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Establishment of a system of registration for craniofacial anomalies: problems, pitfalls and potential

4.1 Guidelines for population-based birth-defect registries at a national and regional level

To implement a registry of birth defects with a guided system to help health personnel involved in different fields follow a methodology that has been formalized and standardized, the following four basic “w” questions need to be considered:

- **Why** to register?
- **Who** must be registered?
- **When** to register?
- **Where** to register?

Guidelines and recommendations represent an operative tool derived from the best and most recent scientific know-how e.g., evidence-based medicine (EBM), and the practice in congenital malformations (CM) management, registration and surveillance settings. In the field of CM registration and surveillance, an evidence-based system (EBS) can be defined as a set of indicators that are both theoretical and empirical, to each of which a different value can be assigned, according to the indicator’s reliability and strength.

The main features of a CM registration system are its effectiveness and ability to adapt to the social and health settings in terms of clinical activities, epidemiological surveillance, public health organization and research. Therefore, the crucial feature of the guidelines must be a focus on adaptability to different situations. The guidelines have to be both formal and flexible at the same time. In fact, the guidelines should not be a rigid protocol to be applied wherever and whenever, but a reasoned set of rules that provide the best assistance for setting up a registry. General knowledge and guidelines are closely connected and play an important role in the decisional process in setting up a registry. It is important to consider that:

- by definition, general knowledge covers a greater area than that of guidelines since guidelines are defined on the *basis* of general knowledge; and
- the ratio of general knowledge to guidelines that is informative for decision-making depends directly on the main purpose of the registry (surveillance, public health and/or research).

The aim in creating guidelines is to streamline the decision-making process of the different stages and make it as objective as possible, to promote quality assessment of registration, to improve cost-effectiveness of the public health services involved, and to set up indicators that are able to control all procedures. Theoretically, from a methodological point of view, the adoption of good quality guidelines is important because:

- they limit behavioural variability in dealing with analogous problems;
- they provide standards that reduce differences in activities such as classification, codification and variables aggregation; and
- they facilitate the production of useful training tools for physicians and assistants, as well as for public health service managers.

The priority goals of guidelines for a CM registry are to provide a useful tool for those who want to implement a birth-defect registry, by defining a methodological standard by which to assess registries already in place or to reset or revise unsatisfying situations, and to contribute to the development of an assessment methodology of the guidelines themselves.

BOX 13

Criteria to be used in preparing the guidelines

- Define of the area of interest, evaluating the impact of selected anomalies in terms of mortality, morbidity, prevention, costs (not only social and economic, but also in terms of health care and human suffering).
- Create a multidisciplinary panel at the preliminary and review stages.
- Identify an independent panel to certify and control activities undertaken with respect to guidelines.
- Review the evidence in literature.
- Consider issues in defining a “gold standard” and a “golden range”.
- Make recommendations based on the strength of both practical and theoretical evidence (i.e., based on the knowledge of running a registry).
- Establish a flexible structure that will allow for the guidelines to be updated.
- Make allowances for different alternatives to be selected if different priorities are chosen (this should relate to cost-effectiveness and risk/benefit assessment).

4.1.1 *Guideline assessment by indicators*

Indicators of guideline evaluation must concern: scope, objectives, involvement of active subjects (including media, stakeholders, decision-makers), involvement of users/persons/associations, rigorous development in terms of relevance and appropriateness, technical and scientific validity, clarity and simplicity of presentation (user-friendly presentation), applicability and repeatability, social and health impact, independence (interest conflict) and ethical issues.

Processes or structures covered by the guidelines are: objectives, resources, procedures, observation stage, registration, validation (ascertainment of full cases), confirmation (by linkage with other sources), classification, analysis, interpretation, presentation and output (communication, reports, etc).

4.1.2 *Setting up the registry*

Guidelines must provide the following flow-chart:

- 1) **Definitions and selection of birth defects** to be registered (terminology, naming and operational definitions, classification and coding), with an explanation of reasons and criteria for selection; changes of definitions and completeness of diagnoses (from prenatal to infant period) must be considered over time.
- 2) **Definitions of the type of fetus/birth** to be registered (spontaneous abortion, terminated pregnancies, stillbirths, live births).
- 3) **Definitions of the registration periods** (early prenatal period, prenatal, neonatal, post neonatal, infant), depending on the level of resources available and possibility to link with other information systems.
- 4) **Definition of the registration base** (hospital versus population).
- 5) **Ascertainment features** (active case-finding and use of multiple sources of information).
- 6) **Coding and classification procedures** to be followed; specification of the person/s who will be in charge and responsible for the coding activities; recommendations to regulate specific and more detailed classifications that are different from standard systems (e.g. for CFA).
- 7) **Clear indication of the person/s in charge of the codification** of congenital malformations (e.g. physicians, expert on CM or nurses where the diagnosis is made, panel of experts working in the postnatal period on the basis of the description of anomalies).

