Viorel PRISACARU

GENERAL EPIDEMIOLOGY WITH MEDICINE BASED ON EVIDENCE

CHIŞINĂU - 2015

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General Epidemiology with medicine based on evidence

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The book concerns such subjects as the mechanisms of emergence and spread of pathological phenomena in human population and measures of their prevention and control. Particular attention is given to the method of epidemiological studies in infectious and noninfectious diseases and the use of principles medicine of based on evidence in decisions making and assessing the effectiveness and safety measures for prevention and control of human diseases, including diagnosis and treatment. It contains elements of classical epidemiology, clinical epidemiology, epidemiological bioethics and health promotion.

The book is intended for students, physicians, residents, and physicians of all specialties interested in making correct decisions and evaluation of diseases.

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"The belief root is experience"
(Nicolae Iorga)

INTRODUCTION

The epidemiology departments train medical specialists in a wide range of epidemiological knowledge and practices - epidemiology of infectious and noninfectious diseases, according to the Bologna process. They will be able to detect the causes, risk factors and mechanism of formation (spread) of morbidity in the human population, develop and interfere with effective measures to prevent and combat human diseases.

Epidemiological research method has proved to be useful in all fields of medicine, including diagnosis and treatment efficiency, and now is considered a basic tool in medicine by evidence.

Depending on the field of application of epidemiological research method, arose various branches of epidemiology, such as clinical epidemiology, epidemiology of disasters, ecological epidemiology, molecular epidemiology, regional and global epidemiology etc.

An important element of contemporary epidemiology is epidemiological diagnosis at the population level. The duty of clinician (therapist, surgeon, etc.) is to ascertain the diagnosis of disease and to treat the patient, on the other hand the epidemiologists' duty is to diagnose pathology in population (community) and to take measures for its recovery.

Another element that was implemented very quickly in contemporary epidemiological theory and practice is the notion of epidemiological surveillance of public health, which requires refinement of both surveillance and control of infectious and non-infectious diseases.

Epidemiological surveys are increasingly effectively used in early screening and elaboration of measures to prevent infectious and noninfectious diseases. In this regard, appeared concepts of primary, secondary and tertiary prevention. Currently, the curative activity of specialists, in addition to knowing the natural determination of forming human population morbidity and tactics of intervention measures to prevent and combat significantly increased necessity properties of epidemiological aspects relating directly or indirectly to the curative process. First, this element is objective assessment, of evidence-based medicine through the criteria, the main means and methods of diagnosis and treatment. It is proved that the medicine is the evidence of successful joint result of different methods of assessment: epidemiological and clinical.

A special attention is given to specific epidemiological research methodology, methods and means of prevention and control of diseases at contemporary level.

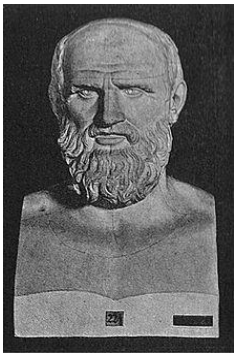
Bibliographic studies and the author's experience in epidemiology over than 30 years were considered in writing this manual.

I would like to express my gratitude and to thank prof. Dr. Aurel Ivan, prof. Dr. Constantin Ciufecu, prof. Dr. John Stelian Bocşan, Dr., assoc. Prof. Irina Brumboiu, Dr. Vasile Turcan, Dr. Vasile Sofrony for the generous contribution to this textbook writing, Mr. Nicolae Prodan, PhD, associate professor (USM) for consulting the chapter "The statistical method of research".

HISTORY AND TRANSFORMATION OF EPIDEMIOLOGY

Epidemiology was born in antiquity, because of the necessity to study epidemics and to explain the essence of these phenomena. The concept of epidemic means nothing else that manifestations of the morbidity in population. Thus, the ancient people spoke about the epidemics of smallpox, plague, malaria, scurvy, pellagra, etc., which usually were widespread among people, and were characterized by high morbidity and mortality. Because at that time the etiology of this phenomenon was not known, they were considered as negative events, invasions or misfortunes fallen on the people (from the Greek words epi - over; demos - people) and this is the origin of the name epidemic. After attaching the prefix *logos* (science) was formed the word *epidemiology* - the science of epidemics, that is the science trying to descovery the objective causes producing the disease or science explaining what is happening to people's health.

As a historical document of great value, proving the existence of epidemiology as a science, serve treatises of Hippocrates (460-377 BC), these seven books about epidemics influenced by previous experience in fighting against the epidemic. Hippocrates rightly can be considered the father of epidemiology.



• Hipocrate

Development stages of epidemiology as a science are conditioned by the development of the society, of all the sciences, including medicine, biology, mathematics, etc. and of course, the development of epidemiological methods of the study about the essence of epidemics.

In the ancient world, miasmatic hypothesis was formulated regarding the causation of epidemics. According to this hypothesis, epidemics occur after entry into the body miasmas, which means harmful substances such as gas emanations which appeared in the air as a result of volcanic elimination, earthquakes or the appearance of comets.

Thereafter, based on a comparison of time and place of the occurrence of epidemics, as well as showing the constitutional character of their hypothesis was formulated by hypothesis of epidemics. According to this hypothesis, epidemics occur in certain places and seasons and are related to the structure of the natural environment (physical geography, flora and fauna, climate) as well as to the human population characteristics from the respective environment.

Hypothesis of epidemics, mostly observational, receives descriptive and analytical meanings at the Hippocratic stage, but the relationships between

causality and disease are explained on the objective and material base as well. As an eloquent argument serves the work of Hippocrates "On Air, Water and Places". The Hippocratic era marked a major step toward the scientific approach to the concept of health and disease, and prevention was raised to the rank of doctrine. Thereby health and disease are determined by natural and social structures of the human ecosystem, Hippocratic School paved the way to knowledge and acceptance of the causes and mechanisms of disease occurrence, which were seen as a result of the imbalance of the internal environment, human relationships due to its conditions of life, natural and social laws (A. Ivan).

Thus, during the Hippocratic period there were attempts to identify the endogenous and exogenous factors, such as the risk of consumption of contaminated water, danger of polluting residues etc. These observations served as a reason to build the facilities to supply with drinking water and other sanitation measures in Rome.

Miasmatic-constitutional hypothesis is based mainly on observational method and description of phenomena. This method prevailed until the XVII-XVIII centuries.

Thomas Sydenham

One of the exponents of the miasmatic-constitutional hypothesis that explained the essence of epidemics in that period was the illustrious English physician Thomas Sydenham (1624-1689), called "the father of English medicine" or "English Hippocrates". He was noted in the history of epidemiology through his work "Medical Notes" ("Medical observations"), in which he described several human diseases and their epidemiology. Although Sydenham described several infectious diseases such as measles, whooping cough, smallpox, cholera, scarlet fever, malaria, fever comatose (flu epidemic) etc., he remained on the position that miasmatic constitution was the cause of illnesses.

Sydenham's conception about outbreaks is reflected in his study "About the constitution of epidemics", explaining its appearance as a result of of harmful substances (miasma) and changing atmospheric factors (weather conditions).

Taking into account the development of epidemiology, is important to note that during this period, called period before Pasteur or pre bacteriological, development progress of epidemiology as a science was influenced by the progress of the development of mathematics as a science, in particular the development of statistical methods to study the phenomena. Peculiarities of epidemics were confirmed by using statistical methods to study the morbidity, constitutional

hypothesis of epidemics were investigated; diseases were diffrentiated according to the clinical and epidemiological peculiarities.

Fundamentals of statistical methods to study the epidemics were elaborated by the Englishman John Graunt, in the publication of 1662, the work about the evaluation of epidemiological processes of diseases starting from the analysis of "tickets of death". In this study, Graunt found differences between men and women, children and adults, towns and villages, seasonal variations, according to the description of quantitative feature of the mortality. In 1747 I. P. Semmelweis realized first retrospective epidemiological investigations of nosocomial infections. In 1839, W. Farr published epidemiological observations on the various causes of morbidity and population groups. W. Farr developed concepts of risk, prevalence, incidence, retrospective and prospective studies. In 1850, was held "the meeting of Epidemiological Society" in London, with the participation of many epidemiologists and specialists in medical statistics. At this meeting Babington said that "medical science gives us new and effective means of demonstrating the truth in medicine" [18].

John Graunt

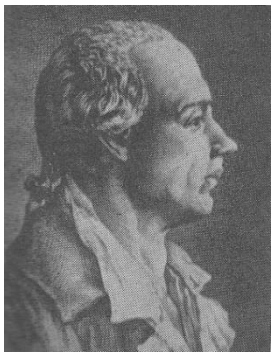
Statistical method of research provides the opportunity to evaluate quantitatively the observed phenomena; to establish comparative characteristics of various epidemics and diseases; to determine the intensity of spread of epidemics in different territories; the dynamic of the morbidity; to determine the level of damage to population by some diseases; to establish relationships between different diseases and public health through environmental factors; to develop measures to prevent and combat the diseases. In 1854, after the analysis of cholera outbreak in London (1853-1854) John Snow established that the risk of illness is associated with the consumption of water supplied from certain sources. J. Snow proposesed measures to prevent and combat the disease by improving water consumption of the inhabitants of London long before they discovered the causative agent of cholera, and epidemiological investigation method he used in that study was used later in epidemiological investigations (studies).


John Snow

Therefore, at that period epidemiology moved from


Girolamo Fracastro

observation and description of phenomena to the analysis of causes and peculiarities of spreading and manifestation of the epidemic, becoming a science with specific methodology addressed to public health problems at the population level.



Danila Samoilovici

An important event in the history of epidemiology occurred in the first half of the sixteenth century. The Italian physician Girolamo Fracastoro (1478-1553) formulated a new vision of the essence of epidemics, its development through living contagiousness that is presented in his work "Study about living contagiousness, diseases and their treatment" (1546). According to this hypothesis, epidemics appear after the contamination with live contagions, that are invisible pathogens, which are transmitted from the sick to the healthy person.

Edward Jenner

One of the supporters of the contagions hypothesis was Russian doctor Danila Samoilov (1744-1805). He was noted for fighting against plague, including in Moldova. Another scientist supporting the hypothesis was Russian doctor Andreevskie S.S. (1760-1818), who for the first time demonstrated contagious nature of plague and conditions of its transmission from animals to humans by self-contamination with the blood of animals infected with anthrax.

In XVIIIth century happened the event of great historical importance, when Edward Jenner discovered how to prevent smallpox by inoculating cows' smallpox to people, thus was initiated the period of immunoprophylaxis of diseases.

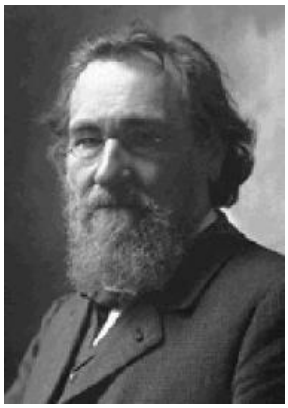
L.Pasteur

For the first time was discovered the world of microorganisms by Dutch scientist A. Leeuwenhoek (1632-1723), who in 1678 published his letters about "tiny living animals" ("animalicula viva"), and in 1695 published his "Secrets of nature discovered by Antonius van Leeuwenhoek ". A. Leeuwenhoek's findings aroused great interest in the scientific world and served as an encouragement to study this small universe.

R.Koch

However, only in the second half of the nineteenth century, because of published works of L. Pasteur (1822-1895), R. Koch (1843-1910), I. Mechnikov (1845-1916), D. Ivanovski (1864-1920) etc., was settled pathogens' role as etiologic factors (causative agents) in infectious diseases, thus started the

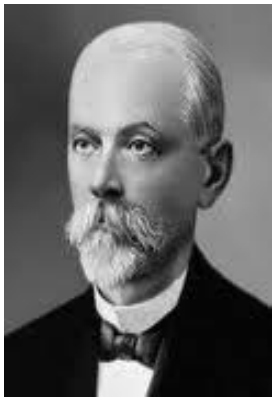
bacteriological period in explaining the essence of epidemics. In the same period I. Mechnikov formulated the theory of immunity, which played a crucial role in explaining the epidemiological phenomena.



I.Mecinikov

These great discoveries of microbiology influenced epidemiologists. Many of them later used the term "epidemic" only for infectious diseases (contagious). Note that this theory belonged to epidemiologists from the former Soviet Union as well.

The truth is that this attitude was influenced by the fact that in the seventeenth century, after the industrial revolution, intense migration of the population, frequent wars, human population faced numerous contagious diseases. An epidemic expansion, or even pandemic one had smallpox, plague, cholera, influenza, typhus, typhoid, diphtheria, tuberculosis, etc.. This situation was a catalyst for the development of medical microbiology and epidemiology of infectious diseases.



D.Ivanovschi

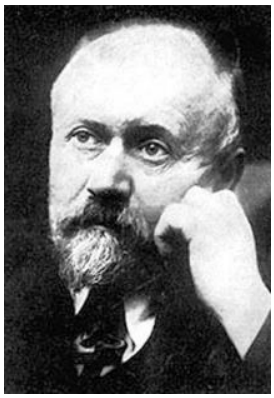
Soon, because of the development of microbiology, were established the causative agents of most infectious diseases with epidemic spreading, specific preparations were made for the prevention and treatment of infectious diseases (vaccines, serums, immunoglobulins, etc.). Application of these preparations resulted in a decrease of the morbidity and lethality in many key diseases such as smallpox, diphtheria, hydrophobicity etc.

Even in the first years after the discovery of pathogens of infectious diseases, the enthusiasm of many scientists, including epidemiologists to microbiology was so great that it led to underestimation of traditional epidemiological research methods. Over time, however, it became increasingly apparent that only basic microbiological research could not establish the peculiarities and real conditions for the spread of disease and as a result, could not be taken effective measures to prevent and combat them.

A true renaissance of epidemiology happened during the first half of the XXth century. Illustrious epidemiologist researchers: Zabolotnîi, Stallybrass, Gromaşevski, Başenin etc.contributed to this event.

Zabolotnîi D.K. (1866-1929) is rightly considered the founder of epidemiology of infectious diseases. In 1922, he founded the first department of epidemiology in the world in Odessa. He is the author of the first textbook "Fundamentals of epidemiology" (1927). He proposed the first definition of epidemiology as a science: "Epidemiology is a science about the epidemics dealing

with the study of the causes of occurrence and spread of epidemics, determines the conditions that favor their spread and proposes measures of combating based on scientific and practical data."



D.K Zabolotnîi

In 1930 Stallybrass C.O. * described the fundamental law of the epidemiology of infectious disease and ranged it as a specific independent science.

At the same period, Ioan Cantacuzino (1863-1934), who is the disciple of I. Mechnikov, CEO of Health Services in Romania (1907), founder of the Institute of Sera and Vaccines (1921), which today bears his name, was carrying out a research on Vibrio cholera and cholera vaccination and active immunization against typhoid fever. Cantacuzino I. introduced vaccination of infants against tuberculosis with BCG in Romania (in 1926, it was the second country in the world after France). In addition, he organized companies to combat epidemic outbreaks of typhus, cholera, malaria, scarlet fever. He was the first to obtain the streptococcus serum for the treatment of patients with scarlet fever. Cantacuzino I. was a member of the Committee of Hygiene of the League of Nations.

Ioan Cantacuzino

Bashenin V.A. (1882-1977) developed the statistical method and demonstrated its role in epidemiological research, he considered epidemiology as a science designed to study the epidemiology of all human pathologies.

V.A.Bashenin

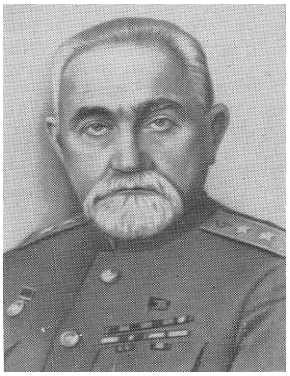
Gromashevski L.V. (1887-1980), was a famous epidemiologist, who defind epidemiology as a science about peculiarities of the epidemic process, which underlies the maintenance and spread of the causative agent of contagious diseases. The author described the theory of the mechanism of transmission of pathogens, and the theory of the component parts of epidemic process. The theory led to the formation of the system to combat the infectious diseases worldwide and it is actual up to date.

L.V.Gromașevschi

In the second half of the twentieth century, epidemiological investigations were directed to study deeper the nature of the epidemic process.

Pavlovskiy E.N. (1884-1966) described the phenomenon of natural focus characteristic of some diseases, which has

made a valuable contribution to the study, discovery and description of the epidemiology of diseases with natural focus.



E.N.Pavlovskiy

Skreabin K.I. (1878-1972) is the founder of helminthology school, author of the eradication theory (devastation) of helminthiasis.

Beleakov V.D. (1921-1997) developed the theory of self-regulation of epidemic, which has radically changed the concept regarding the nature of the epidemic process. He is one of the first Soviet epidemiologists who recognized the existence of two branches of epidemiology: epidemiology of infectious diseases and non-communicable diseases. He defined epidemiology as a universal science of medicine.

K.I.Screabin

Cherkasskiy B.L. (1934-2007) formulated the theory of the socio-ecological nature of epidemic, determined the levels and operational system of epidemic process from the molecular level to the global.

Şleahov E.N. (1920-2006) founded in 1967 the epidemiology course, and later on (1970) the Epidemiology Department in the framework of the State University of Medicine and Pharmacy "Nicolae Testemiţanu" in Moldova, being CEO until 1990. Professor E.N Şleahov made a significant contribution to the development of scientific and practical epidemiology. He developed Epidemiological classification of infectious diseases . He studied all aspects of zooanthroponosis, pathogenesis and immunology of anthrax. He is the author of diagnostic preparations "Antraxina" and "Tetanina". In 1998 the World Health Organization recommended to use the preparation "Antraxin" in medicine and veterinary. The preparation developed by scientists in Moldova has been recommended by the most influential global organization for the first time in history. The researches of Professor E.N.Şleahov about the changes in the immune process after the vaccination, infectious disease prevention, vertical mechanism of transmission, are highly appreciated by specialists. The great value for doctors and students has "Practical Epidemiology", published in five editions in

V.D.Beleacov

B.L.Cherkaskiy

E.N.Șleahov

Moldova and France. E.N. Șleahov was the leading epidemiologist of Moldova (1974-1990), also President of the Scientific Society of Epidemiologists, Microbiologists and Parasitologists of Moldova (1964-1990).

So, the twentieth century is marked by numerous large studies and valuable finds in epidemiology of infectious diseases, which can be considered as a revolution in epidemiology. The essence and laws of the epidemic process were revealed. In addition, the secret of maintaining and spreading of pathogenic microorganisms in nature was disclosed. The epidemiology of infectious diseases was practically studied. At the same time, the source (reservoir) of pathogens, the mechanism of transmission and factors, the role of receptivity and collective immunity, social and natural factors in epidemic process were studied, were developed measures to prevent and combat each infection separately, formulated the concept of epidemiological surveillance of infectious diseases etc.

New vaccines, disinfectants, antibacterial and antiviral serum and immunoglobulins have been developed and successfully implemented in anti-epidemic practice. Implementation of these scientific achievements led to decreasing of the infectious morbidity for the first time in human history. There were no epidemics of smallpox or plague. Many diseases are recorded at sporadic level, and others, in some territories, have been eradicated.

For example, in the second half of the twentieth century, infectious diseases with widespread in the past were eradicated in Moldova, such as recurrent typhus, glanders, trachoma, malaria, brucellosis, tularemia, polio [16].

Successful eradication and control of diseases have significantly increased the prestige of epidemiology.

However, at this stage epidemiology has accumulated a rich arsenal of methods and effective means, including analytical, and research of the public health and disease.

The epidemiological method of research is increasingly used in the study of non-communicable diseases such as cardiovascular disease and cancer, trauma and congenital malformations, etc. In addition, it is used more widely in clinical medicine as evidence-based medicine.

Nowadays, epidemiology makes still larger finds in its field of action, becoming a science that provides services in all areas of medicine.

DEFINITION AND SUBJECT OF STUDY OF MODERN EPIDEMIOLOGY

Epidemiology is the science that deals with the study of the causes, conditions and mechanism of formation of the morbidity in the human population, the development of methods and means for the study, prevention and control, monitoring continually the health promotion.

It is easy to understand, especially for specialists, that this definition does not include the entire content of the study and intervention of the epidemiology. In reality, it is much broader and includes various aspects of human pathology such as supervision and control of public health system, organization and implementation of measures to prevent and combat, evaluating the effectiveness of prevention, diagnosis and treatment, etc.

Throughout history, the epidemiology studies not only epidemics, revealing peculiarities of occurrence and spread of diseases in human populations, but develops measures and even the system of protection of population as well, with the main goal to prevent the appearance of the disease.

Some diseases have been eradicated at global level (smallpox) or in different geographic areas, in others the morbidity is decreased up to the sporadic level, many of which currently can be seen on anti-eradication stage.

However, at the beginning of the millennium, the society faces new epidemiological issues related primarily to the emergence and re-emergence of infectious diseases.

Only in the last 20-30 years in the world appeared or have been discovered dozens of new infections and invasions such as yersiniosis, campylobacteriosis, hepatitis E, C, F, G, rotavirus infection, infection with Escherichia coli 0157: H7, Vibrio cholera 0:139 Bengal infection, Haemophilus influenzae, legionellosis, borreliosis, chlamidioza, infections caused by viruses Marburg, Lassa and Ebola infection, sarcocistozis, cryptosporidiosis, microsporidiosis, izosporoza, cyclosporoza HIV infection, atypical pneumonia with severe acute respiratory syndrome and recently avian and pandemic flu of new type (H1N1). Last four infections caused panic around the world.

More frequently is observed phenomenon of re-emerging because of social disturbances, inefficient measures, and ignorance of all epidemiological peculiarities of infectious diseases. In the last 10-20 years for the Republic of Moldova as an example of re-emerging infections can serve diphtheria, tuberculosis, syphilis, mumps.

In such circumstances, the main goal of epidemiology of infectious diseases is to study the peculiarities of occurrence and spread of them and to develop measures to prevent and combat the disease at any level of development of the epidemic. It is important to develop both the reduced time of combat measures in emerging diseases and to change the tactics to fight and eradicate the infection at any stage.

Doctors, including epidemiologists, face various atypical epidemic manifestations and clinical manifestations of different nosological forms in daily work. At the contemporary stage, more frequently are registered mild or asymptomatic forms of infections, as a result of the widespread use of antibiotics, vaccines, immune preparations etc. However, many infections are characterisede by the carriage of causative agents. These phenomena lead to the maintenance of a latent epidemic process. It is much more difficult to diagnose, but that leads to the maintenance and spread of the causative agents of infectious diseases, increasing the risk of contamination of population. In these circumstances, it is necessary to know the epidemiological characteristics of each disease separately. The specialist must possess theoretical knowledge of the epidemiology of these infections to detect easily the disease and take measures to prevent and combat it.

Currently, there are created conditions to generate epidemics, because of the complexity of the relationship between human and environment, the demographic explosion, the dramatic increase of migration, armed conflicts and bioterrorism, profound changes of the ecosystem and genetics of macro-and microorganisms.

In these circumstances, more obvious is the increase of prevalence of non-communicable diseases - an increasingly important object of study of epidemiology. Even the study of the epidemiology of these diseases at the population level and neutralization of risk factors may lead to the decrease of morbidity caused by them.

Therefore, both terms *epidemiology* and *epidemiological research method* can be used effectively in the study of infectious and non-infectious diseases. Epidemiological departments are formed in many clinical centers such as centers of cardiovascular diseases and cancer.

As the proof of this element of service to the universal science of epidemiology in studying the human pathology at the population level serves fig. 1. Vertical lines are medical sciences that are formed according to principle of studied pathology (cardiology, oncology, nephrology, ophthalmology, neurology, infectious pathology, etc.) and horizontal lines - medical sciences studying human pathologies at different levels of organization of life: molecular (biochemistry, biophysics, molecular biology), cellular and tissue (cytology, histology, microbiology), the body (therapy, surgery) and population (epidemiology). At the

intersection of vertical lines with horizontal lines are usually formed the interdisciplinary sciences.

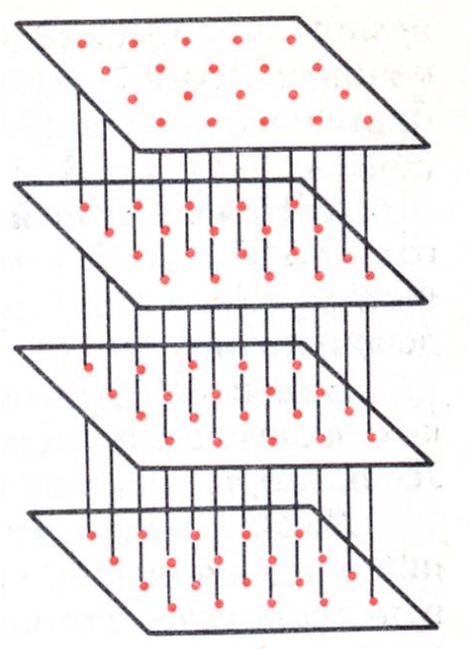


Fig. 1. The structure of medical sciences (V.D. Beleakov, 1989)

Thus, the epidemiological method is common in the study of infectious and non-infectious pathology, with some deviations (specifications) for the first one, but differs from the clinic one by the fact that it is directed to the study of disease at organism (individual) level, while epidemiological method provides pathology study at the population or collective level (Table 1).

Table 1

Clinical and epidemiological approaches in human pathology study
(E.N. Şleahov, 1987)

Criterion	Method of approach	
	clinical	epidemiological
Study subject	Sick	Disease
Level of study	Organism	Population
Medical definition of health disorders	Disease	Morbidity
Diagnostic object	Determination of cause of disease	Determination of cause-consequence of morbidity
Intervention goal	Treatment and individual prophylaxis	Morbidity control and its eradication
Control of the effectiveness of intervention	Follow up and rehabilitation measures of the sick	Analysis of the result at the population level, groups. Epidemiological surveillance.

As an analogy, we can make the following comparison: the clinician sees in front of him the tree, epidemiologist - forest, necessarily in relation to the environment.

In other words, epidemiology concerns fully the pathology of population, pathology of groups of population in relation to environmental, natural and social factors, following the development of measures to improve public health.

In 1967, was noted at the Symposium of Epidemiologists' International Society held together with the European Regional Office of WHO and dedicated to teaching epidemiology, that the world feels the need for training large numbers of epidemiologists and public health managers, well equipped with epidemiological knowledge in prevention of morbidity. In 1971 was published a guide for teaching epidemiology in the medical education system, in order to optimize training the teachers in this area. The emphasis was placed on teaching basic epidemiological methods.

Epidemiology is the subject present in all medical schools. Training of doctors in epidemiology is held at all faculties, with different study programs. Epidemiology is studied by clinical doctors and it is necessary in order to achieve thinking skills at the population level in achieving prophylactic and anti-epidemic measures. An important issue is learning of clinical epidemiology bases of medicine by evidence.

Study program of Epidemiology at the Public Health Faculty aims at training of future epidemiologists, followed by postgraduate residency training (master).

An acute problem of contemporary epidemiology is organizing epidemiological surveillance system of public health at the regional, national and global level. Today, all epidemiological schools in the world have focused on improving the system of epidemiological surveillance. This became a concern of the WHO that encourages the organization of supervision of public health, at the national and international level.

The base and principles of management of the national epidemiological surveillance was constructed by making several serious studies in the last 10-20 years in Moldova. Nowadays it is very important to improve this system for more efficient embodiment, national coordination and integration in the European and global epidemiological surveillance.

Another objective of the contemporary epidemiology is improving of epidemiological diagnosis in public health assessment based on epidemiological analysis and operational review. The essence of pathology or epidemic process, political, economicalo, cultural, ecological, and medical issues can be evaluated by retrospective epidemiological analysis. The epidemiological analysis serves as a strategy of epidemiological surveillance of public health. Therefore, the

epidemiological method is more effective as a branch of public health diagnostic in infectious and non-contagious diseases.

Nowadays, epidemiological methods are used more and more frequently in clinical medicine as argumentation methods and evaluation of protocols for diagnosis, treatment and prevention, being basic methods in medicine by evidence.

At the contemporary stage, the epidemiology can achieve its objectives only through cooperative actions with other medical and non-medical disciplines in which epidemiology plays a synthesis of these sciences, outreach and guidance to fight human diseases. Epidemiology is guided by the data of these sciences to elucidate the nature of the disease, it is the link between morbidity and determinants, from which develop measures to prevent disease and reduce morbidity, the aim being eradication of diseases in communities (human population).

The structure of modern epidemiology, in terms of research objectives, includes three main areas:

- epidemiology of communicable diseases;
- epidemiology of non-communicable diseases;
- other (clinical epidemiology, epidemiology of disasters etc.).

Structure of epidemiology as a science, the methodological point of view, includes two sections:

- General epidemiology;
- Special epidemiology.

Epidemiology studies the general principles of (spread) morbidity in the human population, methods and means of research, prevention and control. It includes the following sections:

1. Epidemiological methods of research (Basis of epidemiological diagnosis and medicine based on evidence).
2. Theoretical concepts concerning regularities of epidemic process.
3. Means and methods to prevent and control.
4. Epidemiological surveillance system of public health.

Special epidemiology studies of epidemiological peculiarities, means and methods to prevent and control of some diseases or disease groups separately.

STRUCTURE AND CONTENT OF EPIDEMIOLOGICAL METHODS OF INVESTIGATION

The term "method" comes from the Greek "methods" - research, or way of knowing the essence of natural and social phenomena, but also effective implementation of research results.

Epidemiological method is a set of specific procedures or methods themselves, which provide as full an understanding of epidemiological phenomena, especially those of health, which can be divided into 4 groups:

- observation and description;
- experimentation and description;
- laboratory;
- statistics.

1. Method of observation and description

Method of observation and description is probably the oldest method of studying phenomena, but today successfully is used in various medical studies, for example, by clinicians in studying the evolution of clinical manifestations. An example in this respect can serve observational studies conducted by famous infectionist Filatov. He watched 4 days of the clinical evolution of patients with measles and later described them, these features are included in textbooks as a classic presentation of measles.

Method of observation and description obtained is wider used in studying the epidemiology of infectious diseases to prevent the natural epidemic. For example, before being known the ethiology of diseases through epidemiological observations have been described characteristics for cholera (Snow, 1854), typhoid (Budd, 1873), polio (Wickman, 1905).

Description of epidemiological phenomena, though their essence remains unknown, was followed by specific recommendations. An example in this respect can serve observations of E. Jenner, who in 1796, noting the lack of human smallpox disease among people who previously did cow pox, smallpox vaccination developed, which resulted in to the global eradication of this infection. Throughout the history, observations were made on both the human population morbidity and morbidity on specific events in relation to the development of natural and social phenomena. Long before it was noted that with heating air, in summer, increases incidence of digestive infections, anthrax, and malaria. Conversely, during the cooling air in winter, reduces incidence of these infections,

but increases the incidence of typhus, diphtheria, whooping cough. Some infections affect especially children (measles, pertussis, polio), others - adults (anthrax, malaria, brucellosis). Some diseases are more prevalent in some areas, like in other geographical spreading areas (fever, malaria, yellow fever etc.). Studying the distribution of morbidity of various diseases depending on geographical spreading areas led to the birth of a new branch of epidemiology - geographical epidemiology. The causation, clinical manifestations, sources of pathogens, mode of transmission, etc are specific for infectious diseases.

Methods of analysis of morbidity according to the mentioned signs (place, time, person, etc.) are called descriptive. Means used for identification of determinants of disease processes are called analytic.

Therefore, the method of observation and description includes both descriptive methods and analytical epidemiological phenomena assessment. Descriptive processes are designed to characterize epidemiological situations at all population groups or cohorts of the population and partly under different conditions. Finally, this process is directed towards the formation of hypothesis on the causes and conditions of occurrence and spread of the epidemic in specific situations, it constitutes the first step in studying the epidemic. The results serve as a basis for organizing of analytical investigations, which will reveal the real causes of the spread of the epidemic process that eventually will be established the epidemiological diagnosis of the situation on the ground, under which anti-epidemic measures will be determined.

A typical use of the observational method in daily medical practice can serve investigating of outbreaks of infectious diseases (see epidemic outbreak investigation).

2. The experimental method is used to evaluate the quantitative description of the means and methods of prevention and treatment (see section "Types of epidemiological research studies"

3. The laboratory method

The role of the laboratory method in contemporary epidemiology has increased considerably. It expans the field of action to improve disclosure etiologies, to define the scale of processes of epidemiological surveillance techniques to improve the health status of population modeling techniques to promote more effective measures for control and prevention [26].

Laboratory investigations are necessary in the experimental study of different aspects of the epidemic such as, for example, determining the causative agents in

infectious diseases and identification of sources (reservoir) of infection transmission factors, the immune status of the population, viability determination of causal agents in the external environment, the effectiveness of antibacterial preparations (disinfectants, antiseptics, antibiotics), effectiveness of immunobiological preparations (vaccines, immune sera etc.), the effectiveness of disinfection measures, vaccinoprophylaxis or antibacterial therapy etc.

Laboratory investigations are of great importance in confirming the diagnosis of disease, as defined in the standard case, with light or inapparent forms (asymptomatic) and in carriers detection. Only sensitive laboratory methods can find the disease in prenosologic form. In these people can be applied measures to prevent the progression of the disease.

In addition, only by laboratory method can be studied both causative agent movements in affected human body and the external, physical (soil, water, and air) and biological (animals, insects, protozoa etc.) environments.

Laboratory investigations have found wide application in the diagnosis and study of efficacy in non-infectious and infectious diseases based on changes in blood and other biological tissues - urine, saliva, etc.

Laboratory investigations used in epidemiological studies are following: bacteriological investigations, virological, parasitological for determining the causative agents in infectious diseases and invasive investigations called direct confirmation of the presence or movement of pathogens. The results of these investigations show an unanswerable argument, for example, in establishing the diagnosis. They can be used at all stages of epidemiological investigation of infectious disease outbreaks, to obtain objective information on the status of the epidemic process components (source factors, responsiveness) in the diagnosis and sources of pathogens to elucidate the possible pathways of contamination and determining factors for the transmission of the causative agent in determining the risk of developing the infection, the epidemiological surveillance of contacts, as indicators of the health of infected persons or those in contact with them. Microbiological investigations serve as bacteriological indicators in assessing epidemiological environment, including water, soil, air, food - factors in infectious disease transmission in pollution pathogens and thus the possibility of their participation in the transmission of infection. Of particular importance were helminthology investigations in the diagnosis and treatment effectiveness in helminthiasis, parasitological and virological investigations in the study of natural foci of infection. Detection of causative agents of infectious diseases both in human body (animal) and in other biological and physical factors of the external environment is the basis, as unanswerable argument in conducting anti-epidemic and preventive measures.

• immunological investigations - confirmation indirect investigations of the diagnosis or circulation of causative agents' through the determination of the specific antibodies present in the investigated body.

• molecular investigations, including molecular genetic determination of the genotype of both the macro and the microorganism, and molecular-biological investigation - for determination of the phenotype signs (features) of organisms, including microorganisms (e.g. tests in microbial antibioticoresistence and enzyme immunoassay tests). The increasing use of molecular investigations in deciphering the essence of the epidemic process and in determining both the particularities of the various components of the epidemic, especially the populations of microorganisms - causative agents and the macro-host and their use in medical practice led to the formation of a new section in epidemiology - molecular epidemiology. An example of this can serve using the method of polymerase chain (PCR) and enzyme immunoassay in the diagnosis of influenza infection caused by new influenza virus A (H1N1).

• clinical laboratory investigations, such as hematological, morphological, biochemical, based on the changes in the constitution of tissues and body fluids in normal and pathological state. For example, infections caused by bacteria increase the leukocyte count in the blood (leukocytosis) in those ones caused by viruses, reduce the number of white blood cells (leukopenia), and the infections caused by helminths - increase then normal number of eosinophils in the blood (eosinophilia). In viral hepatitis, the level of enzymes in the blood serum, such as alanine aminotransferase (ALT), aspartataminotrasferaza (AST), bilirubin increases. The enzymes may be determined by biochemical investigations. The successful use of clinical laboratory investigations in epidemiological studies, assessing the efficacy through various technical means and drugs, gave birth to another new branch of epidemiology - clinical epidemiology, including pharmacoepidemiology. The microbiological, parasitological, biochemical, morphological investigations are made when needed. However, the duty of Epidemiology, family physician, clinician's task is to formulate proper investigation to assess the results of investigations and to know the following:

a) the period of the disease, depending on the particular disease pathogenesis, it is appropriate to harvest pathological material from the sick and in what amount;
b) pathological material that can be taken in pathology and in what ways. It is necessary to choose the most appropriate laboratory methods with maximum efficiency to investigate the object of the study, sensitive and specific methods, for which it is necessary to know the full range of offers proposed by laboratory;

c) transporting laboratory conditions (packs, temperature regime, precautions, etc.);
d) time when the laboratory is required to give a definitive the result after receipt of the material;
e) the degree of safety and obtained investigation results, and additional methods that can be used to confirm the diagnosis;
f) the methodology for the interpretation of laboratory data. To effectively use the results of laboratory investigations, it is necessary to know in advance the essence and characteristics of tests.

4. The statistical method (Biostatistics)

Statistical method includes both epidemiological investigation with mathematical techniques and statistical indices and evaluation of phenomena and finding the truth of epidemiological studies. Using statistical methods in epidemiological studies include the notion of Biostatistics, which is applyied in statistical and mathematical methods in medical-biological and demographic phenomena studies. Biostatistics develops and uses mathematical methods of systematization, processing and interpretation of phenomena at the population level in medical research and practice. Epidemiological study of diseases or other events with positive or adverse effect on human health is not conceivable without the use of statistical methods of evaluation. Epidemiological studies frequently resort to mathematical models, the construction of which requires to use quantitative characteristics of determinants: biological, medical, social, behavioral, antropurgici, weather, economic, psychological, political, etc.
So, epidemiological statistics aims at the development of health assessment processes of the population and deciphering causal relationships between disease and the environment.

Biostatistics is indispensable in clinical trials evaluating the efficacy of treatment means. Laboratory methods also require statistical analysis and interpretation. However, biostatistics medicine needs to combat empiricism, superficiality and errors.

4.1. Indicators of health status of the population

Measurement of health state of the population is achieved by means of indicators. They can be grouped into: indicators that reflect the level of population health (level indicators) and indicators reflecting the determinants of population health (indicators' factors).

4.1.1. Level indicators

4.1.1.1. **Morbidity** is the phenomenon that is subjective or objective deviation from the normal state of health manifested by illness occurring in a defined population in a specified period of time. It can be of several types:

General - mass phenomenon of all nosological forms of diseases;

Specific - according to nosological forms, gender group, living environment (rural, urban), etc .;

hospital (hospitalized) - the frequency of disease in hospital conditions (the ratio of people with the disease studied "x" and the total number of persons admitted multiplied by 100 or 1000);

real - includes all cases of disease existing in the community (population);

diagnosable - includes existing illness cases in the community, but can be diagnosed using diagnostic techniques;

morbidity with temporary or permanent incapacity for work cases of temporary or permanent disability to work as a result of illness;

incidence of concomitant diseases represents categories of patients with concomitant diseases;

successive morbidity dynamics is the study of morbidity between two consecutive studies.

