I N T R O D U C T I O N

Very Rare Defects: What Can We Learn?

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The International Clearinghouse for Birth Defects Surveillance and Research conducted a study on very rare defects (VRDs) to test methodologies in their population surveillance and to increase the knowledge of their epidemiology. Eight VRDs: acardia (AC), amelia (AM), bladder exstrophy (BE), cloaca exstrophy (CE), conjoined twins (CT), cyclopia (CY), ''true'' phocomelia (PH), and sirenomelia (SI) were selected, all of whom showed prevalences in the order of 1/100,000 births, except for BE: 1/48,000 births. Materials in this investigation from 25 million pregnancy outcomes, were provided by 22 Clearinghouse-member programs. The study protocol provided a working definition, a summary of the phenotypic characteristic, and a list of ICD-9 and ICD-10 codes for each VRDs. Learned lessons include: (1) The suspected associations of decreasing risk with advancing maternal age in AM and SI, and increasing risk in BE, and increasing frequency of twins in SI, were confirmed. (2) Morphologically similar defects showed dissimilar epidemiological characteristics, namely, AM and PH, and BE and CE. (3) Heterogeneity in total prevalences for most VRDs among different surveillance programs were attributed to operational reasons, except for SI and CT in which Amerindian ethnicity seems to be associated with higher prevalence. (4) Verbatim description is essential and must be stored in electronic files. In addition to codes. (5) Dysmorphologists or clinical geneticists are an essential part of the coordinating team of the surveillance program. (6) ICD coding system is insufficient. (7) Surveillance programs should be a valuable source of information on exposures to risk factors during pregnancy.

KEY WORDS: clearinghouse; ICBDSR; rare congenital anomalies; rare defects; rare anomalies

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INTRODUCTION

The International Clearinghouse

The International Clearinghouse was conceived in 1974, at a meeting in Helsinki, where representatives of surveillance programs in 10 countries decided to create a non-governmental organization named the ''International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS)''designed to regularly exchange data on the current prevalence of selected malformations [Anonymous, 1991]. From today's perspective such a decision may not seem remarkable, since birth defects surveillance has many other aims [Correa and Kirby, 2010]. But it must be noted that at that time (almost 40 years ago) the thalidomide disaster was still a concerning topic that demonstrated national and regional borders were irrelevant in an epidemic of birth defects. International and worldwide collaboration represented an important advancement in evaluating possible new clusters in the shortest time period. In 1994 a meeting was held in Rome to re-evaluate and expand the objective of the Clearinghouse (Box I). As a result of that meeting the name was updated to ''International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR).'' The Clearinghouse network includes 46 surveillance programs from 37 countries on the five continents [ICBDSR Annual Report, 2009].

In this introductory article we summarize the objectives of the Clearinghouse and its collaborators in the investigation of very rare defects (VRDs), the theme of this special AJMG Seminars issue, and describe the methodology used in all eight of the articles. In addition we highlight the results of the analyses accomplished on these eight VRDs.

WHY VERY RARE DEFECTS?

Sufficiently large case-series of VRDs are difficult to obtain under a uniform ascertainment framework. Even large birth-defect programs require long observational periods to attain a large number of cases. For instance, to collect a series of 100 cases of a defect with a birth prevalence of 1 in 50,000,

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Box 1. Objectives and Functions of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

The objective of the Clearinghouse is to prevent birth defects and ameliorate their consequences.

The Clearinghouse will:

(A) Operate an international program for regular exchange of information amongst its members on birth defects in populations covered by the members' surveillance and research programs;
(B) Cooperate in investigations and research changes in the occurrence of birth defects;
(C) Conduct joint epidemiological studies on the causes of birth defects;
(D) Advance the skills in surveillance and research into the occurrence of birth defects for the purpose of more effective identification of these conditions;
(E) Provide effective training in the surveillance and research of birth defects;
(F) Be an advocate for the surveillance, research and prevention of birth defects;
(G) Conduct assessments of preventive and therapeutic interventions for birth defects.

50 years of data would be required from a nationwide program registering 100,000 births per year such as Cuba, Czech-Republic, or Hungary. Observations made over a long period would be heterogeneous because of changes in observation accuracy, the development of new diagnostic techniques, changes in the staff, as well as actual changes in the observed population, such as maternal age, socioeconomic status, new and abandoned exposures, and other variables still unidentified as risk factors for abnormal fetal development. Furthermore, very few, if any, birth defect surveillance programs in the world have accumulated data for 50 or more years, with the only exception possibly being Canada-British Columbia. Nevertheless, precise starting dates are difficult to establish for the older systems since the early programs evolved from previous ones that recorded frequencies of persons with disabilities and not always including infants with structural birth defects. Other programs triggered by the thalidomide-phocomelia pandemic in the early 1960s were established: Czech-Republic in 1961, Sweden in 1964, and Norway, Atlanta and South America-ECLAMC[1] in 1967. Even though the Clearinghouse merged data from several programs that have variations in working definitions and methodologies, some similarities are shared [Källén et al., 1992]. Analyses are likely more comparable among them than those obtained from literature reviews or cases series, which are the other primary sources of data available for VRDs.

