Chapter 15

A NEW DIRECTION OF MODERN VACCINOLOGY DEVELOPMENT

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INTRODUCTION

In the 21st century, infectious diseases claim a significant number of lives and remain a pressing issue in the healthcare systems of many countries worldwide. Advances in science and their implementation in practical healthcare have significantly reduced the incidence and mortality rates of many common infections. Some, like natural smallpox, have been successfully eradicated globally through vigorous implementation of massive and targeted interventions, including mandatory active specific prevention measures, while others, such as poliomyelitis, persist in only a few countries. However, humanity has not achieved a final victory over infectious diseases thus far. This is evidently linked to the interplay between the human macroorganism and microorganisms. Currently, the most effective and environmentally friendly means of combating infectious diseases and preventing them is vaccination.

Mass specific prevention of controlled infections is aimed at creating collective immunity. Its effectiveness is evaluated using serological monitoring. The results of such monitoring show that even in the presence of collective immunity, there are always groups of people who do not have a protective level of antibodies[1]. Post-vaccination immunity is characterized by various clinical and immunological variants that affect the ability of a child's immune system to respond to infectious antigens both in natural conditions and during vaccination. In healthy children, normal variations in the structural and functional characteristics of immune system indicators are usually compensated for. In children with complicated heredity (genetically determined), these variations can reach values that border on pathology (borderline states). The genetically determined intensity of immune response to various antigens, including infectious ones, manifests as both insufficient post-vaccination immunity and overall weak anti-infectious resistance of the

[1] Prediction of a specific humoral immune response based on the initial parameters of the immune status of children vaccinated against measles, rubella and mumps / Toptygina A. P., Asiatseva V. V., Savkin I. A. et al. *Immunology*. – 2015. T. 36 (1). P. 34–41.

immune system. Immunogenetic examination before vaccination should be conducted to obtain information about the individual characteristics of the immune system of children of different age groups; the capabilities of the child's immune system in terms of forming post-vaccination immunity; individual specific sensitivity to each vaccine; genetic predisposition to this[2].

Each person's immune response to vaccination is individual. Individuals who respond poorly to one vaccine may respond well to another. The primary importance in this phenomenon is the genetic features of the organism, which are well studied in experiments on inbred mice when using synthetic peptides containing 8–12 amino acids as antigens[3]. Any high molecular weight antigen used for vaccine preparation contains several determinant groups. Each of them elicits its own immune response. The immunological reaction to the vaccine is essentially a sum of responses to peptides, so differences between groups strongly and weakly responding to the vaccine are smoothed out. An even more complex mosaic of immune responses arises with the administration of complex vaccines aimed at preventing several infections. In this case, most vaccinated individuals respond well to several components of combined vaccines simultaneously, but groups of people who respond weakly or strongly to one or two or several types of monovalent vaccines included in the preparation can always be identified.

Until recently, medical practice in vaccinology relied on vaccinating all individuals in the population with the same set of vaccines according to a universal schedule, in the absence of contraindications. However, there are several assumptions underlying this approach. One of these assumptions is that each individual will produce similar levels of protective antibodies with almost negligible rates of corresponding side effects. It is also assumed that each individual is at approximately the same level of disease prevention and that vaccine doses and the quantity necessary for the development of robust immunity are the same for the entire population. The main purpose of this approach was the paradigm of population-level immunity, which allowed to control to some extent many infectious diseases. The main drawback of this approach is that it ignores individual variability in the immune response to different types of vaccines and any genetic predisposition to reactogenicity, as well as differences in doses and schedules required to create robust, lasting immunity. At the same time, advancements in immunology, genetics, molecular biology, and bioinformatics demonstrate the value of a personalized approach to vaccine selection and dosing. Thus, a new approach in

[2] Decade of Vaccines — Global Vaccine Action Plan 2011-2020. Режим доступу: /http://www.who.int/immunization/global_vaccine_action_plan/ DoV_GVAP_2012_2020/en/.

