Infectious Disease Epidemiology

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W. Ahrens, I. Pigeot (eds.) *Handbook of Epidemiology, 2nd edition*,
DOI 10.1007/978-0-387-09834-0_34,

51.1 Introduction

51.1.1 Specifics of Infectious Disease Epidemiology

Most textbooks dealing with the epidemiology of infectious diseases address the epidemiological features (also named biology) of specific infectious diseases. In this chapter, the focus is placed on the concepts and methods more specific to the general epidemiological study of infectious diseases. At a later stage, implementation of these methods must be adapted to the specific infectious disease under consideration. Then, detailed knowledge of the disease biology is of capital importance.

Epidemiologists focus their study on population groups (or "herds") rather than on individuals. In addition, infectious disease epidemiology also considers the interaction between individuals within the population group. For non-infectious diseases, each case and his/her risk factors are personal and independent from the neighbor (your neighbor's risk factors for heart disease have no influence on your risk factors). On the contrary, for infectious disease, the interaction between cases and contacts is of prime importance; this special feature of infectious disease epidemiology is discussed in the section transmission and basic concepts important to infectious diseases.

Although not entirely specific of infectious disease epidemiology, some characteristics are more often found in this field of study; for example, infectious disease epidemiology is:

- The closest to "shoe leather" epidemiology, meaning going into the community, talking to patients, contacts, practitioners, observing the environment (living conditions, activities, food preparation, water supply, etc.)
- Direct understanding and "closeness" to data
- Small-scale investigations
- Immediate results
- Easy understanding of etiology

51.1.2 The Global Burden of Infectious Diseases

Infectious diseases are a major cause of human suffering in terms of both morbidity and mortality throughout human history. The spread of infectious diseases was influenced by various steps in human civilization. For example, parasitic and zoonotic diseases have become more common after domestication of animals, airborne viral and bacterial infections after large settlements and urbanization. Throughout the ages, humanity suffered from large pandemics such as plague, smallpox, cholera, and influenza but also from the more silent killers of chronic infectious diseases such as tuberculosis and syphilis.

Morbidity due to infectious diseases is very common in spite of the progress accomplished in recent decades. According to the World Health Organization's (WHO) annual estimates, there are globally 300–500 million cases of malaria, 333 million cases of sexually transmitted diseases (syphilis, gonorrhea, chlamydia,

Table 51.1 Top ten causes of death worldwide (WHO 2008)

	Deaths in millions per year	% of all deaths
Ischemic heart disease	7.25	12.8
Stroke and other cerebrovascular disease	6.15	10.8
Lower respiratory infections	3.46	6.1
Chronic obstructive pulmonary disease	3.28	5.8
Diarrheal diseases	2.46	4.3
HIV/AIDS	1.78	3.1
Trachea, bronchus, lung cancers	1.39	2.4
Tuberculosis	1.34	2.4
Diabetes mellitus	1.26	2.2
Road traffic accidents	1.21	2.1

and trichomonas), 33 million cases of HIV/AIDS, 14 million people infected with tuberculosis, and 3–5 million cases of cholera (WHO 2010).

Even though infectious diseases are much more common in the non-industrialized world, the prevalence of infection is still very high for some infectious diseases in the industrialized world. Annually, approximately 48 million episodes of diarrhea are leading to 128,000 hospitalizations, and 3,000 deaths due to diarrheal illnesses are occurring in the United States (Centers for Disease Control and Prevention (CDC) 2011; Mounts et al. 1999). Every year, influenza virus circulates widely, infecting from 10% to 40% of the world population. Based on CDC estimates, there were 59 million infected during the 2009/2010 H1N1 pandemic (CDC 2011). Furthermore, serological surveys found that by young adulthood, the prevalence of antibodies was 80% against herpes simplex virus type 1, 15–20% against type 2, 95% against human herpes virus, 63% against *Hepatitis A*, 2% against *Hepatitis C*, 0.5% against *Hepatitis B*, and 50% against *Chlamydia pneumoniae* (American Academy of Pediatrics 2006; Mandell et al. 2000).

Not surprisingly, there is also a large imbalance in mortality rates due to infectious diseases between non-industrialized and industrialized countries. Globally, every third death is due from an infectious disease. In 1990, estimated 17 million deaths were due to communicable diseases, along with malnutrition and maternal and perinatal diseases with about 95% of these deaths occurring in the poorest parts of the world, mainly India and sub-Saharan continent (University of California 2011). According to the WHO, the most common causes of infectious disease deaths were lower respiratory infections (3.46 million), diarrheal diseases (2.46 million), HIV/AIDS (1.78 million), tuberculosis (1.34), malaria (1.1 million), and measles (900,000) (WHO 2008) (see Table 51.1).

51.1.3 The Importance of Infectious Disease Epidemiology for Prevention

It is often said that "Epidemiology is the basic science of preventive medicine." To prevent diseases, it is important to understand the causative agents, risk factors,

and circumstances that lead to a specific disease. This is even more important for infectious disease prevention, since simple interventions may break the chain of transmission. Preventing cardiovascular diseases or cancer is much more difficult because it usually requires multiple long-term interventions requiring lifestyle changes and behavior modification, which are difficult to achieve.

In 1900, the American Commission of Yellow Fever, headed by Walter Reed, was sent to Cuba. The commission showed that the infective agent was transmitted by the mosquito *Aedes aegypti*. This information was used by the then Surgeon General of the US Army, William Gorgas, to clean up the 200-year-old focus of yellow fever in Havana by using mosquito proofing or oiling of the larval habitat, dusting houses with pyrethrum powder, and isolating suspects under a mosquito net. This rapidly reduced the number of cases in Havana from 310 in 1900 to 18 in 1902 (Goodwin and Gordon Smith 1996).

A complete understanding of the causative agent and transmission is always useful but not absolutely necessary. The most famous example is that of John Snow who was able to link cholera transmission to water contamination during the London cholera epidemic of 1854 by comparing the deaths from those households served by the Southwark and Vauxhall Company versus those served by another water company. John Snow further confirmed his hypothesis by the experiment of removing the Broad Street pump handle (Wills 1996a).

51.1.4 The Changing Picture of Infectious Disease Epidemiology

Over the past three decades, more than 40 new pathogens have been identified, some of them with global importance: *Bartonella henselae*, *Borrelia burgdorferi*, *Campylobacter*, *Cryptosporidium*, *Cyclospora*, *ebola virus*, *Escherichia coli* 0157:H7, *Ehrlichia*, *hantaan virus*, *Helicobacter*, *hendra virus*, *Hepatitis C* and *E*, *HIV*, *HTLV-I* and *II*, *human herpes virus 6* and *8*, *human metapneumovirus*, *Legionella*, new variant Creutzfeldt-Jakob disease agent, *nipah virus*, *norovirus*, *Parvovirus B19*, *rotavirus*, severe acute respiratory syndrome (SARS), etc.

While there are specific causative agents for infectious diseases, these agents may undergo some changes over time. The last major outbreak of pneumonic plague (*Yersinia pestis*) in the world occurred in Manchuria in 1921. This scourge, which had decimated humans for centuries, is no longer a major threat. The plague bacillus cannot survive long outside its animal host (humans, rodents, fleas) because it lost the ability to complete the Krebs cycle on its own. While it can only survive in its hosts, the plague bacillus also destroys its hosts rapidly. As long as susceptible hosts were abundant, plague did prosper. When environmental conditions became less favorable (lesser opportunities to sustain the host to host cycles), less virulent strains had a selective advantage (Wills 1996b).

51.1.4.1 Changes in Etiological Agent

The influenza virus is the best example of an agent able to undergo changes leading to renewed ability to infect populations that had been already infected and immune. The influenza virus is a single-stranded RNA virus with a lipophilic

envelope. Two important glycoproteins from the envelope are the hemagglutinin (HA) and neuraminidase (NA). The HA protein is able to agglutinate red blood cells (hence its name). This protein is important as it is a major antigen for eliciting neutralizing antibodies. *Antigenic drift* is a minor change in surface antigens that result from point mutations in a gene segment. Antigenic drift may result in epidemics, since incomplete protection remains from past exposures to similar viruses. *Antigenic shift* is a major change in one or both surface antigens (H and/or N) that occurs at varying intervals. Antigenic shifts are probably due to genetic recombination (an exchange of a gene segment) between influenza type A viruses, usually those that affect humans and birds. An antigenic shift may result in a worldwide pandemic if the virus can be efficiently transmitted from person to person.

51.1.4.2 Changes in Populations at Risk

In the past three decades throughout the world, there has been a shift toward an increase in the population of individuals at high risk for infectious diseases. In industrialized nations, the increase in longevity leads to higher proportion of the elderly population who are more prone to acquiring infectious diseases and developing life-threatening complications. For example, a West Nile virus (WNV) infection is usually asymptomatic or causes a mild illness (West Nile fever); rarely does it cause a severe neuroinvasive disease. In the 2002 epidemic of West Nile virus in Louisiana, the incidence of neuroinvasive disease increased progressively from 0.3 per 100,000 in the 0 to 14 age group to 9 per 100,000 in the 60- to 75-year-old age group and jumped to 32 per 100,000 in the age group 75 and older. Mortality rates showed the same pattern, a gradual increase to 0.7 per 100,000 in the 60 to 75 age group with a sudden jump to 11 per 100,000 for the oldest age group of 75 and older (Balsamo et al. 2003).

Improvement in health care in industrialized nations has caused an increase in the number of immune-deficient individuals, be it cancer survivors, transplant patients, or people on immunosuppressive drugs for long-term autoimmune diseases. Some of the conditions that may increase susceptibility to infectious diseases are cancers, particularly patients on chemo- or radiotherapy, leukemia, lymphoma, Hodgkin's disease, immune suppression (HIV infection), long-term steroid use, liver disease, hemochromatosis, diabetes, alcoholism, chronic kidney disease, and dialysis patients. For example, persons with liver disease are 80 times more likely to develop *Vibrio vulnificus* infections than are persons without liver disease. Some of these infections may be severe, leading to death.

In developing countries, a major shift in population susceptibility is associated with the high prevalence of immune deficiencies due to HIV infections and AIDS. In Botswana, which has a high prevalence of HIV (sentinel surveillance revealed HIV seroprevalence rates of 36% among women presenting for routine antenatal care), tuberculosis rates increased from 202 per 100,000 in 1989 to 537 per 100,000 in 1999 (Lockman et al. 2001), while before the HIV/AIDS epidemics, rates above 100 were very rare.

Changes in lifestyles have increased opportunities for the transmission of infectious disease agents in populations previously at low risk. Intravascular drug injections have increased the transmission of agents present in blood and body fluids (e.g., HIV, Hepatitis B and C). Consumption of raw fish, shellfish, and ethnic food expanded the area of distribution of some parasitic diseases. Air travel allows people to be infected in a country and be halfway around the globe before becoming contagious.

By the same token, insects and other vectors have become opportunistic global travelers. *Aedes albopictus*, the Asian tiger mosquito, which is the vector for dengue, eastern equine encephalitis, and other viruses, was thus imported in 1985 to Houston, Texas, inside Japanese tires. Subsequently, it has invaded 26 US states.

51.1.4.3 Changes in Knowledge About Transmission of Disease Agents

With the advent of nucleic acid tests, it has become possible to detect the presence of infectious disease agents in the air and environmental surfaces. For example, the use of air samplers and polymerase chain reaction analysis has shown that *Bordetella pertussis* DNA can be found in the air surrounding patients with *B. pertussis* infection, providing further evidence of airborne spread (Aintablian et al. 1998) and thus leading to reevaluate the precautions to be taken. However, the presence of nucleic acids in an environmental medium does not automatically mean that transmission will occur. Further studies are necessary to determine the significance of such findings.

51.1.4.4 Bioterrorism Adds a New Dimension

Infectious disease agents, when used in bioterrorism events, have often been reengineered to have different physical properties and are used in quantities not usually experienced in natural events. There is little experience and knowledge about the human body's response to large doses of an infectious agent inhaled in aerosol particles that are able to be inhaled deep into lung alveolae. The probably best examples are the 2001 anthrax attacks in the United States. One week after the September 11 attacks, letters containing anthrax spores were mailed to several news media offices and two US Senators, killing a total of 5 persons and infecting 17 others. During the course of these anthrax letter events, there was considerable discussion about incubation period, recommended duration of prophylaxis, and minimum infectious dose for aerosolized and reengineered anthrax spores. The lack of knowledge base has led to confusion in recommendations being made.

51.2 New Approaches

Although the basics of infectious disease epidemiology have not changed and the discipline remains strongly anchored on some basic principles, technological developments such as improved laboratory methods and enhanced use of

informatics (such as advanced mapping tools, web-based reporting systems, and statistical analytical software) have greatly expanded the field of infectious disease epidemiology.

51.2.1 Improved Laboratory Methods

Molecular techniques are being used more and more as a means to analyze epidemiological relationships between microorganisms. Hence, the term molecular epidemiology refers to epidemiological research studies made at the molecular level (see also chapter ▸Molecular Epidemiology of this handbook).

The main microbial techniques use target plasmids and chromosomes, more specifically, plasmid fingerprinting and plasmid restriction endonuclease (REA) digestion, chromosomal analysis including pulse field gel electrophoresis (PFGE), restriction fragment length polymorphism (RFLP), multi-locus sequence type (MLST), and spa typing to name a few of these techniques. Polymerase chain reaction (PCR) is used to amplify the quantity of genomic material present in the specimen. Real-time PCR detection of infectious agents is now possible in a few hours. These techniques are becoming more widely used, even in public health laboratories for routine investigations. For more detailed information on these molecular techniques, please read a book on molecular biology.

Applications of molecular epidemiology methods have completely changed the knowledge about infectious disease transmission for many microorganisms. The main application is within outbreak investigations. Being able to characterize the nucleic acid of the microorganisms permits an understanding of how the different cases relate to each other.

Molecular epidemiology methods have clarified the controversy about the origin of tuberculosis cases: Is it an endogenous (reactivation) or exogenous (re-infection) origin? On the one hand, endogenous origin postulates that *Mycobacterium tuberculosis* can remain alive in the human host for a lifetime and can start multiplying and producing lesions. On the other hand, exogenous origin theory postulates that re-infection plays a role in the development of tuberculosis. The immunity provided by the initial infection is not strong enough to prevent another exposure to *Mycobacterium tuberculosis*, and a new infection leads to disease. In countries with low tuberculosis transmission, for example, the Netherlands, most strains have unique RFLP fingerprints. Each infection is unique, and there are hardly any clusters of infections resulting from a common source. Most cases are the result of reactivation. This is in contrast with areas of high endemicity where long chains of transmission can be identified with few RFLP fingerprinting patterns (Alland et al. 1994). In some areas, up to 50% of tuberculosis cases are the result of re-infection.

Numerous new immunoassays have been developed. They depend on an antigen-antibody reaction, either using a test antibody to detect an antigen in the patient's specimen or using a test antigen to detect an antibody in the patient's specimen.

An indicator system is used to show that the reaction has taken place and to quantify the amount of patient antigen or antibody. The indicator can

be a radioactive molecule (radioimmunoassay [RIA]), a fluorescent molecule (fluorescent immunoassay [FIA]), a molecule with an attached enzyme that catalyzes a color reaction (enzyme-linked immunoassay [ELISA or EIA]), or a particle coated with antigen or antibody that produces an agglutination (latex particle agglutination [LA]).

The reaction can be a simple antigen/antibody reaction or a "sandwich" immunoassay where the antigen is "captured" and a second "read out" antibody attaches to the captured antigen. The antibody used may be polyclonal (i.e., a mixing of immunoglobulin molecules secreted against a specific antigen, each recognizing a different epitope) or monoclonal (i.e., immunoglobulin molecules of single-epitope specificity that are secreted by a clone of B cells). It may be directed against an antigen on an epitope (i.e., a particular site within a macromolecule to which a specific antibody binds).

51.2.2 Mapping as an Epidemiological Tool

Plotting diseases on a map is one of the very basic methods epidemiologists do routinely. As early as 1854, John Snow, suspecting water as a cause of a cholera outbreak, plotted the cases of cholera in the districts of Golden Square, St. James, and Berwick in London. The cases seemed to be centered around the Broad Street pump and less dense around other pumps. The map supplemented by other observations led to the experiment of removing the handle on the Broad Street pump and subsequent confirmation of his hypothesis (Frost 1936).

Geographic Information Systems (GIS) have been a very useful tool in infectious disease research. GIS are software programs allowing for integration of a data bank with spatial information. The mapping component includes physical layout of the land, towns, buildings, roads, administrative boundaries, zip codes, etc. Data may be linked to specific locations in the physical maps or to specific aggregates. A GIS system includes tools for spatial analysis. Climate, vegetation, and other data may be obtained through remote sensing and combined with epidemiological data to predict vector occurrence.

However, these tools should be used with caution. They can be useful to generate hypotheses and identify possible associations between risk of disease and environmental exposures. Because of potential bias, mapping should never be considered as more than an initial step in the investigation of an association. "The bright color palettes tend to silence a statistical conscience about fortuitous differences in the raw data" (Boelaert et al. 1998). See chapter ▸Geographical Epidemiology of this handbook.

51.2.3 Computer Reporting and Software Progress

Web-based reporting, use of computer programs, and developments of sophisticated reporting and analytical software have revolutionized epidemiological data collection and analysis. These tools have provided the ability to collect large

amounts of data and handle large databases. However, this has not been without risks. It remains crucial to understand the intricacies of data collected to avoid misinterpretation. For example, one should be aware that diseases and syndromes are initially coded by a person who may not be very software proficient, using shortcuts and otherwise could enter data of poor quality.

51.3 Basic Concepts

Too often one sees epidemiologists and statisticians preparing questionnaires, carrying out surveys, gathering surveillance information, processing data, and producing reports, tables, charts, and graphs in a routine fashion. Epidemiology describes the distribution of health outcomes and determinants for a purpose. It is important to question the goals and objectives of all epidemiological activities and tailor these activities to meet these objectives.

The description of disease patterns includes analysis of demographic, geographical, social, seasonal, and other risk factors.

Age groups to be used differ depending on the disease; for example, diseases affecting young children should have numerous age groups among children; sexually transmitted diseases require detailed age groups in late adolescence and early adulthood. Younger age groups may be lumped together for diseases affecting mainly the elderly. Gender categorization, while important for sexually transmitted diseases and other diseases with a large gender gap (such as tuberculosis), may not be important for numerous other diseases.

Geographical distribution is important to describe diseases linked to environmental conditions but may not be so useful for other diseases.

51.3.1 Biology or Natural History of Infectious Diseases: The Intersection of Biology, Microbiology, Climatology, Ecology, and Epidemiology

The natural history of an infectious disease is the way in which the disease is transmitted, how it develops over time from the earliest stage of its prepathogenesis phase to its termination as recovery, disability or death in the human population, in the absence of treatment or prevention.

Epidemiologists dealing with an infectious disease issue are best served by taking the time to study the natural history or biology of that specific infectious disease. Facts to be studied are the nature of the infectious agent (parasite, bacteria, fungus, virus, or prion), the natural hosts, mode of entry into the host and exit from the host, distribution in the host tissues, incubation period, signs and symptoms of illness, natural reservoir in animals or environment, resistance to environmental factors, and geographical distribution of the agent and of human illness (which may be slightly different).

51.3.2 Infectious, Communicable, Contagious, Transmissible Diseases

An infectious disease is a disease due to a specific infectious agent or its toxic products that arises through transmission of that agent or its products from an infected person, animal, or reservoir to a susceptible host, either directly or indirectly through an intermediate plant or animal host, vector, or the inanimate environment (Porta et al. 2008).

Infectious diseases are caused by an infectious agent (helminth, protozoa, fungus, bacteria, virus, or prion, sometimes referred to as microorganisms, although helminths are really not microorganisms).

This definition is apparently simple but may get more complicated:

- The infectious agent does not need to be present all the time. The infectious agent may trigger a pathological process that will continue on its own, even after the agent is gone.
- Other factors may be necessary to trigger the disease; the infectious agent alone cannot cause the disease. The infectious agent may be necessary but not sufficient for the infectious disease. Most agents causing opportunistic infections in AIDS patients cannot cause any disease in normal individuals. They can only cause disease if the host is severely immune-compromised.

The term *communicable disease* is specific to those diseases that can be transmitted from an infected individual to another one directly or indirectly. It is sometimes used interchangeably for infectious diseases (Porta et al. 2008). Sometimes communicable diseases are defined as a subset of infectious diseases that can spread from person to person.

The term *transmissible or contagious disease* is often synonymous to communicable disease.

