and systemic inflammation. The role of pro-inflammatory cytokines in the development of endothelial dysfunction, remodeling of the myocardium and the progression of CHF is noted. An independent factor of pathogenetic changes in the development of CHF is hypoestrogeny in postmenopause. Mechanisms of activation of pressor systems in conditions of estrogen deficiency and mediated effects are presented, including molecular mechanisms of connective tissue dysmetabolism, cardiohemodynamic consequences and their interrelationship. Common links were found in the pathogenesis of hypertension, CHF and processes accompanying postmenopause. The pro-inflammatory signaling cascades involved and activated in the mechanisms of CHF formation in postmenopausal women, in particular, with the participation of interleukin ST2, osteoprotegerin, are described in detail. The importance of hypoestrogenia in the activation of pro-inflammatory mechanisms with the development of osteodysmetabolism, myocardial fibrosis and remodeling and their relationship through the prism of systemic inflammation is substantiated. Potential early markers of the development of CHF are presented, and possible directions of therapeutic influence are indicated.

Conclusions. The review systematizes modern ideas about the pathogenetic mechanisms of the development of CHF in postmenopausal women against the background of hypertension, which determines the prospects for solving the problematic issues of diagnosis and treatment of CHF.

Key words: chronic heart failure, arterial hypertension, postmenopause, pathogenetic mechanisms.

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PROGRESS AND PROBLEMS OF VACCINATION AGAINST CORONAVIRUS INFECTION COVID-19

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This article is devoted to the main achievements and problems associated with vaccination against the COVID-19 coronavirus infection. This problem remains relevant as the coronavirus infection is a highly contagious disease that spreads widely worldwide. Vaccination is currently the most effective way to prevent the occurrence of a coronavirus infection or its severe consequences. The difficulty is that vaccination against COVID-19 is effective only when the antigenic structure of the circulating virus matches the antigens contained in the vaccine (or, in the case of RNA and DNA vaccines, the viral antigens programmed into the genetic code). However, the coronavirus is constantly changing its genetic structure, resulting in new strains that differ from circulating variants and have pandemic potential, against which existing vaccines may be ineffective. This study aimed to determine the main approaches to creating a vaccine's advantages and disadvantages of vaccination through bibliographic analysis. A literature search was conducted among published peer-reviewed articles, books, textbooks, and monographs. The obtained data were systematized and processed. Attention was paid to the main approaches to creating vaccines against COVID-19; the problems of immunological imprinting and antibody-dependent enhancement of infection were assessed. It was established that strategies based on the use of DNA and RNA vaccines to solve the problem of their low immunogenicity in humans are a real alternative for the future development of medicine in the prevention of infectious diseases.

Key words: *vaccination, coronavirus infection, COVID-19, vaccine, immunological imprinting, antibody-dependent enhancement of infection.*

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Introduction. Coronavirus infection is a highly contagious infectious disease that spreads widely worldwide [1, 2]. This disease leads to a violation of the general homeostasis of the body, acting on it as a vital stress factor, which leads to changes not only in the organs of the respiratory system but also in the entire body as a whole, and requires the search for the most optimal methods of treatment and prevention [3-6]. Currently, vaccination is considered the most effective way to prevent coronavirus infection or its severe consequences. The difficulty is that vaccination against COVID-19 is effective when the antigenic structure of the circulating virus matches the antigens contained in the vaccine (or, in the case of RNA and DNA vaccines, the viral antigens programmed into the genetic code). However, the coronavirus is constantly changing, resulting in new strains that differ from circulating variants and have pandemic potential, against which existing vaccines may be ineffective [7]. In addition, after vaccination, a person, having entered the state of the infectious process, becomes more vulnerable to the disease for some time [8].

When developing vaccines and carrying out mass vaccinations, one should also consider the possible prospect of complications due to antigenic imprinting and antibody-dependent enhancement of infection (ADE) [9, 10].

The phenomenon of antibody-dependent enhancement of infection must be taken into account when developing vaccines against viruses that usually replicate in macrophages, inducing the production of a large number of antibodies with a poor ability to neutralize homologous viruses and capable of persistent infection [11]. Complications associated with these phenomena may appear many years after the previous vaccination or epidemic. Vaccination carried out without taking them into account can complicate the epidemic process or cause the development of an epidemic of a closely related virus in those regions where this virus and another against which the vaccination was carried out circulate simultaneously. Therefore, it would be more correct to speak not about total vaccination but selective vaccination based on monitoring of immunological status. Individual diagnosis of the immune status of a specific person at the time of vaccination makes it possible to significantly reduce the likelihood of side effects and mortality from complications in general.

