20

Outbreak Investigation

The essentials of the epidemiological approach in determining the specific etiologic agent of a disease are demonstrated in their simplest form by the investigation of the etiology of a food poisoning outbreak.—A. M. Lilienfeld (1976, p. 15)

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Chapter Addendum 1 (Case Study): Drug–Disease Outbreak

Chapter Addendum 2 (Case Study): Food-Borne Outbreak in Rhynedale, California

This chapter considers the investigation of outbreaks and epidemics. The following 10 investigatory steps, as prescribed in the Centers for Disease Control and Prevention (CDC) training materials, are considered: (1) preparation for field work, (2) establishing the

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existence of an outbreak, (3) verifying diagnoses of cases, (4) establishing a case definition and searching for additional cases, (5) conducting descriptive epidemiologic studies, (6) developing hypotheses, (7) evaluating hypotheses, (8) refining hypotheses and performing additional studies, (9) implementing control and prevention measures, and (10) communicating findings.

20.1 BACKGROUND

Initial Detection of Epidemics and Outbreaks

Outbreaks come to the attention of public health agencies in two primary ways. Either (a) epidemiologic surveillance systems warn of an emerging health problem or (b) individuals directly or indirectly affected by the outbreak (e.g., caregivers, cases, relations) notify the authorities directly.

Epidemiologic surveillance systems are organizations and structures set in place for the express purpose of collecting, analyzing, and interpreting outcome-specific health data for planning, carrying out, and evaluating public health practices (Thacker & Berkelman, 1988). Surveillance methods are distinguished by their practicability, uniformity, and rapidity. It is important to note that surveillance systems are often limited in scope and accuracy. They are often incomplete (i.e., missed cases) and lack information on important contribution to disease for those cases that are reported. They are thus insensitive to subtle changes in occurrences and are limited in their ability to evaluate the cause of apparent increases. When increases are evident, they may indicate an artifact of the system. Consequently, a common way to become aware of an outbreak is by direct notification from an affected individual. The initial detection of acquired immunodeficiency syndrome (AIDS) provides an interesting illustration.

One of the first clues that led to the discovery of AIDS came from an astute pharmacist responsible for filling prescriptions for the drug used to treat *Pneumocystis* pneumonia (CDC, 1981a,b). Normally, *Pneumocystis* pneumonia occurs only in immune-compromised individuals, such as those undergoing chemotherapy for cancer. When physicians treating cancer-free young men started requesting the drug in increasing numbers, the astute pharmacist suspected something was amiss. This led to an investigation and eventual discovery of the new form of immunodeficiency now called AIDS.

When Are Outbreaks Investigated?

The decision whether to mount a large-scale investigation of an apparent outbreak is based on some of the following factors:

- The ability to confirm that the observed number of cases is significantly greater than expected (see Chapter 19)
- The scale and severity of the outbreak
- Whether the outbreak disproportionally affects an identifiable subgroup
- The potential for spread
- Political and public relations considerations
- Availability of resources

Goals of Outbreak Investigations

The goals of outbreak investigations are:

- To assess the range and extent of the outbreak
- To reduce the number of cases associated with the outbreak
- To prevent future occurrences by identifying and eliminating the source of the problem
- To identify new disease syndromes
- To identify new causes of known disease syndromes
- To assess the efficacy of currently employed prevention strategies
- To address liability concerns
- To train epidemiologists
- To provide for good public relations and educate the public

Components of Outbreak Investigations

Outbreak investigations have **diagnostic** (research) and **directed action** components. These components are not mutually exclusive. The epidemiologist researching the outbreak must clearly define the problem, describe the epidemiology of the outbreak, formulate hypotheses as to cause and transmission, test causal and prevention hypotheses, and draft conclusions and specific recommendations (Table 20.1).

Who Investigates Outbreaks?