Morbidity may be presented by the consequences of the disease: deficiency, disability and handicap.

Deficiency means any loss or abnormality of structure or physiological, psychological or anatomical function.

Disability (inability) is any restriction or lack of ability to perform an activity in the manner or at the level considered normal for humans.

The handicap is a disadvantage for a given individual, resulting from an impairment or a disability that limits or prevents the realization of normal functions.

Measuring disease has important consequences both in developing preventive measures (vaccination against hepatitis B leads to cirrhosis and liver cancer prevention which is a disability and rubella vaccination of pregnant women fetal congenital cataract avoids causing disability) and in determining health care needs and staff planning, as well as evaluating the significance of pathology.

Morbidity study is used for:

• disease control in the community;
• planning and implementation of preventive measures;
• care planning;
• analyzing the determinants;
• estimate the economic importance of the disease;

• etiological research and clinical aspects of the disease etc.

4.1.1.2. **Mortality** reflects deaths in a population. Data on mortality are considered most important by their certainty.

The types of mortality:

• Overall mortality or gross rate of death is the total number of deaths registered in a certain period of time within a population. This indicator is global and does not take into account the influences on their age, sex, race etc .;

• specific mortality is calculated based on age, sex, race, occupation, living environment, other contingent cause of death etc .;

• Infant mortality is deaths in children aged under one year, relative to the total living newborns for one year;

• perinatal mortality includes fetal mortality (stillbirths new index), neonatal mortality (deaths produced at the age of 1-27 days recorded during the year, relative to the number of live births registered in that year multiplied by 1000) and postneonatal (the number of deaths occurred between the ages of 28 days and 12 months, compared to the number of live births in the same period multiplied by 1000);

• Maternal mortality is the number of deaths in pregnant women with complications of pregnancy, childbirth and puerperium recorded during the year, relative to the number of live births registered in that year multiplied by 1000;

• hospital mortality is the number of deaths in hospital reported by the number of patients admitted multiplied by 100.

4.1.1.3. **Lethality** is the proportion of deaths in each disease, but may represent the share of deaths grouped by certain criteria (gender, age, residence, cause of death) to all deaths.

4.1.1.4. Fatality rate is index that reprezent number of deaths per 100 sick. It is an indicator of epidemiological assessment of disease severity.

4.1.1.4. **The birth rate** is the number of live births reported in the population of a territory for a calendar year multiplied by 1000. The official document for the study of birth information is medical birth certificate. Birth is the most objective indicator of natural movement of population.

4.1.1.5. **Fertility** is the ratio of live births population and female population of reproductive age (15-49 years) multiplied by 1000. This indicator allows a more accurate expression of the reproductive power of the female population to study birth phenomena and helps assess the indices of pregnancy, education, socioeconomic, etc. It is reflected by birth certificates.

4.1.1.6. Life expectancy at birth, or average life expectancy is the average number of years of expected life of the generation born in a given lifetime year. It reflects the expected survival time of a generation or a person who has reached a certain age. This indicator is obtained by knowing longitudinal mortality age of a population. This indicator of the health of the population is largely dependent on socio-economic development of society. It is influenced by infant mortality, mortality of juvenile and adult population up to 65 years.

4.1.2. Indicators of factors:

• biological (immune stratum of population, genetic peculiarities etc.);
• the environment (air temperature, the level of rainfall, humidity, etc.);
• behavior (knowledge, skills, attitudes in the family, society);
• health services (access to medical services, etc.).

4.2. Epidemiological indicators

Determination and assessment of public health problems is effected by means of statistical indices, rates or proportions, which present a numerical expression that can be characterized using a phenomenon.

Rates are measures of frequency of phenomena. Key indicators of the kind commonly used in practice are epidemiological incidence and prevalence.

4.2.1. The incidence is mass phenomenon that reflects the frequency of new cases of incidents (illness, births or deaths, etc.) in a defined population during the observation period (month, year, time of year).

Incidence measures how quickly the disease occurs in the population or frequency of new cases of disease. It expresses the probability of disease risk and is always calculated for a defined period of time. A variation of incidence is the index of attack, which is determined in populations or specific areas for a short period of time and applies to epidemics. This index expresses the speed of development of the epidemic.

4.2.2. Prevalence is the total number of cases (old or new) existing in defined population at a given time (prevalence of moment) or a period (period prevalence). Prevalence is present in population health, relative to a period of time. It is used to measure chronic diseases (e.g. Tuberculosis, HIV / AIDS, cardiovascular diseases) and is conditioned by the long duration of disease, prolonged life cases with or without treatment, the increase in the number of new cases, improved means of diagnosis, population migration , improving sanitary conditions etc. Therefore, in the determination of one and the same phenomenon, for example, when referring to the morbidity, the incidence of the occurrence of the disease is indicated, while the prevalence of the disease indicates its presence. The incidence may be high, while the low prevalence, such as influenza, mumps, measles, and

vice versa, the incidence may be low, while high prevalence, such as tuberculosis and HIV / AIDS.

Both the incidence and prevalence serve as indicators to measure the phenomenon entirely (such as general morbidity) and its structural components (specific conditions) such as morbidity structure by sex, age, occupation, place of living depending on the influence of risk factors, preventive or therapeutic measures.

Incidence and prevalence as basic epidemiological indicators are used successfully in the health service activity in achieving population health scientific research, argumentation and development of health programs.
The incidence and prevalence of phenomena can be determined by calculating various statistical indices, called frequency indices.

4.2.3. Statistics indices of frequency

4.2.3.1. Absolute values express the absolute number or amount of events. They are used in epidemiological studies when the phenomenon can be characterized by absolute numbers, such as the number of cases of illness or other phenomena related to them, increase of defined population in a specified period of time or the number of deaths, loss of capacity work etc. Absolute data are also used when the number of cases of disease is low. For example, after global polio eradication phase WHO shall report annually on the number of new cases recorded in the world, including different continents to assess the dynamics of morbidity and risk territories.

4.2.3.2. Cumulative indices represent total cases of increasing portions of time (days, weeks, months, years). Using cumulative index is only possible when the groups under investigation (surveillance) and time periods are the same. One example is the cumulative record of cases of HIV / AIDS in Moldova over the years since the first case was detected (Fig. 2). The same methodology was used by the WHO information on the evolution of the new flu pandemic A (H1N1) since April 2009, when information indicated the number of countries affected daily and cumulative number of cases and deaths confirmed influenza illness (fig. 3).

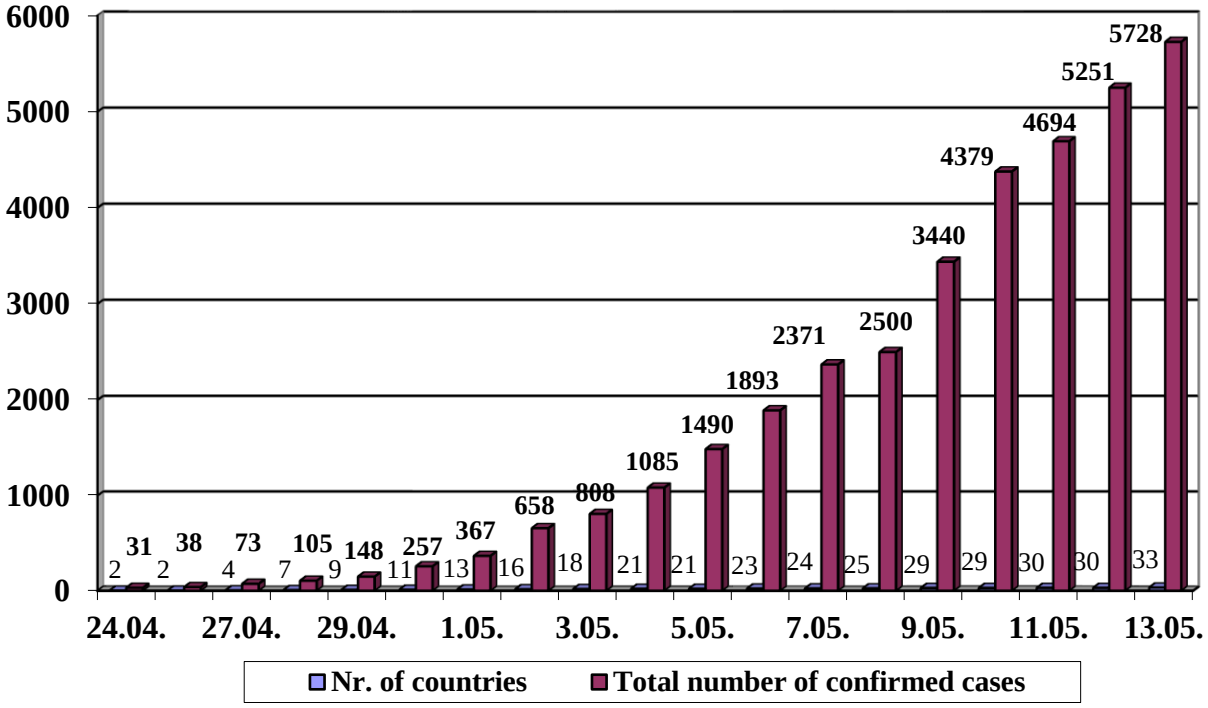


Fig. 2. Evolution of the new pandemic human influenza virus by A (H1N1) 24.04 period. - 13.05.2009

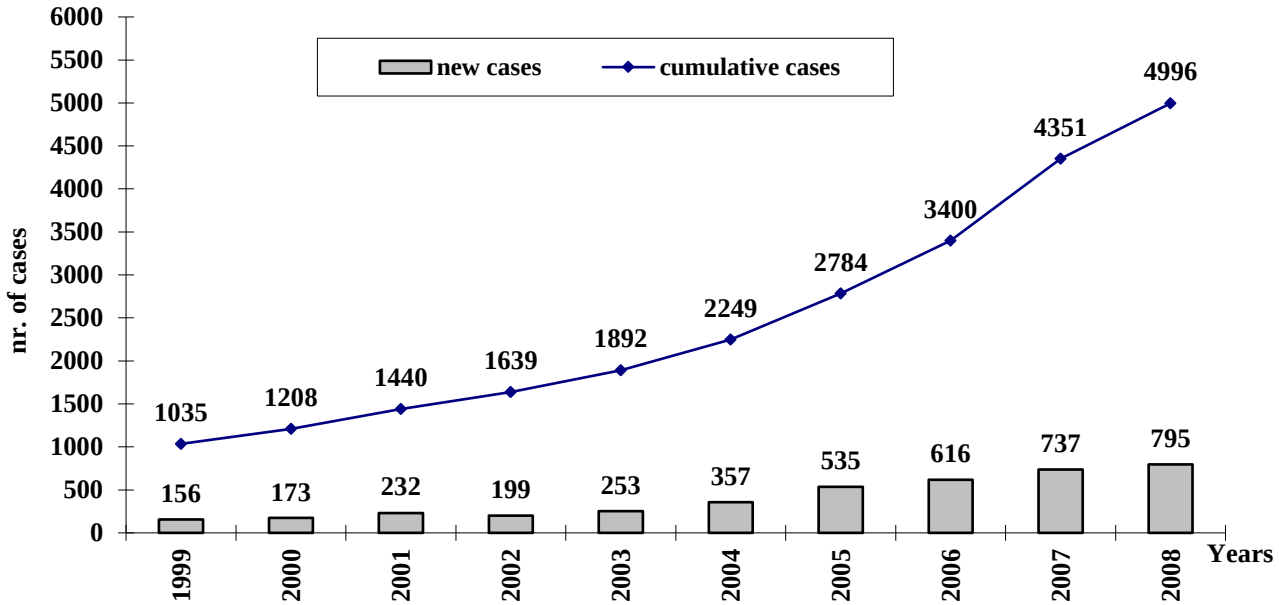


Fig. 3. Dynamics of multiannual morbidity by HIV/AIDS in Moldova, period 1999 - 2008

4.2.3.3. Intensive indices indicate the intensity of a phenomenon (general or specific morbidity, morbidity with temporary disability, general or specific mortality etc.) in a defined population during the period of observation. It is given by:

$$I.I.= \frac{a}{b} \times k \text{ , where}$$

I.I. – intensive index;

a – number of people who contracted the disease in a given period of time;

b – estimated population at risk for the same period;

k – relationship with a constant number of population (10n).

Therefore, intensive indices resulting from reporting an absolute size to another absolute magnitude, the result multiplied by a factor of 10, and can be expressed in per thousand - ‰ (one case per 1,000 people), prodecimile -% oo (a case 10 000 persons) or procentimile -% ooo (one case per 100 000 persons).

4.2.3.4. Extensive or structural indices are relative values of distribution and structure of the phenomenon, which shows the ratio of part and whole, the latter being always considered equal to 100. They are also known as rate because they show the share given to each part to the total phenomenon and is expressed as a percentage. It is given by:

$$I.E. = \frac{n}{N} \times 100 \text{ , where}$$

I.E. - Extensive index;

n - the absolute value of the part;

N - the absolute value of the whole.

Through the extensive index can be easily determined nosological structure of morbidity, nosologic forms prevalent in general morbidity, morbidity distribution for the months of the year (seasonality), the distribution of morbidity by age groups, sex, area of residence, structure of patients after clinical forms, according to severity, development, clinical outcomes, composition lethality, mortality, demographic phenomena etc.

4.2.3.5. Demonstration indices serve for comparing magnitudes of dynamic values, where the original size (but a different size string), taken as a basis, is equal to 100, and the other array sizes are recalculated with respect to the original size. It is expressed as a percentage.

Demonstration index allows abstraction from real comparative sizes, but also clearly demonstrates the difference between them and the trend of change (tab. 2).

Table 2

Incidence of scarlet fever in the city C., the years 1990-2005

Years	Absolute values	Intensive indices (per 100 thousand population)	Demonstration indices from absolute values	Demonstration indeces from intensive indeces
1990	282	37,96	100,0	100,0
1991	257	34,50	91,13	90,88
1992	164	21,99	58,15	57,92
1993	202	27,27	71,63	71,85
1994	279	37,67	98,93	99,23
1995	166	22,39	58,86	58,98
1996	127	16,89	45,03	44,49
1997	162	21,48	57,44	56,58
1998	260	34,53	92,19	90,96
1999	136	18,09	48,22	47,65
2000	122	15,88	43,26	41,83
2001	150	19,39	53,19	51,08
2002	127	16,40	45,03	43,20
2003	115	15,20	40,78	40,04
2004	145	18,20	51,41	47,94
2005	101	13,36	35,81	35,19

Table 2 and Fig. 4 show that the index demonstration, keeping the real ratio between sizes, reveals clear differences in disease frequency in the dynamic of scarlet fever.

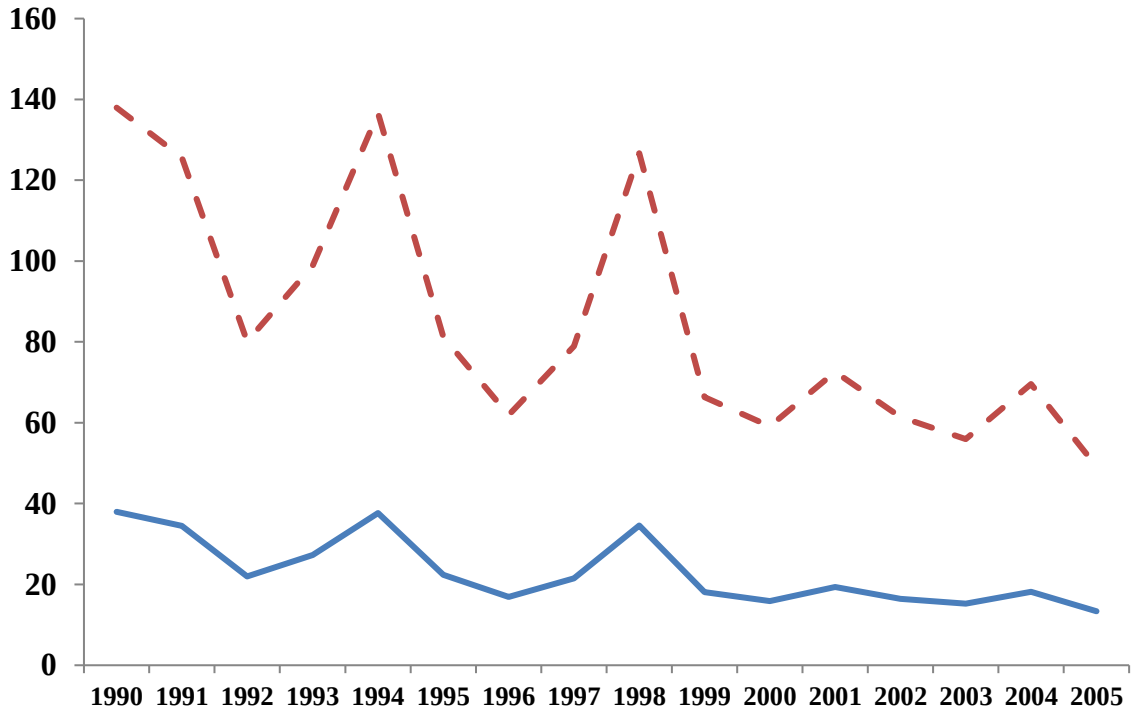


Fig. 4. Dynamics of morbidity of scarlet fever in the city C.,
during the years 1990-1995, presented in:
1 - strength indicator (per 100 thousand population);
2 - indices demonstrator based on strength indicator.

4.2.3.6. The proportions expressing the ratio of two separate amounts, for example, registered sex ratio illness or death of two groups of populations. As an indicator of the proportions is used index report, which is expressed by the relationship between the numerator and denominator and is calculated as follows: a = x / y.

TYPES OF STUDIES IN EPIDEMIOLOGICAL RESEARCH

The literature describes numerous classifications of epidemiological studies, based on different criteria. Overall, epidemiological studies can be classified into observational and experimental.

Observational studies describing and measuring health phenomenon in the natural development, without the intervention of the investigator. They are based on two types of studies: descriptive and analytical. Descriptive studies allow overall description of the phenomenon of disease, while the analytical - determining factors that influence the phenomenon, i.e. identifying the causes and determinants of morbidity.

Descriptive studies may be individual (case report and case series) and population (collective).

Analytical studies can be of three types: ecological (correlation), cohort and case-control.

Although observational studies do not provide direct occurrence of the phenomenon in the natural health, they, however, require intervention actions on the phenomenon investigated.

Experimental studies provide active influence of the researcher on the studied phenomenon of intervention actions (e.g.: treatment, vaccination, neutralization of risk factors etc.). They can be of three types: randomized, field studies and intervention studies of population.

Depending on the time or subject tracking mode, all epidemiological studies can be classified into transverse (for now) and longitudinal. Longitudinal studies are: retrospective and prospective.

One of the epidemiological studies is metaanalysis.

1. Observational studies

1.1. Descriptive studies

Descriptive epidemiological studies aimed at describing phenomena to see that the phenomenon exists to determine the characteristics and particularities. Each type of descriptive studies provides information primarily about people affected by the disease, where the disease occurs (place), when the disease appears (time) and the information on the characteristics, distribution of risk factors, the effectiveness of intervention etc. Without the application of descriptive studies it is impossible to realize the existing problem, its importance, of making assumptions about the etiology of the phenomenon or submit rational proposals to change the situation.

Descriptive study represents the first stage of a complex epidemiological investigations and followed as a rule, by the the analytical study. I mentioned

above that there are two types of descriptive studies: individual (case report or case series) and population (collective).

1.1.1. Individual descriptive studies

Case report is a description of an unusual case of disease or risk factors. Unusual case assumption is made on the basis of comparison with what is known previously. Description of a particular case, but unusual one can reprezent the first observation in finding new diseases, the effects of exposure, and the first step in observational studies or primary information for decision-making. The advantages of these studies are:

- progress in the medical field;
- identification of a new clinical entity;
- identification the consequences of exposure to risk factors;
- preliminary decisions intervention.

The disadvantages of this study are the following:

- observations are unique, isolated, and can be random, subjective;
- it is not possible to confirm correlative cause / effect.

The series of cases is a description of several cases with a similar disease occurring in a short period of time.

These reports of similar cases often became the starting point for defining a new nosological entity or a new epidemic. For example, the description by Michael S. Gottlieb et al., in 1981, of four cases of Pneumocystis carinii pneumonia diagnosed in young homosexual (USA) within 6 month period (1980-1981) paved the way for epidemiological studies dedicated to HIV / AIDS.

Such studies can generate etiological hypotheses testing requires other studies. The advantages of these studies are that they already allow the definition of new clinical manifestations, generate hypotheses to be confirmed by other studies and require the application of research strategies -epidemiologicalo, microbiological, therapeutic etc. These studies are provided with surveillance programs for suggesting the emergence of new diseases or epidemics.

The disadvantages of these studies are that they are often the result of experience only of a single author, without information on the frequency of the phenomenon, have no statistical confirmation of the lack of a comparison group.

An example of use in everyday practice of this method of investigation - case report or case series - is infectious disease outbreak investigation with single or multiple cases (see section 7.2).

1.1.2. Population descriptive studies

It is important to understand that the population descriptive studies on human pathologies are epidemiologically valuble. Usually, they follow a health problem and, most often, contribute to solving this problem at the population level or collectively. In all situations of population health in all epidemics particularly effective intervention measures may be taken only based on descriptive study. Although these studies do not contain a default assumption, however, they generate hypotheses that lead to analytic studies and operational actions. Population descriptive studies are complex studies often complicated both in terms of methodology for analysis of quantitative information, and accumulating data collection, and from the point of view of the multitude of possible variables that can be included in epidemiological analysis, relative to person, time, place, frequency, efficiency etc. Such epidemiological analysis requires special training. The major objectives of a population descriptive study are:

• to assess the significance of the phenomenon of health, which can serve as a serious argument in the development and advancement of health programs;

• to determine the epidemiological characteristics, level and trends of evolution of the studied phenomenon, graphic modelling, description and to compare them with other territories or countries;

• to formulate hypotheses on the etiology of the disease, which will be subsequently checked by analytical studies;

• substantiation of intervention measures.

In studying health, usually several variables are used as fully reflecting the epidemiology of the phenomenon. Quantitative characteristics (numeric) variables are obtained from existing official reports or epidemiological surveys. Descriptive study usually begins with determining the incidence and prevalence rates of the disease in the territory subject to study, i.e. measuring the phenomenon, comparing and evaluating it. Then proceed to analyze the characteristics of the phenomenon, which can be multiple.

Characteristics of a person, for example, which usually answer the question: "Who develops the disease?", include variables such as age, gender, personality type, ethnic group, religion, educational level, occupation, lifestyle, physical constitution , manifestations of disease, presence of concomitant diseases, individual and collective immunity etc. The individual features can be used and information on a range of social variables and behaviors that characterize a person. To social variables belong, for example, socioeconomic status, family characteristics, cultural habits, physical activity, marital status, presence of alcoholism, parental age at childbirth etc. In behavioral variables can be included smoking, nutrition, drugging, hygiene knowledge and skills etc.

Characteristics established place where the disease occurs more frequently. It refers to the geographical distribution of the disease and determines the prevalence of the disease in different parts of the country, in urban or rural areas, towns, institutions, countries, geographical landscapes etc. These features are specific nosological forms and are largely determined by some natural factors and social factors. These studies usually lead to specific pathologies' cartograms with certain territories, to compare them and to develop hypotheses about the etiology of the disease. The disadvantages of these studies is the difficulty of comparisons between countries because of the existence of different disease reporting systems. The time characteristics can be studied as disease frequency, which is also specific nosological forms, which are in direct function of the influence of social factors and natural. Time variables are expressed in hours, days, months, years. For example, the variables in hours or days are used in the study of acute infections, poisoning and food poisoning, acute epidemiological states and indicate the involvement of epidemiological risk factor or stae of emergency. Distribution of morbidity in the months leading to the determination of disease seasonality and descriptive study of the multiannual dynamics provide us with data on the evolution of the disease, cuurent and previous situation and, from which can be easily predicted future phenomenon (see Fig. 2 , 3, 4).

Descriptive studies ultimately lead to the identification of population groups at risk for contracting the disease, descovering teritory or environment time risks. They determine the evolutionary changes in the epidemiology and clinical disease, determine the effectiveness of the intervention, etc. All descriptive studies can be compared with patterns of morbidity and lethality in different countries or administrative territories at different time intervals etc.

The advantages are that descriptive studies are available quantitative information based on data, reported in current information systems and statistical reports on the results of medical tests of population, medical reports from hospitals or other services, other reports, such as vaccination campaigns, consumption of drugs etc., or obtained through studies of epidemiological investigation. Typically, these studies are cheap, quick and easy to perform. At the same time, the results of descriptive studies are valuable because they identify health problems, epidemiological and clinical peculiarities of the disease, provide basic information about the possible determinants of disease, allow the formulation of hypotheses that can be tested in further analytical studies, and the formulation of measures of intervention.

Descriptive studies provide useful information (highly valuable) for planning prevention and education programs and allocate necessary resources. The disadvantages of the descriptive studies are: they provide, as a rule, the

individual population data; some data are not available or have a form other than that required in the study; absence of standard diagnostic methods; lack of an appropriate control group; there is no temporally differentiation of relationship between exposure and disease and there is no posibility to test the etiological hypothesis, although in some cases correlative investigations can be used in descriptive studies.

1.2. Analytical epidemiological studies

The analytical studies investigating associations between risk factors and disease, are aimed to establish the quantitative assessment of the causes of the emergence and spread of diseases in human populations.

The analytical studies verified the hypotheses developed by epidemiological descriptive studies. They answer the question "how?" and "why" has occurred investigated disease by epidemiologic diagnosis.

In other words, analytical studies are directed to reveal the causes and conditions that determine health phenomena (morbidity, manifestations of epidemic process), detected after descriptive analysis, and serve to disclose the cause-effect relationship in the formation of mechanism of morbidity (development of epidemic) of different etiology, under practical conditions of place or time to establish more concrete ways of intervention.

Identifying the causes of disease and the modality of intervention in their neutralization is one of the priorities of contemporary epidemiology and medicine in preventing, combating and controlling diseases and health promotion.

1.2.1. The phenomena "cause and effect"

The cause always precedes effect, which is well known. It is prerequisite for the emergence effect. However, in medicine causal dependence disease or morbidity risk factor or another is different. Therefore, in addition to the term "cause" and other terms are used causative such as "necessary cause (main, obligatory)", "sufficient cause", "constituing causes", "complementary causes" and "risk factors" .

Must be considered causes without which there can be outbreaks or spread of disease. For example, without pathogen contamination with infectious diseases can not occur; it can not take place without the presence of susceptible persons as well. Sufficient reasons are considered in the presence of which usually occurs outbreak or spread of disease. Very often this type of case is singular. Typically, they involve a set of factors and conditions that lead to the production of the disease and the emergence of morbidity. Identification of all these components is not mandatory, because the removal of at least one component of this complex can

prevent disease. For example, the rabies illness occurs not only because of the rabies virus contamination, and lack of emergency prophylaxis. Another example might be: neutralization of at least one of the links leads to the interruption of epidemic process.

Often the risk and spread of diseases, especially those of non-infectious action are determined by several factors. Complex of sufficient factors causing or spreading disease determine constituent causes.

Additional causes usually complement the main causes. For example, the source of infection transmission mechanism and responsiveness of population are constituent causes or obligatory in spreading of infectious diseases. In fact, the spread of infectious diseases requires not only these three components of the epidemic process, but also a number of natural and social factors, some of them provide the functioning of these three components, the development of the epidemic process and as a result, increase of the morbidity. Other factors, on the contrary, lead to the reduction of morbidity.

Thus, the emergence and spread of diseases is related to the influence of several causes. Some of them belong to the main constituent and different combinations of causes are sufficient for the emergence and spread of disease.

For a simple causality, i.e. causal links between risk factors and disease, can be created different models, one of which (Rothman KJ, 1976) is shown in Fig. 7.

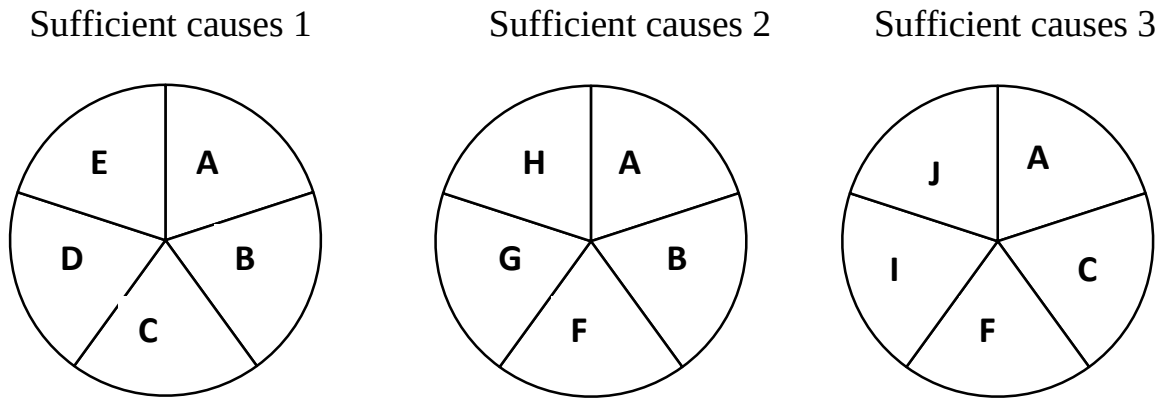


Fig. 7. Structure of causes of hypothetical disease

FIG. 7 shows that only Case A can be found in all sufficient cases. Only Case A is mandatory for this disease. All other constituit cases are complementary (additional).

Time diagram is useful in selecting measures to prevent diseases. The abolition of at least one of the causes leads to equal effect share value data component. Elimination of all causes or at least the main cause (A) will lead to the total prevention of the disease.

The literature highlights two concepts: "risk factors" and "causal factors". Factors, preceding the occurrence of health state that act indirectly are called risk factors but causal factors always induce direct effect [3].
The diversity of risk factors is practically unlimited. They include physical geography, flora and fauna planetary climate, natural events and antropurgice, social and attitudinal environment etc.

The effects of risk factors on population health are varied and complex. Some factors facilitate health state, others, through their action cause pathological conditions. However, the effect of several causal factors involved in the same body or the same population can be synergistic, antagonistic or additional.

1.2.2. Types of analytical studies

The main types of analytical epidemiological studies include:

1. ecological or correlational epidemiological studies;
2. epidemiological case-control studies;
3. epidemiological cohort studies.

1.2.2.1. Ecological or correlational epidemiological studies

This type of study is investigating the health of a population or groups of people (collective) depending on risk factors. They serve to determine the cause-effect relationship in formation mechanism of action morbidity and power (influence) of the determinants and their consequences. Correlational relationship demonstrates ratio function (interdependence) between the numerical values of the investigated variables.

So, the correlation is understood as statistical link of dependence between two or more variables of some phenomena. In other words, it is a correlation between exposure and effect. It was found, for example, that the greater the consumption of tobacco, the greater the number of deaths.

In ecological studies, although the object of study is the population, do not use special forms of evidence for each person. The selection of study group is performed on the territorial or social principle with common conditions.

In ecological studies there is no precise dividing of the population investigated in basic and control groups. At the same time, even within a territory, different groups of the population with different morbidity can be considered as case-control group. As an example is the investigation of the link between the level of drinking water supply of the population in different regions or localities and morbidity digestive infections.

The correlation (covariance)

To estimate the degree of association between cause and effect, dependent and independent variables, correlational analysis is used when, for example, we

compare the numerical indices of pathology (health phenomenon) and quantitative characteristics of the studied factor (factors) of assumed risk.

We distinguish two types of correlations: functional correlations and stochastic (statistical) correlations, both of which can be direct or inverse (indirect).

The functional correlations express a perfect rapid and accurate reciprocity, between phenomena and their variables. For example, between the A and B sides of the square there is a functional accurate and rapid correlation, where (A = B), a = b; A = A + B + b (FIG. 8).

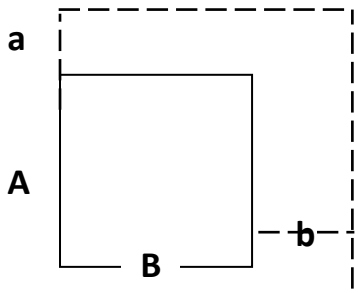


Fig. 8. Example of functional correlation

In case that both phenomena or variable values, which is a correlation between them, change in the same direction, we speak of a direct correlation, shown schematically in Fig. 9, which means that with increasing phenomenon (x) increases and the phenomenon (y), and at the same time with decreasing of (x) decreases and the phenomenon (y).

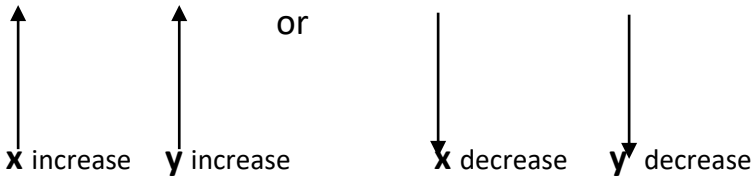


Fig. 9. Direct functional correlations

Indirect functional correlations, conversely, when the phenomenon (x) increases, the phenomenon (y) decreases, i.e. the phenomenon changes in the opposite direction (fig. 10).

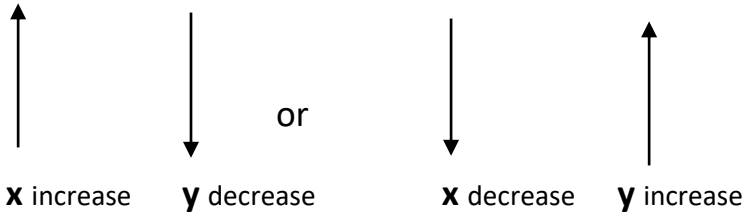


Fig. 10. Inverse functional correlations

Calculation of Pearson correlation coefficient (r)

In epidemiological research it is often necessary to establish the relationship between observed phenomena or subject of observation and the intensity of this relationship.

In these cases, if we want to know to what extent two quantitative variables correlate, calculate the Pearson correlation coefficient (r), which is a measure of relation (function) between two variables (i.e. between the dynamics of infectious diseases morbidity and immunoprophylaxis volume in this disease). Pearson linear correlation coefficient is calculated as follows:

$$r = \frac{\sum d_x \cdot d_y}{\sqrt{\sum (d_x)^2 \cdot \sum (d_y)^2}}$$, where:

r - correlation coefficient;
x and y - series correlative;
dx and dy - simple deviation from the average of two series (x) and (y);
dx^2 and dy^2 - squared deviations from simple arithmetic series x and y variants;
Σ - sum.

Example. We want to calculate the character of association between increasing number of vaccinations and the incidence of measles during 9 years in the locality B. Stages of calculation are presented in Table 12.

Table 12

Table for calculation of liner correlation coefficient

x – number of people vaccinated	y – number of illnesses by measles	d_x – the average deviation for the string **x**	d_y – the average deviation for the string **y**	d_x^2	d_y^2	$d_x \cdot d_y$
110	26	– 44	+ 10	1936	100	– 440
126	25	28	+ 9	784	81	– 250
132	19	– 22	+ 3	484	9	– 66
140	16	– 14	0	196	0	0
153	12	– 1	– 4	1	16	– 4
169	15	+ 15	– 31	225	1	– 15
177	16	+ 23	0	529	0	0
183	8	+ 29	– 8	841	56	– 232
196	7	+ 42	– 9	1764	81	– 378
$\bar{x}$ =154	$\bar{y}$=16	Σ = 0	Σ = 0	Σ = 6760	Σ = 344	Σ = –1385

$$r = \frac{-1385}{\sqrt{6760 \cdot 344}} = \frac{-1385}{\sqrt{2325440}} = \frac{-1385}{1524{,}94} = -0{,}908$$

Therefore, the figures show a reverse correlation between the incidence of measles and vaccination as a preventive measure, ie with increasing number of people vaccinated against measles decreases the number of illnesses caused by this infection.

Depending on the value of the correlation coefficient, the degree of association can be considered as strong, moderate, weak or negligible (tab. 13).

Table 13

Interpretation of the correlation coefficient values

The absolute values of **r**		The degree of association
+1,0 – +0,70	-1,0 – -0,70	strong
+0,69 – +0,40	-0,69 – -0,40	moderate (medium)
+0,39 – +0,20	- 0,39 – - 0,20	week
+0,19 – 0,0	- 0,19 – 0,0	negligible

1.2.2.2. Case-control epidemiological studies

The aim of the study "case-control" is to determine the causes of the emergence and spread of diseases. In studies "case-control" the likelihood cause-effect relationship is not substantiated by different incidences of morbidity, but the incidence (influence) different risk factor is involved in surveyed basic and control groups.

Studies "case-control" start assessing exposure and effect. By their nature studies "case-control" are retrospective. We present and examine disease risk factors in the past, according to the scheme of Fig. 16.

In studies "case-control" subjects are selected based on the presence or absence of a particular disease. The core group includes patients suffering from the disease and the control group (control) includes people who do not suffer from this disease. For example, take the study patients with lung cancer and non-cancer individuals (controls). Determine the frequency of smoking as a risk factor in all studied individuals.