Thus, the study of the phenomenon of antibody-dependent enhancement of infection in the process of development, preclinical and clinical research of vaccines, and diagnosis of immune status during mass vaccinations are necessary conditions for the effective and safe use of immunoprophylaxis against COVID-19.

The aim of the study. Identification of the main approaches to creating vaccines, advantages, and disadvantages of vaccination through bibliographic analysis.

Object and research methods. This bibliographic analysis is based on published peer-reviewed articles, books, textbooks, and monographs. For this systematic review, a literature search (relating to the study of the main approaches to creating vaccines, the advantages and disadvantages of vaccination) was carried out on the worldwide Internet, domestic and foreign sources of literature, the scientific and electronic library of the Poltava State Medical University using the following keywords: "virus", "coronavirus infection", "COVID-19", "entrance gate of infection", "vaccination", "immune system", "phenomena of immunological imprinting", "antibody-dependent enhancement of infection". The search period covered the period from 2011 to 2022; some valuable data from earlier years are included in the review, as these literary sources have a significant scientific value.

The following inclusion and exclusion criteria were used:

- inclusion criteria: original articles published in journals and conference proceedings, books, textbooks, monographs; publication language: Ukrainian, English;
- exclusion criteria: reviews, case studies, editorials, letters, etc., not reviewed for review; a language of publication: others.

Research results and their discussion. Like all medicinal products, vaccines against COVID-19 are first tested in the laboratory (for example, studies of their pharmaceutical quality and studies related to verification of effectiveness in laboratory tests and animals) [12, 13]. Vaccines are then tested on human volunteers in studies called clinical trials. These tests help confirm the effectiveness of vaccines and, importantly, assess their safety and protective effectiveness.

The main approaches to creating a vaccine against COVID-19:

1. Vaccines based on a weakened virus. This is how vaccinations against measles, mumps, rubella, and chicken pox work. The principle is simple. When the human virus is forcibly "transplanted" into an animal cell culture, it will begin to mutate. After each cycle of infection, the virus will better adapt to the host's body and, at the same time, become less pathogenic. A positive effect is that the weakened virus causes a persistent immune response in a person for a long time. Disadvantages: in the process of creating a live vaccine, the virus can mutate, and it is difficult to predict this process.

2. Inactivated vaccines. Such vaccines include viruses that cannot infect cells. A similar principle is the basis of vaccinations against poliomyelitis and whooping cough. The creation process is when the virus is heated and irradiated with ions and disinfectants. In fact, they kill. But a "dead" virus can also trigger an immune response. Safety is a positive effect. Disadvantages: the effect is short-lived and not as strong as in the case of live vaccines.

3. Vector vaccines. Completely different viruses are used as a basis, which serves as a vector (or, more simply, a vehicle) for delivering the desired virus to the cell. A small gene of the selected virus is inserted into the vector virus. As a result, proteins-antigens of the desired virus appear in the envelopes of harmless viruses. Once inside the human body, they provoke an immune response, as effective as "live" ones, but they protect against virus mutation, so they are much safer. The disadvantages of this type of vaccine can be considered their lack of research. There have been attempts to develop such vaccines for HIV, Ebola, and influenza, but none have been approved for humans.

4. Protein vaccines. They are produced based on antigen proteins and provoke an immune response entering the human body. In fact, the prototype of such a vaccine was already used in practice when severe patients with a coronavirus infection were transfused with the plasma of convalescents. Such a vaccine is considered the safest; it can be quickly produced. But it is complicated to get enough of the same proteins, and the immunity will likely not be so stable. According to the WHO, no protein vaccine has yet crossed the threshold of preclinical trials. And even if successful, the production of such a drug will be too expensive. Nevertheless, the safety of this vaccine and the possibility of the rapid output are positive. Disadvantages: difficulties in obtaining a large number of antigen proteins, short-lived effect, high price.

5. Vaccines based on DNA and RNA nucleic acids. The DNA vaccine contains a circular DNA molecule (plasmid), which includes "instructions" for creating a viral protein. Once inside the human body, circular DNA becomes part of the genome and reprograms the host organism's cells, triggering the antigen production process. The high efficiency of this vaccine can be noted among the advantages. However, the disadvantages are insufficient to study; the risk of integrating foreign DNA into the host's genome can cause severe mutations and new diseases. So far, only one vaccine of this type is used – vaccination against the Zika virus (Flaviviridae family) for horses. In fact, DNA vaccines are artificial viruses [14].

The principle of action of the RNA vaccine is different. It contains a viral molecule – matrix RNA (mRNA). This molecule is a "template" from which the viral protein is directly read. The hypothesis is based on the fact that this mRNA, having entered the human body, causes protein synthesis, is recognized by the immune system, and includes protective forces – it starts the production of antibodies.