The responsibility of investigating outbreaks usually falls on the shoulders of the local health department. However, if the investigation requires further resources, attracts substantial public concern, or is associated with a high attack rate or serious complications

TABLE 20.1. Components of Outbreak Investigations

1. *Define the Problem*
   - Confirm diagnoses
   - Show that an epidemic exists (observed number of cases is significantly greater than expected)
2. *Describe the Epidemiology of the Outbreak*
   - *Time:* determine dates and times of onset; draw epidemic curve; determine attack rates over time
   - *Place:* draw spot map of cases; consider environments of home, work, recreational, and special meeting places
   - *Person:* calculate attack rates by age, sex, occupation, ethnic group, and other personal factors; consider rates of infection, disease and death; note possible means of transmission; address both common denominators and notable exceptions
3. *Formulate Hypotheses*
   - Source of infection
   - Method of contamination and spread
   - Possible control mechanisms
4. *Test Hypotheses*
   - Conduct special epidemiologic, laboratory, and environmental investigations
5. *Draw Conclusions and Devise Practical Applications*
   - Long-term surveillance
   - Prevention

Source: Evans (1982, p. 7) (some modification), reproduced with permission of Plenum Publishing.

(hospitalization or death), state and federal agencies are called in. Outbreaks of national importance are investigated by the CDC. In fulfillment of this responsibility, the CDC has prepared excellent outbreak investigation training materials. Much of the discussion in this chapter is based on these materials.

20.2 INVESTIGATORY STEPS

Ten Investigatory Steps

Although no single way to investigate an outbreak applies to all situations, some common steps prevail. For the sake of efficiency and completeness, the CDC (1992a) recommends the following 10-step approach:

1. Prepare for field work.
2. Establish the existence of an outbreak.
3. Verify diagnoses of cases.
4. Establish a case definition and search for additional cases.
5. Conduct descriptive epidemiologic studies.
6. Develop hypotheses.
7. Evaluate hypotheses.
8. As necessary, reconsider or refine hypotheses and conduct additional studies.
9. Implement control and prevention measures.
10. Communicate findings.

Step 1: Prepare for Field Work

Preparation for an investigation includes completing the administrative and personal measures required to begin the inquiry. Travel preparations must be made, supplies and equipment readied, knowledge updated, and administrative and scientific contacts established. Investigators must have a clear understanding of their role in the field and must know the chain of authority involved in the process.

Step 2: Establish the Existence of an Outbreak

One of the first tasks in outbreak investigation is to confirm that the reported cases represent a true outbreak with a common cause. Often, purported outbreaks represent sporadic occurrences of unrelated disease. The investigator must therefore identify and confirm all prospective cases and submit each case to standard diagnostic criteria. After confirming all cases, the observed rate of occurrence must be compared to an expected rate. Expected rates of occurrence can be gleaned from public health surveillance databases, national morbidity and mortality statistics, special registries (e.g., cancer or birth defect registries), data from neighboring states, or special surveys. Comparisons must account for both chance and systematic sources of variation. Quantifying the role of chance involves comparing the observed number of cases to the expected number under the Poisson model (see Sections 19.2 and 19.3). Systematic fluctuations in the number of

cases can be due to any of the biases discussed in Chapter 12. Some of the important biases to consider when evaluating potential outbreaks are:

General Information Bias: Has there been a change in the reporting procedure or case definition, thus resulting in an artifactual increase in the number of cases? Does the increase represent a fad or false alarm?

Change in Population Size: Can a sudden increase in population size, such as might occur in a resort area, college town, or farming area with migrant labor, reflect an increase in the population at risk rather than a change in the rate of disease?

Diagnostic Suspicion Bias: Can diagnostic suspicion bias, such as might occur with improved diagnostic procedures, screening campaigns, or a new physician or infection control nurse in town, explain the apparent increase?

Publicity Bias: Can publicity bias, such as might occur when media attention stimulates the reporting of cases that would have previously gone unnoticed, explain the apparent increase?

The task of verifying an outbreak is made simple if a common cause is identified (as might be expected with food-borne illnesses). When this is the case, mechanisms of transmission and means of control will be well known, allowing for routine and rapid completion of the investigation.

Steps 3 and 4: Verify Diagnoses of Cases and Search for Additional Cases

If the initial signal of an outbreak is verified, the next task is to establish a reliable case definition. Briefly, the case definition is the set of standardized criteria used to decide whether an individual should be classified as having the disease in question (see Chapter 5). Once a reliable case definition is established, the epidemiologist submits each prospective case to these standard criteria for confirmation of case status.

