VOLUME 1, ISSUE 3

FOCUS on Field Epidemiology

Embarking on an Outbreak Investigation

CONTRIBUTORS

Author:

Amy Nelson, PhD, MPH

Reviewers:

E. Danielle Rentz, MPH

FOCUS Workgroup*

Production Editors:

Lorraine Alexander, DrPH

Gloria C. Mejia, DDS, MPH

Editor in Chief:

Pia D.M. MacDonald, PhD, MPH

* **All members of the FOCUS workgroup are named on the last page of this issue.**

The North Carolina Center for Public Health Preparedness is funded by a cooperative agreement between the Centers for Disease Control and Prevention and the Association of Schools of Public Health, Project # A1011-21/21

Outbreak! The word conjures up images of scientists in space suits gingerly creeping through abandoned villages in remote jungles, searching for clues about the transmission of a terrifying new disease. In reality, it may not be quite so dramatic, but outbreak investigation is a vital role of Public Health. In an outbreak investigation, practitioners of epidemiology become the FBI of disease agents. In most states, health departments have a legal mandate to investigate cases of disease that may pose a threat to the health of the public.

Before donning your space suit or whipping out your EBI badge (Epidemiology Bureau of Investigation, of course) and running out to stop an outbreak in its tracks, there are a few things you need to know.

One thing to keep in mind is how excess cases of a particular disease are brought to your attention in the first place. States and localities have disease surveillance mechanisms, aimed at keeping track of how many cases of disease occur every day throughout the year. Cases of specific diseases that the state has deemed "notifiable" are reported to local and statewide disease surveillance systems by health care practitioners and laboratories. While all states have these surveillance mechanisms, not all outbreaks are detected this way. Many outbreaks are detected when a clinician or pharmacist notes an unusual number of cases of disease and calls the health department. Alternatively, community members such as school administrators or parents may call the health department with health concerns among students or other groups.

After you have been notified of cases, there are two vital issues that you should consider. First, if cases of a disease are reported to you, how do you know that the reports are true cases of that disease? Second, how do you know that the number of cases reported to you signify an outbreak? Once you have answered these questions, you need to create a case definition. That is, exactly what signs or symptoms have to be present to be included as a case in this outbreak? Is a laboratory test required? In this issue of FOCUS, we will consider each of these questions.

Verify the diagnosis

One of the first steps in outbreak investigation is to verify the signs, symptoms and test results of the patients that led to the diagnosis. You want to ensure that time and resources are spent appropriately investigating real disease clusters that are a threat to the health of the public. It is always possible that reports of disease are mistaken. For instance, there could have been an error in conducting the lab test that led to the diagnosis; clinical symptoms reported might have been unclear or very general; a physician might not recognize a rare disease s/he has not seen before and misdiagnose it. This potential for diagnostic error should be ruled out before launching a full investigation.

- For example, say that you hear about a number of cases of severe respiratory illness. You

gather personnel and rush out to find all the cases and conduct a full-blown investigation. However, one of the cases turns out to be flu, one turns out to be a severe cold, one is bronchitis, one is pneumonia, and all are unrelated to each other. This "outbreak" did not need to be investigated, because there was no outbreak!

How do you reduce diagnosis error?

1. In the laboratory, always rely on standardized, proven laboratory tests. If you are not the expert, work with a qualified lab technician to verify that the correct tests were done appropriately.

2. Verify the clinical symptoms. If you are not a health care provider, work with one to visit a few patients. Confirm that the symptoms were reported accurately, and that they are compatible with the diagnosis given.

3. For rare diseases of public health concern that health care providers might not be routinely familiar with, such as anthrax, communicate with health care providers and educate them about the signs and symptoms, so they are aware of that disease as a potential diagnosis.

Diagnosis in an outbreak. There are two ways in which a disease might present during an outbreak situation.

1. There could be a known or highly suspected agent causing the disease, or
2. The disease could be described by a number of similar symptoms (a syndrome), but with an unknown causative agent.