51.3.3 From Exposure to Disease

The infectious process may be broken down into the following steps. If the infectious disease agent does not gain a foothold, the person was only *exposed* and the infectious disease process ends. If the disease agent gains a foothold but no reaction is occurring, the person will be *colonized* but not infected. An infection occurs when the disease agent attaches itself to the epithelium and begins to multiply. The infectious disease agent will release cytotoxins which will damage the cells and injure the tissue which leads to the dissemination through the human body. Even after dissemination, humans might not show any signs and symptoms and are therefore considered *asymptomatic* or show clinical signs and symptoms and are then considered *symptomatic*.

Exposed means that a person is placed in a situation where effective transmission of an infectious agent could occur. Being exposed does not always mean that transmission did occur. For example, being in the same room as an infectious tuberculous patient is being exposed since tuberculosis is transmitted by droplet

nuclei. However, being in the same room with a person with HIV does not meet the criteria for exposure because conditions are not met for transmission to occur.

Exposure definition relies on information that may not be all known:

- Being in the same room with a tuberculous patient means being exposed if the patient is infectious (pulmonary tuberculosis with positive sputum). If the patient is not infectious, then exposure does not occur.
- Sharing a meal that resulted in a food poisoning outbreak is being exposed. If we know that only the potato salad was contaminated, then only those who ate the potato salad were exposed.

Infection: The entry and development or multiplication of an infectious agent in the body of humans or animals. Infection is not synonymous with disease. Disease implies some signs and symptoms or some negative impact on the health status of the individual.

Colonization: Porta et al. (2008) define in the Dictionary of Epidemiology infection and colonization as the same concept. However, in hospital-acquired infection control programs (often abbreviated as "infection control"), a distinction is made between colonization and infection: Colonization is the presence of a microorganism in or on a host with growth and multiplication but *without* any overt clinical expression or immune reaction in the host at the time the microorganism is collected (Brachman 1998). In contrast, infection entails some reaction from the host, either only on an immunological level or on an immunological and clinical level.

A *carrier* is an individual that harbors a specific microorganism in the absence of discernible clinical disease and serves as a potential source of infection. A carrier may be an individual who is colonized, incubating the disease, infected and asymptomatic, or convalescent from acute disease. The period of the carrier status may be short or lengthy. The portal of exit may be urine, genital secretions, feces, and respiratory, or the carrier may not excrete the agent (agent is circulating in the bloodstream).

Clinical infection: Clinical infection may result in signs and symptoms. Some of these may be less obvious or very minor. At the end of the spectrum is the individual with no sign, no symptoms who has an *asymptomatic infection or subclinical infection*. Asymptomatic infection does not mean that "all is quiet." It may cover some very active processes as in the asymptomatic phase of HIV infection, tuberculosis infection, or Hepatitis B carrier state.

51.3.4 Case, Index Case, Primary Case, and Secondary Case

A *case* is an operational definition. It denotes usually a person with a specific infectious disease.

A *surveillance case definition* is not a clinical diagnosis, both have very different purposes. A surveillance case definition is usually very precise and fairly restrictive so as to eliminate subjectivity, as much as possible. It uses a fixed set of indicators

to classify disease status regardless of differences between individuals. In contrast to that, a clinical diagnosis' purpose is to ensure best treatment options to the patient and the diagnostic procedures may therefore vary between individuals.

A *diagnosis* is an expression of the clinical judgment of the physician that leads to the therapeutic decisions to be taken.

An *index case* is the earliest documented case of a disease that is included in an epidemiological study or the very first case of an infectious disease that was identified in an outbreak.

A *primary case* is the first individual (case) who brought the infection in the group of population studied. The primary case is not always the index case. The index case may have triggered an investigation, and in the course of the investigation, the primary (or original) case is identified.

A *secondary case* is a case that was infected from the primary case and consequently occurred at a later date. There may be tertiary cases and so on. Usually one does not define cases further than secondary cases. If cases are somewhat synchronized, one may speak of *generations* or waves of cases.

51.3.5 Source, Reservoir, Vehicle, and Vector

A *reservoir* is any person, animal, plant, or environmental medium (soil, water) in which the microorganism normally lives and multiplies, on which it depends primarily for survival, and where it reproduces itself in such a manner that it can be transmitted to the susceptible host. Consider the following examples: Humans are the only reservoir for *Mycobacterium tuberculosis*, measles, chickenpox and smallpox. Numerous animal species are reservoirs for *Salmonella*; rodents are reservoirs for plague. Surface water and water systems are reservoirs for *Legionella*. Soils and the gut of some animals (horses) are reservoirs for tetanus bacteria (*Clostridium tetani*).

A *source of infection* is the actual person, animal, or object from which the infection was acquired.

A *source of contamination* is the person, animal, or object from which environmental media are contaminated. For example, the cook is the source of contamination of the potato salad.

A *vehicle* is an inanimate object which serves to communicate disease, for example, a glass of water containing microbes or a dirty rag.

A *vector* is a live organism that serves to communicate disease. Best known examples are *Anopheles* mosquitoes and malaria as well as *Ixodes* ticks and Lyme disease.

51.3.6 Transmission and Chain of Infection

When describing transmission, one should consider the source of the infectious agent and the portal of entry in the human.

51.3.6.1 The Source of Infectious Material

There are very different sources from where the potential infectious material is coming from. It might be blood splashed on a medical employee during a procedure or a person coming in contact with someone else's blood after a motor vehicle accident. It might be internal body fluids (such as cerebrospinal, pericardial, pleural, peritoneal, synovial, and amniotic fluids), and most of these exposures would occur in the medical setting. For genital fluids (vaginal, prostatic secretions, semen), sexual contact is the main mode of transmission through mucous membranes. Furthermore, transmission of Hepatitis B virus (HBV) and herpes simplex virus (HSV) to the newborn can occur during delivery as the newborns are exposed to vaginal secretions. Both internal and genital fluids can contain blood-borne pathogens (such as HIV, Hepatitis B virus, Hepatitis C virus (HCV), and cytomegalovirus (CMV)). Both secretions (saliva, nasal discharge, sweat, tears, breast milk) and excretions can be infectious. Urine might be contaminated with schistosoma eggs or leptospira bacteria, and feces can contain numerous enteropathogens. Persons can be infected via sexual contact of mucosal membranes (nasal, oropharyngeal, rectal, genital). Contact with contaminated tissue can occur in transfer of human or animal tissue: blood transfusion, blood components (factor VIII), organ transplants, or tissue grafts. Some hormones and proteins may be extracted from the tissue but still carry the infectious microorganisms, for instance, prions of Creutzfeldt-Jakob disease (CJD) in human growth hormone extract. The rabies virus is normally transmitted through animal bites, but also human bites could potentially (however never documented) infect the bite victim with Hepatitis B or C virus. Last but not least, environmental materials such as food, water, air, or even contaminated dust play a major role in the transmission of infectious diseases.

51.3.6.2 The Portal of Entry into Humans

Infectious disease agents can enter the human body through very different paths. They can be inhaled with the air (the respiratory system). Eating contaminated food and drinking contaminated water (gastrointestinal system) can infect persons and of course through sexual activities. Transplacental or intrauterine transmission will pose a risk for the fetuses. Persons also can be infected with viruses, bacteria, rickettsia, and parasites through arthropod bites such as mosquito or tick bites.

51.3.7 Classification of Transmission

51.3.7.1 Droplet Transmission

There are many infectious diseases which are transmitted by droplets (see Box 51.1). Droplets are generated in the upper respiratory tract during talking, singing, spitting, sneezing, and coughing. They are also produced during suctioning, sputum induction, bronchoscopy, and other respiratory procedures. The droplets produced vary in size from 1 to 100 micron (μm). Droplets will fall to the floor; the speed of fall is related to droplet size (see Table 51.2).

Box 51.1. Infections transmitted by droplets

Haemophilus influenzae, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Corynebacterium diphtheriae*, *Yersinia pestis* (pneumonic plague), *Bordetella pertussis*, *Mycoplasma pneumoniae*, *Streptococcus group* A (pharyngitis, pneumonia, scarlet fever), adenovirus, influenza, mumps virus, parvovirus 19, and rubella virus

Table 51.2 Droplet falling rates

A droplet of (μm)	Will fall in	
100	10 seconds	Droplets above 5 μm are trapped in the nose and upper respiratory tract and usually do not make it to the bronchi
40	1 minute	
20	4 min	
10	20 min	
5–10	30–45 min	May reach the lower respiratory tract
≤5	Droplet nuclei	May be inhaled into the alveoli

Droplet transmission occurs by direct hit when these droplets are propelled from the infected host to the recipient's mouth, nasal mucosa, or conjunctivae. As a rule of thumb, this method of transmission is common within 3 feet of the infected patient. Inhalation of a droplet occurs also while it floats; however, this occurs only during a short period of time since the droplet is falling to the floor. Contact with surfaces contaminated with droplets is the main mode of transmission for rhinoviruses and respiratory syncytial viruses (RSV). Concentrations of rhinoviruses are much higher on the hands than in aerosols. Droplets are created by aerosolization of infectious material: The success of such aerosols reaching susceptible individuals depends on the environmental conditions: humidity, temperature of the air, air currents, and distances of the host. The use of suction devices, catheters in intensive care units (ICU), and blood products in hemodialysis may produce some aerosols containing infectious particles.

In nature, soil particles contaminated with rodent urine have been aerosolized and thought to be responsible for the transmission of hantaviruses. *Legionella* are frequently present in waters (surface waters, hot water systems, and condensation from air conditioning or ventilation systems). When water is sprayed (cooling towers, showers, and cool mist over produce), aerosols containing *Legionella* are generated.

The degree of infectivity depends on the microorganism concentration in the droplets emitted. This varies from one virus to another, from one strain to another. The infecting dose is variable. For some viruses, it may be quite small: seven virions for adenoviruses. Experiments made with influenza virus showed that for similar

viral titer in lung tissue, some strains will have very high titer in bronchial secretions while others will not (Schulman 1970).

51.3.7.2 Airborne Transmission

Droplet nuclei or dust particles are responsible for this mode of transmission. Droplet nuclei are small droplets less than 5 μm in diameter. They result from evaporation of larger droplets or from direct formation of smaller droplets (particularly during coughing or during aerosol generating medical procedures). The transmission may occur over a long distance from the source patient.

Tuberculosis (TB) is one of the most important diseases transmitted by airborne means (see Box 51.2). Active pulmonary tuberculosis cases with acid-fast bacilli (AFB) on sputum smear are the cases that are infectious. Tuberculosis is almost exclusively transmitted by droplet nuclei (small particle of 1–5 μm) that contain *Mycobacterium tuberculosis*. The droplet nuclei must reach the pulmonary alveoli to start an infection. Large droplets are swallowed or get stuck in the trachea and bronchus; from there they are brushed back up and swallowed. The rare TB bacilli reaching the stomach are inactivated there. The role of droplet nuclei in the transmission of tuberculosis was demonstrated in several studies. In 1956, Riley and colleagues showed that air coming from rooms occupied by TB patients could infect guinea pigs (Riley et al. 1956). Coughing is the major producer of droplet nuclei. Speaking and singing also produce droplet nuclei, but these do not last very long (see Table 51.3).

Pulmonary tuberculosis cases may have up to 10,000,000 TB bacilli/milliliter (ml) of sputum. A typical sputum smear is about a hundredth of one ml (0.01 ml) and is covering about a 10,000 high power field (magnification ×100 for the oil immersion lens and ×10 for the eye piece). The probability of finding an acid-fast bacillus depends on the concentration of AFB in the sputum, and the number of microscopy fields examined (Toman 2004) (see Table 51.4). In a study carried out among

Box 51.2. Infections transmitted by droplet nuclei

- Tuberculosis (*Mycobacterium tuberculosis*)
- Measles (*Morbilli virus*)
- Chickenpox and shingles (*Varicella zoster* including disseminated zoster)

Table 51.3 Droplet production with coughing and singing

One good cough	⇒ 465 droplet nuclei
30 min after	228 are still airborne (49%)
Counting from 1 to 100	⇒ 1,764 droplet nuclei
30 min later	106 are still airborne (6%)

Table 51.4 Number of AFB per smear and number of immersion fields to be screened

No. of bacilli/ml/sputum	No. of AFB/smear	No. of immersion fields/AFB
10,000	100	100
100,000	1,000	10
1,000,000	10,000	1

Table 51.5 Proportion of infected contacts after index case coughed

Index cases coughed	Proportion of infected contacts (%)
>48 coughs/night	44
<12 coughs/night	27

Box 51.3. Infections transmitted by contact

- Gastrointestinal, respiratory, skin, wound infections
- Colonization with multidrug-resistant bacteria
- Enteric infections, enteroviral infections in infants
- Respiratory syncytial virus (RSV), parainfluenza
- Infectious skin infections: herpes simplex virus (HSV), impetigo, cellulitis, scabies, staphylococcal furunculosis
- Viral hemorrhagic conjunctivitis, viral fevers
- Some respiratory infections, bronchiolitis in infants, children
- Abscess, draining wound

contacts of smear-positive pulmonary cases, Loudon and colleagues showed that the more the index case coughs, the more infected individuals are to be observed among the close contacts (Loudon et al. 1969) (see Table 51.5).

51.3.7.3 Direct and Indirect Contact Transmission

Direct contact transmission results from a direct body surface to body surface contact and physical transfer of microorganisms. Direct contact occurs when shaking hands, taking pulse, turning a patient over, and having sexual intercourse.

Different viruses and bacteria can be transmitted by contact (see Box 51.3). Indirect contact transmission involves contact with the intermediate of an object. Indirect contact occurs through a contaminated dressing, instrument, or glove as well as door handles and keyboards.

51.3.7.4 Gastrointestinal Transmission: Fecal-Oral Route

Transmission by the fecal-oral route is the second most important mode of transmission after the respiratory tract for several infectious disease agents (see Box 51.4). The fecal-oral route refers to the mode of transmission of microorganisms excreted

Box 51.4. Infections transmitted by gastrointestinal transmission: fecal-oral route

- Typhoid fever
- *Shigella* spp.
- Cholera (*Vibrio cholerae*)
- Polio
- Coxsackie virus, echovirus, reovirus
- Norovirus
- Rotavirus
- Hepatitis A, Hepatitis E

by the feces and transmitted to the oral portal of entry through contaminated food, water, milk, drinks, hands, and flies.

The site of entry may be the oropharynx for some microorganisms or the intestinal tract for most viruses. *Surviving through the upper GI tract is essential*. Viruses with envelopes do not survive exposure to hydrochloric acid in the stomach, bile acids in the duodenum, salts and enzymes of the gut. Small enteroviruses without envelope (norovirus, rotavirus, polio, and coxsackie viruses) are able to resist. Hepatitis A and E are also transmitted by the fecal-oral route. For adenoviruses and reoviruses, this route is of minor importance.

Some of these pathogens are essentially found in humans (*Shigella*), while others may survive or multiply in the environment for long periods of time (*Vibrio cholerae*, poliomyelitis virus). This mode of transmission is more amenable to control measures than the respiratory route. Good personal hygiene (mostly proper hand washing), purification of drinking water, pasteurization of milk and dairy products, and sanitary preparation of food are all highly effective prevention measurements for these types of infectious diseases.

51.3.7.5 Gastrointestinal Transmission: Animal Host and Contaminated Food Products

Salmonellas infect a wide variety of domestic animals, birds, and other wildlife. Foods derived from salmonella-infected animal (eggs, dairy products, meat) are the major source of infection if improperly prepared. Salmonella is less often transmitted by water or direct contact. Other microorganisms such as Campylobacter, Yersinia, and Listeria are also transmitted through contaminated food products (see Box 51.5).

Food poisoning overlaps both classes of gastrointestinal transmission. Food poisoning may result:

- From consumption of food from an infected animal or undercooked eggs, for example, chicken and eggs with *Salmonella* or *Listeria* in unpasteurized milk

Box 51.5. Infections transmitted by gastrointestinal (GI) transmission: animal host and contaminated food products

- Salmonella
- Campylobacter
- Yersinia
- Listeria

- From consumption of food contaminated in the environment, for example, *Vibrio vulnificus* or *Vibrio cholerae* in raw oysters or undercooked seafood
- From food contaminated during preparation from an infected food item, for example, potato salad contaminated with *Salmonella* from raw chicken because the uncooked chicken and the salad ingredients were cut on the same cutting board
- From food contaminated by a human source, for example, typhoid fever carrier

51.3.7.6 Skin or Mucous Membrane Transmission

Transmission through the skin is the third most common mode of transmission of infection. Penetration through the intact skin is unlikely. Break in the skin barrier may result from needle injection, cut during a surgical procedure, accidental cut, crushing injury, and bite (rabies).

Transmission of blood-borne pathogens (Hepatitis B and C viruses (HBV, HCV) and HIV) does not occur if the blood was splashed exclusively on intact skin. Penetration through the skin is necessary. In the case of HIV, it takes injury with a hollow bore needle or other sharp object (lancet, glass, and scalpel) with blood to cause an infection. Solid needles do not carry sufficient quantities of blood to cause an infection. The viral titer is the best predictor of risk of infection. After percutaneous exposure to blood from infected patients, the risk of infection in the recipient is 30% for HBV (eAntigen positive), 3% for HCV, and 0.3% for HIV. This follows the ranking of viral titers.

Mucosal membranes allow penetration by blood-borne pathogens. Data from 21 studies worldwide on mucosal membrane exposure to HIV showed only one conversion in a total of 1,107 health-care workers (HCWs). The proportion of conversion was 0.09% (1/1,107).

Some parasites are able to penetrate actively through the intact skin: hookworm larvae and schistosoma cercariae.

51.3.7.7 Sexual Transmission (Mucous Membrane Transmission)

The genital tract is a special case for transmission through the mucosal membranes. The bacteria and viruses listed are present in the genital fluids and on the mucosal membranes (see Box 51.6). They may be transmitted to the mucosal membranes

of the partner during sexual acts: Membranes involved may be the vagina, penile urethra, anus and rectum, or oropharynx. Some of microorganisms such as *Shigella* spp. and *Campylobacter* spp. are primarily considered to be transmitted to the gastrointestinal (GI) tract. However, due to transmission when the rectum is involved in sexual activities, they are also listed as sexually transmitted disease (STD) agents.

The presence of lesions on the recipient partner seems to predispose to acquisition of infection, particularly for HIV.

51.3.7.8 Perinatal Transmission (Mucous Membrane Transmission)

These infections (see Box 51.7) occur when the newborn goes through the birth canal, from the cervix or vagina to the newborn.

Box 51.6. Sexual transmissions (mucous membrane transmission)

- *Neisseria gonorrhoeae*, *Chlamydia trachomatis*
- *Treponema pallidum* (syphilis)
- *Hemophilus ducreyi*
- *Mycoplasma hominis*, *Ureaplasma urealyticum*
- *Calymmatobacterium granulomatis*
- *Shigella* spp., *Campylobacter* spp.
- Group B streptococci
- Bacterial vaginosis-associated bacteria
- Herpes simplex virus (HSV) 1 and 2
- Cytomegalovirus (CMV) or herpes virus 5
- Hepatitis B virus (HBV)
- Human papilloma virus
- Molluscum contagiosum virus
- HIV (human immunodeficiency virus) 1 and 2
- *Trichomonas vaginalis*
- *Entamoeba histolytica*, *Giardia lamblia*
- *Phthirus pubis*
- *Sarcoptes scabiei*

Box 51.7. Perinatal transmission (mucous membrane transmission)

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- HBV
- HSV

Box 51.8. Transplacental transmission or vertical transmission

- *Treponema pallidum* (syphilis)
- *Toxoplasma gondii*
- CMV, HBV
- HIV
- HSV
- Rubella, varicella

51.3.7.9 Transplacental Transmission or Vertical Transmission

The microorganisms in this case are present in the blood of the mother and are able to go through the placenta to infect the fetus (see Box 51.8). In some cases, it is difficult to differentiate between perinatal or transplacental transmission, since both modes of transmission are known to occur.

51.3.7.10 Urinary Transmission

Although some bacteria (typhoid fever, leptospirosis) and viruses (CMV, measles) may be excreted in the urine, the role of urine is a minor one in the transmission of diseases. In urinary schistosomiasis, the adult worms live in the venous plexus around the urinary bladder. They lay their eggs in the lining of the bladder. The eggs are excreted in the urine. If they reach water, they hatch into larvae which look for a suitable intermediate host (freshwater mollusk).