The investigation team also searches for previously unidentified cases. In searching for additional cases, the investigator checks local hospitals, clinics, and clinical laboratories that are likely to diagnose or treat cases. It often proves useful to directly question those individuals who might treat or encounter the disease. For example, in studying a disease of the blood, the investigator might query hematologists and laboratory personnel who might treat or study the disease; in studying neoplastic diseases, the investigator questions oncologists, cancer registry personnel, cancer support groups, and other people likely to encounter prospective cases. Because direct inquiry may require a fair amount of walking about, it has traditionally been called **"shoe-leather" epidemiology.**

Previously unreported cases may also be discovered by issuing a plea for reports through a media appeal or by direct mailing of requests to physicians. Note, however, that blanket requests such as these may elicit duplicate reports, false-positive cases, reports of old cases irrelevant to the current outbreak, and other dubious information.

Step 5: Conduct Descriptive Epidemiologic Studies

Objectives Descriptive epidemiology is used to explore and describe the general pattern of disease in the population at risk. This type of analysis is done early in the

investigation, when little is known about the outbreak. To begin descriptive epidemiology, we collect the following information:

- Case identification information (name, address, telephone number, and other information that will allow investigators to contact the subjects for notification or follow-up purposes)
- Demographic information (age, sex, race, occupation, and other "person" factors that allow for the description of rates)
- Clinical information (time of disease onset, time of exposure to the etiologic agent, signs, symptoms, and test results as are relevant to the case definition)
- Risk factor information (relevant exposures and extraneous factors that might influence the occurrence of disease; specific items must be tailored to the disease in question)
- Reporter information (to allow for further questioning and follow-up, if needed)
- Denominator data (census and *ad hoc* information that might provide reasonable estimates of denominators for prevalence and incidence calculations)

Once data are collected, the investigator describes the outbreak according to the **epidemiologic variables** of time, place, and person (see Section 2.4). Descriptive epidemiology has the following objectives:

- To assess data quality for completeness and accuracy
- To learn about the range and extent of the outbreak
- To assess the possible source of exposure, mode of transmission, incubation period, environmental contributors, host risk factors, and agent characteristics
- To generate hypotheses about the outbreak

Although principles concerning the description of disease according to person, place, and time have already been considered in Section 2.4, a brief review relevant to outbreak investigation is in order.

Time Epidemiologic analyses of outbreaks by **time** are routinely presented in the form of an **epidemic curve**. Epidemic curves provide pictorial insights into:

- The past and future course of the epidemic
- The incubation period of the disease
- Whether this is a point-source or propagating epidemic

The y axis of an epidemic curve represents the number (or percentage) of incident cases at a given time. The x axis represents a time line. In selecting a time scale for the x axis, we use units (e.g., hours, hour groupings, days, day groupings, weeks, months, years) appropriate to the incubation period of the disease. The CDC suggests, as a rule of thumb, using a time unit that is one-eighth to one-third the average incubation period (CDC, 1992a, pp. 363–364). For example, if the typical incubation period is one week, the x axis might be displayed in single-day units. However, since time analyses are sensitive to the choice of intervals, and inappropriate aggregations may mask relevant detail, it is best to

draw several epidemic curves using different time scales and then select the one that best demonstrates temporal patterns. When drawing the curve, the x axis should begin before the epidemic period (to show the endemic level of disease prior to the outbreak's onset) and extend to the period after the epidemic is over (to demonstrate whether disease levels have returned to normal).

Epidemic curves are useful for predicting the past and future temporal course of an epidemic. For example, Figure 20.1 shows an epidemic curve for the 1854 cholera epidemic investigated by John Snow (see Section 1.4). Ironically, this graph suggests that removal of the handle from the Broad Street pump had little to do with ending this notorious outbreak, thus contradicting the folklore surrounding this decisive (and largely symbolic) act. Sir A. Bradford Hill (1955) eloquently describes the course of events:

> Though conceivably there might have been a second peak in the curve, and though almost certainly some more deaths would have occurred if the pump handle had remained *in situ*, it is clear that the end of the epidemic was not dramatically determined by its removal. (p. 1010)

John Snow (1855), himself, recognized that the epidemic might have burned itself out before the pump handle was removed.

