

# Chapter 2

## Definitions

*This chapter deals with a number of the definitions and concepts necessary for understanding the literature on infectious disease epidemiology.*

Every self-respecting branch of science needs to have its own language and concepts. Sometimes it borrows words that have certain connotations in everyday language and gives them a strict definition with a slightly different meaning. Philosophy, sociology and psychiatry contain a number of such examples, but even within somatic medicine they are not uncommon. For example, a ‘positive test result’ can mean something quite different to the doctor and to the layman, and ‘stress’ now denotes a well-defined response of the neuroendocrine system, and not an everyday situation of significant concern.

The purpose of such words is not to deter the novice, but rather to lay a foundation for precise communication. The words of everyday language often have an ambiguity that creates misunderstandings. Some examples are listed below.

1. What do we mean by saying that a disease is common? Do we mean that many have it, or that many will get it?
2. If we say that ‘the mortality in disease X is high’, do we mean that X is a common cause of death, or that a large proportion of those who contract X will die?
3. What does ‘infected’ mean? Does it mean that a person is ill, or that they soon will be?
4. If we state that ‘the risk of becoming infected with Y is high’, do we mean that there is a high probability of meeting someone with Y, or that the risk of transmission is high once we meet someone who demonstrably has Y?

### SOME GENERAL DEFINITIONS

#### Incidence

Incidence is defined as the number of individuals who fall ill with a certain disease during a defined time period, divided by the total population. If the time period is not stated, it is usually assumed to be one year. Thus the state-

ment that 'the incidence of hepatitis B in Sweden is about 2 per 100 000' means that for every 100 000 inhabitants in Sweden, some two individuals contract hepatitis B each year. For common diseases, the incidence may be expressed as a percentage or 'per 1000 population', while for rare diseases a greater denominator is used – for example, 'the annual incidence of Creutzfeldt–Jakob's disease in most Western countries seems to lie between 1 and 2 per 1 million inhabitants'.

In most instances, incidence is calculated from clinical cases, but by following people with serological tests it is possible to detect the subclinical cases, and thus to obtain an incidence figure for the true number of infections.

If incidence is measured over a longer time period, it is often replaced by the term *cumulative incidence*. If we find that 40% of 5-year-olds have antibodies to varicella virus, we can say that the cumulative incidence during the first 5 years of life is 40%, but we do not know exactly how the incidence has varied over these years.

### Prevalence

The prevalence of a disease is the number of people who have that disease at a specific time, divided by the total population. For example, 'The prevalence of HIV infection in several African countries is above 20 per 100 population.'

A person who falls ill adds 1 to the incidence of the disease. He will also add 1 to the prevalence for the duration of his disease, until he either recovers or dies. If the average daily incidence of a disease is  $I$  and the average duration is  $D$  days, then the average prevalence  $P$  will be:

$$P = I \times D$$

Alternatively, expressed in words, 'prevalence is the product of incidence and duration'. Most infectious diseases have such a rapid course that 'prevalence' becomes a rather uninteresting measure. Even disregarding the fact that it would be very difficult to count every individual who had, say, campylobacter diarrhoea in a country on any single day, the seasonal variations are so large as to render prevalence figures rather meaningless. The prevalence of influenza A infection in England can be several per cent in January for certain years, but zero in July.

For chronic or protracted infections, matters become somewhat different. Prevalence figures can be very interesting for hepatitis B carriage, chlamydia infection or HIV infection. For such diseases, the prevalence gives some indication of the risk of exposure to others in the population. For example, if we assume that a person with acute hepatitis B is infectious over a period of 2 months, then the prevalence of individuals who are infectious with hepatitis B at the present time will be equal to the number of carriers plus one-sixth of

the yearly incidence (assuming an even incidence over the year and also including subclinical infections).

When using serology to determine the percentage of a population that shows markers of having had a disease, we often use the term *seroprevalence*. One could argue that this is stretching the term, and that the proportion of a population with markers is really a measure of the cumulative incidence, but it would be cumbersome to put *sero-* in front of that term.

