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VACCINOLOGY: HISTORICAL MILESTONES, ACHIEVEMENTS AND PROBLEMS

Svitlana Kalinichenko, Artur Martynov, Valery Minukhin , Tetyana Kordon, Petro Ovetchin

Mechnikov Institute of Microbiology and Immunology of the National Academy of Medical Sciences of Ukraine

Vaccines are immunobiological preparations from bacteria, viruses, or their vital products, which are used for active immunization of people and animals for specific prevention of infectious diseases. The widespread use of vaccines ensures the formation of acquired active immunity to the corresponding infections, which can cause infectious diseases and pandemic outbreaks. That is why, in the modern world, vaccination is one of the main methods of preventing epidemics.

Historical background. More than 3000 years later, in China, there was a method of protection against smallpox by transferring the contents of the pustules of patients to healthy people. Then, this method began to be used in India (in any case, in 900, Arab scientists wrote about variolation), Asia Minor Africa, and Europe. In Europe, vaccination was introduced at the end of the 18th century by Edward Jenner (1749 - 1823), who is still considered the "father" of vaccinology. The impetus for this was a conversation between the scientist and a peasant woman who sold milk.

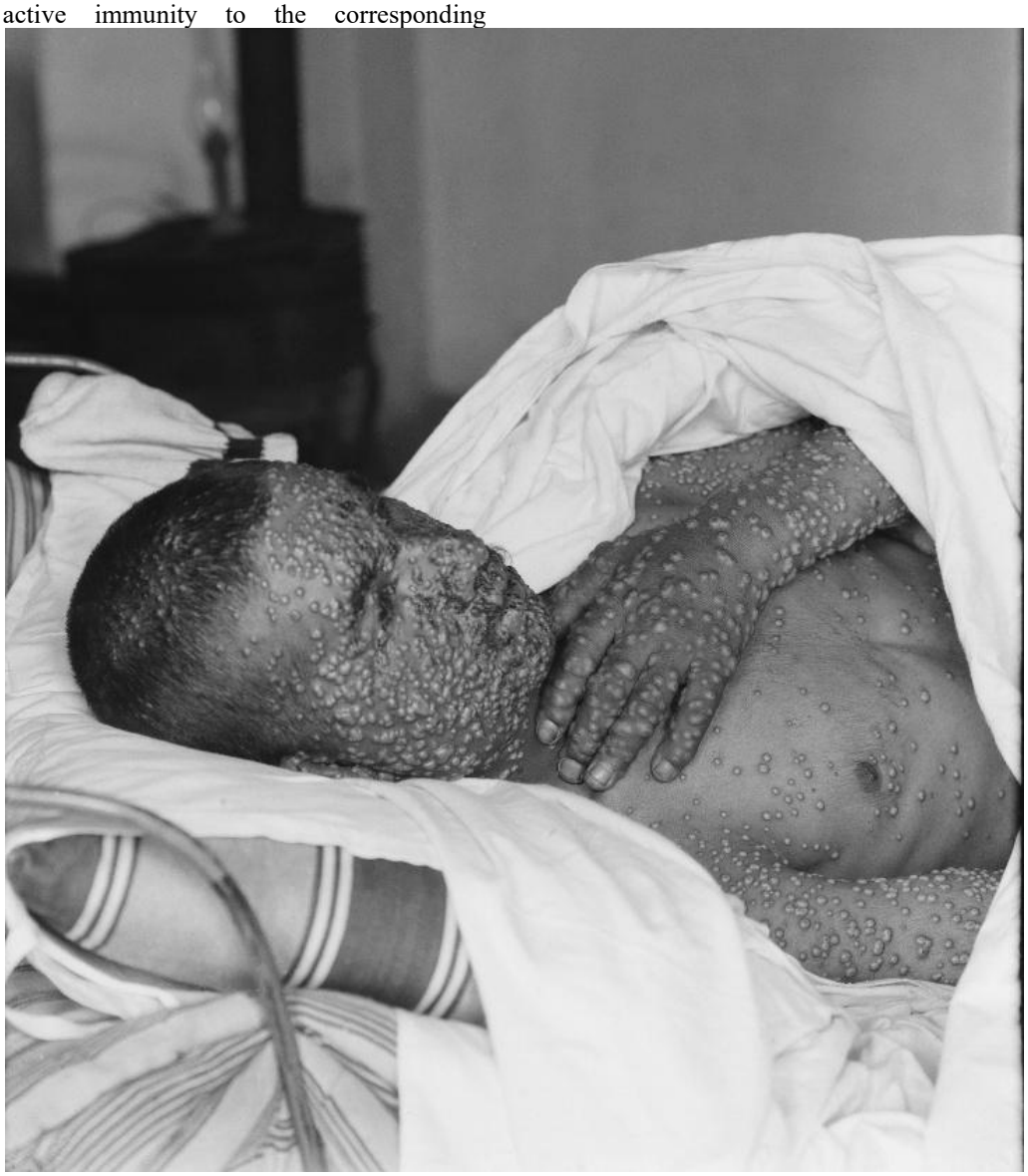

Fig.1. A boy with a heavily pockmarked face, arms and hands from smallpox in Palestine, ca. 1900-1925. (Shutterstock Photo)

She claimed that she could not get natural smallpox since she had already had cowpox. E. Jenner began to observe and collect all known cases of cowpox and found that not only did milkmaids not get smallpox, but also cavalrymen, who often encountered horsepox, did not get smallpox.