> ...but the attacks had so far diminished before the use of the water was stopped, that it is impossible to decide whether the well still contained the cholera poison in an active state, or whether, from some cause, the water had become free from it. (pp. 51–52)

Analysis of the **incubation period** associated with the disease is another important element of descriptive epidemiology. Recall that (a) the incubation period of a disease is the time interval between invasion of the agent into the host's body and appearance of first signs or symptoms of disease and (b) the incubation period of an agent may vary according to the pathogenicity of the agent, level of exposure, and susceptibility of the host. If the

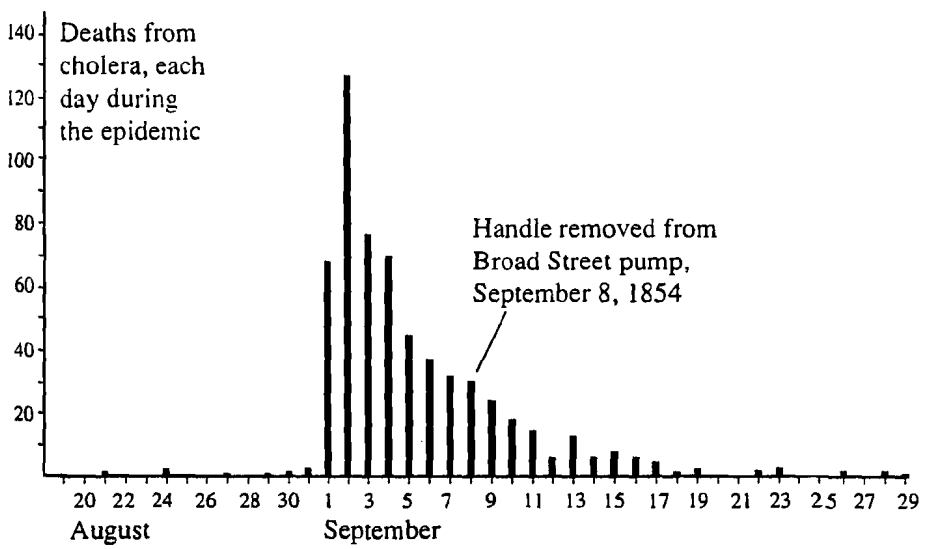

Figure 20.1. *Epidemic curve. London cholera epidemic of 1854 (data from Snow, 1855, p. 49).*

this picture with other sources of information, John Snow was able to support his idea that the cholera agent was waterborne.

A problem with dot maps, however, is that they fail to account for the number of people at risk in a given area. If populations in areas being compared are unequal in size, dot maps can be misleading. Tufte (1997) puts it this way:

> If the population of central London had been distributed just as the deaths were, then the cholera map would have merely repeated the unimportant fact that more people lived near the Broad Street pump than elsewhere. (p. 35)

To compensate for this inherent weakness of dot maps, the epidemiologist might choose to map area-specific rates. One such map of an Ebola virus outbreak is shown in Figure 20.3. This figure displays Ebola disease attack rates (per 100 inhabitants) in the epidemic zone. The attack rates are centered around Yambuku, Zaire, the town where the mission hospital was located. The decreasing attack rates with increasing distance from the hospital supported a hypothesis of iatraogenic spread of the agent (i.e., acquired during the course of treatment).

Person Description of disease rates by **person variables** is useful in identifying high-risk groups. Risk, in turn, is related to the opportunity or exposure or susceptibility to disease once exposed. Examples of person factors relevant to outbreak investigation include demographic characteristics (age, sex, ethnicity), personal activities and practices (occupation, customs, leisure activities, religious activities, knowledge, attitudes, and beliefs), genetic predispositions, physiologic states (pregnancy, parity, distress, nutritional status), concurrent diseases, immune status, and marital status.

Description of disease frequency by personal characteristics may be limited by the availability of numerator (number of cases) or denominator (size of the population at risk) information. At minimum, the frequency of disease is described by age and sex. Other analyses according to person variables cater to the type of disease being investigated. For example, when investigating AIDS, the epidemiologist is interested in describing disease rates according to sexual practices and contacts, intravenous drug use, and iatrogenic exposures.

Step 6: Develop Hypotheses

A hypothesis is a tentative explanation that accounts for a set of facts that can be tested by further investigation. In the investigation of outbreaks, hypotheses should address the most likely source of exposure to the etiologic agent, the means of transmission, the next steps in the investigation, and future control measures.