In 2005 the Clearinghouse launched a study on VRDs. We identified two main reasons for the study: to test methodological approaches in the population surveillance of defects with an extremely low prevalence; and to learn more on the epidemiological and clinical characteristics of eight selected VRDs: acardia (AC), amelia (AM), bladder exstrophy (BE), cloaca exstrophy (CE), conjoined twins (CT), cyclopia (CY), "true" PH, and sirenomelia (SI). In this study VRDs were defined as having an expected total prevalence lower than 1 in 30,000 births. Thus, the eight anomalies were selected; notably the total prevalences were in the order of 1 in 100,000 births for most of them (see Fig. 1). Our Clearinghouse study led to the idea for this *Seminars in Medical Genetics* series.

Rare or VRDs had been and may be in the future the phenotypes that can be caused by new teratogens introduced in the environment. The epidemic of PH caused by thalidomide is a well-known example. Another is the cluster of femoral focal a/hypoplasia observed by the Rhone-Alps/Auvergne surveillance program in France [Robert et al., 1981], and just few years ago a cluster of CY and SI observed in Cali, Colombia [Castilla et al., 2008]. CT and teratomas have been reported to be more frequent in the Polissia region near to Chornobyl, Ukraine [Wertelecki, 2010].

It is also well known that new or still unproven teratogens may cause isolated

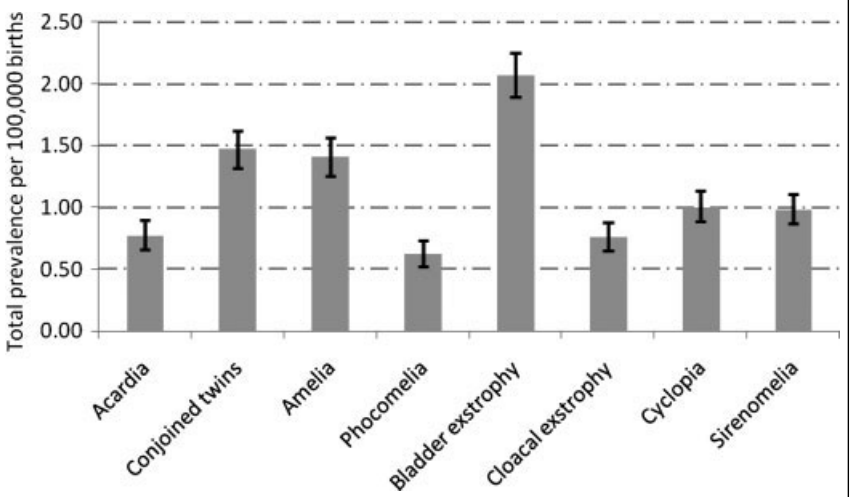

Figure 1. Total prevalence of eight very rare defects per 100,000 births. Very rare defects study International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). Column, total prevalence; vertical line, 95% confidence interval.

[1]ECLAMC: Estudio Colaborativo Latino Americano de Malformaciones Congénitas.

rare defects (e.g., scalp defects by methimazole), and rare defects may occur as a component in a constellation of defects (e.g., microtia is one the most typical defects of the isotretinoin syndrome). Learning how to be more efficient in the surveillance of rare defects represents a timely objective. Choosing eight VRDs as "case studies" will serve as a good starting point and could provide us with additional clinical and epidemiological information on these selected defects. Rare defects are in fact commonly described as a single case report or small series of cases.

Discrete and Continuous Developmental Defects

Some of the VRDs covered in this issue result from an alteration in a given stage of a given developmental process, thus representing a dysmorphologic entity within a continuous spectrum: SI within the caudal defect complex, CY in the holoprosencephaly developmental field complex, conjoined-twins, and AC within the twinning spectrum, AM, and PH, perhaps both within a continuum of transverse limb deficiency defects, either terminal or intercalary. Even when the inclusion of one or more of these eight VRDs could be controversial, the concept of a spectrum of dysmorphology remains valid. The most severe end of the spectrum is obviously represented by a very rare, conspicuous serious defect. Rareness could be due to a low frequency of occurrence of the primary defect, as well as to a high embryo-fetal lethality. The mildest end of the spectrum is expected to be difficult to evaluate because of its continuity with a normal trait and its variants, its lack of conspicuousness, and an expected lack of medical interest. However, the refinement in identifying sub-phenotypes is now acquiring special interest for the study of expressivity for genetic traits such as oral clefts [Weinberg et al., 2006; Marazita, 2007; Neiswanger et al., 2009].

On the other hand, discrete VRDs could also reflect truly rare dysmorphogenetic mechanisms, or a very low prenatal survival threshold. AC and PH could, at least in some cases, fit into this latter category. Finally, even when bladder and cloacal extrophies are difficult to have a dysmorphological interpretation, they can be placed within a spectrum having epispadias at a milder level, and the OEI and OEIS complex at a more severe one.

THE VERY RARE DEFECTS PROJECT, COMMON METHODOLOGIES

Data Extraction

For this series of articles all Clearinghouse members were invited to participate in the project; 22 of the programs joined. The Clearinghouse Centre Director (Pierpaolo Mastroiacovo) and two Clearinghouse members (Csaba Siffel and Eduardo E. Castilla) prepared the study protocol [ICBDSR Annual Report, 2007]. All participating birth defects surveillance program directors were requested to extract for the longest period of time all cases of the following VRDs: AC, AM, BE, CE, CT, CY, "true" PH, and SI. For each defect the study protocol provided the working definition, a summary of the phenotypic characteristic, and a list of International Classification of Disease codes (ICD-9 and ICD-10) most commonly used to code these eight VRDs.