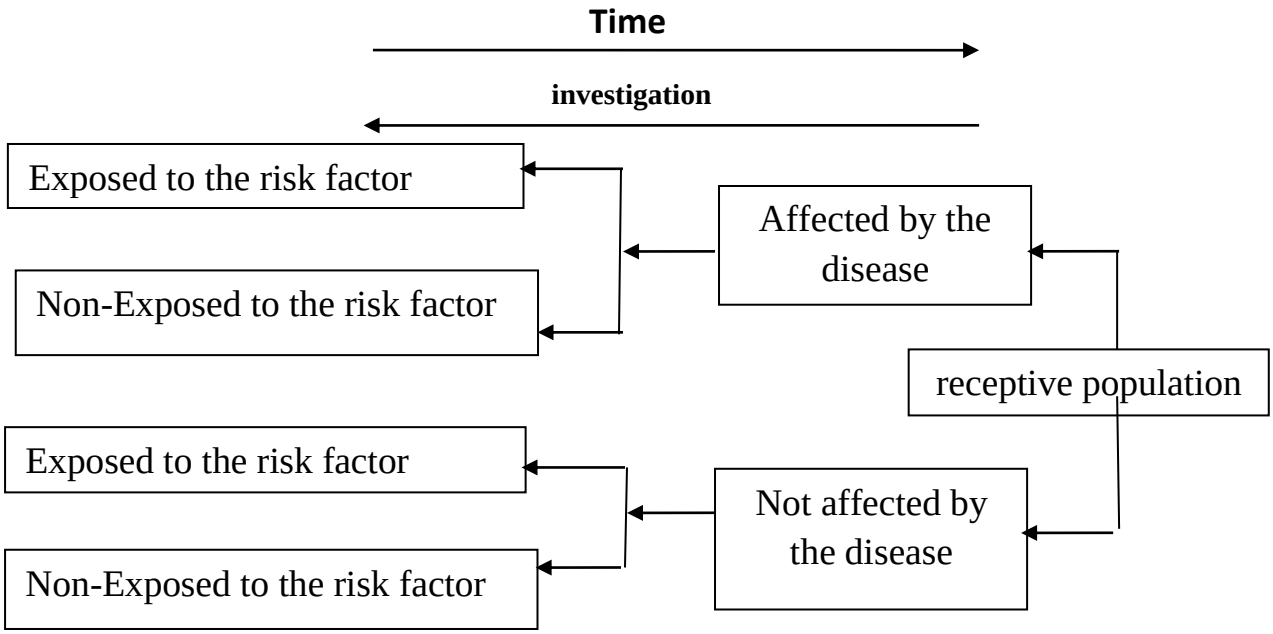


Fig. 16. Scheme of research in epidemiological studies of "case-control"

Assuming that smoking is a risk factor for cancer as a result will lead to a higher proportion of smokers among lung cancer patients than among those without cancer. The important point is onset and duration of exposure both in patients and in controls. This type of study is used more in assessing disease risk factors in low frequency and long latency. Typically, it begins with the selection of the cases of disease in a population and without the disease in cases of the same population. At the same time, these studies are useful in pharmacoepidemiology in the assessment of side effects. For statistical association between exposure and disease to be valid, it is essential for comparability of cases and witnesses, that lots must be homogeneous. It is important to establish strict criteria for disease diagnosis time because diseases, even very similar, may have different etiology, such as chronic hepatitis or primary liver cancer have different etiology.

Choosing the lots is based on the presence or absence of the disease, both groups having the same characteristics (age, sex, socio-economic status). Particular attention is paid to case control group. The selection of cases is used more frequently in patients treated in a hospital or medical service, or all people with the disease in a defined population, or randomly chosen a group representing the given population.

It is important to count on recent cases of disease than prevalent cases in which patients usually change their behavior towards harmful factors. These cases have initial appeal to history and influence of harmful factors throughout their action.

The influence of the risk factor is determined based on the query of people in both groups, their relatives, based on historical data, the study observation records or other legal documentation. Statistical results were analyzed using contingency table 2 x 2 for this model of studies (tab. 14).

In the model presented in tab. 14, we compare the results obtained in both groups, cases and controls, according to the formulas:

1. in the main group - present disease cases:

$$\frac{a}{a+b}$$

2. blank group - people without the disease:

$$\frac{c}{c+d}$$

If the index obtained in the group of patients is much higher compared to that for batch-control, we recognize the role of studied risk factor for disease.

Epidemiological studies of "case-control" are relatively inexpensive, easy to make, able to investigate the involvement of several risk factors, are useful in research on rare diseases outbreaks and causality. However, these studies can be a source of errors, particularly in selecting the batch-control, measurement action factors (amount and time of exposure) etc.

1.2.2.3. Epidemiological cohort studies

Although the purpose of cohorts is the same - to determine the causes of the occurrence and spread of disease in these studies, unlike those of "case-control", they start from exposure and till the effect is reached. In other words, they start from the sick, as in the case studies "case-control", but from a disease-free population group called cohort, which fall into two groups - exposed and not exposed to potential causes of disease e.g. smoking - nonsmoking. Both groups are followed up for a specific time to determine how many individuals exposed and not exposed to the risk factor of this disease contracted the disease. Then rates of disease in these two subgroups of the population are compared.

A prerequisite for this type of research is inclusion in in the cohort of persons the only ones without the disease, which probably may occur during the study, and it will form statistically representative group.

Therefore, cohort studies, in both groups - people exposed and unexposed to a riskfactor (factors) - are selected without the presence of these pathologies, but also homogeneous.

Research scheme of cohort studies is as follows (fig. 17).

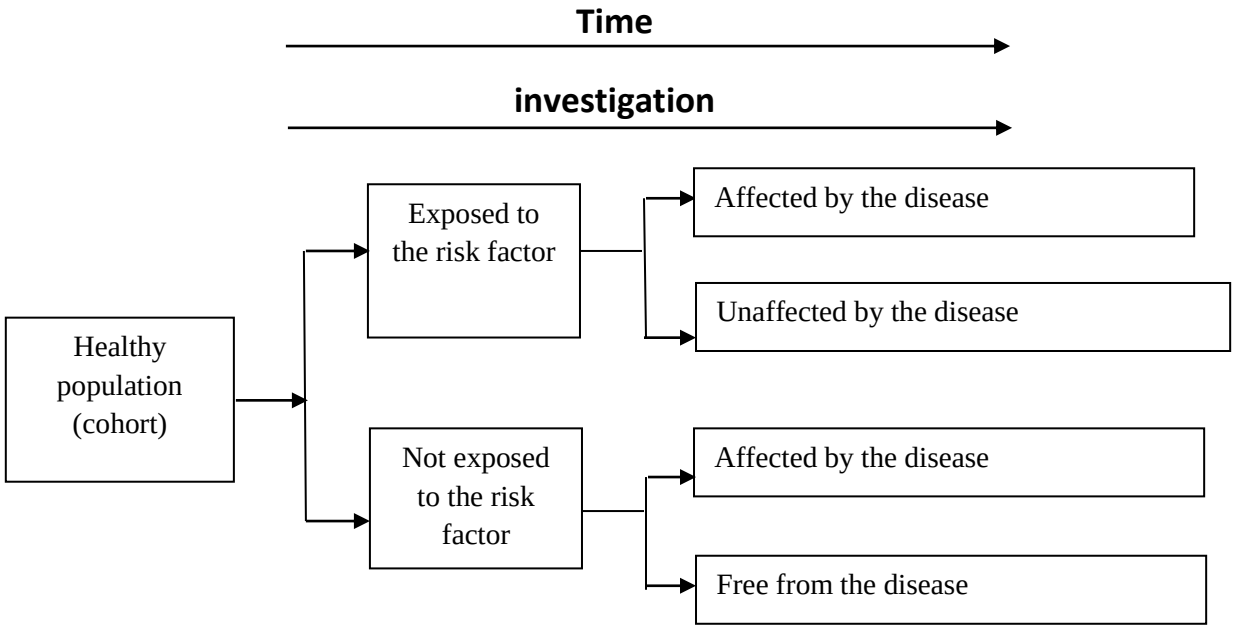


Fig. 17. Research scheme of epidemiological cohort studies

By their nature, cohort studies are observational because they do not interfere with anything in their evolution, and prospective (forward time tracking is suposed), subjects are followed for the entire study period, therefore these studies are called "tracking ". Follow-up period depends on the latency of the disease, i.e. subjects following up during the disease may occur (in infectious diseases, for example) the maximum incubation period.

During surveillance study participants in both groups undergo periodic medical examination to identify expected changes.

At the end of the study subjects are classified into 4 groups: group A - sick among risk factor exponents; group B - healthy people among representatives of risk factor; group C - patients in the control group (control); group D - healthy subjects in the control group (control).

Table 15

2 x 2 contingency table for research cohort

groups	Cases of illness		Total
	present	Absent	
Basic group (exposed to the risk factor)	a	b	a + b
The control group (not exposed to the risk factor)	c	d	c + d
Total	a + c	b + d	a + b + c + d

The disease incidence in the core group, according to tab. 15, will be equal to:

$$\frac{a}{a+b}$$

The disease incidence in the control group will be equal to:

$$\frac{c}{c+d}$$

2. Experimental epidemiological studies

Experimental epidemiological studies aim to evaluate quantitative means and methods of prevention and treatment.

This type of study requires the intervention of the researcher in the course of events related to human health or determinants, for example, assessing harmlessness, effectiveness and efficiency of medical interventions aimed at prevention, diagnosis or treatment, so, they are called intervention studies or experimental epidemiological studies.

There are several types of experimental epidemiological studies:

- controlled experimental studies;
- uncontrolled experimental studies;
- natural experiment;
- modelling of epidemic process (or pathological).

2.1. Controlled experimental studies

Controlled experimental studies are strictly determined by an initial protocol. This type of study is used usually in the evaluation of new preparations (vaccines, immunoglobulins, drugs), new medical technologies, screening programs, such as assessing of the sensitivity of a test for diagnosis of prenosological phase or a new method of healthcare management etc. As a result of these studies can be expected not only prevention, recovery or, conversely, disease, death, but also evaluation of some laboratory tests (paraclinical) to determine subjective signs, obtained from the query subjects in the study, and some changes in the environment. For example, the implementation of effective programs to control nosocomial infections in medical institutions not only will diminish the morbidity of nosocomial infections, but will produce changes in the level of staff training and behavior management measures for the prevention, treatment and diagnosis, revision of priorities and so on.

2.1.1. Randomized controlled trials

Such studies may have the widest application in epidemiological research trials.

Randomized controlled trials methodology is very similar to that of cohort studies in which a group of patients with the same morbid condition is randomly divided into two subgroups, one of them subjected to that intervention requires assessment, the second one subjected to "placebo" therapies or other therapies for comparison (control group), with the follow-up of two sub-groups for a predetermined time and further determination of comparative effectiveness and efficiency, on the basis of statistical analysis methods, (fig. 18).

Because subgroups of study are identical except for the intervention from the theoretically point of view any differences in the obtained results in the two subgroups are determined by intervention.

Randomized controlled trials show the gold standard of methodological and practical underpinning of evidence-based medicine.

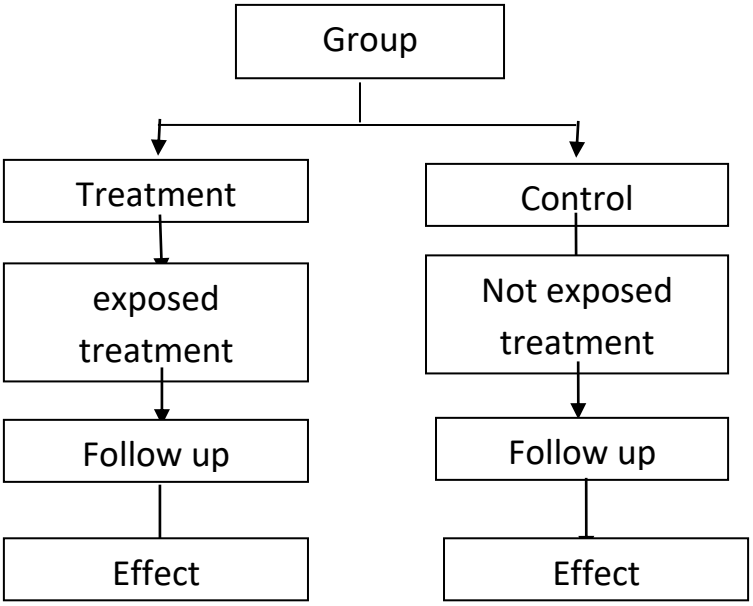


Fig. 18. Randomized scheme of controlled trials

2.1.2. Experimental studies of land

Experimental study includes persons who do not have the pursued disease, but are at risk of contracting it. The method is useful in assessing control measures intended to reduce exposure to a causative factor without necessarily required causal factor determining the effects on health. One of the groups to be compared is "protected" and the other "unprotected".

2.1.3. Uncontrolled experimental studies

These studies are used in clinical practice to assess the effectiveness of action. Usually there are population studies, which are based on studying the effect of measures already taken, but nonrandomized, due to this fact they are exposed to a higher degree of error. As a good example may serve decreased morbidity after mass vaccination, which may coincide with natural decrease as a result of periodicity of multiannual epidemic dynamics.

2.1.4. Natural experiment

Natural experiment means a situation in which increase or decrease of morbidity are caused by natural or antropurgical factors, some that do not depend on the will of the researcher, such as floods, earthquakes, heat, unusual increase of population of insects or rodents, activation of population migration, industrial accidents with risk factors on health, commissioning of the water supply network, armed conflicts etc. Such a situation can provide unique epidemiological data that can not be obtained by routine experimentation (planned) and the study of the obtained data of a natural experiment can also lead to very valuable conclusions.

2.1.5. Modelling of epidemic process

The essence of the process is to build the beginning of the experimental model of epidemic or disease process, examine the functioning of this model in the experiment, and then using the obtained data in clarifying natural processes. At the current stage in epidemiological studies are used mathematical models, epizootological models, modelling of the epidemic process of intestinal infections, by using strains of E. coli M-17, modelling of epidemic process in nosocomial infections using bacteriophage, modeling of septic -purulent process on laboratory animals. Creating facilitates experimental models of studing the possibilities of natural processes related to human health.

3. Epidemiological transversal studies

Cross-sectional studies measure the prevalence of a disease in a defined population in a short time, so they are also called prevalence studies. The morbidity of a population is studied at a given time, that presents a photographic snapshot of a moment.

In other words, the purpose of the transversal studies is to obtain a full information on the prevalence of morbidity at a time or in a short period of time. If necessary, such research may be repeated.

Transversal studies can assesse to both the disease and its characteristics and the presence or absence of risk factors.

Therefore, transversal studies provide data for calculating some health indicators and the knowledge risk factors of studied disease, but without specifying whether it succeeds exposure precedes effect. These studies are usually used as the first stage of an epidemiological study, especially in descriptive studies; they describe a health problem and often allow the start of analytical or experimental studies of health programs.

The advantages of transversal studies:

• they are easy and low cost;

• allow the analysis of health issues and detrmine the priority of response actions;

• generate hypotheses that can then be confirmed by analytical studies;

• requires observing subjects in a short period of time;

• serve as a first step in deciphering outbreaks with unknown cause.

Disadvantages of cross-sectional studies:

• do not allow the temporality on exposure and disease;

• do not provide evidence on the association of disease and risk factors;

• not useful for assessing incidence;

• not applicable for rare diseases;

• There is a risk of confounding factors;

• There is a risk of errors in history.

4. Longitudinal epidemiological studies

Longitudinal studies refer to examination of health problems in dynamics. They can be of two types: retrospective and prospective.

4.1. Retrospective studies will examine the information on morbidity (death) and risk factors collected in the past in a certain period of time (days, months, years). An important source of information in retrospective studies can serve the registration system and evidence of patients, such as history sheets and epidemiologal papers of infectious diseases.

Retrospective studies can be both descriptive and analytical. A typical retrospective descriptive study is a retrospective epidemiological analysis of morbidity by a certain disease in a defined population (administrative area) or active diagnosis of nosocomial infections, based on retrospective analysis of records of observation. An example of an analytical study is the intervention of the

possible link between health phenomenon and the risk factors occurred in the past (case-control study).

4.2. Prospective studies provide information examination on the extent new cases of disease emergence, which were not present at the beginning of the research. Prospective studies are based on the likelihood of new cases of infection in a population subject to a risk factor. It is in pursuit of a group exposed to a risk factor over time.

Prospective studies can only be analytical. A typical example is the cohort study.

5. Meta-analysis

Meta-analysis (meta-analysis, survey research) is the use of statistical methods in order to synthesize the results of several independent studies devoted to a problem, the final result is presented in the form of synthesized unique result. Therefore, statistical meta-analysis summarizes the numerical results of several independent research that addresses the same problem. It is a particular type of study, based on previous studies in which the researcher has not collected personally the data for the study, the researcher was not in direct contact with the test subjects, but collected the data from literature studies, both data are to be combined.

Stages of meta-analysis

The first step is the search and selection of all publications on the subject of the investigation safer in terms of their execution quality and authenticity of the results.

The second step consists in estimating the degree of correspondence of publication research with planned metaanalysis criteria.

The third stage is the union of quantitative information from selected studies. Subsequently, by means of statistical methods the synthesized result is calculated. Like other studies, meta-analysis should be planned in advance and must follow a research protocol that includes working hypothesis, sampling strategy, inclusion criteria, the method of analyzing information.

5. Determining the risk

Epidemiology task is not only to determine the factors that influence health, but also in evaluating the risk of disease, i.e. the probability of disease according to certain characteristics of risk factors.

In epidemiological practice following indicators are used to determine the risk: absolute risk, attributable risk, relative risk, odds ratio.

6.1. The absolute risk (R) is the probability of an event in concrete terms, without reference to another probability. When referring to the disease, the absolute risk is expressed normally in the incidence of disease in the population investigated.

An example may serve the incidence by disease of the morbidity in the certain territory or environmental space.

In the case when it comes to people exposed and unexposed, start from 2x2 contingency table (Table 16).

Table 16

Contingency table “2x2”

	sick	healthy	Total
Exposed	a	b	a + b
unexposed	c	d	c + d
Total	a + c	b + d	a + b + c + d

incidence of disease in the exposed (risk of disease in those exposed):

$$I_e = \frac{a}{a+b};$$

incidence of disease in the unexposed (risk of disease in the unexposed):

$$I_{ne} = \frac{c}{c+d}.$$

6.2. Attributable risk (AR) is the absolute difference between two risks called "risk gap".

The attributable risk provides information about the overall effect of exposure or measures excess risk of disease in those exposed compared with those not exposed, that is the partially incidence is due to the risk factor. RA shows with greater risk to those exposed to those not exposed factor (factors) and risk difference is calculated as the cumulative incidence (risk difference) of two groups compared, according to the formula:

$RA = I_e – I_{ne}$, or, according to contingency table „2x2”,

$$RA = \frac{a}{a+b} - \frac{c}{c+d}.$$

The attributable risk can range:

1) equal to 0, when the risk is the same in people exposed and unexposed;
2) greater than 0, the exposure has adverse health effect;
3) less than 0, the exposure is protective (Table 17).

6.3. The relative risk (RR) measures the force of epidemiological association, or the number of times risk of disease is greater in people exposed to the unexposed, or the probability of contracting the disease in the exposed group compared to the unexposed. RR answers the question: how many times it is more likely to contract the disease for subjects exposed to unexposed ones? RR is used especially in cohort studies and it is the ratio of the incidence of the disease in the exposed group (Ie) and the corresponding incidence in unexposed group (Ine). The formula is:

$$RR = \frac{I_e}{I_n} = \frac{a/(a+b)}{c/(c+d)} \quad .$$

In cohort studies to calculate the cumulative incidence (CI) calculation formula is:

$$RR = \frac{IC_e}{IC_n} .$$

6.4. Odds ratio (OR)

In case-control studies can not be calculated incidence rates for compared groups, therefore, we can not find the relative risk. In case-control studies, subjects are formed on the basis of knowledge regarding the disease status, and exposure is not possible to determine the proportion of subjects who will develop the disease, as in cohort studies, because the proportion of individuals exposed in the reference population is not known. In such cases, the proportion of persons subjected to exposure to the risk factor in the group of patients, on the one hand, and in the group of healthy (control), on the other hand, that is, it presents a reverse calculation to that in the cohort study. You can not directly calculate the RR cohort study, but it can be estimated by calculating the ratio of quotas (odds ratio) by the following formulas:

a) Rate of (odds) exposure among cases:

$$\frac{\text{The proportion of exposed cases}}{\text{The Proportion of exposed cases}} = \frac{a/(a+c)}{a/(a+c)} = \frac{a}{c};$$

a) Rate of (odds) exposure among controls:

$$\frac{\text{The proportion of exposed in controls}}{\text{The proportion of unexposed in controls}} = \frac{b/(b+d)}{d/(b+d)} = \frac{b}{d};$$

b) Proportion of rate (*odds ratio*):

$$OR = \frac{\text{Rate of exposure among cases}}{\text{Rate of exposure among controls}} = \frac{ad}{bc}.$$

The odds ratio can range:

a) equal to 1 when there is no difference between the groups compared;
b) greater than 1, the exposure has adverse health effects;
c) less than 1, the exposure (intervention) was effective in reducing the risk factor (protection) (Table 17). When the frequency of events is very small relative risk and odds ratio are similar.

Table 17

Scheme of Risk Analysis

Attributable Risk	Relative Risk	Odds ratio	Conclusion
RA > 0	RR > 1	OR > 1	risk factor
RA = 0	RR = 1	OR = 1	indifferent factor
RA < 0	RR < 1	OR < 1	factor of protection

7. Epidemiological investigation

Epidemiological investigation presents an investigation based on survey sheets and can be of several types: investigation of a health status at a time (epidemic outbreak with single cases epidemic eruption etc.), public health investigation of a situation that is related to population, community, population quotas etc.

7.1. Epidemiological investigation of outbreaks of infectious disease with single cases

7.1.1. The notion of epidemic outbreak

The "epidemic outbreak" is understood as the place to find out the source of pathogens and within the surrounding territory, where the causative agents can be transmitted from the source to other people.

There are two elements that characterize outbreaks: the existence in space and time, i.e. spatial limits (boundaries) and temporal limits of outbreaks. Spatial and temporal limits of infectious disease outbreaks in each period are determined by infectivity, transmission mechanism, causative agent characteristics and actual conditions of natural and social environment (ambient), which determines the possibilities and dimensions of achieving the transmission mechanism, furthermore, incubation period of the infectious disease.

7.1.2. The concept of epidemiological investigation of the outbreak

Epidemiological investigation of the outbreak is a specific method of investigation of the outbreak of infectious disease based on epidemiological triad and used to determine the cause of its occurrence, tracing pathogens, pathways,

factors and conditions of transmission and the people at the risk of contamination and disease and, finally, finding and developing complex epidemiological measures, aimed at locating an outbreak.

Epidemiological investigation of outbreaks is an important element in epidemiological practice and efficient implementation of anti-epidemic measures. Their fullfilment by epidemiologists or doctors requires deep knowledge in general and special epidemiology, depending on the particular focus and nosological form of the disease.

7.1.3. Tasks of (goals) epidemic outbreak investigation are:

1. The diagnosis of disease.
2. Detection of people affected by the disease.
3. Determining the boundaries of the spread of the outbreak.
4. tracing factors and ways of transmission of the causative agent.
5. Determination of the terms, conditions and cause of epidemic outbreak.
6. Formulation of epidemiological diagnosis.
7. Development of measures to locate and liquidate outbreak.
8. Evaluation of the quality and efficiency of anti-epidemic measures carried out in the outbreak.

7.1.4. The methodology of investigation of outbreaks of disease with unique cases.

The investigation of single cases outbreaks of disease includes the following steps:

- preparing to conduct epidemiological investigation;
- investigation of outbreaks;
- formulation of epidemiological diagnosis and recommendation of measures for tracking and eradication;
- supervision of outbreak.

7.2. Epidemiological investigation (research study) based on questionnaire

The questionnaire is a list of questions, the answer to that would shed light on an issue of health, social, behavioral and other problemsetc.

Following terms of implementation, based on questionnaire investigation can be of 3 types:

• investigation of the interview;

• investigation by the person completing the questionnaire (on site or by mail);

• questionnaire data from documents: archives, records, observation sheets, clinic sheets etc.

The subject-based questionnaire should start from a health problem, for example, the incidence increased or maintained at a high level of disease in a population, or one of the subpopulations, deciphering of epidemic eruptions, finding population health issues etc.

8. Epidemiological analysis of morbidity

In practice, both prevention and combat of infectious diseases and the non-infectious morbidity, epidemiological analysis underly the diagnosis and epidemiological surveillance of public health.

After analysing epidemiological situation can be determined regularities of formation and spread of morbidity, epidemiological peculiarities, epidemiogical situation in the past, present and future, epidemiological and socio-economic importance of the disease, based on which measures to prevent and combat are proposed.

8.1. Retrospective epidemiological analysis

Retrospective epidemiological analysis is a kind of stand-alone analysis, which includes various types of epidemiological research - descriptive, analytical, experimental, mathematical modelling.

The term retrospective epidemiological analysis means that it is based on epidemiological situation reflected in the past, to a time before, analyzed, in order to obtain information for predicting the situation and planning motivated intervention measures.

8.1.1. Stages of retrospective epidemiological analysis:

1. Conducting research project.
2. The accumulation of information.
3. Grouping and aggregation of information.
4. Descriptive analysis of information gathered and advance of hypotheses.
5. Hypothesis testing on the link "cause and effect" (analytical phase).
6. Evaluation of the effectiveness and efficiency of prevention and control measures.
7. Formulation of epidemiological diagnosis.
8. Developing program of intervention measures in order to reduce morbidity and disease eradication.
9. Estimating of epidemiological situation.

8.1.1.1. Analysis of multi-annual dynamic of morbidity

Studying the dynamics of multiannual morbidity is the starting point in retrospective analysis of morbidity in each nosological form part.

Description of multiannual morbidity dynamics permits the assessment of evolutionary change in the epidemiological situation for a certain time, the launch of hypotheses about possible causes that have led to changes in data and forecast future situation. Dynamics of morbidity is seen as a reflection of action causative factors (fig.19).

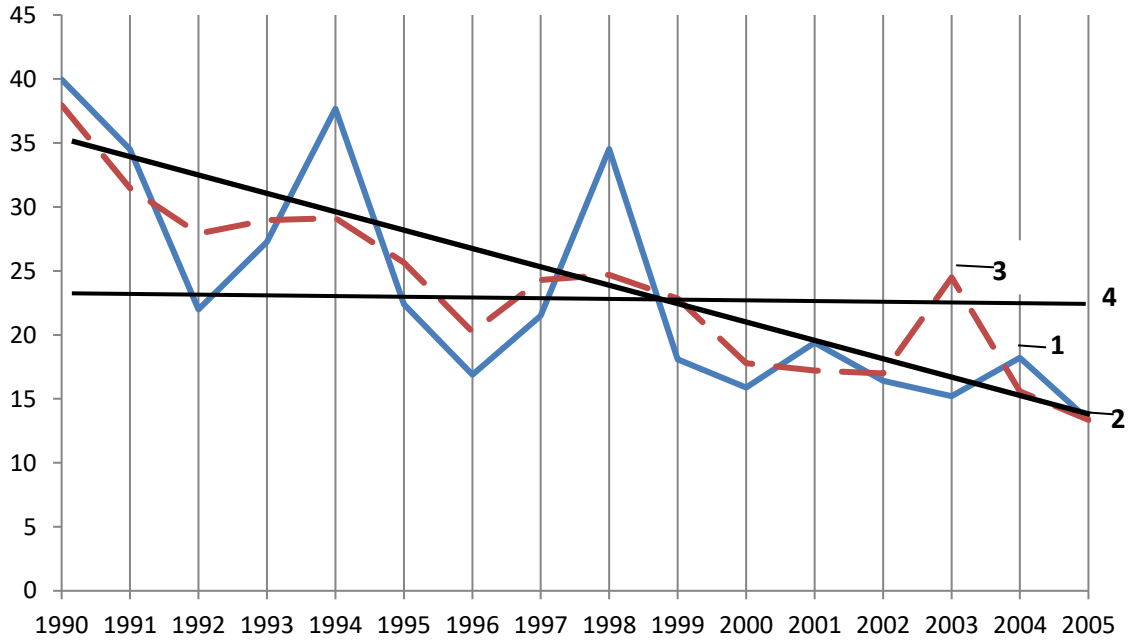


Fig. 19. Dynamics of morbidity of scarlet fever trend in the municipality. C., during 1990 - 2005 years (1 - morbidity per 100 thousand population; 2 – tendency of morbidity; 3 - Gliding average; 4 - annual average).

8.1.1.2. Analysis of growth of morbidity in annual dynamic

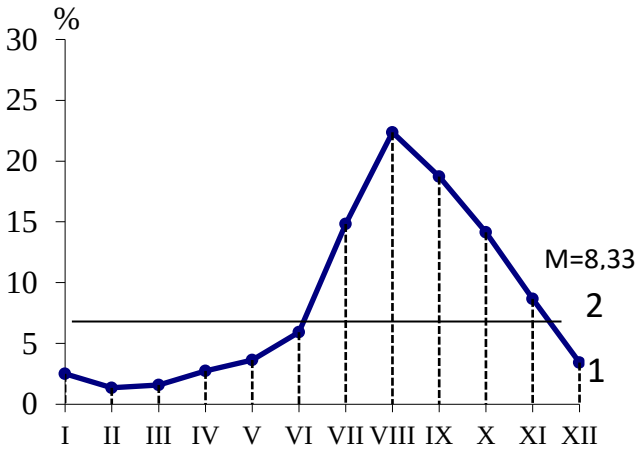
Analysis of morbidity in the annual growth rate is a very important section of retrospective epidemiological analysis because this study is determined by both the evolution of annual and seasonal peculiarities - the year with increased incidence, i.e. "time risk" in that disease and factors (natural, social, human) enhancing disease affecting different times of the year.

To calculate the seasonality of the morbidity is required the distribution of cases in the studied period (year, years, during epidemic or vice versa) during months of the year, according to Table 20. In the given table is presented the distribution of morbidity respective months of the year and calculations on the leptospirosis model.

Table 20

The distribution of leptospirosis morbidity in Moldova during the years (1993 - 2010)

Indexes	months												Total
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	
Abs.	11	6	7	12	16	26	65	98	82	62	38	15	438
%	2,51	1,36	1,60	2,74	3,65	5,94	14,84	22,37	18,72	14,15	8,67	3,42	100,0
Average	0,35	0,21	0,22	0,40	0,52	0,87	2,10	3,16	2,73	2,00	1,27	0,48	1,19
Seasonal variation index	29,4	17,6	18,5	33,6	43,7	73,1	176,4	265,5	229,4	168,0	106,7	40,3	
Month Average	abs = 36,5; % - 8,33.												



1 – annual dynamics; 2 – month average.

Fig. 21. Seasonality of morbidity in Leptospirosis in R. Moldova, 1993–2010 (line diagram)

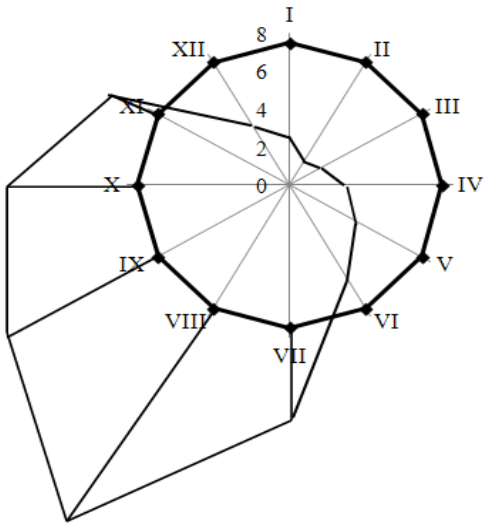


Fig.22. Seasonality of morbidity in leptospirosis in R. Moldova, 1993–2010 (polar diagram)

8.1.1.3. Analysis of geographical distribution (spatial) morbidity

This means the distribution of morbidity on administrative or geographic territories, which differ in both intensity (level) morbidity and morbidity in terms of training, hence the name "geographical epidemiology".

The extent different regions differ in demographic characteristics, socio-economic and geographical (natural) equally manifestations morbidity by disease or another are different.

Table 21

The territorial distribution of morbidity _____ , years_____

*Name of territory	Area of territory	Nr of population	Morbidity **			Other statistical indexes
			absolute	to 100000 population	to 1 km^2 ***	

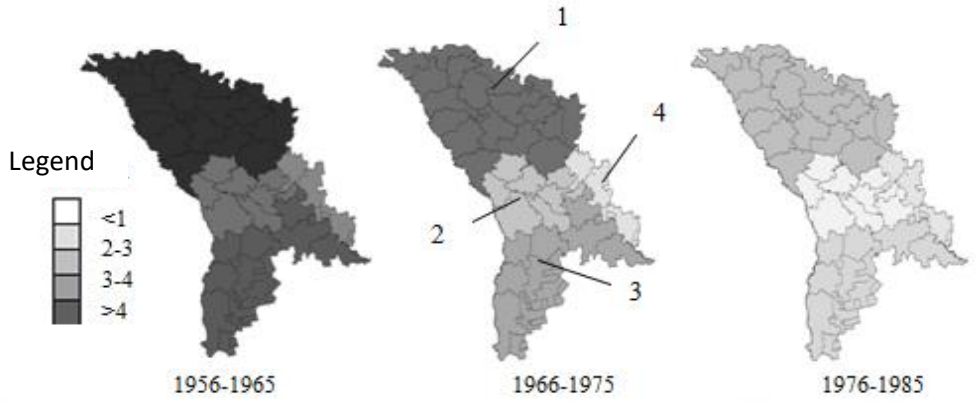


Fig.25 The intensity of epidemic process in anthrax in RM (nr.of cases of diseases per 100 km^2), 1956-1985, according to geographical distribution: 1-North, 2- Centre, 3-South, 4-South-Est. (V.Prisacari,1990)

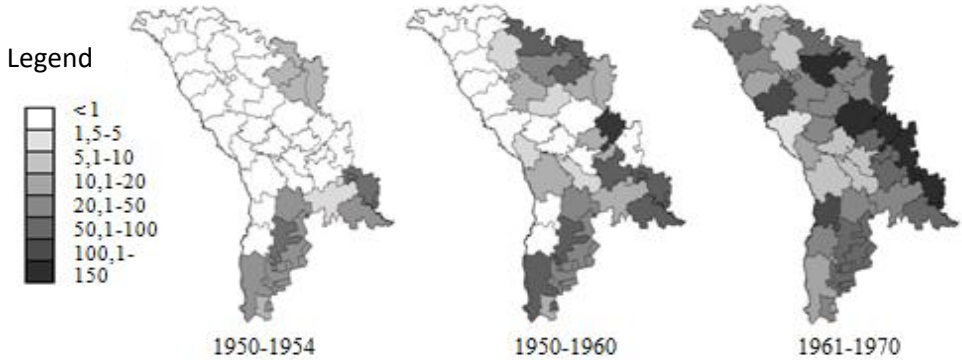


Fig.26 The intensity of epizootic process in leptospirosis in RM in domestic animals (nr.of cases of diseases per 100 km^2), 1950-1970

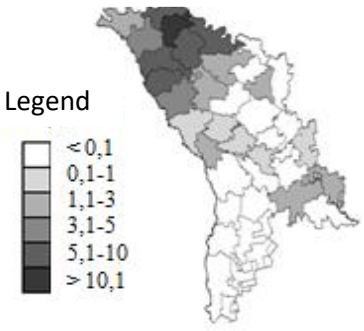


Fig.27 The intensity of epizootic process in L.grippotyphosa in RM, 1981-1986 (% seropositive samples from total number of investigated rats)

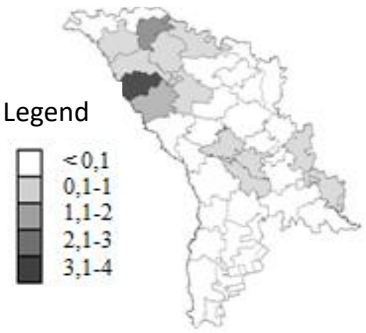


Fig.28 The intensity of epidemic process in L.grippotyphosa in RM, 1981-1986 nr.of illness per 100 km^2)

8.1.1.4. Determining the risk groups

This section of retrospective epidemiological analysis (classical) refers to the analysis of the characteristics related to the person or the host population in infectious diseases in all respects (see comp. Descriptive studies of population). According to the principle of heterogeneity of populations, individuals in a population are different. However, after some signs, they can be grouped based on race, sex, age, area of residence, occupation, susceptibility etc. Since the degree of sensitivity and contamination conditions, diagnosis, treatment etc. differs in different populations, so the risk of developing the disease will be different, namely, the level of morbidity in these groups will also be different.

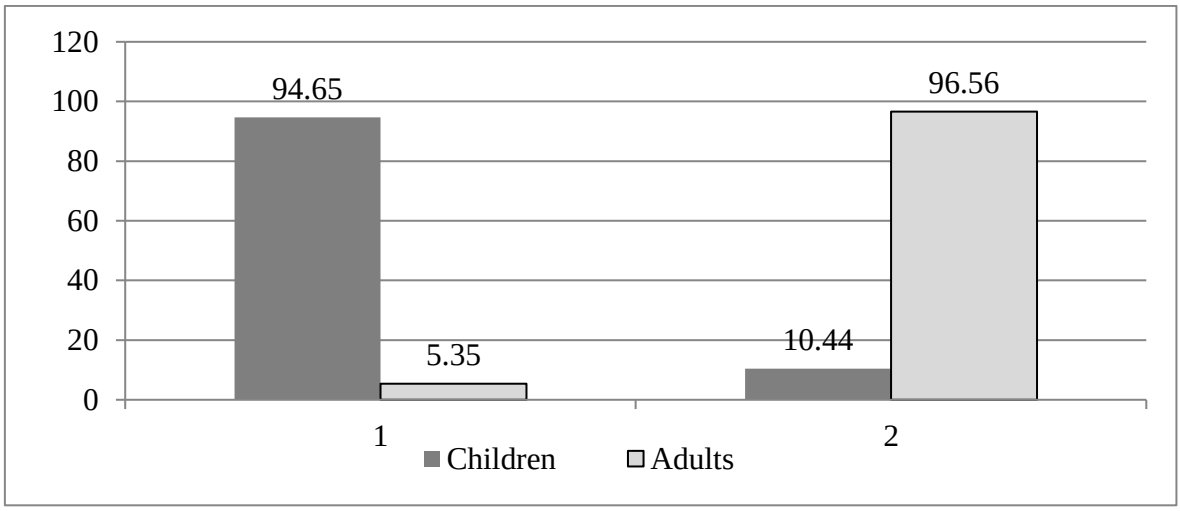


Fig. 29. Comparative distribution of scarlet fever morbidity (1) and leptospirosis (2) in the group of children 10 - 17 years and adults, years 1998-2009

8.2. Operative epidemiological analysis

Operative epidemiological analysis is a logical continuation of the retrospective analysis, i.e. studying the dynamics of the situation taking into account the assessments of epidemiological retrospective analysis. In other words, operational analysis provides constant supervision of the situation using the same methods as in the retrospective analysis.

Basically, it comes from epidemiological analysis of the situation every day or every week, month, quarter, year. One example is the annual epidemiological analysis of the situation in the supervised territory based on obtained data during the year and determines changes in epidemiological situation, including the structure and level of morbidity, level of involvment in the epidemic of different population groups in the territorial distribution and dynamics of morbidity.

8.3. Planning intervention measures

As mentioned above, retrospective and operative epidemiological analyses have as the final aim rational and efficient planning of intervention (control), i.e. the available measures, but with low prices cost and high effectiveness.

Intervention measures can be classified into:

• primary prevention measures - aimed at protecting the health of the population by neutralizing or reducing action of risk factors;

• secondary prevention measures - screening and therapeutic measures aimed at early detection (reversible stages) and effective therapeutic intervention in order to stop bullying disease;

• tertiary Prevention - treatment and recovery measures, aimed at reducing complications of already manifested disease, significantly improving the health of the individual patient and his social integration.

