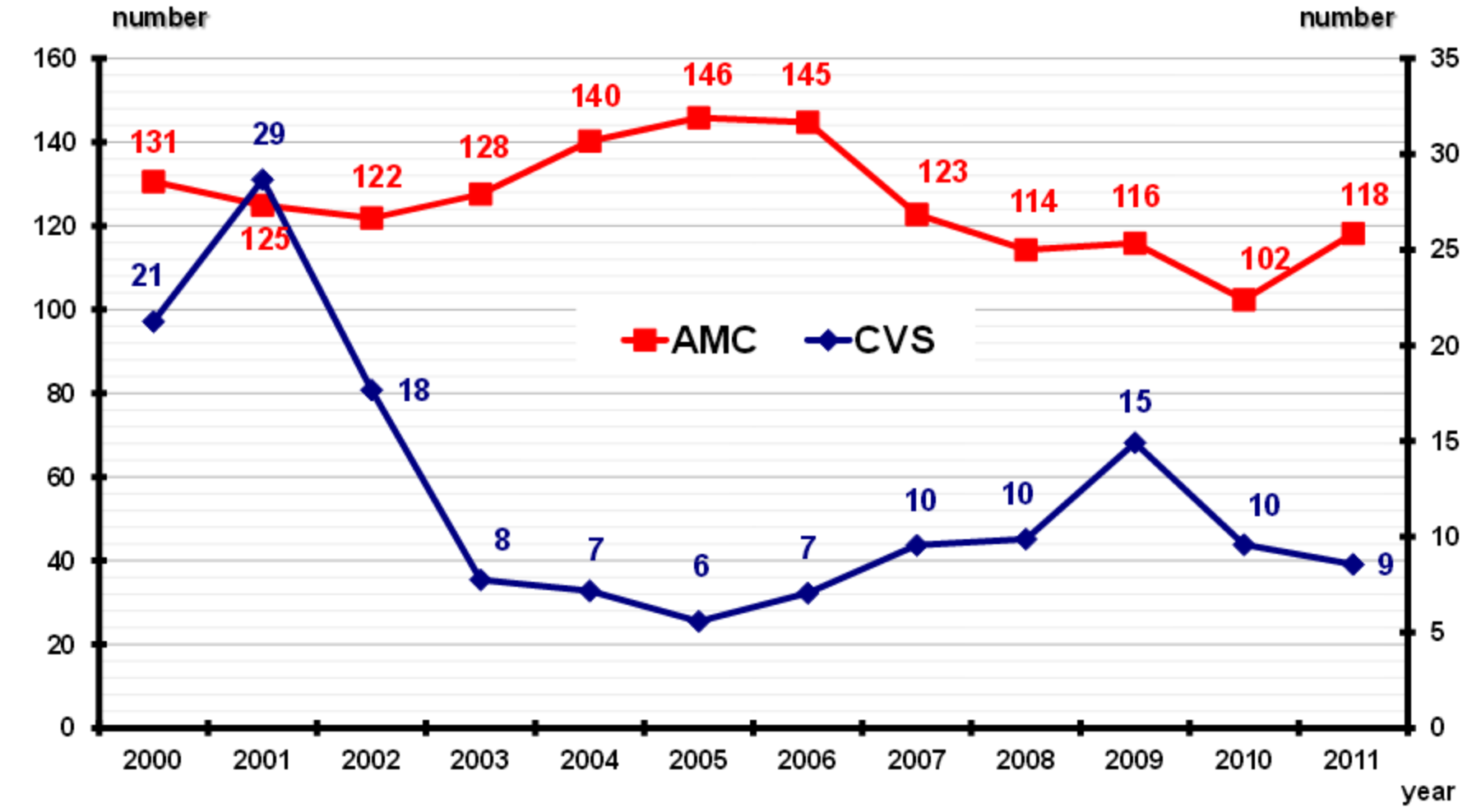
Prenatal Diagnosis, Czech Republic, 1994 - 2011



