

# Washington State Department of Health Guidelines for Investigating Clusters of Chronic Disease and Adverse Birth Outcomes

Revised July 2007

These guidelines are intended to assist Washington State Department of Health (DOH) employees respond to concerns about potential clusters of chronic diseases and adverse birth outcomes in a standardized and coordinated manner. Coordination is needed, because people sometimes report concerns to more than one unit within DOH. The guidelines describe how to track these events. Tracking enables DOH employees to obtain historical information when an individual reports a concern that is the same or similar to one reported previously. The guidelines also serve as a reminder about the importance of communicating and coordinating with other agencies and stakeholders, including the local health agency that has jurisdiction over the geographic area where the potential cluster occurs.

This protocol pertains only to clusters of non-infections diseases, such as cancer and birth defects. It does not apply in emergency situations such as infectious disease outbreaks, terrorism events, or unplanned chemical or radiological releases.

The process described below for the most part parallels the cluster investigation guidelines published by the Centers for Disease Control and Prevention (CDC) in the July 1990 *Recommendations and Reports* series of Morbidity and Mortality Weekly Report (MMWR). The CDC report contains significantly more detail than the general guidelines presented here.

Although these guidelines outline a linear process, investigative elements presented under specific stages may occur at relatively earlier or later stages, depending on the effort involved. In practice, the process is rarely strictly linear.

Background and other information for investigating clusters of chronic disease and adverse birth outcomes is available to DOH employees at Y:\Clusters\.

## ***STAGE 1: COLLECT INITIAL INFORMATION AND PROVIDE EDUCATION AND INFORMATION TO THE INFORMANT.***

Goal: Obtain sufficient information to complete an initial assessment, communicate with appropriate parties, and log information for DOH records.

1. In most cases, individuals with concerns about potential clusters of chronic disease or adverse birth outcomes contact DOH by phone. However, e-mail is becoming more common. Because e-mail is not a secure medium, phone contact for collecting information about specific individuals is preferable to e-mail. Additionally, talking with the concerned individual (the informant) can facilitate a better understanding of the informant's emotional connection to the concern and, thus, might provide a better medium for establishing rapport and for determining the informant's expectations. The DOH person initially responding to the call or e-mail obtains sufficient information to 1) complete an initial assessment of the reported concern; 2) communicate with the informant and with the appropriate local health jurisdiction (LHJ); and 3) complete the

tracking form in Y:\Clusters\Restricted\Tracking. The following list provides guidance on what types of information to collect. Bolded items are needed for the tracking form.

- Contact information for the informant, including name, telephone number, e-mail, and/or mailing address
- **Type of illness(es)**
- Number of people reported with the same illness
- The ages of the people affected
- Time period during which people became ill
- **Where the alleged cluster has occurred, including the appropriate county(ies) and the city or town**
- **Whether the informant suspects a specific environmental exposure and if so, what**
- Others the informant has contacted about the cluster (include other DOH personnel, LHJs, and other agencies)
- **Organizational affiliation of the informant (e.g., health official, private physician, concerned citizen, employer representative, etc.)**

If the concern is outside the area of knowledge of the DOH staff originally contacted, he/she may refer the call or e-mail to the appropriate person listed in Y:\Clusters\Information\Contacts, who then contacts the informant and collects the information listed above. It is the responsibility of the person originally contacted to obtain information so that DOH can contact the informant. The informant should not simply be referred to another person in DOH.

In many cases DOH staff might be able to give information that satisfies the informant during this initial call. Often, people just need help understanding and interpreting their observations. Use Y:\Clusters\Restricted\Resources\Quick\_Background\_Info for guidance.

## 2. **Decision Point**

Following the phone conversation, the person collecting the information (the investigator), checks the tracking form at Y:\Clusters\Restricted\Tracking to determine if a similar cluster has been reported previously in the geographic area of concern. If so, the investigator should see whether there is documentation at Y:\Clusters\Unrestricted\DOH\_Letters and contact the DOH and/or LHJ contact or the State Epidemiologist for Non-Infectious Conditions to obtain information on the previous investigation. **(If an initial voice mail or e-mail provides sufficient information, this step should be taken before contacting the individual.)** The person then contacts the LHJ<sup>1</sup> and others as appropriate, such as others in DOH or Labor and Industries (L&I), to determine whether to close the case or investigate further.

