Science
Against
the Pandemic

Vaccinations against **COVID-19**. Innovative technologies and efficiency.

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Some of the legal regulations described in this document represent a local situation and do not apply outside the territory of Poland and the European Union.

Version 2

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Introduction

Ladies and gentlemen,

the global COVID-19 pandemic, caused by the spread of the SARS-CoV-2 virus, has forced us to make changes in virtually every area of everyday life, from work or study to spending free time and family life. Many people have died in the wake of this pandemic, as a result of contracting COVID-19 or due to overloading health systems.

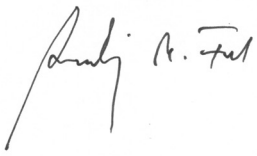
Today, thanks to the advent of vaccination, we have a chance to gain control of the SARS-CoV-2 virus and gradually return to the way of life before the pandemic. However, the positive effects depend largely on the mass vaccination coverage – the achievement of the appropriate level of immunization of the general public – and therefore on the common sense, knowledge, and decisions of each of us.

In the history of medicine development, immunization is one of the most outstanding achievements, a discovery that saved millions of people's lives. This contributed to the eradication of fatal and disabling diseases. Public health, understood as a holistic approach to medicine and healthcare in the fight against infectious diseases, has never had a more effective weapon.

Many Poles are extremely skeptical, even hostile, about vaccinations. The scientific community is aware that only overcoming social fears and actions based on substantive, reliable, and proven knowledge can change Poles' attitudes towards vaccination and thus contribute to high vaccination coverage and stopping the pandemic. That is why I invited a group of over a dozen renowned experts in various fields for years working for public health: infectious diseases, vaccinology, virology, chemistry and biochemistry, family medicine, to unite in the initiative 'Science Against the Pandemic' and to prepare a white paper entitled 'Vaccinations against COVID-19. Innovative Technologies and Efficiency' which is a compendium of knowledge about vaccination, its technology, and validity in fighting the pandemic.

The contents contained in the book support the medical community and medical services who have daily contact with patients and are usually the first source of knowledge for them. It is also a source of knowledge for the media and the general public, all who need science-based knowledge about vaccination against COVID-19, types of vaccines, and how they work.

In an era of overwhelmingly contradictory or unreliable information, as a group of authors, we hope that the white paper will clear up at least some of the doubts about the global COVID-19 pandemic, especially regarding the technology of mRNA vaccination, which is intensely developed in relation to this disease, and which is currently the only significant weapon we have in the fight against SARS-CoV-2.



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Warsaw, December 2020

Summary

Coronaviruses are a large family of RNA viruses that include species that infect humans and animals. In the 1960s, it was discovered that certain species of animal coronaviruses could also infect humans. In 2019, another animal coronavirus (later named SARS-CoV-2) became able to transmit and spread in humans, and the first outbreaks of COVID-19 appeared in China. On March 11, 2020, the WHO announced a pandemic, the epicenter of which quickly moved from Asia to Europe and North America. In Poland, at the beginning of December 2020, the total number of identified COVID-19 cases exceeded one million. COVID-19 can be life-threatening, especially among high-risk groups, and the epidemic spread of the disease, with such a high proportion of patients requiring hospitalization, rapidly overburdens the healthcare system.

Unfortunately, contracting COVID-19 does not equal the development of permanent immunity to the disease. So, we are faced with the simple choice of getting vaccinated against COVID-19 or taking part in the hard to predict lottery related to the disease and further deepening the health and economic crisis. However, the scale of the COVID-19 pandemic and the ease of human movement mean that only global action, including mass vaccination, will disrupt the virus's circulation. Vaccinations are the safest way to acquire immunity against COVID-19. In the case of SARS-CoV-2 vaccines, mRNA vaccines are currently under development. Research on this technology has been carried out for about 20 years, and it has great potential not only for the development of vaccines but also for the treatment of, e.g., cancer. mRNA vaccines are considered to be very safe due to the lack of the possibility of modifying the patient's DNA, the lack of the possibility of infection, the rapid degradation of the vaccine mRNA into harmless components and its similarity to the mRNA naturally occurring in cells, and a very small dose necessary to produce a therapeutic effect. Importantly, high titers of SARS-CoV-2 neutralizing antibodies were obtained seven days after the second vaccination in 90% of people. It is also worth noting that vaccines against COVID-19, like other vaccines available on the EU pharmaceutical market, undergo rigorous clinical trials and marketing authorization procedures. After COVID-19 vaccines are approved for use on the market, their safety will continue to be closely monitored according to legal standards. Moreover, their conditional approval, valid for one year, means that the European Medicines Agency will soon have to analyze the data on using these vaccines in clinical practice.

Logistics plays an essential role in an enterprise on such a scale as the distribution of COVID-19 vaccines. That is why the European Commission has issued a communication to the Member States recommending what a common vaccination strategy should look like, especially concerning vaccine distribution. On December 8, 2020, the National Immunization Program was adopted, taking into account the European Commission's above recommendations. Due to the massiveness, manufacturing procedure, and distribution of vaccines, the vaccination action will be phased. The order of priority groups, according to which vaccination will be carried out, has been established. Healthcare professionals will be able to get vaccinated first while being an example and the main source of knowledge for patients. In this context, patient education is essential – making them aware of the importance of immunization, their role in preventing COVID-19, and thus in restoring the quality of family, social, and economic life.

Medical rationales for vaccinations

Examples of viral pandemics in history and the use of vaccines with success

Vaccinations changed the history of the world. One of the diseases eliminated thanks to vaccination is smallpox, which was one of the greatest threats to human health and accompanied people for nearly 3,000 years. The disease was very severe – the average mortality rate was 30%, and of those who survived, many had visual defects and unsightly scars. In the 20th century alone, smallpox killed about 300 million people worldwide. The first effective vaccine against this disease appeared in 1796 thanks to the English doctor Edward Jenner, but the lack of massive and universal vaccination in the world did not interrupt the virus's circulation. It was only thanks to the introduction of the universal vaccination program 'True Smallpox Eradication Program' in 1967 in every corner of the world that enabled the World Health Organization (WHO) to issue the long-awaited message on May 8, 1980 – the world was free from smallpox.

Poliomyelitis, or widespread childhood paralysis, was one of the greatest threats to children and young people worldwide in the 20th century. The disease was easily transmitted from person to person, and although only about 1% of those infected developed symptoms of paralysis of the limbs, and sometimes paralysis of the respiratory muscles leading to death, the mass incidence of the disease meant that in 1988 every day around the world 1,000 children underwent paresis and paralysis. The poor epidemic situation in the field of widespread childhood paralysis in the world was the reason for the launch of the World Initiative for the Eradication of Poliomyelitis in 1988. Since then, 2.5 billion children in over 200 countries were vaccinated worldwide with the help of 20 million volunteers. As a result, in 2020, only two countries still suffer from poliomyelitis. As of December 9, 2020, there were 56 cases in Afghanistan and 82 in Pakistan. In more than 30 years, the number of poliomyelitis cases worldwide has been reduced by 99%, but the ultimate goal of eradicating the disease has yet to be achieved.

What has the history of fighting smallpox and poliomyelitis taught us? Both examples show that the production of an effective vaccine is only the beginning of the path to increasing population immunity. Mass vaccination is the only way to stop the circulation of the virus and prevent further infection of hundreds of thousands of people. In the modern world, thanks to modern communication and the ease of moving from one corner of the world to another, it is difficult to achieve the success of local programs. Therefore, only global action will allow the virus to be eradicated and the history of a given disease to be completed. The example of poliomyelitis shows that if contamination occurs in one region, even remote from us, it still poses a threat to the rest of the world, necessitating continued mass immunization.

Why is the vaccine the best support to fight viral diseases?

Viruses that can cause disease in humans are those that, by finding a way to enter the cell through the receptor, multiply inside the cell, using its resources. The viral replication cycle is closely related to the metabolism of the cells in the infected organism. So far, few drugs are effective against the viruses inside our cells. The available ones are directed against specific viruses (e.g., herpes, HCV, HIV) and act on specific enzymes. The drugs used so far to treat COVID-19 are effective only in the first phase of infection, inhibiting viral replication, which is most intense before symptoms appear. So far, however, there is no drug with very good efficacy that would show effect after the first week of the disease.

The immune system can effectively protect us against infection with pathogenic viruses, but only if it has acquired this property through prior contact with the virus or its fragment. Vaccinations are the safest way to acquire a controlled resistance to infection. A vaccine is a biological preparation that introduces antigens against which immunity is to be generated. It presents to the immune system the elements of the virus that it wants to recognize. Re-contact with the virus is no longer a surprise to the organism, and the antibodies and sensitized cytotoxic lymphocytes produced by vaccination protect the vaccinated person from the disease.

Many viruses that cause human disease are transmitted by airborne droplets, airborne transmission, or direct contact between an infected person and a sensitive person. Outbreaks, epidemics, and even pandemics arise among vulnerable people. If an infected person appears among those who are immunized, she/he will not infect them. Mass immunization of the majority of society leads to the development of population immunity, also known as collective or herd immunity. In such a community, the infectious agent, unable to find sensitive organisms in which it could multiply, loses the possibility of transmission between persons. Therefore, population immunity offers protection to people who, for various reasons, cannot be vaccinated or for whom the vaccine is ineffective.

The course of the epidemic depends on the mutual proportions of infecting, susceptible, and convalescent people. In the absence of immunization, a reduction in the number of cases occurs when the number of susceptible people decreases, and the number of convalescents who have acquired immunity in a natural way increases.

The use of vaccinations accelerates the increase in the number of resistant people (vaccinated people, like convalescents, acquire immunity) while reducing the number of susceptible people. As a result, the epidemic loses the conditions for further spread

The scale of the current pandemic, including the number of victims, attempts to fight it, and the lack of effective drugs

In December 2019, there were rapidly spreading outbreaks of unspecified severe viral pneumonia in Wuhan, China. The etiological factor of these diseases turned out to be a new coronavirus, the transmission of which has not been found in the human population so far. The World Health Organization named it SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus-2) and COVID-19 (Corona Virus Disease-2019) – the disease it causes. On March 11, 2020, WHO announced the COVID-19 pandemic. Soon its epicenter moved from Asia to Europe and North America.

