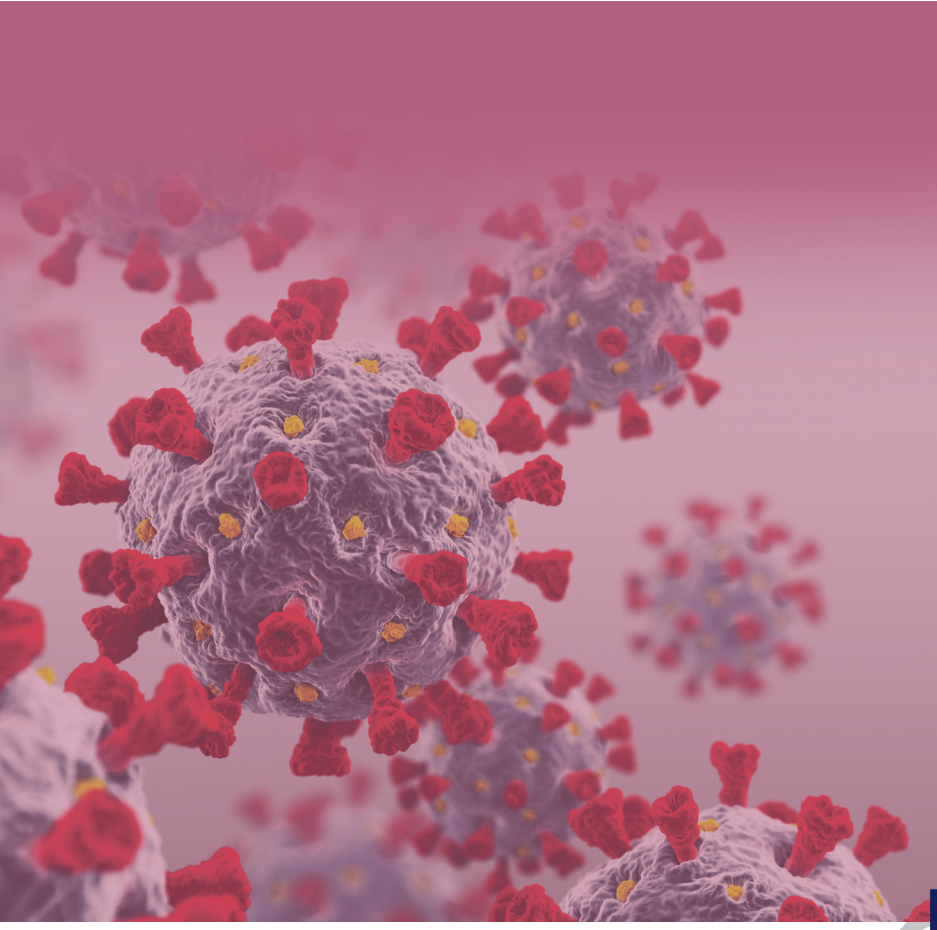

Chapter I

INTRODUCTION

Dragan Lepur, Lorna Stemberger Marić

1. THE IMPORTANCE OF INFECTIOUS DISEASES

Thanks to their prompt effect on the epidemiological situation in developed countries during the 20th century, the discovery of antimicrobials and vaccinology misled us to the naive conclusion that the threat generated by infectious diseases has been eliminated. These predictions and conclusions were beyond optimistic, as new challenges had already arisen towards the end of the 20th century. Despite the development of diagnostic methods, antimicrobial therapy, and new vaccines, infectious diseases have had a significant global influence – even in the 21st century.

Poverty, hunger, lack of fresh water, and associated infectious diseases remain a global problem without an imminent solution. For instance, one in every three African children diagnosed with pneumonia is treated with antimicrobials. In contrast, infections in immunocompromised patients, nosocomial infections, and infections in the elderly also represent major issues and require significant resources in developed countries. If we also consider the global political instability, continuous military conflicts, major population migrations and the (consequent) high risk of (bio)terrorism, it is obvious that we are far from 'defeating' infectious diseases.