Using recombinant DNA and RNA is still a relatively new way to create vaccines. Despite the failures of clinical trials of DNA vaccines and the fact that many RNA vaccines are still under development, these technologies have great potential. First of all, this is due to the simplicity and versatility of the creation of plasmids/RNA and the technological process, as a rule, based on the cultivation of E. coli. However, in recent years, the revival of interest in DNA and RNA vaccines has been associated with the success of the use of plasmids and RNA in gene therapy, as well as the creation of more effective genetic constructs, the improvement of delivery technologies, and the emergence of new promising technologies (iDNA, PPLAV, self-amplifying RNA) **(fig.)** [15].

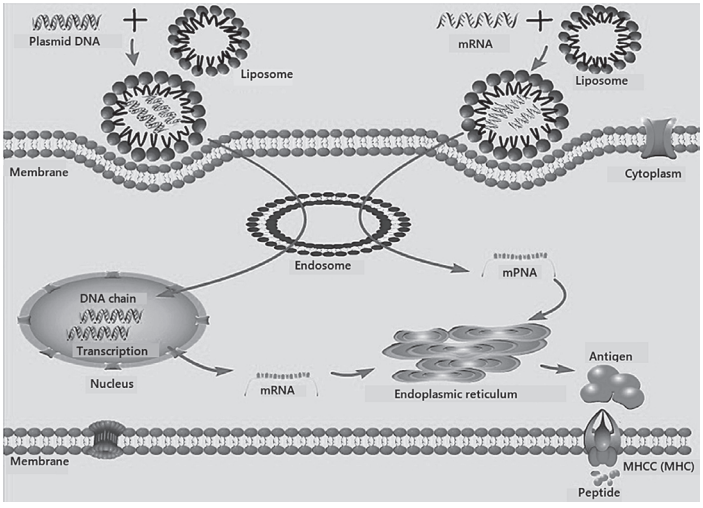

Figure – Schematic representation of the mechanism of action of DNA and RNA vaccines.

Transcription is the process of RNA synthesis using DNA as a matrix, which occurs in all living cells; in other words, it is the transfer of genetic information from DNA to RNA.

Processing, co-transcriptional modification, and post-transcriptional modification are the maturation of the newly synthesized RNA molecule to its functionally active form.

Gene expression is a process in which the genetic information of genes (nucleotide sequence) is used to synthesize a functional product: protein or RNA.

The translation synthesizes proteins from amino acids, which is catalyzed by a ribosome on a template RNA (mRNA) matrix. The translation is one of the stages of protein biosynthesis, which, in turn, is part of the process of gene expression.

Post-translational modification (PTM) is a chemical modification of a protein after its translation. This is one of most proteins' last stages of the protein biosynthesis process.

The major histocompatibility complex (MHCC) is a group of closely linked genes of the 6th chromosome, encoding mainly immunologically significant molecules of three classes (MHC antigens of classes I, II, III). It was discovered during the work on allogeneic transplantation MNS antigens got their name thanks to their ability to cause a transplant rejection reaction when these antigens of the donor and the recipient do not match.

DNA vaccines and RNA vaccines work differently. At the stages between immunization with a DNA template and expression of the target antigen, the DNA must cross the cytoplasmic membrane and nuclear envelope of the cell, be transcribed into mRNA and move back into the cytoplasm to initiate translation.

Immunological imprinting and antibody-dependent enhancement of infection:

1. Phenomena of immunological imprinting and antibody-dependent enhancement of infection. In the early 1950s, Davenport F.M., etc. unexpectedly discovered that the blood serum of people older than 28 years who got sick with influenza before the 1950s, that is, before mass vaccination of the population against influenza, contained low titers of antibodies to the virus serosubtype A (H1N1), used in the preparation of the vaccine, but an increased content of antibodies to the influenza virus that circulated epidemically earlier [16]. The most significant number of people with this distribution of titers of specific antibodies is attributed to the age group of 35-38 years, which survived the "Spanish" flu pandemic in 1918. Similar results were later obtained for influenza virus serotype B and its antigenic variants. To explain the immunological phenomenon, Davenport F.M., etc. suggested that during the first infection with the influenza virus, even in childhood, the immune system focuses on some dominant an-

tigen among the circulating strains of the virus. Further exposure to influenza viruses, antigenically related to the previous one, causes a rise in the level of antibodies not to their antigens but to antigens of the strain of the virus that caused the first infection.

