Appendix D

Surveillance for Birth Defects

Rocky Mountain Arsenal Medical Monitoring Program Recommendation
Surveillance for Birth Defects

I. Objectives: Use the Colorado Department of Public Health and Environment's (CDPHE) existing birth defects registry data base (Colorado Responds to Children with Special Needs, CRCSN), established data collection capabilities and community referral system to satisfy the following objectives (see Figure 1):

Objective 1: Establish baseline rates for birth defects occurring in the communities surrounding the Rocky Mountain Arsenal (RMA);

Objective 2: Describe and analyze rates for significant temporal changes during and after clean-up activities;

Objective 3: Describe and analyze spatial occurrence of birth defects and normal birth outcomes in these communities;

Objective 4: Connect families of children with birth defects in these communities to early intervention and support services.

Objective 5: Use preestablished, scientifically sound criteria to determine the need for, and type of appropriate follow-up investigations, based the findings of objectives 2 and 3.

II. Population to be addressed/served: Parents and children living in communities surrounding RMA.

III. Expertise Required: CDPHE staff familiar with birth defects, vital record data , temporal and spatial statistical analysis, geographic information systems (GIS), public health epidemiology, health education, and RMA remedial and medical monitoring activities.

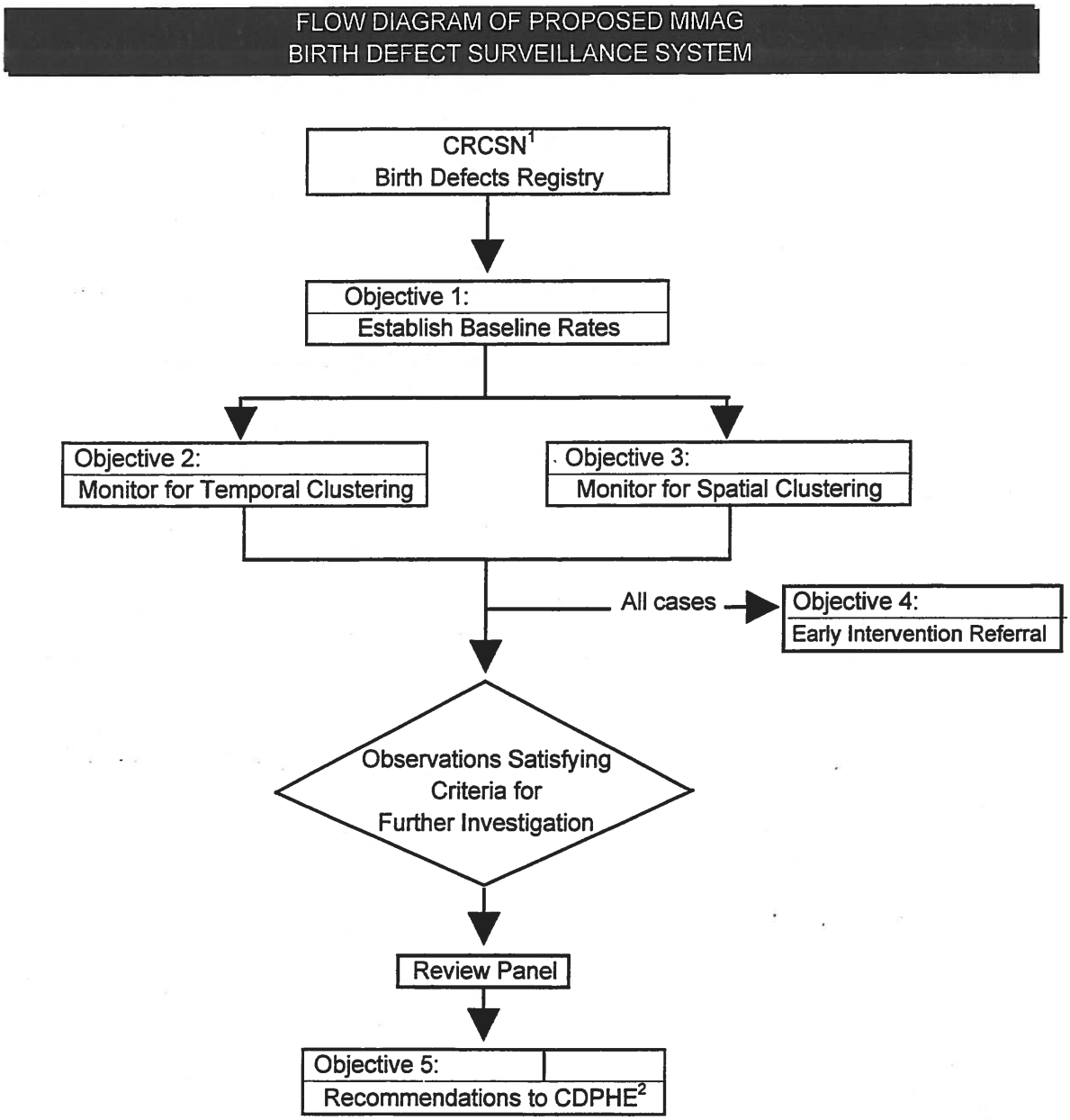
IV. Strategy:

A. General Description

Confidentiality of personal identifying information of persons and families contained in the CRCSN Registry is strictly governed by State law and protocols are currently in place which assure compliance.

The human fetus is sensitive to exogenous physical and chemical agents and therefore it is important that birth outcomes be monitored. This proposal provides for special measures which will ensure vigilance by the RMA Medical Monitoring Program. Latency is not an issue as with other diseases such as cancer, where there may be 30 years between exposure and the diagnosis of disease and the subsequent efforts of studying health risks.

Figure 1



1. Colorado Responds to Children with Special Needs
2. Colorado Department of Public Health and Environment

a:mmag.xls

The birth defects surveillance component of the RMA Medical Monitoring Program will incorporate three data resources currently available at CDPHE: The birth defects registry, birth certificates and the Department's GIS.

Most birth defect cases are reported to CRCSN monthly and current efforts are in place to improve the timeliness of reporting to less than 90-180 days. Pertinent questions to be answered prior to finalizing the design will include: Which defects should be monitored based on biological plausibility, and can etiologic homogeneous groups be defined. Biological plausibility refers to a reasonably strong possibility that a defect is associated with exposure to an agent based on information about mechanisms of action, structure-function relationships, etc. An etiologically homogeneous group is two or more defects which appear to share a common causative agent.

Objective 1: Establish baseline rates for birth defects occurring in communities surrounding RMA.

Prior to monitoring for changes in the occurrence of birth defects, it is necessary to establish baseline rates. Since the CRCSN began statewide data collection in 1989, several years of data are now available to estimate baseline birth defect rates for the area of interest. Place of residence is registered by CRCSN based on the mother's address at the time of birth, and therefore these data will be used to select eligible cases.

Diagnostic data for cases will be obtained from CRCSN which maintains a centralized statewide system for epidemiologic monitoring of birth defect and developmental disabilities. Strengths of ascertainment in this program include an extended age range for ascertainment of a condition (up to three years of age), a diversity of reporting sources covering the entire state, and the ability and authority to undertake active cases review and surveillance when deemed necessary for special studies.

Live birth and fetal death data for the area of interest is currently available from the Health Statistics Section of the CDPHE and will be used as the denominator in calculating birth defect rates[1].

Mothers' street residence address at the time of birth would be obtained as reported on the Colorado birth certificate and used to determine geographic location of both cases and normal births.

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[1] The denominator is the total number of live births and fetal deaths in the area of interest, regardless of whether the child or fetus is defective, and allows an estimation of the rate, or frequency, of births with a defect within that population. For example, among 322,562 live annual births to Colorado residents in 1989-1994 (the denominator), 14,828 were reported born with major congenital anomalies; a rate of 459.69 per 10,000 live births, or approximately 5 percent.

Objective 2: Describe and analyze rates for significant temporal changes during and after clean-up activities;

To achieve this objective, the frequency of birth defects (per unit time) will be monitored and compared to the baseline rate determined in Objective A. An appropriate statistical method for this monitoring effort is the cumulative sum (CUSUM) statistic (see Attachment 1).

A CUSUM statistical method will be designed to monitor, and observe changes in, rates over time. This will help to provide the earliest possible indication (or flag) of a true shift (change in the baseline rate to a new level, e.g., an increased rate) versus observing normal or expected fluctuation around a stable baseline rate of disease occurrence[2]. Flag levels will be determined through statistical analysis as a collaborative effort among CDPHE-CRCSN and -RMA Medical Monitoring Program staff, ATSDR and community representatives. These flags will be selected for specific birth outcomes (all and/or specific types of defects) and with an awareness of the sensitivity or power of the data and statistical methods to observe non-random changes in birth defect frequency. In other words, before monitoring begins, a clear picture of the magnitude of change that can be detect and the ability of the system to detect them, must be determined in at least a semi-quantitative manner.

Objective 3: Describe and analyze the spatial occurrence of birth defects and normal birth outcomes in these communities.

