

# Chapter 9

## Outbreak Investigations

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### 9.1 Introduction

The aim of outbreak epidemiology is to study an epidemic in order to gain control over it and to prevent further spread of the disease. Generally outbreak means a “sudden occurrence,” while in the epidemiological sense an outbreak is defined as a sudden increase in the disease frequency, related to time, place, and observed population. Thousands of outbreaks among humans and animals have been reported and investigated during the last two centuries, among them the most numerous being outbreaks of cholera, plague, malaria, smallpox, influenza, SARS, measles, salmonella, chikungunya, and various foodborne outbreaks.

Traditionally, outbreak investigations are an essential part of infectious disease epidemiology. During the 18th and 19th century, epidemics of different diseases were widespread in Europe. Epidemiologists like Edward Jenner (1749–1823), who, as a country doctor, had observed the devastating epidemic of smallpox in England in the late 18th century, based on his observation had introduced a preventive vaccination against it, and John Snow (1813–1858), who had found contaminated water to be the cause of the cholera outbreak in London in the 1850s, undoubtedly created the fundamentals of modern outbreak investigations (Gordis 2009).

Today there are new challenges for studies of infectious diseases. On the one hand, due to global and regional changes in the environment, industry, food processing, transportation of goods and food, and behavioral changes, new infectious diseases emerge. On the other hand, people are confronted with already forgotten diseases, which are no longer considered to be a danger to public health (Dwyer and Groves 2001). Chapter 3 provides a comprehensive overview of emerging and reemerging infectious diseases. Furthermore, the increasing density of populations, growing megacities in the developing world, an increasing number of subpopulations at risk, and other socio-demographical factors influence the way communicable diseases spread (see Chapter 2). Considering the changing

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nature of modern infectious diseases, outbreak investigations play a crucial role in understanding their nature and subsequent control.

This chapter provides information on the objectives and the use and planning of outbreak investigations as well as on methods of conducting and reporting an outbreak. In addition, we provide simple examples of how to apply different study designs to investigate an outbreak.

## 9.2 Defining an Outbreak

The term “outbreak” is most commonly associated with a number of cases significantly higher than the background expected number of cases in a particular area over a given period of time. Beyond a simple increase in the number of cases, there can be an indication of an outbreak when the same exposure (risk factor) causes a *cluster* of cases (two and more cases simultaneously) with the same disease; the number of disease cases in a cluster must not necessarily be higher than expected (Ungchusak 2004). For instance, a cluster of five cases with hemolytic uremic syndrome (HUS) was identified in one community in southwest France in 2005. The outbreak investigation showed that all patients had consumed one brand of frozen beef burgers in the week before the onset of symptom. *Escherichia coli* O157:H7 (*E. coli* O157:H7) was identified as the cause of the disease (King et al. 2008). An outbreak investigation should also take place even if only one case of an *unknown or an unusual* disease occurs and if this disease is life threatening [e.g., avian flu and severe acute respiratory syndrome (SARS)] (Timmreck 1994).

Typical for any outbreak is that it occurs suddenly and requires direct measures to be taken. A well-conducted outbreak investigation may serve several aims. First of all, an outbreak investigation serves the detection and elimination of a potential epidemic’s cause and provides postexposure prophylaxis to affected individuals. Next, outbreak investigations often result in discovering new infections and diseases. The last quarter of the 20th as well as the first years of the 21st century was rich regarding the discovery of new etiologic agents and diseases, among which were *Legionella* spp. and *legionellosis*, toxic shock syndrome associated with tampon use, *E. coli* O157:H7 – potentially causing fatal hemolytic uremic syndrome, Ebola virus (which was sensationalized in the news media) – causing viral hemorrhagic fever, and severe acute respiratory syndrome (SARS), just to name a few (see Chapter 3 and Weber et al. 2001; Dwyer and Groves 2001; Hawker et al. 2005; Towner et al. 2008; Oxford et al. 2003). The recent outbreak of influenza A (H1N1), which started in Mexico in April 2009, led to the raise of the highest level of influenza pandemic alert (phase 6) by the World Health Organization.

Outbreak analysis may deliver information about the spread of a well-known pathogen to new geographical areas. Infectious agents may be introduced into new areas with immigrants, tourists, imported animals, and contaminated food and goods (Weber et al. 2001). Successful outbreak investigations contribute to the development of knowledge about infectious diseases by identifying new modes of

transmission. For example, *E. coli* O157:H7 infection had previously been associated with eating undercooked hamburger meat; however, numerous outbreak investigations registered *E. coli* O157:H7 transmission via unpasteurized cheese and apple drinks, swimming pools, lakes, municipal water, and person-to-person transmission (Center for Disease Control and Prevention 1993; Cody et al. 1999; Honish et al. 2005; Bruneau et al. 2004; Belongia et al. 1993; Weber et al. 2001).