The phenomenon of immunological imprinting was first described by Francis (1953). Its essence is that each antigen is represented by several epitopes (areas of the antigen that differ from each other). In response to antigen penetration into the body, chemically heterogeneous antibodies are formed that differ in their specificity. When a virus that has some, even minimal, similarity to the previous pathogen enters the body, the body does not see it, and a previously familiar antigen produces antibodies. That is, upon repeated contact of the immune system with a pathogenic microorganism and/or vaccine antigens, the differences between the old version of the antigen epitope and its new version may not be noticed by the immune system. Then in the process of antigenic stimulation, memory B cells are the first to be activated, which "remembered" the previous antigen. Next, they differentiate into plasma cells that produce antibodies against this antigen, although the immune system does not come into contact with it. The antibodies that were formed cannot effectively neutralize the infectious disease's causative agent. The production of antibodies specific to the new pathogen is inhibited due to the suppression of "naive" B-cells by activated memory B-cells. It leads to an aggravation of the infectious process (antibodies to the new pathogen are not produced) and a more accessible virus spread in human populations.

The forgotten immunological phenomenon had to be remembered by researchers not related to the vaccine business when they began to study the consequences of mass vaccinations imposed on the population by the WHO and pharmaceutical corporations under the pretext of averting the transition of the swine flu pandemic to the "Spanish flu".

Four epidemiological studies of the distribution of the pH1N1 pandemic influenza virus carried out in British Columbia (Canada) in 2009 revealed an increased risk of developing influenza in persons previously vaccinated with the trivalent activated influenza vaccine (TIV), which was used for seasonal prevention the flu The authors associate it with the phenomena of antigenic imprinting, antibody-induced enhancement of infection and other, as yet unknown factors, on the need to study which they draw the attention of other researchers.

Due to antigenic imprinting, multiple vaccinations and previous flu illnesses lead to specific low-avid antibodies that cross-react with flu viruses but do not have a protective effect circulate in a person's blood serum.

Antibody avidity or functional affinity is the strength of the bond between an antibody and an antigen.

For example, according to Monsalvo A.C. et al., in deceased middle-aged patients and those with severe influenza, specific low-avid antibodies (IgG) formed immune complexes with the virus, which were deposited in the lung tissue and caused pulmonary edema, peribronchial mononuclear cell infiltration and, as a result, – hypoxemia. The higher the titer of such anti-influenza antibodies, the more severe the disease was. No neutralizing pH1N1 antibodies were detected in the patients, and influenza virus was found in lung tissue in high titers.

The role of antigenic imprinting in epidemic, infectious and post-vaccination processes is as follows:

1) antigenic imprinting, which developed in response to an infectious or vaccine process (or their combination), accompanies a person throughout his life and determines the reaction of the immune system in infectious processes and the structure of population morbidity during epidemics (pandemics) caused by the same causative agent of an infectious disease;

2) in case of complete antigenic coincidence of the new causative agent of the disease with the causative agent that formed memory B cells in the past, these cells produce specific antibodies that have a protective effect, and the development of the infectious process may not occur. The retrospective epidemiological analysis will reveal age groups of the population that are little involved in the epidemic (pandemic);

3) if there is no antigenic match between the pathogens of the infectious disease that caused the first and subsequent (second) infectious processes, but the antigenic distance between them is so tiny that the immune system cannot distinguish the strain (serosubtype) of the pathogen of the infectious disease from the one that formed B -memory cells during the first infectious process, then plasma cells synthesize antibodies specific to the strain (serosubtype) of the causative agent of the infectious disease that spread during the pandemic when memory B cells were formed. As a result, the immune system "works off the wrong target", and the protective effect is absent. A retrospective epidemiological analysis will reveal the age groups of the population that suffered the most significant losses in this pandemic;

4) during the development of the phenomenon of antigenic imprinting in response to the causative agent of an infectious disease or vaccination, in addition to antibodies specific for the antigen first recognized by the human immune system, antibodies will be formed that cross-react with pathogens of strains close in antigenic structure, but have a low affinity to them avidity and are capable of intensifying the infectious process (the effect of antibody-dependent enhancement of infection);

5) if the antigenic distance between the strain (serosubtype) of the causative agent of infectious disease, which caused an infectious process in the past and which caused a new infectious process, is so great that the immune system recognizes it, then the immune response can be directed against this strain (serosubtype). At the same time, new memory B-cells will be formed, which will react with the causative agent of the disease as described above during further outbreaks of the same infectious disease;

6) when a person is repeatedly infected with serosubtypes of the causative agent capable of inducing the development of the antigenic imprinting phenomenon, the serology of the disease is distorted, and establishing the subtype of the causative agent is possible by molecular genetic methods;

7) with the development of the phenomenon of antigenic imprinting, multiple vaccinations and transferred infectious diseases make the responses of the immune system to re-infection with the same pathogens of the infectious disease less predictable: from immunity that

prevents the development of the infectious disease to its weighting with fatal outcomes in patients.

