



College of Nursing



Investigation of an Outbreak

- Introduction to Outbreak Investigations
- Steps of Outbreak Investigations

Christopher W. Blackwell, Ph.D., ARNP-C
Assistant Professor, College of Nursing
University of Central Florida

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Introduction to Investigating an Outbreak

- Uncovering Outbreaks:
 - An outbreak is the occurrence of more cases than expected
 - These occur frequently; often they are undetected
 - One way to assess for outbreaks is to closely monitor surveillance data; assess for commonalities among these data to determine relationships
 - Also detected through regular, timely analysis of surveillance data that reveals an ↑ in reported cases or an unusual clustering of cases by time and place
 - Syndromic surveillance found large ↑ in gastroenteritis in NYC in 2003 following a large-scale blackout; attributed to eating of spoiled meats
 - Infection control practitioners in hospital and clinic settings also collect data to ascertain if nosocomial infections are ↑; eg: taking wound isolates to determine ↑ in MRSA
 - Most outbreaks come to the attention of health authorities because they are notified by astute and concerned clinicians
 - An outbreak of West Nile Virus was detected after an MD treated 2 pts. w/ encephalitis in 1999; the same occurred in FL in 2001, when an astute MD notified health officials regarding a Dx of inhalation anthrax
 - Patients also notify health officials themselves sometimes, reporting illness, for example, after consuming food at a particular establishment or reporting an ↑ of a particular Dx within a community (eg—CA)



Introduction to Investigating an Outbreak

To uncover outbreaks:

- Review routinely collected surveillance data
- Astutely observe single events or clusters by clinicians, infection control practitioners, or laboratorians
- Review reports by one or more patients or members of the public

Epidemic: the occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time. Usually, the cases are presumed to have a common cause or to be related to one another in some way

Outbreak: epidemic limited to localized increase in the incidence of disease

Cluster: aggregation of cases in a given area over a particular period without regard to whether the number of cases is more than expected



Introduction to Investigating an Outbreak

- Deciding Whether to Investigate a Possible Outbreak:
 - Deciding on whether or not to investigate a potential outbreak depends on the severity of the illness, the # of cases, the source, mode of ease of transmission, and the availability of prevention and control measures
 - Most health depts. are apt to investigate an outbreak if:
 - # of persons affected is large; highly severe and life-threatening diseases that are easily ID and prevented are somewhat of an exception (botulism)
 - The disease is severe (high risk of hospitalizations, complications, or death)
 - Effective control measures exist
 - The potential to affect others unless prompt control measures are undertaken
 - At the state or national level, the unusual presentation of disease may spur an investigation; as may occurrence of a new or rare disease
 - Field investigation place a burden on health depts.; so, we must also consider availability of staff and resources and competing priorities
 - Field investigations are justified for one or more of the following reasons:
 - Control or prevention of the health problem
 - Opportunity to learn (research opportunity)
 - Public, political, or legal concerns
 - Training



Introduction to Investigating an Outbreak

– Control and Prevention:

- Most important public health reasons for investigating an outbreak are to help guide disease prevention and control strategies
- Control efforts depend on:
 - Knowledge of the agent
 - Natural course of the outbreak
 - Usual transmission mechanism of the disease
 - Available control measures
- For example:
 - A health dept. learns of an outbreak of Hep A (known agent), in which one of the victims is a restaurant cook
 - To prevent a second wave of cases (control measures):
 - » The dept. can offer immunoglobulin within 14 days of exposure (timing)
- Control measures aren't always necessary; often, if the outbreak follows a time cycle and is nearing its end, it is more essential to determine why the outbreak occurred and what could be done to eliminate it in the future
- The balance between control measures and further investigation depends on how much is known about the cause, the source, and the mode of transmission



Introduction to Investigating an Outbreak

Table 6.1 Relative Priority of Investigative and Control Efforts During an Outbreak, Based on Knowledge of the Source, Mode of Transmission, and Causative Agent

		<u>Source/Mode of Transmission</u> (How people are getting exposed to the agent)	
		Known	Unknown
Causative Agent	Known	Investigation + Control +++	Investigation +++ Control +
	Unknown	Investigation +++ Control +++	Investigation +++ Control +

+++ = highest priority

+ = lowest priority

Source: Goodman RA, Buehler JW, Koplan JP. The epidemiologic field investigation: science and judgment in public health practice. Am J Epidemiol 1990;132:9-16.



Introduction to Investigating an Outbreak

– Opportunity to Learn (Research Opportunity):

- Because randomized trials can not truly occur in public health, we must take advantage when the situation naturally arises
- For a newly recognized disease, field investigation provides an opportunity to characterize the natural history– including agent, mode of transmission, and incubation period– and the clinical spectrum of disease
- Investigators also attempt to characterize the populations at greatest risk and to ID specific risk factors
 - Acquiring such info. was an important motivation for investigators studying such newly recognized diseases as Legionnaire’s disease in Philadelphia in 1976, AIDS in the early 1980s, hantavirus in 1993, severe acute respiratory syndrome (SARS) in 2003, and avian flu in 2005
- Even for diseases well characterized, an outbreak may provide opportunities to gain additional knowledge by assessing the impact of control measures and the usefulness of new epidemiology and laboratory techniques



Introduction to Investigating an Outbreak

– Public, Political, or Legal Concerns:

- Important to note: While media and other public or political influences may pressure investigations into clusters of disease (eg: cancer in a community), RARELY do such investigations identify a causal link between exposure and disease
- Public concerns can also be alleviated by documenting and ID the *correct* cause of an outbreak instead of popular “theories”
- Some investigations are legally mandated: for example, National Institute for Occupational Safety and Health (NIOSH) must investigate risks to health and safety in the workplace if requested to do so by a union, three or more workers, or an employer

– Program Considerations:

- An outbreak of a disease targeted by a public health programs may reveal a weakness in that program and an opportunity to change or strengthen program efforts
- ID the outbreaks causes may ID populations that have been overlooked, failures in intervention strategies, or changes in the agent

– Training:

- Investigating an outbreak requires a combination of diplomacy, logical thinking, problem-solving ability, quantitative skills, epidemiologic know-how, and judgment—All of which improves with experience!



Introduction to Investigating an Outbreak



Exercise 6.1

During the previous year, nine residents of a community died from cervical cancer. List at least 4 reasons that might justify an investigation.

Nine cases of cancer in a community represents a cluster — a group of cases in a given area over a particular period of time that seems to be unusual, although we do not actually know the size of the community, the background rate of cancer, and the number of cases that might be expected. Nonetheless, either the health department or the community or both is concerned enough to raise the issue. Under these circumstances, an investigation may be justified for several reasons.

1. Because the number of expected cases is not known (or at least not stated), one reason to investigate is to determine how many cases to expect in the community. In a large community, nine cases of a common cancer (for example, lung, breast, or colon cancer) would not be unusual. If the particular cancer is a rare type, nine cases even in a large community may be unusual. And in a very small community, nine cases of even a common cancer may be unusual.
2. If the number of cancer cases turns out to be high for that community, public health officials might choose to investigate further. They may have a research agenda — perhaps they can identify a new risk factor (workers exposed to a particular chemical) or predisposition (persons with a particular genetic trait) for the cancer.
3. Control and prevention may be the justification for additional investigation. If modifiable risk factors are known or identified, control and prevention measures can be developed. Alternatively, if the cancer is one that can be treated successfully if found early, and a screening test is available, then investigation might focus on why these persons died from a treatable disease. If, for example, the nine cases were cancers of the cervix (detectable by Pap smear and generally nonfatal if identified and treated early), a study might identify: a) lack of access to healthcare; b) physicians not following the recommendations to screen women at appropriate intervals; and/or c) laboratory error in reading or reporting the test results. Measures to correct these problems, such as public screening clinics, physician education, and laboratory quality assurance, could then be developed.
4. If new staff need to gain experience in conducting cluster investigations, training might be a justification for investigating these cases. More commonly, cancer clusters generate public concern, which, in turn, often results in political pressure. Perhaps one of the affected persons is a member of the mayor's family. A health department needs to be responsive to such concerns, and should investigate enough to address the concerns with facts. Finally, legal concerns may prompt an investigation, especially if a particular site (manufacturing plant, houses built on an old dump site, etc.) is accused of causing the cancers.



Steps of an Outbreak Investigation

- Once the decision to investigate is made, working should be quick and focus on getting the right answer
- “Quick and Clean” not “Quick and Dirty”

Table 6.2 Epidemiologic Steps of an Outbreak Investigation

1. Prepare for field work
2. Establish the existence of an outbreak
3. Verify the diagnosis
4. Construct a working case definition
5. Find cases systematically and record information
6. Perform descriptive epidemiology
7. Develop hypotheses
8. Evaluate hypotheses epidemiologically
9. As necessary, reconsider, refine, and re-evaluate hypotheses
10. Compare and reconcile with laboratory and/or environmental studies
11. Implement control and prevention measures
12. Initiate or maintain surveillance
13. Communicate findings



Steps of an Outbreak Investigation

- Step 1: Prepare for Field Work:
 - Not always the 1st step since some investigations are spurned before confirming an ↑ in cases and verifying Dx's
 - Preparations to conduct a field investigation are grouped as scientific and investigative issues and mgmt. and operational issues
 - Scientific and Investigative Issues:
 - You must have the appropriate scientific knowledge, supplies, and equipment to carry out the investigation before departing to the field
 - Discuss the situation with an official who might have some experience with a similar case—consult the literature about similar cases
 - Contact the laboratory that will conduct bio testing—What are the appropriate collection, storage, and transportation techniques?
 - Determine what kind of protective equipment you'll need—gowns, gloves, masks (N95 vs. droplet mask)
 - Define your objectives and design a plan of action defining what will be done first, second, and third—"Hit the ground running"



Steps of an Outbreak Investigation

– Management and Operational Issues:

- Most investigations are conducted by a team—so the primary investigator must be a good epidemiologist, leader, manager, and coordinator
- Make up your team based on the needs of the investigation; do you need a:
 - Laboratorian?
 - Veterinarian?
 - Translator/ Interpreter?
 - Computer specialist?
 - Entomologist?
 - What is the role of each? Who is in charge?
 - If you are the consultant, are you expected to lead the investigation? What is your precise role expectation?
 - Who are your potential collaborators?:
 - » If the outbreak has an animal source = Food & Drug Administration
 - » If bioterrorist/ criminal intent suspected = Fed. Bureau Inves (FBI)
 - » If a natural disaster is involved, Federal Emergency Management Agency (FEMA)



Steps of an Outbreak Investigation

- Communication plans (including how often and when to provide conference calls or press sessions) must also be established to ensure fast and effective dissemination of information to public health officials and clinicians; this was highlighted in the West Nile, SARS, and anthrax outbreaks
- When a federal agency is involved in the survey of 10+ individuals, the White House Office of Management and Budget must provide clearance
- Operational and logistics are also essential:
 - Bring a phone card, cell phone, laptop computer, camera
 - Arrange where and when to meet local officials if traveling to a new area
 - Follow the strict budgetary constraints of the paying agency to arrange travel, lodging, and local transport
 - Obtain a passport, visa, etc. for international investigations



Steps of an Outbreak Investigation

- Step 2: Establish the Existence of an Outbreak:
 - In an outbreak or an epidemic, the cases are presumed to have a common cause or to be related to one another in some way
 - Note that an outbreak is an epidemic limited to localized \uparrow in the incidence of a disease
 - A cluster is an aggregation of cases in a given area over a particular period without regard to whether the number of cases is more than expected
 - Clusters aren't always true \uparrow in the incidence of a disease; for example, if cancer is more common in a particular neighborhood, the denominator reflecting the entire community or the prevalence of a certain type of cancer might be an expected level of prevalence

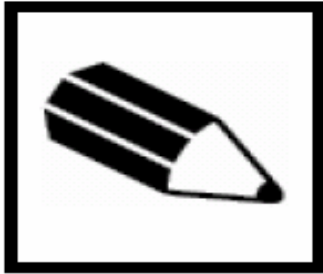


Steps of an Outbreak Investigation

- To determine if a true cluster of a condition is occurring, compare observed with expected
- The “expected” # is usually the # from the previous weeks or months, from a comparable period during the previous few years; but it can also come from hospital DCs, state/national data, registries, etc.
- Outbreaks are not always defined by ↑ in #s; severity of illness, potential for spread, availability of control measures, politics, public relations, resources, etc. also play a role
- ↑ in the # of reported cases (exceeding expected #s) doesn't always indicate true ↑:
 - Changes in local reporting?
 - Changes in case definitions?
 - ↑ awareness due to national/local press attention?
 - ↑ due to a new MD or infection control nurse reporting?
 - Misdiagnosis or lab errors?
 - Is there a change in the denominator? Eg: ↑ in pop. size in migrant areas, college towns, etc.