Finally, outbreak investigations serve as a basis for the development of public health regulations and prevention guidelines. Scientific knowledge makes it possible to draw general conclusions, detect new trends, and show ways to new prevention measures. The study of outbreaks is therefore an important component of public health practice.

The investigation of an outbreak makes simultaneous use of epidemiological, microbiological, toxicological, and clinical methods in order to develop and test hypotheses about the causes of the outbreak. In the following sections, the most important methodological aspects of planning and conducting an outbreak investigation are described and explained using examples.

### 9.3 Suspicions of an Outbreak and Risk Communication

Outbreak investigations differ from other types of epidemiological studies, particularly in the way that they often start without clear hypotheses and require the use of descriptive analysis in order to analyze the situation in terms of time, place, person, and scope of the problem (Brownson 2006).

An outbreak can be suspected if data from several cases display common characteristics (e.g., occurrence of many cases of a disease in the same period of time, in the same area, and with similar manifestations). In order to assess *the existence of an outbreak*, diagnosis of the suspected cases should be confirmed and then the number of detected cases should be compared with the baseline rate for the disease and setting. Possible biases which can influence the evaluation of an outbreak must be taken into account; first of all, changes in reporting practices, changes in population size, improved diagnostic procedures or screening campaigns (detection bias), or increased interest of the public and media in certain diseases (Gerstman 2003). Often it might also be helpful to interview several representative cases. That can help to understand the clinical picture of the disease and obtain additional information about the affected individuals. The collection of epidemiological data is important for the development of prevention and control measures. Based on the initial information, an epidemiological investigation can be planned and control measures can be implemented immediately to stop further transmission of a disease (Dwyer and Groves 2001).

In case of a confirmed outbreak, the relevant public health authorities should be notified immediately and all important findings should be shared with involved individuals and parties. It is important to carefully record data and maintain both internal and external communication. Internal communication concerns the team

of outbreak investigators, whereas external communication concerns selection and presentation of the information to the news media as well as the contact of stakeholders. Investigators should avoid unnecessary speculation and identify key points to communicate and provide relevant background information of the epidemic as well as methods of its evaluation and control (Weber et al. 2001).

General control and prevention measures can already be implemented at the initial stage of the outbreak investigation. For instance, suspicious foods can be taken out of the trade, sick individuals who commercially have to deal with manufacturing or processing of groceries are restricted from their respective activities, or the population can be informed about risk-bearing products.

## 9.4 Descriptive Analysis

The main components of an outbreak investigation are summarized in the flowchart in Fig. 9.1. These steps need not necessarily be performed in the described sequence. Moreover, several steps, as many authors emphasize, often occur simultaneously (Gerstman 2003; Weber et al. 2001). The sequence and completeness of these steps would most likely depend on the urgency of the situation, the availability of human and other resources, and the process of obtaining data (Dwyer and Groves 2001).

In outbreak investigations, descriptive epidemiology is given one of the key roles. It illustrates an outbreak using the three standard variables, time, place, and person, and makes it possible to set up specific hypotheses about causes and sources of

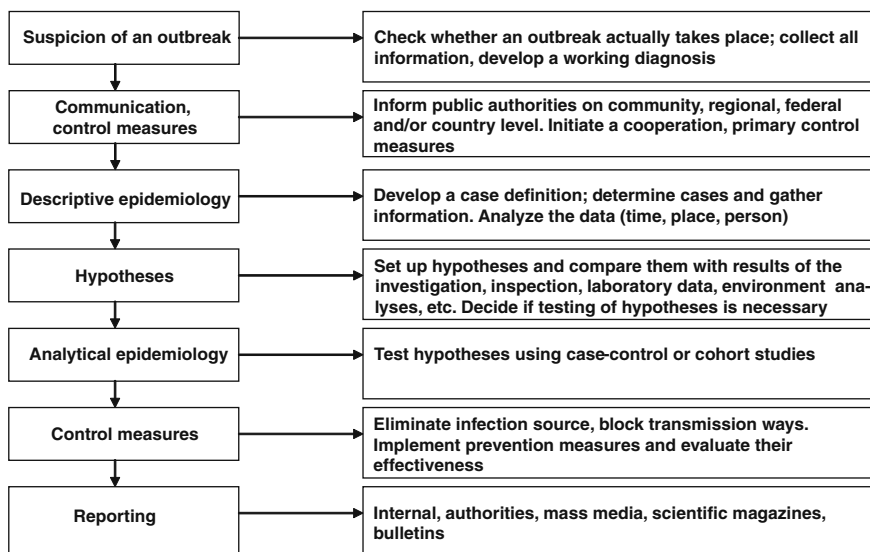


Fig. 9.1 Flowchart for outbreak management

infection and modes of transmission. The components of the descriptive process are discussed in the following sections.

