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Sources of Variability in Birth Defects Prevalence Rates

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ABSTRACT

Background: The characteristics and methodologies of state-based birth defect surveillance systems might influence reported prevalence rates, making comparisons among states difficult. Standardizing methods to minimize variability beyond true differences in prevalence will aid national surveillance efforts and birth defects prevention programs.

Methods: Using data provided in the January 2000 Congenital Malformations Surveillance Report from the National Birth Defects Prevention Network, we characterized the surveillance methodologies among all sites. We then identified prevalence rates that are highly varied among systems that use each of our specified methodologies. We also examined the standards used by other collective health registries that exist across geographical boundaries.

Results: Large differences in prevalence rates across case ascertainment methods (active, passive, or combination of both) were observed for some conditions, but not for others. We identified additional factors which may influence prevalence rates, including case ascertainment sources, case inclusion criteria, and inclusion of elective terminations and stillbirths. The impact of each of these factors on prevalence rates may be defect-specific.

Conclusions: We conclude that while some variability is expected due to differences in the true prevalence of birth defects, extreme differences among states are more likely due to differences in surveillance practices. The Birth Defects Prevention Act prompted new initiatives to develop birth defect surveillance systems, but there are no nationally agreed upon standards in existence to guide the process. This study was performed in support of developing standards that will influence new and existing state surveillance systems.

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INTRODUCTION

Timely and accurate national data on the prevalence of birth defects in the United States are becoming increasingly important for the evaluation of prevention programs, identification of causes of birth defects, and dissemination of information that will influence public health policy and resource allocation. The recent report by the Pew Environmental Health Commission ('99) emphasized the need for increasing standardized national surveillance to confirm possible regional increases in certain birth defects. Without the national standardization of birth defects registries, U.S. public health officials and researchers cannot examine the effectiveness of various prevention programs. For instance, as a measure to prevent neural tube defects (NTDs), the Food and Drug Administration mandated the fortification of certain grain products with 140 μg of folate/100g of product, effective January 1998. However, assessing the preventive benefits of fortification relative to its cost or to the possible consequences of masking pernicious anemia in certain populations is difficult (Mills, '00). Rapid and complete ascertainment of NTDs is critical to evaluating the success of mandated fortification and other national programs such as the National Folic Acid Campaign, which encourages women of childbearing age to take a supplement containing 400 μg of folic acid daily.

Although folic acid deficiency is one of the few known risk factors for birth defects, many more studies are identifying additional factors, including genetic influences and environmental exposures, that may contribute to the development of congenital malformations (Khoury, '00). Approximately 94% of the genes on human chromosomes have been mapped, and researchers predict that the Human Genome Project will be complete by 2003. As the availability of genetic data increases, the field of genetic epidemiology will advance at a faster pace than ever. Public health officials and researchers will need large numbers of cases to provide sufficient statistical power analyses to study the effects of candidate genes and gene-environment interactions on the risk of birth defects. For appropriate analyses, data are required from several different birth defects registries, for studies such as the National Birth Defects Prevention Study. The validity of results based on pooled data is strengthened if case ascertainment methods and inclusion criteria are standardized across participating registries.

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TABLE 1. Reported prevalence of selected birth defects by state (per 10,000 births)