By combining CRCSN, birth certificate and GIS resources, mapping of the exact location of birth defects and normal birth outcomes will be possible. This capability directly addresses the public and scientific quandary of how to evaluate the frequency distribution of health outcomes, in this case, birth defects, without the bias introduced by arbitrarily grouping these events within administrative or political boundaries. Once mapping is accomplished, analysts will then examine the data for possible non-random geographical occurrence, or statically significant clusters[3]. Such clusters may be attributed to a variety of factors, including possible environmental exposures, and may warrant further investigation. An appropriated statistical method for this analysis is the spacial scan statistic (see Attachment 2).

The spatial scan statistic developed by Kulldorf (1995) will be used to analyze these data. This methodology scans the case distribution over the geographic area of interest and provides the location of the most likely cluster for that data set. A statistical test of

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[2] This analytical approach will allow program staff to know when there is an increase in the number of birth defects, i.e., a number greater than the baseline number. The statistical method takes into account the normal variation of the baseline number of birth defects in a community and therefore helps to determine when an increase exceeds this expected normal variation. A "flag" is posted when such an increase is reported. For example, if the baseline average number of defects is 2, with normal variation of 1 to 3, a report of 5 defects may be flagged as unusual.

[3] The benefit of this spacial, or geographical, analysis is that the actual location of birth defect cases and normal birth outcomes can be tracked. Follow-up investigation may, for example, be called for if, say, three cases of a rare defect occur in the same neighborhood.

significance is then provided as guidance in deciding if the pattern of cases in this location was unlikely to be produced by chance. On an ongoing basis, this spatial monitoring will help prioritize areas for investigation and help reduce controversy associated with "perceived clusters." Pertinent questions to be answered prior to the implementation of such a system will be how and on what basis will the study area be defined.

Objective 4: Connect families of children with birth defects in these communities to early intervention and support services.

The ability of CRCSN to provide useful information to families about birth defects and inform families of available services is already established in the CDPHE Community Notification and Referral program and can be easily focused on the communities surrounding the RMA. The aim of this program is to prevent secondary disabilities in children identified in the Registry by connecting their families with services and supports in their local communities. Examples of the many types of services that families can learn about or be referred to are Special Supplemental Food Programs for Women, Infants and Children (WIC), immunization clinics, well-child clinics, grief counseling, parent support groups, Supplemental Security Income (SSI), specialty medical clinics, early intervention programs, and developmental clinics. As with other reportable disease data and their use, confidentiality and privacy are carefully protected throughout the referral process.

Objective 5: Use preestablished, scientifically sound criteria to determine the need for, and type of appropriate follow-up investigations, based the findings of Objectives 2 and 3.

Criteria will be developed which will be used to determine when the statistical observations made in satisfying Objectives 2 and 3 warrant follow-up investigation. A variety of follow-up actions may be considered and tiered according to the strength of the findings of the information subsequently collected. For example, and initial follow-up of a finding meeting the criteria of statistical significance could include careful examination of environmental monitoring data. Another early follow-up action may include residence determination of the mothers during gestation to ascertain whether residency is a potentially important factor (i.e., did the mother live in the vicinity of the RMA during her pregnancy).

A higher tier of follow-up may be the referral of the observation to an independent ad hoc expert panel for review and development of recommendations back to CDPHE (e.g., initiation of a case-control study).

B. Protocol Development

1. General

a. For all objectives, identify exact geographic boundaries for monitoring.
b. Evaluate contaminants of concern for known teratogenicity.

c. Select specific defects and diagnostic groupings based on etiology for monitoring.
d. Develop criteria for determining the need for investigation of observed clustering and for referral to the Review Panel.
e. Develop review panel criteria and identify potential investigative options.

2. Objective-Specific

Objective 1:
a. Determine the time period for establishing baseline rates.
b. Obtain appropriate data for denominators (birth counts and fetal deaths) once time period is established.

Objective 2:
a. Prepare monitored birth numbers vs. strength of the teratogen vs. population exposure tables to characterize sensitivity of temporal monitoring statistical method.
b. Determine the frequency of analysis (e.g., example monthly, weekly, quarterly) that fits assumptions of the statistical model.
c. Define statistical significance (i.e., what constitutes a significant increase, or decrease, in the observed defect frequency (e.g., percent change, doubling of the rate, etc), acceptable periods of data acquisition leading to a "flag level" and duration of acceptable/expected "non-flag" elevations in rates.

