UNIVERSITY OF PÉCS
Faculty of Health Sciences

# EPIDEMIOLOGY

**Edited:**
Prof. Dr. Imre Boncz, Dr. Réka Vajda, Dr. Zsuzsanna Kívés

**Reviewed by:**
Prof. Dr. János Sándor

Translated by: Györgyi Daru

**Publisher:**
University of Pécs Faculty of Health Sciences

Technical support by: Gábor Varga

This book has been produced in the framework of a project registered as „EFOP-3.4.3-16-2016-00005 Modern university in the modern city: Value-centeredness, openness and inclusive approach in a 21st century model of higher education".

**Authors:**
Prof. Dr. József Bódis
Prof. Dr. Imre Boncz
Prof. Dr. Mária Figler
Dr. Andrea Gubicskóné Kisbenedek
Dr. Krisztina Juhász
Oszkár Juhász
Prof. Dr. István Kiss
Dr. Zsuzsanna Orsós
Dr. Zsuzsanna Kívés
Dr. Katalin Krisztalovics
Dr. Réka Vajda
Dr. Anna Páldy
Dr. Viktória Prémusz
Dr. Mária Szücs Dr. Vidáné

SZÉCHENYI 2020
HUNGARIAN GOVERNMENT
European Union
European Social Fund
INVESTING IN YOUR FUTURE

This book has been produced in the framework of a project registered as
„EFOP-3.4.3-16-2016-00005 Modern university in the modern city: Value-centeredness, openness and inclusive approach in a 21st century model of higher education”.

ISBN: 978-963-626-075-0
University of Pécs Faculty of Health Sciences

Pécs, 2022.

# Authors

**Prof. Dr. Imre Boncz**
medical doctor and health services manager, Department of Public Health Medicine, Faculty of Health Sciences, Institute for Health Insurance, professor, director of institute, vice dean, University of Pécs Clinical Centre vice chairman for strategic affairs

**Prof. Dr. József Bódis**
professor of obstetrics and gynaecology, University of Pécs Clinical Centre Department of Obstetrics and Gynaecology, MTA doctor, leader of the National Laboratory of Human Reproduction, ELKH-PTE Head of Human Reproduction Research Group, University of Pécs, Faculty of Health Sciences, Institute for Health Insurance, Universitas Quinqueecclesiensis Foundation Chairman of the board of trustees

**Prof. Dr. Mária Figler**
specialist in internal medicine, University of Pécs, Faculty of Health Sciences professor emerita, Dean's representative of scientific and quality assurance

**Dr. Andrea Gubicskóné Kisbenedek**
food quality assurance engineer, University of Pécs, Faculty of Health Sciences Institution of Nutritional Science and Dietetics, Department of Dietetics, senior lecturer, deputy director of institute, head of department

**Dr. Krisztina Juhász**
specialist in preventive medicine and public health, Government Office of Baranya County District Office of Pécs Department of Public Health, district medical officer

**Oszkár Juhász**
biologist, University of Pécs, Faculty of Health Sciences Institute of Nursing Sciences, Basic Health Sciences and Health Visiting, Department of Basics of Health Sciences subject teacher

**Prof. Dr. István Kiss**
specialist in preventive medicine, MTA doctor, University of Pécs, Medical School, Department of Public Health Medicine, professor, director of institute

**Dr. Zsuzsanna Kívés**
registered nurse, University of Pécs, Faculty of Health Sciences, Institute for Health Insurance senior lecturer

**Dr. Katalin Krisztalovics**
specialist in public health and epidemiology, colleague of the Epidemiological Department of the National Centre for Epidemiology between 1998–2017

**Dr. Zsuzsanna Orsós**
biologist, University of Pécs, Medical School, Department of Public Health Medicine senior lecturer

**Dr. Anna Páldy**
specialist in public health and epidemiology, master of epidemiology, candidate, consultant of National Center for Public Health (the retired deputy director of the predecessor institution, National Institute of Environmental Health)

**Dr. Viktória Prémusz**
sociologist, a University of Pécs, Faculty of Health Sciences, senior lecturer, research fellow of the National Laboratory of Human Reproduction, Secretary of The Doctoral School of Health Sciences, science organization and performance evaluation coordinator

**Dr. Réka Vajda**
Expert in Public Health, epidemiologist, University of Pécs, Faculty of Health Sciences, Institute for Health Insurance senior lecturer

**Dr. Mária Vidáné Szücs**
specialist in public health and epidemiology and preventive medicine, epidemiologist, Tolna County Balassa János Hospital, medical director

# Table of Contents

# I. Introduction

Réka Vajda, Zsuzsanna Kívés, Imre Boncz

## Definition of epidemiology

What is epidemiology? A 1964 definition (Concise Oxford Dictionary) defined it precisely, though not very usefully, as the "science of epidemics". Then, in 1970, MacMahon and Pugh were a bit more precise, formulating it as a "study of the distribution and determinants of diseases". Their definition briefly identified two central elements of traditional epidemiology: among whom (where and when) and why do diseases develop? The final wording, from the Dictionary of Epidemiology (Last JM. 2001), extends its validity not only to diseases but also to general health by two steps, and highlights its role in disease surveillance. Thus:

***"Epidemiology is the study of the distribution of health-related conditions or events and the factors influencing their occurrence in a particular population and the application of its results in the treatment of health problems".***

The key concepts in this definition reflect some important principles of epidemiology.

***Study*** - Epidemiology is a scientific discipline. It uses data-centric, systematic, and unbiased scientific methods to collect, analyze, and interpret data. Epidemiological methods are usually based on careful observation and the use of valid control groups to assess what is being experienced, such as the number of illnesses in a given area over a given period or the frequency of exposure among those suffering from the disease. It also relies on methods from other disciplines, including biostatistics, computer science, biology, economics, and social and behavioral sciences. In fact, it is often described as a basic science in public health, and for a good reason. It examines health-related phenomena, including risk factors for disease development, morbidity and mortality data, and includes evaluations of public health measures and the effectiveness of health care.

***Distribution*** - Epidemiology deals with the frequency and pattern of health-related events in a population:

Frequency refers not only to the number of disease-related events (such as the number of cases of meningitis or diabetes in a population), but also to the proportion of that number to the size of the population. The resulting ratio allows epidemiologists to compare the incidence of diseases in different groups.

The pattern refers to the occurrence of health-related events according to time, place, and person-specific characteristics. Patterns of time can be annual, seasonal, weekly, daily, hourly, weekdays or weekend, or any other time breakdown that may affect the incidence of diseases or events. Location patterns include geographical differences, urban / rural differences, and the location of jobs or schools. Person-specific characteristics include demographic factors that may be associated with the risk of illness, injury, or disability, such as age, gender, marital status, and socioeconomic status, as well as behavior and exposure to environmental risks. Descriptive epidemiology characterizes events by time, place, and person.

***Influencing Factors*** - Any factor, event, characteristic, or other identifiable entity that alters a health condition or other specified characteristic. Epidemiology is also used to search for determinants. Epidemiologists assume that the disease does not occur randomly in a population, but only if there is an appropriate accumulation of risk factors or determinants. To identify these determinants, we use analytical epidemiological studies to answer the questions "why?" and "how?". We examine whether groups with different disease numbers differ in their demographic, genetic, or immunological characteristics, behaviors, envi-

ronmental exposure, or other so-called potential risk factors. Ideally, the results provide sufficient evidence to take immediate and effective public health action.

***Health-Related Conditions or Events*** - Epidemiology originally focused on infectious disease epidemics, later shifting the focus to endemic infectious and non-communicable diseases. By the middle of the 20th century, advanced research methods had been developed and applied in the fields of chronic diseases, injuries, birth defects, and youth, occupational, and environmental health sciences. They then began to examine behaviors related to health and well-being. Nowadays, molecular testing methods can take important steps in the study of genetic markers of disease risk. In fact, the term health-related conditions or events can be considered anything that affects the well-being of the population. Nevertheless, unfortunately, the term "illness" continued to be used to refer to health-related conditions and events.

***Specific populations*** - Epidemiologists and clinicians have different interpretations of the "patient". The clinician focuses on the health of the individual, while the epidemiologist focuses on the health of the community, and the population. The "patient" of the clinician is the individual; the "patient" of the epidemiologist is the community. For example, when a patient presents with diarrhea, the clinician focuses on treating and caring for the individual, while the epidemiologist focuses on identifying the exposure or source that is causing the disease and prevents the opportunity for further spread in the community.

***Application*** - Epidemiology is not only the study of the health status of the population, it also includes the synthesis of the knowledge gained during the studies, and its transfer to community-based practice. The clinician uses his or her scientific knowledge, experience, and patient preferences to make a diagnosis and treatment. The epidemiologist also draws on the scientific methods and experience of descriptive and analytical epidemiology, while using an understanding of the epidemiological situation and local conditions to assess community health.

The shift to evidence-based medicine and evidence-based decision-making in the clinical setting and in health care in general is a direct benefit of the field of clinical epidemiology, with a focus on applied decision-making to improve patient outcomes. Therefore, the principles and methods of epidemiology are applied to the evaluation or application of clinical research regarding prevention, diagnosis, prognosis improvement, and treatment of patients.

## History of the development of epidemiology

Although epidemiology as a discipline has flourished since World War II, epidemiological thinking began in the wake of Hippocrates (460-370 BC). Hippocrates, the father of medicine, among other things, studied the external and internal causes of illness. He observed the geographical specificity of some diseases, such as the higher incidence of malaria or yellow fever in wetlands. He recognized that lifestyle and the physical environment play key roles in the development of diseases and the maintenance of health.

The average life expectancy at birth in medieval society was 30 to 35 years, due to epidemics of plague, influenza, tuberculosis, and typhus. ***John Graunt***'s ***(1620-1674)*** work, "The Nature and Political Observations Made Upon the Bills of Mortality" published in 1662, which analyzed London births and deaths, can be seen as a defining milestone in development. He was the first to write about higher birth and death rates for men, high infant mortality, and seasonal fluctuations in mortality rates. He recognized the importance of routine data collection in the study of diseases, thus laying the foundations for modern epidemiology. However, practical application of the new methods was delayed for nearly two centuries. Then in 1839, the English physician, ***William Farr (1807-1883)*** organized a routine registration of the cause and number of deaths at the Central Registry of England and Wales. He compared mortality data of married and single people as well as different occupational groups. The introduction of a number of new concepts and methods can be linked

to his name, such as the precise definition of the population exposed to a risk factor, control group, and other factors influencing the disease (age, duration of exposure, general health).

In the 19th century, in addition to previously known epidemics, diseases that were concentrated in large cities and clearly linked to poor hygiene were becoming more frequent, and a solution for one of them was due to the findings of another physician, ***John Snow (1813-1858)***. He was researching outbreaks of cholera to find out the cause of the disease and prevent it from recurring. He made a map showing the location of the water pumps and then looked for a connection between the households with cases of cholera and the location of the pumps. Based on these, he recognized the territorial inequalities in mortality, which suggested that water was the source of the infection. To confirm his assumptions, he gathered information about where the cholera sufferers got their water from. He noticed that there were more affected households around pump A ("Broad Street") than around pump B or C. Water consumption from pump A was thus the only common factor among cholera patients. After Snow presented his findings to municipal officials, the pump handle was removed and the epidemic ended. During his study, Snow examined the frequency and distribution of cholera and determined the source of the infection.

In his later study, Snow observed that cholera mortality rates were significantly dependent on water providers in London, due to differences in the location of water extraction and the application of water treatment procedures. At the time of the cholera epidemic, two providers, the Lambert Company and the Southwark and Vauxhall Company, provided water to the areas with the highest mortality rates. At that time, both companies were extracting water from the River Thames, form the part where London's sewage had already significantly polluted it. In 1952, the Lambert Company relocated the water extraction site to the part of the River Thames where the river was still free of London sewage. The incidence of cholera then declined significantly in the areas supplied by the Lambert Company, while remained unchanged in the areas supplied by the Southwark and Vauxhall Company. These data were consistent with the hypothesis that water from the sub-London section of the River Thames was the source of cholera. Snow demonstrated in his epidemiological studies that water was the source of infection and that epidemiological information could be used to guide immediate public health measures.

From the mid-19th century onwards, major epidemics abated, with local epidemics and infectious diseases taking over. For this reason, this period was mainly characterized by learning about the triggers.

The activities of ***Ignaz Semmelweis (1818-1865)*** created the modern hospital hygiene conditions. He was the first to show that high-lethality hospital epidemics were spreading through physicians and nurses, and also pointed out that consistent application of antisepsis and asepsis rules could prevent them. With this recognition, we consider him to be the founder of the etiology of post-partum fever. His main work was published in Vienna in German in 1861 (Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers: Aetiology, Concept and Prevention of Post-partum Fever). Semmelweis's recommendation was, "Any medical student or physician who enters a ward for examination should wash their hands thoroughly, namely in a chlorine-lime solution, located in appropriate washbasins near the entrance to the ward. This disinfection appears to be sufficient prior to the visit. Between each examination, the hands are to be washed only with soap and water (1847)".

The interpretation and approach of ***modern epidemiology*** later expanded. Classical epidemiology dealt almost entirely with the epidemic of infectious diseases. However, in the 1930s and 1940s, the methods of the discipline were extended to non-communicable diseases. The period since the Second World War has seen an explosive development in the theoretical foundations of research methods and epidemiology. It has been applied to a full range of health-related conditions, behaviors, and knowledge and attitudes. The principles of study design, data collection and analysis techniques were formulated after World War II to

help clarify and assess the risk factors for chronic diseases. Doll and Hill's study of the link between lung cancer and smoking, a study of cardiovascular disease among residents of Framingham, Massachusetts, are two examples of how pioneer researchers have used epidemiological methods to learn about chronic non-communicable diseases since World War II. As early as the 1980s, epidemiological methods were used to study injuries and violent incidents. In the 1990s, related fields of molecular and genetic epidemiology also emerged. Meanwhile, infectious diseases continue to be a challenge with the emergence, re-emergence or alteration of new infectious agents (Ebola virus, Human Immunodeficiency virus (HIV) / Acquired Immunodeficiency Syndrome (AIDS)), Resistant Mycobacterium tuberculosis, avian influenza, SARS-CoV - Severe acute respiratory syndrome coronavirus).

## References


1. Boncz I. (szerk.) Kutatásmódszertani alapismeretek. Pécsi Tudományegyetem Egészségtudományi Kar, Pécs, 2015.
2. Doll R, Hill AB. Lung cancer and other causes of death in relation to smoking. Br Med J. 1956; 2(5001): 1071-1081.
3. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: a preliminary report Br Med J. 2004; 328(7455): 1529-1533. doi: 10.1136/bmj.328.7455.1529.
4. Dawber TR, Moore FE, Mann GV. Coronary heart disease in the Framingham study. Am J Public Health. 1957; 47, 4-24.
5. Graunt J. The Nature and Political Observations Made Upon the Bills of Mortality. London, 1662.
6. Greenwood M. Epidemics and crowd diseases: an introduction to the study of epidemiology, Oxford University Press, 1935.
7. Hippocrates. Vol 7. Translated by WD Smith. Cambridge, MA: Harvard University Press, 1994.
8. Jones DS, Podolsky SH, Greene JA. The burden of disease and the changing task of medicine. N Engl J Med. 2012; 366: 2333-2338. DOI: 10.1056/NEJMp1113569
9. Last JM. (editor) Dictionary of epidemiology. 4th ed. Oxford University Press, New York, 2001.
10. Snow J. On the prevention of cholera. Medical Times and Gazette, 1853; 367-369.
11. Snow J. Snow on cholera. London: Humphrey Milford: Oxford University Press, 1936.
12. Thacker SB. Historical development. In: Teutsch SM, Churchill RE, editors. Principles and practice of public health surveillance, 2nd ed. New York: Oxford University Press; 2002. p. 1-16.
13. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention Principles of Epidemiology in Public Health Practice Third Edition. Office of Workforce and Career Development, Atlanta, 2011.
14. Webb P, Bain C. Essential Epidemiology An Introduction for Students and Health Professionals. Cambridge University Press, Cambridge, 2010.

# II. Fundamentals of Epidemiology

Réka Vajda, Zsuzsanna Kívés, Imre Boncz

The main field where epidemiology is used is the identification of the causes of diseases, which is essential in all areas of public health science. If we can find out what leads to deteriorating health, we can work on prevention. The most commonly used epidemiological indicators are discussed below, including how they are calculated and the strengths and limitations of their application. The chapter will then review test methods that can be used to measure the incidence of diseases and will also outline possibilities for the comparison of different populations.
The calculation of relative risk and odds ratio is presented for each research type separately.

## Basic types of epidemiological indicators

### Types of calculated indicators

The easiest way to get information about a particular disease is to count the number of people with that disease. However, although it is undoubtedly a very important piece of data, its further use is limited. To move forward, it is also essential to know how many patients (how large a population) we may need to cover over what period of time. See Table 1:

- ***Proportion*** describes the ratio of the value of a variable to an integer. The formula = A / N, where A is the fraction of N, can be expressed in %.
- ***Ratio*** compares the frequency of a variable's value with another variable's value. Formula = A / B, where A is not part of B.
- ***Rate*** A measure of the value of a variable relative to another measured quantity. Shows the rate at which events accumulate.

### Ratios

Ratio is the quotient of two related data. The general formula is V = A / B, where A = reference quantity, B = reference base, V =ratio.
It is generally classified into three major groups, each of which is essential in the area for which it has been developed.

**Distribution ratio**

- shows the size of a part of a population relative to the whole population.
- general shape: part / whole × 100
- dimensionless quantity, usually used as a percentage to measure internal ratios. Its value varies to a certain extent, from 0.0% to 100.0% in percentage form and from 0.0 to 1.0 in coefficient form.
- Intensity ratio
- a quotient of two different but related data.
- it measures the frequency (intensity) of a given phenomenon in the observed medi-

Table 1: Formulas for calculating proportion, ratio and rate:

| | numerator | denominator |
|---|---|---|
| proportion | persons with a particular disease | all people (with or without a disease) |
| ratio | persons with a particular disease | people free of a specific disease |
| rate | persons with a given disease at a given time | all people (with or without a disease) at a given time |

um. The observed medium is usually the population or a group thereof.
- typical types: birth rates, mortality rates, performance indicators, density indicators (e.g. population density)
- general figure: number of events during a given time / average number of observed population during the same time × k
- *The value of k (constant) depends on the frequency of the phenomenon. It is usually 1000, or 10,000 or 100,000 when measuring rare events or phenomena. When choosing a value, the goal is to make sure the whole part of the ratio is not zero.*
- Dynamic ratio
- a ratio expressing change through time; it is the quotient of data from two time periods or two dates
- the period or date to be compared is called the current or reporting period, and the period or date on which the comparison is based is called the base period
- the general form: data of the examined period (date) / data of the base (comparison) period (date) × 100
- comparison over time may relate to: duration / time, longer / shorter time, absolute numbers / derived indicators
- can be used to analyze time series and determine the extent of deviations from the mean

### Mean values

Mean values represent typical values for the data.

Arithmetic mean (arithmetic mean / simple average)
- Calculation: dividing the sum of all values in the given data/population divided by a total number of values in the data set / population.
- Moving average
- procedure used to determine long-term trends in time series. It averages adjacent elements of longer time series into equal periods so that the averaging begins at each step with the next data in the original data series (second, third, etc.).
- due to its practical importance in reducing fluctuations and sliding the values to be merged by one, the nature of the change can also be traced in the new time series.
- Geometric mean
- it is used for data where the serial relationship is relevant instead of the summary.
- Position means (median, mode)
- the median is the middle value of a data set, the data that is located in the middle of the data set, when the dataset is ordered in an ascending or descending order. If there is an even number of datasets, the arithmetic mean of the two adjacent data in the middle gives the median.
- mode: the most common/frequent value or item in a dataset. It is used for data where the serial relationship is relevant instead of the summary.

### Indicators for the description of a disease

Morbidity refers to the frequency of a particular disease observed in a given population. General formula: number of patients in one year / average number of inhabitants in the same year × 100,000. The incidence of the disease can be characterized by two fundamentally different data.

One of the data gives the number of new cases (people with the disease) detected in *a given period*. This is called incidence. The other type of data gives the proportion of people with a particular disease at a given time. This is called prevalence.

## Incidence

Incidence compares the number of new patients observed over a period of time to the average number of the population at risk (population at risk) over a given period. A member of the population at risk is considered to be any person who is still free of the disease at the beginning of the study period, but may possibly get the disease/become ill during the observation/study period, ie will become a case. There are two types of incidence indicators.

The first is the ***cumulative incidence***, which is calculated for a period of time and the number of new patients is measured for the same time interval. For example, if the follow-up is annual, we compare it to the mid-year population.

$$I = \frac{\text{new cases during the given time period}}{\text{at-risk population}} \times k$$

Depending on how the population at risk is defined in the denominator, the calculation can give different results. Cumulative incidence assumes that the population as a whole was observed from the beginning to the end of the study period. In practice, however, many participants do not participate in the study from the beginning (they join later) or quit before it ends (die, move). As a result, the follow-up time in a 5-year study may vary significantly from participant to participant.
Example: Morbidity rate - compares the number of new cases to the population at risk of infection.
Morbidity rate - example: out of 67 people who attended a work dinner, 15 had gastroenteritis - morbidity rate: (15 / 67) × 100 = 0.223 × 100 = 22.3%
Another type of indicator, the so-called **person-year incidence**, takes the above phenomenon into account when calculating the incidence. That is, the denominator includes total person-time. A person's time is the sum of each individual's time spent at risk and is usually expressed in the years of the person at risk. That is, how much time each person spent exposed to a risk factor. When a subject develops the disease, dies, or discontinues participation in the study, he or she no longer contributes to the personal time unit.

$$PYI = \frac{\text{number of new patients during the study period}}{\text{all particpants-years during the study period}} \times k$$

The term person-year incidence is used in the Hungarian literature while in international literature it is referred to as incidence density. There are some limitations to its use that need to be mentioned. To prevent systematic errors (bias), it is necessary to calculate the incidence for each subperiod throughout the study. It is important to analyze whether people discontinuing participation or excluded from the study form a well-defined group or not. It is also important to accurately define the number people/populations at risk in the denominator. For example, if you want to specify the incidence of uterine cancer, men will automatically be excluded from the population. However, another factor is that the number of women who undergo hysterectomy increases with age, but as they will not develop the disease in the future, they are not part of the population at risk any more.

## Prevalence

To calculate **point prevalence,** the number of patients at a given time is compared to the number of the population. Therefore, it is always a specified number of patients at a specific time (e.g. January 1 or December 31) that is used.

$$P_0 = \frac{\text{persons with the disease at a given point in time}}{\text{population at risk}} \times k$$

**Duration prevalence** measures the number of patients over a given period of time (e.g. one year, two months).

$$P_t = \frac{\text{umber of patients at the beginning of a period + new patients}}{\text{population at risk}} \times k$$

The relationship between prevalence and incidence can be imagined as follows: the water flowing into the tank (number of new patients) represents the incidence, while the water in the tank (total number of patients) represents the prevalence. In addition to new cases, the arrival of a person with the observed disease in the population (e.g. moving away) also contributes to an increase in prevalence. Water flowing out of the tank indicates a decrease in prevalence that may result from spontaneous or therapeutic healing, death, and migration (leaving the observation population, e.g. moving).
Mortality rates presented in detail later are typi-

cally incidence indicators, regardless of whether they indicate a raw or cause- specific mortality rate. They measure the incidence of death in the population as the final stage of deterioration in health.

**Lethality** measures the rate of death relative to the number of people suffering from a given disease. In other words, it shows the patient's risk of death. It is not a mortality rate, as it does not compare deaths to the population. It can be used as a measure of the severity of the disease and the risk of death due to the particular disease. It is usually expressed as a percentage. E.g.: What percentage of women diagnosed with malignant cervical cancer die from the disease.

A specific prevalence indicator is the incidence of congenital malformations or specific developmental abnormalities in neonates.

Mortality essentially refers to an incidence in the population at risk, however, mortality rates related to pregnancy, giving birth, and birth, such as perinatal mortality or loss of the fetus, are generally not considered to be incidence indicators. Perinatal mortality can be interpreted as duration prevalence, as the sum of stillbirths (point prevalence) and deaths in the first 7 days of life (incidence) compared to the number of births (live and stillbirth).

## Mortality indicators

Mortality refers to the frequency of deaths observed in a given population.

Mortality is an indicator based on the quantification of death as an event. We consider death to be the definitive cessation of all signs of life at any time after the birth of a person, without the capacity for resurrection.

Fetal mortality in this way is not part of mortality statistics but a separate statistic. In practical terms, regardless of the above definition, a death event is one for which a document declaring the fact of death is issued according to the rules and regulations of a given country (death certificate, death report).

### Mortality rates

**The crude rate** is the value calculated for the entire population. For the determination of the mortality rate, the following result is presented in our example analyzing cancer mortality in 1980 below.

That is, 183.8 deaths per 100 000 population per year.

**Age specific mortality rate** which is the most commonly used category is a specific indicator – showing mortality rates within an age group. Here we divide number of deaths in a given age group by the number of people in that age group.

**Group-specific mortality rates** are calculated for a given group, usually for particularly vulnerable groups (e.g. refugees, orphans).

**Period-specific mortality rate** is the incidence rate of mortality in a given period (e.g. mortality rate in a given month, mortality rate in the pre-epidemic/epidemic/and post-epidemic period).

**The cause-specific mortality rate** is the rate of death from a given cause in a population (e.g. stroke mortality).

The standardized mortality rate indicator is used to compare the mortality of multiple populations. In this case, population mortality data are calculated by weighting the age distribution of a common, standard-chosen population. The CSO weights the Hungarian mortality data published in its yearbooks by the age distribution of the WHO standard European population.

$$\text{Mortality}_{\text{crude,1980)}} = \frac{\text{416.481 deaths}}{\text{in 226.546.000 population}} = 183{,}8/10^5/\text{year}$$

$$\text{Mortality}_{\text{35-39 age group,1980}} = \frac{\text{4.684 deaths}}{\text{in 13.965.000 population}} = 33{,}5\ /10^5/\text{year}$$

## Derived indicators

### Life expectancy indicators

**Life expectancy at birth** is the average year that people born in a given year can live on average under the age-specific mortality conditions of that year, assuming that all conditions affecting mortality remain unchanged (medical status, lifestyle, environmental effects, economic and social conditions, etc.). In practice, this does provide information about the life expectancy of the newborn, but of the population. The actual life expectancy of those born in a given year is usually much better than the value calculated using the above methodology. Life expectancy at birth is calculated based on mortality table data. It is the most common indicator of mortality in a given population.

**Life expectancy at a given age** is the average number of years that people of different ages can still expect under the mortality conditions of a given year, assuming that conditions do not change and are always subject to age-specific mortality rates for the year of calculation. Similar to life expectancy at birth, it is calculated based on the mortality table. Its value is not the same as the difference between life expectancy at birth and that given age, as over time, someone who reaches a certain age has better chances of reaching longer old age.

***Health-Adjusted Life Expectancy*** **(HALE)** refers to the number of years an individual can expect to spend in complete health at a given age (usually at birth), without any impairment, assuming that his or her circumstances do not change and it is calculated based on mortality and disease characteristics of the given year. It is calculated on the basis of life expectancy at birth, but also takes into account not only mortality but also morbidity.

### Premature death

Premature deaths are deaths that, given the current advances in medicine, could have been prevented with adequate application (avoidable mortality) of these. We distinguish two groups of indicators:

1. "Avoidable mortality" means death that can be avoided by appropriate medical treatment.
2. "Preventable mortality" means mortality that can be avoided by applying appropriate preventive measures.

Due to different geographical and socio-economic characteristics, the opinion of experts differs as to the age at which deaths may be considered avoidable. In developed countries, there is now an increasing emphasis on detecting avoidable deaths and keeping them as low as possible:

### Potential life years lost

It is a measure of premature mortality that shows the loss of life years due to premature deaths in a given population as a result of the conventionally expected average life expectancy (at the time of the agreement: 70 years). It shows the number of years not lived out of the potential 70 years of life expectancy. An indicator calculated from mortality data can be provided by gender, globally, but also for a specific disease or group of diseases. Thus, it allows for the determination of the role of different causes of death in premature mortailty, and provides a possibility to plan prevention and treatment measures.

The following rates are calculated:

- crude ratio: which gives the number of years not lived from the potential life expectancy of 0-70 years per given population, usually per 100 000 inhabitants.
- standardised ratio: where the number of years not lived from the potential life expectancy of 0-70 years per given population group is calculated by weighting the age distribution of the common population chosen as a basis for comparison. The CSO weights the Hungarian mortality data published in its yearbooks by the age distribution of the WHO standard European population.

### Excess mortaliy

It measures the mortality of a selected population against a reference mortality rate. In practice, this is usually a mortality rate set as a target to be achieved. Excess mortality thus measures the deviation of the actual mortality observed in the study population from the reported mortality rate. Its method of measurement is primarily indirect standardization, and the resulting index is one of the indices.

### Disability-adjusted Life Years

DALY (Disability-Adjusted Life Years) summarizes in a single indicator the number of years of life lost due to premature death – i.e.mortality (YLL) and the number of years of lived with disability (YLD). A „DALY" equals one year of life lost that could have been lived in complete health. This indicator has been developed to measure and quantify the burden of a disease.

## Basic epidemiological studies

The grouping of epidemiological studies is shown in Table 2.

### Observation studies

In these cases, the investigator is only an observer: they do not interfere in any way with the development of the processes. They only observe and measure the incidence of a health-related event or disease, and occasionally compare exposed or non-exposed groups to try to find risk factors associated with a particular event or disease.

### Descriptive studies

Descriptive epidemiology examines the distribution of diseases, particularly the affected population or subpopulation (e.g. by age, sex, occupation), the geographic areas it is the most or least common at, and how frequency of the disease has changed over time. Different types of studies measure a given phenomenon based on the simultaneous examination of three aspects: person, place, and time.

*Time*

The incidence of certain diseases changes over time. Some of these changes happen on a regular basis, while others are unpredictable. There are diseases which occur at the same time each year, such as the flu. In contrast, for example, hepatitis B infection or salmonellosis can occur at any time. In the case of seasonal diseases, their occurrence can be anticipated; control measures (for example, an influenza vaccination campaign) can be implemented. In the case of sporadic diseases, studies are carried out to identify the causes and modes of transmission and appropriate target measures will be developed to monitor and prevent the further occurrence of the disease. In both

Table 2: Main types of epidemiological studies (table by authors)

| **Type of study** | | **Unit of study** |
|---|---|---|
| **Observational studies** | | |
| Descriptive studies | | |
| | Case report | an individual |
| | Case series | an individual |
| | Cross-sectional (prevalence) study | an individual |
| | Ecological (correlation) study | population |
| Analytic studies | | |
| | Ecological (correlation) study | population |
| | Cross-sectional (prevalence) study | individuals |
| | Case-control study | individuals |
| | Cohort study | individuals |
| **Intervention (experimental) studies** | | |
| | Randomised controlled (clinical)studies | patients |
| | Areal intervention studies | individuals |
| | Community intervention studies | communities |

cases, visualization of disease incidence through time patterns through time is important. Time data is usually displayed on a two-dimensional graph. The y-axis represents the number of cases; and the x-axis represents time. The time scale may encompass years or even decades depending on the given disease but may only indicate days or hours. In the case of chronic diseases, long-term tendencies are more important, while in the case of a food-borne infection, the time scale ould usually represent only hors or days. Timely occurrence of a disease is usually depicted using a line graph or a histogram.

*Place*

Local description of the occurrence of the disease helps to determine the geographical extent and geographical variations of the problem. The characterization may include not only the place of residence but also the geographical area relevant to the occurrence of the disease. It could be, for example, the place where the diagnosis was made, place of birth, school, hospital unit, or even the most recent travel destination. The unit can be a continent or country, or even an address, a hospital wing, or an operating room. Sometimes it does not refer to a specific place, but to a category of place (for example: urban or rural, domestic or foreign). Analysis of the data based on location can identify communities at increased risk for the disease. Location data can also be displayed in table, but representation on a map is often more useful in everyday practice.

*Persons*

As personal characteristics can influence the disease, personalization and analysis of data can relate to people's internal characteristics (age, gender), biological characteristics (immune status), acquired characteristics (marital status), activities (occupation, leisure activity), health behavior characteristics (physical activity, nutrition, alcohol consumption) or living conditions (socio-economic situation, access to medical care). Age and sex are usually included in all data sets as they are the two most commonly studied characteristics. However, depending on the disease and the available data, it may be necessary to analyze other personal variables. Personal information is usually displayed in tables or graphs.

Descriptive epidemiology thus attempts to answer the questions "Who?", "Where?" and "When?". It can focus on individual data collection, description of a disease for a single person (case study) or even data from national health surveys in several countries (prevalence study). In addition, most routinely collected population-level data, including their appearance in different geographical areas and their time-varying proportions (time trends), are also covered by descriptive epidemiology. Descriptive studies and reports are essential to identify health-related problems and make suggestions that may answer the question „Why?". This allows the generation of a hypothesis that can be used as the basis for analytical epidemiological studies presented in the next section. In this chapter, we take a close look at the most common types of descriptive data, where they come from, and review some examples of how to use these data.

**Case presentation and series of cases**

The identification of a new or recurrant problem often begins with studies based on individual data, which may involve a description of a case or the preparation of a so-called case series. These are detailed descriptions of one or more diseases that are unusual for some reason. This may be because the disease has not been seen before, or it has occurred in people who are not usually expected to develop the disease, possibly or in an area where it has not been reported before. The significance of the above is that we are able to generate a hypothesis about a given problem based on the information from the descriptions. One classic example of a case report is a 1961 publication reporting the case of a 40-year-old premenopausal woman receiving oral contraceptive treatment for endometriosis. She developed pulmonary embolism 5 weeks after starting treatment. Previous evidence suggests that pulmonary embolism is more common in older postmenopausal women, so the notifying physician hypothesized that the drug may have been the trigger in this case.

An example of a series of cases was the diagnosis of Pneumocystis Carinii pneumonia in five previ-

ously healthy homosexual young men within half a year in 1980-1981 from 3 Los Angeles hospitals. This form of pneumonia used to affect almost exclusively immuno-suppressed elderly people, which meant it was a new, unknown disease which was then called acquired immune deficiency syndrome. (Acquired Immunodeficiency Syndrome = AIDS). In 1982, advanced Kaposi's sarcoma and a disease of fever of unknown origin, lymphadenopathy, were reported in Denmark, in 4 previously healthy homosexual men, one of whom later died. Subsequent studies revealed that the patients' immune systems were severely damaged. Three of the four patients had never been to the U.S. where acquired immuno-deficiency syndrome was described, but the possibility arose among European homosexual men admitted to hospital with fever of unknown origin, splenic lymph node lesion, opportunistic infection, or Kaposi's sarcoma. The following example also highlights the importance of case studies. In Australia, 78 babies were born in 1941 with cataract and some with heart failure. The cases occurred in a similar form over a certain period of time, in different areas. Based on these facts, Norman McAlister Gregg hypothesized that there was an association between the occurrences and that a severe Australian rubella epidemic, between 1940-41, was responsible for the congenital abnormalities. They developed as a result of an infection suffered during early pregnancy. Of the 78 children born with cataract, 68 mothers contracted the infection during pregnancy. Based on all this, a congenital triad (deafness, cataract, heart failure) resulting from the mother's rubella infection was described in 1943. Due to the selective nature of these descriptions and the limited amount of information they contain, they provide little evidence of causal relationships and cannot say much about patterns of disease occurrence. However, they can help identify health-related problems, thus generating a hypothesis and providing a basis for further detailed studies to facilitate health promotion activities.

**Crossectional study (prevalence)**

In these studies, data are collected on a ‚cross-section' of the population on health status and / or factors affecting it at a given time (or in practice for a short period of time during the study). There are both descriptive and analytical forms. The characteristics of the descriptive form are outlined below. It is not suitable for the exploration of a causal relationship; it only shows whether the risk factor was present at the given time, i.e. the point prevalence.

Numerous surveys have been conducted to measure the prevalence of various aspects of health, including diseases that are not recorded in other routine statistics but relate to more common disease groups (obesity, diabetes), health behavioral characteristics (smoking, sunbathing, nutrition), or access to and utilisation of healthcare services. These surveys are essential to gain information about health burden, needs, and services beyond hospital data. A wide range of sampling and data collection options are available for conducting surveys as described above, including questionnaire surveys, phone and in-person interviews, and sometimes very detailed physical examinations such as the NHANES- National Health and Nutrition Examination Survey in the USA.

A classic example of prevalence studies in the United States, following the publication of the National Health Survey Act in 1956, was the periodic data collection on the prevalence of acute and chronic diseases and health care utilization. This included personal interviews in households, standard physical examinations and laboratory tests. The protocol was supplemented in 1971 with a Health and Nutrition Examination Survey investigating dietary habits of a randomly selected population.

Studies of this kind are primarily aimed at surveying a sample of the population in order to learn about the prevalence of diseases and determinants in the community, often to promote health promotion measures.

During the cross-sectional examination, the results are recorded in a 2x2 contingency table, and then the point prevalence of the examined disease / health behavior/ characteristic and the selected risk factor is calculated (Table 3.).

Table 3: Structure of the cross-sectional study

| | | PATIENT | | Total |
|---|---|---|---|---|
| | | Yes | No | |
| EXPOSED | Yes | a | b | a + b |
| | No | c | d | c + d |
| Total | | a + c<br>a + c | b+ d<br>b + d | N = a+b+c+d |

Point prevalence of the disease examined ($P_B$) in the exposed population:

$$P_{B,\text{in the exposed population}} = \frac{a}{a+b} \times k$$

in the non-exposed population:

$$P_{,\text{in the non-exposed population}} = \frac{c}{c+d} \times k$$

in the whole population:

$$P_B,\ P_{K,\text{in the whole population}} = \frac{a+c}{N} \times k$$

Point prevalence of the examined risk factor ($P_K$) among patients:

$$P_{K,\text{in the diseased population}} = \frac{a}{a+c} \times k$$

in the healthy population:

$$P_{K,\text{in the healthy population}} = \frac{b}{b+d} \times k$$

in the whole population:

$$P_{K,\text{in the whole population}} = \frac{a+b}{N} \times k$$

**Ecological (correlation) studies**

A descriptive epidemiological study based on aggregated data is called an epidemiological study using ecological or aggregated data. An example is when we map the average alcohol consumption per capita in each country. It does not show who consumes how much alcohol in each country or what the distribution is behind the averages, with regard to individuals or over time. All it reveals is the amount of alcohol consumed per capita per year and the differences between the values in the countries included in the study.

Although descriptive epidemiology cannot provide strong evidence for the causes of diseases, the creative use of its methods can provide new ideas about causation, thus helping to generate new hypotheses. These hypotheses should then be tested through analytical studies capable of proving causal relationships, which will be discussed in the next chapter.

## Analytical studies

Analytical epidemiology examines the causal factors in the development of diseases. It seeks to find a relationship between the incidence of the disease being studied and the presumed causes (e.g. the relationship between lung cancer and smoking), testing a hypothesis to determine whether a factor considered as a causal factor may actually cause (or prevent) the disease studied. It makes comparisons between sick and healthy people and between those with and without exposure to the disease. They try to answer the questions, "Why and how do some people get the disease?" and "How strong is the relationship between exposure and outcome?". According to different principles, we have the opportunity to group the methods of epidemiological studies, but ultimately, almost everything goes back to the same basic principles. The difference lies in the health condition examined and the influencing factors. Therefore, it is important to remember that the approaches dis-

cussed in this chapter are general and applicable to all areas of health research.

**Ecological (correlation) studies**

Although this type of study has already been discussed in the previous chapter, it should be mentioned here as well, since if we examine the relationship between an assumed risk factor and a characteristic of a health condition, they can also be considered as analytical studies. These studies are also called correlation studies, and accordingly, the relationship between the phenomena studied is often plotted on a correlation point diagram, and the relationship between the parameters is evaluated using the correlation coefficient.

The advantage of this type of study is that it can be performed quickly and at relatively low cost as it usually compares existing data with morbidity, mortality data, or health system utilization data.

However, without the knowledge of individual data, they can only be considered as hypothesis-generating studies, not hypothesis testers.

The main limitation of their application is that risk factors cannot be linked to the disease in a given person; they allow for establishing population-level associations. That is, even if we explore the association between alcohol consumption and chronic liver disease, individual risk cannot be inferred even in the case of a close population relationship. If this happens, and individual-level changes are inferred from population-level data it is an ecological mistake.

An example for an ecological study was a study conducted in 1975 in which Armstrong and Doll reported an association between cancer and dietary and other variables, based on data from 23 countries. Diet was shown to have been strongly associated with several types of cancer, particularly meat consumption and colon cancer. Countries with low daily meat consumption per capita had the lowest rates of colon cancer. The study suggested that dietary factors play a role in the development of tumours, leading to flourishing research in this area.

Another survey conducted in China in 1990 examined the association between Helicobacter pylori morbidity and gastric cancer mortality in 46 counties. It was observed that counties with a higher prevalence of H. pylori infection had higher rates of gastric cancer, low rates of H. pylori, and lower rates of gastric cancer. This suggests that H. pylori may play a role in the development of gastric cancer. However, the fact that H. pylori has a high prevalence but a low rate of gastric cancer in some counties suggests that infection alone is not enough to cause cancer. There must be other contributing factors. This was later confirmed by several analytical epidemiological studies.

**Cross-sectional (prevalence) studies**

It has already been mentioned in a previous chapter, but we shall highlight it here as well, as if we collect data on health condition and the factors influencing it, the main aim is to try to find a correlation between these two, or if we examine the effect of a risk factor on a particular disease we are conducting analytical epidemiological studies. The so-called surveys are typical cross-sectional studies. The quantity and quality of information thus collected allows for a much deeper analysis in determining the relationships between health behaviors and individual conditions.

For example the Australian National Health Survey is done in every three years; they collect information on the health behaviour (alcohol consumption, smoking, physical activity) and health status (diabetes, injuries, mental problems) of articipants with the aim to find associations between factors survey. According to data collected for the period between 2004–2005, people reporting high levels of anxiety were more likely to have been physically inactive than those with low anxiety levels.

**Cohort studies**

Cohort studies are used for establishing supposed casual relationships between a risk factor and a disease or illness. In an ideal case, we could theoretically test who are and who are not exposed to a particular risk factor but this would in many cases be unethical (people cannot be deliberately exposed to a supposed risk), or unpractical. In such cases a cohort study is performed (which, most often, is a prospective, longitudinal study).

Initially, a cohort can be a group of healthy individuals who are followed up, to detect and observe disease incidence or a gruop of patients who are studied to investigate the outcome of a disease i.e. the prognosis. Two groups are studied, the exposed group and the non-exposed group. The word 'cohort' in a classic interpretation refers to a subgroup of the populations established on the grounds of the individuals belonging to this subgroup sharing a particular characteristic which does not change over time (e.g. born in the same year), the shared feature can also be exposure/or lack of exposure to the same risk factor. When choosing the exposed cohort to be observed incubation time should be taken into consideration as it may influence follow-up time. The level of exposure should also be determined, it may relate to the amount of alcohol consumed, the extent of radiation, or time spent doing physical exercise. In such cases, subgruops can be formed according to levels of exposure allowing for separate analyses required for adequate evaluation.

There are two ways of choosing groups/cohorts to be studied. Cohort studies *to be conducted on the general population* are usually preceded by a cross-sectional study which helps differentiate people with and without a disease and we can also study the presence of a risk factor. These studies, however, are quite costly and time-consuming which limits their widespread use.

An example is the classic Framingham Heart Study started in 1948 with the prior aim to identify biological and environmental factors which may contribute to the increase in cardio-vascular mortality and related disability. 5209 persons aged between30-60 years, residents of the city of Framingham were included (both males and females) and examined regularly to identify risk factors for coronary heart disease. The study was later continued in 1971 with the inclusion of the children and spouses of participants belonging to the original cohort (5 124 persons); in 2002 the third generation (grandchildren) were included and followed up. The more than 50 years of data collected from residents of Framingham helped identify risk factors associated with the increased risk of cardio-vascular disease including smoking (1960), high cholesterol levels and high blood pressure (1967), and obesity and low levels of physical activity (1967). The identified risk factors formed an integral part of therapeutic and prevention strategies in clinical practice.

The other method is a study based on special exposed cohorts, which can also be used to analyze risk factors that are rare in the general population. Uranium miners, for example, are such a special group. The control group may be an external group with regard to exposure, such as the general population or another selected cohort. A major advantage of the general population is the availability of mortality rates as a benchmark. Its use, however, can be limited by the high proportion of the special exposure cohort studied within the population. In such cases, the control group can only be an external, selected cohort.

Of all the observational studies, cohort studies generally provide the best information about the causes of the disease and allow for the most direct measurements of the risks of developing the disease. Exposure data that are sufficiently accurate for the study may be collected continuously during follow-up; which also allows for the detection of change. Importantly, however, if a cohort study has a very long follow-up period and exposure data were only collected at baseline, people may have changed their observed habits over time, e.g. smoking.

In addition, it is possible to compile a retrospective or historical cohort, which can shorten the otherwise long follow-up time. To this end, accurate recording and traceability of past exposures of cohort members is essential to determine their current health status. In the past, such studies were more common, for example in the military, where, in addition to precise personnel records, birth characteristics (e.g., birth weight and height) were also used to study the development of diseases. However, in the absence of close follow-up, such studies are usually limited to the study of mortality or the outcome of cancer, given the lack of data collection on other non-fatal endpoints.

Marking required for analyzing data from the cohort study are shown in Table 4. Here again, the

Table 4: The structure of a cohort study

| | | CASE | | Total |
|---|---|---|---|---|
| | | Yes | No | |
| EXPOSED | Yes | a | b | a + b |
| | No | c | d | c + d |
| Total | | a + c<br>a + c | b+ d<br>b + d | N = a+b+c+d |

standard 2 x 2 contingency table is used. A part of individuals who were heathy at the onset of the study become cases, so they are placed in the "a" field if exposed, and in the "c" field if they were not exposed.

For cohort studies, the incidence rate, for characteristics, see the section on basic types of epidemiological indicators, can be calculated as follows:

$$I_{\text{exposed cohort}} = \frac{a}{a+b}$$

$$I_{\text{non-exposed cohort}} = \frac{c}{c+d}$$

Given that incidence data can be calculated in a cohort study (as opposed to a case-control study), they can be used to calculate relative risk (RR). This expresses the number of times the incidence of the disease is higher among those at risk than among those without risk. The higher the value of the indicator, the more likely it may be that the risk factor has an influential role.

$$RR = \frac{I_{\text{exposed}}}{I_{\text{non-exposed}}}$$

The additional risk (AR), which is the additional incidence caused by exposure in the exposed group, can be calculated as follows:

$$RR = I_{\text{exposed}} - I_{\text{non-exposed}}$$

The additional risk ratio [ARR (%)], which shows the proportion in which incidence would decrease among the exposed population if the risk factor was not present, calculation is as follows:

$$ARR(\%) = \frac{I_{\text{exposed}} - I_{\text{non-exposed}}}{I_{\text{exposed}}} \times 100 = \frac{AR}{I_{\text{exposed}}} \times 100$$

Main advantages and disadvantages of cohort studies are summarised below (Table 5).

One of the most significant follow-up studies was the British Doctors Study launched in 1951 by Richard Doll and A. Bradford Hill. The cohort consisted of 34 439 English physicians with a follow-up of 50 years. The aim was to compare the risks of different smoking habits among men of different ages and to examine the risk-reducing role of smoking cessation at different ages. They found that smoking cessation at 60, 50, 40, or 30 years increased life expectancy by about 3, 6, 9, or 10 years.

**Case control study**

In case-control studies, instead of identifying people based on their exposure status and waiting to see who develops the disease, data is collected in reverse order, moving backwards. The study is therefore, focused on the past, i.e. retrospective. We select the people who developed the disease studied (cases) and a representative sample of non-patients from the population from which the cases came (control) and then survey their previous exposure status. (Some authors prefer to call the control group the "reference" group). For example, if we wanted to know if smoking was associated with lung cancer, we could compare lung cancer and non-lung cancer groups to see if their smoking habits were different.

The case group is composed of individuals with the disease under study (or with a particular health

Table 5.: Advantages and disadvantages of cohort studies

| Advantages | Disadvantages |
|---|---|
| can be used in rare exposure cases | cannot be used in rare diseases |
| can measure several effects of one risk factor | prospective study is costly and time-consuming |
| can measure the transitional relationship between the risk factor and the disease | loss of particpants to follow u por discontinuation significantly affects the validity of results |
| it allows for measuring incidence in both the exposed and non-exposed cohort based on which RR can be calculated which can then be used to calculate additional risk fractions | loss of particpants to follow u por discontinuation significantly affects the validity of results |
| allows for the exact measurement of exposure | |

behaviour factor). The most important selection criterion is the precise definition of the disease and the detailed breakdown of the disease groups. Optimally, newly diagnosed patients should primarily be included in the study. In the case of rare diseases, where the number of cases is very low, this cannot be solved. Patient selection is usually based on the patient material of the institution conducting the study. The advantage of this is that information about the patients'past medical history is also available. However, it should be noted that if patients are mainly from an institution's catchment area, certain specific risk factors may occur cumulatively (e.g. in mining areas).

The other popular selection criterion is the territorial principle when patients living in a given area (city, county, region, etc.) are examined.

Controls should be representative of the population from which the cases originated, so that their frequency of exposure is very similar to the total non-patient population. A hospital control group can also be used, in which controls are selected from patients admitted to the same hospitals only for diseases other than the condition being studied. Although this is a more efficient and economical process than the selection of population control, it obviously also has significant disadvantages. This is because the controls themselves are sick and thus different from most healthy people who live in the source population from which the cases originate. In fact, the distribution of risk factors (such as smoking, alcohol abuse, etc.) may be much more similar to its cases than to its source population, leading to distortion.

The principle of matching the cases means that the members of the control group have similar characteristics to the persons belonging to the case (patient) group. The most common of these characteristics is gender or age. For example, the pair of 40-year-old male patient in the patient group should also be around 40 years of age in the control group. Matching can be very time consuming, labor intensive, and costly, as it may be more difficult for some patients to find a control pair.

An important issue in the selection of both cases and controls is that they should be selected regardless of their exposure status. For example, in the case-control study of the use of an oral contraceptive pill and deep vein thrombosis, whether or not a woman is taking a pill does not affect her chances of being selected as a case or control. Knowledge of an individual's exposure status can lead to a distortion in recruitment of participants, which is called *selection distortion*.

Another type of distortion occurs when the information collected from cases and controls is not comparable. This may occur if the interviewer generates or interprets exposure information differently when the individual's disease status is known (interviewer distortion), or because those with the disease remember their exposure or experience more accurately than those without the

disease, or differently than non-sufferers (*recollection distortion*).

Table 6.: Structure of the case-controlstudy

| | | CASE | | Total |
|---|---|---|---|---|
| | | Yes | No | |
| EXPOSED | Yes | a | b | a + b |
| | No | c | d | c + d |
| Total | | a + c<br>a + c | b+ d<br>b + d | N = a+b+c+d |

During the analysis of the data, i.e. when evaluating the association between the disease and the presumed risk factor, we examine the proportion of those exposed in the two groups. The designations refer to Table 6

$$OR = \frac{a/(a+b)}{c/(c+d)} = \frac{a/b}{a/b} \approx \frac{ad}{bc}$$

The ratio of exposed:
in the patient (case) group:

$$E_{\text{group case}} = \frac{a}{a+c}$$

in the control group:

$$E_{\text{control group}} = \frac{b}{b+d}$$

Risk measurement is not feasible in case-control studies. This is because the incidence data required to calculate the risk (relative risk, additional risk indicators) cannot be determined. For this reason, in such studies, a relative risk estimate is performed by providing an odds ratio. The odds ratio (OR) compares the odds ratio of exposure and non-exposure in the case group (a/c) and the control group (b/d). According to this, if the disease is rare (low incidence), the number of patient cases is low in both the exposed and non-exposed groups. Thus, the total number of exposures (a + b) can be approximated by the number of exposures in the control group (b), while the total number of non-exposures (c + d) is approximately equal to the number of non-exposures in the control group (d).
The following formula is used:

$$OR = \frac{a/(a+b)}{c/(c+d)} = \frac{a/b}{c/d} \approx \frac{ad}{bc}$$

As already mentioned, additional risk indicators cannot be calculated for case-control studies. However, using the odds ratio, we can also estimate the *additional risk ratio* here, if we substitute the relative risk with the odds ratio in the formula:

$$ARR(\%) = \frac{RR - 1}{RR} \times 100 \approx \frac{OR - 1}{OR} \times 100$$

The main advantages and disadvantages of case-control studies can be summarized as follows (Table 7).

A classic case-control study was conducted in Germany in 1961. Mothers of children born with an unusual disorder of limb development (cases) were compared with mothers of healthy children (control) in terms of exposure during pregnancy. Of the 46 case mothers, 41 (89%) but none of the 300 control mothers took thalidomide in early pregnancy. This strongly suggested that the use of thalidomide in early pregnancy may be responsible for birth defects. This study was prompted by data from an earlier series of cases.
Another example is a study in Tasmania, Australia, on the causes of Sudden Infant Death Syndrome (SIDS). Based on data from 58 cases and 120 control infants, it was formulated that infants placed on the abdomen were found to be four times more

Table 7.: Advantages and disadvantages of case-control studies

| Advantages | Disadvantages |
|---|---|
| relatively fast and cheap | not suitable for the assessment of rare risk factors |
| excellent for evaluating long latency disease | it is usually not possible to calculate an incidence directly |
| optimal for the study of rare diseases | it is sometimes difficult to elucidate the causal relationship between exposure and disease |
| several etiological factors can be examined in relation to a disease | particularly sensitive to distortion (selection and memory) |

likely to develop SIDS than infants put to sleep in other positions. In addition, the risk increases if the child is dressed too hot, sleeping in an overheated room and if he or she has recently suffered from an illness. The results of the study led to the launch of campaigns that encourage parents to make their children sleep on their back to reduce the risk of having SIDS.

A modern version of the design of case-control studies is the embedded case study, which is similar in principle to the case-control study, combining its advantages with the advantages of prospective data collection in the cohort study. In fact, it is a case study that is "embedded" in an existing cohort study. The cases are the cohorts that developed the studied disease, but this time the controls are selected from the cohorts that were disease-free at the time the cases were diagnosed.

### Interventional (expierimental) studies

Interventional (experimental) epidemiology uses experimental methods to confirm the results of observational analytical epidemiology. These interventions are performed in the human population under close ethical control. Intervention studies seek to demonstrate a causal relationship between the suspected pathogen and the development of the disease. Researchers "intervene" to change something in the hope that it will improve participants' future health. We can study the effects of therapeutic or preventive interventions. Therapeutic interventions can be performed at the level of individual, while preventive interventions can be performed at the levels of individual and population.

#### Randomized controlled (clinical) study

Here we study a procedure that is defined by a specific so-called reference population to be used later. Such a reference population may be, for example, women over the age of conception, and the study is a drug that has been developed for this target population. We must first precisely define the reference population mentioned above, and then select from this population the voluntary sample in which the test is to be performed.

The best way to evaluate a new therapy is to identify a group of patients with the same condition and then randomly assign them to different treatments. Preventive testing differs only in that it involves people who are free of the disease but are at risk of developing the disease.

Participants are randomly assigned to one of two or more groups defined in the study; this is called randomization, which ensures that each group is as similar as possible at the beginning of the study. Members of the control group do not undergo treatment, but members of the other group receive some form of treatment. One or more control or comparison groups may be used to compare the results of the treated group with those of the untreated group. Generally, patients in the control group will either not receive treatment or, if possible, will receive placebo (similar to real treat-

ment but not active). If an acceptable standard treatment is available, the control group should be given this - it would be unethical to withhold it - and this is compared to the new therapy. In practice, a treatment that has previously been shown to be effective is usually supplemented with a new therapeutic element, and a comparison of the conventional treatment with the supplemented one is performed. The two groups therefore differ only in this respect, in terms of the intervention factor examined. The effectiveness of the intervention (treatment) is the difference between the outcome indicators measured in the members of the intervention and the control group. Because of this aspect of randomized controlled trials (RCTs) - the close similarity of the groups in all respects other than the intervention - is generally considered to provide the best evidence of all epidemiological studies.

RCTs are prospective studies because their design precedes the study itself. The real experimental setup includes an intervention, randomization, and control group.

Another important aspect is the encryption of the treatment, since, for example, the study of placebo effect can only be performed if the participant does not know whether he or she has received real or placebo treatment. The experimental design, i.e. the group to which the participants belong, is reported only after the end of the treatment. The layout can be a single-blind experiment when only participants do not know their classification. In the double-blind experiment, neither the patient nor the persons conducting the experiment know who belongs to the experimental and who to the control group. And the more recent triple-blind experiment means that the classification will remain secret until the study results are fully evaluated and are not known to participants, experiment conductors, or data analysts.

Of Hungarian descent, László Tabár and his coresearchers studied the effect of mammographic breast screening on breast cancer mortality in two Swedish counties (Östergötland, Koparberg) in a population-based randomized controlled clinical trial. The results of the 7-year follow-up show a 25% reduction in the incidence of stage II or higher advanced breast cancer and a 31% reduction in breast cancer mortality.

### Community intervention study

These are preventive studies in which the intervention is carried out at the community level, usually when it would be impossible to carry out or evaluate the intervention at the level of the individual.

An example of this is water fluoridation and dental health studies conducted in different countries. To assess the effect of adding fluoride to water on dental health, it is obviously impossible for some to fluoridate water but not to others, so entire cities have been designated to participate in the study. The controlled study was conducted in Newburgh and Kingston, New York, USA. After 10 years of fluoridation, children from 6 to 16 years of age in Newburgh had a DMF index (decayed, missing, or filled teeth) 50% lower than children in Kingston, where no fluoridation of drinking water was performed. The assumption underlying the result was that there was no significant difference between the cities other than water, which could explain the effect (i.e., it was not confusing). (Although this and other studies have clearly shown the benefits of low fluoride level for dental health, the ongoing debate about the possible harmful effects of fluoride on other organs in the body, especially bones, has meant that universal fluoridation of the water supply has not taken place.)