The doctor analyzed the ways of transmission of the contents of pustules from infected material to humans and, on May 14, 1796, first vaccinated 8-year-old James Phipps, the son of a farmer, with the contents of a pustule taken from a milkwoman sick with cowpox. The vaccinated person suffered a mild infection and acquired resistance to the causative agent of smallpox. E. Jenner studied the infectious nature of smallpox and cowpox for a long time, discovered the high infectious resistance of dried material from pustules, and researched the reduction of the infectious activity of the material under the influence of adverse environmental factors. In 1798, E. Jenner published the article " An Investigation into the

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Causes and Action of Cowpox "at his own expense since the Royal Society of Sciences distrusted the doctor's research and refused to publish it. Doubts disappeared when the British army and navy soldiers were forcibly vaccinated, and nothing bad happened to them. Thus, E. Jenner was the first in Europe to propose a method of vaccination - the use of a pathogen with a low degree of pathogenicity (cowpox virus) to create resistance to infection with a pathogen with a high degree of pathogenicity (smallpox virus). E. Jenner also described signs of allergy during repeated vaccinations against smallpox and manifestations of delayed-type hypersensitivity. Official recognition of E. Jenner's method occurred only in 1807 when a commission of the British Parliament unanimously recognized the high efficiency of the introduced method.