Except for a few minor changes, infectious diseases remain among the top ten leading causes of death worldwide, especially in developing countries. Among them, the most significant diseases are respiratory infections (pneumonia), diarrhoeal diseases, and tuberculosis, followed by human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and malaria, as well as preventable diseases such as measles and tetanus (Tables I-1 and I-2). It should be mentioned that HIV is no longer among the top 10 causes of death in the world.

The constant presence of emerging and re-emerging infectious diseases, especially the HIV pandemic in developing countries, poses a special challenge for the treatment of infectious diseases in the 21st century.

Table I-1. Leading causes of death worldwide in 2016.

Disease	Numbers of deaths (millions)	Number of deaths/100,000 population
1. Ischaemic heart disease	9.43	126
2. Stroke	5.78	77
3. Chronic obstructive pulmonary disease	3.04	41
4. Lower respiratory tract infections	3.0	40
5. Alzheimer disease and other dementias	1.99	27
6. Cancers of the trachea, bronchi, and lungs	1.71	23
7. Diabetes mellitus	1.59	21
8. Traffic accidents	1.40	19
9. Diarrhoeal disease	1.38	19
10. Tuberculosis	1.29	17

Table I-2. Leading causes of death in developing countries in 2016.

Disease	Number of deaths/100,000 population
1. Infections of the lower respiratory tract	75.8
2. Diarrhoeal disease	58.2
3. Ischaemic heart disease	52.9
4. Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)	44.3
5. Stroke	42.2
6. Malaria	37.6
7. Tuberculosis	34.3
8. Complications associated with premature birth	32.2
9. Perinatal asphyxia and trauma	30.5
10. Traffic accidents	29.4

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1.1. Emerging and re-emerging infectious diseases

In addition to established, current infectious diseases with well-known incidence and prevalence, the persistent threat generated by emerging and re-emerging infections is also well documented. **Emerging** infections are defined as previously unknown diseases – the most popular example being HIV. The most recent (August 2020) paradigm of emerging disease is the 2019 novel coronavirus (COVID-19; Coronavirus disease - 2019) pandemic, which emerged in Wuhan, Hubei, China. **Re-emerging** infections are well-known diseases appearing after a period of absence, usually in more severe and virulent forms than before and in modified epidemiological circumstances. Influenza A pandemics appearing every 30–40 years are a prototype of re-emerging infections. A couple of years ago (February 2016), the Zika virus epidemic re-emerged, originating from Southern and Middle America. The virus is spread via mosquito bites and causes microcephaly in children born to mothers who were infected by the virus during pregnancy.

The HIV pandemic, which appeared during the last two decades of the 20th century, sparked pessimistic forecasts, which, thanks to antiretroviral therapy (ART), did not become a reality. Furthermore, the number of deaths associated with HIV/AIDS is in constant decline. Even so, HIV remains a major global issue and accounts for 1.1 million deaths worldwide each year. Moreover, only two-thirds of HIV-positive child-bearing women in developing countries are treated with antiretroviral medicines to prevent vertical transmission of the disease. As with HIV/AIDS, malaria has also lower mortality rates than earlier; its incidence has declined by 37% in the last 15 years and the mortality risk has declined by 60% due to preventive measures and treatment.

1.2. Infectious causes of chronic and malignant diseases

The association between infectious diseases and various chronic and malignant diseases has been suspected for a very long time, although, in most cases, it has never been confirmed. Most of these infectious agents account for a large number of chronic illnesses that cause significant public health issues on a global scale (e.g., chronic hepatitis B and C and human papillomavirus [HPV]). For most of these diseases, preventive measures do exist (immunisation, treatment of the existing infection), but these are not universally available, resulting in a large number of malignant diseases due to these organisms in the long term. Table I-3 displays infectious agents and the associated chronic/neoplastic diseases. An estimated 18% of all malignant neoplasms are directly or indirectly associated with various infections with other potential causes whose relationships remain unproven. According to some estimates, infections are second only to smoking among the causes of malignant disease. The incidence of some tumours of viral origin is increasing noticeably; for example, planocellular carcinoma of the oropharynx is associated with HPV infection.