Prenatal Diagnosis, Czech Republic, 1994 - 2011

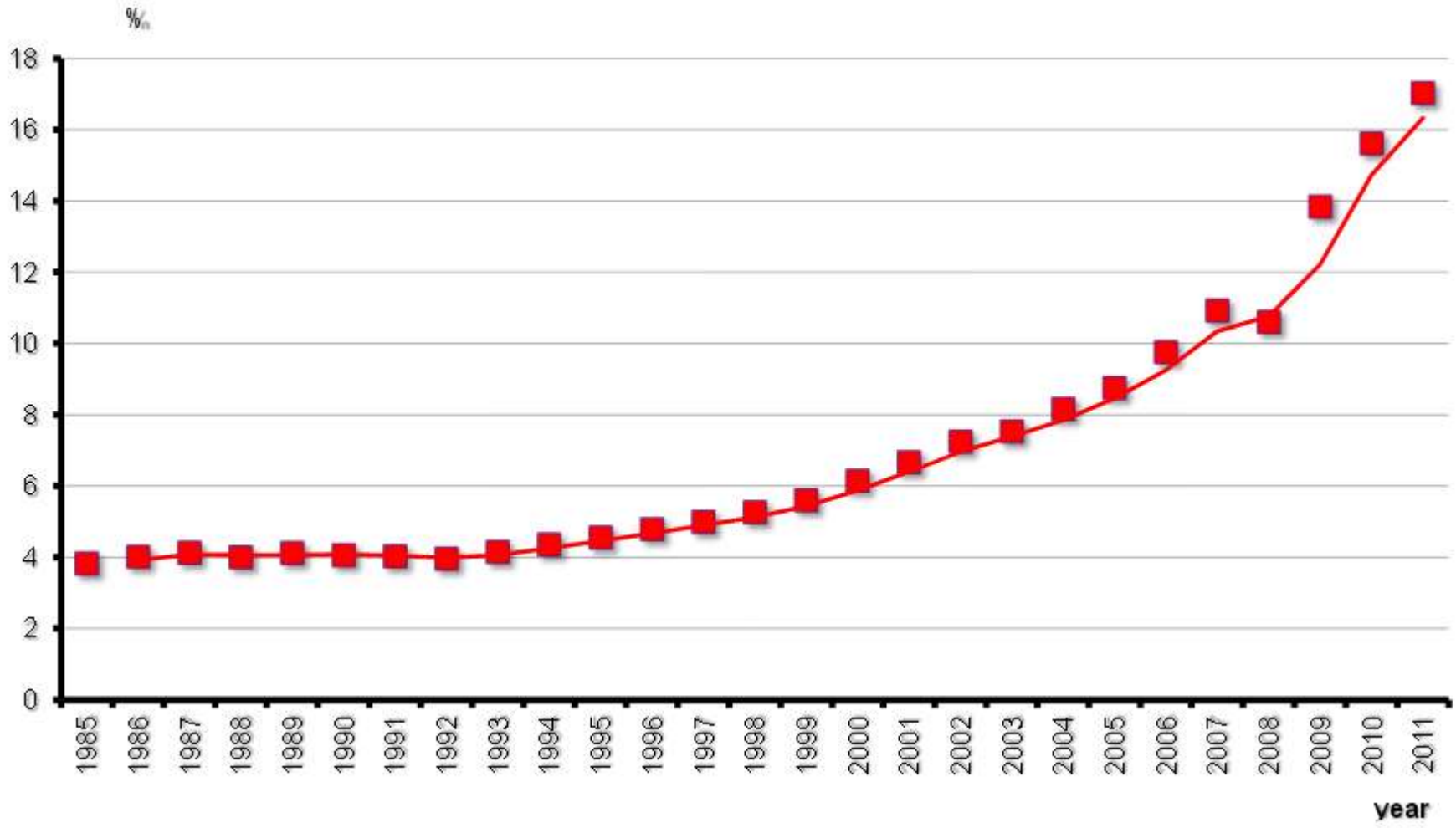


Down Syndrome, Czech Republic, 1994 - 2011



Vrozené vady