Objective 3:
a. Obtain address data (all births), edit (clean-up) and incorporate into GIS for assigning longitude and latitude.
b. Determine periodicity of this analysis.

Objective 4:
a. Adjust existing protocol to the communities monitored (especially where program crosses county lines).

Objective 5:
a. Develop criteria for appropriate, tiered follow-up to observations reported out of Objectives 3 and 4.
b. Establish independent ad hoc review panel protocol.

V. Advantages of this Plan:

A) Reliable data sources already exist.
B) Baseline data will be available for comparison to future data.
C) Multiple reporting methods are already in place and authorized access to medical records strongly counter recall/reporting bias noted in earlier RMA health studies where data were self-reported.
D) The ability to identify all resident births occurring in the study area would overcome the low participation rates noted as a limiting factor in earlier RMA health studies.
E) Expertise in medical record review and disease investigation is already established

in the Disease Control and Environmental Epidemiology Division of the CDPHE (also the location of CRCSN).

F) The spatial analysis proposed directly addresses the problem of multiple comparisons.

G) Provides for multiple levels of data review and tiered follow-up.

VI. Limitations of this Plan:

A) The geographic distribution of birth outcomes is reported to the CRCSN based on the mother's place of residence at the time of birth. While it is feasible to determine the history of residency during gestation for births to mothers residing near the RMA, births occurring elsewhere, but with some portion of gestation occurring near the RMA, may be lost to follow-up.

B) As in all epidemiological investigations, a variety of factors influence observational ability. Factors such as population size, normal frequency of a birth defect are examples of factors which will need to be considered when interpreting the findings of this plan.

Attachment 1
Cumulative Sum Statistic

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Statistical methods for surveillance of congenital malformations: when do the data indicate a true shift in the risk that an infant is affected by some type of malformation?

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Key words: Birth defects; Surveillance; CUSUM

Statistical methods for surveillance are reviewed for use with both hospital-based systems and central registries. In the hospital-based system the surveillance methods are applied as each new case occurs and the methods focus on the number of unaffected births between each case. In centralized systems, it is usually more convenient to observe the number of cases in time intervals of fixed length. Methods for calculating exact confidence limits about the number of cases, the proportion of malformed cases and the observed-to-expected ratio are reviewed, as are methods allowing evidence to accumulate over several time periods. Examples are given to illustrate the use of the different methods.

Introduction

Initiated in the aftermath of the thalidomide episode, the objective of birth defects surveillance has been to detect and explain temporal changes in the occurrence of birth defects. Theoretically, this activity should enable preventive measures to be taken at an earlier stage. We describe here some statistical methods that can be used to evaluate fluctuations in the occurrence of congenital malformations. Most of these methods have been inherited from the early days of quality control [1,2]. In focusing on hypothesis testing and decision rules, these control-chart methods are different from other statistical methods used in modern

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Attachment 2
Spacial Scan Statistic

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STATISTICS IN MEDICINE,

SPATIAL DISEASE CLUSTERS: DETECTION AND INFERENCE

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SUMMARY

We present a new method of detection and inference for spatial clusters of a disease. To avoid *ad hoc* procedures to test for clustering, we have a clearly defined alternative hypothesis and our test statistic is based on the likelihood ratio. The proposed test can detect clusters of any size, located anywhere in the study region. It is not restricted to clusters that conform to predefined administrative or political borders. The test can be used for spatially aggregated data as well as when exact geographic co-ordinates are known for each individual. We illustrate the method on a data set describing the occurrence of leukaemia in Upstate New York.

1. INTRODUCTION

The statistics of disease clustering is of interest to epidemiologists and has been studied for many decades. Such studies are useful to detect and monitor potential public health hazards. A review of several existing methods to detect spatial clustering of disease appears in Marshall[1] and in Hills and Alexander.[2] For more recent developments see Jacquez.[3]

The epidemiologist is typically interested in clusters of disease cases only after having adjusted for spatial variations in the density of the background population itself. Thus, on a map representing the cases as a spatial point pattern, an apparent disease cluster in a particular area could be misleading because it may be explained simply by a clustering of the population itself in that area. In this paper, we present a method that detects the location of possible disease clusters in a population with inhomogeneous spatial density, and simultaneously uses methods of inference to test for significance.

Upton and Fingleton[4] have pointed out two major approaches used for the analysis of spatial point patterns in general. both have been applied to disease clustering. One approach uses a test statistic based on measuring distances between the disease cases while the other is based on studying the variability of case counts in certain subsets of the study region, often called quadrats. The former approach broadly defines the so-called distance methods, of which Whittemore *et al.*[5]

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