Cluster Inquiries: An Extension of Epidemiologic Surveillance

Robin C. Leonard\textsuperscript{1}, Kim H. Kreckmann\textsuperscript{1}, Craig Marshall\textsuperscript{2}

\textsuperscript{1} DuPont Haskell Laboratory, Newark, DE
\textsuperscript{2} Critical Path Services, Newark, DE

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What makes a “cluster” a problem?

- A cluster is a perceived increase of disease in TIME and SPACE.
  - “perceived”. How much time? How large a “space?”
  - Define disease—down to a 4-digit ICD or is “cancer” or “respiratory disease” sufficient.
  - What about symptoms, e.g., dizziness, loss of memory?

- Epidemiology is a population science; epidemiologists like big numbers.
Approaches to cluster investigation

- **Missouri Model—State of MO Health Dept.**
  - Process is a 4-level inquiry, with specific criteria for moving up the levels

- **American Industrial Health Council**
  - 8-step process, with decision criteria

- **DuPont Epidemiology Review Board**
  - 7-task procedure, focused on exposure control and communications
Procedures for cluster inquiries: The Missouri Model

Level 1
Initial Contact and Response

Communication
Report to interested parties

Level 2
Evaluate the information
Is there a cluster?

Level 3
Collect more data
Broaden case ascertainment, if necessary

Level 4
Etiologic Investigation
AIHC Eight-Step Process

1. Document Concern
2. Form Response Team
3. Develop Communication Plan
4. Validate Concern

Stop. Communicate and consider additional monitoring.
AIHC Eight-Step Process

5. Frame Question
   - Yes
   - No

6. Develop Research Strategy
   - Yes
   - No
     - Rework and go to Step 5. If no strategy available, then Stop. Communicate and consider additional monitoring.

7. Answer Question
   - Yes
   - No
     - Develop new strategy (Go to Step 6.) Frame new question (Go to Step 5). Raise new concern. (Go to Step 4) Stop. Communicate, consider additional monitoring.

8. Take Appropriate Steps
   - Yes
   - No
**Level 1 Inquiry**  
**Missouri**

- Initial contact and response
  - Collect information
  - Educate contact about the disease
  - Send contact a letter and other information (i.e. brochures, newsletters, web links)
  - Inform others (i.e. site leaders, your friendly epidemiologist, HSMT, etc.)

**Steps 1-3**  
**AIHC**

- Document concern
- Form response team
- Develop communication plan
Move to Level 2? √ ERB  Step 4
Missouri AIHC

The following must be met:
- All cases verified
- A definable disease is reported
- Only one type of disease is reported
- A specific exposure or cause is suggested
- There is a plausible route of exposure
- No evidence of competing risk factors

√ Validate concern
√ Verify cases
- √ Same disease
- √ Putative exposure

Chemical inventory, new process or equipment
Move to Level 2?  
Missouri

At least two of the following must also be met:

- A common type of disease is occurring in an unexpected age group
- The disease is rare
- The suspected exposure is plausibly linked to the disease of concern
- The known latency of disease matches with the estimated time cases were exposed

Step 4  
AIHC

- Unusual age of onset
- Potential exposures occurred before disease onset
- Complete job histories of all cases
Level 2
Missouri

- Review literature to identify risk factors
- Determine if there is a statistical cluster (spatial and temporal)

Step 5
AIHC

- Frame question
- Develop hypothesis
- Use population-based incidence or prevalence rates to get expected number of cases
Continue to Level 3?  Missouri

The following conditions must be met:

- Case ascertainment is completed
- There are at least 5 adult cases of one type of disease
- Statistical calculations indicate a cluster
- Population is large enough

Feasibility assessment

Develop research strategy

Step “5A” or 6 AIHC
Level 3 Inquiry
Missouri

- Continue literature searches
- Broaden case ascertainment (time/space)
- Recalculate cluster
- Collect more information on the environmental concern

Step __
AIHC

- Cycle back to earlier steps for more information
- Consider monitoring
- Monitoring of the health endpoint(s) for a time interval should be planned to track future incidence
Level 4 Inquiry
Missouri

- Committee decision
- Feasibility study
- Major etiologic investigation

Step 7
AIHC

- Answer question
- Do the research and analyses

Step 8 Follow up as appropriate

- Chemical control program in area of concern should be closely examined for maximum feasible extent of control
What are the appropriate steps?

- Communication—to study subjects and other workers
- Prepare publication
- TSCA 8(e) report
- Modify MSDS if necessary
- Reduce or eliminate exposure
- Consider medical monitoring
Methods for examining pancreatic cancer among workers in glycolic acid areas

- Standardized mortality (SMR) for all causes of death were calculated
  - For pancreatic cancer, mortality rates are very close to incidence rates
  - Best (valid) reference rates are for mortality
  - Observed vs. expected
    - observed cancers are based on Cancer Registry reports and ascertainment through medical insurance files
    - Observed deaths ascertained through Benefits and/or NDI
    - expected based on regional DuPont population
- Need at least 5 expected cases of same disease in order to calculate meaningful SMR/SIR
Regional Population

- Comprises all individuals who ever worked for DuPont in 8 states:
  - Indiana, Kentucky, North Carolina, Ohio, Pennsylvania, Tennessee, Virginia, West Virginia
- Should provide some control for the healthy worker effect as well as local characteristics of culture, diet, ethnicity, and mortality coding

- Total person-years in reference = 1,980,948.5
- Total person-years in study cohort = 142,951.3
- Plant population removed from its state population
### Cause-specific SMRs and 95% CI

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Observed</th>
<th>Expected</th>
<th>SMR</th>
<th>LL 95% CI</th>
<th>UL 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>2662</td>
<td>2624.8</td>
<td>101.4</td>
<td>97.6</td>
<td>105.3</td>
</tr>
<tr>
<td>All cancers</td>
<td>677</td>
<td>631.8</td>
<td>107.2</td>
<td>99.2</td>
<td>115.5</td>
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<tr>
<td>All GI tract cancers</td>
<td>151</td>
<td>160.4</td>
<td>94.1</td>
<td>79.7</td>
<td>110.4</td>
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<tr>
<td>Pancreatic cancer</td>
<td>29</td>
<td>31.7</td>
<td>98.0</td>
<td>20.2</td>
<td>286.3</td>
</tr>
</tbody>
</table>
Summary of SMR analyses

- There was no increased risk for the specific type of cancer identified as a cluster.
  - Expansion to all GI tract also showed no elevation, with narrower confidence limits

- Sufficient person-years and length of follow-up to provide reasonable estimates.
Next steps

- Get work histories of all cases
  - Only 8 complete records found
- Work histories for plant populations to develop case-control analysis potential
  - Only about 3% available for historical population
- Planning is underway to access archived records from plant site, as well as corporate HR for detailed work history information
- Continue surveillance, with particular attention to pancreatic cancer