State	Year of data collection	Hypoplastic left heart	Anencephaly	Gastroschisis	Spina Bifida	Hydrocephalus	Renal agenesis	Tricuspid valve atresia and stenosis	Atrial septal defect
Alaska	1996	0	2	4	1	3	2	0	44.8
Ark.	1996	1.4	4.9	3.8	9.3	25.4	7.4	27.8	36.3
Ariz.	1991	1.6	1	4.7	4.4	6.6	4.6	17.6	39.7
Calif.	1995	1.8	2	2.6	3.6	5.8	NA	NA	NA
Colo.	1996	2.9	1.8	NA	3.7	8.2	5	1.6	47
Conn.	1994	0.9	1.1	NA	3.3	7.4	1.8	0.44	NA
Ga.	1996	3.2	2.2	1.7	3.4	8.1	6.1	28.4	56.7
Hawaii	1996	1	4.6	3.6	7.2	14	8.3	98.5	125.9
Iowa	1996	3.2	5.1	0.8	5.1	6.2	4.8	2.1	20.9
Ill.	1996	1.3	2.3	NA	3.3	6.1	1.8	0.38	18.7
Kans.	1996	NA	3.8	NA	6.3	7.9	1.6	NA	NA
Mass.	1996	1.7	0.5	3.2	2.1	4.5	3	0.1	11.1
Md.	1996	NA	1.8	NA	1.8	1	NA	NA	NA
Mo.	1996	2.6	1.6	NA	5.6	5.8	4.3	0.14	21.3
N.C.	1996	2.7	2.9	NA	6.4	8.9	3.8	0.7	31.1
Nebr.	1996	2.6	3.4	3.4	7.7	5.1	3.8	7.7	47.8
N.J.	1996	2.1	0.44	1.1	3	3.5	4	0.79	64.9
N. Mex.	1996	2.2	3.6	5.4	2.9	0	0.7	1.1	19.7
N.Y.	1996	2	0.38	1.2	2.6	5.4	2.5	5.8	36.2
Okla.	1996	2.6	3.4	3.7	8.8	10.6	6.9	1.5	52.3
S.C.	1996	NA	0.97	NA	1.7	2.7	35.7	NA	NA
Tenn.	1993	2.6	1.9	NA	3.1	6.1	2.7	0.6	10.6
Tex.	1995	2.1	4.7	3.2	5.7	5.1	5.4	NA	NA
Utah	1996	NA	2.4	NA	3.6	NA	NA	NA	NA
Va.	1996	1.3	0.1	NA	3	2.4	1.2	1.1	18.8
Wis.	1996	0.74	2.1	5.8	4.9	4.9	2.4	0.7	19.7
Range		0–3.2	0.1–5.1	0.8–5.8	1.0–9.3	0–25.4	0.7–35.7	0.1–98.5	10.6–125.9

Timely and accurate surveillance provides data for advocacy and grant-writing efforts toward increasing funding for birth defects research and prevention. Additionally, in 1998 the Birth Defects Prevention Act became law. As a result, Congress requires increased reporting of "information regarding the incidence and prevalence of birth defects and the extent to which birth defects have contributed to . . . infant mortality" and "information . . . specific to various racial and ethnic groups." Because states' divisions of land are based on geography and on arbitrary political considerations, and are not necessarily relevant to the causes and occurrence of birth defects, collection of uniform national data is essential. In this paper, we examine prevalence rates of selected defects and propose ways that methodological differences among registries might affect those rates. We performed these analyses in support of developing national standards for surveillance in this field of increasing priority in public health policy and research.

METHODS

Using data provided in the January 2000 Congenital Malformations Surveillance Report from the National Birth Defects Prevention Network (NBDPN, '00), we identified differences in surveillance methodologies among states and attempted to evaluate the impact these differences may have on the reported prevalence rates. Because so many differences exist between the states' registries, the *Teratology* report discouraged the combining of prevalence rates to generate overall rates for the country. In fact, because surveillance systems may change over time, changes in rates of specific defects over time, even within states, should be evaluated cautiously. We hypothesized that while some variability is expected because of differences in the true prevalence of birth defects, extreme differences are more likely to result from differences in surveillance practices. We compared rates across the surveillance systems, not to identify extremes in the reported rates for a particular defect, but to identify the possible sources of variability in reporting between systems.

We evaluated defects representing a range of likelihood of diagnosis at birth and diagnostic certainty based on physical exam (Table 1). We then compared prevalence rates for these defects across state registries. For example, gastroschisis, spina bifida, anencephaly, and bilateral renal agenesis are easily diagnosed at birth. In contrast, because of the increasing frequency of early discharges following birth, some infants with hypoplastic left heart syndrome will be discharged as newborns before that condition is diagnosed. Some congenital heart defects, such as ventricular septal defects and atrial septal defects, are often not diagnosed until after the newborn period. To identify additional sources of variability, registries were stratified by mode of ascertainment, age limit at the time of diagnosis, and outcome of pregnancy, where possible (Table 2).