In the spring and summer of 2020, the greatest number of cases outside the USA was recorded in Italy, Spain, France, and the United Kingdom. At that time, Poland was one of the countries with one of the lowest daily numbers of positive results detected, which was tried to be explained with hypotheses about the influence of previous vaccination against tuberculosis or genetic factors. In retrospect, it is known that early restrictions were imposed, including primarily the closure of schools and other places, increasing the risk of transmission of infection. Until September, the daily number of identified infections did not exceed one thousand. However, at the beginning of the school year, there was a sharp increase in the number of infections, which on November 7 reached nearly 28,000 identified positive results for SARS-CoV-2. At the beginning of December, the total number of cases identified in Poland exceeded one million. However, it is estimated that the actual number of people who had contact with the coronavirus and acquired at least temporary immunity is 5-10 times higher. However, this is not enough to reach the threshold, ensuring population immunity in 2021. It must not be forgotten that the process of acquiring immunity through the further spread of SARS-CoV-2 in society will cost many people deaths. It is estimated that in November alone, about 20,000 people died due to COVID-19, and at least twice as much died due to the pandemic's disruptions in accessing healthcare facilities.

According to the analysis of hospitalized patients registered in the SARSTer database, the COVID-19-related mortality was 6.2% and 7.3% when considering only the adult population. However, mortality clearly increases after the age of 60. Every fifth person over 80 who requires hospital treatment dies, and among patients requiring mechanical ventilation (connection to ventilators), the mortality rate reaches 67%. Therefore, halting the spread of the pandemic and related deaths requires accelerating the development of population immunity through mass vaccination. During the pandemic, mainly based on clinical experience, the use of many drugs was proposed. No doubts as to the effectiveness and safety are raised only in case of the use of oxygen therapy and low molecular weight heparin in patients requiring hospitalization. However, it is supportive treatment.

The lack of optimal, causal COVID-19 therapy is an additional, powerful argument for intensifying preventive measures, emphasizing vaccinations.

How long are we likely to wait for the effect of vaccination on SARS-CoV-2? How long is the effect? And how does mass vaccination coverage (population vaccination coverage) contribute to these issues?

Pandemic and the unpredictable course of COVID-19, over 7% mortality in the age group 60–80 years and nearly 20% in the age group over 80 years, difficult to understand and complex pathogenesis of infection, lack of effective drugs and negation of the existence of the SARS-CoV-2 virus by specific environments is the basis and target for all activities necessary to inhibit the spread of infections. The primary goal is to achieve population immunity, which is guaranteed by patients who will never become infected for unknown, possibly genetically determined reasons, patients who have contracted COVID-19, and patients who have been vaccinated. As mentioned above, undoubtedly, the worst method of achieving population immunity is to allow the infection to spread freely in the population. This leads to large human losses and is a massive burden on a given country's health service and economy. There is also no guarantee that all those infected will develop immunity, nor there is certainty about how long it will last. The data on the nature, degree, and duration of humoral and cellular immunity and its dependence on the presence or coexistence of other diseases, other preventive vaccinations, age, race, sex, genetic characteristics, or even eating habits are still incomplete, and sometimes even contradictory. It was confirmed that the immune response to SARS-CoV-2 infection varied significantly in terms of time, quality, and quantity between individual patients. This heterogeneity is a specific feature of infection with this virus. It is known that neutralizing antibodies to SARS-CoV-2 persist for at least six months. Historically, we know that in patients with SARS-CoV-1 infection, high titers of neutralizing IgG antibo-

dies were maintained for five months and then decreased to undetectable values within 2–3 years. However, in patients infected with another coronavirus – MERS, the presence of neutralizing antibodies was observed 34 months after the disease. However, it should be remembered that the detection of neutralizing antibodies in the IgG class is not synonymous with the persistence of the immune response, just as the absence of these antibodies is not the same as the absence of a permanent immune response. This is due to the existence of, in addition to the humoral immunity conditioned by antibodies, the cellular immunity related to the activity of T lymphocytes.

Binding data on the persistence of the immune response after SARS-CoV-2 infection, and also after vaccination, will be obtained in 2–3 years. Regarding the time needed for immunity after vaccination, people vaccinated against SARS-CoV-2 with an mRNA-based vaccine did not achieve high levels of neutralizing antibodies until seven days after the second vaccination. However, it is important that it concerned over 90% of people.

Basic technologies in vaccines against COVID-19

Principles of specific immunity – active and passive

The immune system uses a number of mechanisms to protect the body against microbes. These mechanisms are divided into non-specific (congenital) and specific (acquired). Non-specific mechanisms are fully developed and practically unchanged throughout a person's life (many of them are already active before birth), so they are fully operational before microbes enter the human body. Unfortunately, this type of immunity is sometimes insufficient to suppress microbes and does not retain permanent immune memory.

Specific immunity develops only 10–14 days after the penetration of microorganisms, but it is very effective and precise – unlike the non-specific response, the activation of which is associated with tissue damage. Specific immunity works with almost surgical precision, effectively eliminating only microorganisms and cells infected by them. Two types of lymphocytes participate in specific immunity – T and B lymphocytes. For simplicity, only the mechanisms by which B lymphocytes participate will be described. On the surface of these cells, there are receptors (called immunoglobulins or surface antibodies) that are able to recognize (bind) specific fragments of microorganisms (so-called antigens) in an amazingly specific way.

To put it simply, this means that a given B-cell receptor can bind strongly to only one antigen. Each B lymphocyte has tens of thousands of these receptors in its membrane, but they are all identical, that is, only capable of recognizing one antigen. Hundreds of millions of B lymphocytes are produced in the marrow every day, each of which may have completely different surface antibodies, so each of these cells can recognize different antigens.

At the time of the first contact with a microbe, only a handful of B lymphocytes in the human body could recognize the microbial antigens. Only during the infection, the few B lymphocytes are activated in the lymphatic organs, which starts the multistage process of transforming these cells into plasma cells, releasing soluble (secreted outside the cell) antibodies. The first step in this process is the intensive division of the lymphocytes, which recognizes the antigen with low affinity.

In the course of these divisions, changes in the structure of antibodies occur, which affect their specificity, i.e., the ability to recognize an antigen specifically. These changes are random and lead to the generation of millions of diverse B lymphocytes capable of producing antibodies with different specificities. Only a few of these cells can produce such antibodies that will specifically recognize the antigen of the microorganism, and their multiplication and transformation into plasma cells occur as a result of further selection processes. The number of these cells increases to many millions, and the soluble antibodies produced by them bind to the surface of microorganisms and eliminate them from the body (most often not directly, but with the participation of non-specific mechanisms, e.g., in the process of phagocytosis, or as a result of activation of the complement system). Unlike B lymphocytes, which release antibodies, T lymphocytes are activated into cells that are able to kill cells infected by microbes directly. After eliminating the microorganism, most lymphocytes die, and only a few memory lymphocytes remain (which can survive in the body for several dozen years). These cells already have developed antibodies that recognize the antigens of the microorganism with high affinity and can rapidly become involved in the body's defense when repeatedly exposed to the same pathogen.

Exactly the same mechanisms as those needed to develop active immunity naturally occur in the body after administering the vaccine. The vaccine also activates B lymphocytes and leads to changes in 'refining' antibodies and plasma cells' formation.

The difference is that one does not have to be infected with the vaccine to acquire immunity (some severe infections may lead to permanent disability before immunity develops, or even death).

The immunity produced by vaccination is called active artificial immunity. There is another type of immunity – passive, based on administering antibodies isolated, for example, from a convalescent to a sick person or a person susceptible to infection. Unlike active immunity, passive immunity is short-lived and lasts up to several months.

Vaccine types

A vaccine is a biological preparation, the task of which is to imitate an infection with a microorganism and thus obtain immunity similar to the passing of a real disease, but in a much safer way. The vaccine may contain live, weakened or dead microorganisms or their fragments (e.g., mRNA vaccine). Vaccines containing virus fragments are considered very safe, and the technology of their production has been developed for about 20 years. In the case of the SARS-CoV-2 virus, which causes COVID-19, this type of vaccine is most intensively developed.

mRNA vaccines

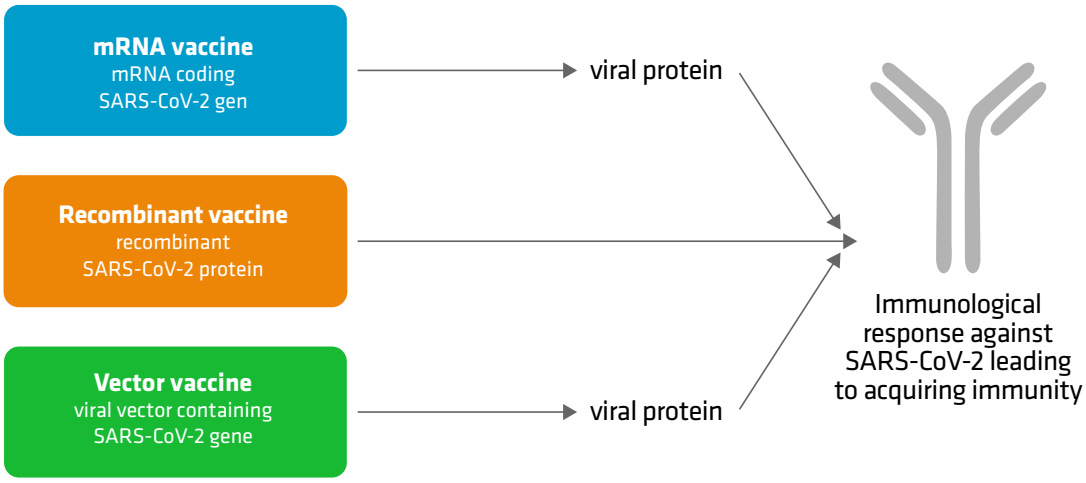
Such a vaccine uses ribonucleic acid (RNA) as a template for producing viral proteins intended to trigger antibodies' production. The RNA itself administered in the vaccine is not stable and degrades rapidly (therefore, low temperatures are required for its storage). In the case of an mRNA vaccine, the virus's genetic material never becomes integrated into the human genome. Examples of such vaccines are those obtained against SARS-CoV-2 by Pfizer/BioNTech and Moderna.