Steps of an Outbreak Investigation



Exercise 6.2

For the month of August, 12 new cases of tuberculosis and 12 new cases of West Nile virus infection were reported to a county health department. You are not sure if either group of cases is a cluster or an outbreak. What additional information might be helpful in making this determination?

First, you should check the dates of onset rather than dates of report. The 12 reports could represent 12 recent cases, but could represent 12 cases scattered in time that were sent in as a batch.

However, assuming that all 12 reports of tuberculosis and the 12 of West Nile virus infection represent recent cases in a single county, both situations could be called clusters (several new cases seen in a particular area during a relatively brief period of time). Classifying the cases as an outbreak depends on whether the 12 cases exceed the usual number of cases reported in August in that county.

Tuberculosis does not have a striking seasonal distribution. The number of cases during August could be compared with: a) the numbers reported during the preceding several months; and b) the numbers reported during August of the preceding few years.

West Nile virus infection is a highly seasonal disease that peaks during August-September-October. As a result, the number of cases in August is expected to be higher than the numbers reported during the preceding several months. To determine whether the number of cases reported in August is greater than expected, the number must be compared with the numbers reported during August of the preceding few years.



Steps of an Outbreak Investigation

- Step 3: Verify the Dx:
 - Addressed at the same time as verifying the outbreak
 - Significant because it ensures proper ID of the disease and verified control measures and r/o lab error as the basis for ↑ error
 - First, review the clinical findings and lab data; if the lab data is inconsistent with the epidemiologic data, ask a laboratorian to review the lab techniques
 - Second, visit an actual pt. with the disease; bring a specialist with you if necessary; ask them:
 - What were their exposures before becoming ill?
 - What do *they* think caused the illness?
 - Do they know anyone else with the illness?
 - Do they have anything in common with others who have the disease?
 - Third, summarize the clinical features using frequency distributions; these are essential in characterizing the spectrum of illness, verifying the Dx, and developing case definitions



Steps of an Outbreak Investigation

- Step 4: Construct a Working Case Definition:
 - A case definition is a standard set of criteria for deciding whether an individual should be classified as having the health condition of interest:
 - Contains clinical criteria and—in an outbreak setting—restrictions by time, place, and person:

restrictions by time, place, and person. The clinical criteria should be based on simple and objective measures such as “fever $\geq 40^{\circ}\text{C}$ (101°F),” “three or more loose bowel movements per day,” or “myalgias (muscle pain) severe enough to limit the patient’s usual activities.” The case definition may be restricted by time (for example, to persons with onset of illness within the past 2 months), by place (for example, to residents of the nine-county area or to employees of a particular plant) and by person (for example, to persons with no previous history of a positive tuberculin skin test, or to premenopausal women). Whatever the criteria, they must be applied consistently to all persons under investigation.



Steps of an Outbreak Investigation

- The case definition must not include the exposure of risk factor you are interested in evaluating
- EG: If a hypothesis is that persons on the west wing are at greater risk of disease, structure the case definition as: “illness among persons who worked in the facility between ___ and ___.”
 - Then conduct the appropriate analysis to determine whether or not those on the west wing really *do* have higher prevalence
- Usually, due to a degree of uncertainty, cases are defined as confirmed, probable, possible, or suspect; this is helpful when lab results are pending:
 - Complete confirmation usually requires laboratory verification
 - Probable = clinical features without lab confirmation
 - Possible = fewer of the typical clinical features



Steps of an Outbreak Investigation

- In an outbreak setting, time and place must be specified in the case definition
- For example, looking at an outbreak of meningitis must have a defined time period, as well as meeting PAHO case definitions:

Meningococcal Disease — PAHO Case Definition

Clinical case definition

An illness with sudden onset of fever ($>38.5^{\circ}\text{C}$ rectal or $>38.0^{\circ}\text{C}$ axillary) and one or more of the following: neck stiffness, altered consciousness, other meningeal sign or petechial or puerperal rash.

Laboratory criteria for diagnosis

Positive cerebrospinal fluid (CSF) antigen detection or positive culture.

Case classification

Suspected: A case that meets the clinical case definition.

Probable: A suspected case as defined above and turbid CSF (with or without positive Gram stain) or ongoing epidemic and epidemiological link to a confirmed case.

Confirmed: A suspected or probable case with laboratory confirmation.

Source: Pan American Health Organization. Case Definitions Meningococcal Disease. Epidemiological Bulletin 2002; 22(4):14–5.



Steps of an Outbreak Investigation

- Few case definitions are 100% accurate in their classifications
- Sometimes, those with S/S are included but not true cases while those with similar S/S may be included
- However, epidemiologists must always strive for few or no false-positives

More About Case Definitions

Early in an investigation, investigators may use a "loose" or sensitive case definition that includes confirmed, probable, and possible cases to characterize the extent of the problem, identify the populations affected, and develop hypotheses about possible causes. The strategy of being more inclusive early on is especially useful in investigations that require travel to different hospitals, homes, or other sites to gather information, because collecting extra data while you are there is more efficient than having to return a second time. This illustrates an important axiom of field epidemiology: *Get it while you can*. Later on, when hypotheses have come into sharper focus, the investigator may tighten the case definition by dropping the "possible" and sometimes the "probable" category. In analytic epidemiology, inclusion of false-positive cases can produce misleading results. Therefore, to test these hypotheses by using analytic epidemiology (see Step 8), specific or tight case definitions are recommended.

Other investigations, particularly those of a newly recognized disease or syndrome, begin with a relatively specific or narrow case definition. For example, acquired immunodeficiency syndrome (AIDS) and severe acute respiratory syndrome (SARS) both began with relatively specific case definitions. This ensures that persons whose illness meets the case definition truly have the disease in question. As a result, investigators could accurately characterize the typical clinical features of the illness, risk factors for illness, and cause of the illness. After the cause was known and diagnostic tests were developed, investigators could use the laboratory test to learn about the true spectrum of illness, and could broaden the case definition to include those with early infection or mild symptoms.



Steps of an Outbreak Investigation



Exercise 6.3

In 1989, a worldwide epidemic of a previously unrecognized syndrome occurred. This condition was characterized by severe myalgias (muscle pains) and an elevated number of a particular type of white blood cell called an eosinophil. The illness was given the name eosinophilia-myalgia syndrome. Public health officials initially used the following case definition:²⁵

Eosinophil count $\geq 2,000$ cells/mm³ in the absence of any other known cause of eosinophilia (in particular, parasitic or fungal infection, end-stage renal disease, leukemia, allergic disorder, or drug reaction)

Using the information in the line listing below, determine whether or not each should be classified as a case, according to the initial case definition above.

Table 6.3 Line Listing of 7 Persons with Suspected Eosinophilia-myalgia

Patient #	Eosinophils (per mm ³)	Other Known Cause	Myalgias	Severe Myalgias*	Case? (Initial Def)	Case? (Revised Def)
1	535	No	Yes	No	_____	_____
2	12,100	No	Yes	Yes	_____	_____
3	2,310	No	Yes	Yes	_____	_____
4	2,064	No	Yes	No	_____	_____
5	2,250	No	Yes	Yes	_____	_____
6	1,670	No	Yes	Yes	_____	_____
7	2,115	Leukemia	Yes	Yes	_____	_____

* Severe enough to affect the patient's ability to pursue usual daily activities

Eventually, public health officials agreed on the following revised case definition:²⁶

1. A peripheral eosinophil count of $\geq 1,000$ cells/mm³;
2. Generalized myalgia at some point during the illness severe enough to affect the patient's ability to pursue usual daily activities;
3. No infection or neoplasm that could account for #1 or #2.

Reclassify each patient using the revised case definition.



Steps of an Outbreak Investigation

Exercise 6.3

Initial Case Definition

Patient 1: No, eosinophil count < 2,000 cells/mm³

Patient 2: Yes

Patient 3: Yes

Patient 4: Yes

Patient 5: Yes

Patient 6: No, eosinophil count < 2,000 cells/mm³

Patient 7: No, other known cancer of eosinophilia

Revised Case Definition

Patient 1: No, eosinophil count < 1,000 cells/mm³ and myalgias not severe

Patient 2: Yes

Patient 3: Yes

Patient 4: No, myalgias not severe

Patient 5: Yes

Patient 6: Yes

Patient 7: No, other known cancer of eosinophilia

This illustrates that a case definition is a method for deciding whether to classify someone as having the disease of interest or not, not whether they actually do or do not have the disease. Patients 1 and 4 may have mild cases, and Patient 7 may have leukemia and eosinophilia-myalgia syndrome, but are classified as non-cases under the revised definition.



Steps of an Outbreak Investigation



Exercise 6.4

*In December 2003, an outbreak of gastroenteritis occurred among tenth-grade students who had participated in a city-wide field trip. Half of the students traveled from December 2 to December 7 (Tour A); the other half traveled from December 3 to December 8 (Tour B). The itineraries were similar. Although teachers and other adult chaperones accompanied the students on both tours, no adult reported illness. In addition, no illness was reported among students who did not go on the field trip, and no cases of *E. coli* O157 were reported in the community that week.*

*A line listing of 26 persons with symptoms of abdominal pain and/or diarrhea is presented below. Using the information in the line listing, develop a case definition that you might use for the outbreak investigation. [Note that persons infected with *E. coli* O157 typically experience severe abdominal cramps, bloody diarrhea, and low grade fever after a 1- to 8-day incubation period (usually 2-4 days).]*

Table 6.4 Line Listing of 26 Persons with Symptoms, School District A, December 2003

Patient #	Grade & School	Age	Sex	Tour	Onset Date	Severe Abdominal Pain?	No. Times Diarrhea	Stool Testing
1	10-1	17	M	A	Dec. 8	Y	3	Not done
2	10-1	16	F	A	Dec. 6	N	1	Negative
3	10-2	16	M	A	Dec. 10	Y	2	<i>E. coli</i> O157
4	10-2	17	F	A	Dec. 8	Y	3	Not done
5	10-2	16	F	A	Dec. 5	Y	8	<i>E. coli</i> O157
6	10-2	16	M	A	Dec. 6	Y	3	Not done
7	10-3	17	M	A	Dec. 7	Y	4	Not done
8	10-3	17	F	A	Dec. 8	Y	2	<i>E. coli</i> O157
9	10-3	16	F	A	Dec. 7	Y	3	Negative
10	10-4	17	F	A	Dec. 7	Y	2	<i>E. coli</i> O157
11	10-4	16	M	A	Dec. 8	Y	3	Not done
12	10-4	16	M	A	Dec. 9	Y	3	Negative
13	10-5	16	F	A	Dec. 8	Y	3	Not done
14	10-6	17	F	B	Dec. 8	Y	3	<i>E. coli</i> O157
15	10-6	16	F	B	Dec. 9	Y	2	Negative
16	10-7	17	F	B	Dec. 6	Y	3	Not done
17	10-7	17	F	B	Dec. 7	Y	5	<i>E. coli</i> O157
18	10-7	16	F	B	Dec. 8	Y	2	Negative
19	10-8	17	F	B	Dec. 6	Y	5	<i>E. coli</i> O157
20	10-8	17	F	B	Dec. 7	Y	3	Negative
21	10-9	16	M	B	Dec. 8	Y	2	Not done
22	10-9	16	F	B	Dec. 7	Y	3	Negative
23	10-9	16	F	B	Dec. 7	Y	3	<i>E. coli</i> O157
24	10-10	17	F	B	Dec. 9	Y	3	<i>E. coli</i> O157
25	10-10	17	M	B	Dec. 7	N	1	Negative
26	10-10	16	M	B	Dec. 6	Y	3	Not done



Steps of an Outbreak Investigation

Exercise 6.4

A case definition is a set of standard criteria for determining whether an individual should be categorized as having a particular disease or health-related condition. For an outbreak, a case definition consists of clinical criteria and specification of time, place, and person. A case definition can have degrees of certainty, e.g., suspect case (usually based on clinical and sometimes epidemiologic criteria) versus confirmed case (based on laboratory confirmation).

