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CALIFORNIA
BIRTH DEFECTS
MONITORING
PROGRAM

INVESTIGATING BIRTH DEFECTS CLUSTERS:

A Systematic Approach

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Investigating Birth Defects Clusters:

A Systematic Approach

Jackie White Wynne, BA
John Harris, MD, MPH
Sonja Bentley, MA
Liz Stierman, MS

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A cluster reported by a health professional or other community member may provide the first clues leading to discovery of a teratogen, an environmental cause of birth defects. The California Birth Defects Monitoring Program takes all reports seriously. We investigate clusters to learn more about birth defects causes and to address public concerns. This document explains the procedures followed in evaluating reports and serves as a reference for future use.

Cluster reports by health professionals and parents may help identify birth defects causes.

The California Birth Defects Monitoring Program takes seriously and encourages reports of suspected clusters of *birth defects*.[1] A *cluster* is more than the expected number of cases of a birth defect in a population group for a defined geographic area and for a specific period. If you suspect you are seeing a cluster, please refer to Appendix B to report.

WHY STUDY CLUSTERS?

There are scientific and public health reasons for investigating suspected clusters:

- **Cluster investigations can generate new clues about causes of birth defects** – Because most birth defects cannot be explained, generating ideas about possible causes is essential. Cluster investigations can be important sources of new information. Solid hypotheses resulting from cluster investigations can then be tested in large *epidemiologic studies*.
- **Cluster investigations can allay community concerns** – When an investigation shows no increased risk, the public is reassured. Other times the investigation may not find a cause, but it may rule out environmental concerns, such as tainted wells, factory emissions and hazardous waste sites. Even if a cluster is not verified, an investigation can help focus attention on legitimate environmental problems that can be addressed by other agencies.

[1]Terms in italics are discussed in the Glossary, Appendix A.

WHO REPORTS CLUSTERS?

Ideas from health professionals and parents have had great scientific merit in the past. They are likely again to help identify new *teratogens*.

- **An alert health professional is often the first to notice a possible cluster** – Clinicians observed and reported clusters involving cataracts caused by rubella (German measles), limb defects in babies whose mothers took thalidomide, and spina bifida caused by valproic acid.

  Health professionals are the first to hear the concerns of parents. They are in the best position to have a clinical "feel" that something unusual is happening. Their access to relevant medical records allows them to begin searching for clues, and they often have good ideas about possible teratogens.

  Some clinicians initiate their own studies to evaluate suspected malformation causes. The Program can provide data or other assistance – our goal is to encourage and advance all efforts to identify new teratogens.

- **County public health officials may note changes in birth defects rates** – When profiling local health data or monitoring environmental conditions, the health department may look at birth defects as one indicator of public health. In addition, they are likely to receive reports concerning suspected occupational or other hazards. The Program can provide *expected rates* and determine if birth defects are linked to identified environmental concerns.

- **Parents and other community members also report clusters** – Parents played instrumental roles in linking both thalidomide and rubella with the birth defects these exposures caused.

  Concerned parents, news reporters and public officials often understand their environments better than anyone else. Community members have helped in cluster investigations by soliciting the cooperation of other parents, researching exposures and providing historical knowledge about relevant local events.

Characteristic elements seen in earlier teratogen-caused clusters provide the framework for today's investigations.

Birth defects, like other health outcomes, often occur in clusters. In a large state like California, many birth defects clusters occur every year. Most happen by chance alone due to normal fluctuation of birth defects rates over time.

The purpose of a cluster investigation is to identify the rare cluster caused by a teratogen – an environmental exposure which causes birth defects. Once a teratogen is identified, history teaches us that it often can be removed or avoided, preventing many birth defects.