9. Screening

Screening is mass examination, which consists of applying a set of methods and techniques of investigation to population group in order to diagnose a disease or suspected abnormalities and risk factors.

Therefore, screening implies investigation of persons who consider themselves healthy, but can carry a disease or abnormality, especially during latency. However, screening is used to detect risk factors in healthy individuals, such as smoking, harmful habits etc.

Screening research is increasingly present in both infectious diseases and non-infectious, in connection with the implementation of the new system to prevent disease, and primarily reflects the interests of secondary prevention, i.e. early stage of treatment of the disease, when the effectiveness and intervention effectiveness can be much higher.

Tasks of screening

• Maintaining health and preventing disease by identifying and removing risk factors. From this point of view, screening may be assigned primary prevention measures.

• Early detection and treatment of disease. From this point of view, screening may be assigned secondary prevention measures.

• Determine the prevalence of disease or risk factors. Through this screening purpose can serve as a basis for planning and programming of health.

• Determine the health of a community.

• Evaluation of programs or actions.

There are two types of screening:

• screening as a prophylactic measure;

• the screening method used in epidemiological research.

10.Determination of the size of the studied group

Epidemiological studies are classified into two types: complete and selective.

Exhaustive studies involve research of all individuals of a population (the population of administrative territory, population of women or men, children or adult population). An example of exhaustive investigation may serve systematical population census or medical research of all newborns or pre-military. Basically, a research is recommended when the whole population "x" is not too high, to avoid expences that may outweigh the conclusions drawn.

Selective studies (partial) involve research of only a part of this population (group of subpopulation), and the subjects of the research are regarded as exponents of this population. Thus, the term "sample" means a part of a population, by which the whole population can be represented and the sampling is the formation of samples (groups of subjects) for the study.

10.1 Determination of group size

When planning a study, for example, to determine the efficacy of a vaccine or drug implications, it is required to calculate in advance the number of subjects that will be necessary for research. Planning can prevent extreme situations, when the sample size is too small, and the results - incorrect or vice versa, when the sample size is unnecessarily large and leads to unnecessary expenses.

To determine the sample size is used formula:

$$n = \frac{t^2\ p\ q}{\varepsilon^2}$$, where:

n - first estimation;
t – confidence (95% will use the value 1.96);
p – the proportion of individuals with characteristics measured in the target population (when it is not known p = 0.5);
q – 1,00 – p
Ɛ – precision (usually 0.05 or 0.01).

This is followed by the final estimation of the size of the studied group according to the formula:

$$n_f = \frac{n}{1+\frac{n}{N}}, \text{ where:}$$

n_f –final size of the group;
n – first estimation;
N –size of the target group of population.

GENERAL EPIDEMIOLOGY OF INFECTIOUS DISEASES

1. Epidemic process. Regularities maintenance, development and decreasing of morbidity

1.1. Basic principles

The epidemic process in contagious diseases is recognized as a specific complex element of human ecosystem that underlies the maintenance of pathogenic microorganisms in nature.

Social and biological nature of the epidemic process, its structure and peculiarities were revealed by following the epidemiological studies. The great scientific discoveries of the last century, which are rightly considered as major public health concerns, led to the effective control of infectious diseases.

It is necessary to understand that during the development of the science about the epidemic process were formulated several theories, concepts, views on the essence of epidemic process, structural organization and operating system. All these concepts, at first sight contradictory, is nothing else than a set of new knowledge on the structural and operating system of epidemic process as a phenomenon fully autonomous and self-regulating .

These successive findings complementing each other are at the base of current study about essence of the epidemic process, which can rightly be considered the theoretical foundation in the development of surveillance and control programs in all diseases.

According to A. Ivan (2000), baseline knowledge about structure of epidemic process is considering it as a whole, as external attributes ("overall structure"), followed by decomposition of the assembly elements and their research in terms of dynamic characteristics ("structural element"). Further is performed research concerning relations between elements. The epidemic process of diseases with its structures and interrelations expresses the structural and functional aspects of human ecosystem, whose knowledge is a fundamental value in developing programs for prevention and control of diseases.

1.2. Concept, structure and mechanism of development of the epidemic process

1.2.1. The concept and basic structure of epidemic process

For the first time L.V. Gromaşevski (1949) assessed the epidemic process as a consecutive chain of infectious state from manifested till unapparent.

Manifested epidemic process is considered in cases of the epidemic process composed of infectious manifested statements, e.g. influenza (fig. 36). In cases

where the epidemic process is composed of unapparent infection status (unfold), it is latent epidemic process (non-manifested), and if the epidemic process consists of infectious manifested and non-manifested states, it is considered as epidemic process partily or non-manifested, for example, diphtheria or polio. (fig. 37)

The epidemic process is developed in the human population but infectious states are part of society and individuals are considered biological components of epidemic process.

A law of the epidemic process is that any infectious state is preceded by another infectious state. They are successive in turn and may lead to an other new infectious state. The morbidity is higher when the development of epidemic process at the horizontal level is more intense. The epidemic process has social-biological nature, as it includes both infectious conditions and social conditions that determine their reproductive possibilities and developing of epidemic process.

The emergence and development of the epidemic process are conditioned also by the existence and interaction of three mandatory elements called chains of the epidemic process:

- source of pathogens;
- specific mechanism of transmission of pathogens;
- receptivity of population.

These three components of epidemic process (fig. 38) are the core or base of any communicable disease. They are closely related and the relationship is permanent is in interconnection. Excluding one of the chain usually leads to the termination of the epidemic process. This element was the basis of the modern system to control the infectious diseases, which provides three main epidemic groups of measures:

- measures aimed to neutralize the source of pathogens;
- measures aimed to neutralize mechanism of transmission of the causative agent;
- measures aimed to increase the immune state of population.

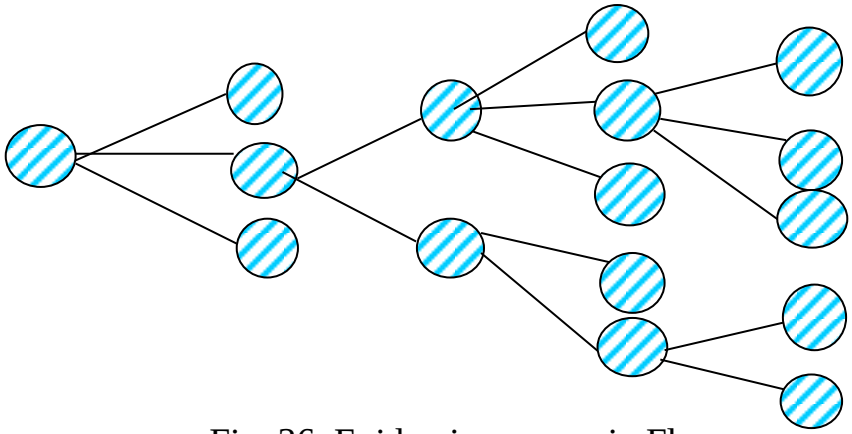


Fig. 36. Epidemic process in Flu

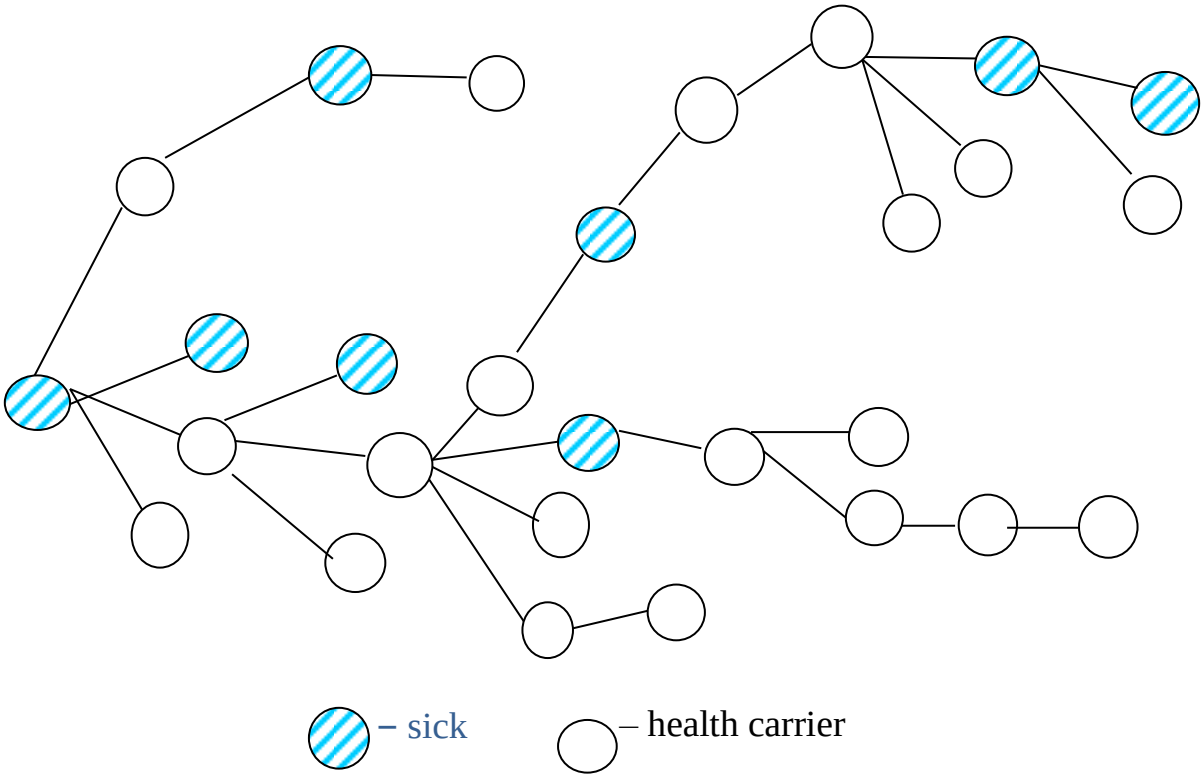


Fig. 37. Epidemic process in Polio

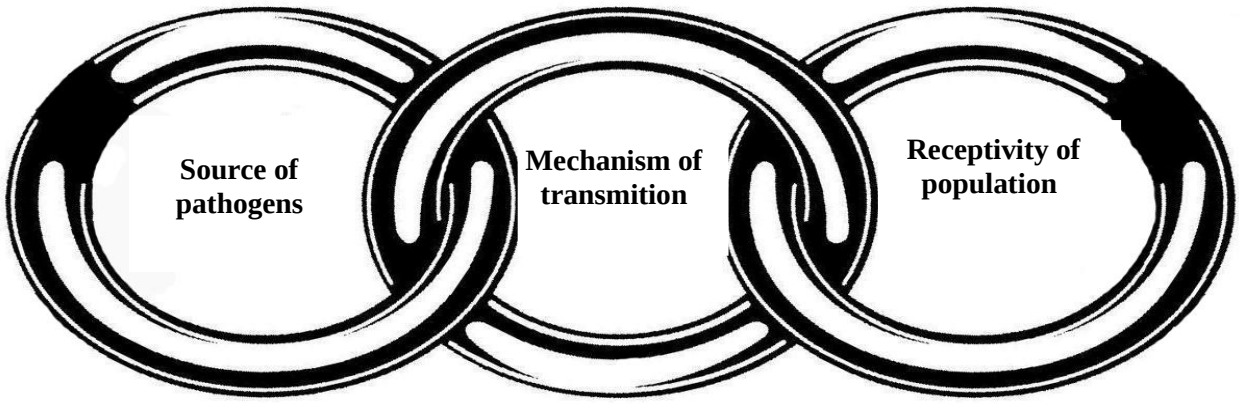


Fig. 38. The structure of epidemic process (L.V. Gromaşevski)

1.2.2. Source of pathogens

Initially, Gromaşevski L.V. (1949) defined the concept of source of pathogens as represented by the human body or animal where infectious germs, because of their development of adaptation, have found their natural living where they multiply, accumulate and are eliminated in external environment in viable state.

Later, it was found that the definition is not an absolute axiom because the causative agents in some diseases use the natural environment for living (water, soil, air, etc.).

Pathogenic microorganisms that use for the natural living exclusively human body, cause the disease only in humans and are included in the notion of "anthroponosis" from the Greek words anthropos - man and mannose - disease, characteristic only from human population, such as, for example, measles, rubella, mumps, whooping cough, typhoid, hepatitis A, etc..

In cases where the natural environment for living of pathogen serves only body of animals, caused diseases refer only to animals and include the term "zoonoses" (zoon - animal, mannose - illness) only typical diseases of animals, such as, for example, poultry leucosis, pigs fever, dogs fever, etc.

Pathogenic microorganisms that use as living environment the body of animal species and the human body, cause the diseases refering to "zooanthroponosis" (zoon - animal anthropos - human mannose - illness), diseases common for animals and humans, such as, for example, anthrax, brucellosis, tularemia, leptospirosis, rabies, plague; some helminthiasis - tenioza, difilobotrioza, echinococcosis etc.

Pathogenic microorganisms that use natural external environment for living (air, water, soil), which enter the human body causing illness, these diseases are included within the definition of "sapronosis", for example, legionellosis, cholera, cryptococcosis, actinomicosis etc..

Infectious diseases can be classified into four groups according to the natural environment of living of causative agents:

- Anthroponosis;
- Zoonosis;
- Zooanthronosis;
- Sapronosis.

Anthroponosis and sapronosis are the subject of medicine, including epidemiology. Zoonosis are the subject of veterinarians, including epizootiology. Zooanthroponosis is the subject of medicine and veterinarians, including epidemiology and epizootiology.

1.2.2.1. Sources of pathogens in anthroponosis

There are two categories of sources of pathogens in anthroponosis:

• infectious patients;

• carriers of infectious germs.

1.2.2.1.1. Infectious patients as a source of pathogens. Epidemiological importance of different forms and periods of infection.

Illness in humans caused by infectious diseases can manifest different forms: according to the gravity, there are severe, medium and light, according to clinical manifestations they are classified in light manifested and non-manifested.

Infectious patients with typical evolution (severe or pronounced) of the disease eliminate in the environment, as a rule, a considerable number of pathogenic agents. However, these patients, being more or less grave, usually, address doctor, and based on clinical signs of disease they are treated.

Patients with atypical forms of diseases (subtle or mild), although eliminate a smaller number of pathogens in the environment have a higher epidemiological risk because these patients often neglect to go to the doctor. At the same time they are attend public places (school, kindergarten, place of work, use public transportation, etc..) contaminating the environment. However, detection of these infections is more difficult, that can have serious epidemiological consequences because, being detected later or remain undetected, they lead to the dissemination of pathogens in the environment.

The situation becomes more difficult in case of unapparent clinical manifestations of disease. In this case, the sick may not suspect the disease due to the absence of clinical manifestations, and can be diagnosed only based on laboratory investigations. In most cases, the disease remains undetected. At the same time, these people apparently are healthy, but contagious and eliminate infectious germs in the environment. Unapparent forms of disease are common in hepatitis A, mumps, Shigellosis etc. Laboratory investigations play important role in diagnosis of unapparent forms of the disease.

Therefore, atypical clinical forms create difficulties in early detection and neutralization of sources of pathogens in anthroponosis.

Recently, unapparent forms of illness caused by infectious diseases appear more frequently because of the widespread use of antibiotics and immune preparations.

Epidemiological importance of disease evolution periods

The period of the infectivity of infectious patients is different in different diseases. Have been established the following epidemiological and clinical studies in infectious diseases. They directly depend on the clinical periods of the disease: incubation, prodromal, clinical manifestation, and recovery.

Example: The onset of infectiousness period in hepatitis A, (elimination of causative agents in the environment) starts in incubation period (10-15 days before the onset of the prodromal period) continues throughout the prodromal period and

stops on 7th - 14th day of the clinical manifestation (after jaundice appearance) of the disease (fig. 39). C

Contagious period begins in classical measles in the prodromal period and continues four days from the onset of specific clinical signs – appearance of the rash (Figure 39). Contagious period begins in shigellosis with the onset of specific clinical manifestations and continues throughout the disease, until complete recovery (Fig. 39). Period of infectiousness starts in typhoid from the 12th day of clinical manifestation and continues throughout the disease, and in 10-30% cases, pathogens continue to be eliminated after clinical recovery period (fig. 39).

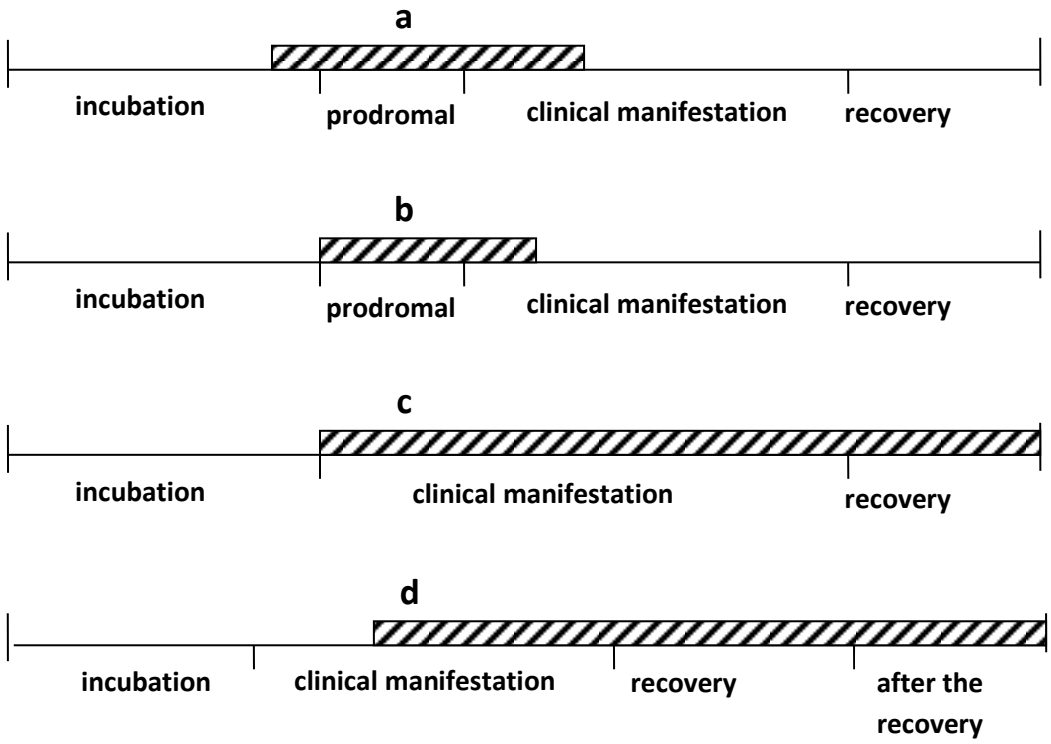


Fig. 39. Contagious periods of patients with: a) hepatitis A, b) measles, c) dysentery, d) typhoid fever

Therefore, the state of infectivity such as duration and intensity differs from one to another disease.

The contagious periods in some infectious diseases are shown in Table 26.

Table 26

Contagious periods in infectious diseases in human population

Infectious disease	Periods of evolution of the disease				
	Incubation	Prodromal	Clinical manifestation	Recovery	After clinical recovery
Amebiasis	–	±	+++	++	+
Hepatitis B and C	+	+++	++	+	±
Rabies	–	–	+++	–	–
gonorrhea	+	+++	++	±	±
Influenza	–	+	+++	±	–
Diphtheria	–	+	+++	±	±
Intestinal yersiniosis	–	+	+++	++	±
HIV	+	++	+++		
Meningococcal infection	–	+++	++		
Rotavirus infection	±	++	+++	+	±
Streptococcal infection	–	±	+++	++	+
Campylobacteriosis	–	–	+++	++	±
whooping cough	–	+++	++	±	–
Rubella	–	++	+++	–	–
Leprosy	–	++	+++	–	–
Yellow fever	–	++	+++	–	–
Malaria	–	–	+++	++	++
Chickenpox	–	+	+++	–	–
Smallpox	–	–	+++	++	–
Mumps	–	++	+++	++	–
Polio	±	++	+++	++	±
Salmonellosis	–	±	+++	++	±
Syphilis	–	+	+++	–	–
Exanthematic typhus		++	+++	+	–
Tuberculosis	–	+	+++	+	±
Cholera	–	++	+++	++	±
Natural plague (pulmonary form)	–	–	+++	++	–
E.Coli infection	–	–	+++	++	±

1.2.2.1.2. Carriers of pathogens. Classification, epidemiological importance.

The notion of "carrier of pathogens," or "state of carriage" means a healthy person hosting in the body a pathogen for a certain period, eliminating it in the environment.

Not all infectious diseases have carriage state. It is characteristic only for some diseases, for example, staphylococcal infections, streptococcal infection,

meningococcal infection, diphtheria, typhoid fever, poliomyelitis, hepatitis B, hepatitis C, etc..

Note, that carriers of pathogenic microorganisms as sources of the causative agents of infectious diseases have important epidemiological significance compared to sick patients, not only because of the lack of clinical manifestations and difficulties in detection, but also because these people are actually healthy and active to do their usual activity. Carriers are dangerous in cases of direct contact with food, sources of drinking water, children, and the surgical patients who do not meet proper hygienic behavior.

There are distinguished several categories of pathogens carriers.

Convalescent carriers - people who have suffered an acute infection but, although clinically they are cured, continue to host and eliminate pathogens in the environment after the period of recovery (typhoid, hepatitis B, etc.). People are considered as temporary convalescent carriers in cases of persisting carriage up to 3 months of recovery. People are considered chronic convalescent carriers in cases of carriage over 3 months and may continue for years, and sometimes even lifelong.

Immune carriers - persons who have been infected or vaccinated, who possess a level of specific immunity. Sometimes, people exposed to recontamination will not develop the disease, but become carriers of the pathogen. The Corynebacterium diphtheria carriers represent a typical example of immune carriage. Carrier status to such persons may be repeated several times until recontamination happens.

Healthy carriers - healthy people, that host pathogen but did not do any acute infection or carriage state may be linked to asymptomatic infection. Carriers of pathogenic staphylococci is a good example (Staphylococcus aureus).

Transitory carriers - people, who eliminate pathogens a short period of time (2-3 days), usually are found after bacteriological investigations during prophylactic examination of risk group of population.

Carriers can be divided depending on the pathogen tropism into: intestinal, nasopharynx, biliary, urine, and blood carriers.

Active detection of all kinds of carriers, based on epidemiological significance, is necessary to organize by laboratory means, in order to prevent and control communicable diseases.

1.2.2.2. Sources of pathogens in zooanthroponosis

Modality to maintain and movement of pathogens in zooanthroponosis as biological species is realization of epizootic process, namely the maintenance and spread of pathogens among different animal species. The epidemic process in zooanthroponosis may manifest also illness in humans, but the epidemic process in

this case is not a mandatory condition of existence of pathogens as species in nature. This is explained by the fact that in the process of evolution, due to the reduced transmission of pathogens in animal populations, due to their considerable dispersion compared to the human population, these species of microorganisms have acquired more properties, the ability to live and to multiply in different species, including the human body. At the same time, human infection is an occasional phenomenon, conditioned by social and human factors. The human body is not natural environment for pathogens in these infections. The transmission among human population is interrupted or limited. In most cases of zooanthroponosis, usually, does not develop any other infectious states among humans, even among animals. The epidemic chain is, practically, interrupted in illnesses among humans, with some exceptions (fig. 40).

The sources of infection in zooanthroponosis for human population are normally carriers or sick animals.

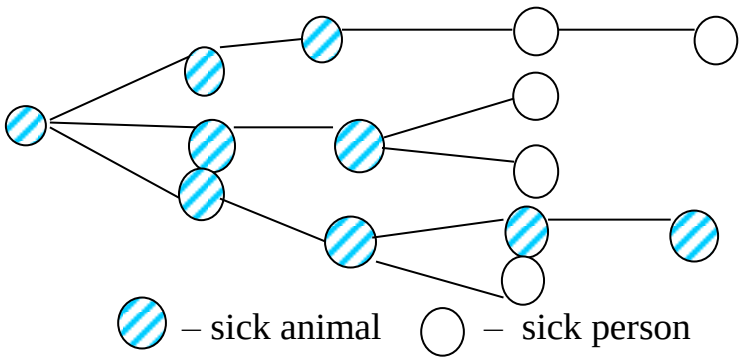


Fig. 40. Epidemic process in zooanthroponosis

The zooanthroponosis can be classified into three groups depending on the potential to spread the infection among human population:

1. Zooanthroponosis where the human can be contaminated only from animals. Maintaining and circulation of these pathogens in nature occur only because of animals (tularemia, tick encephalitis, tick typhus relapsing etc.).
2. Zooanthroponosis where transmission from human to human can occur theoretically, but practically it is very rare. Usually, humans acquire these infections from animals but the main role in the maintenance and circulation of the microorganisms in nature is made by animals called ***epizootic process*** (anthrax, brucellosis, rabies, Q fever, leptospirozele etc.).
3. Zooanthroponosis where the maintenance and circulation of pathogenic microorganisms are provided by transmitting of infection among human population and animals as well (lung fever, yellow fever, tuberculosis, some salmonellosis).

Animals can be divided into several groups based on the big variety of species of animals that can serve as sources of pathogens for humans, as well as the level and form of human contact with animals:

Domestic animals - animals whose existence is in direct relation with human activity (dogs, cats, farm animals and poultry). Human population acquires infection from domestic animals and develop such infections as anthrax, brucellosis, rabies, teniosis, teniarinhoza, echinococcosis etc.

Human contamination from domestic animals occurs during daily contact with them, use of animal products for food and other necessities, during livestock raw material processing, and animals slaughter or handling sick or dead animals etc.

Synanthropic animals - wild animals, that live around humans, pets such as mice or rats, from which person can acquire tularemia, leptospirosis, salmonellosis using food contaminated by these animals. This group of animals includes some birds, pigeons and parrots – which are sources of pathogens in Ornithosis and Psittacosis. An important epidemiological factor concerning synanthropic animals is that they can live in natural and human conditions.

Wild animals (xenantrope) what live in nature with specific biotopes (wolf, fox, wild boar, hare, water rat, several species of murine and microtine etc.). Xenantrope animals are sources of pathogens of such infections as rabies, tularemia, leptospirosis, natural fever, trichinosis, etc.). Natural focality is specific for xenantrope wild animal.

The notion of natural focality

The natural focality means the particularity of pathogens, usually in xenantrope zooanthroponosis, to circulate permanently in natural areas with specific geographical configurations, called biotopes where evolutionary were formed some relationships between different species of pathogens, wild animals and hematophagous arthropods.

Human contamination in natural focus results from human activity (hunters, mowing, foresters, swimming in natural pools etc.). The manipulations of hunted animals and bites products contribute to human contamination with pathogens in natural foci. Also, human contamination occurs frequently in result of stings by different haematophagous arthropods (mites, insects) produced in natural outbreaks.

1.2.2.3. Sources of pathogens in sapronosis

The existence of sapronosis pathogens in nature is dependent on the saprophytic living environment in the objects of the external environment (water, soil and other organic matter), where before the human contamination they pass

through the multiplication and accumulation where temperature and humidity are similar to those of the human or animal body.

For example, multiplication of Legionella in air conditioners, shower devices, water taps etc.; Yersinia – in the rotten vegetables from storage depots; cholera bacteria - in water.

Sometimes, causative agents in sapronosis have two living areas - body of vertebrate animals and soil, but regular exchange of environment (animal-soil-animal) provides their existence as biological species. Example: anthrax, tetanus, clostridium, leptospirosis, yersinia, pseudotuberculosis, listeriosis.

According to Cerkasski B.L. (2001), the natural environment of living of all pathogens always is associated with the notion of biological environment because different specific pathogens are related to life processes, multiplication, accumulation and sustainability causative agents of infectious diseases.

The human body is not a natural environment for the microorganisms in sapronosis and zooanthroponosis. Once the human is contaminated with microorganism specific for sapronosis and zooanthroponosis the epidemic process will stop. (Fig. 41).

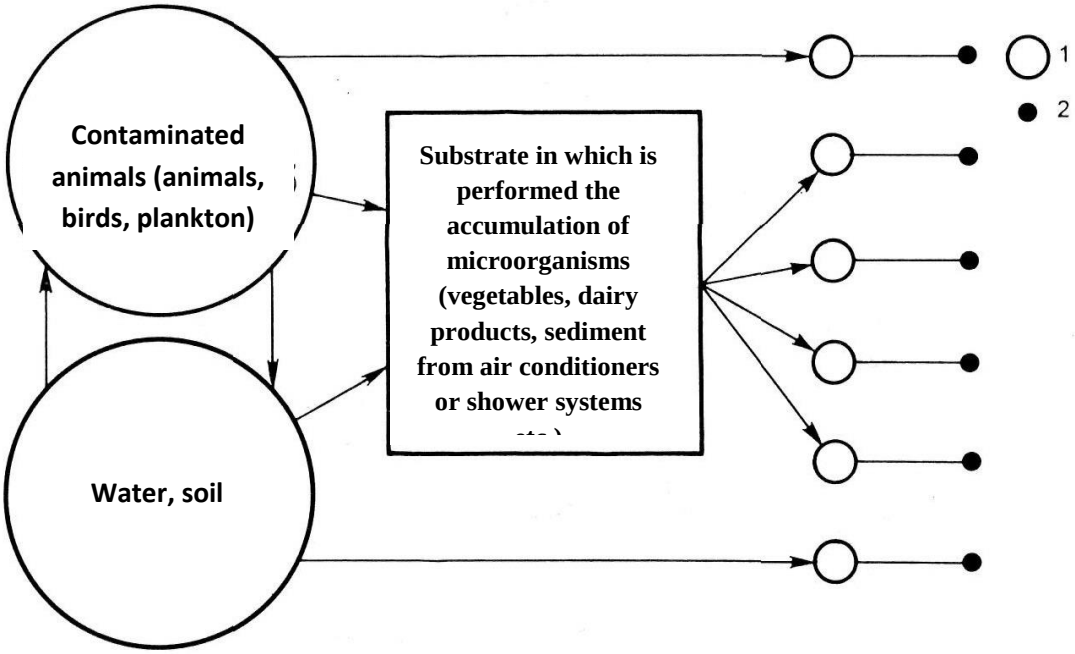


Fig. 41. Epidemic process in sapronosis (B. L Cerkasski, 2001):
1 – sick person; **2** – interupted chain.

E.N. Şleahov and V. Litvinov (1989) proposed the following classification of ecological and epidemiological infectious diseases that affect human population (tab. 27).

Sources of pathogens can be divided into the basic (primary) and secondary (additional) sources.

The main sources constitute the natural environment of existence, the environment in which the multiplication and accumulation of the pathogen in nature is realized, while secondary sources are usually casual, temporary chain of movement of the pathogen.

Table 27

Ecological and epidemiological clasification of infectious diseases

Class	Group	Main reservoir of infection	Example
Anthroponosis	Intestinal, blood-borne, respiratory, skin-borne, „vertical”	Humans	Typhoid fever, hepatitis A, polio, measles, rubella, smallpox, diphtheria, mumps, chicken pox and others.
Zooanthroponosis	Domestic and sinantrope animals	Animals	Brucellosis, anthrax, ornithosis, rat-bite fever**,** others.
	Xenantrope animals	Animals	Plague**,** tularemia, tick rickettsiosis, tick borelliosis rabies. etc
Sapronosis	Saprozoonosis	Animals + extern environment	Anthrax, Yersiniosis, Listeriosis etc.
	Water-borne sapronosis	Water	Legionelosis, melioidosis, Listeriosis ş. a.
	Soil-borne sapronosis	soil, plants	Clostridiosis, botulism, actinomycosis, histoplasmosis and other mycoses.

Only basic sources ensure the maintenance of pathogen agent as a species in nature and are associated with the notion of "reservoir". For example, measles main sources are sick people, in typhoid fever – carrier of S. typhi, the rabies - wolves, foxes, dogs, cats, anthrax - cattle, sheep, horses, pigs and soil (see Table 28) .

Table 28

Main sources (reservoir) of pathogen agent in some infectious diseases

Infectious disease	humans	Dogs, cats	monkeys	farm animals	Xenantrope carnivores animals	Xenantrope ruminant animals	Rats	Birds	fish, sea products	ticks, mosquitoes	abiotic objects of extern environment
1	2	3	4	5	6	7	8	9	10	11	12
Anthrax				+		+					+
Amebiasis	+										
Gonorrea	+										
Botulism				+		+	+	+	+		+
Brucelosis				+							
Diphtheria	+										
Tick encephalitis				+		+	+			+	
Esherihiosis	+										
Hemoragic fever with renal syndrome				+	+		+				
Yellow fever	+		+								
Lassa Fever	+		+								
Typhoid fever	+										
Flu	+										
Rabies		+		+	+	+	+				
Viral hepatitis	+										
Cholera	+								+		
Yersiniosis	+	+		+	+	+	+	+			
HIV	+		+								
Influenza	+										
Meningococcal infection	+										

1	2	3	4	5	6	7	8	9	10	11	12
Staphylococcal infection	+										
Streptococcal infection	+										
Rotaviral infection	+										
Campilobacteriosis	+			+		+	+	+			+
Leprosy	+										
Leptospirosis		+		+		+	+				+
Listeriosis	+	+	+	+	+	+	+		+	+	+
Glanders	+			+	+	+					
Mumps	+										
Ornithosis								+			
Plague	+			+		+	+			+	
Poliomyelitis	+										
Pseudotuberculosis		+		+	+	+	+	+	+		+
Measles	+										
Rubella	+										
Salmonellosis	+			+	+	+	+	+	+		
Shigellosis	+		+								
Syphilis	+										
Tetanus				+		+	+	+			+
Endemic typhus	+										
Tuberculosis	+	+		+				+			
Tularaemia							+			+	
Whooping cough	+										
Chicken pox	+										
Smallpox	+										

1.2.3. The mechanism of transmission of pathogens

The mechanism of transmission of pathogens is the second essential component of the epidemic process, which ensures the transmission of pathogens from host body to another – responsive body.

The notion of transmission mechanism means a set of procedures formed during the evolution of the causative agents of infectious diseases, which ensures transmission of microorganism from source (host body) to another responsive body.

The mechanism of transmission is the way to change the host body, as a condition to maintain the pathogens as species, based on their parasitic nature. As a parasite, pathogen uses the human or animal body as a living environment, but to maintain the species in nature it must necessarily change the host body. Otherwise, pathogenic microorganisms will be killed because of death of host organism or due to immunological changes in the body and consumption of living products. If pathogens of infectious diseases were not adapted to change the body, the microorganisms would disappear as species and it would lead to disappearance of infectious diseases at all.

The transmission mechanism is a process of several steps, including three successive stages:

- elimination of pathogens from infected organism (host) in the external environment;
- maintenance of pathogens for a period of time in the external environment;
- entering of the pathogens into another responsive body. (Fig. 42).

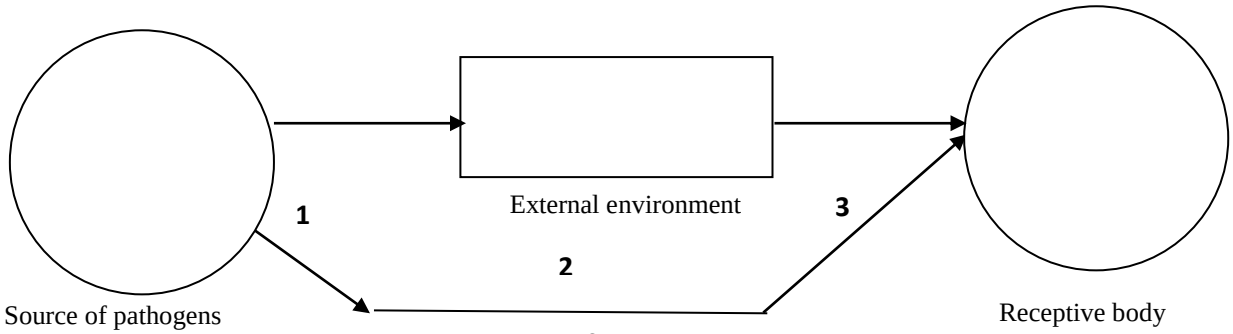


Fig. 42. Stages of transmission mechanism:
1 – elimination of pathogens; 2 – maintenance in the environment;
3 – entrance into the receptive body .

Phases of mechanism of transmission are specific to species of pathogenic microorganisms and constitute the result of their adaptation both to attack the body, elimination, tropism of pathogens in the host organism and their adaptation

to survival in the external environment to ensure continuity of biological species in nature.

The first phase - elimination of pathogens from the host body- is done through various physiological reactions of microorganisms (defecation, urination, breathing, speech) and by various pathological reactions as a result of damage to the body (diarrhea, vomiting, coughing, sneezing, ulcers, wounds or abrasions of the skin or mucous coatings etc.).

Epidemiological significance of elimination phase of pathogens from infected body is directly related to duration, concentration and nature of the causative agent, and dissemination ways in the environment. Ways or gates to eliminate the causative agents are in relation to their location in the body and vary from one to another disease.

In the case of infection with circulating of microorganisms in a closed system (blood or lymph systems), their elimination takes place naturally - through the hematophagous arthropods, or artificially (for example, medical maneuver). The second phase begins with the elimination of the pathogen in the external environment and ends with penetration of another macroorganism (body). It is in direct function of possible duration of pathogen to survive outside the host body. The resistance of pathogenic microorganisms in the external environment differs from one species of microorganisms to another, and depends on the degree of virulence as well as some external environmental factors (temperature, moisture, organic matter content, etc.). If the virulence of microorganism is low, the resistance in the environment will be high and vice versa. Low temperatures also contribute to the longer duration of survival of pathogenic microorganisms in the external environment. Some pathogens can even multiply and accumulate in the external favorable conditions (optimal temperature and humidity, nutrient substances).

Pathogens of some diseases take other forms in the external environment as a response to the faced harsh conditions, such as spore forms in anthrax, tetanus, botulism or small forms of vibrios in cholera, which can survive in nature (soil, water) for decades, keeping clinical and epidemiogenic potential.

In other contagious infections or invasions this stage is mandatory in multiplication process or maturation of pathogens. For example, in enterobiosis maintenance in the external environment is a mandatory stage of maturation of eggs of E. vermicularis, in Strongiloidosis - compulsory stage of development of Strongyloides stercoralis larvae is in the soil, and for malaria, the passing of causative agent, Plasmodium, into the mosquito organism is an obligatory stage for multiplcation of sporozoites.

Phase of entrance of pathogens into the host body is specific for microorganism species and occurs both through natural cavities (oral cavity, nose) and through the injuries of skin or damage of mucosal coatings, called "gates" of entrance. Each infectious disease pathogen has specific gate of entrance, which can usually be single for anthroponosis or multiple for zooanthroponosis.