The outbreak appeared to be limited to students (no adults reported illness), but included both tour groups. Some students had severe abdominal pain and diarrhea and stool cultures positive for *E. coli* O157. Clearly these should be counted as case-patients. Some students had the same symptoms but negative cultures. Should they be counted as case-patients? Still others had the same symptoms but no stool testing. Should they be counted as case-patients? Finally, two students had single bouts of diarrhea, but no abdominal pain and negative cultures.

No one case definition is the absolutely correct case definition. One investigator could decide to include those with symptoms but without testing as suspect or probable cases, while another investigator could exclude them. Similarly, one investigator might put a great deal of faith in the stool culture and exclude those who tested negative, regardless of the presence of compatible symptoms, while another investigator might allow that some stool cultures could be “false negatives” (test negative even though the person actually has the infection) and include them in a suspect or probable or possible category. The two students with single bouts of diarrhea but no abdominal pain and negative cultures seem least likely to have true cases of *E. coli* infection.

Similarly, the beginning time limit could be set on December 2, the date that Tour A departed, or could be set later, to account for the minimum incubation period.

So, one case definition might be:

- PERSON: Any tenth-grade student who went on either tour
- PLACE: Limited to students at city high schools
- TIME: Onset since December 2? 3? 4?
- CLINICAL: Confirmed stool sample positive for *E. coli* O157:H7, regardless of symptoms
- SUSPECT: Self-reported severe abdominal pain and diarrhea >2 episodes/day, with stool culture not done; or self-reported abdominal pain and diarrhea >2 episodes/day and stool culture negative



Steps of an Outbreak Investigation

- Step 5: Find Cases Systematically & Record Data:
 - Because such a small % of cases brought to the attention of health depts. are determined to be real cases, public health workers must look for additional cases to determine the true geographic extent of the problem and affected pop.
 - Enhanced passive and active surveillance are typically the first efforts
 - Sometimes, the media is alerted regarding a potential outbreak (contaminated turkey w/ listeriosis in 2002)
 - If cases are more restricted, often a survey is conducted of the entire population via questionnaire
 - Regardless of what instrument is used to collect the data, it is essential to obtain certain information



Steps of an Outbreak Investigation

- **Identifying information.** A name, address, and telephone number is essential if investigators need to contact patients for additional questions and to notify them of laboratory results and the outcome of the investigation. Names also help in checking for duplicate records, while the addresses allow for mapping the geographic extent of the problem.
- **Demographic information.** Age, sex, race, occupation, etc. provide the **person** characteristics of descriptive epidemiology needed to characterize the populations at risk.
- **Clinical information.** Signs and symptoms allow investigators to verify that the case definition has been met. Date of onset is needed to chart the time course of the outbreak. Supplementary clinical information, such as duration of illness and whether hospitalization or death occurred, helps characterize the spectrum of illness.
- **Risk factor information.** This information must be tailored to the specific disease in question. For example, since food and water are common vehicles for hepatitis A but not hepatitis B, exposure to food and water sources must be ascertained in an outbreak of the former but not the latter.
- **Reporter information.** The case report must include the reporter or source of the report, usually a physician, clinic, hospital, or laboratory. Investigators will sometimes need to contact the reporter, either to seek additional clinical information or report back the results of the investigation.



Steps of an Outbreak Investigation

Table 6.5 Line Listing of Demographic, Clinical, and Exposure Characteristics of 22 Cases of Bioterrorism-Related Anthrax—United States, 2001

Case No.	Onset Date, 2001	Date of Anthrax Diagnosis by Lab Testing	State ^a	Age (yrs)	Sex ^a	Race ^a	Occupation ^a	Case Status ^b	Anthrax Presentation ^b	Outcome	Diagnostic Tests ^a
1	9/22	10/19	NY	31	F	W	NY Post employee	Suspect	Cutaneous	Alive	Serum IgG reactive
2	9/25	10/12	NY	38	F	W	NBC anchor assistant	Confirmed	Cutaneous	Alive	Skin biopsy IHC+ / serum IgG reactive
3	9/26	10/18	NJ	39	M	W	USPS machine mechanic	Suspect	Cutaneous	Alive	Serum IgG reactive
4	9/28	10/15	FL	73	M	W, H	AMI mailroom worker	Confirmed	Inhalational	Alive	Pleural biopsy IHC+ / serum IgG reactive
5	9/28	10/18	NJ	45	F	W	USPS mail carrier	Confirmed	Cutaneous	Alive	Skin biopsy IHC+ and PCR+ / serum IgG reac.
6	9/28	10/12	NY	23	F	W	NBC TV news intern	Suspect	Cutaneous	Alive	Serum IgG reactive
7	9/29	10/15	NY	0.6	M	W	Child of ABC employee	Confirmed	Cutaneous	Alive	Skin biopsy IHC+ / blood PCR+
8	9/30	10/4	FL	63	M	W	AMI photo editor	Confirmed	Inhalational	Dead	Cerebrospinal fluid culture +
9	10/1	10/18	NY	27	F	W	CBS anchor assistant	Confirmed	Cutaneous	Alive	Skin biopsy IHC+ / serum IgG reactive
10	10/14	10/19	PA	35	M	W	USPS mail processor	Confirmed	Cutaneous	Alive	Blood culture + / serum IgG reactive
11	10/14	10/28	NJ	56	F	B	USPS mail processor	Confirmed	Inhalational	Alive	Blood PCR+ / pleural fluid cytology IHC+ / serum IgG reactive
12	10/15	10/29	NJ	43	F	A	USPS mail processor	Confirmed	Inhalational	Alive	Pleural fluid IHC+ / bronchial biopsy IHC+ / serum IgG reactive
13	10/16	10/21	VA	56	M	B	USPS mail worker	Confirmed	Inhalational	Alive	Blood culture +
14	10/16	10/23	MD	55	M	B	USPS mail worker	Confirmed	Inhalational	Dead	Blood culture +
15	10/16	10/26	MD	47	M	B	USPS mail worker	Confirmed	Inhalational	Dead	Blood culture +
16	10/16	10/22	MD	56	M	B	USPS mail worker	Confirmed	Inhalational	Alive	Blood culture +
17	10/17	10/29	NJ	51	F	W	Bookkeeper	Confirmed	Cutaneous	Alive	Skin biopsy IHC+ and PCR+ / serum IgG reactive
18	10/19	10/22	NY	34	M	W, H	NY Post mail handler	Suspect	Cutaneous	Alive	Skin biopsy IHC+
19	10/22	10/25	VA	59	M	W	Government mail processor	Confirmed	Inhalational	Alive	Blood culture +
20	10/23	10/28	NY	38	M	W	NY Post employee	Confirmed	Cutaneous	Alive	Skin biopsy culture +
21	10/25	10/30	NY	61	F	A	Hospital supply worker	Confirmed	Inhalational	Dead	Pleural fluid and blood culture +
22	11/14	11/21	CT	94	F	W	Retired at home	Confirmed	Inhalational	Dead	Blood culture +



Steps of an Outbreak Investigation



Exercise 6.5

Review the six case report forms in Figure 6.1. Create a line listing based on this information.

FIGURE 6.1

STATE DISEASE REPORT FORM		
NAME	AGE	PHONE
Clifton, R	46	555-2110
ADDRESS	SEX	RACE
361 Chander St.	Male	White
CITY, STATE	COUNTY	
Springdale, VA	Columbia	
DISEASE	DATE OF ONSET	LAB CONFIRMED?
Lyme Disease	8/1/2004	Yes
HOSPITAL ALERTED? HOSPITAL NAME	ADMISSION DATE	DISCHARGE DATA
Yes		
LAB TEST RESULTS	COMMENTS (CLINICAL DESCRIPTION, IMMUNIZATION THEORY, ETC.)	
WB IgM+	Erythema migrans, fatigue, sweats, chills	
POSSIBLE EXPOSURE		
PHYSICIAN REPORTING	PHONE	DATE OF REPORT
Dr. Snow	555-1200	11/24/04

STATE DISEASE REPORT FORM		
NAME	AGE	PHONE
Houston, M.	56	555-4897
ADDRESS	SEX	RACE
4890 Pleasant St.	Female	White
CITY, STATE	COUNTY	
Arlington, VA	Columbia	
DISEASE	DATE OF ONSET	LAB CONFIRMED?
Lyme Disease	8/2/2004	Yes
HOSPITAL ALERTED? HOSPITAL NAME	ADMISSION DATE	DISCHARGE DATA
Yes		
LAB TEST RESULTS	COMMENTS (CLINICAL DESCRIPTION, IMMUNIZATION THEORY, ETC.)	
WB IgM+; WB IgG+	Erythema migrans, arthritis, fatigue, sweats, fever	
POSSIBLE EXPOSURE		
PHYSICIAN REPORTING	PHONE	DATE OF REPORT
Dr. Farr	555-1313	11/24/04

STATE DISEASE REPORT FORM		
NAME	AGE	PHONE
Mason, M.	40	555-3756
ADDRESS	SEX	RACE
34 Winifred Ave.	Female	White
CITY, STATE	COUNTY	
Brookville, VA	Columbia	
DISEASE	DATE OF ONSET	LAB CONFIRMED?
Lyme Disease	8/17/2004	Yes
HOSPITAL ALERTED? HOSPITAL NAME	ADMISSION DATE	DISCHARGE DATA
Yes		
LAB TEST RESULTS	COMMENTS (CLINICAL DESCRIPTION, IMMUNIZATION THEORY, ETC.)	
WB IgM+; WB IgG+	Erythema migrans	
POSSIBLE EXPOSURE		
PHYSICIAN REPORTING	PHONE	DATE OF REPORT
Dr. Howard	555-1950	11/24/04



Steps of an Outbreak Investigation

STATE DISEASE REPORT FORM		
NAME Michael, S.	AGE 53	PHONE 555-4899
ADDRESS 48 Valley Hill Dr.	SEX Male	RACE Black
CITY, STATE Brookville, VA	COUNTY Columbia	
DISEASE Lyme Disease	DATE OF ONSET 9/02/2004	LAB CONFIRMED? Yes
HOSPITAL ALERTED? HOSPITAL NAME Yes - Columbia Medical Ctr	ADMISSION DATE 9/18/04	DISCHARGE DATA
LAB TEST RESULTS: WB IgM+; WB IgG-		
COMMENTS (CLINICAL DESCRIPTION, IMMUNIZATION THEORY, ETC.) Erythema migrans		
POSSIBLE EXPOSURE		
PHYSICIAN REPORTING Dr. Fine	PHONE 555-1951	DATE OF REPORT 11/24/04

STATE DISEASE REPORT FORM		
NAME Rollins, W.	AGE 45	PHONE 555-4771
ADDRESS 127 Midland St.	SEX Male	RACE White
CITY, STATE Portland, VA	COUNTY Columbia	
DISEASE Lyme Disease	DATE OF ONSET Mid May 2004	LAB CONFIRMED? Yes
HOSPITAL ALERTED? HOSPITAL NAME	ADMISSION DATE	DISCHARGE DATA
LAB TEST RESULTS: WB IgG+		
COMMENTS (CLINICAL DESCRIPTION, IMMUNIZATION THEORY, ETC.) Arthritis, arthralgias, headache, fatigue, sweats, chills		
POSSIBLE EXPOSURE		
PHYSICIAN REPORTING Dr. Howard	PHONE 555-1950	DATE OF REPORT 11/24/04