If the agent is known or suspected, you can verify the diagnosis through established lab techniques. Not every single reported case has to be verified in the laboratory, as long as all cases have similar symptoms. Many times you can just verify enough cases to know a good portion of your cases are infected with the agent. You will want to work with an experienced lab technician if you do not know how to evaluate the lab test yourself. Check to see if biological samples were handled appropriately and if the correct tests were conducted (future FOCUS issues will deal with these topics). You should also gather information on who collected the specimen to be tested (health care provider), how it was handled, and where the lab test was performed. For current and future cases, make sure that the appropriate biological samples get collected, in case these patients need to be lab-confirmed.

- An example of a known or suspected agent was a listeriosis outbreak in Winston-Salem, North Carolina (1). The diagnosis of listeriosis was clinically verified by several physicians from the local hospital. Infection with *Listeria monocytogenes* has distinct symptoms that were obvious in this outbreak. Hospital physicians alerted the health department of three pregnant patients with listeriosis within two weeks who were recent Mexican immigrants. Among pregnant women, infection with *L. monocytogenes* can result in stillborn babies or premature birth. Specimens for lab testing were placental tissue or normally sterile fluids. Using the samples collected, hospital labs verified the diagnosis using standard tests for the agent. CDC labs verified through molecular methods that these and other patients were linked. The investigation revealed that the listeriosis cases had purchased non-commercial fresh Mexican-style cheese made from raw milk. The milk was traced to a dairy farm that had *L. monocytogenes*-contaminated milk storage tanks (1).

If you do not have a suspected agent, but a number of people with similar symptoms being reported, then you should try to find a probable agent. How?

Examine the symptoms – are they respiratory? Gastrointestinal? Are any symptoms characteristic of a particular diagnosis? If standard lab diagnostic tests have not been done, they should be. If there are no positive results, standard tests can be used to rule out a diagnosis, and you can then hypothesize about which agents that were not tested are most likely. Other clues as to what the agent might be are age of patients, apparent incubation period, and season.

Verifying the existence of a true outbreak is critical to proceeding with an investigation. If it is obvious that the cases have a common link (for example person, place, or

Useful resources on critical aspects of outbreak investigation

- Field Epidemiology. Gregg MB, ed. Oxford University Press, 2002.
- Epidemiologic Methods for the Study of Infectious Disease. Thomas JC and Weber DJ, eds. Oxford University Press, 2001.
- CDC Nationally Notifiable Infectious diseases: http://www.cdc.gov/epo/dphsi/PHS/infdis.htm
- Case Definitions for Infectious Conditions Under Public Health Surveillance. *MMWR* May 2, 1997; v. 46(RR-10), available at: http://www.cdc.gov/epo/dphsi/casedef/index.htm
- Principles of Epidemiology: An Introduction to Applied Epidemiology and Biostatistics Dicker RC, et al. Centers for Disease Control and Prevention, 1992.

time) or that they are the same illness, you can investigate without knowing the agent. If it seems that the cases are not related and they do not appear to have a common exposure, you may not want to investigate.

- A common example of a syndrome that is reported without an agent is gastrointestinal illness. Patients may present with diarrhea, fever, or abdominal cramps, and many different kinds of pathogens can cause these symptoms (such as *Salmonella*, rotavirus, Norwalk-like viruses, *E. coli*, and *Campylobacter*). Talk to the lab and see if any cases were tested for specific agents. If not, see if these diagnostic tests can be conducted. Find out which other tests not in the standard lineup of tests usually performed could be used. For example, determining that *Salmonella* is the cause of the illness depends on laboratory tests that identify *Salmonella* in the stools of an infected person. The test exists, but is sometimes not performed unless the laboratory is instructed specifically to look for the organism.

Remember: if you have many cases of the same illness, but they are all from different agents, then you do not have an outbreak. The only exception to this is when the source of disease contains multiple pathogens, such as sewage contamination of drinking water. In this case, however, you should be able to link cases based on their common exposure to the contaminated source.