### a) **Criteria for continuing the investigation and moving to Stage 2 include:**

- I. There are at least 3 cases of the same or similar conditions, or in the case of birth defects, developmentally similar conditions, OR

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<sup>1</sup> LHJ refers to the local health officer and other local health personnel, e.g., administrative director, epidemiologist, assessment coordinator, or environmental health director. DOH will always notify the local health officer at this stage of the investigation. DOH may also notify other LHJ contacts. If the investigation proceeds to additional stages, the LHJ will determine the primary LHJ contact for DOH.

- II. A specific exposure of concern, including a potential route of exposure, is alleged as the cause of the cluster. The potential exposure must not be etiologically implausible due latency periods or other knowledge about the cause of the reported disease.
- b) When a decision has been made, the DOH staff member (or supervisor or designee for those without write rights to the tracking form):
- I. Notes in the tracking form (Y:\Clusters\Restricted\Tracking) either that case is closed, including noting that it was closed at Stage 1 or if conducting further investigation, records names of a secondary DOH contact and an LHJ contact.
  - II. E-mails<sup>2</sup> a short summary of the concern and the decision to
    - DOH DL Agency Cluster,
    - LHJ (local health officer, assessment coordinator, or other local health contacts, such as environmental health director),
    - L&I Safety and Health Assessment and Research for Prevention (SHARP), if the concern occurred in an occupational setting (contacts listed in Y:\Clusters\Information\Contacts), and
    - Other state and local agencies, such as Department of Ecology, that might have an interest in the report or on-going investigation.
  - III. Provides feedback to the informant, after allowing time for feedback from local health and others.
    - If the investigation is closed, an e-mail or letter to the informant should summarize the reason for closing the investigation. (See Y:\Clusters\Restricted\Resources\Sample\_Letter for a sample letter template and Y:\Clusters\Unrestricted\DOH\_Letters for examples.) The investigator can provide relevant information (see Y:\Clusters\Unrestricted\Resources) and referrals for environmental assessment, if appropriate. The local health officer or his/her designee and others should review the letter as appropriate before sending.  
**NOTE:** There may be instances in which the investigator deems that the informant was satisfied with the information provided during the initial contact and that there is no further benefit of written closure.
  - IV. If the investigation is closed, posts a copy of the letter (step 2.b.III), or if a letter is not written, the e-mail (step 2.b.II), to the appropriate county file at Y:\Clusters\Unrestricted\DOH\_Letters.<sup>3</sup>
  - V. Notifies the DOH media office if media involvement is anticipated.

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<sup>2</sup> Personal health information is confidential. To protect patient privacy, all e-mail communications should omit personal identifiers.

<sup>3</sup> Note that the sub-folders are listed by the county or counties over which an LHJ has jurisdiction. There is also a file for clusters in multiple counties that involve multiple LHJs.

## **STAGE 2: PROVIDE AN INITIAL ASSESSMENT OF THE MAGNITUDE OF THE REPORTED CLUSTER.**

Goal: Provide a quick, rough estimate of the likelihood that a statistically significant excess has occurred.

1. If the investigation is not closed in Stage 1, the investigator confirms the need for further action with the State Epidemiologist for Non-Infectious Conditions (or designee) who confers with the people listed in Y:\Clusters\Information\Contacts to determine who within DOH should be involved on the cluster investigation team. This decision is based on skills, availability, and approval by the team members' direct supervisors. The LHJ is invited to participate on the team and to take the lead. (If the concern is occupational in nature, L&I is encouraged to participate on the team and take the lead.) If other entities do not have staffing or expertise to take the lead, DOH takes the lead. In these instances, the DOH team designates a lead person who is responsible for coordinating information gathering, maintaining files with documentation and materials, keeping other team members informed and communicating with the informant. For continuity, if the team leader is not the original investigator, the team leader may ask the original investigator to maintain communication with the informant. If the LHJ or other agency takes the lead, DOH team members decide on a DOH lead who is responsible for communicating with the lead agency, maintaining DOH records, and communicating within DOH.
2. The team develops an initial case definition and gathers information on the natural history of the disease, common risk factors, and background rates (if readily available). Also at this time, the team may ask the informant to assist in gathering additional information.<sup>4</sup> If the diagnosis can be confirmed using readily available data, the team should do so. However, if this is not possible, all reported cases are treated as real.
3. If there is a specific exposure of concern, a review of scientific literature and consultation with other investigators or experts might be necessary at this stage. The purpose of the literature review is to assess biologic plausibility, strength, consistency, temporal association and evidence of a dose-response gradient to support an association between the reported exposure and disease.
4. Investigators use standard methods to determine whether there is an excess of disease. Standard methods include using pre-existing data and/or community reports to assess the ratio of observed to expected numbers of cases or comparing rates in the area of concern to background rates. For these analyses, the team needs to
  - a) Define the appropriate geographic area and time period in which to study the cluster. Defining the geographic area and time period too narrowly can result in falsely identifying a cluster; defining too broadly can result in missing a cluster.
  - b) Determine the most appropriate reference population for which there is pre-existing data.Standard methods can also include use of software designed specifically to identify clusters, such as SatScan. The advantage of SatScan is that the team does not need to identify pre-defined geographies or background rates.