STATE DISEASE REPORT FORM		
NAME TURLEY, L.	AGE 13	PHONE 555-1539
ADDRESS 12 Elmwood Rd.	SEX Male	RACE Black
CITY, STATE Salem, VA	COUNTY Columbia	
DISEASE Lyme Disease	DATE OF ONSET 2003	LAB CONFIRMED? No
HOSPITAL ALERTED? HOSPITAL NAME	ADMISSION DATE	DISCHARGE DATA
LAB TEST RESULTS		
COMMENTS (CLINICAL DESCRIPTION, IMMUNIZATION THEORY, ETC.) Arthritis, arthralgias, fatigue		
POSSIBLE EXPOSURE		
PHYSICIAN REPORTING Dr. Steere	PHONE 555-1234	DATE OF REPORT 11/24/04



Steps of an Outbreak Investigation

Exercise 6.5

ID #	Age	Sex	Race	Disease	Date of Onset	Lab Results	Signs, Symptoms	Physician
1	46	M	W	Lyme disease	8/1/2004	WB IgM+	EM,Fat,S,C	Snow
2	56	F	W	Lyme disease	8/2/2004	WB IgM+, WB IgG+	EM,A,Fat,S, Fev	Farr
3	40	F	W	Lyme disease	8/17/2004	WB IgM+, WB IgG+	EM	Howard
4	53	M	B	Lyme disease	9/18/2004	WB IgM+, WB IgG-	EM	Fine
5	45	M	W	Lyme disease	mid-May 2004	WB IgG+	A,Arthral, HA,Fat,S,C	Howard
6	13	M	B	Lyme disease	2003		A,Arthral,Fat	Steere

A = arthritis

Arthral = arthralgias

C = chills

EM = erythema migrans

Fat = fatigue

Fev = fever

HA = headache

S = sweats



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Steps of an Outbreak Investigation

- Step 6: Perform Descriptive Epidemiology:
 - After ID and gathering basic information on the persons with the disease, systematically describe some of the key characteristics of those persons
 - This process of characterizing an outbreak by time, place, and person is descriptive epidemiology
 - This step is crucial for several reasons:

- Summarizing data by key demographic variables provides a comprehensive characterization of the outbreak — trends over time, geographic distribution (place), and the populations (persons) affected by the disease.
- From this characterization you can identify or infer the population at risk for the disease.
- The characterization often provides clues about etiology, source, and modes of transmission that can be turned into testable hypotheses (see Step 7).
- Descriptive epidemiology describes the where and whom of the disease, allowing you to begin intervention and prevention measures.
- Early (and continuing) analysis of descriptive data helps you to become familiar with those data, enabling you to identify and correct errors and missing values.

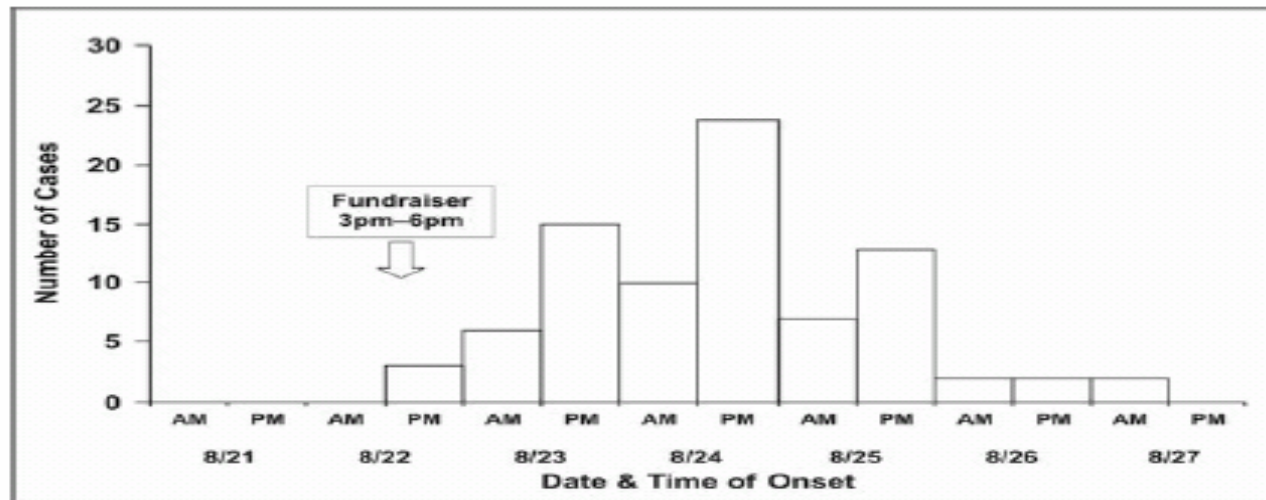


Steps of an Outbreak Investigation

– Time:

- The time course of an epidemic is plotted on a graph called an epidemic curve, which displays the outbreak's magnitude and time trend
- The classic epidemic curve graphs the number of cases by date or time of onset of illness:

Figure 6.2a Outbreak of *Salmonella* Enteritidis Gastroenteritis—Maryland, 2003 (Epidemic Curve by 12-Hour Intervals)



Source: Castel AD, Blythe D, Edwards L, Totaro J, Shah D, Moore M. A large outbreak of *Salmonella* Enteritidis infections associated with crabcakes at a church fundraiser—Maryland, 2003. Presented at 53rd Annual Epidemic Intelligence Service Conference, April 19-23, 2004, Atlanta.



Steps of an Outbreak Investigation

Epidemic curves are a basic investigative tool because they are so informative (see Lesson 4).

- The epi curve shows the magnitude of the epidemic over time as a simple, easily understood visual. It permits the investigator to distinguish epidemic from endemic disease. Potentially correlated events can be noted on the graph.
- The shape of the epidemic curve may provide clues about the pattern of spread in the population, e.g., point versus intermittent source versus propagated.
- The curve shows where you are in the course of the epidemic — still on the upswing, on the down slope, or after the epidemic has ended. This information forms the basis for predicting whether more or fewer cases will occur in the near future.
- The curve can be used for evaluation, answering questions like: How long did it take for the health department to identify a problem? Are intervention measures working?
- Outliers — cases that don't fit into the body of the curve — may provide important clues.
- If the disease and its incubation period are known, the epi curve can be used to deduce a probable time of exposure and help develop a questionnaire focused on that time period.



Steps of an Outbreak Investigation

Figure 6.2b Outbreak of *Salmonella* Enteritidis Gastroenteritis—Maryland, 2003 (Epidemic Curve by 6-Hour Intervals)

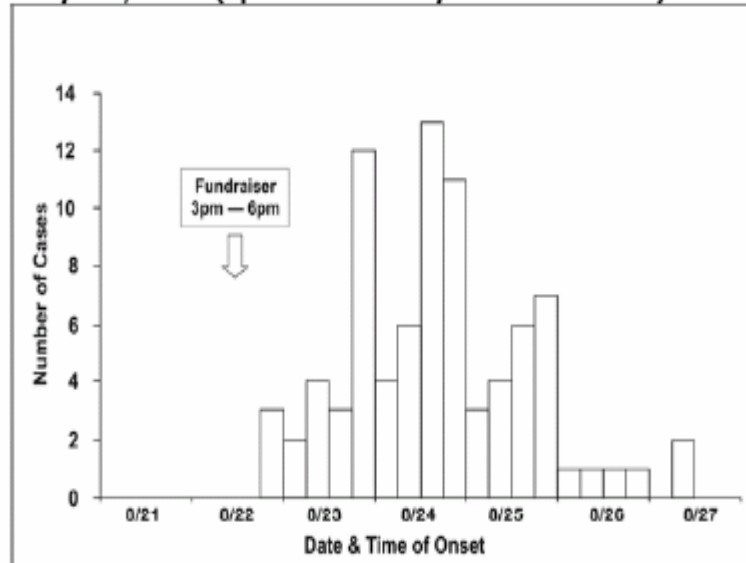


Figure 6.2c Outbreak of *Salmonella* Enteritidis Gastroenteritis—Maryland, 2003 (Epidemic Curve by One Day Intervals)

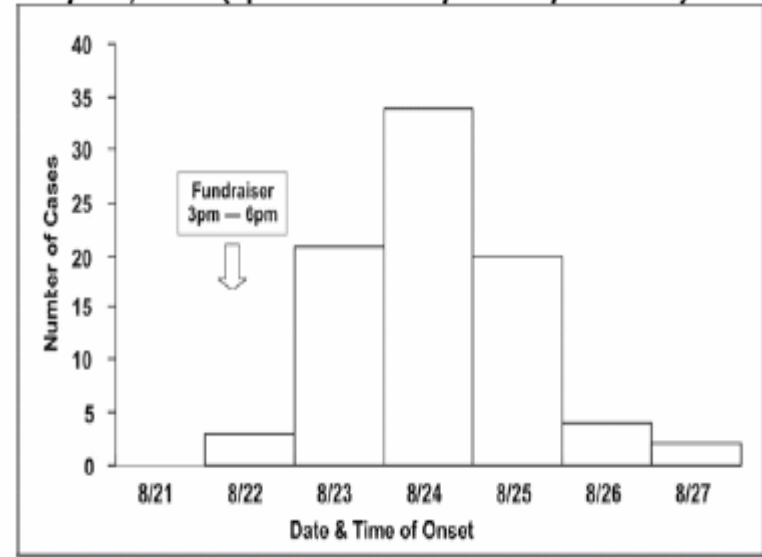
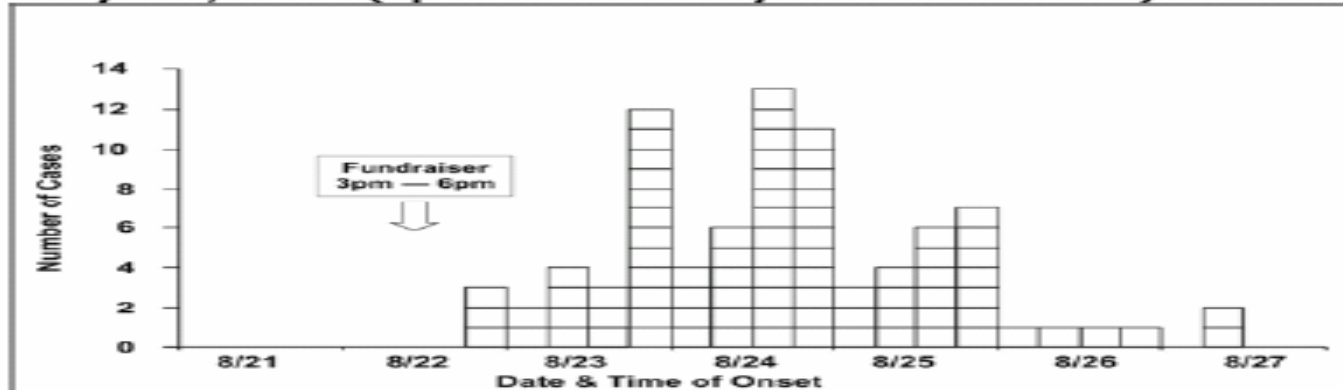