### 9.4.1 Case Definition

It is essential to establish a simple and workable case definition for both the description of an outbreak and a possible analytical investigation. In the present context, the epidemiological case definition also includes orienting variables related to time, place, and person. This is in addition to clinical and, where appropriate, laboratory medical criteria. The case definition must be applied equally to all cases under investigation from the beginning. Obviously, early or preliminary case definitions can be based only on information about signs and symptoms of a disease or an infectious agent. For example, a primary definition of a foodborne outbreak can be formulated as follows:

A case of illness is defined as any vomiting, diarrhea, abdominal pains, headache, and fever that developed after attending an event X.

This definition does not imply any common risk factors for affected individuals, and thus emphasizes the *sensitivity* to detect disease cases. However, as the investigation goes on, the case definition should be reviewed and refined to increase *specificity*. The previous case definition of a foodborne outbreak may then be reformulated as:

A case of illness is defined as vomiting or diarrhea with onset within 4 days (96 hours) of consuming food served at the event X.

Here the definition has higher specificity and aims to exclude cases of gastroenteritis or other illnesses (Dwyer and Groves 2001).

Investigators can sometimes divide cases into “definite” (e.g., confirmed in a laboratory), “probable” (e.g., cases who have objective signs and symptoms contained in the case definition), and “possible” (“suspect”) (e.g., cases who have subjective signs and symptoms contained in the case definition) (Weber et al. 2001).

The following definition was formulated for “possible” cases in the outbreak of the influenza A (H1N1): “Defined as an individual with an acute febrile respiratory illness (fever  $>38^{\circ}\text{C}$ ) with onset of symptoms:

- Within 7 days of travel to affected areas; or
- Within 7 days of close contact with a confirmed or a probable case of influenza A (H1N1).”

One of the definitions for “probable” cases of the influenza A (H1N1) ran as following: “An individual with a clinically compatible illness or who died of an

unexplained acute respiratory illness that is considered to be epidemiologically linked to a probable or a confirmed case.

“Definite” case of the influenza A (H1N1) would be “an individual with laboratory confirmed Influenza A (H1N1) virus infection by one or more of the following tests:

- Real-time polymerase chain reaction (RT-PCR);
- Viral culture;
- Four-fold rise in Influenza A (H1N1) virus specific neutralizing antibodies” (European Centre for Disease Prevention and Control 2009; World Health Organization 2009a, 2009b).

### ***9.4.2 Finding Cases and Collecting Information***

Usually investigators know only about a part of the cases which occur during an outbreak. The main reasons for that are the following:

- Not all sick individuals visit a physician. Many of them feel no need to do so.
- Physicians do not always send a sample to a laboratory for microbiological analysis.
- Laboratory investigations do not always succeed in identifying a causal pathogen.
- Not all positive findings are reported to the public health department.
- Some patients avoid being reported.

Thus, in addition to the cases already known, there are cases which might have been missed or overlooked, and investigators should search for them. Only then the extent of an outbreak can be objectively estimated and the outbreak population defined. Hence, active search for cases might be carried out using certain case-finding techniques, for example:

- Searching in surveillance data and laboratory data (e.g., summaries of illnesses, morbidity reports from local health departments)
- Surveying physicians, personnel of clinical microbiological laboratories, and hospitals to check logs about diseases or diagnoses typical for the current outbreak
- Questioning known outbreak cases to find secondary cases (e.g., based on guest or participant lists of an event), public announcements in the local press, radio, and other mass media (More about surveillance systems in Chapter 8).