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<sup>4</sup> The "Initial Inquiry Report Form," developed for use by communities conducting their own investigations, might also be useful when asking the informant to gather additional information. (Y:\Clusters\Unrestricted\Resources\DOH\_Resources\Initial\_Inquiry\_Report\_Form)

## 5. Decision Point

The cluster investigation team meets to discuss the information gathered and to decide whether to take the investigation to Stage 3.

- a) Criteria which serve as guidelines for beginning Stage 3 include the reporting of a least **three** cases of the same condition, an excess of cases that is **at least marginally statistically significant**, **AND** one or more of the following:
  - I. The disease is of known etiology and there is **potential for exposure to the causal agent** OR
  - II. Scientific literature supports an **association between the reported exposure and the reported condition** OR
  - III. The disease is of unknown etiology and there is potential for exposure to a **rare or unusual substance** (i.e., these exposures are unique to an area or an occupation and are not commonly found in other places in Washington or the United States) OR
  - IV. The **disease is extremely rare**.
- b) When a decision has been made, the DOH lead<sup>5</sup> (or supervisor or designee, as needed)
  - I. Notes in the tracking form (Y:\Clusters\Restricted\Tracking) that the case is closed, including noting that it closed at Stage 2, or if the investigation is continuing, notes the status in the comment field.
  - II. E-mails a short synopsis of the decision to DOH DL Agency Cluster. Other team members determine how best to notify other parties who were consulted during Stages I and 2.
  - III. Provides feedback to the caller. If the investigation is closed, the team leader or designee
    - Sends an e-mail or letter to the caller, summarizing the concern, the steps taken during the preliminary assessment, the results of investigative activities, and the rationale for closing the investigation. The local health officer, other team members, and any consultants (e.g., Ecology or L&I) should review the letter before sending.
    - Sends copies of the letter or e-mail to agencies that have been involved in the investigation.
    - Posts a copy in the appropriate subfile at Y:\Clusters\Unrestricted\DOH\_Letters.
    - Sends supporting documentation and material to the State Epidemiologist for Non-Infectious Conditions (or designee).

### ***Stage 3: Verify initial assessment***

Goal: Verify the initial assessment with a more refined analysis of both health and environmental data.

1. The team may expand its membership to include DOH, LHJ personnel and others who could contribute to the development and implementation of activities. The team members, in coordination with their supervisors, decide on whether and how the team needs to be expanded, including decisions on public involvement.

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<sup>5</sup> The DOH lead is only responsible for the first two bulleted activities in step III if he/she is also the team lead.

2. The cluster investigation team develops a plan for verifying the reported illnesses, as well as the exposure of concern (if one has been reported). Typically, the following steps will take place during this stage.
  - a) If indicated, the team refines the geographic area and time period of interest. The refinements should be based on information gathered during Stage 2 concerning latency periods, available data (both geographically and temporally) and plausibility of exposure to the risk of concern.
  - b) The team obtains information on all reported cases to verify diagnosis, time of onset and exposure profile. Depending on the amount of information needed, this can be often be accomplished using a combination of routinely collected data and verifying community reports for those cases that are too recent to be included in routinely collected data. If this step is relatively easy and inexpensive, it may be carried out in Stage 2.
  - c) If necessary, the team refines the case definition.
  - d) If case ascertainment is likely to be incomplete, the team needs to consider active case finding. This step might involve reviewing additional databases or medical records, or obtaining additional information from the community. Generally, obtaining additional information from the community would **not** be a formal survey. Formal surveys generally occur in Stage 5 and investigators need to be careful not to bias people who might eventually be recruited for Stage 5 activities. For the same reason, investigators need to be cautious in using the media or other public notification procedures to ascertain cases.
  - e) The team determines whether there is a statistically significant excess using standard analytic methods as described in Stage 2 step 3.
  - f) When there is a specific potential source of exposure, the team should conduct a preliminary environmental assessment. This assessment might include a site visit, a review of existing data including engineering and other land-use records, and a review of any existing environmental sampling data. Activities at this stage typically will **not** involve the collection of new data through environmental sampling. If potential exposure sources are verified, exposure pathways and biological plausibility of the suspected contaminants as etiologic factors for the disease need to be delineated.
  - g) The team might review existing information about other risk factors for the condition (e.g., lifestyle or genetic factors). As with environmental exposures, activities at this stage typically will **not** involve the collection of new data, such as conducting surveys or collecting biological samples.