### **Denominator**

The above two definitions highlight a central concept in epidemiology, that when comparing incidence (or prevalence) between two groups one must take into account the size of the groups – the denominator. The incidence of meningococcal meningitis in Sweden is about 1 per 100 000 inhabitants per year, whereas in Denmark it is considerably higher. Since the population of Denmark is about half that of Sweden, the same number of meningitis cases in both countries during a year would mean that the Danish incidence is about twice as high. Three cases of tuberculosis in a small town would give a high local incidence for that town, but may not affect the figure for national incidence very much. Figures given for various events and conditions in epidemiology should always be divided by the number of individuals in the population under consideration.

There is some confusion in the epidemiological literature here. Especially in older texts, incidence and prevalence were taken to be the actual number of cases, regardless of the denominator. The corresponding measures divided by their denominators were then usually called the *incidence rate* and *prevalence rate*. I would discourage the use of these terms, and maintain that figures for incidence and prevalence should only be given with a denominator as above. Such practice encourages awareness of the crucial denominator concept in our epidemiological thinking. Sometimes, this denominator might be implicit. For example, ‘The incidence of reported salmonella in Sweden in 2000 was 4848’ implicitly means ‘per 8.9 million population’, and is thus less satisfactory, since not everyone will know the population of Sweden offhand.

If the denominator cannot even be defined, you should not use the word ‘incidence’ at all. Thus the statement ‘the incidence of gonorrhoea among gay men in London in 1999 was X’ is meaningless, since no one would know the denominator. The correct statement would be ‘there were X cases of gonorrhoea among gay men in London in 1999’.

In real life you will find that practice varies as to whether figures for incidence and prevalence have already been divided by a denominator or not, but it is usually clear from the content which definition is being used. I also believe that practice is gradually moving towards the definitions that I provided above.

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## Population at risk

National statistics on infectious diseases usually give the annual incidence per 100 000 inhabitants, with the population counted at mid-year. In other instances it may be less evident what the denominator should be.

For diseases that could only affect one of the sexes, such as orchitis or salpingitis, the denominator should just include the number of individuals of the respective sex in the population. If the incidence of a disease is expressed by age group, the denominator should be the number of individuals in each age group in the population. This is important, since the size of different age groups may vary considerably.

One recurrent issue in infectious disease epidemiology is whether the incidence for diseases that lead to immunity should have the total population, or just those who have not yet contracted the disease, in the denominator. Since the proportion who are immune is often not known, the former is generally used, but if one does know how many have already had the disease, one should divide by the number of individuals who are still susceptible.

In general, one should strive to include only those who *could* get the disease in the denominator (i.e. the *population at risk*).

## Case fatality rate or lethality

The term 'case fatality rate' is almost exclusively used in infectious disease epidemiology, whilst people outside our field tend to use the term 'lethality' (or inversely the 'rate of survival', which has a more positive ring to it). They both mean the same thing, namely the proportion of people who will die of a certain disease out of those who contract it. For acute infections, one needs some time limit from the start of the illness, and the case fatality rate for measles is thus often measured as those who die within 4–6 weeks after the rash appears.

Figures for the case fatality rate are largely dependent on how many of the milder cases escape diagnosis. The very high figures initially cited for the case fatality rate in haemorrhagic fevers, such as Lassa fever, were probably largely explained by the fact that many of the more benign cases remained undetected by the local health authorities.

## Mortality

This measure indicates what proportion of the entire population die from the disease each year.

In Western Europe a disease such as rabies has a high case fatality rate but low mortality. All of those infected die, but the number of deaths is only a few per year. Conversely, influenza A has a low case fatality rate (most cases survive) but may carry a high mortality. During an influenza epidemic the

percentage of all deaths in the country that are due to influenza can be seen to rise markedly. Since influenza is responsible for a sizeable proportion of all deaths during an epidemic, mortality from all other causes may show a slight temporary decrease.

People frequently talk about ‘mortality’ when they mean ‘case fatality rate’.