SCIENTIFIC PRECEDENT

Many human teratogens have been discovered through cluster investigations –

- In 1941, an Australian ophthalmologist treated several babies with congenital cataracts. Because all had the same rare defect, he gave serious thought to a common etiology. Based on the babies' birthdates, he estimated that their embryonic development corresponded with the height of the 1940 rubella epidemic. From this clue, scientists later verified this virus as a teratogen.
- Between 1959 and 1962, several thousand babies were born in Europe and Australia with missing arms and/or legs. Two astute clinicians and a determined parent linked the children's problems to a sedative their mothers had taken during pregnancy. The drug was thalidomide.

- In the 1980s in France, a physician providing genetic counseling to parents of children with spina bifida noticed many of the mothers had epilepsy treated with valproic acid. Her review of data from existing birth defects registries in France and Italy confirmed the association between valproic acid and spina bifida.

CHARACTERISTIC ELEMENTS

The framework for investigating birth defects clusters is based on those involving rubella, thalidomide and valproic acid. All had 3 elements in common, now regarded as the attributes of a cluster caused by a teratogen:

- Large excess of the same defect
- Biologically plausible exposure among most cases AND
- Characteristic pattern of defects.

Large Excess of the Same Defect

The teratogens discovered through cluster investigations have all been potent and therefore caused large increases in relevant birth defects. The rate of limb defects in babies prenatally exposed to thalidomide was 240 times the expected rate.[1] In babies exposed to valproic acid, spina bifida increased 40 times.[2]

Scientists assume there are subtle teratogens which cause less dramatic increases. The less potent the teratogen, the more cases needed to verify an association.

Cluster reports usually do not contain enough cases to discover an association between a mild teratogen and a birth defect. Experience shows that if a teratogen increases the occurrence of a defect 10 or more times the expected rate, a cluster investigation may be able to detect an association. A cluster investigation cannot detect a teratogen causing a lesser increase. Only large epidemiologic studies evaluating hundreds or even thousands of pregnancies are likely to detect these mild teratogens.

Biologically Plausible Exposure

People are exposed to many potentially harmful substances each day, however, most do not result in adverse reproductive outcomes. Several factors render an exposure a biologically plausible birth defects cause:

- **Findings from human and animal studies:** Biological plausibility is established when epidemiologic studies, case reports or animal studies suggest an increased risk with particular exposures.

  Isotretinoin (Accutane), a vitamin A derivative used to treat severe cystic acne, was known to cause birth defects in several species of animals before receiving FDA approval for human use. Consequently, when mothers taking isotretinoin had children with birth defects, scientists were quick to focus their investigation on this medication.

[1]Knightly P, Potter E, Wallace M (1979): *Suffer the Children: The Story of Thalidomide*, New York: Viking Press, page 99.
[2]Robert E, Rosa FW (1983): Valproate and birth defects (letter), *Lancet* 2:1142.

People are exposed to many potentially harmful substances each day; however, most are not biologically plausible birth defects causes.

- **Timing:** A teratogen usually causes structural defects during the critical period of organ formation, 2-12 weeks after fertilization. Within this sensitive period, narrower time frames have been identified pinpointing the development of specific organ systems. If an exposure occurs after the affected organs have formed, it is not a biologically plausible cause. For example, the lip is formed by the 42nd day after fertilization. Consequently, an exposure after that time could not cause cleft lip.

- **Pathway:** There must be a verifiable route by which the pregnancy was exposed. In the 1950s, Minamata Bay, Japan was contaminated with methyl mercury. Most mothers who had children with mercury-related cerebral palsy had eaten poisoned fish from the bay.

  Many people are worried about toxic waste dump sites close to their homes. However, if negligible amounts of these chemicals are in the air or drinking water, it is unlikely a pathway exists for pregnancy exposure.

  In general, an agent must be able to cross the placenta for the pathway to be complete. This capability is determined by the substance's chemical characteristics.

Characteristic Pattern of Defects

When a number of pregnancies are exposed to a teratogen, all birth defects will not increase – instead, a characteristic pattern of defects results. Each teratogen acts on specific tissues and organs. The vulnerable sites are different for each agent, resulting in distinctive and characteristic patterns of malformations.