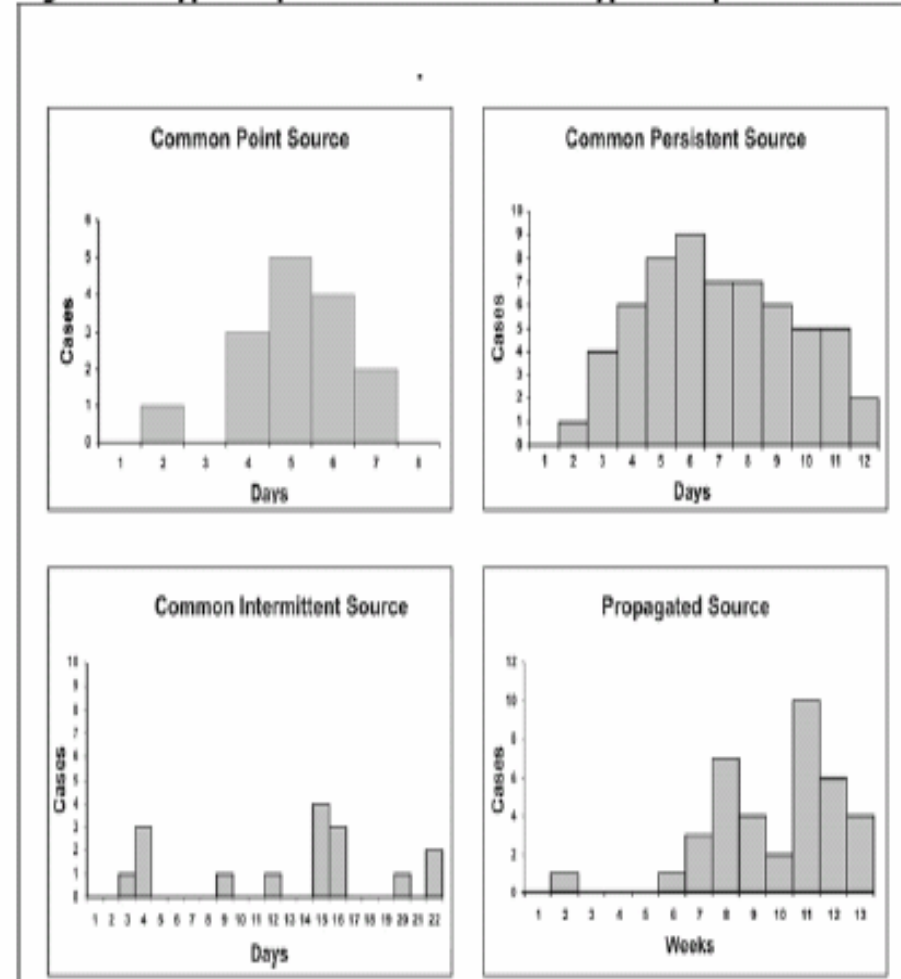
Figure 6.2d Outbreak of *Salmonella* Enteritidis Gastroenteritis—Maryland, 2003 (Epidemic Curve by 6-Hour Intervals)



Steps of an Outbreak Investigation

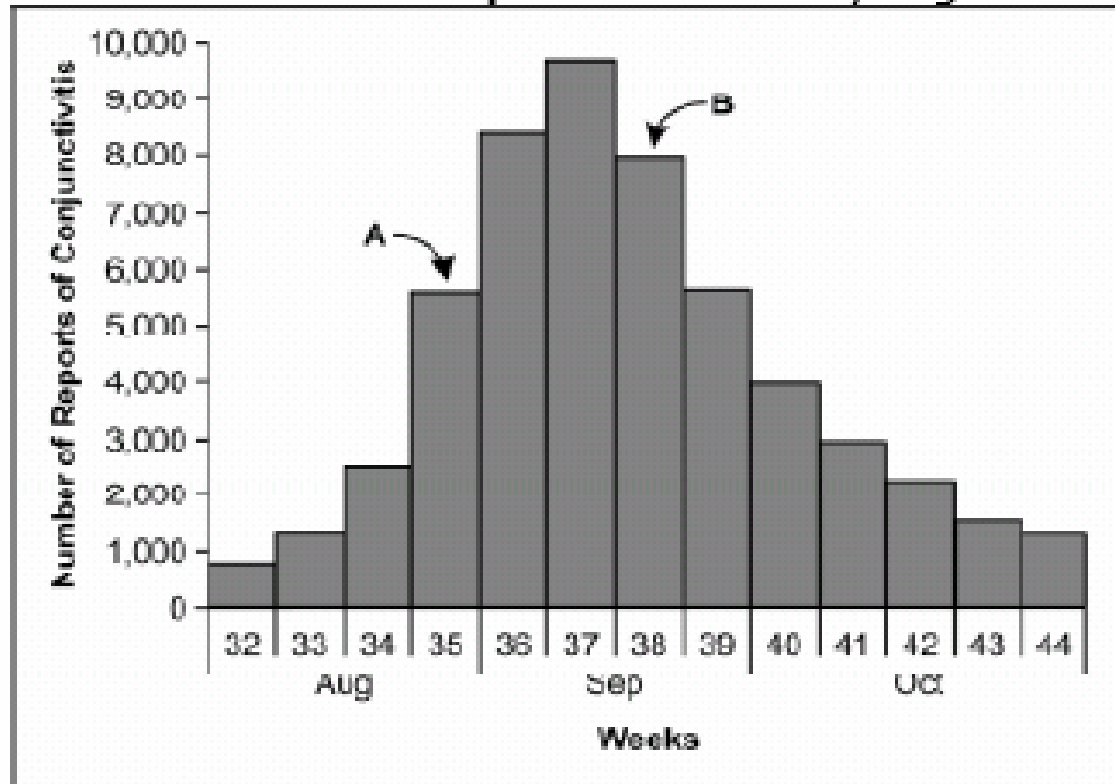
- Interpreting an Epidemic Curve:
 - 1st step is to look at the overall shape, determined by the epidemic pattern, the period of time over which susceptible persons are exposed, and the min., avg., and max. incubation periods for the disease
 - An epidemic curve that has a steep upslope and a more gradual down slope is point source, persons are exposed to the same source over a relative brief period: any \uparrow in cases suggests sudden exposure to a common course one incubation period earlier:

Figure 6.3 Typical Epi Curves for Different Types of Spread



Steps of an Outbreak Investigation

Figure 6.4 Number of Cases of Acute Hemorrhagic Conjunctivitis, By Month and Week of Report—Puerto Rico, August 7–October 30, 2003



Adapted from: Acute hemorrhagic conjunctivitis outbreak caused by Coxsackievirus A24—Puerto Rico, 2003. MMWR 2004;53:632–4.



Steps of an Outbreak Investigation

- Cases that stand apart may be just as important as the overall pattern
- An early case may represent a background or unrelated case, a source of the epidemic, or a person who was exposed earlier than most of the cases
- Late cases may represent unrelated cases, or persons exposed later than most other; or can be miscoded or erroneous data
- All outliers are worth examining carefully because if they are part of the outbreak, they may have an easily identifiable exposure that may point directly to the source
- In a point-source epidemic of a known disease with a known incubation period, the epidemic curve can be used to ID a likely period of exposure
- To ID the likely period of exposure from an epidemic curve:
 - Look up the avg. and min. incubation periods of the disease (available on the WWW from CDC or *Control of Communicable Diseases Manual*)
 - ID the peak of the outbreak or the median case and count back on the X-Axis one avg. incubation period, note the date
 - Start at the earliest case of the epidemic and ct. back the min. incubation period and note this date as well



Steps of an Outbreak Investigation

- Ideally, the 2 dates will be similar, which is the probable period of exposure
- Widen the probable period of exposure 20-50% on either side of the dates; ask about exposures during this widened period in an attempt to ID the source
- If the time of exposure and the times of onset of illness are known but the cause is not known, the incubation period can be estimated from the epidemic curve:
 - Subtract the time of onset of the earliest cases from the time of exposure to estimate the min. incubation period
 - Subtract the time of onset of the median cases from the time of exposure to estimate the median incubation period
 - Compare the incubation period with those of established diseases which might be the possible etiology



Steps of an Outbreak Investigation

EXAMPLE: Interpreting an Epidemic Curve

Consider, for example, the outbreak of hepatitis A illustrated by the epidemic curve in Figure 6.5. The incubation period for hepatitis A ranges from 15 to 50 days (roughly 2 to 7 weeks), with an average incubation period of 28–30 days (roughly one month). Because cases can occur from 15 to 50 days after exposure, all cases from a point source exposure should occur within a span of $50 - 15 = 35$ days.

Figure 6.5 Hepatitis A from Sub Shop—Massachusetts, 2001



Adapted from: Foodborne transmission of hepatitis A—Massachusetts, 2001. *MMWR* 2003;52:565–7.



Steps of an Outbreak Investigation

Is this epidemic curve consistent with a point-source epidemic? (That is, do all of the cases occur with one incubation period?)

Yes. The date of onset of the first case was during the week of October 28. The date of onset of the last known case was during the week of November 18, less than one month later. All of the cases occur within the range of incubation periods expected for a point source exposure. Therefore, the epidemic curve can be used to identify the likely period of exposure.

What is the peak of the outbreak or the median date of onset?

Both the peak of the outbreak and the median case occurred during the week of November 4.

When is the likely date(s) of exposure, based on one average incubation period prior to the peak (median date) of the outbreak?

Since both the peak and the median of the outbreak occurred during the week of November 4, the most likely period of exposure was a month earlier, in early October.

When is the beginning of the outbreak?

The earliest case occurred during the week of October 28.

When is the likely dates of exposure, based on the minimum incubation period before the first case?

Subtracting 2 weeks from the week of October 28 points to the week of October 14.

Thus you would look for exposures during the weeks of October 7 and 14, plus or minus a few days. This turned out to be the exact period during which a restaurant employee, diagnosed with hepatitis A in mid-October, would have been shedding virus while still working. In summary, the graph reflects an outbreak (number of cases clearly in excess of usual) beginning during the week of October 28, peaking during the week of November 4, and ending during the week of November 18. Based on these data and knowledge of the incubation period of hepatitis A, the period of exposure was probably in early to mid-October.



Steps of an Outbreak Investigation



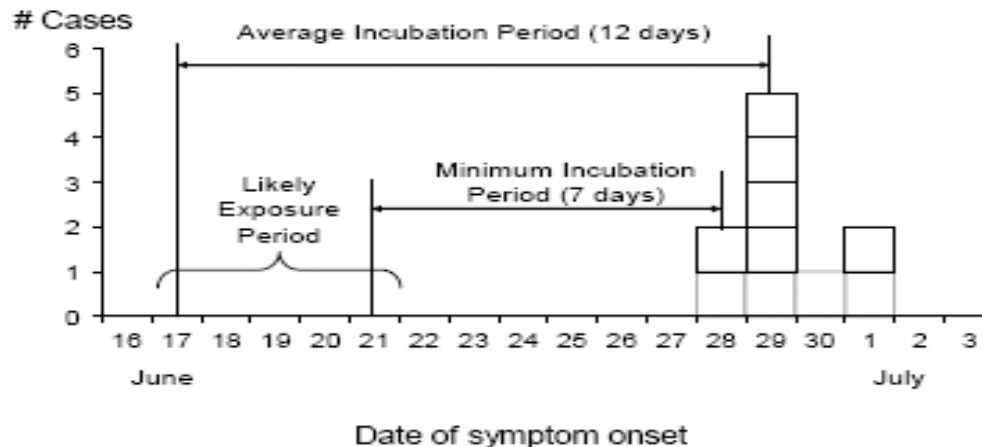
Exercise 6.6

An outbreak of an acute respiratory disease, *coccidioidomycosis*, occurred among volunteers, group leaders, and archaeologists who began working at a Native American archaeological site in Utah on June 18.³⁰

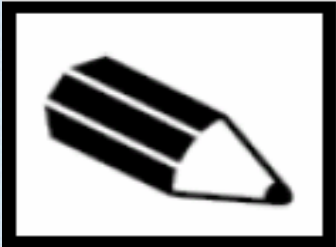
A. Using the dates of onset listed below, draw an epidemic curve. Graph paper is provided at the end of this lesson.

<u>Case #</u>	<u>Date of Onset</u>	<u>Case #</u>	<u>Date of Onset</u>
1	6/28	6	6/29
2	6/28	7	6/29
3	6/29	8	6/30
4	6/29	9	7/1
5	6/29	10	7/1

PART A



Steps of an Outbreak Investigation



Exercise 6.6

An outbreak of an acute respiratory disease, coccidioidomycosis, occurred among volunteers, group leaders, and archaeologists who began working at a Native American archaeological site in Utah on June 18.³⁰

- B. The average incubation period for coccidioidomycosis is 12 days, with a minimum incubation period of 7 days. Using your epidemic curve and the average and minimum incubation periods for coccidioidomycosis, identify the likely exposure period.*

PART B

The date of onset of the earliest case was June 28. Subtracting the minimum incubation period (7 days) from June 28 points to June 21. The median and modal date of onset was June 29. Subtracting the average (say, 12 days) from June 29 points to June 17. So the most likely exposure period was sometime around June 17 through June 21, give or take a day or two on either side. Indeed, the investigators determined that exposure most likely occurred on June 19, when all ill persons either actively participated in or were nearby the sifting of dirt that probably harbored the organism.