## **DEFINITIONS USED IN INFECTIOUS DISEASE EPIDEMIOLOGY**

There are a number of definitions that are chiefly or only used in infectious disease epidemiology. The first concerns the subject itself. What exactly does the term ‘infectious diseases’ encompass?

One could make a distinction such as the following.

- Infectious diseases – all diseases caused by micro-organisms.
- Communicable diseases – diseases that can be transmitted from one infected person to another, directly or indirectly.
- Transmissible diseases – diseases that can be transmitted from one person to another by ‘unnatural’ routes.

In the above, each group is a subset of the previous one.

Legionnaire’s disease and tetanus are examples of diseases that are infectious but not communicable. Measles, influenza and shigellosis are all both infectious and communicable. Creutzfeldt–Jacob’s disease can be passed from one patient to the next via neurosurgical instruments or corneal transplants, neither of which is a ‘natural’ route, and it is thus a transmissible disease. (In this context, it is interesting to note the term ‘sexually transmitted disease’ (STD), which hints at an underlying moralistic conception that sexual contact is a non-natural transmission route. ‘Sexually communicable disease’ (SCD) would be a better term than STD.)

In this book we shall not make any distinction between *infectious* and *communicable* diseases. The John M. Last *Dictionary of Epidemiology* defines infectious disease as follows:<sup>1</sup>

An illness 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.

*Contagious disease* is a slightly obsolete term, but if used nowadays it usually means ‘highly infectious’.

We shall now go on to discuss several other important definitions.

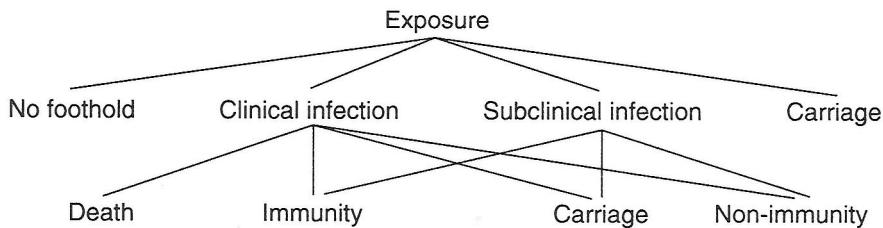
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Someone who has met with an infectious agent in a way that we know from experience may cause disease has been *exposed*. You will immediately notice that this definition is circular, since our concept of exposure will rely on our current biological knowledge of transmission mechanisms. Someone who passes a patient with a salmonella infection in a corridor has not been exposed to salmonella. However, a child who has been playing in the same room as another child with pertussis has been exposed to whooping cough.

If the infectious agent manages to get a foothold in the exposed person, that individual becomes *infected*. Sometimes this will lead to changes that are clinically evident or can be assessed by laboratory tests. The most obvious outcome is that he falls ill (i.e. has a *clinical infection*). Frequently the infected person will not display any symptoms, but can be shown serologically to have reacted to the infectious agent. He has then had a *subclinical* (or *asymptomatic*) *infection*.

Both types of infection can lead to a *carrier state* for some diseases. A carrier harbours the pathogen, and is able to transmit it, but shows no clinical signs of infection. Such a state may be prolonged compared to the acute infection. Examples include hepatitis B and salmonella infections.

The different outcomes of exposure to an infectious agent are shown in Figure 2.1.



**Figure 2.1** The possible outcomes of exposure to an infectious agent.

For a few bacteria a somewhat different carrier state is also possible. The best example is that of staphylococci, which a person might carry on their skin or in their nose and transmit to others. In this carrier state the person is not really infected with the bacteria, but rather they are locally *colonized*.

The two different carrier states are not identical, and should really have two different names.

The role played by subclinical infections and carrier states in the spread of infectious diseases constitutes an important part of modern infectious disease epidemiology, and is one of the phenomena whereby this branch of epidemiology most clearly displays its distinctive traits.