Another randomized, controlled community study evaluated the effect of vitamin A supplementation to prevent childhood death, in 229 villages in Indonesia, children aged 1–5 years received two doses of vitamin A, while in 221 control villages, children received vitamin A only after the study. Mortality of children in control villages was 49% higher than in villages receiving vitamin A supplementation.

## References


1. Ádány RV, Hajdú P. Epidemiológiai szótár. Medicina Könyvkiadó, Budapest, 2003.
2. Egészségtudományi Fogalomtár Állami Egészségügyi Ellátó Központ Available from: https://fogalomtar.aeek.hu/index.php/Kezd%C5%91lap [Letöltve: Pécs, 2021. november 2.]
3. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer. 1975; 15: 617-631.
4. Ast DB, Schlesinger ER. The Conclusion of a Ten-Year Study of Water Fluoridation. Am J Public Health Nations Health. 1956; 46(3): 265-271. doi: 10.2105/ajph.46.3.265.
5. Boncz I, Vajda R, Horváthné Kívés Zs. Epidemiológiai alapismeretek In: Boncz I. (szerk.) Kutatásmódszertani alapismeretek. Pécsi Tudományegyetem Egészségtudományi Kar, Pécs, 2015; pp. 60-113.
6. CDC. Pneumocystis Pneumonia – Los Angeles. MMWR 1981. 30(21): 1-3.
7. Decsi T. A bizonyítékokon alapuló orvoslás. Medicina Könyvkiadó Zrt., Budapest, 2011.
8. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. Br Med J. 2004; 328(7455):1519. doi: 10.1136/bmj.38142.554479.AE.
9. Ember I, Kiss I, Cseh K. (szerk.) Népegészségügyi orvostan. PTE ÁOK, Pécs, 2013.
10. Fidy J, Makara G. Biostatisztika. InforMed 2002 Kft., Budapest, 2005.
11. Forman D, Sitas F, Newell DG, et al. Geographic association of Helicobacter pylori antibody prevalence and gastric cancer mortality in rural China. Int J Cancer. 1990; 46: 608-611.
12. Gerald M. Framingham Heart Study: The First 20 Years. Prog Cardiovasc Dis. 2010; 53(1): 55-61. doi: 10.1016/j.pcad.2010.03.003.
13. Gerstoft J, Malchom-Moller A, Bygbjerg I, et al. Severe acquired immunodeficiency in European homosexual men. Br Med J. 1982; 285: 17-19. doi:10.1136/bmj.285.6334.17
14. Gregg NM. Congenital cataract following German measles in the mother. 1941. Epidemiol Infect. 1991; 107(1): 3-14 doi:10.1017/s0950268800048627.
15. Jordan WM. Pulmonary embolism. Lancet, 1961; 278(7212): 1146-1147. doi:10.1016/S0140-6736(61)91061-3.
16. Karamánné Pakai A, Oláh A. Elméleti áttekintés a tudományos kutatásokról. In: Ács, P. (szerk.) Gyakorlati adatelemzés. Pécsi Tudományegyetem Egészségtudományi Kar, Pécs, 2014; pp. 9-32. (ISBN:978-963-642-682-8).
17. Mellin GW, Katzenstein M. The saga of thalidomide: neuropathy to embryopathy, with case reports of congenital anomalies. N Engl J Med. 1962; 267: 1184-1193, 1238-1244. doi: 10.1056/NEJM196212062672305.
18. Mental health in Australia: a snapshot, 2004–05. Available from: https://www.abs.gov.au/ausstats/abs@.nsf/mf/4824.0.55.001 [Letöltve: Pécs, 2021. október 20.]
19. Paffenbarger RS, Hyde RT, Wing AL, et al. Physical activity, allcause mortality, and longevity of college alumni. N Engl J Med. 1986; 314(10): 605-613. doi: 10.1056/NEJM198603063141003.
20. Pakai A, Kívés, Zs. Kutatásról ápolóknak, Mintavétel és adatgyűjtési módszerek az egészségtudományi kutatásokban. Nővér. 2013; 26(3): 20-43.
21. Ponsonby AL, Dwyer T, Gibbson LE, et al. Factors potentiating the risk of sudden infant death syndrome associated with the prone position. N Engl J Med. 1993; 329(6): 377-382. doi: 10.1056/NEJM199308053290601.
22. Sommer A, Djunaedi E, Loeden AA, et al. Impact of Vitamin A supplementation on childhood mortality: A Randomised Controlled Community Trial. Lancet, 1986; 327(8491): 1169-1173. doi:10.1016/S0140-6736(86)91157-8.
23. Tabar L, Yen MF, Vitak B, et al. Mammography service screening and mortality in

breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet. 2003; 361(9367): 1405-1410. doi: 10.1016/S0140-6736(03)13143-1.

24. Tabar L, Fagerberg CJ, Gad A, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the breast cancer screening working group of the Swedish National Board of Health and Welfare. Lancet, 1985; 1(8433): 829-832. doi:10.1016/s0140-6736(85)92204-4.
25. V. Hajdú P, Boján F. Demográfiai és epidemiológiai módszerek a népegészségügyben. Literatúra Medica Kiadó, Budapest, 1996.
26. Webb P, Bain C. Essential Epidemiology An Introduction for Students and Health Professionals Cambridge University Press, Cambridge, 2010.

# III. Epidemiological tasks in public health

Réka Vajda, Zsuzsanna Kívés, Imre Boncz

## Introduction

Due to lack of space, this chapter is not intended to discuss general and detailed areas and aspects of epidemiology in depth. Principles and aspects of classic epidemiology have been outlined in several textbooks in great detail. These textbooks were primarily written for medical doctors, with the aim to help the preparation for the specialist exam in communicable diseases and preventive medicine. The information such textbooks provide, may, on the one hand prove too much, or from another aspect too little, for students studying public health. Public health officers do not take part in treating patients; therefore, they may not benefit form detailed descriptions of various therapeutic modalities, while individual epidemiological examinations and investigation procedures might not be detailed adequately in these works.

Due to the low number of resident physicans in the area of public health, and the fact that several positions offered at government or district offices do not require candidates to have a specific higher education degree, fresh public health graduates can mainly rely on the knowledge they gained during their university studies. Public health officers are expected to do most of their tasks and duties on their own, including: updating and managing databases of the National Public Health Center, providing training and continuous information for data providers working in their area, analysing and interpreting surveillance data, preparing documents on individual public health decisions and forwarding these to the head of the district public health authority and the county chief medical officer.

It was an integral part of the work of Dr. Ilona Straub, the Chief Director of the National Center for Epidemiology, to provide practical training for colleagues involved in public health work in area and to further highlight the necessary theoretical background. We would hereby like to express our gratitude to our mentor.

## Surveillance

*Surveillance = Sufficient information for action.*
Surveillance (World Health Organisation [WHO] definition)
*Public health surveillance is the continuous, systematic analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice and timely reporting of these to decision-making authorities.*

### Principles of surveillance

Surveillance can be described as active supervision: information for action with which we can prevent or control the spread of disease.
It is a widely applied method for the assessment and evaluation and follow-up of not only infectious diseases but any other healthcare phenoma. In order to be able to cut back on, or eliminate a particular infectious disease according to health policy plans, prior to implementing targeted measures, it is imporant to know the incidence and prevalence of the disease in terms of time and space, and group(s) of the population affected. Data collection therefore, is a vital preceding step. A uniform definition has to be formulated to enable the comparison of collected data both in time and space. The subsequent step includes the continuous collection, validation and analysis of data,

and the preparation of information which is than presented to decision makers in the form of reports which would then facilitate the initiation of adequate measures. Data collection continues, but at this stage, with the aim to monitor *the change a given measure or intervention has resulted in*, if implemented measures have manifested in the expected change, whether the targeted issue has been resolved or if novel problems have surfaced. It is not only decision-makers (local, county/regional, national) who have to be aware of surveillance data in time, but data providers also need to be provided regular feedback as this generates motivation at reporting and seems to improve the quality of data they provide.

Surveillance is employed in all areas of public health as this is the guiding principle encompassing the entire thinking in epidemiology-related work. Surveillance data are not only used for containing infectious or communicable diseases but also for gainingfurther in-depth knowledge about various aspects of these diseases (which populations are more severely affected etc.), in order to be able design and implement more precisely targeted treament (age, sex, occupation- specific) and thus, to further increase the potential of prevention measures and to contribute to the development of science with new information highlighting previously unkown associations.

## Types of surveillance

- *passive surveillance:* is the routine collection of automatic reports containing surveillance data submitted by hospitals, clinics and public health units to health authorities;
- *active surveillance*: regular contact is established (via phone or e-mail etc.) with healthcare surveillance data providers in order to facilitate active research into particular cases during an epidemic (e.g. to identify the cause of an accumulation of cases observed upon analysing surveillance data or to conduct an international search for given cases during an epidemic etc.);
- *integrated in-patient surveillance:* generates a report from data collected through two channels (evaluation of indicators and events) with regard to a particular healthcare problem.

**indicator-based surveillance (IBS) –**

- *institutional* surveillance: healthcare institutions send reports daily/weekly/monthy based on an indicator (e.g. absence rate, number of respiratory infections etc.);
- *case-based* surveillance: a collection of predefined data on specific cases reported by healthcare provider physicians who are obliged to reporting these (e.g. defined clinical symptoms and laboratory results) (infectious/communicable cases) and subsequent analysis of the epidemiological situation with regard to the given disease with the aim to plan intervention;
- *sentinel* surveillance: involes a pre-arranged, representative set of healthcare providers (sentinels, physicians looking after a certain percentage of the population) who are obliged to report certain diseases; it serves to help estimate the prevalence and incidence of common infectious diseases (influenza, STDs) in the general population;
- *syndrome-based* surveillance: entails collection of data on patients presenting with a pre-defined set of symptoms/clinical picture without laboratory tests, focusing only on the presence of symptoms. It allows for a rapid, sensitive collection of data, although not as specific as case-based surveillance, whereby, they collect data on etiologically clarified cases;
- *laboratory-based* surveillance: relies on the collection of information on the number of positive samples sent by healthcare institutions. It helps monitor change in the epidemiology of a given disease based on its incidence, regional occurrence, and specific characteristics of the pathogen (serotype, antibiotic-sensitivity etc.)
- *surveillance of disease-specific care providers*: relies on disease-specific data provided by instituions providing care for specific conditions and diseases e.g.TB-, STDs-,

HIV/AIDS;

*event-based surveillance* (EBS): Event-based surveillance (EBS) is defined as the organized collection, monitoring, assessment and interpretation of mainly unstructured ad hoc information regarding health events or risks, which may represent an acute risk to public health:

- unexpected accumulation, epidemic of a particular disease or syndrome and/or sudden change in disease characteristics (change in symptomatology, disease progession, increase in the number of severe cases, mortality, changes in the age-spectrum, changes in response to routine therapy, disease manifestation despite vaccination, changes in the pathogen);
- occurrence of a disease among animals that may be harmful to humans (*zoonosis*), contaminated food or drinking water, environmental pollution (chemicals, radiation);
- threat of exposure to harmful biological or chemical substances, or radiation, natural or man-made disasters.

Information on such events is easily accessible in the media, on internet websites, blogs, soical media sites etc. Data included in event-based reports should be confirmed prior to forwarding.

## Case definition

Explanation of concepts: The epidemiological situation regarding a particular disease or condition is best characterised by numbers: where? (area/region), *when*? (time, period), *among whom*? (e.g. age, sex, group/community) *what*? (disease/symptoms) *in what number? has it been* detected. The *case definition* made *for epidemiological purposes* is not necessarily the same as the *clinical case defintition,* as a disease may present with various clinical pictures and a combination of several different symptoms, therefore, the aim of clinicians if to identify atypical cases beside those manifesting with the typical symptomatology, in order to gain further knowledge about the disease in question, and develop treatment modalities. Epidemiology, however, aims at identifying and exploring a *standard group,* out of all cases of a particular disease, which may then be *uniformly described,* so that its prevalence values (in numbers) could be compared in terms of time, space and population and consequently, trends and sizes could be assessed and evaluated. Case definition *may vary* with time.

The question arises: how can we uniformly describe and define a single disease case i.e. to provide an answer to the What? question from among all the aspects pertaining to a given public health situation detailed above.

**Structure of a case definition**

A case definition usually contains *symptoms and/or epidemiological characteristics and/or laboratory test results.*

For example a patient is a confimred case of COVID-19 infection if ,

- they present with at least two *symptoms* out of the following: dry cough, fever, shortness of breath, sudden loss of smell or taste,

**AND**

- *as an epidemiological* prerequisite, during the latency period
  - they were in close contact with a with a COVID patient, OR
  - are residents of an institution where they treat a COVID patient, OR
  - have visited an area where COVID-19 has been spreading among the population

**AND**

  - their smear test *was positive for* SARS-CoV-2.

**Levels of case definition refer to the likelihood of a potential diagnosis:**

- *suspected*– the given disease is only slightly likely (e.g. only symptoms occur)
- *possible* – the given disease is moderately likely (e.g. symptoms and epidemiological features occur)
- *confirmed*– the given disease is high likely (e.g. based on symptoms and laboratory test results ).

**Sensitive and specific case definition**

Data collection may be described s*ensitiv*e: *Several cases may fulfil* this more general case definition, resulting in a larger database about the actual situation, which may however, be quite heterogenous in quality. For example, if a disease is only defined by its symptoms (syndrome-based surveillance, e.g. fever, cough), among the cases collected, there will be many patients suffering from different diseases but presenting the same symptoms. This is a fast method that does not require much resources and equipmen,t but cannot distinguish among diseases caused by various respiratory viruses (e.g. clinical surveillance of flu: flu-like illness)

On the other hand, if the data collection is more *specific* (e.g. besides symptoms, the detection of a give pathogen is also required e.g. SARS-CoV-2), there will be *a smaller number* of cases, the data collection process *will be slower* (e.g. sample taking and laboratory test - rapid test or PCR will be needed), consequently, this will be more costly and due to the equipment needed but will therefore, be more informative with regard to the particular disease.

Uniform data collection enables a *comparison* of data, which is important because, if our aim is to collect data about a certain disease or medical condition, we have to be able to compare these data with those collected by other *systems* (national, European, Global databases) to make sure that it is the same phenomenon we are dealing with.
Surveillance data need to allow for monitoring changes in the prevalence of a disease *through time*; using a uniform case definition makes it possible to convert data reflecting change in the epidemiology of a disease through time into numbers. However, in order to be able to evaluate data in the long term, it is also important to know how surveillance changed throughout the given period: what was the exact case definition used in that given period, what platform was used for the collection of information (paper-based, digital) and whether there were changes in the diagnostics of the disease in question etc.

Data have to be comparable in time and *space* as well in order to allow for the comparison of the epidemiological situation of different regions with each other.
There may be several case definitions for the same disease or medical condition depending on what the information is intended to be used for.

## Steps of surveillance

1. *Identification and documentation of the case* into a record system – first, it has to be examined whether the case meets the criteria of the given case definition, and what level evidence the diagnosis is based on (suspicious, likely, confirmed). The *time* of data collection also has to be registered (identification and recording has to be performed immediately upon receiving information about the case). *Exactness, precision and completeness of data* are crucial : all data required/rubrics should be completed if possible (e.g. reception of infectious case report forms by the National Professional Information System (OSZIR);
2. *reporting*: promptly, within the *time interval* defined by the surveillance (24 hours/ one week, etc.) the case has to be reported to the surveillance centre (on a general or disease-specific, unique examination sheet);
3. *analysis* (time, location, person) and *interpretation of data.* Data analysis has to be *continuous and regular* in order to detect significant changes of trends in time (e.g. weekly, monthly, annual analyses and reporting );
4. *detecting and confirmation of registered cases/events*: local investigation, further data collection (precise identification of disease onset, patient characteristics, predisposing factors, special exposure), the use of a more specific case definition, laboratory confirmation, identifying people at risk (those exposed and their contacts), (reported cases, case accumulation, investigation of an epidemic), preventive measures (education of those exposed and diagnosed patients, prophylaxis, vaccinations etc.) based

on the location and the cases;

5. *increased preparedness*: assessment of availability of staff with regard to their number, qualification, educational/training background and equipment needed (diagnostic equipment, vaccines, prophylaxis, care centers for the exposed cases, medication supplies etc.) ;
6. *response steps* (intervention planning, coordination steps, risk communication plan, community acceptance);
7. *risk communication:* positive feedback on reporting information, real-time exchange of information, recommendations, opinion sharing, informing those at risk;
8. *monitoring, assessment, supervision, revision and feedback* with the aim to develop the surveillance system, it provides assessment on efficacy of surveillance and response actions: timeliness, information quality , preparedness (levels, management of cases),and the implementation of all the above steps. Feedback to the health care staff that has sent the report with the aim to motivate their future cooperation and facilitate timely, quality reporting.

**Characteristics of surveillance in operation:**

- public health significance of the disease under surveillance,
- aims and operation of surveillance,
- resources required,
- evidence for…
  - usefulness,
  - characteristics of the system,
  - simplicity,
  - flexibility,
  - data quality,
  - acceptability,
  - sensitivity,
  - positive predictive value,
  - representativeness,
  - timeliness,
- stability.

**Planning surveillance**

1) *The scope of surveillance* (disease,health-care condition/phenomenon)
   - selection of a disease/ phenomenon that has a significant *public health impact* (high morbidity and/or mortality, considerable burden of disease on society),
   - … is effectively *preventable* by evidence-based public health measures
     - *via aspecific* measures (using hygienic interventions targeting the source of infection, source of transmission or suspected organism e.g. through isolation, disinfection, sterilisation within the transmission medium e.g. food, drinking water hygiene etc. ),
     - applying disease-*specific measures* (e.g. vaccination).
2) *Aims of surveillance*
   - *follow-up* of a phenomenon with known epidemiological characteristics and the evaluation of the efficacy of introduced measures,
     - *endemic disease*: the aim is to keep the occurrence of diseases below a certain level, to detect an epidemic, to detect accumulation of a disease, to contain, and in the long run, to eliminate disases/an epidemic,
     - *importable diseases,* a disease capable of spreading: the aim to alert the population, to stop the disease from spreading and to eliminate it from a given country;
   - *novel disease*, phenomenon: definition of fundamental epidemiological characteristics (*in time:* seasonality, cyclicity; *in space*:endemic areas; *regarding sexes*: female/male dominance; *regarding age*: high risk age groups, cohort: age-specific nature, lethality); identification of factors relating to exposure and risks, intervention planning etc.)
3) *Database design*
   - decision about the format (excel, etc.);
   - single disease/case/event, single record,

single line-identifier (ID identity (person/case/event identifier);
- application of grouping principles (time and areal units, age groups, sexes etc.) respecting national traditions and customs, and disease characteristics;
- determination of the features of records (data fields: onset, site/location, name, date of birth etc. , format – text/ numeric; principles: self-administered/min-max values/ dictionary);

### Analysis of surveillance data

1.) *Data cleaning*: filtering out duplicates, validation of registered data (quality check of data fields);
2.) checking *completeness* of data
   - have reports been received from all/ most data providers: identify lack of data, non-supplier institutions and the reasons;
   - completeness of all *fields* of a record – lack of data in a field, quantity check – a characterisitc of surveillance;
3.) checking timeliness of data ( time interval between the creation and receiving of data– min/max/average/optimal – determines the effectiveness of response to data, upon late receival of data, response and actions taken might lose acuity or may result in decreased efficacy– a vital element of surveillance;
4.) *calculation of summed values* (all cases/all deaths reported per area for a time period etc.);
5.) *generation of rates and indices*
   See chapter on the fundamentals of epidemiology.

## Disease accumulation and epidemics

### Explanation of concepts

#### Accumulation

Cumulative occurrence of an infectious disease, symptoms or a pathogen within a given time period or location that is more than *the usual or expected* number of cases.;

#### Epidemic

- refers to an often sudden, *significant increase* in the number of cases *above what is normally expected* or *over a certain threshold in* a given population or area during a period of time,
- at least *two cases that are epidemiologically associated* and the association can be proven by public health evidence;
- *Therefore, from a public health perspective, it is not the absolute value of case numbers that matters,* it can only be determined whether there has been an increase in the prevalence of a particular disease or phenomenon in the preceding days/weeks/or during same time periods of previous years, through comparison (if the disease shows seasonal variance).
- Disease accumulation is identified through analysing surveillance data obtained from functioning, ongoing surveillance systems. Actual data are always *compared to* those obtained *on previous days/weeks or corresponding seasons of previous years, and if increased* case numbers are detected an accumulation is confirmed. It is important to examine and *evaluate the extent of change*: minor change can be completely random but bigger changes (eg: above 5%)should be *taken into consideration*.
- Thereafter, the *cause of an accumulation* should be investigated:
- has there been a change in surveillance? (Has the reporting system, or the case definition changed? Have data providers received feedback and whether they have beed alerted? etc).
- has there been a change in laboratory diagnostics?,
- is the seeming increase in case numbers due to delayed reporting? etc.,
- or is there a real epidemiological reason in the background (potent infection source or medium).
- Upon detecting disease accumulation, the focus is not on individual cases, at this stage there is no information about their potential

epidemiological connection; only the rise in case numbers t is detected.

**Detecting an epidemic**

a.) The detection of an epidemic is not necessarily based on *reporting.*

b.) The presence of an epidemic can also be suspected if the analysis of *surveillance data* reveals that a part/the majortiy of cases indicating an accumulation seem to be *connected* not only *in time, but also in space* e.g. (patients are from the same town or community), and/or share other *characteristics* (e.g. belong to the same age-group).

c.) Connection between two individual cases can be established by their epidemiological examination. Two cases show an epidemiological connection:
- if one infected patient or symptomless individual was in contact with the other infected patient or symptomless individual during the latency period of the disease which may have resulted in transmitting the infection (links in the chain of infection) or,
- both have been in contact with the same infection source (*live* organism) or,
- both individuals have been exposed to the same agent (*environmental* exposition: water, food, aerosol etc.).

d.) Laboratory surveillance can also detect an epidemic by identifying a given sub-group of a certain pathogen *through a laboratory typing* (serotype, phage type, etc.)in some of the reported cases.

It is important to gain as much information as possible from *the reporting institution*/*or person*. Subsequent to thorough questioning, data should be precisely recorded and an official report *should be compiled*.

*Regarding the reporting person/institution, the following information should be provided*: name, occupation, status and involvement with respect to the epidemic, (e.g.head of institute, subordinate employee, infected person, and patient with diagnosed disease), contacts including a phone number the person can be contacted at.

*Regarding the epidemic*: location including exact adress , the community involved, the event, information about onset, number/potential patient size, place of care ( home/health care institution– severity, the site of the public health examination ), suspceted medium/media (contaminated food, airborn infection etc.) if known.

**Investigation of an epidemic**

1.) **Preparation for field work**

In public health, *time lost* cannot be made up for! With regard to dangers and extent of damage, the point at which a chain of infection is interrupted by implemeting measures has considerable impact e.g. at the second or fifth generation of patients. The investigation of a suspected epidemic is *an emergency task in public health*. Work does not end until the confirmation of an epidemic and its size are determined (whether additional help is required for the investigation, whether the epidemic exceeds county or district boundaries), irrespective of work hours, weekends or holidays.

Although social media platforms are potential sources of suspicious happenings and situations an epidemic *requires personal investigation*. *Availabilities* should be colllected of all persons possible who can provide information including those in leadership positions, employees, event partiipants, affected patients, exposed persons, acquintances etc. Although phone numbers or email addresses may suffice for immediate contacting, personal and *on site collection of information* may prove useful upon collecting personal or sensitve data - health/ medical information – which may also support credibility and trust.

*Superiors, county/national level authorities* should be notified about a suspected epidemic and also about planned investigations.

Information has to be collected about previous epidemiological situations with regard to the given *syndrome/disease* in the affected region, including social and societal im-

pact, public transport, institutional/organisational structures etc.

A *team of investigators* should be assigned and *travel* to the investigation site should be arranged (logistics). Furthermore: communication, sample taking equipment, questionnaires, record books, documents and stamps etc. should be arranged and provided.

2.) **Confirmation of an epidemic and clinical diagnosis**

The questions an epidemiologist wants answers for include: Who? Where? When?

An epidemic has to be investigated *immediately*!

The investigation starts with data collection. At first, an experienced professional has to *interview at least 6-8 diagnosed patients in great detail* about the disease, the circumstances of disease onset with the aim to find commonalities. The interviews should mainly be conducted through *open-ended* questions that allow patients to enlarge upon their own personal experience. Based on these interviews, a fixed, multi-question, detailed, so-called *hypothesis-generating survey* should be completed and subsequently analysed *to highlight similarities* of the cases which will also help identify at risk populations/groups.

Further information should be collected about the results of potential, *earlier* clinical and microbiological laboratory *examinations*, if they are still in progress, when to expect the results, where the results are, and if it is possible to arrange for more detailed examinations. **Case definition and search for further cases**

A new case definition has to be formulated for the epidemic that is different from the one used in surveillance: the new definition entails only cases of the current epidemic. Levels of this case definition (suspicious, likely, confirmed) indicate how likely it is, that the case belongs to the current epidemic. Case definitions change throughout an epidemic. Initially, it is more useful to apply a more general, *sensitive* definition in order to identify ma larger number of cases.

The next step is to detect potential patients (the more the patients identified, the easier it is to know how the disease spreads, and statistical analyses are also more accurate). Data can be collected from the patients themselves, or in the case of minors/elderly from parents/family members, kindergarten/school staff, GP, paediatric GP, hospital physician (treating physician, pathologist) or laboratory.

*The most important issues include*: disease onset, symptoms, body temperature, physician visit, medications prescribed, and whether these improved symptoms, whether the patient has a history chronic diseases, what medications they take for these, and the current status of the patient. Patients need to be warned about the importance of seeing a doctor with their symptoms.

Patient data are first collected in *a database which is later* converted into an expendable version to allow for novel aspects of the epidemic to be added.

*The next stage is the confirmation* of the surveillance of the given disease/syndrome i.e. the data source - e.g. GP, laboratory - data provider persons/institutions are informed about the epidemic and the importance of reporting cases. They should receive information about possible, specific, diagnositic measures, therapeutic interventions and institutions providing care. Search for cases is carried out by health care facilities (hospital, GP's surgeries, outpatient care units). Patients are divided into those exposed but symptomfree (controls) and, those sick with the disease based on systematically interviewing those at risk.

3.) **Identifying at risk populations**

Knowing the common points of the hypothesis-generating survey and characteristics of the most common infectious diseases (source of infection, characteristic ways of spreading) it becomes possible to outline

the development and spread of the epidemic, and thus, we can *determine the populations that have been potentially exposed and those at risk*.

In case of an endemic, a competent person has to be asked to make a list of all persons belonging to the community, which helps detemine the extent of the endemic in terms of *the number of people potentially exposed* at kindergartens, schools per group or class,; in factories, e.g. per shift and office workers separately.

*In the case of an airborne endemic,* usually the whole community is considered as potentially exposed*,* it may, however, happen that the disease manifests only in smaller groups, e.g. among people attending the same class. *In the case of a foodborne outbreak* those considered exposed will obviously include those that have consumed the food and the kitchen staff. The further spread of the pathogen *through contact* should continuously be monitored which may result in an increase in both the number of those exposed and that of those diagnosed during the investigation.

A shorter, hypothesis-testing questionnaire containing closed (yes/no) questions should be constructed from the long, hypothesis-generating surveycontaining open-ended questions which should then be administered to as many diagnosed patients and members of the exposed (at risk) population as possible. The results of this survey will form the basis of the statistical analysis which will then reveal evidence for sources of the infection and media of transmission.

4.) **Taking microbiological samples**

It is essential to know if *samples have already been taken* from the patient and whether there are results pending. If there have been no prior efforts at an a*etiological diagnosis*, no laboratory examination has been ordered, it is essential to take steps in this direction as soon as possible, as in public health “time lost cannot be made up for”, as with time passing it becomes more and more difficult to identify the pathogen from patient samples. Physicians, and in the case of an enteral illness, patients and their family members, should be provided *sample-taking kits/tools*, the most effective way is, when these are handed over during a public health examination subsequent to a short instruction on how they should take the sample, and how to complete the examination request form.

Samples should be collected from *10% of patients involved in an epidemic, at least 10 patients,* in order to be able to more securely identify the pathogen. No conclusion can be drawn from one positive sample, as the presence of one particular pathogen can arise from mere chance or can be a side result as well. Results thus received cannot be used for drawing aetiological conclusions. However, if several pathogens are identified by the laboratory it has to be decided which are responsible for the outbreak and which are mere side results.

If a *large number of samples* are expected to arrive at the laboratory, it is crucial to logistically facilitate fast and safe reception of these samples (*official/authorised delivery* as the investigation of an epidemic is an official duty). Laboratories always *have to be informed* about the potential arrival of samples and about *the examinations requested:* whether they will require culture media etc., so that the staff can prepare for the fast examination of samples. Laboratories may receive samples at weekends or holidays as well in the case of a large-scale epidemic buti n such cases the laboratory staff has to be alerted in due time.

If, based on the hypothesis, the disease does not only spread from human to human but and environmental vector (water, food,other media) plays a role in the spread of the disease, a *microbiological sampling should possibly be carried out* in collaboration with a co-authority. If a pathogen is identi-

fied from such a sample it is of confirmative value, however, lack of success does not necessarily prove that there is no common vector. (Only, there is no proof e.g. as it has been destroyed etc.).

5.) **Data analysis, making a hypothesis**
The first step is descriptive epidemiological analysis which determines the onset and location of the epidemic, the number of patients affected, their epidemiological features (age, sex distribution, most typical symptoms, severity of symptoms, laboratory results), and finally a *disease curve* is drawn. These are inevitable steps during the investigation of an epidemic. **Statistical analysis for the verification of a hypothesis**
First, the statistical survey is first planned (retrospective cohort, case-control study), calculations are made; results are evaluated to see if the statistical analyses support the initial hypothesis. If they do, it explains how the epidemic is spreading but if they do not, we will have to change the hypothesis and test it again until it is proven correct.

6.) **Planning and implementation of action**
Once the spread of an epidemic has been proven and understood, it can then be effectively targeted by designing and implementing *specific disease control measures.* These will need a supply and routine use of tools and equipment (e.g. disinfectant, vaccines, chemoprophylaxis, and training). The implementation of measures and actions should continuously be monitored. Meanwhile supervision of data is started through the analysis of verified *surveillance data,* which also reveals, whether implemented measures have been effective or not, and whether these have resulted in *a slow-down* of the epidemic. If the spread of the epidemic seems to be slowing down, the hypothesis was correct (indirect evidence), in case it is not, we need to reconsider the initial hypothesis and implement adequate, new measures and assess the effectiveness of these afterwards.

7.) **Final report**
The final report summarises the most important *facts* established throughout the investigation *(who? - where? - when?)*, it provides a description of the *pathogen* and the possible *mechanism* that led to the development of the epidemic (hypothesis) together with epidemiological, microbiological and statistical *evidence* in support of the previously mentioned facts. Final reports outline the measures implemented and provide information on their efficacy (whether the epidemic in question could be contained), together with further *recommendations* with regard to preventing similar situations *in the future*.

## Public health surveillance-systems in Hungary

### Reporting of infectious cases

**Aims**: Infectious case reporting involves the contiunous reporting of certain infectious/communicable diseases in order to assess and evaluate the effectiveness of previously introduced measures in case of an increased prevalence of these diseases or an epidemic, and thereby, to facilitate the implementation of novel action to contain a pending epidemic.
It is the first treating physician who is responsible for *reporting a suspected case* of a communicable disease that falls within the scope of those diseases that are to be reported within 24 hours of suspecting or diagnosisng such a disease, to the state health care authority the patient belongs to. The reporting physician or health care worker should notify the authorities through the National Professional Information System by submitting a Communicable disease report form *electronically*. Notifying physicians usually are GPs, paediatric GPs, or infectologists. Cases found post mortem are reported by the *physician making the declaration of death*. In inpatient institutions (hospitals, clinics), *hospital hygiene services and infection*

*control services* assist the work of other departments in this respect. It is often epidemiology nurses attending regular ward rounds at hospital departments who may actually call the attention of treating physicians to fulfil their duties in this respect.

Treating physicians are obliged *to report deaths that have occured due to the given infectious disease cases with complications and those of full recovery*.

The same applies to the reporting of cases where there are no documents of identification available, or cases reported for surveillance purposes (HIV/AIDS, STDs).

Public health officals enter information received from reporting health care workers into the infectious disease database subsequent to evaluation and validation of these data (A sub-system of the infectious case reporting system of the National Professional Information System, and HIV/AIDS, STDs sub-system).

### Case invesigation

Besides the clarification and confirmation of data, the aims of investigating a reported infectious/communicable disease also include the identification of:

- location where the patient is recovering, whether they are isolated (if isolation is required ),
- the potential source of infection (live organism),
- the potential trasmission medium/media, (water, food, aerosol, etc.) through which the pathogen may have entered the patient's body,
- contact tracing (contact search, isolation/ observation),
- people who may have been infected through contact with the patient (contact search, isolation/ observation),
- level of protection at the time the patient possibly got infected (vaccinated status, previous infection etc.)
- persons the patient may have infected, those that may possibly be in the latency period and individuals who may need official observation ,
- whether the case was single/sporadic or accumulated as part of an epidemic (case evaluation).
- There are *general* (enteral, airborne etc.) and *disease-specific* forms used in the investigation process (electronic forms are available from: the National Professional Information System). These forms contribute towards a uniform description of cases and circumstances, and thereby, facilitate professional, high-quality reporting nationwide.

*Processing* of information and data collected through these forms (analysis of a single database) may call attention to previously unidentified disease accumulation and can thus raise the suspicion of an ongoing epidemic. Such information may facilitate the identification of a common pathogen or medium and aid their subsequent elemination (e.g. a particular food available nationwide).

### Special surveillance of infectious/communicable diseases with additional significance

Besides data included in the infectious disease reports, it may be indicated to collect detailed further clinical or epidemiological information for rapid reporting purposes toward the National Public Health Centre. Infomation gained help design and implement adequate prevention measures at local, regional and a national levels.

### Mortality surveillance

Upon investigating death declaration certificates issued in the disctrict/area, *the aim is to* :

- *with regard to diseases that fall under reporting obligation:* comparing these data with the public health database provides a more accurate picture of actual cases, related deaths i.e. more exact morbidity, mortaliy and lethality numbers – the real disease burden of the disease upon the society.
- *with regard to diseases that do not fall under reporting obligation:* monitoring change in mortality data may highlight whether disease-specific surveillance is to be initiated to improve the control of diseases becoming more prevalent in the future.

- *with regard to non-communicable diseases:* the aim is to be able to determine the importance of causes of death within the population, including rates, trends with the further aim to plan, and implement primary, secondary and tertiary screening and prevention programmes.

Surveillance of *mortality data from infectious diseases,* which may seem belated, can however, provide importent information. The diagnosis should be made by the physician who declares *the cause of death*; data should be entered in row 25.I.d on the death certificate. In such cases, it is of crucial importance to review data and to obtain laboratory and epidemiological confirmation of the cause. When the clinical picture raised the suspicion of an infectious disease which was also confirmed by laboratory findings but the disease identified *was not the cause of death,* the *disease should be entered as a concomittant disease* onto the death certificate in row 25.II.

## Reporting an epidemic

*Aims*: to identify the source, medium/media and thus to prevent further spread of a current epidemic and to prevent the development of future epidemics. *In the case of multiple endemics occurring at the same time and location, caused by the same pathogen* (e.g. household epidemic) further investigation is required to identify the common infectious source and transmission to ensure adequate prevention strategies are implemented.

Anyone can report a disease to public health authorities who notices or learns about there being an accumulation of cases. Reporting is possible via letter, phone, or e-mail. Public health officials are obliged to receive all reports and need to register and to file them according to rules and regulations into the system of the concerning public health authority. There is a function within the infectious case reporting sub-system of the National Professional Information System which provides the possibility for health care workers to submit direct reports electrically to the database of the public health authority about a disease outbreak they detected, let it be household, communal or regional. Upon submitting a report the notifying person or health care worker gains access to information about the disease on the National Professional Information System website.

All reports are to be taken seriously even if they seem trivial or unimportant as they may actually turn out to be threatening the health, or life of people. Information may happen to come from the media. Even in such cases a public health investigation should be commenced.

If all the information point towards a real disease outbreak, after starting an investigation, event data should be registered into the public health database, subsequently, updated and finally closed after the outbreak is over.

If there is no outbreak detected, this fact has to entered into the file as well, but it remains important to pay close attention to incoming infectious case reports, as they may actually help towards identifying a disease.

### Enteral-surveillance

*Aims*: Epidemiological evaluation of a pathogen (species, subtype, or other characteristics based on other typing methods), characteristics of the resulting epidemic, investigation of household, community or regional outbreaks, identification of the transmission medium/media (e.g.: water, food) in order to introduce action towards removing the given medium from public access, implementing stricter and more comprehensive measures to prevent further spread of the disease in the community.

An in-depth epidemiological analysis, mainly allows for the study of a given *syndrome* (gastroenteritis), its prevalence, changes in time and space, and differences with regard to different age groups (if local health care workers report suspected cases, not only those confirmed by laboratory results). Even at this stage, the aim is to investigate disease accumulation in time, space and age group.

Matching data received from *microbiological surveillance*, especially those that are greatly detailed (species of a pathogen, serotype, phage type, PFGE-type, and type of sequence) with the cases enable a more precise selection and grouping of

data based on the description of the pathogen according to e.g. sero-type, phage type etc. Based on previously mentioned data, monthly analyses are performed which detail the incidence and prevalence of the disease *according to the pathogen/ causing agent*, including:

- disease location (districts/areas/region),
- typical patient characteristics according to *demographic indices* (sex, age group) and,
- epidemiologic features (sporadic/epidemic).

Furthermore, data are collected about new *outbreaks* per month, per pathogen, (household, community, regional), onset of outbreaks, location, exact pathogen (type), the number of people exposed, the number of patients diagnosed, the means of transmission, the medium and all evidence confirming the above.

If there is a considerable increase in the number of 'sporadic' cases caused by the same species/ type pathogen through several months it may indicate the presence of an *undetected, ongoing, regional epidemic,* as in this case, individual cases do not occur within the same community, and there is no other epidemiological connection among them, apart from contact with/exposure to the same pathogen, which is unknown at the time cases have been reported and investigated (therefore: the outbreak qualifies as 'sporadic'). In such situations public health officials need to *repeatedly check* the report forms of these cases and search for similarities which may point towards exposure to the same pathogen (e.g. participation on the same event, ordering from the same supplier etc.) If, based on all the above, there is no suspected medium, *knowing the pathogen, patients who have been identified as sporadic cases need to be surveyed again* with targeted questions in *the direction of potential, typical transmission media (e.g. drinking water, bath water, foods, prepared meals, etc.)***.** New information gained through repeated survey may increase the chances of investigating a previously unidentified local/regional epidemic.

**Flu surveillance**

Influenza virus can cause more disease and death cases within a few weeks than all other communicable diseases falling under the obligation of reporting together, in a year. Consequently, special preparedness is required prior to flu seasons.
Flu-surveillance in Hungary is based on three pillars:

- *Collection of morbidity* data – syndrome-based clinical surveillance,
- *Collection of microbiological* data (Respiratory pathogen monitor),
- Monitoring absence from communities.

Flu–surveillance is ordered by the chief medical officer, data collection from the 40th week of the given calendar year until the 20th week of the following year. Apparently, preparation for the flu season starts earlier so that all roles, functions and tasks are properly allocated by week 40.

Collection of morbidity (clinical) data
It is essential that data collection be performed using a uniform *case definition*. There is a predetermined set/number of symptoms that indicate the diagnosis of a flu-like illness e.g.sudden onset fever, weakness, muscle pains, headache, dry cough and other symptoms. (In the elderly, it is often not easy to diagnose flu, especially at the onset of the flu season, as many older patients may not develop fever, and the only symptom they may present with is confusion.) Given the fact that approx. 200 pathogens can cause flu-like symptoms, the clinical picture may often not suffice for the identification of the exact aetiological cause. Nonetheless, the trend of the incidence of flu-like illnesses can clearly indicate the onset and the end of a flu epidemic.
General practice services are key to collecting morbidity data. It is district health officers who invite general practitioners from their administrative region whose practices represent districts from geographical and population statistics aspects (sentinel –physicians). In practice, this means that these should include adult, paediatric and mixed GP's practices providing care for 20% of the population of the given district in total, representing the population in terms of *age group* as well. Data

providers should be selected so that there are GP practices from *cities, towns, large and small villages* as well. General practitioners thus chosen are obliged to send reports every Monday on the number of flu-like cases they diagnosed including the age distribution of patients.

**Collection of microbiological data (Respiratory Disease Monitoring)**

As an aetiological diagnosis cannot be established based on flu-like symptoms, it is of great importance to know which pathogens circulate in the immediate or wider environment during the flu season.

It is the Chief medical officer who determines the number of GPs who can take part in Respiratory Disease Monitoring in a given year. From among GPs, paediatric GP s or those running mixed practices, who take part in clinical data collection, it is approximately *100 who can participate in sample taking*. GPs chosen receive detailed instructions about the number of patients, presenting at at an early stage of the illness, they can take non-invasive airway samples from on a weekly basis. Samples taken should be collected and transported by a delivery service to the assigned laboratory.

Physicans taking the samples and public health authorities receive results from the laboratories electronically. Patients will usually have recovered by the time they receive their lab results. *On a community level*, however, *it is essential to know* which pathogens are present in the district/ region as this information may have significant prognostic value.

**Monitoring absences from communities**

As respiratory pathogens spread very easily in communities, monitoring absence from communities may provide useful public health information. It is the disctrict health officer who invites directors of various communities (nurseries, kindergartens, schools) to submit a report *upon noticing an absence above 30%.* Upon receiving a report, public health autorities initiate an epidemiological investigation with the aim to collect data on the epidemic, to facilitate microbiological examinations (to clarify the aetiology of the disease outbreak via airway samples), and *to introduce public health measures,* and thus, to prevent the further spread of the disease.

Flu-surveillance means a more than half-year long process, which is often complicated by an increased awareness and attention among the population.

**Duties of public health officers during surveillance**

*Upon receiving the circular sent by the Chief medical officer,* the initial task is to appoint participants of the three-pillar surveillance system. Timely and exact allocation of information, *cooperation* among staff and *meeting deadlines* are crucial.

*The second task involves supervising clinical data collection*: it needs to be checked hours *prior to deadlines* who did and who did not supply data and also the quality of data that have been submitted. This allows contacting those who have not yet sent data, as it is of considerable importance to have a representative database for the region. Shortness of time pressure is often responsible for missing data. Another typical issue, upon *not applying the case definition precisely enough,* is that patients with upper respiratory symptoms are entered into the database, who only had a simple cold, and flu was not even suspected. On such occasions reporting health care workers should be made aware of adherence to the case defintion.

*The third task involves* supervising whether the physician appointed to take part in sample- taking is sending airway samples regularly. If they fail to do so, they need to be contacted. *Reasons for* lack of samples may include: lack of patients in the given practice who would meet case definition criteria, e.g. due to the epidemic being mild, or the physician being overburdened, or having simply forgotten to report cases.

*The fourth task is to construct a database* that enables the continuous monitoring and analysis of events and the drawing of graphs which can graphically demostrate the epidemiological situation of a given region for each reporting physician, district and age-groups. *By creating indices* (flu-like illness-index = % of patients presenting

with flu-like symptoms, patients diagnosed with flu-like illness in each age-group) important information can be gained. Monitoring *absence from communities* is a good predictor of an epidemic, therefore, it needs to be included in the analysis.
Data collected and analysed throughout the years, using the same method, may reveal *trends*; however, these trends only provide information with regard to a given district/region. To see where we stand globally, it is incidence data that need to be calculated and compared between areal units (district, county, regional, national). Such comparison reveals the position of a given disctrict/region compared to the national average or other areal units during an outbreak.
*The fifth task* is the evaluation of LKM data, which will idenityl the pathogen circulating in the given area. It is important to know, from an epidemiological perspective, for example, if it is Influenza Type A or Type B, as Type A is usually responsible for larger epidemics, while Type B more commonly causes local outbrakes. On the other hand, virus typing allows for the *comparison of the circulating virus with strains contained by vaccines*. If there is a considerable overlap/similarity, we can expect lower number of infections in the vaccinated population. On the contrary, a big difference between the virus strains may foreshadow a more severe outbrake.
*The sixth task involves compiling a regional report* based on the national, weekly report format which should contain an evaluation of the current situation and recommendations for prevention. Sending this report to health care providers aims to provide feedback and may serve as a form of training and intends to encourage reporting efforts.
*Task seven is the organisation of vaccination schemes.* It is primarily the duty of GPs to inform eligible patients and to organise, manage and document vaccinations. The logistics of allocating free vaccines is the tasks of public health services. Vaccinating physicians receive a list of eligible individuals, who are mostly patients receiving treatment for chronic conditions, the elderly or certain occupation groups. The vaccination programme should be organised so that vulnerable patients are protected by the time the flu outbreak is expected to intensify i.e. vaccinations can begin in the second half of October.

### Hepatitis-surveillance

*Aims:* Syndrome-based surveillance helps monitor individual patients who belong to an aetiologically varied and epidemiologically very different communicable disease group with the aim to decrease the prevalence of that particular disease in the country, and consequently, to reduce the related disease burden by identifying factors responsible for the spread and also to introduce of preventive measures.

**Hepatitis A**

Resulting from public health measures introduced during the past decades (water and food hygiene regulations), and the general improvement of public health conditions (settlement, and personal hygiene), there has been a considerable increase in the number of people vulnerable to faeco-oral infections. Consequently, single contaminated individuals may trigger large-scale outbrakes in our country. Therefore, close monitoring is required including the incidence of aetiologically verified cases to detect disease accumulation as early as possible. This underlines the significance of individual public health investigations which search for the source of single incidences and potential members/links of the infectious chain.

**Hepatitis B**

Acute hepatitis B used to be the most prevalent among health care workers. As a response, a mandatory vaccination programme was introduced among students of institutions offering training in fields of health care within a timeframe which allows for the development of an adequate level of protection prior to the start of practice sessions. Health care workers have to be vaccinated against Hepatitis B which they also have to prove by a certificate. Maintaining public health security has been greatly supported by the introduction of a ompulsory vaccination programme through school campaigns, in 1999, among teenagers.

**Hepatitis C**

10-20% of cases manifest in the form of an acute illness; 70-80% result in chronic infection with aspecific symptomatology; liver involvement is most commonly revealed by specific examinations. Hepatitis C leads to liver cirrhosis in about 20% of the cases which may later result in the development of primary hepatocellular carcinoma. Although there are no primary prevention methods to date, and there is no vaccination against the indfection, beside secondary prevention modalities (blood product safety, search for hidden morbidity) there has been significant advancement in therapeutic methods resulting in a curability rate of 95% of the cases.

**Acute flaccid paralysis – AFP surveillance**

*Aims:* The WHO initiated the acute flaccid paralysis (AFP programme) for the verification of polio-free status at a global scale. The programme is a syndrome-based surveillance. It was started to ensure that *all cases of flaccid muscle paralysis of non-traumatic and non-mailgnant origin* among children under 15 years of age, who fulfil the clinical, diagnostic criteria of acute, anterior poliomyelitis, are reported. The aim of this surveillance programme is to verify and document that a given clinical presentation is not due to an infection with the wild polio virus.

As a result of age-specific, mandatory vaccinations, there have been no acute, anterior poliomyelitis cases detected in Hungary for decades. Upon changes in the public health situation it is important, therefore, to perform epidemiological and *laboratory investigations* of every case that meets criteria included in the case definiton of the syndrome. On suspicion of the diagnosis of acute, anterior poliomyelitis, the noticing physician should immediately report the case to the public health department of the competent regional authority or to the county public health department.

An investigation has to commence *immediately*. As the epidemiological situation in Hungary has been safe for decades, it is mainly *diseases brought into the country from abroad we have to look for. Urgency* is crucial in today's world of global travel and movement of populations.

In this case, the investigation initiated involves collection of personal data, clinical and epidemiological data, and information on vaccination status, the commencement of *laboratory examinations* in due course of time and the establishment of a preliminary diagnosis

Preferably as soon as possible, but within 14 days from the onset of paralysis, 2 stool tests are to be taken, one day apart, and 2 further sterile samples 14 days apart with any anticoagulant therapy suspended.The samples should be sent to the assigned reference laboratory of the National Public Health Centre accredited annually by the WHO.

Missed stool testing or delayed sending of samples threatens the efficacy and success of *isolating the virus* and significantly reduces the chances of correct diagnosis. Absence of *paired serology testing* makes it more difficult to prove whether, despite a negative stool test, symptoms could still have been caused by an immunological reaction triggered by the polio virus.

*Rapid reporting forms* have to be submitted to the National Public Health Centre by a given deadline, where, beside investigations, officials can initiate seeking international legal aid (to search for sources of infection and/or international search for exposed individuals), and reports are submitted to international surveillance centres as well.

48 hours from receiving information on a suspected case of AFP, the public health officer assigned to investigate the case has to submit a detailed report by completing the *"Epidemiology report form on an individual case of acute flaccid paralysis"* to the public health department of the National Public Health Centre. The aim of this reprort is to inform the superior authority on data that have been revealed and thus to assist the initiation of action.

The results of a *60-day clinical follow-up* of a reported case of AFP close the case. It is often not easy to establish the diagnosis, i.e. to actually identify the cause in the background of the peripheral paralysis, several consultations may be required among physicians involved and patient documentation has to be submitted to an expert commitee. S*urveillance* is *sensitive enough* if the number of reported and investigated, suspicious

cases of AFP among the population, under age 15, is *1:100 000/year*.

**Invasive meningococcal disease- – meningococcus-surveillance**

*Aims:* to initiate near real-time chemoprophylaxis of people in potential contact with the patient who are at risk (individual) and furthermore, to collect data rapidly and in detail about changes in the *epidemiology* of the disease (e.g. sero-group change, appearance or spread of a clone causing a more serious disease) with the aim to be able to plan and implement effective large-scale preventive measures (risk communication, campaign targeting population groups etc.).

Infectious meningococcus is seasonal infectious disease mostly occurring in winter and spring. Infants and small children are more susceptible. During other seasons, approximately 5% of the population is affected, in winter and spring prevalence of carriers may reach 80%. Despite the widespread availability of intensive patient care, the disease has a *very rapid progress and is associated with high morbidity.* Survivors often suffer from long-term complications caused by nervous system damage, or various thrombotic vascular obstructions that significantly impact quality of life.

*The concomittant presence of other respiratory viruses may compicate diagnosis* (infections caused by such viruses can help Neisseria meningitidis bacterium to penetrate through the mucosa, consequently, a concommitant disease may occur). The fact that the disease is *relatively rare* may also hinder timely diagnosis. A GP for example, may not have met a single case during 50 years of practice. Therefore, public health officials are highly recommended to call up a meeting for GPs praticing in their area, prior to the beginning of winter, to inform them about the epidemilogical situation of the area. Such meetings should also facilitate building stronger contact and may provide information update. Regular *contact with health care institutions providing inpatient care* is also crucial, as these institutions report most of the cases.

Apparently, cases of menigococcus infection require an urgent public health investigation. The investigation should primarily aim at gathering a minimal amount of data that would suffice for the completion and submission of the *"Rapid report form of Invasive meningococcal disease"*. The rapid report should be submitted to the National Public Health Centre by an official from a district authority of the public health department. As disease progress is very rapid only a few hours are left for initiating treatment, therefore, *laboratory tests should be commenced* as soon as possible, as it is a further goal of surveillance to evaluate the situation based on the exact aetiology and to initiate adequate action (e.g.vaccination).

A *public health investigation* should be started in all cases. It is often a very difficult task emotionally to visit a family who has lost their child or to talk to a community the person belonged to but the identification of those who would need chemoprophylaxis is *an urgent task.* Cooperation with the disctrict GP or paediatric GP may be needed as parenteral prophylaxis can often secure the best protection.

The document entitled "*Public health report form of Invasive meningococcal disease*" has to be submitted to the Public Health Department of the National Public Health Centre within two weeks subsequent to the closing of the case and receiving reports on progress and outcomes. This report should include information on the patient, the disease, details of a local investigation performed, results of the search for exposed individuals and the prophylaxis therapy applied.

Vaccines are currently available at public pharmacies against Neisseria meningitidis; they can be administered from two months of age. Vaccines include ones that are effective against serotype Neisseria meningitis B which is the most common in Europe. The current epidemiological situation of A N. meningitidis does not indicate making vaccinations mandatory. Nevertheless, we should remember that protection of an individual serves the interest of the community.

**Legionellosis-surveillance**

*Aims:* Identification of sources of infection/ exposure (contaminated air-conditioners, a perlators,

humidifiers etc.) that may lead to the development of the disease. The epidemiological importance of legionellosis was primarily raised by cases ofvulnerable, immune-compromised patients, the aging of populations, the development of a built environment and the increased mobility of populations that lead to an increased number of outbrakes.

*Travel-associated legionellosis has to be reported with urgency* upon receiving a report about a case so that epidemiological data can be forwarded to the "Travel-associated legionnaires' disease surveillance system" database of the WHO. (Travel criteria: within 2-10 days prior to their travel, the patient spent at least one night outside his/her home, at a rented accommodation, within their country of residence or abroad. Getting infected while staying at relatives' or friends' homes does not have to be reported toward European surveillance authorities.)

**Lyssa-surveillance**

*Aims:* In case of a danger of a 100% lethal infection, the cooperation among human and animal health experts has to be established rapidly and effectively inorder to protect the person or persons in danger from getting infected. -

The elimination of lyssa is a global human and animal health concern. There have been no Humane lyssa cases detected of since 1994, in Hungary. This does not mean however, that Hungary is free of lyssa as there have not been any three consecutive years without rhabies being diagnosed from animal samples (recently, most commonly from bats). Elimination of lyssa is hard to achieve as there are several countries in the region, where rhabies in endemic among wild animals, and domesticated animals living in the wild can also cross borders easily; swimming across rivers is no obstacle consequently, *the infection entering the country from abroad is a constant threat.*

Reporting cases of injury that may have resulted in getting infected with lyssa is an emergency as the long incubation period limits intervention time. It is also an urgent task to *inform animal health authorities (also in writing). The observation of* the animal responsible for causing the injury that may have resulted in getting infected with lyssa is to be organised by the *authorised veterinary physician,* as it may have legal consequences. It needs to ensured that *the physician attending to the case has infromed the authorised veterinary* responsible for the area in which the injury happened as this may not always happen. Deadlines should also be strictly kept including whether the report on the health status of the animal submitted by the veterinary has been received. All the above stress the need for a close collaboration with the autorised veterinary.

Furthermore, it is crucial to investigate and *record all details about the circumstances of the injury promptly,* as these data may serve as the basis of the indication of vaccination. The main aspect that has to be considered is whether the animal causing the injury can be identified and found. If yes, a vaccination is not necessary as the 14-day observation of the animal will clearly show whether it had rhabies (it dies) or not (it survives). Thus it is an important task to collaborate with the owner of the animal during the observation (make sure the animal cannot roam away, or get out fromits enclosure e.g. to avoid the animal getting run over by a vehicle, that it is properly fed and taken care of, under all weather conditions) so that it would survive the observation period.

The authorised veterinary has to be immediately informed about *any change in the animal's condition or its death.* It is forbidden *to get rid of the corpse* (to bury or to burn it) as a *laboratory examination is mandatory*.

If the injured person *has to be vaccinated*, there is nothing to wait for, the vaccination has to be organised. As the vaccinating physician is most often the GP, paediatric GP or a GP running a mixed practice, and they are most likely to be using the vaccine approx. once every two-three years it is recommended to inform them about the required *vaccination intervals*. It is also necessary to get to know whether the injured has received a rhabies vaccine in the previous five years as this could modify the number of vaccines needed. The vaccination protocol has to be followed as described in the methodological letter. Exact dates cannot be delayed even if it happens to be on a weekend or

during a public holiday. It may, however, happen even with all efforts taken, that the person to be vaccinated comes late; in such cases an expert of the National Public Health Centre is to be consulted.

*Lactating dairy cows suspected of being infected with lyssa* are a special challenge. In such cases the National Public Health Centre is to be contacted to discuss diagnostics and prevention.

Rules and regulations allow persons, who are at risk of a lyssa infection (injured, exposed through milk), to reject post-exposure prophylaxis. Nonetheless, all efforts have to be taken to prevent such cases. If such a situation arises, it has to be well documented that the subject involved has clearly understood and is fully aware of the consequences such conduct may lead to.

### HIV/AIDS-surveillance

*Aims:* To follow-up the epidemiological situation of the infection/disease on the basis of an anonymous surveillance system, and thereby, to notice changes to them and to identify affected population groups with the aim to implement viable, target measures for the prevention (risk communication, screening, contact tracing) and therapy (establishing new treatment centres, expand the availability of medications).

The identification of an HIV infection and the diagnosis of AIDS require a verified *HIV-positive result.* The reporting physician is the doctor who makes the diagnosis. Patient care is carried out in designated centres. Prevention may include local, regional or national programmes and initiatives. It is of pivotal importance *to improve health education/awareness and diagnostic awareness together with* the education of the population about the disease. *Target groups* are mainly adolescents and older younger populations who are the most vulnerable *not only due to their sexual behaviour but also due to other forms of risk behaviour*.

*HIV-screening* may be open or anonymous. Tests can be taken free of charge at screening stations without a referral. Those who prefer an anonymous screening do not have to give their personal identification, only a password with which they can take the test and receive the results.