The organizers (PM and EC) recommended that the participating programs search for cases corresponding to the given working definitions using every code that could reveal a case. We stressed that only "true" or complete PH defects were to be included and a special attention was given to CE since this defect lacks a specific code and could be confused with persistent cloaca or with BE.

For each case identified at local level the study protocol requested a standardized spreadsheet be sent to the Clearinghouse Center with the following information: code(s) and verbatim description of the VRD, laterality for AM and "true" PH, code(s) and verbatim description of associated defects, code and name of a syndrome if identified, diagnostic lab examination(s) (e.g., karyotype), pregnancy outcome, sex, plurality, date of outcome, date of last menstrual period, gestational age, birth weight, maternal and paternal age, parity, previous abortions, consanguinity, history of pregestational diabetes or epilepsy, folic acid use during the periconceptional period, history of fever, smoking, and medication use during first trimester, maternal education, and maternal occupation.

The information received from the participating surveillance programs was first reviewed at the Clearinghouse Center by one of the authors (PM and first authors of the articles) in order to clean the data and solve major problems of inconsistency with the study protocol. In turn each principal investigator in charge of a specific defect (first author of the articles in this issue) reviewed all the case-by-case information. Principal investigators and program directors collaborated on case-by-case inclusion/exclusion, especially for CE, PH, and SI.

Characteristics of the Participating Programs

The main characteristics of the participating programs are summarized in Table I. Ten surveillance programs are based on the deliveries of resident population irrespective where the delivery occurred (real population-based programs), seven are based on the deliveries occurring in the covered area irrespective to the mother' residence, and one on the deliveries of resident mothers but excluding mothers with an outside residence. Four programs are hospital-based, usually without any a priori selection except the willingness to participate. These four hospital-based programs survey consecutive birth series, and they all are located in countries having $<5\%$ of domiciliary births. Hospital-based programs should not be confused with clinical-based series of cases for a given disease since hospital-based programs evaluate all the infants with a congenital defects without any selection linked to the severity, need of treatment, survival or other characteristics.

TABLE I. Main Characteristics of the International Clearinghouse Surveillance Programs Participating to the Very Rare Defects Project

Surveillance program	Coverage	ETOPFA	Source of ascertainment	Criteria defining stillbirths	Information provided by the Surveillance Program to the Clearinghouse Centre		
					Code	Extension	Description
Australia, Victoria	PP1	P, R	M	20 w or 400 g	ICD9	BPA	DS
Canada, Alberta	RP	P, R	M	20 w or 500 g	ICD9 + ICD10	BPA − RCPCH	No
China, Beijing	PP1	P, NR	S	20 w	ICD9	BPA	No
Finland	RP	P, R	M	22 w or 500 g	ICD9	BPA + CDC	DS
France, Central East	RP	P, R	M	22 w or 500 g[a]	ICD9	BPA	No
Germany, Saxony-Anhalt	PP2	P, R	M	500 g	ICD10	BPA + LDE	DS
Hungary	RP	P, R	M	24 w or 500 g[b]	ICD9	BPA + LDE	DS[c]
Israel	H	P, R	S	20 w or 500 g	ICD9	BPA	No
Italy, Campania	PP1	P, R	S	180 days	ICD10	—	DS
Italy, Emilia Romagna	PP1	P, R	S	180 days	ICD9	BPA	No
Italy, North-East	PP1	P, R	S	180 days	ICD9	BPA	No
Italy, East Sicily	PP1	P, R	M	180 days	ICD9	BPA	DS
Italy, Tuscany	RP	P, R	M	180 days	ICD9 + ICD10	BPA	No
Mexico, RYVEMCE	H	NP	S	20 w or 500 g	ICD9	BPA + LDE	DS
Northern Netherlands	RP	P, R	M	24 w	ICD9 + ICD10	BPA	DS
Slovak Republic	PP1	P, R	S	28 w or 1,000 g	ICD10	—	No
South America, ECLAMC	H	NP	S	500 g	ICD9	BPA + LDE	DS
Spain, ECEMC	H	P, NR	M	24 w or 500 g	ICD10	BPA + LDE	No
USA, Atlanta	RP	P, R	M	20 w	ICD9	BPA + CDC	DS
USA, Texas	RP	P, R	M	20 w[d]	ICD9	BPA + CDC	DS
USA, Utah	RP	P, R	M	20 w	ICD9	BPA + CDC	DS
Wales	RP	P, R	M	24 w	ICD10	BPA	DS

Surveillance Program: *Coverage*: RP = resident population, when it includes only subjects born to mothers with the residency during gestation in the area covered by the registry, wherever the delivery took place, and it excludes all the subjects born to non-resident mothers that delivered in the area covered by the registry. PP1 = present population type 1, when it includes all subjects born to mothers that delivered in the area covered by the surveillance program, wherever they had the residence during gestation. The surveillance program does not cover subjects born outside the area, even if the mother is resident in the area. PP2 = present population type 2, the same as PP1 but the surveillance program excludes subjects born to mothers that had the residence out of the area. H = hospital based, when it includes only a proportion—even near to 90%—of all subjects delivered in the area covered by the registry. *ETOPFA*: P, permitted by country's legislation; NP, not permitted; R, reported; NR, not reported. *Source of ascertainment*: S, single source; M, multiple sources. *Information provided*: ICD, International Classification of Diseases; BPA, British Pediatric Association-Classification of Diseases; BPA-RCPCH, BPA classification adopted by the Royal College of Pediatric and Child Health; LDE, local developed extension codes to identify more precisely some subtypes of defects; DS, diagnostic description.