### 3. **Decision Point**

The cluster investigation team meets to discuss the new information and to decide whether to take the investigation to Stage 4. Since further activities are likely to be resource intensive, a consensus about the decision is important, including support by management within DOH and the LHJ.

- a) Criteria for moving to Stage 3 include meeting **all of the first three criteria and either IV or V** below.
- I. At least **five cases** of the disease.
  - II. A ratio of the number of observed cases to the number of expected cases (O/E) that is **at least two when there are 50 or more people** with the same or etiologically related diseases and **increases as the number of cases decreases**, ending with an O/E of 20 for 5 cases. To determine the O/E ratio for a specific number of cases, divide 100 by the number of cases. If the result is less than 2, use 2 as the criterion. The following table illustrates results using this method.

Number of cases	Minimum O/E
5	20.0
10	10.0
15	6.7
20	5.0
25	4.0
40	2.5
>50	2.0

- III. The investigation is **likely to have a public health impact**. For example, a cluster in which data suggest the cause is an environmental contaminant that has already been cleaned up would not require further study<sup>6</sup> other than to confirm adequate decontamination. A cluster in which data suggest a stable persistent problem could indicate the need for further study.
- IV. For diseases of **known or suspected etiology**, there must be a **plausible exposure and route of exposure**, including proper latency between the exposure and the onset of disease.
- V. For diseases of **unknown etiology**:
  - There must be a **unique** exposure (i.e., an exposure which is not commonly found in other areas in Washington or the United States where there are not clusters) and a **plausible route of exposure**, AND
  - The weight of the evidence from scientific literature should not render an association between the disease and the exposure **unlikely**.

**Note:** The experience of the California Birth Defects Monitoring Program shows that an investigation is unlikely to uncover a new teratogen unless the following conditions are met:

- There is a large excess of the same defect, with a relative risk 10 or more times the expected rate.
- There is a biologically plausible exposure, including exposure to the teratogen at the critical period of organogenesis. (The critical period varies depending on the organ or organ system involved.)
- There is an unusual pattern of anomalies. Because each teratogen acts on specific tissues and organs, the resulting defects tend to show characteristic patterns. For example, the rubella virus causes heart defects, cataracts, chorioretinitis, deafness and developmental disabilities, while thalidomide causes limb defects.

<sup>6</sup> However, if the effects of a historical exposure could be mitigated by a specific action, investigators should notify those who had been at risk of exposure.

- b) When a decision has been made, the DOH lead (or supervisor or designee, as needed)
- I. Notes in the tracking form (Y:\Clusters\Restricted\Tracking) that the case is closed, including noting that it closed at Stage 3, or if the investigation is continuing, notes the status in the comment field.
  - II. E-mails a short synopsis of the decision to DOH DL Agency Cluster. Other team members determine how best to notify other parties who were consulted as part of the investigation.
  - III. Provides feedback to the caller.<sup>7</sup> If the investigation is closed, the team leader or designee
    - Sends an e-mail or letter to the caller, summarizing the concern, the steps taken during the investigation, the results of investigative activities, and the rationale for closing the investigation. The local health officer, other team members, and any consultants (e.g., Ecology or L&I) should review the letter before sending.
    - Sends copies of the letter or e-mail to agencies that have been involved in the investigation.
    - Posts a copy of the letter or e-mail in the appropriate subfile at Y:\Clusters\Unrestricted\DOH\_Letters.
    - Sends supporting documentation and material to the State Epidemiologist for Non-Infectious Conditions (or designee).

#### ***STAGE 4 DETERMINE UTILITY AND FEASIBILITY OF FURTHER EPIDEMIOLOGIC STUDY***

Goal: Determine the feasibility of performing an epidemiologic study to determine whether the health event and putative exposure are associated.