*There is councelling* p*rior to the blood test and after receiving the results.* This is a discussion between the patient and a counsellor with the counsellor giving information and advice with the aim of prevention. During councelling the patient receives information about various forms of *risk behaviour* that may lead to getting infected with HIV infection and also about possible prevention and risk-lowering measures. This prior consultation may help build trust which might prove very useful in the situation when the patient *is informed about the results*. It is very important for the patient to accept the help offered in the form of a *professional network of specialists*. Although there is no cure for either HIV, or AIDS, *individualised treatment* can help achieve a good quality of life and maintain the ability to work for patients in the long run as well, turning the infection/disease into a chronic illness.

Apart from those mentioned above, the *timely and precise completion and submission* of other case-specific epidemiological report forms are also of great importance but these shall not be listed here due to lack of space.

## Vaccination surveillance

### About vaccines

As pandemics have become less and less frequent during the past century populations have lost their fears about infectious/communicable diseases. In the 1980s, the view that, with the the advancement of antiobiotics and the spread of their use, infectious diseases no longer pose a problem for healthcare became widely shared among the general population, and health policy makers as well, and as a result, infectious disease wards and bed numbers have started to be considerably reduced or eventually closed. How much we are at mercy of pathogens have been clearly demonstrated by the 2009 H1N1/09 flu-pandemic, the 2012 MERS-CoV pandemic and the way more massive SARS-CoV-2 pandemic, starting at the end of 2019. Pandemics paralysed tourism, cultural life and caused severe long-lasting damage to economies worldwide, they have had serious negative impact on

education not to mention long-term consequences on people's health that is still to be researched. The most recent Covid pandemic challenged health care systems at various levels, even though non-communicable diseases were managed 'only' at the emergency level by AE units resulting in tremendous harm and considerable excess mortality. The situation was further aggravated by *those that denied the existence* of the virus, and their regular appearance on social media. This was a global, not only a typical Hungarian phenomenon. The fact that some of these people actually got infected, ended receiving intensive care treatment and were trying to send messages from behind an oxygen mask admitting that they had been wrong or the fact that some of them died, did not change the situation considerably.

The pandemic has provided numerous scientific evidence for the efficacy of *aspecific protection measures* in preventing the spread of infection (e.g. personal and food hygiene, social distancing, isolation, wearing masks covering the nose and mouth etc.).

It gave a glimpse of hope that SARS-CoV-2 vaccines were developed relatively fast, within about a year. Naturally, however, *anti-vaccine propaganda* appeared soon after. Undermining the belief and trust of the population in nature and science has resulted in a very high number of preventable deaths and health impairment. Many people refused the offered disease-specific vaccination protocols, despite the fact, that this is the most potent way of fighting a pandemic at a global scale. Aspecific protective measures cannot replace specific protection modalities and it is the combination of the two that has beenproven to be the most effective.

## The role of vaccines in controlling epidemics, basic principles and concepts

Nowadays, mathematics and informatics are basic prerequisits for the successful work of epidemiologists. Mathematical modelling of and calculations made from data collected by epidemiologists can effectively support decision-making in health care and can further contribute to the implementation of adequate action in due time.

The level of vaccination required for containing an epidemic or pandemic depends on the basic reproduction rate: $R_o$.

According to the definition, $R_o$ = average number of secondary cases in a totally susceptible population who got infected via contact with the same person. That is, if one infected person spreads the infection onto two susceptible persons, it is described as: $R_o = 2/1 = 2$. Consequently, if

- $R_o > 1$, the pathogen spreads effectively and an epidemic develops as the number of infected cases is less than that of people/the next generation who got infected via contact with them.
- If $R_o = 1$, the pathogen is circulating in the given area; it is endemic, thus we need to expect the occurrence of infected cases but at numbers that are likely to remain roughly the same through generations
- If $R_o < 1$, the epidemic is in remission as the number of newly infected cases is less than the number of those spreading the infection.

Using the basic reproduction rate, the mass mmunization threshold can be calculated.

The equation used: mass mmunization threshold = $1 - 1/R_o$, the number has to be multiplied by 100- to get the result in %. The equation shows that the higher the $R_o$, the smaller the number which is to be subtracted from 1, that is the higher the mass mmunization level that has to be achieved to ensure that the disease goes into remission and will not develop into an epidemic. To achieve this aim the mmunization level will by all means have to exceed the calculated value.

So far, it has been mostly mathematics and numbers but life is unfortunately, much more complicated. First and foremost, there is no vaccine with 100% *effectiveness*, that is, we cannot expect all people who have received the vaccines to show antigen numbers that reach *the protective level.* Several factors may modify, and thus, mmunizat the response of an individual to a vaccine (the antigen producing ability) for example, age, health status, chronic diseases, medication therapies etc. These may have an impact on antigen titers, persistence, and the need of booster shoots.

There are always people for whom the vaccination

is contraindicated i.e people who would normally be offered the vaccination but due to e.g. an acute disease causing fever they cannot be vaccinated, and there are individuals for whom a given vaccine is contraindicated for a lifetime due to e.g. a previous anaphylactic reaction against the vaccine or one of its components. These people will remain susceptible for either a period of time or lifelong and thus may contribute to the circulation of the pathogen. If these people are only sporadically present in populations we may rely on aspecifc protection measures or the development of herd immunity.

Themmunization of vaccination schemes can best be measured by continuous, short- and long-term monitoring of the incidence and prevalence of the disease at local and national levels.

Unfortunately, there will always be people who are against vaccines or a particular vaccine irrespective of the amount of fees they were made to pay repetitively for refusing vaccinations. These people will remain susceptible, and apparently, may get infected and infect others.

In Hungary, the situation with regard to vaccination levels is favourable and safe in many diseases, as most parents accept the vaccination protocols offered and the custom of getting children vaccinated is passed down from generation to generation.

Table 1.: Basic reproduction rate ($R_0$) and mass mmunization threshold (%) of some infectious diseases

| Infection | $R_0$ | Mass immunisation threshold (%) |
|---|---|---|
| Diphteria | 6-7 | 85 |
| Pertussis | 12-17 | 92-94 |
| Morbilli | 12-18 | 83-94 |
| Mumps | 4-7 | 75-86 |
| Rubella | 6-7 | 83-85 |
| Polio | 5-7 | 80-86 |

Source: CDC

Rules and regulations on the tasks and duties with regard to vaccinations are discussed in detail by the health law and the related executive regulations; specific areal duties are outlined by regulation 18/1998. (VI.3.) NM. An appendix entitled 'Vaccination methodology letter' is considered the 'Bible' for the given year.

## The structure of the vaccination methodology letter is as follows

*I.* *Introduction*: summary of the legal background.

*II.* *Contraindications for vaccines*: There are several diseases and conditions which do not contraindicate getting vaccines (e.g. alimentary egg white allergy, controlled epilepsy).

*III.* *Vaccinations for special conditions to be considered individually*: in general, these are conditions or diseases that interfere with the immune status. A special group is vaccines for neonates. A hypothesis/practice that was prevalent for years was to wait with vaccinations until the baby or infant catches up with his/her peers. Today, on the contrary, it is believed that it is these very small babies who are the most vulnerable and therefore, when they reach the age they should be vaccinated so that they are at least protected from diseases against which there are vaccines available.

*IV.* *Vaccinations of children who are foreign nationals* (Examination of the vaccination booklet/certificates will be discussed later.)

- Vaccination diary
- Mandatory age-specific vaccinations
- Continuous vaccinations
- Campaign vaccinations
- Time intervals between vaccinations
- Minimum time intervals between the administration of human blood and/or plasma products or vaccines containing live viruses

- Recommended time intervals between vaccinations and surgical interventions
- Administering missed, mandatory, age-specific vaccinations
- Recording and reporting about mandatory, age-specific vaccinations

This document sets the fundamental principles for vaccination schemes for the whole year. The present chapter contains useful information about sources that could be used as reference when answerning questions received through phonecalls.

It can be generally stated that human blood and/or plasma products are being gradually removed from the market to prevent transmittable prion diseases (e.g.TSE: Creutzfeldt-Jakob-disease, variant Creutzfeldt-Jakob-disease).

*V.* *Mandatory vaccinations given at risk of disease*: Special attention is given to the care and treatment of injuries that are suspicious of for a lyssa infection, and tasks relating to the care of babies born to HBsAg-mothers are going to be outlined in detail as well.

*VI.* *Voluntary, preventive vaccinations free-of-charge*: Atypical example is the influenza vaccine which has already been mentioned in connection with flu -surveillance.

*VII.* *Work-specifc vaccinations:* This chapter may prove useful for those working in occupational health services.

*VIII.* *Travel vaccinations:* The chapter gives a summary of non-free vaccinations that are administered by GPs or at national vaccination centers. Consult the WHO pages for valid, up-to-date information about vaccines required prior to travel to given regions of the world. At present, the vaccine against yellow fever is mandatory in endemic regions. A yellow-coloured vaccination certificate is issued by vaccination centers upon a person receiving the vaccine. Neither the certificate, nor the vaccine is publicly available in order to prevent forgery and thereby, to maintain public health safety.

*IX.* *Supply, storage and allocation of vaccines*: This chapter details logistics of free-of-charge vaccines provided through the public health system. Tasks with regard to situations that fall outside the scope of strict storage regulations are also outlined here.

*X.* *Ensuring conditions required for the adequate management, recording and reporting of vaccinations*: The part on Adverse events after vaccination-surveillance provides further details on the topic.

*XI.* *Vaccination with other vaccines*: This chapter elaborates on prescription vaccinations authorised by the National Institute of Pharmacy and Nutrition, registered by the European Union, that are available in public pharmacies.

## Local vaccination management

1.) A function of the "*Vaccination letter*" (appendix to VML): in larger settlements where there are several paediatric GPs providing care for the population, and where the area belonging to the paediatric GP, and that of the health visitor, do not overlap. A GP can be in contact with more health visitors and a health visitor can be in contact with more GPs. Health visitors' service areas are fixed as they encompass given streets of a settlement. Health visitors contact expecting mothers and their family is during the pregnancy, and keep a record on the pregnancy and the baby and takes newborn babies into account when ordering the first (at eage 3 months) and further vaccinations. Health visitors keep record of only those vaccinations which they and the paediatric GP jointly administered. Health visitors however, should receive information about vaccines administered by other paediatric GPs through a vaccination report. Therefore, it is a very important task of health visitors to keep up-to-date records on vaccinations received by babies and infants belonging to their service area. These vaccination databases are to be regularly updated, and upon noticing missing records or delayed administration of vaccinations, they should

contact the parents and the paediatric GP as soon as possible.

In smaller settlements, mixed-practice GPs provide care for under 18 populations.

2.) *Reporting on missed vaccinations*. In case of a delay in vaccinations that exceed a period of two months, the appointed physician sends a report using the designated report form to the district health visitor who will than register this report into the National Professional Information System. Based on the information and data provided in the report, an official at the public health department of the disrict authority shall investigate the case and may initiate an official procedure.

3.) *Report on age-specific vaccinations administered through school campaigns*: school health visitors are obliged to submit reports on vaccinations administered to the public health department of the disrict authority by a given deadline.

4.) *Tasks and duties with regard to the care of HBsAg-positive pregnant women and their newborn.*

Hepatitis A and B viruses are oncogene viruses. During pregnancy care, besides other types of test, expectant mothers have to undergo *HBsAg* screening by the 12th week of gestation. Mandatory vaccination against Hepatitis B was introduced to schools in 1999, with eigth graders receiving the vaccine, as a result of which, HBsAg positivity has decreased significantly among women of child-bearing age. Nonetheless, alertness has to be maintained as vaccines do not give 100% protection, and unfortunately, there still are many disadvantaged women living under difficult circumstances who might not be aware of being sero-positive.

Authorised laboratories, which carry out the screening examinations, report positive cases to the respective main public health department of the county government office, which shall then forward it to the responsible district authority. The physician requesting the examination is also informed about the result. The task is, therefore, twofold: the district health visitor records the screening result into the pregnancy record book; the public health officer performs the case-specific investigation. The aim of this investigation is to check whether there are family members of the expectant mother who may have been exposed to the virus through contact with her. Those at risk of exposure should be offered a free vaccination protocol. The vaccination protocol should be carried out with the collaboration of the GP. A public health investigation should be repeated with every other pregnancy of the patient as there may occur changes in their circumstances that can only be noticed when they are visited at their home.

The subsequent task is to make sure the institute where the woman is going to deliver the child receives both the active and the passive vaccine one month prior to the due date of delivery. The label on the vaccine should bear the name of the mother and her health insurance number. It is recommended to consult the head physician of the neonatal unit to make sure it is the newborn who the vaccine is rightfully meant for, who finally receives it. Vaccines are to administered within 12 hours after delivery; this is appointment 0. Then the vaccination protocol is to be continued one and six months after receving the first shot. The successful delivery of the vaccination protocol requires the joint effort and cooperation of the public health officer, the paediatric GP and the health visitor. Vaccination documentation and reports have to be completed and submitted as defined by rules and regulations by given deadlines.

Check-up examinations have to be performed at age 15 months, to ensure prevention was successful, including a HBsAg test and an antigen test. Lab results will indicate if there are steps to be taken which including recommended treatment or the need of booster shots, if the antigen titer against HBV is low. As the time between the birth

and the check-up is more than a year, public health officers are recommended to write a reminder note in their diaries about these vaccinations. They are also responsible to arrange check-up examinations, and if needed, to make sure vaccinating physicians receive vaccines in time. It is also among the duties of public health officers to check vaccination reports.

In cases where pregancy care does not go according to regulations, and *the mother's HBsAg-status is not known,* it is vital to perform a test as soon as possible. The test can be done at the laboratory of the institute where the delivery is going to take place. In such cases the newborn should receive an anti-HBV vaccine within 12 hours after birth. If lab results of the mother come back positve for HBsAg an HBV immunoglobulin should be administered as soon as possible or maximum one week after birth. If the administration of an immunoglobulin is not indicated and more than one week has passed since birth; the newborn should receive fast-acting, active immunisation.

Persons in the immediate environment of the expectant HBsAg-positive mother should also undergo public health screening and upon testing positive, they should be encouraged to undergo vaccination.

If prior to giving birth, the mother tests negative for a HBsAg, active immunisation of the newborn should, nonetheless, be initiated and completed, meaning that babies receive the second and third vaccines as described above. In these cases, however, passive immunisation and serology test at age 15 months are not indicated.

## Common tasks with regard to vaccines

*a) The vaccine*

The fact that vaccines *are precious commodities* has already been emphasized. What does this actually mean? It does not necessarily refer to vaccine development and production, as these fall under the competence of the National Institute of Pharmacy and Nutrition. However, after a vaccine leaves the factory every company, instituion or person who has anything to do with it bears a responsibility. This is because the goal is *not only vaccination, but immunisation!* – a prerequisite for achieving this goal is to ensure the vaccine maintaining its quality thoughout transportation, i.e. from leaving being produced until they are administered.

*b) Ordering vaccines*

At present, local officers are responsible for ensuring and controlling economical vaccination allocation. Vaccines are ordered by vaccinating physicians in collaboration with health visitors and assistants. Ordering is done online with adequate IT support. Orders are supervised and reviewed by a member of the distric public health department of the loca government authority. For the successful completion of this task they need to know the exact number of persons who are elligible for vaccination, the amount of vaccine previously allocated and used; vaccination movement between physicians and further data e.g. loss of vaccines due to inadequate refrigeration.

The next level of supervision is the main public health department of the county government office. The work carried out here aims at distributing currently available stocks first. It is highly recommended to withstay the pressure suggesting there should be 'spare' vaccines kept in refrigerators locally. *Close supervision of vaccine-management is crucial.*

It is a fundamental principle to try to avoid having to discarde vaccines due to carelessness or lack of organisation. How can this be achieved? It is recommended not to draw up mulitple doses of vaccines in advance. Contraindications may occur and vaccines that have already been drawn into a syringe cannot be used up later, which may lead to having to discard them. Vaccines may have to be discarded for several reasons even upon taking adequate precautions: e.g. upon removing air from syringe a small amount

of vaccine may be lost, or the ampoulle may be dropped by mistake etc. As all drops of a vaccine are precious they should be handled with utmost care and precaution.

c) *Vaccine Storage*

Vaccines should be stored according to instructions. It is a generally applicable rule that vaccines should not be kept in refrigerator door bins as the temperatures there may not be adequate for vaccination storage. Vaccines should be kept grouped according to expiry date and those with the nearest expiry date should be dispensed and used first. It is recommended to keep track of vaccines dispensed from and put into refrigerators. It is not possible to utilise the whole refrigerator volume, as boxes containing the vaccines *are not allowed to touch the wall,* as they may absord moisture and lead to the freezing and consequent damage of vaccines. It is important to provide proper circulation of cold air in storage spaces and shelves and thus to ensure the same temperature everywhere in the refrigerator. All refrigerators used for storing vaccines or medicines should have a *digital display unit* which can give information on the actual storage temperature without having to open the door. Storage temperatures *need to be entered into a diary* including the year, month, day, hour, minute, the name and signature of the supervising person. Storage temperatures should be checked at least twice daily, upon starting and finishing work.

Distant monitoring of refridgerators through the internet is considerably safer. Such systems have the advantages of continuously monitoring and registering adjusted parameters, and upon registering change, they alert the person who can then intervene and has the right and means to enter the building (entry code, keys to main door etc), on public holidays as well. It is recommended to keep records including these colleagues and such events.

Vaccine storage rooms should be protected from entry by any unauthorised persons as for example if someone unplugs a refrigerator and forgets to plug it back by mistake it can lead to the refrigerator melting which could then lead to having to discard all vaccines.

Besides vaccines, only medicines are allowed to be stored in the same refrigerator. Under no condition can human samples (e.g. blood, stool or liquor), food stuffs (foods, drinks) or anything else be stored together with vaccines. It is essenetial for refrigerators to be in proper technical condition. Upon purchasing a new refrigerator, it is the new machine that has to be used for the storage of vaccines and the other can then be used for other purposes. (e.g. storing dangerous medical waste that is delivered away after 48 hours).

It is essentail to make sure the storage space of refrigerators is disinfected regularly. This procedure is best performed at times when there are fewer vaccines stored, meanwhile, adequate storage temperatures are continuously provided.

d) *Transportation of vaccines*

Nowadays, vaccines are delivered by professional delivery services in closed refrigerated containers that have a temperature monitor. The organisation of delivery is centralised. Upon opening the container boxes for the first time, all information is available on temperatures from the moment of preparing the vaccines for transportation. This should be documented upon handing over and receiving the boxes.

The delivery can be made to the address of the county or district auhority or that of the vaccinating physician. If this is not possible, it has to be ensured that vaccines are delivered and then refridgerated through the shortest way possible.

e) *Preparation of vaccines*

The fact that vaccines are precious and should therefore be used with utmost care, inorder to avoid wasting them, has alread been mentioned. There are a few further aspects that need to be considered. It is im-

ortant to observe the adequate hand hygiene protocol and to provide a work environment which can guarantee that vaccines do not get contaminated. The first step is choosing the vaccine, followed by checking the validity date of both the vaccine and the dilutant, in case a dilutant is needed. Ampoulles should be disinfected, a separte needle is to be used for drawing up the vaccine; the needle has to be of adequate length and diameter. It is imortant to make sure the needle is tightly attached to the syringe to make sure it will not move due to the pressur occurring upon injecting the vaccine. Until the vaccine is actually injected, the cap should be kept on the needle. Empty ampoulles should be placed next to the vaccines drawn up so that the vaccinating physician can check them and thereby avoid vaccination accidents.

*f) Administration of vaccines*

According to law, vaccines can only be administered by physicians but there may occur other circumstances. Hand hyigiene is of pivotal importance. Disinfecting the injection area should be done by spraying one puff of disinfectant on the skin surface where the needle is going to penetrate. It is forbidden to remove/wipe off the disinfectant or to touch the area with the fingers even with protective gloves on. Time should be given for the disinfectant to abdorb and evaporate as presribed by instructions on the bottle. There is no need for further puffs, the vaccine can then be injected through the needle. Upon wiping the disinfectant off or not waiting long enough for the disinfectant to evaporate it may either not take proper effect or the remnants of the liquid may damage the vaccine.

*g) Documenting vaccinations*

What data should be documented? When is a vaccine legally valid?

To ensure the legal validity of a vaccination, the following information/data need to be provided:

- Personal details of the *vaccinated person* (name, date of birth, address, health insurance number).
- *Name of the vaccinating physician*, their signature, address of the vaccination centre, copy of the physician's registered stamp.
- Name of the vaccine, manufacturing number, the date of the administration of the vaccine, the administration route, tthe body part and side of administration.

The vaccinating physician has to record these data onto the medical database system used and provide paper-based documentation about the vaccination to the vaccinated person (e.g. via documenting the vaccination into the vaccination booklet). District health visitors, school health visitors, and in some cases, employers (work-specific vaccinations) are under an obligation to record vaccinations.

Health care provider institutions (vaccination centres) have to keep health care records for 30 years.

*h) Vaccination of foreign nationals*

It is Chapter IV of Government Decree VML which details rules and regulations regarding the vaccination of children who are foreign nationals. The same rules and regulations apply for people settling in Hungary from other countries. Upon making a vaccination plan, only those vaccines can be taken into consideration which have been documented as described above. It is of utmost importance to check and verify that the given documentation truly belongs to the person in question. A vaccine which is not documented 'does not exist'.

Upon making a specific vaccination plan for an individual the following has to be considered: age, previous vaccinations, and dates of previous vaccinations. This has to be compared with the Hungarian vaccination requirements and a Hungarian vaccination diary which will then give a clear picture about the vaccines the child still needs to receive and the age by which these vaccines will have to or should be administered. In

case of delayed or missed vaccinations the administration is officially ordered.

**Benefits of the Hungarian vaccination system**

- *It is free-of -charge*
  The term 'free' should be avoided; vaccinations are given free-of-charge for elligible persons. Vaccines and all the tools and equipment needed for their administration have considerable costs, not to speak of the salaries payed for employers, the maintenance of the infrastructure required and additional expenses (water, electricity, cleaning, disinfection, collection, transportation and elimination of dangerous waste etc.). We should be aware of the fact that public health safety costs the government billions covered by the income from taxpayers contributions. This is why economical vaccination management is crucial.
- *Available for all*
  All Hungarian children have equal rights to vaccinations irrespective of the finantial situation of their families. If a child missed a vaccine, and there is no contraindication, the vaccine should be administered as soon as possible upon the child reaching the required age.
- *Time of vaccinations is optimised*
  Vaccination time – the age at which a child should receive the vaccine – is determined by the pathogen. The aim, here, is to make sure the child is protected by the time morbidity in the given age-group reaches a peak during the natural course of an infection with the pathogen, i.e. immunity will have developed, at least 14 days have passed since the day of receiving basic immunisation.
  It is not the parent who should decide when their child is vaccinated. The most common misconception is that a child's immune system is not strong enough, and thus, the vaccination should be delayed. Pathogens infect unprotected organisms immediately.
- *Use of safe vaccinations*
  Only authorised vaccines are used; refridgeration chains are monitored and documented to ensure we do not only vaccinate but immunise the population.
- *It is a dynamic system*
  Depending on the actual situation, the system can be modified if necessary: novel vaccines can be introduced, vaccination times can be modified, certain vaccines can be discontinued for the proir aim to contain and eliminate diseases… etc.

## Surveillance of mandatory vaccinations by authorities

**Monitoring vaccination coverage**

High *vaccination coverage* and *adequate vaccination schedules* are the major prerequisits for maintaning public health safety. Surveillance is supported by an up-to-date IT system.

Vaccination reports on *conitnuous vaccinations* have to be submitted by a certain deadline every month for each district. The reason(s) for vaccinations delayed for more than two months also have to be reported.

Analyses of data received thereby have to be carried out every month for each district, county and at country level too, highlighting tendencies and possible need for intervention. The same applies for school vaccination campaigns.

**Continuous vaccination monitoring**

Basic documents are printed for every district after monthly deadlines. First, acute monthly reports on continuous vaccinations are reviewed; these monthly reports should contain the *number of people to be vaccinated* and *those who have been vaccinated* for each type of vaccine.

This allows us to calculate the monthly *vaccination coverage* = (number of people who have been vaccinated / number of people to be vaccinated) x 100 (to receive the rate in %). Evaluation of these data is very easy, for example, if all babies born in a given months undergo vaccination it gives a 100% vaccination coverage. The *number of people to be vaccinated* may vary in a given district due to moveg in or moving away from the area belonging to the competent district authority. Apparently, in case of missed vaccinations, vaccination

coverage is less than 100%. Vaccination coverage is an important and useful index despite the fact, that it does not give information on the progress of vaccination coverage.

Why is it important to have information on the *progress of vaccination coverage*? The answer is: for the sake of maintaining public health safety, as the prior goal is to make sure every elligible child/ person is vaccinated as soon as possible when reaching the designated age, so that the vaccine can activate immune cells, and thereby, can contribute toward reducing at risk populations.

The table below presents data on progress of vaccination coverage for a given month. Columns are to be analysed *from bottom up*. The last entry in the column showing year /month of birth refers to the actual month. The next column gives the age of the infant in full months.

For example: *if a child was born on 21.03.2015, he/she child* is two months old on 21.05.2015 but on 22.05.2015 he/she has passed age of two months that is, they become elligible for the vaccine to be received at two month of age on this day.

Before the evaluation of the progress of vaccination coverage it should be considered that the last row in all the columns refers to the actual month, which means, that this is not a completed month, and therefore, these data cannot be evaluated. Data in *the two rows* immediately above show vaccination coverage in the two months subsequent to the month the child is due to receive the vaccination. Vaccination progress is considered to be quite good if the rate reaches at least *98%*. If it is reached only by the third month, it is regarded to be *good*, if only by month four, it is considered *average*, if the required rate is reached by month five, it is termed as *prolonged*, if it requires half a year or longer it is *significantly prolonged.*

Should monthly reports reveal a worsening tendency or lack or improvement of an unfavourable situation, an investigation into the causes should be initiated, and both district- and county-level authorities should plan and implement adequate preventive measures to avoid more serious potential problems.

Comparing the above two tables, we can identify children who remained unvaccinated even after two months of becoming elligible for each vaccine type. To give an example: if the progress of vaccination coverage goes beyond 98% in two consecutive months we need to check the number of children to be vaccinated from the report (DPT4, HIB4, IPV4 = 4 persons). In the table on "*Missed vaccines* " the persons/children can be identified by entering the date of birth and the vaccination type, of course ,only if such data have been registered and reported. The next task is to thoroughly investigate the *underlying cause*. For the clarification of the situation the public health officer working on the case may have to contact the child's paediatric GP, health visitor, or vaccination consellor. It is very important to remember that the main duty of public health officers is to help maintain public health safety and not to succumb to parental pressure or pressure from other persons to issue a certificate of exemption from vaccination on unvalid, illegal grounds.

Upon organising *school campaigns,* it is important to provide new dates within the given time period for missed vaccination appointments to ensure as high vaccination coverage as possible. *Vaccination covergage* should then be assessed and evaluated based on the reports submitted. Upon detecting a deteriorating tendency, school directors, and parents should be contacted with the aim to find an adequate solution for the problem of missed vaccines.

It is also important to devote some words to the *vaccination of adults*. The new corona virus (COVID) epidemic has been a great example; in other cases it is mainly the devotion of GPS to the cause of facilitating vaccinations that is the most determinant factor in this respect. It would be very important to ensure that the elderly are vaccinated at least against pathogens there are vaccines for (e.g. Streptococcus pneumoniae), as they are considered immune-supressed due to their age, and are more likely to use health care service, as they often suffer from a variety of chronic illnesses.

Table 2. REPORT
On the state of continuous vaccination at the end of March 2015., Public Health Department of the District Authority at the area of the County Government Office

| Date of birth year/ month | To be vacci-nated | vaccinated | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | BCG | DPT1 | HIB1 | IPV1 | DPT2 | HIB2 | IPV2 | DPT3 | HIB3 | IPV3 | MMR | DPT4 | HIB4 | IPV4 |
| ... | | | | | | | | | | | | | | | |
| 2013/05 | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 |
| 2013/06 | 78 | 78 | 78 | 78 | 78 | 78 | 78 | 78 | 78 | 78 | 78 | 78 | 74 | 74 | 74 |
| **Total** | **422** | **422** | **422** | **422** | **422** | **421** | **421** | **421** | **421** | **421** | **421** | **421** | **417** | **417** | **417** |
| 2013/07 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 60 | 60 | 60 |
| 2013/08 | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 90 | 73 | 73 | 73 |
| 2013/09 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 72 | 70 | 50 | 50 | 50 |
| 2013/10 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 73 | 69 | 0 | 0 | 0 |
| 2013/11 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 72 | 0 | 0 | 0 |
| 2013/12 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 64 | 48 | 0 | 0 | 0 |
| **Total** | **446** | **446** | **446** | **446** | **446** | **446** | **446** | **446** | **446** | **446** | **446** | **413** | **183** | **183** | **183** |
| 2014/01 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 0 | 0 | 0 | 0 |
| 2014/02 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 0 | 0 | 0 | 0 |
| 2014/03 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 0 | 0 | 0 | 0 |
| 2014/04 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 63 | 0 | 0 | 0 | 0 |
| 2014/05 | 58 | 58 | 58 | 58 | 58 | 58 | 58 | 58 | 58 | 58 | 58 | 0 | 0 | 0 | 0 |
| 2014/06 | 77 | 77 | 77 | 77 | 77 | 76 | 76 | 76 | 76 | 76 | 76 | 0 | 0 | 0 | 0 |
| **Total** | **395** | **395** | **395** | **395** | **395** | **394** | **394** | **394** | **394** | **394** | **394** | **0** | **0** | **0** | **0** |
| 2014/07 | 85 | 85 | 85 | 85 | 85 | 85 | 85 | 85 | 85 | 85 | 85 | 0 | 0 | 0 | 0 |
| 2014/08 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 90 | 0 | 0 | 0 | 0 |
| 2014/09 | 81 | 81 | 81 | 81 | 81 | 81 | 81 | 81 | 78 | 78 | 78 | 0 | 0 | 0 | 0 |
| 2014/10 | 74 | 74 | 74 | 74 | 74 | 74 | 74 | 74 | 67 | 67 | 67 | 0 | 0 | 0 | 0 |
| 2014/11 | 87 | 87 | 87 | 87 | 87 | 82 | 82 | 82 | 40 | 40 | 40 | 0 | 0 | 0 | 0 |
| 2014/12 | 88 | 88 | 86 | 86 | 86 | 57 | 57 | 57 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | **505** | **505** | **503** | **503** | **503** | **469** | **469** | **469** | **360** | **360** | **360** | **0** | **0** | **0** | **0** |
| 2015/01 | 81 | 79 | 63 | 63 | 63 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2015/02 | 66 | 66 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2015/03 | 83 | 79 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | **230** | **224** | **63** | **63** | **63** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |

Table 3.: Progress of Vaccination coverage for March 2015.
Public Health Department of the District Authority at the area of the County Government Office

| Date of birth year / months | Full months | BCG | DPT1 | HIB1 | IPV1 | DPT2 | HIB2 | IPV2 | DPT3 | HIB3 | IPV3 | MMR | DPT4 | HIB4 | IPV4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ... | | | | | | | | | | | | | | | |
| 2013/05 | 22 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% |
| 2013/06 | 21 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 94,9% | 94,9% | 94,9% |
| 2013/07 | 20 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 93,8% | 93,8% | 93,8% |
| 2013/08 | 19 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 80,2% | 80,2% | 80,2% |
| 2013/09 | 18 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 98,9% | 69,4% | 69,4% | 69,4% |
| 2013/10 | 17 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 97,2% | | | |
| 2013/11 | 16 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 94,5% | | | |
| 2013/12 | 15 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 87,8% | | | |
| 2014/01 | 14 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 75,0% | | | |
| 2014/02 | 13 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | | | | |
| 2014/03 | 12 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | | | | |
| 2014/04 | 11 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | | | | |
| 2014/05 | 10 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | | | | |
| 2014/06 | 9 | 100,0% | 100,0% | 100,0% | 100,0% | 98,7% | 98,7% | 98,7% | 98,7% | 98,7% | 98,7% | | | | |
| 2014/07 | 8 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | | | | |
| 2014/08 | 7 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | | | | |
| 2014/09 | 6 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 96,3% | 96,3% | 96,3% | | | | |
| 2014/10 | 5 | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 100,0% | 90,5% | 90,5% | 90,5% | | | | |
| 2014/11 | 4 | 100,0% | 100,0% | 100,0% | 100,0% | 94,3% | 94,3% | 94,3% | 46,0% | 46,0% | 46,0% | | | | |
| 2014/12 | 3 | 100,0% | 97,7% | 97,7% | 97,7% | 64,8% | 64,8% | 64,8% | | | | | | | |
| 2015/01 | 2 | 97,5% | 77,8% | 77,8% | 77,8% | | | | | | | | | | |
| 2015/02 | 1 | 100,0% | | | | | | | | | | | | | |
| 2015/03 | 0 | 95,2% | | | | | | | | | | | | | |

## Adverse events reported after vaccination

Aims: to conclude the quality control process of a vaccine. Unfortunately, the significance of this type of surveillance has not yet gained sufficient appreciation among physicians either.

*According to the defintion:* adverse events subsequent to vaccination include any unwanted event (symptom, death) upon the occurrence/noticing of which it may be suspected (or more precisely, it cannot be excluded) that it is associated with the vaccination.

*Who can report an adverse event after a vaccination?* The noticing person (physician, pharmacist, the vaccinated person, and an acquaintance) or the vaccinating physician can report adverse events to the public health department of the district/regional authority and to the National Institute of

Pharmacy and Nutrition.
*What is the form of reporting*? Reporting can be done on-line or by completing documents in paper. Regarding details consult the corresponding methodological letter. [National Public Health Center of Hungary: Protocol on the management of adverse events after vaccinations (2019.)]
The investigation is to be performed by the public health department of the district govenment authority. Data collection is based on a uniform questionnaire. The public health officer responsible for the investigation of the adverse event has to collect all data available which requires *contacting the vaccinated person* or their family members, the vaccinating physician and to *carry out an investigation at the premises*. Besides personal interviews, it is also necessary to check *medical documents* including information on *vaccination storage and administration.* Their responsibilites, however, do not include the investigation of eligibility or that of contraindications; these are physicians'competencies.

The report then has to be forwarded to a gremium of experts for processing and evaluation.

## Sero-epidemiological examinations

Sero-epidemiological examinations may reveal valuable information on the health status of the population, for example, the level of protection or vulnerability of a given segment of the population against a particular disease. Such examinations can well monitor *the effectiveness of vaccinations and the persistance of antibodies at population level*, for all age-groups. Highlighting *regional inequalities* can help identify disadvantaged population groups, which may benefit from rapid interventions or may point toward the need to initiate targeted campaigns. Sero-epidemiological examinations may forecast recurrence of infectious diseases (e.g. diphteria), or the possibility of a repeated outbreak based on detected increase in the number of susceptible individuals amids a favourable epidemic situation (e.g. Hepatitis A outbreak registered in 2006 in a Somogy, Baranya and Tolna counties; 2021 small outbreaks of COVID-19 in 2021 in areas of low vaccination coverage).
A disadvantage of sero-epidemiological examinations is that they are resource intensive. Information on available resources is required in order to be able to plan examinations, to supply the tests and to prepare the laboratories. Samples examined have to be *representative of the population in terms of the age, sex, geographical and urban environment (city, town, village).*
By observing corresponding data protection laws and regulations, sample collection is relatively easy as hundreds of diagnostic blood tests are performed daily. Serologicial tests can continue by using the *blood remaining* after diagnostic tests. A difficulty arising here is, how the samples get to the labs which carry out the serological examinations in processable condition. Laboratory work requires highly trained professional staff and considerable finantial resources.

## Microbiological and laboratory examinations, taking of samples

Although several symptom-based surveillance systems work without laboratory tests, these mainly serve acute emergeny situations. Epidemiological phenomena (disease accumulations, outbreaks, epidemics, pandemics) require targeted and effective measures which necessitate the analysis of data on diseases of verified aetiology.
The Appendix to Government Decree (18/1998. (VI.3.) issued by the Ministry of Public Health is to be consulted upon questions regarding *type of samples to be taken*, and *type of examinations to be performed,* to ensure the most precise *epidemiogical diagnosis*. The Hunagrian health care system has a *multi-level system of laboratories* for this purpose.

*Clinical laboratories* can dentify clinical parameters of an infection (aspecific immune response to an infection: RBC sedimentation rate, quality blood count, CRP). The network of *microbiological laboratories* (local, regional, reference values) can, on the one hand, identify *pathogens* with continuously advancing diagnostic technologies,

at increasing levels of detail, and on the other hand, can detect *specific-immune responses* of the organism to a given pathogen (serological tests). Clinicians are guided by local protocols that describe which samples to take, for what purpose and where to send them for laboratory testing and evaluation. Logistics is provided by the system of clinical institutions in the case of individual samples, but if the samples are to be evaluated for epidemiological diagnostic purposes logistics is managed by the public health authorities system.
Precise completion of the *examination request form* is crucial, as besides personal details of the patient, this form includes public health data as well (onset of the disease, clinical symptoms, whether the case belongs to an epidemic), health data, regular medications taken, and vaccination status (if relevant). Based on the clinical picture and the medical history, clinicians often do not order further examinations *post mortem*. *However,* on suspicion of a reportable infectious disease this is not acceptable *from an epidemiological perspective for several reasons*. As for example, sepsis can be caused by several different pathogens. Liquor samples should be taken as soon as possible, in post mortem cases prior to transportation of the deceased to the pathology in order to avoid the samples getting infected.
It is a basic requirement that the examination request form and the sample container should be *identifiable*, because if there cannot be matched up, the laboratory will not be able to perform the tests. Test samples should be wrapped by making sure request forms do not get contaminated. Inadequate data supply may cause financing issues for the lab. By completing the examination request form properly, the laboratory staff may be able to perform further tests so that they can identify the given pathogen more precisely. Samples should be delivered to the labs as fast as possible and should, subsequently, be stored as required by the sample type (microbiologists can provide help).
*Rapid tests* are useful in identifying viruses, or for example, in the differential diagnostics of capsulated bacteria as they can be performed within minutes or hours. At present, there are rapid test for the identification of e.g. the rota virus, SARS-Cov-2, N. meningitidis, H. influenzae, E. coli, Penumococcus and Streptococcus. Further tests including chemical, microbiological and other specific typing tests may also be carried out. Liquor *culture* is fundamental as besides confirming the diagnosis, its results may indicate *antibiotic resistance* and further in-depth characteristics of the pathogen may also be revealed. If the patient received an antibiotic prior to the liquor biopsy, a PCR test can help identify the bacterium/bacteria.

Nowadays, test results are available online. There are rules and regulations which determine which test results should microbiological laboratories make available for the microbiological sub-system of the National Professional Database System. This is the basis the collaboration between the public health services system and *microbiological surveillance* is built upon.

## Hand hygiene

Public health officers do not take part in patient care directly, but through their involvement in different types epidemiological work, e.g. case investigations, supervising hospital/institution hygiene, official investigations etc., they may have to enter patient zones or patient care zones.
*Patient zone:* is defined as surfaces/items in his/her sorroundings, also including the patient, that are temporarily and exclusively dedicated to him/her i.e. all items touched directly or indirectly by the patient or touched by health care workers while delivering care.
*Patient care zone:* all areas of the hospital where direct patient care is delivered and where patient diagnostic or treatment procedures are performed.
*Basic prerequisites of hand hygiene*:

- Healthy, intact skin
- Short, clean nails (accepted length:≤ 0,5 cm over finger tip)
- Artificial nails or wearing nail varnish is forbidden!
- Jewellery is forbidden!

**Hand hygiene indications:**
Using an alcoholic disinfectant is more effective

than washing the hands with soap or disinfectant soap. Washing the hands with soap is only recommended if the hands are apparently contaminated.

Public health officials are required to precisely know all 5 indications of the WHO handhygiene guidelines, according to which hands should be disinfected:

1. prior to direct contact with patients;
2. prior to aseptic interventions;
3. subsequent to contact with body fluids;
4. subsequent to direct contact with patients;
5. subsequent to any contact with items touched directly or indirectly by the patient.

**Use of gloves is mandatory:**

1. Steril gloves prior to surgical interventions.
2. Examination gloves prior to potential contamination with an infectious material.
3. Examination gloves prior to contact with isolated patients.
4. Gloves worn on the hand are just as potent sources of infection as unprotected, bare hands. It is important to disinfect the hands before putting on and after removing medical gloves with an alcohol-contaning disinfectant.

Alcoholic hand disinfectants should be continuously available for office workers as well.

## Surveillance of General practitioners

GPs are key players in maintaining public health safety. Contact with primary care physicians is a fundamental interest of the public health services system.Databases managed by district authorities may prove valuable *indicators* of the public health work conducted by local GPS. Routinely reported data - reported infectious cases, number of outbreaks, laboratory tests perfomed per case, vaccinations, annual reports on the management of health waste data etc. – can help identify GPs who need to be visited first.

It is advisable to *schedule visits* based on a prior plan. Pre-announced surveillance visits to GPs best be scheduled for early summer or early autumn as flu seasons will likely have ended and catarrhal diseases with with fever may have not started yet. Summer is not an optimal period as many physicians may be on holiday and those who work are likely to be substituting colleagues. Surveillance visits may be *ordered by* the Chief medical officer or might be prompted by an *acute outbreak*.

Surveillance of GPs' surgeries reveals hygienic conditions, tidiness and cleanliness of the place. With the help of the nurse/assisstant, the public health officer conducting the surveillance may find unreported cases by checking laboratory results from the medical database or by coming across recorded diagnosed cases. Meanwhile, the chief medical officer can discuss about the GP's reporting routine, may call attention to adherence to guidelines and the importance of documenting cases. Vaccination storage, disinfection and sterilisation practices, cleaning and waste management and disposal (dangerous, communal) should also be in focus during such visits.

Surveillance visits also provide an opportunity for allocating information, highlighting problems, searching for solutions and trust-building among physicians and other health care workers. A surveillance report is finally compiled, which may result in further action.

## Authority surveillance, authority documentation

During their work, public health officers represent the public health authority of the country. Therefore, they are required to be always well-prepared professionally, and to behave and dress accordingly. As their work almost always entails writing a report they are advised to have a general sample report form at hand containing the *essential parts* (file number, site or surveillance, start and finish times, personal details of persons present, their availabilities, legal staus, subject, the ground upon which the surveillance was ordered, letter sent to the person under surveillance detailing his/her rigths and duties, data of the physician under surveillance, conclusions, declarations, number of pages and number of original copies, signatures).

The surveillance report records *facts and data*

with great precision and detail, and will serve as the basis for the resolution/decision. Anything left out of the report *cannot be referred to or acted upon.*

**Decisions made during administrative procedures (**judgements/resolutions)
Administrative procedures result in decisions that fall within the scopes of substantive and/or procedural law. An example for the first is ordering a mandatory vaccination; one for the latter is a judgement about a procedural fine payable.
Decree CL/2016 on the regulation of public health procedures decisions are to be issued in the form of a judgement or resolution. The designated authority makes *resolutions on the case* and all other decisions made during the procedure make up a *judgement*.
The regulation contains the following:

1. the appointed authority, all data required for identifying the client and the case,
2. a part about the judgement *including*:
   - the *decision* made by the authority,
   - the resolution of the expert commitee,
   - information about the *appeal* filed in
   - arising *procedural costs,*
3. *reasoning* should include:
   - a circumstances and facts,
   - evidence,
   - reasons for decisions made by *a professional authority*,
   - reasons for discretion and the final decision,
   - laws, rules and regulations referred to in decision-making
4. resolutions have to be adequately signed ,
5. and dated.

*In cases requiring immediate legal action,* the client may receive the resolution/judgement *in words* the preparation of a preliminary document in writing may be omitted. In such cases, a written document compiled and sent by the authorities later.

## Communication

Colleagues working for public health services often realise that rules and regulations are often ignored, not because they are not comprehensible enough, or those who should abide by them do not know them, or do not understand them properly, it is rather because they are not aware of the scientific background of and evidence behind these rules and regulation and therefore, do not clearly understand how important they actually are. For this reason, the best strategy of handling non-compliance is to start by providing information and educate health care workers. Such strategies may prove beneficial as they may further enhance trust and cooperation between the public health officer and the health care worker involved. These strategies will not undermine respect towards the authorities, or generate unnecessary conflict; on the contrary, they may actually result in building the grounds of effective, long-term cooperation.

The measures authorities employ may vary at a large scale: enacting decisions, suspension of operations, warnings given on matters involving personal responsibility or issuing serious fines. Consequently, *the extent of non-compliance, and whether it was committed negligently or intentionally*, recurrent cases of such behaviour shall all be considered when authorities decide upon the measures to be taken. The aim is to *enforce compliance with rules and regulations by causing the least human or financial/economic harm*.
Public health surveillance is not aimed at *finding scape goats*. It is crucial to avoid any form of external pressure that would point in this direction. An infection, disease, or outbreak does never develop as a result of non-compliance of one particular individual but is always a multi-factorial phenomenon (including non-compliance with rules and regulations, incomplete or imprecise surveillance, understaffing, time pressure etc.).

## References


1. Az egészségügyről szóló 1997. évi CLIV. törvény
2. Az egészségügyi és a hozzájuk kapcsolódó személyes adatok kezeléséről és védelméről szóló 1997. évi XLVII. törvény
3. A fertőző betegségek jelentésének rendjéről szóló 1/2014. (I. 16.) EMMI rendelet
4. A fertőző betegségek és a járványok megelőzése érdekében szükséges járványügyi intézkedésekről 18/1998. (VI. 3.) NM rendelet
5. A várandósgondozásról szóló 26/2014. (IV. 8.) EMMI rendelet
6. Az egészségügyi ellátással összefüggő fertőzések megelőzéséről, e tevékenységek szakmai minimumfeltételeiről és felügyeletéről szóló 20/2009. (VI. 18.) EüM rendelet
7. Az egészségügyi szolgáltatónál képződő hulladékkal kapcsolatos hulladékgazdálkodási tevékenységekről szóló 12/2017. (VI. 12.) EMMI rendelet
8. Az általános közigazgatási rendtartásról szóló 2016. évi CL. törvény
9. http://www.oltasbiztonsag.hu/
10. http://www.veszettsegmentesites.hu/
11. https://hivszures.hu/http://www.oek.hu/oek.web?nid=444&pid=2&to=16&lang=hun
12. https://www.antsz.hu/felso_menu/temaink/jarvany/modszertani_levelek
13. https://www.who.int/teams/integrated-health-services/infection-prevention-control/hand-hygiene
14. Kertai Pál: Megelőző orvostan, Medicina Könyvkiadó 1999, ISBN: 963-242-334-8
15. Fertőző betegségek járványtana I-III., szerkesztette: Jurányi Róbert, Semmelweis Egyetem Egészségügyi Főiskolai Kar, Budapest, 2005.
16. Ádány Róza: Megelőző orvostan és népegészségtan, Medicina Könyvkiadó Zrt., 2007.
17. Népegészségügyi orvostan, szerkesztették: Ember István, Kiss István és Cseh Károly, PTE ÁOK, 2013.
18. Népegészségügyi medicina, szerkesztették: Ádány Róza, Kárpáti István, Paragh György, Medicina 2014, ISBN: 978 963 226 508 7
19. Paulik Edit: Megelőző orvostan és népegészségtan, JATEPress, 2014.
20. Fertőző betegségek, szerkesztette: Maródi László, Medicina Könyvkiadó Zrt., 2016.
21. Infektológia, szerkesztette: Ludwig Endre, Medicina, 2020. ISBN szám: 978 963 226 769 2

# IV. Epidemiology of non-communicable diseases

Zsuzsanna Kívés, Réka Mihály-Vajda, Imre Boncz

In 2019, 55% of the total global mortality of 55.4 million was caused by the 10 most common causes of death. Global causes of mortality, in terms of total years of life lost, were associated with the following disease groups: cardiovascular (ischaemic heart disease, stroke), respiratory (chronic obstructive pulmonary disease, lower respiratory tract infections) and mortality related to neonatal conditions.

Globally, in 2019, according to the Global Burden of Disease (GBD) data, 7 out of 10 leading causes of mortality were non-communicable diseases. These 7 causes were responsible for 44% of all mortality and amounted to 80% of the 10 leading causes. In 2019, all non-communicable diseases accounted for 74% of mortality worldwide. The leading cause of mortality was ischaemic heart disease accounting for 16% of total global mortality. Between 2000-2019, it increased by 2 million, up to 8.9 million. Stroke and chronic obstructive pulmonary disease were the second and third leading causes of death accounting for 11% and 6% of total mortality. Mortality due to pharyngeal, bronchial and pulmonary cancers increased from 1.2 million to 1.8 million being the sixth most common cause of death today. Diabetes became one of the ten most common causes of mortality as there has been a significant, 70% increase, since 2000, in deaths associated with diabetes.

According to data retrived from the Hungarian Central Statistical Office, there were 129 600 deaths in 2019. Major causes of death included: 49.5% (64 100 persons) were due to diseases of the circulatory system, 25.5%were due to cancer (33 000 persons), and the third most common cause was respiratory diseases (6.7%, 8 000 persons), followed by diseases of the digestive tract (4.9%, 6 400 persons) and deaths caused by violent action (accidents, suicide) (4.2%, 5 500 persons).

Due to lack of space, this chapter is going to outline the epidemiological importance and prevention possibilites of only the most important diseases. The epidemiology of obesity is described in more detail in the chapter on the epidemiology of nutrition.

## The Epidemiology Of Cardiovascular Diseases

Cardiovascular diseases include diseases caused by atheromatous changes in the coronary heart arteries, cerebral- and peripheral arteries.

Cardiovascular diseases (CVDs) are responsible for the death of 3.9 million people in Europe and more than 1.8 million people in the European Union (EU) in a year. Cardiovascular diseases account for 45% of total mortality in Europe and 37% of total mortality in the EU. Half of the mortality associated with cardiovascular diseases is due to ischaemic heart disease, out of which, the prevalence and mortality of acute myocardial infarction has been showing a decreasing trend in Western countries since the 1980s, while Asian countries have seen an increase in this respect. These trends can be due to an increase in life expectancy, rapid economic growth and the spread of Western lifestyle. In Hungary, according to data from the National Myocardial Infarction Registry, (with 93 hospitals contributing data at present) there were 14 462 patients and 14 766 events registered in 2016.

Risk factors contributing to the development of cardiovascular diseases can be grouped along various considerations:

***Causal/conventional risk factors, which*** significantly increase the risk or cardiovascular diseases: smoking, high blood pressure, diabetes mellitus and elevated LDL cholesterol levels.
***Predisposing factors***: overweight, obesity, physical inactivity, male sex, early onset coronary heart disease in the family history, socio-economic factors, insulin resistance.
***Conditional risk factors***: homocistein, fibrinogen, lipoprotein (a), LDL cholesterol, C-reactive protein.
***Newly identified risk factors*** (e.g. oxidative stress markers, some allele polimorphisms).

A large international study (INTERHEART) revealed that potentially modifiable risk factors associated with myocardial infarction do not show significant differences in terms of ethnic origin or country of origin. Early onset cardiovascular disease in the family history is a significant risk factor, and while the mechanism is multifactorial; it may be significantly associated with and influenced by lifestyle including smoking, diet, obesity and physical inactivity. Evidence has shown that there is a close association between genetic polimorhism and lifestyle-related risks.
Data collected within the framework of the Cardiovascular Lifetime Risk Pooling Project including 18 cohort studies and an overall 257 384 afroamerican and caucasian males and females revealed that people with an optimal overall risk profile had a significantly lower risk for cardiovascular diseases than those with one major risk factor (1.4% versus 39.6% in men, 4.1% versus

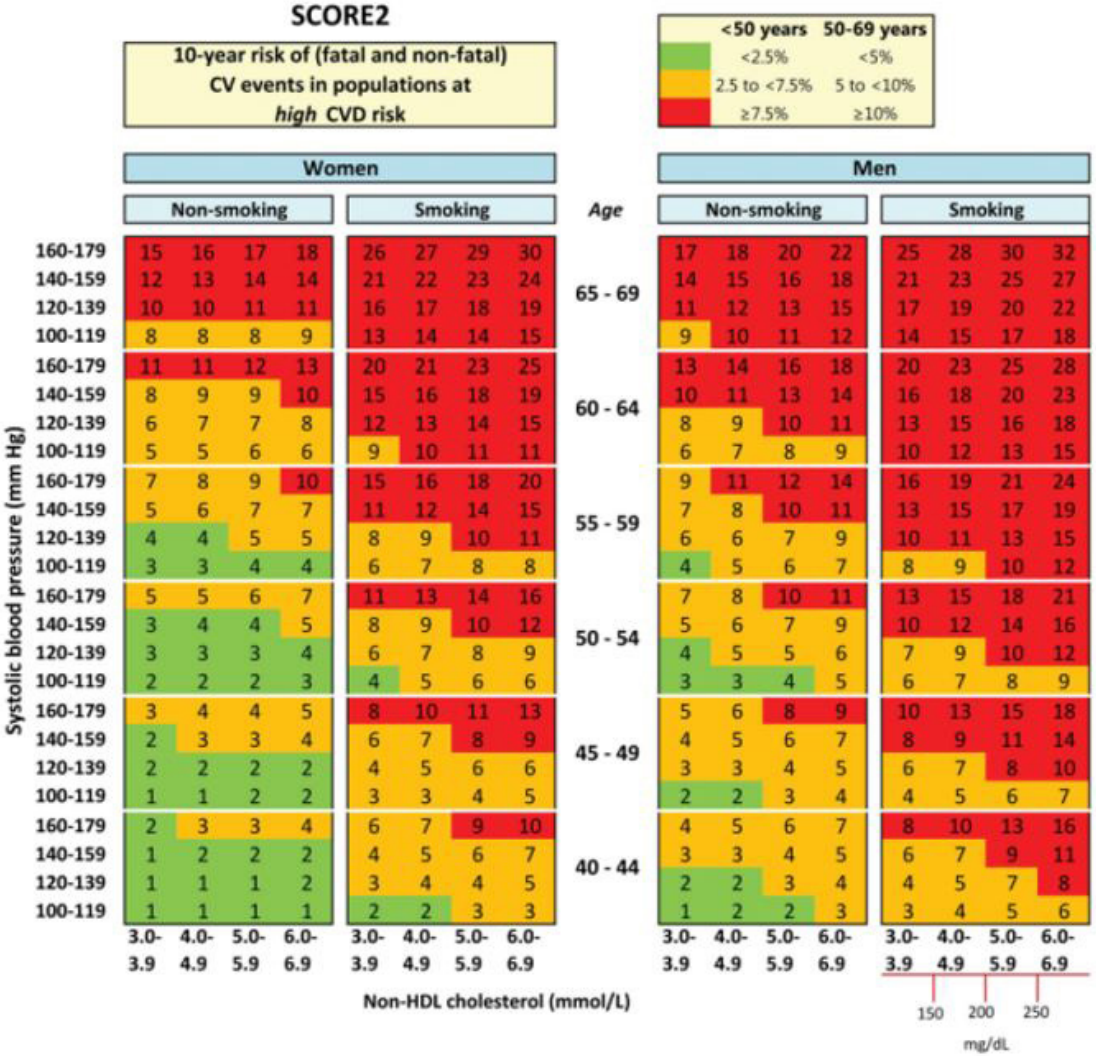


Figure 1.: The risk of a cardiovascular event within 10 years according to the European Society of Cardiology (2021)

20.2% in women). Having more than two risk factors increased lifetime risk further with 49.5% in males and 30.7% in females. Main risk factors included: diabetes, high blood pressure, low HDL, high LDL, higher trigliceride levels, sex, age. Absolute cardiovascular risk was found to have been twice as high among diabetic patients compared to the non-diabetic population.

***Absolute cardiovascular risk*** refers to the likelihood of an individual to have a cardiovascular event (disease) induced by atherosclerotic change over a given period of time taking into consideration all risk factors. (Cardiovascular diseases: high blood pressure, coronary artery disease, heart failure, cardiomyopathy pericardial diseases, cerebrovascular diseases, transient ischaemic attacks, stroke, peripheral aretrial disease, gangrene, aneurysm, vasculitis).

Risk assessment tools help assess risk of individual patients and facilitate adequate therapeutic decisions. The current guideline of the European Society of Cardiologists, to so-called SCORE (Systematic Coronary Risk Evaluation), aims to assess the above mentioned risk factors (age, sex, smoking, blood pressure, cholesterol levels), and taking all these into consideration it is used for the calcualtion of the 10-year the risk of a fatal coronary event Diseases affecting the coronary arteries: Coronary heart disease (CHD), and Coronary Artery Disease (CAD) which may lead to angina (chest pain) or heart attack (myocardial infarction).

In Europe, separate scores are used for low- and high-risk countries. Hungary is among high-risk countries.

Asymptomatic patients are recommended to undergo risk assessment at annual check-up examinations in the following cases: 1. the patient has one or more cardiovascular risk factors 2. there is early onset cardiovascular disease in the family history 3. the patient has symptoms suggesting a cardiovascular disease; if the patient is diagnosed with a cardiovascular disease it immediately puts him/her into the very high risk category and therapy to reduce risks should be commenced, or 4. upon the patient's request.

## The Epidemiology of Hypertension

Hypertension is diagnosed when a person's blood pressure average, based on two measurements out of three taken on three different occasions (at least one week apart) in the office or clinic, reaches or is above 140 Hgmm systolic and/or 90 Hgmm diastolic pressure. Upon measuring blood pressure at home, it indicates hypertension if the blood pressure is 135/85 Hgmm or higher; blood optimal blood pressure is 120/80 Hgmm. Table one presents normal and abnormal blood pressure values measured in a medical setting.

