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A sustainable solution for the activities of the European network for surveillance of congenital anomalies: EUROCAT as part of the EU Platform on Rare Diseases Registration

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\textbf{ABSTRACT}

The European Commission through its Directorates-General Joint Research Centre (DG JRC) and Health and Food Safety (DG SANTE) is developing the European Platform on Rare Diseases Registration (EU RD Platform) with the objective to set European-level standards for data collection and data sharing. In the field of rare diseases the EU RD Platform will be a source of information on available rare disease patient data with large transnational European coverage. One main function of the EU RD Platform is to enable interoperability for the > 600 existing RD registries in Europe. The second function is to offer a sustainable solution for two large European surveillance networks: European Surveillance of Congenital Anomalies (EUROCAT) and Surveillance of Cerebral Palsy in Europe (SCPE).

EUROCAT is European network of population-based registries for the epidemiological surveillance of congenital anomalies. It covers about one third of the European birth population. The Central Database contains about 800,000 cases with congenital anomalies among livebirths, stillbirths and terminations of pregnancy, reported using the same standardised classification and coding. These high quality data enables epidemiological surveillance of congenital anomalies, which includes estimating prevalence, prenatal diagnosis and perinatal mortality rates and the detection of teratogenic exposures among others. The network also develops recommendations for primary prevention in the Rare Diseases National Plans for medicinal drugs, food/nutrition, lifestyle, health services, and environmental pollution.

The network has received the European Commission’s support since its inception. In order to offer a sustainable solution for the continuation of EUROCAT activities, it was agreed that EUROCAT would become part of the EU RD Platform. In 2015, the European level-coordination activities and the Central Database were transferred to the DG JRC, where the JRC-EUROCAT Central Registry is now located. This paper describes the functioning of EUROCAT in the new setting, and gives an overview of the activities and the organisation of the JRC-EUROCAT Central Registry.
1. Introduction

The EUROCAT network was established in 1979, bringing together professionals and researchers working in population-based congenital anomaly registries across Europe.

The aims of the network are to collect population data and perform epidemiological surveillance on congenital anomalies in Europe. Over the years EUROCAT achieved standardisation of definitions, diagnoses and terminology, principally by the development of the EUROCAT guides and software for data management. Owing to the high level of data harmonisation and interoperability, the EUROCAT methodology is recognised worldwide and is used by many research groups. The data are used also to facilitate early warning of new teratogenic exposures, to evaluate the effectiveness of primary prevention and to assess the impact of developments in prenatal screening.

These results of the network are relevant for informing European public health authorities and may lead to public health actions. The network acts as an information system and resource centre for health professionals and the public regarding increasing or decreasing trends or the occurrence of clusters indicating potential changes in exposures to risk factors. It also provides a resource for collaborative research on the causes and prevention of congenital anomalies.

The EUROCAT Central Registry was initially located in Belgium (Catholic University of Louvain and later Scientific Institute for Public Health), in 1999 moved to the London School of Hygiene and Tropical Medicine, and from 2000 to 2014 was hosted by the University of Ulster (Belfast, Northern Ireland) (Boyd et al., 2011). The central coordinating activities of EUROCAT were from the beginning funded by grants received from the EC. The organisation and activities of EUROCAT before the transfer to the DG JRC in 2015 are described in Boyd et al. (2011). The reason for the transfer of the Central Registry to DG JRC was to provide a sustainable solution for the continuation of EUROCAT activities, to secure the results of previous work and to keep the network functioning (Martin et al., 2016). EUROCAT is now an integral part of the European Platform on Rare Diseases Registration (EU RD Platform) developed by the DG JRC in close collaboration with the EC’s Directorate for Health and Food Safety (DG SANTE).

2. The European Platform on Rare Diseases Registration

The development of the EU RD Platform is part of the implementation of the EU policies in the field of rare diseases (European Commission, 2014). The Platform’s main objective is to cope with the enormous fragmentation of RD patient data contained in hundreds of patient registries across Europe by providing solutions for interoperability between the RD data sources, for data collection and data sharing. By addressing the above goals, the EU RD Platform will essentially support knowledge generation on RD, allowing the identification of patients with a given condition across Europe. This will help reaching the required numbers to conduct epidemiological, clinical, translational, pharmacological studies and research for advancing diagnosis and treatment for RD patients.

In particular, the EU RD Platform develops, provides and promotes European-level standards for RD data collection and information exchange. The European RD Registry Infrastructure (ERDRI), developed as a core component of the Platform, supports semantic interoperability for RD data via the Central Metadata Repository, which is linked to the European Directory of RD Registries. These tools make RD patient data searchable and findable at EU level. This requires patient data to be pseudonymised, a further function offered by ERDRI. Thus, the Platform supports existing RD registries to become interoperable and helps creation of new registries including the ones inside the European Reference Networks (ERNs). These are 24 virtual networks involving healthcare providers across Europe which concentrate knowledge and resources for diagnosis and highly specialised treatment of rare and complex diseases (European Reference Networks, 2018).