After all the cases are identified, comprehensive information about them is collected. The individuals can either be interviewed personally (or per telephone) or given a standardized questionnaire to fill in. Regardless of the type of disease, the

following basic information is necessary to describe the general pattern of it to the population at risk (Gerstman 2003; Dwyer and Groves 2001):

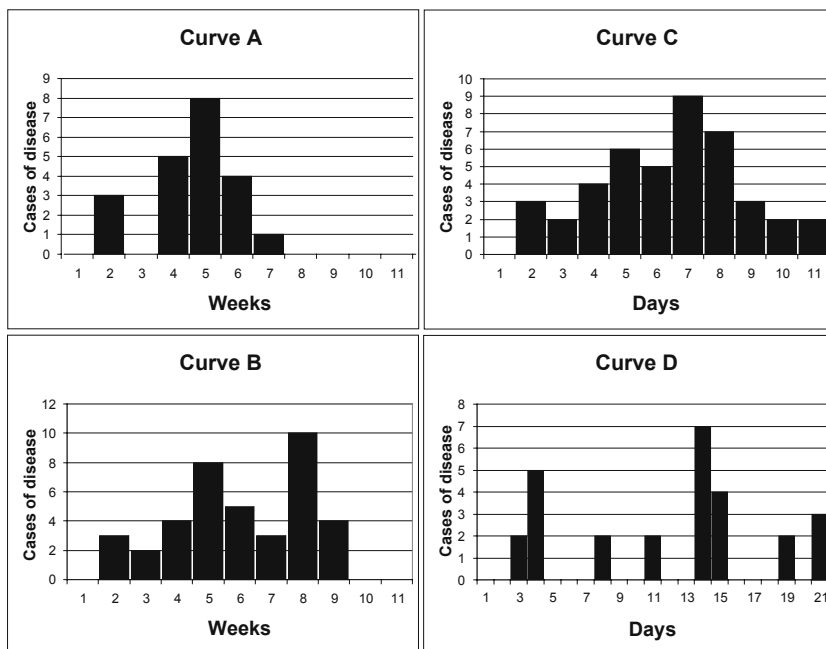
- Case identification (name, address, etc.),
- Demographical background,
- Clinical information (disease onset, time of exposure to the infectious agent, signs, manifestation, laboratory test results), and
- Potential risk factors (exposure or factors that might influence the probability of disease).

Following the collection of this information on cases, it is possible to structure the data in terms of *time, place, and person*. The goal of the descriptive epidemiology here is to find answers to the following questions: What do the patients have in common? Is there any increasing frequency in relation to sex, age groups, occupation as well as to demographical or geographical variables and variables related to time? In order to simplify answering these questions, it is often helpful to present the collected data in diagrams, tables, and maps and to calculate the attack rate.

### 9.4.3 Time: Epidemic Curves of Outbreaks

For the purpose of graphical description of cases by time of onset of illness, an epidemic curve can be drawn in which the occurrence of cases is shown over an appropriate time interval. Graphically, such a curve is constructed by putting the number of cases on the *y*-axis and the date of onset of illness on the *x*-axis. An epidemic curve helps to keep track of the time course of the events and gives clues about ways of transmission, exposure, and incubation period of the investigated disease. Disease cases, whose time course strongly deviates from that of the other cases (“outliers”), can give important clues to the source of infection (Gordis 2009). An epidemic curve can also help in distinguishing between common and propagated source epidemics.

Four examples of typical epidemic curves are given in Fig. 9.2a–d, modified from Checko (1996). Examples A and B represent an epidemic curve for a *propagated (continuing or progressive) source outbreak*. Propagated outbreaks depend on transmission from person to person or continuing exposure from a single source (Gerstman 2003). Curve A illustrates an outbreak (e.g., measles, influenza, or chickenpox) with a single exposure and index cases (index cases are those that first come to the attention of public health authorities) (Friis and Sellers 2004). Curve B shows the incidence of secondary and tertiary cases, typical, for example, for hepatitis A (secondary cases are those who acquire disease from contact with primary cases and tertiary cases are those who acquire disease from contact with secondary cases). In such a propagated outbreak, as it is shown in part B, there first occurs an increase in cases after exposure, then a fall in the incidence of cases; later there occurs a second increase in cases eventually infected by person-to-person transmission from primary cases. Curves C and D of Fig. 9.2 are examples of *common source outbreaks*. In such outbreaks most cases are exposed to one risk factor. Part C is a possible example for



**Fig. 9.2** (a–c) Examples of epidemic curves; (a and b) propagated or continuing source outbreak; (c and d) common source outbreak. Source: Modified from Checko 1996

an outbreak when the number of cases rises suddenly and then slowly falls again. This is characteristic of a common source outbreak with a point exposure when the population at risk is exposed simultaneously within a short period of time. In this instance the epidemic ends, unless secondary cases occur, which is typical for food-borne outbreaks. Another example of the point source outbreak is Legionnaires' disease, which broke out among people who attended a convention of the American Legion in Philadelphia in 1976 (Arias 2000).

