GLOSSARY

Infectious diseases epidemiology

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In this glossary the authors have reviewed old and new terms contemporarily used in the infectious disease epidemiology. Many of these concepts were established throughout the 19th century and at the beginning of the 20th century (classic terms), however, the meanings of old terms have been revised and new terms are continually being added. This glossary has therefore reviewed the classic and the more recently established terminology defining the most relevant terms contemporarily used in this field.

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Infectious diseases constituted the most serious health issue in the world until the beginning of the 20th century when chronic degenerative diseases began to dominate this scenario in developed countries. Plagues and cholera used to devastate significant proportions of the populations of the great European cities.[1 2]

In his classic *Plagues and Peoples*,[3] McNeill analyses the importance of infectious diseases in the history of humanity and concludes that the role of infectious diseases in the set of factors that defined the course of the historical evolution of human civilisation has been underestimated, and considers that this role was as important as that of economic and military determinants. The importance that the occurrence of these diseases, principally in the form of epidemics, had in forming the dominant political, social, and theological opinion of the different human societies in medieval and modern times was fundamental in the definition and adoption of many of the pathways that led to civilisation.[4] The explosive characteristics and unpredictability of epidemics are a cause of fear, insecurity, and panic even today, as could be clearly seen during the recent SARS epidemic.[5]

The search for explanations regarding the causes of these occurrences has stimulated human imagination throughout the ages and has been the object of reflection of many important thinkers. In ancient times, Hippocrates[6] established the existence of links between the occurrence of diseases and the environment in which populations lived. The idea that some diseases could be transmitted between people (or be contagious) is also old and became the basis for the institution of preventive actions even before the existence and importance of microbian agents had been scientifically proved. In 1546, in Italy, Fracastoro wrote the first theorisation of the concept of the transmission of diseases between people through minute particles.[7] However, it was not scientifically shown before the middle of the 19th century, when Snow's indicated the water used by the population as a possible source of transmission of cholera.[8] However, it was only at the end of the 19th century that the idea of contagion finally overthrew its opponent, the miasmatic theory, in the intellectual battles nurtured by new scientific advances that truly reflected different visions and philosophical perspectives on the world, on society, and on its diseases. The advances in microbiology that took place during that century, particularly the works of Koch and Pasteur, confirmed the role of live microscopic agents as an immediate, fundamental cause of a wide range of morbid entities, thereby provoking profound changes in the understanding of the causes of infectious diseases and the consequent strategies for their prevention.[9–12]

The terminology and concepts used today in epidemiology of infectious diseases (EID) did not evolve from a unified body of ideas or from one single discipline but from a complex set of scientific fields that studied their agents, their causes and determinants, the dynamics of transmission and diffusion of these agents, and their means of prevention. Many of these concepts were established throughout the 19th century and at the beginning of the 20th century (classic concepts), however, the old concepts have been revised and new concepts are continually being added.[13–19] Bearing in mind that in its early phases of development EID constituted epidemiology itself, many of the concepts used in epidemiology are derived from this time. More recently, an inverse phenomenon has taken place in which terms used in EID have originated from other areas of epidemiology or other disciplines. Therefore, this glossary will only define terms contemporarily used in EID.

DEFINITIONS

The unequivocal demonstration in the second half of the 19th century that microscopic beings caused diseases revolutionised existing theories of causality and in subsequent decades the advances resulting from this discovery enabled new concepts to enrich the field of EID, consequently adding numerous new terms to its glossary. *Infectious agent* was the name given to all micro-organisms or macro-organisms capable of producing an infection or an infectious disease (more recently it was found that even some proteins, known as prions, can be infectious). *Infectious disease* (or *communicable disease*) is defined as an illness caused by a specific *infectious agent* or its toxic product that results from 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 inanimate environment.[20] *Infection* is the term that defines the entrance and development of an *infectious agent* in a human or animal body, whether or not it develops into a disease. The detection of this state in which there are no signs of a recognised related disease is called *unapparent infection*. The limits between infection and disease are not always clear and may change with the development of new diagnostic techniques able to detect earlier signs of the action of the infection in the organism or as a result of the discovery confirming a causal relation between a disease and an infectious agent already known (for example, *Helicobacter pylori* as the aetiological agent of peptic ulcer[21 22]).