Keep in mind, however, that hypothesis generation and development is more art than science. It begins when the first clues that an epidemic might exist come to light and continues until the investigation is complete. Hypothesis development requires an understanding of the disease process and population at risk. It is supported by discussions with patients, health-care providers, local public health officials, community activists, and other interested parties, and should include the review of all relevant clinical, epidemiologic, and laboratory information. In generating and developing hypotheses one should consider:

- What is generally known about the disease
- All relevant clinical and laboratory findings
- What patients say about the disease

probable time of exposure to the agent is known, the incubation period can be summarized by its minimum, maximum, and average (Fig. 20.2). The average incubation period can be expressed as an arithmetic average, geometric average, or median. Knowledge of incubation is helpful in identifying the etiologic pathogen.

The shape of the epidemic curve is useful in determining the epidemic pattern of the disease. **Point-source epidemics** are caused by exposure to the agent from a single source over a brief time. When this is the case, the epidemic exhibits a sudden rise followed by a rapid falloff (Figs. 2.15*c*, 20.1, and 20.2). **Propagating epidemics** depend on serial propagation from person to person or continuing exposure from a single source. Propagating epidemics exhibit a plateau or continual rise in the number of cases (Fig. 2.15*d*).

Place Describing the occurrence of cases by **place** can provide supportive evidence about the cause and transmission of the agent. Epidemic maps may take the form of simple dot maps or more complex maps of area-specific rates.

Dot maps may serve to document the geographic extent of the problem and provide evidence of clustering. Snow's celebrated dot map of clustering of cholera deaths around the Broad Street pump (Fig. 1.14) provides an important historical example. By combining

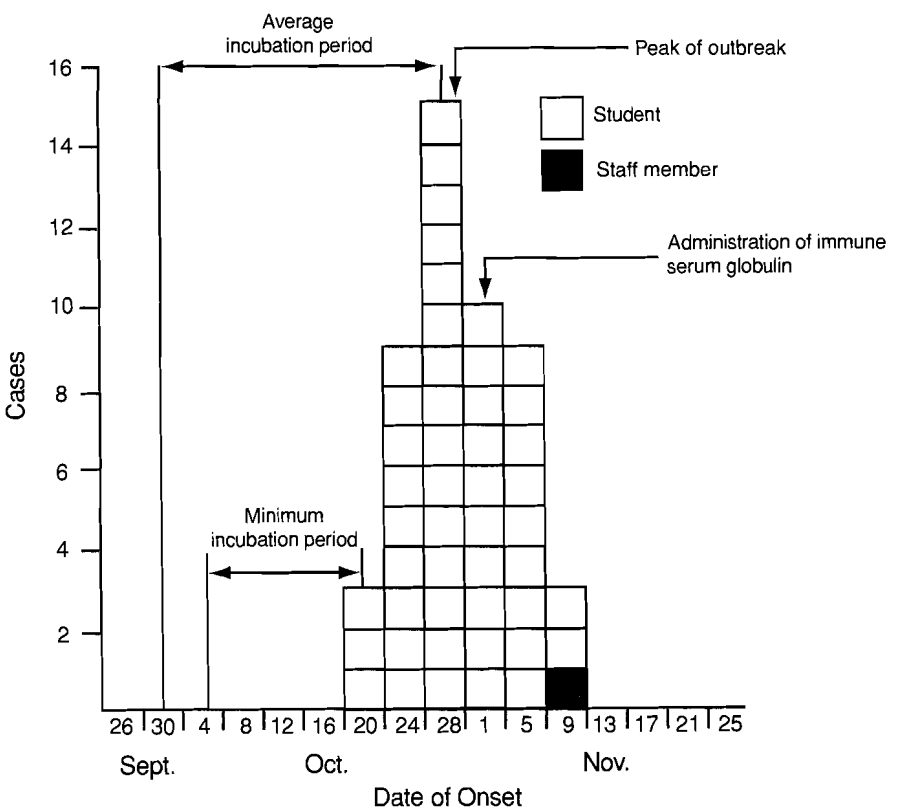

Figure 20.2. *Epidemic curve, hepatitis A outbreak, Colbert County, Alabama, 1972. (Source: CDC, 1992a, p. 367.)*