1. Having verified through Stage 3 activities that there is an excess number of cases of a specific illness (or etiologically related illnesses) in the defined community/population and that further investigation might be warranted, the first step in Stage 4 is to determine whether the team needs to be expanded to include others within DOH; the LHJ; other state agencies that can provide environmental sampling, such as the Department of Ecology or the Department of Agriculture; the members of the community and/or persons with specific areas of expertise, such as CDC, university personnel and other state or local health departments. The team members, in coordination with their supervisors and the State Epidemiologist for Non-Infectious Conditions (or designee), decide on whether and how the team needs to be expanded.
2. The team's main objective is to review the information obtained in the investigation up to this point and examine the potential that further investigation might find a relationship between the observed cluster and a specific exposure. The team needs to consider
  - The statistical power to find a relationship if one exists.
  - Issues of bias due to potential response rates or other factors.
  - The ability to distinguish exposed from unexposed individuals (i.e., the ability to identify an appropriate control population). Unexposed individuals might be from

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<sup>7</sup> The DOH lead is only responsible for the first two bulleted activities in step III if he/she is also the team lead.

the geographic area of the cluster or from a broader population for which average levels of exposure are known.

- Appropriate study design (for example case series, case-control, nested cohort), with attendant costs and expected outcomes.
- What data need to be collected and the logistics of data collection, including survey methods, environmental sampling, and physical and laboratory measurements.
- Potential social, financial and environmental implications of different decisions and study outcomes.
- The total resources required by the study itself and by alternative study findings.

**NOTE:** According to Rothman (AJE, 1990) systematic studies of clusters of diseases are not likely to be fruitful in identifying causes of disease unless there is a **single causal mechanism** for the disease. Rothman further states that single causal mechanisms are most frequently seen for diseases that are **extremely rare or suddenly** increasing.

**NOTE:** Other characteristics which indicate that an investigation might be fruitful include:

- The etiologic agent is easy to measure:
  - ✓ It persists in the environment
  - ✓ It is detectable and measurable
  - ✓ It is rare in the general population and leaves a physiological response in the bodies of those exposed
- There is an ability to select an appropriate control group, i.e., the exposure is heterogeneous.

### 3. Decision Point

- a) Criteria for moving to Stage 5 include a determination that an etiologic investigation is
  - I. **Technically feasible** AND
  - II. **Adequately resourced** AND
  - III. **Likely to have a public health impact**
- b) When a decision has been made the DOH lead (or supervisor or designee, as needed)
  - I. Notes in the tracking form (Y:\Clusters\Restricted\Tracking) that the case is closed, including noting that it closed at Stage 4, or if the investigation is continuing, notes the status in the comment field.
  - II. E-mails a short synopsis of the decision to DOH DL Agency Cluster. Other team members determine how best to notify other parties who were consulted as part of the investigation.
  - III. Provides feedback to the caller.<sup>8</sup> If the investigation is closed, the team leader or designee
    - Sends an e-mail or letter to the caller, summarizing the concern, the steps taken during the investigation, the results of investigative activities, and the rationale for closing the investigation. The local health officer, other team members, and any consultants (e.g., Ecology or SHARP) should review the letter before sending.

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<sup>8</sup> The DOH lead is only responsible for the first two bulleted activities in step III if he/she is also the team lead.

- Sends copies of the letter or e-mail to agencies that have been involved in the investigation.
- Posts a copy of the letter or e-mail in the appropriate subfile at Y:\Clusters\Unrestricted\DOH\_Letters.
- Sends supporting documentation and material to the State Epidemiologist for Non-Infectious Conditions (or designee).

### ***STAGE 5. CONDUCT DETAILED ETIOLOGIC INVESTIGATION***

Goal: To perform an etiologic investigation of a potential disease-exposure relationship.

1. The primary purpose of this stage of the investigation is to pursue the epidemiologic or public health issues that the cluster generated. In this context, this stage represents a standard epidemiologic study, for which all the preceding work has been preparatory.
2. Based on the information collected and decisions made in Stage 4, develop a protocol and implement the study, expanding the team and changing the team lead as needed. At this point the remaining investigative steps will be unique to each study and further guidelines are outside the scope of this document.
3. The team is responsible for sharing the results of the investigation with the community and other appropriate groups. Depending on the findings, the team should recommend interventions to prevent further disease.
4. The DOH lead, post a copy of the final report in the appropriate subfile at Y:\Clusters\Unrestricted\DOH\_Letters and sends supporting documentation and material to the State Epidemiologist for Non-Infectious Conditions (or designee).