51.3.7.11 Arthropod-Borne Transmission

Mosquitoes, flies, fleas, true bugs, ticks, and lice may transmit various microorganisms by two mechanisms (see Table 51.6):

1. Passive transmission: the insect acts as a live syringe. It picks up microorganisms from blood or superficial lesions and passes them on to another human. There is no incubation time, no multiplication of microorganisms while carried by the arthropod. This mode of transmission is not specific; a wide variety of microorganisms may be transmitted, but the transmission is not very efficient.
2. Active transmission involves multiplication of the microorganisms in the arthropod. This applies only to some microorganisms with a definite set of arthropods. This mode of transmission may be very effective: The microorganisms may be multiplied a thousand to a million times. This mode requires a period of multiplication in the arthropod.

51.3.7.12 Common Vehicle Transmission

The microorganisms have contaminated the "common vehicle" and are persisting over a long period of time in/on the common vehicle. The common vehicle can

Table 51.6 Arthropod-borne diseases

Disease (infectious agent)	Vector/intermediate host
Bacteria	
Plague (*Yersinia pestis*)	Fleas
Borrelia	
Lyme disease (*Borrelia burgdorferi*)	*Ixodes* ticks
Relapsing fever (*Borrelia recurrentis*)	*Ornithodoros* ticks
Rickettsia	
Epidemic typhus (*Rickettsia prowazekii*)	Lice, Pediculus humanus
Murine typhus (*Rickettsia typhi*)	Fleas
Scrub typhus (*Rickettsia tsutsugamushi*)	Larval mites
Rickettsialpox (*Rickettsia akari*)	Mouse mite
Rocky Mountain spotted fever (*Rickettsia rickettsii*)	*Dermacentor, Amblyomma* ticks
Trench fever (*Rickettsia quintana*)	Lice
Virus	
Dengue	*Aedes aegypti*
Flaviviridae	Mosquitoes
St. Louis encephalitis	*Culex* mosquitoes
Japanese encephalitis	*Culex* mosquitoes
Tick-borne encephalitis	*Ixodes* ticks
Powassan	*Dermacentor* ticks
Togaviridae: Alphavirus	
Eastern equine encephalitis	Mosquitoes
Western equine encephalitis	Mosquitoes
Venezuelan equine encephalitis	Mosquitoes
Bunyaviridae	
California encephalitis, La Crosse	Mosquitoes
Crimean-Congo hemorrhagic fever	Ticks
Kyasanur forest hemorrhagic fever	Ticks
Yellow fever	*Aedes* mosquitoes
Protozoa	
Malaria (*Plasmodium* sp.)	*Anopheles* mosquitoes
Chagas disease (*Trypanosoma cruzi*)	*Triatoma* sp. (bugs)
Sleeping sickness (*Trypanosoma gambiense*)	*Glossina* sp. (tsetse flies)
Leishmaniasis (*Leishmania* sp.)	*Phlebotomus* (sandflies)
Helminths	
Bancroft's filariasis (*Wuchereria bancrofti*)	*Culex*, *Aedes*, and *Anopheles* mosquitoes
Malayan filariasis (*Brugia malayi*)	*Culex*, *Aedes*, and *Anopheles* mosquitoes
Mansonella ozzardi	*Culicoides*, *Simulium*
Acanthocheilonema perstans	Gnats, *Culicoides*
Onchocerciasis (*Onchocerca volvulus*)	Black gnats, *Simulium*
Loiasis (*Loa loa*)	Mango flies, *Chrysops*

be food, water (either drinking the water or swimming in the water), soil (tetanus bacteria), medications, medical devices, or equipment.

51.3.8 Different Roles in Transmission: Indicator, Maintenance, and Amplifier

For some infectious diseases, different segments of the population play different roles. The best example for that is foot-and-mouth disease (FMD), a viral disease which rarely affects humans. Cloven-hoofed animals (such as cattle, goats, sheep, and pigs) are susceptible to FMD. FMD viruses are transmitted by air from one infected animal to another. Pigs are considered to be the amplifier host because they may exhale up to 1 million viral particles/ml of air. Sheep are an important reservoir of the virus and are considered maintenance hosts. They are usually asymptomatic when infected with foot-and-mouth disease. When these sheep mix with cattle, the cattle develop severe clinical signs and are therefore easily detected (*indicator host*).

51.3.9 Incubation Period, Latent Period, and Serial Interval

51.3.9.1 Incubation Period

The incubation period is the time interval between the invasion by a microorganism and the first signs or symptoms of disease (onset of disease). The concept of incubation period relies on the assumption that the disease is not asymptomatic and that the onset is clearly identifiable. For asymptomatic cases or carriers, incubation periods are irrelevant. For some infections, a person may get exposed to the agent, become colonized, and sometime in the future become a case. If this happens, incubation is also irrelevant. Incubation periods are only useful if infection is followed by disease within a certain period of time. Incubation periods are useful tools when carrying out infectious disease investigations. A person usually can tell when the first symptoms of a specific disease appeared. From that date, subtracting the incubation period, epidemiologists may estimate the date of infection (within a certain interval). It is also important for follow-up on potential contacts to the primary case that the primary case might have been already infectious before exhibiting any clinical signs and symptoms (see Fig. 51.1). In many instances, a person may be infectious toward the end of the incubation period but before the appearance of the first symptoms. The incubation period varies according to numerous factors:

- Portal of entry: The closer the portal of entry to the site of disease, the shorter the incubation period.
- Type of infection (local or systemic): Diseases caused by local multiplication of a microorganism have short incubation periods. Those that require systemic dissemination and secondary localization have longer incubation periods.
- Pathogenesis: Diseases due to a preformed toxin have very short incubation periods. Diseases due to direct involvement of epithelial surfaces have short incubation periods, for example, streptococcal sore throat, bacterial pneumonias,

Primary Case	⇩ Infection	⇩ Onset	
	Incubation	**Disease**	
	Latent period	**Infectious period**	
Secondary Case	⇩ Infection		
		Incubation	**Disease**
	Onset of primary ⇨	Serial interval	⇦ Onset of secondary

Fig. 51.1 Incubation, latent period, and serial interval

shigellosis, cholera, and gonorrhea. In contrast, *Mycoplasma pneumoniae*, diphtheria, and pertussis as well as diseases like syphilis, brucellosis, and typhoid fever have long incubation periods (2–3 weeks).

- Immune status of the host: It is important that the notion of incubation is relative. HIV provides a good example. Infection of an individual with HIV is followed by a flu-like syndrome. It includes fever, headache, miscellaneous aches (neck and back), malaise, lymphadenopathy, and rash. The incubation period for this primary syndrome is 2 weeks to 2 months. The patient then enters into a remission period with no clinical signs. However, during this period, the HIV multiplies at variable rates, destroying CD4+ lymphocytes which are generated as fast as they are destroyed. The latent remission ends when the patient's organism is no longer able to produce CD4+ lymphocytes in sufficient quantities. Immune defenses fail rapidly and opportunistic infections develop. This phase is considered as the AIDS (acquired immune deficiency syndrome) disease. The incubation period for AIDS diseases ranges from 2 to 10 years, with less than 10% having an incubation period greater than 10 years.

In rabies, the incubation period depends on the length of time it takes the virus to progress along the neurons to reach the brain. Once the brain is reached, the disease becomes manifest. The incubation may be as short as 9 days if the bite was in the face or as long as 1 or 2 months if the bite occurred in the leg. The longest incubation period known for rabies virus is 9 years.

The incubation period is useful for tracing the source of infection and contact, determine the period of surveillance, allow for prophylaxis to become effective (diseases with a long incubation period may be prevented by immunization if administered early), identification of point source or propagated epidemics.

Incubation period in a vector is the time interval between entry of the microorganism in the vector and the time the vector becomes infective. This is also called the extrinsic incubation in contrast to the intrinsic incubation period in humans.

51.3.9.2 Latent Period

The latent period of infection is the length of time between infection and the beginning of the infectious period. It is also a period during which no symptoms occur, an asymptomatic window in the disease (latent period of syphilis, of HIV infection).

51.3.9.3 Serial Interval

A serial interval for diseases spread from person to person is the time between successive generations of cases, that is, the time between appearances of symptoms in successive generations. If a person is infectious before onset of symptoms, the serial interval may be lower than the incubation period.

51.3.9.4 Infectious (Infectivity) or Communicability Period

The infectious (infectivity) period is the length of time a person may transmit a microorganism. There are several patterns for infectious periods:

- Short period at the end of the incubation period and at the beginning of the disease (measles, chickenpox)
- Short period and a few individuals become chronic carriers (Hepatitis B)
- Throughout the disease (open cases of active pulmonary tuberculosis, malaria).

Measuring infectivity is difficult. It is seldom the result of well-controlled studies. It is often the interpretation of observational studies on the occurrence of secondary cases. Factors such as amount of infectious agents put out by the source, closeness, length of contact, and susceptibility of the target contacts have to be considered. In recent times, nucleic acid testing has been used to find remnants of infectious disease agents in human or environmental materials, but their significance to transmission is difficult to interpret.

51.3.10 Distribution Pattern in the Population

For a better understanding of the distribution of infectious diseases in populations, the below terms have to be defined: Epidemiologists define *sporadic* cases as the occurrence of single illnesses in irregular or random instances. *Endemic* defines the occurrence of cases of an illness with a constant frequency. Depending on the intensity of the occurrence, the terms holoendemic, hyperendemic, or hypoendemic are used. *Epidemic is defined as the* occurrence in a community of cases of an illness with a frequency clearly in excess of normal expectancy. If this occurrence of an epidemic occurs worldwide or affects numerous countries, epidemiologists consider it a pandemic. The most recent pandemic was declared in June 2009, when the WHO declared a pandemic of novel influenza A (H1N1). At the time, more than 70 countries had reported cases of novel influenza A (H1N1) infection, and there were ongoing community level outbreaks of novel H1N1 in multiple parts of the world. An *outbreak* is defined as two or more related cases with the identical infectious disease agent suggesting the possibility of a common source or transmission between these cases. It also could be defined as a very limited epidemic; however, the word "epidemic" is usually avoided when the number of cases is relatively small so as not to scare the public. *Elimination of disease* is the reduction to zero of the disease incidence in a defined geographical area (e.g., neonatal tetanus) compared to the *elimination of infections* which is defined as the reduction to zero of incidence of infection in a defined geographical area (e.g., measles, poliomyelitis).

Table 51.7 Infectious dose and attack rates

Dose (no. of organisms)	Attack rate (%)
Experimental human salmonellosis	
125,000	17
695,000	33
1,700,000	67
(McCullough and Eisele 1951)	
Typhoid fever	
1,000	0
100,000	28
10,000,000	50
100,000,000	89
1,000,000,000	95
(Hornick et al. 1970)	

If there is a permanent reduction to zero in the worldwide incidence, the disease is considered *eradicated*, such as smallpox was in 1980.

51.3.11 Infectious Dose

The dose of pathogens received by the exposed individual is an important aspect of infectivity. There is also a close correlation between dose and type of contact. A closer, more direct type of contact delivers a higher dose.

It is rarely possible to have an exact measure of the infecting dose. In the past, experiments have been carried out with human volunteers. In one experiment, *Salmonella bareilly* was given to several groups of six volunteers (McCullough and Eisele 1951). A case was defined as one experiencing clinical diarrhea with *S. bareilly* isolated from the stools. Some of the cases excreted *Salmonella* for 1 day, some for 2 days. The corresponding attack rates, that is, percentage of volunteers experiencing a clinical diarrhea, are displayed in Table 51.7. The attack rate depends heavily on the working case definition.

From this type of data, one may calculate an infectious dose 50 (ID50) = the dose of pathogenic microorganism that will cause disease in 50% of the susceptible exposed. In some outbreaks, particularly foodborne outbreaks where contaminated food is saved, it may be possible to estimate the infectious dose. The dose may also be important in determining the severity of disease. To give an example, 1,000 *Vibrio cholerae* bacteria produce asymptomatic infections, 10,000 to 1 million bacteria produce simple diarrhea in 60%, and at least 1 million bacteria produce severe diarrhea with dehydration in 25–50% of volunteers.

51.3.12 Environmental Factors

There are several factors which influence the spread of microorganisms in the environment. The spread of infectious diseases depends on:

1. The stability of the microorganism in the physical environment required for its transmission including resistance to desiccation, high or low temperature, and ultraviolet light
2. The amount of microorganisms in the vehicle of transmission
3. The virulence and infectivity of the microorganisms
4. The availability of the proper vector or medium for the transmission

Environmental characteristics play a role on different levels:
1. Survival of the virus in the environment
2. Influence on the route of transmission
3. Influence on the behavior of the host

A warm environment enhances the transmission of microorganisms transmitted by water. In tropical and temperate areas, summer increases contacts between humans and surface water. Summer brings more people outside, particularly in the evening, and increases contacts between humans and mosquitoes and other arthropod vectors.

In the cooler seasons in temperate climates, in the rainy season in tropical climates, people tend to stay and congregate indoors promoting transmission by airborne or droplet mechanisms. Long stays in the hot and dry environment indoors impair the protective mechanisms of human mucous membranes and may facilitate the attachment of viruses onto the upper respiratory mucous membranes. The incidence of upper respiratory infections is as high in the middle of winter in the temperate climates as in the middle of the monsoon or rainy season in the tropical climates.

51.3.13 Host Factors

51.3.13.1 Extrinsic Host Factors

Exposure to infectious disease agents depends on both intrinsic (internal) and extrinsic (external) host factors. Extrinsic host factors are the method of transmission of the microorganism as well as the host behavior. Exposure to microorganisms which are transmitted by droplet or airborne modes is very common. Anyone who is out in the public is likely to be exposed to these microorganisms. Microorganisms which are transmitted by vectors result usually from special occupations or special settings (hobbies or leisure activities). For example, persons who love to be outdoors (camping, hiking, or working on fields or in the forest) are more likely to be bitten by ticks or mosquitoes and therefore more likely to develop one of the zoonotic diseases which are transmitted by these arthropods. Exposure to sexually transmitted microorganisms depends entirely on the sexual activities, number of sex partners, and/or lifestyle of the hosts and the carriers of these diseases.

51.3.13.2 Intrinsic Host Factors

The transmission of infectious diseases is also regulated by intrinsic factors that influence the host response. It depends on how many microorganisms are transmitted (dose), how virulent the strain is, and how the microorganisms enter the

human body. The person's age at time of infection is important, too. In general, the probability of clinical disease increases with age (e.g., polio, Hepatitis). Preexisting level of immunity to the disease, the nutritional status of the host, as well as any preexisting disease will influence a successful transmission as well. Individuals with impaired immune response (HIV, patients on immunosuppressive therapy for cancer or transplant) have a higher risk of developing severe disease. Also personal habits or lifestyle factors such as smoking, drinking alcohol, drug abuse, or exercise can influence the host response. Smoking depresses the ciliary function of the bronchial tree and increases susceptibility to infections (e.g., tuberculosis). Alcohol consumption increases the risk for chronic Hepatitis infections. Also psychological factors such as motivation and attitude toward disease can contribute to the transmission of infectious disease agents.

51.4 Occurrence of Infectious Diseases

Especially in outbreak situations, epidemiologists investigate the occurrence of disease by asking the following questions:

- When did the disease occur (time)?
- Where do the cases come from (place)?
- Who got infected with the disease (person)?

51.4.1 Time

51.4.1.1 Epidemic Curve

An epidemic curve is the standard graphic representation of cases occurring over time. It is a histogram with number of cases plotted along the vertical axis and time along the horizontal axis. The time unit may be in hours (rapid outbreak such as foodborne outbreaks due to a toxi-infection), days, or weeks. It is important to have a good time unit applied; if the time unit is too short or too long, one does not get a visual picture of the outbreak dynamics.

The examples in Figs. 51.2 and 51.3 show the epidemic of a Saint Louis encephalitis (SLE) outbreak that occurred in Louisiana in September to October 2001. Figure 51.2 uses days as a time unit, and Fig. 51.3 uses weeks. Figure 51.3 provides a better understanding of the outbreak.

An epidemic curve may provide some clues about the nature of the outbreak. A point source outbreak is relatively contracted in time, while a continuous source outbreak is more stretched out. In the beginning of an outbreak which is due to person-to-person transmission, one may see the successive generations.

51.4.1.2 Seasonal and Annual Variations

Seasonal variations are important for some infectious diseases, particularly those which are heavily influenced by the environment such as water, food, and arthropod

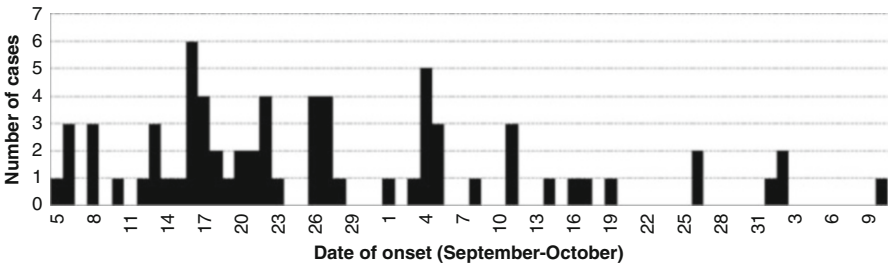

Fig. 51.2 Saint Louis encephalitis (SLE) outbreak, Monroe, Louisiana, September–October 2001, epidemic curve by day of onset

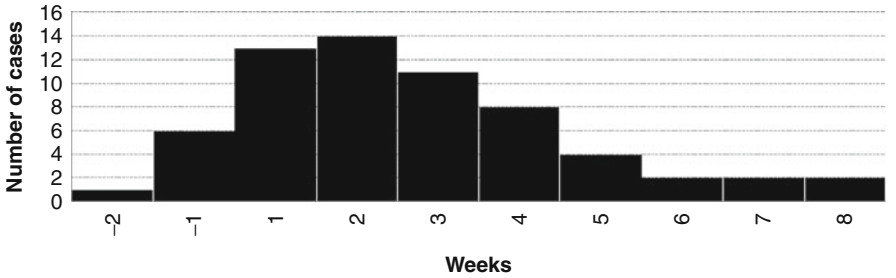

Fig. 51.3 Saint Louis encephalitis (SLE) outbreak, Monroe, Louisiana, September–October 2001, epidemic curve by week of onset. Week 1 = notification of SLE cases. Some cases actually had onset before notification (hence week −1 and week −2)

vectors. These are more prevalent during the warmer months of the year. Respiratory infections on the other hand are more prevalent during the winter in temperate areas or the rainy season in tropical areas.

Annual variations are thought to be mostly the result of accumulation of immune people after epidemics of an infectious disease. Once the proportion of the immune population has reached a certain threshold, there are very few susceptible individuals. In the absence of large epidemics, the pool of susceptible builds up back again, and herd immunity is down again. Then the circumstances are right for another epidemic. These cyclical patterns vary, every other year for measles before the advent of the vaccine, every 3–4 years for pertussis.

51.4.2 Place

Mapping cases is a very common tool used in infectious disease epidemiology. The map may range from a facility to a city, county, province, or country. Maps may be spot maps or rates in boundaries. Mapping may also provide some clues as to the etiology and evolution of an outbreak.

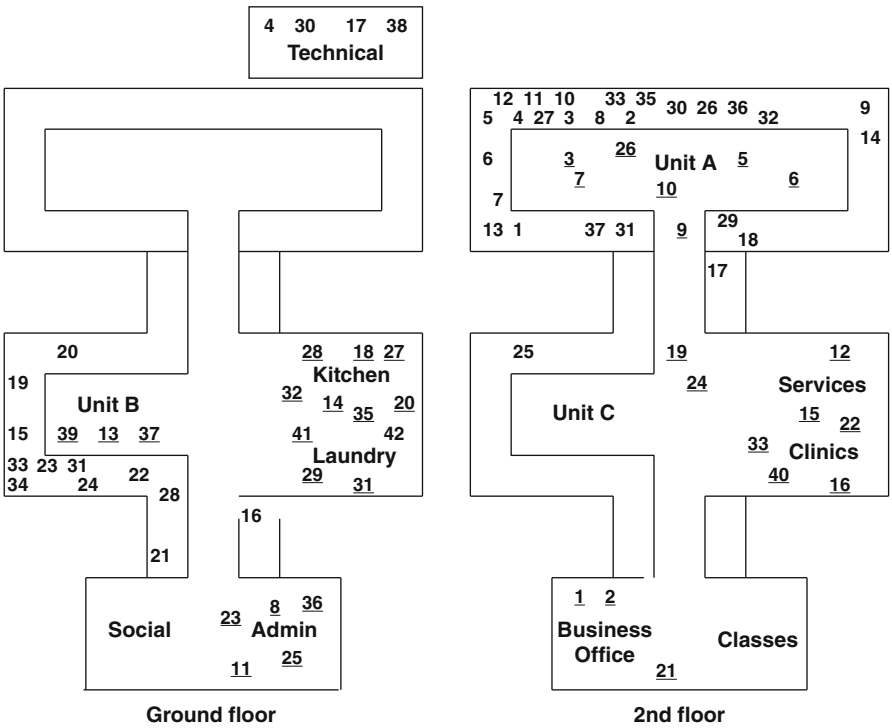

Fig. 51.4 Norovirus outbreak, nursing home, New Orleans 2005

Figure 51.4 shows a map of a nursing home outbreak that occurred in New Orleans in April 2005. Cases are plotted according to their location and are numbered in sequence as they were diagnosed. Cases among employees are underlined compared to cases among patients which are not underlined. The outbreak started with two unattached employees (as indicated as numbers 1 and 2 in Fig. 51.4); they infected an employee in A Unit (number 3). This was followed by a large outbreak in the Unit A. Then an employee in the Unit B was infected and soon after the outbreak was continuing in Unit A but also spreading in Unit B while it also spread among unattached employees. The Unit C was mostly vacant, so there were few cases.