[3] Heterogeneity in vaccine immune response: the role of immunogenetics and the emerging field of vaccinomics / Poland G. A., Ovsyannikova I. G., Jacobson R. M., Smith D. I. *Clin Pharmacol Ther*. 2007. № 82 (6). P. 653–664.

vaccinology is emerging between the traditional view of population-based public health and a new paradigm of individual level, which recognizes unique individual variations in response to biological agents[4].

1. The main links of the immunopathogenesis of the vaccine response

The elimination of these diseases can only be achieved through the establishment of a robust collective immunity against infections within the population. Therefore, the main efforts were directed towards ensuring high coverage and timeliness of vaccinations. However, as it turned out, these measures could not provide effective population immunity. This necessitates the search for factors that hinder this.

In implementing the vaccination-controlled infectious diseases (VCID) elimination program under conditions of low vaccination coverage, increasing incidence rates, and public distrust of vaccinations, the role of serological monitoring significantly increases. This allows for the timely identification of high-risk groups and territories and elucidates the reasons for the increase in the number of seronegative individuals. This involves organizing extensive laboratory testing for the intensity of immunity to VCIDs among all healthcare workers, service industry employees, individuals working with children and adolescents, and screening various groups of the pediatric and adult population. Comprehensive and reliable information not only about the incidence but also about the state of specific immunity in different age groups of the population will allow for predicting the epidemiological situation and implementing differentiated operational measures in different territories.

Long-term observations and special studies have shown that several main variants of immune response to vaccination can be observed in individuals, which are conventionally divided into hyperergic, normoergic, and hypoergic types[5]. Different clinical variants of post-vaccination immunity formation observed in practice are based on various variants of general immunity.

Historically, cytokines and their roles have been primarily mentioned in relation to the regulation of the immune response. Cytokines that control the strength and form of the specific immune response are produced by Th1 (gamma-interferon and tumor necrosis factor-beta) or Th2 (interleukins-4, -5, -6, -10, -13) cells. The first group of cytokines favors cellular immune response over humoral, while the second group favors humoral immune response over cellular. For example, the Th2 product interleukin-4 inhibits most functions of macrophages activated by gamma-interferon. Interleukin-

[4] Hood L. Balling R., Auffray C. Revolutionizing medicinemin the 21st century through systems approaches. *Biotechnol. J.* 2012. Vol. 7 (8). P. 992–1001.

[5] Ljungman P. Viral infections: current diagnosis and treatment. *Hematology J.* 2011. № 5. P. 63–68.

10 inhibits antigen presentation, production of pro-inflammatory cytokines, and synergizes with IL-4. The Th1 product gamma-interferon suppresses the functions of B-lymphocytes involved in the humoral response. Thus, the character of the specific immune response can change under the influence of specific cytokines and their combinations[6].

This means that the effectiveness of anti-infectious protection depends on the balance of cytokines, as effective cellular defense mechanisms act against intracellular parasitic microorganisms, while specific humoral immunity works more effectively against extracellular parasitic microorganisms. Cytokines function as intercellular mediators that transmit signals of activation or inhibition from one cell to another. Currently, the assessment of cytokine concentrations in blood serum is conducted in clinical practice to determine the degree of intensity of regulatory mechanisms of the immune response. However, this only confirms the fact of their elevation or reduction in a particular individual, without considering their genetic constitution. It is worth noting the contradictory results of numerous studies, which may be due to the peculiarities of the genotypes of the studied populations. These circumstances determine the relevance of studying the role of cytokines in the formation of the immunopathogenesis of the vaccine response.

As products of the immune system cells, cytokines naturally play a crucial role in its functioning. The inflammatory reaction formed with the participation of cytokines serves as the basis for the development of the immune response. Moreover, the effects of cytokines are even more pronounced and diverse during the antigen-specific phase of the immune process. According to the cytokine theory of diseases, health is characterized by the constant balanced production of cytokines at a low level necessary to maintain homeostasis. However, hyperproduction of certain cytokines can lead to various diseases, including allergic ones. Regarding the functional activity and predominance of one subclass of T-helper cells, judgment is made based on the secretion products of these cells. For Th1 type, gamma-interferon is considered a marker, while for Th2 type, interleukins IL-4, IL-5, IL-6, IL-10, IL-13 are indicative.