The EU RD Platform was also conceived to offer a sustainable solution for two large European surveillance networks: EUROCAT and Surveillance of Cerebral Palsy in Europe (SCPE). For both networks, the European level-coordination activities and the central databases were transferred to DG JRC. For these two particular networks the EU RD Platform also functions as a data repository.

3. The JRC-EUROCAT Central Registry

The transfer of the EUROCAT Central Registry to DG JRC was an intensive and complex process. This required completion of many legal and technical procedures, including specifying the pathway for data protection notification at the European level, and the creation of new structures such as secure IT systems for data transfer and data management (Martin et al., 2016). The new JRC-EUROCAT Central Registry is now fully operational and the routine surveillance of congenital anomalies in Europe, developed by the network, continues effectively.

The role of the Central Registry is to maintain and further develop the EUROCAT Central Database according to established coding methodologies, ensure secure data transmission and data management from all registries. Data management includes data checking, data harmonization, quality assessment; the validated data included in the Central Database are then used by the Central Registry to perform routine statistical analysis for epidemiological surveillance. The Central Registry also supports and participates in the coordinating activities of the network, by maintaining regular contact with individual registries, issuing a regular newsletter, preparation (content, logistics) and follow-up of routinely planned meetings: Annual Registry Leader's meeting, Scientific Symposia, Management Committee, Coding and Classification Committee. The DG JRC also supports the work of the Registry Advisory Service and EUROCAT Working Groups (WG) - Environment WG, Genetic WG, Health Inequalities WG, Prevention WG, Prenatal WG, Website WG - established to develop the scientific activities of the network. The Central Registry also maintains the relationship with the individual registries and gives advice for the implementation of EUROCAT procedures. Moreover, the Central Registry has an important role in the dissemination of the network's results through scientific reports and publication of the relevant information on the JRC-EUROCAT website.

3.1. Coordination of the EUROCAT network

Currently there are 39 active population-based registries from 23 countries (Fig. 1) covering more than 29% of European births (1.7 million) per year. All EUROCAT registries have a defined geographical coverage: in some countries all births are covered by a registry and in some countries less than 10% of that country's birth population are covered by a registry (Table 1).

All EUROCAT registries use multiple sources of information to ascertain cases in live births, late fetal deaths (≥20 weeks gestational age), and terminations of pregnancy for fetal anomaly at any gestational age. Depending on the registry, the data sources include maternity, neonatal, and paediatric records; fetal medicine, cytogenetic, pathology, and medical genetics records; specialist services including paediatric cardiology; and hospital discharge and child health records. The information collected by the registries is summarised in Table S1 (Supplementary Information), while the more detailed registry descriptions can be found on the EUROCAT website (Complete list of EUROCAT members, 2018).

In addition to full and associate members, there are six affiliate member registries (Bulgaria, Slovenia; Spain, Navarra) who do not transmit data but participate in meetings and projects. These are registries with an active interest in congenital anomaly surveillance which do not fulfill the requirements for full or associate memberships, but are still working towards the requirements. It is important to mention that the network is
also expanding and 14 new registries from Italy, the UK, Slovakia, Lithuania and Iceland are in the process of becoming EUROCAT members. Information about the EUROCAT membership criteria and the process of how to become a member can be obtained from the EUROCAT website (EUROCAT Membership Criteria, 2018).

3.2. The EUROCAT Central Database

The EUROCAT Central Database contains over 800,000 cases of congenital anomalies, and is an invaluable collection of data used for routine surveillance and research. Data are collected and coded according to EUROCAT standards, using validated international classification systems where possible, which are defined in the EUROCAT Guide 1.4 (EUROCAT Guide 1.4, 2016). A standard data set of 95 coded variables (33 core variables) includes general information about the baby and mother, the diagnosis of malformations (ICD10 codes, prenatal diagnosis, genetic test and karyotype, gestational age at discovery), exposure of the mother, family history and socio-demographic variables.

The Central Database is regularly updated. Data are transmitted by individual registries to the JRC-EUROCAT Central Registry twice a year, in February and October, via a secure web-portal. The data that are sent are usually cases that have been born two years before (e.g. in 2018 the registries are reporting cases born in 2016).