The floor map is accompanied by an epidemic curve showing the cases by their location (A = patients in Unit A, a = employee in Unit A, similarly for unit B and C, and e for employee not attached to a specific unit) (Fig. 51.5).

51.4.3 Host Immunity

The immune status of individuals plays a major role in their susceptibility to infectious agents.

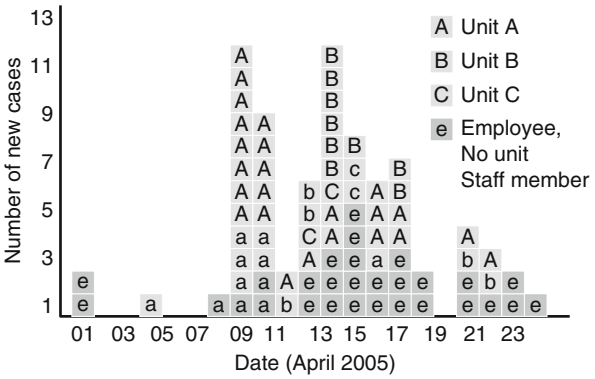

Fig. 51.5 Epidemic curve of a Norovirus outbreak in a nursing home, New Orleans, April 2005

51.4.3.1 Specific Immunity

After acquiring an infectious disease, the immune system reaction may (or may not) lead to protection against another attack of the disease. This so-called refractory period is the time period where no other infection of this disease can occur. It may last from a few days up to lifetime depending on the infectious agent. For some infections such as gonorrhea and *Chlamydia*, there is hardly any protection. A person may become re-infected soon after being cured of the previous infection. For some diseases such as syphilis, a person may not be super-infected while being already infected (immunity of premonition). Once treated, the immunity disappears. For others, the immunity may last for years or even a lifetime (measles, chickenpox). Lifetime immunity may be boosted by repeated contacts with the infectious agents. Immunity may have been acquired following an overt clinical bout of disease or following an unapparent infection. Eighty percent of children in the USA are immune to cytomegalovirus (CMV) infection, and the majority have had a completely asymptomatic infection.

The herd immunity is the immunity of the group. It is related to the sum of immune individuals over the total population. If a high proportion of a population is immune to a disease, one speaks of herd immunity. Above a certain threshold, the incidence of infections may decline. For example, invasive pneumococcal disease decreased dramatically after the pneumococcal conjugate vaccine (PCV7) for young children was introduced in 2000 in the USA. The modeled incidence of pneumococcal disease covered by this vaccine decreased by 76.6% in the unvaccinated population if the three-dose vaccination was completed in children before 15 months of age based on an estimated vaccine coverage between 38.1% and 54% in this population (Haber et al. 2007).

51.4.3.2 Immunocompetence

Immunocompetence is the ability of the immune system to respond to foreign substance and provide adequate protection. Humans with normally functioning immune systems are protected against a wide variety of infectious agents.

Immunocompetence is not fully developed in newborns and is weakened by age or by numerous chronic, acute diseases or medical treatments. Deep depression of the immune system is called immune deficiency. Infection by the HIV virus leads to a profound acquired immune-deficiency syndrome (AIDS). The spread of an infection may be very different depending on the prevalence and distribution of immune-deficient individuals. For example, levels of tuberculosis disease reach the highest incidence in countries with high prevalence of HIV infection.

51.4.4 Contacts: Patterns, Networks, and Structures

Contacts (the persons who are the recipients of the infectious agent) and contact patterns are important in infectious disease epidemiology. Contact may be defined as the type of interaction (or situation) between a person acting as a source of an infectious agent and a person susceptible when the interaction may lead to transmission of the infectious agent.

51.4.4.1 Contact and Interaction

The types of contact vary widely with the type of transmission. Direct contact occurs when the infected host and the susceptible recipient have their skin or mucous membranes touching, for example, by shaking hands, kissing, or having sexual intercourse. Indirect contact occurs when the transmission between both persons involve an inanimate object (fomite) or a mechanical vector (e.g., fly).

When exposure occurs through the air, droplets or droplet nuclei are the vehicles of the infectious agent. The circumstances of the "contact" require a precise definition. For example, a contact of an infectious pertussis case is a person who (1) had face-to-face interaction at less than 3 ft for at least 10–15 min or (2) shared confined space for 1 hour or (3) had a child in a crib located 3–6 ft away or (4) had direct contact with oral, nasal, or respiratory secretions or (5) had shared food, drink, or eating utensils or (6) kissed or (7) was in a medical setting during examination of mouth, throat, intubation, or cardiopulmonary resuscitation (CPR). This type of very detailed definitions is useful to determine the persons at risk of infection and place them under surveillance or prophylaxis.

51.4.4.2 Contact Patterns: Sociograms

Sociograms were developed to analyze choices or preferences within a group. They can diagram the structure and patterns of group interactions. A sociogram consists of nodes (people) and links (contact meeting the definition of a possible transmission).

The nodes on a sociogram who have many choices are called stars. Those with few or no choices are called isolates. Individuals who choose each other are known to have made a mutual choice. One-way choice refers to individuals who choose someone, but the choice is not reciprocated. Cliques are groups of three or more people within a larger group who all choose each other (mutual choice).

The following is an example of a sociogram for sexual contact patterns in a hypothetical high school (Fig. 51.6). Squares represent males, circles females, and

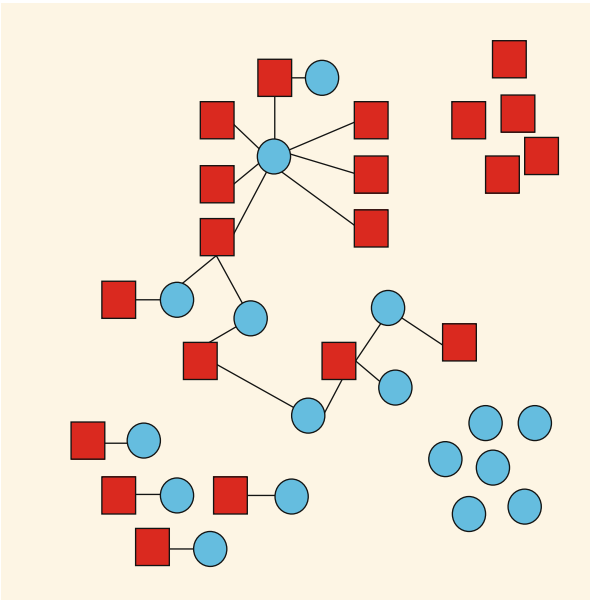

Fig. 51.6 Example of a sociogram depicting sexual relations in a hypothetical high school. Square = male, circle = female

links sexual relations. There are celibate males and females, isolated pairs and a large network of individuals having sexual relations, some with a single partner, and some with multiple partners. Such sociograms may be useful to describe and understand an outbreak, but it may also be useful to describe contact patterns in the absence of any specific disease. It would then help understand what would happen if an outbreak would occur in the population.

51.4.5 Risk Measures

Incidence rate (cumulative incidence), incidence density, and prevalence are commonly used (see chapter ▸Rates, Risks, Measures of Association and Impact of this handbook). The numerator may be the number of cases or the number of persons with serological evidence of past infections for example. Depending on the circumstances, the denominator may be the entire population or the number of persons exposed. All rates used in epidemiology are also used in epidemiology of infectious diseases. However, attack rate and case fatality rates are especially common to infectious disease epidemiology.

51.4.5.1 Attack Rate

The *attack rate* is the proportion of those exposed to microorganisms that develop the disease. Attack rates are frequently used in infectious disease epidemiology. They are heavily influenced on the used definition of exposure and disease. If a segment of the population is immune (previous natural infection or immunization), it will not be susceptible to the disease, and therefore, the attack rate will be

underestimated. Attack rate is a misnomer. The attack rate is a cumulative incidence of cases that occurred during an outbreak.

51.4.5.2 Case Fatality Rate

The case fatality rate is the proportion of people who will die of a certain disease over those who have the disease. Since it is a rate, a time period has to be specified. It is different from the mortality rate which is the proportion of the entire population which dies from a certain disease during a definite period of time (usually 1 year).

51.4.5.3 Reproductive Rate

The reproductive rate is the average number of cases that will result from an index case. The reproductive rate depends on the:

- Probability of transmission in a contact between infected and susceptible
- Frequency of contacts in the population
- Duration of infection
- Proportion already immune in the population

51.4.6 Study Designs

Although any design is used in infectious disease epidemiology studies, the most common designs are descriptive and case-control studies (see previous sections in this handbook).

Case reports are detailed descriptions of single cases with exposure, clinical, treatment, and other relevant information. Description of single cases exposed under unusual circumstances may have profound consequences on the prevention of infectious diseases (case of HIV transmitted by a dentist, cases of rabies transmitted by unspecified contact with bats, case of West Nile virus infection transmitted by transfusion or transplantation).

Case series are descriptions of a cluster of cases with detailed exposure, clinical and outcome data without controls. Such case series description has led to the identification of AIDS (cluster of Kaposi's sarcoma and of *Pneumocystis carinii* among homosexual men) and Lyme disease (*Borrelia burgdorferi*) (cluster of arthritis in children in Lyme, Connecticut).

Case-control and *cohort studies,* even though important for infectious disease epidemiology, are not discussed here since the methodology is described in detail in earlier chapters (e.g., see chapters ▸Cohort Studies, ▸Case-Control Studies, ▸Modern Epidemiological Study Designs, ▸Epidemiological Field Work in Population-Based Studies, and ▸Exposure Assessment of this handbook).

51.5 Surveillance Issues

Surveillance is the continuous scrutiny of all aspects of occurrence and spread of a disease that are pertinent to effective control (Porta et al. 2008; see also chapter ▸Emergency and Disaster Health Surveillance of this handbook).

The basic activity in surveillance is to identify new cases. Surveillance, both active and passive, is the systematic collection of data pertaining to the occurrence of specific diseases, the analysis and interpretation of these data, and the dissemination of consolidated and processed information to contributors to the program and other interested persons (CDC 2001b). Surveillance has multiple purposes. It provides quantitative data on the magnitude of an illness, documents the distribution throughout the population and the geography leading to information on the natural history of the disease, allows detecting outbreaks, monitors changes in illness patterns, and evaluates the effects of control measures.

51.5.1 Passive Surveillance

In a *passive surveillance system*, the surveillance agency has devised and put a system in place. After the placement, the recipient waits for the provider of care to report. *Passive case detection* has been used for mortality and morbidity data for decades throughout the world. Many countries have an epidemiology section in the health department that is charged with centralizing the data in a national disease surveillance system collecting mortality and morbidity data.

In theory, a passive surveillance system provides a thorough coverage through space and time and gives a thorough representation of the situation. Practically, compliance with reporting is often irregular and incomplete. In fact, the main flaws in passive case detection are incomplete reporting and inconsistencies in case definitions.

The main advantages are the low cost of such a program and the sustained collection of data over decades. The purpose is to produce routine descriptive data on communicable diseases, generate hypotheses, and prompt more elaborate epidemiological studies designed to evaluate prevention activities.

Some conditions must be met to maximize compliance with reporting:

1. Make reporting easy: provide easy to consult lists of reportable diseases, provide prestamped cards for reporting, and provide telephone or fax reporting facilities.
2. Do not require extensive information: name, age, sex, residence, and diagnosis. Some diseases may include data on exposure, symptoms, method of diagnosis, etc.
3. Maintain confidentiality and assure reporters that confidentiality will be respected.
4. Convince reporters that reporting is essential: provide feedback; show how the data are used for better prevention.

Case definitions are important to ensure that data are consistent over time and multiple jurisdictions. On a global basis as well as for pandemics (e.g., the novel H1N1 flu pandemic in 2009), this data consistency is achieved by adhering to WHO case definitions for the respective infectious disease. In the USA, case definitions are regularly updated and published by the Centers for Disease Control and Prevention (CDC) in the Morbidity and Mortality Weekly Report (MMWR) (CDC 1997).

Table 51.8 Hepatitis A case reporting by physicians' specialty and by active/passive sample category, Kentucky, 1983 (Hinds et al. 1985)

	Active sample[a]			Passive sample[b]		
Specialty	*N*	Cases	Rate[c]	*N*	Cases	Rate[c]
General practice/family practice	71	4	5.6	73	2	2.7
Pediatrics	74	7	9.5	71	3	4.2
Internal medicine	71	3	4.2	72	0	0.0
All[d]	216	14	6.5	216	5	2.3

[a]Samples were obtained through weekly phone calls to health-care providers (HCPs)
[b]Samples were sent to the health department without prior phone calls to HCPs
[c]Cases per 100 physicians
[d]Active sample/passive sample rate ratio, adjusted for specialty = 2.8 (95% CI: 1.1–7.2)

Confidentiality of data is essential, particularly for those reporting health-care providers who are subject to very strict confidentiality laws. Any suspicion of failure of maintaining secure data would rapidly ruin a passive surveillance program.

51.5.2 Active Surveillance

In an *active surveillance system*, the recipient will actually take some action to identify the cases. In an active surveillance program, the public health agency organizes a system by searching for cases or maintaining a periodic contact with providers. Regular contacting boosts the compliance of the providers. Providers are health agencies, but also as in passive case detection, there may be day-care centers, schools, long-term care facilities, summer camps, resorts, and even the public involved in reporting diseases to the public health agency.

51.5.2.1 Active Surveillance Through Interaction with Providers

The agency takes the step to contact the health providers (all of them or a carefully selected sample) and requests reports from them at regular intervals. Thus, no reports are missing.

Active surveillance has several advantages:

- It allows the collection of more information. A provider sees that the recipient agency is more committed to surveillance and is therefore more willing to invest more time her/himself.
- It allows direct communication and opportunities to clarify definitions or any other problems that may have arisen.

Active surveillance provides much better and more uniform data than passive case detection (Table 51.8). Active case detection is much more expensive; however, for certain diseases such as Hepatitis A virus (HAV), the benefit normally outweighs the cost. Based on 9 HAV cases and 38 contacts, the total costs for active

Table 51.9 Costs and benefits of a 22-week active surveillance program for Hepatitis A, Kentucky 1983 (Hinds et al. 1985)

Costs		Benefits	
Activity	Dollar estimate	Activity	Dollar estimate
Central office surveillance		Medical costs averted[b]	$5,273
Personnel	$3,764	Indirect costs averted[b]	$8,748
Telephone	$535		
Local health offices[a]			
Contact tracing			
Personnel	$647		
Telephone	$149		
Travel	$31		
Contact prophylaxis			
Personnel	469		
Immune Serum Globulin (ISG)	21		
Total	$5,616		$14,021

[a]Costs of tracing and prophylaxis of 38 additional active surveillance-associated Hepatitis A contacts

[b]Based on 7 Hepatitis A cases prevented among 38 contacts of 9 additional Hepatitis A cases identified by active surveillance. Indirect costs are primarily due to productivity losses

surveillance were estimated to be $5,616; however, the benefits (medical and indirect costs) of 7 HAV cases prevented in among the 38 contacts were $14,021 (Table 51.9).

51.5.2.2 Active Surveillance Through Active Case Detection

Active surveillance systems are usually designed when a passive system is deemed insufficient to accomplish the goals of disease monitoring. This type of surveillance is reserved for special programs, usually when it is important to identify every single case of a disease. Active surveillance is implemented in the final phases of an eradication program. Best examples are the smallpox and poliomyelitis eradication programs and African guinea worm eradication program in some selected countries. Active surveillance is also the best approach in epidemic or outbreak investigations to elicit all cases.

In the smallpox eradication program, survey agents visited providers, asked about suspected cases, and actually investigated each suspected case. In the global polio eradication program which was launched in 1988, all cases of acute flaccid paralysis were investigated.

Thanks to the distribution of water filters, education about the transmission of the parasite, as well as enhanced active surveillance for guinea worm (*Dracunculus medinensis*) there are only five African countries left where dracunculiasis is still endemic. The disease might be eliminated by 2015 which would make guinea worm the first parasite to be eradicated.

51.5.3 Syndromic Surveillance

With increasing concerns about infectious disease outbreaks caused by bioterrorism or emerging infectious agents, it became important to detect health events (illnesses) before final diagnosis or laboratory confirmation. The assumption is that early detection will lead to better prevention. Timeliness and validity of the information are the two most important factors in a successful syndromic surveillance system.

In a syndromic surveillance system, the data collected is not about diagnoses but about indicators of the early stages of an outbreak. Requests for laboratory tests may be part of a syndromic surveillance system, while results of lab tests that may take hours or days would be considered in a passive surveillance system. Other examples of data that may be used are syndromes elaborated from the chief complaints from emergency department records, clinical impressions on ambulance worksheet, prescription filled, retail drug and product purchases, and school or work absenteeism (Buehler et al. 2004).

Framework for evaluating public health surveillance systems for early detection of electronic reporting of data is instrumental in obtaining a rapid transfer of data which is essential for early detection. Statistical tools for pattern recognition and aberration detection are necessary to identify subtle outbreak patterns.

51.5.4 Case Register

A case register is a complete list of all the cases of a particular disease in a definite area over a certain time period. Registers are used to collect data on infections over long periods of time. Registers should be population based, detailed, and complete. A register will show an unduplicated count of cases. They are especially useful for long-term diseases, diseases that may relapse or recur, and diseases for which the same cases will consult several providers and therefore would be reported on more than one occasion.

Case registers contain identifiers, locating information, disease, treatment, outcome, and follow-up information as well as contact management information. They are an excellent source of information for epidemiological studies. In disease control, case registers are indispensable tools for follow-up of chronic infectious diseases such as tuberculosis and leprosy.

The contents and quality of a case register determine its usefulness. It should contain:

- Patient identifiers with names (all names), age, sex, place and date of birth, and complete address with directions on how to reach the patient
- Name and address of a “stable” relative that knows the patient’s whereabouts
- Diagnosis information with disease classification and brief clinical description (short categories are better than detailed descriptions)
- Degree of infectiousness (bacteriological, serological results)
- Circumstances of detection

- Initial treatment and response with specific dose, notes on compliance, side effects, and clinical response
- Follow-up information with clinical response, treatment regimen, compliance, and side effects
- Locating information (for some diseases, contact information is also useful)

Updating a register is a difficult task. It requires cooperation from numerous persons. Care must be taken to maintain the quality of data. It is important to only request pertinent information for program evaluation or information that would remind users to collect data or to perform an exam. For example, if compliance is often a neglected issue, include a question on compliance. Further details concerning the use of registries in general are given in chapter ▸Use of Health Registers of this handbook.

51.5.5 Sentinel Disease Surveillance

For sentinel disease surveillance, only a sample of health providers is used. The sample is selected according to the objectives of the surveillance program. Providers most likely to serve the population affected by the infection are selected; for example, child health clinics and pediatricians should be selected for surveillance of childhood diseases. A sentinel system allows cost reduction and is combined with active surveillance.