The pattern may include one or more major birth defects, as well as characteristic facial features or minor anomalies. Often the teratogen's presence is recognized because of increased occurrence of a rare birth defect, such as the epidemic of limb defects seen with thalidomide. Table 1 shows some examples of patterns associated with specific teratogens.

Potential Teratogens

Environmental causes of birth defects may include anything to which the pregnancy is exposed: illness; infection; medications; chronic health conditions; alcohol and illicit drugs; chemicals in the workplace, home, community and hobbies; dietary deficiencies and supplements; starvation.

The diversity of known teratogens demonstrates that an agent does not have to be harmful to the mother to cause birth defects. Therapeutic drugs such as isotretinoin and valproic acid can damage a developing embryo. Most of the mothers in Minamata, Japan who ate contaminated fish suffered no ill effects, yet their babies were born with severe neurological defects.

No teratogen causes birth defects in 100% of those exposed. Isotretinoin, one of the most potent teratogens, causes defects in about 25%. The fact that similar exposures can result in no effect, mild or very serious structural defects is thought to be related to genetic differences in the mother and embryo as well as timing of the teratogenic exposure.

Patterns Associated with Some Known Teratogens

Alcohol	Pre- and postnatal growth retardation; microcephaly; characteristic facial features, including small eyelid openings, thin upper lip and smooth philtrum; developmental disability.
Rubella	Heart defects, cataracts, chorioretinitis, deafness, developmental disability.
Accutane	Ear anomalies, including absence or stricture of auditory canal, absence of auricle and microtia; thymus abnormalities; reduction malformations of the brain; hydrocephalus; heart defects.

Table 1

A multidisciplinary team follows up all reports.

EXPERIENCE AND RESOURCES

The California Birth Defects Monitoring Program began evaluating clusters in 1983. Since then staff have investigated over 140 reports.

A multidisciplinary team follows up all cluster reports. Investigations are initiated by the community liaison, who serves as a single point of contact and maintain ongoing communication with the person reporting and the public. The team also includes a pediatrician, geneticist, epidemiologists and data collection specialists.

The Program's birth defects *registry* is the key to efficiently and accurately evaluating perceived clusters. Reports can be assessed in the context of expected rates in the local area, selected population groups and the general population. The registry ensures timely identification and verification of cases.

CONDITIONS INVESTIGATED

The Program investigates suspected clusters of more than 200 structural birth defects for which the causes are unknown or not well understood. These include abnormally developed internal and external organs and limbs (heart or kidney defects, cleft lip, missing limbs or digits); chromosome abnormalities (Down syndrome and trisomy 18); and syndromes (fetal alcohol syndrome).

PUBLIC INFORMATION & COMMUNICATION

Community Response

In most instances the public is not widely aware that a suspected cluster has been reported and is being investigated. However, when they are, we recognize that an investigation can raise considerable anxiety. The community may be frustrated that long-standing concerns have been ignored and may be distrustful of public agencies. Prospective parents may feel anxious about the lack of available information and the safety of their neighborhood or workplace.

The Program addresses public concerns about the investigation process and outcome by:

- Answering questions
- Discussing how and when the investigation will proceed
- Providing realistic expectations about possible outcomes
- Communicating investigation status regularly
- Sharing findings openly
- Participating in community meetings and/or using a panel of community representatives in the investigation
- Working closely with the local health department
- Working with the media to facilitate communication.

Progress Reports

A cluster investigation can take 6 months to 2 years, depending on how many facilities have to be visited, the number of cases and how much routine data has already been collected. The Program gives periodic verbal and written updates to the person reporting the cluster, the public health officer and other interested persons.