Recombinant vaccines

Recombinant vaccines are created by incorporating the genetic material of a microorganism into mammalian cells or yeast cells. The resulting recombinant proteins are isolated and purified and then administered to the patient to induce antibodies' production. These are classic vaccines developed by many companies against SARS-CoV-2, but none of them has yet been approved.

Vector vaccines

In the vector vaccines, the active viruses were modified to minimize the risk of infection. It is often a virus that safety and applicability in vaccines have been confirmed in the past or viruses not present in humans. These viruses are modified to trigger the production of a protein from the organism against which immunity is to be built when administered as a vaccine. Examples of such vaccines are those obtained against SARS-CoV-2 by AstraZeneca and Johnson & Johnson.



mRNA and vector vaccines contain genetic material of the SARS-CoV-2 virus, from which in the organism a viral protein is created and recognized as an antigen. This leads to acquiring immunity against the virus.
A recombinant vaccine directly contains the viral protein. Therefore, there is no stage of its production by the human organism.

Figure 1. Vaccine types

mRNA technology and its application in vaccination

Expression of genetic material.
mRNA – the biological role

In eukaryotic cells (including all humans, animals, and plants), the genetic information about proteins is encoded in enormous DNA molecules called chromosomes. For a given protein to be synthesized in a cell, the appropriate chromosome fragment called a gene must be transcribed into mRNA sequences, constituting a specific cellular 'protein recipe'. This 'recipe' is transported from the cell nucleus to the cytoplasm, where the process of translation takes place, i.e., the translation of the genetic code written in the form of RNA sequences into the amino acid sequence of proteins. Based on one mRNA molecule, many molecules of a given protein can be created – just like in the kitchen, one recipe can prepare a given dish many times. Yes, to put it simply, with mRNA's help, proteins are created in our cells, which are involved in almost all processes taking place in our bodies.

RNA is unstable. When it does its job, and the protein is made, RNA is enzymatically degraded in cells by enzymes called ribonucleases, and the resulting nucleotides are used by the cell. So, it can be said that there is no trace left of the degraded mRNA, except for the protein it encoded.

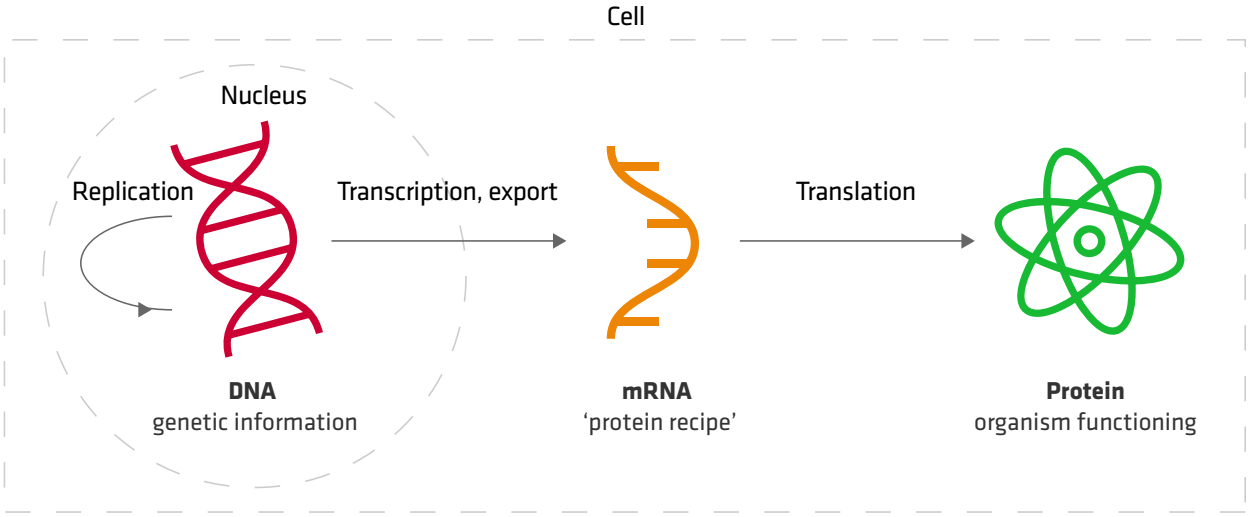


Figure 2. Expression of genetic information from DNA, by mRNA, to proteins

Development of gene therapy

Most traditional drugs are small-molecule chemicals that interact with various proteins to affect their activity. However, many diseases are challenging to treat with conventional drugs (e.g., cancer, genetic disorders, some viral diseases). Therefore, already in 1970s, the concept of gene therapy was created, in which information about a therapeutic protein is delivered to cells in the form of a genetic recipe.

Gene therapy can be performed in two ways: by providing DNA or mRNA encoding a given protein. Initially, scientists were inclined to use DNA. Still, for the genetic material to be expressed in the form of DNA (i.e., to produce mRNA and then proteins on its basis, see Fig. 2), it must be integrated with the patient's genetic material. Even nowadays, it is not effective enough and difficult to control. It is entirely different from mRNA expressed in the cytoplasm. mRNA never reaches the cell nucleus, the effect is transient, and the mRNA itself is a rapidly degrading molecule.

The most important thing, however, is that in human cells, there is no mechanism for transcribing sequences from mRNA to DNA and integrating such DNA into the genome. This means that incorporating the viral genetic material from the mRNA vaccine into the human genome and influencing it is absolutely impossible, making mRNA therapy completely safe in this respect.

The last 20 years have been marked by intensive work on the development of therapeutic mRNAs and several discoveries have enabled mRNA use in therapy. The main achievements in this field include increasing the stability of mRNAs, reducing their immunogenicity (i.e., the ability to induce a response from the immune system), or solving the problem of mRNA delivery inside cells. All this so that enough protein is produced from as little mRNA as possible to have a therapeutic effect.

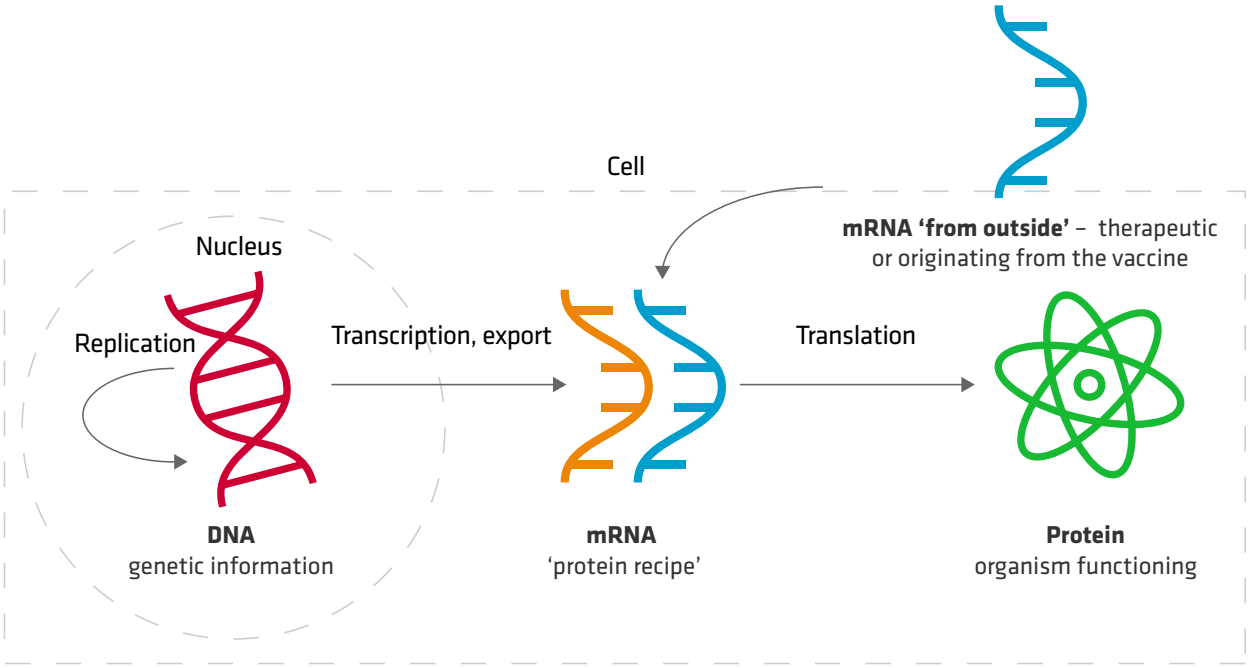


Figure 3. Therapeutic protein from mRNA supplied from the outside is produced by a natural translation process occurring in the cell

Therapeutic mRNA

mRNA therapy consists of delivering mRNA encoding a therapeutic protein to the patient's cells. It could be a protein that is not working correctly in the given patient or is being made too little because of the disease. It can also be a protein characteristic of some pathogen which task is to activate the immune system against that pathogen. The latter case is used in the development of an mRNA vaccine.

One of the great advantages of this technology is that by changing only the nucleotide sequence in a therapeutic mRNA once developed, we can obtain almost any protein because the method of obtaining and purifying mRNA of any sequence is the same. mRNA is received in a test tube by a biochemical reaction, and its production can be easily scaled up. The development of a therapeutic against one disease makes developing another one against other diseases much more straightforward, cheaper, and quicker. This is especially important in a pandemic situation. Clinical trials for mRNA vaccines against cancer and non-SARS-CoV-2 viruses, as well as mRNAs that treat rare genetic diseases, have been underway in many companies for over ten years. This explains why we have got the first SARS-CoV-2 vaccines so quickly and why mRNA vaccines are winning this race. It also gives hope that the acceleration of work on this technology caused by the pandemic will translate into progress in treating other diseases in the near future.

Why is the mRNA vaccine safe?