The mechanism of transmission is directly related to both the location (tropism) of the pathogen in the host organism and the gates of entrance and elimination ways from a body to another.

Infectious diseases are classified into four groups depending on the gate of entrance and tropism of pathogens in the host organism:

1. Digestive infections (typhoid fever, shigellosis, esherichiosis, malaria, food poisoning, viral hepatitis A, enteroviral infections, etc.);
2. Respiratory infection (influenza, measles, rubella, smallpox, chickenpox, mumps, diphtheria, streptococcal infection, meningococcal infection, whooping cough, tuberculosis, etc.);
3. Blood infections (malaria, endemic typhus, yellow fever, hepatitis B,C and D, HIV, etc.);
4. Infections of the skin and mucous membranes (anthrax, tetanus, erysipelas, dermatomycoses, syphilis, gonorrhea, trachoma, conjunctivitis, etc.).

The pathogenic microorganisms have adapted during the evolution process not only to the specific environment of living, but to the various mechanisms of transmission from a body into the receptive host.

An important role in the formation of mechanism of transmission plays pathogens tropism into the host body. Some microorganisms multiply and affect only certain types of tissues. For example, influenza virus infect the upper respiratory mucosa, bacillus dysentery - the lining of the small intestine, viral hepatitis - liver tissue. These microorganisms are called monotrope. Apart from them, other microorganisms can parasitize in various tissues and organs – they are called polytrope. However, the higher epidemiological significance in infectious diseases has the location in which it becomes possible to transmit the pathogen from infected body to responsive body. As a good example of this can serve meningococcal infection. The primary location of the causative agent is in the nasopharynx mucosa, thereafter it is multiplying in brain membrane. However, the second location has only clinical importance, because elimination of meningococal pathogen in the external environment occurs only through excretions of nasopharynx.

There are five types of transmission mechanisms of pathogens:

Fecal-oral - the elimination of pathogens from the host organism occurs through the excretion with feces and then they must get the new body by oral cavity to ensure their biological existence through multiplication and accumulation in other responsive body (Fig. 43A).

For example: typhoid fever, shigellosis, cholera, viral hepatitis A and E, salmonellosis, rotavirus infection, etc.

Respiratory - pathogens affect the upper or lower airways. Infectious pathogens are eliminated from the host body in the external environment with breath and other body penetration, necessarily, by the inspiration, inhaling contaminated air (fig. 43B). For example: influenza, measles, mumps, diphtheria, whooping cough, tuberculosis, etc. These infections are called "respiratory infections". Exceptions are some zooanthroponosis (eg. Tularemia), the pathogens can be acquired through other means, including via inhalation of contaminated aerosols.

Parenteral - the causative agent entering the body or the body's elimination occurs only through skin or of damage mucosal coatings. Typically, this mode of transmission is specific for blood infections and transmission of the causative agents occurs through contaminated blood (fig. 43C).

In this category fall both anthroponosis whose source of infection is the human population (typhus, recurrent typhus, malaria, hepatitis B and C, HIV) and zooanthroponosis (tularemia, plague, encephalitis, hemorrhagic fever, fever Q etc.) whose sources of infection are animals.

The main feature of the mechanism of transmission of blood infections group is that pathogens in the host body are in a closed system of the bloodstream and are not eliminated in the external environment independently.

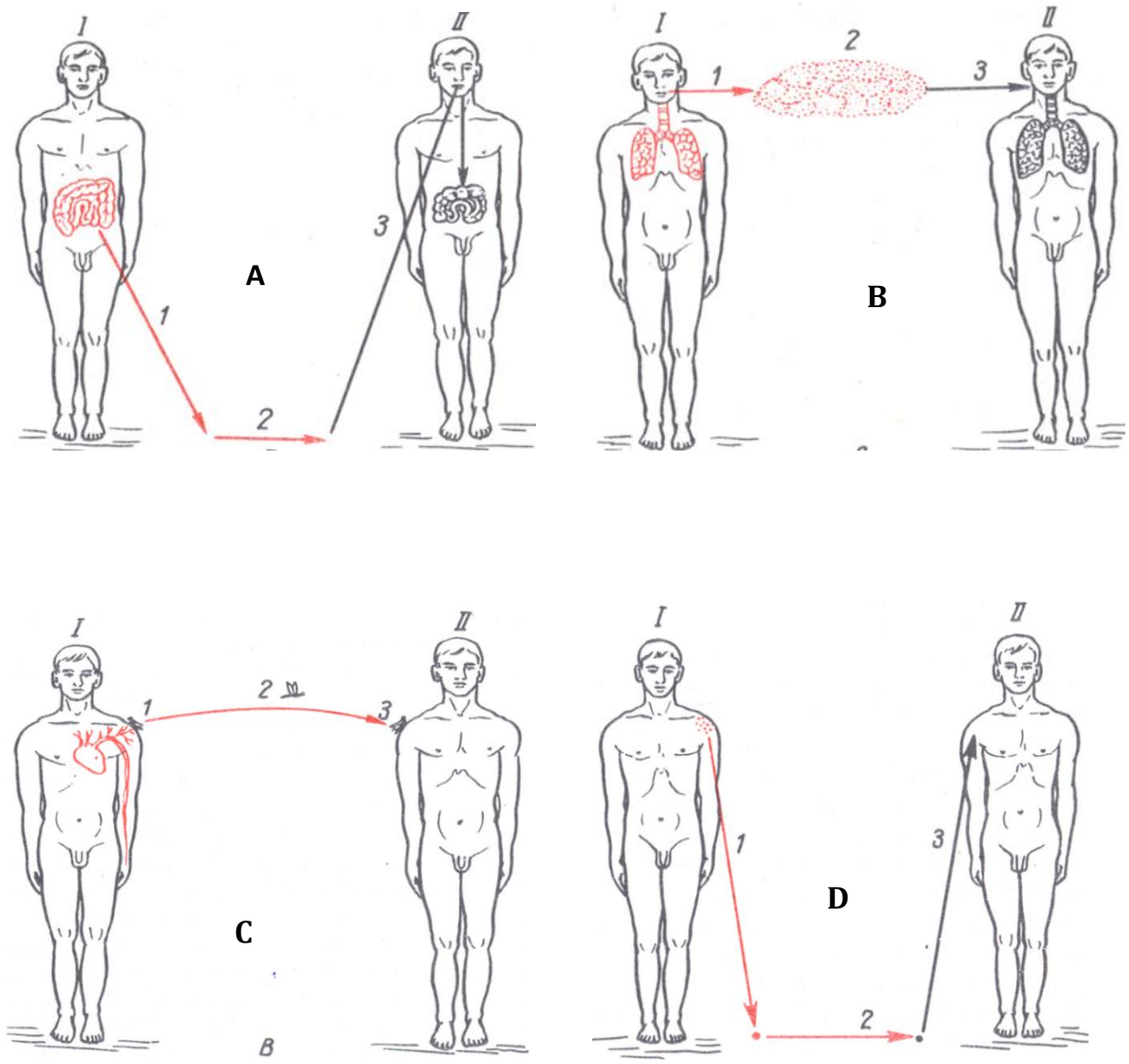


Fig. 43. Types of horizontal mechanisms of transmission of pathogens (L.V. Gromaşevski):

A – fecal-oral; B – respiratory; C – parenteral; D – direct or indirect contact.
I – host body; II –receptive body;
1 –elimination stage; 2 – maintenance in the external environment;
3 – entrance stage into the receptive body.

There are two modes for parenteral transmission:

1) Natural - when pathogens are removed (eliminated) from the host body and are inoculated into other responsive body by biologically active vectors - hematophagous arthropods, such as plague, tularemia, yellow fever, Q fever etc. Biologically active vectors provide a specific stage of multiplication of pathogens or maturing in their body in some blood diseases (malaria, endemic typhus and others). The natural parenteral way

of transmission can be attributed to the transmission of pathogens in blood infections through sexual contact (HIV, hepatitis B and C).

2) Artificial - when the pathogens are eliminated from the host organism and inoculated into another responsive body through invasive instruments and medical devices (syringes, surgical or dental instruments, probes, blood transfusion, etc.) used in diagnosis and treatment. Also, it can be through the tools of shaving and manicure. In this way can be easily transmitted causative agents of hepatitis B and C, HIV, etc.

Through direct or indirect contact. This mode of transmission of pathogens from the host body to receptive one is specific for skin and mucous infections. The transmission of pathogen by direct contact involves direct touching with the infected body without the participation of the external environment (e.g. Syphilis, gonorrhea, rabies, etc.). Indirect contact involves the transmission of pathogens by touching the damaged skin or mucous membranes with contaminated objects of the environment - clothing, dressing material, water, soil etc. (anthrax, tetanus, erysipelas, septic-purulent infections, dermatomycosis) (Fig. 43D).

Vertical - from mother to child in uterus when fetal nutrition occurs through mother's cord blood. The theory of this mechanism is not completely studied. However, since the 80s of the twentieth century, there is growing evidence that demonstrates the functionality of the mechanism of transmission of pathogens. So far, its functionality was demonstrated in toxoplasmosis, syphilis, rubella, herpes, hepatitis B virus, HIV, influenza, listeriosis, Q fever, etc. This mechanism is called “vertical transmission” because pathogens transmission occurs from mother to child during embryonic development, from one generation to another.

Thus, four transmission mechanisms described above were horizontal because pathogen transmission occurs in a population from one individual to another.

1.2.4. Factors and transmission routes of pathogens

As mentioned above, between the elimination phase from the host body and entrance phase into responsive body (excluding transmitted by direct contact) is maintained a period in the external environment, but to keep it as the biological species they must be transported to another responsive body, in a viable state. This movement is achieved through various elements of the environment (water, soil, air, household objects, insects, etc.), contaminated by pathological excretions of infectious patients or carriers of germs.

All elements of the external environment, which ensures the movement of pathogens from the host body to the receptive one, ensuring continuity of the epidemic process are called **factors of transmission**.

The pathogens have adapted to some or other specific factors of transmission, which varies from one disease to another. Also, transmission mechanism is realized via specific factors. For example, fecal-oral mechanism of transmission occurs by following elements of the environment: water, food, soil, contaminated hands, computers, flies, various household items (dishes, towels) etc.

Factors of transmission can be divided into primary and secondary. For example, fecal-oral mechanism of transmission is realized mainly by water and food, factors which ensure the penetration of pathogens into the recipient.

The main factor of transmission of pathogens in respiratory mechanism of transmission is the air. Due to this fact, infections from this group are called **airborne**. However, in certain infections (influenza, measles, mumps etc.) the transmission of pathogens occurs through liquid aerosol (droplets) and in the others (diphtheria, tuberculosis, streptococcal infection) - with liquid aerosols and solid aerosol (powdered).

The realization of parenteral mechanism of transmission in blood infections involves a relatively large number of biologically active vectors, such as ticks, mosquitoes, phlebotomy, fleas, lice, haematophagous flies. Some species of pathogenic microorganisms, in the evolution process, have adapted to this mode of transmission from the host body to receptive one via some active vectors. For example, causative agents in malaria are mosquitoes of the Anopheles genus, yellow fever - Aëdes Aegyptus mosquito, in leishmaniasis - mosquitoes of the genus Phlebotomies, in plague - fleas Xenopsylla cheopis, in tick encephalitis - ticks of the genus Ixodes, in endemic typhus - lice (Pediculus vestimenti). In some diseases (malaria, endemic typhus), pathogens undergo a compulsory stage of biological development cycle, thus fulfilling the role of reservoir.

Artificial parenteral mechanism of transmission of pathogens in blood infections is realized by all invasive medical instruments, manicure instruments and tattoo, etc. It is important to note that in these cases the main factor in transmissionm is considered contaminated blood.

The direct contact mechanism of transmission of pathogens is realized without the participation of environmental elements, by direct touch in sexual contact (syphilis, gonorrhea), bites (rabies) etc. Transmission factors in indirect contamination in these infections can serve: clothing, soil, laundry, contaminated hands, water tanks etc.

Way of transmission is a set of factors or some main factors of transmission through which direct contamination of receptive body occurs.

Thus, digestive infections are transmitted by food or water, respiratory infections – aerogenic way and blood infections - blood way of transmission.

Therefore, the mechanism of transmission of pathogens in infectious diseases should be seen as a complex process that depends on both the characteristics of direct sources and routes of elimination, and by many factors, conditions and ways of transmission (fig. 44, 45).

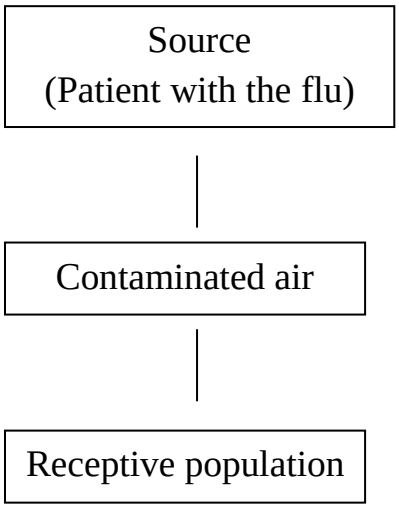


Fig. 44. Transmission of pathogen agents in Flu

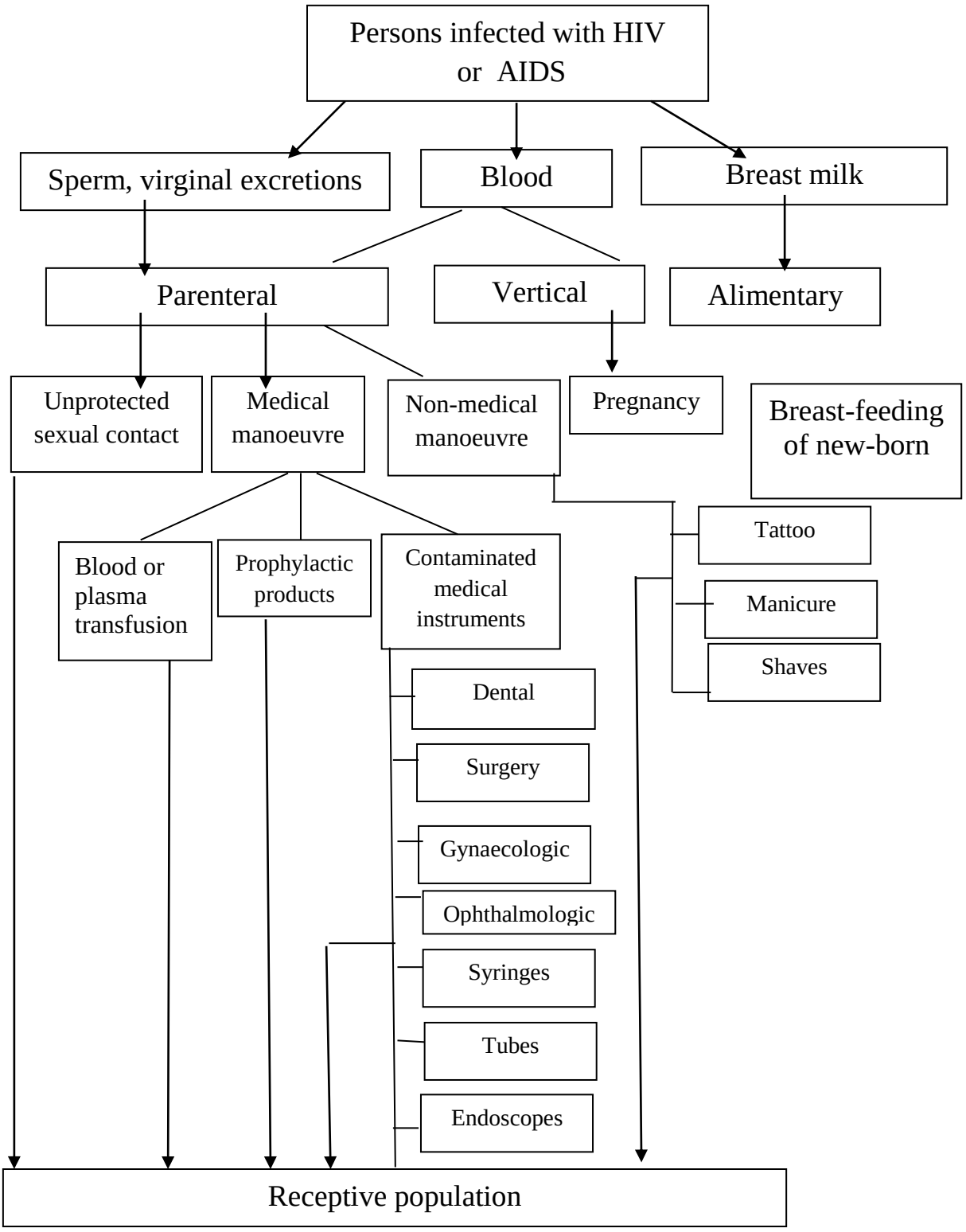


Fig. 45. Transmission of pathogen agent in HIV

1.2.5. Population receptivity

The receptivity (responsiveness) is the property of organisms to serve as a living environment at the species level (biological host) for pathogenic microorganisms - causative agents of infectious diseases. Only a receptive body can develop an infectious process (infectious state) in response to pathogen penetration.

They are considered **unresponsive** (non-receptive) if the human or animal body is not a favorable living environment for pathogenic microorganisms.

There are specific and nonspecific factors that participate in protection function of the body. The nonspecific factors that participate in protection against pathogens are: protective function (mechanical and bactericidal) of skin and mucos, secretions of organs (bactericidal property gastric juice and bile, saliva, tear fluid), the antagonistic action of the body's normal microflora effects inflammation, phagocytosis, and a number of humoral products such as antibacterial action of the complement system, interferon, lysozyme, lymphokines, prostaglandins, ceruloplasmin, etc.

Specific immunity is the resistant state of the body against different species of pathogenic microorganisms and can be innate and acquired during the life.

Innate immunity can be**: hereditary** - formed in the human phylogenesis as a species and transmitted by hereditary from generation to generation and manifested to some species of pathogenic microorganisms, such as human non-receptivity to virus of pigs plague or birds leucosis and reverse – non-receptive animals to measles or whooping cough; and **maternal -** when specific antibodies formed in the process of life, are passed from mother to child by transplacental way. This immunity protects the newborn and infant. It is characteristic of some infections, such as measles and mumps, being of short duration until a year.

Acquired immunity is dependent on the presence of specific antibodies (humoral immunity) or protective capacity of anti-infective cells (cellular immunity) produced in the interaction with pathogens. Acquired immunity can be of two types - natural and artificial.

Natural immunity is obtained from natural infectious process development, due to this fact it is called **post-infectious immunity**. Note, that after some infections (smallpox, measles, diphtheria and other.) the immunity lasts life-long. Natural immunity can be obtained from the contamination of the body with small repeated doses which are not able to produce the disease, but also sufficient to stimulate the formation of immune antibodies (latent immunization or habitual called in medical practice "**premonition**"). As example, may serve lower

sensitivity of Indian population in the Bengal Bay (natural outbreak of cholera) to Vibrio cholera, which is explained by the effect of immunization with small but often doses of vibrio cholera.

Artificial immunity can be **active** when the body produces specific antibodies in response to the artificial introduction of microorganisms - causative agents of infectious diseases - live attenuated or inactivated (killed) and their products (toxoids) and **passive** resulting from introduction into the body of preparates containing the specific antibody, such as immune sera or immunoglobulin preparations containing specific immunoglobulins (fig. 46).

Receptive and unreceptive bodies to various pathogenic microorganisms are always present among human population. The ratio of responsive and unresponsive individuals in the population (collective) to infectious diseases is called immunological structure of the population (group). This indicator is constantly in dynamic variability and can be assessed only in time.

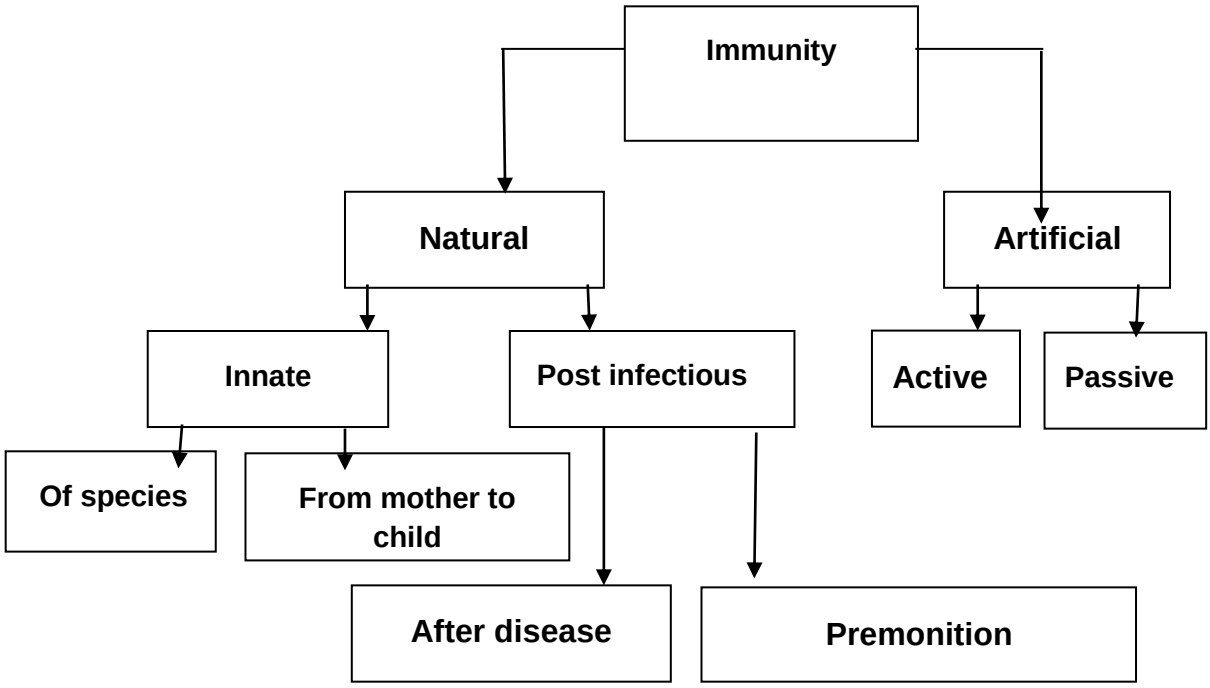


Fig. 46. Clasification of immunity

The intensity of the epidemic development is directly related to the immunological structure of the population. The high proportion of receptive population leads to less unreceptive population that contributes to the favorable conditions in development of the epidemic process. Unreceptive population is called **immune fund** or **immune coverage** of the population, which can be assessed by serological methods. In addition, vice versa, if the immune stratum of the population is high, the conditions for the spread of the epidemic process are reduced.

So, the number of immune people to a particular infection determines the capacity of immune coverage of population and is an important factor in regulating or "directing" epidemic process by vaccination.

The assessment of immunological structure or immune coverage of population (group) allows the estimation and forecast the epidemiological situation now or in perspective, being an important factor in developing of epidemiological surveillance program and intervention decisions, including vaccinations.

1.2.6. Manifestations of epidemic process

There are four forms of manifestations of the epidemic process (morbidity) depending on the number, duration and spatial spread of diseases in human populations: **sporadic, eruption, epidemic, pandemic.**

Sporadic manifestation is a reduced morbidity, expressed by a small number of cases of disease, unique cases without apparent connections between them, dispersed throughout the country. It is often assessed as a minimum, usuall spread of disease. Sporadic manifestation of the epidemic process usually reflects satisfactory epidemiological morbidity and an appropriate activity in epidemiological surveillance, prevention and control. However, sporadic occurrence indicates maintaining of epidemics in the territory and the onset or end of the epidemics, such as the flu. Sporadic level of morbidity precedes the final stage of eradication of a disease. Usually, the morbidity is decreasing after the effective application of the eradication measures, taking sporadic manifestation as occurred in poliomyelitis or currently occurs in measles. Imported cases of the diseases in the population can be included in sporadic manifestation where the disease has not been eradicated, for example, currently imported malaria from endemic countries and effective measures of epidemiological surveillance and control lead to stopping their spread.

Eruptive manifestation ("epidemic eruption", "disease in group") means an outbreak of cases of disease compared with the normal level in a territory (region) or in a collective (kindergarten, school, company) without disease dissemination outside of the collective or certain region.

Epidemic manifestation as a phenomenon reflecting the intensification of the epidemic process, essentially exceeded normal levels, sporadic illness in the human population, but that is limited to the borders of a country or contains some common foreign countries. As example may serve epidemics of mumps registered in 2008 year in Moldova, when in one year were officially registered about 30,000 cases of illness, exceeding the usual morbidity by about 20 times.

Epidemic manifestation can be divided depending on transmission routes: air-borne, food-borne, water-borne, vector-borne etc. Epidemics may also be

characterized by: the nature of the onset ("explosive", "slow"), extensivity ("excess morbidity"), and severe ("excessive complications and mortality"), duration of evolution (short, medium, long), finishing mode (sudden, slow) period between epidemics (short, medium, long) [19].

In some cases, the epidemic can be latent (unmanifested), the spread of pathogens in the human population does not lead to disease manifestations but leads to carriage states. An example of latent epidemic process, which takes place today, is that of diphtheria.

Pandemic manifestation (pandemic) represents unlimited spreading in place or an accumulation of outbreaks that cover several countries or even whole continents. Pandemic may lead to global spread when spreads are registered on every continent populated by humans. As example may serve pandemics of cholera, including the seventh pandemic caused by Vibrio cholera El Tor, which covered practically all continents, pandemic flu, including pandemic influenza or the new type caused by influenza A (H1N1). Another example of pandemic spreading of virus infection can serve HIV, which is rightly considered one of the worst pandemics. Pandemics of smallpox, plague, syphilis, typhus, diphtheria, etc., are considered classics in the history of Epidemiology.

Endemic morbidity is a form of epidemic process recorded only in territories where illness from a specific disease is very common for this region, zones or countries. **Exotic diseases are** cases of diseases imported into the country from another territory with unstable situation.

However, disease is characterized by specific manifestations of morbidity and multi-annual dynamics, distribution in place, groups of population, and groups by age, occupation, living environment, clinical appearance, focus character, specific sources, factors, conditions and mechanism of formation etc.

THE SYSTEM OF PROPHYLACTIC AND CONTROL MEASURES IN COMMUNICABLE DISEASES

Based on the structure of the epidemic process (see section 2.2.1), prophylactic and control measures can be divided into three groups:

- Measures aimed to neutralize the source of pathogens;
- Measures aimed to neutralize the transmission mechanism;
- Measures towards the formation of specific immunity of the population (immunoprophylaxis).

1. Measures aimed to neutralize the source of pathogens

1.1 Measures directed to the source of pathogens in anthroponosis

The source of pathogens in **anthroponosis** is neutralized by yearly detection, isolation and treatment of patients and carriers of infectious germs. An example of a prophylactic measure to detect infectious germs sources can serve systematic bacteriological investigation or epidemiological indications of risk groups to carriage of pathogens - causative agents of gastrointestinal infections (service personnel in schools and day care, food industries, drinking water stations, etc.), carriers of pathogen Staphylococcus (health-care workers in surgical department), HbsAg carriers (blood donors) etc.

All children in schools and pre-schools are mandatory investigated during morning examining and monitoring throughout the day for early detection of infectious diseases and carriers.

Detection of infectious patients or carriers of pathogens includes usual anti-epidemic measures (isolation, treatment and follow-up, etc.).

Isolation is achieved by hospitalization of patients with infectious diseases, isolation at home, isolation in temporary isolator of children's institutions, campus, ships, trains, etc.

Isolation of patients with hospitalization is required for a number of infectious diseases: typhoid fever, epidemic typhus, diphtheria, tuberculosis (active form), anthrax etc.

Isolation into the hospital is compulsory for patients, and people who have contacted with them as well, in case of the conventional diseases (cholera, plague).

Regarding other infectious diseases (measles, mumps, whooping cough, dysentery, salmonellosis, etc.), isolation of patients is performed according to epidemiological and clinical indications.

The epidemiological indications are:

- First emerging or re-emerging cases of infections;

- Sick persons residing (finding permanent) in campus, boarding schools, barracks, orphanages etc.;
- Lack of isolation conditions at home;
- Families with children that are susceptible to infection;
- Families where somebody practices a profession at risk to contaminate others;
- Patient is from a risk group of population.

Clinical indications are:

- Severe forms of infection;
- Associated complications.

However, based on epidemiological indications, patients can be isolated at home in case of uncomplicated mild form, where they receive the treatment, but this decision must be coordinated with epidemiologists.

Investigation of patients is required after finishing their treatment in case of infections with the potential risk to become a chronic carrier of pathogens (typhoid, shigellosis, salmonellosis, diphtheria, tuberculosis, hepatitis B and C, etc.) and further follow-up in order to detect relapses of the disease or convalescence carrier.

All cases of infectious disease or suspected cases should be entered into the record, and higher epidemiologic authorities should be informed within 24 hours. Medical personnel informs through the urgent notification form (form 058/e) about detection of infectious disease, intoxication, food poisons and/or acute professional diseases, side effects after vaccination - approved by MoH of 11.01.2011, no. 13. Notification is immediate in case of conventional infections. Information can be conducted electronically, by phone or fax and requires further confirmation in a written form. At the same time, an alert message is sent to Automated Information System for Surveillance of infectious diseases, established by Decision No. MS available. 477-d of the 31.07.1999.

The following measures are undertaken in the focus of infectious disease epidemic aimed to neutralize the source of pathogens:

- Detection of contact persons;

- Clinical investigation of contact persons or persons suspected of disease;

- Emergency prevention among people who have contact with patients, depending on the disease: antibiotics, immunoglobulins, vaccines, bacteriophage. Emergency prophylaxis is aimed to interrupt the infectious process during the incubation period;

- Daily medical examinations of contact persons during the maximum incubation period of the respective infection, which include questioning, examination, thermometry, clinical investigation. Supervision of these individuals aims at early detection of patients and their isolation. Daily medical examination of

contact persons in outbreaks is made by family doctors and lasts maximum incubation period from the contact with the source of infection.

1.2. Measures aimed to neutralize the source of pathogens in zooanthroponosis

Measures organized in zooanthroponosis include immunoprophylaxis of farm animals, isolation and treatment of sick animals, and in some cases - the mass slaughter of diseased cattle (i.e. in brucellosis), with further processing of output, reducing the number of homeless animals (dogs, cats) and wild animals, for example, foxes, as main measure in prophylaxis of rabies.

Xenantrope and sinantrope zooanthroponosis, where sources of infection are different species of rodents, can be controlled by zoo recognition and reduction of their population densities.

1.2.1. Deratization is rodent control measures, which are sources of pathogens in infectious and invasive diseases.

1.2.1.1. **Rodent control measures** can be divided into two groups: prophylactic and extermination or destroying.

Preventive measures include such conditions that prevent rodents from penetrating into the occupational environment and human habitat with its population, in order to exclude contamination by various diseases.

Preventive measures may be sanitary-hygienic, sanitary-technical and agro-technical .

Sanitary and hygienic measures are directed towards to maintain permanent housing, auxiliary rooms, warehouses and other structures and adjacent territory in hygienic conditions. It is important to respect sanitary-hygienic requirements for the collection, storage and use of liquid and solid waste, storing and preserving of food. Particularly important is to respect the sanitary and hygienic measures at catering enterprises and trade of food, processing of milk, meat, fish, food production and food in education institutions and training of children, medical institutions and other objects of epidemiological importance.

Sanitary-technical measures. One of the basic requirements to avoid the entrance of rodents in homes, production facilities, warehouses etc. is the periodic review of their sanitary condition. Special technical means of protection need to be provided during designing of new buildings and repair or reconstruction of old ones against rodents and prevent their entry into rooms (foundation and basement walls must be of brick, metal fencing to vents must be installed at a height of up to 80 cm from the ground, etc.).

Agro-technical measures are particularly focused on outdoor rodents, not allowing their multiplication and include:

• reaping in time, in short terms; immediate threshing of grain on land well designed and storing it in elevators;

• Autumn deep processing of agricultural land;

• protection of animals and birds from rodents;

• zoo recognition of the presence and density of rodents.

Rodent destroying methods

Destroying of rodents includes the following methods: mechanical, physical, chemical, biological and combined.

Mechanical method is one of the oldest methods of capture and extermination of rodents and the most harmless to humans and the environment. Mechanical methods to reduce rodents are performed by catching and crushing using various mechanical means (trapping, crushing, pots etc.).

Physical methods - use of the following means of capture and extermination of rodents: water (hot and cold), hot steam under pressure, sticky pasta, electricity, and ultrasound.

Biological control method includes some means or methods of extermination of rodents: use of bacterial strains pathogenic to rodents, the involvement and protection of natural enemies of rodents - mammals and birds, use of chemical sterilizing remedies and immunodepressant.

Chemical method of control includes destroying of xenantrope and sinantrope rodents with rodenticides, which can be classified according to:

A. origin: organic and inorganic, natural and artificial.

B. the state of aggregation: solid, liquid, gaseous, amorphous.

C. preparative form: solutions, gas, baits.

D. organoleptic properties: fragrant, gustatory.

E. action: quick, chronic, combined, systemic.

F. Hazardous.

General strategy for selecting the conditions of their production and use is determined in accordance with the hazard class of rodenticides. There are 4 classes of known preparations:

- Class I - extremely dangerous preparations;
- Class II - very dangerous preparations.

Substances and concentrates of these two classes are used only in chemical industries which have license to work with these substances; their application in practice is prohibited.

- Class III - Moderate dangerous means, which include concentrated rodenticides necessary for preparation of ready bait and means of surface

coating, whose production is allowed only under laboratory conditions. Rodenticides class III can be applied both by specialists and the population, in strict accordance with the normative-methodical instructions.

- Class IV - less dangerous means - include forms of ready prepared baits for the application by professional contingent and population without special restrictions in use, regardless of conditions etc.

2. Measures aimed to neutralize the transmission mechanism

Measures aimed to interrupt the transmission mechanism of causative agents include: disinfection, sterilization, disinsection.

2.1. Disinfection

Disinfection is the removal or destruction of the causative agents of infectious and invasive diseases.

The aim is to neutralize ways and interrupt the transmission mechanism of causing agents from the host organism to the receptive one by performing decontamination measures.

Tasks:

- Ensure efficient and safe disinfectant preparations.
- Creating a database of information on the circulation of disinfectant products, means and methods of use.
- Developing laws and procedures for ensuring effective and harmless circuition and use of disinfectant products.
- Creation of technical and material resources to ensure efficient performance of disinfection measures.
- Permanent and continuous study of the occurrence and development of resistance of microorganisms to disinfectants.
- Development and use of methods, including identification of the substance / active substance in preparations of working solutions and the surfaces treated with disinfectants.
- Supervision of realization time of disinfection depending on the viability of microorganisms in the environment and the time of action of disinfectant preparations.

2.1.2. Types of disinfection

Disinfection can be of two types: prophylactic and focus (outbreak). **Prophylactic disinfection** is all decontamination methods and means, which are applied regardless of the presence or absence of pathogens in the environment in order to prevent infectious diseases appearance.

Epidemiological importance of prophylactic disinfection is that the source of infection, often undetected, presents hazard for spreading of pathogens in the environment. Prophylactic disinfection can be applied depending on the epidemiological significance of environmental objects and substrates - temporarily, periodically or permanently.

Objects treated by prophylactic disinfection are of the epidemiological and social-hygienic significance, such as drinking water sources, catering, social facilities (saunas, pools, train stations, libraries, hotels, theaters, homes, transportation, etc.), training and education institutions (nurseries, kindergartens, schools, colleges etc.), medical assistance and health recreation facilities (hospitals, clinics, dispensaries, sanatoria and rehabilitation centers, laboratories, pharmaceutical institutions, dental units, etc.).

Disinfection in focus (**focus disinsection**) is carried out in case of epidemic outbreak and constitutes a compulsory eradication process. Disinfection of the outbreak may be "current" or final depending on the presence of the source of infection.

Current disinfection is carried out during the presence of source of infection in the outbreak or in case of a threat to disseminate the pathogens into the environment. Current disinfection has epidemiological importance in hospitals, foci when the source of infection is isolated and treated at home, and in some medical institutions with special admission and treatment of patients, microbiological, virological, parasitological, and biochemical laboratories.

Final disinfection is carried out in the focus, only once, after removing the source of infection (hospitalization, isolation, death), after the expiry of infectiousness period or change of residence.

2.1.2.1. Methods of disinfection

The following methods are used in disinfection: physical, chemical, biological and combined.

2.1.2.1.1. Physical method is based on removing pathogens and other microorganisms from objects and the external environment through the mechanical and thermal means, and radiant energy. Mechanical disinfection includes ventilation, filtration, extraction, washing and cleaning. Due to mechanical aspiration of dust are removed by 98-99% of microorganisms. The ventilation of rooms during 15 min and filtering of water, lead to decreasing the number of pathogenic microorganisms in the air or water.

In order to ensure a high harmlessness of filtration of water and other liquids, are used such means as ultrafiltration and hyper filtration.

Thermal disinfection can be used in two forms: high temperatures and low temperatures.

The high temperatures are: buckling flame, ironing, cooking, boiling, drying, incineration, pasteurization, hot dry air, water vapor.

Buckling flame (buckling). It is used in laboratory practice for decontamination of laboratory devices. For this purpose is used the lamp with alcohol, gas, and other sources of high temperature.

Boiling in water at 100 ° C allows destroying vegetative forms in 2 minutes, viruses within 20 - 30 min., and spores in 1-6 hours. For example, anthrax spores are killed in 45-60 min., tetanus - 3 hours, botulism - more than 6 hours.

Hot dry air acting on the microbial cell, resulting in destruction of protoplasm, which is dehydrated and coagulated. Vegetative forms of microorganisms at temperature of 100 ° C are killed within 1 - 1.5 hours, and spore forms are destroyed at temperature of 140-170 ° C in 1.5 - 2 hours.

Table 28

Temperature regime of destroying of microorganisms
(after Vilkovici V.I.)

Microorganisms	Temperature regime of destroying of microorganisms (in min)							
	60°	80°	100°	110°	120°	140°	150°	170°
Vibrio cholera	60	15	10	–	–	–	–	–
Dysentery	–	120	30	15	10	–	–	–
Pathogen of diphtheria	–	120	30	30	20	10	–	–
Pathogen of Typhoid fever	–	–	120	60	20	10	–	–
E.coli	–	–	–	30	30	10	–	–
Staphylococcus	–	–	–	60-120	30	15	10	–
anthrax spores	–	–	–	–	120	60	30	10

Dry hot air is used for disinfection at 50-60 ° C in special ovens. Table 28 includes the bactericidal properties of dry hot air in correlation with temperature, relative humidity and exhibition.

Pasteurization is used for the destruction of microorganisms by heating the liquid, or food to temperature of 70-80 ° C within 30 min.

Low temperatures. Artificial freezing of pathogens to minus 270 ° C does not cause their destruction, but with time, the number of microorganisms is reduced considerably.