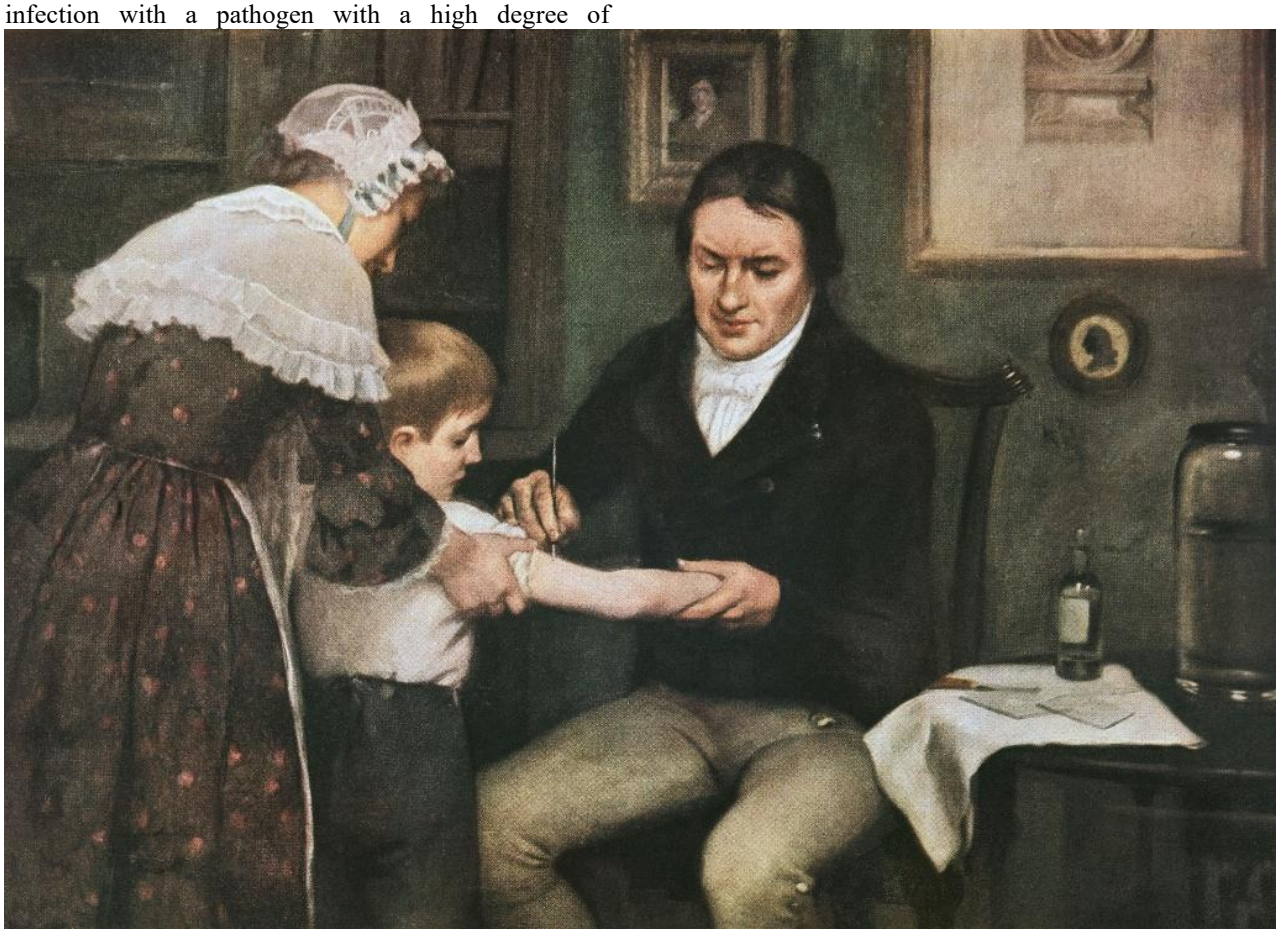

Fig.2. Dr. Edward Jenner (1749-1823) performing his first vaccination against smallpox on James Phipps, a boy of 8, May 14, 1796, oil on canvas by Ernest Board (1877-1934), 1920-1930, U.K.

Jenner's Louis Pasteur, who, out of respect for the works of E. Jenner, proposed to call vaccines preparations based on the principle of creating artificial immunity (from the Latin word “vacca” - cow) and the science that studies the regularities of vaccinations - vaccinology. In the second half of the 19th century, Louis Pasteur formulated the idea of the specificity of the action of various pathogens. While studying the causative agent of chicken cholera, L. Pasteur 1879 discovered that a culture left in a thermostat for a long time without reseeding lost its pathogenic properties and caused not a disease in chickens but a stable immunity. The researcher called the weakening of the pathogenic properties of microorganisms under the influence of various factors *attenuation*. Later, attenuation began to be actively used to obtain vaccines. When creating vaccines against anthrax, "swine rubella" and rabies, L. Pasteur determined that vaccines can be prepared in laboratory conditions in any quantity. This made it possible to carry out mass vaccinations of animals and prevent their mass death. Thus, L. Pasteur theoretically and practically proved that vaccination is a universal way to prevent infectious diseases. In each case, his methods of weakening the virulence properties of pathogens were used to create vaccines. At this time, L. Pasteur is the founder of medical microbiology and, along with E. Jenner, of vaccinology.