- *The genetic material of the virus contained in the vaccine cannot modify a patient's DNA*
- *a recipe is provided for only one virus protein (out of several dozen viral proteins and the genetic material of the virus necessary for its existence), thanks to which there is absolutely no possibility of infection*
- *mRNA is a natural component of our cells*
- *mRNA lasts a short time (hours) in cells, then it degrades into harmless, natural components*
- *a very small dose of the vaccine is enough to produce a therapeutic effect. E.g., in the Pfizer / BioNTech vaccine, it is 30 micrograms, which is over 100,000 times less than the sugar in a teaspoon*
- *therapeutic mRNA, its effectiveness and safety have been studied in patients in the context of various diseases for many years (first clinical trials using mRNA[1]: 2001; direct administration of mRNA to a patient[2]: 2009)*

1) Clinical trials started in 2001 – the first delivery of mRNA to dendritic cells and introduction of these cells into the patient's body described by Heiser, A. et al. Autologous dendritic cells transfected with prostate-specific antigen RNA stimulate CTL responses against metastatic prostate tumors. J. Clin. Invest. 109, 409-417 (2002).

2) Clinical trials started in 2009 – first direct injection of mRNA into the patient's body described by Weide, B. et al. Direct injection of protamine protected mRNA: results of a phase 1/2 vaccination trial in metastatic melanoma patients. J. Immunother. 32, 498–507.

Vector vaccine technology

Vector vaccines are based on natural viruses that are not dangerous to humans. For this purpose, viruses that do not cause disease in humans or viruses that are unable to replicate in human cells are used. Their safety and applicability in vaccines have been confirmed. There are, therefore, two main types of vector vaccines: replicating and non-replicating. In such vaccines, these safe viruses serve as a carrier that contains instruction for the cell on how to produce a specific antigen - the protein of the microorganism to which immunity is to be obtained.

All presently counting vaccines in this group against COVID-19 are based on non-replicating adenoviruses. Examples of formulations of this type include AstraZeneca (animal adenovirus), Russian Sputnik (adenovirus 26 and 5), CanSino (adenovirus 5) and Johnson & Johnson (adenovirus 26).

What are adenoviruses?

Adenoviruses are DNA viruses whose tiny genome (26,000 – 48,000 base pairs) is contained in a spherical capsid devoid of a lipid envelope (Fig. 4). These viruses infect humans and many animal species, and several dozen of their types are known today. They cause various diseases, including infections of the upper and lower respiratory tract, ear, digestive system, bladder, and eye. Adenoviruses, due to their relatively small genome, were recognized some time ago as a convenient tool for the transfer of information to the cell, especially since it is possible to develop variants that are unable to reproduce or even to use viruses that do not naturally infect humans and are unable to replicate in human cells and do not cause disease.

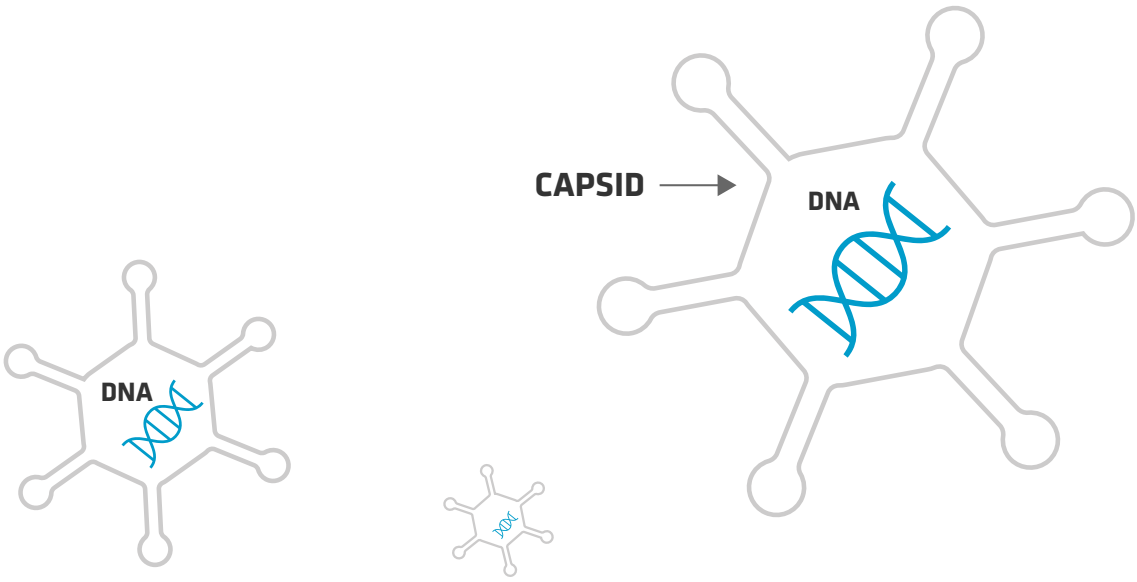


Figure 4. A simplified structure of an adenovirus

How does the vector vaccine work?

The currently counting vector vaccines against COVID-19 use adenoviruses that are unable to replicate, i.e., they cannot also mutate in our body and regain the ability to multiply and spread - without replication, there is no mutation. During natural infection and during transduction, the virus's genetic material is introduced into the cell's nucleus. However, it does not integrate with our genome but remains in the nucleus as a separate, episomal molecule. These vectors are classified, among others, by the European Medicines Agency as non-integrating.

The use of such a vector eliminates the risk of spontaneous multiplication of the virus in human cells but also guarantees that vaccinated people will not have antibodies that recognize this virus as a result of previous infections. Such pre-existing immunity would mean that before the vector enters the cell, it is removed by our immune system, and the vaccine would not work.

The mechanism of action of vector vaccines is presented in Figure 5. A DNA fragment that codes for the S protein of the coronavirus is inserted into the adenovirus genome. After entering the cell, the virus introduces its DNA into the cell's nucleus, where it is naturally transcribed, i.e., transcribed into an mRNA molecule. The resulting mRNA molecule from the cell's nucleus is transported to the cytoplasm. In the cytoplasm, the resulting mRNA serves as a matrix for our ribosomes, which allows the production of the S protein. The resulting protein is processed correctly inside the cell and then presented on its surface by the major histocompatibility complex proteins. This allows cells of the immune system to recognize a new element – the S protein of the coronavirus – and then trigger further processes to build an

immune response, both cellular and associated with antibody production. This allows the vaccinated person's immune system to recognize the virus or infected cells when it is later exposed to SARS-CoV-2 and block replication and, consequently, the disease.

How is a vector vaccine different from an RNA vaccine?
The main difference is how instructions are provided for human cells: how to make the coronavirus S protein. In the case of RNA vaccines, it is a messenger RNA (mRNA) molecule, while in a vector vaccine, information is transported in the form of DNA, and only in the cell it is translated into mRNA. The next steps are identical for both types of vaccines.

An essential difference between mRNA-based vaccines and vector vaccines are the conditions in which they must be stored. While the former require very low temperatures, the latter are not frozen and can be stored in a refrigerator (2-8°C) for a long time.

Another difference concerns the efficacy reported in the third phase clinical trials. As long as the mRNA vaccines reveal the efficacy of approx. 95%, the adenovirus-based vector vaccines exhibited a significantly lower level of protection. However, the efficacy in these trials is defined as the level at which symptomatic infections are prevented. The studies reveal that vector vaccines can effectively prevent severe COVID-19 and hospitalizations.

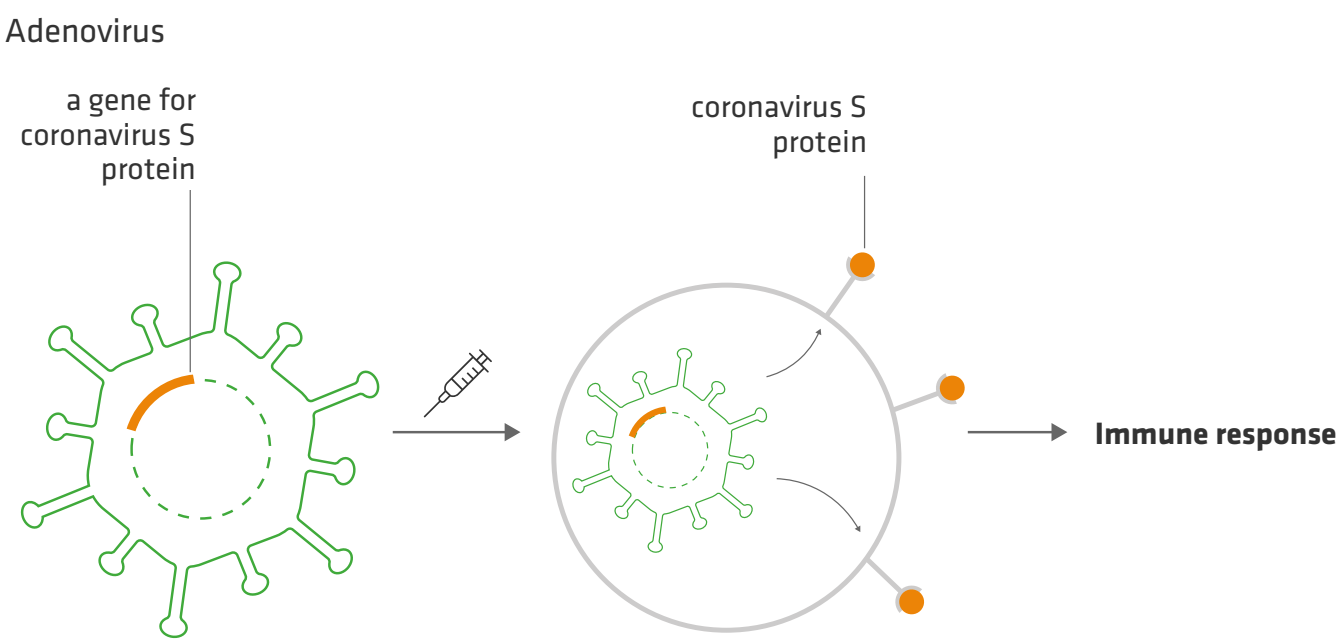


Figure 5. The mechanism of action of the vector vaccine

SARS-CoV-2 as the cause of a global pandemic

What are coronaviruses?