Mothers over 35 years , Czech Republic, 1994 - 2011



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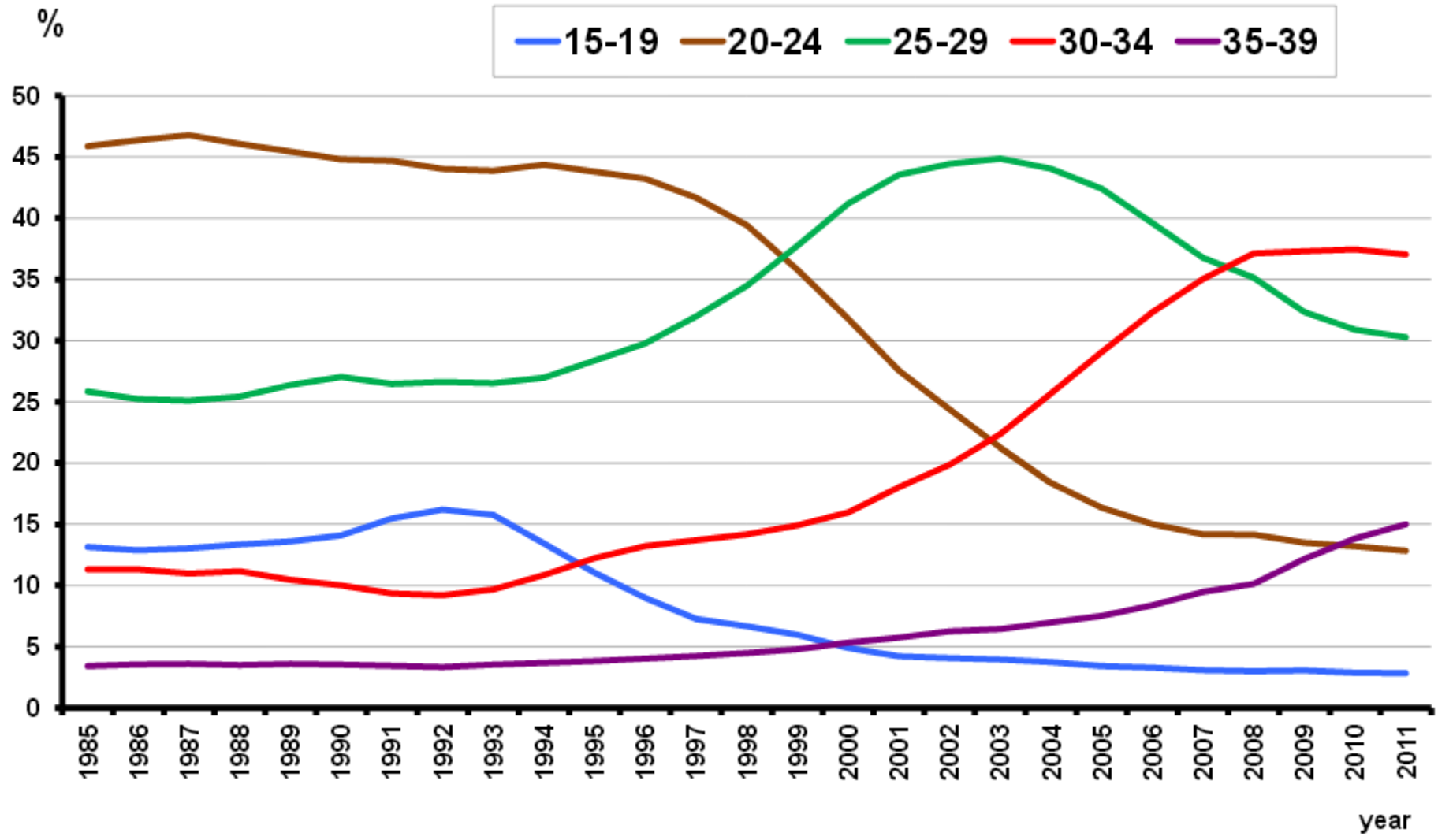
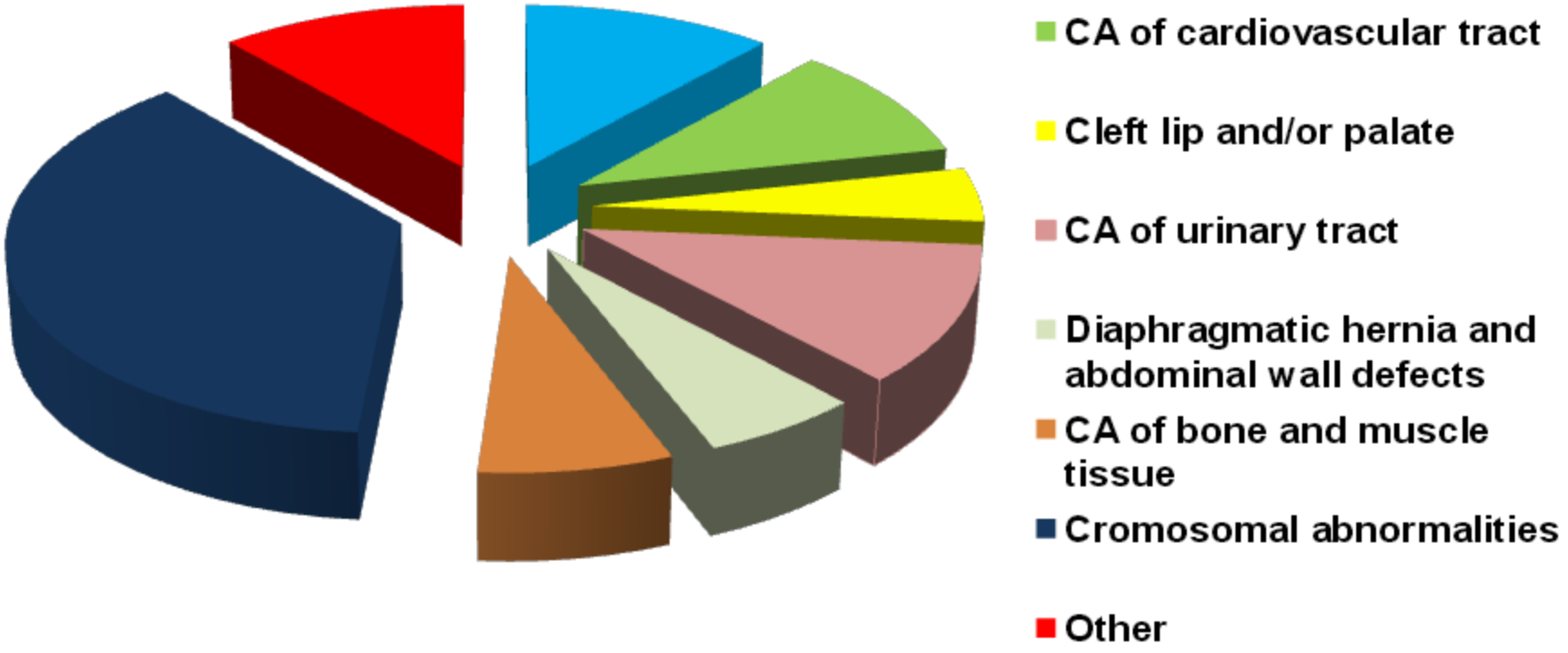