Subsequent work in the field of vaccination followed a medical line. First, it concerned the development of methods for the production and use of anti-rabies vaccines [1-8].

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Fig. 3. Rabies Virus (https://galaklc.com/rabies-virus-one-step-purification/)

A turning point in vaccinology was the discovery of phagocytosis by I.I. Mechnikov (in 1882) in Messina while studying the reaction of starfish larvae to introducing rose thorns into them. The observation prompted I.I. Mechnikov to create a theory of phagocytosis, inflammation, and cellular immunity [9, 10]. Many of I.I. Mechnikov's contemporaries, including R. Koch, did not believe phagocytes could kill microbes and believed that phagocytes could only absorb dead microbes, acting as passive "garbage collectors" [9]. Other researchers believed that living microbes could penetrate cells. Still, the latter was only a nutrient medium for them, while phagocytes did not have a bactericidal effect and spread the live pathogen throughout the body. Therefore, the work of I.I. Mechnikov's work, "Sensitivity and mobility, the ability to absorb solid bodies and produce substances that can destroy and digest microbes - these are the main factors of phagocyte activity," in which the author considered phagocytosis as a factor of active protection of the body and one of the main mechanisms of immunity development, made a big splash in the scientific community of that time [10]. With his works, I.I. Mechnikov radically changed the idea of inflammation as a harmful process: "Inflammation is a healing reaction of the body, which consists in eliminating harmful elements using phagocytosis" [10]. "Only in rare cases do aliens (i.e., microbes) adapt to live inside phagocytes and become parasites of the latter; most often, they die under the influence of these amoeba-like cells and are digested by them like other foreign bodies" [10]. The conclusion made by I.I. Mechnikov 100 years ago sounds prophetic: " ....phagocytes act due to their vital properties and ability to exert an enzymatic effect on pathogenic agents. The mechanism of this action has not yet been fully elucidated. Future researchers have a wide and fruitful field of research in this direction" [10]. Indeed, this field turned out to be fruitful; after the works of I.I. Mechnikov, great successes were achieved in the study of new functions of macrophages. Among them, the most significant is the participation of macrophages in antigen presentation and the ability of macrophages to produce mediators of cell interaction and respond to cytokines formed in other cells [1].

Along with the theory of cellular immunity of I.I. Mechnikov, a new direction was developed - humoral immunity. The founder of this direction was the German pharmacologist Paul Ehrlich, who 1882 put forward the

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theory of "side chains" [11]. According to this theory, specific receptors for antigens exist in cells. An antigen, contacting receptors, causes intensive production and release into the general circulation of certain "side chains" (antibodies). I.I. Mechnikov recognized the existence of antibodies and antitoxic immunity: "Antitoxic sera turned out to be not only beneficial preventive measures against diphtheria and tetanus, but also reliable therapeutic drugs." I.I. Mechnikov was close to solving the nature of cells that produce antibodies. He put forward a hypothesis about the origin of antibodies from phagocytes. The limited technical capabilities at that time did not allow for a more precise conclusion. Emphasizing the importance of the foundations of cellular immunity, I.I. Mechnikov wrote: “If, on the one hand, due to the weakening of phagocytosis, immune animals can suffer from a fatal disease, despite the large number of antibodies in their body fluids, then, on the other hand, there are cases when immunity is preserved even in the absence of humoral antibodies” [9, 10]. To date, great progress has been made in establishing the relationship between humoral and cellular factors in the development of immunity; however, even today, in the discussion of the nature of anti-infective resistance, one can hear a phrase similar to the one written by I.I. Mechnikov 100 years ago: “And even for tetanus and diphtheria — these two infections that were the first to form the basis of the antitoxic theory — the latter could not fully explain the mechanisms of immunity.” In 1908, I.I. Mechnikov and P. Ehrlich were awarded the Nobel Prize as a sign of the solemnity of two branches of science in studying the nature of immunity [1, 2, 9].