[a]Before 1993: 22 weeks; since 1993: 20 weeks.

[b]Before 1998: 28 weeks; since 1998: 24 weeks.

[c]Photographic documentation was provided for the majority of conjoined twins cases.

[d]Before 2001: 20 weeks. Since 2001: all stillbirths with documented birth defects included.

All programs register cases observed in live births (LB) and stillbirths (SB) and in elective termination of pregnancy for fetal anomalies (ETOPFA) if legally permitted. In two programs ETOPFA are not permitted, although some illegal ones may be performed (South America, ECLAMC and Mexico, RYVEMCE[2]). In two programs the ETOPFA are permitted but not registered (Spain, ECEMC[3] and China, Beijing). The source of case's ascertainment is multiple in 13 programs, while it is based on a

[2]RYVEMCE: Registro Y Vigilancia Epidemiológica de Malformaciones Congénitas.

[3]ECEMC: Estudio Colaborativo Espanol Malformaciones Congenita.

single source in 9 programs, usually those based on an ad hoc reporting form for birth defects from the maternity hospitals. Informed consent for registration of cases is requested by five programs.

Not all programs contributed to the 8 very rare selected defects. All of them provided data on BE. For the remaining seven defects the number of participating programs ranged between 18 (AC) and 21 (CT). The reasons for the lack of participation were either no observed case or difficulties in retrieving the cases according to the inclusion/exclusion criteria given in the study protocol.

Phenotype Descriptions and Classification

The last three columns of Table I show the information sent by each program for transmitting centrally the VRDs diagnosis of the cases. Other than codes a verbatim description was sent by 14 programs. Almost always the description sent was in "diagnostic style," defined as such when the verbatim description was limited to the naming the diagnosis; for example, just "sirenomelia" and not a more complete description including for instance: fusion of lower limbs in a single malformed limb without evidence of feet. The same "diagnostic style" was used for the related or unrelated associated defects. However, it must be noted that even a single worded "diagnostic style" verbatim description is more informative than a code when no specific slot for a given anomaly is available in the most commonly used coding systems, as ICD. For several anomalies in this investigation, and their associate defects, a single diagnostic style word had brought together more than one code in some of the contributing programs, after laborious data mining.

Cases of AM, BE, CY, SI, and PH, were classified as isolated, multiple congenital anomalies (MCA) and syndromes. The classification was done centrally and independently by each principal investigator and by the ICBDSR Centre Director following the guidelines suggested by the National Birth Defects Prevention Study in United States [Rasmussen et al., 2003]. Discrepancies among them were discussed and when necessary involved the data providers and program directors. Minor or mild malformations were not considered. MCA were defined as the presence of two or more major unrelated defects. Related defects of the eight VRDs are defined in each single article of this issue. Unless otherwise specified, syndromes were defined mainly by the data contributor program directors.

Statistical Methods

To express the frequency of each defect we have used the term "total prevalence." Total prevalence is a ratio between the number of cases observed in LB, SB, and ETOPFA as numerator and the number of births (LB + SB) as denominator. The total number of ETOPFA is not usually available on vital statistics.

In the programs where ETOPFA are not permitted the total prevalence was obviously computed using as a numerator only SB and LB. In the programs where the ETOPFA are permitted but not registered, the total prevalence may be biased, lower than the actual prevalence, the size of bias being related to the unknown proportion of the ETOPFA performed in the area covered by the program for that specific defect.

Total prevalence estimates were computed for each program (LB + SB + ETOPFA cases/LB + SB births, per 100,000 births) with its 95% confidence interval according to the Poisson distribution. The "overall" total prevalence was computed summing up all the cases in each program and dividing these by the sum of all births of all participating programs. Total prevalence for AC and CT were also computed using as a denominator the number of twin births or the number of monozygotic twins (derived by the like-sex twin births). Since no difference between each program's prevalence was found compared to total number of births prevalence, we did not present these results.

Comparison among programs of the total prevalence estimates of each defect was evaluated computing first the expected number of cases in each program (number of births multiplied by the overall total prevalence) under the hypothesis of a homogeneous total prevalence among all programs; then the exact Poisson probability of observing N or more cases in each program was computed, using the expected number of cases [P ($N \geq x$), where N is the observed number of cases and x is the expected number of cases computed multiplying the overall total prevalence by the number of births in the surveillance program]. Statistical significance was set to $P < 0.05$ with Bonferroni correction for multiple testing (0.05/n, where n is the number of programs). Marginally statistically significant differences with $P < 0.05$ without Bonferroni correction were also noted.

The 5-year maternal age prevalence ratio was also computed for non-syndromic cases (isolated and MCA) and for syndromes when the number of cases with syndromes was more than 20. The maternal age <20 years was most commonly used as reference group. Trend across maternal age group was tested with the chi square for trend.

The exposure to many variables (e.g., medication use or fever in the first trimester) was either: not originally available, not sent by some surveillance programs or sent as data of unknown information. For most cases the following variables were available for analysis: sex, pregnancy outcome, birth weight, gestational age, parity, previous spontaneous abortions, plurality, maternal age, paternal age difference, and maternal education.