Final Report

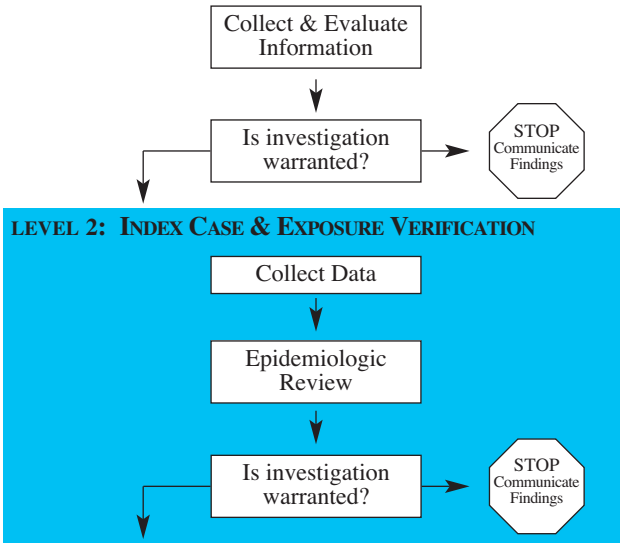
When an investigation is concluded, staff prepare a written report summarizing the process, findings and final action. Findings are conveyed by phone and in writing to the person who initiated the report and to the public health officer. If there was communication with parents or other community members, they receive written findings as well. The final report is a public document available at no cost.

Confidentiality

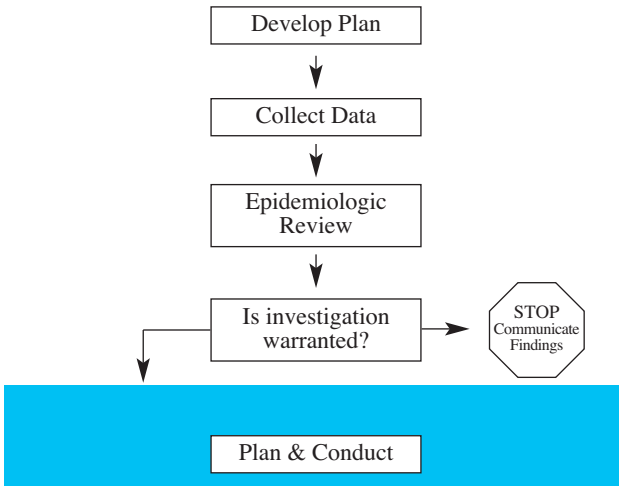
Under state law all identifying information from the registry, cluster investigations and scientific studies is kept strictly confidential. Program staff follow rigorous procedures to safeguard confidentiality.

The California Birth Defects Monitoring Program has developed a systematic procedure for investigating reports. The protocol does not prescribe a rigid process, rather it is a set of guidelines enabling the scientific team to assess the public health significance of each report. A decision to stop or continue is made at the end of each level based on criteria designed to distinguish clusters caused by teratogens.