Table 1.: Categories of normal and abnormal blood pressure values measured in a medical setting (Hungarian Society of Hypertension)

| Category | Systolic blood pressure (Hgmm) | | Diastolic blood pressure (Hgmm) |
|---|---|---|---|
| optimal blood pressure | < 120 | and | < 80 |
| normal blood pressure | 120-129 | and/or | 80-84 |
| elevated- normal blood pressure | 130-139 | and/or | 85-89 |
| Grade 1. hypertension | 140-159 | and/or | 90-99 |
| Grade 2. hypertension | 160-179 | and/or | 100-109 |
| Grade 3. hypertension | >180 | and/or | >110 |
| isolated diastolic hypertension | < 140 | and | >90 |
| isolated diastolic hypertension | >140 | and | <90 |

80-85% of hypertension is primary hypertension which typically takes years to develop. 15-20% of people develop high blood pressure as a consequence of, or paralel with, another disorder or organ dysfunction (e.g. obstructive sleep apnoea, kidney disease, tumours of the suprarenal gland, thyroid problems, certain hereditary vascular disorders), or it may develop as a result of taking certain medications/pharmacotherapy (e.g. contraceptive pills, cold remedies, OTC pain killers, illegal drug use: e.g. cocaine, amphetamines).

## Prevalence

Around 1.13 billion people have hypertension globally and the number is expected to increase upto 1.5 billion by 2025. Prevalence of hypertension is around 30-45% in the adult population based on measurements performed in a medical setting and shows an increasing tendency with age. Prevalence is above 60% in people aged 60 and above. At present, there are around 3-3.5 million people living with hypertension in Hungary, the prevalence in the adult population is over 35%. In adolescents, hypertension prevalence is 2.5%, in the whole population 32.7% in women and 34.1% in men.

According to a 2019 health survey the risk of developing hypertension increases with age; in the 35–44 age group it is 16%, in people aged 75 and above it is more than 90%. Prevalence is higher among women than among men, which is mostly due to the differences in age distribution. Risks of hypertension show significant social differences in the population above 25 years, with only a quarter of the people with a higher education degree having high blood pressure compared to those with only 8 years of elementary education or less. In the population above 18 years of age the prevalence is 25% less among people belonging to the highest income group compared to those in the lowest income group.

## Risk factors

- Risk increases ***with age***. About two-thirds of people over 65 suffer from hypertension. The risk of developing hypertension in people who have normal blood pressure aged 55 is 90%.
- Until about 64 years of age high blood pressure is more common ***among men***. ***Women*** are more likely to develop high blood pressure after age 65.
- HBP is very common in the ***afro-american race***. The prevalence is nearly double in the ***Roma*** population compared to the total Hungarian population.
- Regarding the effect of ***family history***, children with hypertensive parents are more likely to develop the disease with a slightly stronger correlation found between mother and child. In the case of hypertension in adolescence, there is a positive family history in 86% of the cases.
- ***Regarding obesity or overweight every*** 1 kg/m$^2$ increase in BMI increases the risk of hypertension with 12%. Every 10 kgs of weight gain increases the systolic pressure with 3 Hgmm, and diastolic pressure with 2.2 Hgmm.70.6% of hypertensive patients have an abnormal waist circumference. Birth weight and blood pressure in adolescence show a negative correlation. Low birth weight is associated with a higher incidence of hypertension in adulthood. According to data, in Hungary, more than 80% of patients having hypertension are overweight, 89% have an above normal waist circumference and 33% of those who are overweight have hyperension. (Kiss, 2014).

**Further risk factors include:** physical inactivity, active or passive smoking, high sodium, and low potassium intake through diet, excessive alcohol consumption, high stress levels, and certain chronic conditions. Socio-economic factors also play a significant role; HBP prevalence is 33% higher among women in the lower income group.

## Symptoms

High blood pressure remains asymptomatic until complications develop in target organs. Vertigo, flushed face, headache, fatigue, nosebleed or nervousness may be the early signs. Severe high blood pressure may lead to serious cardiovascu-

lar, renal, retinal or neurological complications (e.g. symptoms of coronary atherosclerosis, heart failure, hypertonic encephalopathy, kidney insufficiency).

## Prevention

**Primary prevention**

Lifestyle changes are important and highly recommended next to pharmacotherapy as well. Main steps include:

- Reducing intake (< 5g daily).
- Reducing alcohol intake: in men, down to 14 units/week (175 g/week), in women, down to 8 units (100 g/week), heavy drinking should be avoided.
- Diet rich in vegetables, fresh fruit, fish, whole grains, nuts, saturated fatty acids (olive oil), and low fat dairy products. Red meats should be avoided (Dietary Approaches to Stop Hypertension (DASH) diet).
- Bodyweight control: in case of overweight or higher waist circumference (>102 cm in men, >88 cm in women); target values are: BMI 20-25 kg/m$^2$ and waist circumference in men <94 cm in women <80 cm.
- Regular, moderate or high intensity training/physical exercise can decrease systolic blood pressure with 11 Hgmm and diastolic blood pressure with 5 Hgmm. At least 150 minutes of moderate exercise or 75 minutes of intense aerobic exercise weekly, or the combination of moderate and intense exercise is recommended. Interval training (repetitive exercises combining high intensity with low intensity exercises, or passive periods of resting) and muscle strengthening exercises performed at least twice weekly are also beneficial and effective.
- Stress release techniques aimed at reducing stress levels, and the use of adequate coping techniques are also very helpful (muscle relaxation, deep breathing, regular physical activity, getting enough sleep).
- Regular blood pressure monitoring at home (blood pressure diary) helps patients develop awareness about their condition and may provide helpful data to physicians as well.

**Secondary prevention**

Blood pressure measurements should be a part of at any routine doctor-patient encounter. Blood pressure checks should be carried out based on age and risks as follows:

- Patients under 40 with optimal blood pressure who have no risks should have their blood pressure checked *every 5 years*, patients with normal blood pressure values every three years and those with elevated-normal BP values should be checked every year.
- Between 40–65 years of age, if the patient has an optimal blood pressure it is enough to have a BP check every three years, those with normal blood pressure every two years and patients with elevated-normal blood pressure should have their blood pressures taken every year in an office/sclinic setting.
- Patients who are at higher risk should have a BP check *every three years* if they have an optimal blood pressure, those with normal blood pressure should have their BP checked every two years and patients with elevated-normal values should have their blood pressure taken annually.

# The Epidemiology of Stroke

From a public health perspective, stroke is the most significant cerebrovascular disease group. Stroke is a sudden nervous system dysfunction caused by decreased cerebral blood flow. The clinical symptoms of a focal or extended functional disturbance last at least 24 hours or may be fatal and the cause is only of vascular origin.

Ischaemic stroke is the most common type accounting for 80% of strokes caused by an obstruction of a cerebral vessel. It is most commonly due to atherosceloris, thrombosis, or embolism. Another type is haemorrhagic stroke, the most important risk factor of which is hypertension; in this case a vessel leaks or ruptures causing bleeding into the brain. Strokes may originate from several conditions affecting vessels e.g. uncontrolled high blood pressure, overtreatment with anticoagulants, aneurysms, trauma (e.g. traffic ac-

cident), and protein deposits in vessel walls leading to weakened vessel walls. 8-12 % of patients who have had an ischaemic stroke and 37-38% of patients who have had a haemorrhagic stroke die within a month. Mortality within a year after a stroke is 25% in women and 22% in men.
A special form of stroke is the so-called transient ischaemic attack (TIA) which is characterised by temporary stroke-like symptoms but it does not cause permanent damage. TIA is caused by a transitory disturbance in cerebral blood supply which may last up to five minutes.

## Incidence, mortality, prevalence

In 2019, the global incidence of stroke was 12.2 million, global prevalence was 101 million, DALY was 43 million (133–153), and mortality was 6.55 million cases (6.00–7.02). Stroke is the second leading cause of death worldwide amounting to 11.6% of total mortality and 5.7% of total DALY 5.7 in 2019. Between 1990 and 2019, absolute number of stroke was 70.0% higher, and its prevalencia was 85.0% higher. Mortality due to stroke was 43.0% higher; loss of DALY due to stroke increased by 32.0%. During the same period, age-standardised incidence decreased by 17.0%, mortality decreased by 36.0%, prevalence by 6.0% and DALYs by 36.0%. Prevalence of stroke in people younger than 70 years of age increased by 22.0% and incidence by 15.0%. In 2019, major risk factors of stroke included high systolic blood pressure, high BMI, elevated starving plasma glucose, environmental pollution and smoking.
Age-specific mortality due to cerebrovascular disease has been the lowest in Western European countries, in both sexes, and the highest in countries of the former Soviet Union.
In Hungary, around 40 000 new cases are registered annually (41 703 cases in 2009). According to the National Statistics Office of Hungary, in 2018, 4 851 men and 6 416 women died due to cerebrovascular disease. The mortality rate was 103.8 persons among males and 125.8 among females per 100 000 population.

## Symptoms

Typical symptoms of stroke include *sudden -characteristically monolateral- paralysis in the arms, legs or face*. Sudden speech disturbance may also occur; patients cannot formulate words or cannot understand what they are told. *Visual disturbance* is also common, with a typically one-sided loss of peripheral vision. *The mouth may be* drooping, patients are unable to form an 'o'with their mouth. Vertigo is also common, mostly the spinning type, difficulty swallowing (dysphagia), imbalance or complete paralysis of the lower extremities, and loss of consciousness lasting a few moments may also occur. Sudden strong headache is also common with subsequent vomiting, dizziness or disturbed consciousness.

## Risk factors

- ***Life-style-associated risk factors*** (overweight, obesity, physical inactivity, excessive alcohol intake, cocain use, use of metamphetamin).
- ***Further risk factors include***:high blood pressure**,** active or passive smoking**,** high cholesterol levels, diabetes, obstructive sleep apnoe, cardiovascular diseases (e.g.heart failure, atrial fibrillation), stroke in the medical history or family history, previous heart attack of TIA**,** Covid-19 infection, age ≥55years, male sex, afroamerican ethnicity, taking contraceptive or oestrogen-containing hormone tablets. Untreated hypertension is the most important risk factor for recurrent stroke. Five years after a stroke, 24–42% of patients have a recurrent episode with more severe outcomes.

## Complications

Stroke may lead to temporary or permanent disability depending on how long the obstruction in the cerebral blood flow lasts and which part of the brain is affected. Complications may include:

- paralysis or loss of muscle movement,
- difficulty speaking or swallowing,
- difficulty understanding speech,
- problems with reading or writing,
- loss of memory, disturbed cognition,

- emotional problems,
- pain,
- numbness or other unusual sensations in the affected area,
- changes in behaviour or self-care.
- Patients may become more withdrawn after having a stroke and may need help with self-care and managing daily tasks.

### Prevention

Several stroke prevention strategies are the same as those used for the prevention of heart disease. Recommendations with regard to healthy lifestyle are generally the following:

- Reducing and controlling (high) blood pressure: a metaanalysis including 14 large randomised trials found that, by reducing diastolic blood pressure by 5-6 Hgmm, the relative risk of a stroke is reduced by 42%. Based on more than 40 randomised, controlled trials, reducing blood pressure down to 115/75 Hgmm in the 60-79 age group significantly reduces the risk of all cerebrovascular events: risk is 30% lower with every 10 Hgmm decrease. Reducing blood pressure to 120/70 Hgmm decreases the risk of getting a stroke continuously (reference).
- Reducing the amount of cholesterol and saturated fats in the diet. The CARE study found that pravastatin reduced stroke risk by 32% in patients with coronary heart disease having average total cholestrol levels. Every 10 % reduction in LDL-cholesterol decreased total stroke incidence by 16.5%. According to a Hungarian recommendation, the reduction of LDL-C levels with pharmacotherapy including statins and non-statin lipid-lowering drugs is of pivotal importance to reduce cardiovascular mortality and morbidity.
- Smoking cessation reduces risks gradually.
- Further prevention strategies include: management of diabetes, achieving and maintaining an optimal bodyweight, following a Mediterranean diet based on using olive oil, rich in fruits, nuts, vegetables, whole grain products, regular physical (aerobic) exercise, moderate alcohol consumption, the treatment of obstructive sleep apnoea, and the avoidance of drug use.
- It is crucial to recognise signs and symtoms of stroke/TIA with regard to the future prognosis of patients. Successful therapy is only possible within a certain time window, consequently, the aim is to minimalise loss of time and to start adequate treatment as early as possible. Therefore, wide scale education of the population (organised awareness raising) is very important.

## The Epidemiolgy of Lung Cancer

There are two main types of lung cancer based on the microscopic appearance of tumour cells. Small cell lung cancer accounts for approx. 15% of the cases, mostly occurring among smokers. Small cell lung cancer usually has a bad prognosis, survival is around 20 months, 5-year survival rate is 20%. In advanced cases, 5-year survival is under 1%. Non-small cell lung cancers make up the remaining 85% of cases and include several different types of lung cancer: squamous cell carcinoma, adenocarcinma, large-cell carcinoma). Five-year survival rates vary depending on cancer stage; in stage I.cases, it is around 60-70%, in stage IV, it is less than 1%. Patients with metastases have an average survival of 6 months; those who receive treatment may have a longer survival of nine months.

### Incidence, mortality

Regarding global cancer incidence, lung cancer is the third (22.4 persons/100 000 population) following breast (47.8 persons100 000 population) and prostate cancer (32.7persons/100 000 population). In terms of mortality, lung cancer is the leading cause (18.0 persons/100 000 population). Based on incidence data, it is the fourth most common type of cancer in Europe after breast (74.3 persons / 100 000 population), prostate (63.4 persons/100 000 population) and colon cancer (30.4 persons / 100 000 population). It is the leading cause of cancer mortality in Europe (22.6 persons / 100 000 population).

Regarding individual countries, Hungary has the highest incidence rate (50.1 persons/ 100 000 population), followed by Serbia with 47.3 persons per 100 000 population. Mortality statistics show the same picture with Hungary having 42.4 persons /100 000 population, and Serbia with 40 persons per 100 000.

According to the Korányi Bulletin, lung cancer incidence in 2016 was 4926 cases.

Total prevalence in 2020 was 21 874, which was a significant decrease compared to previous years (incidence ranged between 22 263 - 22 671 between 2010 - 2019). In 2020, as a result of restrictions due to the Covid epidemic, incidence rates were lower (3 601 persons), similar rate was last seen in 1980 (3 960 persons). During the past decade, male incidence ranged between 56-65%- and female incidence was between 35-44% with the highest female incidence in 2019 and 2020 (44% and 45%).

## Risk factors

- ***smoking*** is the most significant risk factor (associated with 85% of the cases), the risk increases with the number of cigarettes smoked/day and the years of smoking. Cancer risk decreases after quitting smoking but will never reach that of never smokers. 15-20% of patients suffering from lung cancer never smoked or only smoked minimally. Quitting at any age decreases the risk of developing lung cancer.
- ***radiation therapy*** for another type of cancer,
- ***family history of lung cancer,***
- ***air pollution, using marihuana, exposure to cigar smoke or passive smoking or exposure to carcinogenic substances*** (e.g. asbestos, radiation, radon, arsenic, chromates, nickel, chloride-metylene-ethers, polycyclic aromatic carbohydrogens, mustard gas,coke oven gases),
- ***chronic inflammation:*** COPD (chronic obstructive pulmonary disease), alfa-1-antitripsin deficiency and pulmonary fibrosis (e.g. silicosis) increase the risk of developing lung cancer.
- other types of pulmonary disease (e.g. tuberculosis),
- ***genetic mutations*** (e.g. secondary or additional mutations in cell-growth stimulating gene mutations inhibiting tumour suppressor genes). Although oncogenic mutations may cause lung cancer and may contribute to the development of the disease in smokers, these mutations are most likely to cause cancer in never smokers. In 2014, the Lung Cancer Mutation Consortium (LCMC) found major mutations in 64% of 733 lung cancer cases including both smokers and non-smokers. (Kris, 2014)

## Symptoms

Early stage lung cancer usually does not cause symptoms, they typically appear at advanced stages.Symptoms may include: unresolving cough, haemoptysis (even if only small amounts), dyspnoea, chest pain, hoarseness, weigthloss without dieting, pain in the bones, headaches.

## Prevention

### Primary prevention

Except for smoking cessation, active prevention strategies targeting lung cancer have not proven successful. Although reducing the radon levels of private apartments eliminates the radiation known to be associated with carcinogenesis, it has not been shown to decrease lung cancer incidence.

### Secondary prevention

Lung cancer screening may be beneficial for people at an early stage of the disease, especially, for patients having operable, non-small cell lung cancer who can undergo early stage resection. Screening is now recommended for high risk populations as well. According to a study, annual screening with **low-dose CT** resulted in 20% decrease in lung cancer mortality compared to screening with chest X-ray. – The study (Aberle, 2011) revealed that high-risk patients were, mostly, past, or current smokers (mainly aged 55-74), with at least 30 pack years of smoking, and those who quit during the previous 15 years. Recent research based on screening high-risk patients showed better surviv-

al among patients screened with low-dose CT (de Koning, 2020). Pack -years is defined as: N refers to packs of cigarettes smoked per day, T refers to years of smoking, the two values muliplied indicates pack years smoked (N x T = PY).
The U.S. Preventive Services Task Force (USPSTF) recommends annual screening for people aged between 50 and 80 years having no symptoms with 20 pack years of smoking history and for those who quit less than 15 years ago.
Screening should be stopped if the person has not been smoking for more than 15 years or if they are diagnosed with a medical condition, which is likely to significantly lower life expectancy, or eligibility for surgery for the type of lung cancer diagnosed or the willingness of the patient to undergo such surgery.
In the future, lung cancer screening may possibly include molecular analysis of genetic markers (e.g. K-ras, p53, EGFR), sputum cytometry and the detection of carcinogenic volatile organic compounds (e.g. alcane, benzol) in expired air.

## The Epidemiology of Colorectal Cancer

A part of colorectal cancers are caused by hereditary factors:

1. Familiary adenomatous polyposis (FAP) characterised by hundreds or thousands of adenomas in the small intestine or rectum which are likely to turn into adenocarcinoma. The disease usually manifests before age 35. FAP is a monogenic, autosomal, dominant disorder.
2. Lynch-syndrome, an autosomal dominant disorder, accounts for around 5% of hereditary, non-poliposus, colorectal cancers.
3. Peutz-Jeghers syndrome develops by age 20 with affected patients being highly susceptible to developing other types of cancer. 61-65% of sporadic, non-hereditary colon cancers develop on the grounds of a polip or colon infection.
4. Prognosis largely depends on the stage of the disease. Five-year survival of cancers located in the mucosa is nearly 90%; in the case of those penetrating the wall it is 70-80%, if there are positive lymph nodes it decreases down to 30-50%, and in metastatic cases <20%.

### Incidence, mortality

In 2020, based on Globocan global incidence data, colon cancer was the fourth (19.5 cases/100 000 population), after breast (47.8 persons), prostate (30.7 persons) and lung cancer (22.4 persons). It was the third in Europe (30.4 persons), following breast (74.3 persons) and prostate cancer (63.4 persons). Colon cancer was the third leading cause of mortality worldwide (9.0 persons) after lung (18.0 persons), and breast cancer (13.6 persons). In Europe, it was also the third leading cause of death (12.3 persons) following lung (22.6 persons), and breast cancer (14.8 persons).
Hungary reported the highest incidence rate in the world: 45.5 cases per 100 000 population, followed by Slovakia (43.9 persons) and Norway (41.9 persons). With regard to mortality, Slovakia had the worst rate (21.0 persons) followed by Hungary (20.2 persons) and Croatia (19.6 persons).
According to the National Cancer Registry, in 2016 there were 3 530 registered persons among men aged 3 041women aged 0-X. According to Hungarian Central Statistical Office data, in 2018, 2 836 men and 2 198 women died from malignant colorectal cancer. Among men, the mortality rate has been constantly increasing, however, since 2000, the rate of increase has been slower. Among women the mortality rate has been more or less constant.

### Risk factors

- colon cancer can manifest ***at any age*** but the majority of patients are older than 50,
- the ***afro-american population has been shown to have a higher risk***,
- ***rectal cancer or polips in the family history or medical history***,
- ***chronic inflammatory diseases of the colon*** (Ulcerative Colitis, Crohn's disease)
- ***low-fibre, high-fat diet***
- a daily intake of 100 gramms of ***red meat***

increases the risk by 12%
- in the case of ***processed meat products*** , consuming a daily amount of 50 g – about one hot dog – increases the risk by 16% (Colorectal Cancer Report, 2017). (Processed meats include: meat products preserved by smoking, curing, salting or addition of other preservatives or taste enhancers. Rajabi et. al (2021) conducted a cohort study with the inclusion of 26 218 participants and revealed that it is possibly only processed red meat that is responsible for the development of cancer, consequently, this study largely contributed to improving guidelines.
- ***physical inactivity***,
- ***diabetes*** (diabetes–colon cancer: RR 1.38, 95% MT 1.26-1.51, diabetes-rectal cancer: RR 1.20, 95% MT: 1.09-1.31)
- ***obesity,***
- ***smoking*** (RR: 1.18; 95% MT: 1.11-1.25). There is a stronger association between smoking and rectum cancer, polips, and Lynch-syndrome. Smoking 40 cigarettes (two packs) a day increases the risk of colon cancer by 40% and nearly doubles mortality risks.
- ***alcohol consumption*** (moderate alcohol consumption: RR=1.21, 95% MT: 1.13-1.28), significant consumption (4 drinks/day): RR: 1.52, 95% MT: 1.27-1.81). (Moderate alcohol consumption: <14g/day in women, <28g/day in men)
- ***earlier radiation therapy of the abdominal region*** received as part of cancer treatment

## Symptoms

Colorectal adenocarcinomas grow slowly, thus it may take time for the first symptoms to appear. Symptoms largely depend on the site, the type, extent of the cancer and the complications.

Symptoms may include: occult bleeding, fatigue and weakness due to severe anaemia, partial or complete bowel obstruction, blood-streaked stool or blood mixed in the stool, tenesmus or feelings of incomplete emptying of the bladder. Pain is common on perirectal involvement. Some patients experience symptoms and signs of metastatic illness first (e.g. hepatomegaly, ascites, enlargement of supraclavicular lymph nodes).

## Prevention

**Primary prevention**

- red meat consumption should be limited to a maximium of three portions per week (three portions equal approx. 350–500 g cooked volume, 500 g cooked red meat equals approx. 700-750 gr raw meat),
- vitamin D intake, mainly via food (oily fish, e.g. salmon, trout, sword fish, tuna, eggs, mushroom, milk, soy milk, almond milk, orange juice, grains). The recommended daily dose is 600 NE for people aged between 1 and 70 years. Under age 1 it is 400 NE, and above 70 a daily intake of 800 NE is recommended. According to a study by McCullough (2019), a higher level of circulating 25(OH) D has a significant association with a lower risk of colon cancer. The optimal, risk-lowering concentration of 25(OH) D is 75-100 nmol/L
- moderate alcohol consumption (one drink for women and two drinks for men per day)
- cessation of smoking,
- maintaining an optimal bodyweight,
- regular physical exercise of minimum 30 minutes daily, (A metaanalysis including 126 studies by Liu, published in 2016, found that patients who were doing regular physical exercise had 19% less risk of developing colon cancer than those who were less active.),
- higher dietary fibre intake - especially in the form of whole grain products – is probably – not provenly – associated with lower colon cancer risk.

**Secondary prevention**

There are two main early diagnostic screening methods.

1. **Faecal occult blood testing**
   Faecal occult blood tests detect blood that may derive from polips of tumours. They only indicate the presence of blood but

cannot give information on the amount or source of the bleeding, this requires colonoscopy. Most cancers do not bleed at all, or only bleed periodically, that is why stool tests should be taken during successive (2-3) bowel movements. Occult blood can be detected by chemical or immunochemical methods, however, their sensitivity may often vary.

a) To chemically detect faecal haemoglobin – ***Guajac faecal occult blood test,*** **gFOB** or "haemoccult test" – guajak-based, colour reaction tests are used, in which the blue colour of the guajak results from the peroxidase-like activity of the haemoglobin. As the reaction is not specific to human haemoglobin false positive results are not uncommon. Therefore, to avoid both false negative and false positive results, sample-taking is to be preceded by observing strict dietary restrictions and suspending certain medication therapies.
b) ***Immune faecal occult blood test – iFOBT*** *or FIT* – is based on detecting an antigen reaction targeting receptors of the globin part of human haemoglobin, thus it is specific to components of human blood. Therefore, no dietary restrictions are recommended.

2. ***sDNA-FIT*** (stool DNA test with faecal immuno-chemical test) – detects DNA fragments in stool characteristic of certain cancer types with immunological methods (FIT-DNA). This examination is based on a molecular analysis of the DNA of cells detaching from the wall of the colon (healthy mucosal lining, adenoma, and tumor) and entering the lumen. It is a rather expensive but easy-to-perform test; several samples are needed; wrapping and delivery of samples are to be done with utmost care. Nonetheless, its sensitivity is not much better than that of other tests.
3. **Endoscopic methods**
   ***a) Flexible sigmoidoscopy (FS)*** the instrument can be inserted 60 cm into the rectum up to the sigmoid colon and a part of the descending colon. Its disadvantage is that it cannot detect around one third of disorders. In non-negative cases, a colonoscopy is required.
   ***b) Colonoscopy*** can help examine the entire length of the colon, its sensitivity can reach 90–95%. It allows for the surgical removal of 90% of polips. This is the 'gold standard', as it is a highly reliable, one-step screening method. It is used for the clarification of non-negative findings obtained with other screening methods. Disadvantages are that it requires a quality instrument, time, expertise and is not without dangers.

**Screening recommendations**

The so-called **'one-step strategy'**means the use of colonoscopy as the only screening method. The **'Two-step approach'** refers to first, a faecal occult blood test performed followed by colonoscopy insearch for cancer or precancerous change in non-negative patients.

According to USPSTF recommendations, screening should include the population between 50-75 years who are at general risk for colorectal cancer. Their 2021 guidelines recommend the inclusion of the 45-49 age group into the screening programme as 94% of new cases occur in adults aged 45 or older. Recommended screening methods are: high-sensitivity gFOBTannually, FIT test every 1-3 years, sDNA-FIT every 1-3 years, CT every 5 years, flexible sigmoidoscopy every 5 years, flexible sigmoidoscopy every 10 years + a FIT test annually or colonoscopy every 10 years.
In Hungary, the first step of the two-step approach is an iFOB test followed by a colonoscopy in non-negative cases. Screening is done bi-annually, including the population aged between 50-69 years who have an average risk of colon cancer but have no symptoms or complaints. Screening is the task of family practitioners with the support of the Oncology Screening System (OSZR).

# The Epidemiology Of Breast Cancer

Breast cancer is a disease originating from breast cells - most commonly the glandular tissue or the mucosa lining the walls of milk ducts – affecting both men and women.

## Incidence and mortality

Globally, in 2020, it is the WHO European region which had the highest incidence rate with 69.7 cases / 100 000 population, followed by America with 68.0 cases per 100 000. The mortality rate in Europe was 14.8 cases per 100 000 population. The highest mortality rate was in the African region, where, despite a relatively low incidence (38.7cases / 100 000 population), the mortality rate was 19.1 cases per 100 000. Within *Europe,* Belgium showed the highest incidence (113.2 cases/100 000 population) followed by the Netherlands (100.9 cases), Luxemburg (99.8 cases) France (99.1 cases), Denmark (98.4 cases) and Finland (92.4 cases). The mortality rate in these countires ranged between 12.1-15.6 per 100 000 population. In Central and Eastern Europe, Hungary reported the highest incidence (77.3 cases), followed by the Czech Republic with 77.2 cases. The mortality rate was the highest in the Republic of Moldova (18.3 cases), followed by Poland (17.9 cases) and Hungary (17.3 cases).

Regarding cancer mortality, based on incidence rates, in Eurpoe, breast cancer is the leading cause in both sexes with 74.3cases followed by prostate (63.4 cases), colon (30.4 cases) and lung cancer (29.4 cases). Looking at women only, it is the leading cause of mortality (14.8 cases) followed by lung (12.9 cases) and colon cancer (9.5 cases). *In Hungary,* it is the most common type of cancer among women and the second leading cause of mortality. In 2011, regarding cancer mortality of Hungarian women aged 25-64, breast cancer mortality was 1.2-times higher compared to EU15-countries. In 2018, according to data retrived from the Hungarian Central Statistical Office, breast cancer was responsible for the death of 2 127 women. According to the National Cancer Registry breast cancer incidence, in 2018, was 8 638 out of which 242 were men.

## Risk factors

- ***Women are at much higher risk than men***.
- Risk increases with age, with the majority of cases occurring above age 50,
- earlier ***breast biopsy***,
- ***personal medical history*** (in situ or invasive breast cancer predisposes to the development of breast cancer in the contralateral breast after mastectomy at a rate of 0,5-1%/year),
- ***breast cancer running in the family:*** diagnosis of breast cancer among first degree relatives (mother, sister or daughter) especially when diagnosed at a young age increases the risk. (if more than two persons had a positive diagnosis: RR= 5-6, if only one: RR=1.5-3),
- around 5-10% of women with breast cancer carry a ***gene mutation*** in one of the two most commonly known breast cancer genes, BRCA1 orBRCA2. Lifetime risk of developing breast cancer is 50-85% in women having a BRCA mutation. The risk of developing breast cancer until age 80 is around 72% in people with BRCA1 mutation and 69% in those carrying the BRCA2 mutant gene. In women having a BRCA1 mutation, there is a 20-40% risk of developing ovarian cancer. Men with BRCA2 mutation have a higher risk for developing breast cancer. Mutations are more common among the ashkenazi jewish (2.3%),
- ***radiation therapy*** before age 30 (radiation therapy given for Hodgkin-lymphoma makes the risk four-fold in the subsequent 20-30 years,
- ***in situ lobular carcinoma means a 25-times higher risk*** of developing an invasive carcinoma,
- ***gynaecological history****:* early menarche (prior to age 12), late menopause (above age 55) late first pregnancy (after age 30), or no pregnancies,
- ***taking oral contracepives*** (approx. 5 cases more /100 000 women), the risk decreases gradually during 10 years after stopping contraceptive use,

- ***post-menopausal hormone replacement therapy (HRT)*** (oestrogen plus one progestine) moderately increases risks even after 3 years of treatment, taking HRT for 5 years increases the risk up to 7 or 8 cases/10 000 women with every year of taking HRT (relative risk has been shown to increase by 24%). Using oestrogen only has not been proven to increase the risk of breast cancer. The risk decreases with the cessation of HRT.
- ***lifestyle factors:*** smoking, alcohol consumption; breast cancer mortality has been shown to be 40% lower among those doing regular physical activity compared to the less active population. Physical activity decreases the risk of post-menopausal breast cancer among patients with a positive family history.

## Prevention

### Primary prevention

- Maximum 1 alcoholic drink per day.
- At least 30 min. of physical exercise on most days of the week.
- Avoding postmenopausal hormone
- Maintaining an optimal bodyweight.
- Healthy nutrition: meditarreanean diet using extra virgin olive oil, nuts may help reduce the risk of breast cancer.

### Secondary prevention

Mammography is one of the most commonly used preventive screening methods, other options are the physical examination performed by trained professionals and magnetic resonance imaging (MRI) recommended for high-risk individuals.

There has been no scientific proof supporting the efficacy and usefulness of perfoming the other screening tests alone (physical examination, self-test, ultrasound etc.) in the case of breast cancer.

The aim of screening the 45-65-year-old population with mammograpy is to detect breast cancer early at a non-palpable stage. Regular screening with mammograpy can detect 70% of breast cancers. Experience is Sweden shows that 20% of breast cancers diagnosed early require only surgery, 80% require radiotherapy and only 20% of patients need adjuvant therapy besides radiotherapy.

According to USPSTF guidelines, mammography screening is recommended every two years for women aged 50 – 74 years. Advantages include: high diagnostic accuracy (true positive rate is 90% in clinical practice, and 80% through screening examinations), breast cancer can usually be diagnosed two years prior to the appearance of clinical symptoms. Evidence has shown that regular screening can decrease breast cancer mortality by half. Disadvantages of mammography are the following: exposure to ionising radiation, rate of false negative findings (10% in clinical practice and 20% with screening examinations and 5% during screening).

High-risk patients are recommended to attend mammography screening annually, after age 30, if needed an ultrasound or MRI may also be performed. Screening the 40-49 group has been recommended in the literature for several years. It is also recommended to continue screening after 65 years of age if the patient does not have any other severe disesase which would considerably lower life expectancy (limiting survival to 3-5years). Screening this population is important as 45% of all newly diagnosed breast cancer cases are carcinomas in women aged above 65; 45% of breast cancer mortality also occurs in this age group. Several recent international statements recommend an annual screening protocol. Rate of interval cancers is higher at young age. Smaller tumour size shows a close association with longer survival.

Mammography screening is voluntary and is provided free for women between 45-65 who have health insurance coverage. Those elligible receive a letter of invitation every two years.

Self-examination of the breasts is not enough; nonetheless, getting to know ones breasts and self-examining them may help find unusual changes or lumps which can motivate people to see a doctor.

# The Epidemiology of Cervical Cancer

Cervical cancer is an intraepithelial neoplasia of the cervix (CIN) the most important, necessary, but not exclusive risk factor of which is the human papilloma virus (HPV) infection. 90% of the cases are caused by HPV-16, -18, -45, -31, -33, -35, -52, and -58 strains. Development of cervical cancer is a slower, gradual process that has several stages. Invasive cervical cancer develops at the meeting point of squamous cells of the portio and the cervical canal, the so-called transition zone, through a series of mucosal change of increasing severity.

## Incidence and mortality

Based on IARC Globocan (2020) data on cancer incidence, cervical cancer is the 7th with 10.7 cases/100 000 population; regarding mortality, it is the fifth with 3.8 ecases per 100 000 population. From among WHO regions, African populations have the highest incidence (30.9 cases) and mortality (21.5 cases) rates. Europe takes the fourth place both in terms of incidence, and mortality. Within Europe, the highest incidence was found in Montenegro with 26.2 cases per 100 000 population. Hungary was tenth with 17.2 cases per 100 000. The same ranking is true for mortailty, Montenegro having 10.5 cases, and Hungary 4.5 cases per 100 000.

Based on data retrieved from the Hungarian Central Statistics Office, in 2018, mortality due to cervical cancer was 8.0/100 000 population. Unfortunately, there has been no marked decrease in cervical cancer mortality during the past decades (7.9 cases / 100 000 in 2010), despite the introduction of cytological screening in 1960 for the population aged 20-65 years as part of routine gynaecological examinations. There were around 1.3 million smear tests perfomed in the 80s. Nevertheless, the improvement expected, namely, that the screening programme would decrease mortiality, did hardly manifest at a population level. The reason probably was that despite a high number of screening examinations the population coverage remained low.

The introduction of the cervical cancer screening programme offered by health visitors has improved coverage to some extent. Low levels of participation is supposedly due to inadequate health awareness, and knowledge among the female population, lack of taking responsibility for one's health, lower education levels and the associated socio-economic situation resulting in increasing differences in access to health care. Widespread availability and acceptance of the Cervical Cancer Screening Programme by Health Visitors is a significant issue for public health. The active involvement of local/district health visitors is key to increasing the efficacy of preventive efforts targeting socially disadvantaged populations.

## Risk factors

- Younger age at the first sexual intercourse, high number of sex partners through a lifetime,
- having had other STDs (e.g. chlamydia, gonorrhoea, syphilis, HIV/AIDS),
- compromised immunity,
- smoking,
- pregnancy under age 20 trebles risks compared to those giving birth after age 25 and they have a four-fold risk compared to those who have never been pregnant,
- number of deliveries,
- inadequate genital hygiene.
- HPV infection is responsible for 6.7% of all cancers and 99.7% of cervical cancers. 70% of infections remain hidden as the immune system eliminates it within a year. Infection rate is very high in the USA with 19-46% of sexually active women being infected. HPV is more common under age 25 and mostly eliminates spontaneously, it is less common above 35 but at this age group it is more likely to persist.

## Symptoms

Early stage cervical cancer may remain symptomless. Advanced stage disease may cause irregular bleeding after sexual intercourse, spontaneous bleeding inbetween periods or after the menopause. In more severe cases, spontaneous bleed-

ing, foul-smelling vaginal discharge, lower pelvic pain, or pain on intercourse may occur.

**Prognosis:** sqamous cell carcinomas only give distant metastases in advanced or recurrent stages. Five-year survival rates are as follows: Stage I.: 80-90%, Stage II.: 60-75%, Stage III.: 30-40%, Stage IV.: 0-15%. 80% or recurrent disease manifests within two years.

### Prevention

**Primary prevention**

- Safe sex, preventing STDs (using condoms, limiting the number of sexual partners),
- avoiding smoking,
- HPVvaccination.

**Secondary prevention**

The aim of cervical cancer screening is to detect changes in the cervical lining as early as possible. According to guidelines of international institutions such as the International Agency for Research on Cancer (IARC), the *Union for International Cancer Control* (UICC), and the EU regular screening started at age 25, lasting until age 65 provides an opportunity for preventing cervical cancer. This type of screening is also one of the most effective ways of spending resources. A cytological smear taken from the upper layers of the cervical lining and the vaginal wall through the vagina has been proven to be an effective screening method to be started when the person begins her sex life but at age 21 at the latest.

There are two screening tests for detecting cervical abnormalites: the Pap test and the HPV test**.** The American Cancer Society issued novel guidelines in 2020 with regard to cervical screening including the following:

Screening should begin at age 25.

If a primary HPV-DNS test is available it should be started at age 30 and performed regularly every 5 years, in such cases no cytology (Pap-test) is needed.

If a primary HPV test is not available, a Pap-test should be perfomed every 3 years or a co-test every 5 years (Pap-test and HPV-test). It is important to continue screening after child birth, receiving an HPV vaccination. Above age 65; however, if tests came back negative during the previous 10 years (no CIN2 or more severe findings) – no further screening is required.

USPSTF recommends cervical cancer screening, with only cervical smear taken, every three years for women aged between 21 and 29 years. For women aged 30-65 years the same time interval of three years is recommended with cervical cytology test only. If the patient goes for screening every 5 years only high-risk HPV test or a co-test is recommended. Above age 65, with negative screening history, after hysterectomy, or in the case of an absence of risk factors and under age 30 and HPV test is not indicated.

Hungary provides a cytology-based organised screening for the 25-65-year-old female population. Women who have not had screening for more than 3 years receive a letter by mail.

(Based on suggestions aimed at up-dating current guidelines screening is recommended every 3-5 years for women aged between 21-65 years irrespective of risks or previous screening results. (Koiss, 2017))

In May 2020, the Executive Board of the WHO accepted the global strategic framework which set out to reduce incidence per 100 000 females in all countries down to under 4 cases. This comprehensive approach includes the prevention, early detection and effective treatment of precancerous laesions. To achieve the above aim by 2030, the following targets were set: • to increase HPV vaccination coverage up to 90% among girls (aged 15 and above);

• screening 70% of the female population (between 35-45 years using high sensitivity tests);

• treating 90% of women diagnosed with malignant cervical cancer (treating 90% of women at precancerous stage, and 90% of women with invasive stage cancer).

## The Epidemiology of Diabetes Mellitus

Diabetes mellitus is a metabolic disorder resulting from alternating or constantly high levels of blood glucose, inadequate insuline production or uptake. Main types include diabetes Type-I and

Type –II, gestational diabetes and other special types. In Type-I diabetes the pancreas does not produce enough insuline (the level of the circulating hormone is less than required).

Type-II diabetes (adult-onset or non-insulin-dependent diabetes) is caused by two counter-dependent issues. On the one hand, muscle, fat and liver cells become resitant to insuline (cells don't connect with insuline, and thus do not take up glucose); on the other hand, due to increased demand, the pancreas can no longer produce enough insuline to decrease blood glucose levels. The exact cause of this process is not fully known, but physical inactivity and obesity are key predisposing factors. Due to Type-II diabetes being an important public health concern the present chapter is devoted to the epidemiology of this type of diabetes.

## Incidence, prevalence

In 2019, according to the Diabetes Atlas, there were around 463 million people living with diabetes in the 20-79 age group (prevalence: 9.3%). This number is estimated to increase globally by 2030 to 578 million (prevalence: 10.2%). In 2019, the number of diabetic patients aged 65 and above was around 111.2 (prevalence: 19.9%).

Due to a lack of a central registry in Hungary, there are no data available on the exact number of adult diabetic patients. According to estimates it is around 6-7% with the majority having Type II diabetes. Results of a Hungarian representative screening study published in 2010 suggested weighted diabetes prevalence to be 8.65% in the 20-69 age group, which means a 7.47% prevalence in the total population aged 20-69. According to data published in the IDF Atlas, diabetes prevalence in the same age group was 7.51% in 2014 in Hungary. Based on data from the National Health Insurance Fund of Hungary, in 2014, there were 727 000 patients on antidiabetic treatment for diagnosed Type II diabetes, prevalence for the whole population was 7.3%. Incidence of Type II diabetes was 29 100 persons in 2016. Registered point prevalence cases registered on 01.01.2016 were 714 978 persons (males: 324 702, females: 390 276), average age of males was 64.2 years, average age of females was 67.6. Prevalence in the whole population was 7.27% (males: 6.93%, females: 7.59%).

## Symptoms

Symptoms and signs of Type II diabetes develop slowly; patients may remain asymptomatic for years. Most common signs and symptoms include: increased thirst, frequent urination, increased appetite, weight loss, tiredness, blurred vision, slow wound healing, frequent infections, numbness or the feeling of pins and needles in the hands or feet. The appearances of darker skin areas, usually in the axillary region or on the neck often indicate insuline resistence.

## Risk factors

- Main risk factors are ***obesity or overweight***. Abdominal fat accumulation means higher risk (waist circumference in males above: 102 cm, in females above: 89 cm),
- ***sedentary lifestyle, lower levels of physical activity,***
- ***type-2 diabetes in the family history,***
- ***certain ethnic races*** are more predisposed (Afroamerican, Hispanic, Indian and Asian,or those living in the Pacific region compared to Caucasian populations),
- ***low HDL cholesterol,***
- ***high triglicerideleves,***
- risk increases **with age** especially above age 45
- untreated prediabetes (Prediabetes is a condition in which the blood glucose level is above the normal but is not high enough to meet the diagnostic criteria for diabetes),
- gestational diabetes, and mothers giving birth to babies weighing more than 4 kilogramms,
- policystic ovarian syndrome.

## Complications

Inadequately controlled hyperglicaemia in diabetic patients can, through many years, result in mulitple, mainly cardiovascular, complications affecting smaller or larger vessels or both. Microvascular: retinopathy, nephropathy and neu-

ropathy. Diabetes risk factors are also risks of developing other chronic disorders. Treatment of diabetes and adequate blood glucose control can help prevent complications and reduce the risk of comorbidities.

***Diabetic retinopathy*** has no early signs or symptoms, but eventually manifests in blurred vision, detachment of the retina or the vitreous body, partial or complete loss of vision; progression may vary considerably. Early diagnosis and tratment is vital to prevent loss of vision.

***Diabetic nephropathy:*** is the leading cause of chronic kidney disease. It is initially asymptomatic until nephrotic syndrome or kidney failure develops. Diagnosis is via a urine albumin test. Excretion of albumin >300 mg/day albumin indicates elevated albuminuria or open proteinuria and is a sign of advanced diabetic nephropathy.

**Cardiovascular diseases**: Diabetes increases the risk of developing heart disease, stroke, hypertension, and vascular narrowing.

**Neuropathy in the extremities:** High blood glucose levels lead to neuronal damage manifesting in numbness, pins and needles, or burning sensation in the extremities, which may lead to pain or loss of sensation beginning at the tip of the toes or fingers and spreading further up.

**Other neuronal damage:** Damage to the heart nerves lead to arrythmia. Impaired gastrointestinal nerve function may cause nausea, vomiting, diarrhoea or constipation. Nerve damage may cause impotence in men.

**Further complications**: cataract, glaucoma, skin problems (bacterial or fungal infections), hearing impairment, sleep apnoe, Alzheimer disease or other forms of dementia. Untreated cuts, wounds, or blisters may turn into severe infection (ulcer) which may be difficult to treat. In severe cases, minor or major (above the ankle) amputation may be indicated.

## Prevention

In prediabetes, ***lifestyle changes*** may slow down or eventually stop the development of diabetes. Lifestyle changes include ***a low fat, low calorie diet*** consisting of high fibre foods including fruit, vegetables and whole grain products.

• Weekly moderate 150 min. or longer, or more intensive ***aerobic-type*** exercise is recommended. Long-term sitting should be avoided; one should stand up every 30 minutes and move a little.

• ***Weightloss:*** losing 7-10% of the bodyweight can decrease the risk of diabetes at the prediabetic stage.

• In the case of prediabetic patients, metformin, and oral antidiabetic drugs can help reduce the risk of developing Type II diabetes, it is recommended especially for adults who are overweight and who cannot lower their blood sugar levels by changing their lifestyle.

**Secondary prevention:**

The American Diabetes Association recommends routine Type II diabetes screening with diagnostic tests for adults aged 45 or older and in the following groups:

- people younger than 45 who are overweight or obese, and have one or more risk factors,
- who have gestational diabetes,
- diagnosed prediabetes,
- an overweight or obese diabetic person in the family.

Hungarian recommendations also include screening tests for Type II diabetes and its preceding conditions. Screening may involve an oral glucose tolerance test with 75 g glucose (OGTT), or the standard method for detecting HbA1c. Screening should also include identifying classic cardiovascular risk factors (lipids).

At a population level, risk-based screening is recommended in smaller or larger cohorts which means that as a first step, they identify high-risk individuals by using a questionnaire and laboratory examinations are only performed in people at increased risk. The FINDRISC questionnaire is an effective tool in family practice or primary care settings. Based on this questionnaire, high-risk patients (total score >12) can have a standard OGTT with 75 g glucose. Measuring starving glucose is another screening method which means a blood test performed after starving for 12 hours as this should give the lowest blood sugar level. If it is higher than 7 mmol/l the blood test should be

repeated on another day to confirm the diagnosis of diabetes.
Everybody should undergo screening above 45; if the result is negative it is recommended to have a test every three years. Subsequent to gestational diabetes, if the OGTT is negative, screening is recommended every 1-2 years, in prediabetes, every year, and under age 45, in high-risk individuals, every three years.

### Diagnosis

Type II diabetes is usually diagnosed with a **glycaeted haemoglobin (HbA1c) test** which indicates the average blood sugar level for the preceding two-three months (value ranges are: normal under 5.7%, values between 5.7-6.4% indicate prediabetes, values higher than 6.5% or higher means the patient has diabetes). If a HbA1c test is not available, or it cannot be performed due to certain conditions an **ad hoc blood glucose test can be performed** the result of which, - irrespective of the time the patient last ate – indicates diabetes if it is 200 mg/dl (11.1 mmol/l) or higher especially if the patient has signs of diabetes e.g. extreme thirst and frequent urination.
**Starving blood glucose test:** if the value is less than 100 mg/dl (5.6 mmol/l) it is normal, 100-125 mg/dl (5.6-6.9 mmol/l) indicates prediabetes and values of 126 mg/dl (7 mmol/l) or higher on two measurements performed at different times confirm the diagnosis of diabetes.

## The Epidemiology of Osteoporosis

Osteoporosis is a generalised, progressive metabolic disease of the skeletal system characterised by decreasing bone mass, impaired microarchitecture of the bones and deterioration of bone quality resulting in increasing fragility of bones. Associated low-impact fractures are more common. In post-menopausal women, trabecular bone loss is most dominant leading to cortical bone loss with aging. In women, 95% of fractures, in men around 80% of fractures are primary fractures. Prevalence of secondary fractures may also increase due to diseases of other organs and taking certain medications.

### Incidence, prevalence

According to the European Vertebral Osteoporosis Study, the disease affects around 600 000 women and 300 000 men above age 50 years. The clinical significance of osteoporosis lies in the associated pathological fractures (vertebrae, radius, humerus and hip fractures) the most important of which is hip fracture, as 12-20% of patients die within a year after the fracture. Half of patients having had a hip fracture need lifelong care.

### Risk factors

The interaction of several contributing factors is responsible for the increased risk of osteoporotic fractures including clinical, iatrogenic, behavioural, nutritional and genetic factors.
Peak bone mass is a significant determinant of the bone mass of an elderly individual. Deveoping peak bone mass already starts during intrauterine life and typically ends by age 40. It is significantly influenced by bone mass gained through adolescence.

Main risk factors are the following:

- ***aging***, 25% of fractures affect people aged above 80,
- ***female sex***
- ***lower peak bone mass***,
- ***low bodyweight*** (under 58 kg) or low ***BMI index*** (under 22 kg/m$^2$),
- ***weight loss***: losing 10% or more of the bodyweight,
- bone loss accelerates during the first years of the menopause when ovarian function stops, continues to decrease with age. In ***post-menopause,*** women having a low body mass index, low body fat, and low body weight have an increased risk.
- *hip fracture in the family history,*
- ***earlier fractures*** ,
- hypogonadisms (lack of oestrogen),
- steroid treatment lasting more than three months,
- excessive effects of thyroid hormones,
- ***malnourishment***/malabsorption/maldigestion(calcium, protein or vitamin deficiency),
- renal hypercalcuria,

- ***long-term immobilisation***, long term sitting, physical inactivity,
- chronic liver and kidney disease,
- ***smoking,***
- ***excessive alcohol consumption*** (1 glass of beer, 1 dl wine, 2 cl of spirit).

### Symptoms

At early stages, osteoporosis has no symptoms. Advance stage osteoporosis may cause: backache caused by a fractured or collapsed vertebra, gradual loss of height and bent posture.

### Prevention

Adequate calcium and vitamin-D intake are key to prevention together with sufficient levels of physical exercise.

#### *Calcium*

Men and women aged between 18 and 50 years need a daily amount of 1000 mg calcium This increases up to 1200 mg in women over 50 and men over 70 years. After the menopause, women are recommended to take 1500 mg of calcium daily.
Recommended sources of calcium include: low-fat dairy products, dark green leafy vegetables, salmon or tinned sardines with bones, soy products (e.g. tofu), cereals enriched with calcium and orange juice. If the diet does not provide suffient levels of calcium, it can be taken in the form of a dietary supplement. Higher than necessary intake of calcium has been associated with kidney stones, therefore, it is not recommended to take more than 2000 mg/day even after age 50.

#### *Vitamin-D*

Vitamine D improves calcium uptake in the body and facilitates bone health in various different ways. Sources include: cod liver oil, tuna, salmon, eggs, and mushrooms. Milk and whole grain products are often fortified with vitamin D. Average recommended daily dose is at least 600 NE. After age 70, and after the menopause it is 800 NE. Those who do not have other sources of vitamin D, especially people who spend very limited time outdoors in the sun may need to take a supplement. Most multivitamins contain 600 - 800 NE vitamin D.

#### *Physical activity*

The most beneficial is regular physical exercise started in childhood and maintained throughout life. A combination of muscle strengthening, weigth-bearing and balance exercises are very effective for example: walking, jogging, running, stair climbing, skipping rope, skiing, and sports that involve physical impact (hits) to the legs, hip bones and the lower vertebrae. Balance exercises, which aim to decrease the impact of falls, may be beneficial for the elderly.

## The Epidemiology of Asthma

Asthma is a heterogenous disease typically characterised by inflammation of the airways. A Medical history typically includes airway symptoms – wheezing, difficulty breathing, chest tightness, and cough – which vary in time and intensity. Symptoms are caused by various degrees of expiratory flow obstruction. Asthmatic airway inflammation leads to airway hypereactivity resulting in recurrent eposides of wheezing, dyspnoea, chest tightness and cough. Symptoms usually occur during the night, or in the early morning aggravate on exertion and cause extensive airway obstruction of varying degrees which may subside spontaneously or may be reversed by pharmacotherapy.

### Incidence, prevalence

Today, around 300 million people suffer from asthma globally; its prevalence is estimated to increase with another 100 million by 2025. Average asthma prevalence is 5-10% in most countries of Europe. Prevalence, severity and mortality associated with asthma shows considerable geographical variations. Prevalence is the highest in high-income countries, mortality is the highest in low- and middle-income countries.
In Hungary, the number of patients registered at pulmonary care institutes was 321 714 patients (197 515 women, 124 199 males) in 2020. This number is supposedly higher as it does not include patients presenting at outpatient units of different pulmonological inpatient institutions and, patients

treated by family practitioners. The past twenty years have seen a slow but gradual increase in the prevalence of asthma. In 2000, there were 128 809 registered patients. The number of registered cases between 2000 and 2019 was between 13 420 and 19 298; in 2020 it decreased down to 9 181 most probably due to restrictions introduced in response to the Covid-19 pandemic. The ratio of allergic to non-allergic cases of asthma was 2/3-1/3 as earlier. Prevalence of severe asthma is estimated to be around 5-10% in the world.

Mortality associated with asthma does not correlate with asthma prevalence. The disease is responsible for the death of around 250 000 people worldwide. In Europe, mortality is around 5/100 000 asthma patients per year. Asthma has a significant impact on society as it affects a large number of people, mostly the active population. Direct health care costs (medications, hospital treatment, emergency treatment etc.) and indirect non-health care costs (early mortality, absence from work etc.) show a straightforward association with asthma severity and level of asthma control. Asthma control implies that it is not the disease that controls patients' lives as it is under control through therapy.

### Causes of asthma, causes of flare ups and exacerbations

Causes of asthma are not fully known, the disease is probably due to a combination of environmental and hereditary (genetic) conditions.

***Genetic factors:***

- genes predisposing to atopic illnesses;
- genes predisposing to airway hyperreactivity;
- genetic constellations determining expression of inflammatory markers and immune response rates,
- obesity,
- female sex

***Environmental and other factors:***

- exposure to various irritating substances (allergens) that can cause an allergic reaction may trigger signs and symptoms of asthma,
- airborne allergens (e.g. pollen, house dust mites, mold spores, pet dander, cocroach waste particles),
- airway infections,
- physical activity,
- cold air,
- air pollutants and irritants e.g. smoke,
- smoking (active, passive),
- certain medications (beta-blockers, aspirin, non-steroidal anti-inflammatory drugs),
- strong emotions, stress,
- sulphites and preservatives,
- gastrooesophageal reflux.

### Prevention

Besides cessation of smoking during pregnacy (during and after pregnacy) there is no other uniformly proven prevention strategy. Breast feeding, taking antioxidants and a diet rich in fish may have a protective effect.

Prevention of symptoms and exacerbations: avoiding and eliminating specific (allergens) and non-specific agents (viral infections, air pollutants, certain medicaments etc.) from the environment of the patient may help control asthma and may lead to lower doses of drugs needed. In most cases, however, the factors which contribute to the development of asthma cannot be avoided as they are continuously present in the environment. Smoking cessation may prove beneficial.

Medications given for preventing asthma help reduce inflammation and also the sensitivity of the airways to these allergens. That is why adherence, taking the prescribed medications regularly, in the correct dose, is of great importance.

## The Epidemiology Of Chronic Obstructive Pulmonary Disase (COPD)

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable population disease characterised by persisting and generally progressive airway obstruction. Increased resistance of airflow results from an abnormally intense inflam-

matory reaction in the lungs triggered by inhalation of gases and particles harmful for lung tissue. In Hungary, 21% of registered patients have mild, 48%-have moderate, 23% have severe, and 8% have very severe COPD based on spirometry test results.

### Incidence, prevalence

COPD is the 4th-6th most common cause of mortality globally. According to a report by the Burden of Obstructive Lung Disease (BOLD) programme, in 2010, the estimated number of patients suffering from COPD was 384 million which corresponded to the 11.7% (95% CI: 8.4%-15.0%) global prevalence. Due to a continuous increase in prevalence an estimated 5.4 deaths are expected to be associated with COPD in the upcoming 40 years, by 2060.

In Hungary, in 2020, COPD incidence was 7 996 persons (4 176 males, 3 820 females). Between 2010 and 2019, the number of incident cases ranged between 17 744 and 12 256. Low incidence numbers in 2020 were associated with restrictions implemented due to the Covid-19 pandemic. Prevalence in 2020 was 193 725 (96 989 males, 96 736 females). Prevalence has been higher than 100 000 since 2007; in 2000 there were only 48 795 registered cases.

### Risk factors

- Genetic factors (inherited alpha-1 antitripsin deficiency which is a recessive autosomal deficiency)
- factors responsible for individual sensitivity and genetic polymorhisms e.g. AB0 secretor state, glutation-S-transpherase, epoxid-hidralase enzymes or alpha-1-chimotripsin allele polymorphism.
- Smoking is the most important risk factor; however, COPD develops only in 15-20% of chronic smokers. 40 pack years or higher of smoking is an important preditor, relative risk of smokers is 12-fold higher.
- concomitant asthma,
- increased airway hyperactivity,
- any form of impaired development of the lungs,
- occupational exposure to dust or chemicals,
- outdoor and indoor air pollutants,
- severe airway infections in childhood.

### Prevention

Smoking cessation is the first most important step. Heavy smokers may benefit from nicotine replacement products or other drugs (eg: vareniklin). Abstaining from smoking during and after pregnancy, avoiding the exposure of the child to passive smoking can also help reduce the risk of airway diseases in childhood.

## The Epidemiology of Depression

Depression is a mood disorder manifesting in prolonged sadness and loss of interest in previous activities. It may severely interfere with daily routine and patients may feel that they have no meaning in their lives

The exact cause of depression is not known, but hereditary factors, changes in neurotransmitter levels, changes in neuroendocrine function and psychosocial factors may all play a role in the development of the condition. Depression may need long-term therapy. Depressive disorders may present at any age, but prevalence is higher in adolescence, in the mid-20s or mid-30s. 30% of patients presenting at primary care service providers complain of symptoms of depression, but severe depression is only present in 10% of these cases.

