

The Epidemiological Approach (1.4)

As with all scientific endeavors, the practice of epidemiology relies on a systematic approach. In very simple terms, the epidemiologist:

- **Counts** cases or health events, and describes them in terms of time, place, and person;
- **Divides** the number of cases by an appropriate denominator to calculate rates; and
- **Compares** these rates over time or for different groups of people.

Before counting cases, however, the epidemiologist must decide what a case is. This is done by developing a case definition. Then, using this case definition, the epidemiologist finds and collects information about the case-patients. The epidemiologist then performs descriptive epidemiology by characterizing the cases collectively according to time, place, and person. To calculate the disease rate, the epidemiologist divides the number of cases by the size of the population. Finally, to determine whether this rate is greater than what one would normally expect, and if so to identify factors contributing to this increase, the epidemiologist compares the rate from this population to the rate in an appropriate comparison group, using analytic epidemiology techniques. These epidemiologic actions are described in more detail below. Subsequent tasks, such as reporting the results and recommending how they can be used for public health action, are just as important, but are beyond the scope of this lesson.

Defining a case

Before counting cases, the epidemiologist must decide what to count, that is, what to call a case. For that, the epidemiologist uses a case definition. A case definition is a set of standard criteria for classifying whether a person has a particular disease, syndrome, or other health condition. Some case definitions, particularly those used for national surveillance, have been developed and adopted as national standards that ensure comparability. Use of an agreed-upon standard case definition ensures that every case is equivalent, regardless of when or where it occurred, or who identified it. Furthermore, the number of cases or rate of disease identified in one time or place can be compared with the number or rate from another time or place. For example, with a standard case definition, health officials could compare the number of cases of listeriosis that occurred in Forsyth County, North Carolina in 2000 with the number that occurred there in 1999. Or they could compare the rate of listeriosis in Forsyth County in 2000 with the national rate in that same year. When everyone uses the same standard case definition and a difference is observed, the difference is likely to be real rather than the result of variation in how cases are classified.

To ensure that all health departments in the United States use the same case definitions for surveillance, the Council of State and Territorial Epidemiologists (CSTE), CDC, and other interested parties have adopted standard case definitions for the notifiable infectious diseases. These definitions are revised as needed. In 1999, to address the need for common definitions and methods for state-level chronic disease surveillance, CSTE, the Association of State and Territorial Chronic Disease Program Directors, and CDC adopted standard definitions for 73 chronic disease indicators.

Other case definitions, particularly those used in local outbreak investigations, are often tailored to the local situation. For example, a case definition developed for an outbreak of viral illness might require laboratory confirmation where such laboratory services are available, but likely would not if such services were not readily available.

Components of a case definition for outbreak investigations

A case definition consists of clinical criteria and, sometimes, limitations on time, place, and person. The clinical criteria usually include confirmatory laboratory tests, if available, or combinations of symptoms (subjective complaints), signs (objective physical findings), and other findings. Case definitions used during outbreak investigations are more likely to specify limits on time, place, and/or person than those used for surveillance. Contrast the case definition used for surveillance of listeriosis (see box below) with the case definition used during an investigation of a listeriosis outbreak in North Carolina in 2000.

Both the national surveillance case definition and the outbreak case definition require a clinically compatible illness and laboratory confirmation of *Listeria monocytogenes* from a normally sterile site, but the outbreak case definition adds restrictions on time and place, reflecting the scope of the outbreak.

Listeriosis — Surveillance Case Definition

Clinical description

Infection caused by *Listeria monocytogenes*, which may produce any of several clinical syndromes, including stillbirth, listeriosis of the newborn, meningitis, bacteriemia, or localized infections

Laboratory criteria for diagnosis

Isolation of *L. monocytogenes* from a normally sterile site (e.g., blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid)

Case classification

Confirmed: a clinically compatible case that is laboratory confirmed

Source: Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. *MMWR Recommendations and Reports* 1997;46(RR-10):49-50.

Listeriosis — Outbreak Investigation

Case definition

Clinically compatible illness with *L. monocytogenes* isolated

- From a normally sterile site
- In a resident of Winston-Salem, North Carolina
- With onset between October 24, 2000 and January 4, 2001

Source: MacDonald P, Boggs J, Whitwam R, Beatty M, Hunter S, MacCormack N, et al. Listeria-associated birth complications linked with homemade Mexican-style cheese, North Carolina, October 2000 [abstract]. 50th Annual Epidemic Intelligence Service Conference; 2001 Apr 23–27; Atlanta, GA.

Many case definitions, such as that shown for listeriosis, require laboratory confirmation. This is not always necessary, however; in fact, some diseases have no distinctive laboratory findings. Kawasaki syndrome, for example, is a childhood illness with fever and rash that has no known cause and no specifically distinctive laboratory findings. Notice that its case definition (see box below) is based on the presence of fever, at least four of five specified clinical findings, and the lack of a more reasonable explanation.

Kawasaki Syndrome — Case Definition

Clinical description

A febrile illness of greater than or equal to 5 days' duration, with at least four of the five following physical findings and no other more reasonable explanation for the observed clinical findings:

- Bilateral conjunctival injection
- Oral changes (erythema of lips or oropharynx, strawberry tongue, or fissuring of the lips)
- Peripheral extremity changes (edema, erythema, or generalized or periungual desquamation)
- Rash
- Cervical lymphadenopathy (at least one lymph node greater than or equal to 1.5 cm in diameter)

Laboratory criteria for diagnosis

None

Case classification

Confirmed: a case that meets the clinical case definition

Comment: If fever disappears after intravenous gamma globulin therapy is started, fever may be of less than 5 days' duration, and the clinical case definition may still be met.