LEVEL 1: INITIAL REPORT EVALUATION



LEVEL 3: COMPLETE CASE ASCERTAINMENT



POSSIBLE OUTCOMES

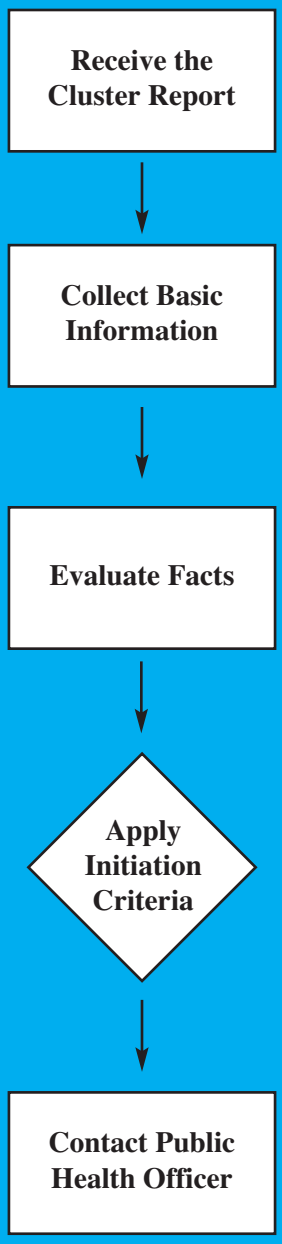
No Further Investigation

- **No excess** – The California Birth Defects Monitoring Program finds no excess in 95% of investigations. The birth defects most frequently reported are congenital heart defects, Down syndrome, neural tube defects and oral clefts. Because these conditions occur more frequently than is commonly realized, normal patterns of occurrence may seem excessive.
- **An excess less than 10 times the expected rate where the cases do not have an exposure in common** – In this instance, experience dictates the cluster is usually due to normal fluctuation in rates, improved diagnosis, changed referral patterns or a subtle teratogen.

Further Epidemiologic Study

- **A biologically plausible exposure among many of the cases, regardless of the rate** – Since generating hypotheses about undiscovered teratogens is a main purpose of studying clusters, those where most of the mothers have the same exposure and the defects are the same or developmentally-related are of particular interest. In this instance, an investigation may be warranted with as few as 3 cases.
- **An excess of more than 10 times the expected rate** – There is a strong possibility this cluster is related to an undiscovered teratogen, or increased exposure to a known teratogen.

INITIAL REPORT EVALUATION



LEVEL 1: INITIAL REPORT EVALUATION

1.1 Health professionals and community members may report suspected clusters by calling the community liaison.

1.2 The community liaison asks a series of questions to evaluate the initial report (Appendix B). Crucial to developing the case definition are:

- Information on each *index case,* including name of mother and baby, date and hospital of birth, diagnosis
- Ideas about exposures or possible teratogens.

1.3 The community liaison evaluates the information. Often the cluster reflects normal occurrence patterns – birth defects are more frequent than many people realize. Table 2 shows the frequency of some malformations commonly reported in suspected clusters.

The report should concern birth defects which are developmentally-related, as this is a characteristic element of a teratogen-caused cluster. Conditions that look similar, such as limb reduction defects, may actually be the result of very different processes in structural development. Others, such as neural tube defects, may appear different clinically but are related developmentally.

1.4 The Program will initiate an investigation if:

- At least 3 cases exist with the same or developmentally-related birth defects
- There is sufficient information to verify the index cases and to establish the time period, geographic area and/or population group AND
- No other immediate explanation is evident.

1.5 If an investigation is initiated, the community liaison contacts the public health officer, solicits information and discusses roles and responsibilities for conducting the investigation.

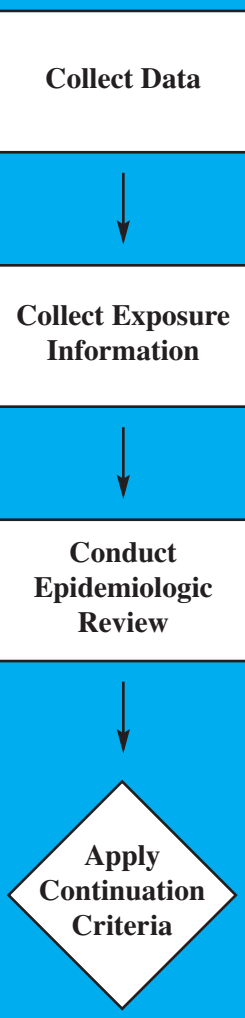
RATES OF COMMON BIRTH DEFECTS
PER 1000 LIVE BIRTHS

Congenital heart defects	5.91
Oral clefts	1.73
Down syndrome	1.06
Neural tube defects	0.67
Limb defects	0.67

California Birth Defects Monitoring Program registry data, 1983-1989

Table 2

INDEX CASE & EXPOSURE VERIFICATION



LEVEL 2: INDEX CASE & EXPOSURE VERIFICATION

2.1 To verify index cases born in the current or previous year, data collection staff visit every hospital where the children were treated and review medical records. Demographic and complete diagnostic information is abstracted using the Program's standardized procedures. Cases born 2 or more years prior can be retrieved from the Program's computerized registry file.