**Diagnosis** is based on the presence of a mood disorder and the accompanying symptoms. Depression is confirmed if 5 of the following symptoms are present for at least two weeks; the first symptom group always has to be present: 1. Bad mood, sadness, feelings of emptiness and hopelessness throughout most of the day 2. Loss of interest in most previously enjoyed activities (e.g. sex, hobby or sport). 3. Significant increase or decrease of body weight and or BMI. 4. Sleep disorders (insomnia and/or excessive sleepiness, sleeping too much) nearly every day. 5. Anxiety, irritability or restlessness. 6. Loss of energy, fatigue, even small tasks require a lot of energy. 7. Feelings of guilt and uselessness, most of the time. 8. Difficulty concentrating. 9. Slow thinking, speech,

movement. 10. Loss of motivation. 11. Recurrent thoughts about death and suicide.

## Incidence, prevalence

Depression is a global epidemic, affecting an estimated 3.8% of the population out of which, 5.0% are adults and 5.7% are over the age of 60. Around 280 million people suffer from depression. As a result of the COVID-19 epidemic, especially reduced physical activity levels and higher daily rates of infection have been associated with increased prevalence of major depression and anxiety. The epidemic affected women and younger people more. In 2020, the incidence and prevalence of depression and anxiety disorder increased more markedly in countries with higher Covid rates. 54.1 million further cases are estimated globally (suggesting an increase of 28.1%). Total prevalence of depression increased up to 3 164.5 cases per 100 000 population. In total, major depression accounted for 49.5 million DALYs, anxiety disorder was responsible for 45.3 million (30.7–63.8) DALYs worldwide.

In Hungary, according to the European population survey of 2014, depresssive episodes occurred in 20% of men and 30% of women with 3.5% showing signs of severe depression. Severe forms of depression are more common among women (4.3%); men are less affected (2.6%). Depression occurs more frequently with age, more than 10% of the population over 74 years of age sufffering from severe depression. People with a lower educational background and/or in an unfavourable financial situation are more predisposed.

## Risk factors

- Women are more frequently diagnosed with depression than men, which is partly due to the fact that women are more likely to seek professional help. Men are more likely to use alcohol or other forms of addiction as a coping strategy, therefore, the diseases these forms of behaviour lead to may mask depression. High stress levels and hormonal changes affecting women may also contribute to the higher prevalence.
- ***earlier depressive episodes***,
- certain personality traits (e.g. low self-esteem, extreme dependency, pessimism, lack of independence, need of control, conformist behaviour),
- ***traumatic or stressful events*** (e.g. physical or sexual abuse, loss or death a beloved person, relationship issues, financial difficulties),
- sexual abuse in childhood, any other forms of abuse, mental disease of parents, divorce of parents;
- ***depression in the family history***, bipolar disorder, alcoholism or suicide ***in the family history***;
- non-supportive environment in the case of people with lesbian, gay, bisexual or transgender sexual orientation, or in the case of people with maldevelopment of genital organs;
- ***other mental disorders*** (e.g. anxiety, eating, posttraumatic stress),
- ***alcohol or abuse of recreational drug***s;
- ***severe or chronic disease***,
- ***use of certain medications***, for example certain anti-hypertension drugs or sleeping pills;
- ***low socio-economic status***, poverty;
- ***certain chronic diseases*** e.g. stroke, mental illnesses, hormonal disturbances; smoking (risk remains higher for 6 months after quitting);
- ***anxiety disorders***;
- sleep disturbances;
- **hormonal changes** (pregnancy, post-partum period, thyroid problems, menopause)

## Prevention

### Primary prevention

Effective community-level prevention strategies include school-based mental health development programmes aimed to facilitate positive coping mechanisms among small children and adolescents. Interventions programmes offered for the parents of children having behavioural problems may help relieve depression symptoms of parents and thereby, improve their children's condition as well. According to recent research, regular physi-

cal exercise helps prevent the development of depressive symptomatology.

**Secondary prevention**

Several short-form questionnaires are available for screening depression. A questionnaire survey, however, does not suffice for establisheing the diagnosis but may be useful in identifying people at risk who may need further, more in-depth assessment and evaluation. Frequently used measures include a Patient Health Questionnaire-9 (PHQ-9) and the Beck Depression Scale.

## References


1. A 2014-ben végrehajtott Európai lakossági egészségfelmérés eredményei. Összefoglaló adatok Központi Statisztikai Hivatal, 2018.
2. A cerebrovascularis kórállapotok elsődleges megelőzése agyérbetegségek 2004;10(4):4-8.
3. A cerebrovascularis kórállapotok másodlagos megelőzése Agyérbetegségek 2004;10(4):9-12.
4. Aberle DR, Adams AM, National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. New Engl J Med 365 (5):395-409, 2011.
5. American Cancer Society: Survival Rates for Breast Cancer. Accessed on 8/31/20.
6. Antal E, Ilyés I, Jancsó Z, et al. Kardiometabolikus rizikótenyezők - kardiovaszkuláris rizikóbecslés és kockázatbesorolás – rizikómenedzsment az alapellátásban. Gottsegen György Országos Kardiológiai Intézet.
7. Az Emberi Erőforrások Minisztériuma egészségügyi szakmai irányelve a diabetes mellitus kórismézéséről, a cukorbetegek antihyperglykaemiás kezeléséről és gondozásáról felnőttkorban 2020. EüK. 12. szám EMMI irányelv https://www.hbcs.hu/uploads/jogszabaly/3172/fajlok/2020_EuK_12_szam_EMMI_iranyelv_4.pdf
8. Az Emberi Erőforrások Minisztériuma szakmai irányelve az asztma diagnosztikájának, kezelésének és orvosi gondozásának alapelveiről felnőttkorban 2018. EüK 13. szám EMMI szakmai irányelv.
9. Barna I, Daiki T, Dankovics G, Kékes E, Kiss I. A hypertonia lakossági vizsgálata Magyarországon – 2011. Magyarország Átfogó Egészségvédelmi Szűrőprogramja 2010–2020. Hypertonia és nephrologia, 2013; 17, 1, 28-33.
10. Bogos Krisztina, Ostoros Gyula. Tüdőrák Korányi Bulletin 2021. 1. szám p.30-39.
11. Bősze P, Gőcze P, Hernádi Z, Pap K, Ungár L. (2009) A méhnyakrák szűrésének szempontjai: hazai irányelvek. In: Nőgyógyászati Onkológia, 14, pp 11-17
12. Böszörményi Nagy György. COPD Korányi Bulletin 2021. 1. szám p. 24-29.
13. Canfell, K. Towards the global elimination of cervical cancer. Papillomavirus Res. 2019, 8,100170. doi: 10.1016/j.pvr.2019.100170.
14. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: Detection, evaluation, and management: A Scientific Statement From the American Heart Association. Hypertension 72:e53-e90, 2018.
15. Cole SR, Young GP. Effect of dietary restrictions on partici- pation in fecal occult blood screening for colorectal cancer. Med. J. Aust. 175: 195-198. 2001.
16. COVID-19 Mental Disorders Collaborators. Estimating the global prevalence and burden of depressive and anxiety disorders in 2020 due to the COVID-19 pandemic. The Lancet. 8 October 2021. doi: 10.016/S0140-6736(21)02143-7.
17. Csoma Zsuzsanna. ASZTMA Korányi Bulletin 2021. 1. szám p.18-23.
18. de Koning HJ, van der Aalst CM, de Jong PA, et al. Lung-cancer mortality With volume CT screening in a randomized trial. New Engl J Med 382:503-513, 2020.
19. Döbrőssy L, Kovács A, Budai A, Simon J, Horváth AR, Cornides Á, Tulassay Zs. (2011). A vastag- és végbéldaganatok szűrésének vitatott kérdései: klinikai nézőpontok és a népegészségügyi nézőpon-

tok ütközése. Orvosi Hetilap, 152. évf. 31. sz. 1223-1232.
20. Döbrőssy L. Daganatok szűrése, minőségbiztosítási kézikönyv és módszertani útmutató. Országos Tisztifőorvosi Hivatal, Budapest, 2013.
21. Egészségügyi helyzetkép, 2019 www.ksh.hu
22. Emberi Erőforrások Minisztériuma EGÉSZSÉGÜGYI SZAKMAI KOLLÉGIUM Egészségügyi szakmai irányelv – A krónikus obstruktív tüdőbetegség (chronic obstructive pulmonary disease – COPD) diagnosztikájáról, kezeléséről és gondozásáról 2020.12.31.
23. Farsang Csaba és Járai Zoltán (szerk.). A magyar hypertonia társaság szakmai irányelve. A hypertoniabetegség ellátásának irányelvei 11., módosított, javított és kiegészített kiadás. Hypertonia és nephrologia 2018;22(SUPPL.5):S1-S36
24. Fontham ETH, Wolf AMD, Church TR, et al. (2020) Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society, CA Cancer J Clin 2020.
25. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2021 Report.
26. Global strategy towards eliminating cervical cancer as a public health problem. https://www.who.int/docs/default-source/cervical-cancer/cerv-cancer-elimn-strategy-16dec-12pm.pdf [Pécs, 2020. április 4.]
27. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019 Lancet Neurol 2021; 20: 795-820.
28. Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx). http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b
29. Jermendy G, Kiss Z, Rokszin G, Abonyi-Tóth Z, Wittmann I, Kempler P. Decreasing incidence of pharmacologically treated Type 2 diabetes in Hungary from 2001 to 2016: A nationwide cohort study. Diabetes Res Clin Pract 2019 Jul 19; 155:107788. doi: 10.1016/j.diabres.2019.107788.
30. Jermendy G, Nádas J, Szigethy E, Széles G, Nagy A, Hídvégi T, et al. Prevalence rate of diabetes mellitus and impaired fasting glycemia in Hungary – cross-sectional study on nationally representative sample of people aged 20-69 years. Croat Med J 2010; 51: 151-156. 14. IDF Atlas 6 ed. 2014. www.idf.org/sites/default/files/DA-regional-fact-sheets-2014_FINAL.pdf Letöltés: 2016. júl 24.
31. Jermendy Gy, Kempler P, Abonyi-Tóth Zs, Rokszin Gy, Wittmann I. A cukorbeteg-ellátás mutatóinak alakulása Magyarországon 2001-2014 között: az Országos Egészségügyi Pénztár adatbázis-elemzésének célja és módszertana. Orv Hetil 2016; 157: 1259-1265.
32. Karamánné Pakai A, Németh K, Dér A, et al. A szervezett méhnyakrák-szűrés távolmaradás okainak vizsgálata magyar nők körében. Orvostudományi Értesítő 81: 4 pp. 271-275, 5 p. (2008).
33. Kékes E, Barna I, Daiki T, Dankovics G. A vérnyomás értékek és a magas vérnyomás incidenciájának változása a magyar felnőtt populációban 2010-2018 között, a hazai népegészségügyi szűrés adatai alapján IME XX. évfolyam 2021/1. szám.
34. Kempler P, Putz Zs, Kiss Z, Wittmann I, Abonyi-Tóth Zs, Rokszin Gy, Jermendy Gy. A 2-es típusú diabetes előfordulása és költségterheinek alakulása Magyarországon 2001-2014 között – az Országos Egészségbiztosítási Pénztár adatbázis-elemzésének eredményei. Diabetologia Hungarica 2016; 24: 177-188.
35. Kiss I, Barna I, Dankovics G, Daiki, T, Kékes E. A MÁESZ Programbizottság nevében: Népegészségügyi prevenció Magyarországon II: megalapozott módszerekkel, megfelelő információval, valódi

szűrési eredmények „Magyarország Átfogó Egészségvédelmi Szűrőprogramja 2010-2020” (MÁESZ) – négyéves eredmények. LAM (Lege Artis Medicinæ). 2014; 24, 1-2, 43-48.
36. Kívés Zs, Endrei D, Elmer D, Csák T, Kajos LF, Boncz I, Mangel L, Mihály-Vajda R. A vastag- és végbéldaganat okozta országos epidemiológiai és egészségbiztosítási betegségteher Magyarországon. Orvosi Hetilap. Orv Hetil. 2021; 162(Suppl 1): 14-21.
37. Kívés Zs, Endrei D, Vajda R, Boncz I. A vastagbél daganatok népegészségügyi jelentősége Európában és Magyarországon Egészség Akadémia. 2019; 10(1-2): 36-48.
38. Kívés Zs, Kovács A, Budai A, Döbrőssy L, Vajda R, Endrei E, Boncz I. A Csongrád megyei vastagbélszűrési pilot program minőségi indikátorai és teljesítménymutatói, Magyar Onkológia. 2019; 63:125-132.
39. Koiss R, Boncz I, Hernádi Z, Szentirmay Z (2017). Javaslat a hazai méhnyakszűrési eljárásrend korszerűsítésére Orvosi Hetilap, 158 (52). pp. 2062-2067.
40. Kris Mg, Jhonson BE, Berry LT, et al. Using multiplexed assays of onvcogenic drivers in lung cancers to select targeted drugs JAMA 311 (19): 1998-2006, 2014.
41. Lindström J, Tuomilehto J. The diabetes risk score. A practical tool to predict diabetes risk. Diabetes Care 2003; 26: 725-731.
42. Liu L, Shi Y, Li T, et al. Leisure time physical activity and cancer risk: evaluation of the WHO’s recommendation based on 126 high-quality epidemiological studies. British Journal of Sports Medicine 2016; 50(6):372-378.
43. Marjorie L. McCullough*, Emilie S. Zoltick*, Stephanie J. Weinstein*, Veronika Fedirko*, Molin Wang, Nancy R. Cook, A. Heather Eliassen, Anne Zeleniuch-Jacquotte, Claudia Agnoli, Demetrius Albanes, Matthew J. BCirculating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts JNCI J Natl Cancer Inst (2019) 111(2): djy087.
44. Millei K, Vajda R, Kívés Zs, et al. HPV-fertőzéssel kapcsolatos ismeretek vizsgálata édesanyák és leányaik körében. Egészségfejlesztés 56: 3 pp. 9-16, 8 p. (2015).
45. Németh N, Endrei D, Elmer D, Csákvári T, Horváth L, Kajos LF, Cziráki A, Boncz I. A heveny szívinfarktus okozta országos epidemiológiai és egészségbiztosítási betegségteher Magyarországon Orv Hetil. 2021; 162(Suppl 1): 6-13.
46. Network GA. The Global Asthma Report, Auckland, New Zealand. (2018).
47. Nicole M, Niehoff, Hazel B, Nichols, Shanshan Zhao, Alexandra J, White and Dale P, Sandler. Adult Physical Activity and Breast Cancer Risk in Women with a Family History of Breast Cancer Cancer Epidemiol Biomarkers Prev; 28(1) January 2019.
48. Országos Egészségbiztosítási Pénztár: Osteoporosis következtében kialakuló csonttörés primer prevenciójának finanszírozási protokollja (eljárásrend) Budapest, 2013.
49. Pakai A, Brantmüller É, Vajda, R, et al. Reasons for non-appearance on organized cervical screening in Hungary. Practice and theory in systems of education 11:2 pp.142-154, 13 p. (2017).
50. Pakai A, Dér A, Kriszbacher I, et al. Why don’t Hungarian women take part in organized cervical screening? NEW MEDICINE 2010: 1 pp. 25-28, 4 p. (2010).
51. Rajabi AA, Geraldine LS, Alianu KA, et al. Towards refining World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations for red and processed meat intake: insights from Alberta’s Tomorrow Project cohort Br J Nutr 2021 Apr 8;1-12.
52. Rátgéber L, et al. The effect of physical exercise on arterial stiffness parameters in young sportsmen. (2015) ACTA CARDIOLOGICA 0001-5385 70 1 59-65.
53. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. IDF Diabetes Atlas Committee: Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results

from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019 Nov; 157:107843. doi: 10.1016/j.diabres.2019.107843.
54. SCORE2 working group and ESC Cardiovascular risk collaboration: SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe European Heart Journal (2021) 42, 2439-2454.
55. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement US Preventive Services Task Force JAMA. 2021;325(19):1965-1977.
56. Screening for Lung Cancer US Preventive Services Task Force Recommendation Statement JAMA. 2021;325(10):962-970.
57. Spei ME, Samoli E, Bravi F, et al. Physical activity in breast cancer survivors: A systematic review and meta-analysis on overall and breast cancer survival. Breast 2019; 44:144-152.
58. Szőcs I, Bereczki D, Belicza É. [Results of stroke care in Hungary in the frame of international comparison]. Orv. Hetil., 2016, 157(41), 1635-1641.
59. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. (2012) 12:5. 10.1186/1471-2458-12-204.
60. Vajda R, Pakai A, Éliás Zs, et al. A méhnyakrákkal kapcsolatos ismeretek és szűrővizsgálaton való részvételi mutatók vizsgálata. Lege Artis Medicinae 24:3 pp.118-125 (2014).
61. Vajda R, Kívés Zs, Éliás Zs, et al. A humán papillómavírussal (HPV) kapcsolatos attitűdvizsgálat. Magyar Nőorvosok Lapja 77:3 pp.18-25 (2014).
62. Veettil SK, Wong TT, Pharm B; Loo SY, et al. Role of Diet in Colorectal Cancer Incidence Umbrella Review of Meta-analyses of Prospective Observational Studies JAMA Network Open. 2021;4(2):e2037341. doi:10.1001/jamanetworkopen.2020.37341
63. Vértes A, Szabados E. Cardiovasculáris prevenció – 2016 Orv. Hetil., 2016, 157(38), 1526-1531.
64. Winkler G, Hidvégi T, Vándorfi Gy, Balogh S, Jermendy Gy. Kockázatalapú diabetesszűrés háziorvosi praxisokban, felnőtt egyének körében. Diabetologia Hungarica 2011; 19: 111-122.
65. World Cancer Research Fund/American Institute for Cancer Research Recommendation and public health and policy implication, 2018.
66. World cancer research Fund/American Institutefor Cancer Research: Colorectal cancer report 2017.
67. World Health Organization The top 10 causes of death https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
68. Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288 (3):321-333, 2002.
69. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study g, on behalf of the INTERHEART Study Investigators Lancet 2004; 364: 937-52.

# V. Genetic Epidemiology

Oszkár Juhász

## What is genetic epidemiology?

Population genetics deals with the quantitative characterization and interpretation of intra-species diversity and the exploration of processes influencing diversity. Its methods, terminology and general results are used in many fields that apply the caoncept of population (e.g. systematics, ecology, nature conservation, anthropology).

Genetic epidemiology is a young discipline that originally evolved from population genetics, more precisely, from the combination of human quantitative genetics and epidemiological methodology. Its subject is the study of how genes and environmental factors affect human characteristics as well as human health and disease. During its development, the discipline has been defined in several ways by researchers. The term was first used by Morton and Chung (1978), by their definition, a science that deals with the etiology, distribution, and follow-up of diseases among relatives and the hereditary causes of diseases within populations. According to Mitchell L. Cohen (1980), it examines the combined role of the environment and genetic factors in the development of diseases, in addition to taking into account the different effects of environmental agents on both familial and non-familial genetic backgrounds. King et al. (1984) defined it based on how and why diseases accumulate in families and ethnic groups. In 2003, Morton's definition was further developed by Muin J. Khoury, Julian Little, and Wylie Burke to create the term "human genome epidemiology," which uses methods of epidemiology to understand the impact of genomic variations on health and disease, going beyond the effects of individual genes. James V. Neel, founding president of the International Society for Genetic Epidemiology (IGES), says it deals with „the study of the genetic components of complex biological phenomena." It can be seen from the above - as is the case with other young disciplines - the definition is still evolving.

Today's modern epidemiological genetics covers all diseases. For this reason, many advances in the epidemiology of genetic diseases are related to seemingly simple hereditary disorders (e.g., cystic fibrosis, sickle cell disease). However, the results also indicated that even monogenic disorders can be extremely complex due to the interactions of epigenetic factors, disease genes, with environmental factors. In addition to a broad focus on genetic diseases, genetic epidemiology includes various aspects of epidemiology.

Genetic epidemiology is of practical importance in several respects. First, exploring the etiology of a disease facilitates the understanding of the mechanisms of the disease and the development of logically targeted diagnostic, preventive, or therapeutic treatments. Second, in theory, if we know the genetic factors behind the disease, risk profiles can be determined. In this way, for example, asymptomatic relatives of patients who have undergone genetic testing may help to assess the risk of developing the disease. Third, clinicians will be able to select the appropriate therapy in the future based on pharmacogenetics — the genetically determined chances of a good, bad, or unfavorable response to a drug. Finally, the examination of known mutations allows a more accurate diagnosis of certain diseases, such as typing in acute lymphoblastic leukemia (which allows specific therapy to be used).

## Subject of genetic epidemiology

Genetic epidemiology basically tries to answer 2 questions: (1) is there a genetic component to the disease, and (2) what genes play a role in its development?

To understand genetic epidemiology, we also need

to be on familiar terms with three topics. The first is basic genetics, so we need to know the nature of hereditary material, the concept of chromosomes in alleles, and the basic laws of genetics. The second is research methodology, as thorough design of the studies is essential. The third topic requires statistical knowledge for the interpretation and evaluation of the results of the research.

Whether a disease has a genetic component can be determined by studying relatives. If the disease appears more frequently than expected in the patient's relatives, it is reasonable to conclude that it is a disease with hereditary components. [3] There are diseases for which familial accumulation is evident, their pattern of inheritance is clearly visible, these are called monogenic or Mendelian diseases. Mendelian diseases are caused entirely by a single genetic mutation in either or both alleles. Mendelian inheritance can take place in several ways. For example, the vast majority of cases of Stargardt's macular dystrophy are caused by a mutation in an autosomal recessive gene. This means that for the development of the disease, both alleles of the gene involved must be abnormal, i.e., a single normal copy of the allele can prevent expression of the gene. In contrast, in the case of autosomal dominant inheritance, such as in vitelliform macular dystrophy, only a single pathological allele is sufficient for the disease to develop. There is even codominant inheritance, which can occur if both alleles contribute to phenotyping.
Most diseases are not inherited according to simple Mendelian laws, but are the result of more complex multifactorial processes, which is why they are called complex. Such diseases are caused by the combined, small effects of each component. These can be genetic or non-genetic environmental factors such as age or smoking. Susceptibility to multifactorial disease can be increased or even decreased by different genetic variants.

## Identifying the genetic factors of a disease

The genetic component of multifactorial diseases such as AMD (age-related macular degeneration) was traditionally explored by examining family members. Epidemiological studies have shown that relatives of patients with AMD are more likely to develop AMD. If the appearance of the phenotype to be studied is monitored within families (e.g., diabetes, glaucoma, or schizophrenia), segregation analysis can be used to determine whether or not we can talk about family accumulation. That is, in each generation, the number of people showing the phenotype to be tested is counted. In general, the family accumulation of multifactorial diseases is modest, which may indicate that the effect of any genetic component is also weak. If a disease is frequently observed in relatives, it may indicate that genetic factors also influence the development, but it is not sufficient, as several other environmental or other factors may accumulate in the family because relatives in the same household are likely to consume the same diet or are exposed to the same toxic fumes from an industrial area near their home, and so on. A specific example is that spouses of patients with lung, colon or stomach cancer are at higher risk of developing the same diseases as second-degree relatives, and there is no genetic relationship between them.

Twin studies can be extremely useful in determining the heritability of a phenotype. If a disease is more common in both members of monozygotic (identical) twins than in dizygotic (fraternal) twins, it is more likely to occur due to genetic effects. This is proven to be the case with AMD.
The disadvantage of segregation analysis is that it does not provide enough evidence alone on the influence of genetic factors, so even genetic testing is needed. In order for the tests to be repeatable, it is essential to specify the expressed nature of the test subject. There are so-called phenocopies, which are inherited diseases that, despite the presence of defective allele(s), do not or less manifest as a result of environmental effects (e.g. under the influence of drugs). In this case, the environment does not actually allow the effect of the faulty gene to be expressed. However, it is possible that a disease with an otherwise genetic background can develop solely due to environmental factors, such

as severe injuries or infections (e.g. deafness caused by rubella infection), despite healthy alleles. We talk about abnormal phenocopy if the phenotype is abnormal despite the normal genotype, and we talk about normal phenocopy if there is a normal phenotype despite the abnormal genotype. Speculatively, for example, there are several different pathological processes that result in symptoms of a particular disease, each with a different genetic predisposition, and each may be specific to different ethnic groups, geographic regions, or family trees. If different genetic changes in different individuals can lead to the same disease, then we can talk about locus heterogeneity. In addition, incomplete penetrance may occur when the (percentage) expression of the same genotype differs between different individuals. The same genotype may be expressed in different ways due to several effects: another unknown epistatic gene (one allele of the gene does not allow the other to express) and/or untested epigenetic factors such as DNA backbone methylation, which affect gene expression. (The science of epigenetics is looking for answers on how the expression of inherited traits is affected by environmental influences. These external influences affect the function of genes by altering the nucleotide sequence of DNA but altering the chemical structure of DNA). Furthermore, the effect of a gene may depend on exposure to an environmental factor. For example, one of the risk factors for AMD is smoking, so the exact genetic contribution may depend on smoking habits. Although this is obvious, the changing exposure to unknown environmental factors makes it difficult to analyze the effect of genes. The task for the future will be to study together the genes in distant parts of the genome that affect each other, and to study the myriad possible interactions between gene expression and environmental factors.

These processes can also be studied at levels of the family and population, which have both advantages and disadvantages. Which procedure is worth using depends on exactly what the study wants to accomplish and what resources are available. Family tree-based studies are particularly useful in selected families with a high incidence or severe or early-onset type of disease. Such families are worth studying, because they increase the number of cases of common genetic basis and increase the strength of the test used to detect genetic effects, especially when a rare mutation causes susceptibility. For example, in breast cancer, mutations in the BRCA genes increase the risk of developing it. There are many types of mutations in the BRCA gene, and because each mutation is rare and may only occur in a particular family, it may not be detectable in population-based studies, so family-based studies are needed.

However, there are drawbacks to studying family trees. There may be potential statistical pitfalls in the interpretation of data obtained by nonrandom selection methods, and the calculations required for evaluation may be complicated. Gathering large numbers of families with affected members is a time consuming and cumbersome process. Furthermore, in the case of age-related conditions, the number of families that can be tested is limited, as it is unlikely that the patients' parents and possibly siblings are still alive, and in the case of the disease in old age, it is not possible to know whether it appears in the offsprings, as they are too young to produce symptoms.

The problem with population-based studies is that the sampled population may contain hidden subgroups that may differ in terms of risk factors. For example, analysis of a sample of multiple ethnic origins may obscure or exaggerate a genotype-disease relation that appears in only one subgroup. In population-based studies, it should be ensured that the sampled population is as homogeneous as possible and that cases can be divided into separate subgroups based on potential confounders. It is also important that patient and control samples can be compared in each subgroup as well. However, information on relevant confounders may be incomplete, thus defining subgroups can be quite cumbersome.

## Identification of the gene or genes concerned

### Mendelian diseases

The first diseases associated with specific genes had a simple Mendelian inheritance process. For example, Huntington's disease, Duchenne muscular dystrophy (DMD), and cystic fibrosis (CF) have also been shown to be cumulative among relatives and follow Mendel's pattern of inheritance. DNA samples from members of the affected families were subjected to genetic mapping, during which markers at selected points in the DNA strand were selected and followed their intergenerational pathway in the affected families. This method is analogous to genetic experiments in Morgan's lab (they studied a phenotypic marker through generations of fruit flies, for example, their monogeneously inherited eye color).

Since the entire human genome sequence is known thanks to the Human Genome Project, a single-nucleotide polymorphism (simple or single nucleotide polymorphism), better known as SNP, is now used as a marker instead of the now-classical molecular markers. According to the original definition, a single-nucleotide polymorphism is a variant DNA sequence resulting from a change in a nucleotide that occurs in at least 1% of the population. Today, their definition has been partially modified: SNPs are all kinds of deviations involving a single nucleotide, but the frequency of the rare allele (MAF = Minor Allel Frequency) must be provided in each case. MAF is not yet precisely defined, but is generally considered common if > 5%, low if it is between 0.5 and 5%; and rare if it is <0.5% (in some publications the latter is only 0.3%). SNPs can be used as codominant markers of Mendelian hereditary, have a low mutation rate, and can be analyzed by statistical methods based on genotype frequency. SNPs can often be associated with adaptive features and have different consequences depending on where they occur in the genome. SNPs can appear at any section of the genome, in the coding or non-coding regions of genes, or even in intergenic regions. In the coding section, a distinction is made between synonymous (causing a "silent" mutation) and non-synonymous (causing a "missense" or "nonsense" mutation) SNPs. SNPs in the non-coding region may be intergenic, or in the UTR regions of exons (untranslated regions, that is, non-protein-translated regions), or in introns, in regulatory regions, and consequently may affect transcription, translation, mRNA maturation, splicing, the binding of transcription factors. SNPs occur in the human genome on every 100-300 nucleotides on average; they are universal, and the most common polymorphism markers. There are several methods for its detection, such as direct sequencing of amplicons (PCR products) and targeted re-sequencing. In the latter process, the samples are compared to a known reference genome. It is also possible to use Genotyping By Assay (GBA) methods, which operate indirectly on the basis of different motility of DNA fragments. In addition, methods based on hybridization are used on a target sequence immobilized on a microchip. Next Generation Sequencing eliminates the need for targeted marker development, allowing comparative analysis of large amounts of sequences. One such new generation method is Genotyping By Sequencing (GBS). The advantage of this method is that SNPs are identified and genotyped simultaneously.

Due to the continuous development of genotyping, several methods are usually applied together. The choice of the appropriate method is based on the cost, efficiency, and available resources of the process. Traditional techniques include PCR-based SNP-RFLP analysis (RFLP: restriction fragment length polymorphism) and SNP-SSCP (single-strand conformation polymorphism) analysis, or also called PCR-RFLP and PCR-SSCP, however, they have the disadvantage that they are slow and difficult to perform.

SNP-RFLP analysis and SNP-SSCP analysis are based on PCR (or Southern blot). PCR (polymerase chain reaction) is an in vitro DNA synthesis method that allows short DNA segments to be chain-reacted in millions of copies in a matter of hours. In the process, the nucleic acid to be tested (DNA or RNA) is cleaved with restriction enzy-

mes (cleaved nucleic acids at a specific sequence). Following denaturation, synthetic oligonucleotides are attached to the DNA preparations (by complementary base pairing). These oligonucleotides function as primers, so that DNA polymerase attaches nucleotides defined by the template strand to the 3' end of the primer during synthesis. In the process, both strands are duplicated. PCR consists of a cyclic repetition of 3 steps: 1. denaturation (95 °C); 2. primer binding (55 °C); 3. DNA synthesis (72 °C). The repetition of the cycles is ensured by a computer-controlled PCR (thermocycler). The mixture must contain the substrates required for the process and the DNA polymerase. Since the process requires high temperatures, DNA polymerase (e.g., Taq polymerase) is isolated from bacteria living in heat sources. The essence of SNP-RFLP analysis is that due to point mutations, known restriction sites may shift or even disappear, resulting in fragments of a different size than the wild type. During PCR, these fragments are amplified and detected by electrophoretic methods (e.g., gel electrophoresis).
The first step in SNP-SSCP analysis is also PCR. This is followed by denaturation and immediate cooling of the double-stranded PCR product formed in the process, resulting in single-stranded DNA strands, which can also be evaluated using electrophoretic methods. In the case of SSCP, polymorphism is not due to the different size of the fragments, but to the different migration rates resulting from the secondary spatial structure determined by the base sequence of the single-stranded DNA strands.

In the case of multifactorial diseases, the search for the responsible genes is much more complicated, thus several procedures are used. One such method is called "Linkage Analysis" and is suitable for monitoring the intergenerational inheritance of genetic markers. In addition, it is an effective tool for determining the chromosomal location of the disease-causing gene.
In the case of multifactorial diseases, genetic mapping can be performed by the application of association studies. When examining the polymorphism of a candidate gene, association means that a given allele occurs significantly more frequently with a given phenotype than would be expected. Association studies hypothesize that a genetic variant is more common in individuals with the disease than in those without the disease. It can be assumed that multifactorial diseases are defined to some extent by a group of alleles that may be common (with a frequency of at least 1%) in the population but have no significant effect on the disease or the predisposition to the trait under study. Association studies have greater statistical power than linkage studies if we want to detect a gene with a mild effect. However, their application to separate complex diseases presents challenges. The reliability of a test used to detect genes for susceptibility to a disease depends on the size of the sample, the frequency of the alleles involved, and the magnitude of their effect. Therefore, a large number of samples are usually required to identify low-impact genetic changes. The results of the studies should be combined in meta-analyzes to increase their statistical power. Association studies can be divided into two groups: candidate gene studies and genome-level association studies. Candidate genes play a key role in the development of the disease. When testing candidate genes, a gene is selected within the gene that is thought to cause susceptibility. Variants are tested on patient and control samples for association with disease or trait. The basic assumption regarding the association is that the gene plays an important role in the development of the disease. The gene is selected based on experimental data. We know that susceptibility loci usually occur in the introns of DNA, but current knowledge is not sufficient to predict which variants actually have an effect. Therefore, candidate loci are usually derived from the coding or promoter regions. If a candidate gene can be associated with the disease, it does not necessarily have a causal relationship, as the mechanisms of multifactorial diseases are poorly understood. The exact effect of an SNP or haplotype can also be speculative. Therefore, studies should be repeated in different populations.
Genome-level association studies are screenings that examine thousands of markers in a large number of samples throughout the whole geno-

me. This method has a high chance of identifying a group of markers that may be associated with the disease. This suggests that there may be a link between the markers and the susceptibility gene, thus they may be relatively close to each other. A number of markers need to be examined in association studies. Although technological advances have made it possible to analyze thousands of markers rapidly and at an acceptable cost, association studies are believed to be ineffective enough to detect small effects. If researchers do not find a significant correlation during their studies, they usually conclude that a larger sample size or denser marker coverage would have shown the monitored effect. The HapMap project could be a solution to eliminate this problem. HapMap, short for "haplotype map," is a catalog of unique SNP variations that eliminates the need to track large amounts of markers at one time. The advantage of haplotypes is that it is sufficient to select a single SNP in each haplotype because it can represent the entire haplotype. Thus, information on any haplotype can be analyzed by measuring a single SNP.

One of the potential pitfalls of association testing is that tens of thousands of SNPs need to be tested in many thousands of individuals to ensure the reliability of an association study, which can be costly and cumbersome. Consequently, it is inevitable that many SNPs will be associated with the disease merely by chance. If the significance level is set to 0.05 or less, 5% of the associations tested will be positive. Therefore, it is important to perform a post-hoc analysis of the results (showing whether the relationship between two measured parameters is significant). Testing with such a large number of items will inevitably show some statistically significant correlation, thus it is necessary to repeat the test several times. therefore, when a positive association cannot be re-detected, it is likely that the original result was false positive. (There are statistical methods to solve the problem of multiple comparisons.) Another possibility is that the cause of the failure is to be found in deviations from the original studies. Studies that presumably have the same correlations may differ in many ways, for example, samples may differ in their ethnic or environmental exposure. Different SNPs can be tested; in the case when only one non-synonymous SNP per gene type is tested in one experiment, while another known SNP is tested for the same gene type in another experiment. Different levels of experimental error may also occur during genotyping (or sequencing) of SNPs. Due to the different types of the disease, different control samples can be selected and different levels of statistical significance can be set to compensate for other errors. Most association studies are case-control-based (retrospective) and are therefore subject to potential for error in all case-control studies. Other variables that affect the phenotype may not be measured, potentially leading to erroneous conclusions. Accurate measurement of environmental factors is difficult because, in general, testers should rely on the subject to recall the level of exposure. Family-based association studies can eliminate potential confusing effects by testing families sampled from a given population instead of comparing randomly selected cases and controls, for example, it is possible to examine a siblings, one of whom has the disease while the other does not. With the same sample size, such arrangements provide better performance, but sufficient families to meet the conditions must be found, and tracking family members can be problematic.

## Common genetic diseases

Mendelian inherited diseases are caused by a mutation in a high-impact gene, three types can be distinguished within the group: Autosomal dominant, autosomal recessive, and X-linked.

Autosomal dominant diseases can affect structural or receptor proteins, and in some cases, the mutant protein interferes with the function of the normal protein ("negative dominant effect"). In such cases, decreased penetrance and variable expression are observed, and symptoms usually begin later, only in young adulthood. If one parent is involved, in principle, 50% of the offspring will show the abnormal phenotype. Such diseases include: Huntington's disease; Neurofibromatosis; Tuberous sclerosis; Marfan syndrome; Ehlers-Danlos

disease; Osteogenesis imperfecta; Achondroplasia; Polycystic renal disease; Polyposis familiaris coli; Familiar hypercholesterolemia; Porphyria acute intermittens; Hereditaer spherocytosis; von Willenbrand disease.

- Huntington's disease is a genetic disorder affecting the central nervous system. It causes progressive degeneration of brain cells, leading to degeneration of motor skills and cognitive abilities, as well as behavioral difficulties. It is a rare disease that affects men and women equally (only 7-10 out of 100,000 are affected). Therapy consists of treating the symptoms of the disease.
- In neurofibromatosis, in addition to characteristic skin lesions, benign tumors develop in the nerve fibers and nerves in the brain. It affects 1 in 2,500 people (twice as many boys as girls). Depending on which defective gene the child inherited, two types of neurofibromatosis are distinguished: neurfibromatosis I (NF1) and neurfibromatosis II (NF2). Increased formation of malignancies can be expected in some types.
- In Sclerosis tuberosa, naturally benign tumors develop in several vital organs. It affects 1 in 12,000 people, but new gene mutations (i.e. not inherited from parents) are common: they occur in 58-68% of cases. Since the brain, kidneys, heart, lungs, and skin can be affected, the symptoms are very varied: seizures, developmental abnormalities, behavioral problems, skin lesions, and lung and kidney disease. The symptoms caused by the diagnosed diseases can be treated, but the disease itself cannot be cured. The symptoms are caused by the Tuberosus Sclerosis Complex 1 and 2 (TSC1/2) genes, which encode peptides called hamartin and tuberine, which can affect cell proliferation.
- Autosomal recessive diseases are the largest group of diseases with Mendelian inheritance. If the parents are heterozygous, 25% of the offspring will be ill and it will manifest in early childhood. Its expression is much more uniform compared to the dominant diseases, characterized by 100% penetrance. Enzyme proteins are most commonly affected. Such diseases include: Cystic fibrosis (Mucoviscidosis); Haemochromatosis; Phenylketonuria; Galactosaemia; Sickle-cell anemia; Homocystinuria; Thalassemia; Alkaptonuria; α1-antitrypsin deficiency; Friedreich ataxia; Wilson's disease; Spinal muscular atrophy.
- Cystic fibrosis is the most common type of disease in Europe, 1-2 patients out of four thousand in Hungary, while 4-5 percent of them carry the disease. The symptoms are caused by a malfunction of the cell wall transport protein, which is responsible for the moisture of the outer and inner mucous membranes and the density of the secreted mucus, thus the glands in the body produce much denser secretions than normal. Symptoms can include digestive problems, infertility, and even life-threatening lung infection. The dense mucus clogs the passages of the separating glands, which become which cystically (nodularly) enlarged, hence the name of the disease. Its formation is due to mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene; the coding site for the defective protein is on chromosome 7 in DNA.
- Phenylketonuria is caused by a gene defect on chromosome 12. The enzyme that breaks down phenylalanine (an amino acid that is involved in building of proteins) does not function or malfunctions. As a result, phenylalanine builds up, which the body tries to break down in other ways, but this leads to the formation of toxic, abnormal end products that damage various organs. The disease can be diagnosed in 1 to 10 cases per 1 million live births, mostly in boys The disease is rare, it is diagnosed in 1 sick child per 1 million live births in Hungary.
- Sickle-cell anemia is caused by an inherited point mutation on chromosome 11. It is common in the Mediterranean and African regions, but we can also find it in Hungary. The disease in the red blood cells changes the hemoglobin composition; a molecule

called HbS is formed in large proportions, which is able to suppress normal hemoglobin. The HbS molecule, on the other hand, assumes the characteristic sickle shape in small vessels in an oxygen-deficient environment due to slow flow and precipitates. The abnormal HbS molecule is thus unsuitable for oxygen transport and also blocks small blood vessels, causing infarction in some organs.

- All sex chromosome-bound diseases are X chromosome bound because most of the genes on the Y chromosome are responsible for the development of the male gonad. In the case of these mutations, the person is infertile (e.g., Del Castillo's syndrome: aspermiogenesis). In hemizygotic men who carry the mutant X chromosome-bound gene, the disease is expressed. Male children of such men will be healthy, and all their daughters will be heterozygous (carrier) if the mother has a healthy sex chromosome. In heterozygous women, the disease may be partially expressed due to random X inactivation (lyonization). Examples of such diseases are: Duchenne muscular dystrophy; Wiskott-Aldrich syndrome; Haemophilia A and B; Hyper IgM syndrome; Chronic granulomatous disease; Diabetes insipidus; Glucose-6-phosphate dehydrogenase deficiency; Lesh Nyhan syndrome; Agammaglobulinemia (Bruton); Fragile X syndrome.
- In Duchenne muscular dystrophy, muscle cells are gradually replaced by adipose tissue and connective tissue that are unable to perform muscle work, and the patient becomes weaker and eventually self-sufficiency also becomes challenging. It is mainly expressed in boys, occurring in 0.27% of live-born boys. Girls are much less likely to develop the disease, but more likely to carry the disease (heterozygotes). Spontaneous onset of the disease may occur. 30% due to some mutagenic effect (e.g. ionizing radiation). Symptoms of the disease are caused by the lack or synthesis of a protein called dystrophin. Due to lack of protein activity, calcium ion concentration in muscle cells rises drastically, causing them to die.
- Wiskott-Aldrich syndrome causes microthrombocytopenia, combined immunodeficiency (recurrent infections), and eczema. The disease can be diagnosed in 1 to 10 cases per 1 million live births, mostly in boys. The genetic defect is that the Wiscott-Aldrich syndrome protein is not present in hematopoietic (blood-forming) cells at all or only in insufficient amounts.
- The cause of the disease is a fraction of the level of coagulation factor VIII in hemophilia A and of coagulation factor IX in hemophilia B, approx. 1-5 percent, of normal value. Due to the failure of the coagulation cascade, bleeding of varying severity occurs at certain parts of the body, mainly affecting the skin, skeletal muscles and joints, but can occur in almost any organ (stroke, gastric bleeding, etc.). Vast majority of bleeding occurs in areas of the body subjected to increased stress, in large joints load-bearing joints (knee, hip, shoulder, wrist, elbow). Incidence of haemophilia: one in 5,000 neonates. Hemophilia B accounts for 15 percent of cases. Hemophilia is very rare in women and they may be more likely to be carriers of the disease.
- Chronic granulomatosis is an immunodeficiency disease caused by a defect in phagocytic cells. Under the influence of pathogens, granulomas can appear in many parts of the body: in the skin, mucous membranes, lymph nodes and internal organs, joints and bones. In essence, due to the malfunction of phagocyte oxidases, granulocytes and mononuclear phagocytes are unable to convert extracellular oxygen into toxic metabolites, thereby lacking the ability to eliminate pathogens. The disease usually occurs in young childhood, but in rare cases, it can also manifest in adulthood.
- The cause of the symptoms of diabetes insipidus is that, due to the disease, the body is unable to retain water. There are two

types, central diabetes inspidus and nephrogenic diabetes insipidus. In central diabetes inspidus, the hypophysis (pituitary gland) is characterized by a partial or complete lack of production or excretion of ADH vasopressin and affects 1 in 25,000 people per year (the incidence is the same in men and women). The central variety is characterized by a partial or complete lack of production or excretion of vasopressin. It is a chronic disease that can start suddenly and end suddenly. Central diabetes insipidus is an uncommon disease; one in 25,000 people develop the disease every year. It is equally common in women and men. In nephrogenic diabetes insipidus, the kidneys will be completely resistant to the hormone produced or to exogenous hormone preparations, thus the water-binding effect will not prevail.

## References


1. Guerra, S. and Meaney, F. John (2016, August 4). Genetic epidemiology. Encyclopedia Britannica. https://www.britannica.com/science/genetic-epidemiology
2. Williams MA, Carson R, Passmore P, Silvestri G, Craig D. Introduction to genetic epidemiology. Optometry. 2011 Feb;82(2):83-91. doi: 10.1016/j.optm.2010.01.014. Epub 2010 Oct 13. PMID: 20947437.
3. Burton PR, Tobin MD, Hopper JL. Key concepts in genetic epidemiology. Lancet 2005;366(9489):941-51.
4. Toth Gy, Endre & Attila, Köbölkuti & Andrzej, Pedryc & Maria, Höhn. (2015). SNP markerek és használatuk fenyőfajok molekuláris genetikai vizsgálatainál (Review). Kertgazdaság. 47. 79.
5. Nachman, MW. (2001). Single nucleotide polymorphisms and recombination rate in humans. Trends in Genetics, 17. (9): 481-485.
6. International Human Genome Sequencing Consortium. (2001): Initial sequencing and analysis of the human genome. Nature, 409: 860-921.
7. Duran, C, Appleby, N, Clark, T, Wood, D, Imelfort, M, Batley, J. Edwards, D. (2008): AutoSNPdb: an annotated single nucleotide polymorphism database for crop plants. Nucleic Acids Res., 37: 951-953.
8. Pyhajarvi, T, Hufford, MB, Mezmouk, Ross-Ibarra, J. (2012): Complex patterns of local adaptation in teosinte. arXiv:1208.0634 FALUS, 2006.
9. Brutlag, D, Das, R, Sherlock, G, Snyder, M, Karp, P. (2014). Computational Molecular Biology, http://biochem218.stanford.eu/
10. Pavy, N, Parsons, L, Paule, C, Mackay, J, Bousquet, J. (2006): Automated SNP detection from a large collection of white spruce expressed sequences: contributing factors and approaches for the categorization of SNPs. BMC Genomics.
11. Andolfatto, P, Davison, D, Erezyilmaz, D, HU, T. T., Mast, J., Sunayma-Morita, T, Stern, D. L. (2011). Multiplexed shotgun genotyping for rapid and efficient genetic mapping. Genome Res, 21:610–617. (Jehan et al., 2006.)
12. Sebastiani, F, González-Martínez, CS, Vendramin, GG. (2003). Review on single nucleotide polymorphisms (SNPs) and population genetic studies in conifer species. Euforgen. Conifers Network, Report of the fourth meeting, 19-27. (Jehan et al., 2006; Rafalski et al., 2002).
13. Puck, J. M, Candotti, F.: Lessons from the Wiskott-aldrich syndrome. N Engl J Med, 2006, 355,1759-1761.

# VI. Molecular epidemiology

Zsuzsanna Orsós, István Kiss

Molecular epidemiology is one of the most dynamically developing fields in recent decades, yet for many it is still a bit of an elusive concept. Advances in medicine have increasingly required us to exactly know the mechanisms that lead to the development of the disease.

At the beginning, regarding the process by which a symptomatic disease develops in a healthy individual as a result of adverse exposures little or no was known. Traditional epidemiology marked the longer, shorter period that elapses between different exposures to the body and the disease as a black box. We were not aware of the molecular changes / processes taking place in our body, their background was covered in darkness. The black box of molecular epidemiology has become an adage (Figure 1).

Due to the extremely rapid development of molecular biology, this box now contains fewer and fewer black spots. To date, molecular epidemiology has largely revealed numerous markers of exposure, effect, and disease, and we are also increasingly aware of individual sensitivity factors for the development of disease (Figure 2). Without molecular testing methods and the precise definition of molecular biological factors, medical diagnostics and individualized treatment would be inconceivable. It is important to mention that nowadays, as the emphasis shifts more and more from healing to prevention, the role of molecular epidemiology in prevention is becoming even more emphasized.

Molecular epidemiology now provides the basis for both primary and secondary prevention. Throughout our lives, we encounter countless compounds, both directly and indirectly. Many are exposed to various harmful factors due to their occupation and others due to their lifestyle. The 21st Century test methods can be used to determine concentrations of pollutants in soil, air or water and to limit the quantities of emission. Thus, at the level of primary prevention, we may be able to protect everybody from harmful exposures. But molecular epidemiology provides even more accurate options for determining the level of individual exposures and biological effects, respectively. Metabolites and biomarker molecules formed as a result of exposure to the body can now be measured very precisely. They can be used to screen for high-risk individuals and even change their lifestyle or occupation before the disease occurs. Personalized risk assessment is clearly the way forward for the future and is currently the most dynamically evolving field in molecular epidemiology.

Research in appropriate biomarkers offers an immense opportunity to detect diseases at an early stage, thus reducing the risk of developing serious

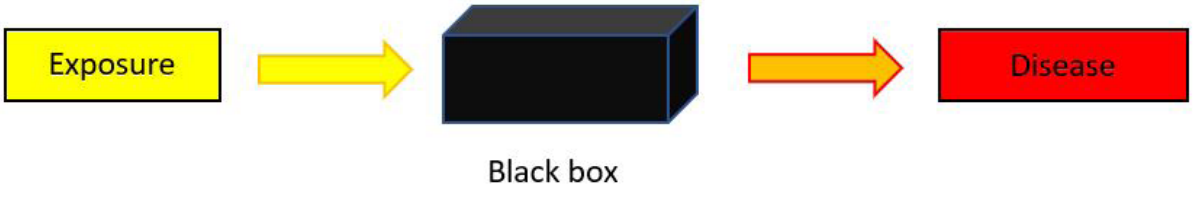


Figure 1.: Traditional epidemiology

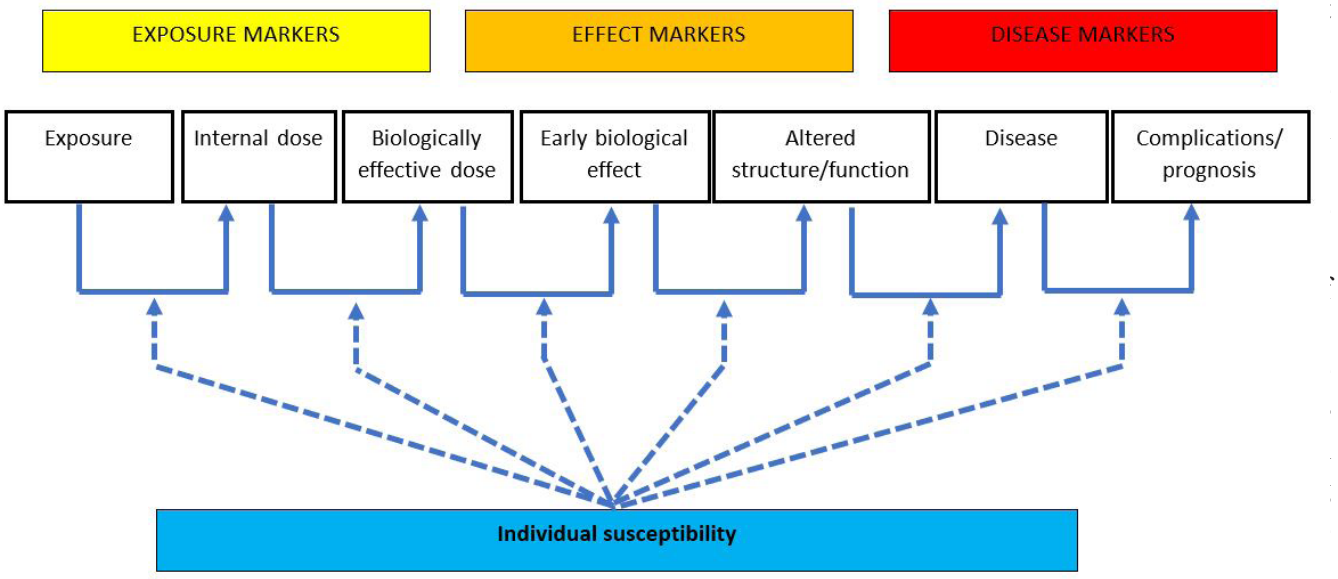


Figure 2. Molecular epidemiology

effects - for example, the development of personalized therapy for the targeted treatment of tumors is spectacular. The most rapid way to determine the appearance of complications during therapy is to use biomarkers.

## The black box

Scientific research on molecular biology in recent decades has introduced us to the complicated and highly dependent and complex path that leads from exposure to the onset of disease. Molecular epidemiology has assigned biomarkers to the different steps of the exposure-disease process, which can be used to accurately describe these stages and the progress of the process.

**Exposure** to various chemical, physical, or biological agents may result in the accumulation of either the agent itself or its metabolites in measurable amounts in the body (Figure 2). This stage is called the **internal dose**. By characterizing the internal dose, i.e. the concentration of the test substance measured in blood and body fluids, exposure can be described much more accurately than if only the environmental concentration of the compound in question was monitored. The compound entering the body reaches practically everywhere through the bloodstream, but for the development of the disease in question, that part oncogene activation, and tumor suppressor gene inactivation. Our body has a number of mechanisms (repair, apoptotic) with which it tries to preserve its internal integrity. Therefore, the above mentioned early biological effects do not necessarily cause substantial changes — DNA repair enzymes, for example, can repair DNA damage or damaged cells are eliminated by apoptosis. If the body is unable to prevent damage, changes (**altered structure / function**) may soon be detected at the level of the particular cells / tissues. This is the case, for example, with an abnormal cytological finding obtained during cervical cancer screening. The process sooner or later progresses to the development of a disease with clinical symptoms (**disease**). Molecular biomarkers can also facilitate early diagnosis of the disease (e.g., detection of tumor cell-specific DNA in feces for colon cancer screening) or more accurate diagnosis. Properly selected biomarkers can also help in assessing the likelihood of **complications** and expected prognosis. For example, activation of metastasis-specific genes in some tumors indicates a higher likelihood of developing metastases.

In real life we also experience that the speed of the exposure-disease process and the rate of progression from one stage to the next show significant individual differences - these can be characterized by biomarkers of **individual sensitivity**. Indivi-

dual sensitivity to specific exposures or diseases is affected by a number of factors, e.g. nutritional status or the current state of the immune system. Perhaps the most important factor of these is our inherited traits, our genetic factors. Their role is discussed in more detail in the molecular epidemiology of each disease group.

## The beginnings

The most important milestone in the development of molecular epidemiology is the Human Genome Project. The Human Genome Consortium and the Celera Genomics Biotechnology Company began a tremendous amount of work in 1990 to map the entire human genetic pool. The three main goals of the company, which had huge funding, were:

1. Map the location of different genes on a chromosome (gene map). (This method was already known and used in genetics at this time).
2. Determine the size (nucleotide length) of genes, map the distance between genes within a DNA molecule (physical map)
3. Explore the complete, coding and non-coding DNA sequence of the human genome (sequencing).

In June 2000, the President of the United States and the British Prime Minister of that time (the latter joined via video call) and the leaders of the Human Genome Project announced at a joint press conference that 90% of the Human Genome Project had been completed. The diverse and sometimes surprising results of the project were published in the two most important scientific journals, Science and Nature. It turned out that the number of human genes estimated at 100 000 is actually approx. 23 000 (we've known this even more accurately since then: in fact, even less than 20,000). Our genome is made up of 3.2 billion bases, less than 2% of which encode proteins, and the remaining 98% have diverse functions, and some are still unknown to us today. The Human Genome Project has shown that 99% of the people of different races on Earth have the same DNA pool and that only 1% of the variability in the human genome is responsible for, to the naked eye, the seemingly huge differences. The so-called Single Nucleotide Polymorphisms (SNPs) are responsible for approx. 90% of this variability, whose number was estimated at 1.4 million in 2001 and then at 10 million by 2010, and today we estimate it at 2-300 million. We have learned that almost half of our genetic pool consists of repetitive sequences. 3% of these are simple repeats, 5% are duplications of large chromosomal segments, and almost 50% are transposons, i.e. their position is not fixed but variable in the DNA molecule. (Transposons are also called „jumping genes," or DNA sequences that can change location.)

The 100% completion of the Human Genome Project in 2006 and the co-development of next-generation sequencing procedures opened a new era for science, including the fact that DNA sequencing could become part of routine diagnostics. Understanding the genetic background of hereditary diseases has been revolutionized by new molecular technologies. It has similarly influenced the field of tumor research, in particular, the somatic mutations underlying tumor formation. Medicine has since identified a myriad of biomarkers of extremely high diagnostic value that have invaluable value in both prevention and cure. All of these contributed significantly to the fact that we have now been able to add a lot of information to our black box so far.

However, the results of the Human Genome Project and the development and spread of molecular genetic / genomic methods have raised many ethical issues. Who owns the genetic information? Who has the right and opportunity to use genetic data? Can anyone request genetic information for any reason (e.g. employer)? When and what genetic tests should be performed and in what form should the results be communicated to the data subject? When is it reasonable to perform genetic tests and when is it not reasonable? Are the direct-to-consumer tests justified and, if so, in what cases? For the time being, there is no single and reassuring answer to all these very exciting questions. In general, it can be said that in the vast majority of democratic countries, the law seeks to strengthen autonomy regarding genetic data and

genetic information as much as possible, and thus to entrust the individual with the authorization of their use. It is needless to say that this can also have limitations (e.g., DNA identification in connection with a crime or deciding paternity issues), and setting these boundaries is often a very difficult task for bioethics. The current situation in this field is that science is ahead and law and ethics are trying to catch up and respond appropriately to new situations.

## Molecular epidemiology of tumors

At least 65-70% of tumors develop sporadicaly-ly due to somatic mutations, while classic hereditary tumors and cases of familial accumulation accounting for only 25-30% of all. Nevertheless, tumor development follows specific molecular mechanisms in each case. The classic model of carcinogenesis was first presented by Fearon and Vogelstein in connection with colorectal tumors. The model revolutionized the understanding of the process of carcinogenesis and the publication, which has been cited nearly 15 000 times since, formed the basis of a very complex science in the molecular epidemiology of tumors (Figure 3).