A typical surveillance program for influenza infections includes a selected number of general practitioners who are called every week to obtain the number of cases with influenza-like Illness (ILI) presented to them (Fig. 51.7). This

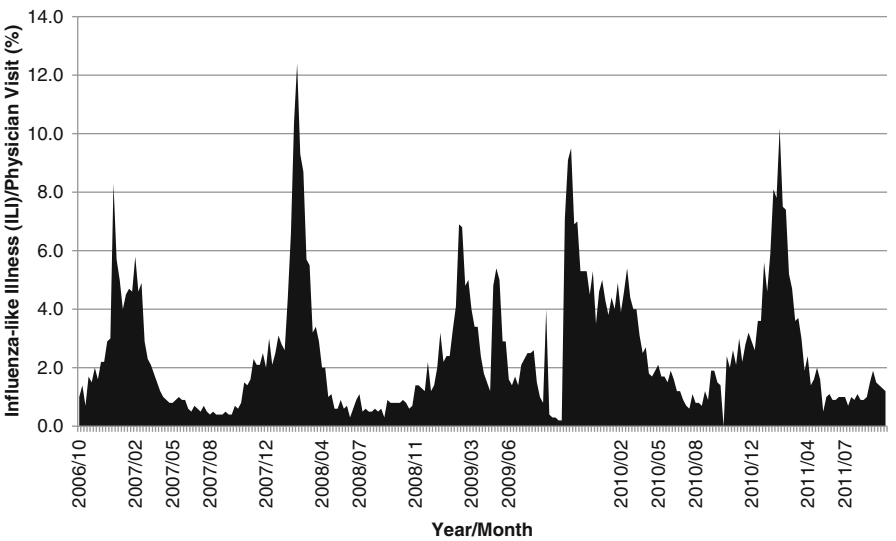

Fig. 51.7 Influenza sentinel surveillance, Louisiana 2006–2011

program may include the collection of samples for viral cultures or other diagnostic techniques. Such a level of surveillance would be impossible to maintain on the national level.

51.5.6 Evaluation of a Surveillance System

Surveillance systems are evaluated on the following considerations (CDC 2001b):

- *Usefulness*: Some surveillance systems are routine programs that collect data and publish results; however, it appears that they have no useful purpose – no conclusions are reached, no recommendations are made. A successful surveillance system would provide information used for preventive purposes.
- *Sensitivity* or the ability to identify every single case of disease is particularly important for outbreak investigations and eradication programs.
- *Predictive value positive* (PVP) is the proportion of reported cases that actually have the health-related event under surveillance. Low PVP values mean that non-cases might be investigated, outbreaks may be exaggerated, or pseudo-outbreaks may even be investigated. Misclassification of cases may corrupt the etiological investigations and lead to erroneous conclusions. Unnecessary interventions and undue concern in the population under surveillance may result.
- *Representativeness* ensures that the occurrence and distribution of cases accurately represent the real situation in the population.
- *Simplicity* is essential to gain acceptance, particularly when relying on outside sources for reporting.
- *Flexibility* is necessary to adapt to changes in epidemiological patterns, laboratory methodology, operating conditions, funding, or reporting sources.
- *Data quality* is evaluated by the data completeness (blank or unknown variable values) and validity of data recorded (see also chapter ▸Quality Control and Good Epidemiological Practice of this handbook).
- *Acceptability* is shown in the participation of providers in the system.
- *Timeliness* is more important in surveillance of epidemics.
- *Stability* refers to the reliability (i.e., the ability to collect, manage, and provide data properly without failure) and availability (the ability to be operational when it is needed) of the public health surveillance system.

51.5.7 Elements of a Surveillance System

The major elements of a surveillance system as summarized by the WHO are mortality registration, morbidity reporting, epidemic reporting, laboratory investigations, individual case investigations, epidemic field investigations, surveys, animal reservoir and vector distribution studies, biologicals and drug utilization, and knowledge of the population and the environment. Traditional surveillance methods rely on counting deaths and cases of diseases. However, these data represent only a small part of the global picture of infectious disease problems.

51.5.7.1 Mortality Registration

Mortality registration was one of the first elements of surveillance implemented. The earliest quantitative data available on infectious disease is about mortality. The evolution of tuberculosis in the USA, for example, can only be traced through its mortality. Mortality data are influenced by the occurrence of disease but also by the availability and efficacy of treatment. Thus, mortality cannot always be used to evaluate the trend of disease occurrence.

51.5.7.2 Morbidity Reporting

Reporting of infectious diseases is one of the most common requirements around the world. A list of notifiable diseases is established on a national or regional level. The numbers of conditions vary; it ranges usually from 40 to 60 conditions. In general, a law requires that health facility staff, particularly physicians and laboratories, report these conditions with guaranteed confidentiality. It is also useful to have other non-health-related entities report suspected communicable diseases such as day-care centers, schools, restaurants, long-term care facilities, summer camps, and resorts. Regulations on mandatory reporting are often difficult to enforce. Voluntary compliance by the institution's personnel is necessary. Reporting may be done in writing, by phone, or electronically in the most advanced system. Since most infectious diseases are confirmed by a laboratory test, reporting by the laboratory may be more reliable. The advantage of laboratory reporting is the ability to computerize the reporting system. Computer programs may be set up to automatically report a defined set of tests and results.

For some infectious diseases, only clinical diagnoses are made. These syndromes may be the consequences of a large number of different microorganisms for which laboratory confirmation is impractical.

When public or physician attention is directed at a specific disease, reporting may be biased. When there is an epidemic or when the press focuses on a particular disease, patients are more prone to look for medical care and physicians are more likely to report. Reporting rates were evaluated in several studies. In the USA, studies show report rates of 10% for viral Hepatitis, 32% for *Hemophilus influenzae*, 50% for meningococcal meningitis, and 62% for shigellosis.

51.5.7.3 Morbidity Case Definition

It is important to have a standardized set of definitions available to providers. Without standardized definitions, a surveillance system may be counting different entities from one provider to another. The variability may be such that the epidemiological information obtained is meaningless.

Most case definitions in infectious disease epidemiology are based on *laboratory tests*; however, some clinical syndromes such as toxic shock syndrome do not have confirmatory laboratory tests. Most case definitions include a brief *clinical description* useful to differentiate active disease from colonization or asymptomatic infection. Some diseases are diagnosed based on epidemiological data. As a result, many case definitions for childhood vaccine preventable diseases and foodborne

diseases include epidemiological criteria (e.g., exposure to probable or confirmed cases of disease or to a point source of infection). In some instances, the anatomic site of infection may be important; for example, respiratory diphtheria is notifiable, whereas cutaneous diphtheria is not (CDC 1997).

Cases are classified as a confirmed case, a probable, or a suspected case. An epidemiologically linked case is a case in which (1) the patient has had contact with one or more persons who either have/had the disease or have been exposed to a point source of infection (including confirmed cases) and (2) transmission of the agent by the usual modes is plausible. A case may be considered epidemiologically linked to a laboratory-confirmed case if at least one case in the chain of transmission is laboratory confirmed. Probable cases have specified laboratory results that are consistent with the diagnosis yet do not meet the criteria for laboratory confirmation. Suspected cases are usually cases missing some important information in order to be classified as a probable or confirmed case.

Case definitions are not diagnoses. The usefulness of public health surveillance data depends on its uniformity, simplicity, and timeliness. Case definitions establish uniform criteria for disease reporting and should not be used as the sole criteria for establishing clinical diagnoses, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, or providing standards for reimbursement. Use of additional clinical, epidemiological, and laboratory data may enable a physician to diagnose a disease even though the formal surveillance case definition may not be met.

51.5.7.4 Data for Which Stage of Disease Should Be Collected? The Morbidity Iceberg

Surveillance programs collect data on the overt cases diagnosed by the health-care system. However, these cases may not be the most important links in the chain of transmission. Cases reported are only the tip of the iceberg (see Fig. 51.8). They may not at all be representative of the true endemicity of an infectious disease.

There is a continuous process leading to an infectious disease: exposed, colonized, incubating, sick, clinical form, convalescing, and cured. Even among those who have overt disease, there are several disease stages that may not be included in a surveillance system:

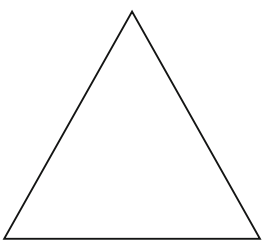

Fig. 51.8 The iceberg concept

– Some have symptoms but do not seek medical attention.
– Some do get medical attention but do not get diagnosed or get misdiagnosed.
– Some get diagnosed but do not get reported.

Infectious disease cases play different roles in the epidemiology of an infectious disease; some individuals are the indicators (most symptomatic), some are the reservoir of microorganisms (usually asymptomatic, not very sick), some are amplifiers (responsible for most of the transmission), and some are the victims (those who develop severe long-term complications). Depending on the specific disease and the purpose of the surveillance program, different disease stages should be reported. For example:

- In a program to prevent rabies in humans exposed to a suspect rabid animal (usually a bite) needs to be reported. At the stage where the case is a suspect, prevention will no longer be effective.
- For bioterrorism events, reporting of suspects is of paramount importance to minimize consequences. Waiting for confirmation causes too long of a delay. In the time necessary to confirm cases, opportunities to prevent coinfections may be lost, and secondary cases may already be incubating, depending on the transmissibility of the disease.
- Surveillance for West Nile viral infections best rests on the reporting of neuroinvasive disease. Case reports of neuroinvasive diseases are a better indicator than West Nile infection or West Nile fever cases that are often benign, go undiagnosed, and are reported haphazardly.
- For gonorrhea, young males are the indicators because of the intensity of symptoms. Young females are the main reservoir because of the high proportion of asymptomatic infections. Females of reproductive age are the victims because of pelvic invasive disease (PID) and sterility.
- A surveillance program for Hepatitis B that only would include symptomatic cases of Hepatitis B could be misleading. A country with high transmission of Hepatitis B from mother to children would have a large proportion of infected newborns becoming asymptomatic carriers and a major source of infection during their lifetime. Typically in countries with poor reporting of symptomatic Hepatitis, the reporting of acute cases of Hepatitis B would be extremely low in spite of high endemicity which would result in high rates of chronic Hepatitis and hepatic carcinoma.

51.5.7.5 Individual Cases or Aggregate Data?

Most morbidity reporting collects data about individual cases. Reporting of individual cases includes demographic and risk factor data which are analyzed for descriptive epidemiology and for implementation of preventive actions. For example, any investigation leading to contact identification and prophylaxis requires a start from individual cases.

However, identification of individuals may be unnecessary and aggregate data sufficient for some specific epidemiological purposes. Monitoring an influenza epidemic, for example, can be done with aggregate data. Obtaining individual

case information would be impractical since it would be too time consuming to collect detailed demographics on such a large number of cases. Aggregate data from sentinel sites consists of a number of influenza-like illnesses by age group and the total number of consultants or the total number of "participants" to be used as denominators. Such data is useful to identify trends and determine the extent of the epidemic and geographical distribution.

Collection of aggregate data of the proportion of school children by age group and sex is a useful predictive tool to identify urinary schistosomiasis endemic areas (Lengeler et al. 2000) without having to collect data on individual school children.

51.5.7.6 Investigations of Cases, Outbreaks, Epidemics, and Surveys

Epidemics of severe diseases are almost always reported. This is not the case for epidemics of milder diseases such as rashes or diarrheal diseases. Many countries do not want to report an outbreak of disease that would cast a negative light on the countries. For example, many countries that are tourism dependent do not report cholera or plague cases. Some countries did not report AIDS cases for a long time.

Case investigations are usually not undertaken for individual cases unless the disease is of major importance such as hemorrhagic fever, polio, rabies, yellow fever, any disease that has been eradicated, and any disease that is usually not endemic in the area.

Outbreaks or changes in the distribution pattern of infectious diseases should be investigated, and these investigations should be compiled in a comprehensive system to detect trends. While the total number of infectious diseases may remain the same, changes may occur in the distribution of cases from sporadic to focal outbreaks. For example, the distribution of WNV cases in Louisiana shifted from mostly focal outbreaks in the first year (2002) the West Nile virus arrived in the state to mostly sporadic cases the following years (2003–2004) (Fig. 51.9).

Surveys are a very commonly used tool in public health, particularly in developing countries where routine surveillance is often inadequate (see chapter ▸Epidemiology in Developing Countries of this handbook). Survey data needs to be part of a comprehensive surveillance database. One will acquire a better picture from one or a series of well-constructed surveys than from poorly collected surveillance data. Surveys are used in control programs designed to control major endemic diseases: spleen and parasite surveys for malaria, parasite in urine and stools for schistosomiasis, clinical surveys for leprosy or guinea worm disease, and skin test surveys for tuberculosis.

51.5.7.7 Surveillance of Microbial Strains

Surveillance of microbial strains is designed to monitor, through active laboratory-based surveillance, the bacterial and viral strains isolated. Examples of these systems are:

- In the USA, the *PulseNet program* is a network of public health laboratories that performs DNA fingerprinting of bacteria causing foodborne illnesses (Swaminathan et al. 2001). Molecular subtyping methods must be standardized to allow comparisons of strains and the building of a meaningful data bank.

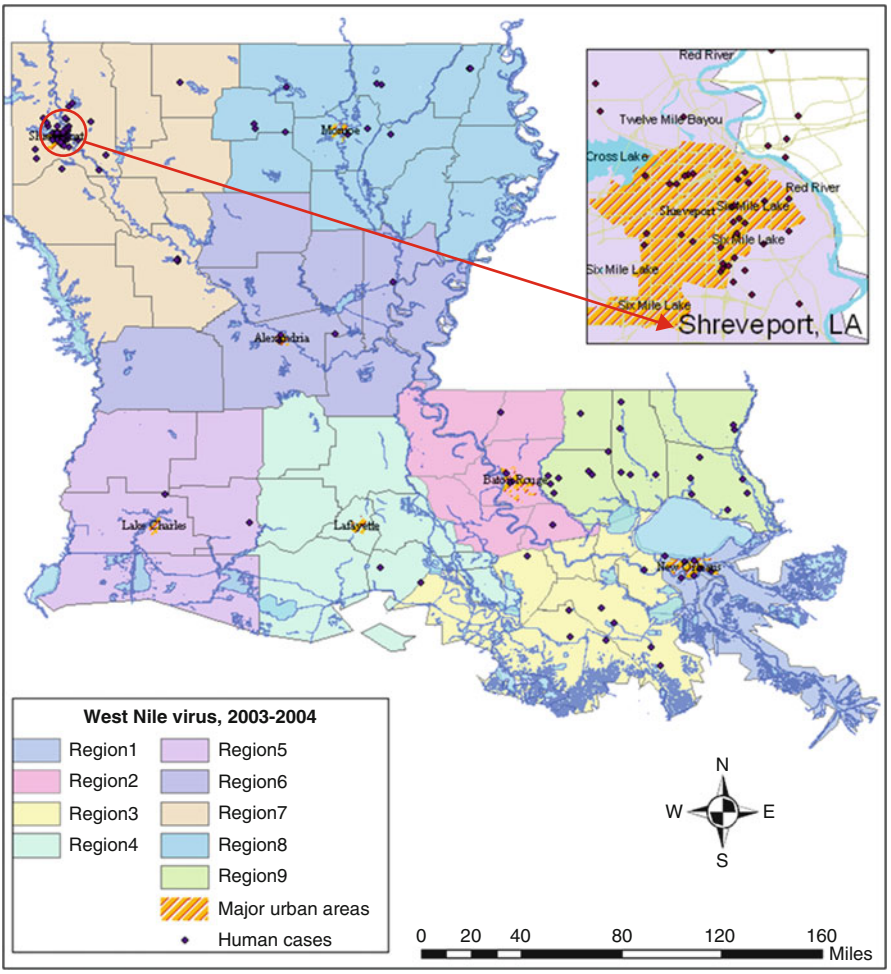

Fig. 51.9 Human West Nile neuroinvasive disease cases in Louisiana, 2003–2004

The method used in PulseNet is pulse field gel electrophoresis (PFGE). The use of standardized subtyping methods has allowed isolates to be compared from different parts of the country, enabling recognition of nationwide outbreaks attributable to a common source of infection, particularly those in which cases are geographically separated.

- The US *National Antimicrobial Resistance Monitoring System* (NARMS) for enteric bacteria is a collaboration between CDC, participating state and local health departments, and the US Food and Drug Administration (FDA) to monitor

antimicrobial resistance among foodborne enteric bacteria isolated from humans. NARMS data are also used to provide platforms for additional studies including field investigations and molecular characterization of resistance determinants and to guide efforts to mitigate antimicrobial resistance (CDC 2006).
- Monitoring of antimicrobial resistance is routinely done by requiring laboratories to either submit all or a sample of their bacterial isolates.

51.5.7.8 Surveillance of Animal Diseases

Surveillance for zoonotic diseases should start at the animal level, thus providing early warning for impending increases of diseases in the animal population.
- Rabies surveillance aims at identifying the main species of animals infected in an area, the incidence of disease in the wild animals, and the prevalence of infection in the asymptomatic reservoir (bats). This information will guide preventive decisions made when human exposures do occur.
- Malaria control entomologic activities must be guided by surveillance of *Anopheles* mosquito populations, their biting activities, and *Plasmodium* infection rates in the *Anopheles* mosquitoes.
- Infection rates in wild birds, infection in sentinel chickens, and horse encephalitis are all part of West Nile encephalitis surveillance. These methods provide an early warning system for human infections.
- The worldwide surveillance for influenza is the best example of the usefulness of monitoring animals prior to spread of infection in the human population. Influenza surveillance programs aim to rapidly obtain new circulating strains to make timely recommendations about the composition of the next vaccine. The worldwide surveillance priority is given to the establishment of regular surveillance and investigation of outbreaks of influenza in the most densely populated cities in key locations, particularly in tropical or other regions where urban markets provide opportunities for contacts between humans and live animals (Snacken et al. 1999).

51.5.7.9 Rationale of Selecting Diseases for Surveillance Purposes

The rationale for selecting infectious diseases and an appropriate surveillance method is based on the goal of the preventive program. Table 51.10 shows a few examples of different surveillance methods based on the disease and the objectives of the surveillance.

51.6 Outbreak Investigations

Outbreaks of acute infectious diseases are common, and investigations of these outbreaks are an important task for public health professionals, especially epidemiologists. In 2001, a total of 1,238 foodborne outbreaks with 25,035 cases involved were reported in the USA (CDC 2004) with norovirus being the most common confirmed etiological agent associated with these outbreaks (see Table 51.11).

Table 51.10 Examples of different surveillance methods based on the disease and the objectives of the surveillance system

Disease	Objectives	Surveillance method
Anthrax	Limit bioterrorism event	Active or passive syndromic surveillance
Antibiotic resistance	Description	Active laboratory reporting of antibiograms
Aseptic meningitis	Sentinel event for West Nile Identification of outbreak	Passive surveillance by health-care providers
Gonorrhea	Description of epidemic Treatment of cases	Passive case detection by health-care practitioners Systematic screening of young females (family planning, prenatal, student health services, etc.)
Hepatitis B	Description of endemicity	Survey of representative groups
Hepatitis B	Prevention of perinatal transmission	Screening of pregnant women
Influenza	Quantify endemicity	Sentinel surveillance with aggregate data from physicians' offices, emergency departments, nursing homes, and schools
Poliomyelitis	Identification of residual cases before complete eradication	Active surveillance of acute flaccid paralysis
Rabies	Prevent human cases	Passive reporting of exposure to potentially rabid animals
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Provide information for management of suspected staphylococcal infections	Active laboratory surveillance of aggregate data on proportion of staphylococci resistant to methicillin
Vancomycin-resistant *Staphylococcus aureus* (VRSA)	Identification of an emerging infection	Laboratory submission of specimens
Tuberculosis	Description of endemicity Case management	Case register
West Nile	Early warning for public and mosquito control	Passive reporting of dead birds by the public, passive reporting of encephalitic horses, sentinel chicken serology, survey of wildlife by serological methods
West Nile	Description of endemicity	Passive and active case finding of neuro-invasive disease

Table 51.11 Confirmed etiological agents of foodborne outbreaks in the USA in 2001

Etiology	Number of outbreaks
Bacillus cereus	5
Brucella spp.	1
Campylobacter spp.	16
Clostridium botulinum	3
Clostridium perfringens	30
Enterohemorrhagic *Escherichia coli*	4
Enterohemorrhagic *Escherichia coli* O157:H7	16
Enterotoxigenic *Escherichia coli*	2
Listeria monocytogenes	1
Salmonella spp.	112
Shigella spp.	15
Staphylococcus aureus	23
Vibrio spp.	4
Yersinia enterocolitica	3
Total bacteria	**235**
Ciguatera	23
Histamine	10
Other chemical	1
Scombroid	18
Total chemical	**52**
Cyclospora cayetanensis	2
Giardia lamblia	1
Trichinella spp.	2
Total parasitic	**5**
Hepatitis A	6
Norovirus	150
Total viral	**156**

Source: CDC Foodborne Outbreak Response and Surveillance Unit (2004)

Outbreaks or epidemics are defined as the number of disease cases above what is normally expected in the area for a given time period. Depending on the disease, it is not always known if the case numbers are really higher than expected and some outbreak investigations can reveal that the reported case numbers did not actually increase. The nature of a disease outbreak depends on a variety of circumstances, most importantly the suspected etiological agent involved, the disease severity or case fatality rate, population groups affected, media pressure, political inference, and investigative progress. There are certain common steps for outbreak investigations as shown in Table 51.12. However, the chronology and priorities assigned to each phase of the investigation have to be decided individually, based on the circumstances of the suspected outbreak and information available at the time.