Prenatal Diagnosis, Czech Republic, 1994 - 2011



Vrozené vady

International Cooperation

ICBDSR

ICBDSR - International Clearinghouse for Birth Defects Surveillance and Research

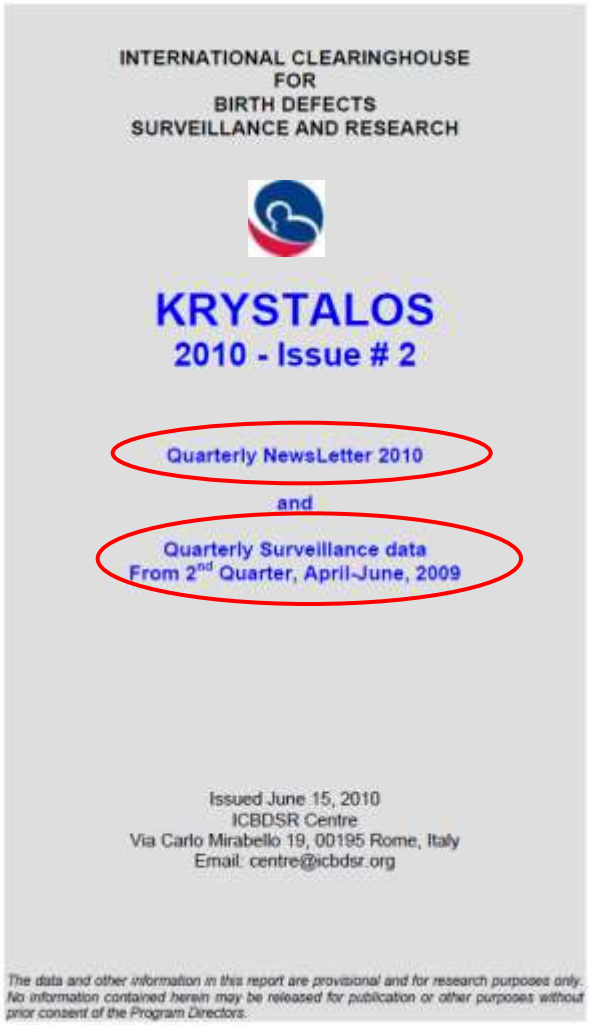
Founded in 1974

ČR (ČSSR) was the founding member

49 membere registires World-wide

http://www.icbdsr.org/

ICBDSR



INTERNATIONAL CLEARINGHOUSE
FOR
BIRTH DEFECTS
SURVEILLANCE AND RESEARCH

KRYSTALOS
2010 - Issue # 2

Quarterly NewsLetter 2010

and

Quarterly Surveillance data
From 2nd Quarter, April-June, 2009

Issued June 15, 2010
ICBDSR Centre
Via Carlo Mirabello 19, 00195 Rome, Italy
Email: centre@icbdsr.org