2.2 Medical records document alleged exposures or provide new exposure information. Data collection specialists review these records and note all relevant information.

Environmental health and infectious disease specialists in the local health department help verify alleged exposures such as toxic factory emissions or tainted water. Whenever possible, the boundaries of an exposure are defined so they can be compared to the geographic distribution of cases.

2.3 Epidemiologic staff review index case and exposure information. Cases are excluded for any of the following reasons:

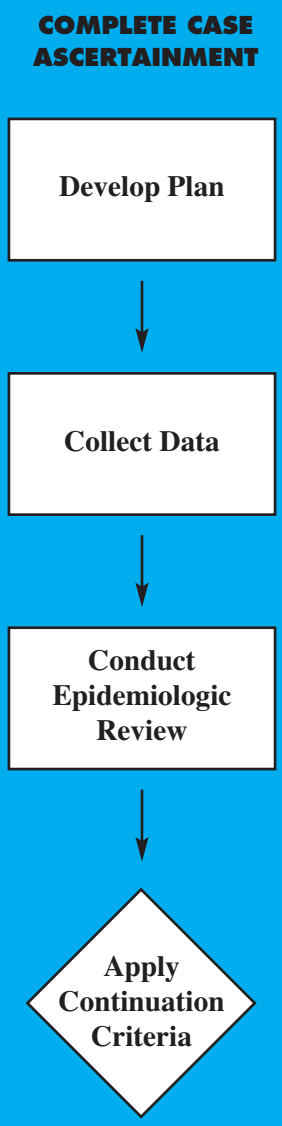
- Residence is outside the geographic boundaries of the cluster
- Complete diagnostic information rules out the initial diagnosis
- The malformation is part of an underlying condition (congenital heart defect in a child with Down syndrome)
- The condition cannot be systematically diagnosed (a heart murmur of no functional significance would not be considered a case of congenital heart disease)
- Physical findings do not meet specific diagnostic criteria established by a geneticist or appropriate specialist.

Epidemiologists evaluate the evidence of a cluster in the context of their existing understanding of the condition and the population group in question. They verify that cases meet the initial case definition and calculate whether the rate is unusual.

2.4 Staff will continue an investigation if analysis of the index cases indicates:

- There are at least 3 cases with the same or developmentally-related birth defects AND
- Case verification supports evidence of a cluster.

The investigation is discontinued if the above criteria are not met.



LEVEL 3: COMPLETE CASE ASCERTAINMENT

3.1 If the Level 2 continuation criteria are met, staff will develop a plan for ascertaining all children meeting the case definition. The elements of the case definition may be revised to thoroughly evaluate what is occurring. Diagnostic criteria may be broadened to determine whether the occurrence of related conditions has increased. A teratogen causing an increase in Down syndrome also might cause an increase in other trisomies. Similarly more than one congenital heart defect might have the same cause.

3.2 The sources for data collection are the same as in Level 2. Birth, death and fetal death records may be examined for additional demographic information.

3.3 An epidemiologist and, where appropriate, a pediatrician and/or geneticist review all data to confirm compliance with the case definition. Cases are excluded for any of the reasons listed in section 2.3.

A "worst case" approach is used to calculate the *observed rate* in the cluster population: the shortest meaningful period and/or smallest geographic area are used to determine the denominator.

The observed rate is compared to the expected rate for a similar population. The registry generates expected rates by race, sex, parental age, geographic area and time. When available, prior year rates for the condition and geographic area in question are examined for comparison.

The cases are plotted on a map to see if there is geographic clustering or relationship to an alleged exposure. Evidence of seasonal patterns or other time clustering are assessed.

Epidemiologists analyze the data to evaluate the public health significance of the suspected cluster. They address these questions:

- Is the apparent increase meaningful?
- Are there known epidemiologic patterns which may provide clues for analysis?
- Are certain agents suspected of contributing to the defect?
- What is the vulnerable period for the embryologic development of this defect?