E. Behring and S. Kitazato in 1890 showed that serum from mice immunized with tetanus toxin protects animals from a lethal dose of the toxin [12]. In 1891, in the clinic of the University of Berlin, anti-diphtheria serum was administered to a boy dying of diphtheria, thanks to which the boy was saved. The serum of laboratory animals contained antibodies in low titers, so in 1894, high-titer anti-diphtheria serum from horses was organized. The use of immune sera for prophylactic and therapeutic purposes was called seroprophylaxis and serotherapy. Treating patients with tetanus and diphtheria with immune sera was the most outstanding achievement of applied immunology, which was ahead of the development of the theoretical foundations for creating passive immunity [1].

R. Kox (1843-1910) discovered the causative agent of tuberculosis and obtained tuberculin [13]. A. Calmette and S. Guerin (1914) were the first to obtain a live vaccine from attenuated tuberculosis pathogens [14]. R. Ramon, in 1924-1925 pp., developed a method for obtaining toxoids (anatoxins) by neutralizing toxins with formalin [15]. A significant milestone in vaccinology development was Max Theiler's research in 1937, which consisted of the attenuation of the yellow fever virus by serial passages in mouse and chicken embryos [16]. The virus, developing in atypical conditions outside the human body, became less virulent in the mutation process while retaining immunogenicity. Max Theiler was awarded the Nobel Prize in Physiology or Medicine for his discovery in 1961, and his vaccine derivatives are still used today [1]. The second half of the twentieth century was full of discoveries, the basis of which was the method of Theiler [17], but in the early 1960s, Albert Sabin developed a live oral polio vaccine (OPV) by serial passages in monkey kidney and testicular cells [18, 19]. Vaccines were then developed for measles (1963), mumps (1967), rubella (1969), chickenpox (1995), and rotavirus (2008). [20]

Richard Mulligan and Paul Berg took another extremely important step in 1980 by describing the process of transfecting *Escherichia coli* genes into monkey kidney cells. *Coli*, which causes monkey cells to produce the bacteria's proteins. This led to the development of recombinant DNA technology, making vaccines against hepatitis B (1986), human papillomavirus (2006), and influenza (2013) possible [20].

At this time, humanity has entered the fifth era of vaccinology – the era of mRNA vaccines, thanks to the discovery of Catalin Carico and Drew Weissmann regarding modifications of nucleoside bases. The new class of vaccines does not contain viral proteins but uses mRNA, DNA, or viral vectors to provide the cell with information on producing such proteins. Vaccines make it possible to protect a person from 25 infections [21-23]. According to BOO3, vaccines save the lives of 3 million children annually. It is predicted that with the help of new vaccines that will be developed over the next 5-15 years, it will be possible to prevent the deaths of another 8 million children per year [24].

Challenges in vaccine development

With the development of scientific and technological progress, vaccines have changed: the composition of vaccines and the technology of their production. Now, vaccines can be conditionally divided into the following types [25-30]:

•Live attenuated vaccines (for polio, rubella, measles, mumps, tuberculosis, plague, anthrax). Live vaccines with a weakened (attenuated) pathogen reproduce the infection in the body without developing the disease. Live attenuated Vaccines induce a complex immune response (cellular and humoral) and stimulate immune surface protection of mucous membranes (mucosal immunity). This immune response is close to natural, so vaccines of this class are more effective than other types of vaccines. Live vaccines have both positive and negative properties. Along with genetic fixed loss pathogenic properties, vaccine strains are capable of multiplying in the city introduction, lymph nodes, and internal organs. A clinical picture of the disease does not accompany vaccine infection but leads to the formation of strong and durable immunity, similar to postinfectious. Unfortunately, living vaccines are hard and deliver biocontrol. They are extremely sensitive to high temperatures and require unwavering compliance with cold storage chains. In addition, a live vaccine usually contains a big number (up to 99%) of ballast structures that may lead to increased reactogenicity. Also, one cannot pay attention to the possibility of reversion of virulent forms that can cause diseases in patients who are vaccinated. For sufficient security, live vaccines must have genetically stable, homogeneous, attenuated strains and undergo constant control to reverse virulence pathogens [25, 29, 30].