In part D there is a continued (intermittent) exposure of individuals; cases of disease occur suddenly after the minimum incubation period, but do not disappear completely, because more individuals continue to be exposed to the source of infection.

#### **9.4.4 Place: Spatial distribution**

The spatial description of an outbreak can provide useful evidence about the geographical distribution of the cases, the size of an outbreak, and under special circumstances about the underlying source. For example, this might give information about specific locations within closed environments (e.g., a hospital), sites of routine activities (e.g., fast-food restaurant, public pools), or the place where affected individuals live (Weber et al. 2001). It is practical to present geographical information in the form of maps, for example, dot density maps and choropleth



maps. Dot density maps may serve to graphically present the geographical extent of the problem and provide information on clustering. Probably the most famous dot density map was drawn by John Snow, showing the cholera deaths near the Golden Square in London (where the outbreak occurred) in 1854 (McLeod 2001). From his map, one could recognize the connection between clustering of cholera cases around the Broad Street pump, thus, the water-borne nature of the infectious agent (Gerstman 2003). However, the disadvantage of dot density maps is that they do not provide any information concerning the number of people at risk in a mapped area, which can be confusing when populations of these areas are unequal in size. Another option is to build a map, which shows area-specific disease rates, for example, disease attack rates per 100 inhabitants showing epicenters of an epidemic.

In any case, visual representations are beneficial to understand more about the spread of an outbreak of disease. In addition to the above mentioned, there are more complex methods [e.g., Geographic Information Systems (GIS)], which combine both geographical and other information. For advanced treatment of these methods, please see Chapter 10.

### ***9.4.5 Person: Portraying the Outbreak Population***

Person-based variables can be used for portraying the outbreak population. An increasing frequency of cases in a certain population group can point to groups at high risk (for example, increased occurrence of cases among workers in a certain part of a factory or among visitors of a local restaurant). Person-based factors include demographical characteristics (age, sex, ethnicity), marital status, personal activities (occupation, habits, leisure activities, knowledge, attitudes, and behavior), genetic factors, physiological conditions (nutritional status, distresses, pregnancy, etc.), current diseases, and immune condition (Gerstman 2003). Furthermore, investigations of specific diseases, like STDs or HIV/AIDS, require the use of variables related to sexual behavior, sexual practices, number of sexual partners, and in specific cases also intravenous drug use.

#### **Exhibit 9.1 Use of mathematical methods in outbreak investigation**

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The elementary analysis of data as sketched above is meant to detect a *possible* outbreak but does not lead to a definitive statement about its existence. We *suspect* an outbreak if the epidemic curve looks unusual, in particular, if we find incidences that are significantly higher than expected if there is no outbreak. Such a purely qualitative judgment may suffice in a relatively simple and clear-cut setting as in the following examples of food poisoning, especially if supported by an a posteriori epidemiological analysis of the kind made there. In many situations, however, given the consequences of actions to be taken depending on the result of the investigation, a more precise decision rule will be necessary. We have to state what we mean by “significantly higher than expected.”

If we base our conclusion exclusively on the epidemic curve, which amounts to disregarding the spatial component of the data on cases, the problem may be formulated as follows: how can we determine a “threshold value”  $t$  such that, in the *absence* of an outbreak, an incidence exceeding  $t$  for a given period has a “very small” probability. We will then declare that there is an outbreak if the epidemic curve passes to values above  $t$ . What we mean by a “very small” probability needs to be defined in advance, depending on the risk we are willing to face for overlooking an outbreak.

Mathematically, this approach bears some similarity with the so-called theory of dams.

There we are interested in the probability that a dam built to contain water in a reservoir, e.g., for an electrical power station, will overflow during a given period of the future, given data from the past. Some research along these lines was indeed done within the framework of outbreak investigations but has not gained much importance because it became increasingly clear that the larger part of relevant information is usually contained in the spatial component of the data on cases. This led to the so-called cluster analysis, both for noninfectious and infectious diseases. The basic idea is similar to the one formulated before, namely to describe in a rigorous quantitative way what kind of clustering is, in the absence of an outbreak, still to be considered as “normal” and arising purely by random effects. We cannot enter into details here; some of the methods are presented in Chapter 11. There is an introductory text by Waller and Gotway (2004). For an advanced treatment, see the book by Lawson and Kleinman (2005), especially its chapter by Kulldorff on “Scan Statistics for Geographical Disease Surveillance: An Overview.”