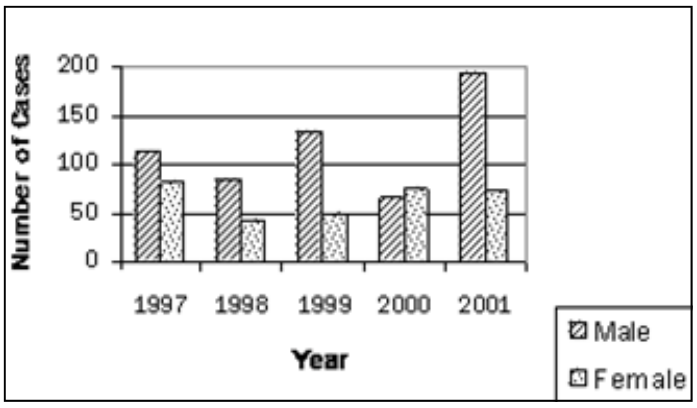
To investigate or not to investigate

If you have verified that case-patients are all due to the same agent or have the same diagnosis, how do you know that there are enough cases to really be considered an outbreak?

Take a moment to determine whether to investigate this potential outbreak at all. Potential outbreaks may turn out to be true outbreaks with a common cause, or may be unrelated cases of the same disease. "By chance" there could have been a number of unrelated cases at the same time. Other factors in considering whether or not an investigation should be undertaken are the severity of the illness, its potential as a threat to the health of the public (how transmissible it is), and possibly local politics, public concern, or resources available to investigate.

Usually, the key determinant in deciding whether to investigate a number of cases is knowing whether that number is an "unusually high" number of cases, or if it falls within what might be the expected number of cases for that population at that time of year, etc. But how do you define "unusually high"? It often depends on the disease, but can loosely be defined as "more cases than expected."

Figure 1. Hepatitis A cases, North Carolina 1997-2001



- For example, during February, 50 cases of respiratory illness at a primary school might not be high. However, 50 cases of rash at a primary school might be very unusual.
- In North Carolina, an unexpectedly high number of Hepatitis A infections were noted in the year 2001 (2). From 1997 to 2000, there were 135-194 cases per year, while in 2001, there were 266 cases (see Figure 1). Health department investigators noted that the increase took place completely among men, and determined that transmission was occurring among men who have sex with men (MSM). This resulted in the recommendation that all MSM receive the Hepatitis A vaccine.

If a disease has never been seen before in an area, such as West Nile Virus or SARS, any case report might be a cause for alarm. For some diseases, even one case-patient is considered an outbreak. Examples are Botulism, anthrax or other potential bioterrorism agents, and meningococcal disease.

For notifiable diseases, each health department has records on how many cases of particular diseases have been seen, and on which dates, over the years. These numbers of cases are obtained from surveillance mechanisms (to be discussed in detail in future issues). To determine if the number of cases you have is higher than expected, compare current reports of disease with previous weeks, or with reports during the same month or season in previous years. If the current numbers seem unusually high, you may have an outbreak on your hands.

For non-notifiable diseases or conditions, there are a variety of ways to determine approximately what the expected number of cases or the expected rate might be.

1. Check local hospital discharge records, mortality statistics, cancer registries, birth defect registries, or other available records.

2. If no local data are available, data from neighboring counties or states can be used to estimate rates.
3. Conduct a telephone survey of local health care providers to see if they have seen an unusually high number of cases of a particular disease.
4. Conduct a telephone survey of the community and ask about recent episodes or past occurrences of a particular disease to estimate rates.

Case definitions

Creating a case definition allows for a simple, uniform way to identify cases, and "standardizes" the investigation by having clear criteria for who should be considered a case and who should not. A case definition is unique for every outbreak situation, but is always based on objective measures (3). Every case definition includes three characteristics: person, place and time.

1. Person: age, gender, other relevant characteristics where applicable (occupation, sexual orientation, etc.)
2. Place: neighborhood, school, city, state, or attendance at a specific event where exposure was thought to take place
3. Time: dates during which exposure is thought to have been possible

A case definition can emphasize getting all possible cases (sensitivity), or can emphasize having only the exact illness you are investigating as cases (specificity). Generally, you start with a "loose" definition early in the investigation, which lends itself to identifying anyone who might possibly be a case (this is a *sensitive* case definition). The idea is to play it safe: it is better to gather too much information than too little. For instance, getting information about patients that later end up not being true cases is better than having to go back and find cases that you mistakenly ruled out early on. Likewise, gathering information from potential cases about many exposures that turn out not to be related to the outbreak is easier than going back, trying to contact cases again, and asking more questions about exposures you did not include in your early investigation because of a narrow case definition. As you become more sure of the symptoms and the agent, the place of exposure, and the time frame, you can safely narrow the case definition.