• Inactivated vaccines (against encephalitis, meningococcal infections, rabies, typhoid fever, hepatitis A) are in stock, in which the exciter is fully inactivated.

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Such vaccines are not able to cause diseases by definition; therefore, in themselves, they are safer than the disease. Such vaccines contain viruses and bacteria killed by high temperature or chemical means (as in vaccines against pertussis, polio) or individual particles of viruses or bacteria (as in vaccines against Hib infection, modern vaccines against pertussis, hepatitis B). To obtain inactivated pathogen vaccines, virulent properties are deprived by heating and processing with formalin, acetone, alcohol, etc. This provides reliable inactivation and minimal damage to structural antigens, but due to process inactivation, the immunogenicity of such vaccines is reduced by orders of magnitude. Lyophilic drying vaccines provide high-stability drugs and reduce the concentration of some impurities, but at the same time, the immunogenicity of vaccines is reduced by orders of magnitude. Inactivated vaccines, in general, are less effective than those that are alive, but upon reintroduction, they create enough stable immunity. In production, inactivated vaccines are necessary, and special attention is needed to deactivate vaccines completely. This class includes subunit and split vaccines with low reactogenicity, a high degree of specific safety, and sufficient immunogenic activity. The viral lysate used to prepare such vaccines is usually obtained with the help of a detergent, and various methods are used to purify the material, allowing for a high degree of purification (> 95%). To increase the immunogenicity of vaccines of this type, adjuvants are used - substances that increase or diversify the immune response of a microorganism, for example, aluminum hydroxide. This significantly increases the effectiveness of inactivated vaccines [25, 30].

•Anatoxins (vaccines against pertussis, tetanus, and diphtheria) are exotoxins of various microorganisms inactivated by formalin. Such vaccines are usually adsorbed on aluminum hydroxide. They provide the formation of antitoxic immunity (induction of the synthesis of antibodies against anatoxins), which does not prevent bacterial carriage. Artificial adjuvant vaccines are based on natural antigens and synthetic adjuvants. Combined vaccines include components that provide protective immunity against several infections. The most famous is the DTP vaccine, consisting of inactivated *Bordetella* pertussis bacteria and purified diphtheria and tetanus toxoids adsorbed on aluminum hydroxide [25, 26]. The main problem in recombinant, synthetic, and inactivated vaccines is their insufficient immunogenicity, much lower than that of their predecessors, live and whole-cell vaccines. Inactivation of the pathogen and/or toxin with formalin or propiolactone leads not only to a decrease in immunogenicity by orders of magnitude but also to forming covalent bonds between formalin and toxin proteins. These new undesirable, abnormal antigenic determinants increase the reactogenicity and allergenicity of such vaccines [26, 30].

•Molecular or biosynthetic vaccines (hepatitis B, human papillomavirus, influenza) [30].

•Nucleic acid-based (DNA/RNA) vaccines are safer, easier to manufacture, and cheaper. A person is directly injected with messenger RNA (mRNA), which programs the human cell to produce an antigen to which an immune response is induced. Their production requires only the acquisition of genetic material, not the virus [30].