Post-vaccination complications associated with antigenic imprinting may appear decades after its implementation. Vaccination with the same vaccine can give opposite results in population groups with different epidemic histories and previously repeatedly vaccinated with the same vaccine.

2. The phenomenon of antibody-dependent enhancement of infection. In the early 1970s, Western researchers discovered antibody-dependent enhancement of infection (ADE) during the development of an epidemic process [17]. The presence of antibodies in the blood serum of a convalescent, remaining after mild cases of Dengue fever, upon re-infection with DENV of a different serotype leads to a severe course of the disease.

The essence of the phenomenon of antibody-dependent enhancement of infection is the enhancement of the infectious process by antibodies specific to the causative agent of the infectious disease. Such antibodies form complexes with the causative agent of an infectious disease or its toxin. With the help of the Fc-fragment, the antibodies interact either with the Fc-fragment-specific receptor (Fc-receptor, FcR) or with the complement receptor (complement receptor, CR) on the surface of phagocytic cells. Intensification of the infectious process occurs due to the reproduction of the microorganism in phagocytic cells.

Fc-fragment of Ig (fragment of crystallizable immunoglobulin, fragment crystallizable region, Fc-region) is the final part of the immunoglobulin molecule that interacts with the Fc-receptor on the cell surface and with some proteins of the complement system. Fc-fragments of antibodies of the same class are conservative.

Fc receptors are molecules, each recognizing immunoglobulin of one or more related isotypes. Receptors of this type are part of the immunoglobulin superfamily. Fc-receptors for immunoglobulins are on the surface of mononuclear leukocytes, neutrophils, normal killer cells, eosinophils, basophils, and mast cells. Interacting with the Fc region of immunoglobulins of different isotypes, these receptors stimulate, for example, phagocytosis, antitumor cytotoxic activity, and degranulation of mast cells.

The interaction of the "Antibody – infectious agent" complex with Fc receptors and complement receptors of monocytes/macrophages helps to change the tropism of the infectious agent during the infectious process.

Example 1. The severe acute respiratory syndrome coronavirus (SARS-CoV) does not infect human monocytes/macrophages at the initial stage of the infectious process because there are no receptors on the surface of these cells that it can recognize [18]. However, antibodies to the spike of the coronavirus envelope, produced by the human immune system in response to infection, contribute to the penetration of SARS-CoV-2 into monocytes and macrophages through the Fc receptor and complicate the course of the disease.

Example 2. Parvovirus B19 (parvovirus B19, B19V) in vitro shows a strict tropism towards erythroid progenitor cells and causes their death. The clinical manifestations of parvovirus infection are usually consistent with these ideas about the specificity of the virus.

In healthy children, the infection often manifests itself only in the form of benign infectious erythema. In adult patients, skin lesions are less common, but there are cases of acute and chronic cardiomyopathy with a high content of parvovirus B19V DNA in the endothelial cells of the myocardium, which contradicts the results of experiments performed in vitro, which showed the impossibility of such an infection. Kietzell K. and others found that the absorption of B19V by endothelial cells is based on a mechanism that uses antibody-dependent enhancement of infection. Antibodies specific to B19V, forming a complex with the virus and interacting with the surface glycoprotein of the endothelium CD93 – the receptor for the temperature-sensitive complement factor C1q, increase its absorption by the endothelial cells of the myocardium almost 4000 times. The scientists above consider this mechanism the main one in developing myocardial lesions in parvovirus infection.

Antibody-dependent enhancement of infection complicates the course of an infectious disease caused by a closely related microorganism (or a microorganism of the same serocomplex) if cross-reacting antibodies are present in the patient's blood. The same problem was encountered by Japanese epidemiologists who discovered a severe course of Dengue fever in initially infected residents of the southern regions of Japan, endemic to Japanese encephalitis (Japanese encephalitis, JE), who traveled to areas of Southeast Asia endemic to Dengue fever. Up to 2% of such residents suffer from Japanese encephalitis during their lifetime and have neutralizing antibodies to its causative agent – the Japanese encephalitis virus [19]. Their number among people younger than 50 years is constantly increasing due to the implementation of various programs for vaccination of the population against Japanese encephalitis, thereby increasing the risk of hemorrhagic course of Dengue fever during primary infection with the Japanese encephalitis virus. Japanese encephalitis and Dengue viruses belong to the Flaviviridae family and share common epitopes.

The phenomenon of antibody-dependent enhancement of infection is most characteristic of infectious processes caused by viruses and has the following features:

a) they are usually replicated in macrophages;

b) induce the production of a large number of antibodies with cross-specificity and a low ability to neutralize homologous viruses;

c) are capable of persistent infection, characterized by prolonged viremia.