Someone who has contracted an infection (clinical or subclinical) with a certain pathogen – or who has been vaccinated against it – so that he shows no clinical signs of infection on renewed exposure to this pathogen, is said to be *immune*. However, it is sometimes possible to show by laboratory methods that an already immune person has reacted to the exposure with an

increased antibody titre, and this is called a *natural booster*. Those who are not immune to a disease, and who are thus potentially infected by an exposure, are said to be *susceptible*.

An important factor that determines the risk of becoming infected is the *dose* (i.e. the actual number of micro-organisms that are attacking the person). Whereas a low number of bacteria or virus particles may be fended off directly by the body, a massive dose is almost certain to lead to infection in a susceptible individual.

### **What is a case?**

Much of routine infectious disease epidemiology relies on reports of notifiable diseases. Using such figures, cases may be compared over time or between regions and countries. The above graph of possible outcomes following exposure makes it clear that the definition of a case is far from simple.

To be registered as a case in the classical sense, the following criteria have to be met.

1. The patient:

- has to experience symptoms from the infection; and
- has to be ill enough to seek medical care or advice.

2. The physician:

- has to suspect the correct diagnosis; and
- (usually) has to send a sample to the laboratory.

3. The tests in the laboratory:

- must come out positive; and

4. The case must be reported.

Finally, the case must be filed correctly by some central agency.

It is obvious that the number of cases included in regional/national statistics will underestimate the true number of infections to varying degrees for different diseases.

The increasing use of laboratory methods to ascertain subclinical diseases complicates the picture even further. For example, if we start a large screening programme for genital chlamydia infection (which is often asymptomatic), the number of reported chlamydia cases will rise sharply, which might give the impression of a sudden epidemic. Furthermore, for some diseases that are mainly diagnosed by serology, such as hepatitis B and syphilis, there can be ambiguity as to whether the patient represents a new case or just has

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markers of an old infection, and even if they can be shown just to have markers of an old infection, they must still have been a case at some point between conception and the present.

### Attack rate

This is defined as the proportion of individuals who are exposed to an infectious agent who become (clinically) ill. Obviously any calculation of the attack rate will depend on how accurately exposure and disease are measured. If some of the individuals who were exposed were not counted, the calculated attack rate would be too high, and if instead some of the cases were missed, the attack rate would appear too low. Moreover, for most calculations of attack rate one would want to exclude individuals who were exposed and who were already immune to the disease (i.e. only include the population at risk).

### Primary/secondary cases

For infections that are spread from person to person, the individual who brings the disease into a population (where the population can be any defined group of people, such as a school class, a group of restaurant visitors, or even a country) is called the *primary* case. The people who are infected by this individual are called *secondary* cases. If all of the secondary cases are infected at about the same time, then the *tertiary* cases will also appear approximately simultaneously, and we can talk about waves or *generations* of infection.

### Index case

This is the first case to be discovered by the health care system during an outbreak. The finding of this individual leads to an investigation of the outbreak, during which many more cases may be discovered. Often it will be found that there were cases who had fallen ill before the index case was diagnosed.

Thus it is important to note that the index case and the primary case may not be the same person – and in real-life outbreaks they usually are not. However, the terms are frequently used incorrectly.

### Reproductive rate

The potential for a contagious disease to spread from person to person in a population is called the *reproductive rate*. It depends not only on the risk of transmission in a contact, but also on how common contacts are – a person with measles who meets no one will not transmit the infection. In a similar way the average rate of acquisition of new sexual partners in a population will influence the spread of sexually transmitted diseases.

The principal determinants of the reproductive rate are as follows:

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1. the probability of transmission in a contact between an infected individual and a susceptible one;
2. the frequency of contacts in the population;
3. how long an infected person is infectious;
4. the proportion of the population that is already immune.

Point 2 above is really the most interesting from an epidemiological point of view, and also the most frequently overlooked. The spread of infectious diseases depends not only on the properties of the pathogen or the host, but also in at least equal degree on the contact patterns in the society (who meets whom, how often, and what type of contact they have). We shall examine this further in Chapter 11.

### Vector

A vector is an animal, most often an arthropod (e.g. an insect), which picks up the pathogen from an infected person and transmits it to a susceptible individual. The best example is the *Anopheles* mosquito, which is responsible for the spread of malaria.