In some instances, microorganisms directly cause malignant diseases, while in other cases they are only partially involved, such as weakening the immune system, consequently allowing the expression of oncogenes. The details of these mechanisms and of oncogenic transformation are not well understood; however, tumorigenesis probably requires more than just infection alone. Other factors such as immunosuppression, somatic mutations, genetic predisposition, and carcinogen exposure may also be necessary, and their roles vary according to the causative agents and the specific tumours.

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Table I-3. Examples of chronic and malignant diseases caused by infections

Causative agent	Disease
Bacteria	
Helicobacter pylori	Peptic ulcer disease, carcinoma, and lymphoma of the stomach
Tropheryma whipplei	Whipple disease
Borrelia burgdorferi	Chronic arthritis
Viruses	
Human papillomavirus (types 16,18,31,33,45,52, and 58)	Carcinoma of the cervix, vulva, vagina, anus, and oropharynx
Human papillomavirus (types 6 and 11)	Genital warts
Hepatitis B and C virus	Hepatocellular carcinoma
Epstein–Barr virus (EBV)	Burkitt lymphoma, nasopharyngeal carcinoma
Human immunodeficiency virus (HIV)	Lymphomas, Kaposi sarcoma
Human T-lymphotropic virus (HTLV) type 1	T-cell leukaemia and T-cell lymphoma in adults
Human herpes virus 8 (HHV-8)	Kaposi sarcoma
Parasites	
Schistosoma haematobium	Urinary bladder carcinoma
Opisthorchis viverrini	Cholangiocarcinoma
Clonorchis sinensis	Cholangiocarcinoma

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Oncogenes can cause changes to cell membranes that result in tumorigenesis. While chronic viral infections (e.g., hepatitis C) disable cell regeneration, other processes following such infections also confer oncogenic potential, including resistance to insulin, oxidative stress, and steatosis. Some bacteria and parasites stimulate oncogenesis via antigens and toxins or by the release of hormones such as oestrogen, whose metabolites have a high affinity for host cell DNA. HIV is the most well-known causative agent of strong immunosuppression that predisposes malignoma formation (e.g., lymphoma)

In conclusion, the main characteristic of oncogenic microbes is the potential to establish chronic infections, which may result in malignant transformation via various mechanisms.

The infectious causes of malignancies are, in most cases, preventable or treatable; thus, the availability and quality of health care are of crucial importance in preventing these diseases. Although the benefit of immunisation, screening, and treatment of potentially oncogenic infections is unquestionable, these procedures, as well as improvements in sanitary conditions, remain unavailable to most patients.

1.3. Systemic diseases caused by infections of the oral cavity

The importance of oral, especially odontogenic, infections, has long been recognised and forms the basis for the theory of focal infection that was especially popular during the 19th and a large part of the 20th centuries. Since diagnostic methods were relatively modest during

Table I-4. Pathogenic mechanisms by which commensal microorganisms in the oral cavity cause systemic diseases

Pathogenic mechanism	Systemic disease
Metastatic infections due to bacteraemia	• Subacute infective endocarditis • Acute bacterial myopericarditis • Brain abscess, lung abscess • Septic thrombosis of the cavernous sinus • Sinusitis, orbital cellulitis • Osteomyelitis, septic arthritis
Circulating bacterial toxins	• Stroke, acute myocardial infarction • Fever of unknown origin (FUO) • Toxic shock syndrome (TSS) • Low birth weight
Circulating immune complexes	• Behçet's disease • Crohn's disease • Chronic urticaria • Uveitis (iridocyclitis)

this time, most teeth were extracted without solid indication or proof of infection. As this method did not lead to regression of systemic diseases, it was ultimately abandoned.

Thanks to numerous epidemiological, microbiological, and clinical studies, our understanding of the importance of oral infections today is more realistic and rational. It is well known that bacteria that are part of the oral flora, in addition to bacterial products, their components, and immune complexes, can easily enter the bloodstream to cause bacteraemia. Inadequate oral hygiene results in a tenfold increase in the number of bacterial colonies, which, combined with disrupted physical, electrical, and immune barriers, predisposes patients to (usually) gram-negative anaerobic bacteraemia.