For example, in 2002, 21 outbreaks of acute gastroenteritis on cruise ships with travel destinations outside the USA were reported to the CDC (CDC 2002). In only

Table 51.12 Fourteen steps in outbreak investigations

#	Step
1	"Outbreak" detected based on initial report or analysis of surveillance data
2	Collect basic numbers and biological specimens
3	Investigate or not?
4	Think prevention first
5	Get information on the disease or condition
6	Sometimes numbers do not count
7	Is the increase real or artificial?
8	Verify the diagnosis
9	Prepare a case definition
10	Put the information in a database
11	Find additional cases
12	Basic descriptive epidemiology (time, place, and person)
13	Hypothesis testing and measures of association
14	Final report and communications

5 of these outbreaks, about 1,400 persons, with an average 280 cases per cruise, had symptoms of viral acute gastroenteritis. Norovirus outbreaks begin usually as a food- or waterborne disease but often continue because of the easy person-to-person transmission in a closed environment and low infectious dose (100 viral particles can be infectious) (CDC 2001a).

51.6.1 Basic Steps in Outbreak Investigations

51.6.1.1 The Initial Report

The original report can originate from very different sources. Examples are:

- A physician is calling the local or state health department about an increase of number of patients seen and diagnosed with a specific disease.
- A high number of patients with similar signs and symptoms are showing up in the emergency room.
- A school principal or day-care owner is reporting a high number of absent students.
- A nursing home health-care professional is seeing a lot of residents with gastrointestinal illnesses.
- A person is complaining to the health department that she/he got sick after eating at a certain restaurant.

Another way to detect an increase of cases is if the surveillance system of reportable infectious diseases reveals an unusually high number of people with the same diagnosis over a certain time period at different health-care facilities.

Outbreaks of benign diseases like self-limited diarrhea are often not detected because people are not seeking medical attention and therefore medical services are not aware of them. Furthermore, early stages of a disease outbreak are often

undetected because single cases are diagnosed sporadically. It is not until a certain threshold is passed that it becomes clear that these cases are related to each other through a common exposure or secondary transmission.

Depending on the infectious disease agent, there can be a sharp or a gradual increase of number of cases. It is sometimes difficult to differentiate between sporadic cases and the early phase of an outbreak. In the 2001 St. Louis encephalitis (SLE) outbreak in Louisiana, the number of SLE cases increased from 9 to 18 between weeks 1 and 2, and then the numbers gradually decreased over the next 9 weeks to a total of 63 cases (Jones et al. 2002).

51.6.1.2 Basic Information

After the initial report is received, it is important to collect and document basic information: Contact information of persons affected, a good and thorough event description, names and diagnosis of hospitalized persons (and depending on the presumptive diagnosis their underlying conditions and travel history), laboratory test results, and other useful information to get a complete picture and to confirm the initial story of the suspected outbreak. It also might be necessary to collect more biological specimens such as food items and stool samples for further laboratory testing.

51.6.1.3 Decision to Investigate

On the one hand, based on the collected information, the decision to investigate must be made. It may not be worthwhile to start an investigation if there are only a few people who fully recovered after a couple of episodes of a self-limited, benign diarrhea. Other reasons not to investigate might be that this type of outbreak occurs regularly every summer or that it is only an increase in number of reported cases which are not related to each other.

On the other hand, however, there should be no time delay in starting an investigation if there is an opportunity to prevent more cases or the potential to identify a system failure which can be caused, for example, by poor food preparation in a restaurant or poor infection control practices in a hospital or to prevent future outbreaks by acquiring more knowledge of the epidemiology of the agent involved. Additional reasons to investigate include the interest of the media, politicians, and the public in the disease cluster and the pressure to provide media updates on a regular basis. Another fact to consider is that outbreak investigations are good training opportunities for newly hired epidemiologists.

Sometimes lack of data and lack of sufficient background information make it difficult to decide early on if there is an outbreak or not. The best approach then is to assume that it is an outbreak until proven otherwise.

51.6.1.4 Prevention Comes First

Prevention of more cases is the most important goal in outbreak investigations, and therefore a rapid evaluation of the situation is necessary. If there are precautionary measures to be recommended to minimize the impact of the outbreak and the spread to more persons, they should be implemented before a thorough investigation is

completed. Most likely control measures implemented by public health professionals in foodborne outbreaks are:

- Recall or destruction of contaminated food items
- Restriction of infected food handlers from food preparation
- Correction of any deficiency in food preparation or conservation

51.6.1.5 Natural History

After taking immediate control measures, the next step is to know more about the epidemiology of the suspected agent. The most popular books for public health professionals include the "Red Book" (American Academy of Pediatrics 2006), the "Control of Communicable Diseases Manual" from the American Public Health Association (APHA 2008), or other infectious disease epidemiology books as well as the CDC website (www.cdc.gov). If the disease of interest is a reportable disease or a disease where surveillance data are available, baseline incidence rates can be calculated. Then a comparison is made to determine if the reported numbers constitute a real increase or not. Furthermore, the seasonal and geographical distribution of the disease is important as well as the knowledge of risk factors. Many infectious diseases show a seasonal pattern such as rotavirus or *Neisseria meningitides*. For example, in suspected outbreaks where cases are associated with raw oyster consumption, the investigator should know that in the US Gulf states, *Vibrio* cases increase in the summer months because the water conditions are optimal for the growth of the bacteria in water and in seafood. This kind of information will help to determine if the case numbers show a true increase and if it seems likely to be a real outbreak.

51.6.1.6 Number of Cases

For certain diseases, numbers are not important. Depending on the severity of the disease, its transmissibility, and its natural occurrence, certain diseases should raise a red flag for every health professional, and even a single case should warrant a thorough public health investigation. For example, a single confirmed case of a rabid dog in a city (potential dog-to-dog transmission within a highly populated area), a case of dengue hemorrhagic fever, or a presumptive case of smallpox would immediately trigger an outbreak investigation.

51.6.1.7 Artifact

Sometimes an increase of case numbers is artificial and not due to a real outbreak. In order to differentiate between an artificial and a natural increase in numbers, the following changes have to be taken into consideration:

- Alterations in the surveillance system
- A new physician who is interested in the disease and therefore more likely to diagnose or report the disease
- A new health officer strengthening the importance of reporting
- New procedures in reporting (from paper to web-based reporting)
- Enhanced awareness or publicity of a certain disease that might lead to increased laboratory testing
- New diagnostic tests

- A new laboratory
- An increase in susceptible population such as a new summer camp

51.6.1.8 Misclassification

It is important to be sure that reported cases of a disease actually have the correct diagnosis and are not misdiagnosed. Is there assurance that all the cases have the same diagnosis? Is the diagnosis verified and were other differential diagnoses excluded? In order to be correct, epidemiologists have to know the basis for the diagnosis. Are laboratory samples sufficient? If not, what kind of specimens should be collected to ascertain the diagnosis? What are the clinical signs and symptoms of the patient?

In an outbreak of restaurant-associated botulism in Canada, only the 26th case was correctly diagnosed. The slow progression of symptoms and misdiagnosis of the dispersed cases made it very difficult to link these cases and identify the source of the outbreak (CDC 1985, 1987).

51.6.1.9 Case Definition

The purpose of a case definition is to standardize the identification and counting of the number of cases. The case definition is a standard set of criteria and is not a clinical diagnosis. In most outbreaks, the case definition has components of person, place, and time, such as the following: persons with symptoms of X and Y after eating at the restaurant Z between Date1 and Date2. The case definition should be broad enough to get most of the true cases but not too narrow so that true cases will not be misclassified as controls. A good method is to analyze the data, identify the frequency of symptoms, and include symptoms that are more reliable than others. For example, diarrhea and vomiting are more specific than nausea and headache in the case definition of a food-related illness.

51.6.1.10 Database

What kind of information is necessary to be collected? It is sufficient to have a simple database with basic demographic information such as name, age, sex, and information for contacting the patient. More often, date of reporting and date of onset of symptoms are also important. Depending on the outbreak and the potential exposure or transmission of the agent involved, further variables such as school, grade of student, or occupation in adults might be interesting and valuable.

51.6.1.11 Case Finding

During an outbreak investigation, it is important to identify additional cases that may not have been known or were not reported. There are several approaches:

- Interview known cases and ask them if they know of any other friends or family members with the same signs or symptoms.
- Obtain a mailing list of frequent customers in an event where a restaurant is involved.
- Set up an active surveillance with physicians or emergency departments.
- Call laboratories and ask for reports of suspected and confirmed cases.

Another possibility is to review surveillance databases or to establish enhanced surveillance for prospective cases. Occasionally, it might be worthwhile to include the media for finding additional cases through press releases. However, the utility of that technique depends on the outbreak and the etiological agent; the investigator should always do a benefit risk analysis before involving the media.

51.6.1.12 Descriptive Epidemiology

After finding additional cases, entering them in the database, and organizing them, the investigator should try to get a better understanding of the situation by performing some basic descriptive epidemiology techniques such as sorting the data by time, place, and person. For a better visualization of the data, an epidemic or "epi" curve should be graphed. The curve shows the number of cases by date or time of onset of symptoms. This helps to understand the nature and dynamic of the outbreak as well as to get a better understanding of the incubation period if the time of exposure is known. It also helps to determine whether the outbreak had a single exposure and no secondary transmission (single peak) or if there is a continuous source and ongoing transmission. Figures 51.10 and 51.11 show "epi" curves of two different outbreaks: a foodborne outbreak in a school in Louisiana (Fig. 51.10) and the number of WNV human cases, stratified by clinical diagnosis of fever only and meningoencephalitis, in Louisiana in the 2002 outbreak (Fig. 51.11), respectively.

Sometimes it is useful to plot the cases on a map to get a better idea of the nature and the source of an outbreak. Mapping may be useful to track the spread by water (see John Snow's cholera map) or by air or even a person-to-person transmission. If a contaminated food item was the culprit, food distribution routes with new cases identified may be helpful. Maps, however, should be taken with caution and carefully interpreted. For example, WNV cases are normally mapped by residency but do not take into account that people might have been exposed or bitten

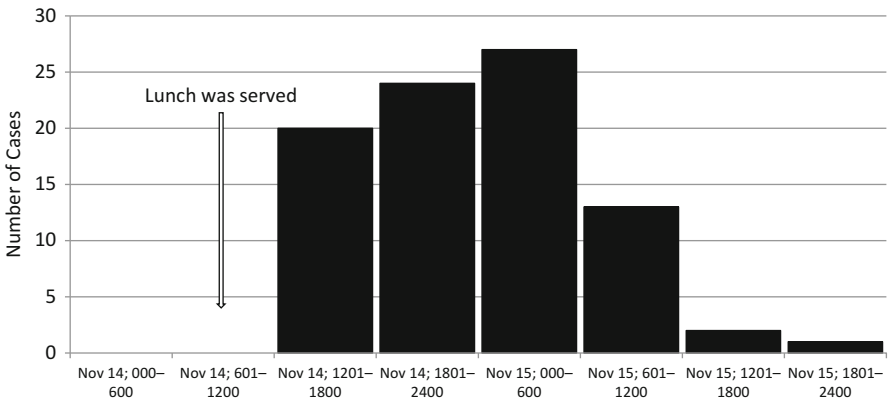

Fig. 51.10 Gastroenteritis outbreak in a school in Louisiana, 2001

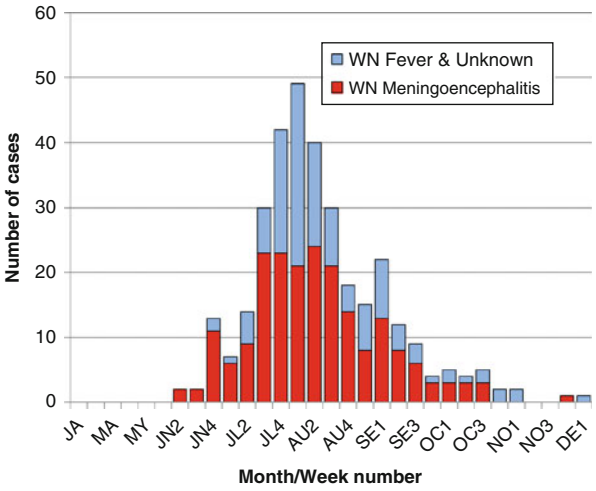

Fig. 51.11 Human West Nile virus cases, Louisiana 2002

by an infective mosquito far away from where they live. For outbreak investigations, spot maps are usually more useful than rate maps or maps of aggregate data.

Depending on the outbreak, it might be useful to characterize the outbreak by persons' demographics such as age, sex, address, occupation, and health status. Are the cases at increased susceptibility or at high risk of infection? These kinds of variables might give the investigator a good idea if the exposure is not yet known. For typical foodborne outbreaks, however, demographic information is not very useful because the attack rates will be independent of age and sex. More details on methods used in descriptive epidemiology are given in chapter ▸Descriptive Studies of this handbook.

51.6.1.13 Hypothesis Forming

Based on the results of basic descriptive epidemiology and the preliminary investigation, some hypotheses should be formulated in order to identify the cause of the outbreak. A hypothesis will be most likely formulated such as "those who attended the luncheon and ate the chicken salad are at greater risk than those who attended and did not eat the chicken salad." It is always easier to find something after knowing what to look for, and therefore a hypothesis should be used as a tool. However, the epidemiologist should be flexible enough to change the hypothesis if the data do not support it. If data clues are leading in another direction, the hypothesis should be reformulated such as "those who attended the luncheon and ate the baked chicken are at greater risk than those who attended and did not eat the baked chicken."

To verify or deny hypotheses, measures of risk association such as the relative risk (*RR*) or the odds ratio (*OR*) have to be calculated (as described in chapters ▸Rates, Risks, Measures of Association and Impact, ▸Cohort Studies, and

►Case-Control Studies of this handbook). The CDC has developed the software program "Epi Info" which is easy to use in outbreak investigations and, even more importantly, free of charge. It can be downloaded from the CDC website (http://www.cdc.gov/epiinfo/). Measures of association, however, should be carefully interpreted; even a highly significant measure of association cannot give enough evidence of the real culprit or the contaminated food item. The measure of association is only as good and valid as the data. Most people have recall problems when asked what they ate, when they ate, and when their symptoms started. Even more biases or misclassifications of cases and controls can hide an association. A more confident answer comes usually from the laboratory samples from both human samples and food items served at time of exposure. Agents isolated from both food and human samples that are identified as the same subtype, in addition to data results supporting the laboratory findings, are the best evidence beyond reasonable doubt.

51.6.1.14 Final Report

As the last step in an outbreak investigation, the epidemiologist writes a final report on the outbreak and communicates the results and recommendations to the public health agency and facilities involved (see Table 51.12). In the USA, public health departments also report foodborne outbreaks electronically to CDC via a secure web-based reporting system, the National Outbreak Reporting System (NORS).

51.6.2 Types of Outbreaks

51.6.2.1 The "Traditional" Foodborne Outbreak

The "traditional" foodborne outbreak is usually a small local event such as family picnic, wedding reception, or other social event and occurs often in a local restaurant or school cafeteria. This type of outbreak is highly local with a high attack rate in the group exposed to the source. Because it is immediately apparent to those in the local group such as the group of friends who ate at the restaurant or the students' parents, public health authorities are normally notified early in the outbreak, while most of the cases are still symptomatic. Epidemiologists can start early on with their investigation and therefore have a much better chance to collect food eaten and stool samples of cases with gastroenteritis for testing and also to detect the etiological agent in both of them.

In a 2001 school outbreak in Louisiana, 87 persons (67 students and 20 faculty members) (see Fig. 51.10) experienced abdominal cramps after eating at the school's annual "Turkey Day" the day before. Stool specimens and the turkey with the gravy were both positive for *Clostridium perfringens* with the same pulse field gel electrophoresis (PFGE) pattern (Merlos 2002). The inspection of the school cafeteria revealed several food handling violations such as storing, cooling, and reheating of the food items served. Other than illnesses among food handlers, these types of improper food handling or storage are the most common causes of foodborne outbreaks.

51.6.2.2 New Types of Outbreaks

A different type of outbreak is emerging as the world is getting smaller. In other words, persons and food can travel more easily and faster from continent to continent and so do infectious diseases with them. Foodborne outbreaks related to imported contaminated food items are normally widespread, involving many states and countries, and therefore are frequently identified. In 1996, a large outbreak of *Cyclospora cayetanensis* occurred in 10 US states and Ontario, Canada, and was linked to contaminated raspberries imported from South America. Several hundred laboratory-confirmed cases were reported, most of them immunocompetent persons (CDC 1996).

A very useful molecular tool to identify same isolates from different geographical areas is subtyping enteric bacteria with PFGE. In the USA, the PulseNet database allows state health departments to compare their isolates with other states and therefore increase the recognition of nationwide outbreaks linked to the same food item (Swaminathan et al. 2001).

In a different scenario, a widely distributed food item with low-level contamination might result in an increase of cases within a large geographical area and therefore might be not get detected on a local level. This kind of outbreak might only be detected by chance if the number of cases increased in one location and the local health department alerts other states to be on the lookout for a certain isolate.

Another type of outbreak is the introduction of a new pathogen into a new geographical area as it happened in 1991 when *Vibrio cholerae* was inadvertently introduced in the waters off the Gulf Coast of the United States.

Food can not only be contaminated by the end of the food handling process, that is, by infected food handlers, but also can be contaminated by any event earlier in the chain of food production. In 1996, an outbreak of *Salmonella enteritidis* in a national brand of ice cream resulted in 250,000 illnesses. The outbreak was detected by routine surveillance because of a dramatic increase of *Salmonella enteritidis* in South Minnesota. The cause of the outbreak was a basic failure on an industrial scale to separate raw products from cooked products. The ice-cream premix was pasteurized and then transported to the ice-cream factory in tanker trucks which had been used to haul raw eggs. This resulted in the contamination of the ice cream and subsequent salmonella cases (Hennessy et al. 1996).

51.7 Surveys

Surveys are useful to provide information for which there is no data source or no reliable data source. Surveys are time consuming and are often seen as a last choice to obtain information. However, too often unreliable information is used because it is easily available. For example, any assessment of the *Legionella* problem using passive case detection will be unreliable due to underdiagnosis and underreporting. Most cases of legionellosis are treated empirically as community-acquired pneumonias and are never formally diagnosed.

In developing countries, surveys are often necessary to evaluate health problems since data collected routinely (disease surveillance, hospital records, case registers) are often incomplete and of poor quality. In industrialized nations, although many sources of data are available, there are some circumstances where surveys may be necessary.

Prior to carrying out surveys involving human subjects, special procedures need to be followed. In industrialized countries, a human subject investigation review board has to evaluate the project's value and ethics. In developing countries, however, such boards may not be formalized, but it is important to obtain permission from medical, national, and local political authorities before proceeding.

51.7.1 Survey Methods

Surveys of human subjects are carried out by mail, telephone, personal interviews, and behavioral observations. In infectious diseases, the collection of biological specimens in humans (i.e., blood for serological surveys) or the collection of environmental samples (food, water, environmental surfaces) is very common. Personal interviews and specimen collection require face-to-face interaction with the individual surveyed. These are carried out in offices or by house-to-house surveys.

Non-respondents are an important problem for infectious disease surveys. Those with an infection may be absent from school, may not answer the door, or may be unwilling to donate blood for a serological survey, thus introducing a systematic bias into the survey results.

Since surveys are expensive, they cannot be easily repeated. All field procedures, questionnaires, biological sample collection methods, and laboratory tests should be tested prior to launching the survey itself. Feasibility, acceptability, and reliability can be tested in a small-scale pilot study. More details on survey methods are to be found in chapter ►Epidemiological Field Work in Population-Based Studies of this handbook.

51.7.2 Sampling

Since surveys are labor intensive, they are rarely carried out on an entire population but rather on a sample. To do a correct sampling, it is necessary to have a sampling base (data elements for the entire population) from which to draw the sample. Examples of sampling bases are population census, telephone directory (for the phone subscriber population), school roster, or a school list. In developing countries, such lists are not often available and may have to be prepared before sampling can start. More information on sampling designs can be found in chapter ►Epidemiology in Developing Countries of this handbook.