- 8) **Listing of any further variables** on reproductive history, delivery, babies and parents (e.g. previous pregnancies; parents' occupation and exposures, use of drugs, lifestyle, etc).

The above factors will be strongly influenced by the kind of collection. The need to collect a wide and detailed core of information must be balanced with the difficulties in obtaining valid data (e.g., interviews).

Collected data can be used to:

- carry out investigations when excesses, trends, patterns or clusters are reported by the surveillance system or health personnel;
- design and implement new etiologic studies, including GEI studies;
- obtain information on exposure by linkage with other sources (e.g. envirovigilance data).

It is essential that a birth-defect registry can be integrated into the public health system ...

Collection of data must be planned in view of different study design needs (e.g. level of exposure – in particular for individual or community measures, selection of healthy or sick controls, availability of parental data for triad designs). The registration form must take all these needs into account. It is essential that a birth-defect registry can be integrated into the public health system at the same administrative level (regional, national) so that results can be effectively used in the setting that has produced the information.

The general guideline methodologies and procedures will focus on a CFA registry, presenting performance indicators of the CFA registration activity.

4.2 ICBDMS: interregional experience

The International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) was established in 1974 to encourage an international exchange of data and collaborative research in the field of birth defects. It is an independent, non-profit organization, accepted in 1986 as an NGO in official relations with WHO.

The International Centre for Birth Defects (ICBD), located in Rome, Italy, serves as the headquarters for ICBDMMS, coordinating its monitoring activities and collaborative studies, regularly producing an annual report, newsletters and reports on monitoring.

The major activity of the ICBDMMS is to monitor changes in the prevalence of birth defects and, with all its participating programmes combined, to monitor a very large population with almost three million births each year. At present (2002), there are 36 participating programmes, representing 34 countries spread across the five continents. One programme (in South

America) includes hospitals in 12 different countries, while several countries – Canada, China, France, Italy and the USA – are each represented by two or more programmes.

The ICBDMMS performs international collaborative research on a very large scale; the problems it faces because of the heterogeneity of the various registries are counterbalanced by the beauty of diversity. The final results are regularly published in international scientific journals.

Further information on the ICBDMMS can be found at www.icbd.org.

4.3 ECLAMC: the Latin American experience

This description of the Latin American Collaborative Study of Congenital Malformations (ECLAMC) concentrates on the present pitfalls to function as a registry of OC, in an attempt to identify possible solutions for the future. ECLAMC is a hospital-based, non-institutional, non-governmental, voluntary, collaborative research project for congenital anomalies and has operated in about 100 South American maternity hospitals since 1967.

4.3.1 Oral clefts epidemiology and the DNA bank

The epidemiology of oral clefts in ECLAMC can be summarized as follows:

- **For both CL/P and CP:** stable secular trends over the 33-year period (1967-1999) for isolated cases, and significantly rising trends for syndromic cases.
- **For CL/P:** a significant association with high altitude (above 2000 metres), male sex, twinning, low socioeconomic class, maternal illnesses, self-medication and parental consanguinity.
- **For CP:** a significant association with the female sex, twinning, low socioeconomic class and self-medication.

Since January 2000 ECLAMC has maintained a DNA bank for all major malformations, as well as for a randomly selected sample of non-malformed newborns. Until July 2001, the stored material included DNA samples from 7546 healthy newborns and 1447 malformed newborn/mother dyads, including the following CFA:

- 336 cleft lip, with or without cleft palate,
- 73 cleft palate,
- 40 microtia, and
- 46 holoprosencephaly cases.

4.3.2 ECLAMC – pitfalls as a registry

Incomplete coverage: Hospital-based systems are best applied in low- to middle-income countries where statutory statistics are unreliable or missing. However, unlike their counterpart (population-based systems) they fail to cover real populations. In South-America, the ± 100 reporting hospitals that are scattered over 9 of the 10 participating countries failed to identify 3 known geographical clusters for OC. Those were:

- the Baurú syndrome in São Paulo state, Brazil – where this meeting took place (Gorlin, Cohen & Hennekam, 2001) ;
- non-syndromic CL/P associated with a mutation of PVRL1 in Margarita Island and the Cumaná seaside in Venezuela (Sözen et al, 2001); and
- a high prevalence rate for OC, based on a longstanding “rumour”, in Patagonia (Castilla & Sod, 1990).

Hospital-based systems fail to cover real populations ...