The process will take many years, even decades, providing an opportunity to track changes by using biomarkers.
In a broader sense, tumor development begins with some carcinogenic exposure. When measuring the external concentration of carcinogens from various environmental or occupational or lifestyle factors, the actual exposure is much better characterized by the so-called **internal dose**. This is the measured concentration of the carcinogen itself or any of its metabolites in tissues, body fluids or excreta. By monitoring the internal dose, we can learn how much of the harmful compounds from the environment and lifestyle factors have actualy-ly entered the body. Internal dose depends on the amount of molecules taken up and the metabolism and excretion of the test compounds / components, so it is much more unique and accurate than measuring the environmental concentration.
The **biologically effective dose** already shows the relevant amount of a substance that causes a health effect in the body more accurately than the internal dose. It is relevant because it takes into account only the part of the substance in the body that has reached the specific target organ, and even within that, the target cells that are important for health damage. It is most often characterized by measuring and describing the amount of DNA or protein adducts (the compound(s) in question are covalently bound to the DNA or proteins) from the target organs. If measurement from the target organ is difficult to perform, the use of alternative biomarkers will often be required. For example, exposure to tobacco smoke can often show 7-methylguanine adducts in the lung or liver (or 4-aminobiphenyl adducts in the placenta in pregnant women), but instead of lung or liver biopsies, these adducts can also be measured in white blood cells. Detection of protein or DNA adducts can also be performed by HPLC, mass spectroscopy or immunoassay.

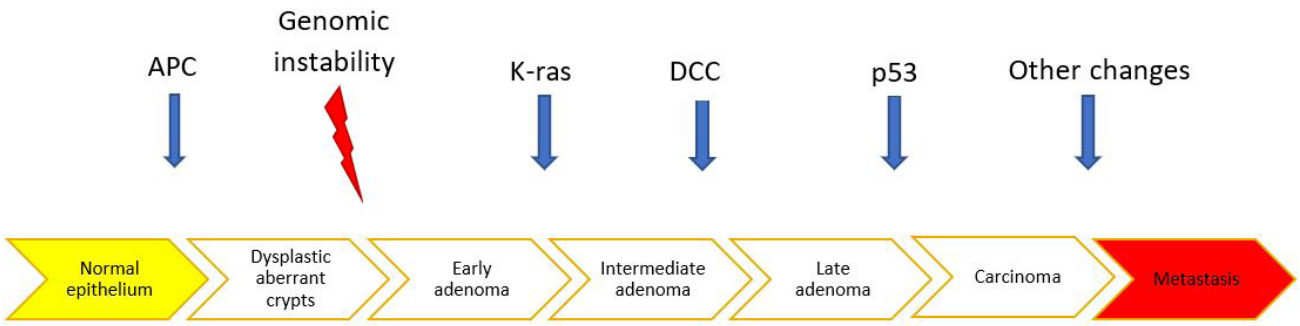


Figure 4: Vogelstien's adenoma – carcinoma model
Source: Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990; June 1;61(5):759-67.

In contrast to the previous two stages, the **early biological effect** indicates the first actual effect, change. These include point mutations or other genetic changes in tumorigenesis. If point mutation affects a functionally important gene, such as an oncogene or a tumor suppressor gene, this mutation can lead to malignant transformation. We often try to infer the point mutation from the location or type of the mutating agent. A typical example is that ultraviolet (UV) radiation creates thymeric mutations in the skin, significantly increasing the risk of developing skin cancer. Similarly, an aflatoxin-induced mutation in codon 249 of the p53 tumor suppressor gene is known to cause the possible development of liver tumors. Other carcinogens, such as hepatitis viruses, always cause mutations at different positions. One characteristic marker for measuring early biological effects associated with chemical carcinogens is a mutation in the ras proto-oncogene. Ras mutation can be caused by a number of genotoxic agents. Classic chemical carcinogenesis studies have shown that N-methyl-N-nitrosourea (MNU) targets the second base of codon 12 of H-Ras and K-Ras and generates G12D mutations, whereas UV radiation often results in a mutation in Ras Q61. Mutations that activate proto-oncogenes (H-Ras, K-Ras, and N-Ras) most commonly affect codons 12, 13, or 61. Despite the high degree of similarity between ras genes, K-Ras mutations are much more common in tumors.

Changes greater than point mutations may be observed upon carcinogenic exposure. Frequent and relatively easy to study early biological effects include sister chromatid exchange and the development of chromosomal aberrations (e.g. deletion, inversion, translocation). These changes are often caused by industrial pollution, exhaust fumes, or smoking. At the same time, the importance of lifestyle is shown by the fact that many carcinogenic components can be added to our plate in connection with food processing and preservation. During grilling and smoking, polycyclic aromatic hydrocarbons, nitrosamines may be added to food, or trans-fatty acids may be formed during frying at high temperatures in fats with inappropriate fatty acid compositions. All of these compounds are highly mutagenic and carcinogenic.

Minor or major early abnormalities can occur in the form of **structural or functional changes** over time from intracellular changes detectable by molecular biological methods. A typical example is papillomavirus infection and the development of cervical cancer. For many years after infection, no changes in structure or function are seen in the gynecological examination of women (but as an early biological effect, integration of the viral genome already occurs). However, after 15-20 years, structural changes in the epithelial cells of the cervix can be seen even under a light microscope, and later the histological structure of the

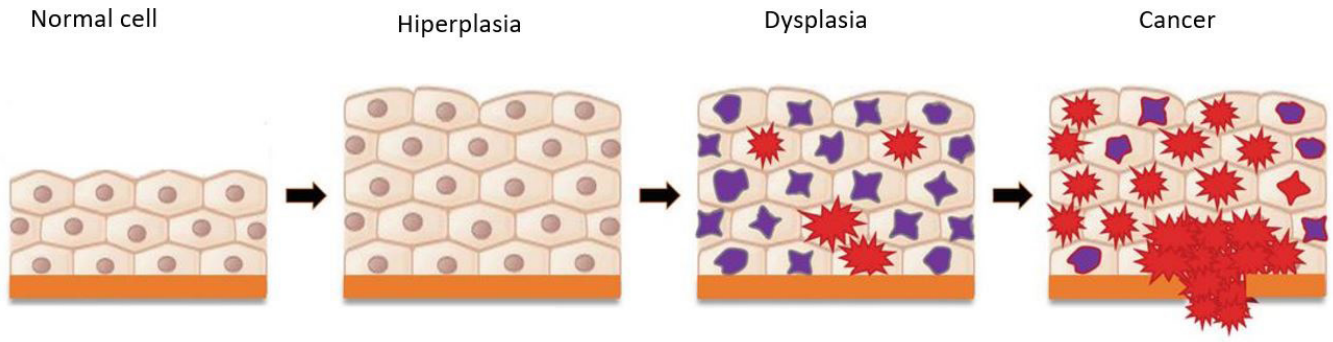


Figure 5.: Precancerous conditions of the cervix

Source: Source: Nwachuku, K., Johnson, D.E., Grandis, J.R. The Mutational Landscape of Head and Neck Squamous Cell Carcinoma: Opportunities for Detection and Monitoring Via Analysis of Circulating Tumor DNA. In: El Assal, R., Gaudilliere, D., Connelly, S.T. (eds) Early Detection and Treatment of Head & Neck Cancers. Springer, Cham. 2021; pp 107-122.

cervix also changes. Based on this, we can distinguish between low- and high-grade squamous intraepithelial lesion (LSIL, HSIL). These stages are called precursor lesions or precancerous conditions (Figure 4). Structural changes are already emerging in these early stages, but we are not yet talking about cervical cancer. With proper treatment, complete recovery is expected, while at a more advanced stage, the likelihood of survival is greatly reduced.

Medicine has also undergone a tremendous development regarding the detection and diagnosis of the **disease**. The use of tumor markers facilitates and simplifies the detection of tumors. They are expressed at an early stage, their concentration is directly proportional to the size and advanced state of the tumor. They are usually tumor-specific.
Two main types of tumor markers can be distinguished: Circulating tumor markers and tumor tissue markers.

**Circulating tumor markers:** These biomarkers are found in the blood, urine, feces, or other body fluids of the subjects. Elevated circulating tumor marker level may indicate the presence of a tumor, but it is important to emphasize that levels of certain tumor markers may be elevated for other reasons, such as inflammation or benign tumors. The level of tumor markers also shows individual variability, making them difficult to use for screening or diagnosis. In general, measurement of circulating tumor markers is combined with the results of biopsies or imaging examinations for accurate diagnosis. Monitoring of tumor markers might be most useful during therapy and for detecting relapses. In this case, the later values are compared to the patient's own tumor marker level measured before the therapy, so that individual variability no longer plays a role in this case. Regular measurements can be used to monitor changes in the levels of tumor markers, so that effective treatment can reduce the level of the tumor marker, while an increase in concentration may indicate progression or failure of therapy or later (months or years), tumor recurrence.

**Tumor tissue markers:** A tumor that generates abnormal cell proliferation expresses different molecules. Some of these enter the circulation and can be detected there (circulating tumor markers). However, others are found in or on the surface of tumor cells. Therefore, they can only be detected in the tumor tissue - these are called tumor tissue markers. They are usually obtained from a biopsy taken during the diagnostic procedure or from the tumor itself during surgical procedure. Some of these biomarkers are used as genetic tests to conclude information regarding tumor growth and other biological features. These biomolecular characteristics help the practitioner determine which treatment to provide for the individual that will be the most effective in fighting the tumor in his or her body. Thus, tumor tissue markers are of great importance in the selection of adequate, precise targeted therapy. One of the earliest and best-known examples is testing estrogen and progesterone receptors in biopsies of women with breast cancer. These receptors, as tumor tissue markers, provide guidance for the physician on how a person (more specifically, the tumor) responds to hormone therapy.

Some tumor markers can also be used as prognostic markers. For example, overexpression of the oncogene erb-B2 has a prognostic value in breast cancer, unfortunately with a worse outcome.
It is not yet used as a routine test, but such biomarkers are known that are secreted by the tumor and can be detected in the blood, where blood acts as a liquid biopsy specimen. These liquid biopsies have several benefits. Since they do not involve surgery, they are available even when surgical biopsy is not possible, such as when tumors are difficult to reach or patients do not tolerate surgery.

## Markers of individual sensitivity

The Human Genome Project has also drawn attention to the millions of single nucleotide polymorphisms (SNPs) in human DNA. At the same time, the study of the relationship and interaction of environmental and genetic factors has become

Table 1.: Use of biomarkers.

| Circulating tumor marker | Tumor tissue marker |
|---|---|
| Using it for screening purposes can help detect the disease at a very early stage | Assists in making an accurate diagnosis |
| When diagnosing a disease, it can help determine the exact stage | Helps determine the exact stage of the disease |
| Helps to estimate the outcome and prognosis of the disease | Helps to estimate the prognosis |
| It is also suitable for indicating the effectiveness of treatment | It can help to choose the right, targeted treatment |
| Detection of tumor recurrence | |

one of the key areas of molecular epidemiology. Serious diseases with Mendelian inheritance are usually rare in the population, but due to the high penetrance of the genetic factor, the disease develops in practically all cases. The influence of environmental factors is negligible, the genetic factor alone is strong enough to express itself. Such a genetic factor characterizes Duchenne muscular dystrophy. This X-linked genetic disease in young boys is associated with chronic muscle wasting due to a lack or insufficient function of the protein dystrophin that is required for muscle function. The incidence of this rare, sex-linked, recessive inherited disease is 1: 3 500, but there is an even more rare (approximately 1: 30 000) disease, also a hereditary muscular dystrophy (Becker's muscular dystrophy), which has milder symptoms and course than Duchenne dystrophy.

In contrast, we know of an extremely large number of genetic factors (allelic variants) that have very high incidence but low penetrance (phenotype-genotype relationship). These factors are called individual susceptibility genes. These types of genetic factors do not develop disease on their own, but may already play an important role when interacting with the modifying role of the environment. A typical example of genetic factors of individual sensitivity is the number of polymorphisms in our metabolizing enzymes. A protein of similar name transcribed from the glutathione S-transferase M1 (GSTM1) gene is a so-called phase 2 metabolizing enzyme. This means that it neutralizes harmful substances and their metabolites by conjugating them to glutathione, thus reducing carcinogenic effects. Substrates of the GSTM1 enzyme include a number of well-known environmental carcinogens, reactive radicals, and chemotherapeutic agents. The most important of these are: polycyclic aromatic hydrocarbons, alkyl halides, hydroperoxides, various epoxides (polycyclic aromatic hydrocarbon diol epoxides). GST genes play an important role not only in metabolic processes, but also in the processes of drug metabolism and the development of drug resistance. The null allele polymorphism of the GSTM1 gene is well known. In some people, GSTM1 gene encodes an ineffective GSTM1 enzyme due to deletion which results in loss of function (affecting a relatively large segment of the gene). This is less interesting in heterozygotes, but homozygotes have no functional GSTM1 enzyme at all. Frequency distribution of GSTM1 genotypes shows an interesting pattern among different populations. On our planet, the frequency of the null allele increases in the north-south direction, in Hungary, for example, about 50% of the population has the null genotype. Thus, in individuals with the null genotype, the detoxification capacity of GSTM1 is lost; therefore, the risk of some tumors may be slightly higher. Of course, this does not mean that these individuals are completely vulnerable

to adverse environmental exposures, as some of the metabolic enzymes may overlap in substrate specificity, so other metabolic enzymes may be involved in neutralizing and depleting carcinogenic metabolites.

One or two low-penetration genetic factors, such as carrying the null allele of GSTM1, do not in themselves pose a significant risk. However, it is important to emphasize that in this case the environmental factors become much more important. In individuals who may be in the high-risk group for more than one gene, small factors add up and have a higher level of exposure at the individual level, in which case they should be more careful about relevant adverse environmental exposures. Let's look at two specific examples.
The N-acetyltransferase 2 (NAT 2) gene encodes an enzyme that is capable of activating and deactivating arylamine and hydrazine metabolites. More than 60 alleles of the gene are known, which, based on phenotype, are classified into fast, medium, and slow acetylation groups. Rapid acetylators are those that carry the wild-type allele in a homozygous or heterozygous form. In this case, the arylamine and hydrazine substrates are acetylated extremely rapidly, so they do not burden the body for a long time. In contrast, in individuals with a slow acetylating genetic type, potential carcinogens can exert their cell-damaging effects for quite some time because acetylation occurs slowly. Regarding NAT2 fast / slow allelic polymorphism, there are also extremely large differences between different populations on Earth. In the populations of the Caucasus, the incidence of those with a higher risk of slow acetylation capacity is 50–60%, compared to an only 10-15% of incidence in Asia. Polymorphisms in the NAT2 gene are also associated with a higher incidence of drug toxicity.
During the processing, preservation or grilling of red meat, quite a few carcinogenic compounds filtrate into the meat. For individuals carrying a slow acetylation gene variant, arylamine and hydrazine metabolites pose a much higher risk than for fast acetylators. Similarly, for example, the risks of the consumed alcohol vary individually.
The genes of dehydrogenase and acetaldehyde dehydrogenase enzymes, which are responsible for breaking down alcohol, are also polymorphic. 7 alleles of human alcohol dehydrogenase gene are known. Different alleles functionally encode other proteins that play a major role in our relationship to alcohol or the harmful consequences of alcohol. If we inherit an alcohol dehydrogenase allele that is low in enzyme activity or inactive (ADH1B*2, ADH1B*3), then consuming alcohol makes us feel very uncomfortable (flushing, rapid breathing, headache, stomach problems). This syndrome is also called "flushing syndrome". In Europe, this genotype is rare, barely 20%, while in Asia its incidence can be as high as 70-80%. With this genotype, individuals do not want to re-consume alcohol. At this point, the genetic background protects the body from harmful exposure caused by alcohol. In contrast, in the presence of other gene variants, alcohol consumption will be recorded as a pleasant experience and the risk of developing alcohol addiction will be much higher.

These examples show that, depending on our individual sensitivity markers, different environmental factors pose different risks to us. With personalized risk assessment, we would be able to communicate much more effectively to maintain our health.

## Epigenetics

The Human Genome Project has also contributed to the development of the science of epigenetics. The appearance of methods and technologies in new generation molecular biology has allowed us to get to know the process of inheritance as precisely as possible. Previously, we thought that only mutations in gametes appear in the offspring. Today, this misconception has been dispelled. One of the biggest challenges today is to recognize and understand epigenetic factors. The word epigenetics is of Greek origin; means "beyond genetics". This suggests that it is possible to regulate gene activity without altering the DNA sequence of the hereditary material, which is inherited in the offspring or even in future generations. Epigenetic

inheritance draws attention to the fact that the role of environmental factors is significantly more important than previously thought. Over the past decade, many studies have shown that many lifestyle factors, such as smoking, diet, alcohol consumption, sports, or even aging, cause changes in cells that can periodically turn certain genes on or off. Some of this can be also passed on to offsprings. The phenotype in the offspring is estimated to be up to 60-70% dependent on non-genetic changes. The three major pathways of epigenetic regulation are DNA methylation; post-translational histone modification and non-coding RNAs (ncRNAs), including microRNAs.

In animal experiments, there is ample evidence that parental environmental exposures generate transgenerational effects. In animal models in rats and mice, it has been shown that consuming a high-fat diet during pregnancy also increases the incidence of obesity and metabolic syndrome in the offspring. Increased body size was maintained in two generations of mice.

It is also a nutritional factor, but this time the epigenetic effect of excessive calorie restriction was seen in those born / conceived during the Dutch famine. Several countries struggled with food shortages during World War II, but one of the biggest famines was in the Netherlands. In September 1944, Dutch railwaymen wanted to stop the transport of Nazi troops, so they went on strike. This was retaliated against by the Nazi forces and as a punishment, blocked food supply in the Netherlands. During the period known as the ‚Dutch Hunger Winter' (until May 1945, when the Netherlands was liberated), more than 20 000 people died of starvation. Subsequent research has shown that children conceived / born during starvation were in poorer health as adults: were more likely to be obese, had higher lipid levels, and were more likely to have cardiovascular diseases and high blood pressure. The explanation - at least in part - may be that during the famine the body tried to avoid any unnecessary waste and energy loss, and these changes, coded in the offspring, already led to excessive fat accumulation with normal energy intake.

There are also many examples of gene-environment interactions in human studies. Children's Health Study found that grandmother's smoking during pregnancy doubled the development of asthma in grandchildren. If both the child's mother and grandmother smoked during pregnancy, the child was even more likely to develop asthma. In a Norwegian cohort study, grandmother's smoking during pregnancy generated a 15% and 21% higher relative risk of developing asthma at 3 and 7 years of age, respectively.

The mechanisms of epigenetic regulatory processes are not yet fully understood, but we now know for sure that environmental factors interact with genetic factors and that the interactions between them are partially passed on to our offsprings (even for several generations). As the examples mentioned above show, it is certain that the environmental effects on parents can affect the offspring as well as the third generation. This influencing effect can certainly cause not only negative effects but also positive changes.

Nutrigenomics is now extensively studying the effects of nutritional factors on inter- and transgenerational inheritance. With its help, we can help and shape the preservation of our health by taking into account individual genetic characteristics, even with personalized nutritional recommendations.

Learning about epigenetic regulation draws even more attention to the importance of health awareness. Today we can no longer say that this is my life… After all, what we do in our present life is an imprint on the structure of DNA and has an effect on our offspring as well. The risk-increasing effects of a dangerous or unhealthy lifestyle affect not only our own lives but also the life prospects of our unborn child.

## References

1. Aguilar F, Hussain SP, Cerutti P. Aflatoxin B1 induces the transversion of G-->T in codon 249 of the p53 tumor suppressor gene in human hepatocytes. Proc Natl Acad Sci USA. 1993; Sep 15;90(18): 8586-90.
2. Amitava Dasgupta: Genetic polymorphisms of alcohol metabolizing enzymes associated

with protection from or increased risk of alcohol abuse. in Alcohol, Drugs, Genes and the Clinical Laboratory, 2017.
3. Edenberg HJ. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health. 2007; 30(1): 5-13.
4. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990; Jun 1;61(5): 759-67.
5. Garte S, Gaspari L, Alexandrie AK, et al. Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev. 2001; 10: 1239-48.
6. Handy DE, Castro R, Loscalzo J. Epigenetic modifications: basic mechanisms and role in cardiovascular disease, Circulation. 2011; 123: 2145-2156.
7. Hayes JD & Pulford DJ. The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Critical Reviews in Biochemistry and Molecular Biology, 1995; 30: 445-600.
8. https://www.ncbi.nlm.nih.gov/gene/10
9. Li YF, Langholz B, Salam MT. & Gilliland FD. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. Chest. 2005; 127: 1232-1241.
10. Lumey LH, Van Poppel FW. The Dutch famine of 1944-45: mortality and morbidity in past and present generations. Soc Hist Med. 1994; Aug;7(2): 229-46.
11. Magnus MC, Håberg SE, Karlstad Ø, et al. Grandmother's smoking when pregnant with the mother and asthma in the grandchild: the Norwegian Mother and Child Cohort Study. Thorax. 2015; Mar;70(3): 237-43.
12. Mahmood S, Smiraglia DJ, Srinivasan M. & Patel MS. Epigenetic changes in hypothalamic appetite regulatory genes may underlie the developmental programming for obesity in rat neonates subjected to a high-carbohydrate dietary modification. J. Dev. Orig. Health Dis. 2013; 4: 479-490.
13. Nwachuku, K., Johnson, D.E., Grandis, J.R. The Mutational Landscape of Head and Neck Squamous Cell Carcinoma: Opportunities for Detection and Monitoring Via Analysis of Circulating Tumor DNA. In: El Assal, R., Gaudilliere, D., Connelly, S.T. (eds) Early Detection and Treatment of Head & Neck Cancers. Springer, Cham. 2021; pp 107-122.
14. Perera FP, Weinstein IB Molecular epidemiology: recent advances and future directions. Carcinogenesis, 2000; 21(3): 517-24.
15. Polimanti R, Carboni C, Baesso I, et al. Genetic variability of glutathione S-transferase enzymes in human populations: Functional inter-ethnic differences in detoxification systems. Gene. 2013; 512:102-107.
16. Schulte PA and Perera FP. Molecular epidemiology: Principles and practices. San Diego: Academic Press, 1993.
17. Tiffon C. The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. Int. J. Mol. Sci. 2018; 19, 3425.
18. Tiis RP, Osipova LP, Galieva ER, et al. N-acetyltransferase (NAT2) gene polymorphism and gene network analysis. Biomed Khim. 2021; May;67(3): 213-221.
19. Törmänen VT, Pfeifer GP. Mapping of UV photoproducts within ras proto-oncogenes in UV-irradiated cells: correlation with mutations in human skin cancer. Oncogene. 1992; Sep; 7(9): 1729-36.
20. Vogelstein B, Fearon ER, Hamilton SR et al. Genetic alterations during colorectal-tumor development. N. Engl. J. Med. 1988; 319: 525-532.
21. Zarbl H, Sukumar S, Arthur AV, Martin-Zanca D, Barbacid M. Direct mutagenesis of Ha-ras-1 oncogenes by N-nitroso-N-methylurea during initiation of mammary carcinogenesis in rats. Nature. 1985; May 30-Jun 5; 315(6018): 382-5.

# VII. Reproductive epidemiology

Viktória Prémusz, József Bódis

## The subject of reproductive epidemiology

Reproductive epidemiology is basically an area of epidemiology dealing with reproduction. In more detail, it deals with the study of the distribution and determinants of conditions or events associated with reproductive health, i.e., the reproductive system, its functions, and processes, in human populations to promote overall physical, mental, and social well-being.

For providing useful epidemiological information to improve reproductive health, it is essential to identify the risk factors of reproductive health conditions or events, the individuals, and populations most at risk, monitor public health problems, and evaluate the effectiveness and efficiency of prevention and treatment programs.

Both at the level of public health and the individual, epidemiological information can help make informed decisions about, i.a. sexually transmitted diseases, family planning, reduction of unwanted pregnancies, safe and effective contraception, maternal morbidity and mortality, perinatal and infant health (Merill, 2010).

**Indicators of global monitoring of reproductive health**

1. Total fertility rate
2. Contraceptive prevalence
3. Maternal mortality rate
4. Pregnancy care cover
5. Childbirth assisted by qualified medical personnel
6. Availability of basic obstetric care
7. Availability of comprehensive essential obstetric care
8. Perinatal mortality rate
9. Prevalence of low birth weight
10. Prevalence of positive syphilis serology in pregnant women
11. Prevalence of anaemia in women
12. Percentage of obstetric and gynaecological abortion-related admissions
13. Reported frequency of female genital mutilation
14. Prevalence of infertility
15. Prevalence of HIV infection in pregnant women
16. Knowledge of HIV prevention practice

## Primary reproductive trends

Reproduction, the essence of all known life, is the biological process by which living organisms produce offspring (Steadman, 2005). In connection with human life, additionally, demography can also help us in the study of population processes at the population level, in the description of population transition, i.e. changes in population from birth to death (AEEK, 2021).

The Population Division of the United Nations Department of Economic and Social Affairs of the United Nations Department of Economic and Social Affairs has issued a warning overview of global demographic trends and prospects for **the size, composition and distribution of the population**, given that projection of the world's population is expected to reach 9.7 billion by 2050 and 11 billion by the end of the 21st century. Although the number of countries experiencing population decline is increasing, growth rates vary widely from region to region: many countries are moving towards an ageing population due to increasing life expectancy, postponed childbearing and declining fertility rates (UN, 2019; Sobotka 2004, Sobotka 2019).

Similarly to other developed countries, the declining birth rate, declining population and rising average age are serious challenges in Hungary. The phenomenon was due to the relatively high

mortality rate compared to other European countries in the 1980s, but the low fertility rate has been a significant factor since the 1990s.
Since 1981, the population of Hungary has been declining with varying intensity, but continuously. As of January 1, 2020, there were 9,890,640 people, approximately 820,000 less than 40 years ago. Changes in the population structure are well illustrated by the 120-year-old interactive population pyramid of the Central Statistical Office (CSO). This application shows the development of the number and age structure of the Hungarian population by gender from 1870 to 2060 (KSH, 2019).

According to the Demographic Snapshot of the CSO, despite a slight increase after the absolute low of 2011 (88,049 births/year), the number of live births still has not reached the level of the time before the 2008 global economic crisis (96,000 births/year). In 2020, the number of live births was still only 92,000, a decrease of 52% compared to 1975 (188,000).

## Total Fertility Ratio

However, we have more appropriate comparative indicators than the annual birth rate. **Age-specific fertility rate** (ASFR) is the fertility rate within selected age groups and is calculated as a 5-year age group breakdown for reproductive age (15–49 years) (Merill, 2010):

$$ASFR = \frac{\text{Live births in a given year for women aged Xl}}{\text{Number of women aged X in the middle of the given year}} \times 1000 \text{ women}$$

Using the current age-specific fertility rates as an indicator, the **total fertility rate** (TFR) can be calculated, which shows the average number of children a woman would have in her lifetime if the fertility data for a given year were constant.

$$TFR = \frac{\sum AFR \times 5}{1000}$$

In which case ∑ASFR is the aggregate result of the above age-specific rates. If the TFR is greater than two, it provides population replacement, so 2.1 can be considered the **replacement rate** (RR) for reproduction, as in this case it is ensured that the generations of society reproduce themselves. Reproduction under RR requires continuous immigration and/or a steady increase in life expectancy to maintain the population.

As a basic trend, mortality has improved in most countries around the world, while fertility has declined. In the 1950s, women gave birth to an average of five children globally. The United Nations World Population Prospects reported in 2019 that today the global TFR, which was 3.2 births for all women in their lifetime in the 1990s, fell to an average of 2.5 by 2019, thus, globally, fertility remains above 2.1 births per woman (UN, 2016). However, in the EU-28, there was an average of 1.59 live births per woman in 2017, with the lowest extremes in Malta being 1.26 and the highest in France with 1.90 (Eurostat, 2017).
TFR changed positively in Hungary: compared to 1.24 in 2011, it was around 1.54 in 2017. The fertility rate per woman in Hungary was 1.56 in 2020, the forecast expects a further slow increase in the long run, we are expected to reach 1.6 in 2031, it may be above 1.7 in 2070, i.e. the level required for reproduction is not reached in the long run (CSO, 2021).
While Hungary's relative position in TFR rankings has improved and the overall fertility rate has risen, there has been no significant increase in the birth rate. After 2010, the number of births and the total fertility rate no longer moved together, which, according to Kapitány and Spéder, is justified by the specific age composition of the Hungarian population. Although WHO defines the reproductive age of 15 to 49 years for women (WHO, 2006), in our culture, the desire to have children between the ages of 25 and 40 is much more pronounced, and the number of women in this age group has declined rapidly since 2012. Thus, it may have happened that while fertility per woman increased, the number of live births did not change (Spéder, 2015; Spéder, 2018).

## Relationship status and childbearing, the importance of marriage

The total first marriage rate (TFMR) shows the chances of a man or woman getting married during their lifetime. For more than 30 years after the Second World War, TFMR was above 0.9 in Hungary, and then began to decline before the change of regime, after which it switched to "freefall" and reached its historic low in 2010. It increased 1.5 times in 2018, and an increase of around 30% in 2019, is the highest number of marriages in thirty years. In 2020, the rise continued, with more than 67,000 couples getting married in Hungary. (CSO, 2021a)

Why is this question important for reproductive epidemiology? Women can also be examined for marriage in connection with childbearing. Based on Hungarian data, the form and stability of the relationship play an important role in having a child. The proportion of married women in the female population was exceeded by the proportion of children born in wedlock, suggesting higher fertility among married women.

According to the data of the CSO, in 2018, half of the first children were born in or out of wedlock, and the second and third children, with the highest rate, were born in wedlock at 62% and 64%, respectively. It may suggest that after the first children are born out of cohabitation, couples get married before the second or third child arrives. However, the rate of out-of-wedlock births in the fourth and subsequent children is rising again and the half-to-half rate seen in the case of the first children is restored.

The intensifying propensity to marry in recent years has moderated and then halted the declining proportion of married women among women of childbearing age. Married women are still in the minority (36% married, 64% unmarried). At the time of the change of regime, the opposite was true (CSO, 2019).

## Postponed childbearing: trends and consequences

Figure 1 indicates two alarming trends. On the one hand, the number of women aged 15-49 (considered to be of reproductive age according to the WHO definition) decreased in Hungary between 2010 and 2018. On the other hand, even within this age group, the age structure has changed, with a sharp increase in the proportion of women over the age of 30. Postponing the childbearing age has begun to slow in recent years. In 2017, the average age of women at the birth of their first child was 28.0 years in Hungary, compared to the EU-28 average of 29.1 years. The average age of women, including all children, was 29.8 years at birth, compared to 30.7 years in the EU-28 (CSO, 2016, Eurostat 2017b). Experience has shown that postponed childbirth does not always occur later and may have reproductive health consequences. The opinion of the Commission of the American College of Obstetricians and Gynecologists (ACOG) warns of a decline in female-related fertility, namely that female fertility is gradually but significantly declining from the age of 32 to age 37. After which the rate of decline accelerates (ACOG, 2014).
The decline in the female population of reproductive age and postponing childbearing raise a higher incidence of abnormalities affecting fertility and a higher risk of pregnancy loss (ACOG, 2014).

## Fertility disorders and their treatment: prevalence of infertility

The clinical definition of infertility according to the International Classification of Diseases (ICD-11) is a disorder of the reproductive system that results in no clinical pregnancy within one year of regular unprotected sexual intercourse (WHO, 2018).
In 2012, McLaren and her co-authors described the global prevalence of one-year infertility at around 12% –15% (McLaren, 2012). In contrast to the fact that the infertility rate has remained roughly unchanged over the past two decades, an

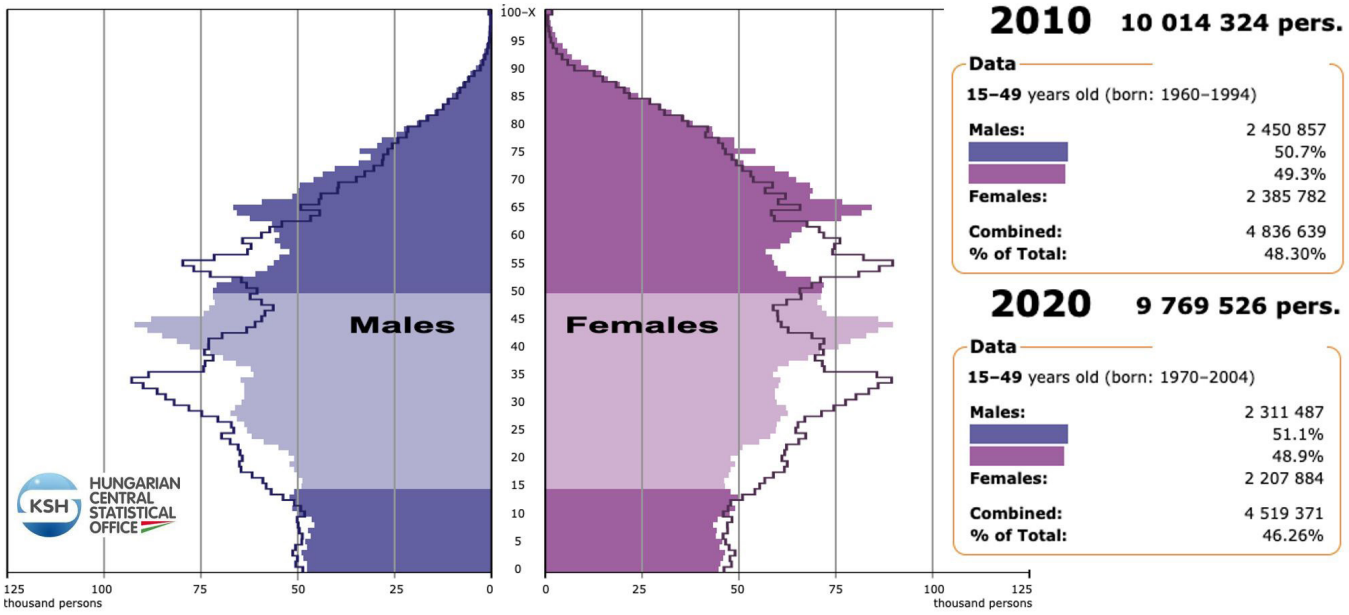


Figure 1.: Changes in the population of reproductive age (15-49 years) in Hungary on January 1, 2010-2018.
Lines indicate 2020 data and the filled colors indicate 2010 data.
(Source: https://www.ksh.hu/interaktiv/korfak/orszag_en.html)

increasing trend in the number of fertility treatments can be reported (ESHRE, 2001). 1978 and 2012 a total of 5 million newborns and in 2018, a total of 8 million, i.e., 1-4% of all newborns were born with the help of assisted reproductive technology (ART) (Bauquis, 2012, (De Geyter, 2018)). However, it is difficult to find reliable and up-to-date reports on current global trends. The latest global report was published in 2021, but with the reference year of 2014, by the International Committee for Monitoring Assisted Reproductive Technologies (ICMART), presenting aggregated data from 76 countries and 2746 clinics, accounting for 66% of the total cases. In the treatment year 2014, it is estimated that more than 439,000 newborns were born out of 1,929,905 cycles in the reporting countries. The success rates for two infertility treatments, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) per fresh aspiration (per initiated treatment) and per frozen embryo implantation cycles were 19.9% and 24.3%, respectively (Chambers, 2021).

Approximately 50% of fertility treatment cycles occur in Europe. (ESHRE Capri Group, 2001). The monitoring report of the European Society of Human Reproduction and Embryology (ESHRE) reports an increasing rate of ART treatments. We can read about 940,503 cycles started in 2017, a 4.63-fold increase in the number of cycles compared to 1997 since data collection on ART treatments in national registries began and doubled, compared to the data from ten years earlier. The most common treatments are intracytoplasmic sperm injection (ICSI, 391,379 cycles), frozen embryo implantation (FER, 271,476 cycles), and in vitro fertilization (IVF, 165,379 cycles) (EIM, 2021).

In the Scandinavian countries and Belgium, the application of ART is traditionally high in the number of cycles per million inhabitants, while in Russia and Spain, a significant increase in the number of treatments has been described. The proportion of babies born with ART in Europe ranges between 5.6% (Denmark, Iceland) and 1.1% (Malta), while the proportion in the US is estimated to be around 1.0% of all births. Although the number of treatments is increasing dynamically, the rates of clinical pregnancies for in vitro fertilization (IVF) treatments per aspiration (all initiated treatments) and per transfer were 26.8% and

34.6%, and for ICSI 24% and 33.5% for the year 2017 (De Geyter et al., 2018; ESHRE, 2001; ESHRE, 2015; ESHRE 2017).

Bernard and Krizsa reported a similar situation in Hungary in the 2000s, with 10-15% of couples of childbearing age having fertility problems (Bernard et al., 2006). In 2012, the World Health Organization (WHO) reported a 12-15% incidence of fertility disorders and one of the highest age-standardized secondary infertility prevalence in Central and Eastern Europe at 18.0% (13.8% -24.1%) (Mascarenhas et al., 2012).
Regarding ART treatments, data for Hungary in 2012 were as follows: 920 IVF and 3502 ICSI treatments were performed, with 31.7% and 34.5% pregnancy rates per aspiration, respectively (Calhaz-Jorge et al. 2016). Despite an increase in the frequency of treatments between 2012 and 2014 (1179 IVF and 3857 ICSI), ESHRE reported 25.0% and 28.8% clinical pregnancies for IVF and ICSI, respectively.

According to the publication of the EIM Consortium, 170,163 ART infants were born in 2014, which means that one in 50 children in Europe conceives and is born with ART treatment (De Geyter et al., 2018).

In Hungary, the National Healthcare Service Center and, before 2015, its predecessor, the National Institute for Quality- and Organizational Development in Healthcare and Medicines, are responsible for providing data on the frequency, indication, procedure type, and success rate of ART procedures due to the 339/2008. (XII. 30.) Government Decree on "Mandatory disclosure of efficacy data for human reproduction procedures".
Relevant data are currently made public between 2010 and 2014, during which five years the majority of patients were in the 30-34 age group (38.26%) and typically the first (48.95%) or second (27.25%) cycle. Of these patients, 34.40% were diagnosed with an indication of female origin. Regarding the type of treatment, only IVF and ICSI data were reported consistently, with the number of cases increasing by 28.71% and 31.72%, respectively, with the ratio of ICSI being approximately three times that of IVF.

The number of clinical pregnancies also increased from 1649 to 1803, by 9.34%. Pregnancy rates ranged from 25.67% to 32.36% per initiated treatment cycle (per aspiration) and from 28.72% to 35.14% per embryo transfer (per transfer), but no clear upward trend can be described (AEEK, 2010 -2014). However, the pregnancy rate should be interpreted with caution because statistics from the National Health Insurance Fund do not state with certainty whether births following an IVF procedure occurred as a result or independently. Obstetric events were considered if they occurred within 290 days after ART. In addition, the database only contains service procedures financed by the National Health Insurance Fund.

## Early childbearing

It is estimated that 15 percent of young women worldwide give birth before the age of 18. Pregnancy or childbirth in early adolescence can prevent girls from becoming healthy adults and can have a negative impact on their education, subsistence, and health.

Obstetric fistula, eclampsia, maternal endometritis, and systemic infections are just some of the serious conditions they can face in the short and long term. Globally, maternal conditions are the fourth leading cause of disability-adjusted life years (DALY) and the second leading cause of death among 15- to 19-year-old girls (the first being tuberculosis). Not only mothers but also children who are born may have a higher-than-average health risk due to early childbearing; therefore, reducing the fertility rates of young women is essential to maintain the health of these women and their children. (UNICEF, 2021)

Within Europe, Hungary has one of the highest rates of childbearing among young women aged 15–19, rising from an average of 18 to 25 per thousand between 2010 and 2016, and then declining to a fertility rate of 22 per thousand in 2017-2018.

For girls aged 10–14, the proportion remains low at 0.2–0.4 per thousand.
Compared to the member states of the European Union, we can see that the Hungarian data are high, as in the EU the number of newborns per a thousand women decreased in the 15–19 age group from 12 per thousand in 2010 to 9 per thousand in 2018, and in the 10–14 age group from 0.18 per thousand to 0.15 per thousand. In Europe, only in Slovakia, Romania and Bulgaria is the fertility rate of 15-19 year olds higher than in Hungary. (KSH, 2021c)

## Premature birth and low birth weight

The prevalence of low birth weight (LBW) is the percentage of liveborn newborns weighing less than 2,500 g based on the newborn's first (immediate postnatal) weight. The limit is based on epidemiological observations that newborns weighing less than 2,500 g are about 20 times more likely to die than born with a higher weight. Very low birth weight is less than 1500 g and extremely low birth weight is less than 1000 g.

$$\text{LBW} = \frac{\text{number of newborns born with less than 2500 g}}{\text{number of live births}} \times 100$$

LBW is an aggregate indicator of a number of factors, including maternal nutrition, lifestyle, and other exposures during pregnancy. Nutrition during childhood, adolescence, conceiving, and pregnancy should be considered when evaluating maternal nutrition. Alcohol, smoking, and drug use are primary lifestyle variables that are also often considered. Finally, environmental exposures may include infectious diseases, toxic chemicals, ionizing radiation, and altitude. (Merill, 2010)
Not only the weight of the fetus is used to determine the development and biological maturity of the newborn; but based on the combined assessment of gestational week and birth weight, neonates can be divided into four categories:
1. a mature preterm infant born before the 37th week of pregnancy but not less than 2500 grams;
2. a low birth weight, premature infant born before the 37th week of pregnancy and weighed less than 2,500 grams;
3. a light birth weight, term infant born after the 36th week of pregnancy but weighed less than 2,500 grams;
4. a mature, term infant born after the 36th week of pregnancy and with at least 2500 grams.

According to UNICEF, more than 20 million babies worldwide, 15.5 percent of all births, have low birth weight, 95.6 percent of them in developing countries. The level of low birth weight in developing countries (16.5%) is more than twice that of developed regions (7%). Half of the low-birth-weight infants are born in South Central Asia, where more than a quarter (27%) of infants weigh less than 2,500 g. In sub-Saharan Africa, low birth weight is about 15%. On average, in Central and South America and Oceania, rates are much lower (10%), while in the Caribbean this level (14%) is almost as high as in sub-Saharan Africa. (UNICEF, 2004)

WHO estimates that 15 million newborns per year, about 10.6% of the world's live births, are born prematurely (before the 37th full week of pregnancy), and that number is rising. Premature birth complications are the leading cause of death among children under the age of 5, accounting for approximately 1 million deaths in 2015, three-quarters of which could have been prevented with currently in practice, cost-effective interventions.

In the 184 countries studied, the rate of premature births ranges from 5% to 18% of babies born. (WHO, 2018b). In 2014, Asian and sub-Saharan African countries accounted for 78.9% of live births and 81.1% of premature births. (Chawanpaiboon, 2018)
After Cyprus (12%) and Greece (11.3%), the rate of premature births in Hungary is the third highest in Europe: 8.7%. The proportion still reached 10.2% in the 1980s but has not changed much in the last twenty years, ranging between 8.1 and 9% (Szabó, 2021).

## Prevalence of contraception

Contraceptive prevalence (CP) is the proportion of women of reproductive age (15–49 years) who (or their partner) apply a contraceptive method at a given time. Contraceptive methods include natural methods, mechanical and chemical methods, intrauterine contraceptives, hormonal methods, artificial infertility (female and male), and pharmacological inhibition of spermatogenesis.
The use of contraceptives in developing countries increased from 10% in the early 1960s to 59% in 2000. In the 1990s, a 1% increase in contraception in countries of Africa, Asia, the Pacific Ocean, Latin America, and the Caribbean was accompanied by a 0.06 decrease in TFR. However, regional disparities in birth control remain significant: prevalence is 24% in sub-Saharan Africa, 53% in the Middle East and North Africa, 46% in South Asia, 79% in East Asia and the Pacific, 71% in Latin America and the Caribbean, and 65% in Central and Eastern Europe and the Commonwealth of Independent States. In contrast, it was 75% in Canada, Germany, France, and New Zealand; 79% in the Netherlands; 81% in Spain; 82% in Switzerland; 84% in the UK; and 76% in the United States. (Merill, 2010)

Contraception has also been integrated into the United Nations Sustainable Development Goals (Sustainable Development Goals, Target 3.7.1) and set the universal access to sexual and reproductive health services, including family planning, information and education, and the integration of reproductive health into national strategies and programs as a goal. (UN, 2015)
According to the UN Population Division's global report on contraceptive use (World Contraceptive Use 2019), which was based on 1247 surveys of 195 countries or territories around the world, in 2019, out of 1.9 billion women of reproductive age (15-49 years old) in the world, 1.1 billion women take care of family planning in some way, i.e. either they are currently using contraception - 842 million are using modern contraception, 80 million are using traditional methods - or have a need for family planning that they cannot solve - 190 million women want to avoid pregnancy but do not use any method of contraception.
According to 2019 data, sterilization is currently the most common method of contraception worldwide, with 23.7 percent, 219 million women using contraception, opting for female sterilization. Three other methods have more than 100 million users worldwide: condoms (189 million), intrauterine devices (IUD) (159 million), and hormonal contraceptive pill (151 million). Overall, 45.2 percent of contraceptive users rely on permanent or long-acting methods (female and male sterilization, IUD, contraceptive implants), 46.1 percent on short-acting methods (e.g., condoms, pills, injections, and other modern methods), and 8.7 percent on traditional methods (interrupted intercourse, natural rhythm methods, and other traditional methods). (UN, 2019b)

The "Contraception Revolution" took place in Hungary from 1953 to 1993. The proportion of people using contraception is almost complete: the number of women who protect themselves against unwanted pregnancies has risen from 58% to 94%, with modern methods taking precedence over traditional methods, the use of them increasing from 21% to 87%, in which the use of pills and intrauterine devices jumped, while the proportion of those who had interrupted intercourse fell. (Frejka, 2008).
According to the third data of the "Turning Point in Our Lives" ["Életünk Fordulópontjai"] survey of the Demographic Research Institute in 2009, 87% of women aged 15-45 and 91% of women under 42 protect themselves against pregnancy, with most women using condoms (37%), pills (31%), or IUD (18%) as a contraceptive, 13 of 100 women applied natural contraceptive methods. (Makay, 2014)

## Abortion

The other aspect of birth control is the termination of the pregnancy or induced abortion (abortion on demand). An indicator of the relationship between abortions and births is the relative proportion of the two obstetric events, i.e. the number of in-

duced abortions per 100 live births. A more accurate picture is obtained, if we do compare both obstetric events with the number of women of appropriate childbearing age, rather than the absolute numbers, to show the frequency with which women at certain stages of childbearing age have children or an abortion.
The **total abortion rate** (TAR), the sum of age-specific frequencies, is an indicator that hypothetically shows how many abortions women would go through during their lifetime if the number of abortions at a given age were to persist for the entire life cycle of their childbearing age. Its indicator pair, the total fertility rate (TFR), estimates the average number of children conceived in the event that fertility frequencies at a given age are maintained. Hypothetical indicators project the registered abortions and live births of the observed period (year) to female members of a specific birth cohort (year).

Long-term trends in TAR and TFR are sensitive to external stimuli or disincentives, such as changes in the legal framework for authorization, availability of modern contraceptives, level of education of women, preferred age for childbirth, or provisions to encourage childbirth or the lack or withdrawal thereof. In Hungary, trends can be examined from the mid-1950s, since then, relatively reliable data on the number of abortions have been made available.
In 1953, Ratkó's (Minister of Health) ministerial order, together with several other measures, punished illegal abortion with imprisonment. From June 1956, however, abortion was essentially granted unconditionally at the request of the mother, and then between 1959 and 1973, more abortions than live births were registered each year. In 1964, there were the most, 140 abortions per 100 live births.
From 1974 onwards, an improving trend began to emerge, with the number of births exceeding the number of abortions each year. A significant change took place from the mid-1990s (79,000 abortions) to 2016 (30,400 abortions). Although the number of abortions fell by less than half, there was still one induced abortion for every three births (93,100 births in total).
Bason on TAR, there were 278 induced abortions per 100 women in their lifetime in 1969, compared to less than a fifth in 2016 (49 abortions). Following the change of regime, the age-specific incidence of abortion decreased by 60% between 1990 and 2016.

At the time of the change of regime, 63% of all induced abortions were among married women, and two-thirds of women aged 15-49 were married. In 2016, however, single women took over the dominant role. According to marital status, single people were already in the majority and 70% of all induced abortions were among them, while the share of married people was barely 23%.
Conscious family planning and birth control practices are closely related to women's educational level. The incidence of induced abortions decreases with a higher educational level. In 2016, the difference between the abortion rates of women who did not complete 8th grade (48.8 per thousand) and women with tertiary education (4.3 per thousand) is eleven, but it is also seven and a half times higher between women who have completed 8th grade and those with tertiary education. (KSH, 2017)

## Miscarriage and stillbirth

Desired conceptions can be broken down into live births and fetal deaths. Fetal mortality is when the fetus does not give any sign of life after being separated from the mother's body, as defined in Act LXXIX of 1992 (labour protection regulation) on the protection of fetal life.
The **fetal mortality rate** is the proportion of fetal deaths out of all conceptions per thousand women, broken down into early and middle-term (spontaneous abortions) and late fetal deaths (stillbirths). Early and middle-term fetal death (spontaneous abortion, miscarriage) is when the fetus has been in the mother's body until the 24$^{th}$ gestation week or less, or if the age since conception cannot be calculated but weighs less than 500 grams and the body length is less than 30 cm. Late fetal death (stillbirth) is when the fetus has been

in the mother's body for more than 24 weeks (until 1997, up to a full 28 weeks) or the age of the fetus cannot be determined but reaches the above weight or length parameters, or in the case of twin births, regardless of the age of the fetus if at least one fetus is born alive.
The cause of miscarriage is often difficult to identify; known risk factors include hormonal problems, infections or maternal health problems, obesity, lifestyle (e.g., drug use, malnutrition, and smoking), maternal age, cancer medications, certain ethylene glycol ethers, lead, ionizing radiation, and hard physical work (e.g. prolonged standing, heavy lifting).

At the age of 30, female fertility begins to decline slowly and at an ever-increasing rate over the age of 35. However, considering all outcomes of planned conceptions other than abortion (live birth or early, middle, and late fetal death), with age, the rate of live births decreases and the rate of fetal deaths increases. The chances of live birth have not changed significantly in recent decades, with 88% at age 30, 80% at age 36 and 65% at age 40. After the reproductive age (15-45 years), even if the desired conception occurs, there is a higher chance of fetal death than of live birth (Kamarás, 2012, Mayo Clinic, 2022). A favourable trend has been observed since 2010, with a decrease in fetal mortality and an increase in the number of live births in Hungary among women aged 30 and older (CSO, 2019c).

## Perinatal mortality

Two indicators need to be distinguished: perinatal (late fetal and early neonatal) and infant mortality.
Based on the Act of CLIV of 1997 on health care, perinatal death is if the death within the uterus occurs after the 24th week of pregnancy, or similarly to fetal death, if the fetus died within the uterus is or over 30 centimetres in length or weighs 500 grams. When a death occurs in the week following the birth of a newborn (within 168 hours), regardless of the newborn's height or weight, we speak of neonatal mortality. A born child is a newborn up to the age of 28 days and is an infant from the age of one month to the age of one year.

Perinatal mortality rate (PMR) is the number of perinatal deaths per 1,000 births.

$$PMR = \frac{\text{Perinatal (fetal and early neonatal deaths)}}{\text{Number of live births}} \times 1000$$

Perinatal, neonatal and infant mortality is an indicator of high importance, an internationally recognized indicator regarding the development level of a country's health care system and the standard of pregnancy and newborn care and plays a key role in the development of life expectancy at birth since the probability of death before reaching the age of one is remarkably high compared to the risks of death at a later age.
In 2006, WHO data reported 10 deaths in industrialized regions, 50 in developing regions and 61 in the least developed countries per 1000 children. The proportion showed high regional variability: 62 in Africa, 50 in Asia, 13 in Europe, 21 in Latin America and the Caribbean, 7 in North America, and 42 in Oceania (WHO, 2006).
In 2020, nearly half of deaths under the age of five (47%) still occurred in the first 28 days of life. This is even a relative increase compared to 1990 (40%) as on the global level, under five years of age mortality has declined faster than neonatal mortality. According to regional data for 2020, sub-Saharan Africa has the highest neonatal mortality rate in the world (27 (25–32) deaths per 1,000 live births), followed by South Asia (23 (21–26) deaths per 1,000 live births). A child born in sub-Saharan Africa is 11 times more likely to die in the first month of life than a child born in Australia and New Zealand; the risk of death for a child born in a high-income country is only one-tenth that of a child born in a low-income country. By country, neonatal mortality rates ranged from 1 death per 1,000 live births (Singapore, San Marino, Japan) to 44 (Lesotho) in 2020, and the risk of death before the 28th day of life in children born in the country with the highest mortality rates is about 56 times higher than the in the country with

the lowest mortality rate (UNICEF, 2021).
In Hungary around 270 per thousand (one in four newborns died before the age of one year) in the 1890s, then there was no improvement in the deaths of 226 per thousand in 1900 (the loss of one in five infants) until the end of the First World War. Between 1920 and 1944, neonatal mortality decreased almost by half (from 193 to 103 per thousand), by a third between 1947 and 1968, and again by four-tenths in the two decades following the change of regime (CSO, 2019b).
Since the change of regime, infant mortality has fallen by a quarter, from 14.8 per thousand in 1990 to 3.6 per thousand in 2017. According to CSO data, infant mortality decreased from 5.9 per thousand to 3.6 per thousand between 2007 and 2017. According to the UNICEF database, it has fallen further to 2.1 per thousand by 2020. Looking at long-term trends, overall, there is no demographic indicator that has shown as much improvement as infant mortality.

## Maternal mortality

**Maternal mortality rate (MMR)** is the number of maternal deaths (i.e. deaths during pregnancy or within 42 days after the termination or delivery) per 100,000 live births in a given period, usually within one year. Maternal mortality consists of death due to a pregnancy-related or exacerbated cause (pregnancy, delivery, postnatal period) or its treatment (interventions, defaults, or improper treatment) (WHO, 1992).
The indicator also represents the social situation of women and the functioning of the health care system.
In 2000, maternal mortality rates in industrialized countries were 13, 440 in developing countries and 890 in the least developed countries. In sub-Saharan Africa, the rate is 940, 220 in the Middle East and North Africa, 560 in South Asia, 110 in East Asia and the Pacific, 64 in Central and Eastern Europe and the former Soviet Union, 190 in Latin America and the Caribbean. The rates were 6 in Canada, 17 in France, 16 in the Netherlands, 7 in New Zealand, 4 in Spain, 7 in the United Kingdom and 17 in the United States.
The UN estimates that between 2000 and 2017, the **global maternal mortality rate** fell by 38 per cent - from 342 to 211 deaths per 100,000 live births. Nevertheless, more than 800 women die every day from complications during pregnancy and childbirth. In addition, for every woman who dies, about 20 others suffer a serious injury, infection, or disability.

The distribution of data remains unchanged, where two regions, sub-Saharan Africa and South Asia are responsible for 86 percent of maternal deaths worldwide. Sub-Saharan Africans suffer from the highest maternal mortality rate - 533 maternal deaths per 100,000 live births, or 200,000 maternal deaths per year. This is more than two-thirds (68%) of all maternal deaths worldwide. South Asia is second with a maternal mortality rate of 163, or 57,000 maternal deaths per year, or 19 percent of global mortality (UNICEF, 2019).
In Hungary, between 2010 and 2018, the proportion of women who died due to complications during pregnancy and childbirth decreased by 35%, with more or fewer fluctuations. There were 15 maternal deaths in 2010 per 100,000 live births and 10 maternal deaths in 2018. (CSO, 2021c)
It can be seen that regional and global averages tend to show large differences both within and between countries. Almost all maternal deaths could be prevented, as evidenced by the huge differences between regions and between the richest and poorest countries.

Bleeding remains the **leading cause of maternal mortality**, accounting for more than a quarter (27%) of deaths. A similar rate of maternal mortality was indirectly caused by pre-existing medical conditions exacerbated by pregnancy. Pregnancy hypertensive disorders, especially eclampsia, and

$$MMR = \frac{\text{Number of maternal deaths in a given period (year)}}{\text{Number of live births}} \times 100\,000$$

complications of sepsis, embolism, and unsafe abortion also claim a significant number of lives. The **lifetime risk of maternal mortality** is the likelihood that a 15-year-old girl will die from complications of pregnancy or childbirth during her lifetime. The indicator takes into account both the maternal mortality rate and the total fertility rate (average number of births per woman in her reproductive years at current age-specific fertility rates). Thus, a woman in a high-fertility environment is more likely to be at risk of maternal death and will have a higher risk of death during her lifetime than in a low-fertility environment.

The global risk of maternal mortality fell by almost half between 2000 and 2017, from 1:100 to 1:190. Like maternal mortality rate, the lifetime risk of maternal mortality varies greatly from country to country. In 2017, low-income countries had an overall lifetime risk of maternal mortality of 1:45, compared with 1:5400 in high-income countries. Among the regions, women in sub-Saharan Africa are at the highest risk of life (1 in 38), followed by South Asia (1 in 240). 1 in 4,300 women in Europe and Central Asia and 1 in 11,900 women in Western Europe lose their lives for the above reason. (UNICEF, 2019)

## COHORT'18 - Hungarian Birth Cohort Study

In Hungary, a new initiative on reproductive health is worth mentioning. The Population Research Institute of the CSO launched a longitudinal study among those born in 2018/19. The participating children were born in the same period (1 April 2018 to 30 April 2019), i.e. they form a common cohort (generation).