- Descriptive epidemiologic findings
- Other intuitive insights

Table 20.2 is a checklist of items that may be used when generating and developing hypotheses. When generating hypotheses, we search for common characteristics and

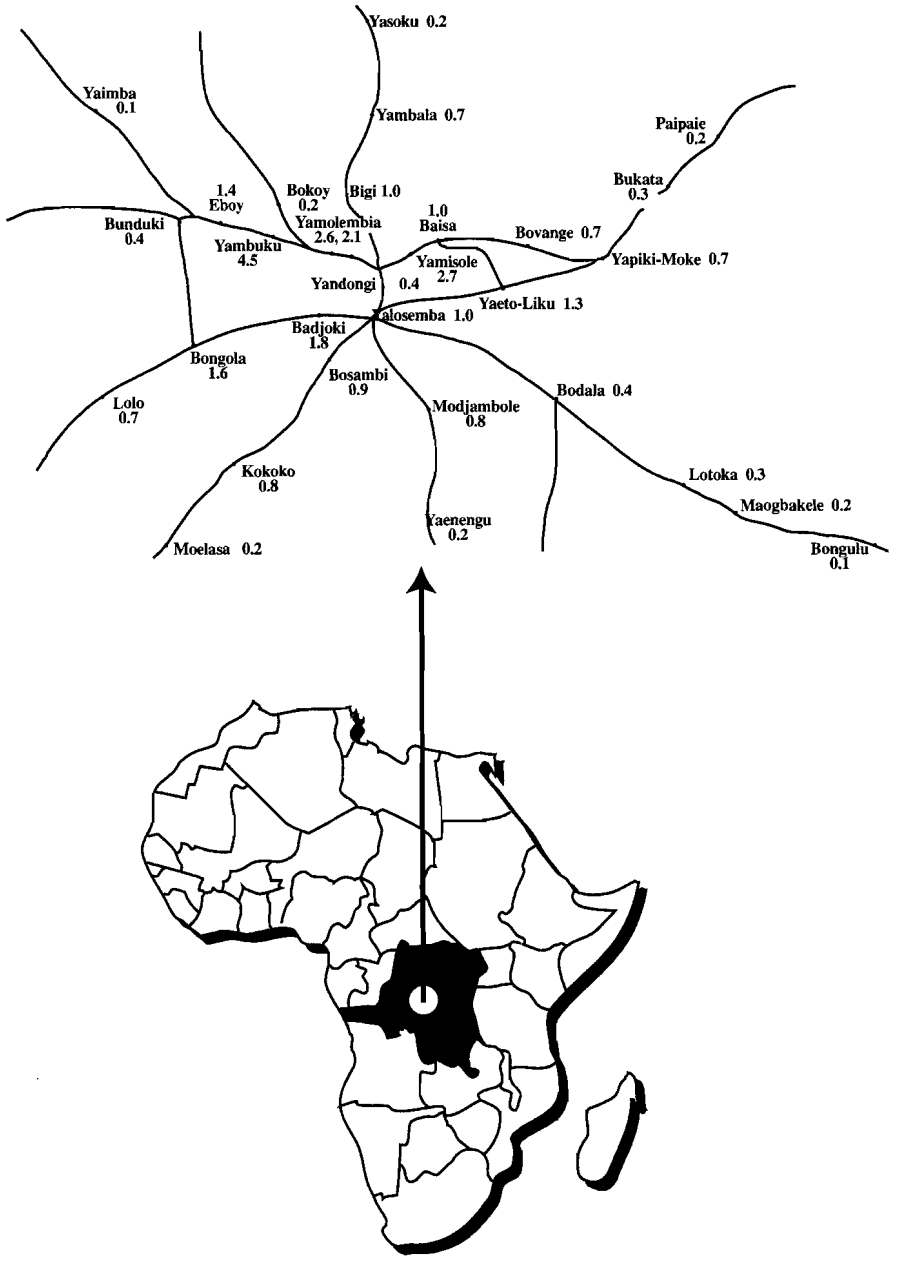

Figure 20.3. *Ebola virus epidemic zone, Zaire, 1976. (Source: Adapted from CDC, 1992b, p. 10.)*