For five defects: AM, BE, CY, PH, and SI these variables were analyzed comparing cases of MCA without known syndromes with the cases with an isolated defect. The proportion of MCA varied widely among programs. Considering all the five defects together and excluding syndromes the mean proportion of MCA out of the total of isolated plus MCA cases was 44.9% with a range between 12.5% (Slovack Republic) and 76.5% (Germany Saxony-

Anhalt). This was most probably due to the different capability to detect associated malformations in the various programs. Given this so wide different proportion of MCA recorded in the various programs and given the small sample size in each program, the odds ratios (OR) of the association between the independent variables (sex, pregnancy outcome, etc.) and the MCA was adjusted (aOR) by program according to its tertile category of the proportion of MCA observed and computed with the logistic regression model.

For all articles, a clinical/epidemiologic perspective was provided along with a brief literature review. This was considered to be important considering the rarity of these defects.

SUMMARY OF MAIN RESULTS

The total prevalence by program, the maternal age prevalence ratio, the main phenotypic and epidemiological characteristics, and when suitable the comparison of some variables between isolated and MCA cases of each VRDs are presented in each article of this issue. The total prevalence is presented in tabular form and as a figure. The table lists the surveillance programs in order of geographic location (north to south and west to east) to appreciate possible similarities between the nearest areas. The figure shows the programs by decreasing order of total prevalence to appreciate the differences among them. In the present article the summary of main results is shown in Figure 1 and in Tables II and III. Figure 1 shows the observed overall prevalence of the eight VRDs. Frequency range between 2.07 per 100,000 births (CI 1.90–2.25) for BE to 0.62 per 100,000 births (CI 0.52–0.73) for PH.

Table II shows the variation in the total prevalence among programs. The marginally statistically significant findings and those statistically significant considering the multiple testing are shown. The interpretation of this variation is challenging. Some low total prevalence may be explained by the most common of the epidemiology problems: under-registration of cases. Under-registration is a different issue from under-ascertainment. The case may have been diagnosed in the target population, may have been ascertained by the program but may be under-registered for many reasons, for example, wrong coding, wrong or uncertain central classification, clinical records not found or ad hoc forms for birth defects not transmitted (these two last problems are probably more common for rare defects). Another issue is over-registration. The clearest examples among the VRDs here discussed is "true phocomelia" and AM, since the classification of these defects requires often the availability of good clinical and imaging documentations: pictures and radiographs. Some variation may be true, especially those that are significantly higher than in other programs. At the end of this project the results that require further exploration include the high prevalence of BE in Finland, CT in South America and Finland, and SI in Mexico.

Table III summarizes the main results by defect. Results are given only for nonsyndromic cases.

What Have We Learned?

In conducting this project of VRDs we have learned several lessons:

On these eight selected VRDs. (1) Some associations, suspected in previous studies between defects and risk factors, were now, with a larger sample size, scientifically established, namely: decreasing risk with advancing maternal age in AM and SI, and increasing risk in BE, and increasing frequency of twins among SI cases.

(2) With materials from a single data set, and under similar working definitions and methodologies, morphologically similar anomalies showed different epidemiological characteristics, especially for cases of AM and PH, and bladder and cloacal exstrophies.

(3) Most studied VRDs had different total prevalences in the participating surveillance programs. For most defects this heterogeneity was attributed to operational reasons, except for SI and CT in which Native American ethnicity seems to be associated with significant higher prevalence.

On methodology. (1) Verbatim description is essential and must be stored in electronic files. The most important lesson we have learned is that in a birth defect surveillance program the original verbatim description of all defects should be stored in electronic files as well as the codes. Codes are useful to retrieve a case, but the full verbatim description is necessary to validate the code, or to better classify a case when needed. The use of "diagnostic style" description, as defined in the methods section, should be discouraged, except perhaps for cases that are very typical. When only the diagnostic style description is available in original records, it should be specified. When possible, the imaging (pictures, radiographs), necropsy, and laboratory reports should be stored. The quick availability of all this information may be needed to review and re-evaluate cases.

A guide to describe and code the eight VRDs approached in this issue is presented in Box II.

(2) Dysmorphologists or clinical geneticists are an essential part of the coordinating team of the surveillance program. Ideally, a birth defects surveillance system should have the original description written by the physician that actually examined the affected infant or fetus, including pediatricians, ultrasonographers, and pathologists, and accompanied by suitable documentation: photographs, radiographies, ultrasongraphies, surgical, pathological, and other reports. At the central level, cases should be reviewed by dysmorphologists or geneticists, who should have an active participation in final coding of each case, as well as in follow ups and subsequent corrections needed in coding [Lin et al., 2009].