However, dissemination of bacteria via the bloodstream with consequent formation of distant infectious foci (endocarditis, lung or brain abscess, osteomyelitis) is not the only mechanism associated with oral infections and systemic diseases and conditions. Bacterial exotoxins and/or endotoxins (products of bacterial decomposition) can enter the bloodstream and induce inflammatory reactions. Moreover, parts of microorganisms can enter the bloodstream and, after binding to antibodies, create macromolecular complexes (immune complexes) that cause various acute and chronic inflammatory reactions (Table I-4).

In this context, the most important diseases are periodontal infections; more specifically, periodontitis, which is the most common infection of the oral cavity. Unfortunately, periodontitis does not receive much-needed attention due to its minimal symptomatology and duration. Periodontitis caused by a pathogen originating from dental plaques, most commonly *Aggregatobacter* (*Actinobacillus) actinomycetemcomitans, Porphyromonas gingivalis,* and *Bacteroides forsythus.* It is also related to other systemic diseases because of some common risk factors (tobacco smoking, stress, old age) and the subgingival biofilm, which serves as an active source of gram-negative bacteraemia and inflammatory mediators.

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Frequent bacteraemia and endotoxaemia cause vascular responses, including inflammatory infiltrates in vascular walls, proliferation of smooth muscles in vascular walls, vascular fatty degeneration, and intravascular coagulation. Endotoxaemia (LPS; lipopolysaccharide) causes and promotes the synthesis of interleukin-1 (IL-1), tumour necrosis factor (TNF-α), and thromboxane-A2 (TXA_2), resulting in an inflammatory reaction, aggregation of thrombocytes, and accumulation of lipids and cholesterol in blood vessels, which is the foundation of cardiovascular and cerebrovascular diseases. The periodontium also contains high concentrations of proinflammatory cytokines (TNF-α, IL-1β), gamma-interferons, and prostaglandins (PGE_2), which can also enter the bloodstream to promote thrombus formation. One example is the correlation between poor oral hygiene and the incidence of stroke. The activity of the aforementioned inflammatory mediators is also correlated with preterm childbirth and low birth weight (<2500 g), and periodontitis alone is an independent risk factor for preterm childbirth.

The pathogenesis of infective endocarditis is explained in a similar way and almost always occurs on damaged or changed heart valves. Endocarditis is most probably caused after multiple episodes of bacteraemia accompanied by hypercoagulability, resulting in damage to the endothelium, aggregation of thrombocytes, and nonbacterial thrombotic endocarditis (NBTE). During later bacteraemia, virulent pathogens more easily adhere to and colonise the pre-conditioned valves, resulting in severe endovascular infection.

In addition to inhalation and haematogenous dissemination, aspiration is one of the most important mechanisms involved in the pathogenesis of pneumonia. Aspiration pneumonia usually develops in conditioned patients (elderly patients, patients with diabetes mellitus, tobacco users, patients on mechanical ventilation, patients with psycho-organic syndrome, or immobile patients) by aspiration of oropharyngeal secretions. The most common causative agents include *A. actinomycetemcomitans, Actinomyces israelii, Capnocytophaga* spp., *Eikenella corrodens, Prevotella intermedia*, and *Streptococcus constellatus*. Patients with poor oral hygiene have a higher incidence and die more commonly of aspiration pneumonia.

Furthermore, the connection between periodontitis and diabetes mellitus is also well known. Diabetes is a risk factor for severe periodontitis and vice versa, because periodontitis aggravates the regulation of glycaemia in patients with diabetes and further aggravates the disease. Treatment of periodontitis (mechanical and antimicrobial) usually contributes to better glycaemic control, which indicates the importance of oral hygiene and oral infections in patients with diabetes.