We also reviewed and describe the policies of two large health surveillance systems, the European Registration of Congenital Anomalies and Twins (EUROCAT) and the North American Association of Central Cancer Registries (NAACCR) (Table 3). The procedures established by these organizations may aid in efforts to

TABLE 2. Range of selected birth defects by surveillance system characteristics (rates per 10,000 births)

Condition	Case ascertain method			Age at diagnosis		Elective terminations	
	Active	Passive	Active and passive	0 to 1 year	0 to 2 or greater	Yes	No
Anencephaly	0.5–5.1	0.1–3.8	0.4–3.6	1.0–7.7	1.7–9.3	1.0–5.0	0.1–5.1
Atrial Septal Defect	11.1–125.9	18.8–64.9	10.6–36.2	22.5–32.3	10.6–125.9	36.3–125.9	0.7–64.9
Gastroschisis	0.8–4.7	1.1–5.8	1.2–5.4	0.8–4.7	1.2–5.8	3.2–3.8	0.8–5.8
Hypoplastic Left Heart Syndrome	1.0–3.2	0.0–2.9	1.3–2.7	0.0–3.2	0.74–3.2	1.0–2.9	0.0–3.2
Hydrocephalus	2.7–25.4	1.0–8.2	0.0–8.9	1.0–14.0	0.0–25.4	5.1–25.4	1.0–10.6
Renal Agenesis	3.0–35.7	0.8–5.0	0.7–3.8	0.8–4.7	1.2–35.7	5.0–8.3	0.7–35.7
Spina bifida	1.7–9.3	3.0–7.7	2.6–6.4	1.0–7.7	1.7–9.3	1.7–9.3	1.0–8.8
Tricuspid Valve Atresia and Stenosis	0.12–98.5	1.1–7.7	0.38–5.8	0.0–98.5	0.7–28.4	1.6–98.5	0.0–28.4

TABLE 3. EUROCAT Prevalence rates, 1995–1996 (per 10,000 pregnancies)

Congenital Anomaly	Range of reported prevalence rates
Gastroschisis	0.2–4.1
Hypoplastic Left Heart Syndrome	0.4–5.5
Congenital Heart Disease	26.0–126.9
Spina bifida	1.1–20.7
Unilateral Renal Agenesis	0.7–10.8
Bilateral Renal Agenesis	0.4–2.8
Hydrocephalus	1.4–16.1
Anencephaly	0.5–9.0

identify strategies for increasing uniformity in birth defects case ascertainment.

RESULTS

The conditions examined in this report are shown in Table 1, from that with the least variability to that with the highest, among birth defects registries in 26 states (NBDPN, '00).

Potential sources of variability in reported rates

Case ascertainment methods. We hypothesized that a portion of the variability in prevalence rates across monitoring systems may result from differences in active versus passive case ascertainment methods. In fact, we expected the reported rates to be higher among systems with active case ascertainment.

Differences across case ascertainment methods (active, passive, or combination of both) in prevalence rates were larger for some conditions than others. For instance, the reported rates of anencephaly and spina bifida were quite similar across the modes of case ascertainment (Table 2). This supports the results of a study that compared the prevalence rates of spina bifida reported by 16 state birth defects surveillance programs and the Centers for Disease Control and Prevention's (CDC's) Birth Defects Monitoring Program. Similar prevalence rates and trends were reported by active and passive systems (Lary and Edmonds, '96). In contrast, the prevalence rates for atrial septal defects (ASDs), tricuspid valve atresia and stenosis, and hydrocephalus reported by active surveillance systems varied more than those reported by passive systems or for those systems using both passive and active methods of ascertainment. For all defects except gastroschisis, the highest prevalence rates were reported by active surveillance systems (Table 2).