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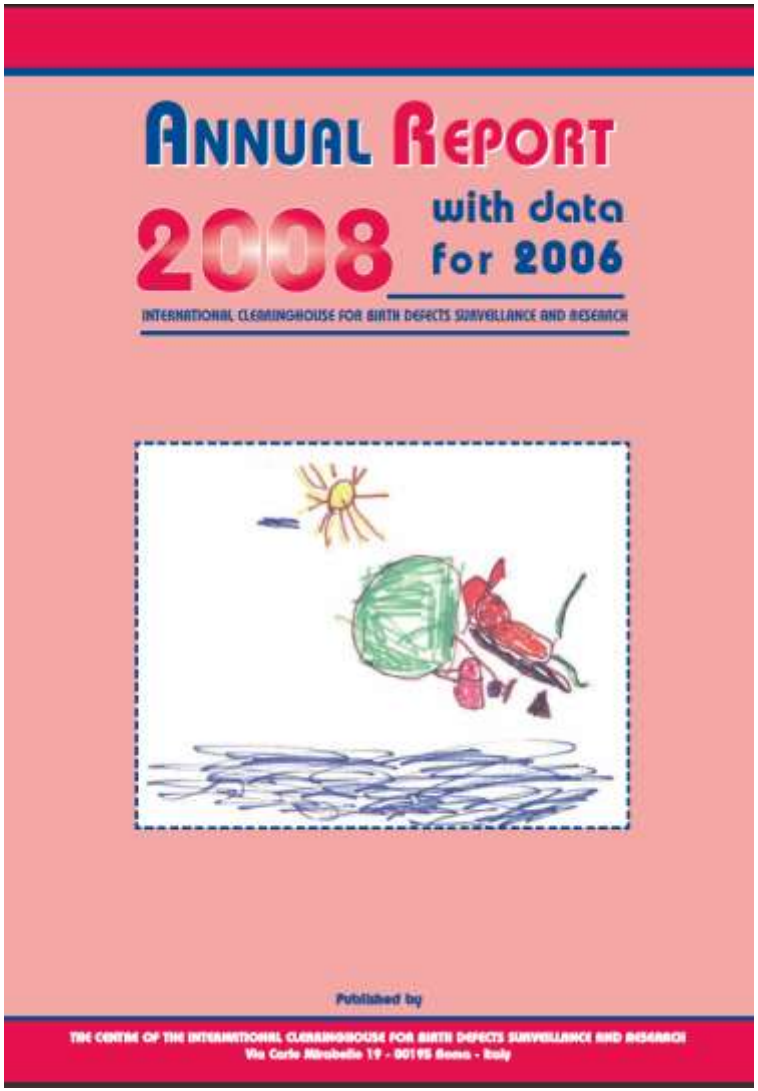
Krastalos