2. EPIDEMIOLOGY OF INFECTIOUS DISEASES

During the 20th century, human life expectancy has increased in developed countries, from 50 to 80 years. This increase is related to multiple factors including the decline of morbidity and lethality from infectious diseases. This is mostly because of improvement in sanitary and hygienic conditions; and in the socioeconomic status. The development of effective vaccines has significantly reduced the incidence of infectious diseases, and the discovery of antimicrobials has allowed the successful treatment of otherwise fatal infections. Although a number of diseases have been practically eradicated thanks to vaccination (diphtheria, poliomyelitis), certain diseases

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(e.g. measles) occasionally cause epidemics in developed countries, serving as a reminder of the importance of proper immunisation coverage and a coordinated approach in disease control, ranging from prompt identification to epidemiologic service notification and urgent interventions directed against the epidemic.

The most important infectious diseases today in terms of mortality are acute infections of the lower respiratory tract, tuberculosis, diarrhoeal diseases, HIV/AIDS, malaria, measles, hepatitis B, pertussis, neonatal tetanus, and haemorrhagic fevers. In developed countries, mortality due to infectious diseases is low thanks to improvements in living standards and advances in medicine and public health. However, the structure of mortality caused by infectious diseases has been unchanged in the last few years. Individuals still die from active tuberculosis, influenza (lethality 0.01%), pneumonia, bacterial meningitis, leptospirosis, salmonellosis, AIDS, gastrointestinal infections, encephalitis, legionellosis, tetanus, and hepatitis B.

Among infectious diseases, acute respiratory infections are the leading cause of mortality worldwide. Even though infection of any part of the respiratory system may have fatal outcomes, it is most commonly associated with pneumonia in patients younger than 5 and older than 65 years old.

Mortality due to gastrointestinal infections is highest among children in developing countries. The most common causative agents are rotaviruses, enterotoxic *Escherichia coli* (ETEC), *Shigella*, and *Campylobacter*. Among children in developed countries, rotaviruses are an important cause of diarrhoea and hospital admission. The rising importance of gastrointestinal infectious diseases is linked with food trade, climate change, a larger number of immunocompromised patients, and travel to different parts of the world.

The 2014 Ebola epidemic highlighted a global epidemiological effort to contain this dangerous infectious disease. In 2015, intense preparations were also made for MERS-CoV (*Middle East Respiratory Syndrome-Coronavirus*) infection, for *Zika virus* at the end of 2015, as well as for COVID-19 in January 2020.

While, for centuries, humankind was troubled by epidemics caused by the plague, cholera, typhus, smallpox, influenza, and other diseases, the larger current epidemiologic problem is the increase in the number of microorganisms resistant to antimicrobial drugs. Multi-drug resistant *Mycobacterium tuberculosis, Streptococcus pneumoniae, Staphylococcus aureus, Neisseria gonorrhoeae, Plasmodium falciparum,* etc. have emerged. This phenomenon can be explained by demographic changes, changes in human behaviour, the influence of industrialisation, economic development and changes in the exploitation of the environment, increased international travel and transport of trade goods, adaptation and changes of causative agents, and negligence of proper public health measures. Important changes have occurred regarding environmental factors, host characteristics, and causative agents, all of which together play an important role in the emergence of infectious diseases.

Recently, changes have been noted in the pattern of infectious disease emergence and the dynamics of their transmission, suggesting changes in the appearance of emerging and re-emerging diseases. These diseases are usually caused by extremely pathogenic microorganisms, usually drug-resistant, which can be usually found on the list of microorganisms that could be used as weapons of bioterrorism. Between 1940 and 2004, 335 emerging diseases were registered. More than 70% of emerging and re-emerging diseases are zoonoses and vector-borne infectious diseases. Zoonoses are diseases transmitted from domestic and wild animals to

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humans. Emerging diseases are narrowly linked to socioeconomic and ecological factors and have an important effect on public health and global economy. Factors that may influence the appearance and evolution of emerging diseases include demographic changes, climate changes, tourism and international travelling, the ability of microorganisms to adapt to new conditions, and inadequate utilisation of public health measures during natural disasters and warfare. Although these diseases are highly contagious and dangerous, most of them have no specific cure.