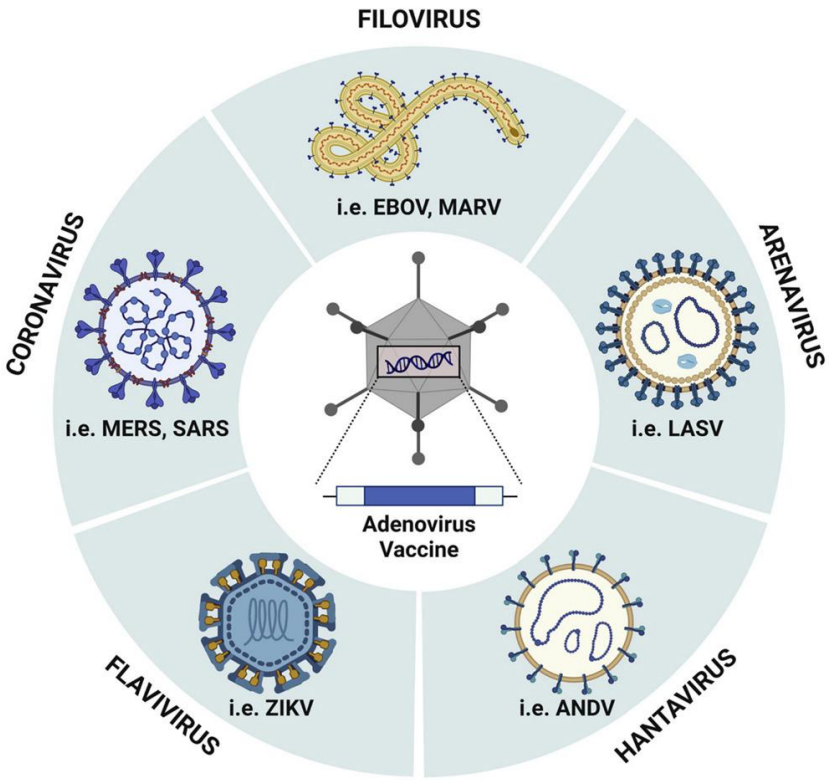

Fig.3. Adenovirus-based vaccines—a platform for pandemic preparedness against emerging viral pathogens

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• Recombinant vector vaccines—a non-pathogenic virus transports other antigens to which an immune response is generated. Such vaccines are generally safe and induce a strong immune response. However, the presence of immunity to the virus that serves as the vector may reduce the vaccine's effectiveness. Regular booster doses are required to induce long-lasting immunity [30, 31].

Modern features of vaccinology and vaccine development

On average, every 1-2 years, the world medical practice receives one new vaccine and several modified vaccines. A feature of modern vaccination is the development and implementation of vaccine generations based on artificial synthesis, genetic engineering, and the latest technology. The molecular structure of many infectious disease pathogens has been deciphered, artificial viral and bacterial peptides have been obtained, and large-scale cell cultivation methods have been developed, which are used to produce viral vaccines, monoclonal antibodies, cytokines, and other immunobiological drugs. The production of recombinant vaccines and vaccines with protein carriers and artificial adjuvants has begun. Fundamentally, new vaccines are being developed (vector vaccines, mRNA, DNA vaccines, plant vaccines, etc.), new combination vaccines capable of creating immunity to 7-8 infections, and new methods of vaccine application (intranasal, cutaneous, mucosal, and others).

The type of production of immunoprophylaxis agents has changed. Enterprises use modern biotechnology based on artificial synthesis and genetic engineering. Cell lines devoid of the disadvantages of primary cell cultures are increasingly used as a substrate for producing viral vaccines. In industrial conditions, it is possible to obtain kilogram quantities of monoclonal antibodies. Many enterprises operate in conditions of computerization of basic production processes and convergence of GMP requirements.

Modern diagnostic methods (PCR, immunoblotting, ELISA modifications, biosensor systems, etc.) are highly sensitive (to a picogram amount of antigen or antibody) and allow diagnosis in the early stages of disease development. Many existing vaccines, while retaining their names, have been improved over the decades and are now significantly better than their predecessors. However, all vaccines (domestic and foreign) have shortcomings and require further improvement.