Source: Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. *MMWR Recommendations and Reports* 1990;39(RR-13):18.

Criteria in case definitions

A case definition may have several sets of criteria, depending on how certain the diagnosis is. For example, during an investigation of a possible case or outbreak of measles, a person with a fever and rash might be classified as having a suspected, probable, or confirmed case of measles, depending on what evidence of measles is present (see box below).

Measles (Rubeola) — 1996 Case Definition

Clinical description

An illness characterized by all the following:

- A generalized rash lasting greater than or equal to 3 days
- A temperature greater than or equal to 101.0°F (greater than or equal to 38.3°C)
- Cough, coryza, or conjunctivitis

Laboratory criteria for diagnosis

- Positive serologic test for measles immunoglobulin M antibody, or
- Significant rise in measles antibody level by any standard serologic assay, or
- Isolation of measles virus from a clinical specimen

Case classification

Suspected: Any febrile illness accompanied by rash

Probable: A case that meets the clinical case definition, has noncontributory or no serologic or virologic testing, and is not epidemiologically linked to a confirmed case

Confirmed: A case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a confirmed case. (A laboratory-confirmed case does not need to meet the clinical case definition.)

Comment: Confirmed cases should be reported to National Notifiable Diseases Surveillance System. An imported case has its source outside the country or state. Rash onset occurs within 18 days after entering the jurisdiction, and illness cannot be linked to local transmission. Imported cases should be classified as:

- International. A case that is imported from another country
- Out-of-State. A case that is imported from another state in the United States. The possibility that a patient was exposed within his or her state of residence should be excluded; therefore, the patient either must have been out of state continuously for the entire period of possible exposure (at least 7-18 days before onset of rash) or have had one of the following types of exposure while out of state: a) face-to-face contact with a person who had either a probable or confirmed case or b) attendance in the same institution as a person who had a case of measles (e.g., in a school, classroom, or day care center).

An indigenous case is defined as a case of measles that is not imported. Cases that are linked to imported cases should be classified as indigenous if the exposure to the imported case occurred in the reporting state. Any case that cannot be proved to be imported should be classified as indigenous.

Source: Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. *MMWR Recommendations and Reports* 1997;46(RR-10):23–24.

A case might be classified as suspected or probable while waiting for the laboratory results to become available. Once the laboratory provides the report, the case can be reclassified as either confirmed or “not a case,” depending on the laboratory results. In the midst of a large outbreak of a disease caused by a known agent, some cases may be permanently classified as suspected or probable because officials may feel that running laboratory tests on every patient with a consistent clinical picture and a history of exposure (e.g., chickenpox) is unnecessary and even wasteful. Case definitions should not rely on laboratory culture results alone, since organisms are sometimes present without causing disease.

Modifying case definitions

Case definitions can also change over time as more information is obtained. The first case definition for SARS, based on clinical symptoms and either contact with a case or travel to an area with SARS transmission, was published in CDC's Morbidity and Mortality Weekly Report (MMWR) on March 21, 2003 (see box below). Two weeks later it was modified slightly. On March 29, after a novel coronavirus was determined to be the causative agent, an interim surveillance case definition was published that included laboratory criteria for evidence of infection with the SARS-associated coronavirus. By June, the case definition had changed several more times. In anticipation of a new wave of cases in 2004, a revised and much more complex case definition was published in December 2003.

CDC Preliminary Case Definition for Severe Acute Respiratory Syndrome (SARS) — March 21, 2003

Suspected case

Respiratory illness of unknown etiology with onset since February 1, 2003, and the following criteria:

- Documented temperature > 100.4°F (>38.0°C)
- One or more symptoms with respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or radiographic findings of pneumonia or acute respiratory distress syndrome)
- Close contact* within 10 days of onset of symptoms with a person under investigation for or suspected of having SARS or travel within 10 days of onset of symptoms to an area with documented transmission of SARS as defined by the World Health Organization (WHO)

* Defined as having cared for, having lived with, or having had direct contact with respiratory secretions and/or body fluids of a person suspected of having SARS.

Source: Centers for Disease Control and Prevention. Outbreak of severe acute respiratory syndrome—worldwide, 2003. MMWR 2003;52:226–8.

Variation in case definitions

Case definitions may also vary according to the purpose for classifying the occurrences of a disease. For example, health officials need to know as soon as possible if anyone has symptoms of plague or anthrax so that they can begin planning what actions to take. For such rare but potentially severe communicable diseases, for which it is important to identify every possible case, health officials use a sensitive case definition. A sensitive case definition is one that is broad or “loose,” in the hope of capturing most or all of the true cases. For example, the case definition for a suspected case of rubella (German measles) is “any generalized rash illness of acute onset.” This definition is quite broad, and would include not only all cases of rubella, but also measles, chickenpox, and rashes due to other causes such as drug allergies. So while the advantage of a sensitive case definition is that it includes most or all of the true cases, the disadvantage is that it sometimes includes other illnesses as well.

On the other hand, an investigator studying the causes of a disease outbreak usually wants to be certain that any person included in a study really had the disease. That investigator will prefer a specific or “strict” case definition. For instance, in an outbreak of *Salmonella* Agona infection, the investigators would be more likely to identify the source of the infection if they included only persons who were confirmed to have been infected with that organism, rather than including anyone with acute diarrhea, because some persons may have had diarrhea from a different cause. In this setting, the only disadvantages of a strict case definition are the requirement that everyone with symptoms be tested and an underestimation of the total number of cases if some people with salmonellosis are not tested.