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ORIGINAL ARTICLE

Value of sharing and networking among birth defects surveillance programs: an ICBDSR perspective

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Abstract

Birth defects (BD), also known as congenital anomalies, are structural or functional abnormalities present at birth as a result of abnormal prenatal development. Their cause can be broadly categorized as genetic, environmental, or a combination of both. It is estimated that approximately 3–6% of newborn infants worldwide are affected by BD, many of which are associated with serious morbidity, mortality, and lifelong disabilities. The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), founded in 1974, promotes worldwide birth defect surveillance, research, and prevention through the ongoing sharing of data, expertise, and training. In this review, we show value and contribution of BD surveillance systems in pursuing these aims. In the time of personalized medicine for many rare and common diseases, there are still massive gaps in our understanding of the causes and mechanisms of many birth defects, especially structural congenital anomalies. The main aim of the Sustainable Development Goals (SDGs), adopted by the United Nations in 2015, is to ensure healthy lives and promote well-being for all children. One specific goal is to end preventable deaths of newborns and children less than 5 years of age by 2030. The SDGs also underscore the need to consider BD as a priority in the global child health agenda. It can be said that *counting BD helps BD to count*. By sharing data and expertise and joining in surveillance and research, BD surveillance programs can play a major role in increasing our understanding of the causes of BD, and promoting prevention.

Keywords Birth defects · Congenital anomalies · Registries · ICBDSR · Surveillance · Research

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Introduction

Birth defects (BD)—also called congenital anomalies—are structural or functional abnormalities that are present at birth as a result of the alteration of prenatal development. Their causes broadly can be categorized as genetic, environmental, or a combination of both. Serious BD are estimated to affect approximately 3–6% of newborn infants worldwide (CDC 2017; ICBDSR 2014). Because BD are present at birth, their challenges are lifelong. Individuals and their families must deal with their consequences in terms of increased morbidity, mortality, and disability. The associated loss of productivity has economic consequences not only for the individuals but also for their families and the community. Christianson et al. (2006) estimated that overall 7.9 million children are born each year with serious BD of genetic or partially genetic origin, and additional hundreds of thousands more are born with serious BD of post-conception origin. Moreover, at least 3.3 million children die from BD each year under 5 years of age (Zarocostas 2006), and there is an

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increasing proportion of perinatal and infant deaths attributed to BD. While during the Millennium Development Goals (MDGs) era, the under-five mortality rate reduced by an impressive 53% globally, congenital abnormalities were the most important cause of death in countries with low and very low under-five mortality rate (Liu et al. 2016). This means that BD are becoming an ever increasing public health concern leading to early mortality.

Additionally, an estimated 3.2 million of those who survive may face lifelong disabilities (Zarocostas 2006). A definite etiology can be established in only around 20% of cases (Feldkamp et al. 2017). Some preventive measures are already known; however, a major gap remains in our knowledge of the causes and effective prevention strategies. These considerations underscore how BD, most of which are considered "rare diseases", deserve greater attention from clinicians, society, researchers, and policy makers.

Here we present, from the perspective of ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research), the value of sharing data and experiences through networking among programs registering BD with the aim of their surveillance and also focusing on research on their causes, and the final goal of their prevention through a better knowledge of their epidemiology.

Need for birth defect surveillance systems and the advantage of networking

The thalidomide epidemic (Lenz and Knapp 1962; Lenz 1961) led to the early development of surveillance systems to monitor BD. Thalidomide provided evidence that medications were able to cross the placenta, previously thought to protect the fetus from harm, and this brought to light the need to establish systems that could identify any agent that could damage the developing embryo and fetus. A major goal of those initial surveillance programs was to serve as an early detection system for unexpected increases in the frequency of BD resulting from the introduction of teratogens (new and old) in the population. Such systems were thought also to help discover new causes of birth defects, which would then become the target of preventive measures to reduce the occurrence of birth defects (primary prevention). This reasoning led to the specific systems to register BD, because it was quickly realized that general available data systems such as vital statistics (e.g., birth certificates or fetal death certificates) in most countries lacked the capacity for BD surveillance. The crucial importance of high-quality birth defects surveillance programs was recently reinforced by the Zika virus-related epidemic of microcephaly and brain anomalies. These basic principles—high-quality data and timely and ongoing dissemination—are still valid: BD registries and epidemiological studies (descriptive and analytic) based on registry data are the main tools for effective BD surveillance and prevention. For these purposes, the organization of registry networks in the field of BD has been a natural evolution of the initial programs, since all have to face the same problems. Also, as for some BDs, the number of cases is small in each specific program, it is logical to try putting together the registered cases in order to better study their characteristics. Moreover, there is a need to check if some local epidemiological findings can affect broader areas, and networking makes the communication among programs easier.