2.1. Basic epidemiological terms in infectious diseases

Soon after the isolation of the first infectious agent, challenges arose regarding the determination of causative relationships between the agent and the disease. Therefore, Henle and Koch defined the Henle-Koch postulates, four conditions that determine possible causative relationships between the agent and the disease (Table I-5).

Infectious diseases in humans can appear in an *endemic form* (continuous appearance in an expected frequency over a certain time period over a specific geographical area) or *epidemic form* (a frequency larger than expected in a certain time period over a specific geographical area). To declare an epidemic, the normal incidence of a disease is the key parameter. A large number of individuals infected with a common infectious agent does not necessarily indicate an epidemic; however, a relatively small number of people infected with a very rare infectious disease may be declared an epidemic. A *pandemic* is defined as an infectious disease that spreads over a large number of countries or continents and infects an exceptionally large number of people. An epidemic limited to a small geographical area or a small population is called a local epidemic or outbreak.

Table I-5. Henle-Koch postulates

1	The same agent must be found in every case of the disease.
2	The agent should be isolated and ocultured in the laboratory.
3	The agent must be able to produce the disease in experimental animals.
4	The agent should be recovered from the experimental animal.

The organism in which a specific microorganism resides is called the *host*. The host that contains the causative microorganism in its mature or sexually active stage is called the *definitive* host, while a host containing the causative microorganism in its larval or asexual stage is called an *intermediate* host.

In the event of an epidemic, identifying the source of infection is of utmost importance. Looking backward at the chain of transmission, we usually arrive at the *reservoir* and the *source of infection*. The reservoir of the infection is the primary habitat of the infective agent, where it lives and multiplies in quantities sufficient for transmission to a susceptible host. To secure the survival of its species, the infective agent must continually search for and infect new, non-immune organisms.

The *primary*, or so-called *index case* is the first recognised case of the disease, identified at the start of the epidemic. The time period between the onset of symptoms of the index and secondary cases—the time period necessary for the index case to generate the next group of patients— is defined as the *infective period.*

The *reproductive rate of infection* is the average number of new cases during the infective period. The traditional idea of *infection*, defined as the spread of disease from one organism to another via direct transmission, was later re-

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vised to include the possibility of transmission via various means (indirect transmission). The *routes of transmission* are the means by which the pathogen crosses from its source to a vulnerable host. These routes depend on the pathogen and host characteristics. *Direct transmission* is accomplished through close contacts (touch, bite, kiss, sexual intercourse) or by direct exposure of the eyes, nose or mouth to infected droplets (mostly at a distance of up to 1,5 meters). *Vertical transmission* is a special form of direct transmission from mother to child during pregnancy or childbirth. A disease may also be transmitted *indirectly* from the source via an object (toys, clothing, utensils, medical equipment, water, food, blood products) or insects (vectors). A vector can be a mechanical carrier and hold no importance in the development of the infective microorganism or may be a biological carrier, in which case the microorganism requires the vector for development. Extermination of the vector can result in the eradication of the disease carried by the vector (e.g., mosquitoes and malaria). An aerosol is a suspension of tiny solid or liquid particles that contain parts of, or the entire microorganisms that may persist in the air for a longer period of time. Viruses are especially easily transmitted by this route (e.g., measles).

For infection to occur in a new host, *exposure of a non-immune host* to the infective agent must occur. Successful transfer to a new host requires *effective contact. Infectivity* is the ability of a pathogen to establish infection in a susceptible host. In directly transferable diseases, infectivity is measured by the ability to cause secondary infections, which reflects the percentage of non-immune hosts that are infected after exposure to the index case.

The *infective dose* is one of the factors that determines the disease incidence and severity and marks the required number of agents needed for the disease to occur. While some infectious diseases require just a single agent (e.g. *Coxiella burnetii*), other infective doses are measured in the hundreds of thousands (e.g., salmonellosis). Among multiple factors that determine if the disease will clinically manifest after being successfully transmitted, host *susceptibility* is the most important. A susceptible individual is a member of the population that is at risk of infection due to their non-immune status, while the *source of infection* is the place from which infection stems. The source can be *endogenous* (e.g., the host's own endogenous commensal flora) or *exogenous* (outside of the organism). Onset of the disease also depends on host factors including age, genetic predisposition, sex, race, nutritional status, and previous contact with the same agent that may result in resistance or immunity.