Antibody-dependent enhancement of infection can be a consequence of antigenic imprinting if low-avid antibodies that cross-react with dominant antigenic epitopes are formed during repeated infection in a person.

There is indirect evidence of the involvement of antibody-dependent enhancement of infection in the progression of tuberculosis infection and Ku-fever.

Antibody-dependent enhancement of infection can contribute to developing diseases that are usually considered somatic. Type 1 diabetes is associated with the destruction of β-cells of the pancreas, which synthesize insulin. Hereditary factors are considered the basis of the development of such pathology. In recent years, other causes of β-cell death have been clarified. Epidemiological studies of populations of people with a similar genetic profile made it possible to establish a close

relationship between genetic factors and environmental factors in the pathogenesis of type 1 diabetes.

Coxsackie virus type B (Coxsackie virus-B, CV-B), an enterovirus of the Picornaviridae family, is considered the primary candidate for such an external factor, according to epidemiological and experimental studies [20]. The human immune system easily recognizes this virus by its dominant antigen – structural protein VP4 (viral protein, VP). VP4 is located on the surface of the virion and protrudes from it in the form of a spike. It binds to receptors on the surface of target cells and directs the introduction of the virus into the cell. But antibodies to VP4 do not block the infection but start the mechanism of its antibody-dependent strengthening. Antibodies to VP4 bind CV-B, and the "Antibody-CV-B" complex formed interact on the surface of monocytes with CV-B and adenovirus receptors (Coxsackie virus and adenovirus receptor, CAR) and Fc receptors (FcγRII and FcγRIII). As a result, the "Antibody-CV-B" complex penetrates the cell, and the viral RNA is released into the cytoplasm and stimulates the synthesis of IFN-α. At the same time, CV-B reproduction occurs in the cell, and viral particles enter the blood, intensifying the infectious process.

Re-infection of CV-B in combination with the phenomenon of antibody-dependent enhancement of infection stimulates the non-physiological synthesis of IFN-α, which contributes to the development of autoimmune reactions against β-cells of the pancreas in patients genetically predisposed to the development of type I diabetes. At the same time, monocytes play the role of a "Trojan horse", spreading CV-B on β-cells of the pancreas.

Antibody-dependent enhancement of infection develops in two stages:

1. Extrinsic antibody-dependent enhancement of infection (extrinsic ADE, eADE) is a virus-specific antibody that forms a complex with the virus through the interaction of its Fc fragment with the Fc receptor (FcR) and/or with complement receptors (complement receptor, CR) on the surface of phagocytic cells, increases the spread of the virus on phagocytic cells.

2. Internal (intracellular) antibody-dependent enhancement of infection (intrinsic ADE, iADE) – "virus-specific antibody" complexes that interact with a phagocytic cell through Fc receptors and complement receptors, trigger signaling mechanisms that block its antiviral defense, and thereby contribute intracellular reproduction of the virus.

It is worth citing examples of some viral and bacterial infections accompanied by the antibody-dependent enhancement of infection: Ebola fever, hepatitis C, HIV/AIDS, tick-borne encephalitis, rabies, measles, an acute respiratory syndrome caused by a coronavirus, tuberculosis [21]. However, the most probable development of antibody-dependent strengthening of the infection is in persons who were previously vaccinated against viruses, pathogens of infectious diseases represented by the families: *Orthomyxoviridae, Paramyxoviridae, Rhabdoviridae, Coronaviridae, Retroviridae, Parvoviridae, Filoviridae, Flaviviridae, Togaviridae, Picornaviridae,* as well as pathogens of tuberculosis.

The phenomenon of antibody-dependent enhancement of infection develops against the background of sensitization caused by vaccination. Complications after vaccination, which arise as a result of antibody-dependent enhancement of infection, have not been the object of systematic research until now, so information about them is scattered. Nevertheless, the phenomenon of antibody-dependent enhancement of infection in a previously vaccinated person may be associated with insufficient immunization; with the features of the interaction of the causative agent of an infectious disease; with the human immune system; with the features of the epidemic focus in which vaccination is carried out.

The cause-and-effect relationship of antibody-dependent enhancement of infection with inadequate immunization is studied in detail using the examples of inactivated measles vaccine and inactivated vaccine against the respiratory syncytial virus (RSV). Both vaccines are obtained by inactivating viruses with formaldehyde [22]. In the early 1960s, after mass immunization of the population against measles with formalin-inactivated vaccines, cases of so-called atypical measles (severe measles) were noted among vaccinated people. Iankov I.D. etc., showed that the basis of its development is the phenomenon of FcR-ADE, which is caused by antibodies to hemagglutinin of the virus (surface protein H).