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## 9.5 Analytical Epidemiology

To remind the reader, the goal of an outbreak investigation is fundamentally not only to identify and describe the causative agent but also, more specifically, to find a pathogen source of the disease and modes of transmission in order to develop control and prevention measures. In outbreak investigations, analytical studies are applied mainly in order to assess the centre, source, and cause of infection independently from laboratory methods.

The first important and probably the most difficult step in the analytical epidemiology is formulating and testing hypotheses. A formal testing of hypotheses can under certain circumstances be omitted, provided all the collected information clearly supports the generated hypotheses. In case some important issues remain unclear, further investigations are needed.

It is characteristic of analytical epidemiological studies to use a comparison group that allows quantifying a possible association between specific exposures and the disease under investigation. The two most frequently used study designs are case-control studies and cohort studies. Methodological aspects of these and other types of epidemiological studies are presented in Chapter 11.

### 9.5.1 *Formulating a Hypothesis*

Based on the findings of the descriptive analysis of the cases, the laboratory analysis, inspections carried out on site, and clinical investigations, the researchers are able to set up qualified hypotheses about the cause of infection, possible source of the pathogen, modes of transmission, and specific exposures. After developing the first hypotheses, a list of potential risk factors related to the infection can be developed. For instance, collected information may strongly suggest that members of a certain community supplied by a specific water system are at high risk to get ill or visitors of some event may report a disease with common manifestations (Gregg 2002).

### 9.5.2 *Assessing Risks: Historical Cohort Studies*

The choice of an appropriate study design may depend on various factors, like timing of the investigation, available resources, experiences of investigators, the size of the affected population, the exposure prevalence, and disease incidence (Gerstman 2003). If an outbreak occurs in a limited, closed population group (for example, participants of a celebration, a party, or patients of a hospital), the historical cohort study can be preferred to other study designs. In such a study the total population is divided into persons who were exposed to the potential risk factor and persons who were not exposed to the risk factor. After that the risk-specific attack rates are calculated and compared in both groups. The risk-specific attack rate is normally presented as a percentage:

$$\text{Attack rate} = \frac{\text{No. of cases in the population at risk}}{\text{Total } N \text{ of people at risk}} \times 100$$

The attack rate does not explicitly take a time variable into account, but as soon as the period from the exposure to the onset of most cases is known, the time is implicitly included in the calculation of the attack rate (Gordis 2009).

An example of a hypothesized foodborne outbreak is given below. A foodborne disease outbreak (FBDO) is defined as an incident in which two or more persons experience a similar illness resulting from the ingestion of a common food (Center for Disease Control and Prevention 2008). The example provides the calculation of attack rates and the identification of food or drink items which could possibly have caused the outbreak. In case of such an outbreak, first, investigators list all food and drinks served at the dinner. Next, they divide guests into those who consumed a certain food or drink and those who did not. After that the attack rate in each of the groups is calculated using the formula for attack rate given above. The next step is to find a difference in attack rates between the two groups. The food or drink items which show the biggest differences in attack rates can be responsible for an outbreak of disease (Friis and Sellers 2004). Exhibit 9.2 summarizes the steps in the reporting of a foodborne outbreak, as recommended by the US Centers for Disease Control and Prevention (Center for Disease Control and Prevention 2008).

## Exhibit 9.2. Guidelines for reporting in investigations of a foodborne outbreak

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### *Investigation of a foodborne outbreak: reported information and guidelines*

1. *Report type* (final or preliminary report during an outbreak)
2. *Number of cases* (laboratory/confirmed and presumptive cases; if necessary estimated number of cases)
3. *Dates* (dates where the first and the last known case patients got ill; dates of the first and the last known exposure; attached epidemic curve)
4. *Location of exposure* (use of country-specific cities' name abbreviations)
5. *Approximate percentage of cases in each age group* (identification of patterns of age distribution, age groups most affected)
6. *Sex of cases*
7. *Investigation methods*
8. *Implicated food(s)*
  - The contaminated ingredient(s)
  - Reasons for suspecting the food (e.g. laboratory analysis)
  - Methods of preparation
9. *Etiology* (identification of bacterium, virus, parasite, or toxin, according to the standard taxonomy)
11. *Contributing factors* [evidence of contamination, proliferation (increase in numbers), and survival factors responsible for the outbreak]
12. *Symptoms, signs, and outcomes* (number of patients with outcomes)
13. *Incubation period* (the shortest, the median, and the longest incubation period measured in hours or days)
14. *Duration of illness* (the shortest, the longest, and the median duration of illness measured in hours or days)
15. *Possible cohort investigation* (report of attack rate with formula)
16. *Location of food preparation*
17. *Location of exposure* (where food was eaten)
18. *Traceback* (if any traceback investigation)
19. *Recall* (recall of any food product related to the outbreak)
20. *Available reports* (if any additional reports)
21. *Agency reporting the outbreak* (contact information)