Under-ascertainment of minor forms: In spite of the fact that ECLAMC registers minor defects including birthmarks on the skin, some microforms of oral clefts are under-ascertained. These include sub-mucous CP, uvula bifida, and notched gum at the maxillary-palatal junction level. Registered birth prevalence rates per 100 000 are:

- sub-mucous CP: 0.6,
- uvula bifida: 1.2, and
- notched gum: 1.1.

Even though some of these microforms may be unrelated to typical OCs, actual evidence is still needed, as shown by the following findings on congenitally “healed” cleft lip. The epidemiology of congenitally “healed” or “frustre” cleft lip was first reported in the combined material of ECLAMC and ECEMC (a similar Spanish study). Twenty-five cases were ascertained from four million observed births (1/160 000 births). The lack of previously published figures caused difficulty in establishing the ascertainment rate for this defect, but under-registration was likely. This anomaly could be a variant of CL, as suggested by its preponderance in the male sex and on the left side. The combined data also had a record of two families with joint segregation of open CL and healed CL. The existence of ipsilateral notched vermilion and collapsed nostril favours the pathogenesis of an intra-uterine spontaneously repaired cleft (“healed” in the English literature), rather than an incomplete cleft (“frustre” in the French literature) (Castilla & Martínez Frías, 1995).

Under-ascertainment of syndromes: Most of the nearly 300 recognized syndromes, including OCs, are seldom registered by ECLAMC in newborn infants.

Incomplete family histories: Even though ECLAMC records complete family histories for all malformed and matched control infants, relatives are not examined by the reporting physician. Thus, there is no careful examination of the lower lip or searching for bilateral pits even in the mother who is present during the history-taking before discharge from the maternity hospital. As a result, only four cases of van der Woude syndrome have been recorded among the four million examined births. This is considered to be under-registration for such a well-known syndrome.

4.3.3 Possible solutions

Some of the above-mentioned pitfalls in the ECLAMC system could be reduced by implementing the following strategies:

- **A malformation-specific registry** could be nested into the ECLAMC system. An OC registry could easily extend its geographical coverage in this way, following up cases and families for a minimum period of two years and interacting with the community (support organizations) and local health authorities for the benefit of patients and their families.
- **Oral physical examination of the newborn**, a no-man's land lying between the responsibilities of medicine and dentistry, is frequently disregarded. Participant paediatricians should be trained in transillumination and digital palpation of the palate, careful observation of the gum, gum-labial bands, tongue ties, lower lip pits and fistulas, both in the newborn and in the mother.
- **A postnatal follow-up** would greatly improve the detection and identification of syndromes for the benefit of families through sound genetic counselling. Follow-ups can be ensured by OC registries since they exist with other registries (congenital heart diseases, cytogenetics, cancer, twins, etc.) (Last, 1995). Such other registries may easily overlap with pre-existing birth-defect surveillance systems (Källén & Winberg, 1979) or could even become the bases for future systems if there were none in the area.

4.4 EUROCAT: European experience

The EUROCAT project, supported by the European Union, represented by the Commission of European Communities, focuses on the epidemiological surveillance of congenital anomalies in Europe. Surveillance is based on a network of regional registries coordinated by a central registry. The participating registries use the same epidemiological

methodologies and their general characteristics have been described elsewhere (De Wals, Weatherall & Lechat, 1985). The EUROCAT database provides the opportunity to perform a large descriptive epidemiological survey on OC throughout Europe and obtain further insight on OC epidemiological and genetic features.

Further information on EUROCAT can be found on its web site: www.eurocat.ulster.ac.uk.

BOX 14

Aims of the EUROCAT Registry

- Provide essential epidemiological information on congenital anomalies in Europe.
- Facilitate the early warning of teratogenic exposures.
- Evaluate the effectiveness of primary prevention.
- Assess the impact of developments in prenatal screening.
- Act as an information and resource centre regarding clusters or exposures or risk factors of concern.
- Provide an established collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children.
- Act as a catalyst for the setting up of registries that will collect comparable, standardized data throughout Europe.

4.4.1. The EUROCAT Oral Cleft Project

The 1980-1996 EUROCAT database includes 9553 cases with CP, or CL/P collected by 31 registries. This European network of population-based registries for the epidemiological surveillance of congenital anomalies, covers more than 900 000 births per year. It also comprises data on terminated pregnancies, in accordance with the EUROCAT guidelines. Validation and classification procedures have been performed on a sub-file that includes all eligible OC cases provided by the EUROCAT central database. Each individual record is classified into isolated, multiple congenital anomalies, chromosomal anomalies, sequence, syndromes and/or recognized conditions.