As soon as the first infectious agent was isolated, a crucial scientific and philosophical problem appeared: the necessity to show the cause-effect relation of specific agents with specific diseases. This concern was elaborated by Jacob Henle and later adapted by Albert Koch, who established the necessity of observing four presuppositions (*Henle-Koch's postulates*[20]) to show a possible cause-effect relation between an aetiological agent and a specific disease. The expansion of biomedical knowledge and the identification of new morbid situations in which the possible involvement of infectious agents was suspected, stimulated a revision of *Henle-Koch's postulates* and, about one century after being written, they were revised in the so called *Evans' postulates*.[23]

Infectious diseases occurrence in human populations could be in *endemic* form (the continuous occurrence at an expected frequency over a certain period of time and in a certain geographical location; when a high level of infection is registered beginning at a young age and predominantly affecting the young population it is called *holoendemic*; and when it equally affects all age groups it is called *hyperendemic*) or in *epidemic* form (the occurrence of a disease that is definitely greater than that expected in a certain geographical region). When the epidemic is generalised and involves different countries and a large population it is called a *pandemic*; on the other hand, when the epidemic is restricted to a small geographical area or population, it is called an *outbreak*; and when the *epidemic* is restricted to a non-human population, it is called an *epizootic*.

The simple or complex organism that is the target of an infecting action of a specific infectious agent was named the *host*. The host that harbours an agent in a mature stage or in a sexually active phase is called the *definitive host* and the host that harbours the agent in a larvae stage or asexual developmental stage is the *intermediate host*.

The ancient idea of contagion (defined as the transmission of an infection from one individual to another—that is, *direct transmission*) was later reviewed as contagion between individuals that could be mediated by different means. This is called *indirect transmission*. This mediator could be the surrounding air (*airborne transmission*), a living being acting as vector (*vector borne transmission*) or even an inanimate object (*vehicle borne*).

Contamination is a situation in which one person or object hosts an infectious agent and thus converts itself into a potential vehicle of dissemination of this agent. Any animate being (insects or other animals) or inanimate substance (water, air, food, soil) that transports an aetiological agent is defined as a *vehicle of dissemination*. When the transmission of an agent is intermediated by an arthropod, this arthropod is called a *vector*. The vector may be simply mechanical—that is, it may merely carry the agent that accidentally contaminated it but it is not fundamental to the perpetuation of the agent, or it may be *biological* when the infectious agent obligatorily requires the vector to pass from one phase to another in its development, meaning that the eradication of this vector may also lead to the suspension of transmission by this agent. *Vectorial capacity* is a property of the vector, measured by means of parameters such as abundance, survival, and house infestation rates, and has a direct influence on the capacity of transmission of an infectious agent.

Reservoir of infection, also called *primary source of infection*, is a location (person, animal, arthropod, plant, soil, or substance) in which the infectious agent finds conditions that permit it to survive and multiply and from where it can be transmitted to another susceptible host.

For the infection of a new host to occur, there must be an opportunity for a susceptible host to be exposed to the infectious agent—that is, there must be *contact* between the agent and the host. This may be direct or indirect depending on the *mode of transmission* of the agent. When this agent is effectively transferred to a new host, there is an *efficient contact*. One of the factors that influence the appearance and seriousness of the illness is the *infective dose*, which is the number of units of the infectious agent required to produce the disease.

The great variation seen between the different infectious agents regarding the period of time between the host becoming infected and developing the disease or becoming a new transmitter of the agent resulted in the need to define these different periods.[24] *Incubation period* is the interval between the effective exposure of the susceptible host to an infectious agent and the appearance of signs and clinical symptoms of the disease in that host (in the field of non-infectious diseases the period between exposure to a specific cause and the appearance of signs and symptoms of the disease is known as the latency or induction period); *latent period* is the time from infection to onset of the ability to infect; *prodromic period* is the time between the perception of illness by the host and the appearance of signs and symptoms based on which a clinical diagnosis of the disease is possible; *communicable period* (or *duration of infectiousness*) is the time interval during which the infected host, ill or not, eliminates an agent to the environment and new susceptible individuals can become infected.