TABLE 20.2. Hypothesis-Generating Checklist

1. Review what is known about the disease itself:
   - Agent
   - Usual reservoir
   - Mechanisms of transmission (portal of entry, portal of exit, life cycle of agent in nature, etc.)
   - Natural history of disease
   - Clinical spectrum of disease
   - Pathogenic mechanisms
   - Known risk factors
2. Study clinical and laboratory findings:
   - Review clinical and laboratory records
   - Check to see if lab tests are confirmed and the lab is accurate
   - Determine if specialized lab work (e.g., DNA "fingerprinting") is necessary
   - Describe frequency of symptoms, signs, and test results among cases
3. Consider what patients and caregivers say:
   - Determine potentially relevant exposure sources
   - Hear what they think about cause
   - Gain additional insights into clinical features
   - See if they are aware of other cases
   - Infer commonalities and differences in cases
4. Review descriptive epidemiology results:
   - Epidemic curve and pattern (point source, propagating, combination)
   - Geographic distribution
   - Incubation statistics (minimum, maximum, mean, median)
   - Events occurring around the most likely period of exposure of each case
   - Significant "person" risk factors
5. Ruminate critical facts:
   - Deduction
   - Intuition
   - Analogy
   - Coherence
   - Credibility of sources
   - Quality of information
   - Missing keys and explanations
   - Exceptions and outliers

notable exceptions. When searching for common characteristics, the objective is to search for the specific exposure having the strongest association with disease. Important clues, however, may also come from investigating why certain people exposed to the putative agent did not become ill and why apparently unexposed people developed the illness. Exceptions to the observed pattern, or **outliers** as they are occasionally called, can provide important clues about the source of infection and mode of transmission. John Snow, in his classic 19th-century cholera investigations, used this technique on repeated occasions. For example, he pointed out the relative absence of fatal cholera cases in brewery workers living near the epidemic's center (see Fig. 1.2) and attributed this deficiency to avoidance of pump water. (The proprietor of the brewery believed his workers did not drink water at all and most certainly did not obtain water from the pump on the street.) Snow also noted a fatal case in a 59-year-old widow living outside the epidemic area and traced this to water transported from the pump. These notable exceptions provided strong clues in support of the waterborne theory of cholera transmission.

Steps 7 and 8: Evaluate Hypotheses; As Necessary, Reconsider or Refine Hypotheses and Conduct Additional Studies

Hypotheses developed in step 6 are continually reexamined, refined, and tested throughout the investigation. The scientific method is iterative, cyclic, and self-correcting, thus requiring a continual process of hypothesis generation, hypothesis testing, and hypothesis refinement. Since the usefulness of an analytic study is dictated by the clarity and quality of its hypothesis, time devoted to hypothesis refinement is well spent. It is an axiom of epidemiology that if you cannot generate insightful hypotheses, then conducting statistical analyses are likely to be a waste of time (CDC, 1992a, p. 384).

Causal hypotheses can be tested using qualitative or quantitative methods, depending on underlying circumstances. The *CDC Self-Study Course* (1992a) describes a circumstance in which statistical analyses were unnecessary.

> In an outbreak of hypervitaminosis D that occurred in Massachusetts in 1991, it was found that all the case-patients drank milk delivered to their homes by a local dairy. Therefore, investigators hypothesized that the dairy was the source and the milk was the vehicle. When they visited he dairy, they quickly recognized that the dairy was inadvertently adding far more than the recommended dose of vitamin D to the milk. No analytic epidemiology was really necessary to evaluate the basic hypotheses in this setting. (p. 375)

Nevertheless, in most outbreaks, statistical analyses are necessary to draw inferences about the etiology of the outbreak and source of exposure. Analytic studies may take the form of a cohort study, case–control study, cross-sectional study, clinical trial study, or community trial study. The choice of a study design depends on many factors, including the timing of the investigation (i.e., whether the outbreak is ongoing or has resolved), the availability of resources, past experience of the investigator, the size of the population at risk, the prevalence of the exposure, and the incidence of the disease. In general, small, well-circumscribed outbreaks in which the incidence of disease is high are well suited for cohort study. In contrast, outbreaks in large, poorly circumscribed populations in which the disease is rare may be better suited for case–control methods.