The study sample (initial sample: 9000 people) is provided by newborns and their families, the involvement of pregnant women and the first data collection were performed by nurses, the sample included 600 nursing districts, ensuring the representativeness of the research. Data collection extends from children's cognitive, and emotional development through their family and environmental backgrounds to health and social inequalities. The research will follow the life of the Hungarian child and their family from pregnancy to at least pre-school age, but as planned, until they reach adulthood. (COHORT'18)

## References


1. ACOG. Female age-related fertility decline. Committee Opinion No. 589. Fertil Steril. 2014;101(3):633-4.
2. AEEK. Demográfia, In: Fogalomtár. Available from: https://fogalomtar.aeek.hu/index.php/Demogr%C3%A1fia [Letöltés dátuma: 2021. december 1.]
3. Bauquis C. The world's number of IVF and ICSI babies has now reached a calculated total of 5 million. ESHRE, Brussels, 2012.
4. Bernard A, Krizsa F. Generally about infertility. Modern diagnostic and therapy in infertility[A meddőségről általában In: Kaáli, S: A meddőség korszerű diagnosztikája és kezelése] Medicina Könyvkiadó, Budapest, 2006.
5. Calhaz-Jorge C, de Geyter C, Kupka MS, de Mouzon J, Erb K, Mocanu E, és mtsai. Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE. Hum Reprod. 2016;31(8):1638-52.
6. Chambers GM, Dyer S, Zegers-Hochschild F, és mtsai. International Committee for Monitoring Assisted Reproductive Technologies world report: assisted reproductive technology, 2014†. Hum Reprod. 2021;36(11):2921-2934.
7. Chawanpaiboon S, Vogel JP, Moller AB, és mtsai. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health. 2019;7(1):e37-e46.
8. De Geyter C, Calhaz-Jorge C, Kupka MS, és mtsai. ART in Europe, 2015: results generated from European registries by ESHRE. Hum Reprod Open. 2020;2020(1):1-17.
9. ESHRE CWG. Social determinants of human reproduction. Hum Reprod.

2001;16(7):1518-1526.
10. ESHRE. ART Fact Sheet 2016. ESHRE, Grimbergen, 2017.
11. ESHRE. ESHRE Annual Report 2017. ESHRE, Grimbergen, 2018.
12. Eurostat: Fertility indicators: Total fertility rate, 2017. Available from: https://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do [Letöltés dátuma: 2019. július 17]
13. Eurostat. Mean age of women at childbirth and at birth of first child, 2017b. Available from: http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=tps00017&lang=en [Letöltés dátuma 2019. június 6.]
14. Frejka, T. Birth regulation in Europe: Competing the contraceptive revolution. Demographic Res. 2008;19(5):73–84.
15. GYEMSZI. IVF Adatszolgáltatás 2010. Available from: https://okfo.gov.hu/documents/20182/607007/IVF_adatszolgaltatas_2010eves.pdf/079480aa-ff3b-51da-d8a7-595d174b9205; [Letöltés dátuma: 2021. december 1.]
16. Kamarás F. (2012). A születések és a termékenység hazai irányzatai. Demográfia, 55(4), 243-267.
17. Kapitány B, Spéder Zs. Fertility. Demographic portrait of Hungary. 2018. 49-66.
18. Kapitány B, Spéder Zs. Fertility. Demographic portrait of Hungary. 2015. 41-55.
19. KSH. 120-year Interactive Population Pyramid [120 év interaktív korfája]. Available from: https://www.ksh.hu/interaktiv_korfa (2019). [Letöltés dátuma: 2021. december 3.]
20. KSH. Népesedési helyzetkép. Budapest: Központi Statisztikai Hivatal; 2016.
21. KSH. Terhességmegszakítások. 2017 Available from: https://www.ksh.hu/docs/hun/xftp/idoszaki/pdf/terhessegmegsz16.pdf [Letöltés dátuma: 2021. december 27.]
22. KSH. STADAT: Main rates in vital statistics of Hungary (2001–2018), 2019a. Available from:
23. https://www.ksh.hu/docs/eng/xstadat/xstadat_annual/i_wdsd007a.html [Letöltés dátuma: 2019. augusztus 6.]
24. KSH. Csecsemőhalandóság. Statisztikai Tükör, 2019b
25. KSH. Népmozgalom. 2019c Available from: https://www.ksh.hu/docs/hun/xftp/idoszaki/nepmozg/nepmozg19/index.html
26. [Letöltés dátuma: 2021. december 27.]
27. KSH. Népesedési világnap. 2021a. Available from: https://www.ksh.hu/docs/hun/xftp/stattukor/nepesedesi_vilagnap/2021/nepesedesi_vilagnap_2021.pdf [Letöltés dátuma: 2021. december 20.]
28. KSH. Magyarország számokban. 2021b. Available from: https://www.ksh.hu/docs/hun/xftp/idoszaki/mosz/mosz20.pdf [Letöltés dátuma: 2021. december 20.]
29. KSH. Fenntartható Fejlődési Célok, 3. Cél: Az egészséges élet biztosítása és a jóllét előmozdítása minden korosztály valamenynyi tagjának. 2021c Available from: https://www.ksh.hu/sdg/cel_03.html [Letöltés dátuma: 2021. december 1.]
30. KOHORSZ ’18. Available from: https://kohorsz18.hu/ [Letöltés dátuma: 2021. december 29.]
31. Makay Zs. Fogamzásgátlási módszerek alkalmazása párkapcsolatban élő nők körében. In Spéder Zs. (szerk.): A család vonzásában. KSH NKI, Budapest, 2014: 127–156.
32. Mascarenhas MN, Flaxman SR, Boerma T, és mtsai. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012;9(12):e1001356.
33. Mayo Clinic. Miscarriage Available from: https://www.mayoclinic.org/diseases-conditions/pregnancy-loss-miscarriage/symptoms-causes/syc-20354298#:~:text=Women%20older%20than%20age%2035,45%2C%20it’s%20about%2080%20percent. [Letöltés dátuma: 2022. június 15.]
34. McLaren JF. Infertility Evaluation. Obstet Gynecol Clin North Am. 2012;39(4):453-63.
35. Merrill, R. Reproductive epidemiology: principles and methods. Sudbury, MA: Jones & Bartlett Learning, 2010

36. OBDK. Éves jelentés IVF eljárásokról 2014 Available from: http://www.ijsz.hu/UserFiles/ivf_jelentes_2014.pdf [Letöltés dátuma: 2021. december 27.]
37. Sobotka T. Post-transitional fertility: the role of childbearing postponement in fuelling the shift to low and unstable fertility levels. J Biosoc Sci. 2017;49(S1):S20-S45.
38. Sobotka T. Postponement of childbearing and low fertility in Europe. Amsterdam, Dutch University Press, 2004.
39. Stedman TL. Stedman's Medical Dictionary for the Health Professions and Nursing, 5th ed. New York, NY, Lippincott, Williams & Wilkins, 2005.
40. Szabó L, Veroszta Zs. „Várandósság és szülés." Demográfiai portré. 2021:65-82.
41. The European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE), C Wyns, Ch De Geyter, és mtsai, ART in Europe, 2017: results generated from European registries by ESHRE, Hum Reprod Open, 2021(3):, 2021:1-17.
42. UNICEF. Maternal mortality. 2019. Available from: https://data.unicef.org/topic/maternal-health/maternal-mortality/ Letöltés ideje: 2021. december 27.
43. UNICEF. Child mortality data. 2021a. Available from: https://data.unicef.org/resources/dataset/child-mortality/ [Letöltés ideje: 2021. december 28.]
44. UNICEF. Early childbearing. 2021b. Available from: https://data.unicef.org/topic/child-health/adolescent-health/ [Letöltés ideje: 2021. december 27.]
45. United Nations Children's Fund and World Health Organization, Low Birthweight: Country,
46. regional and global estimates. UNICEF, New York, 2004.
47. UN General Assembly. Sustainable development goals. SDGs Transform Our World, 2030.
48. Available from: https://www.undp.org/sustainable-development-goals [Letöltés ideje: 2021. december 19.]
49. United Nations. World population prospects 2019: Highlights. United Nations Econ Soc Aff. 2019a.
50. United Nations, Department of Economic and Social Affairs, Population Division. Contraceptive
51. Use by Method 2019: Data Booklet (ST/ESA/SER.A/435). 2019b.
52. WHO. ICD-10. International Statistical Classification of Diseases
53. and Related Health Problems, 10th revision. Geneva, Switzerland: World Health Organization; 1992
54. WHO. Infecundity, infertility, and childlessness in developing countries. DHS Comparative Reports. 2004;9.
55. WHO. International statistical classification of diseases and related health problems: 11th revision (ICD-11). Geneva: World Health Organization; 2018a.
56. WHO. Preterm birth key facts. 2018b. Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth [Letöltés ideje: 2021. december 21.]
57. WHO. Reproductive health indicators: guidelines for their generation, interpretation and analysis for global monitoring. World Health Organization; 2006.

# VIII. Nutrition Epidemiology

Andrea Gubicskóné Kisbenedek

## Concept of nutrition epidemiology

Nutrition epidemiology is a branch of epidemiology that helps to understand the relationship between nutrition and health and illness. Nutrition epidemiology also examines how dietary factors are associated with the incidence of the disease in individual populations. Epidemiological studies related to nutrition have found a direct connection between certain dietary components and the risk of developing a disease or death. Epidemiological studies have shown that there is a correlation between the intake of trans fatty acids (TFAs) and unfavourable serum lipid levels, so that in several countries authorities have regulated the use of fats containing trans fatty acids in food production. In Hungary, the amount of artificial trans fatty acids in foods has been regulated since 2014. The regulation has achieved its goal, as based on the results of the 2016 impact assessment, the number of foods with a high content of trans fats has drastically decreased, thus also the intake of trans fats by the population. The Hungarian regulation was added to the European Commission's good practice database in 2019 and is available to anyone at the Good Practice Portal.

The design, implementation and evaluation of the results of nutrition epidemiology studies also present many challenges for the researcher, as the exact exposure is much more difficult to determine during these studies. In epidemiology, exposure is defined as the characteristics and lifestyle behaviours of subjects (e.g.: food, medications, such as hormone replacement therapy, tobacco products) with which they may be connected to or at risk of developing a disease. The study of nutrition and food intake is particularly complex for several reasons. If we take smoking as an example, which is a simple activity, individuals can provide information on whether they smoke by ticking yes or no. Smoking is a long-term behaviour, and since it is a habit, most people smoke roughly the same amount each day. In contrast, it is a challenge for consumers to be able to accurately report their food consumption, as an individual can consume hundreds or even thousands of different foods in a single week. The exact marking is further complicated by the fact that the food consumed can also be prepared for the industry (e.g. pre-packaged), so the respondent does not know the details of the preparation (e.g. use of fat or salt during preparation, the portion size is not always clear, either). Assessment of consumption is also complicated by the fact that individuals do not have a constant choice of food, but it can constantly change with the seasons and other life activities (weekends, holidays, vacation). The variety of food consumption from day to day can be so great that it is impossible to identify some sort of consistent dietary pattern in that. In addition, foods often replace the exposure they want to study (e.g. dietary fat or sugar content), which means that researchers must rely on food composition databases to calculate the exposure variable. Given the problems associated with the assessment of dietary intake, it is not surprising that, despite some important contributions previously observed, it is still difficult to substantiate with consistent and robust evidence the impact of diet on disease risk.

The vast majority of nutrition epidemiology researches have focused on the identification of foods and / or specific nutrients in foods over the past twenty-five years. In the focus, substances with such bioactive properties have been identified that prevent or assist in the development / control of chronic diseases (e.g.: cancer, diabetes, cardiovascular diseases). As a result, nutrition epidemiology has developed tools and methods that address scientific issues related to the biology of chronic disease, including the timing and multifactorial nature of the disease.

## Suitable epidemiological methods for the study of nutrition

Nutrition questionnaires are the primary methods by which dietary and nutrient intake estimates can be realized. There are basically three main types of these:
(1) a record of the dietary intake consumed,
(2) recall; and
(3) selection from a pre-compiled fixed list.

In the case of nutrition surveys, the period covered by the survey may cover one or more days, a specific period (e.g. during a pandemic) or even a year. The selection of the most appropriate type of questionnaire for the purposes of our studies requires careful planning, as each of the methods has both advantages and disadvantages.

### 24-hour Dietary Recall

The data collector (who is a person with knowledge of dietetics) records the type and quantity of nutrition, foods and drinks consumed during the previous 24 hours during the interview and the time of consumption. This method provides only approximate information about an individual's eating habits because it relies on memory and the diet of the individual cannot be characterized by one day's diet. It can be done in person, by phone or video call. The use of food albums and portion schedules can help in personal questioning. The respondent often wants to make a positive impression on the interviewer, which distorts the data collected in a healthy direction. Answers can also be influenced by the question itself.

### Food Frequency Questionnaire – FFQ

Respondents indicate the frequency of food consumption on a pre-designed questionnaire. This allows for retrospective data collection. Data collection can be for a month, three months, or possibly a season. The compilation of the list greatly influences the effectiveness of the method, it is difficult to create a sufficiently comprehensive, but not too detailed list of many items. The optimal length and structure of the list must be adapted to the nature of the survey. Inaccuracies can result if the food list provided does not cover all foods, but a larger list can lead to an overestimation of consumption. This method is not suitable for calculating energy and nutrient intake because it only provides information on the frequency of food consumed, not on the amount consumed. If supplemented with an average portion of food, the method may be suitable for energy and nutrient calculations. This version is called the Semi-Quantitative Food Frequency Questionnaire (SQFFQ).

### Food Screener (Brief Dietary Assessment Instruments)

It is a targeted food consumption frequency questionnaire that focuses on a specific eating behavior. Here, too, the frequency of food consumption should be provided, but the questions are only related to a specific food group, such as, for example, fast food or foods with potentially acidic chemical effects in the case of kidney stones. It is characterized by a short, quick-fill, even self-filling method and can be easily complemented with questions related to quantity.

### Diet diary

The examined person makes a dietary record of the food and beverages consumed during the day, indicating the consumed quantity of each, as well. The advantage is that in the case of comparisons, which can be considered standard, if it is carefuly-ly managed, reliable data can be obtained from it. Inadequate cooperative skills of the subject may indicate weakness in the method (e.g.: they do not immediately record consumption, they forget to record, etc.). In addition, the method is time-consuming and labour-intensive. Its standardized format is the three-day diet diary, in which the subject describes the consumption data of two not consecutive weekdays and one day at the weekend, and then these are processed in a weighted manner. The accuracy of the method can be increased by preparing detailed explanatory notes in advance, providing a sample day, and a list of commonly used household units. The method can also help to identify problem foods and raw materials by keeping a so-called symptom diary (e.g. food allergies).

**Nutrition / Diet History**

This method combines the methods listed above. It is extremely time-consuming, although it circumspectly determines the quality and quantity of normal nutrition intake.

It is recommended to collect detailed information on the following items during the diet history:

- allergies, intolerances, food avoidance,
- appetite,
- attitudes towards dining and food,
- chronic diseases, their treatment, medications,
- culture and background (religion, educational background, health beliefs),
- economic situation,
- dental and oral health,
- gastrointestinal factors,
- nutritional problems,
- life and eating patterns at home,
- food supplements, herbs,
- physical activity, leisure, distress.

The use of a diet history can provide sufficiently accurate data on the nutrition of individuals and population groups.

### Validity and reliability of data

The studied population selected according to the objectives of the particular nutrition survey, as well as the use of the appropriate method, are important factors in the reliability of the data collected during the surveys. Errors in performing nutrition surveys may derive from a wide variety of sources. Distortions may occur when sampling the population to be tested. A measurement error may result from the inaccuracy of the respondent's memory, the absence or inaccuracy of a dietary interview folloing the completion.

During processing, data may be miscoded, the size of the portions consumed may be incorrectly assessed, or even deficiencies or errors in the food composition database used during processing may lead to inaccuracies. In addition, these errors can accumulate, greatly reducing the credibility of the results. At all stages of the survey, every effort should be made to eliminate possible errors and distortions as carefully as possible.

## The concept of obesity

„Obesity is a disruption of metabolic processes in connection with genetic, central nervous system, endocrine and environmental effects, that causes a change in energy balance." This process results in an increase in food intake and / or a decrease in energy expenditure and then leads to increased fat storage. In the weight-bearing phase, it is possible to maintain obesity with less energy intake. Even at this stage, further regulatory disturbances and associated diseases may develop. Obesity is thus a chronic disease that requires long-term treatment to lose weight and then to maintain weight.

In other words, an obese person is considered to have a higher-than-normal body fat content.

### Reasons for change in energy balance

Complex endogenous mechanisms manage body weight regulation. If the amount of energy absorbed with food and used for bodily functions and physical activity is in balance, body weight does not change. Even a slight malfunction of the control systems can easily lead to this imbalance, leading to excess weight or obesity. In general, these factors, or a combination of them, contribute to obesity: environmental, genetic, childhood and adulthood, after pregnancy and childbirth, menopause, and certain events (smoking cessation, marriage, sports cessation, vacation, etc.).

### Genetic factors

Due to genetic researches, the number of secondary obesity forms with known heredity and exact genetic background is increasing, but only 2-5% of the obese patients still belong to the latter group. There is still little knowledge regarding the genetic background of exogenous obesity. It is hypothesized that the role of some predisposing genes in today's modern, obesity-promoting environment causes the epidemic of obesity. Thus, the role of genetic factors cannot be neglected either. Genetic factors have an effect, i.e. they can affect appetite, food intake, thermogenesis, energy expenditure, and storage. The combined effect of inherited and environmental factors plays a role in the development of obesity. The main areas of

energy use that is absorbed by food are resting metabolism (60-70%), thermogenesis (10-15%) and physical activity (15-40%).

### Environmental factors

In addition to a number of traditional environmental factors, intrauterine and early neonatal environmental influences may also play a role in the development of obesity and adult chronic diseases. Newborns with higher weights are more at risk for later obesity, but lower birth weight is associated with an increased risk of developing abdominal-type (central) obesity and consequential metabolic syndrome.
The risk of developing obesity in later childhood and adulthood is increased by rapid weight gain in early infancy. Other adverse effects of this rapid weight gain after birth include increased insulin resistance, an increased risk of cardiovascular disease and hypertension, abnormal blood lipid levels, and impaired endothelial function.

### The role of social and economic factors

Obesity and excess weight are serious problems that have become an enormous and increasing financial burden. However, this situation can be mainly prevented by making a reasonable lifestyle change. Nowadays, it is common all over the world for people to consume high-energy foods while being physically inactive and using little energy in their work (sedentary job) and leisure time. Like all chronic diseases, the development of obesity is easier to prevent than to treat. In the food market, the consumption of high-energy foods is significantly higher than necessary due to the advertisments of products that cause weight gain. In Hungary, foods with a beneficial effect on health do not receive enough attention. The difference between the buying and selling prices of vegetables and fruits has an adverse effect on shopping habits. The development of a nutrition culture is also an integral part of prevention.

## Determining the degree of obesity

There are several methods for determining the degree of obesity. The most general and common method is body mass index measurement. Body mass index is the quotient of the weight per the square meter of body height in kilograms. (kg / $m^2$).

According to the World Health Organization (WHO), Body Mass Index (BMI) above 25 kg / $m^2$: a person is considered to be overweight, and a person with a Body Mass Index above 30 kg / $m^2$ is considered to be obese. In addition, width dimensions (abdominal circumference, upper arm circumference, hip circumference, waist-hip ratio, etc.) may be considered. Body composition is the ratio of lean body tissue (muscle, organs, bones, blood) to adipose tissue. Distribution of body fat is more important than its amount. It provides a more precise indicator for the risks of metabolic disorders, heart diseases, high blood pressure, and diabetes. The distribution of fat in our body is determined partly by genetic and partly by hormonal balance. In men with elevated testosterone levels, storage around the abdomen, between the shouldr blades, and around the internal organs is more common. In women with elevated estrogen levels, fat is stored around the breasts and triceps. After menopause, when estrogen level decreases, fat tends to migrate from the hips from and the thighs to the abdomen, changing the shape of women. There are several methods to measure the distribution of body fat, from which it can be more accurately determined how much fat and how much muscle there are in the body. Studies show that dual energy X-ray absorptiometry (DEXA) is the most accurate method for measuring body composition. MRI and CT scans play an important role in determining the distribution of fat (e.g.: subcutaneously, muscle tissue, cardiac) in obesitology centers. Special machines based on the principle of electrical impedance are also used to determine body composition.

## Epidemiology of obesity

According to the WHO, there are more than a billion overweight and obese people in the world. Obesity is a significant health problem - and at the same time, a very serious economic difficulty - not only in developed but also in developing countries. If the current trend continues, by 2030, there

will be 2.16 billion overweight and 1.12 billion obese adults in the world.
„The most significant health and economic challenge today is the epidemic of obesity." According to a 2019 survey in Hungary, more than half of the population over the age of 15 (58.6%) have higher body weight than recommended, and one in five adults is overweight. (HCSO, 2020.)

The main diseases whose development is directly related to obesity are:

- Non-insulin dependent diabetes mellitus (NIDDM)
- Stroke
- Various heart diseases
- Orthopedic disorders
- Immunological dysfunctions
- Reproductive dysfunction
- Certain types of tumors.

## Cardiovascular diseases

Cardiovascular diseases are caused by a disorder of the heart and blood vessels, which include ischemic heart disease and coronary heart disease, stroke, hypertension and peripheral arterial diseases that are due to arteriosclerosis; furthermore, rheumatic heart disease, congenital heart disease, arrhythmias and heart failure that are not due to arteriosclerosis. The most common diseases are due to arteriosclerosis. It is the most common cause of death originating from chronic, non-communicable diseases. Heart attack and stroke are responsible for four-fifths of cardiovascular disease-related deaths.

According to data published by the World Health Organization (WHO), cardiovascular disease-related deaths account for more than half of all deaths in all European countries, outranking cancer and respiratory diseases. The number of cardiovascular diseases and related deaths has been declining in recent years, following a steady rise since the 1960s. However, according to the IDEA study, the incidence of the disease in the Eastern European region is outstandingly high among both men (27%) and women (24%), compared to other regions, where the incidence is between 8% (Canadian women) and 16% (men in northwestern Europe).
Cardiovascular diseases pose a significant health burden at both the level of the individual and the society. The high mortality rate in the Eastern European region has hardly decreased, which is also typical of cardiovascular mortality in Hungary. According to HCSO data, 49.8% of all premature deaths in Hungary are due to diseases of the circulatory system.

### Epidemiology of cardiovascular diseases

In Hungary, too, most people die from diseases of the circulatory system, just like in any country with a developed health culture. Cardiovascular disease-related deaths are responsible for every second person's death. Regarding circulatory system diseases, gender difference is not significant in their mortality rate. This is due to the fact that women generally live to a higher age than men and diseases of the circulatory system affect the senior age group to a greater extent.

### Causes and factors contributing to the development of cardiovascular diseases

Vascular calcification (Arteriosclerosis, atherosclerosis)
Vascular calcification is an inflammatory process that affects the medium to large blood vessels of the entire cardiovascular system. Low-density lipoprotein (LDL) cholesterol, which is deposited in the walls of the arteries, causes chronic inflammation, which causes plaque formation, making the wall of the blood vessels stiffer and thicker, and at the same time, the inner diameter becomes narrower. The disease can be dangerous in two ways: on the one hand, when the plaques rupture, blood clots start to form, which can lead to vascular occlusion, and dilatation due to compensation. Vascular calcification is based on the dysfunction of the inner squamous layer of the vessel wall, an endothelial dysfunction. Abnormal endothelial function is thought to increase the ability of platelets to accumulate and aggregate, and the adhesion of monocytes, which contribute to plaque formation. In addition to endothelial dysfunction

and inflammatory processes, pathological fibrinolytic processes also play a role in the development of vascular calcification.
Diabetes, dyslipidemia, or oxidative stress cause such vascular dysfunction that leads to the development of atherosclerosis, a key pathological underlying cause of cardiovascular diseases. The free radicals produced reduce the bioavailability of nitrogen monoxide (NO) by binding it. Atherosclerosis can be asymptomatic for decades, often with the first symptom being myocardial infarction (as a result of coronary calcification) or sudden cardiac arrest. Symptoms usually appear at a 50% stenosis and are specific to the organ supplied by that vessel. The rate of progression of atherosclerosis depends partly on inherited genetic factors and partly on environmental effects, the latter can be more or less influenced. This includes lifestyle and nutrition. Currently, there is no method to change genetic factors, therefore, controlling the risk factors that can be influenced and influencing the environmental factors in a favourable direction is of high importance.

## Cardiovascular risk factors

In order to reduce cardiovascular diseases and related mortality, population-based epidemiological studies were conducted for decades to help identify the development of the disease, the conditions that contribute to it, and the risk factors. The Framingham Heart Study has identified key risk factors for cardiovascular diseases: high blood pressure, high cholesterol, smoking, obesity, diabetes, and sedentary lifestyle; furthermore, their loss of effects results in endothelial dysfunction, including reduced vascular relaxation. In addition, the role of psychosocial factors has been identified, as well. Smoking is the most significant preventable lifestyle risk factor in developed countries, with some surveys showing that the relative risk of developing ischemic heart disease is 20% higher in smokers than in non-smokers. Smoking promotes the early onset of microvascular complications (retino-, nephro-, neuropathy), increases triglyceride levels and lowers HDL cholesterol, and promotes the development of insulin resistance. All of these increase the risk of developing coronary heart disease and heart attack. Quitting smoking can only slightly reduce blood pressure but can significantly reduce cardiovascular risk. Some epidemiological studies have shown that even unsuccessful quitting's have risk-reducing effect. The role of malnutrition was first raised in the 1940s. The Seven Countries Study, launched in 1958 and running until 1970, looked at the relationship between dietary fat intake and atherosclerosis and related cardiovascular diseases. Based on a study of more than 12,000 male participants aged 40 to 59 years, serum cholesterol levels were low in those who consumed a diet low in saturated fat. On the other hand, participants on a high saturated fat diet had high cholesterol level. A very strong correlation was shown between saturated fat intake and mortality within five years of coronary heart disease. Correlation between saturated fat intake and coronary vessel disease was also confirmed by the 25-year follow-up data.

Global cardiovascular and metabolic (cardiometabolic) risk

Several studies have shown that scoring systems based on traditional risk factor assessment (Framingham SCORE) often underestimate the cardiovascular risk of individuals at moderate risk, especially of women. In addition to cardiovascular (absolute) risk factors, all known risk factors - abnormalities suggestive of metabolic disorder, positive family history, and physical inactivity - have been suggested to assess the prognosis, leading to the emergence of the concept of global cardiometabolic risk. Accordingly, an individual with at least three of the symptoms of smoking, abdominal obesity, hypertension, high cholesterol, and an additional risk factor is also present from other "residual" risk factors, even if, on a typical SCORE value, the cardiovascular risk is moderate.
The role of the Mediterranean diet in cardiovascular diseases

In the case of cardiovascular diseases, Mediterranean diet also has a beneficial effect in reducing its risk factors and also in reducing the severity of the disease developed. A series of studies report that Mediterranean diet lowers blood pressu-

re, cholesterol levels, complications of diabetes, inflammatory marker levels, and endothelial function. In the case of metabolic syndrome, no effect on the frequency of occurance resulting from the Mediterranean diet was found, but the level of inflammatory markers was reduced due to the effect of alpha-linolenic and linoleic acid.

Characteristics of the typical Mediterranean diet:

1. Abundant consumption of vegetable raw materials
2. Consumption of cereal grains in large quantities.
3. Consumption of large amounts of fresh fruits on a daily basis.
4. The main source of fat is olive oil.
5. Regular consumption of sea fish, seafood.
6. Consumption of small amounts of red meat in the diet is typical.
7. Moderate consumption of milk, milk products and eggs.
8. Consume 1-2 glasses of red wine with meals a day.

The effectiveness of the Mediterranean diet is enhanced by antioxidant vitamins (vitamins A, C, E), which are also provided in large amounts by plant sterols and polyphenols. Plant sterols are found in small amounts in many fruits, vegetables, nuts, seeds, legumes, vegetable oils, and other plant sources, and are essential components of the plant's cell membrane.

## The role of nutrition in developing cancer

In Hungary, the second place in mortality statistics is occupied by malignant neoplasms. Unfortunately, their number shows an ever-increasing trend, which is explained by several factors. Among other things, they attribute it to the increase in life expectancy, the development of diagnostic procedures, poor eating habits, lifestyle factors, pollution, and individual sensitivity. The role of nutrition in the development of tumors is estimated at 35%, and they could, in theory, be prevented by developing good eating habits. First, it was Doll and Peto to publish the factors involved in the development of tumors. The majority of diet-related tumors are caused by carcinogens that enter the food as natural contents or contaminants, or during food preparation. Some of the substances that enter the body through food are genotoxic, initiator, while most of them have a promoter effect. The process of tumor formation can be facilitated, i.e. certain macro- and micro-nutrients can act as promoters, which enter our body in a higher or lower proportion than necessary. Throughout our food intake, ingredients that inhibit or slow down the development of tumors, called biologically active substances. Our foods have many ingredients, which is why it is difficult to study the relationship between nutrition and tumors, as it is difficult to study the ingredients independently.

### Carcinogenesis

During the process of carcinogenesis, usually a long time elapses between exposure and onset of the disease, as well as between the onset of clinical symptoms and the appearance of metastases. After all, the development of tumors is considered to be a multi-stage process.

### Exposure

Exposure to a carcinogenic chemical is called exposure. DNA damage depends on the frequency and extent of exposure, therefore, form the composition of the diet and the functioning of the defense mechanisms. The most common carcinogens in our diets are the heterocyclic amines, mycotoxins, polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and their common characteristic is that they are extremely strong reactive substances.

### Initiation

During initiation, the carcinogen comes into contact with the DNA molecule, which is the first step in carcinogenesis. During the process, the molecule that binds to DNA changes the structure of the DNA, which can cause incorrect coding and point mutations during duplication. Becoming a tumor cell is an irreversible change. Against mutations, our bodies defend us through repair mechanisms.

### Promotion

Promotion is in which no irreversible change occurs in the second phase of tumor development. During the long process, the body's repair mechanisms (DNA repair, apoptosis) try to defend against the mutation, and the carcinogenic and tumor-promoting inflammatory processes help the development of more and more mutations.
The carcinogenic effect of nutritional factors has been investigated in several experiments. However, the beneficial effects of some nutrients could also be observed. An example is methionine- and choline-deficient foods, which increase the incidence of liver cancer. In cancerous processes of the pharynx, larynx and esophagus, retinoids slow or inhibit the process.

### Progression

The final stage of cancer formation is a complex process in which initiated cells proliferate, attack the surrounding tissues. Clinical recognition occurs at this stage, the tumor can already be diagnosed, and causes symptoms due to its size or aggression.

### The role of nutritional factors in the development of tumors

- Excessive energy intake
- Abundant animal protein intake
- Excessive intake of animal fat
- Low dietary fiber intake
- Excessive alcohol consumption
- Excessive salt intake
- Excessive consumption of salted, smoked, marinated foods
- Sudden consumption of too hot food

### Anti - carcinogenic substances

Anticarcinogens: This group includes substances that prevent the formation of carcinogens and reactive metabolites from precursors.
Blockers: The second group includes substances that prevent a carcinogenic compound from reaching or reacting with the target molecule, thus blocking initiation.
Suppressors: the third group includes substances with a barrier function; they delay or prevent malignant transformation of cells after carcinogenic exposure by inhibiting promotion or progression.
Vitamin C is an antioxidant vitamin that inhibits the production of carcinogenic metabolites in the intestinal tract. Several studies suggest that high doses of carotenoids inhibit gastrointestinal, breast, and cervical cancer. However, large studies in recent years have not reported success with its chemopreventive use. Vitamin E also has an antioxidant effect, presumably through the inhibition of nitrosamine formation.
Bioactive compounds, also known as phytochemicals, are compounds found in plants that play an active role in preventing or combating the development of diseases. The study of their action mechanism has begun in recent decades, and the compounds alone or in combination with micronutrients block initiation or inhibit the progression of the cancerous process.

Phytochemicals include allium compounds, which are responsible for the smell, aroma, and health effects of bulb vegetables (onion, garlic, chives, shallots, etc.). Garlic contains allin, which decomposes rapidly on contact with air and forms sulfur compounds (diallyl sulphide, allyl methyl trisulphide) at the end of the process. Allium compounds exert their tumor-preventing effect by activating detoxification enzymes and blocking initiation. Due to the bacteriostatic effect of garlic, it also inhibits bacterial activity, thereby converting nitrogen to nitrite.

Glucosinolates are found in all cruciferous plants (broccoli, cauliflower, buds, kale, etc.). Glucosinolates can be converted to isothiocyanates and indoles upon cooking and chewing.
Phytoestrogens include isoflavones, the main sources of which are cereals; and lignans found in flaxseed, sesame seed, strawberry, and blueberry. Their biological activity is diverse, having antiviral, antiproliferative and growth inhibitory effects. Due to their mild estrogenic effects, they are able to bind to various enzymes and receptors, stimulating the production of globulins that bind to sex hormones in the liver - thus affecting the metabolism of the steroid hormone. They inhibit

the proliferation of hormone-dependent tumor cells.

Flavonoids (catechin, anthocyanidin) can intervene in the process of carcinogenesis at several points. They inhibit the formation of DNA adducts; accelerate detoxification, thereby inhibiting initiation. They inhibit promotion as they have anti-inflammatory effects. They induce apoptosis. Quercetin (red wine, apple) have inhibited the action of tumor promoters and some chemical carcinogens in animal experiments, and inhibited the proliferation of colonic epithelial cells. However, other studies have shown an increased risk of bladder and bowel tumors.

## References


1. 37/2014. (IV. 30.) EMMI rendelet a közétkeztetésre vonatkozó táplálkozás-egészségügyi előírásokról. Available form: https://net.jogtar.hu/jogszabaly?docid=a1400037.emm [accessed: September 07, 2019].
2. 71/2013. (XI. 20.) EMMI rendelet az élelmiszerekben lévő transz-zsírsavak megengedhető legnagyobb mennyiségéről, a transz-zsírsav tartalmú élelmiszerek forgalmazásának feltételeiről és hatósági ellenőrzéséről, valamint a lakosság transz-zsírsav bevitelének nyomon követésére vonatkozó szabályokról. Available form: https://net.jogtar.hu/ jogszabaly?docid=A1300071.EMM [accessed: September 07, 2019].
3. Ádány R. (ed.). Megelőző orvostan és népegészségtan. Debreceni Egyetem, Debrecen, 2011. Available from: https://www.tankonyvtar.hu/hu/tartalom/tamop425/0019_1A_Megelozo_orvostan_es_nepegeszsegtan/adatok.html [accessed: August 03, 2019].
4. Alabaster O, Tang Z, Shivapurkar N. (1996). Dietary fiber and the chemopreventive modelation of colon carcinogenesis. Mutat Res. 350:1.185-97.
5. Antal M. (2003). A daganatos megbetegedések. 42-44 o. In: Rodler I. (szerk.): Élelmiszerbiztonság és Táplálkozás-egészségügy. Táplálkozás-egészségügy és táplálkozáspolitika. Fodor József Országos Közegészségügyi Központ Országos Élelmezés- és Táplálkozástudományi Intézete, Budapest.
6. Aschengrau A, Seage GR. Essentials of epidemiology in public health. Third edition, Jones & Bartlett Learning, Burlington, 2019.
7. Balkau B, Deanfield JE, Després JP, Bassand JP, Fox KAA, Smith SC Jr, Barter P, Tan CE, Van Gaal L, Wittchen HU, Massien C, Haffner SM: International day for the evaluation of abdominal obesity (IDEA). A study of waist circumference, cardiovascular disease, and diabetes mellitus in 168.000 primary care patients in 63 countries. Circulation116: 1942-1951, 2007.
8. Bíró Gy. (2004). A helyes táplálkozás In Bíró G, Bíró Gy. Élelmiszer-biztonság, Táplálkozás-egészségügy. Agroinform Kiadó, Budapest 2000.
9. Bíró Gy. (2008). Eljárások és módszerek a magyarországi lakosság tápanyagbevitelének meghatározására a táplálékkal bevitt xenobiotikum terhelés becsléséhez, Élelmiszervizsgálati közlemények, 54:1. 5-22.
10. Biró L. A korszerű tápanyagszámítás szerepe és lehetőségei a táplálkozástudomány területein. Doktori értekezés. Semmelweis Egyetem, Patológiai Tudományok Doktori Iskola, Budapest, 2012. Available from: https://repo.lib.semselweis.hu/bitstream/handle/123456789/199/birolajos.DOIs.pdf?sequence=1 [accessed: September 03, 2019].
11. Boeing H, Schwingshackl L. Reforming Nutritional Epidemiologic Research-Reply. JAMA. 2019; 321(3):309-310. Avail- able from: https://www.researchgate.net/publication/330619379_Comment_Reforming_Nutritional_Epidemio- logic_Research/link/5c4ab891299bf12be3e1ab31/download [accessed: August 10, 2019].
12. Boeing, H. Nutritional epidemiology: New perspectives for understanding the diet-disease relationship? Eur J Clin Nutr. 2013;67(5):424-9. Available from: https://

www.nature.com/articles/ejcn201347 [accessed: August 03, 2019].
13. Breitenbach Z. A táplálkozással kapcsolatos vizsgálatok. In: Figler M (ed.) Klinikai és gyakorlati dietetika. Medicina Könykiadó Zrt., Budapest, 2015; pp. 83-94.
14. Demográfiai jellemzők Magyarországon és az Európai Unióban, különös tekintettel a daganatos megbetegedések okozta halálozásra from http://www.ksh.hu/statszemle_archive/2012/2012_06/2012_06_544.pdf
15. Erdei G, Kovács VA, Bakacs M, et al. Országos Táplálkozás és Tápláltsági Állapot Vizsgálat 2014 – I. A magyar felnőtt lakosság tápláltsági állapota. Orv Hetil. 2017; 158(14): 533-540.
16. European Food Information Resource (EuroFIR). Transforming quality food data into tools and products. From food data to databases. Available from: http://www.eurofir.org/food-information/food-composition-databases/ [accessed: September 07, 2019].
17. European Food Safety Authority. Food consumption data. Available from: https://www.efsa.europa.eu/en/data/food- consumption-data [accessed: September 07, 2019].
18. Gunnar J. Nutritional epidemiology. Dietary assessments: use, design concepts, biological markers, pitfalls and validation. E-published 2014. Available from: http://hh.diva-portal.org/smash/get/diva2:719801/FULLTEXT02.pdf [accessed: August 03, 2019].
19. Hajer GR, van Haeften TW, Visseren FLJ. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J 2008; 29 [24]: 2959–2971.
20. Hammond KA, Mahan LK. Intake: Analysis of the diet. In Mahan L.K, Raymond Jl. (eds.) Krause's food & the nutrition care process 14th Edition, Elsevier, 2017; pp.52-63.
21. Illner AK, Freisling H, Boeing H, et al. Review and evaluation of innovative technologies for measuring diet in nutritional epidemiology. Int J Epidemiol. 2012;41(4):1187-203.
22. Ioannidis JPA. The challenge of reforming nutritional epidemiologic research. JAMA. 2018; 320(10):969-970. Available from: http://statmodeling.stat.columbia.edu/wp-content/uploads/2018/08/jama_Ioannidis_2018_vp_180095.pdf [accessed: August 03, 2019].
23. Kicsák M, Biró L, Vígné Sági K. 1-es típusú cukorbetegségben megbetegedettek energia- és tápanyag-bevitelének multicentrikus vizsgálata. Táplálkozási adatfelvétel, tápanyagszámítás, adatfeldolgozás, gondozási adatok. Available from: http://www.diabet.hu/upload/diabetes/magazine/99040501.htm?web_id= [accessed: September 03, 2019].
24. Kok FJ, Kromhout D. (2004). Atherosclerosis. Epidemiological studies on the health effects of a Mediterranean diet. Eur. J. Nutr., Suppl. 43, I/2–I/5.
25. Központi Statisztikai Hivatal. A háztartások életszínvonala, 2018. Available from: http://www.ksh.hu/docs/hun/xftp/ idoszaki/hazteletszinv/2018/index.html#chapter-0 [accessed: November 07, 2019].
26. Lachat C, Hawwash D, Ocké MC, et al. Strengthening the reporting of observational studies in epidemiology-nutri- tional epidemiology (STROBE-nut): An extension of the STROBE Statement. PLoS Med. 2016;13(6). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4896435/ [accessed: September 03, 2019].
27. Martos É, Kovács VA, Bakacs M, et al. Országos Táplálkozás és Tápláltsági Állapot Vizsgálat – OTÁP2009. I. A magyar lakosság tápláltsági állapota. Orv Hetil. 2012; 153: 1023-1030.
28. Nagy B, Nagy-Lőrincz Zs, Bakacs M, et al. Országos Táplálkozás és Tápláltsági Állapot Vizsgálat 2014 – III. A magyar lakosság makroelem-bevitele. Orv Hetil. 2017; 158(17): 653-661.
29. Nagy B, Nagy-Lőrincz Zs, Bakacs M, et al.

Országos Táplálkozás és Tápláltsági Állapot Vizsgálat 2014 – IV. A magyar lakosság mikroelem-bevitele. Orv Hetil. 2017; 158(21): 803-810.
30. Nelson MC, Lytle LA. Development and evaluation of a brief screener to estimate fast food and beverage consump- tion among adolescents. Am Diet Assoc. 2009; 109(4): 730-734.
31. Országos Élelmezési- és Táplálkozástudományi Intézet. Az Országos Táplálkozás és Tápláltsági Állapot vizsgálat (OTÁP2014) háromnapos táplálkozási naplójának kitöltési útmutatója. Available from: http://www.oeti.hu/down- load/taplnaplootap2014.pdf [accessed: April 03, 2015].
32. Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet (OGYÉI). Európai uniós jó gyakorlat lett a transzzsírsav-tartalomra vonatkozó magyar korlátozás. Available from: https://www.ogyei.gov.hu/europai_unios_jo_gyakor- lat_lett_a_transzzsirsav_tartalomra_vonatkozo_magyar_korlatozas [accessed: August 03, 2019].
33. Park Y-S, Kim J-S: Obesity Phenotype and Coronary Heart Disease Risk as Estimated by the Framingham Risk Score J Korean Med Sci. 2012 March; 27(3): 243-249.
34. Reaven GM. Why Syndrome X? From Harold Himsworth to the Insulin Resistance Syndrome Cell Metabolism JANUARY 2005 VOL. 1.
35. Rodler I. (ed). Élelmezés- és táplálkozás-egészségtan. Medicina Könykiadó Zrt., Budapest, 2008.
36. Rodler I. (szerk) (2008). Biogén aminok. In Élelmezés és Táplálkozás-egészségtan. Budapest, Medicina Könyvkiadó Zrt. pp. 359.
37. Rodler I. (szerk.) (2005). Új tápanyagtáblázat. Medicina Kiadó.
38. Sarkadi Nagy E, Bakacs M, Illé É, et al. Országos Táplálkozás és Tápláltsági Állapot Vizsgálat 2014 – II. A magyar lakosság energia- és makrotápanyag-bevitele. Orv Hetil. 2017; 158(15): 587-597.
39. Satija A, Yu E, Willett WC, Hu FB. Understanding nutritional epidemiology and its role in policy. Adv Nutr. 2015;6(1): 5-18. Available form: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4288279/ [accessed: August 03, 2019].
40. Schreiberné Molnár E, Nagy-Lőrincz Zs, et al. Országos Táplálkozás és Tápláltsági Állapot Vizsgálat 2014 – V. A magyar lakosság vitaminbevitele. Orv Hetil. 2017; 158(33): 1302-1313.
41. Scott SK, Harris RE. Epidemiology of obesity. In: Harris RE (ed.) Epidemiology of Chronic Disease: Global Perspectives Second Edition. Jones & Bartlett Learning, Burlington, 2019; pp. 609-646.
42. St-Pierre AC, Cantin B, Mauriege P, Bergeron J, Dagenais GR, Despres JP, Lamarche B. Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. CMAJ 2005; 172(10):1301-1305.
43. Szűcs V, Szabó E, Bánáti D. Az élelmiszer-fogyasztási adatbázisok múltja, jelene és jövője. Orv Hetil. 2012;153(43): 1692-1700.
44. Thompson FE, Subar AF. Dietary assessment methodology. In: Coulston AM, Boushey CJ, Ferruzzi M, Delahanty L. (eds.) Nutrition in the prevention and treatment of disease, Academic Press, Elsevier, 2017; pp. 5-48.
45. Trinchieri A. Development of a rapid food screener to assess the potential renal acid load of diet in renal stone formers (LAKE score). Arch Ital Urol Androl. 2012;84(1):36-8.
46. Villasĕnor A, Cadmus-Bertram L, Patterso RE. Overview of nutritional epidemiology. In: Coulston AM, Boushey CJ, Ferruzzi M, Delahanty L. (eds.) Nutrition in the prevention and treatment of disease, Academic Press, Elsevier, 2017; pp. 145-166.
47. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediator Inflamm 2010; 2010:535918. doi: 10.1155/2010/535918. Epub 2010 Aug 5.
48. Welch A. Dietary assessment. In: Gandy, J. (ed. in conjunction with the British Dietetic Association) Manual of Dietetic Practice,

Fifth Edition, John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, 2014; pp. 61-66.
49. Willett W. (ed.) Nutritional epidemiology. Oxford University Press, New-York, 2013.
50. Yang W, Kelly T, He J. (2007). Genetic epidemiology of obesity. Epidemiol Rev. 2: 9. 49-61.

# IX. Introduction

Anna Páldy

## Introduction

Diseases associated with environmental factors are difficult to identify because they are the result of a combination of factors. The relationship between the factors of natural and built environment and human health is known, but it is often difficult to identify harmful effects and the cause-and-effect relationship. Environmental effects are characterized by the fact that they usually occur at low levels or concentrations, but over a long period of time, and that health damage develops as a result of a number of effects.
Overall, 13% of deaths in the European Union (EU) are due to various environmental stressors, resulting in 630,000 deaths per year. It is estimated that about 17-22% of the total burden of disease in Hungary is attributable to environmental risk factors (higher than the global average of 11.8%). Within this, air pollution is of the greatest importance in Hungary - primarily fine particulate matter (PM)) outdoors, which accounts for approx. 12% of total morality in 2019. Air pollution is currently the fourth leading cause of global burden of disease and mortality following high blood pressure, smoking and dietary risk.
Health risks of extreme temperatures and heat waves cannot be neglected either. Other environmental factors (radon and lead), risks originating from water (poor quality drinking and bathing water, inadequate hand washing, poor sanitation, and vulnerability of drinking water supplies) and exposure from soil contamination play a smaller role.

## Risk assessment of air pollution from acute to chronic effects

Health risk of air pollution is first assessed by applying the traditional risk assessment method (hazard identification, exposure characterization, dose-response relationship characterization, exposure estimation, risk assessment).
Risk assessment focuses on comparing exposure concentration data with thresholds without examining the effect of above-threshold concentration. The Hazard Index (HI), which is the ratio of the currently measured concentration of an air pollutant to the relevant limit value, is most commonly used. HI can also be used to characterize complex air pollution. Calculation of HI also provides an opportunity to quickly assess the hazard of acute events (e.g. fires of various origins and magnitudes) based on properly designed and performed on-site sampling and measurements. Short-term Acute Exposure Level Guidelines (AEGLs) developed by several U.S. environmental agencies should be used to calculate HI.

The paradigm of risk assessment used in toxicology should also be applied to indoor air quality in public areas according to the Scientific Committee on Health and Environment Risk (SCHER) established by the European Commission in 2004. Where possible, safe exposure limits should also be established or exposure levels should be compared with those based on experimental and human studies to characterize the risk. In 2021, the European Center for Environment and Health (WHO / ECEH) developed a free-to-download tool for estimating the risk of chemical exposure in children's institutions using the HI calculation method.

Environmental health impact assessment is relatively new to the well-defined methodology of risk assessment, which quantifies the expected burden of disease due to a given environmental exposure in a given population. When doing an environmental health impact assessment of air

pollution the following factors should be taken into account : basic health indicators of the study population, number of population, concentration of air pollutant (e.g. PM) and the relative risk of health effects per unit air pollutant (usually determined by the statistical method of time series analysis in multicentre studies). Applying this method, we can estimate the risk of past, present and modeled future exposure, and it is suitable for modeling the impact of planned provisions. The estimate can be quantitative or qualitative, and usually includes estimating the concentration, further the exposure of the target population, and how dangerous the particular concentration is to the exposed population. The result of estimating the health effects of air pollution is most often provided by the number of excess deaths attributable to air pollution. Even within mortality, the most significant problem is early or premature mortality, usually before the age of 65, which is used as a separate indicator among mortality indicators. Losses are often characterized by the number of years of life lost (YLL). Attributable death rate is clearly influenced by the individual's environmental factors, including air quality, socioeconomic status, curability of the disease, state of the health care system, and so on. Disability-adjusted life years (DALY) or change in life expectancy are often used. These indicators can even be used to calculate additional costs and to quantify the health benefits of the policy measures taken. There are softwares that can assist these calculations as well. It is important to mention that in 2014, the European Union developed a formal recommendation to calculate the cost of diseases caused by air pollution, taking into account WHO recommendations.

In addition to the benefits of environmental health impact assessment, its limitations should also be mentioned, the most significant of which is the lack of adequate data: for example, air pollution or population data are not available for a given site, so in many cases the risk assessment is based on estimates. As a result, environmental health impact assessments can involve a lot of uncertainty. Of course, impact assessments only cover health outcomes in which the effects can be quantified.

## Adverse health effects of fine particulate matter (PM)

In 2013, in the context of "Clean Air Programme for Europe", the European Union set a target of reducing the health effects of air pollution, i.e. premature deaths from PM and $O_3$, by 37% by 2025 and an additional 40% by 2030.

Air quality is regulated by harmonized regulations based on EU directives. The WHO recommends stricter guidelines than those laid down in the European Union. The World Health Organization first issued guidelines on air quality in 1987, which have been amended several times in the light of the scientific evidence that has accumulated in the meantime. The last update of the previous air quality guidelines issued in 2005 took place in September 2021. The new air quality guidelines are significantly stricter than those set in 2005. The new ambitious target is to achieve an annual average concentration of 5 μg/m$^3$ for $PM_{2.5}$ size fraction, a maximum concentration of 10 μg/m$^3$ for $NO_2$ and a limit value of 60 μg/m$^3$ for the 8-hour average peak ozone concentration. By comparison, the guideline issued in 2005 recommended 10 μg/m$^3$ for the $PM_{2.5}$ size fraction and 40 μg/m$^3$ for $NO_2$, while no guideline level was available for long-term ozone concentrations. Although the guideline levels are not legally binding, it is hoped that countries will strive to meet these values.

New recommendations are also of paramount importance because there has been a wealth of evidence over the past two decades confirming the serious health effects of air pollution, stressing that it can be harmful to almost every component of the human body. It is important to emphasize that the health effects of air pollution are not only present at significant exposure levels, but also at very low concentrations, so no limit value can be set below which exposure can be considered safe. Regarding air pollutants, fine particulate matter is considered to be the most significant pollutant, with similar scientific evidence of an impact on the health of urban population in all parts of the world. The respiratory and circulatory systems are mainly affected, the extent of which may vary by age groups and by the health status of the popula-

tion. The risk of each effect depends on the concentration and composition of the air pollutants. Epidemiological studies show that particulate matter has harmful effects in both the short and long term.

The results of clinical, experimental toxicological and epidemiological studies demonstrating the effects of fine particulate matter were first summarized and evaluated by the WHO in 2003. PM primarily causes local inflammation, followed by exacerbation of pre-existing respiratory diseases, excessive reactions, oxidative stress, activation of many biochemical processes, and reduction in the defense mechanism of the lungs. PM pollution has been shown to contribute to the mortality and exacerbation of patients with chronic lower respiratory disease. Asthma patients' symptoms also worsen and their need for medication increases during more polluted periods. In 2013, the WHO International Agency for Research on Cancer (IARC) classified air pollution as a proven human carcinogen. Particulate matter pollution has also been treated separately and classified as a Group 1A carcinogen.

Fine dust particles, especially those with a particle size of less than 1 μm in diameter, are absorbed through the alveoli and, on the one hand, cause sterile inflammation in the interstitiun of the lungs, and, on the other hand, entering the bloodstream, they induce the formation of C-reactive protein in the short term, which triggers the blood clotting process, consistently leading to the formation of a blood clot (thrombus). Numerous epidemiological studies have also shown an increase in deaths from cardiovascular disease and a higher number of hospital admissions.

## Risk assessment of air pollution in practice

To assess the environmental health impact of air pollution, the WHO has developed a free-to-use tool to evaluate the attributable health risks of air pollution. From 2020, the latest version of the software, AirQ+ is available, it meets the latest IT requirements and includes the latest scientific findings and evidence on the relationship between air pollution and health risks for different health endpoints.

One of the indicators (3.9.1: deaths from indoor and outdoor air pollution) for the achievement of the UN's Sustainable Development Goals (SDG 3: "Ensure healthy lives and promote well-being for all at all ages") until 2030 can be monitored by using the software. The software can also be used at local level to assess the environmental health impact of new installations in case of having the basic appropriate exposure, population and health endpoint data.

## The health risk of fine particulate matter load in Hungary

In Hungary, data of the National Air Pollution Measurement Network provide information on the levels of individual outdoor air pollutants. However, it is important for both the general public and decision-makers, environmental and health professionals to have adequate information on the health effects of pollution measured by monitoring stations.

AirQ+ software was used to perform a comprehensive assessment based on measured data from domestic monitoring stations for municipalities with operating urban or suburban background stations for the period 2008-2016. The analysis was based on outdoor $PM_{2.5}$ concentrations for routinely collected health endpoints (mortality, hospital admissions). When estimating the total mortality due to long term outdoor $PM_{2.5}$ pollution greater than the non-binding health guideline value (10 μg/m3 annual average) stated by the 2005 WHO Air Quality Guidelines, the estimated number of excess deaths was between 1400 and 1660 in Budapest, between 190 and 230 cases in Miskolc and 137-154 cases in Debrecen on average per year during the examined period.

## Assessment of the short-term health risk of air pollution based on the Air Quality Health Index (AQHI)

Characterization of air quality status is based on the comparison with the limit values, which me-

ans examining the extent and number of exceedances of the limit values. Regulation 4/2011 (I. 14.) of the Ministry of Rural Development on health limit values for air pollution provides information regarding this matter. The regulation also contains information and alert thresholds on the basis of which the smoke alarm response plan is implemented.

Since 2007, the National Public Health Center (hereinafter: NPHC) and its predecessor institutions have been assessing health risks of air pollution on a daily basis for various risk groups (e.g. children, the elderly, people with chronic respiratory and other diseases, especially cardiovascular diseases). The aim is to give a timely information on the short term health effects of the actual air pollution situation and health protection of the vulnerable population groups by relevant advices. Air Quality Health Index (AQHI) rating system is based on the results of the latest international and domestic research. The assessment is updated daily, using validated air pollution data published on the previous day, taking into account the most important air pollutants for health risk: (1) fine particulate matter with a diameter of less than 2.5 micrometres (µm) ($PM_{2.5}$); (2) fine particulate matter with a diameter of less than 10 µm ($PM_{10}$); the concentration of nitrogen dioxide ($NO_2$) and ozone ($O_3$). AQHI is calculated from the 24-hour average concentration values (for $PM_{2.5}$ and $PM_{10}$), the daily maximum of the 8-hour moving average concentrations (for $O_3$) and the daily maximum of the hourly average concentrations (for $NO_2$), by taking into account the latest WHO recommendation.

AQHI includes four categories: (1) acceptable; (2) moderate; (3) unhealthy (4) hazardous. The data required for determining AQHI are provided by the continuously published measurements of the automatic monitoring stations of the National Air Pollution Measurement Network.
Concentration values corresponding to each category are based on the relationships established in international studies between air pollution and the short-term health effects of the concentration of a given air pollutant (Table 1).

## Health risks of indoor air pollution

From the second half of the 20th century onwards, due to the changed economic and social conditions, we spend more and more time indoors - 16 out of 24 hours a day. It is therefore very important that the environment at home, at work and in leisure is of the right quality. Outdoor air quality is well regulated, although it should be mentioned that in addition to routinely measured pollutants, especially during the heating period, the concentration of certain unmonitored substances that are harmful to health may increase significantly. It is known that indoor air quality is greatly influenced by outdoor air, and according to the literature data, concentration of the dominant outdoor pol-

Table 1.: Air Quality Index – categories and classification of air pollutants

| **Categories of Air Quality Index** | **Concentration of air pollutants (µg/m3)** | | | |
|---|---|---|---|---|
| | **$PM^{2.5}$** (24 hours) | **$PM_{10}$** (24 hours) | **$NO_2$** (hourly maximum) | **$O_3$** (maximum of the 8-hour moving average) |
| acceptable | <25 | <50 | <100 | <100 |
| moderate | 25 – 37.5 | 50 – 75 | 100 - 200 | 100 - 160 |
| unhealthy | 37.5 - 50 | 75 – 100 | 200 - 300 | 160 - 240 |
| hazardous | ≥50 | ≥100 | ≥300 | ≥240 |

lutant components (e.g .fine particulate matter) can be higher by 20-80% indoors. The main problem indoors is the high concentration of carbon dioxide due to insufficient air exchange, as well as fine particulate matter, formaldehyde and volatile organic compounds. In many places, another special problem is the presence of biological agents due to the lack of insulation of buildings or, conversely, over-insulation and inadequate ventilation equipment. The latter are also very important for thermal comfort. Indoor radon is an additional problem in some geographic areas, with a non negligible risk of developing lung tumors.
Investigation of the adverse health effects of indoor environment is a very important environmental health task. Public health professionals should be prepared for proper investigation of complaints and perform routine inspections in health and educational institutions, and to assist in creating healthy indoor environment. The methodological recommendation prepared by the NPHC for educational institutions is available on the Centre's website.