The infectious agent, after establishing itself in a new individual and to assure the survival of its species, needs to constantly find and infect new, susceptible individuals. *Infectivity* is the ability of an infectious agent to cause a new infection in a susceptible host, and in directly transmitted diseases it is measured by the *secondary attack rate*, which is the proportion of susceptible individuals that develop the infection after exposure to a primary case. Nevertheless, when an agent is transmitted to a new host, whether the disease occurs or not depends on many factors in addition to the infection dose, one of the most important being *susceptibility*. Therefore, the success of the invasion of an agent depends on a great number of factors regarding the host, such as age, genetics, sex, race, nutritional status, and previous exposure to this agent that could have resulted in the development of a state of resistance to it—*immunity*. This may be *active immunity*, when the immunity is generated either through infection from an agent or by its vaccine (dead infectious agents, attenuated agents, their fractions or synthetics) or *passive immunity* when the immunity is transferred naturally from mother to fetus or artificially by inoculation of specific protective antibodies. *Natural immunity* refers to the innate immunity of humans or other animal species to specific infectious agents. The proportion of individuals in a population with immunity to a specific infectious agent defines the *herd immunity*, this being one of the principal factors that define the transmission dynamics of most agents—that is, its *diffusibility*—a characteristic that depends on the relation between the agent, the route of transmission, and individual and collective susceptibility.

Infected individuals or animals that do not show clinically recognisable symptoms of a given disease upon examination, but who are hosting the respective aetiological agent, are called *healthy or asymptomatic carriers* and this state may be of short (*temporary or transient carrier*) or long duration (*chronic carrier*). The latter is of great importance to public health because of the capacity that these individuals have to disseminate the disease.[25] Some infectious agents may remain silently in the host for long periods of time without any sign of their presence but may eventually cause disease. This condition is known as *latent infection*.

The greater or lesser capacity of an infectious agent to provoke disease after having infected the host is called *virulence* or the *degree of pathogenicity*, numerically expressed as the ratio of the number of cases of the disease in relation to the total number of individuals infected. A measure very often used is the *case fatality rate*, which is the proportion of deaths in relation to the number of cases of a disease within a specified time.

Whereas the use of mathematical models for understanding the dynamics of infectious diseases has already been in practice for more than a century,[26] in recent times this is an area which has grown in popularity to the extent that it is now often confused with epidemiology of infectious diseases itself.[16] *Mathematical models applied to infectious diseases* may be understood as attempts to use equation systems to represent elements of the dynamics of infectious processes, involving agent, host, and environment.

As any model, mathematical models are useful for forming more or less complete representations of the relations between the different components of a system. Mathematical models are therefore useful not only for studying aspects of this relation but also for verifying whether it changes when subjected to certain effects such as control interventions. Although it is a powerful instrument for analysis, for predicting situations, and even for evaluating the potential capacity of certain interventions to change the likelihood of new cases occurring, the difficulty in transforming the complex situations involved in the process of transmission of many infectious agents into mathematical models is a limitation to their use in many situations. These models study the host-parasite population dynamics—that is, the processes that affect the number of parasites and hosts in the population. The population is divided into three states: susceptibles (S) who can acquire infection; infectives (I) who can transmit infection to susceptibles; and removals (R) who are immune or dead as a consequence of infection. This model of endemic infection is therefore known as the SIR model. In a host population in its first contact with the population of agents, obviously $S = 1$ and I and $R = 0$. As the infection disseminates, S decreases and I increases. A key concept is the *basic reproduction number*[27] (originally named as *basic reproductive ratio* or *rate*[16 19]) (R_0) meaning ''the average number of secondary infections produced when one infected individual is introduced into a host population in which every host is susceptible'' (in the case of microparasitic infections)[19] or ''the average number of offspring (or female offspring in the case of dioecious parasites) produced throughout the reproductive life-span of a mature parasite that survive to maturity in the absence of density-dependent constraints to population growth'' (in the case of macroparasitic infections).[19] There are three basic potential situations related to the R_0 value. If $R_0 = 1$, the number of cases is stable and indicates that the disease is endemic, if $R_0 > 1$ the number of cases is increasing and it will eventually become an epidemic; and if $R_0 < 1$ this means that the number of cases is decreasing.