*For advanced reading and downloading the reporting form for foodborne outbreaks, please refer to the Center for Disease Control and Prevention electronic materials, available at <http://www.cdc.gov/foodborneoutbreaks/toolkit.htm>*

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### 9.5.2.1 Example of a Cohort Study in a Hypothetical Foodborne Outbreak

After participating in a wedding dinner, many of the guests became ill with symptoms like nausea, vomiting, and diarrhea. All 150 persons who participated in the wedding meal were asked about the food and drink they had consumed and whether they got sick after that. The investigators suggested that some food or drink could have been contaminated with staphylococcal bacteria. Using the case definition the

**Table 9.1** Analysis of a cohort study

| Risk factor present | Disease, N=50 | No disease, N=100 | Food-specific attack rate (%) |
|---------------------|---------------|-------------------|-------------------------------|
| Ate food X          | 45            | 40                | 45/85=53                      |
| Did not eat food X  | 5             | 60                | 5/65=7.7                      |

attack rates for specific food (for example, food X) was calculated and compared (Table 9.1).

Out of a total of 85 individuals who ate food X, 45 got sick (attack rate 45/85=53%). The attack rate of those who did not eat food X was 5/65 or 7.7%. Food X was assumed to be a possible risk factor for the disease, because of the following reasons:

- Food-specific attack rate among those who ate food X was high (53%).
- Food-specific attack rate among those who did not eat food X was low (7.7%), and therefore the difference (“risk difference”) between the attack rates was high (45.3%).
- The majority of the cases ate food X (45/50 or 90%).

In addition, the relative risk (RR), i.e., the ratio of attack rates, can be calculated:

$$RR = \frac{\text{Attack rate ate food X}}{\text{Attack rate did not eat food X}} = \frac{53}{7.7} = 6.9$$

A relative risk of 6.9 indicates that individuals who ate food X had a 6.9 times higher probability to get ill than those who had not eaten that food. Statistical significance tests can be used to assess that this association was not found due to chance exclusively (see also Chapter 12).

### 9.5.3 Secondary Attack Rate

When a disease spreads from the initial case to other persons, for example, to family members, the secondary attack rate can be calculated. It generally refers to the spread of disease in a family, household, dwelling unit, or another community or group. Here we would like to emphasize the use of definitions of initial cases. If a few cases of a disease occur at about the same time after an exposure, then the first case which gets the attention of the public health authorities is referred to as *an index case*, while the other ones are called *coprimary cases* (Friis and Sellers 2004). A coprimary case is by definition very close in time to an index case; therefore it is considered to belong to the same generation of cases. Therefore a secondary attack rate is defined as follows (Friis and Sellers 2004):

$$\text{Secondary attack rate} = \frac{\text{Number of new cases in group} - \text{initial cases}}{\text{Number of susceptible persons in the group} - \text{initial cases}} \times 100$$

For instance, three cases of measles occurred in a group of 17 children in a summer camp, and it was assumed that exposure took place outside of the camp. Out of

these three cases the first one registered by the camp health authorities was considered to be the index case and two other the coprimary cases. Ten days after the first measles symptoms were noticed in the initial cases, further 11 children in the group got ill.

Thus the secondary attack rate was

$$(11 - 3)/(17 - 3) \times 100 = 57.1\%$$

### 9.5.4 Case–Control Study

A case–control study should be the preferred study design in an outbreak investigation under at least the following three circumstances (Dwyer et al. 1994). First, if the initial population is very large and only a part of the population at risk can be sampled. Second, if the initial population at risk is not defined well enough to determine a cohort to be followed. Finally, a nested case–control study can be applied within a studied cohort when additional hypotheses should be tested. In a case–control study the distribution of exposures in the group of cases is compared with that in a group of healthy individuals (controls). The aim of case–control studies is to find differences in the risk factors to which two examined groups (cases and control persons) were exposed in the past. The questionnaire used to interview persons is identical in both groups.

#### 9.5.4.1 Example of a Case–Control Study in a Hypothetical Foodborne Outbreak

We now look at the above example (Table 9.1) from the angle of a case–control study. This means, in particular, that the two groups of “cases” and “controls” involved had been sampled from larger populations of unknown size.

Ninety percent of all cases ate food X, compared to only 40% of the control persons (Table 9.2). This suggests that consumption of food X is associated with the disease.