Quarterly Report
2/2010

ICBDSR



Souhrnné statistiky

Annual Report

EUROCAT

EUROCAT- European Surveillance of Congenital Anomalies

Founded in 1979

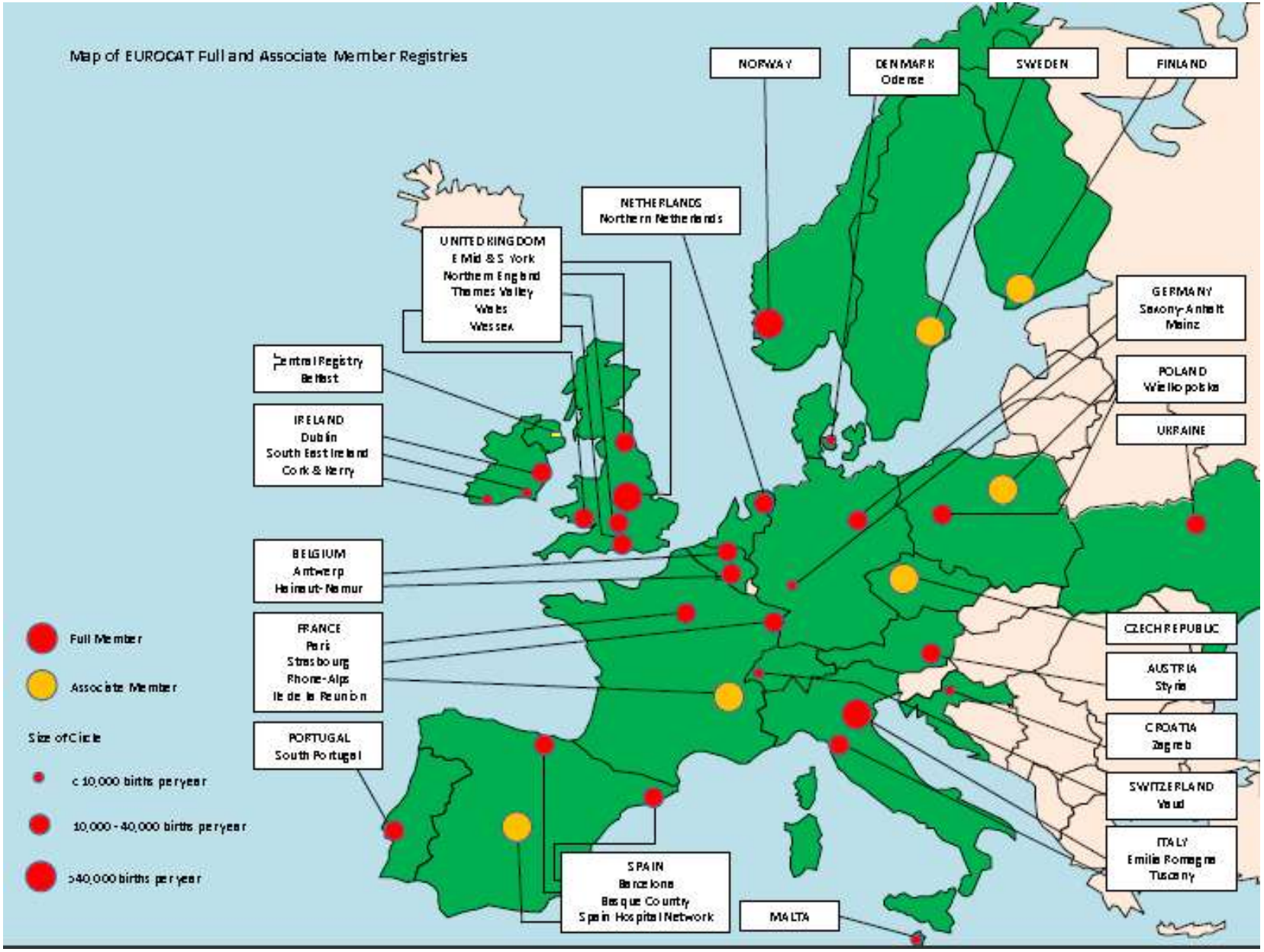
ČR - Associate membership from 2009

Today - 44 member registires from the Evropy

http://www.eurocat-network.eu/

Vrozené vady

EUROCAT



EUROCAT

Birth Defects Research (Part A) 91:S51 S100 (2011)