### Transmission routes

Several different classifications exist for the routes of transmission of different infections. These have been generated mostly for the purpose of grouping similar diseases together in handbooks on preventive measures, and none of them is entirely satisfactory. Common classifications include person-to-person spread, air-borne, water-borne, food-borne and vector-borne infections.

An alternative approach would be simply to divide the infections into those that are transmitted directly and indirectly (see Table 2.1).

Most of the infections in the indirect group can also spread through direct contact. In fact, the diseases that are placed in the ‘indirect’ categories are really just the most infectious ones. If you think about it, there are very few

**Table 2.1** Examples of directly and indirectly transmitted infections

Direct transmission	Indirect transmission
Mucous membrane to mucous membrane – sexually transmitted diseases	Water – hepatitis A
Across placenta – toxoplasmosis	‘Proper’ air-borne – chicken-pox
Transplants, including blood – hepatitis B	Food-borne – salmonella
Skin to skin – herpes type I	Vectors – malaria
Sneezes, coughs – influenza	Objects – scarlet fever (e.g. on toys in a nursery)

infections that could not be transmitted between two people who are as close together as in sexual intercourse. It is only those pathogens that are so weak that they can only spread through this most intimate of contacts that cause what we commonly call sexually transmitted diseases.

The division between sneezes/coughs and ‘proper’ air-borne spread has been made to highlight the fact that for most air-borne infections one has to be reasonably close to the source, whereas an infection such as chicken-pox can actually spread from one room to the next through the ventilation system.

Of course, there are also infections that do not spread from person to person at all. Most of these are caused by bacteria that live in soil or water, such as those responsible for tetanus and Legionnaires’ disease. The epidemiology of such diseases differs very little from that of other illnesses caused by inanimate agents in the environment, such as toxins or radiation.

### **Reservoir vs. source**

A reservoir is an ecological niche where a pathogen lives and multiplies outside humans. For example, freshwater lakes are reservoirs for *Legionella*, voles and other small rodents are probably the reservoir for *Borrelia*, and rodent populations of the Himalayas and Rocky Mountains are reservoirs for *Francisella pestis*.

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

### **Zoonosis**

Zoonoses are infections that can spread from vertebrate animals to humans. Many salmonella infections are zoonoses, as is rabies. Diseases that are spread by insects from person to person, but without a vertebrate reservoir, are not zoonoses.

### **STI**

The term ‘venereal disease’ is not used much nowadays. For the last couple of decades, the term ‘sexually transmitted disease’, or STD, has been the correct one. However, since the epidemiology of infections transmitted during sexual intercourse largely concerns asymptomatic infections rather than diseases, the term STD is now being increasingly replaced by ‘sexually transmitted infection’, or STI, and I shall use this acronym throughout this book.

### **‘Benenson’**

Ever since the First World War, the American Public Health Association has published every five years an updated book with guidelines on the epidemiology and control of a large number of infectious diseases. The title of the

book is the *Control of Communicable Diseases Manual*, but since its editor during the last quarter of the twentieth century was Abraham S. Benenson, it is usually referred to just as Benenson<sup>2</sup>. This book contains a wealth of information, and is indispensable for anyone involved in the practical application of infectious disease epidemiology. Part of its charm stems from the ordering of diseases in strict alphabetical order, so that ‘salmonellosis’ is followed by ‘scabies’ and ‘typhus fever’ by ‘viral warts’.

There are also several definitions of time periods that are important.

### Incubation period

The incubation period is not a fixed number of days for any disease, but rather an interval where the middle values are more common than the extremes, and the actual period is often dependent on the infectious dose (a higher dose usually gives a shorter incubation period). The distribution of incubation periods is often skewed to the left, which means that there will be more people with short incubation times than with long ones, and references usually give the median (or mean) period, plus a minimum and maximum.

The incubation period extends from the moment a person is infected until they develop symptoms of disease. During this time they may be infectious, and in fact for many of the common childhood diseases the period of greatest infectivity is towards the end of the incubation period. This fact has important implications for the control of such diseases, since isolation of cases will often occur too late to prevent spread.