Vaccine development is a long and high-tech process that proves its quality, effectiveness, and safety in protecting healthy people, including children, from infectious diseases.

On average, developing a new vaccine at the current stage takes 5-7 years. The development time depends on the amount of funding and interest in developing this vaccine and the pathogen. The development, production, and introduction of vaccines to mass use can be divided into the following stages [30]:

1. Research phase (vaccine candidate development): The research phase of the vaccine development process is designed to identify natural or synthetic antigens that can help prevent or treat an infectious disease. Such antigens may include weakened strains or parts of the virus.

2. Preclinical research stage. In this stage, vaccine candidate manufacturers investigate tissue or cell culture systems and conduct animal studies to determine whether the candidate will elicit an immune response. Many vaccine candidates do not progress to the next stages of development because they do not meet established criteria or are generally harmful to test animals.

3. The stage of clinical trials of the vaccine candidate, consisting of the following phases:

Phase I. The candidate vaccine is administered to a small group of volunteers (less than 100 people) to determine whether it is safe and to obtain initial data on adverse reactions that may occur after its use. This phase is conducted on as many healthy people as possible to exclude the possible influence of other factors.

Phase II. The candidate vaccine is administered to hundreds of people. This phase aims to obtain information about safety, immunogenicity, immunization schedule, and dose level.

Phase III. This study phase may involve thousands or tens of thousands of people from different target groups. The goal is to continue studying the candidate vaccine's safety (rare adverse reactions sometimes do not occur in smaller groups) and effectiveness. The minimum number of participants for this phase is 3,000.

4. The stage of consideration of materials for the vaccine in the NRA for its registration and approval of regulatory documents.

Suppose the vaccine has passed all three phases of clinical trials. In that case, the developer of the candidate vaccine applies to the National Regulatory Authority with the appropriate package of documents for a registration certificate (license).

5. The vaccine production stage consists of all stages of the production process for obtaining vaccines, their testing methods, proper quality of reagents, and relevant industry standard samples, which must meet the standards defined by the requirements of Good Manufacturing Practice (GMP).

6. The quality control stage and use of the vaccine during its mass use. Throughout the entire life cycle of the vaccine, the relevant regulatory authorities, together with the applicant, monitor whether the vaccine works as claimed and intended (Phase IV study).

Summarizing the review materials, we note that various technologies for their production are used to develop safe and highly effective vaccines, such as inactivation, attenuation, production of nucleic acids, use of viral vectors, production of viral subunits, and viral particles. However, despite the availability of many methods, continuous efforts to measure. The scientific community is focused on developing highly competent and effective vaccines that are simultaneously hypoallergenic, immunogenic, and safe. This review article reflects on the history of vaccine development, reveals modern vaccine development technologies, as human life is saved from various potential diseases, and, thus, highlights an important area of research.

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Vaccinology: historical milestones, achievements and problems

Svitlana Kalinichenko , Artur Martynov, Valery Minukhin , Tetyana Kordon, Petro Ovetchin

Vaccines are immunobiological preparations derived from bacteria, viruses, or their essential products. They are utilized to actively immunize humans and animals to prevent infectious diseases. The extensive application of vaccines facilitates the development of acquired active immunity against corresponding infections, which can cause infectious diseases and pandemic outbreaks. Consequently, in contemporary society, vaccination represents a principal strategy for epidemic prevention. Various technologies are employed in producing safe and highly effective vaccines, including inactivation, attenuation, nucleic acid production, utilization of viral vectors, production of viral subunits, and generation of viral particles. Nonetheless, despite the plethora of available methods, ongoing efforts within the scientific community are concentrated on developing highly competent and effective vaccines that are simultaneously hypoallergenic, immunogenic, and safe. This review article reflects on the historical progression of vaccine development. It elucidates modern vaccine production technologies as human life is safeguarded from various potential diseases, thereby underscoring a significant avenue of research.

Keywords: Vaccines, history, problems, future

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