Review Article

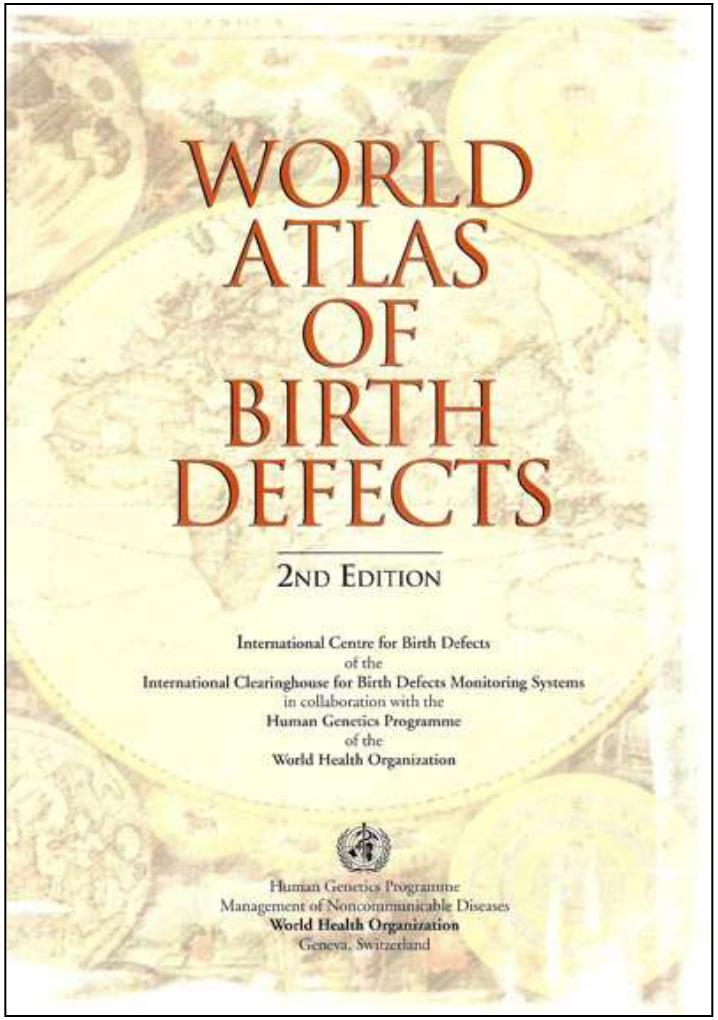
Paper 6: EUROCAT Member Registries: Organization and Activities†

Ruth Greenlees,[1] Amanda Neville,[2] Marie–Claude Addor,[3] Emmanuelle Amar,[4] Larraitz Arriola,[5] Marian Bakker,[6] Ingeborg Barisic,[7] Patricia A. Boyd,[8] Elisa Calzolari,[2] Berenice Doray,[9] Elizabeth Draper,[10] Stein Emil Vollset,[11] Ester Garne,[12] Miriam Gatt,[13] Martin Haeusler,[14] Karin Kallen,[15] Babak Khoshnood,[16] Anna Latos–Bielenska,[17] Maria–Luisa Martinez–Frias,[18] Anna Materna–Kiryluk,[17] Carlos Matias Dias,[19] Bob McDonnell,[20] Carmel Mullaney,[21] Vera Nelen,[22] Mary O'Mahony,[23] Anna Pierini,[24] Annette Queisser–Luft,[25] Hanitra Randrianaivo–Ranjatoélina,[26] Judith Rankin,[27] Anke Rissmann,[28] Annukka Ritvanen,[29] Joaquin Salvador,[30] Antonin Sipek,[31] David Tucker,[32] Christine Verellen–Dumoulin,[33] Diana Wellesley,[34] and Wladimir Wertelecki[35]

[1]University of Ulster, Newtownabbey, United Kingdom
[2]Istituto di Genetica Medica, Ferrara, Italy
[3]Division of Medical Genetics, Lausanne, Switzerland
[4]Registre des Malformations en Rhône Alpes, Lyon, France
[5]Subdirección de Salud Pública, San Sebastian, Spain

Greenlees R, Neville A, Addor MC et al. (2011) ***Paper 6: EUROCAT member registries: Organization and activities.*** *Birth Defects Res A Clin Mol Teratol. [Epub ahead of print]*