Case ascertainment efforts may vary more for active systems than passive systems, or active systems may have more misclassification errors. In fact, completeness of case ascertainment may vary widely across all registry types, because of differences in expertise, training, system auditing, resources, and legislated priority of ascertainment. Those registries, active or passive, with more assertive ascertainment methods, multiple reporting sources, and overall resources may be much more successful in identifying the majority of cases.

Case ascertainment sources. Sources of case ascertainment may also influence variability in birth defect prevalence rates. Some registries include both inpatient and outpatient facilities in their surveillance, while others include only inpatient facilities. This distinction is not likely to affect the reported prevalence of conditions that are more easily diagnosed at birth, such as gastroschisis, or those requiring intensive medical or surgical intervention, such as many congenital heart defects. However, conditions that may be entirely diagnosed and managed through outpatient primary care or subspecialty clinics may be missed by systems that monitor only inpatient facilities. For example, a small ventricular septal defect may be diagnosed and treated entirely through a private pediatrician. Registries that monitor both inpatient and outpatient facilities may monitor any or all of a wide variety of outpatient services, most often pediatric specialty clinics. Unless a registry monitors all possible sources, including private physicians, a potential remains for cases to be routinely missed.

Case inclusion criteria. Variability in prevalence rates may be influenced by case inclusion criteria, which often vary widely from one birth defects surveillance registry to another. Some variable criteria are the inclusion of elective terminations, the age at diagnosis, requirements for diagnostic precision, and the severity of the defect reported. Additionally, simple differences in coding across registries may influence whether certain cases are included in specific analyses.

Inclusion of elective terminations and stillbirths. Table 2 reports the prevalence rates of the selected defects stratified by registries that include elective terminations in their surveillance and those that do not. Most systems do not include elective terminations. States that reported the highest prevalence rates of spina bifida have active surveillance systems that ascertain elective terminations. This source of variability in ascertainment is complicated by the definition and inclusion of stillbirths in calculating birth defect rates (International Clearinghouse for Birth Defects Monitoring Systems, '91). Many malformed fetuses are premature, or are stillborn, yet may not be classified in many surveillance systems. The inclusion of information on stillborn infants varies widely across NBDPN registries. The extreme variation made it difficult to include this as a factor in the analysis. Not all of the registries in the NBDPN include information about stillbirths, and registries apply a wide variety of criteria regarding weight and gestational age in defining stillbirths.

Age limit at time of diagnosis. The age of inclusion varies widely among registries and may affect the reported prevalence of birth defects. Some registries ascertain cases that are diagnosed in the first year after birth, while other systems extend the age of inclusion to two years or even longer. For conditions usually diagnosed in the neonatal period (28 days) rates should be comparable across systems that have different age-inclusion criteria. For example, the prevalence rates of gastroschisis are similar across registries whether the age of inclusion is one year or greater (Table 2). We would expect registries that include cases diagnosed after infancy to report increased prevalence rates for conditions such as fetal alcohol syndrome (FAS) that frequently are not diagnosed until after the first year. For example, the differences in the prevalence of FAS reported by California and Oklahoma may be partially due to differences in the age of inclusion criteria utilized by these two active surveillance systems. California includes only cases diagnosed in the first year after birth and reported a prevalence of 0.82 in 1995. Oklahoma includes cases diagnosed during the first two years and reported 3.6 cases per 10,000 births in 1996.

Methods of diagnosis confirmation. Many opportunities exist for misclassification of diagnoses in birth defects registries. For example, a 1990 study within one registry found that 10% of abdominal wall defects were misclassified or were recorded incorrectly (Torfs, '90). The most frequent misclassifications were gastroschisis recorded as ruptured omphalocele or limb-body wall complex recorded as gastroschisis. The National Birth Defects Prevention Study is attempting to limit misclassification errors by requiring review of all cases by a group of clinical geneticists specialized in clinical dysmorphology. Each of these cases is reviewed by a clinical dysmorphologist at each individual center and at the CDC to ensure uniformity across centers.