The development of molecular biology and the intensive use of its methods in the various aspects of the study of infectious diseases have brought a new set of terms to EID. *Molecular epidemiology* would be ''the use of molecular biology techniques in epidemiologic studies''.[20] The application of methods for molecular analysis in biology has permitted identification of traces of the presence or the effects of infectious agents in different substrates. These traces are generically referred to as *biomarkers* and serve to stratify groups and subgroups in which the epidemiological associations are best observed.

The biomarkers may be related to the agents, to exposure, or to the susceptibility of the hosts.[28] The *agent markers* permit refined differentiation among the various strains of a given infectious agent. The *exposure markers* are used to identify the presence or the passage of the agent by verifying the existence of markers of its presence in different body fluids. The *susceptibility markers* define the degree of susceptibility of the organism in relation to infections in general or with respect to one specific infection. Many of the *exposure markers*, such as some antibodies, are also *susceptibility markers*. An important and very useful concept in the context of new vaccines development is that of *correlates of protection* or *immunological markers of protection*, meaning a measurable immunological parameter (usually an antibody) that correlates with protection against disease.[29]

In recent years, the registration and perception of important changes in the pattern of occurrence of infectious diseases or in the transmission dynamics of their agents has stimulated intense reflection on the factors involved in this process. In 1992 the term *emerging infectious diseases* was defined to refer to ''clinically distinct conditions whose incidence in humans has increased''.[30] In addition, *reemergence* was defined in this publication to describe ''the reappearance of a known disease after a decline in its incidence''.[30] It is important to emphasise that the term *emergence* when referring to infectious diseases, specifically to viruses, had already been used in previous publications,[31 32] while Drotman[33] considered that it was Joshua Lederberg who coined the term *emerging infectious diseases*.

Later, *emerging infectious diseases* was defined as ''diseases of infectious origin whose incidence in humans has increased within the past two decades or threatens to increase in the near future''.[34] In 2003, the Institute of Medicine published an update of a document from 1992 and defined *emerging infectious diseases* as ''either a newly recognized, clinically distinct infectious disease, or a known infectious disease whose reported incidence is increasing in a given place or among a specific population''.[35] Therefore, this update makes the concept more precise from a spatial viewpoint; nevertheless, the imprecision regarding which parameter of magnitude of the incidence should be considered in order to define an infectious disease as an emerging one still persists. Moreover, it should be noted that this definition does not distinguish *emergence* from *reemergence*.

It is worth mentioning a different line adopted by Grmek,[36] in 1993, who associated *emerging disease* to five different conditions: (a) the disease existed before being identified but was overlooked from a medical point of view because it could not be conceptualised as a nosological entity; (b) the disease existed but was not detected until there was a quantitative or qualitative change in its manifestations, for example, until the occurrence of an outbreak or an increase in its lethality; (c) the disease did not exist in a particular region of the world before it was brought there from another region; (d) the disease never existed in a human population but existed in an animal population; (e) the disease is completely new—the causal agent and/or the necessary environmental conditions did not exist before the first clinical manifestations. This makes the characterisation of an infectious disease as emergent more precise and contextualises it with regard to

population, territory, and to the historical time in which it occurs.

In contrast with the situation in the developed countries, in the context of the developing world, the *emerging* and *re-emerging infectious diseases* were an addition to an epidemiological profile in which infectious diseases still had great importance in the morbidity and mortality rates of the population. Consequently, to denominate these highly prevalent infections and diseases simply as *old* is insufficient and we proposed to denominate them as *remaining* (or *persistent*) *infectious diseases*.[37 38]

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