Objectives of the EUROCAT OC Project

- Assess quality of data, i.e., completeness, validity and homogeneity amongst registries.
- Split cases into isolated, associated or recognized conditions.
- Describe the variation of the different types of OCs with regard to geographical patterns and temporal trends.
- Produce an epidemiological description of the different OC types according to selected variables, such as sex ratio, birth weight, gestational length and maternal obstetrical history.

The relevant heterogeneity highlights the need to analyse data of the different OC types ...

4.4.2. Results and comments

A total of 9553 oral cleft cases were recorded among 6 242 763 live births and stillbirths in the EUROCAT database. Among these cases, 65.7 % occurred as isolated anomalies. Among the isolated cases, 73.5% were CL/P. Isolated atypical clefts were diagnosed in four cases. In 1732 cases (18.1 %), an OC occurred with a recognized condition, and in 1610 cases (16.1 %) it occurred with multiple congenital anomalies of an unknown nature. OC in chromosomal aberrations were observed in 1542 cases (16.1%). The birth prevalence rate of all OC cases was 15.3 (CL/P = 9.0 and CP = 6.2) per 10 000 births.

The proportion of terminated pregnancies following prenatal diagnosis was small (4.5 % for CP; 11.8 % for CL/P), and generally related to more severe anomalies associated with OCs. The detection rate diagnosed by ultrasound was 27% for CL/P and 7 % for CP.

The relevant heterogeneity observed among centres highlights the need to analyse data of the different oral cleft types, taking into account the available knowledge of genetics, genetic susceptibility and environmental conditions in the different European areas, particularly with reference to the distribution of gene variants and nutritional habits.

4.5 NBDPN: North American experience

The National Birth Defects Prevention Network (NBDPN) is a group of individuals involved in birth-defect surveillance, research and prevention. The need for such a group was originally discussed in an informal meeting of interested individuals, held in conjunction with the CDC's Maternal, Infant, and Child Health Epidemiology Conference in Atlanta in December 1996. As a result of that meeting, Charlotte Druschel, MD, and

Russell Kirby, PhD, agreed to co-chair the NBDPN during its start-up phase.

Subsequently, in February 1997, several individuals who had expressed interest in serving on the planning workgroup for the NBDPN met at CDC to establish a mission statement and objectives for the new organization. In addition, several committees were formed and a number of priority activities for the network were outlined. To date the NBDPN has held four annual meetings which involved plenary sessions, concurrent workshops and business meetings to elect committee chairs and conduct committee business.

Further information on NBDPN can be found at www.nbdpn.org.

BOX 16

Aims of the NBDPN project

- Improve the quality of birth-defect surveillance data.
- Promote scientific collaboration on the prevention of birth defects.
- Provide technical assistance for the development of uniform methods of data collection.
- Facilitate the communication and dissemination of information related to birth defects.
- Collect, analyse and disseminate state- and population-based birth-defect surveillance data.
- Encourage the use of birth-defect data for decisions regarding health service planning (secondary disabilities prevention and services).

4.5.1 NBDPN results

Based on the experience of the NBDPN, Larry Edmonds from the National Center on Birth Defects and Developmental Disabilities, CDC, presented a comprehensive analysis of the costs involved in registering oral clefts by different systems (Edmonds, 2001).

Birth prevalence rates per 10 000 live births of OCs obtained from various data sources show the expected under-registration of statutory and mandatory systems, as compared with active search for cases. However, the range is minimal, probably due to the conspicuousness of this type of congenital anomaly.

Table 8: Summary of birth prevalence rates

Type of source	Source	Rate
Linked data sources	Colorado, 1990-1991	10.0
Active hospital surveillance	MACDP*, 1990-1991	9.9
Hospital discharge data	BDMP**, 1990-1991	8.6
Birth certificates	1990-1991, excludes 5 States	8.5
Mandatory hospital reporting	New York, 1990-1991	7.8

* MACDP: Metropolitan Atlanta Congenital Defects Program, started 1968.

** BDMP: Birth Defects Monitoring Programme, started 1974.

The estimated costs of birth-defect surveillance (in US dollars) by different methods are summarized in the following table. However, it should be noted that these are *estimates* and can vary greatly depending on the particular methodology used.

Table 9: Costs of birth-defect surveillance by different methods

Method	Quality of data	Cost per live birth	Cost* per case	Cost* for 50 000 births/year
Birth certificates	Poor	None	None	None
Mandatory hospital reporting (no follow-up)	Fair	1-5	25-125	50 000-250 000
Mandatory hospital reporting (with follow-up)	Good	5-10	125-250	250 000-500 000
Intensive surveillance	Best	10-30	250-750	500 000-1 500 000

* Cost in US dollars.

Source: Larry Edmonds, NDBPN

It is clear that the best quality data are obtained from the more expensive, active systems. The ideal source/s of data must be decided upon for each planned study according to aims and resources.