Diagnostic precision. Most registries require a physician diagnosis of a birth defect, but some also require a confirmatory test for specific conditions. For example, before 1998, the Arkansas Reproductive Health Monitoring System included any physician diagnosis of a *probable* or *definite* ASD, regardless of evidence of a confirmatory echocardiogram or other "gold standard." Reliance only on physician diagnoses may result in greater misclassification of cases than if a confirmatory diagnostic test is required for inclusion. Thus, one may expect an artificial elevation of the prevalence rate reported by systems that do not require confirmatory evidence of conditions diagnosed by physical examination alone. A related source of variability is that some states report birth defects listed by a physician as *possible* or *probable*, while other states include only those listed as *definite*.

DISCUSSION

Influence of the national birth defects prevention network

In 1996, representatives from several state birth defect registries recognized the increasing need for a collective surveillance effort and established the NBDPN. The objectives of the NBDPN include improving the quality of birth defects surveillance, providing technical assistance for the development of uniform methods of data collection, and facilitating the communication and dissemination of information related to birth defects. Despite the successes of the NBDPN, a need remains for widely accepted standards and guidelines to ensure completeness, accuracy, reliability, and minimum data quality for congenital malformations monitoring programs in the United States.

The NBDPN established the Surveillance Guidelines and Standards Committee to develop a standards manual for birth defects registries. Using standards and guidelines developed by other established health registries, the Committee is developing recommendations regarding legislation, case definition, case ascertainment methods, data quality and management, statistical methods, and data collection variables. Recognizing the importance of this project, the CDC allocated funds to hire an epidemiologist to work with the Committee and facilitate the development of the manual. This manual will address many of the concerns we present herein, if state registries adopt the standards.

Examples of other health registries

The NBDPN may draw from the experience of other health registries that have made progress in standardizing ascertainment methods across local registries.

EUROCAT. The European Registration of Congenital Anomalies and Twins (EUROCAT) was established in 1979 as a Concerted Action of the Commission of the European Communities (EUROCAT, '97; EUROCAT, '99). The goal was to create a network of population-based registries of children with congenital anomalies in European countries. Objectives of the EUROCAT program include establishing baseline rates of congenital anomalies, monitoring trends and mapping geographic variations, and evaluating the impact of prevention programs. Local case identification procedures are modified to facilitate pooling of data for analysis and surveillance.

For inclusion in EUROCAT, registries must meet several requirements. The registry must be population-based, with the population defined by place of residence, not by place of birth, or location of hospital. The registry must use multiple sources for active case ascertainment. Because some anomalies, particularly cardiac anomalies, may not be diagnosed at birth, the registry must be able to extend its methods to include all cases diagnosed after the newborn period. All registries included in EUROCAT report data using an identical coding system. Up to eight anomalies may be coded for each case, but minor anomalies are not recorded unless they occur in combination with a major anomaly. These requirements for membership in EUROCAT enable comparisons between registries and allow for the development of informative statistics and publications about congenital anomalies on the European continent. Thirty-nine centers in 17 countries participate in EUROCAT, and these registries monitor approximately 430,000 births per year.

EUROCAT rates are reported in three rate groups: live births only, live births and fetal deaths, induced abortions, or a composite rate of all three categories. We used the composite rate to assess differences in the reported prevalence rates of selected conditions (Table 3). For unilateral renal agenesis, per 10,000 pregnancies, the reported EUROCAT prevalence rates ranged from 0.7 in northeastern Italy to 10.8 in the Basque country registry and for bilateral renal agenesis the range was from 0.2 to 3.1 per 10,000 pregnancies. For gastroschisis, the reported prevalence rates ranged from 0.2 in southern Portugal to 4.1 in the Mainz region of Germany. The EUROCAT prevalence rates for congenital heart defects as a whole ranged from 26.0 to 126.9, a difference so large that variation beyond true differences in the prevalence rates is suggested.

Although it is not appropriate to make a direct comparison of prevalence rates reported by EUROCAT and those obtained by the NBDPN, it is important to consider the possible sources of variability in data reported for each type of birth defect. The prevalence rates reported for any particular defect may be influenced specifically by ascertainment methods and diagnostic inclusion criteria.