Steps of an Outbreak Investigation

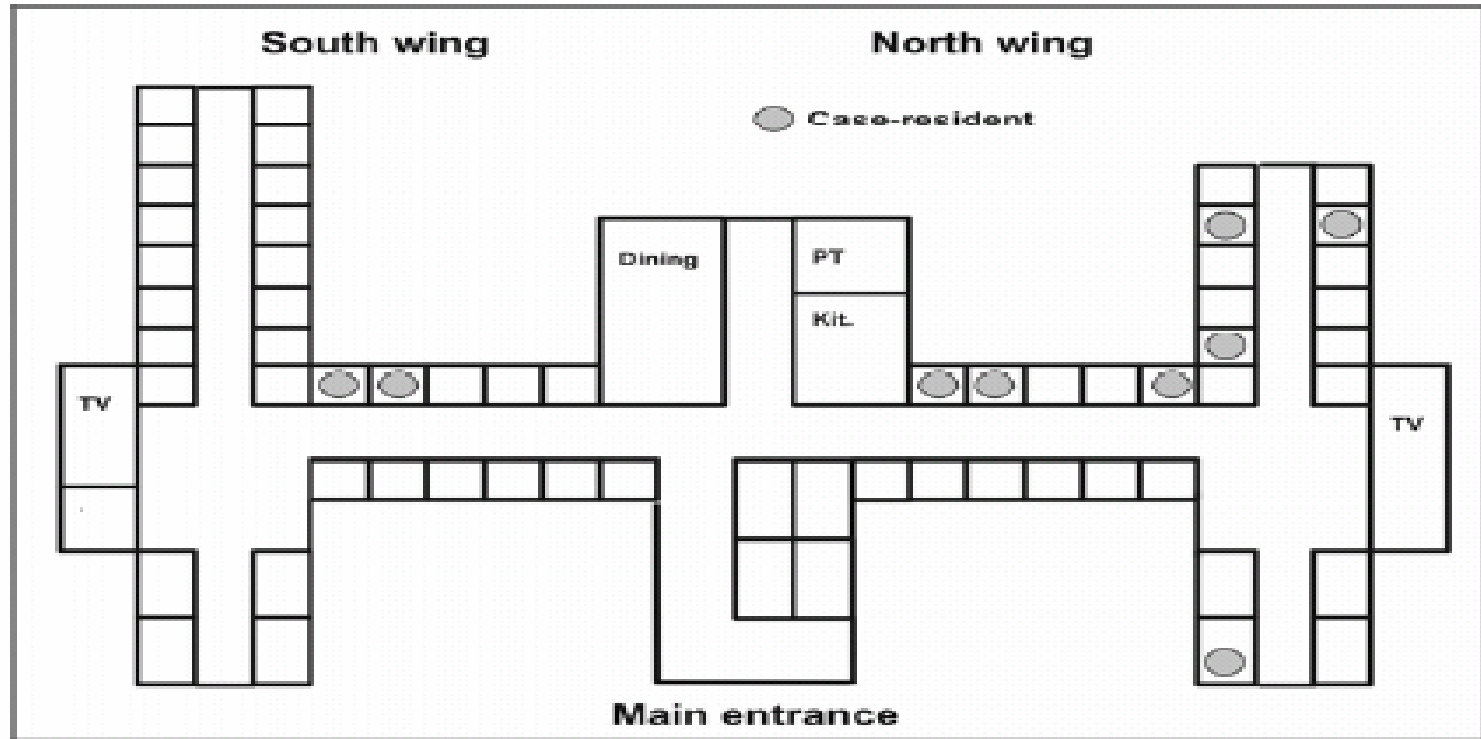
– Place:

- Demonstrates geographic extent of the problem and demonstrated clusters or patterns that provide important etiologic clues
- Spot Maps are excellent at pinpointing exposure locations and assessing geographic trends:
 - If the spot map shows a cluster pattern, look for possible explanations— water supplies, wind currents, or proximity to restaurant or store
 - Clustering of cases in a wing of a nursing home = either focal source or person-to-person spread; scattering of cases throughout a facility is probably common source, like water or dining hall



Steps of an Outbreak Investigation

Figure 6.6 Cases of Pneumonia by Room, Nursing Home A—New Jersey, 2001

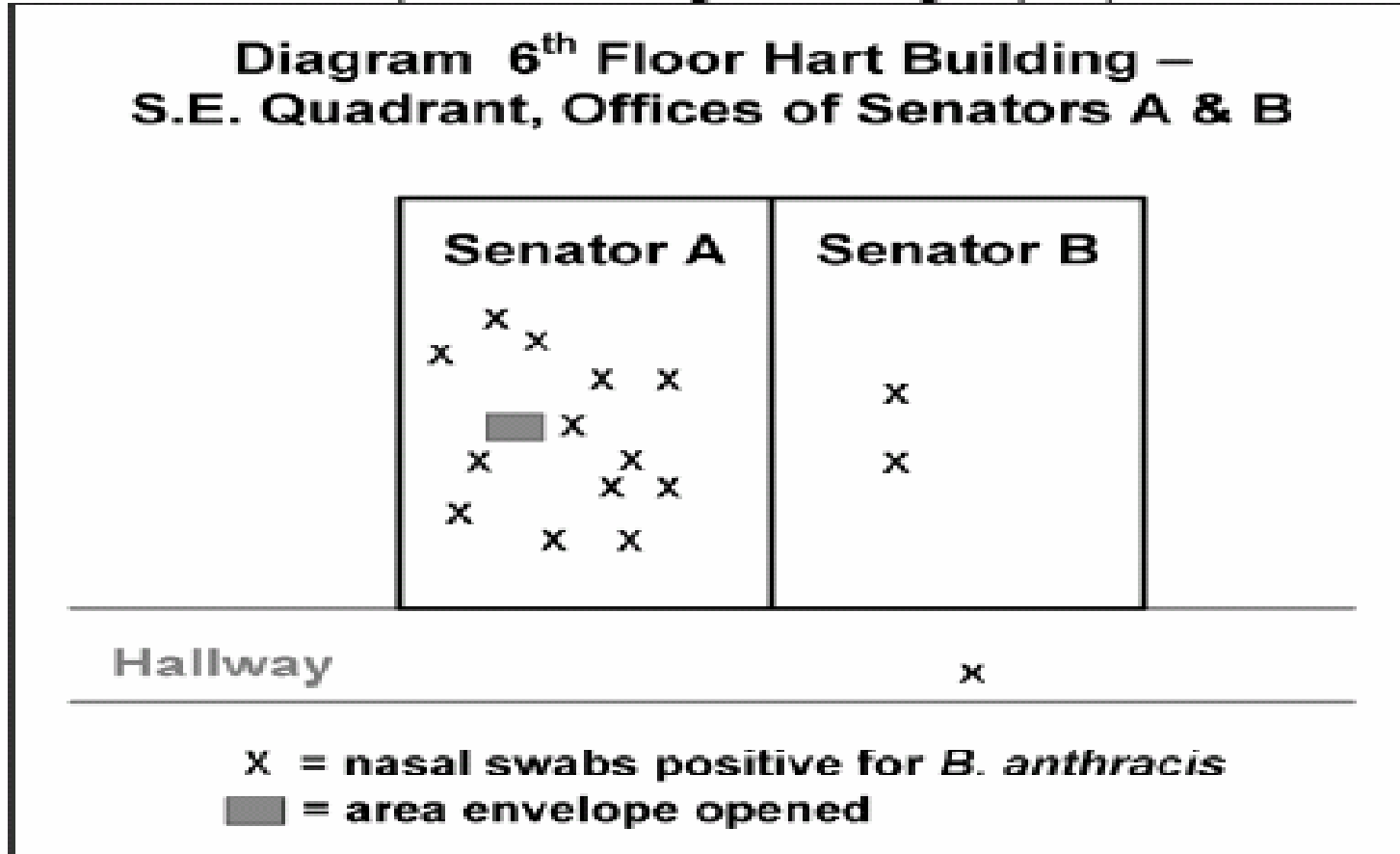


Adapted from: Tan C. A preventable outbreak of pneumococcal pneumonia among unvaccinated nursing home residents in New Jersey during 2001. Infect Control Hosp Epidemiol 2003;24:848–52.



Steps of an Outbreak Investigation

Figure 6.7 Desk Locations of Persons with Nasal Swabs Positive for *Bacillus anthracis*, Hart Building—Washington, DC, 2001



Steps of an Outbreak Investigation

- To assess for an outbreak of surgical wound infections in a hospital, cases may be plotted by OR, recovery room, and ward room
- To assess “Sick Building Syndrome” and problems r/t airflow patterns, cases should be plotted by work location
- Limitation of spot maps is that they do not take geographic size into acct.
- Area maps showing area-specific rates are better at looking at incidence between different areas with different population densities
- Divide the # of cases within a county by the population of the county to determine the county-specific rates can be calculated



Steps of an Outbreak Investigation

Figure 6.8 Cases of Human Granulocytic Ehrlichiosis by County—Wisconsin, May 1996–December 1998

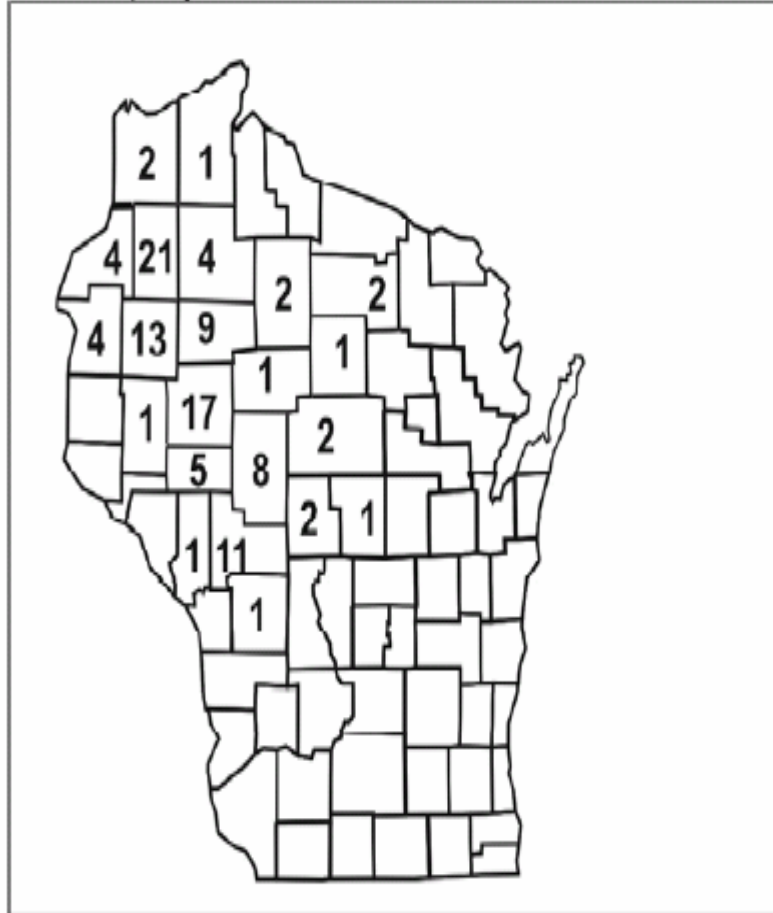
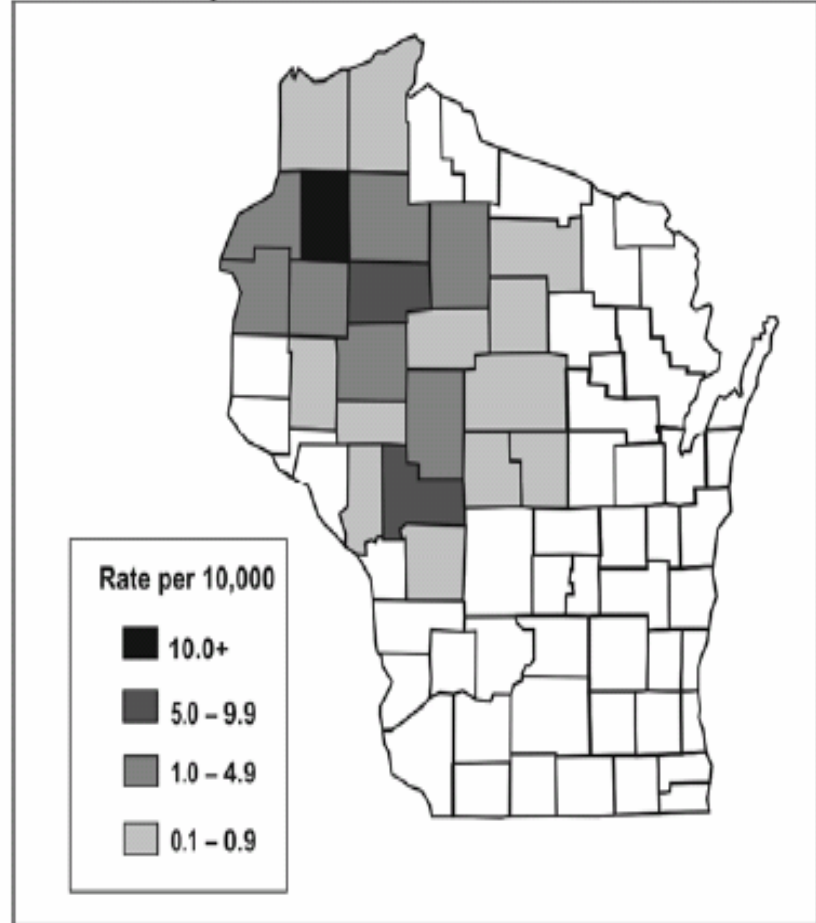