Radiation is electromagnetic waves that are distribuited in space atmosphere as gases or particles exert pathogenic or healthy effects, depending on the dose and exposure time. The main physical properties of electromagnetic waves: wavelength (λ), the frequency (F) and the velocity of propagation (V). Propagation speed and spectral composition of radiation largely depend on the environment. The energy of radiation is inversely proportional to wavelength (since the length is less, the available energy will be higher). Radiant energy depends on the size and frequency of the oscillations.

Ultraviolet radiation (UVR) is the radiation of wavelength between 100 and 400 nm and high energy loads (from 12.40 to 3.10 ev). UVR is classified into three categories:

A - wavelength range of 400-320 nm, the effect of pigmentation.

B - wavelength range 320-280 nm, erythematous effect.

C - below 280 nm, germicidal effect.

Ultraviolet radiation (UVR) can be natural or artificial. The most important natural source is the sungenerated UVR.

Artificial sources of UVR can be grouped into the following categories:

– with gas

–incandescent sources (halogen lamps Tiingsten);

–fluorescent lamps (fluorescent, UV fluorescence emitters).

UVR irradiation is performed by devices equipped with bactericidal tubes (lamps) containing mercury.

In order to ensure an efficient air disinfection of rooms, irradiation devices need to be installed in the calculation of from 1.5 to 2 Vt in $1m^3$ of space. The mechanism of action of UVR is denaturation of proteins by destruction of enzymes' activities.

Ultrasound. The disinfecting effect correlates with the intensity of oscillations, increasing at the same time with their number. Acoustic vibrations with frequencies of 2 x 104 to 2 x 106 Hz are used for disinfecting and sterilizing medical instruments, laboratory glassware.

2.1.2.1.2. Chemical Method

Chemical method of disinfection includes using of various substances and preparations with selective or broad-spectrum antimicrobial activity. It is the most accessible, due to large means and methods, which may be used in disinfection.

2.1.2.1.2.1. Classification of disinfectant preparations

Chemical disinfectants are antibacterial substances and preparations, of diverse origin, physical and chemical composition, destination.

1. *According to the spectrum activity of disinfectant preparations they can be classified into:*
   - 1.1. Preparations with broad spectrum of action (universal) - include disinfectants with destructive actions of all groups of microorganisms (bacteria, viruses and protozoa). Ex: chlorine, bromine, iodine and their compounds, formaldehyde and other disinfectants preparations. This group includes substances and preparations with antibacterial activity against gram-positive and gram-negative bacteria.
   - 1.2. Disinfectants with moderate spectrum of action - include bactericidal disinfectants against several species of gram-positive or gram-negative bacteria and viruses, fungi and viruses, fungi and protozoa.
   - 1.3. Disinfectants with limited spectrum of action. There are disinfectant preparations active against some species of microorganisms, for example, mycobacterial infections, gram-positive and gram-negative bacteria, spores, enteroviruses, pseudomonas, fungus, etc.
2. *According to the chemical structure, they are divided into:*
   - 2.1. Halogens and their derivatives both organic and inorganic.
   - 2.2. Organic and inorganic acids and their derivatives.
   - 2.3. Guanidine.
   - 2.4. Oxidofors.
   - 2.5. Aldehydes.
   - 2.6. Alkaline.
   - 2.7. Heavy metals and their organic and inorganic salts.
   - 2.8. Phenol, cresol, and their derivatives.
   - 2.9. Surface-active preparations.
   - 2.10. Oxidants.
3. *According to the action of substances and preparations disinfection is divided into:*
   - 3.1. Antibacterial.
   - 3.2. Antiviral.
   - 3.3. Antifungal.
   - 3.4. Antiparasitic.
4. *According to the mechanism of action:*
   - 4.1. Destructive.
   - 4.2. Oxidizing.
   - 4.3. Membranous action.

4.4. Antimetabolite.
4.5. Anti-fermentative.

5. *According to the final effect:*
   5.1. Bacteriostatic.
   5.2. Bactericidal.

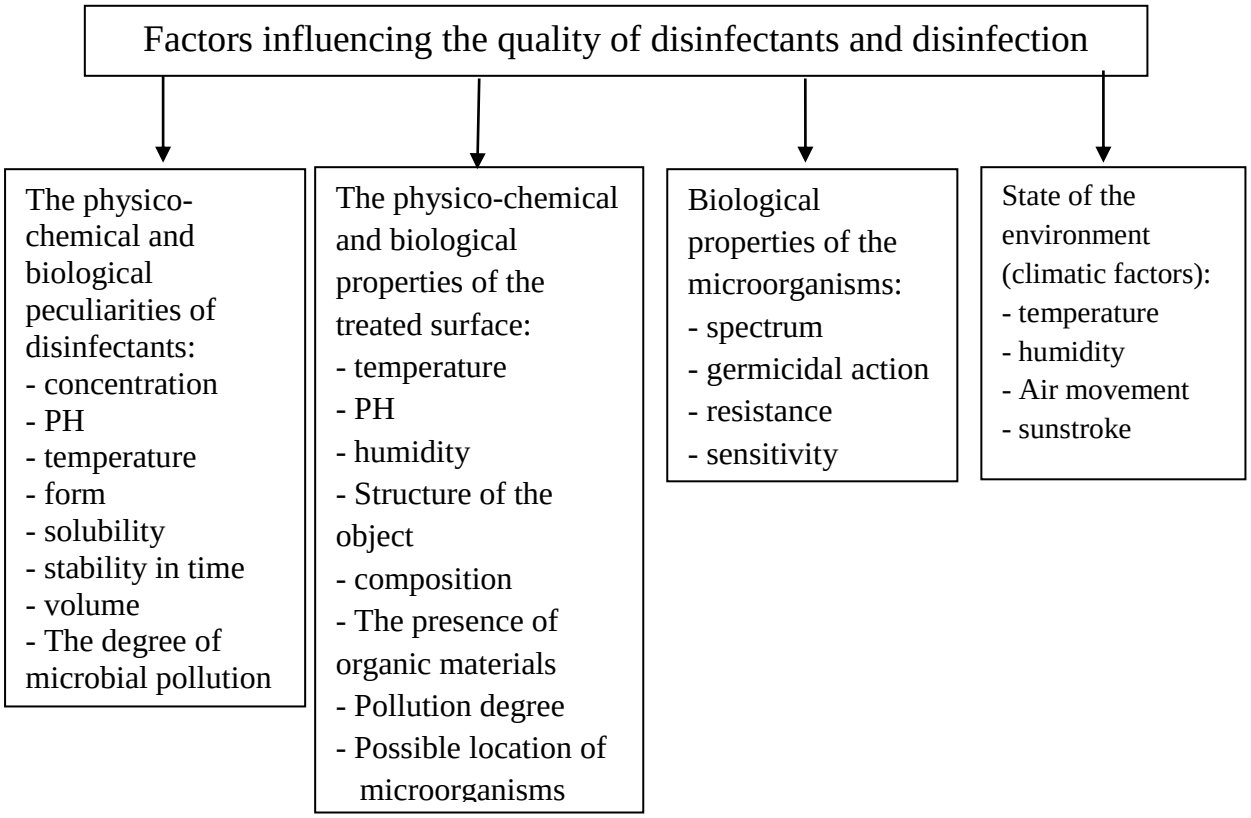
Substances and disinfectant preparations must meet the following requirements:

- to have broad spectrum of antimicrobial activity;
- to possess low toxicity;
- to be sufficiently soluble in water and compatible with surface-active substances, and salts of fatty acids;
- to show high activity in the presence of organic substances;
- to be universal in using (washing, spraying, wiping, dipping, etc.);
- to be harmless at skin contact, inhalation, entry into the gastrointestinal tract;
- not to be aggressive to objects, surfaces, and other items during the disinfection;
- to be non-corrosive to equipment and reusable medical instruments;
- to have minimal bactericidal exhibition;
- to possess superior physico-chemical properties (to be stable, non-flammable, non-explosive, be safe and easy to prepare working solutions);
- to be able to be used in the presence of humans and animals;
- to be possibile to determine the active substance in the basic preparation and working solutions;
- to be accessible to medical institutions and population.

2.1.2.1.2.2. Factors that influence the effectiveness of disinfection

The quality and effectiveness of disinfection are determined by a number of factors (tab. 29), which can be divided into 4 groups:

- Physico-chemical and biological properties of disinfectants.
- Physico-chemical and biological properties of the treated surface.
- The biological properties of the microorganisms.
- State of the environment.



High degree of microbial pollution of treated surface needes more time for disinfection. In determining the factors that influence the effectiveness of disinfection it is necessary to estimate not only the degree of microbial pollution, but location of microorganisms as well. This condition is important in disinfection of apparatus that has canals (endoscopes, fibroscopes etc.).

Most preparations have antibacterial activity against gram-positive and gram-negative bacteria, but expected bactericidal effect of disinfectant may be different because of the sensitivity of various microorganisms.

The presence of substances of organic origin (blood, feces, pus, etc.) diminishes antimicrobial action of disinfectants.

Other factors, which influence the effectiveness of disinfection, are concentration of the preparation, the humidity, the temperature of the environment and the working solution. The optimum temperature of solutions is of 45-50 ° C. Higher temperatures destroy the disinfectant and as a result reduce the effectiveness of disinfection.

One of the most difficult problems is the disinfection of objects at low temperatures. Disinfectants, including chlorine compounds, at temperatures below 15 ° C (V. Turcan, 1997) lose their antimicrobial activity. To enhance the bactericidal effect of disinfectants at low temperatures are used chemicals - activators (NaCl, (NH4) 2SO4 and ammonia).

Destruction of the microorganisms in liquid medium and on different surfaces depends on intensity of the contact between disinfectant and microbial cell. Most efficient is disinfection by using disinfectant in liquid form and compliance with the concentration of the working disinfectant solution. Otherwise, the preparation may have only bacteriostatic action, leading to the formation of the resistance to disinfectant.

2.1.2.1.2.3. Forms and methods of application of disinfectants

Disinfectants can be used in solid form (powders, pills, soap), liquid (solution, suspension, emulsion) and gas (aerosol, mist).

The most used methods for applying disinfectants are: irrigation, washing, wiping, dipping, vaporing, spraying, soaking, wetting, embedding.

Performing an effective disinfection it is necessary to use the most rational form and method suitable for respective disinfectant. Methods that are more effective are: irrigation and washing of the surfaces and objects using the required amount of working solution.

Spaulding scheme provides reasonable disinfection of objects, apparatus and equipment used in caring after the sick, following the methods of disinfection. Based on the scheme all disinfected objects are divided into three categories: critical, non-critical and semi-critical.

Critical objects - present a significant threat to patients and medical staff in case of microbial contamination, including spores of bacteria. This category of objects includes surgical instruments, probes, intravenous solutions, needles, etc. In this case decontamination methods are: heating, autoclaving and chemical sterilization, the objects being cleaned of organic substances.

Semi-critical objects - which are in contact with the mucosa or skin. On the surface of these objects must not persist microorganisms (except bacterial spores). The semi-critical objects are: inhalation and anesthesia equipment, thermometers, gastrointestinal endoscopes. The disinfection of semi-critical objects needs to be of high level, which is usually carried out by the following methods: autoclave and cold sterilization and glutaraldehyde, hydrogen peroxide, alcohol, phenol, iodophorm and its compounds, followed by rinsing and heat drying.

Non-critical objects – which are in contact with the skin, but not mucous membranes (hospital furniture, dishes, linen, books, tonometry cuffs etc.). Non-critical objects can be disinfected and used immediately, without being transported to other rooms for disinfection.

2.1.2.1.2.4. Sensitivity/resistance of microorganisms to disinfectants

The sensitivity of different species of microorganisms to disinfectants varies considerably. The concentration required for killing the microorganisms is different.

High sensitivity to disinfectants have vegetative forms of bacteria, fungi and viruses, followed by M. tuberculosis, and P. aeruginosa. Less susceptible to disinfectants are bacteria spores.

It is important to note that using disinfectant solutions with low bactericidal concentrations favor the formation of resistant microorganisms to the disinfectants.

Acquired resistance to disinfectants is determined by genotypic mechanism (due to occasional mutations in the DNC replication plasmids, chromosomes and transposons) or phenotypically.

Phenotypic resistance to disinfectants is based on the ability of bacteria to form biofilms, which have various microbial membrane surface, which limits access of disinfectant molecules.

The main causes, which lead to the formation of resistance to disinfectants, are:

- incorrect selection of disinfectants;
- irrational disinfection;
- large and long use of disinfectants containing quaternary ammonium compounds;
- incorrect preparation and storage of working solutions;
- use of preparations and working solutions at concentrations below the admissible concentration;
- use of disinfection procedures without discounting features of objects and disinfectant substance;
- lack of microbiological investigations to sensitivity of microorganisms to disinfectants.

Formation of resistance to disinfectants is possible to avoid by:

- respecting strictly disinfectants circle;
- following instructions in organizing disinfection measures;
- selecting disinfectants in accordance with contemporary requirements, depending on the species of microorganisms, sensitivity to disinfectants and object for disinfection;
- keeping records of purchased preparations and their consumption;
- performing monitoring of resistance of microorganisms to disinfectants;

- performing rotation of disinfectant products based on microbiological monitoring results;
- following the rules of storage, and preparation of disinfectants;
- ensuring systematic monitoring of quality and efficiency of disinfection;
- testing the bactericidal activity of disinfectant preparations each semester;
- improving the strategy and tactics of disinfection regime in medical institutions, selection and correction of systematic disinfection regime.

2.1.2.1.2.5. Requirements to terminal disinfection

Terminal disinfection is carried out in outbreaks of infectious diseases and aims to interrupt the epidemic process, to stop the outbreak.

Terminal disinfection is performed compulsory in cases of suspected or confirmed contagious infectious diseases: plague, cholera, relapsing fever, typhoid, typhus, Q fever (pulmonary form), anthrax, diphtheria, salmonellosis, tuberculosis, haemorrhagic fevers of viral etiology, leprosy, ornithosis, micosporosis, tricofitie, scabies. Terminal disinfection is performed usually by specialized institutions in the certain area and by licensed specialists. In case of necessity, fot the terminal disinfection and disinsection can be used steaming. Disinfection of objects, items, clothes, linen, books from outbreaks of infectious diseases is compulsory to do by steaming.

The quality of terminal disinfection is assessed by the following indicators:

- terminal disinfection at least 95% of all recorded outbreaks;
- terminal disinfection in outbreaks within 24 hours from the patient's hospitalisation;
- disinfection of the oven (steaming) - 95% ;
- assessment of the quality of terminal disinfection (visual and bacteriological - at the same time) within 1-3 hours after disinfection (at least 1% of outbreaks at home and at least 10% of outbreaks in communities);
- sampling of at least 10 lavages, 2 samples of the disinfectant solution, 10 samples-specifically in order to identify the disinfectant residuals;
- bacteriological control of the oven, (not less than once per trimester).

2.1.2.1.2.6. Requirements for the organization of current disinfection at home

Health-care workers, who detected the patient with infectious disease, organize current disinfection in outbreak. It is performed until the patient's hospitalization, during the patient's treatment at home, treatment of carriers of

pathogens, and in some infectious diseases (e.g. active tuberculosis) – during the follow up.

Physical methods, mechanical and chemical disinfection can be widely used in outbreaks.

It is necessary to create optimal conditions for safekeeping of disinfectants in order to avoid children's access. Family members, involved in the current disinfection, have to be well-trained in disinfection.

Making current disinfection it is necessary to follow the measures:

1. Use of disinfectants depending on the pathogen of infectious disease.
2. Compliance with the required concentration of the working solution.
3. To insert objects used by sick person which can serve as a transmission factor into disinfectant solution, (if it allows the volume and structure of the object).
4. The disinfectant solution must completely cover the surface of the object.
5. The temperature of the working solution - the parameters of 20-35 ° C.
6. To respect the exhibition and periodicity of disinfection.
7. To avoid concomitant use of two disinfectants or one after another. First disinfectant may inactivate the other.
8. It is necessary to take into account that the excreta of patients (blood, feces, sputum, vomit, urine) containing organic substances, can decrease the activity of disinfectants.

Main quality indicators of the current disinfection are:

- current disinfection within 3 hours from patient’s detection;
- quality control of current disinfection at least in 1% of total outbreaks;
- bacteriological control by taking 10 lavages; one sample of disinfectant and working solution;
- disinfection is qualitative if the number of positive lavages is less than 3%, the number of express samples, specific to identify the active residual substance on the treated objects is ≈ 3%.

2.2. Sterilization

Sterilization is the totality of methods and means used for the destruction or removal of all species of microorganisms that are present in different substrates or on the surface of various objects.

2.2.1. Methods of sterilization

Depending on the species and the particularity of the microorganisms, sterilization can be performed by the following methods: physical, chemical and biological.

2.2.1.1. Physical method

Physical methods of sterilization include: sterilization by dry heat, sterilization with circulating vapors, sterilization by radiation, sterilization at the reduced pressure, ultrasonic sterilization, sterilization by ultraviolet rays, sterilization by filtration, sterilization with electron beams, etc.

2.2.1.1.1. Sterilization by dry heat (oven)

Sterilization by dry air at 160 ° C during two hours or at 180 ° C for one hour is an effective method to sterilize reusable medical instruments, glass and heat-resistant glasses, but does not allow sterilization of soft material (textile) and compresses. It is important to note that the exposure time is considered when the temperature is reached.

Complete sterilization cycle consists of three stages:

- Heating until the indicated temperature for sterilization;
- Maintaining the operating temperature throughout the sterilization;
- Cooling.

Recommendation for dry heat sterilization:

- Heating should be started, preferably, with the open door to decrease air humidity and thus to prevent oxidation of the instruments.
- Never open the door if the temperature exceeds 80 ° C.
- Sterilization in oven is indicated for metal or glass objects.
- Sterilization is not recommended at temperatures above 180ºC (risk of deterioration of the metal).
- Placing the material in the oven must ensure free air circulation between objects.

2.2.1.1.2. Sterilization by steam under pressure (moist heat) in autoclave

Autoclaving is the most reliable and safe method of sterilization, allowing sterilization of the whole material (including textile and rubber). Principle of the method: The water is heated in a tightly closed space, which leads to a higher temperature of 100 ° C in the absence of air (air is evacuated at the start of the sterilization), the pressure and temperature are directly proportional, that allos the temperature to be adjusted by controlling the pressure (tab. 30). Sterilization can be carried out at 121ºC depending on the material (= 1 atmosphere overpressure) and at 134ºC (= 2 atmospheres over-pressure).

Table 30

Sterilization regime of medical items in autoclave

Sterilization material	Temperature		Pressure		Duration
	°C	°F	Atm	PSI	Min.
Instruments, syringes (plastic, glass), rubber	121	250	1	15	30
Bandages (compresses), operation area, gowns)	134	275	2	30	30
	or 121	250	1	15	40
* Overpressure above atmospheric pressure					

2.2.1.1.3. Sterilization by prolonged boiling (30 min.) It is allowed in extreme conditions, in the absence of the possibility of using special equipment.

Recommendations. To ensure effectiveness of sterilization by prolonged boiling process must be considerd the following:

• It is important to prepare tools and materials for sterilization. This binding process is carried out by soaking the instruments for 8-15 minutes in cold water with addition of ammonia or sodium carbonate in a concentration of 1-2%. Syringes and needles are degreased with oil neophaline. Cleaning will be more efficient if the objects before the sterilization are washed with hot water (30-35 ° C) and sodium carbonate in a concentration of 1-2%, then, plentiful rinsing.

- Pour enough water to cover all instruments or reusable material throughout the boling after arranging the material. Water used for sterilization must meet the requirements for drinking water.

• Sterilization time is calculated from the boiling time and must be ≥ 30 minutes.

• Prepared kits can be used during 2 hours, if they remain covered, and extraction of instruments shall fellow aseptic techniques.

2.2.1.1.4. Low-Temperature Sterilization Technologies

This method is used to sterilize technically complicated heat-sensitive medical instruments, but with the possibility to be penetrated by sterilizing agent in the inner cavities.

A priority of this method is the absence of toxic remaining. Special type of sterilizers „Serrada" are used, in order to implement these methods. The device occupies an area of just 1 m^2, is equipped with mechanisms of self-control and self-regulation of working parameters. Sterilization chamber volume is of 100 litters, the sterilization cycle - for 54-72 min.

2.2.1.1.5. Sterilization of water for surgical washing is performed in the autoclave for sterilization, to 1.5 kg/cm^2 pressure and exposure of 30 minutes. Sterile water for surgical washing is prepared in the day of use.

2.2.1.1.6. Sterilization by ionizing radiation

It is currently widely used method (gamma radiation) to sterilize dressing material, medical re-usable instruments (surgical), pharmaceutical preparations, serums and other objects.

Sterilization by ionizing radiation has some advantages over the heat sterilization. The temperature of the item is increasing insignificantly during the sterilization by ionizing radiation. Due to this fact, the process is called "cold sterilization".

2.2.1.1.7. Sterilization by filtration

This method of sterilization requires special equipment - ultra filter (bacterial filters), which remove microorganisms mechanically from the objects for sterilization. Bacterial filters are made of glass, ceramics, asbestos (Mg3CaSi4O12) and other materials.

The technological process is used to remove the heat-sensitive pharmaceutical antibacterial remedies, impossible to be cleaned by other means.

2.2.1.1.8. Sterilization by microwaves

It is shown (Latimer JM et al., 1982) that microwave irradiation of household products such as microwave ovens (2.45 GHz) completely inactivate microorganisms in an exhibition from 60 sec. to 5 min., depending on the species.

2.2.1.2. Chemical sterilization

2.2.1.2.1 Sterilization with strong disinfectants

Chemical method of sterilization is recommended for articles of polymeric, glass and rubber materials, and metals resistant to corrosion.

The process of sterilization consists of cleaning of patient’s care items and rinsing in the effective disinfectants against vegetative bacteria and viruses (including HIV and hepatitis B, C, D). This method is an alternative, if the autoclaving or sterilization are not possible. The efficacy of chemical sterilization is dependent of solution concentration, duration of sterilization ≥ 360 min. and the duration of solutions using (must be renewed at least once a day). Chemical method of sterilization is not recommended to needles and syringes.

2.2.1.2.2. Gaseous Sterilization

This method is used to sterilize surgical instruments, which have mirror surfaces, the optical or radio-electronic apparatus, guts, disable objects and different articles of plastics, synthetic, thermo-resistant (catheters, tubess etc.) that are not resistant to dry-heat sterilization, by water vapor under the pressure or chemical sterilization . Preparations that have sporicidal action, such as ethylene oxide, trioxymethylene, metal bromide, formaldehyde (formaldehyde or formaldehyde gas) and the mixture OB (ethylene oxide and methyl bromide) are accepted for gaseous sterilization.

Sterilization is performed in polyethylene packaging in two layers with a thickness of 0.06 to 0.2 mm, parchment, non-impregnated paper bag for automatic packaging of the food products (brand E). Storage of sterilized polyethylene packs is 5 years and parchment paper - 20 days.

2.2.2. Sterilization of medical items

All re-usable medical items that come in contact with the wound surface, blood or injections, and some articles that contact with mucous membranes and may cause damage to them, must be completely free of microorganisms. Sterilization of medical items consists of 2 phases: anti-sterilization and sterilization.

Anti-sterilization process requires removal by mechanical cleaning of all contaminations of proteins, lipids and drug origin.

Anti-sterilization of medical items is performed immediately after use, when they are going to be reused. In this case, blood contaminated instruments are washed under running water, or immersed in a solution of the corrosion inhibitor (e.g. solution of 1% sodium benzoate), it can be stored up to 7 hours. An effective cleaning of re-usable medical instruments may be achieved by soaking them for 15 minutes in water with the addition of ammonia or sodium carbonate in concentration of 1-2%. Oily substance from instruments can be removed by neofilinum, followed by washing with water (30-35°C) and sodium carbonate 1,5-2% and abundant rinsing.

The quality of sterilization depends on the level of ovens' loading. Sterilizing items are charged in such a quantity that allows free entry of circulating of dry air into the sterilizer chamber.

The recommended capacity of loading packs and surgical dressing material is indicated in Table 31.

Table 31

Capacity of loading packs and surgical and dressing material

Sterilizing items	measures	Model of packs						
		KSK-3, KF-3	KSK-6, KF-6	KSK-9, KF9	KSK-12, KF-12	KSK-18, KF-18	KSPF-12	KSPF-16
Typhon	Grams	150	300	450	600	900	600	800
cotton	Grams	65	130	195	260	390	260	350
Towel	Pieces	1	3	5	7	10	7	9
Sheet	Pieces		1	2	3	5	3	4
surgical caps	Pieces	10	20	30	40	60	40	51
surgical gloves	Pieces	15	30	45	60	90	60	80
dressing gowns	Pieces		1	2	3	5	3	4
Tubes	Kilograms	0,5	1,0	1,5	2,0	3,0	2,0	2,7
shoe covers	Pieces	2	4	6	8	12	8	10
metal instruments	Kilograms	6,0	12,0				15,0	15,0

Storage of sterile items

The shelf life of a packaged sterile item depends on the quality of the wrapper, the storage conditions, the conditions during transport, the amount of handling, and other events (moisture) that compromise the integrity of the package.

If event-related storage of sterile items is used, then packaged sterile items can be used indefinitely unless the packaging is compromised.

Duration of storage of medical items sterilized in packs without filters is 3 days; in parchment paper impervious to moisture, the paper's brand food packaging, wrapping resistant paper enhanced with filter - period is 20 days.

Medical re-usable items sterilized in impregnated paper bag, paper bag impervious to moisture, food paper for automatic packaging brand E, resistant packing paper are stored for 20 days.

Articles sterilized without packaging must be used immediately after sterilization. To maintain the sterility of sterilized items it is necessary to ensure the tightness of containers' boxes with sterile items, store them in closed cupboards. Other materials are forbidden to store in these places.

Immediately after sterilization on the boxes or other wrapping paper applies the following:

- The day and time of sterilization;

- The sterilization device and the cycle number;
- Data about person who performed the sterilization.

Data about the sterilization of medical articles are entered in the register.

2.2.3. Central sterilization department (CSD)

Centralized sterilization units is provided for medical institutions. They are divided into two areas - sterile and non-sterile. The sterile area covers: the sterile sterilization department - autoclaving, sterile material storage and expedition. Others relate to the non-sterile spaces. Access is allowed in sterile room only through sanitary filter.

Sterilization Department performs the following functions:

- Receiving the re-usable instruments and items (materials) for performing the sterilization;
- Segregation, sorting, cleaning of tools;
- Packaging and sterilization of instruments;
- Release of sterilized objects and materials;

Staff is provided with personal protective sanitary equipment that will be possible to be washed and sterilized under hospital conditions, separately from the patients and staffs items. Health staff will pass through the filter at the beginning and end of the work. All the staff of central sterilization department will be subject to periodic (once a year) medical examination, occupational safety and hygiene training.

2.3. Disinsection

Disinsection is a set of measures used to control arthropods (insects) - Vector in transmitting of infectious and invasive diseases.

Latest, in Europe were recorded cases of Chikuugunya, Dengue fever, West Nile virus infection - infectious diseases transmitted by mosquito Aedes albopictus and Aedes aegypti, which lead to the intensification of surveillance activities of diseases transmitted by mosquito species in European countries.

Preliminary studies carried out in Moldova have demonstrated the presence of West Nile in tick species Dermacentor marginatus and Ixodes ricinus.

Natural outbreaks have the potential to be more active under the influence of certain factors, such as temperature and high humidity. At the same time, there is observed the reducing effectiveness of measures in connection with the development of resistant populations of insects.

2.3.1. Methods, sources and means of disinsection

Disinsection measures are divided into preventive and control measures. Both prophylactic and control measures use the following methods: mechanical, thermal, radiant, biological, chemical and combined.

The purpose of prophylactic measures is to create unfavorable conditions for life and reproduction of arthropods, preventing from entering and maintaining their effect in the human environment.

The aim of the disinsection is total or partial destruction measures against selective biological vectors of active or passive transmission of infectious and invasive diseases.

Disinsection methods:

a) Physical, which includes:

• mechanical (extraction, ventilation, nets, special clothing, etc.);

• radiant (ultraviolet, infrared, gamma radiation);

• thermal (dry heat, wet heat, boiling, burning, etc.).

b) Biological (entomopathogenic preparations, fish, aquatic plants, birds, advanced biotechnologies).

c) Chemical (synthetic or natural chemical preparations).

Classification of insecticides and their use

One of the most effective way to combat arthropods is the chemical method, which requires extensive use of chemicals to destroy insects (insecticides). Insecticides are substances and preparations in minimal concentrations acting on the living body, causing destruction or disruption of essential physiological functions, leading even to insects death (from Latin words: insectum - insect and caedo - destroy).

Insecticides can be classified according to the following principles:

A. The nature of biological vector:

- *Acaricide* (control of ticks);
- *Larvicide* (destruction of larvae);
- *Ovicidal* (destruction of arthropods' eggs);
- *Pediculicide* (destruction of lice);
- *Imagocide* (control of mature arthropods).

B. Regulation of the growth, multiplication, location and removal:

- **Repellents** – Insecticides that reject arthropods from the subject;
- **Attraction** – chemicals that attract arthropods in a certain place;
- **Sterilizing -** preparations that cause infertility;
- **Regulating the growth** - chemical means that inhibit the development of arthropods.

C. Dependence on the ways and means of penetration into the body of arthropods and their mechanism of toxic action:

- **Contact**, that enter the body through the body skin (epidermis);
- **Intestinal, that** enter with the bait by water and food;
- **Breathing** (fumigants);
- **combined**, which possess double or even triple action (contact fumigated - intestinal).

D. The chemical structure:

- *Organochlorine;*
- *Organophosphorus;*
- *Carbomice, tiocarbomice;*
- *Nitrophenol etc.*

Currently, medical insecticides used in disinsection are organic and phosphor organic compounds, pyrethroids, vegetable preparations (peretrine) and other substances and preparations from other classes and groups of chemical compounds.

According to chemical structure, contact insecticides are divided into the following groups: Chlororganic, phosphor organic, including fermentation, carbomate, peretroide, piretrine, neonicotinoids, and other chemical compounds.

2.3.2. Forms of insecticides used in medical practice

More frequently are used forms of powder or solid consistency (granules, powder, dusts, capsules, pills, etc.), liquid (solutions, concentrates, suspension, emulsion), semi-solid or semi-liquid (ointments, liniments, paste, glue, sparkling bait etc.), aerosols, gases.

3. Immunoprophylaxis of infectious diseases

Immunoprophylaxis has the goal to prevent appearance of infectious diseases by administering immunological preparations containing antigenic substances or antibodies. Immunoprophylaxis is used in the prevention of more than 30 infectious diseases.

3.1.1. Types of vaccines

The vaccines are immunological preparations, containing a suspension of (bacteria, viruses, rickettsia etc.) live attenuated or inactivated microorganisms ("killed") or fractions (subunits) thereof, given to induce the immunity in order to prevent the disease.

Currently are developed several types of vaccines: corpuscular live attenuated, inactivated corpuscular ("killed"), disaggregated (split vaccines), chemical (subunit, split), toxoids, recombinant vaccines protein carring, vaccines, vaccines with artificial adjuvants, associated vaccines.

3.1.1.1. Live corpuscular vaccines

Live vaccines are a suspension of low-virulence strains of microorganisms attenuated in various ways: by successive passages on unfavorable culture media, or on non-natural animal host, genetically engineered, by inactivating the genome responsible for the virulence factor or genetic mutation that leads to decrease of the virulence.

Thus, strains of live microorganisms, that are genetically attenuated, los the capacity to produce the infectious disease in humans but remain closest thing to a natural infection, keeping the property to multiply in the body, ensuring the maintenance of necessary infectivity in order to provide adequate antigenic stimulation and production of an appropriate immune response. Infectious process after vaccination takes usually several weeks and is not accompanied by clinical manifestations. The immune response after the vaccination is long-lasting, thanks to the immune memory.

The advantages of live vaccines:

• lead to the formation of a strong and long-lasting immunity;

• in most cases it is sufficient a single dose of vaccine;

• they are easy to manage. Can be inoculated into the body by simple methods, such as by scarification or paroral;

• Most live vaccines are produced in lyophilized form, which can be kept longer term (up to one year and more);

• freezing does not essentially influence their activity;

• Live vaccines do not contain preservatives.

However, to ensure complete safety of live vaccines it is necessary to control them systematically because of the reversibility of the original virulence of strain.

It is necessary also to comply with strict requirements to ensure their viability. One of the main conditions is the preservation and transportation exclusively at +2-+8 ° C. Working with live vaccines it is important to comply with aseptic rules. Another important aspect to remember is that before 1-2 days of administration of live bacterial vaccines and 7 days after vaccination it is necessary to avoid using the antibiotics, sulfanilamide or/and immunoglobulins, which can diminish the vaccine response due to its bactericidal action on these preparations.

3.1.1.2. Corpuscular inactivated vaccine ("killed")

Inactivated vaccines are prepared from killed strains of bacteria or viruses, keeping the antigenic activity. Therefore, inactivated vaccine strains lose the property to cause an infectious process, but retain their immunogenic properties. For inactivation of microorganisms are used physical agents (heat) and chemical substances (phenol, formaldehyde, acetone, alcohol, β-propiolactone, hydroxylamine, etc.), which guarantee a safe inactivation with minimum damage to the antigenic complex. Inactive vaccines in liquid form have greater stability compared with live vaccines. Storage and transportation conditions are the same, the temperature of + 4 - + 8 ° C. The freezing of inactivated vaccines leads to decreasing of the activity and increasing adverse reactions to preparation. Inactivated vaccines have a lower immunization capacity than that with live vaccines, however, repeated administration leads to the formation of a stable and strong immunity. The most commonly administration method is parenteral inoculation.

3.1.1.3. Subunit vaccines (chemical) and split-vaccines

Subunit vaccines contain an antigen or an antigenic fraction obtained from the parental strains of microorganisms by various chemical methods. Instead of the entire microbe, subunit vaccines include only the antigens that best stimulate the immune system. The basic principle consists of separation of protective antigen, which provides the specific immunity. Chemical vaccines have low reactogenicity and may be inoculated in high doses for several times. The use of adjuvants enhances vaccine efficacy. Subunit vaccines, in particular the lyophilized, are resistant to the influence of the environment, can be easily standardized, and can be used in combination with other vaccines directed to prevent various diseases.

"Split" vaccines consist of disaggregated antigenic substrate from the parent strains by using detergents. Different methods are used to clean the antigenic material: ultrafiltration, centrifugation and chromatography. In result, there is obtained a high degree of cleaning - >95%. As adsorbent is used aluminum hydroxide (0.5 mg / dose) and as a preservative - merthiolate (50 mg / dose).

Both vaccines "split" and the subunit have low reactogenicity, a high degree of specificity, enough immunogenicity and are harmless.

3.1.1.4. Toxoids

Toxoids are prepared from exotoxins derived from different species of microorganisms. The toxins, neutralized with formalin not to lose immunogenic properties – form the antitoxins. Toxoids are adsorbed by aluminum hydroxide after purification and concentration. They induce the production of antitoxic immunity.

3.1.1.5. Recombinant Vaccines

The principle of preparation is the cloning, in which antigens are synthesized by inserting the coding genes into E. coli or yeast cell as HBV vaccines. Most suitable for cloning is vaccinia virus (cowpox virus) used in smallpox vaccination. In addition to the fact, that the virus has a high potential for replication in the human body, it does not circulate in nature, so it can be genetically manipulated without risk. The isolated viral DNA is non-infectious and the genetic information leads to the synthesis and release of encoded antigens and produces the corresponding immune response to the vaccinated people. This technique has been used to make the vaccine against the hepatitis B virus and influenza virus.

Avirulent strains of S. typhimurium, Shigella, E. coli, etc. can be used for the same purpose. This kind of vaccines has many advantages.

3.1.1.6. Synthetic vaccines (carrier of protein)

This type of vaccine is prepared from the synthetic polypeptide, being a new realization in chemistry. It started from the observation that protein macromolecules' structure of viruses and bacteria carry a large number of determinants, of which only some have a role in inducing the specific protective response.

To obtain synthetic vaccines it is necessary to recognize chemical structure of the natural antigenic determinants and then by chemical synthesis is reproduced the synthetic structure (fragments) of antigenic determinants, analog of the natural ones, that can be made immunogenic by coupling them with various carriers of molecules. By this method is obtained, for example, hepatitis B vaccine containing synthetic polypeptides similar to those of HBsAg. Antigen binding synthetic peptide-carrier protein molecule has a number of beneficial effects on the immune response, primarily by increasing the size of the immunogenic particle. As the carriers of protein, were used hemocianin of Magathura (KLH), tetanus toxoid, as well as some branched synthetic polymers or polymerized peptides.

Advantages of synthetic vaccines are that they have a well-defined chemical nature, can be produced in large quantities, harmless, able to join on the same carrier-molecule more peptides that are immunogenic determinants of various pathogens including bacteria and viruses.

However, synthetic vaccines are relatively less immunogenic compared to the natural one and dictates the need for adjuvants.

3.1.1.7. Associated vaccines

Associated vaccines contain antigens associated with several species of microorganisms. An example is the diphtheria-tetanus-pertussis vaccine. Immunization is done with associated vaccines against several infections, so simplifying vaccination schedule and avoiding overloading it.

There are two types of vaccinations: combined and simultaneous (concurrent).

Combined vaccines contain antigens associated with several species of microorganisms previously mixed during the technologic process or within using the same syringe, being inoculated in the same place. To this category belong diphtheria-tetanus-pertussis (DTP) vaccine, diphtheria-tetanus-pertussis + polio vaccine (DTP-P), trivaccinal measles - mumps - rubella (MMR) and others.

Simultaneosly associated vaccines – administration of several types of vaccines, in different ways and in different areas, but the vaccines are injected with different syringes. In this way can be administrated the following vaccines: polio vaccine (killed) + H. influenza type b (Hib) + DTP + hepatitis B or measles + mumps rubella. Combination of vaccines must ensure the effectiveness of each, and the side effects are not frequent and more severe than those known for each vaccine.

The current schedule of vaccination in Moldova for 2011 - 2015 years provides both concomitant vaccination with pentavalent vaccine (Hep B + DTP + Hib) and pneumococcal vaccine (PC) separately with different syringes and at different injection sites, polio (OPV) and antirotaviral vaccines (RV) - droplets in the mouth at 2, 4 and 6 months. Revaccination with BCG - VPO - DT and MMR at the age 6-7 years; VPO - Td - MMR at the age 15-16 years.

Large application of combined vaccination in the immunization plan as prophylactic vaccination is a global trend that covers interests of children, parents, health workers and society as a whole, as it allows to reduce costs in the management and preservation of vaccines, traumatization of children; and increase the coverage of vaccination of the population.