Apart from these advantages, an added value of registry networks in the field of BD is the harmonization of definitions, procedures for data gathering, methods for interpretation of BD occurrence rates taking into account the possible differences in some methodologies (what can also enable the comparison of the diverse methods), and some other. This also makes possible the comparison of different characteristics, such as the attitudes and rates of terminations of pregnancy due to fetal anomalies in various countries worldwide, the result of the implementation of diverse preventive measures in different places, among others.

The birth and some history of ICBDSR

After thalidomide, the first BD registries tended to work in isolation; however, in 1974, representatives of BD surveillance programs from ten countries met in Helsinki, Finland, and established the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS). Later renamed International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), this network emphasizes the value of combined surveillance and research to achieve the final goal of BD prevention.

Currently, ICBDSR is a voluntary, non-profit, international organization affiliated with the World Health Organization (WHO). It brings together BD surveillance and research programs from around the world. The current membership counts 42 programs from 36 countries (all the continents, except Africa, where some programs are already in contact with ICBDSR), which together monitor more than four million births per year. More detail about updated geographical distribution and characteristics of the programs can be found in ICBDSR's website (www.icbdsr.org). Additionally, there are 19 Affiliate Members; these include people and programs that are beginning or planning to begin BD surveillance, especially in low- and middle-income countries. The mission of ICBDSR is to promote and conduct worldwide surveillance of BD and research into their causes and determinants, with the double aim of prevention as well as better health and lives for those living with BD. The scope of ICBDSR includes fetal and childhood conditions of prenatal origin, and specifically structural anomalies, i.e., malformations, deformations, and

disruptions, which are mostly included in the XVII chapter of the International Classification of Diseases 9 (ICD-9) or the "Q" chapter of ICD-10.

Systematic data collection in BD surveillance programs as the basis for epidemiological studies

Epidemiologic studies are a crucial contribution of BD registries. At the beginning, careful studies are necessary to generate a robust baseline for ongoing surveillance. Once a baseline is satisfactorily established, epidemiology provides the methods to determine whether occurrence is changing (increasing or decreasing) and whether these changes can be extrapolated to the general population if the data come from a sample of the population. In all these analyses, data quality (completeness, timeliness, and accuracy) is crucial and must be evaluated over time. One of the goals of collaborative studies and data sharing in ICBDSR is to help improve global data quality.

ICBDSR's work and contribution of available BD surveillance programs' data

As a result of the successful collaboration and data sharing tradition and experiences, some of the joint ICBDSR activities are summarized below by way of example. ICBDSR:

- Operates an international program for regular exchange among its members of information on BD in populations covered by the member's surveillance and research programs. This information is contributing to understand the magnitude and distribution of the BD, its associated challenges, and its determinants, and is useful to properly plan and allocate the resources (always limited) that are necessary for the care of affected people;
- Is an advocate for the surveillance, research, and prevention of BD;
- Advances the skills in surveillance and research;
- Promotes standards and definitions for conducting surveillance;
- Maintains appropriate standards for confidentiality and security of data;
- Coordinates research activities with the members and other collaborators;
- Cooperates in investigations of clusters and "alarms" (unexplained changes in BD occurrence);
- Conducts joint epidemiological studies of the causes of BD;
- Conducts assessments of preventive and therapeutic interventions for BD;
- Provides training in the surveillance and research of BD;

ICBDSR has been successful in promoting collaborative projects among its member programs. A few examples include the following:

- Annual Reports on the current occurrence and trends of selected BD routinely evaluated by all members, and found on the ICBDSR web page for Annual Reports (ICBDSR 2017).
- Focused studies on the epidemiology of specific BDs in different programs such as holoprosencephaly (Leoncini et al. 2008) or hypospadias (Källén et al. 1986).
- Systematic studies of very rare defects, which require the collaboration of very large birth populations—as seen in the 2011 publication of the *American Journal of Medical Genetics Seminars in Medical Genetics* on very rare defects (Bermejo-Sánchez et al. 2011a, b; Botto et al. 2011; Feldkamp et al. 2011; Mutchinick et al. 2011; Orioli et al. 2011a, b; Siffel et al. 2011).
- Cluster investigations of BD (Castilla et al. 2008).
- Surveillance of adverse fetal effects due to medications (Lisi et al. 2010).
- Confirming the teratogenicity of specific agents (Bjerkedal et al. 1982), after the previous suspicion of another researcher in the group (Robert and Guibaud 1982).
- Evaluating the impact of specific preventive measures, such as folic acid supplementation and fortification in different countries with different baseline prevalence and folic acid-related activities (Botto et al. 2006).