Figure 6.9 Rates of Human Granulocytic Ehrlichiosis by County, Wisconsin—May 1996–December 1998



Steps of an Outbreak Investigation

– Person:

- Provides a description of whom the case-patients are and who is at risk
- Person characteristics are both host (age*, race, sex*, medical status) and exposure (occupation, leisure activities, Rx/illicit-Rx, ETOH, tobacco)—Both influence susceptibility to disease and opportunities for exposure
- * = most described host characteristics due to ease of collection and often r/t exposure to and risk of disease
- Raw numbers are OK at first when looking at overall extent of outbreak or those affected; but focus will eventually be needed:
 - Classify Hep B cases by IV vs. Non-IV Rx users or by sexual contacts; school-based gastroenteritis classified by grade, class, or student vs. teacher/staff
- Raw numbers indicate the burden of disease and useful for planning service delivery
- Rates are essential for identifying groups with ↑ disease risk



Steps of an Outbreak Investigation

- Summarizing by Time, Place, and Person:

- After characterizing by time, place, and person, take a look at what data you have:
 - What does the epidemic curve tell us? Where are we in the epidemic—start, middle, end???
 - Who has higher rates? Women, men, young, old, black, white? Smokers? Clustering by residence or worksite?

- Step 7: Develop Hypothesis

- This step actually occurs very early—i.e., during the first interaction with suspected cases
- The hypothesis may address the source of the agent, the mode of transmission, and the exposures causing disease
- Remember that the hypothesis needs to be testable
- First consider what you already know:
 - What is the agent's usual reservoir?
 - How is it usually transmitted?
 - What vehicles are commonly implicated?
 - What are the known risk factors?
 - “Round up the usual suspects”

“Round up the usual suspects.”

- Capt. Renault
(Claude Rains) to his
policemen after Rick
Blaine (Humphrey
Bogart) had just shot
a Nazi officer,
Casablanca, 1942



Steps of an Outbreak Investigation

- Go back to interviewing the case-patients:
 - If possible, round them up! Put them in a short meeting and interview them together, assessing for common characteristics
 - Ask them for the right to inspect their homes, look through their refrigerators, etc.
- If the epidemic curve points to a narrow exposure period:
 - What events occurred around that time?
 - Why do people living in one area have the highest attack rate?
 - Why are some people with certain characteristics (age, sex, etc.) at greatest risk than people with differing (or even similar) characteristics
- Due to ↑ risk of bioterrorism, be on the suspicion for this in any outbreak:
 - When the epidemiology doesn't match the usual or natural patterns of transmission, think about intentional methods of spread
 - *Salmonella* poisoning of those in The Dalles, Oregon, 1984
- Outliers also essential to examine: In 1985, a breakout of thyrotoxicosis occurred in Luverne, Minn. One case was found 60 miles away—in Sioux Falls, DK. This person obtained ground beef from Luverne when visiting her father!



Steps of an Outbreak Investigation

Table 6.6 Epidemiologic Clues to Bioterrorism

1. Single case of disease caused by an uncommon agent (e.g., glanders, smallpox, viral hemorrhagic fever, inhalational or cutaneous anthrax) without adequate epidemiologic explanation
2. Unusual, atypical, genetically engineered, or antiquated strain of an agent (or antibiotic-resistance pattern)
3. Higher morbidity and mortality in association with a common disease or syndrome or failure of such patients to respond to usual therapy
4. Unusual disease presentation (e.g., inhalational anthrax or pneumonic plague)
5. Disease with an unusual geographic or seasonal distribution (e.g., tularemia in a non-endemic area, influenza in the summer)
6. Stable endemic disease with an unexplained increase in incidence (e.g., tularemia, plague)
7. Atypical disease transmission through aerosols, food, or water, in a mode suggesting deliberate sabotage (i.e., no other physical explanation)
8. No illness in persons who are not exposed to common ventilation systems (have separate closed ventilation systems) when illness is seen in persons in close proximity who have a common ventilation system
9. Several unusual or unexplained diseases coexisting in the same patient without any other explanation
10. Unusual illness that affects a large, disparate population (e.g., respiratory disease in a large population may suggest exposure to an inhalational pathogen or chemical agent)
11. Illness that is unusual (or atypical) for a given population or age group (e.g., outbreak of measles-like rash in adults)
12. Unusual pattern of death or illness among animals (which may be unexplained or attributed to an agent of bioterrorism) that precedes or accompanies illness or death in humans
13. Unusual pattern of death or illness among humans (which may be unexplained or attributed to an agent of bioterrorism) that precedes or accompanies illness or death in animals
14. Ill persons who seek treatment at about the same time (point source with compressed epidemic curve)
15. Similar genetic type among agents isolated from temporally or spatially distinct sources
16. Simultaneous clusters of similar illness in noncontiguous areas, domestic or foreign
17. Large number of cases of unexplained diseases or deaths



Steps of an Outbreak Investigation

- Step 8: Evaluate Hypotheses Epidemiologically:
 - Hypotheses are usually tested using a combination of environmental evidence, laboratory science, and epidemiology
 - Evaluate hypotheses by comparing the hypotheses with the established facts:
 - Used when clinical, laboratory, environmental, or epidemiologic evidence obviously supports the hypothesis
 - Formal hypothesis testing becomes unnecessary
 - EG: Hypervitaminosis D in Mass in 1991
 - Or by using analytic epidemiology to quantify relationships and assess the role of chance:
 - Conducted when evidence is not compelling or circumstances not as straightforward
 - Involves comparison of expected pattern with a non-exposed control group with observed pattern of an exposed experimental group
 - Allows ability to quantify relationships between exposures and disease and test hypotheses about causal relationships
 - Most common are retrospective cohort studies and case-control studies



Steps of an Outbreak Investigation

– Retrospective Cohort Studies:

- Study of choice in a small, well-defined population
- Investigator contacts each member of the defined population, determines each person's exposure to possible sources/ vehicles, and notes whether the person later became ill with the disease in question
- Next, an attack rate is calculated for those exposed and those not exposed:

1. The attack rate is high among those exposed to the item.
2. The attack rate is low among those not exposed, so the difference or ratio between attack rates is high.
3. Most of the case-patients were exposed to the item, so that the exposure could "explain" or account for most, if not all, of the cases.



Steps of an Outbreak Investigation

- Relative and Attributable Risk:
 - Comparison of the attack rate in the exposed vs. non-exposed group (Risk Ratio or Relative Risk):
 - » When the attack rate for the exposed group is the same as that of the unexposed group, it is equal to 1.0 (the exposure is not associated with the disease)
 - » The greater the difference in attack rates between the exposed and unexposed groups, the larger the relative risk and stronger the association between exposure and disease

Method for calculating risk ratio:

*Attack rate (risk)
in exposed group*

*Attack rate (risk)
in unexposed group*



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Steps of an Outbreak Investigation

Table 6.7 Attack Rates By Items Served at Company A's Holiday Banquet—Virginia, December 2003

Food Items Served	Number of Persons who ATE Specified Food				Number of Persons who DID NOT EAT Specified Food				Risk Ratio
	Ill	Not Ill	Total	Attack Rate	Ill	Not Ill	Total	Attack Rate	
Beef	53	28	81	65%	4	31	35	11%	5.7
Ravioli	43	35	78	55%	14	24	38	37%	1.5
Cajun sauce*	19	11	30	63%	37	48	85	44%	1.5
Pesto cream*	37	29	66	56%	19	30	49	39%	1.4
California rolls*	21	14	35	60%	34	44	78	44%	1.4
Mushrooms*	32	26	58	55%	24	31	55	44%	1.3
Broccoli*	34	30	64	53%	22	29	51	43%	1.2
Carrots*	34	30	64	53%	23	28	51	43%	1.2
Potatoes*	39	41	80	49%	17	17	34	50%	1.0

*Excludes 1 or more persons with indefinite history of consumption of that food.

Table 6.8 Risk of Gastroenteritis By Consumption of Beef—Virginia, December 2003

		Ill	Not Ill	Total	Attack Rate (Risk)
Ate beef?	Yes	53	28	81	65.4%
	No	4	31	35	11.4%
Total		57	59	116	49.1%

$$\text{Risk ratio} = 65.4 / 11.4 = 5.7$$

$$\text{Proportion of cases exposed} = 53 / 81 = 65.4\%$$

$$\text{Population attributable risk percent} = (65.4 - 11.4) / 65.4 = 82.6\%$$



Steps of an Outbreak Investigation

– Another way to assess risk more quantitatively is through attributable risk for each exposure:

- » The proportion of illness in the entire study population that could be attributable to a given exposure, assuming those who became ill in the unexposed group must be attributable to something else
- » May actually underestimate in many outbreaks, since it does not take into acct. such common occurrences as cross-contamination of foods or sampling from partner's plate

Method for calculating population attributable risk percent:

$$\frac{(AR_p - AR_U)}{AR_p}$$

AR_p

AR_p = Attack rate (risk) in total population

AR_U = Attack rate (risk) in unexposed group

Table 6.8 Risk of Gastroenteritis By Consumption of Beef—Virginia, December 2003

		Ill	Not Ill	Total	Attack Rate (Risk)
Ate beef?	Yes	53	28	81	65.4%
	No	4	31	35	11.4%
Total		57	59	116	49.1%

Risk ratio = 65.4 / 11.4 = 5.7

Proportion of cases exposed = 53 / 57 = 93.0%

Population attributable risk percent = (49.1 - 11.4) / 49.1 = 76.7%



Steps of an Outbreak Investigation

- Statistical Significance Testing:
 - Start with a null hypothesis:
 - » The relative risk = 1.0; exposure is not related to disease
 - Next, compute a measure of association (risk or odds ratio)
 - Calculate a chi-square, which indicates the probability of finding an association as strong or stronger than the one you observed if the null hypothesis were really true (i.e., the exposure does not cause disease):
 - » If the p value is very small ($<.05$), discard or reject the null hypothesis (i.e., the exposure DOES cause the illness)
 - » Note that a Chi-Square value > 3.84 corresponds to a p value $<.05$; thus reject the null if Chi-Square > 3.84
 - » P value is not always absolute; in small studies with relatively few persons, p tends to be $>.05$ although the null may actually be true; p can also be $<.05$ by chance and not be a true explanation of an outbreak
 - » Chi-Square good for studies w/ > 30 participants