Coronaviruses are a large family of RNA viruses that include many species that infect humans and animals. Coronaviruses consist of a large (approx. 30,000 nucleotides) molecule of single-stranded RNA closely bound to the N protein, which forms the core that protects and stabilizes this sensitive molecule. This core is surrounded by a membrane in which the virus's structural proteins are embedded – envelope protein E, membrane protein M, and the most important – the protein S (spike), responsible for recognizing the host cell and initiating the infection process (Fig. 6). While coronaviruses exhibit greater variability than DNA viruses, or even more so with higher organisms, they are far from other RNA viruses, such as the influenza virus, in this respect. Contrary to them, they have a system for correcting errors arising in replicating the genetic material. As a result, they change significantly more slowly.

The first species of coronaviruses were discovered in the 1940s in samples taken from sick animals. Further research showed that these viruses can be pathogenic, causing diseases of the respiratory and digestive systems, viral hepatitis, or infectious peritonitis. However, different species of these viruses vary in virulence – while infection with some does not lead to serious clinical conditions, infection with others invariably leads to death. In the 1960s, it was discovered that some members of the coronavirus family could also infect humans. Two species – HCoV-229E and HCoV-OC43 – were associated with the common cold and diseases of the upper and, less frequently, lower respiratory tract. For many years, the coronaviruses were not the subject of detailed studies because their clinical significance was low. However, at the end of 2002, one of the animal viruses, SARS-CoV beta-coronavirus, became capable of infecting humans. In the 2002–2003 season, the virus infected about 8,000 people, causing severe acute respiratory syndrome (SARS), with a high mortality rate of approximately 10%. Fortunately, the virus's ability to travel between humans and humans decreased drastically with the advent of higher temperatures, and structured countermeasures such as contact tracing and isolation effectively cut infection pathways. As a result, the SARS epidemic was extinguished entirely. The advent of SARS-CoV electrified the world of science and medicine. It was proven that some coronaviruses have a high ability to spread from animals to humans and can pose a real epidemic and medical threat. Extended research resulted in the identification of two more 'human' coronaviruses – HCoV-NL63 and HCoV-HKU1 - which in the vast majority of cases cause relatively mild respiratory disease. Also, at that time, the first research was initiated to develop effective methods of preventing coronavirus infections and their therapy – vaccines and active substances. However, they were largely dropped in the preclinical stage as the SARS-CoV virus disappeared.

Another major coronavirus-related epidemic occurred in 2012 when human infections with the highly pathogenic MERS-CoV species were detected in the Arabian Peninsula. This virus's infection leads to the so-called Middle-East respiratory syndrome (MERS), characterized by a high mortality rate of 35%. Due to frequent travels MERS-CoV infections were identified in various Asian countries, as well as in Europe and Africa; however, the virus is relatively difficult to transmit from person to person. Most infections occur due to human contact with camels, which are the main reservo-

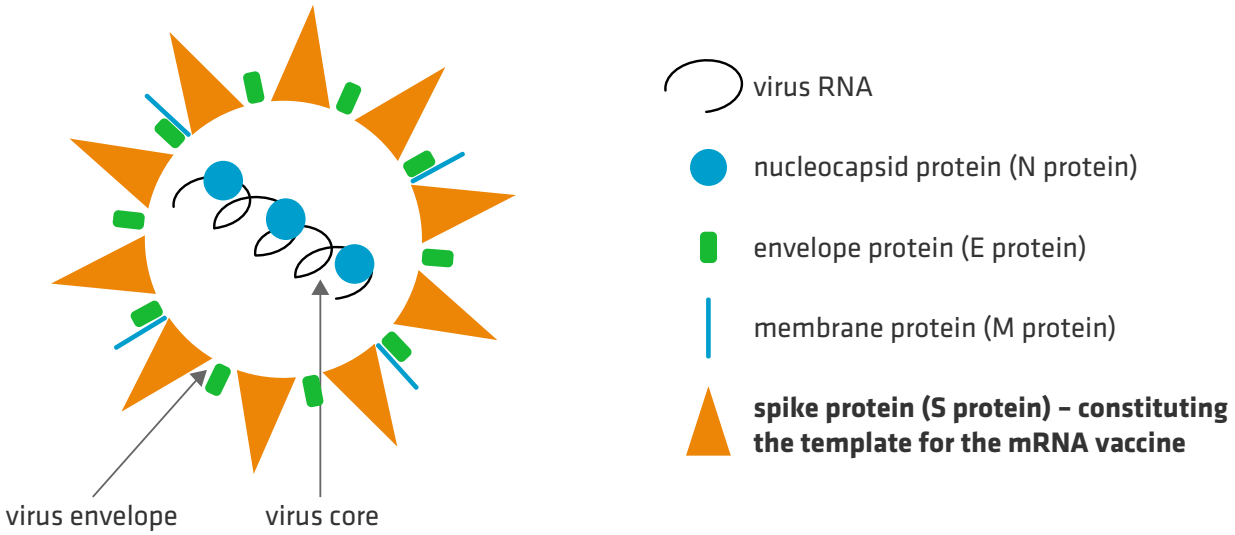


Figure 6. A simplified SARS-CoV-2 structure

ir of MERS-CoV. Consequently, while MERS-CoV is with us today, its occurrence is primarily restricted to the Arabian Peninsula. As in the case of SARS-CoV, after the appearance of the MERS virus, work began on effective methods of preventing and treating its disease. Simultaneously, voices began to appear more and more often, suggesting that zoonotic coronaviruses could pose a significant threat in the coming years. Analyzes of samples from wild animals showed that bats were the true reservoir of coronaviruses. Their organisms contain thousands of varieties belonging to this family of viruses, which continuously adapt to the effective immune system of animals and are continually evolving. Considering the high risk of transmitting these viruses to humans and increasing human interference in the natural environment, this threat has become very real.

SARS-CoV-2

In 2019, another animal coronavirus gained the ability to spread to humans, as well as further spread human-to-human. On December 31, 2019, the first report of pneumonia cases of unknown etiology in the Hubei province was released. Ten days later, Chinese scientists published the entire genome sequence of the causative agent – beta-coronavirus. The International Committee on Taxonomy of Viruses named it SARS-CoV-2 and classified it under the Sarbecovirus subgenus, the same to which the previously discussed SARS-CoV belongs. The genetic relationship between these viruses indicates that while both viruses are derived from the same evolutionary lineage, SARS-CoV is not a direct ancestor of SARS-CoV-2. However, it should be remembered that the relationship among viruses is much more distant than that of other living organisms. At the genetic level, they are less similar to each other than humans are to mice.

The appearance of the SARS-CoV-2 virus in China initially aroused limited emotions in Poland. It was not assumed that it could reach our country or affect our lives to such an extent. However, it happened otherwise. After the initial wave of infections in Southeast Asia, a storm hit Europe that wreaked terrible havoc in some countries. The rapid spread of SARS-CoV-2 was driven not only by globalization and associated international transport but also by the virus's characteristics. It is worth mentioning the most important ones here: the virus is transmitted by droplets without the need for close contact, the long period of incubation of the disease allows transmission over long distances, an infected person becomes contagious before the appearance of symptoms and a relatively high percentage of people pass the infection with mild symptoms or almost asymptomatic, which facilitates the spread of the virus.

But why has the SARS-CoV-2 virus stopped the world? Of course, it is a serious threat to life, especially among people at high risk. These include the elderly, people with cardiovascular diseases, people with obesity, cancer patients, people with type 2 diabetes, chronic kidney disease, and chronic respiratory diseases. The second problem is the epidemic spread of the disease. With such a high percentage of patients requiring hospitalization, the healthcare system is overloaded very quickly. Patients, who do not receive help, die both due to COVID-19 as well as for other medical conditions. The complicated clinical picture of COVID-19 aggravates the situation. Although the virus travels through the respiratory system, SARS-CoV-2 can infect many other organs. It can be found in the nervous system, heart muscle, vessels, pancreas, intestines, and many other parts of our body. In addition, in many cases, the virus modulates the immune system tragically, and our own immune system becomes a lethal threat to us. It should also be noted that the convalescence after SARS-CoV-2 infection is in some cases long-lasting, and in some people, the disturbing changes remain even after a mild disease. We still do not know if the traces of infection in some of the convalescents will be permanent. In Poland, an early and decisive reaction at the beginning of a pandemic, consisting in the introduction of the so-called lockdown, allowed for a significant reduction in the number of COVID-19 cases in the spring. The lack of rapid increases in the number of cases and victims of the disease, also observed in the summer, while returning to normalcy, gave the impression that the threat passed. On the other hand, the arrival of the autumn period began to favor the transmission of the virus due to frequent stay in confined spaces and the characteristics of the pathogen itself, as well as confusing COVID-19 symptoms with seasonal respiratory infections. As a result, a very dynamic increase in the number of cases was recorded, leading to a crisis in the health service and forcing the return of restrictions. While the number of cases is now lower than in mid-fall, it remains high, and the death toll remains shocking.

The complex nature of COVID-19 causes the conscious pursuit of the so-called population resilience can be considered a dangerous fallacy that leads to high deaths, healthcare system failure, and catastrophic economic consequences. It should be noted that the available data suggest that COVID-19 disease is not associated with the generation of a sustained immune system response to SARS-CoV-2, and the reports of reinfection are not optimistic in this regard.

Today, we are faced with the simple choice of getting vaccinated against COVID-19 or taking part in a difficult to predict lottery related to the disease and the further deepening of the economic and health crisis.

This choice is only possible thanks to international efforts, which have allowed vaccine research to be conducted at an unprecedented pace, but with an assessment based on the three most essential pillars: safety, immunogenicity, and efficacy. If we compare the multifaceted consequences of the disease and the potential side effects of vaccination, which do not differ from those seen with other vaccinations against viral diseases, the choice should seem simple.