A EUROCAT Data Management Programme (EDMP) was developed by the network to obtain high quality data for surveillance in a timely manner (EDMP User Guide, 2018). The system ensures that all data are coded according to agreed specifications and verifies each case before submission achieving an “a priori” data harmonization. The EDMP software is provided to all Member registries, which are requested to use it for checking their data and formatting prior to transmitting data to the Central Registry. In addition, the ability to create different types of reports/data analysis at both the local level and by the Central Registry allow results to be shared with and approved by the registries before being disseminated on the network’s website. The EDMP software is regularly updated, depending on the needs (e.g. implementation of new checks, addition of new variables). The most recent update was carried out in January 2018.

A similar programme called EUROCAT Central Database (ECD) was developed to be used only by the Central Registry with the aim to manage in a standardized manner data from all registries, to perform the routine statistical monitoring with standardized and validated...
3.3. Surveillance of congenital anomalies

The core activity of the Central Registry is to provide timely updates of prevalence, prenatal diagnosis and perinatal mortality data, which are published on the EUROCAT website (EUROCAT Prevalence Tables, 2018; EUROCAT Prenatal Detection Rates, 2018). The dynamic website allows extracting tailored reports combining registries, years and anomalies. Since 2015, after the transfer of the central database from the University of Ulster, the JRC-EUROCAT Central Registry has managed seven data submissions. This has increased the number of cases in the database by 12%. Tables have been updated three times with prevalence rates for 92 congenital anomaly subgroups, giving detailed information concerning the different pregnancy outcomes (livebirths, Stillbirths, Terminations of pregnancies).
stillbirths and terminations of pregnancy for fetal anomaly) by each Registry and by birth year from 1980.

Another important output of the Central Registry is the annual statistical monitoring report, which includes: a) the analysis of clusters identified for every anomaly subgroup in every registry over a 5-year period, and b) 10-year Pan-European trends to detect/monitor any significant variation in frequency of congenital anomalies at European level. The most recent report for the birth years 2005–2014 was prepared for the first time by the JRC-EUROCAT Central Registry and published in January 2018 (Lanzoni et al., 2017).

Apart from routine data analysis, EUROCAT data are widely used for various research studies. The wide use of EUROCAT data is highly encouraged, and both EUROCAT members, as well as scientists not associated with EUROCAT can request data following a well-defined procedure (Requesting EUROCAT Data, 2018).

3.4. Governance structure

The DG JRC and the EUROCAT network member registries established a legal framework – the Collaboration Agreement - for the transfer and the continuation of EUROCAT European level coordinating activities at the JRC in the context of the EU RD Platform. The Collaboration Agreement, signed by the JRC and the individual registries, covers the objectives of the collaboration, roles and responsibilities of the parties, governance and coordination, and protection of the results of the collaboration. It establishes that registries remain the owners of their data. For every use and publication of the data the Central Registry requires formal approval from the registries.

The Collaboration Agreement foresees the joint JRC-EUROCAT Management Committee, which coordinates the EUROCAT activities. The roles of the Management Committee are to ensure the continued scientific integrity of the EUROCAT database and any research arising from it, decide on membership issues, supervise the security and confidentiality of data held at the Central Registry including data transmission. The Management Committee also supervises the organisation of meetings, workshop and working groups, and takes decisions on application for research studies, data release and authorship; finally it approves the publication of the annual statistical monitoring report. The JRC-EUROCAT Management Committee meets regularly 3–4 times a year.

Another very important body is the EUROCAT Coding and Classification Committee. The main aim of this committee is to improve standardised coding and classification of congenital anomalies in EUROCAT. The committee reviews the coding of congenital anomalies and gives advice and guidance to all registries to ensure harmonization of the data. It provides feedback to the registries via the JRC-EUROCAT Central Registry. In addition, the Coding Committee examines cases with multiple congenital anomalies, and reviews the cases included in clusters and trends with feedback to local registries that are involved in the statistical monitoring. An important task of the committee is to regularly review EUROCAT subgroups for routine prevalence data and to create validation routines with the Data Management Working Group when needed.

4. Conclusions

The development of the EU RD Platform started with a comprehensive activity in order to secure a sustainable solution for the internationally recognised, long-lasting network of population-based registries for the surveillance of congenital anomalies in Europe, EUROCAT. Overall, this process was not simply a ‘transfer’, but the establishment of a whole new system, with new structures, which required a deep analysis of the processes with solutions for every legal and technical, aspect involved. It was a challenging experience which allows for continuing the work on the surveillance of congenital anomalies in Europe in a new setting.

The JRC-EUROCAT Central Registry will disseminate the results of the network’s scientific activities to provide evidence to policy makers and to facilitate linkage of EUROCAT data with other databases available at the JRC (e.g. environmental, socio-economic indicators).

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2018.03.008.

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