It was established that antibodies to antigenic proteins of measles and RSV viruses, inactivated by formaldehyde, have a reduced protective capacity compared to antibodies obtained against the same antigens of live vaccines. It is because antigenic proteins treated with formalin have an increased number of active carbonyl groups, leading to disruption of epitopes' tertiary structure.

Antibody-dependent enhancement of infection is a phenomenon characteristic of the interaction of the causative agent of an infectious disease with the human immune system. Suppose antibody-dependent enhancement of infection develops during the infectious process. In that case, there is reason to believe that the phenomenon will occur in vaccinated people and animals if they are infected with the virus against which they were vaccinated.

There are indicative results of experiments with vaccines developed for the specific prevention of retroviral infections in animals – infectious anemia in horses and immunodeficiency in cats. They also aimed to model HIV vaccination strategies. Although these experiments were performed in the 1990s, they have not yet aroused the interest of HIV vaccine developers.

Infectious anemia in horses is caused by the equine infectious anemia virus (EIAV) from the Retroviridae family. The disease has a non-cyclical nature and is manifested by fever, anorexia, and anemia syndromes; recovery does not occur [23]. Exacerbation of the disease infected with EIAV in vaccinated horses and ponies is indicative if antibodies induced by the vaccine's introduction were present in their serum. Issel C.J. etc. used viremia as a criterion for the severity of the disease and demonstrated that vaccination with an inactivated whole-virion vaccine could not prevent the development of viremia and clinical signs of the disease in an animal injected with a virulent strain of the virus.

Retrovirus, the causative agent of the feline immunodeficiency virus (FIV), after infection of cats vaccinated with the membrane recombinant protein of this virus, was detected in their blood even earlier than in unvaccinated animals [24]. In similar studies conducted

with various recombinant FIV vaccines, it was established that in response to vaccination, antibodies to the FIV membrane protein, poorly neutralizing the virus in vitro, are detected in the blood of animals. In vaccinated animals, the viral load was significantly higher than in non-vaccinated ones. As the titers of antibodies to the FIV core protein increased in cats, the clinical signs of the disease increased.

Similar results were obtained in experiments on humans to study the protective effect of the HIV vaccine, conducted in South Africa by Merck.

Indirect evidence of the development of antibody-dependent enhancement of infection during the tubercular process is well consistent with the observations of Noreiko B.V., who showed that in people vaccinated with the BCG vaccine (BCG, Bacillus Calmette-Gurin), secondary forms of tuberculosis are prone to progress with the development of such complications, as the destruction of lung tissue with bacterial secretion and bronchogenic dissemination (from dissemino – to scatter, – the spread of microbes or tumor cells from the primary focus throughout the body). However, from this point of view, the dissemination of the tuberculosis process was not considered by him since the phenomenon of antibody-dependent enhancement of infection is unknown to clinicians.

Wallace M.J. etc., in experiments on mice, established that antibodies to Japanese encephalitis virus in subneutralizing concentrations increase viremia and mortality among mice infected with Murray valley encephalitis virus (MVEV). Based on these data, they assumed that the phenomenon of antibody-dependent enhancement of infection might contribute to the replacement of one epidemic process by another. Therefore, the researchers believe that programs to vaccinate the population against the Japanese encephalitis virus in those areas where MVEV also circulates at the same time may contribute to the development of the Murray Valley encephalitis epidemic. In addition, later works discussed the association of previous Japanese encephalitis vaccination with severe dengue fever in Japanese residents.

Antibody-dependent enhancement of infection is a problem on the way to creating a new vaccine against coronavirus (for example (SARS-CoV). One of the most unpleasant features of coronaviruses is that many have the phenomenon of antibody-dependent enhancement of infection [25]. Like some other RNA viruses during reproduction (self-copying in the host cell), they make many mistakes, due to which the composition of proteins on the surface of the virus envelope can change significantly.

In practice, this can lead to sad consequences. For example, let's say that a person has passed the coronavirus without symptoms. Then he is vaccinated against the coronavirus – but it is far from a fact that the "vaccine" copy of the same coronavirus that entered his body later will be correctly "recognized" by immunity. Instead, an immediate, heightened immune response may begin, accompanied by inflammatory processes. At the same time, the concentration of antibodies after the introduction of the vaccine may not have time to reach the safe threshold necessary to neutralize the virus.

In this case, the presence of a person's immunity to the first type of coronavirus will make it easier for the second type of coronavirus to penetrate the body's cells. The problem is that the older relative SARS-CoV-2 (properly SARS) shows antibody-dependent amplification.