(3) The standard International Classification of Disease (ICD) coding system is insufficient. The ICD.10 offers specific codes for half of the eight VRDs dealt with in this project,

TABLE II. Summary of Statistically Significant Total Prevalence Variations of 8 Very Rare Defects Among ICBDSR Surveillance Programs

Surveillance program	Acardia	Amelia	Bladder exstrophy	Cloaca exstrophy	Conjoined twins	Cyclopia	Phocomelia	Sirenomelia
Overall total prevalence	0.77 (0.66–0.90)	1.41 (1.26–1.57)	2.07 (1.90–2.25)	0.76 (0.65–0.88)	1.47 (1.32–1.62)	1.00 (0.89–1.14)	0.62 (0.52–0.73)	0.98 (0.87–1.11)
Canada Alberta, births = 1,062,483				1,51 (0.86–2.45), ↑ $P = 0.0088$				1.60 (0.93–2.56), ↑ $P = 0.038$
USA Utah, births = 380,706	2.10 (0.91–4.14), ↑ $P = 0.011$							
USA Atlanta, births = 1,283,999	—							
USA Texas, births = 2,054,788					**0.63 (0.34–1.08), ↓↓$P = 0.0004$**			
Mexico RYVEMCE, births = 1,058,885		2.36 (1.53–3.49), ↑ $P = 0.011$	3.21 (2.22–4.49), ↑ $P = 0.010$		2.27 (1.45–3.37), ↑ $P = 0.027$	1.70 (1.01–2.69), ↑ $P = 0.024$		**2.36 (1.53–3.49), ↑↑P *0.0001***
South America ECLAMC, births = 4,556,173			**0.77 (0.54–1.07), ↓↓P *0.0001***	**0.37 (0.22–0.60), ↓↓$P = 0.0007$**	**2.37 (1.94–2.86), ↑↑P *0.0001***		**0.15 (0.06–0.32), ↓↓P *0.0001***	1.36 (1.04–1.74), ↑ $P = 0.0088$
Finland, births = 713,494			**4.63 (3.18–6.50), ↑↑P *0.0001***		**3.22 (2.04–4.84), ↑↑$P = 0.0005$**			
Wales, births = 222,309		—		2.25 (0.73–5.25), ↑ $P = 0.029$			—	
Northern Netherlands, births = 369,658							—	
Germany Saxony Anhalt, births = 355,184								—
Slovak Republic, births = 318,257	—			—				
Hungary, births = 3,022,194		—		0.46 (0.25–0.78), ↓ $P = 0.032$		**0.26 (0.11–0.52), ↓↓P *0.0001***	—	**0.33 (0.16–0.61), ↓↓P *0.0001***
France Central East, births = 2,500,214	1.16 (0.78–1.67), ↑ $P = 0.024$							
Italy North East, births = 1,186,497	**0.08 (0.00–0.47), ↓↓$P = 0.001$**	**0.42 (0.14–0.98), ↓↓$P = 0.0008$**			**0.08 (0.00–0.47), ↓↓P *0.0001***	1.77 (1.10–2.71), ↑ $P = 0.011$	0.17 (0.02–0.61), ↓ $P = 0.023$	1.69 (1.03–2.60), ↑ $P = 0.017$
Italy Emilia Romagna, births = 558,176				—		—		—
Italy Tuscany, births = 336,744	—			—				
Italy Campania, births = 643,962	—	0.47 (0.10–2.36), ↓ $P = 0.020$		—	0.47 (0.10–1.36), ↓ $P = 0.016$	0.31 (0.04–1.12), ↓ $P = 0.044$		0.16 (0.00–0.87), ↓ $P = 0.013$
Italy Sicily, births = 216,257	—				—	—		
Spain ECEMC, births = 2,054,751		0.73 (0.41–1.21), ↓ $P = 0.035$			0.78 (0.45–1.27), ↓ $P = 0.004$			
Israel, births = 151,562								—
China Beijing, births = 1,927,622	0.36 (0.15–0.75), ↓ $P = 0.019$	**2.44 (1.79–3.24), ↑↑$P = 0.0004$**	**0.52 (0.25–0.95), ↓↓P *0.0001***			1.50 (1.01–2.16), ↑ $P = 0.024$		
Australia Victoria, births = 1,390,179	**1.94 (1.28–2.83), ↑↑P *0.0001***		**3.67 (2.73–4.82), ↑↑P *0.0001***				**1.44 (0.88–2.22), ↑↑$P = 0.0006$**	

In brackets 95% confidence interval; P-value computed according to the exact cumulative Poisson test: ↓ = lower than the overall total prevalence, $P < 0.05$; ↑ = higher than the overall total prevalence $P < 0.05$; bold and ↑↑ or ↓↓ = statistical significance with Bonferroni correction for the number of surveillance programs compared ranging from $P < 0.022$ when all programs were participating and $P < 0.029$ when 17 programs were participating); — = not participating program.

TABLE III. Selected Characteristics of Eight Non-Syndromic Very Rare Defects

	N	M/F	SB (%)[#]	ETOPFA (%)	Birth weight <2,500 g[§,#]	Twins (%)[#]	Prevalence by maternal age
Amelia	319	1.52★	26.4	34.3	54.5	8.3	Decreases with advancing age[&]
Phocomelia	127	1.23	18.9	19.4	49.4	3.3	No variation
Bladder exstrophy	537	1.85★★	3.7	5.2	14.2	3.4	Increases with advancing age[&]
Cloaca exstrophy	186	0.85	15.6	18.5	54.5	10.6	No variation
Acardia	164	1.08	82.8	23.4	—	—	No variation
Conjoined twins	383	0.50★★	27.2	50.7	40.9	—	No variation
Cyclopia	178	0.65★	34.8	39.5	75.0	2.5	No variation
Sirenomelia	249	0.94	28.5	45.9	88.2	9.3	Decreases with advancing age[&]

ETOPFA = elective termination of pregnancy for fetal anomalies, computed only in surveillance programs where ETOPFA are permitted and registered.

[#]Missing value (<20%) were excluded. [§]Computed only for live births. ★$P < 0.05$; ★★$P < 0.01$ at chi square test. [&]Chi square for trend $P < 0.01$.