Immunity can be *active*, developing after the patient recovers from infection (natural) or by vaccination, or *passive*, developing by transfer of mother's antibodies to the foetus during pregnancy (natural) or by parenteral application of protective antibodies (artificial).

The percentage of individuals in a population that is immune to a specific infective agent represents *collective immunity,* which is one of the main factors defining the dynamic of microorganism transfer. Collective immunity appears when vaccination of a considerable percentage of the population offers protection even to individuals who have not developed immunity. It is assumed that the chain of transmission is broken when most of the population is immune or less susceptible to the disease (the causative agent does not 'circulate' among the populace).

Other than *patients*, disease can also be transmitted from an infected person without any clinical symptom of the disease but who is still a carrier. These persons are called *healthy* or *asymptomatic carriers.* Prolonged carrier status is a public health issue because of the risk of

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further spread of the disease. Additionally, some agents can cause *latent infection* and persist in the host for a long period and still cause disease after a certain amount of time.

The *mortality rate* is the proportion of the number of deaths in relation to the number of ill people over a certain time span.

3. BASIC TERMS AND DEFINITIONS

Contamination refers to the accidental input of infectious material such as bacteria, fungi, moulds, viruses, prions, parasites, their toxins, or other products into biological material. It does not require interaction between the microorganism and the host; thus, it is not labelled as an infection but merely as coexistence (*commensalism*) of the microorganism and the host.

Colonisation is the first phase in the microorganism-host relationship and marks the invasion of the microbe in the host and the beginning of the microorganism's population process. This usually happens on bodily surfaces, which the microorganism uses as the location of entry into the host (mucosa of the respiratory, gastrointestinal, and urogenital systems and also the skin). Colonisation is a process that begins immediately after birth and results in the formation of the so-called normal (saprophytic) flora that is most abundant in the bowel, mouth and on the skin.

The *saprophytic flora* consists of bacteria that do not multiply in a living organism during normal conditions but that live on its surfaces and feed on cell detritus. They usually do not cause disease in immunocompetent hosts, although some microorganisms may cause damage via the toxins they excrete.

The *carrier state* can be a chronic infection due to the ineffectiveness of the defensive mechanisms in eliminating pathogens; as such, the infected individual becomes a reservoir and can transfer microorganisms to other (non-immune) individuals. This type of infection develops after the patient recovers from the disease (e.g., hepatitis B) and lasts for the remaining life span without endangering the host. The carrier state can also follow after recovery from an infectious disease and may disappear after some time. That is the so-called reconvalescent carrier state, which is common after infectious diarrhoea (e.g. *Campylobacter, Salmonella enteritidis*, rotavirus). Furthermore, the carrier state does not have to follow an infectious disease at all but can emerge as its own an entity (e.g., a meningococcal carrier state which may evolve into an active disease but does stimulate specific immunity). In addition, a carrier state can exist without infection but merely as colonisation of bodily surfaces, which does not stimulate formation of immunity in the host (e.g., non-typeable *Haemophilus*, *S. aureus*). Although carriers are a source of microorganisms and have the potential to spread them to others, some strains cause only a carrier state and differ from infectious strains. These are generally less invasive strains, and it is uncertain if they cause disease in immunocompetent hosts (e.g., *S. pyogenes*). The duration of the carrier state may be temporary, periodic (intermittent), or permanent (persistent).

Parasitism refers to the presence of microorganisms that exploit the host as a source of nutrients.

Pathogenicity is the ability of a microorganism to penetrate into the human organism, remain and multiply, and finally disseminate via the blood and lymph throughout the body and cause disease. The pathogenicity of an organism, namely its ability to cause disease, is determined by virulence factors. Pathogenic microorganisms are microorganisms that cause

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