"Joint Action EUROCAT 2011-2013 Funded by the Public Health Programme 2008-2013 of the European Commission"

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Abstract Congenital anomalies (CA) are an important cause of morbidity and mortality in infants and children. More than 100,000 children with CA are born in EU each year.
The European Surveillance of Congenital Anomalies (EUROCAT) is a network of population based congenital anomaly registries in Europe currently surveying 31% of EU birth population. EUROCAT has been awarded funding for 2011-2013 as a Joint Action between EU and member states. The Joint Action EUROCAT aims to use harmonised data on CA across EU to assess prevalence of all birth outcomes, the impact of primary prevention, and developments in prenatal screening. Joint Action EUROCAT will serve as an early warning of teratogen exposures, and act as an information centre regarding clusters, and exposures to risk factors of concern, including new medicine used in pregnancy, ail pollution, swine flu vaccination, and chronic maternal diseases as obesity and diabetes.

Sažetak. Kongenitalne anomalije su važan uzrok smrtnosti i pobola u dječjoj dobi. U Europskoj zajednici svake se godine rodi više od 100000 djece s prirođenim manama. The European Surveillance of Congenital Anomalies (EUROCAT) je mreža populacijskih registara prirođenih mana koja trenutno obuhvaća 31% poroda u EU. U razdoblju od 2011-2013 financirana je kao zajednička akcija Europske zajednice i zemalja članica. Cilj ove zajedničke akcije je da se prikupljanjem standardiziranih podataka u zemljama članicama utvrdi prevalencija svih ishoda trudnoća, učinak mjera primarne prevencije i razvoja prenatalne dijagnostike. Zajednička akcija EUROCAT služiti će za otkrivanje ranih signala izloženosti teratogenima te kao informacijskih centar u slučajevima uočavanja nakupljanja anomalija u vremenu/prostoru kao i izlaganja rizičnim čimbenicima, uključujući nove lijekove koji se koriste u trudnoći, zagađivače zraka, cijepivo protiv influence te kronične bolesti majke kao što su debljina i šećerna bolest.

Keywords: EUROCAT, congenital anomalies, surveillance, registries, prevalence, prevention, epidemiology, prenatal screening

Congenital anomalies (CA) are structural defects mainly of unknown/complex origin, but also caused by chromosomal aberrations, single gene defects, or teratogen exposure. They are one of the leading causes of embryonic, foetal, and infant deaths and childhood morbidity and mortality in developed countries. Affected individuals often suffer from serious physical, mental and social consequences and require long-term multidisciplinary follow-up and treatment. After the thalidomide accident, networks of registries for the surveillance of congenital anomalies have been set up in different parts of the world in order to collect epidemiologic data, to develop and evaluate prevention programmes and promote research in the field of CA. The EUROCAT network of registries for CA was started in 1979 as a concerted action of the European Commission for the epidemiologic surveillance of CA. EUROCAT is today a large network surveying more than 1.7 million births per year. It includes 41 registries that cover 31% of EU birth population. Members of the EUROCAT network are population-based registries using multiple sources of information and registering cases among live births, stillbirths/late foetal deaths from 20 weeks gestation, and terminations of pregnancy following prenatal diagnosis (1).

The objectives of EUROCAT are: to provide essential epidemiologic information on congenital anomalies in Europe, to monitor trends in prevalence and to assure the continuous evaluation of the impact of programmes of primary prevention and of prenatal screening and diagnosis. The network acts as an information system that can respond quickly to unusual

patterns suggestive of adverse environmental influences including nutrition, drugs, infections, and chemical and physical agents. EUROCAT aims to respond to inquiries from public health care providers and governmental agencies and to provide data to other institutions. The database serves as a source of cases for aetiological, clinical, or health service research. Over the years EUROCAT has also functioned as a model for congenital anomaly surveillance, operating as a catalyst for the setting up new registries throughout Europe and ensuring that they collect standardized and comparable data. The work and organisation of EUROCAT network are recently described in detail (2).

The Centre for Maternal, Fetal and Infant Research, School of Health Sciences, University of Ulster, home of Eurocat Central Registry, acts as a World Health Organization (WHO) Collaborating Centre for the Epidemiologic Surveillance of Congenital Anomalies. Since CA have been identified as one of the major groups of rare diseases needing concerted action across Europe, the European Commission (EU) is funding EUROCAT activities as a Joint Action between EU and the member states in the field of rare diseases for the 2011-2013 period.

EUROCAT- Joint Action aims to secure a high quality and easily accessible information system for CA in Europe. This goal is in line with the Communication from the Commission on Rare Diseases: Europe's challenges of November 2008 and the Council Recommendation of 8 June 2009 (3, 4).