51.7.3 Community Surveys (House-to-House Surveys)

Most community surveys are carried out in developing countries because reliable data sources are rare. The sampling base often ends up to the physical layout of the population. A trip and geographical reconnaissance of the area are necessary. The most common types of surveys undertaken in developing countries are done at the village level; they are based on maps and a census of the village.

In small communities, it is important to obtain the participation of the population. Villagers are often wary of government officials counting people and going from door to door. To avoid misinterpretations and rumors, influential people in the community should be told about the survey. Their agreement is indispensable, and their help is needed to explain the objectives of the survey and particularly its potential benefits. Increasing the knowledge about disease, disease prevention and advancing science are abstract notions that are usually poorly understood or valued by villagers who are, in general, very practical people. If a more immediate benefit can be built into the survey, there will be an increase in cooperation of the population. Incentives such as offering to diagnose and treat an infection or drugs for the treatment of common ailments such as headaches or malaria enhance the acceptance of the survey.

In practically all societies, the household is a primary economic and social unit. It can be defined as the smallest social unit of people who have the same residency and maintain a collective organization. The usual method for collecting data is to visit each household and collect samples or administer a questionnaire.

Medical staff may feel left out or even threatened whenever a medical intervention (such as a survey) is done in their area. A common concern is that people will go to their medical care provider and ask questions about the survey or about specimen collection and results. It is therefore important to involve and inform local medical providers as much as practical.

A rare example of a house-to-house survey in an industrialized nation was carried out in Slidell, Louisiana, for the primary purpose of determining the prevalence of West Nile infection in a southern US focus. Since the goal was to obtain a random sample of serum from humans living in the focus, the only method was a survey of this type. A cluster-sampling design was used to obtain a representative number of households. The area was not stratified because of its homogeneity. Census blocks were grouped so that each cluster contained a minimum of 50 households. The probability of including an individual cluster was determined by the proportion of houses selected in that cluster and the number of persons participating given the number of adults in the household. A quota sampling technique was used, with a goal of enlisting ten participating households in each cluster.

Inclusion criteria included age (at least 12 years of age) and length of residence (at least 2 years). The household would be included only if an adult household resident was present. A standardized questionnaire was used to interview each participant. Information was collected on demographics, any recent febrile illness, knowledge, attitudes, and behaviors to prevent WNV infection and potential exposures to mosquitoes. A serum sample for WNV antibody testing was drawn.

In addition, a second questionnaire regarding selected household characteristics and peridomestic mosquito reduction measures was completed. Informed consent was obtained from each participant, and all participants were advised that they could receive notification of their blood test results if they wished. Institutional review board approvals were obtained.

Logistics for specimen collection, preservation, and transportation to the laboratory were arranged. Interpretation of serological tests and necessary follow-up were determined prior to the survey and incorporated in the methods submitted to the ethics committee.

Sampling weights, consisting of components for block selection, household-within-block selection, and individual-within-household participation, were used to estimate population parameters and 95% confidence intervals (CI). Statistical tests were performed incorporating these weights and the stratified cluster sampling design.

In this survey, 578 households were surveyed (a 54% response rate), including 1,226 participants. There were 23 Immunoglobulin M (IgM) seropositive persons, for a weighted seroprevalence of 1.8% (with a 95% confidence interval of 0.9–2.7%) (Michaels et al. 2005).

51.8 Microbiological and Serological Issues

51.8.1 Case Confirmation

Definitive confirmation of a case relies on the identification of the infectious agent in the patient in some specific body sites. The site is important for agents that may be pathogens or colonizers. For example, identification of *Neisseria meningitidis* in an upper respiratory fluid could be due to colonization, while isolation from cerebrospinal fluid or blood would mean definite invasive disease.

Identification of infectious agents is more frequently done by genotyping of the agent nowadays. The reliability of these identifications depends on the methods being used. Many of the tests are developed "in house." The tests that identify a single gene are less reliable than those that identify several specific genes.

51.8.2 Serological Issue and Seroepidemiology

Serological tests have long been used to diagnose the cause of an infectious disease. In most instances, these methods are reliable, but this is not always so. The old serological methods (agglutination, hemagglutination, complement fixation, etc.) often resulted in a false-positive/false-negative result. Dilutions were used to quantify the reactions. In general, positive reactions at low titers were meaningless, while positivity at high dilutions was indicative of a recent infection. A fourfold increase of positivity (e.g., from a 1:16 to 1:64 dilution) over a 2-week period was usually considered confirmatory based on the dilution factor that meets the

criteria for positivity in the laboratory test. A good example for this is *Brucella* sp. (a zoonotic disease where humans are accidental hosts) where a fourfold or greater rise in the *Brucella* agglutination titer between acute (specimen taken while patient is symptomatic) and convalescent (specimen taken while patient is recovering from the disease) serum specimens obtained 2 or more weeks apart is considered positive. Serological diagnosis is often discouraged because of difficulties of collecting follow-up serum samples if the patient has recovered and is not in medical care anymore.

Newer techniques such as enzyme immunoassays (EIA) do quantify the amount of antibodies present, but do not allow for the "fourfold increase."

The serological response to an infection consists of several types of antibodies: IgM at first, Immunoglobulin G (IgG) antibodies later, and also Immunoglobulin A (IgA) antibodies. The usual assumption is that IgM antibodies are produced early (before IgG antibodies) and for a limited length of time (usually 2–3 months). However, the postulate "IgM means recent infection" is not always true. Onset and length of production of IgM antibodies depend on the infectious agent. For West Nile infections, IgM production starts a few days after infection but may last for several years; in fact, 1 year after infection, 40% of the patients are still reported IgM positive by most criteria established by laboratory definitions.

51.8.3 Sensitivity, Specificity, and Predictive Value of a Positive Test

Issues of sensitivity, specificity, and predictive value are particularly relevant to serological testing. The methods are similar to those described in chapter ▸Clinical Epidemiology and Evidence-Based Health Care of this handbook. The predictive value of a positive test (*PVPT*) depends on its sensitivity, specificity, and prevalence. Its formula is the following:

$$PVPT = \frac{PR^{*}SE}{(PR^{*}SE) + [(1 - PR)^{*}(1 - SP)]},$$

where *PR* denotes the prevalence, *SE* the sensitivity, and *SP* the specificity.

It is heavily influenced by the prevalence. Even if the tests have the highest sensitivity and specificity (99% for both in Table 51.13), the predictive value is poor

Table 51.13 Predictive value of a positive test

Sensitivity (%)	Specificity (%)	Prevalence (%)	*PVPT* (%)
99	99	5	83.9
99	99	1	50
99	99	0.1	9
95	95	5	50
95	95	1	16.1
95	95	0.1	1.9

when the prevalence is low. This has implications for case definitions in situations of very low prevalence or disappearing infectious diseases (example of measles and rubella in the USA).

51.9 Nosocomial Infection Epidemiology

Epidemiology plays a major part in prevention programs against nosocomial (hospital-acquired) infections. Surveillance should provide systematic and continuous observations on the occurrence and distribution of nosocomial infections within the hospital population. Surveillance is the focal point for infection control activities. The term surveillance implies that the observational data are regularly analyzed.

Surveillance activities may provide valuable epidemiological data such as the identification of outbreaks, priorities for infection control activities, and the elucidation of important secular trends, such as shifts in microbial pathogens, infection rates, or outcomes of hospital-acquired infection. Surveillance activities provide the additional benefits of increasing the visibility of the infection control team in the hospital during the infection control practitioners' ward rounds and of allowing an opportunity for informal consultation and education for both nurses and physicians.

Ideally, the surveillance of hospital-acquired infection should be a continuous process that consists of the following elements:

1. Definition of categories of infection
2. Systematic case finding and data collection
3. Tabulation of data
4. Analysis and interpretation of data
5. Reporting of relevant infection surveillance data to individuals and groups for appropriate action

51.9.1 Definitions

The use of consistent definitions of nosocomial infection is critical in developing data on endemic infection rates. Definitions must be simple, requiring only clinical information or readily available laboratory data.

51.9.1.1 General Definitions

A nosocomial infection is either:

1. An infection which is acquired during hospitalization and which was not present or incubating at the time of admission or
2. An infection which is acquired in the hospital and becomes evident after discharge from the hospital or
3. A newborn infection which is the result of passage through the birth canal.

An infection is defined as hospital acquired if the patient (1) has an infection, not a simple colonization, (2) was not infected at the time of admission, and (3) had sufficient time to develop infection.

True Infection and Not Colonization or Contamination Infections are accompanied by signs and symptoms of infection (fever, malaise) and in localized infections: swelling due to inflammation, heat, pain, and erythema (tumor, dolor, rubor, or calor). Immunocompromised patients do not show signs of infection as easily as normal patients. Neutropenic patients ($\leq$500 neutrophils/cubic millimeter) show no pyuria, no purulent sputum, little infiltrate, and no large consolidation on chest X-ray. An antibiotic treatment by a physician is a presumption of infection.

No Infection at Time of Admission Several criteria may be used to establish prior negativity: history, symptoms and signs documented at the time of admission, lab tests, and chest X-rays done in the early days in the hospital. Normal physical examination, absence of signs and symptoms, normal chest X-ray, negative culture, and lack of culture are useful.

Sufficient Time to Develop Infection For diseases which have a specific incubation period, the hospital-acquired infection can only develop if the patient has stayed in the hospital for a stay $\geq$ incubation period. Numerous infections do not have well set incubation periods (e.g., staphylococci and *E. coli* infections). However, these infections rarely develop in less than 2 days.

To establish a nosocomial infection meeting the definition criteria, it is sufficient that there is no need to have proof beyond the shadow of a doubt.

51.9.1.2 Specific Definitions

To carry out surveillance, very specific definitions are necessary, not only regarding the major nosocomial infections (surgical site infection, bloodstream infections, pneumonia, and urinary tract infections) but regarding all possible sites of nosocomial infections.

51.9.2 Scope/Strategy of Surveillance

Active surveillance is much more effective than *passive surveillance*. Using active surveillance increases the sensitivity of identifying infections.

51.9.2.1 Case Finding

Case finding can be *retrospective*, *prospective*, or both. Prospective or concurrent surveillance means monitoring the patient during hospitalization. Prospective surveillance may include the post-discharge period. In contrast, retrospective surveillance involves review of the medical record after the patient has been discharged. Prospective surveillance provides increased visibility for infection control personnel and timely analysis of data and feedback to clinical services, but this type of surveillance is more expensive. Retrospective methodology is cheaper to implement but requires more controls to verify how effective the infection control personnel are as follows:

- Patient-based case finding relies on evaluating medical records and doing rounds in hospital wards. It allows assessing risk factors, procedures, and practices related to patient care.
- Laboratory-based surveillance relies on identifying positive cultures for pathogens. Then, further investigations are necessary to verify if this is a health-care facility-associated infection, a community-associated infection, a colonization, or a contamination.

A major issue is determining the scope of surveillance. Choices can include three major strategies: hospital-wide surveillance, surveillance by objective, and limited or targeted surveillance.

51.9.2.2 Hospital-Wide Surveillance

Comprehensive or hospital-wide surveillance implies a continuous surveillance of all patients for all types of nosocomial infections in all hospital wards.

This strategy is time consuming. Efficiency is increased by using "clues" to identify patients whose charts should be reviewed. A hospital-wide surveillance provides a global view of the hospital, but the cost and the labor involved may be prohibitive. Critics of whole-house surveillance argue that collecting and analyzing data may be overwhelming; time may not permit developing objectives for surveillance, and many of the identified infections may not be preventable. A modification of this strategy includes doing hospital-wide surveillance for 1 year, or part of a year.

51.9.2.3 Surveillance by Objectives

Surveillance by objectives focuses on specific outcome objectives defined for surveillance purposes. Levels of surveillance effort are prioritized. Prioritization focuses on types of infections to be prevented, and levels of effort may be adjusted to the relative seriousness of the problem. Considerations in setting these priorities would include morbidity and mortality data, costs of treating infections, length of stay, frequency of occurrence of infection, and percentage of infections that are thought to be preventable. If baseline rates (before objectives are met) are not established, the identification of clusters and epidemics would be difficult. Areas that were not included in the objectives could not be evaluated.

51.9.2.4 Targeted Surveillance

Targeted surveillance can be site specific, unit specific, rotating, or limited to outbreak surveillance.

Site-specific surveillance focuses on specific infection sites such as surgical wounds or urinary tract infections. In contrast to surveillance by objective, this strategy lacks a defined objective. It is flexible, because this strategy can be used concurrently with alternating components such as continuous and rotating surveillance as well as special projects.

Unit-directed surveillance targets specific units or areas with highest risk. Surveillance activities are limited to the areas of highest risks such as intensive

care units, burn units, and hematology and oncology units. Targeting critical care and oncology units, for example, would capture the majority of all bloodstream infections. The rate of infection in these units is high, yet a relatively small number of patients are actually treated. This approach may prevent infections in patients at greatest risk.

Rotating surveillance is periodic and systematic surveillance in a given unit for a specific time period. This technique is less time consuming and more cost effective than other forms of surveillance because all areas of the hospital are covered at sequential periodic intervals using careful continuous surveillance. Ideally, rotating surveillance involves an annual, detailed, and directed infection-control evaluation for each hospital unit. One type of rotating surveillance, the prevalence survey, can identify infection control risks; however, it can also miss clusters in areas that are not currently under surveillance.

Outbreak surveillance requires an alert hospital staff who report any unusual cluster of events that, when based on surveillance data, extend beyond threshold units.

Whichever surveillance strategies are selected, they should allow personnel to recognize and workup clusters of infections or events.

51.9.3 Calculating Rates

51.9.3.1 Numerator

The numerators may be the number of infections or the number of patients infected. Decisions must be made on how to count infections caused by multiple organisms at the same site (usually counted as one infection), infections in a patient with a second nosocomial infection, a patient with an extension of another infection, and so forth.

51.9.3.2 Denominators

If incidence rates are warranted, a common denominator is number of patients admitted or discharged. If incidence density rates are calculated, number of hospital days or numbers of device days are usually used. The choice of denominator depends on the purpose of calculating these rates.

Hospital-Wide Nosocomial Infection Rate per 100 Admissions A hospital-wide nosocomial infection rate/100 admissions for a given period (month, quarter, or year) is commonly calculated but has little significance because it does not take into account (1) the risk posed to the patient by procedures (intravenous (IV) lines, urinary catheters, or ventilators) and (2) the severity of the patients' conditions. A small hospital with little use of invasive procedures and relatively healthier patients will have lower rates of infection.

In this rate, a patient who has two infections is actually counted twice. This rate can be calculated as

$$\frac{\text{number of nosocomial infections}^{*}100}{\text{number of patients admitted}}.$$

Hospital-Wide Patient Infection Rate per 100 Admissions Hospital-wide patient infection rate/100 admissions are used to avoid the pitfall of multiple infections in the same patient. This rate may be calculated for a given period: month, quarter, and year. In this rate, a patient with two infections is counted only once:

$$\frac{\text{number of patients infected}^{*}100}{\text{number of patients admitted}}.$$

Patient Infection Rate per 1,000 Hospital Days The risks of infections are much higher in some units of the hospital such as intensive care units (ICUs) and coronary care units. Calculating ward-specific rates is useful to look at the trends in specific units or compare between units. The number of patients admitted to an ICU may be difficult to determine because some patients are admitted in the ward 1 day, spend a few days, be discharged to a regular ward, and after a few days be readmitted into ICU. To avoid the problem posed by the same patient admitted and discharged several times from the ICU to the wards, the rate of infection is expressed in number of patients infected/1,000 hospital days. This rate also takes into account the duration of hospitalization which is a risk factor for nosocomial infection. It allows comparison between wards where duration is different and can be calculated as

$$\frac{\text{number of infections}^{*}100}{\text{number of hospital days}}.$$

Device-Specific Rates and Procedure-Specific Rates The risk of infection is related to the extrinsic risk factors (use of devices such as ventilator, central line intravascular catheter, urinary catheter, surgical operation). To compare the risk associated with these devices or procedures, the following rates are best suited:

$$\text{surgical site infection rate} = \frac{\text{number of surgical site infections}^{*}100}{\text{number of patients operated on}},$$

$$\text{ventilator associated pneumonia rate} = \frac{\text{number of ventilator associated pneumonia}^{*}1{,}000}{\text{number of patients on ventilator days}},$$

$$\text{catheter related bloodstream infection (BSI) rate} = \frac{\text{number of catheter related BSI}^{*}100}{\text{number of patients on IV line days}},$$

where it may be difficult to obtain the number of intravascular line days. Ideally, the number should be line specific, for example, central line (which is a catheter (tube) that is passed through a vein to end up in the thoracic (chest) portion of the vena cava or in the right atrium of the heart) days and peripheral line (which is a catheter (tube) placed into a peripheral vein) days

$$\text{utilization rate} = \frac{\text{number of device days }^{*}100}{\text{number of patients days}},$$

where the device utilization rate (DUR) is the proportion of patient days for which a certain device is used. The DUR is specific to a certain device: catheter, IV line, and ventilator. The DUR reflects the amount of devices used and is a reflection of the patient severity.

51.10 Epidemiological Aspects of Infectious Disease Prevention

51.10.1 Antibiotic Resistance

There are an almost daily increasing number of publications on antibiotic resistance creating the impression that the resistance is growing worldwide. However, there is no comprehensive surveillance system for antibiotic sensitivity and no comprehensive database documenting the spread of resistance in the USA or worldwide. One of the best data sources for the USA comes from the *National Nosocomial Infection Surveillance* (NNIS), now the *National Healthcare Safety Network* surveillance which documents sensitivity of nosocomial infections, an estimated 4% of bacterial infections occurring in the USA.

On a very global aspect, antibiotics are still very effective. For many hospitals, antibiotic sensitivity patterns are not very different nowadays than what they were 10 years ago, except for very few pathogens. Reports obtained from the medical literature are not representative of the whole hospitals, and even of the whole "world" of bacteria. Many of the resistance reports from the literature come from single institutions where antibiotic resistance was the consequence of overuse of an antibiotic. Very few reports attempt to compare several institutions. There is no randomized, non-selective, multicentered data to evaluate the scope of resistance and its evolution. Most of the US data is reported from large metropolitan hospitals affiliated with medical schools in the northern USA. These hospitals treat the more severely ill patients who often have been treated unsuccessfully at community hospitals and have probably become resistant during previous attempts at treatment.

The impression is that the most severe cases of resistance are generated in the tertiary care hospitals (these are specialty hospitals dedicated to specific subspecialty care including ICUs). It may well be that resistance is generated in primary (health care was provided by a general practitioner or other health professional) and secondary care facilities (health care provided by hospital clinicians) and those cases who did not respond to antibiotics were referred to tertiary care hospitals.

51.10.1.1 Active Surveillance

The goal of an antibiotic sensitivity active surveillance system is to estimate the proportion of selected bacteria that are resistant to antibiotics by the reporting of laboratory aggregate data. This surveillance system can only monitor a few pathogens. In the USA, the most common pathogens monitored in such programs are methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *Streptococcus pneumoniae* (DRSP), and vancomycin-resistant *Enterococcus* (VRE). Laboratories are asked to report:

1. The total number of drug-resistant or drug intermediate-resistant isolates excluding duplicates (one isolate per patient per month if possible) (numerator)
2. The total number of isolates of the bacterial species of concern (denominator) from a given laboratory for each month

51.10.1.2 Antibiograms

Another approach to establish an antibiotic sensitivity surveillance system is to use the hospital antibiograms. In 2001, the *National Committee on Clinical Laboratory Standards* (NCCLS) now known as the *Clinical and Laboratory Standards Institute* (CLSI) issued guidelines on how to analyze and present cumulative antimicrobial sensitivity test data from antibiotic sensitivity testing performed on health-care facility patients. The data show the percent sensitivity for the first isolate from a patient within an analysis period (generally 1 year), the specimen source, and the total number of isolates tested (minimum ten for each organism to avoid describing sensitivity on a sample of less than ten patients).

The compilation of individual hospital antibiograms over time is useful in monitoring antibiotic sensitivity. The CDC conducted a study to compare data from the resource-intensive active surveillance collection of antibiotic resistance patterns to the data collected using hospital antibiograms. The study found the proportions of drug-resistant isolates from antibiograms were within ten percentage points of those from isolates obtained through active surveillance, thereby providing a relatively simple and accurate way to monitor antibiotic resistance (Van Beneden et al. 2003).