Box 2. Guide to Describe and Proper Codification by ICD.10-BPA System

Definition	Description guide	Coding
Acardia: Absent heart. Frequently associated with acephaly (absent head). A complex congenital malformation seen in multiple births, usually in monozygotic twins but also in triplets and quadruplets In all cases, the heart is lacking and many other structures may be missing or are significantly malformed. In the more common occurrence, head and upper torso are missing (acardius-acephalus), with relative preservation of the lower body, which however can still be significantly malformed. More rarely, some cephalic structures remain (anceps). In a few cases, the reverse situation is observed cephalic structures are present with little or no truncal development (acormus). Finally, all cephalic and truncal differentiation may be lacking (amorphous), such that the fetal remnant resembles a teratoma. However, unlike a teratoma, the amorphous fetus has an umbilical cord and maintains some skeletal organization	Describe parts of the body and organs which are: absent, present, and abnormal; plus weight and length	ICD-10—Q89.8: Other specified congenital malformations ICD-10-BPA—Same as ICD.10
Cloacal exstrophy: A very rare abdominal wall defect composed by Omphalocele, hemi-bladders Exstrophy and Imperforate anus (OEI), sometimes with renal malformations and Spine defect (OEIS complex). The hemibladders flank the openings of the small intestine and blind-ending large intestine and contain the orifices of the ureters and vasa deferentia in males and the uterovaginal canal in females	Describe external aspect of the abdomen, visualized internal structures, presence of anus, where the urine and the meconium are excreted from, X-ray of spine	ICD-10—Q45.8: Other specified congenital malformations of digestive system ICD.10-BPA—Q64.10: Cloacal exstrophy
Sirenomelia: A congenital malformation characterized by different degrees of between the lower limbs "A limb anomaly in which the normally paired lower limbs are replaced by e single midline limb" [Stevenson, 2006]. Most cases have bilateral renal agenesis, affecting post-natal survival and impairing prenatal diagnosis by ultrasound because of the resulting oligoamnios	Sirenomelia could be grouped into 7 types of semi-continuous progressive severity according to Stocker and Heifetz [1987]	ICD.10—Q87.2: Congenital malformation syndromes predominantly involving limbs ICD.10-BPA—Q87.24: Sirenomelia syndrome

Box 2. (*Continued*)

Amelia: A congenital malformation characterized by total absence of skeletal structures of one or more limbs	Describe 4 details Affected limb/s Absent bones Present and abnormal bones: hypotrophic, deformed, fused, etc. Present and normal bones	ICD.10—Q71.0: Congenital complete absence of upper limb(s); Q72.0: Congenital complete absence of lower limb(s); Q73.0: Congenital complete absence of unspecified limb(s) ICD.10-BPA—Same as ICD.10
Complete phocomelia: A congenital malformation characterized by total absence of skeletal structures of the long bones of the limbs (humerus, radius, ulna/femur, tibia, fibula), with the presence of a normal or abnormal hand/foot directly attached to the trunk	Describe 4 details Affected limb/s Absent bones Present and abnormal bones: hypotrophic, deformed, fused, etc. Present and normal bones	ICD.10—Q71.1: Congenital absence of upper arm and forearm with hand present; Q72.1: Congenital absence of thigh and lower leg with foot present; Q73.1: Phocomelia, unspecified limb(s) ICD.10-BPA—Same as ICD.10
Conjoined twins: Conjoined twins (CT) are a very rare embryologic developmental accident a couple of monozygotic twins (MZ) do not fully separate each other and continue their normal embryologic development, but induce the jointedness of both embryos originating a couple of conjoined twins	Describe the complete set of twins as being Symmetric or asymmetric Avoid technical latin nomenclature Part/s of the body of union, as detailed as possible Shared organs, if any Total number of limbs External genitalia For medical and statutory use, decide whether the set of conjoined twins conforms one or two (or more) human beings. For this purpose use common sense and your judgment as possibility to survive once separated surgically	ICD.10—Q89.4: Conjoined twins ICD.10-BPA—Q89.4: Conjoined twins; Q89.40: Dicephaly Two heads; Q89.41: Craniopagus Head-joined twins; Q89.42: Thoracopagus Thorax-joined twins; Q89.43: Xiphopagus, Xiphoid and pelvis-joined twins; Q89.44: Pygopagus, buttock-joined twins; Q89.45: Double monster; Q89.48: Other specified conjoined twins
Cyclopia: (also cyclocephaly or synophthalmia) is part of the facial aspect in *holoprosencephaly*, a congenital malformation characterized by the failure of the embryonic *prosencephalon* to properly divide the *orbits* of the eye into two cavities	Describe Number of orbits, eye globe, corneas, pupils Brain lobules from XRay, surgery, autopsy Other facial structures: nose, lips, mouth, ears, etc.	ICD.10—Q87.0: Congenital malformation syndromes predominantly affecting facial appearance ICD.10-BPA—Q87.03: Cyclopia [cyclops] [cyclopism][synophthalmia]
Bladder exstrophy: Complex malformation characterized by a defect in the closure of the lower abdominal wall and bladder. Bladder opens in the ventral wall of the abdomen between the umbilicus and the symphysis pubis. It is often associated with epispadias and structural anomalies of the pubic bones	Describe external aspect of the abdomen, visualized internal structures, presence of anus, where the urine and the meconium are excreted from	ICD.10—Q64.1: Exstrophy of urinary bladder ICD.10-BPA—Same as ICD.10

namely AM (Q71.0, Q72.0, Q73.0), complete PH (Q71.1, Q72.1, Q73.1), BE (Q64.1), and CT (Q89.4); nonspecific collective codes are given for two: SI (Q87.2 congenital malformation syndromes predominantly involving limbs), and CY (Q87.0 congenital malformation syndromes predominantly affecting facial appearance); and two are not mentioned at all: AC, and cloacal exstrophy.