Registration and marketing authorization of medicinal products in relation to SARS-CoV-2 vaccines

According to the current nomenclature, vaccines are a group of medicinal products (as opposed to medical devices and biocidal products). Although they do not treat, they meet the legal definition of a medicinal product because they protect vaccinated people against viral and bacterial infections. Even in situations where the vaccinated person becomes ill because of a weaker response from their own immune system, the disease's course will be much lenient.

Registration of a medicinal product (marketing authorization of a medicinal product)

Pursuant to the requirements of the pharmaceutical law, registration of a medicinal product is called marketing authorization. Admission to the market of a medicinal product is based on the declaration by a competent authority, based on the documentation submitted by the applicant, that the product is safe, effective, and of good quality. Positive evaluation of a medicinal product concerns the knowledge available at the time of issuing the decision. The Marketing Authorization Holder (MAH, i.e., the company that applied for the marketing authorization of the medicinal product, usually its manufacturer) has a legal obligation to observe the medicinal product already on the market and respond to all new, relevant from the therapeutic point of view, information. As a result of the data collected this way, the medicinal product remains on the market or is withdrawn from it.

In the European Union, there are three routes for obtaining Marketing Authorization in several EU countries at once, which differ in the process, but the required documentation remains the same. It is also possible to obtain a marketing authorization at the national level (then it only applies to the country in which it was issued). In Poland, the decision-making body in this matter is the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products (URPL). Most of the SARS-CoV-2 vaccines will be assessed by the European Medicines Agency as part of the central procedure. If it is positively recommended, the vaccine will obtain marketing authorization from the European Commission (Fig. 7). This means that these vaccines will be authorized simultaneously in all European Union countries. More information on this procedure can be found on the European Medicines Agency website linked in the 'Verified Resources of Knowledge' appendix. In the event of free access to a medicinal product (e.g., to a vaccine against SARS-CoV-2), the Agency for Health Technology Assessment and Tariffication must give an opinion, which will reassess the effectiveness and safety in the defined indication for reimbursement, i.e., it will answer the question whether it is worth spending budget money for free vaccination of Polish citizens against SARS-CoV-2.

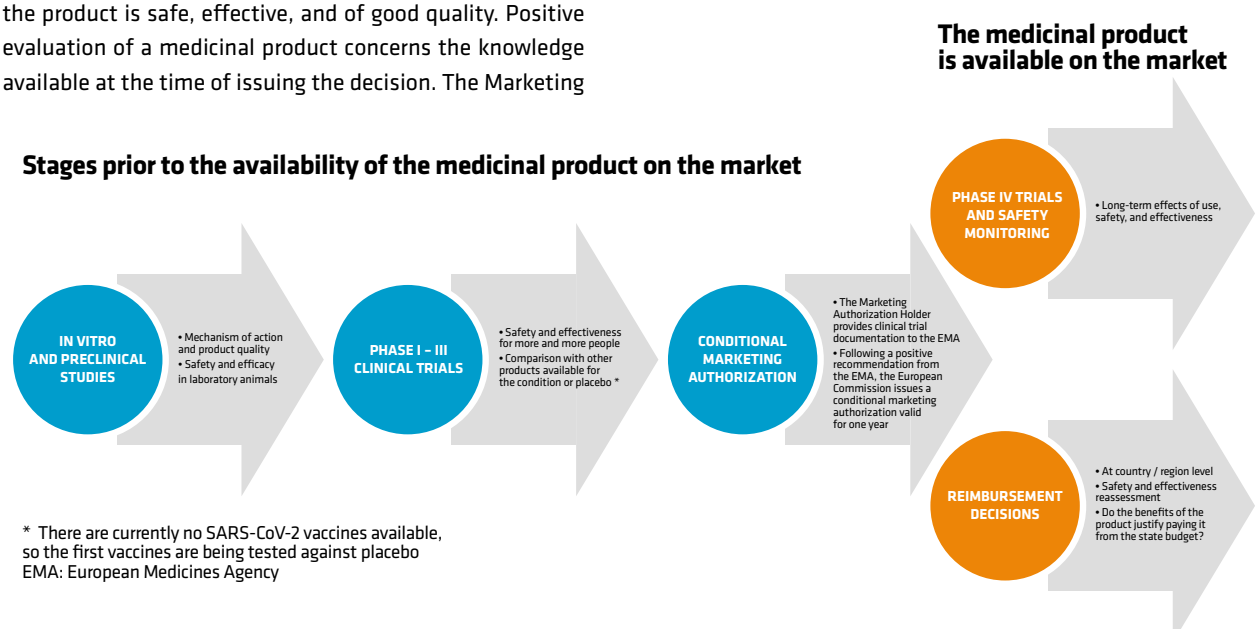


Figure 7. The process of evaluating a medicinal product before and after marketing authorization

Competent bodies

Medicines licensing authorities are called competent authorities. Each country has a Registration Agency or Department within the Ministry of Health. In Poland, it is the URPL mentioned above. In addition, the European Union also has the aforementioned European Medicines Agency (EMA), which associates the competent authorities of 27 member states. Otherworld agencies that influence drug registration include the Food and Drug Administration (FDA) in the USA, Canadian Agency, Australian Agency or Japanese Agency. Of these, the FDA has the greatest reach and is the benchmark and legislative model for the registration proceedings conducted in the countries of the Americas, Asia, and Africa.

Conditional registration

Conditional registration is an important concept for SARS-CoV-2 vaccination. It allows the use of a medicinal product in everyday clinical practice based on less comprehensive studies than those necessary to obtain a standard marketing authorization. The conditional procedure is used in relation to medicinal products that, at the stage of phase I or phase II studies, have shown efficacy in the treatment or prevention of clinical situations in which there has been no proven effective treatment method so far, and the patients are in a state of the immediate threat to their life or health. To sum up, this method of registering a medicinal product applies to situations where it is not possible to compare a medicinal product with others because such products do not exist in a given indication. In the literature, such a situation is referred to as an unmet medical need. The reason for this decision is the ethical aspect. It is also worth noting that the conditional registration procedure is not new and was not created to fight the SARS-CoV-2 pandemic. This procedure has been in place since 2006, and in the first ten years of its application, none of the 30 conditional marketing authorizations issued had to be revoked or suspended.

Indications for the use of the medicinal product

The medicinal product can be used in clinical practice in accordance with the indications for use described in the summary of product characteristics. These indications are based on clinical trials conducted with the product. Sometimes the treating physician decides, at his own risk, to use a given product outside the indications for use included in the summary of product characteristics. This is an off-label use that carries a potential additional risk of use due to the lack of previous comprehensive clinical trials. However, it is unlikely that off-label use issues will apply to SARS-CoV-2 vaccination.

New medicinal product

A medicinal product that has just been authorized is admittedly a new product on the market, but it has undergone long tests in clinical trials. Positive results from large phase III trials with an appropriately selected control group are sufficient to apply for marketing authorization. Still, they are not the end of the road for a medicinal product. On the contrary, a product already admitted to trading is observed in everyday use (the so-called real-world experience). Its safety is closely monitored according to the applicable Polish and European legal standards. Often, products already authorized on the market are subject to phase IV clinical trials to gather additional information on the long-term safety and efficacy of the product. Such a study may be imposed by the competent authority that granted the marketing authorization or taken on the MAH initiative.

Clinical trials

Phase I – the medicinal product's safety is determined, and the optimal dosing regimens are established.

Phase II – the therapeutic efficacy and safety of the medicinal product are determined.

Phase III – confirms the effectiveness, safety, and dosing schedules.

Phase IV – these are the aforementioned post-registration clinical trials. They are therapeutic trials in medical practice, needed when changes are made in terms of indications, dosage, type of packaging, and changes in pharmaceutical form. Clinical trials in pregnant women are not carried out, but the safety of already authorized products in pregnant women is monitored.

Clinical trials conducted on children, the so-called pediatric clinical trial, rely on separate regulations.

Suspension and recall of a medicinal product

A medicinal product may be suspended or withdrawn from the pharmaceutical market by:

- Main Pharmaceutical Inspector – due to quality defects.
- President of URPL – if there are data about insufficient safety of use or therapeutic effectiveness. The Minister of Health substantively supervises both institutions, and the President of URPL is formally subordinate to the Prime Minister of the Polish government.

Collecting information about side effects, including vaccine side effects

In the event of adverse drug reactions to medicinal products, including post-vaccination reactions, the frequency and severity of adverse events are essential. Information on side effects and post-vaccination reactions is collected in Poland by:

- Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products. Contact details of the Registration Office: fax 22-49-21-309 or e-mail: ndl@urpl.gov.pl. You can also contact the office using the Mobit Skaner mobile application or by traditional mail.

- Marketing Authorization Holders (as defined above; the Marketing Authorization Holder's name for a given product can be found in the Summary of Product Characteristics).

- PNational Institute of Hygiene – National Institute of Public Health – only post-vaccination reactions.

- Bodies:

• State Sanitary Inspection – only post-vaccination reactions.

• State Sanitary Inspection of the Ministry of the Interior – only vaccine reactions.

• Military Sanitary Inspection – only post-vaccination reactions.

Side effects of medicinal products, including vaccines, are obligatorily reported by doctors, pharmacists, nurses, midwives, and paramedics. However, patients and their statutory representatives or actual guardians also have the option to report side effects to the above-mentioned authorities. Medical professionals should report severe side effects of medicinal products within 15 days from the date of receiving information about their occurrence.

However, the Act on infectious diseases requires to notify about vaccine adverse events (VAE) within 24 hours.

The Act of December 5, 2008, on the prevention and combating of infections and infectious diseases in humans, Journal of Laws 2008, No. 234, item 1570 provides as follows: Art. 21.1. A doctor or a feldsher, who suspects or recognizes the occurrence of an undesirable post-vaccination reaction, is obliged within 24 hours from suspecting its occurrence to report such a case to the state district sanitary inspector competent for the place of suspicion.

From a legal point of view, the notification must include:

• name of the medicinal product,

• description of the adverse reaction (at least one of the symptoms),

• patient data (initials, gender, or other identifying data of the patient),

• data of the reporting person (name, surname, address, telephone number, e-mail address).