Steps of an Outbreak Investigation

Table 6.9 Standard Notation of a Two-By-Two Table

	Ill	Well	Total	Attack Rate (Risk)
Exposed	a	b	a+b = H ₁	a / a+b
Unexposed	c	d	c+d = H ₀	c / c+d
Total	a+c=V ₁	b+d=V ₂	T	V ₁ / T

One formula for the chi-square test:

$$T(ad-bc)^2$$

$$H_1 \times H_0 \times V_1 \times V_2$$

Table 6.10 Table of Chi-Squares

Degrees of Freedom	Probability						
	.50	.20	.10	.05	.02	.01	.001
1	.455	1.642	2.706	3.841	5.412	6.635	10.827
2	1.386	3.219	4.605	5.991	7.824	9.210	13.815
3	2.366	4.642	6.251	7.815	9.837	11.345	16.268
4	3.357	5.989	7.779	9.488	11.668	13.277	18.465
5	4.351	7.289	9.236	11.070	13.388	15.086	20.517
10	9.342	13.442	15.987	18.307	21.161	23.209	29.588
15	14.339	19.311	22.307	24.996	28.259	30.578	37.697
20	19.337	25.038	28.412	31.410	35.020	37.566	43.315
25	24.337	30.675	34.382	37.652	41.566	44.314	52.620
30	29.336	36.250	40.256	43.773	47.962	50.892	59.703



Steps of an Outbreak Investigation

- Confidence Intervals:
 - An alternative to calculating p values
 - Confidence Interval of 95% = $p < .05$
- Case-Control Studies:
 - Because during an outbreak the population is not well-defined and because speed of investigation is so important, case-control study becomes the design of choice
 - Questions are asked about exposures to the case-patients and to a comparison group (controls—without the disease)
 - Next, an odds ratio is calculated to quantify the relationship between the various exposures and disease
 - Finally, a p value is calculated;
 - Choosing Controls:
 - Controls should be similar to the cases, but not with the disease
 - » Population-based controls from random telephone/household surveys
 - » Neighbors of case-patients*; pts. from same MD/hospital w/o disease*; friends of case-pts.* (* = greater risk of bias)
 - Logistical issues must also be considered:
 - » How to contact controls, gain their cooperation, ensure they are free of disease, and obtain appropriate exposure data
 - » Size of the sample needed (In outbreaks of 50+, use a 1:1 ratio of controls to cases; in smaller outbreaks, ↑ this to 2, 3, or 4+ controls per case)



Steps of an Outbreak Investigation

- Odds Ratios:
 - In most case-control studies, the population is not well defined, and the total # of people exposed/unexposed is not known; thus, attack rates cannot be calculated
 - An odds ratio is selected
 - Approximates the relative risk found if a cohort study had been feasible
 - Perform Chi-Square

Method for calculating the odds ratio:

$$\frac{\left(\begin{array}{c} \text{Number of exposed cases} \\ X \\ \text{Number of unexposed controls} \end{array} \right)}{\left(\begin{array}{c} \text{Number of exposed controls} \\ X \\ \text{Number of unexposed cases} \end{array} \right)}$$

OR

$$ad / bc$$



Steps of an Outbreak Investigation



Exercise 6.7

You are called to help investigate a cluster of 17 persons who developed brain cancer in an area over the past couple of years. Most, perhaps all, used cell phones. Which study design would you choose to investigate a possible association between cell phone use and brain cancer?

Cell phones are quite popular. Noting that most if not all of the 17 patients had used cell phones does not indicate that cell phones are the cause of brain cancer. An epidemiologic study that compares the exposure experience of the case-patients with the exposure experience of persons without brain cancer is necessary. A case-control study is the design of choice, since 17 persons with the disease of interest have already been identified.

As many as possible of the 17 persons with brain cancer should be enrolled in the case-control study as the case group. A group of persons without brain cancer need to be identified and enrolled as the control group. Whom would you enroll as controls? Remember that controls are supposed to represent the general exposure experience in the population from which the case-patients came. Controls could come from the same community (randomly selected telephone numbers, neighbors, friends) or the same healthcare providers (e.g., patients treated by the same neurologist but who do not have brain cancer). Once case-patients and controls are identified and enrolled, each would be questioned about exposure to cell phones. Finally, the exposure experience of case-patients and controls would be compared to determine whether case-patients were more likely to use cell phones, or use particular types of phones, or used them more frequently, or for longer cumulative time, etc.

The alternative to a case-control study is a cohort study. For a cohort study you would have to enroll a group of cell phone users (“exposed group”) and a group of persons who do not use cell phones (“unexposed group”). You would then have to determine how many in each group develop brain cancer. Since brain cancer is a relatively rare event, you would need rather large groups in order to have enough brain cancer cases for the study to be useful. Therefore, a cohort study is less practical than a case-control study in this setting.



Steps of an Outbreak Investigation



Exercise 6.8

Investigators conducted a case-control study of histoplasmosis among industrial plant workers in Nebraska.⁴¹ The following table shows the number of case-patients and controls who worked in Building X, near a recently excavated site.

	Cases	Controls	Total
Building X	15	8	23
Other Building	7	23	30
Total	22	31	53

1. What is the appropriate measure of association?

The appropriate measure of association for a case-control study is the odds ratio.

2. Calculate this measure.

2. The odds ratio is calculated as the cross-product ratio: ad / bc .

$$\text{Odds ratio} = 15 \times 23 / 8 \times 7 = 6.16 = 6.2$$

The chi-square is 9.41, and the 95% confidence interval is 1.6–25.1. How would you interpret your results?

3. With a chi-square of 9.41 and a 95% confidence interval of 1.6–25.1, this study shows a very strong (odds ratio = 6.2) association between histoplasmosis and working in Building X. This finding is quite statistically significant (chi-square = 9.41 corresponds to a p-value between 0.01 and 0.001). And although the 95% confidence interval indicates that the study is compatible with a seemingly relatively wide range of values (1.6–25.1), most of these values indicate a strong if not stronger association than the one observed.



Steps of an Outbreak Investigation



Exercise 6.9

Consider the following data from an outbreak of gastroenteritis among college football players.⁴² At which meal do you think the critical exposure occurred?

Meal	Ate Meal			Did Not Eat Meal		
	#Ill	(% Ill)	Total	#Ill	(% Ill)	Total
9/18 Breakfast	9	(90)	10	45	(46)	98
9/18 Lunch	50	(62)	81	4	(15)	27
9/18 Dinner	45	(52)	87	9	(43)	21
9/18 Late dinner	34	(54)	63	20	(44)	45
9/19 Breakfast	42	(49)	85	12	(52)	23
9/19 Lunch	39	(51)	76	15	(47)	32

The first step in answering this question is to compare the attack rates (% ill) among those who ate the meal and those who did not eat the meal. Since the % ill is a measure of risk of illness, you could calculate a risk ratio for each meal.

					Risk Ratio
9/18	Breakfast	90% vs. 46%	=	2.0	
9/18	Lunch	62% vs. 15%	=	4.1	
9/18	Dinner	52% vs. 43%	=	1.2	
9/18	Late dinner	54% vs. 44%	=	1.2	
9/19	Breakfast	49% vs. 52%	=	0.9	
9/19	Lunch	51% vs. 47%	=	1.1	

Clearly, the September 18 lunch has the highest risk ratio. It has a relatively high attack rate (though not the highest) among those who ate the meal, and the lowest attack rate among those who did not eat the meal. Furthermore, almost all of the cases (50 out of 54) could be “accounted for” by that lunch.

In contrast, although the September 18 breakfast has a high attack rate among those who ate that meal, it has a relatively high attack rate among those who did not eat that breakfast, and most importantly, it can only account for one-sixth (9 out of 54) of the cases. Perhaps the September 18 breakfast was a minor contributor, but most of the illness probably resulted from exposure that occurred at the September 18 lunch.



Steps of an Outbreak Investigation

- Step 9: Reconsider, Refine, and Re-Evaluate Hypotheses:
 - Analytic epidemiology doesn't work if hypotheses aren't solid
 - When analytic epidemiology is unrevealing, rethink hypotheses:
 - Convene a meeting of case-patients together and look for links
 - Visit homes of case-patients and look at shelves!
 - An outbreak of *Salmonella* Muenchen in OH occurred; no food-source could be determined yet only 41% of controls has people aged 15-31 in the home; re-examination looking at risk factors for young adults found contaminated marijuana was the culprit
 - Focus the hypothesis and narrow it down:
 - Although a grocery store was implicated in an outbreak of Legionnaire's –what about the store was significant. Cases walked investigators through the store and all purchased vegetables sprayed with a contaminated ultrasonic mist machine
 - Sometimes, controls need to be more closely matched to cases:
 - Initially, a restaurant was implicated in an outbreak of *Clostridium*; eaters identified a common sandwich—radio ads recruited eaters who didn't become ill—they didn't eat sautéed onions on the sandwich (which were contaminated)



Steps of an Outbreak Investigation

- Keep in mind that beyond initiating control measures, “experiments of nature” (i.e. outbreaks) are excellent research opportunities:
 - The pts. Infected with West Nile Virus in NYC in 1999 were followed for 2 years to determine sequelae of the disease
- Step 10: Compare and Reconcile with Laboratory and Environmental Studies:
 - Coordinate with the laboratory, take pictures of conditions, and bring back physical evidence to be analyzed to confirm associations



Steps of an Outbreak Investigation

- Step 11: Implement Control and Prevention Measures:
 - In practice, implement as early as possible, even before investigation if feasible
 - Confidentiality is critical in many situations; failure to maintain confidentiality can doom effective investigation/Tx
 - Control measures are directed at one or more segments of the chain of transmission (agent, source, mode of transmission, portal of entry, or host)
 - Often, cases need to be cohorted (quarantined) to avoid transmission to others
- Step 12: Initiate or Maintain Surveillance:
 - Begin, continue, and maintain active surveillance to ensure:
 - The outbreak is improving
 - The outbreak hasn't extended beyond its original area



Steps of an Outbreak Investigation

- Step 13: Communicate Findings:
 - Final task is to summarize the investigation, its findings, and its outcomes in a report, and to communicate the report to appropriate health authorities via:
 - An oral briefing for local authorities:
 - Should be in easy to understand terms
 - Should provide appropriate control/ Tx implementations
 - A written report:
 - Prepared in scientific format:
 - » Introduction
 - » Background
 - » Methods
 - » Results
 - » Discussion and Recommendations

Epi-X is the CDC's Web-based communications solution for public health professionals. Through *Epi-X*, CDC officials, state and local health departments, poison control centers, and other public health professionals can access and share preliminary health surveillance information quickly and securely. Users can also be actively notified of breaking health events as they occur. Key features of *Epi-X* include:

- Scientific and editorial support
- Controlled user access
- Digital credentials and authentication
- Rapid outbreak reporting
- Peer-to-peer consultation.



Summary

- Most important reason to investigate outbreaks is to learn about situations to implement control and prevention efforts
- Investigations are conducted quickly and should be well-coordinated with clear communication and a precise plan
- The steps of investigation include:

Table 6.2 Epidemiologic Steps of an Outbreak Investigation

1. Prepare for field work
2. Establish the existence of an outbreak
3. Verify the diagnosis
4. Construct a working case definition
5. Find cases systematically and record information
6. Perform descriptive epidemiology
7. Develop hypotheses
8. Evaluate hypotheses epidemiologically
9. As necessary, reconsider, refine, and re-evaluate hypotheses
10. Compare and reconcile with laboratory and/or environmental studies
11. Implement control and prevention measures
12. Initiate or maintain surveillance
13. Communicate findings