Back in 2011, a scientific paper was published in BMC Proceedings that showed this. The authors of Yip MS and others directly say: "Our data raise reasonable concerns regarding the use of the SARS-CoV vaccine in humans" [9].

In 2016, the same conclusions were repeated by another group of researchers: "The presence of antibody-dependent enhancement in SARS-CoV... indicates the benefit of increased caution when developing a vaccine against it" [16].

Four epidemiological studies of the spread of the so-called "swine" flu H1N1 virus in British Columbia (a province in western Canada) conducted in 2009 showed that mass vaccinations against the flu, carried out without taking into account the phenomenon of antigenic imprinting, may lead. Furthermore, it turned out that the risk of developing flu in persons previously vaccinated with trivalent inactivated influenza vaccine created based on H1N1 virus strains (trivalent inactivated influenza vaccine, TIV) is even greater than in persons not previously vaccinated.

Conclusions. Thus, approaches based on the use of DNA and RNA vaccines in case to solve the problem of their low immunogenicity in humans are a real alternative for the future development of medicine in the prevention of infectious diseases.

When developing vaccines and carrying out mass vaccinations, it is necessary to consider the possibility of complications associated with the phenomena of antigenic imprinting and antibody-dependent enhancement of infection. Complications underlying these phenomena may appear decades after the previous vaccination or epidemic. In addition, the vaccination itself, carried out without taking them into account, can complicate the epidemic process or cause the development of an epidemic of a closely related virus in those areas where this virus and the one against which the vaccination was carried out circulate at the same time.

Prospects for further research. In the future, it is planned to continue work in the direction of evaluating the positive and negative consequences of vaccination because in the pursuit of a scientific breakthrough and in the desire to save all humanity from a new infection, one can forget about another perspective. The world may be plunged into a new pandemic called "Vaccination Consequences".

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ПРОГРЕС І ПРОБЛЕМИ ВАКЦИНАЦІЇ ПРОТИ КОРОНАВІРУСНОЇ ІНФЕКЦІЇ COVID-19

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Резюме. Пандемія коронавірусної інфекції, спричиненої COVID-19 є актуальною проблемою сьогодення. Тому пошук оптимальних та безпечних шляхів профілактики виникнення цієї інфекції або важких її наслідків становить значний інтерес для науковців та клініцистів по всьому світу. Найбільш ефективним шляхом для цього є вакцинація, яка на жаль, у випадку COVID-19 є ефективною лише тоді, коли антигенна структура циркулюючого вірусу відповідає антигенам, що містяться у вакцині. Однак, поява нових штамів, внаслідок здатності коронавірусу постійно змінюватися, які відрізняються від циркулюючих варіантів і володіють пандемічним потенціалом призводить до неефективності раніше запропонованих вакцин. Тому метою даної роботи було визначення основних підходів для створення вакцин, переваг та недоліків вакцинації шляхом проведення бібліографічного аналізу сучасних наукових публікацій. Було охарактеризовано основні підходи в створенні вакцини від COVID-19, зокрема: вакцини на основі ослабленого вірусу, інактивовані вакцини, векторні вакцини, білкові вакцини, вакцини на основі нуклеїнових кислот. Описано основні переваги та недоліки, кожного із запропонованих варіантів. Значну увагу приділено питанню імунологічного імпринтінгу і антитілозалежного посилення інфекції. Проведено детальний аналіз даних феноменів та описано їх вплив на ефективність різних вакцин. Було встановлено, що застосування ДНК і РНК-вакцин, за умови вирішення проблеми їх низької імуногенності у людей, є реальною альтернативою для майбутнього розвитку медицини в питаннях профілактики інфекційних захворювань. Доведено важливість враховування можливості появи ускладнень, пов'язаних з феноменами антигенного імпринтінгу і антитілозалежного посилення інфекції при розробці вакцин і проведенні масових вакцинацій. Оскільки, ускладнення, в основі яких лежать ці феномени, можуть проявитися через десятки років після попередньої вакцинації або епідемії. Крім того, сама вакцинація, проведена без їх урахування, здатна ускладнювати епідемічний процес або викликати розвиток епідемії близькоспорідненого вірусу в тих районах, де одночасно циркулюють цей вірус і той, проти якого вакцинація проводилася**.**

Ключові слова: вакцинація, коронавірусна інфекція, COVID-19, вакцина, імунологічний імпринтінг, антитілозалежне посилення інфекції.

PROGRESS AND PROBLEMS OF VACCINATION AGAINST CORONAVIRUS INFECTION COVID-19

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Abstract. The pandemic of coronavirus infection caused by COVID-19 is an urgent problem today. Therefore, the search for optimal and safe ways to prevent the occurrence of this infection or its severe consequences is of great