Laboratory and environmental studies are used in isolating potential pathogens from cases and the environment. The laboratory investigation should determine the presence of the pathogenic organism and whether it is present in large enough numbers to be considered significant. Environmental and sanitary conditions should be studied to help explain why the outbreak occurred in the first place and what might prevent it from happening again. Special laboratory tests (e.g., DNA, chemical, or immunologic fingerprinting) can occasionally be used to link the agent isolated from patients to specific environmental sites. When available, laboratory evidence can "clinch the findings" established by the epidemiologic investigation. Note, however, that since many outbreaks are investigated after the fact, collection of specimens is precluded.

Step 9: Implement Control and Prevention Measures

Two of the main objectives of outbreak investigation are to bring the current epidemic to a halt and prevent future occurrences. Elements of control should be directed at the weakest link in the chain of infection. This can involve efforts directed toward any of the agent, host, or environmental factors that constitute the ecology of the disease. Elements of infection control are summarized in Table 20.3.

TABLE 20.3. Elements of Epidemic Control

Action	Example
1. Control the source of the pathogen	Remove the source of contamination
	Remove persons from exposure
	Inactivate or neutralize the pathogen at its source
	Isolate and treat the infected person
2. Interrupt the transmission (environmental control)	Sterilize or interrupt animate (vertebrate host) and inanimate (water, food, soil, air) environmental transmission
	Control insect vectors
	Improve sanitation
3. Control or modify the host response to exposure	Immunize susceptibles
	Use prophylactic chemotherapy

Source: Kelsey et al. (1986);

Demonstration of the efficacy of control measures provides support for causal hypotheses. Termination of the outbreak, however, does not offer direct proof since the population may simply have run out of susceptibles or cessation may be coincidental with other events.

Step 10: Communicate Findings

The investigation is not complete until the results are disseminated to the appropriate parties. Study findings should be reported to initial informants, those involved in the

TABLE 20.4. The "What, Why, When, How, Where, and Who" of Outbreak Reporting

What: oral briefings
Why: to disseminate information and defend conclusions and recommendations, to promote good public relations, and to allow for constructive criticism
When: at the beginning and end of the investigation and whenever information for prevention and control comes to light
How: use scientifically objective language (avoid emotional terms), consider the audience (many people may not be epidemiologists), and explain epidemiologic principles and methods (avoid jargon)
Where: the appropriate venue is dictated by the audience; presentations should be given in the locality affected by the outbreak and at the sponsoring agency; findings can also be presented at regional and national professional conferences
Who: audience may vary but should include local, state, and federal authorities and people responsible for control and prevention measures

What: written reports
Why: to document the investigation, to disseminate information and defend conclusions and recommendations, to promote good professional relations, to increase credibility of the work, to allow for constructive criticism, to prevent future occurrences, and to add to the public health information base
When: at the conclusion of the investigation
How: use standard scientific reporting format with introduction, methods, results, discussion, (± recommendations); sponsoring agency may have additional reporting requirements
Where: internal documents should be filed with the local health department and all supporting agencies; if appropriate, a manuscript should be submitted to a general or discipline-specific peer-reviewed journal for publication
Who: audience may vary but might include epidemiologists in training, field epidemiologists, and researchers in the discipline

investigation, local, state, and federal public health agencies, and the community of people affected by the outbreak. This is done in the form of oral briefings and written reports. The "what, why, when, how, where, and who" of reporting are summarized in Table 20.4.

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CHAPTER ADDENDUM 1 (CASE STUDY): DRUG–DISEASE OUTBREAK

Author Joyce Murat Piper

Background

As your first assignment working for the U.S. Food and Drug Administration (FDA), you are to act as an epidemiologic consultant to the division that reviews and approves the use of endocrinologic and metabolic drugs. One day in late February (1985), a medical officer from the reviewing division comes to you with an unusual problem and asks for your help. The medical officer has just received a report of the death of a 20-year-old man with Creutzfeldt–Jakob disease (CJD). It is noted that this case received human growth hormone (hGH) for 13 years as a child, between the ages of 3 and 16 (from 1966 to 1980). You note that hGH is used to prevent pituitary dwarfism when given during the growth years.

Question 1 What is your first step in investigating this case? What is your reaction to this single case of CJD?