3.1.2. Ensuring quality and safety of vaccines

3.1.2.1. The national supervisory authority of vaccines

Every country should have a national supervisory authority to ensure the quality and safety of vaccines, according to WHO recommendations, which fulfil the following functions:

• licensing of vaccines;
• assessing the quality of vaccines;
• improvement Protocol releasing each lot of vaccine;
• testing of each lot of vaccine;
• monitoring the "cold chain";
• certification and licensing of institutions and medical staff in providing immunization services;
• vaccinations' quality supervision in the field.

In Moldova the national authority for carrying out these functions is designated for the National Centre for Public Health.

3.1.2.2. Conditions to vaccine as biological product

Immuno-biological preparations must fit the following conditions:

- Be immunogenic - to determine the specific immune response;
- Be purified - do not contain ballast substances that could cause complications;
- Be concentrated - to have optimal antigenic effect in small quantities;
- Not to be irreversible - for live vaccines;
- Be stable - not to lose immunogenic qualities during storage and transportation;
- Be cheap (affordable, economic).

3.1.2.3. Requirements for the vaccine to be administered

Health worker must take into the account the following factors, before administrating the vaccine:

- label has to be present on the packaging, which should contain the following data:
    • production company;
    • the name of the preparation;
    • content of preparation (in polyvalent vaccines):
    • serial number;
    • number of control;
    • volume and dose of preparation;
    • date of production;
    • timeout limit (shelf life);
    • storage conditions;
    • temperature indicator.

- the packaging must be intact;
- preparation appearance must correspond to accompanying document.

Both preparations with damaged packaging, unlabeled or labeled with incomplete data and those without instruction or expired are prohibited for use. Preparations with changed aspect (color, haze, uncharacteristic sediment) must be non-valid. Content of preparation of solid consistency (lyophilized vaccines) should repeat the form of packaging. In case of incorrect storage or expiration of shelf life, they take shape of balloon or dust. The sediment is allowed for liquid preparations. In such cases, it is compulsory to indicate on the label "Before use it is necessary to be shaken". In the absence of such inscriptions preparation must be transparent and without sediment. Preparations that do not meet the above requirements must be rejected.

3.1.3. Storage conditions

Vaccines are very sensitive biological products that can easily lose immunogenic capacities from exposure to inappropriate temperatures. Once lost, these capabilities can not be restored. Therefore, one of the general conditions of maintaining immunogenicity of immunological preparations is compliance with temperature regime during transportation from manufacture to Management Company and throughout storage and use ("cold chain") -. Most preparations require storage at +2 to + 8 ° C. Keeping at the light (direct sun rays) or at a higher temperature than 10 ° C results in the inactivation of the preparation. Also, unfavorable temperatures are below 0 ° C (but not including vaccines against polio, measles, mumps, rubella and BCG - but not solvent). These vaccines may be frozen and defrosted several times without losing their immunogenic capacity, with condition that in the process of defrost the vaccine’s temperature will not exceed + 8 ° C.

Freezing and defrost are prohibited for the following vaccines: Hep. B, DTP, DT, Td, diphtheria and tetanus toxoids, Hib. These vaccines are deteriorating after freezing. The concrete storage of preparations is described in the instructions. In order to check the compliance with regime of preservation are used different types of chemical or electronic indicators.

3.1.4. Indications for vaccination

Mass vaccination can be of two types:

• planned vaccinations;
• vaccinations according to epidemiological indications.

Planned vaccinations are performed against infections included in the vaccination schedule. Vaccination against these infections is performed regardless of the currently existing epidemiological situation. They are performed on the basis

of legislative acts according to the schedule, and they are mandatory for risk groups listed in the schedule of vaccinations.

Vaccination according to epidemiological indications is carried out against some infectious diseases, according to created situation, WHO recommendations for high-risk groups of population, such as international travelers (tourism, business, trade, cultural exchanges), immigrants, refugees (in case of social, natural or artificial disaster), certain known risk professions, people with certain lifestyle etc. An example may serve mandatory vaccination against yellow fever of all persons who travel to countries at risk of contamination of the disease.

3.1.5. Calendar of vaccinations

Planned vaccination is addressed to some groups, especially children, and is performed in certain periods, therefore, it is necessary to establish a timetable under which to organize vaccination.

Typically, each country makes its own schedule of vaccinations, according to country's specific conditions, which is an official program of vaccination of all persons eligible by age.

Calendar of vaccinations contains data about the management of mandatory vaccination, both during a calendar year and the lifetime of an individual.

Making the vaccination calendar the following factors are taken into account:

- the risk of infection to a certain age;
- age peculiarities of the immune response to the vaccine;
- potential interference of immune response to the presence of passive maternal antibody or antigen overlap;
- risk of complications after vaccination at certain ages;
- optimal intervals in compliance with vaccination schedules for each vaccine individually;
- epidemiological situation in the country and WHO recommendations for each vaccine;
- economic and organizational possibilities for achieving immunization program.

National Immunization Program for 2011-2015 (approved by the Government Decision no. 1192 of 23.12.2010) and vaccination schedule (approved by Order of 16.02.2011 MS of RM no. 2104) provide vaccination against hepatitis B, tuberculosis, polio, diphtheria, tetanus, pertussis, measles, mumps, rubella, Hib infection. Also, in this calendar is provided vaccination plan against rotavirus infection from 2012, and in 2013 - against pneumococcal infection. Timing of vaccination and revaccination and types of vaccines used in the Program (schedule) of current vaccinations are given in tab. 32.

Making prophylactic vaccination according to the calendar at different stages leads to a decreased morbidity (diphtheria, tetanus, pertussis, hepatitis B, measles, mumps, rubella and others. A.) tens and hundreds times compared to pre-vaccination period, and in some infections – eradication of them (smallpox, polio).

3.1.6. Basic principles in organizing and administering of vaccinations

1. Prophylactic vaccination against infectious diseases included in the schedule of immunizations is guaranteed and insured by state (the Republic of Moldova Law regarding the state supervision of public health no. 10 - XVI of 03.02.2009).
2. Vaccinations included in the vaccination schedule are usually performed in vaccination clinics of primary medical institutions or maternity. It is allowed in special cases, conducting vaccinations in other circumstances (pre-school institutions, schools, higher education institutions, enterprises), in compliance with the rules of transportation, storage and administration of vaccines, as well as emergency medical assistance in cases of adverse reactions after vaccination.
3. Parents are informed in advance about the need for childs' immunization, the day the child will be vaccinated, type of used vaccine, possible post-vaccination reactions.

4. Vaccinations are performed by doctors in primary health care system, which provides: preparing the annual plan of vaccinations, informing and mobilizing the population, vaccination schedule, storage and optimal handling of the vaccine, providing the tools necessary for the vaccine (syringes and disposable needles), training and certification of nursing staff participating in the action of vaccination.
5. All health workers participating in vaccination should be trained in vaccinations regarding the indications, contraindications, precautions of vaccination, reporting system about reactions after vaccination, providing conditions for transportation and storage of the vaccine, public education on the value of immunization in preventing infectious diseases.
6. Children subjected to immunization previously are examined by the family doctor (nurse), including the body thermometer, accurate data on the assumptive disease and history of previous vaccinations, allergy to drugs or food etc. A doctor treats all children with chronic diseases, allergic reactions, etc., before the immunization.
7. Vaccinations are applied according to the established timetable.
8. Unimmunized children are vaccinated according to the individual schemes in possible terms, with separate or simultaneous administration of vaccines. Priority application of one or another vaccine is determined depending on the situation on the epidemiological state, age and health state of the child.

9. Each dose of vaccine will be administered with sterile syringe and needle in different parts of the body. During concomitant vaccination it is strictly prohibited in the same syringe combination of two or more vaccines. Do not allow to dissolve lyophilized vaccine with the liquid vaccine of another infection.
10. Minimum interval between the separate administrations of the vaccines is 30 days.
11. After blood transfusion, nonspecific or specific immunoglobulin, passive/active prophylaxis of tetanus and rabies, vaccines (except those against measles, mumps, rubella) will be administrated after 1.5 months. Vaccines against measles, mumps and rubella will be administered after 3 months.
12. The immunoglobulin can be applied 2 weeks after the administration of vaccines. Administration of immunoglobulin, in specific clinical indications or rabies and tetanus immunoprophylaxis, is done regardless of previous immunizations.
13. Tuberculin testing is performed with an interval of one month after application of vaccines and 2 weeks after introduction of immunoglobulin.
14. The vaccines can be administered after tuberculin testing immediately after the reading of the tuberculin reaction.
15. Each person must remain under the supervision of health worker for 30 minutes after applying the vaccine, for early evidence of possible side effects.
16. All adverse reactions appeared after the vaccination, will be diagnosed and reported to public health authorities (Public Health Center), according to the national system for reporting of adverse reactions after vaccination (Form no. 058/s, approved by Order MS no. 13 of 11 January 2011).
17. All vaccinations will be recorded in the medical record documents: vaccination sheet, newborn's sheet, patients' sheet, vaccination certificate.

Table 32

Vaccination schedule in the Republic of Moldova

Age	Immunization against								
	HepB	Tuberculosis **BCG**	Polio **OPV**	Rotaviral infection **RV**	**Hib**	Pneumococcal infection **PC**	Diphtheria, tetanus, pertussis **DTP**	Diphtheria, tetanus, **DT/Td**	Measles, mumps, rubella **MMR**
24 hours	HepB-0*								
2 – 5 days		BCG 1							
2 months	HepB-1		VPO-1	RV-1**	Hib-1	PC-1***	DTP-1		
4 months	HepB-2		VPO-2	RV-2**	Hib-2	PC-1***	DTP-2		
6 months	HepB-3		VPO-3	RV-3**	Hib-3	PC-1***	DTP-3		
12 months									ROR-1
22 – 24 months			VPO-4				DTP-4		
6 – 7 years			VPO-5					DT	ROR-2
15 – 16 years			VPO-6*					Td	ROR-3**
Adults: at 20, 25, 30, 35, 40, 50 and 60 years old								Td	

Note: * - from 2011; ** - from 2012; *** - from 2013

3.1.7. Contraindications to vaccination

Each country independently determines the list of pathological conditions that constitute rejection of a person to vaccination. The list of contraindications to vaccination significantly reduced at present. According to the Ministry of Health Order No.100 of 01/06/94, this list actually corresponds to WHO recommendations.

We distinguish true and false contraindications to vaccination. True contraindications include temporary contraindications and absolute (relative).

3.1.7.1. Absolute contraindications

There is a number of absolute contraindications, which do not allow immunization with vaccines included in the NIP [17].

3.1.7.1.1. Serious side reactions (anaphylaxis, collapse, encephalitis or encephalopathy, convulsions) are observed after the previous dose of the vaccine. These reactions, appeared after vaccination, can be easily determined by the mother or a health worker. The second or third dose of DTP vaccine is not administered to children who have severe post-vaccination reactions observed at the previous dose. In this case, the administration of pertussis component is excluded from vaccination and continue only with diphtheria and tetanus (DT) vaccine.

3.1.7.1.2. Vaccine with cell pertussis component is contraindicated in children with uncompensated neurological pathology (children with epilepsy, whose treatment does not prevent the development of accesses, or children with progressive encephalopathy).

3.1.7.1.3. Vaccines produced of chicken embryos or containing neomycin is prohibited in children who react to chicken eggs or neomycin by symptoms of hypersensitivity (generalized urticaria, difficulty in breathing, larynx edema, collapse, and shock). For example, measles, mumps, rubella (MMR).

3.1.7.1.4. Live vaccines are not recommended for immunocompromised children or children with the weakened immune system due to tumors and due to the treatment or after radiotherapy. Patients with clinical symptoms of AIDS are prohibited to be administrated BCG vaccine and against yellow fever, however, can be administrated measles and polio vaccine. At the same time, vaccination against tuberculosis is administered to children with HIV without clinical evidence of disease.

3.1.7.2. Temporary contraindications

Contraindications to vaccination can be considered temporary illness and acute exacerbations of chronic disease states. In these cases, it is necessary to postpone vaccination until the disappearance of acute signs of disease. Vaccination is carried out immediately after the disappearance of fever in acute respiratory diseases or moderate forms of digestive infections. Many forms of diseases (eczema, dermatitis, asthma, thrombocytopenic purpura, congenital heart defects, arrhythmias, rheumatic carditis, chronic pyelonephritis, chronic glomerulonephritis) allow vaccination only in the period of remission.

3.1.7.3. False contraindications

As false contraindications are recognized the following: perinatal encephalopathy, stable neurological state (e.g. Dawn syndrome and other chromosomal disorders, cerebrospinal paralysis), puerperal trauma, allergic status (asthma or other allergic diseases), dysbacteriosis, mild respiratory infection or diarrhea, temperature not higher than 38.5 ° C, dermatitis, eczema or local lesions of infectious origin of the skin, chronic heart, lung and kidney diseases, chronic hepatitis.

The false contraindications also can be: premature birth, low birth weight, hypotrophy, sepsis, complications of vaccination in the family, family allergy, epilepsy, HIV infection in children without clinical signs of disease, treatment with antibiotics or low doses of steroids, corticosteroids, and its local using.

It is important to note that all health workers involved in vaccination should be guided by the instruction for vaccine application and adhere to rules that refer to temporary or absolute contraindications for vaccination.

3.1.8. The methods of vaccines administration

The effectiveness of immunization is highly dependent on the mode of administration. Each vaccine, according to the specific requirements, is administered in a specific mode and for a certain time. There are several ways of administering vaccines: parenteral, enteral ("orally"), intranasal.

3.1.8.1.Parenteral administration

There are four ways of parenteral administration of vaccines:

- intramuscularly;
- subcutaneously;
- intracutaneously;
- scarification.

Intramuscularly are usually administered vaccines containing aluminum salt as adjuvant (DTP, AD, AT, Td, hepatitis B, etc.). Preferred intramuscular site in children is the anterolateral thigh showing the largest muscle (Fig. 52.1). Intramuscular injection is performed into the deltoid muscle in young children and

adults. It is not recommended to perform injection in M. gluteus because of the risk of nerve ischiadic trauma. It is also necessary to take into account the fact that subcutaneous fat thickness in adult in the buttock region is ≈ 3.5 cm, due to this fact, the injection of the vaccine in the buttock may form a vaccine depot in the deep layer fat, which absorbs hard and causes reduction of immune response.

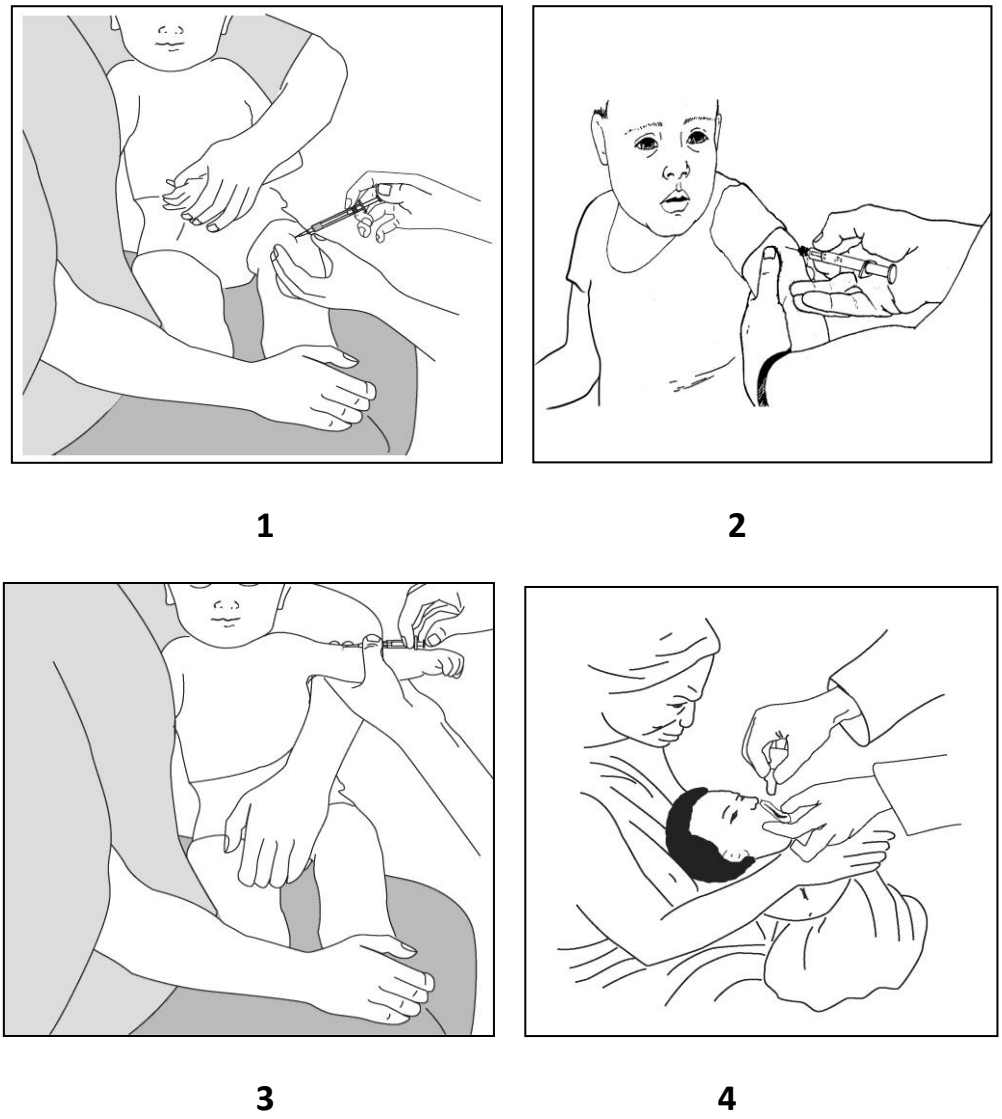


Fig. 52. Correct position of child and needle during the vaccine administration:
1 – Intramuscular; 2 – subcutaneous; 3 – intradermal; 4 – oral.

Subcutaneously usually are administered the following vaccines: measles, rubella, mumps, and their combinations. Preferred site for subcutaneous injection is the upper arm (Fig. 52.2).

Intracutaneously is administered BCG vaccine, which is injected in the skin, to provide a slow release, typically in the left arm on the border between the upper 2/3 and lower 1/3 (fig. 52.3). This method requires certain skills, the vaccine is

introduced under pressure to appear a "lemon peel". Incorrect injection of BCG vaccine risks to form a cold abscess.

Scarification. Vaccination is carried out by light incrustation in the skin, usually on the outside of the arm. It is used in live vaccines: smallpox, tularemia, anthrax.

3.1.8.2. Enteral ("orally", “per os”)

Oral administration of the Salk polio vaccine (Fig. 52.4) is used in the vaccination against polio, in drops. Oral vaccines have low reactogenicity and light allergic reactions. Children easily support them. Immunological and epidemiological effectiveness of other methods do not yield the application of vaccines. "Per os" method of administration is simple and harmless, does not require special equipment and special devices. Vaccination can be carried out under any conditions, is free of disadvantages, there is no danger of transmission of infection, does not cause emotions in the vaccinated person.

3.1.8.3. Intranasal administration

Intranasal vaccination is achieved by applying an aerosol vaccine or vaccine dripping in nasal cavity, where the antigen, with air currents, easily reaches the lungs. It is used in influenza vaccination with inactivated influenza vaccine.

3.1.9. Adverse reactions after vaccination

Adverse reactions after vaccination (VAR) depend on the type of vaccine, the method of administration and individual response to vaccines.

The association reaction with a specific vaccine can be suspected when:
1. the registration of multiple cases of reactions among immunized people in short time after vaccine administration;
2. reactions among vaccinated population are observed much more frequently than among the population of the same age group, that was not vaccinated.

Adverse reactions to vaccination are: local (pain, swelling, edema, hyperemia, nodules, abscesses, necrosis), systemic (fever, headache, malaise, myalgia, arthralgia, drowsiness, thrombocytopenia, paralysis), allergy (hives, swelling of the face and larynx, encephalopathy, collapse, shock).

Can be highlighted:

1. *Side effects induced by vaccine* - caused by vaccine components themselves (lymphadenitis after administration of BCG, measles vaccine, allergic reactions to vaccine components).
2. *reactions hurried by vaccine* – clinical state that could occur in vaccinated individuals, but occurred earlier due to vaccination (ex. Febrile convulsion in a child with neurological history, febrile convulsion in a child predisposed to epilepsy).

3. *Side effects associated with the program* - errors in storage or administration of vaccines.

4. *Coincidences* of s*ide effects* - in cases when clinical sate could appear even if individual is not vaccinated, but coincides with the time after vaccination.

Adverse reactions to live attenuated vaccines are usually infectious and occur later, compared with those produced by inactivated vaccines that usually appear immediately and are based on the mechanism of hypersensitivity. There are two types of vaccine adverse reactions (VAR): common and undesirable.

3.1.9.1. General adverse reactions after the vaccination

The vaccine administered in the body affects the immune system and metabolism and it is manifested through various reactions in the body. Therefore, local reactions, fever and some systemic reactions are part of normal reactions to vaccines. At the same time, some of the components of the vaccine, such as adjuvants, may cause various reactions.

Usual reactions can be considered the following: local pain, swelling or redness in individuals vaccinated with DTP, sterile abscess - after vaccines containing an increased amount of adjuvants, fever and rash - after measles, papule, ulcers and scars that occur over two weeks or a few months after the vaccination with BCG. The frequency of normal reactions after administration of different vaccines is shown in Table 33.

Table 33

The frequency of usual post-vaccination reactions, according to WHO

Vaccine	Local reactions (pain, swelling, redness)	Fever	Malaise, general symptoms
BCG	Frequent	–	–
Hib	5 – 15%	2 – 10%	–
Hep B	Children - up to 55% Adults – up to 30%	1 – 6%	–
MMR, Measles	Up to 10%	Up to 5%	Up to 5%
Polio	–	Less than 1%	Less than 1%*
DT, Td	Up to 10%**	Up to 10%	Up to 25%
DTP***	Up to 50%	Up to 50%	Up to 60%

* Diarrhea, headache and/or muscle pain.

** At buster doses up to 85%.

*** using acellular vaccine of pertussis, the rate will be lower.

Usual post-vaccination reactions occur within 24-48 hours after vaccine administration, except fever and general symptoms after measles and MMR, which

can be observed 5-12 days after immunization, and local reactions after BCG. These are normal post-vaccination reactions that do not require special treatment or to be declared. However, vaccinated child should be followed up, and parents should be consulted regarding possible side effects.

3.1.9.2. Undesirable side effects after vaccination

Undesirable side effects after vaccination are more rare. In most cases they refer to seizures, thrombocytopenia, hypotonia and hyporeflexia, persistent crying. These effects are short-lived and do not cause major health problems.

Table 34

The frequency of undesirable side effects and time of appearance after the vaccination

Vaccine	undesirable side effects	Occurrence interval after vaccination	Rate per million doses of vaccine
BCG	Suppurative lymphadenitis, Osteitis, Disseminated BCG,	2– 6 months 1 – 12 months 1 – 12 months	100 – 1000 1 – 700 2
Hib	They have not been observed		
Hep B	Anaphylaxis Guillain Barr syndrome (SGB)	0 – 1 hour 1 – 6 weeks	1 – 2 5
Measles/MMR*	Febrile seizures Thrombocytopenia Anaphylaxis	5 – 10 days 15 – 35 days 0 – 1 hour	333 33 31 – 50
Polio	Paralytic poliomyelitis vaccine associated	4 – 30 days	1,4 – 3,4**
Td, DT	Brachial neuritis Anaphylaxis Sterile abscess	2 – 28 days 0 – 1 hour 1 – 6 weeks	5 – 10 1 – 6 6 – 10
DTP	Persistent crying (more than 3 hours) Seizures Hypotonic syndrome Anaphylaxis/shock Encephalopathy	0 – 24 hour 0 – 3 days 0 – 24 hours 0 – 1 hour 0 – 3 days	1000 – 60.000 570*** 570 20 0 – 1

* Reactions (except anaphylaxis) occur more frequently among children primary vaccinated; in children less than 6 years febrile seizures are not observed;

** Risk is higher after the first dose compared with secondary doses;

*** Febrile seizures depend on the child's health status, medical history, age - the risk is lower in children up to 4 months.

Serious reactions can be encephalitis following vaccination against measles and mumps, encephalopathy after pertussis vaccine, live polio vaccine-related paralysis, local lymphadenitis and long lasting ulceration scars after the vaccine with BCG, anaphylactic shock after administration of DTP.

Although serious undesirable post-vaccination reactions are rare, however, they are observed more frequently than serious complications as a result of supported disease. For example, a case of paralysis after vaccination can be found in 2.5 million doses of OPV, and a case of encephalopathy per million vaccinated against measles, while the complication in patients with measles is 500-4000 times more frequent. The frequency of undesirable side effects and the time of possible occurrence is given in tab. 34.

3.1.10. Reactions associated with the program

They are related to technical errors in the storage and administration of vaccines. They may be as follows:

- Improper storage and transport of the vaccine (time, place, temperature conditions);
- Ignoring the requirements for vaccine before the vaccination;
- Too much vaccine administered per dose;
- Inoculation in a disallowed place;
- Compromising the sterility of the syringe and/or needle;
- Dissolving improperly the vaccine diluent;
- The use of an incorrect amount of diluent;
- Substituting the diluent with a drug;
- Contaminated vaccine or diluent;
- Ignoring contraindications.

Errors associated with the program may make an outbreak of side effects. For example, vaccinations are at risk of developing abscesses, septicemia, blood-borne infections in case of non-compliance with the aseptic rules of vaccination.

Adverse reactions associated with post-vaccination program can be prevented by continuous training of staff that provide immunization services, correct management, use of equipment that ensures the security of injections and continuous supervision of storage and administration of vaccines, epidemiological investigation and analysis of cases.

3.1.11. Vaccination of children with allergic diseases

Children with allergic diseases are vaccinated individually. The vaccination of these children is to comply with the following criteria:

- Children with allergic diseases are vaccinated against all infections included in the vaccination schedule. Immunization is recommended against flu as well, especially children with chronic Broncho pulmonary pathology;
- Vaccination of children with allergic diseases is performed only in remission (complete or incomplete), after prophylactic therapy with antihistamines according to age, 2 times a day, 5-6 days before and after vaccination;

- During vaccination children must respect diet to exclude the causative allergen (fish, eggs, honey, chocolate, nuts, cocoa, citrus, strawberries, raspberries, etc.) and avoid using food which had already caused allergic reactions. During this period, is not recommended introduction of new products. The diet must be respected at least one week before and one month after vaccination;
- Children suffering from pollinizes are vaccinated outside plant flowering period. Vaccination of children with allergic diseases regardless seasonal nature may be performed in any season;
- Skin tests with infectious and non-infectious allergens can be made 10 days before vaccination and 1-1.5 months after vaccination;
- Vaccination is carried out 1.5-2 months after complete treatment (exception - epidemiological indications) if the child receives specific hypo-sensitization treatment with infectious or non-infectious allergen or histoglobulin therapy, normal or anti-allergy immunoglobulin. After the vaccination, course of therapy can be started not earlier than 1.5-2 months;
- Children suffering from asthma are vaccinated during stable disease remission (absence of accesses within one month). Vaccination is performed after prophylactic therapy, which volume is determined by the severity of asthma;
- In case of intermittent and mild persistent allergic reactions, average doses of antihistamines are indicated according to age within 2 days before and 7-10 days after vaccination;
- In case of persistent severe evolution of allergic reaction, vaccination is carried out based on prophylactic therapy with topical steroids (Becotide, Becloforte, Flixotide etc.) or in combination with theophylline or Salbutamol;
- Children with severe persistent asthma are vaccinated in the hospitals.
- Children with asthma who have had systematic allergic reactions in anamnesis (anaphylactic shock, Quinke edema, generalized urticaria) require vaccination with DT instead of DTP. Repeated dose of antitoxin is introduced only in hospital together with anti-inflammatory therapy! Antihistamine is indicated 2-3 days before vaccination, and corticosteroids -2 hours prior to vaccination (sometimes 10-15 minutes prior is administering adrenaline).

3.1.12. Vaccination of children with neurological conditions

Children with perinatal encephalopathy, acquired cerebral trauma, neurological infections, metabolic encephalopathy, especially those with history of seizures, acute or chronic poisoning, children with developmental anomalies or genetic diseases, children at risk and those from disadvantaged families should be specially prepared for vaccination.

This preparation aims to decrease the reactivity of the CNS in children and prevent epileptic seizures and non-seizures that are hard to be observed by parents

and even by medical personnel, and cerebral edema, which is the basis of various serious complications after the vaccination.

Preparation for vaccination is carried out by administering 5 mg/kg phenobarbital in 2 rounds morning and evening, with an interval of 12 hours, and glicerophosphat (gluconate) of calcium of 30-50 mg/kg in 3 rounds. These preparations are administered 2-3 days prior to vaccination and 7-10 days after vaccination.

In case that once a child has epilepsy (seizures, blurred bouts of breathing disorders, psychomotor retardation, etc.) will be given phenobarbital 5 to 10 mg/kg every 8 hours over 3 rounds with calcium preparations, during 3 days before vaccination and 10-12 days after vaccination.

If the child makes epilepsy during the vaccination (seizures or loss of consciousness without seizures access) he is given first medical aid by urgent introducing 0.3-0.5 mg/kg diazepam i/v or most convenient - i/rectal. Dose of diazepam needed per kg of body is taken in a syringe and dissolved in 2-3 ml of physiological solution or boiled water, the needle is removed, syringe is lubricated with grease (oil) and administrated intra/rectal. Orally can be administered phenobarbital + calcium and this child is hospitalized urgently in neurology ward for children for investigation and treatment.

In order to prevent febrile seizures, parallel to the phenobarbital, especially in the night, it is recommended to administer doses of paracetamol according to age. Parents are advised to be careful at night to measure the temperature every hour after the child has been vaccinated and administrate antipyretic medicines recommended by doctor.

One should remember, that if mental, verbal or motility disorders occur after vaccination (weakness in the limbs, paresis or paralysis), the child should be immediately hospitalized in neuro-pediatrics profile sections.

3.1.13. Vaccination during pregnancy

For the moment, there is no conclusive assessment of risk regarding vaccination during pregnancy, therefore, except in specific cases, vaccination should be avoided during pregnancy, especially during the first trimester. In some circumstances, the risk resulting from vaccination needs to be estimated compared with the benefits to mother and fetus. The benefits will outweigh the risks in cases when:

- risk of exposure to infection for mother or fetus is high;
- disease presents an especial risk for mother and fetus (eg. Tetanus).

There is an extensive vaccination of pregnant women with inactivated vaccines, toxoids and polysaccharides (ex., Tetanus toxoid) without adverse side effect for pregnancy. Typically, vaccination is postponed for the third timester of

pregnancy, in order to minimize risks to the fetus development and not to cause abortion.

Most live vaccines (BCG, measles, rubella, mumps, chicken pox) are not recommended during the pregnancy to exclude possible congenital malformations. Experience has shown, however, that ignorance regarding administration of rubella vaccine to pregnant women did not lead to anomalies, confirming that abortion is not a justified measure.

3.1.14. Vaccination of persons with HIV/AIDS

Vaccination is safe and beneficial in children with HIV, that is why is not recommended HIV testing.

Most children infected during the first two years of life, possess the ability of immune response, both cellular and humoral. Over the next two years, is observed an evident decline of the response.

People with asymptomatic HIV infection can receive all vaccines except BCG vaccine and the vaccine against yellow fever.

Children with symptomatic HIV infection, at the severe stage of the disease, as well as for other severe diseases will not be vaccinated.

3.1.15. Planning vaccinations

Development of vaccination plan comprises two major objectives:
1. Determination of the number of people requiring vaccination according to the vaccination schedule, and according to epidemiological indications.
2. Establishment of vaccine needs, syringes, and other supplies, boxes for incineration of vaccins, provision of their necessary quantities.

The planning process is usually carried out at the end of the year, for the next one to include information on the achievements about vaccinations realized and that were not made in the current year. Planning is done annually and quarterly bottom-up (medical institution, district, country) in accordance with the schedule of vaccinations and the Ministry of Health Orders regarding population immunizations for each dose of vaccine separately.

Planning the vaccinations will take into account:

1. The number of population by age groups. Family doctor will record and update the register of served population by visiting at home, with further verification by the local administrative organs. Based on the census, will be completed report "Data on the number of living people" from Monthly Register of immunization activities for the next year, according to the Order of No. MS. 901 of 23.11.2011.
2. Data on the number of children born in the last 2 years and estimation the number of children who will be born in the year for whom vaccinations are planned. The number of new-borns for the next year is calculated based on

the average number of new-borns in the last 3 years. If you observed a decline or a significant increase in the birth rate, the estimated number of new-borns will be adjusted for birth trend. The estimated births for the next year are divided by 12 months, to know how many children will be born each month. Estimated figures for the first 6 months can be verified with the number of pregnant women that are registered and their term of pregnancy. It will also consider the growth or decline in birth or other social and demographic phenomena.

The Annual vaccination is composed according to table 35 (see tab. No. 35) and includes data on population requiring vaccination with each dose of vaccine during the year, including monthly and quarterly growth - 3, 6, 9 12 months.

Table 35

Vaccination plan

	Group / Vaccine	Months			3 months	Months			6 months	Months			9 months	Months			Total per year
		I	II	III		IV	V	VI		VII	VIII	IX		X	XI	XII	
0.1	Nr. New-borns in maternity																
0.2	Nr of children <1 year at family doctor																
I	**Primary vaccination**																
I.1	BCG																
I.2	HepB1																
I.3	HepB2																
I.4	HepB3																
I.5	OPV																
I.6	OPV2																
I.7	OPV3																
I.8	DTP+Hib 1																
I.9	DTP+Hib 2																
I.10	DTP+Hib 3																
I.11	DT1																
I.12	DT2																
I.13	MMR1																
II	**Revaccination at 1-6 years**																
II.1	OPV4																
II.2	DTP4																
II.3	DT3																
III	**Revaccination at 7-13 years**																
III.1	OPV5																
III.2	DT5																
III.3	MMR2																
III.4	BCG2																
IV	**Immunization of teens and adults**																
IV. 1	Td -**15** years																
IV. 2	PO 6 -15 years																
IV. 3	Td1																
IV.4	Td2																
IV. 5	Revac.Td-adults																
V	**Vaccination and revaccination not included in NPI**																
V.1	HepB1-gr. risk																
V.2	HepB2-gr risk																
V.3	HepB3-gr. risk																
V.4	HepB4-gr.risk																
V.5	Flu vaccination																
V.6	Rabies vaccination																

3.1.16. Features of vaccines included in the immunization schedule

3.1.16.1. Vaccine against tuberculosis BCG (bacillus Calmette-Guérin)

The preparation contains live attenuated mycobacteria - BCG vaccine strain, lyophilized, white powder, or tablet, or a cream. A vial containing 1 mg of BCG vaccine, comprising 20 doses of 0.05 mg of the preparation.

Biological and immunological properties

Live strains of attenuated mycobacteria multiplying in the body of the person being vaccinated, results in the formation of long-lasting specific immunity against tuberculosis. Following the vaccination occurs activation of cellular immunity (T lymphocyte proliferation, macrophage activation, cytokine secretion, delayed hypersensitivity development etc.).

A papule of 5-10 mm in diameter is developed on the site of intradermal inoculation of BCG vaccine. In neonates, this reaction, is considered normal, appears over 4-6 weeks after vaccination, which then evolves vesicle and ulceration. Decreasing of the reaction lasts for about 3 months (2-5 months). The reaction develops within 1 –2 weeks in individuals that received booster dose. Scars are formed in 90-95% of vaccinated, on the BCG vaccination site with a diameter up to 10 mm, which is an indication that immunization was a success. Lack of scars in vaccinated children against tuberculosis does not mean lack of immune protection and they will not be vaccinated once again. Doctor supervises evolution of cicatrization over 1, 3 and 12 months after immunization with recording the results in child's development sheet, form no. 112e.

Mode, time and dose of administration of the BCG vaccine

BCG vaccine is dissolved with the solvent supplied by the same manufacturer, is injected intradermal in the top layer of skin on the external surface of the upper portion of the left shoulder, usually within the first 3-5 days after birth. If vaccination is performed 2 months after the child birth, prior testing is recommended with 2 IU PPD Mantoux reaction. Vaccination will be performed to children presenting a tuberculin reaction of 0-4 mm size infiltrate or hyperemia of any size more than 72 hours.

Administration dose of BCG vaccine for children under the age of 12 months is 0.05 ml and for children over one year - 0.1 ml. Application of dressings or disinfectants is prohibited after injection of BCG vaccine.

Possible side effects after vaccination

The following common adverse reactions may occur after administration of BCG vaccine:

• Axillary/neck lymphadenitis, which usually goes without treatment. In more severe cases is recommended the treatment of children in specialized hospitals.

• Swelling or cold abscesses. This happens as a result of unsterile syringes and needles used for vaccination, the injection of a large amount of the vaccine, or it is administered subcutaneous instead of intradermal.

The following undesirable side effects may occur after administration of BCG vaccine:

• lipoid local reaction, which usually passes recovering in a few months, keloids tuberculosis and lupus;

• Osteitis or osteomyelitis •;

• tuberculous meningitis and generalized infection caused by BCG vaccine are usually registered among people with immunodeficiency.

Contraindications

1. Temporary Contraindications:

• Children with allergic manifestations;

• Children with skin diseases (pyoderma, furunculosis, eczema);

• Recovering from acute infectious diseases: 1 - 3 months after influenza, measles, scarlet fever and minimum 6 months after acute viral hepatitis. These children will be vaccinated after the recovery.

2. Absolute Contraindications:

• Symptomatic HIV infection (AIDS);

• Positive reaction to tuberculin (PPD).

Allergy test to tuberculin (Mantoux reaction or PPD test).

Tuberculin allergy test aims:

- Effective control of BCG vaccination;
- Establishment of indications to BCG revaccination;
- Detection of oversensitivity to tuberculin;
- Determination of contamination with tuberculosis among population;
- Diagnosis of tuberculosis.

Purified Protein Derivative (PPD) product with 2 IU in 0.1 ml is used to test tuberculin allergy. It is a specific protein substance - prepared by a human mycobacteria which is purified, concentrated and titrated in International Units.

PPD test is administrated on the anterior side of the forearm, after local treatment with alcohol, by intradermal inoculation of 0.1 ml PPD strictly 2 IU. Correct inoculation is confirmed by the formation of a bubble of edema of about 5 mm remaining 10 minutes. If the bubble of edema does not appear after inoculation, take out the needle and inject on the other forearm with the same amount of PPD.

Reading the reaction takes place 72 hours after inoculation, noting the maximum transverse diameter of the papule and possible issues: blistering,

ulceration, necrosis. The reaction is considered positive if the papule diameter is ≥ 5 mm.