The General Objective of this joint action is to facilitate the reduction of the public health burden of congenital anomalies by epidemiological surveillance through the EUROCAT network of population-based congenital anomaly registers.

The main expected outcomes of the Joint Action EUROCAT are:

Available and easily accessible epidemiological information updated to birth year 2011 on prevalence of CA, perinatal mortality due to CA, and prenatal detection rates, on the EUROCAT website [http://www.eurocat-network.eu]

Assessment of the teratogenic impact of new or changing environmental exposures, including swine flu related exposures and maternal chronic diseases.

Evaluation of the potential for linkage between registers and electronic information systems on exposure, including European pollution information systems and prescription databases, and addition of BMI to the common dataset.

A framework for national plans for primary prevention of CA, and evaluation of progress in the prevention of neural tube defects by raising periconceptional folic acid status.

Evaluation of impact of delayed childbearing and changes in prenatal screening techniques and policy on Down Syndrome

The development of EUROCAT's role as a core pregnancy-related pharmacovigilance system in Europe (EUROmediCAT).

The addition of at least 3 new registries to the network, including two new EU countries, and provision of guidelines and software to further interested regions/countries.

Improved coding and classification of CA within EUROCAT and worldwide by training and contribution of EUROCAT expertise to the revision of the International Classification of Disease (ICD).

Two European Symposia on the Prevention of Congenital Anomalies

The detection, appropriate investigation and reporting of clusters and trends in congenital anomaly prevalence, including improving the capacity for rapid response through a new Task Force for Evaluation of Clusters and delineation of responsibilities for response.

The Joint Action EUROCAT has 36 Associated Partners, and nine Collaborating Partners. The work is structured in three horizontal (WP1 – Coordination, WP2 – Dissemination, WP3 – Evaluation) and six core Work Packages (WP4 – Registration, central database and surveillance, WP5 – Coding and classification, and data quality, WP6 – Investigation of trends, clusters and new exposures, WP7 – Primary prevention, WP8 – Prenatal screening, Down Syndrome, and genetic syndromes, WP9 – Medication during pregnancy).

The main results of JOINT Action EUROCAT activities for the first-year period include:

1. Comprehensive epidemiologic information on the prevalence of CA up to year 2009. Data on year 2009 have been collected for the 33 existing member registries and four new ones. All full member registries have used the EUROCAT Data Management Program (EDMP) for data input/import, validation, duplicate checking, and transmission. The EDMP allocated cases to the standard 95 EUROCAT CA subgroups according to their ICD codes. Following data confirmation, the data is uploaded to the live website tables [http://www.eurocat-network.eu/accessprevalencedata/prevalence tables]. The system allows choosing the anomaly(s), the region(s) and the time period of interest and produces prevalence rates among live births, stillbirths and terminations of pregnancy following prenatal diagnosis in a required table format. The website also provides data on prevalence and specific public health indicators for CA such as perinatal mortality, prenatal detection rates and termination of pregnancies due to

severe CA, Down syndrome live birth prevalence, total prevalence of NTD and CA paediatric surgery. Major improvements in the EUROCAT central database (ECD) and EDMP have been undertaken in order to increase the efficiency, accuracy and quality of data collection and processing.

2. Central Registry has preformed statistical monitoring of clusters and trends of CA over time to detect possible signals of new or increasing teratogenic exposures requiring public health action. In 2011, a new "summary" graph showing the average annual percentage change in prevalence for all anomaly subgroups at pan-Europe level was produced. Key findings of this analysis were: a continuous increase of the prevalence of chromosomal autosomal trisomies, an increase in the prevalence of gastroschisis, especially in UK, and an overall decrease of the prevalence of all non-chromosomal anomalies, with marked decreases found for neural tube defects and severe congenital heart defects [http://www.eurocat-network.eu/content/Stat-Mon-Report-2009-Combined.pdf]. Task Force for Evaluation of Clusters (TEC) was established to co-ordinate rapid response to public concern regarding clustering of CA and for evaluation of registry investigation reports into the clusters identified by Statistical Monitoring. Cluster investigation in 2008-2009 period identified no clusters of immediate public health concern. Two studies of trends in prevalence of congenital heart disease have been submitted for publication. Investigation of other trends (hypospadias, multiple births, gastroschisis, Hirschprung disease) is in progress.
3. The current 10th International Coding and Classification System for Diseases (ICD10) has been reviewed by WHO experts and the next version (ICD11) is due in 2015. EUROCAT Coding and Classification Committee has reviewed and commented on the new ICD11 Proposal for Developmental Anomalies [http://www.eurocat-network.eu/content/EUROCAT-Comments-to-ICD11-Proposal-Oct2011.pdf]. The Coding Committee has also produced new coding tips. Data from registries have been reviewed and comments and proposals for improving of coding were forwarded to the registries. A computer algorithm for classification of CA followed by the manual review by clinical geneticists of potentially multiple malformed cases has been developed and uploaded to a secure web-based system for future use. Revision of EUROCAT Guide 1.3 [http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf] and data quality indicators (DQI) for evaluation and improvement of data collection has started.