Additionally, ICD.10 has a specific slot for complete PH but not for incomplete (or atypical), which have to be considered as "other reduction defects" of upper (Q71.8), lower (Q72.8), or unspecified (Q73.8), limb(s). Furthermore, acephaly, a common association found with AC in so called acardio-acephaly, is erroneously placed by ICD.10 under the same code of anencephaly (Q00.0) a completely different defect from the morphological as well as from the pathogenetic standpoints. The much less frequently used ICD.10-BPA, the 5th digit extension of ICD.10 made by the British Paediatric Association, provides specific codes for SI (Q87.24), and CY (Q87.03), but ignores AC, and cloacal exstrophy.

(4) Exposure information is often not recorded or unknown, or it is recorded inconsistently across sites. Surveillance programs are a very valuable source of information on exposures to risk factors during the first week of pregnancy. Without this information for more than 80% of cases in this study, we were not able to conduct any case-control study on medications used during the first weeks of pregnancy or on any other of the requested risk factors because many programs did not register exposure information above the needed percentage threshold to avoid serious biases. Surveillance programs should evaluate routinely the percentage of unknown information by specific defects, even the rarest, to improve their information sources.

CONCLUSION

This series of articles is the first contribution to the literature regarding the knowledge of clinical and epidemiological aspects of eight very rare congenital defects. The results of the analyses include birth prevalence values from worldwide large birth sets, and description of clinical sub-phenotypes and associated risk factors for each defect. Besides methodological lessons, these eight articles provide support for direct associations of maternal age and BE, and indirect association with AM and SI, as well as confirming associations of twinning with SI, and Amerindian ethnic background with SI and CT.

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REFERENCES

Anonymous, Congenital Malformations Worldwide. A report from International Clearinghouse for Birth Defects Monitoring Systems. Amsterdam, New York, Oxford: Elsevier. 1991.

Castilla EE, Mastroiacovo P, López-Camelo JS, Saldarriaga W, Isaza C, Orioli IM. 2008. Sirenomelia and cyclopia cluster in Cali, Colombia. Am J Med Genet Part A 146A:2626–2636.

Correa A, Kirby RS. 2010. An expanded public health role for birth defects surveillance. Birth Defects Res A Clin Mol Teratol 88:1004–1007.

ICBDSR Annual Report, 2007 with data for 2005, Centre of the International Clearinghouse for Birth Defects Surveillance and Research of ICBDSR, Rome, Italy. 2007.

ICBDSR Annual Report, 2009 with data for 2007, Centre of the International Clearinghouse for Birth Defects Surveillance and Research of ICBDSR, Rome, Italy. 2009.

Källén B, Castilla EE, Lancaster PA, Mutchinick O, Knudsen LB, Martínez-Frías ML, Mastroiacovo P, Robert E. 1992. The cyclops and the mermaid: An epidemiological study of two types of rare malformation. J Med Genet 29:30–35.

Lin AE, Rasmussen SA, Scheuerle A, Stevenson RE. 2009. Clinical geneticists in birth defects surveillance and epidemiology research programs: Past, present and future roles. Birth Defects Res A Clin Mol Teratol 85:69–75.

Marazita ML. 2007. Subclinical features in nonsyndromic cleft lip with or without cleft palate (CL/P): Review of the evidence that subepithelial orbicularis oris muscle defects are part of an expanded phenotype for CL/P. Orthod Craniofac Res 10:82–87.

Neiswanger K, Chirigos KW, Klotz CM, Cooper ME, Bardi KM, Brandon CA, Weinberg SM, Vieira AR, Martin RA, Czeizel AE, Castilla EE, Poletta FA, Marazita ML. 2009. Whorl patterns on the lower lip are associated with nonsyndromic cleft lip with or without cleft palate. Am J Med Genet A 149A:2673–2679.

Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA, National Birth Defects Prevention Study. 2003. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 67:193–201.

Robert JM, Guibaud P, Robert E. 1981. A local outbreak of femoral hypoplasia or aplasia and femoral fibula-ulnar-complex. J Genet Hum 29:379–394.

Stevenson RE, Limbs. In: Stevenson RE, Hall JG, editors. Human malformations and related anomalies, 2nd edition. New York: Oxford University Press. 2006.

Stocker J, Heifetz S. 1987. Sirenomelia, a morphological study of 33 cases and review of the literature. Perspect Pediatr Pathol 10:7–50.

Weinberg SM, Neiswanger K, Martin RA, Mooney MP, Kane AA, Wenger SL, Losee J, Deleyiannis F, Ma L, De Salamanca JE, Czeizel AE, Marazita ML. 2006. The Pittsburgh Oral-Facial Cleft study: Expanding the cleft phenotype. Background and justification. Cleft Palate Craniofac J 43: 7–20.

Wertelecki W. 2010. Malformations in a chornobyl-impacted region. Pediatrics 125: e836–e843.