### Serial interval

For diseases that are spread from person to person, the time period between successive generations is called the *serial interval* (or *generation time*). To be exact, this is the time between the appearance of similar symptoms (e.g. rash, cough) in successive generations. Note that if a person is infectious before they develop symptoms, the serial interval will be shorter than the incubation time.

### Infectious period

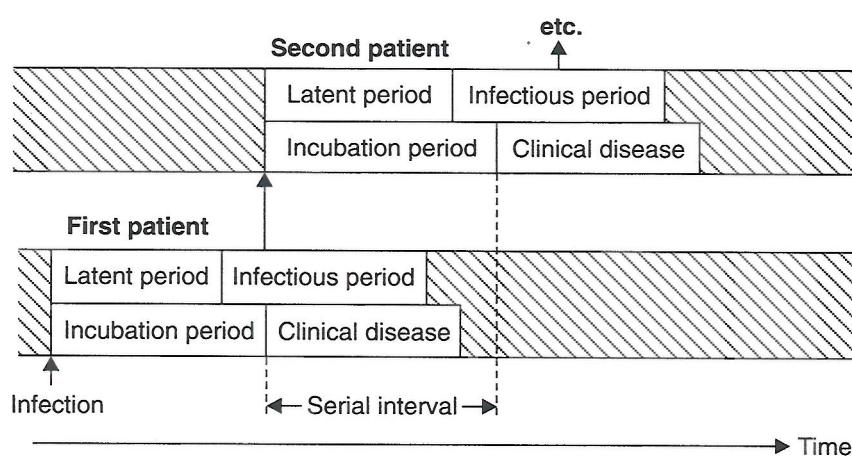
This is the time period during which a person can transmit a disease.

### Latent period

This is the time period from infection until the infectious period starts.

The relationships between all of these time periods are shown in Figure 2.2.

As was pointed out in the previous chapter, a knowledge of these time periods for different diseases is an important diagnostic aid when dealing



**Figure 2.2** The relationships of some important time periods. The patient at the bottom is infected first, and transmits the infection to a second patient.

with individual patients, but it also facilitates tentative diagnoses in outbreak situations. For example, the median incubation time will be much shorter in a calici virus than in a salmonella outbreak. Conversely, if the pathogen that is causing the outbreak is known, knowledge of the incubation time for that disease will make it possible to decide approximately when the exposure must have taken place.

## Epidemic

This is one of the most difficult definitions of all, and many suggestions have been made. My favourite, and one of the shortest, is the one in the *Control of Communicable Diseases Manual*, namely ‘The occurrence in a community or region of cases of an illness (or an outbreak) with a frequency clearly in excess of normal expectancy’. Some people would probably find this definition too wide, and would prefer to include something about a ‘sudden rise in incidence’ or ‘very large number of cases’, while others might want to relate it to the public’s perception of this health problem. There is just no universally useful definition.

The word ‘epidemic’ has an ominous ring to it, and many public health officials prefer to replace it with the more neutral term *outbreak* whenever possible.

When an infectious disease lingers at around the same incidence for a long time, it is called an *endemic*. Many childhood infections may be endemic over a couple of years, only to cause a sudden epidemic every once in a while.

There are also diseases that are endemic in some areas of the world, but which sometimes spread to other places, causing epidemics. The Ganges area is one such endemic area for cholera, a disease that may become epidemic in other places (e.g. Latin America in the early 1990s). In Chapter 11

we shall consider some of the reasons why one disease is endemic and another epidemic.

For the interested reader, the above-mentioned book by John M. Last is a good epidemiological dictionary, and I have tried to adhere to his definitions in this chapter, while adding some personal reflections.

### REFERENCES

1. Last JM. *A Dictionary of Epidemiology*, 2nd edn. Oxford: Oxford University Press, 1988.
2. Chin J (ed.). *Control of Communicable Diseases Manual*, 17th edn. Washington, DC: American Public Health Association, 2000.

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