For example, the case definition from the listeriosis outbreak mentioned earlier was:

- Mother of a stillborn or premature infant infected with *L. monocytogenes*; or a pregnant woman/mother with a febrile illness (person)
- Winston-Salem, NC (place)
- October 24, 2000 to January 1, 2001 (time)

The case definition from a *Salmonella* outbreak in North Carolina caused by eating contaminated eggs might be:

- Culture-confirmed *Salmonella enteriditis* in a North Carolina resident (person)
- North Carolina (place)
- July 1 to September 7, 2001 (time)

Often, investigators prioritize all potential cases as "confirmed," "probable," and "possible" (or "suspected") in order to be sure that no one is missed. The CDC offers general guidelines for these definitions that can be tailored to a unique outbreak setting.

1. Confirmed: symptoms characteristic of the agent, as well as either a lab test confirming the presence of the agent or an epidemiologic link to a lab-confirmed case.

2. Probable: symptoms confirmed to match the outbreak agent, but no lab or epidemiologic link.

3. Possible: symptoms reported to match the outbreak agent, but no confirmation has been obtained.

Conclusion

This issue of FOCUS reviews verifying case reports and laboratory diagnoses, and how to determine expected rates of disease. Deciding whether to conduct an outbreak investigation requires an balance of disease reporting, correct diagnosis, background research, and good judgment.

Glossary

Agent: An infectious agent or disease agent. The micro-organism (virus or bacteria) that causes illness.

Case definition: A set of standard criteria for deciding whether an individual should be classified as having a health condition of interest.

Hepatitis A: A liver disease caused by the Hepatitis A virus. Symptoms can include abdominal pain, jaundice, nausea, diarrhea, and fever. Transmission is by the fecal-oral route.

Listeriosis: A disease caused by bacteria of the *Listeria* species. Symptoms can include fever, muscle ache, and vomiting or diarrhea. Nervous system infection can result in stiff neck, confusion, or convulsions. Infection in pregnant women may cause premature or stillborn birth. Transmission is usually occurs via contaminated foods.

Outbreak: A situation when the observed number of cases exceeds expected number of cases of a specific disease in a given population for a given period of time.

THE UNIVERSITY OF NORTH CAROLINA

North Carolina Center for Public Health Preparedness
The University of North Carolina at Chapel Hill
Campus Box 8165
Chapel Hill, NC 27599-8165

Phone: 919-843-5561
Fax: 919-843-5563
Email: nccphp@unc.edu

If you would like to receive electronic copies of *Focus on Field Epidemiology* periodical please fill out the form below:

- NAME: _____
- DEGREE (S): _____
- AFFILIATION: _____
- E-MAIL ADDRESS: _____
- May we e-mail any of your colleagues? If so, please include their e-mails here:

  _____

  _____

  _____

Please fax to: (919) 919-843-5563

or mail to: North Carolina Center for Public Health Preparedness
The University of North Carolina at Chapel Hill
Campus Box 8165
Chapel Hill, NC 27599-8165

Or go online: http://www.sph.unc.edu/nccphp/focus/

REFERENCES

1. Centers for Disease Control and Prevention. *Outbreak of Listeriosis Associated With Homemade Mexican-Style Cheese — North Carolina, October 2000-January 2001*. MMWR July 06, 2001; 50(26);560-2. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5026a3.htm.

2. Dombrowski, Julie. *Hepatitis A Among Men who Have Sex with Men*. 2002. Available at: http://www.epi.state.nc.us/epi/gcdc/pdf/HepatitisA.pdf.

3. Dicker RC, et al. Investigating an Outbreak. In: *Principles of Epidemiology: An Introduction to Applied Epidemiology and Biostatistics*. Centers for Disease Control and Prevention. 1992; 347-350. Available at: http://www.phppo.cdc.gov/PHTN//catalog/pdf-file/Epi_Course.pdf.

UPCOMING TOPICS!

- Case Finding and Line Listing: a Guide for the Investigator
- Epidemic Curves Ahead
- Hypothesis Generation during Outbreaks
- Designing Questionnaires for Outbreaks
- Interviewing Techniques for Epi Studies
- Introduction to Forensic Epidemiology

We are on the web!
http://www.sph.unc.edu/nccphp