4. The air pollution pilot study started in the Barcelona area. The first draft protocol of the study was circulated in December 2011. Another approach looking at the feasibility of epidemiological investigation in small polluted areas has been explored as well.
5. Joint Action, EUROCAT is analysing CA data in relation to the swine flu pandemic, neuraminidase inhibitors and pandemic vaccine. As a part of this effort a survey of the European pandemic influenza vaccination campaigns was undertaken (5). The results of the investigation of maternal pregestational diabetes and the risk for CA were published (6).
6. In order to collect and review public health actions relevant to primary prevention of CA, two questionnaires (*Policies for primary prevention of neural tube defects with folic acid and folate* and *Public health actions on primary prevention of congenital anomalies*) have been finalized and distributed to the stakeholders. Seven specific issues concerning CA primary prevention were identified (Folic acid and related nutritional aspects, Maternal lifestyles, Chronic and infectious maternal conditions, Environment, home and workplace, Drugs, Food safety, Genetic factors and genetic counselling). In collaboration with EUROPLAN project (www.europlanproject.eu) Joint Action EUROCAT is highlighting the need to include CA primary prevention into the national plans/strategies for rare diseases in EU-MS.
7. To assess the impact of developments in prenatal diagnosis and screening at a population level, data on prenatal diagnosis 2005-2009 for the 21 registries are made available on the EUROCAT website [http://www.eurocat-network.eu]. Overall, 40% of all non-chromosomal and 72% of chromosomal CA were prenatally diagnosed. Differences exist among countries, due to prenatal policies, cultural and demographic characteristics (e.g. maternal age). Protocol was developed for the study on Down syndrome and congenital heart defects. New data on prenatal diagnosis of rare chromosomal abnormalities have been published (7), and analysis of several rare genetic syndromes is in course.
8. One of the tasks of Joint Action EUROCAT was to develop an effective postmarketing surveillance related to the use of medication in pregnancy and risk of CA. A training workshop on ATC coding was organised in order to improve the coding of the drugs. The proposal for new DQI for medication exposure data was adopted. A protocol for prescription data linkage to selected EUROCAT registries has

been developed under the EUROmediCAT project (FP7). 3rd update on Lamotrigine in pregnancy study was prepared.

9. Joint Action EUROCAT is co-ordinating the establishment of new registries throughout Europe collecting comparable, standardised data on CA. Registry Advisory Service (RAS) has been working with applicant members to help them achieve full membership status in EUROCAT. RAS organised a training workshop on EUROCAT methodology and coding that was attended by 12 participants from different EU countries. The Hungarian Congenital Abnormality Registry, and the Congenital Anomalies Registry of Comunitad Valenciana have been awarded full membership status in autumn 2011. The integration of new registries and countries allows the sharing of knowledge and expertise and public health planning at European level. Further data quality monitoring is essential for the sustainability of the new registries and use of the data for all other objectives.
10. As a part of Joint Action activities, EUROCAT hosted successfully the 11th EUROCAT Symposium on Congenital Anomalies in Antwerp, Belgium, 17th June. Main topics were preconceptional and prenatal care, environmental risks for CA and long term outcome of children with a CA. The symposium hosted 232 participants from 25 countries that shared experiences in the prevention, registration and care for CA.

In conclusion, congenital anomalies continue to be an important cause of morbidity and mortality in infants and children. More than 100,000 children with CA are born in EU each year. The EUROCAT Joint Action aims to use harmonised data on CA across EU to assess prevalence of all birth outcomes, the impact of primary prevention, and developments in prenatal screening. EUROCAT network will serve as an early warning of teratogen exposures, and act as an information centre regarding clusters, and exposures to risk factors of concern, including new medicine used in pregnancy, ail pollution, swine flu vaccination, and chronic maternal diseases as obesity and diabetes.

The outcomes of the EUROCAT Joint Action 2011-2013 are expected to have an important impact on future MS policy on rare diseases.

The results of the EUROCAT Joint action will also serve to inform and educate the larger community. Main messages concern healthy lifestyle in childbearing age, recommendations/guidelines for the prevention of CA, evaluation of the use of new drugs in pregnancy, data on teratogenic impact of new environmental exposures, evaluation of the effectiveness of methods of secondary prevention (e.g. prenatal ultrasound or biochemical

screening). Through dissemination of the EUROCAT-Joint Action results we would like to actively engage the community in improving the health status of women in childbearing age.

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