However, the above requirements are too scarce to take optimal action and therefore, the addition of:

• the reason for administering the medicinal product,

• series,

• expiry date,

• pharmaceutical form,

• application routes,

• the type of dosage,

• other medicines used in this disease or coexisting diseases,

• the age, weight, height, and race of the patient.

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Vaccination plan and importance of primary care physicians and nurses

Logistics and distribution of vaccines against COVID-19 is a large-scale undertaking, and so far, such a range of activities has not been undertaken not only in our country but also in the world. The primary scope of this project includes activities such as:

1. Ensuring easy access to vaccines,

2. Introducing vaccines with different properties,

3. Indicating groups and people most exposed or susceptible to infection,

4. Defining and meeting storage and transport needs, in particular in terms of the cold chain, refrigerated transport, and storage options.

There have been several epidemics around the world in recent years. The experience related to combating them may also be useful now, in the face of the pandemic caused by the SARS-CoV-2 virus. In the United States, lessons learned from previous mass vaccinations in the USA and worldwide were analyzed, including the 2009 H1N1 flu vaccination campaign and the 2013-2016 vaccination campaign during the Ebola outbreak in West Africa. They also enabled to define ethical principles and strategies for prioritizing resource allocation. Several of these principles and strategies have been recently developed to distribute rare hospital drugs for COVID-19.

Based on several key lessons learned from previous mass vaccination campaigns regarding distribution, logistics, and communication, it identified the need to develop effective distribution tracking systems; to ensure timely and appropriate distribution of auxiliary supplies; the risk of 'unfulfilled and overstated promises' in planning and communication activities; to provide up-to-date information on vaccine production, stocks and forecasts through stronger and more formal cooperation between central subjects and vaccine manufacturers; to plan a series of vaccine delivery scenarios; to consider using the infrastructure of a childhood immunization program as the basis of adult emergency vaccination distribution programs; to implement limited vaccine supplies fairly and transparently, to use pre-specified, evidence-based criteria for prioritizing allocation; and to use consistent, respectful, and accurate communication to earn, secure, and maintain trust. (2)

Many countries are preparing for and taking these challenges very seriously. On October 15, 2020, the European Commission (EC) presented the Communication from the Commission to the European Parliament and the Council on preparedness in the area of vaccination strategy and the introduction of vaccines against COVID-19. The Communication provides recommendations for the Member States that should start developing a joint vaccination program to distribute vaccines. The Member States should ensure, among others:

- the capacity of the vaccination system to deliver the COVID-19 vaccine, including the provision of qualified personnel and medical and protective equipment;
- easy and inexpensive access to vaccines for target groups;
- distribution of vaccines, taking into account the different storage and transportation needs, in particular the cold chain, low-temperature product transportation, and storage capacity;
- clear information on the benefits, risks, and importance of the COVID-19 vaccination to build public confidence. (3)

On January 19, 2021, another Communication from the Commission to the European Parliament and the Council was released, entitled 'A Common Front to Fight COVID-19'. It defines, among others, the latest European Union (EU) working rules to accelerate vaccination and vaccine delivery. The EC secured 2.3 billion doses of vaccines and indicated the key directions of its activity:

- The Member States should set targets to vaccinate at least 80% of health care and social care workers and those over 80 years of age by March 2021 and at least 70% of the total adult population by summer.
- The Commission, Member States, and the European Medicines Agency (EMA) will work with vaccine manufacturers to maximize vaccine production capacity.
- Based on the Member States data, the European Center for Disease Prevention and Control (ECDC) will publish updated information on doses delivered and administered twice a week.
- The Commission will work with vaccine manufacturers to publish and update delivery schedules.
- By the end of January 2021, vaccination certificates should be harmonized to allow for swift use of certificates from the individual Member States in health care systems across the EU and beyond.
- The Commission is to carry out a large-scale study on the safety and efficacy of the COVID-19 vaccine covering the entire EU population.

- ECDC is to develop a package of logistics advice under stress conditions (temperature, time from opening to administration) for use by the Member States. (4)

On December 8, 2020, the National Immunization Program prepared by the Ministry of Health was released in Poland. Poland decided to enter into five vaccine purchase agreements: AstraZeneca (16 million doses), Janssen Pharmaceutica NV / Johnson & Johnson (16.98 million), CureVac (5.72 million), Moderna (6.69 million), Pfizer / BioNTech (16.74 million) – 62.13 million doses in total. On December 29, 2020, and January 6, 2021, additional contracts were concluded with Pfizer / BioNTech to deliver vaccines in the second and third quarters of this year. Poland will receive a total of 42.9 million doses of the vaccine from this manufacturer.

Overall, the contracts currently concluded will provide Polish patients with 88.22 million vaccines (5). The Material Reserves Agency, which coordinates the entire process, is responsible for the correctness and efficiency of distribution. Storage capacity has been secured, enabling the expected supply of vaccines to be stored in cold chain conditions (2–8°C) and ultra-low temperatures (-75°C). Logistics centers were selected, which constitute storage and distribution facilities. Transport is carried out using a specialized fleet of vehicles with a refrigeration system or in special transport devices that maintain the required low temperature. The entire process is based on the well-functioning distribution networks of two pharmaceutical wholesalers.

Vaccination points scattered all over the country place orders in a dedicated IT system that allows monitoring of orders and the status of deliveries. Also, the accessories required by vaccine manufacturers are provided: syringes, needles, gloves, surgical masks, swabs, and the required saline solution. Their distribution is correlated with the supply of vaccines.

Vaccine tranches from individual manufacturers will be split to ensure that both required doses of vaccine are delivered from the same shipment. As a result, the patient's revaccination after 3 or 4 weeks will be smooth and uninterrupted in accordance with the manufacturers' guidelines. (7)

In Poland, the focus was mainly on the existing network of vaccination points operating mainly within primary health care facilities. They employ medical personnel with many years of experience in the field of vaccinations, particularly for children, in accordance with the current vaccination schedule and meeting all legal requirements in terms of competencies and conditions necessary for the operation of such facilities. The primary health care system is supplemented by dedicated points in specialist outpatient care and other medical facilities. Additionally, mobile vaccination teams will be created to perform vaccinations at the patient's place of residence or stay and vaccination centers in reserve hospitals.

The vaccination procedure is carried out in two ways: individually and in groups. Individual procedures are performed at the vaccination sites. In contrast, group procedures are designed, among others, for healthcare personnel, uniformed services, residents of nursing homes, care and treatment institutions, and nursing and care institutions. Depending on the manufacturer's logistic possibilities and indications, group vaccinations are performed in hospitals divided into nodal hospitals vaccinating the staff of medical entities and pharmacies, pediatric and oncological hospitals vaccinating only their staff, and nursing and therapeutic facilities vaccinating patients and their own staff.

Due to its mass, scale, vaccine production, and vaccine distribution procedure, the vaccination campaign takes place in 5 stages. The priority groups' order to be vaccinated at each stage was established based on four criteria: risk of exposure to infection, risk of serious illness and death, socio-economic conditions, and ease of transmission. Based on the Regulation of the Council of Ministers of January 22, 2021, amending the Regulation on the establishment of certain restrictions, orders, and bans in connection with an epidemic, within the first two groups, from January 23, 2021, new groups were added to the originally specified entitled persons.

In the case of the individual vaccination group, the patient receives invitations in the form of e-referral for vaccination, which are automatically generated in the P1 system (electronic platform of public services in the field of health care) in tranches according to the order of vaccination (for a specific age, professional, etc.). Doctors may also, in some instances, issue an individual e-referral for the patient. The vaccination appointment process is based on a central e-registration system that integrates individual admission schedules for individual vaccination points. In order to make an appointment, the patient may use: a special Helpline, make an appointment electronically through the Internet Patient Account (available at patient.gov.pl), by text message to the number 664 908 556, via the facility where the patient was issued e-referral or directly at the vaccination point. The patient receives confirmation and reminder about the first and second visit via SMS. The patient also receives a vaccination certificate enabling them to take advantage of the amenities. (7)

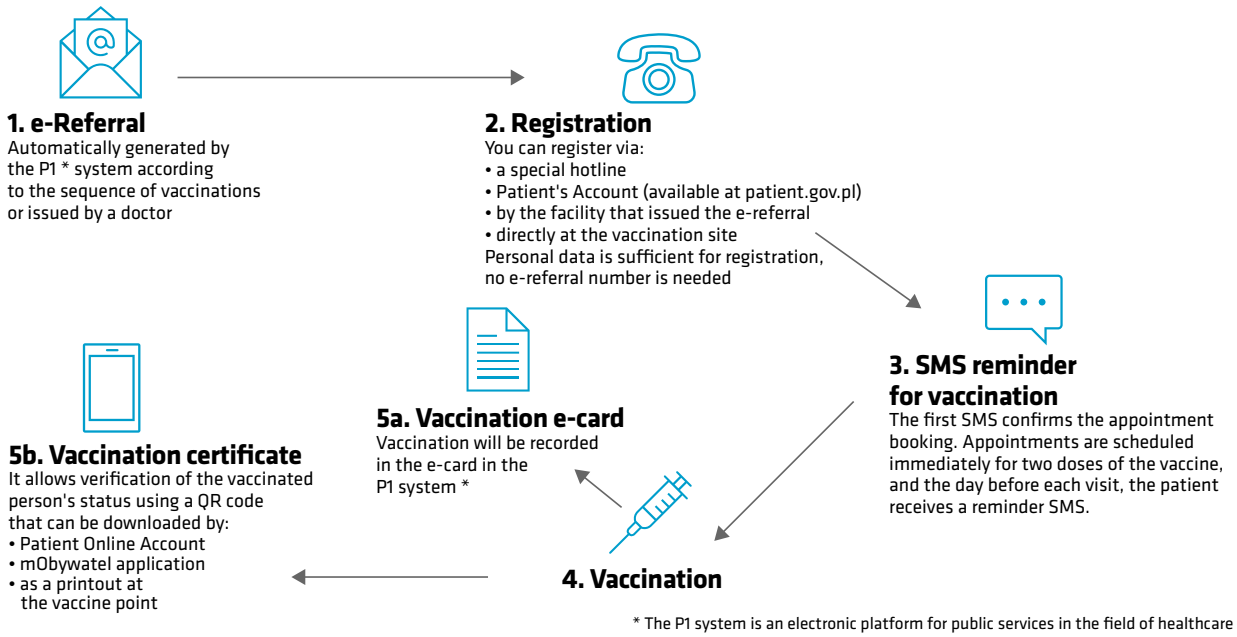

Figure 8. Vaccination course from the patient's point of view

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A strategy to promote vaccination against COVID-19. The role of primary care physicians, medical services, including nurses, in patient's education and activities for high immunization coverage

In the health policy of European societies, immunization is the most effective form of infectious disease prevention. The correct implementation of immunoprophylaxis depends mainly on the education of persons subject to vaccination, which should be carried out by medical personnel of various specialties, including nurses performing vaccinations. It is also extremely important to educate medical personnel and provide physicians with the necessary tools so that they can, in turn, effectively inform patients.