WHO

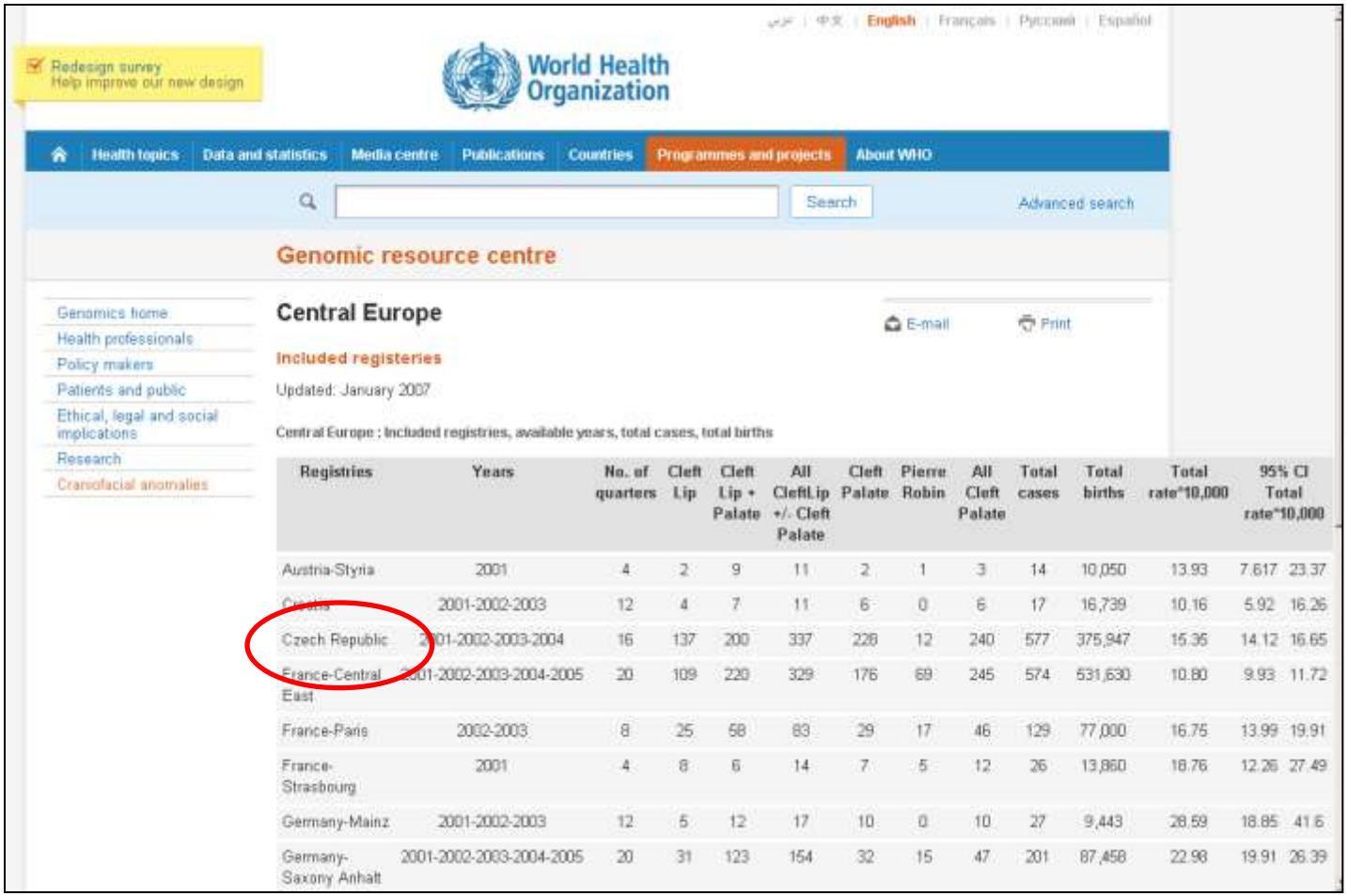


[World Atlas of Birth Defects (supported by WHO)]

World Health Organization

Vrozené vady

WHO



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- Patients and public
- Ethical, legal and social implications
- Research
- Craniofacial anomalies

Central Europe

E-mail | Print

Included registeries

Updated: January 2007

Central Europe : Included registries, available years, total cases, total births

Registries	Years	No. of quarters	Cleft Lip	Cleft Lip + Palate	All CleftLip +/- Cleft Palate	Cleft Palate	Pierre Robin	All Cleft Palate	Total cases	Total births	Total rate*10,000	95% CI Total rate*10,000
Austria-Styria	2001	4	2	9	11	2	1	3	14	10,050	13.93	7.617 23.37
Croatia	2001-2002-2003	12	4	7	11	6	0	6	17	16,739	10.16	5.92 16.26
Czech Republic	2001-2002-2003-2004	16	137	200	337	228	12	240	577	375,947	15.35	14.12 16.65
France-Central East	2001-2002-2003-2004-2005	20	109	220	329	176	69	245	574	531,630	10.80	9.93 11.72
France-Paris	2002-2003	8	25	58	83	29	17	46	129	77,000	16.75	13.99 19.91
France-Strasbourg	2001	4	8	6	14	7	5	12	26	13,860	18.76	12.26 27.49
Germany-Mainz	2001-2002-2003	12	5	12	17	10	0	10	27	9,443	28.59	18.85 41.6
Germany-Saxony Anhalt	2001-2002-2003-2004-2005	20	31	123	154	32	15	47	201	87,458	22.98	19.91 26.39

World Health Organization

International Database on Craniofacial Anomalies (IDCFA)

Thank you

admin@vrozene-vady.cz

http://www.vrozene-vady.cz/