3.4 An epidemiologic study will be initiated if the data meets these criteria:

- The birth defects are the same or developmentally-related AND
- There are at least 3 cases and a biologically plausible exposure which the cases have in common, OR
- 5 cases and an observed rate of more than 10 times the expected rate.

The investigation is discontinued if the above criteria are not met. The community liaison will monitor the situation for at least a year to determine if rates are elevated or if community concern continues.

LEVEL 4: EPIDEMIOLOGIC STUDY

If the cluster warrants further evaluation, the investigation is assigned to a team of epidemiologists. They design a study based on current scientific knowledge about the birth defect in question and the alleged exposure. The study may involve interviewing parents, obtaining biological samples (such as blood) and/or collecting environmental samples. It may be useful to examine data from other similarly exposed areas in the county or in other parts of California.

Birth defects: For the registry and cluster investigations, the Program evaluates major structural abnormalities diagnosed by age 1. Major categories of the over 200 conditions included are found in the International Classification of Disease (ICD) sections 740-759.9.

Structural defects include disabilities due to abnormally developed internal and external organs and limbs (heart or kidney defects, cleft lip, missing limbs or digits); chromosome abnormalities (Down syndrome and trisomy 18); and syndromes (fetal alcohol syndrome). The causes for these conditions are unknown or not well understood.

Cluster: More than the expected number of birth defects cases in a population group for a defined geographic area and a specific period. Birth defects clustering may be the result of a teratogen, normal rate fluctuation over time, improved diagnosis or changed referral patterns.

Epidemiologic study: A research study evaluating the patterns of disease occurrence in populations and the factors that influence these patterns.

Large-scale case-control studies are effective for testing hypotheses about causative and protective factors for birth defects. Information comes from data analysis, personal interviews with parents and biologic sampling.

Expected rate: The number of cases we expect to occur in a given population. The Program's registry provides expected rates by race, sex, parental age, geographic area and time.

Index cases: The cases which first suggest clustering. The initial case definition is determined by characteristics of these cases.

Observed rate: The actual number of cases we observe in a given population. The larger this population, the more reliable the rate.

Registry: The California Birth Defects Monitoring Program's computerized file containing data on all children diagnosed by age 1 with any of over 200 major structural abnormalities. All data are confidential insofar as the identity of an individual patient is concerned.

Staff regularly visit hospitals, genetic centers and labs to collect data. They review medical records and abstract both diagnostic and demographic information following standardized procedures. Demographic information is crosschecked with birth, death and fetal death records.

Teratogen: An environmental exposure which causes birth defects. In this context, the environment includes anything to which the pregnancy is exposed: illness; infection; medications; chronic health conditions; alcohol and illicit drugs; chemicals in the workplace, home, community and hobbies; dietary deficiencies and supplements; starvation.

Program staff elicit as much relevant information as possible when a cluster is reported – responses to all questions are not expected.

1. Person Reporting – name, title, affiliation, address, phone number.
2. How did you become aware of this cluster?
3. What is the birth defect of concern?
4. In whom are these birth defects occurring?

   In what population group?

   In what setting?

   In what time period? How many cases are usually seen in this time period?
5. What ideas do you have about what may have caused these birth defects?

   What do the mothers have in common (race, age, worksite, neighborhood, other exposures)?

   What environmental events/concerns/hazards occurred during the relevant time period? How might the pregnancies have been exposed?
6. Have you discussed your concerns with anyone else (such as local health officials)?
7. Who else can I contact for more information?
8. Index case information – for each case:

   Name

   Current address & address during gestation

   Date and hospital of birth

   Other hospitals where treatment was received

   Diagnosis

   Other history: parents' occupation, medical conditions, other exposures, family history of birth defects

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The California Birth Defects Monitoring Program –
a public health program devoted to finding causes of birth defects –
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and jointly operated with the March of Dimes Birth Defects Foundation.

www.cbdmp.org