**Table 9.2** Analysis of a case–control study

| Exposure                  | Cases      | Controls   |
|---------------------------|------------|------------|
| Ate food X                | 45         | 40         |
| Did not eat food X        | 5          | 60         |
| <i>Percentage exposed</i> | <i>90%</i> | <i>40%</i> |

We compare the odds of the food consumption in the group of the cases (45/5) to the odds of the food consumption in the group of the control persons (40/60). The odds ratio is therefore equal to

$$\text{Odds ratio} = \frac{\frac{P1(E)}{1-P1(E)}}{\frac{P2(E)}{1-P2(E)}} = \frac{45/5}{40/60} = \frac{45 \times 60}{5 \times 40} = 13.5$$

An odds ratio of 13.5 hints at a strong association between falling ill and having consumed the food X. Similar to cohort studies it is possible to calculate the potential influence of chance with the help of statistical tests.

### ***9.5.5 Proving Evidence for Causal Associations***

A statistical association asserted on the basis of an analytical epidemiological study does not mean a causal association.

The likelihood of a cause and effect relationship increases if the following statements are true:

- The exposure preceded the illness. The suspected causation is biologically plausible; in other words, it is consistent with modern biological knowledge.
- The results correspond to those from other investigations, established and known facts about the disease.
- The value of risk or chance (measured by relative risk or odds ratio) is high, which increases the probability of causal association.
- There is evidence which reveals a dose–response association (the risk increases with the consumed quantity of the suspected infectious cause) (For more about postulates for causation, see Gordis 2009 and Hill 1965).

## **9.6 Control Measures and Reporting**

As has already been mentioned in Section 9.1, the main goal of an outbreak investigation is to stop a current outbreak and to avoid future outbreaks or epidemics. In order to stop an outbreak, the infectious source must be removed or transmission ways should be blocked. To avoid further spread of the infection it is necessary that the conditions that caused the outbreak are eliminated with the help of suitable long-term measures and structural changes. The investigation cannot be considered as completed until the preventive measures have been taken and they have been proven to be effective.

Specific measures that can be implemented to control the infectious source are, e.g., callback of contaminated products, closing of a manufacturing plant, cleaning or disinfection, removing persons from the infective source, treating the infected persons. In order to block the transmission, measures such as vaccination or improvement of hygiene, interruption of animate or inanimate environmental transmission, information and educational campaigns can be taken.

Obviously, any outbreak investigation should be completed by the writing of a report and dissemination of results to the involved parties. Detailed guidelines for writing reports of outbreak investigations can be found elsewhere; however,

the following remarks should be taken into account (Ungchusak 2004; Arias 2000; Gregg 2002).

First, the results of the investigations should be carefully documented and sent in the form of a detailed interim and final report to all authorities involved as well as to the administrative staff of the affected facility and the infection control center or committee (Weber et al. 2001; Arias 2000). Study findings should also be reported in the form of oral briefings or reports to all informants, interested local, state, and federal public health departments. In addition, the community of people where the outbreak occurred and study participants should be given feedback about the outcome of the investigation; the public can be informed through the news media. The scientific content of the investigation should be made accessible to specialists through publications in scientific journals and bulletins so that everyone can profit from the experience and insights gained.

During the pandemic of influenza A (H1N1), the World Health Organization provided the guidelines document for preparedness and response encouraging not only governments but also communities, families, and individuals to take active part in mitigating the global and local effects of the pandemic. During an outbreak, civil society groups should play a mediator role between government and communities, taking part in health communication and raising awareness. Taking preventive measures at the level of families and individuals such as regular hand washing, covering sneeze and cough, and isolating ill individuals is crucially important as well. It is furthermore necessary that each household takes care of its own safety in terms of access to precise and update information, medicines, water, and food. Recovered individuals should make use of their illness experience and reach out to other affected people to provide them with information and support (WHO 2009).

## 9.7 Conclusions

In the light of increasing frequencies of epidemics and outbreaks, a systematic and targeted action is needed in order to collect evidence and support decision-making processes. An outbreak investigation requires an application of methods of descriptive and, where appropriate, analytical epidemiology. The outbreak investigation and management includes several steps, among them most important are the establishment of the case definition and case-finding techniques, collection of data, and description of cases in terms of time, place, and affected person. Usually an analysis is required. Although associations found in an outbreak investigation cannot automatically be considered as causal, the simultaneous use of a well-planned epidemiological investigation and clinical and laboratory evidence will almost always provide valid information about causes and modes of transmission of diseases which will be helpful for decision making.



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