According to international experience, the assessment of the indoor environment is carried out either quantitatively or qualitatively. Quantitative assessment is based primarily on visual inspections to identify the cause of visible mold or unpleasant odours in the indoor environment, such as the source of volatile organic compounds. Quality assessments are usually limited to measuring a few parameters (primarily comfort): such as carbon dioxide, temperature, humidity; and some contaminants such as small aerosol particles and all volatile organic compounds.

Based on international publications and domestic experience, the following general recommendations can be made:

- Proposed steps for the environmental health assessment and evaluation of interiors
- On-site inspection, during which a survey sheet must be filled in on the condition of the building and the individual rooms, sources of danger.
- Filling in a questionnaire suitable for personal assessment of the state of health of the exposed subjects.
- Assessment of health complaints using a questionnaire.
- Instrumental examination of the quality of the indoor environment.
- Risk assessment using simple and complex indicators.
- Calculation of indoor air quality index.

A number of indicators are used to estimate health risks, from the *hazard index* for assessing the hazard of each compound to the *Maximal Cumulative Ratio* (MCR), which is an extension of the hazard index to test the combined toxicological effects of mixtures and to various indoor air quality indices. Calculation of the indices is based on specific measurements. When calculating complex indicators, each component is weighted based on their toxicity and health effects.

The WHO's Regional Office for Europe published a book in 2010 based on health risks, entitled "WHO guidelines for indoor air quality: selected pollutants", which sets out guidelines for the most common air pollutants. They are generated indoors and often occur in concentrations harmful to health: benzene, carbon monoxide, formaldehyde, naphthalene, nitrogen dioxide, polycyclic aromatic hydrocarbons (especially benzo(a)pyrene), radon, trichlorethylene and tetrachlorethylene. It should be mentioned that currently there is no European Union or Hungarian legislation in force to be applied for indoor air quality.

## Significance of biological air pollutants

Allergy is an important public health problem of the 21st century. Allergic hay fever (rhinitis) and asthma are two of the most common childhood chronic diseases, which impair the quality of life of those suffering from the disease and cause significant social harm. International data show that the incidence of hay fever was 10-15% in the 2000s, but this rate has practically doubled by now.

International surveys suggest that biological allergens contributing to the development of allergies vary from country to country, and even within countries. The rate of sensitivity to major respiratory allergens (birch, grasses, ragweed, olive, and wall weed pollen), some fungal spores (e.g. *Cladosporium herbarium, Alternaria alternata*), house dust mite (*Dermatophagoides pteronyssinus*), and animal hair (e.g. cat) vary significantly. According to a 2007 European survey, the most frequent sensitization was to dust mite (*D. pteronyssinus*), grass pollen and cat hair, with an average incidence of 22%, 17% and 9% in adults. Hay fever was detected in 19% based on self-report and in 13% based on medical diagnosis.
Respiratory allergic diseases of people living in a given geographical area are mainly influenced by the presence and quantity of native allergic plants; thus, the dominant respiratory allergen differs by climatic zones (e.g. birch in northern Europe, grasses in western Europe, ragweed in the Carpathian Basin, in the Po-valley and southern France, and olive trees in Mediterranean countries). In Hungary, the majority of patients with proven allergies are sensitized to airborne respiratory allergen pollens, most commonly to ragweed and grass pollen.

Based on the above, it can be concluded that pollen grains produced by different wind-pollinated plant species are among the most important atmospheric allergens worldwide. In the case of plants, the degree of allergenicity is determined by a combination of factors, such as the prevalence of the allergy in the population and the severity or duration of the symptoms.
Groups of allergenic plants deserve special attention because sensitization can affect children as well as the elderly. If a person has developed allergy to an allergen, it is more likely develope it for another substance (polysensitivity). In addition to the above, the life of people with allergies is also complicated by cross-reactions - all people with allergy should inform themselves on these reactions.
Knowledge of outdoor air quality, pollen information and the identification of surrounding allergenic plants are important for doctors, professionals and patients primarily in terms of prevention, primary prevention. Even today, the most effective way to alleviate or eliminate the symptoms of respiratory allergies to outdoor allergens is to avoid allergens, for which information on the pollen situation (pollen calendar, reports, and short-term forecast) is an important aid. An important goal of prevention is to reduce the risk of developing allergies, with the help of the informative material prepared by NPHC (Allergies made simple).

Knowledge of allergenic plants is also important for public health in the design of green spaces (public areas, walkways, cycle paths, gardens, parks, playgrounds, sports fields, etc.); the allergenicity of each plant species must be taken into account. It can be said, for example, that it is not recommended to plant vegetation capable of significant pollen dispersal in front of windows, and that it is also important to prevent or limit the spread of weeds that are able to appear en masse in order to protect our health. Information required for the design of row trees and the creation of an allergen-poor environment can also be found on the website of NPHC.

## Health risks of climate change

According to the scientific community, the warming occurred between 1850-2020 (0.99 °C, of which about 0.5 °C in the second half of the 20$^{th}$ century) is most likely of human origin, and it can be practically ruled out that this is a natural fluctuation in the state of our environment. The latest (6$^{th}$) report of the Intergovernmental Panel on Climate Change (IPCC) published in 2021, is clearer than ever before, stating with great certainty that human activity in transforming nature, often in a damaging way, has reached the Earth's climate system.
Changes in the current climate could have a number of adverse effects on the whole world: glaciers are receding, Arctic ice is melting, sea levels are rising, the growing season of plants is changing, and more invasive plant species are emerging. Infectious diseases transmitted by animal carriers

(vectors: insects, rodents, etc.) appear elsewhere in space and time. Diseases that have already been overcome may return to Europe, or hitherto unknown diseases may emerge. The frequency and intensity of heat waves also place a heavy burden on Europe's population, they are considered as the most serious risk. Based on experience to date, these changes cannot be compensated by the human body under normal conditions. The most vulnerable are those with chronic diseases and the elderly over the age of 65. The effects can be partially prevented by reducing greenhouse gas emissions, mitigation and facilitating individual and societal adaptation.

In accordance with the IPCC reports, based on the climate health studies carried out in Hungary since 2000, it has been established that the effects of temperature and extreme temperature events in the Carpathian Basin are currently the most important health risks. This fact is included in the government decision, adopted in the document of 1384/2014. (VII. 17.) "Report on Hungary's national disaster risk assessment methodology and its results".

NPHC's legal predecessor, the National Center of Public Health, developed the heat alarm in 2005, which has occurred 1-6 times per year since then. The alarm threshold temperature is a daily average of 25°C, which corresponds to a value measured at a frequency of 90% during the summer period. According to the Hungarian definition, a period when the average daily temperature exceeds the threshold temperature for at least three consecutive days is considered to be a heat wave. By each alert the public, as well as health and social care systems, municipalities and relevant authorities are well informed. Based on the WHO guidelines and the EU's "Adapting to Climate Change" strategy published in 2013, the National Center of Public Health developed recommendations for the preparation of heat response plans, which are submitted to relevant authorities by the public health network. It should be mentioned that there is no legislation in force requiring preventive measures to be taken.

In 2020, the WHO/ECEH updated the recommendations of the 2008 Heat-Health Action Plan. The supplementary material emphasized the improvement of indoor thermal comfort, with particular reference to health and social care systems. In the long run the ventilation and cooling of buildings needs to be improved both at individual and at institutional level. Air conditioning in buildings is an important option, but in the long run this solution is only recommended using renewable energy. Although air conditioning reduces heat complaints, Although air conditioning reduces heat-related complaints, it also reduces the normal capability to adapt. It should be mentioned that the use of air conditioning equipment promotes the development of other symptoms, e.g. „sick building syndrome" (a term used to describe cases in which occupants/workers in a building complain of acute symptoms and discomfort that appear to be proportionate to the time spent in the building, but which cannot be attributed to any specific illness, or cause, such as difficulty of breathing, fatigue, irritability, headache, etc.). Improper cleaning and maintenance can lead to the so-called Legionnaires' disease. (Legionnaires' disease is a generic term of human illnesses of varying severity, sometimes fatal, caused by environmental bacteria of the genus Legionella. Legionnaires' disease is a respiratory disease that does not spread from person to person, just through an environmental aerosol infected with Legionella.) To mitigate the effects of extreme temperatures, the health care system must also be prepared with measures to ensure the health and well-being of both patients and those working in health care facilities. It is important to educate health and social care professionals about the effects of heat waves and the special care of vulnerable groups.

The most vulnerable to heat waves are those with chronic circulatory, metabolic, respiratory, mental illness, the elderly and children, and pregnant mothers.

The impact of heat waves on mortality varies from year to year; spatial characteristics can also be detected by examining longer time series. Excess mortality is mainly determined by the excess temperature above the threshold temperature on days

warmer than the so-called threshold temperature with a frequency of 90% for the area. Over the past 15 years, the daily average mortality during heatwave days has been increased by 15%, the excess mortality varied between 20 and 1740 cases, with an average of 780 cases registered per year between 2005 and 2014. On the one hand, the number of heatwave days is expected to increase in the future, and on the other hand, heatwave days will be warmer due to the expected climate change. Between 2021 and 2050, the average annual excess mortality in each county is projected to increase by 110-180%, increasing the excess mortality due to heat by about 150% on average. Between 2071 and 2100, based on today's demographic and socioeconomic status, climate change will increase current excess mortality by six to seven times.

## Climate change and communicable diseases

IPCC Reports 5 and 6 also confirm that climate change is expected to affect the spatial and temporal occurrence of certain communicable diseases transmitted by animal vectors (mediators: (insects, rodents) as the habitat of the vectors will spread.

In Hungary, Lyme disease, transmitted by ticks, caused by the bacterium *Borrelia burgdorferi*, will become more common. There is no vaccine against the disease, but it is easily recognized by the characteristic red spot around the tick bite and is well treated with antibiotics. Another important disease, also transmitted by ticks, is viral meningitis and encephalitis that can be prevented by vaccination. The incidence of this disease decreased between 1990 and 2000, but has been increasing again since 2001. Future frequency may be increased by mild winters and changes in the country's forest cover.

Similarly, an increase in the number of cases of the viral disease, West Nile fever, transmitted by the species of mosquito native to Hungary, is expected. The disease caused a minor epidemic in Greece, Bulgaria, but also in Romania and Hungary in 2010. The incidence of the disease is expected to increase in the Carpathian Basin during the 21st century, due to both the increase in extremes characteristic to the continental climate and global warming. (In 2018 alone, 2,083 human infections were registered in Europe. 215 cases were detected in Hungary).

Another risk is the spread of Chikungunya fever. One of the vectors of the virus, the Asian tiger mosquito (*Aedes albopictus*), is present in 12 countries in Europe. It was identified in Hungary in 2015, in the south-western part of Transdanubia. According to the current trends of climate change, due to the warming forecasted to take place by the middle of the century, but not later than the end of the century, this mosquito species may spread throughout the country along with other invasive species (*Ae. Egypti, japonicus, koreicus, etc.)*.

In the long run, the number of cases of malaria transported to Hungary, which is also spread by mosquitoes and causes a serious epidemic problem in the tropics and the Mediterranean, may increase. There is currently no locally developed human malaria infection in Hungary. Today, malaria caused by *Plasmodium vivax* is endemic in Greece being the closest to us; it is probable that this type of malaria will spread to other parts of the Balkans, including our southern neighbors; therefore, due to climate change the re-emergence of temperate zone malaria in Hungary seems possible in the near future.

The appearance of leishmaniasis spread by psychodidae (sand-flies) should also be mentioned as a significant threat. This disease is already a serious problem in tropical and Mediterranean countries, it also affects dogs. Currently, vaccinations are only available for dogs, not for humans yet.

An increase in rodent-borne Hantavirus infections has been observed since the 1990s. It is assumed that this disease is also spreading across the country. The number of cases is currently expected to increase by less than 20 per year.

## Impact of climate change on air pollutants

In connection with the more frequent heat waves, the effect of increasing air pollution during the so-called "summer-type smog" situations must

also be taken into account. The meteorological situation that causes heat waves contributes to the deterioration of air quality, increasing the amount of ground-level ozone and fine particulate matter. Short-term high concentrations of ozone and PM in the summer increase the risk of deaths due to all-causes and to cardiovascular diseases.

### Impact of climate change on UV radiation

Climate change modifies exposure to UV radiation in several ways, depending on your geographical location and current UV exposure. It changes the distribution of clouds, which affects the amount of UV radiation reaching the Earth's surface. Higher outdoor temperatures affect our dressing habits and time spent outdoors, all of which can increase the risk of UV radiation. The 4$^{th}$ IPCC report states that changing UV radiation should be treated as a risk factor for the adverse health effects of climate change. Excessive UV radiation is associated with an increase in the incidence of both melanoma and non-melanoma type skin cancers. Excessive exposure to sunlight should be avoided in accordance with the European Cancer Code, in line with the EU's cancer code.

## Water hygiene

The main sources of information on the health risks of pollutants in water are mainly the WHO Water Quality Guidelines and the EU Directive 2020/2184 on the quality of water intended for human consumption which many countries follow in drafting their own regulations. During the implementation, it is very important to apply the risk-benefit approach, which can be realized in practice during the drinking water safety planning. Microbiological or chemical contaminants that pose a health risk must be taken into account during water use. The task of environmental health is to identify the various hazards associated with use and to ensure concentrations that are beneficial or non-hazardous to human health.

### Water pollution of microbiological origin

Microbiological safety is paramount to water quality, as water-related microbial pathogens cause many more illnesses and even deaths worldwide than chemical ones. In Hungary, water-related diseases are also included in the notification system for infectious diseases. The disease surveillance system is complemented by environmental health surveillance systems (e.g. laboratory tests on the quality of drinking water or bathing water provided). A good example of this is the monitoring of SARS-CoV-2 virus particles in wastewater. NPHC was also involved in the development of the methodology. From October 2021, monitoring is mandatory in EU countries.

In Hungary, the most significant event in the last 20 years was the water pollution in Miskolc in 2006, following the flash-flood, which caused more than 3,000 diseases. Currently, the number of typical bacterial water-borne infections has declined as a result of the spread of wastewater treatment and the improvement of the public health condition. At the same time, the proportion of diseases caused by enteric viruses (norovirus, rotavirus, adenoviruses, hepatitis A and E) resistant to traditional water treatment and water disinfection methods is increasing.

### Chemical water pollution

The vast majority of chemical water contaminants can cause a less common chronic disease after long exposure, the pathogenic factors of which often remain hidden, and only modern epidemiological methods can reveal the causal relationship. The compliance of most chemical parameters in our domestic drinking water is over 99% nationwide. The most significant health risk in recent decades has been the value of above-the-limit concentration of arsenic in drinking water. Domestic studies have shown that chronic arsenic exposure cuased by drinking water poses a significant health risk to both skin and lung cancer and some congenital heart diseases, which, based on internationally recognized scientific evidence, justifies the observance of the 10 µg/l limit value, which is much stricter than before and therefore disputed by many, and requires significant material costs. In 2011, the arsenic content of drinking water was challenged in 343 settlements, which had decreased to 143 by 2015. At present, the

problem can be considered practically solved, in 2020 only 10 settlements in the Southern Great Plain had the As content of drinking water above the limit value. In recent years, the assessment of lead contamination in drinking water has required much attention.

### Health risks of lead contamination in drinking water

Lead (Pb) is a ubiquitous pollutant and potentially toxic element. Routes of human exposure: inhalation, oral, dermal, food consumption, smoking, particulate matter, soil. Lead is stored in the brain, bones, liver and kidneys. The most serious effect is neurotoxicity, which poses a particular risk to young children. In adults, cardiovascular damage and nephrotoxicity are the most severe effects. Lead exposure has been gradually declining since the 2000s. In Hungary, blood lead levels were determined in children aged 4-11 years in 2006. The geometric mean was 30 μg/L. It should be emphasized that the concentration of Pb in biological samples is declining across Europe and that there is no safe concentration of lead.

Pb exposure by drinking water is currently a risk in Hungary. It is known that the quality of drinking water can vary significantly from water source to consumer tap. There are secondary pollutants, including lead, the main source of which is the water distribution network and the internal network of buildings and flats.

Lead cannot be detected in the drinking water bases that form the basis of the drinking water supply or in the public drinking water supply systems; however, it may enter the drinking water in excess of the limit value when dissolved from the substances found in the internal drinking water network of the buildings. The main source of exposure in the internal drinking water network of old houses is the still exisiting lead pipe network.

As children are considered to be the primary risk group, it is extremely important to monitor the lead content of tap water provided in children's institutions. According to NPHC tests, the Pb concentration in 2.3% of the tested samples was above the limit value (10 μg/L) and 7.7% exceeded the target value set by the European Union (5 μg/L). From the point of view of reducing the exposure, it is especially important to inform the population about the possible risks of the lead content of drinking water, about their own exposure, and about the possibilities of intervention. The intake of lead by drinking water can be solved by a complete overhaul of the lead pipes. Small drinking water treatment systems can be used as a temporary solution for lead removal, but not all types are suitable for reducing the lead content of tap water to a sufficient degree and safety. Information available on the website of NPHC provides assistance regarding this matter.

### Nitrate contamination of individual wells

Most of the individual wells are located in an unprotected, near-surface layer, so surface contaminants can easily find their way to the aquifer, i.e. they enter the water of the well. Although water quality of individual wells needs to be checked every 3 years, this is not usually the case. Thus, there is no comprehensive knowledge and data on the health risks associated with the use of individual wells. Private wells are most often investigated in the framework of methaemoglobinaemia prevention, and it is known from these data that nitrate in the water of most private wells exceeds the level specified in 201/2001. (X. 25.) Government Decision. Therefore, examination of wells for pregnant mothers using individual wells is still necessary.

## References


1. 1384/2014. (VII. 17.) Korm. határozat „Magyarország nemzeti katasztrófakockázat-értékelési módszertanáról és annak eredményeiről szóló jelentés” Available from https://net.jogtar.hu/getpdf?docid=A14H1384.KOR&targetdate=&printTitle=1384/2014.+%28VII.+17.%29+Korm.+hat%C3%A1rozat&getdoc=1 [letöltve 2021. november 2.]
2. 314/2005. (XII. 25.) Korm. Rendelet a környezeti hatásvizsgálati és az egységes környezethasználati engedélyezési eljárásról. Available from https://net.jogtar.hu/jogszabaly?docid=a0500314.kor [letöltve 2021. november 2.]
3. 4/2011. (I. 14.) VM rendelet a levegőterheltségi szint határértékeiről és a helyhez kötött légszennyező pontforrások kibocsátási határértékeiről Available from https://net.jogtar.hu/jogszabaly?docid=a1100004.vm [letöltve 2021. november 2.]
4. A screening tool for assessment of health risks from combined exposure to multiple chemicals in indoor air in public settings for children: methodological approach. Copenhagen: WHO Regional Office for Europe; 2021. Licence: CC BY-NC-SA 3.0 IGO Available from https://apps.who.int/iris/bitstream/handle/10665/341708/9789289055611-eng.pdf?sequence=1&isAllowed=y [letöltve 2021. október 28]
5. Air pollution and urban structure linkages: evidence from european cities ENV/EPOC/WPIEEP(2014)15, available at https://one.oecd.org/document/ENV/EPOC/WPIEEP(2015)4/en/pdf [letöltve 2021. október 8]
6. Air quality in Europe – 2019. Available from https://www.eea.europa.eu/publications/air-quality-in-europe-2019 [letöltve 2021. október 25]
7. Airq+ Available from https://www.euro.who.int/en/health-topics/environment-and-health/air-uality/activities/airq-software-tool-for-health-risk-assessment-of-air-pollution. Available from [letöltve 2021. október 28]
8. Allergén növények. Available from https://efop180.antsz.hu/tajekoztatok-kornyezeteu/tajekoztatok-kornyezeteu-tajekoztatok.html. [letöltve 2021. október 8]
9. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rinitisz in Europe. Eur Respir J, 2004;24(5): 758-64. https://doi.org/10.1183/09031936.04.00013904
10. Beszámoló jelentés az 1330/2011. (X.12.) Korm. határozattal elfogadott Kisméretű Szálló Por ($PM_{10}$ részecske) Csökkentés Ágazatközi Intézkedési Programjának végrehajtásáról 2017. Available from https://pm10.kormany.hu/download/6/80/22000/PM10%20besz%C3%A1mol%C3%B3%202017_web.pdf [letöltve 2021. október 28]
11. Bobvos J, Malnasi T, Rudnai T, Cserbik D, Páldy A. The effect of climate change on heat-related excess mortality in Hungary at different area levels. Időjárás 2017; 121(1). 43-62.
12. Bousquet PJ, Chinn S, Janson C, Kogevinas M, Burney P, Jarvis D. Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European Community Respiratory Health Survey I. Allergy, 2007; 62: 301-309. https://doi.org/10.1111/j.1398-9995.2006.01293.x
13. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J. 1994; 7(5): 954-60. doi: 10.1183/09031936.94.07050954.
14. Climate Change: Impacts, Adaptation, and Vulnerability. Summary for Policymakers. In: Aldunce, P. – Ometto, J. P. – Raholijao, N. – Yasuhara, K. (eds.): Final draft of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change 2014. Available from http://www.ipcc.ch/pdf/assessment-report/ar5/wg2/ar5_wgII_spm_en.pdf [letöltve 2021. október 8]
15. Commision Staff Working Document „Adaptation to climate change impacts on human, animal and plant health” accompa-

nying the document“ An EU Strategy on adaptation to climate change” Available from https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52013SC0136 . [letöltve 2021. október 28]
16. D’Amato G, Cecchi L, Bonini S, Nunes C, Annesi-Maesano I, Behrendt H, et al. Allergenic pollen and pollen allergy in Europe. Allergy. 2007; 62:976-90. https://doi.org/10.1111/j.1398-9995.2007.01393.x
17. Egyszerűen az allergiáról Available from https://efop180.antsz.hu/tajekoztatok-kornyezeteu/tajekoztatok-kornyezeteu-tajekoztatok/490-egyszeruen-az-allergiarol.html [letöltve 2021. október 8]
18. GBD 2019 Viewpoint Collaborators. Five insights from the Global Burden of Disease Study 2019. Lancet. 2020; 396(10258): 1135-1159. doi: 10.1016/S0140-6736(20)31404-5.
19. GBD Compare - Viz Hub Available from https://vizhub.healthdata.org/gbd-compare/ [letöltve 2021. október 28]
20. Gundacker C, Forsthuber M, Szigeti T, Kakucs R, Mustieles V, Fernandez MF, Bengtsen E, Vogel U, Hougaard KS, Saber AT. Lead (Pb) and neurodevelopment: A review on exposure and biomarkers of effect (BDNF, HDL) and susceptibility. Int J Hyg Environ Health. 2021; 238:113855. doi: 10.1016/j.ijheh.2021.113855.
21. Hantavirus infection Annual Epidemiological Report for 2019 Available from https://www.ecdc.europa.eu/sites/default/files/documents/AER-hantavirus-2019.pdf [letöltve 2021. október 8]
22. Health Aspects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide. Report on a WHO Working Group, Bonn, Germany 13–15 January 2003. Available from https://www.euro.who.int/__data/assets/pdf_file/0005/112199/E79097.pdf [letöltve 2021. október 28]
23. Health risk assessment of air pollution – general priciples Coppenhagen WHO Regional Office for Europe 2016. Available from https://www.euro.who.int/en/publications/abstracts/health-risk-assessment-of-air-pollution.-general-principles-2016 [letöltve 2021. október 28]
24. Heat and health in the WHO European Region: updated evidence for effective prevention. World Health Organization 2021. Available from https://www.euro.who.int/en/health-topics/environment-and-health/Climate-change/publications/2021/heat-and-health-in-the-who-european-region-updated-evidence-for-effective-prevention-2021 [letöltve 2021. október 28]
25. Hogyan válasszunk kertünkbe fákat, cserjéket? Available from https://efop180.antsz.hu/temak-konyezetegeszsegugy/allergenek-a-levegoben/allergenek-hogyan-valaszszunk-kertunkbe-fakat-cserjeket.html [letöltve 2021. október 8]
26. Kadocsa E. Az allergiás eredetű nátha prevalenciájának meghatározása Szegeden. Fül-Orr-Gégegyógy, 1994; 39: 182-188.
27. Közterületi sorfák Available from https://www.fasember.hu/files/2020_kozteruleti_sorfak.pdf [letöltve 2021. október 8]
28. Levegőhigiénés Index Available from https://www.nnk.gov.hu/) https://www.nnk.gov.hu/index.php/kozegeszsegugyi-laboratoriumi-foosztaly/terkepes-informaciok/levegohigienes-index
29. Magyar D, Páldy A, Szigeti T, Szilágyi A, Orlóci L. A potenciális allergenitás felhasználási lehetősége a zöldterületek minősítésében és az allergén terhelés szabályozásában. Egészségtudomány 2020(4). Available from https://doi.org/10.29179/EgTud.2020.4.57-80
30. Magyar D, Szigeti T, Páldy A, Udvardy O, Zséli Gy, Orlóci L. A növények potenciális allergenitása – áttekintés és módszertani javaslat. Egészségtudomány 2020(4). Available from https://doi.org/10.29179/EgTud.2020.4.30-56
31. Magyarország ivóvíz minősége 2020. Nemzeti Népegészségügyi Központ, available: https://www.nnk.gov.hu/attachments/article/726/Ivovizminoseg_2020.pdf [letöltve 2021. október 8]

32. Módszertani ajánlás az oktatási-nevelési intézmények beltéri levegőminőségének javítására Available from https://www.nnk.gov.hu/attachments/article/78/M%C3%B3dszertani%20aj%C3%A1nl%C3%A1s%20az%20oktat%C3%A1si-nevel%C3%A9si%20int%C3%A9zm%C3%A9nyek%20beltéri%20levegő%C5%91j%C3%A9nek%20javít%C3%A1ra_v2.pdf [letöltve 2021. október 8.]
33. Módszertani útmutató az ivóvíz ólom tartalmával kapcsolatos lakossági tájékoztatáshoz Available from https://efop180.antsz.hu/attachments/article/485/M%C3%B3dszertan%20az%20%C3%B3lomkock%C3%A1zat%20kommunik%C3%A1ci%C3%B3j%C3%A1hoz.pdf [letöltve 2021. október 28.]
34. Navarro A, Gómez L, Sanseverino I, Niegowska M, Roka E, Pedraccini R, Vargha M, Lettieri T. SARS-CoV-2 detection in wastewater using multiplex quantitative PCR. Sci Total Environ. 2021; 797:148890. doi: 10.1016/j.scitotenv.2021.148890.
35. Országos Légszennyezettségi Mérőhálózat Available from http://www.levegominoseg.hu/automata-merohalozat [letöltve 2021. október 8.]
36. Outdoor Air Pollution. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 109. Available from IARC ISBN-13 (PDF) 978-92-832-0175-5 [letöltve 2021. október 28.]
37. Összefoglaló kutatási jelentés ivóvíz utótisztító kisberendezés ólomeltávolítási hatékonyságának vizsgálatáról. Available from https://efop180.antsz.hu/attachments/article/487/%C3%96sszefoglal%C3%B3%20az%20%C3%B3lomelt%C3%A1vol%C3%ADt%C3%A1sra%20vizsg%C3%A1lt%20kisberendez%C3%A9sekr%C5%91l.pdf letöltve 2021. október 28.]
38. Páldy A, Bobvos J. Health Impacts of Climate Change in Hungary – A Review of Results and Possibilities to Help Adaptation. Central European Journal of Occupational and Environmental Medicine. 2014; 20( 1–2): 51–67. Available from https://www.nnk.gov.hu/cejoem/Volume20/Vol-20No1-2/CE14_1-2-06.html [letöltve 2021. október 8]
39. Pollen információk. Available from https://www.nnk.gov.hu/index.php/kozegeszsegugyi-laboratoriumi-foosztaly/256-kornyezetegeszsegugyi-laboratoriumi-osztaly/polleninformaciok-megjelenitese [letöltve 2021. október 8]
40. Public health advice on preventing health effects of heat. World Health Organization 2011. Available from https://cdn.who.int/media/docs/default-source/climate-change/publication-public-health-advice-on-protecting-health-effects-of-heat39cda4ff-5772-4afe-a067-e60ce02b807d.pdf?sfvrsn=5f1494a9_1&download=true [letöltve 2021. október 28]
41. Sóti L, Endre L. A pozitív Prick-reakciót kiváltó leggyakoribb légúti allergének gyakoriságának alakulása 1992 és 2000 között, 2124 légúti allergiában szenvedő gyermek vizsgálata alapján. Orv Hetil, 2005; 146(18): 833-837.
42. Tiszta levegőt Európának program. A Bizottság közleménye az Európai Parlamentnek, a tanácsnak, az európai gazdasági és szociális bizottságnak és a régiók bizottságának Brüsszel, 2013.12.18. com(2013) 918 final Available from https://eur-lex.europa.eu/legal-content/HU/TXT/PDF/?uri=CELEX:52013DC0918&from=EN [letöltve 2021. október 28]
43. Trájer AJ, Bede-Fazekas Á, Bobvos J, Páldy A. Seasonality and geographical occurrence of West Nile fever and distribution of Asian tiger mosquito. Időjárás 2014; 118(1): 19-40.
44. Trájer AJ. és Páldy A. Az antropogén éghajlatváltozás várható növény-, állat- és humánegészségügyi következményei a 21. század második felében. Egészségtudomány 2021(1) Available from https://doi.org/10.29179/EgTud.2021.1.4-29 [letöltve

2021. november 2.]
45. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. World Health Organization 2021 Available from. https://apps.who.int/iris/handle/10665/345329. License: CC BY-NC-SA 3.0 IGO
46. WHO guidelines for indoor air quality: selected pollutants. WHO 2010. Available from https://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. [letöltve 2021. november 2.]

# X. Structure and operation of the public health system

Krisztina Juhász

## International public health institutions and their operation

### World Health Organisation (WHO)

The World Health Organization is a specialized organization of the United Nations. The charter of the organization was adopted in 1946 in New York, which came into force April 7, 1948. Since then, April 7 is World Health Day. It held its first general meeting in 1948, at which the main challenges of the time were identified, such as fight against malaria, protection of the health of children and women, tuberculosis, sexually transmitted diseases, and global inequalities in nutrition and health care. The organization currently has 194 member countries, grouped into 6 regions: Africa, the Americas, Southeast Asia, Europe, the Eastern Mediterranean, and the Eastern Pacific.

The main mission of the WHO is to improve the health of the Earth's population, bring nations together, assist people in maintaining their health, safeguard world security, and to protect the vulnerable. Its constitution states that equal opportunities, a fairer world order and an international health policy would be needed in order to make promotion of health and fight against diseases accessible to all peoples. Each year, the WHO General Assembly formulates the world's health policy guidelines and budgets, evaluates existing global programs, and develops new ones (e.g., smallpox prevention, HIV/AIDS programs, tuberculosis and poverty eradication programs). Based on the 1996 Global Health Survey, the concept called "Health for All by 2000" was formulated, the essence of which was that by the year 2000, peoples of the world would be in a state of health to live an economically and socially productive life.

The WHO has so far declared international emergency six times: in 2009 at the outbreak of the swine flu, in 2014 at the outbreak of polio, in 2014 and 2019 at the outbreak of Ebola, in 2016 at the outbreak of the Zika virus, in 2020 at the outbreak of COVID-19 coronavirus.

### European Centre for Disease Prevention and Control (ECDC)

The Stockholm-based agency, established by the WHO in 2005, provides central surveillance data and scientific advice on various communicable diseases and their health aspects, as well as on epidemics and other public health threats. It works closely with other European institutions and non-EU organizations, such as the European Medicines Agency, the European Food Safety Authority and the World Health Organization. ECDC operates three basic systems: the Early Warning and Response System of the European Union (EWRS), the Epidemic Intelligence Information System (EPIS) and The European Surveillance System (TESSy). These systems help perform a wide range of tasks, including:

- **Analysis and interpretation of data** from European Union countries **on 52 communicable diseases and related health issues.**
- **Scientific advice** to the EU institutions and Member State governments.
- **Early identification and analysis** of emerging threats to the European Union.
- Coordination of the **European Intervention Epidemiology Training Program** and the **European Public Health Microbiology Training Program.**
- Supporting **EU governments** in preparing for epidemics.

### Centers for Disease Control and Prevention, USA (CDC)

The U.S. Centers for Disease Control and Prevention is a U.S. public health institution based in Atlanta. The primary purpose of the CDC is to protect public health and safety through the prevention of disease, injury, and disability in the United States and worldwide. It pays particular attention to communicable diseases, food poisoning, environmental health, occupational safety and health protection, health promotion and injury prevention. In addition to research work, the CDC provides information on non-communicable diseases and is a founding member of the International Association of National Public Health Institutes.

## History and development of the Hungarian public health system

The history of public health in Hungary dates back almost 300 years. We can speak of organized public health activity from the 18th century, when in 1724 the Vienna Government, recognizing the poor health of the population, obliged the counties and major cities to employ paid doctors to treat disadvantaged patients and to perform epidemiological duties. In 1752, Maria Theresa issued such an imperial decree, which can be considered the founding document of the Hungarian Medical Officer Service, which supplemented the physicians' responsibilities for the care of patients with the observation of public health conditions and the call for the improvement of conditions, and then entrusted the work to the newly appointed „county physicists". The first health act was published in 1770, under which the national chief physician, whose work in the counties is assisted by county physicians, may act on behalf of the county council. The National Public Health Council was established in 1868, and in 1874, under the leadership of József Fodor, the first Department of Public Health at the University of Budapest. After World War I, the National Institute of Public Health was established in 1927 under the leadership of Béla Johan, modeled on the Pasteur Institute in Paris. The modern public health system made it possible to implement and control organized prevention and to ensure the efficient operation of health care.

After World War II, a decree of the Council of Ministers of 1951 abolished the medical system and established the Public Health Epidemic Stations (KÖJÁL) on a Soviet model. KÖJÁL, which operated until 1991, was followed by the National Public Health and Medical Officer Service (ÁNTSZ). According to the Act, XI. of 1991, the ÁNTSZ is responsible for the management and supervision of public health, epidemiology and health protection activities, as well as the supervision of health care being a state reponsibilty, and the performance of this task is entrusted to the service under the direct supervision of the Minister of Welfare. The National Office of the Chief Medical Officer (OTH) was established on January 1, 1998, under the leadership of the National Chief Medical Officer.

As of January 1, 2011, government offices have been established in the capital and in 19 counties, whose organizational units perform various public health tasks. Professional and functional tasks are continued to be managed by the national chief medical officer. During the reorganization of the individual background institutions, from 4 April 2017, the OTH became a department of the State Secretariat for Health, whose national chief medical officer duties were performed by the Deputy State Secretary. On October 17, 2018, the National Public Health Center (NNK) was established as the legal successor of the State Public Health and Medical Officer Service (ÁNTSZ) under the leadership of the National Chief Medical Officer.

## Structure of the Hungarian public health system

Activities carried out with the participation of public health, state and local government bodies, economic and non-governmental organizations, as well as individuals, primarily aimed at population groups and communities. Its main goal is to protect and improve health, prevent disease, injury and disability. At present, the participants

of the public health system in Hungary can be identified on three levels. The national level is represented by the Ministry of Human Resources and the central office under its direct control, the National Public Health Centre (NNK). According to Government Decree 385/2016 (XII.2), the national chief medical officer participates in the professional preparation of the decisions necessary for exercising ministerial powers. The decree lists in detail the public health responsibilities of the NNK and county government agencies. Other actors in the public health structure include community-based health promotion offices, local governments, practices, group practices, and the health visitor system. Coordinated operation of the organizational units at different levels of operation is essential in the performance and organization of public health activities. *(Figure 1)*

## Bodies operating at the national level and their role in the public health system

### Ministry

The central government plays a key role in Hungary's public health system. The Ministry of Human Resources (EMMI) is responsible for fields related to the health of the population, such as health care, public health, social affairs, support for social mobility and equality, culture and education, sports, family and adolescent affairs, religion and non-governmental organizations. Accor-

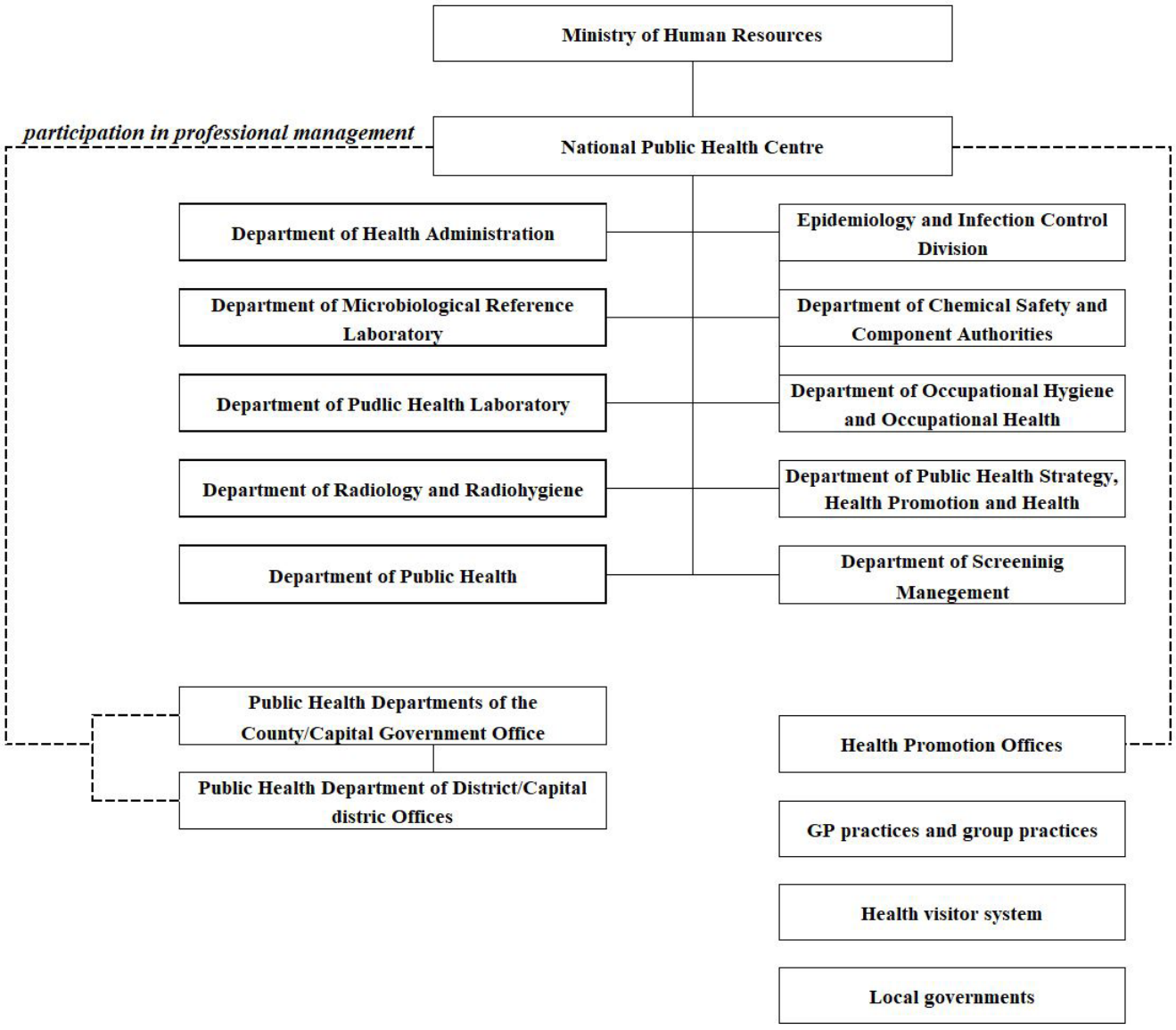


Figure 1.: Structure of the Hungarian public health system

ding to the EMMI regulation 15/2017 (IV.3), the tasks of the ministry include the development of public health strategies, definition of goals and priorities at the national level, coordination of the implementation of the goals defined in the strategies, and the representation of health aspects in all policies. The Secretary of State for Health exercises professional, political control over public health tasks.

The organizational unit, headed by the Deputy Secretary of State, for professional management of health care is the Department of Public Health, which prepares professional proposals for public health legislation and regulatory instruments. The Department of Public Health performs coordination tasks in the fields of health promotion, health education, epidemiology, child, family and adolescent health care, mental health, smoking, drug and alcohol use.

Professional College, as the professional body of the Minister responsible for health, provides advice, recommendation and opinion in the field of health care. In addition, the Hungarian Association of Public Health Training and Research Institutions, the Scientific Society for Public Health, the Hungarian Society of Hygienists, the Hungarian Dietitic Association and the Association of Hungarian Health Visitors play a research and advisory role.

### National Public Health Centre (NNK)

The NNK is a central budgetary body under the direction of the Minister for Human Resources, headed by the National Chief Medical Officer who is appointed by the Minister for Human Resources. His/Her work is assisted by the Deputy National Chief Medical Officers, who are also appointed and dismissed by the Minister.

The NNK performs the assigned tasks in the fields of public health (environmental and municipal health, including spa health, food health, nutrition health, radiation health, health compliance of cosmetic products, chemical safety, children and adolescent health), epidemiology, health promotion (health protection, health education and maintenance, organization and coordination of public health screenings, health monitoring, including epidemiology of non-communicable diseases, health impact assessment), health administration and coordination, and occupational medicine and hygiene. It operates and maintains laboratories accredited for certain activities.

Participates in the performance of tasks related to projects financed by the European Union and in the maintenance of projects subject to the maintenance obligation. Operates and develops professional IT systems required to perform public health tasks of the government office and the district office, as well as the NNK *(Table 1)*.

| | |
|---|---|
| **EFRIR** | Epidemiological Surveillance System and IT System |
| **eGEN** | Operating License Registry and Decision Generating System |
| **HENYIR** | Human Resources Registration System |
| **IRMA-ETEL** | Filing and unit registration programs |
| **KBIR** | Chemical Safety Professional System |
| **NutriComp** | Energy and nutrient calculation program |
| **NVT** | A program for recording checks for the protection of non-smokers |
| **OSAP** | National Statistical Data Collection Program |
| **OSZIR** | National Professional Information System |
| **OSZR** | Oncology Screening System |
| **x TEK** | Territorial Supply Obligation Register |

Table 1.: Professional IT systems operated by NNK

**Departments under the direct supervision of the National Chief Medical Officer Department of Health Administration**

The department operates in Budapest, Debrecen, Győr, Kaposvár, Miskolc, Szeged and Veszprém. Its organizational units are the Department of

Health Authorities and the Department of Professional Supervision.
The department keeps records of **healthcare providers**, authorizes and monitors healthcare providers with inpatient specialist care, inpatient and concurrent outpatient specialist care, rescue services, patient transport, health care for events, blood supply, hemodialysis, cell and tissue banking, in vitro fertilization activities, genetic counseling and molecular genetic laboratory diagnostics services. If necessary, it shall decide on the specialist care capacities, areas of care and reallocation of all public health care providers. It investigates complaints and public interest complaints filed against health care providers licensed by the national chief medical officer. It makes proposals to the owner and the financier regarding the establishment, development and termination of health care institutions, as well as to the organizational and management measures for the improvement of care at all levels of the health care system. It exercises professional supervision over the activities of health care providers. It gives an opinion on modifications concerning the organization and tasks of health care institutions, as well as the proposals for the establishment of district boundaries for health visitors.

Performs official duties related to licensing medical research on humans. It gives its consent to the transport of organs and tissues from Hungary to abroad and from abroad to Hungary, as well as to the performance of official tasks related to organ transplantation, if necessary.
It organizes and coordinates nursing supervision activities within the government office and the district office, and mediates the uniform professional guidelines. It professionally manages, supervises and evaluates the implementation of health visitor tasks.

**Department of Microbiological Reference Laboratory**
The National Reference Laboratory operating in the department and the WHO Reference Laboratories are responsible for the implementation of special diagnostic procedures, professional methodological development and consulting. In the field of epidemiological virology, bacteriology, mycology and parasitology, the diagnostic, clinical and epidemiological microbiological laboratory tests of infectious diseases are performed among the Hungarian laboratories with the highest level of methodological preparedness.

**Department of Public Health Laboratory**
The department participates in the performance and coordination of environmental health (Department of Environmental Health Laboratory) and toxicology (Department of Toxicology Laboratory) tasks. It participates in the management of studies, evaluations and methodological developments aimed at the quality of environmental elements and other media (water, soil, air, and wastes). It performs chemical, microbiological, toxicological and ecotoxicological studies. In addition to developing testing methods, it participates in the preparation of legislation in this field. Prepares professional guides, circulars, brochures; maintains regular contacts with other professional institutes, organizes proficiency tests for domestic testing laboratories. At the national and international level, it carries out scientific cooperation and participates in domestic and international research networks, infrastructures and scientific tenders.

**Department of Radiobiology and Radiohygiene**
In order to achieve the public health goals included in the legislation, the department performs radiohygiene and radiation protection tasks. During its activity, it studies the biological and health effects of ionizing and non-ionizing radiation, examines the factors involved in individual radiation sensitivity, both in terms of radiation protection and radiation therapy. It makes proposals for the regulation of radiation protection at workplace, thereby drafting regulations, standards, methodological letters, and guidelines for the implementation of legislation.

**Department of Public Health**
The department performs professional tasks in

the field of environmental and municipal health care, food and nutrition health, health compliance of cosmetic products, climate change, children and adolescent health, and public health aspects of spas. It provides professional management of government offices and district offices, comprehensive and targeted inspection of county government offices. It participates in the review and preparation of legislation in order to enforce public health competencies.
Its two main organizational units are the Department of Municipal Health, Climate Change and Environmental Health Analysis and the Department of Food, Nutrition, Children and Adolescent Health.

**Epidemiology and Infection Control Division**
*With regard to official tasks in the field of epidemiology, the department:*

- monitors the development of the epidemiological situation in the country. If necessary, it shall propose the ordering of a major epidemic event or measures to be taken in order to eliminate the epidemic threat or epidemic. It provides information on the current epidemiological situation upon request.
- operates disease-specific surveillance.
- collects and registers data on the completion of age-related vaccinations received through a joint database with the district offices and the capital city and county government offices, analyzes and evaluates the performance of vaccinations, as well as the vaccination-related activities of government offices.
- works with other sub-departments in the department to monitor adverse events following vaccination (AEFV).
- compiles an annual vaccination methodology letter.
- liaises with the WHO's epidemiological management and coordination departments.

*With regard to the quality control of immunobiological preparations, the department:*

- assists as an expert on immunobiological products (viral vaccines, bacterial vaccines, blood products, allergens) if requested by the Pharmaceutical Authority.
- prepares an expert opinion on the quality of medicines upon request.

*With regard to infection control and hospital epidemiology, the department:*

- monitors hospital hygiene / infection control activities and the epidemiological situation of healthcare associated infections.
- liaises with representatives of the ECDC, the WHO and the European Commission and monitors their recommendations for infection control and makes recommendations for their implementation in Hungary.
- performs the secretariat tasks of the National Infection Control and Antibiotic Committee, and supports its activities with professional proposals,
- operates the National Nosocomial Surveillance System (NNSS);
- studies the situation of antimicrobial resistance and the use of antimicrobials in Hungary.

*With regard to disinfection, disinsection, deratization and official tasks, the department:*

- develops and manages monitoring and surveillance systems for key indigenous and invasive vectors.
- on notification, is kept informed of the public health damage caused by the occurrence of the health pests that spread the disease and of the measures taken to eradicate them.
- participates in the necessary measures taken against health pests upon request, in order to prevent or handle a natural disaster, other extraordinary event, epidemic or epidemic threat.
- participates as an expert in the review program of biocidal active substances and in the evaluation of the effectiveness of disinfectants, pesticides and repellents.
- performs the microbiological qualification tests required before the market release of sterilization and disinfection equipment, as well as the equipment already in operation

at specified intervals.
- plans the national quantities of vaccines required for vaccination in the national immunization program and to prevent the risk of disease and providing epidemiological reserves.
- provides expertise in the subject of public procurement in public procurement procedures for the procurement of vaccines. It registers the vaccine procured, and distributes and delivers it to government agencies and district offices.

**Department of Chemical Safety and Competent Authorities**
In its capacity as authority, it coordinates the implementation of EU chemicals regulations at Member State level, such as those on industrial chemicals. It participates in the authorization of biocidal products. It operates information services (helpdesks) in connection with their statutory obligations to the industry concerned. It operates the Health Toxicology Information Service (ETTSZ), which provides information on what to do in case of acute poisoning on a toll-free number 24 hours a day.

**Department of Occupational Hygiene and Occupational Health**
In the field of occupational health, the department performs professional-methodological, professional management, scientific research, training, upskilling training and preventive basic institutional tasks.
*Among its core activities to be performed as a state task, it participates in:*
- the substantiation of governmental decisions and strategies related to occupational hygiene and occupational health activities, and in related surveys.
- scientific tasks related to the improvement of the health of employees and the prevention of diseases.
- the process of harmonization of community law and decision-making related to the European Union. It is also involved in solving tasks related to the implementation of domestic and European Union programs related to occupational health.

*In the framework of its core activities, it performs the following tasks:*
- basic and specialist occupational health care tasks;
- specialist examination, review and treatment of occupational patients;
- assisting in the occupational health professional activities of the regional occupational safety inspectorates.

**Department of Public Health Strategy, Health Promotion and Health Monitoring**
The department is responsible for the professional supervision related to the preparation and implementation of assigned projects. Its tasks can be divided into three main groups: health promotion and health preservation (Department of Health Promotion), health monitoring (Department of Health Monitoring), and strategic and coordination tasks related to public health.

**Department of Screening Management**
Among its general tasks, it organizes and coordinates targeted screening for public health purposes. It proposes changes for development and contributes to their implementation in accordance with uniform guidelines. It prepares and continuously develops the screening strategy of NNK, in connection with which it prepares professional policies and guidelines. It initiates their development and contributes to its commenting, mediation and implementation. Its two main organizational units are the Department of Screening Program Management and the Department of Screening Coordination for Public Health.

## Bodies operating at the county level and their role in the public health system

Metropolitan and county government offices are the government's territorial administrative agencies with general powers. The 20 government offices, which form the largest units of the territorial administration, operate in the county capitals, and in the case of the capital and Pest county, in

Budapest. The metropolitan and county government offices consist of organizational units directly headed by a government agent, as well as district and, in the capital, metropolitan district offices. District (metropolitan district) offices are the smallest units of the territorial administration. They operate in 174 cities and 23 districts in Budapest. Their basic task is to manage the public administration matters referred to their competence.

**Public health tasks of the government office:**

- Management, coordination and professional supervision of the professional activities of district offices.
- Exercising official authority in legally specified matters.
- Perform tasks related to:
  - the field of public health (food health, nutrition health, environmental and municipal health, radiation health, health compliance of cosmetic products, chemical safety, child and adolescent health), for which it may operate a chemical, radiological, bacteriological and aerobiological testing laboratory;
  - the field of epidemiology, for which it may operate an examination laboratory;
  - the field of health promotion (health protection, health education and preservation, organization and coordination of public health screenings, health monitoring);
  - the field of health administration and coordination.
- Carrying out tasks related to the operation of professional supervision over health care providers under legislation.
- Performing official duties in relation to infection control responsibilities of healthcare providers.
- Developing public health programs to maintain the health of the population and then participate in their implementation.
- Performing radiation health tasks.
- Exploring public health and epidemiological risks and performing official tasks in relation to ports handling international cargo or passenger traffic and international commercial airports.
- Secondary proceedings in official matters regarding public health, where the district office acted in the primary proceeding.

**The public health tasks of the district office are:**

- Carrying out the licensing procedure for providing health care services and issue operating licenses.
- Keeping reports and records related to infectious diseases. Carrying out epidemiological investigations and measures in case of reported infectious diseases and epidemics.
- Ordering age-related mandatory continuous vaccines and vaccination campaigns. Ensuring proper distribution of vaccines and statutory administration of vaccines.
- Keeping vaccine records. Ordering a person to be vaccinated if he or she does not comply with the law.
- Investigation of public complaints regarding the proliferation of health pests.
- Initiation of official inspections in the field of municipal and environmental health.
- Carrying out public health inspections of drinking water supply facilities and, in certain periods, swimming pools and taking official measures.
- Issuing official permits for the deceased and burial.
- Participation in the permission process for sites subject to notification and licensing.
- Receiving customer reports on activity or changes in activity with hazardous substances and mixtures.
- Controlling the marketing of food supplements, foods for particular nutritional uses and cosmetics in any commercial form. In case of suspicion of possible health damage, sampling of the preparation for accredited laboratory testing.
- Carrying out health checks on food and nutrition.

- Inspection of public health requirements for nurseries, kindergartens, primary and secondary schools, summer camps.
- On-site inspection prior to the operation of a family daycare center and issuing public health resolution. Continuous public health monitoring of family day care facilities already in operation.
- Controls related to the protection of non-smokers.
- Organizing and conducting health promotion programs.
- Fetal protection, family planning and prenatal counseling by health visitors within the framework of the Family Protection Service.
- Providing professional supervision over health visitors in the fields of district health visitors and school nurses by the district chief health visitor.
- The district chief health visitor performs professional supervision of general practitioners and paediatricians, basic dental care, occupational health care, home nursing services, hospice nursing services, outpatient specialist care, professional activities and social institutions operating in the area of competence of the district office.

## Organizations at Community level and their role in the functioning of the public health system

Other actors in the public health structure are the health promotion offices responsible for providing community health promotion services, as well as the practices, group practices, and the health visitor system responsible for providing health promotion services for individuals. Local governments play an important role in maintaining health promotion institutions and developing strategic plans.

### Health Promotion Offices (EFI)

Health promotion offices are key players among Hungarian health promotion organizations. They were established from 2013 onwards. There are 116 offices in a total of 61 districts that provide free health promotion services in the proximity. Professional management and coordination of offices are performed by the NNK. Their area of operation is the district, which has an average population of between 50 and 100,000, but the districts show significant differences in geographical coverage, urbanization, economic development and population.

Basic objectives of establishing EFIs were to support cardiovascular and cancer disease prevention, reduce early and preventable mortality, improve health-determining lifestyles and habits and attitudes that affect health, and to raise public health awareness. The tasks of the health promotion offices are the implementation lifestyle change programs and community-level health education and development programs in various settings (municipal, workplace and school settings), monitoring health promotion activities in the district, improvement of the cooperation between health promotion organizations and networking organizations.

### GP practices and group practices

Within the framework of primary curative-preventive care, tasks of general practitioners include advising the population and mobilizing them for targeted screening for certain public health purposes, examination of the patient, medical treatment, medical rehabilitation and, if necessary, referral to a specialist or inpatient examination and medical treatment. The GP is also responsible for public health, epidemiology and health promotion tasks such as vaccination, infectious diseases, persons, vectors, food poisoning, and participation in health education and awareness.

### Health visitor system

The health visitor system plays a particularly important role in supporting healthy development of fetuses and children, in raising health awareness of families and the population, and in influencing health-damaging habits, and thus in carrying out preventive public health tasks in the proximity of people's homes.

Within the framework of the health visitor system, a special system of senior health visitors has emerged: regarding the professional guidance and supervision of health visitors, the senior district

health visitors operate in the district and capital district offices, senior capital district health visitors manage regional and school health visitors, while in county government offices the senior county health visitors manage these tasks, and in hospitals, family protection services and senior district health visitors are managed by the capital head health visitors.

In 2013, an organized cervical screening program by health visitors was introduced nationwide to increase access to cervical screening for public health purposes and to ensure close proximity to home. Following projects involving training and further training in cervical screening for health visitors, the program has been integrated into the responsibilities of regional health visitors, with the result that nearly 1,500 health visitors can perform cervical cancer screening nationwide.

### Local governments

Local governments at the municipal level have a dual role in health promotion. On the one hand, they are obliged to prepare a settlement development plan every five years, which must also include health promotion and community building interventions. On the other hand, the local government plays a role in the health promotion framework, as it maintains several institutions that deal with health promotion.

## References


1. A fővárosi és megyei kormányhivatal, valamint a járási (fővárosi kerületi) hivatal népegészségügyi feladatai ellátásáról, továbbá az egészségügyi államigazgatási szerv kijelöléséről szóló 385/2016. (XII. 2.) Korm. rendelet.
2. Az Állami Népegészségügyi és Tisztiorvosi Szolgálatról, a népegészségügyi szakigazgatási feladatok ellátásáról, valamint a gyógyszerészeti államigazgatási szerv kijelöléséről szóló 323/2010. (XII. 27.) Korm. rendelet.
3. Az egészségügyről szóló 1997. évi CLIV. törvény.
4. Az emberi erőforrások minisztere 18/2019. (VI. 6.) EMMI utasítása a Nemzeti Népegészségügyi Központ Szervezeti és Működési Szabályzatáról.
5. Az Emberi Erőforrások Minisztériuma Szervezeti és Működési Szabályzatáról szóló 16/2018. (VII. 26.) EMMI utasítás.
6. Az Országos Tisztifőorvosi Hivatal Szervezeti és Működési Szabályzatáról szóló 29/2016. (VI. 24.) EMMI utasítás.
7. 15/2017. (IV. 3.) EMMI utasítás az Emberi Erőforrások Minisztériuma Szervezeti és Működési Szabályzatáról szóló 33/2014. (IX. 16.) EMMI utasítás módosításáról.
8. https://europa.eu/european-union/about-eu/agencies/ecdc_hu [Online].
9. https://www.cdc.gov/about/organization/mission.htm [Online].
10. Ember I, Kiss I és K. Cseh K. Népegészségügyi orvostan, Budapest: Dialóg Campus, 1993, pp. 35-38.
11. Kertai P. és Lun K. 250 éves a magyar tisztiorvosi szolgálat. [Performance]. A megújult ÁNTSZ 10 éves jubileumi ülésén elhangzott előadás alapján, 2007.