The negative reaction allows BCG vaccination/revaccination, whereas positive reaction is an absolute contraindication to BCG vaccination.

The efficacy of BCG vaccination is estimated by:

- Percentage of allergies obtained after vaccination, PPD test beeing the most objective;
- Proportion of persons with vaccination scars;
- Monitoring the incidence and severity of disease among vaccinated individuals.

3.1.16.2. The vaccine against hepatitis B (Hep B)

Hepatitis B vaccine is designed to prevent both acute and persistent infection and its consequences: liver cirrhosis and liver cancer. Vaccination protects infection with HBV virus infection and to HDV.

Vaccination is indicated in children according to schedule and adults with high risk of contamination: blood transfusion service workers, persons employed for the production of biological and donated cord blood, clinical laboratory workers, medical staff and the active during training (students, including medical colleges, residents), hemophiliacs, people in contact with carriers of HBV, intravenous drug users, patients with parenchymal organ transplant or graft etc.

Hepatitis B vaccines currently used in practice are of a recombinant type and are obtained by genetic engineering (recombinant DNA), fractions of immunogenic polypeptide (protein surface S HBsAg) encoded by the corresponding DNA of the HBV genome, cloned, and then inserted into the genomic DNA of yeast (*Sacharomyces cerevisiae*). The obtained product is adsorbed on aluminum hydroxide and is produced in vials with one or more doses or pre-packaged in syringes with self-destructive mechanism.

In addition to the monovalent vaccines there are associated preparations in the form of bivaccines: DTP - Hep B, Hib - Hep B, Hep A - Hep B or 3 component vaccines - DTP - Hep B + Hib, etc. New-born babies receive only monovalent Hep B vaccine.

Scheme, dosing and vaccination

Since 1995 the Republic of Moldova has made universal vaccination of new-borns against hepatitis B according to the following scheme: the first 24 hours after birth, 2 months, 4 months and 6 months (Scheme 0: 2: 4: 6). The dose is 0.5 ml vaccine for children, and those aged more then 15 - 1.0 ml.

Method of administration

Hepatitis B vaccines are inoculated intramuscularly:

- In children under 10 years vaccine is inoculated in muscle external surface of the thigh portion environments;

- In adults in the deltoid muscle.

Hep B vaccine can be administered simultaneously, but in different anatomical areas with BCG, DTP, OPV, Hep A or HIB, without risk of adverse reactions to stress or interference in the immune response.

Possible side effects

Hep B vaccine is one of the most harmless vaccines. Side effects are rare, mild and transient and are manifested by low grade fever and headache (1-6% of vaccinees), which last one or two days after injection of the vaccine, the sensetivity, redness or swelling at the injection site are light and that occurs slightly more often than in 15% of cases of adults and 5% in pediatric cases. Anaphylactic reactions occur rarely.

Contraindications and precautions to vaccination

Hepatitis B vaccination is contraindicated in persons with a history of anaphylactic reactions to yeast or other constituents of the vaccine. To temporary contraindications belong severe febrile illness, prolonged treatment (over 7 days) with corticosteroids. No vaccination is contraindicated in pregnant or lactating women.

3.1.16.3. Polio vaccination

Polio immunization can be achieved by the administration of two kinds of vaccines:

a) inactivated Salk Polio vaccine (VPI), which contains three types of viruses (I, II and III) killed by formalin and heat processing, administrated intramuscular, and induces only humoral immune response, by the appearance of specific antibodies for all three types of polioviruses;

b) live vaccine Sabin type - with types I, II and III of attenuated poliovirus with oral administration and producing of double immunity, both humoral and local (blocking the entrance gate, which makes impossible the multiplication of wild polioviruses in the intestine).

3.1.16.3.1. Inactivated Polio vaccine (IPV)

IPV is obtained by culturing polioviruses substrate Vero cell culture or human diploid cells (MRC - S) and inactivated with formalin and heat.

Storage conditions: temperature between + 2 ° C and + 8 ° C. Avoid freezing as it lowers its immunogenicity.

Vaccination schedule. IPV may be used in polio vaccination programs alone or in the sequential scheme.

IPV vaccination in infants has two or three intramuscular (or subcutaneous) injections at dose of 0.5 ml to 6 months of age (age 2 and 4 months or 2, 4 and 6 months), first re-vaccination at the age of 12-18 months, and the second booster vaccination at the age of 4-6 years.

For vaccination of adults IPV is administered at a dose of 0.5 ml intramuscularly (or subcutaneously) in the deltoid region. Primary vaccination consists of 3 doses: the first two every month or two months and the third within interval of 6-12 months compared with the second dose.

3.1.16.3.2. Live Polio attenuated vaccine (OPV)

The vaccine contains three strains of the polio attenuated virus obtained through serial passages in vitro and in vivo. In addition to attenuated virus strains, preparation of nutrient medium contains magnesium chloride as a thermal stabilizer and phenolftalien as pH indicator.

The preparation is in the form of clear solution, pink, and is delivered in two package types: small dripping plastic tubes and dripping plastic bottles which are supplied separately.

Method of storage

OPV vaccines are kept frozen at -10 ° C for 1 year, and at -20 ° C - for 2 years. After thawing they are not to be stored at temperatures between + 2 ° C and + 8 ° C, vaccines must be used within 30 days after thawing.

Dosages and vaccination

The vaccine is administered orally at dose of 0.2 ml (2 drops) directly into the mouth of the child. The vaccination consists of 3 doses at 2, 4 and 6 months age. Revaccination is carried out from 22 to 24 months, 7 years and 15-16 years old.

In countries where polio cases are recorded, the "zero" dose of OPV soon after childbirth is recomended. 2-month interval between the first and second administration, second and third administration according to the case may be reduced to one month.

3.1.16.4. Diphtheria-tetanus-pertussis (DTP)

Method of storage

The DTP vaccine is maintained at a temperature from + 2 ° C to + 8 ° C. Pertussis Component of vaccine is sensitive to high temperatures. Freezing also leads to damage to the DTP vaccine.

Indications

DTP vaccine is used in the prophylaxis of diphtheria, tetanus and pertussis in

young children. Maximum age that can be administered DTP vaccine containing Bordetella pertussis is 7 years.

Method of administration

Vaccination is the administration of three inoculations at a dose of 0.5 ml at 2, 4 and 6 months of baby's life, intramuscular, deep-lateral external face of the thigh. In children over 3 years vaccine can be inoculated in the deltoid region. Injecting the child in the buttock can lead to achieving the sciatic nerve and is not recommended. Inoculation product is made with another needle than the one used for taking product from the vial. The interval between the first and second dose of DTP and between the second and the third DTP dose can be reduced up to one month.

The first revaccination with DTP applies at age 22-24 months of baby's life. The second revaccination is performed at the age of 6-7 years with DT vaccine containing diphtheria and tetanus purified. The dosage of administration is 0.5 ml. The mode of administration is as in the DTP vaccine.

The following revaccination at age 15-16 years (third revaccination) and for adults (according to the schedule of vaccinations) is performed with Td vaccine containing purified tetanus anatoxine and diphtheria purified anatoxine - in low dose (1/10 of the child' dose) . The manner and dosage of administration are the same as for DT and DTP vaccines - 0.5 ml intramuscularly.

3.1.16.5. Haemophilus influenza type b vaccine (Hib)

Haemophilus b vaccine presents a polysaccharide encapsulated H. influenza type b conjugated with tetanus protein. No preservatives are used. It is produced in two forms: liquid and lyophilized. Each of these forms is available as a vaccine or in combination with other vaccine (DTP + Hib Hep B +).

Indications

Hib vaccine is used in the prophylaxis of invasive infections caused by H. influenza type b (meningitis, pneumonia, sepsis, epiglottitis, otitis, sinusitis, septic arthritis, etc.) in over 60% of cases in children up to 5 years. This vaccine does not induce protection against other types of Haemophilus influenza.

Storage conditions

Hib vaccine is kept at +2 to + 8 ° C. Do not allow freezing.

Immunization schedule

The vaccination is similar to that used in DTP and OPV primary vaccination and includes three doses of 0.5 ml each:

Hib 1 to 2 months;

Hib 2-4 months;

Hib 3 to 6 months.

The minimum interval can be reduced to at least one month between each dose. In some countries the fourth dose at age 12-18 months is used.

Method of administration

In infants, the vaccine is given intramuscularly in the anterolateral thigh. Older children receive the vaccine intramuscularly in the upper arm. It is practiced to combine Hib vaccine with other vaccines: DTP, OPV and Hep B.

3.1.16.6. The monovalent vaccines against measles, mumps, rubella and combined vaccines measles - rubella (MR) and measles - mumps - rubella (MMR)

The monovalent vaccines against measles, mumps and rubella, and combinations of these vaccines - the combined vaccine against measles and rubella (MR) or measles, mumps and rubella (MMR) is live attenuated vaccine delivered in lyophilized powder or pills.

Storage mode

Measles, mumps, rubella, MMR and solvent RR and should be stored at + 2 ° C to + 8 ° C. At higher temperatures they quickly lose their immunogenic capacity. Reconstituted vaccines are sensitive to high temperatures and direct sunlight. The reconstituted vaccine should be administered within up to 6 hours of dissolution of solvent.

Freezing is not harmful for lyophilized vaccine, but it damages the vials with solvent or reconstituted vaccine.

The schedule and route of administration

In Moldova since 2002 monovalent vaccines against measles and mumps were replaced by the combined vaccine against measles, mumps and rubella (MMR) vaccine, which is given to children at the ages of:

- 12 months - primary vaccination (MMR - 1);
- 6-7 years - first revaccination (ROR - 2);
- 15 - 16 years - the second revaccination (ROR - 3).

MMR vaccine is administered subcutaneously in the upper arm at a dose of 0.5 ml, both as vaccination and revaccination.

3.1.16.7. Pneumococcal vaccine (VPC)

Pneumococcal vaccine is intended ahainst infection caused by Streptococcus pneumoniae (S. pneumoniae, or the pneumococcal). Worldwide illnesses caused by S. pneumoniae is a serious public health problem. Among S. pneumoniae infections major public health problems present pneumonia, meningitis, septicemia, endocarditis, otitis, sinusitis, bronchitis, abdominal infection etc. A higher percentage incidence of pneumococcal infection is the children of 2 years

and older persons. According to WHO data for 2005, 1.6 million people die annually because of pneumococcal infection, among them 0.7 to 1.0 million. children. However, the continued growth of pneumococci resistance to antibiotics conditions urgent need for using vaccines to fight pneumococcal infection. Pneumococcal vaccines are of antigenic type containing pneumococcal capsular polysaccharides.

Currently in preventing pneumococcal infection are used two types of pneumococcal vaccine: PCV-7 vaccine and vaccine VPP-23.

7-valent pneumococcal polysaccharide vaccine (PCV-7) includes serotypes comprising 65-80% of all S. pneumoniae serotypes causing pneumococcal infection in young children. Because capsular polysaccharides induce a weak immune response, to improve its vaccine antigens were conjugated to a protein (diphtheria) - conjugate polysaccharide vaccine. Depending on the area and the spread of S. pneumoniae serotypes of pneumococcal polysaccharide vaccines can be produced 7-valent conjugate, 10-valent and 13-valent. Conjugate pneumococcal vaccines are covered easily and possess pronounced immunogenicity for all age groups, but are now used only to vaccinate children up to 5 years, including children aged up to 12 months.

VPP-23 pneumococcal polysaccharide vaccine contains purified capsular polysaccharides, from 23 serotypes of S. pneumoniae, which covers over 90% of the types commonly involved in invasive forms of pneumococcal infection. It is intended to vaccinate adults, but can be used in vaccination of children aged less than 2 years. 23-valent vaccine is indicated for those who are at high risk for development of invasive pneumococcal infection or its complications: immunodeficiency persons older than 65 years, especially those living in nursing homes; persons aged 2 to 65 years with splenectomy or its function disorders, chronic cardiovascular diseases, diabetes, liver cirrhosis, immunocompromised patients, including symptomatic and asimptomatic HIV and with leukemia, malignancy, chronic renal failure, immunosuppressive therapy etc. Pneumococcal vaccines are presented as a single-dose prefilled syringe with 0.5 ml vaccine Solita. Appearance is clear, transparent, colorless. Must be kept in refrigerator at + 2 ° C to + 8 ° C, are not resistant to freezing.

Vaccination schedule

Primary course of vaccination with PCV-7 consists of three applications, intramuscular, starting at 2 months of age, with intervals of 1-2 months. The vaccine can be administered simultaneously with other vaccines (according to the schedule of vaccinations) into the syringe in different anatomical areas. Adults should be given a single dose of 0.5 ml, preferably intramuscularly in the

deltoid, is possible subcutaneous administration in individuals with disorders of hemostasis.

3.1.16.8. Rotavirus vaccines

Rotavirus vaccines are intended for prevention of rotavirus infection, considered as the main cause of severe diarrhea in children, especially those up to 1 year.

There are two types of rotavirus vaccines:

• human monovalent Rotavirus vaccine (RotarixTm);

• pentavalent rotavirus vaccine recombinant (RotaTeq).

Monovalent human rotavirus vaccine - Rotarix is a live oral vaccine obtained on the basis of human rotavirus strains attenuated by growing in series of tissue culture with subsequent recultivation of obtained vaccine strain (RIX4414) in vero cell culture. Randomized controlled trials, widely performed, demonstrated high efficacy and safety of this vaccine (80% in preventing rotavirus infections and 100% in preventing serious rotavirus infections). Currently Rotarix vaccine has found application in many countries.

The vaccine is lyophilized and kept in the original container at +2 - +8 ° C in the dark place. Rotarix is not allowed for freezing.

At the administration of Rotarix, the vaccine is dissolved in the solution of disposable applicator and is administrated to child momentary, perorally in 2 doses. The first dose is given to children aged 6 to 12 weeks (at the latest at 12 weeks after birth), and the second dose - with an interval of 4 weeks. Vaccination should finish at 16 weeks of age and not later than at age of 24 weeks.

Recombinant pentavalent rotavirus vaccine (Rotateq)

Rotateq contains five rotavirus types (genetically modified) obtained on the basis of four human strains (G1, G2, G3 and G4) and a bovine rotavirus strain (P1A).

Efficacy and safety of RotaTeq have been shown in randomized controlled trials and it is currently permitted for use in many countries. Vaccine efficacy is 74% in preventing rotavirus infection and 98% in preventing rotavirus gastroenteritis serious infections.

Rotateq is supplied in plastic dispensers, which allow the vaccine to infants' peroral application. Each dose (2 ml) contains 1.2 x 1012 infectious units. The vaccine is in liquid form. Must be kept in refrigerator at 2 ° C to 8 ° C for 24 months. Contains no preservatives or thimerosal. After removing from the refrigerator vaccine should be administered as soon as possible.

Method and vaccination

Rotateq vaccine is administered perorally in 3 doses to children at the age of 2, 4 and 6 months.

3.2. Use of immune serum and immunoglobulin in the treatment and prevention of infectious diseases

Immune serum and immunoglobulins are used in medical practice of artificial passive immunoprophylaxis and treatment of infectious diseases (Table 37).

Table 37

Immune serum and immunoglobulin used in the prophylaxis and treatment of infectious diseases

Diseases	Homologous			Serums and immunoglobulins specific heterologous
	normal immunoglobulin	specific immunoglobulin	immune plasma	
Antrax				+
Botulism		+		+
Dyphtehria				+
Gangrene	+			+
Hepatitis A	+	+		
Hepatitis B		+		
Flu				+
Leptospirosis				+
Meningococcal Infection	+			
Poliomyelitis	+			
Rotavirus infection	+			
Ebola		+		
Mumps	+	+		
Measles	+	+		
Rubella	+	+		
Rabies		+		+
Tetanus		+		+
Whooping Cough		+		
Infection with proteus			+	
Infection with B. pyogenic			+	
Staphylococcal infection		+	+	
Tick encephalitis		+		+
Herpes infection		+		

3.2.1. Immune serums

Immune sera derived from the serum of man or animals contains antibodies to pathogens or their products of metabolism. Antibodies are produced either naturally after immunization (after illness) or after inoculation of specific antigens in human or animal body (e.g. horses). Due to this fact, as the source, immune sera can be: human (homologous) and animals' (heterologous).

Serum can be used in its native state or as purified and concentrated serum by various physical and chemical methods. The latter presents advantages over native

sera both in terms of reducing accidents due to serum purification and by having a high concentration of antibodies administered per unit of product.

The disadvantage is that the heterologous serum present the foreign protein for humans and they act as allergens, leading to sensitivity phenomena. These reactions occur rarely following serum's purification and concentration until the sera become native because of their lower content of antigenic proteins. The frequency and intensity of serum reactions are based on both the amount of serum administered and the reactivity of the organism and the existence of previous sensitivity (the risk is higher in the second administration of serum) and can be immediate or delayed.

3.2.2. Immunoglobulins

Immunoglobulin preparations can be of two types:

• normal or toal human immunoglobulin, obtained from the mixture of plasma taken from healthy individuals - adult donors;

• specific human immunoglobulin, obtained, as a rule, from convalescent or immunized individuals.

The preparations of purified immunoglobulin are biological products (relieved of other proteins), delivered in a concentration of 16% antibodies (15-18%), which means the concentrations of 16 times compared to gammaglobuline levels in blood.

3.2.2.1. Human immunoglobulin

Immunoglobulins have in their composition antibodies of about 15-18% (IgG) against various pathogens, reflecting the spectrum of infections and immunizations experienced by those donors.

It is delivered in vials of 2 ml and administered only intramuscularly. Normal immunoglobulins are indicated for immunocompromised persons as a prophylactic measure, especially in hepatitis A and measles, providing the administration as soon as possible after the contact with infected patient in outbreak, as an emergency prophylactic measure.

The preparation is administered in measles prophylaxis with amount of 0.2 - 0.4 ml/kg in the first days after the contact with measles infected patient to receptive people under the vaccination age or having contraindications to measles vaccination. Protection is immediate and lasts 3-4 weeks. Administration after 4 days of contact or lower dose is insufficient or leads to the development of atypical measles (mild) with an incubation period of up to 28-30 days.

The hepatitis A prophylaxis is administered in doses of 0.02 to 0.05 ml / kg in the first week of contact. Protection lasts 3-5 months.

Normal immunoglobulin for intravenous administration

These products are also obtained from human plasma, containing only monometric IgG, free of anticomplementary activity with high titer of antibodies. They are used in the treatment of immune deficiency diseases and in the treatment of autoimmune diseases component (e.g. Chronic idiopathic thrombocytopenic purpura) or severe diseases (sepsis, meningitis, severe pneumonia). It is used in concentrations of 200-400 ml/kg at slow infusion.

Contraindications:

• intolerance to blood or blood derivatives due to human immunoglobulins awareness or presence of anti-IgA;
• intramuscular inoculation of immunoglobulins is not performed in patients with coagulopathy;
• allergic response to one of the components of the product;
• if the product is cloudy.

3.2.2.2. Specific human immunoglobulins

Specific human immunoglobulins are biological preparations containing antibodies specific to an antigenic determinant derived from persons previously immunized or infected in the past. Products are purified and does not involve anaphylactic reactions.

benefits:

• can be recommended for both prophylactic and curative purposes;
• do not give sensitization or intolerance;
• doses may be repeated without any risk of anaphylactic shock;
• remain in circulation for a long time, with the half-life of 21-35 days
• do not require any inquiry on inoculations with heterologous therapeutic sera.

Currently are produced and delivered several specific antibodies: against rabies, tetanus, rubella, mumps, cytomegalovirus, herpess, varicella zoster virus, hepatitis B, HIV etc.

GENERAL EPIDEMIOLOGY OF NON-COMMUNICABLE DISEASES

INTRODUCTION

Humanity was threatened by diseases for centuries, some of which are very serious. Many of them showed a clear decline due to measures to improve the living and working conditions of the population, cultural and educational level rise, the discovery of antibiotics, especially the application at the population level the vaccines.

Although, these diseases differ from those that can be controlled by immunization, such as the wide range of acute intestinal infection, most respiratory virus diseases, streptococcal infections, hepatitis, HIV/AIDS, various tropical parasites etc., they constitute major causes of morbidity and mortality in the developing countries, currently dominant human pathology is represented in many aspects by the evolution of non-communicable diseases.

As the causes of many diseases - particularly infectious - lost their importance, now, the spotlight falls on diseases with multifactorial aetiology, so-called "diseases of modern civilization": cardiovascular diseases, chronic diseases of devices and systems, cancer, nutritional disorders, neuro-psychiatric diseases, dental diseases, congenital malformations, genetic diseases, accidents etc. The origine of these diseases and disabilities is the result of the gap between the development of modern society and relatively moderate capacity to adaptation of man undergoing complex of variables that chalange him. In developed countries, the population is exposed to pathogenic effects, sometimes unknown: food additives, pollutants of air and aquatic environment, professional pollutants, radiation, stress, etc. This range of non-infectious harmful factors - known as "risk factors" - often act occultly, asymptomatic or limited by clinical evidence.

Alcohol, tobacco, drugs and various types of traffic accidents, cancer, cardiovascular diseases, nutrition and mental illnesses today cause more victims than most tragic epidemics of past centuries.

Most non-communicable diseases, are the result of people’s living conditions and circumstances wich are influenced by lifestyle. Characteristic insidious onset of non-communicable diseases compared to the severety of acute illnesses, slow evolution of morbid processes makes both the individual and the doctor not often concerned sufficiently about primary health care, the care of such "fallse health", is deteceted in many cases, at the early stages, only by changes in biochemical constants.

In many non-communicable diseases, prevention measures effectiveness depends on the realization of epidemiological studies and population-level

cooperation in the detection of early morbid phenomena, the formation through education in the individual, family, community participatory attitudes to neutralize the action of risk factors and to promote proper behaviour.

Prof. dr. Aurel Ivan

1. The epidemiological process in non-communicable diseases

1.1. Background. Definition. Structure. Levels

Problems concerning the emergence, expansion and various manifestations of disease at the population level concern the protection and promotion of health. Mechanisms and complex factors involved in disease emergence and expanding were found mainly in the twentieth century and continue to be studied.

Epochal scientific progress in various medical and non-medical fields, allowed understanding the causality of relationships and circumstances that may create certain "critical moments", facilitating the association of various causative agents acting on the human body in a relationship of great complexity and diversity of structural and functional intimacy of the human ecosystem.

This enabled us to give the definition of epidemiological process as the following: it is a variety of factors; biological, natural and social mechanisms and phenomena that compete in determinant, dynamic and favouring way with each other at the appearance, expansion and development of morbid state at the population level.

The complexity of the epidemiological process of non-communicable diseases is evidenced by many elements that compose it, their particularities and their interdependence.

Human body is exposed to the aggression of the physico-chemical elements from the human ecosystem by a number of factors such as: the sources generating the aggressive agents, transmission paths belonging to environmental and social factors and they may interfere through direct or indirect mechanisms; receptive population as a result of a reduced non-specific resistance and general immunity and limited adaptive capacity (Fig. 53).

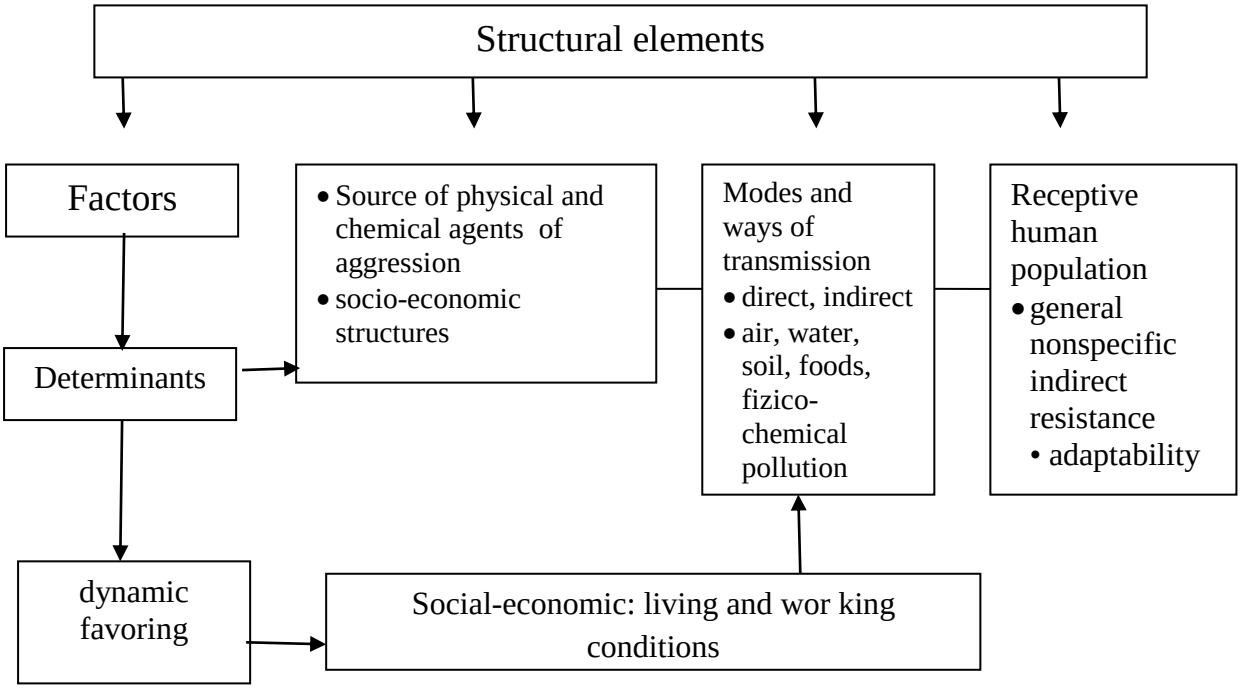


Fig. 53. The general structure of the epidemiological process in non-communicable diseases

Knowledge of the epidemiological process and application elements of theory and structuralism levels, show that its formation mechanisms in both diseases are similar. This explains, why originally developed as a method of study and intervention in diseases, epidemiology expanded its sphere of concern addressing issues of non-communicable diseases. Therefore, epidemiology is currently studying science of health and disease as a phenomenon in population, together with the factors that determine and favour two categories of diseases, in order to take effective measures for prevention and control.

The link between knowledge of the structure and levels of epidemiological modelling as it is seen as a logical development of investigations for assessing and forecasting the evolution of disease and to "optimize" activity in the prevention and combating health programs.

At the same time, we analyse the structure and levels of the common key elements of differentiation and epidemiology of communicable disease process compared to that of non-communicable diseases. We consider: agents of aggression, the nature of causal relations, aggregation, synergism, origins, sources and routes of transmission modes, responsiveness, adaptability, driving-predisposing factors, the possibilities for screening, prevention, control and evaluation of cost / health benefit activities (Table 38).

Although, logically, the epidemiology of non-communicable diseases (NCDs) can only have a general structure similar to that of communicable diseases (CD),

analysis of the factors and mechanisms involved in their formation reveals a number of features that should be considered for the development of programs for prevention and control.

Table 38

Some common elements and differences in the epidemiological process compared to non-communicable diseases

Epidemiological process		
Parametrs	Communicable Diseases	Non- Communicable Diseases
1	2	3
• agents	• microbes, parasites, fungi	• physical, chemical
• causes	• single cause (mono etiology)	• multiple causes (etiology multicausal)
• accumulation	• Establishing minimum infective dose (in short, braking mechanisms involved)	• setting aggressive doses (for a long time, adaptive mechanisms are involved)
• sinergism	• unimportant	• often present
• origin	• living and working environment (changes in human ecosystem brakesformation)	• living and working environment (human ecosystem change accelerates setting)
• sourse	• posed by human or animal bodies (eliminates biological agents)	• represented by: industrial technologies, chemical processing, mechanization, urbanization, intensive exploitation of the soil and subsoil, transforming the natural environment, the accumulation of debris, stressful lifestyle, dietary habits, food additives, increased consumption of drugs, alcohol, tobacco, etc. . (eliminates physical agents and / or chemical)
• mode of transmission	• direct, indirect	• direct, but mostly indirect • air, water, soil, food (contaminated with physical agents and / or chemical)
• ways of transmission	• air, water, soil, food, objects, hands, animated vectors (contaminated)	
• receptivity – unreceptivity	• depends on general non-specific resistance and specific resistance (immunity)	• general nonspecific resistance and adaptability
• dinamization	• socio-economic factors and natural	• socio-economic factors and natural
• detection	• facilitated by characteristic symptoms and laboratory resources available; some situations are useful measures of population screening	• partially, late, uncharacteristic symptoms, long periods, laboratory methods for early stages are inaccessible
• prevention	• General and specific means are available, accessible; measures involving social, economic and public involvement	• efficient means (the "rationalization of life"); inaccessible; involves costly socio-economic measures, with the involvement of many factors; reduced population accessibility
• combat	• special means are available, applied especially by healthcare professionals	• various means, applied towards non-medical staff at the suggestion of the medical one
• evaluation of results	• methodologies are accessible for healthcare body; with results obtained on time, at low cost and with good cooperation with population	• methodologies are difficult to handle by health care professionals; with a high cost, which requires cooperation varied; the population is poor

The nature of interrelationships between non-healthy and healthy or eco-socio-epidemiological froms of human ecosystem structures requires knowledge of the understanding the structural features of epidemiological processes in cardiovascular, lung, nutrition, neuropsychological, mutagenic, teratogenic etc. diseases.

The configuration process of NCDs turned with the evolution of human society. These diseases are a reflection of adverse effects, unwanted, but determined by man in his struggle to transform nature and society. Therefore, they are called "diseases of civilization", "social progress diseases", "diseases of ecological imbalance".

In reality, NCDs have a double determinism: the social and natural condition of human interventions have a dual origin, an eco-socio-genesis, which requires them to carry out the study in the human ecosystem structures with eco-social contribution.

Epidemiology of NCDs appears as an expression of aggregation "adverse reactions" long-term changes due to complex, varied alerts to be recorded in human ecosystem due to human tendency to change their way of life.

Contemporary human ecosystem is increasingly subject to "pressure" exerted by the scientific-technical revolution, which has already written our future by mechanization, automation and robotics based on the development of electronics, microelectronics, precision mechanics, biotechnology, fine chemical synthesis, cybernetics, informatics, unconventional energy, machine building, etc.

The peculiarities of general epidemiological process in NCDs include:

- Multicausal etiology of high complexity due to the difficulties to detect causal interrelations;

- Long incubation, atypical onset, insidious evolution and spread, apparently well-tolerated and difficult to detect early in local population;

- Sources of aggression by physical or chemical agents are extremely varied, and spread in every way of human life and work (in ecosystem structure) and presents a wide range of mechanisms and pathways of elimination; often the same agent may be disseminated by different sources;

- Agents of aggression are extremely varied, can use simultaneously one or more gateways to the body, which may act by accumulation and synergism;

- Transmission of physical and chemical aggression agents from the sources to susceptible organisms, ais realised rarely on case of accidents by direct and indirect mechanisms (modes), and more frequently, using usaul way of dissiminating air, water, soil and food (physico-chemically contaminated); these paths may interfere singularly, but frequently occurring combinations, "chain" dissimination and involvment of various structures of the human ecosystem;

- physico-chemical pollution pathways of transmission are achieved mostly with small aggressive doses, which, however, through repetition and accumulation can lead to dangerous doses "aggressive doses"; in some circumstances, they may be considered "aggressive mixtures" by accidental association of two or more agents of aggression, which you reinforce each action;

- agents of aggression in the composition of environmental factors are difficult to detect, especially when the amount is to be reduced; flora and fauna through changes incurred may constitute "signal elements";

- knowledge in dynamic of environmental dissimination of physical and chemical aggretion agents and of exposed population encount great difficulties, because active dosees at the cellular and tissue levels are hard to estabilish, especially when cumulating processes of both chemical and physical agents and injures produced for long term interfere with each other. The ways of entrance, time interval for the absorbtions and necessary critical dose in a certain place and moment cannot be prmptly identified;

- in case of penetration by physical and chemical of aggression agents, the human body reacts differently, depending on the nature of aggression, general nonspecific resistance and adaptive capacity; long-term tolerance may mean adapting when functional and structural disturbances does not exceed a "threshold" or, conversely, signs of adaptive failure appear and therefore, the occurrence of the disease.

1.2. Determinant factors

To become an epidemiological process of NTDs it is necessary ("critical moment") for 3 determinant factors and tow categories of dynamic and favorable factors to enteract with each other (Table 39).

Table 39

Structural factors of the epidemiological process of non-communicable diseases

Constitutive factors	
Determinant	Dynamic-favoring factors
I. Sources of physical and/or chemical agents 1. Industrial Technologies 2. Mechanization systems 3. Use of chemicals 4. Crowding 5. Operation and transformation of nature 6. Power systems 7. Toxic residues 8. Demographic structure 9. Brewing population 10. Information systems 11. Drug abuse 12. Lifestyle	I. Nature: Cosmic meteorological, climatic, geographic II. Economic and social: 1. Living conditions 2. Occupational conditions
II. The ways and means of transmission of physical and chemical agents 1. Direct and indirect mode 2. Routes of transmission: air, water, soil, food (physico-chemically polluted)	
III. Responsiveness and adaptive failures	

1.2.1. Sources generating agents aggression. Sources are mixed interdependently, each is stimulated and are interdependent. Industrialization stimulates urbanization, chemical processing, mechanization, intensive agriculture, transport, etc. However, by their intrinsic developments of all these process, stimulate industrialization and the cycle continues in what we call the first, second, third etc. industrial and scientific and technical revolution.

1.2.1.1. Industrial technologies. Industrialization, extremely complex, with a variety of technologies and extraordinary mobility that characterizes it, can be considered to be started in 1680 when Denic Papin discovered elastic force of water vapor and James Watt, in 1784, invented machine steam. From now scientific-technical revolution is undergoing various stages with unpredictable speed, changing "face the world" and increasing the problem of industrialization transformation into the active source, generating agents of aggression for contemporary human health and future generations.

1.2.1.2. Mechanization systems. Relations between industrialization and mechanization stimulated diversification of two categories of non-healthy sources of agents.

In addition to industrial technologies, mechanization covered various areas of human life: agriculture, roads, homes, etc.

Trend "toward mechanization of life" modern man has given rise to new types of health aggression agents involved in increasing the frequency of diseases, injuries, infirmities, deaths. These aggressors against human health include: noise, vibrations, dust, gas, mechanical traumas, thermal, electrical, ultrasonic radiation etc.

1.2.1.3. Use of chemicals. Among the sources generating health aggression agents, are particularly those that are varied and disseminate dangerous chemicals. They directly or indirectly especially by air, water, soil and food can reach the human body.

Over 4 million chemical compounds: organic, mineral or synthetic come from natural sources or industrial uses are widely used, creating numerous risks to human health.

1.2.1.4. Urban crowding. The first settlements with elements of urbanization appeared 7-8000 years ago. In the VII millennium BC in the Middle East there were many urban settlements. The population in Ancient Athens was 100 000 and in Rome in the 1st century A.D. had already reached 1 million. In general, old world city dwellers had a small proportion of the total population.

Urbanization reached an important development in the Middle Ages and the Renaissance, so as in the eighteenth century and nineteenth century scientific-technical revolution to step it up, and in the twentieth century in industrialized countries, the urban population to overcome the rural one, phenomenon is constantly expanding.

1.2.1.5. Operation and transforming of nature. Modern civilization has emerged and developed using for the benefit of man, various natural resources. The rapid growth of the population of the Earth and its social and economic emancipation intensified exploitation of natural riches to abusive "conquer" of it, accompanied by the danger of depletion of resources and producing serious imbalances, with profound harmful effects on present and future human.

Beside the intensive exploitation of such riches as oil, gas, minerals (from 1940 to 1970 mankind has used more ore than for the rest of its history; ore consumption will increase by 2020 almost 50 times comparated to 1900), construction materials, forests etc., intensive agriculture (amelioration, irrigation, etc.) contribute to the overexploitation of natural component of the ecosystem and thereby disrupting its healthy interrelations.

1.2.1.6. Energy systems. After the XIII century fossil coal was first used in England to obtain exosomatic energy, after thousands of years of using wood oil followed.

China used oil for lighting 5-6 thousand years ago. Greece and Mesopotamia followed, they used oil for burning, shipbuilding, mortar for masonry etc.

Bucharest was the first city in the world to use gas lighting. In 1857, Romania, which produced 260 tons of oil a year, built the world's first industrial refinery near Ploiesti.

1.2.1.7. Toxic residues. Modern human activities conducted towards the exploitation of their own achievements in industrialization, mechanization, chemical industries etc., have become generatot of aggression agents for health, by accumulation of toxic wastes.

Since the early twentieth century, with the development of intensive industry and its massive production of toxic residues, they were formed into a true "independent source" of physical and chemical aggression agents and thereby harmful for environmental health and man.

Only industrialized countries produce more than 450 million tons of toxic waste, of which 15 million tons are "hazardous waste". These residues have caused a true "trade", which endangers the health of people in different geographic areas of the world, especially in developing countries, subject to such a "toxic aggression" from industrialized countries. Along with various types of toxic waste plus the radioactive one presents even greater danger.

1.2.1.8. Demographic structures. Complex and reciprocal relationship between the evolution of demographic phenomena and processes of socio-economic development of nations is a reality of the contemporary era.

Since the emergence of Homo sapiens and until today, Earth was populated by 80 billion people, half of whom were born in the last 600 years and a quarter after the year 1650. Of these, currently living are over 7 billion, with approximately 80% living in developing countries.

Population forged over millennia history and civilization of our planet. Currently, the population problem is viewed in terms of "population explosion" feature of developing countries, the "zero population growth" and "aging population" universal tendencies, but with a special importance in highly developed countries.

Population explosion. Population - the main component of the human ecosystem is growing and after the previous millennia maintains a certain balance between births and deaths.

1.2.1.9. Information systems. "Information explosion" is the expression of a complex process and accelerated impressive universalization of human relations that has made a crucial source of information in the economy, a dynamic power of modern society, an element of progress, defining strategies development of contemporary human society.

"Explosion", "crisis", "inflation", "pollution" are expressions by means of which information tries to highlight the contradiction which appeared between the

ever-increasing volume of circulating knowledge and inability to access the potential beneficiary scientific and technical information to all its circumscribed sphere of interest.

Different from one population group to another, "information explosion" may be a strain in the element of the health risk factor.

1.2.1.10. Drug abuse. With varied motivations, the man of modern times is exposed to very aggressive health agents from sources which we call current: drug abuse, tobacco, alcohol, hallucinogens or stimulants of the central nervous system. Excess consumption of drugs is related to the euphoria of a modern man to them, because prevention performance and especially their amazing therapeutic and diversification (every day appear 3 to 6 new drugs on the world market), which promotes "self-medication" and "excessive prescribing" . Thus, it was "drug disease" (10 - 30% of iatrogenic diseases), including allergies, poisoning, intolerance, habituation, addiction, drug combinations related disorders, chronic diseases by use etc.

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