Limitations of hospital antibiograms are that they do not sort out community-acquired infections from nosocomial infections and some laboratories may not thoroughly unduplicate their data, thus giving a picture of a larger number of resistant isolates than it is the case.

51.10.2 Immunization

Epidemiology plays a major role at several stages in immunization programs.

51.10.2.1 At the Development Stage

Once a vaccine has been developed, it has to go through a rigorous process to be recognized as safe and efficacious. Once information on the vaccine composition, manufacturing, stability and sterility, and animal testing results have been submitted for review, the vaccine has to go through preclinical and clinical trials. In the preclinical studies, assays are carried out in animals to determine the humoral and cellular responses, the optimal administration route, the dose-response relationship, and the dosing schedule and the adverse or toxic effects. This is followed by the clinical studies. Phase I studies are intended to determine the efficacious dose and safety of the vaccine in a small number of healthy adults. Phase II studies are more extensive "open-label" prospective cohort studies or small randomized controlled trials on all relevant age groups. Their goal is to establish safety and immunogenicity. Phase III studies are randomized double-blind placebo-controlled vaccine efficacy trials. A comparison is made for the incidence rate of a disease in the standard versus a placebo group. The goal is to confirm the efficacy and obtain a comprehensive list of side effects.

51.10.2.2 At the Implementation Stage

Once in public use, the populations receiving the vaccine are much less controlled than during the trials. The designs of epidemiological studies must be adapted to these new conditions. Descriptive studies, surveys, case-control, and cohort studies are then performed with a goal to evaluate efficacy, side effects, and success of a vaccination campaign. The study of outbreaks among unvaccinated populations becomes a very useful tool to evaluate efficacy.

51.10.2.3 When Vaccine Led to Disappearing Illness: Eradication

Once a vaccine has been widely distributed among the population and the herd immunity is very high, the incidence of disease will decrease until elimination. Epidemiological studies are useful to determine if the widespread use of vaccine has led to suppression of disease with continuation of circulation of the agent or to the total disappearance of the infectious agent. With poliomyelitis, the killed vaccine led to elimination of the disease, but the virus was still circulating. The live oral vaccine on the other hand led to a complete elimination of the circulating virus. Epidemiological methods are instrumental in gathering this evidence.

During the final stages of a disappearing illness, active surveillance and detailed case investigation are necessary to detect every suspect and confirm the diagnosis with a definitive laboratory test (under these circumstances, identification of the infectious agent is preferred to a serological/immunological test). For poliomyelitis eradication, surveillance for acute flaccid paralysis is implemented before declaring a country free of the disease.

51.11 Program Evaluation

Program evaluation is a systematic way to determine if prevention or intervention programs for the infectious disease of interest are effective and to see how they can be improved. It is beyond the scope of this chapter to explain program evaluation in detail; however, there is abundant information available, that is, the CDC's Framework for Program Evaluation in Public Health (CDC 1999) as well as many valuable text books on program evaluation.

Most importantly, evaluators have to understand the program such as the epidemiology of the disease of interest, the program's target population and their risk factors, program activities, and resources. They have to identify the main objectives of the control actions and determine the most important steps. Indicators define the program attributes and translate general concepts into measurable variables. Data are then collected and analyzed so that conclusions and recommendations for the program are evidence based.

Evaluating an infectious disease control program requires a clear understanding of the microorganism, its mode of transmission, the susceptible population, and the risk factors. The following example of evaluation of tuberculosis control shows the need to clearly understand the priorities.

Most of tuberculosis transmission comes from active pulmonary tuberculosis cases that have positive sputum smears (confirmed as *Mycobacterium tuberculosis* on culture). To a lesser extent, smear-negative, culture-positive pulmonary cases are also transmitting the infection. Therefore, priority must be given to find sputum-positive pulmonary cases. The incidence of smear-positive tuberculosis cases is the most important incidence indicator. Incidences of active pulmonary cases and of all active cases (pulmonary and extrapulmonary) are also calculated but are of lesser interest. The proportion of all cases of tuberculosis that are pulmonary versus extrapulmonary, smear-positive culture-positive pulmonary versus culture-positive only pulmonary, or culture-negative pulmonary is used to detect anomalies in case finding or case ascertainment. A low proportion of smear-positive cases may result from poor laboratory techniques or excessive diagnosis of tuberculosis with reliance on chest X-rays and low interest in obtaining sputa for smears or cultures.

Once identified, tuberculosis cases are placed under treatment. Treatment of infectious cases is an important preventive measure. Treatment efficacy is evaluated by sputum conversion (both on smear and culture) of the active pulmonary cases. After 2 months of an effective regimen, 85% of active pulmonary cases should have converted their sputum from positive to negative. Therefore, the rate of sputum conversion at 2 months becomes an important indicator of program effectiveness. This indicator must be calculated for those who are smear positive and with a lesser importance for the other active pulmonary cases.

To ensure adequate treatment and prevent the development of acquired resistance, tuberculosis cases are placed under directly observed therapy (DOT). This measure is quite labor intensive. Priority must therefore be given to those at highest risk of relapse. These are the smear-positive culture-proven active pulmonary cases. DOT on extrapulmonary cases is much less important from a public health

standpoint because they are not infectious and the major objectives of any public health program are to prevent transmission.

The same considerations apply to contact investigation and preventive treatment in countries that can afford a tuberculosis contact program. A recently infected contact is at the highest risk of developing tuberculosis the first year after infection; hence, the best preventive return is to identify contacts of infectious cases. Those contacts are likely to have been recently infected. Systematic screening of large population groups would also identify infected individuals, but most would be "old" infections at lower risk of developing disease. Individuals infected with tuberculosis and HIV are at extremely high risk of developing active tuberculosis. Therefore, the tuberculosis control program should focus on the population at high risk of HIV infection.

Often, program evaluation is performed by epidemiologists who have not taken the time to understand the dynamics of a disease in the community. Rates or proportions are calculated, no priorities are established, and precious resources are wasted on activities with little preventive value. For example, attempting to treat all tuberculosis cases, whether pulmonary or not with DOT, investigating all contacts regardless of the bacteriological status of the index case would be wasteful.

51.12 Mathematical Models

51.12.1 Aims of Mathematical Modeling

Mathematical models are an important tool for understanding the transmission dynamics of infectious diseases. In contrast to statistical models, dynamic transmission models are based on first principles. They aim at deriving population level phenomena from a mechanistic description of transmission between individuals of the population. The centerpiece of a dynamic transmission model consists of a term that quantifies the rate with which susceptible and infectious persons have contact with each other and the probability that transmission takes place during such a contact. In its simplest form, this term is modeled as a mass action term. In analogy to the mass action law in chemistry, the underlying assumption is that susceptible and infectious persons mix homogeneously and contact each other with a rate that is proportional to the concentrations of either population group. In more formal terms, if we denote by $X(t)$ the fraction of susceptible persons, and by $Y(t)$ the fraction of infected and infectious persons at time t, the rate at which infectious contacts take place is proportional to $X(t)^*Y(t)$. The proportionality factor β is a product of the contact rate – the number of contacts per unit time – and the probability that upon contact transmission of infection takes place. With the assumption that recovery from the infectious state into the immune state occurs with a constant rate γ, we can now formulate a first simple mathematical model:

$$\frac{dX(t)}{dt} = -\beta X(t)Y(t),$$
$$\frac{dY(t)}{dt} = \beta X(t)Y(t) - \gamma Y(t),$$
$$\frac{dZ(t)}{dt} = \gamma Y(t),$$

where $Z(t)$ is the fraction of immune or recovered individuals at time t. This set of equations is the simplest version of the so-called *susceptible-infected-removed* model that was first introduced in a more elaborate form by Kermack and McKendrick (1927; reprinted 1991). Since then, numerous variants of this simple model have been formulated and analyzed (Anderson and May 1991).

The primary aim of such a model is to gain a better understanding of the dynamics of the system. For example, in the above system of equations, we are interested in how an outbreak evolves in the population after introduction of a small number of index cases. The epidemic curve will depend on the parameters of the model, which in this case are the transmission rate β and the recovery rate γ. Let us see what we can say by just looking at the equations. Let us assume that we start at $t = 0$ in a situation where almost the entire population is susceptible, a small fraction of the population is infected, and nobody is immune. First, we observe that the fraction of susceptibles in the population can only decrease, because the right-hand side of the equation for $X(t)$ is negative. Furthermore, we see that $Y(t)$ will increase if the right-hand side of the equation for $Y(t)$ is positive, which is the case if $\beta X(0)Y(0) > \gamma Y(0)$. This leads to the insight that an outbreak is only possible if $\beta/\gamma > 1$. Here β/γ is the so-called basic reproduction number denoted by R_0 (see also Sect. 51.12.2). We will come back to this important concept later. Finally, we see that the fraction of immune persons in the population is continuously increasing as long as there are infected persons in the population. Figure 51.12 shows the typical time course of an outbreak for the parameters $\beta = 5$ and $\gamma = 1$.

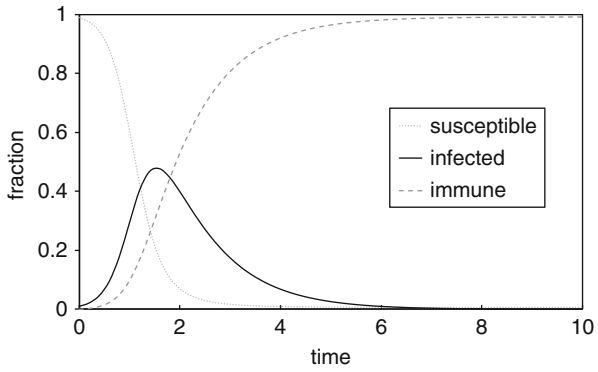

Fig. 51.12 The time course of an epidemic when there is no inflow of new susceptible individuals

After the outbreak has swept through the population and has left a certain fraction of the population immune, no further dynamics are possible in this system. This can only change if new susceptible individuals enter the population.

We want to extend the above model to include a simple demographic process, that is, births into the population with a rate ν and a per capita mortality rate μ. We assume that the mortality is not disease related, but applies to all population groups in the same way. For populations that grow or decrease in size, there are different ways of taking population size into account in the model formulation (Keeling and Rohani 2008). For simplicity, we assume here that $\nu = \mu$, meaning that the population is neither growing nor decreasing in size. With these additions, our model equations can be written as

$$\begin{aligned}
\frac{dX(t)}{dt} &= \nu - \beta X(t)Y(t) - \mu X(t), \\
\frac{dY(t)}{dt} &= \beta X(t)Y(t) - \gamma Y(t) - \mu Y(t), \\
\frac{dZ(t)}{dt} &= \gamma Y(t) - \mu Z(t).
\end{aligned}$$

These additions to the model change the long-term dynamic behavior of the model completely. The demographic process allows for a flow of new susceptible individuals into the population, thereby providing fuel for the transmission process to continue. In the long run, if the transmission rate β is large enough, the system will settle down to an endemic steady state with a prevalence of infection that is constant in time. It is not difficult to compute the endemic prevalence as a function of the model parameters. The result in terms of fractions X, Y, and Z of the population is

$$\begin{aligned}
X &= \frac{1}{R_0}, \\
Y &= \left(1 - \frac{1}{R_0}\right) \frac{\mu}{\gamma + \mu}, \\
Z &= 1 - X - Y.
\end{aligned}$$

In other words, the fraction of susceptible individuals is completely determined by the basic reproduction number R_0, with higher values of R_0 leading to a smaller proportion of susceptible individuals in the population. The endemic prevalence Y increases with increasing R_0 but is also determined by the duration of the infection $1/(\gamma + \mu)$.

Whether to use a model with or without demographic parameters depends on the time scale on which the outbreak takes place. For example, on the time scale of an influenza outbreak that takes a few weeks, the demographic process in the population will hardly influence the shape of the outbreak, and we might also not be interested in what will happen after the first wave. However, for an infection like

HIV, transmission dynamics evolves on the time scale of decades and will therefore strongly interact with the demographic process in the population.

This short introduction into the susceptible-infected-removed (SIR) model shows that (a) the model can provide insight into qualitative features of the transmission process on population level and (b) the exact form of the model to be used depends on the time scale and properties of the specific infection.

51.12.2 Important Concepts

Insights into the dynamics of the SIR model have led to the definition of a number of important concepts that are universal for all models and all infectious diseases. The most important of these concepts is the *basic reproduction number* R_0. The basic reproduction number R_0 is the number of secondary cases caused by one index case during his/her entire infectious period in a susceptible population. In other words, the basic reproduction number is given by the product of the transmission rate (number of new infections per time unit) and the duration of the infectious period. In the above model, the number of new infections per unit time is given by β, while the duration of the infectious period can be computed as $1/(\gamma + \mu)$. Therefore, for the SIR model with demographic process, we get

$$R_0 = \frac{\beta}{\gamma + \mu}.$$

We easily see from the equation describing the dynamics of $Y(t)$ that $Y(t)$ will increase in size if $R_0 > 1$ and decrease otherwise. This is the so-called threshold property that was already in 1927 formulated by Kermack and McKendrick (reprinted 1991) in a more general form. If $R_0 > 1$ an infected individual replaces himself by more than 1 new infected persons, which leads to an expansion of the epidemic. If $R_0 < 1$ the infection cannot establish itself in the population and will die out.

In more generality, one talks about the reproduction number $R(t)$ that describes the number of secondary cases per infected individual in a population that is not necessarily completely susceptible. $R(t)$ depends on the time, because with unfolding of the epidemic outbreak, the proportion of susceptibles in the population decreases and the proportion of immune individuals increases. Therefore, $R(t)$ will decrease with time. If there is no replenishment of the susceptible population, the transmission will stop at some point. The total number or fraction of the population that was infected during the entire course of the outbreak is called the *final size* of the epidemic. In epidemiological terms, the final size is called the attack rate; we denote it by A. The final size can be expressed in terms of the basic reproduction number as $A = 1 - \exp(-R_0 A)$ (Fig. 51.13).

If there is replenishment of the susceptible population by birth or recruitment into the population, the reproduction number may eventually converge to 1 in the endemic steady state. The prevalence in endemic steady state depends on the basic reproduction number with a larger R_0 leading to higher prevalence in steady state.

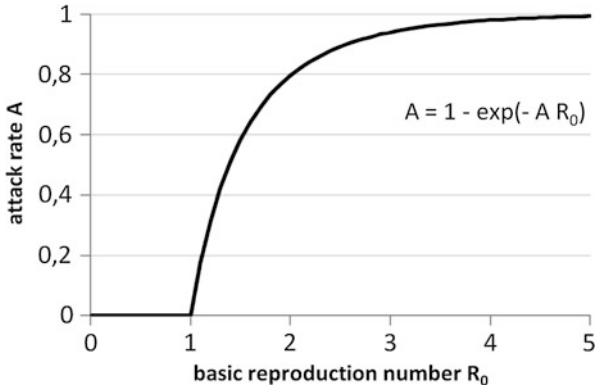

Fig. 51.13 The attack rate A as a function of the basic reproduction number R_0

Incorporating a simple term for infant vaccination with coverage p into the model makes it possible to determine the *critical vaccination coverage*. A model with vaccination is given by

$$\frac{dX(t)}{dt} = \nu(1-p) - \beta X(t)Y(t) - \mu X(t),$$
$$\frac{dY(t)}{dt} = \beta X(t)Y(t) - \gamma Y(t) - \mu Y(t),$$
$$\frac{dZ(t)}{dt} = \nu p + \gamma Y(t) - \mu Z(t),$$

where a fraction p of all newborns enters into the immune compartment immediately at birth, while the remaining fraction $1-p$ remains susceptible. Based on the endemic prevalence for this system of equations, the critical vaccination coverage can be derived as

$$p_{\text{crit}} = 1 - \frac{1}{R_0}.$$

This relationship gives valuable information about the vaccination effort needed to eliminate an infection from a population. It explains why it has been possible to eradicate smallpox with an estimated R_0 of around 5 (Gani and Leach 2001) in contrast to measles, for which the R_0 is estimated at around 20 (Wallinga et al. 2003).

Since the introduction of the SIR model, many different models have been formulated, and the diversity of models has vastly increased. Models have been designed for many specific infectious diseases, and they have incorporated population structure such as age, gender, spatial distribution, and differences in risk behavior. Also, stochastic models have been used to account for effects of chance events.

When choosing a model to answer a particular question in epidemiology or public health, different aims can be achieved, and the model of choice has to be accommodated to the aim. For answering questions about the qualitative dynamics

of an infection, it is preferable to turn to a relatively simple model for which mathematical analysis is possible, while for the purpose of generating quantitative estimates or projections, more complex models are necessary that incorporate more details of the population structure (e.g., age) and more details about the transmission and course of infection. The latter can be simulation models that are implemented as computer code and cannot be formulated in terms of mathematical equations.

51.12.3 Use of Mathematical Models in Epidemiological Studies

Although mathematical modeling has been around for a long time, until recently, it was not much used as a tool for public health, but was considered a specialized research area for applied mathematicians and theoretical biologists. This started to change with the advent of the HIV pandemic, when mathematical models were first used to predict future epidemic spread, and to analyze the impact of behavior change on HIV incidence (Kaplan and Brandeau 1994). However, the breakthrough for mathematical modeling as a public health tool came with the concerns that smallpox virus could be used in a deliberate release and lead to devastating outbreaks in the only partially immune populations of present societies. How can public health policy be developed against threats with pathogens that are not circulating at present? There is no way to conduct epidemiological investigations, and the only available data in the case of smallpox were from before the eradication era. Therefore, to design policy, knowledge from historical smallpox outbreaks had to be combined with data about present-day society, and possible interventions had to be tested on the basis of this available information. Mathematical modeling provided a flexible tool to do that and was used to analyze possible vaccination strategies and other interventions (Ferguson et al. 2003).

Later, the experience with the global spread of SARS – the severe acute respiratory syndrome caused by a novel strain of corona virus – and the threat of a future pandemic with a new strain of influenza A initiated national and international efforts to better prepare for large outbreaks of emerging infections. Mathematical modeling was widely used for investigating optimal strategies for dealing with a new influenza pandemic (Longini et al. 2004; Ferguson et al. 2006). These response plans came into action during the pandemic with new influenza A|H1N1 emanating from Mexico in the spring of 2009. Even as the pandemic was still unfolding, first mathematical modeling studies started to deliver valuable data analyses almost in real time (Fraser et al. 2009).

Besides supporting public health policy in designing prevention and intervention strategies, mathematical modeling of infectious diseases has contributed greatly to increasing the understanding of the intricate relationships between clinical and biological determinants of infection and human contact and risk behavior patterns that lead to transmission. The importance of core groups of high sexual activity in the transmission dynamics of sexually transmitted infections (Hethcote and Yorke 1984), the impact of concurrent partnerships on the spread of HIV (Morris and Kretzschmar 1997), the importance of hosts being infectious before the appearance

of symptoms for disease control (Fraser et al. 2004), and the connectedness of modern societies in a small world network (Watts and Strogatz 1998) are just some examples for how mathematical modeling has shaped the present paradigms of infectious disease epidemiology.

51.13 Conclusions

Today, the world is smaller than ever before, and international travel and a worldwide food market make us all potentially vulnerable to infectious diseases no matter where we live.

New pathogens are emerging such as the SARS or spreading through new territories such as WNV. WNV introduced in the USA in 1999 became endemic in the USA over the next years. Hospital-associated and community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) and resistant tuberculosis cases and outbreaks are on the rise. Public health professionals are concerned that a novel recombinant strain of influenza will cause a new pandemic.

But not only the world and the etiological agents are changing; the world population is changing as well. In industrialized countries, the life expectancy is increasing, and the elderly are more likely to acquire a chronic disease, cancer, or diabetes in their lifetime. Because of underlying conditions or the treatment of these diseases, older populations also have an increased susceptibility for infectious diseases and are more likely to develop life-threatening complications.

Knowledge in the field of infectious disease epidemiology is expanding. While basic epidemiological methods and principles still apply today, improved laboratory diagnoses and techniques help to confirm cases faster, see how cases are related to each other, and therefore can support the prevention of spread of the specific disease. Better computers can improve the data analysis, and the Internet allows access to in-depth disease-specific information. Computer connectivity improves disease reporting for surveillance purposes, and the epidemiologist can implement faster preventive measures if necessary and is also able to identify disease clusters and outbreaks on a timelier basis.

The global threat of bioterrorism adds a new dimension. The intentional release of anthrax spores and the infection and death of persons who contracted the disease created a scare of contaminated letters in the US population.

With all these changes, there is renewed emphasis on infectious disease epidemiology and makes it a challenging field to work in.

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