The main aim of these activities is to convince patients to join the COVID-19 vaccination program based on reliable and credible information. Thus, the constant development of the COVID-19 vaccination program in Poland, in line with the trends of many European countries, justifies the need for constant education. This requires from the medical staff – the doctor and nurse – updated knowledge about vaccinations, communication skills, and building a climate of trust in relationships with patients under care. The basic assumption of education should be its realization as a process of organized action, the result of which is gaining the competence of the educated person to make effective decisions in the field of vaccination.

The assumptions of this program are:

1. Education of medical personnel on vaccination (e.g., vaccination procedures, instructions on possible complications).

2. Educational activities of medical personnel have a decisive impact on changing patients' attitudes and overcoming barriers related to the lack of acceptance of vaccinations.

3. Effective implementation of education by medical personnel requires continuous professional development and personal development (training, webinars, handouts, a dedicated platform for medics, mobile application).

4. The interdisciplinary nature of education may be the desired direction in developing a vaccination program.

A wide variety of tools and materials can be used in carrying out an educational program. Communications to patients should emphasize that immunization has many individual and social benefits. First of all, they prevent contracting COVID-19 and often fatal complications. They contribute to the development of population immunity and generate savings on social and health benefits and the health care system by reducing the number of medical visits and expenses incurred on hospitalization. Thus, they improve family and social life quality, preventing exclusion due to illness and its consequences.

Communications and materials for doctors and nurses could include messages for healthcare professionals about COVID-19 vaccines based on current clinical trial results and reports. In addition, the following materials would be useful: educational materials for facility staff on how to deal with vaccine-negative patients and patient information such as vaccine videos, and a COVID-19 Vaccination Guide (electronic and printed) detailing each of these vaccines and giving answers to frequently asked questions from patients about immunization.

The use of new technologies as part of the educational program may include social media (dedicated profile on Facebook, Twitter, Instagram, YouTube, TikTok), chatbots for medical staff and patients, as well as creating an application for patients informing them about the latest vaccination reports, which also it will perform motivational functions, e.g., show the vaccination rate in the area where the user is (similar ProteGO safe application).

It seems that the model of vaccination promotion against COVID-19 should be based on effective and long-term activities carried out by government institutions with the support of non-governmental organizations and scientific societies, as well as on direct cooperation with patients who can inform the local community about vaccinations and encourage them to their implementation.

Recommendations

Education of medical personnel

Healthcare professionals are among the most important groups to the success of educational campaigns to promote vaccination against COVID-19. On the one hand, doctors and nurses are the main source of information for patients on vaccination, and most patients decide to vaccinate after obtaining a medical or nursing recommendation. On the other hand, as an infectious disease transmitted mainly by airborne droplets, coronavirus can be a serious epidemiological and organizational problem in healthcare facilities.

The increase in the number of COVID-19 cases among medical personnel not only increases the transmission of the disease (both among employees and among patients), but it can also be a source of organizational problems related to the need to deal with staff shortages. Only vaccination provides fully effective protection against COVID-19 (both for staff and patients). At the same time, the use of personal protective equipment, compliance with sanitary and hygienic procedures, although undoubtedly important, may turn out to be insufficient. Therefore, the overriding goal of preventing the spread of COVID-19 is to reduce the incidence of diseases in groups at high risk of complications. Vaccinating healthcare staff against the coronavirus is one way to protect these most vulnerable groups of patients.

Due to contact with sick people or with infectious biological material, healthcare personnel is at high risk of contracting COVID-19, which can be prevented by vaccination. Staff can also be a source of infection for patients (in large part of patients at high risk of complications) and colleagues. Outbreaks of infectious diseases, including coronavirus outbreaks in healthcare facilities, can have serious consequences: financial (the cost of managing an outbreak among patients, including temporary suspension of service activities, absenteeism, staff shortages, the need to organize replacements), image (loss of patient confidence) and legal (claims for damages).

Promotion of vaccination among medical workers against COVID-19 should, in particular, include educational campaigns on vaccination against COVID-19 (lectures, brochures, newsletters distributed by e-mail as well as in a traditional way, posters) presenting the risk of disease and complications among staff and patients, and describing the vaccines against COVID-19 themselves (efficacy, safety, differences between the available preparations). Another important element of vaccination promotion among medical personnel is facilitating access to vaccinations in the workplace, including free vaccines for staff, recommending vaccination against COVID-19 to all people working in health care facilities (both who have direct contact with the patient and technical and administrative workers), vaccinations in a place and time convenient for employees, and readily available information on this subject. One may also find it helpful to motivate people to vaccinate by, for example, vaccinating health practitioners and/or other local opinion leaders, an administrative requirement to vaccinate for a job, or financial incentives.

The level of vaccination against influenza among medical personnel depends on many factors, such as occupation (doctors are vaccinated more often than nurses), specia-

lization (most often vaccinations are performed by pediatricians and family doctors, and least often – by surgeons), work experience (more often vaccinations are performed by employees aged over 60), and the place of work (vaccination is more often performed by inpatient rather than outpatient care workers). These factors show that the vaccination promotion campaign should, in the first place, be addressed to the most skeptical groups of medical personnel.

Education of patients

The recommendations and actions specified in Poland in the National Immunization Program seem justified, including:

1. Creation of a knowledge base for patients – in order to implement a responsible information policy, it is necessary to create a reliable and widely available knowledge platform where citizens will find all the information required on vaccination against COVID-19 – both theoretical and practical.

2. Creation of FAQ – a section of frequently asked questions. The formula of questions and answers will provide information as closely as possible to people's experience and translate procedures and instructions into everyday situations.

3. Automating the information process for patients. In more individual cases, citizens will contact the hotline run by specialists from the National Health Fund.

4. Key participation of experts – experts (scientists, medics, epidemiologists) will play an important role in shaping the information policy. They are a valuable source of knowledge and analyzes that allow rulers to make responsible decisions, but also play an extremely important role in the field of social education.

5. Information campaign in the media and on the Internet. Additionally, it is worth considering the use of new technologies (mobile applications, robots collecting up-to-date information and transmitting it to citizens).

6. Motivational incentives and facilities for vaccinated people, for example:

- the vaccinated person will be able to count on faster service in health care facilities; such person should be treated as if they performed a coronavirus test and it turned out negative
- release from the sanitary regime
- partial release from quarantine. If the person we live with (a parent, a spouse, or a child) becomes infected with coronavirus, the vaccinated people living with them will not be quarantined.
- when there will be restrictions on quarantine in the country after returning from abroad vaccinated people will be released from this obligation.

Glossary

Amantadine: an antiviral drug that stops the multiplication of the virus (mainly influenza)

Episome: a small piece of DNA that remains independent of genomic DNA

Etiological factor: pcauses the formation of the disease

DNA: deoxyribonucleic acid in which human genetic information such as eye or hair color is stored. It is stored in the nucleus of each cell

Microbes: Collective name for organisms that can be observed under a microscope

Epidemic: Increased incidence of an infectious disease in an area

Genome: the entire genetic material of an organism

Low molecular weight heparin: a substance that inhibits blood clotting, used in medicine for anticoagulant purposes

Heterogeneity: non-homogeneity, diversity

Immunogenicity: a property of a substance that allows it to trigger an immune response against itself

Isolation: isolating a person or group of people who are sick or suspected of having an infectious disease. Used to prevent the transmission of diseases from one patient to another

Casuistic: based on cases or examples

Drug: a substance that inhibits the symptoms and development of the disease by modifying physiological processes

Lymphocytes: cells of the immune system that provide a precise response to infections

mRNA: messenger RNA: ribonucleic acid (RNA) serving as a template for the formation of proteins by cells

Nucleotides: organic chemical compounds that are the basic building blocks of nucleic acids (DNA and RNA)

Plasma: the basic fluid component of blood that forms the environment for blood cells and other blood components

Pandemic: A larger-scale infectious disease epidemic that has spread to many continents and even the world.

Pathogenicity: ability to initiate disease

Medicinal product: A substance or mixture of substances with properties to prevent or treat disease in humans or animals

Antibodies (immunoglobulins): proteins that recognize and bind to things that are foreign to the body (e.g., bacteria) and allow them to be eliminated by the immune system. The most common type of antibody is IgG

Remdesivir: an antiviral medicine that inhibits the multiplication of viruses which genetic material is RNA

RNA: ribonucleic acid, the second type of nucleic acid after DNA, also carrying genetic information. In humans, it plays a 'helper' role for DNA but is the only genetic material for some viruses.

SARSTer: a project investigating the effectiveness of various types of COVID-19 therapies used in Poland, implemented by the Polish Society of Epidemiologists and Doctors of Infectious Diseases

Transduction: an introduction of the external genetic material into a cell by a virus

Protective vaccination: administration of an infectious disease vaccine for the purpose of artificial immunization against this disease

Oxygen therapy: a treatment method that consists of increasing the concentration of oxygen in the inhaled air

Immune system: is responsible for how the immune mechanisms work in the body

Virus (Latin: virus, poison): particles containing only one type of DNA or RNA nucleic acid that reproduce by infecting living cells

Cold chain: all activities aimed at the maintenance and monitoring of storage, transport, and distribution conditions in order to maintain the durability and effectiveness of the product

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