NAACCR. Established in 1987, the mission of North American Association of Central Cancer Registries (NAACCR) is

> *"To support and coordinate the development, enhancement and application of cancer registration techniques in population-based groups, so that quality data may be used for cancer control and epidemiologic research, public health programs, and patient care to reduce the burden of cancer in North America."*

To accomplish this goal, NAACCR provides standards for diagnoses, data quality, staff guidelines, case-finding, patient follow-up, and reporting sources. The publication *NAACCR Standards for Cancer Registries* consists of four detailed volumes of ideal registry standards, from legislation and case inclusion criteria to data collection and staffing. Each standard is presented as something that a registry *must*, *should*, or *may* do to operate effectively.

The NAACCR has a Registry Certification Committee and a Uniform Data Standards Committee. The Certification Committee is responsible for establishing certification standards and evaluating registries to determine whether they meet those standards. Because resources for health registries may vary widely, the Certification Committee focuses on the quality of data collected rather than on the collection methods used. The Uniform Data Standards Committee is for ensuring the comparability of data across registries. Public health priority and legislative mandate and fiscal support affect the resources available to all health registries.

A report by the NAACCR published in April 2000, using data from 1993 through 1997 (Chen et al., '00), presented age-adjusted cancer rates by physical site for males and females, to obtain a composite measure across registries. The prevalence rates reported are generally very similar across states. For all cancers in females (per 10,000 individuals), the incidence rates ranged from 27.8 in Utah, to 38.2 in Rhode Island. For all cancers in males the rates ranged from 39.0 in Utah to 54.3 in Michigan. Although some variability in rates exists, the differences are not great. Such consistency in rate reporting should be a goal in national ascertainment of birth defects across registries.

RECOMMENDATIONS

Because state legislators mandate access to data and often allocate funds required to operate registries, complete centralization of U.S. birth defects surveillance may not be reasonable. Nevertheless, a concerted nationwide effort, in conjunction with those of local registries, is needed to develop and sustain a successful network of surveillance programs. The national effort will develop from the experience of local programs, and local programs may benefit from the extensive resources of the NBDPN.

It is essential that standards instituted for birth defects surveillance systems in the United States are acceptable to registries with different modes of case ascertainment. Each potential source of variation should therefore be considered individually for each registry. Because of limited resources, the status of a registry as passive versus active may not be easily changed. However, other factors, especially case inclusion criteria, may be more easily modified in an effort to attain uniformity across registries.

Etiologic heterogeneity in birth defect cases with similar phenotypes is well established. The presence of associated defects, and accurate clinical descriptions of defect types should be used in classifying birth defect cases into etiologically and pathogenetically homogeneous groups. We recommend that in developing standards for birth defect ascertainment that allow for comparability across registries, a sentinel group of defects be chosen as the basis for comparability. These defects can be determined on the same bases used by the National Birth Defects Prevention Study, including consistency in ease of classification, diagnostic criteria, and the consideration that the defect is considered a "major" defect. A birth defect registry can report on defects outside of the shared group of defects, but consistency in inclusion criteria for the shared set of defects will allow for accurate reporting and will impose minimal changes to existing registries or those currently being formed.

On the basis of the prevalence rates and the surveillance system characteristics, we suggested some possible explanations for the variability in the reported rates of specific birth defects. However, we cannot make definitive recommendations to reduce the variability of reporting for specific defects because the differences are multifactorial in origin.

This analysis represents a beginning step in evaluating and reducing variability in national birth defects surveillance. This work must be extended to produce necessary changes in many state registries. Productive discussions on this topic should continue to be part of the agenda of the NBDPN and all those who are working toward preventing birth defects. During the last several years, federal agencies including CDC and the National Institutes of Health have demonstrated an increased interest to fund birth defects surveillance, prevention and research projects. Now is a good time to take advantage of the growth in this area by developing a standardized means to track the birth defects across the country. Without valid data collection methods, intervention programs designed to prevent birth defects will not be fairly evaluated.

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