The core activity at the foundation of ICBDSR is the systematic monitoring of BD by each member program. These data are crucial for informed public health action. For example, the information generated from the data can be used for advocacy, policy development, etiologic studies, outcome studies, and assessment of prevention interventions.

A valuable contribution of BD surveillance networks such as ICBDSR is to train and provide support to those in low- and middle-income countries who wish or plan to develop a surveillance system and are interested in epidemiological research. Thus, new or recent programs and countries can benefit from the wealth of experience of programs that have been in operation for many years. A good example is the development of ICBDSR's training programs and on-line courses for health professionals, often developed in collaboration with international organizations such as World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), March of Dimes Foundation, and Task Force on Global Health (WHO/CDC/ICBDSR 2015; Flores et al. 2015). These training courses are complemented by educational materials and guides aimed at the professionals conducting birth defects surveillance, especially those starting activities in low-resource settings (WHO/CDC/ICBDSR 2014).

Conclusions

Personalized medicine is making significant strides for those conditions with known causes or mechanisms (a necessary condition for developing targeted therapies); however, such progress has been lagging for many birth defects, whose causes (with few exceptions such as folic acid insufficiency for most neural tube defects) still remain mostly unknown.

We want to underline that the WHA63.17 Resolution of the Sixty-Three World Health Assembly (World Health Assembly 2010) on Birth Defects emphasized how lack of epidemiological data may hamper effective and equitable management. It also expressed concern for the limited resources dedicated to prevention and management of BD before and after birth, in particular in middle- and low-income countries. It additionally stated a deep concern because birth defects are not still recognized as priorities in public health. Furthermore, it urged Member States to execute at least 11 critical actions, and requested the Director-General to continue to collaborate with ICBDSR, among other seven key issues. Through the resolution on birth defects of the Sitxty-third World Health Assembly (2010), Member States agreed to promote primary prevention and improve the health of children with congenital anomalies by:

- developing and strengthening registration and surveillance systems
- developing expertise and building capacity
- strengthening research and studies on etiology, diagnosis, and prevention
- promoting international cooperation.

It is also remarkable that the Sustainable Development Goals (SDGs) adopted by the United Nations in 2015 (United Nations 2015a, b) aim at ensuring healthy lives and promoting well-being for all children, among other important objectives. In particular, SDG goal 3 (target 3.2) aims at ending preventable deaths of newborns and children under 5 years, by 2030 (United Nations 2015b).

The global disease burden due to non-communicable diseases in childhood and later in life is rapidly increasing. Therefore, BD are and should always be a priority in the global child health agenda. BD surveillance programs through collaboration and sharing of data and expertise provide a crucial opportunity to increase our understanding on the impact of BD (prevalence and health, burden) and to uncover their genetic and environmental determinants. We cannot afford to lose this opportunity through neglect and underfunding. Too many births remain invisible, because too many countries, especially in low-resource areas, lack even a basic infrastructure for surveillance. BD programs should be adequately supported in all countries, otherwise BD will continue to be common, costly and critical, and the goal of improving lifelong health in children will remain unfulfilled. It all starts by making BD visible to all key stakeholders—professionals, public, and policy makers. It has been said that *counting BD helps BD to count*. This basic task of detecting, registering, and tracking BD must be a public health priority worldwide. Such foundation can then serve not only for advocacy and as a safety net for new teratogenic threats, but also and especially as a stepping stone to broader etiologic research and better prevention.

Acknowledgments ICBDSR wishes to thank all its members, which operate BD surveillance programs, systematically collecting data, sharing data for worldwide surveillance, being advocates in their countries for better knowledge and awareness on BD, contributing to enhance BD surveillance and research in their countries and abroad, and undertaking or participating in collaborative research on BD in the International Clearinghouse for Birth Defects Surveillance and Research, also in collaboration with other organizations in the field, to achieve the common goal of infants being born healthy.

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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