It is considered that host genetic factors are responsible for 90% of the variation in an individual's antibody response to the vaccine. Among these genetic factors, human leukocyte antigen (HLA) genes located on chromosome 6 are of interest, as these highly polymorphic HLA genes play an important role in regulating the immune response, including specific immunity to measles, mumps, and rubella viruses. The main role of HLA class

[6] Клінічна та лабораторна імунологія : [національний підручник] / За загальною редакцією доктора медичних наук, професора Кузнецової Л.В.; доктора медичних наук, професора Фролова В.М.; доктора медичних наук, професора Бабаджана В.Д. К. ООО «Поліграф плюс», 2012. 922 с.

I and II molecules is to present antigens to CD8+ and CD4+ T cells, thereby initiating adaptive immune response[7].

While HLA alleles are highly polymorphic and challenging to fully characterize due to the deficit of some alleles, the functional gene sequences are less diverse. The types of peptides that can bind to HLA and the efficiency of these bindings are influenced by the shape of the binding region and the amino acids present in the peptide-binding domains. This information allows us to consider HLA in terms of further biological consequences and to redistribute HLA alleles into "supertypes" based on their affinity for binding specific peptides. This simplified and practical approach to data processing may be more powerful and offer the most realistic information than attempting to understand the impact of each individual allele[8].

The formation of antibodies in response to antigen stimulation remains the cornerstone for measuring individual responses and protection for most viral vaccines. A significant portion of the variation in individual humoral immune responses to vaccination is genetic. Increasing evidence suggests that single-nucleotide polymorphisms (SNPs) through the formation of specific gene alleles make a significant contribution to phenotypic differences among individuals, including personal characteristics in the development of protective reactions, as well as susceptibility to a range of diseases.

The collection of genes found on chromosome 6, which forms the human leukocyte antigen (HLA) system, provides one of the largest sources of genetic variability in humans concerning their immune responses. Recent studies have demonstrated a significant association between vaccine response and alleles of the human leukocyte antigen system. These associations not only explain why vaccine-induced humoral immune responses differ among individuals and populations, but these differences may also hold the key to the development of future generations of vaccines. The search for susceptibility markers to infection among cytokine gene alleles is a new and promising area of scientific research[9].

The analysis of the role of HLA genes, cytokine genes, and cell surface receptors as examples of how genetic polymorphism leads to individual and population variations in immune responses to vaccines demonstrates the complex mechanisms of immune response in a highly intricate regulatory system. Many researchers refer to this as the new golden age of vaccinology – "predictive vaccinology," which will predict the likelihood of a corresponding response to the

[7] Germain R. N. MHC-dependent antigen processing and peptide presentation: Providing ligands for T lymphocyte activation. *Cell*. 2014. № 76. P. 287–29

[8] Human leukocyte antigen haplotypes in the genetic control of immune response to measles-mumps-rubella vaccine / Ovsyannikova I. G., Pankratz S. V., Vierkant R., Jacobson R. M., Poland G. A. *J Infect Dis*. 2006. № 193(5). P. 655–663.

[9] Jamil K. M., Khakoo S. I. KIR/HLA interactions and pathogen immunity. *J Biomed Biotechnol*. 2011. P. 298–348.

vaccine or an adverse reaction to the vaccine, the number of doses required, and even whether the vaccine can be beneficial (i.e., whether the individual is predisposed to the risk of the vaccine's outcome)[10].

2. Vaccination in Ukraine in wartime and post-war conditions

Infectious diseases persist and proliferate during times of war. Children and adults living in areas partially or fully affected by armed conflict are often the most vulnerable to outbreaks of vaccine-preventable infectious diseases. Additionally, a large number of internally displaced persons in our country currently reside in informal urban settlements, reception centers, and camps. Consequently, poor nutrition, overcrowding, unsanitary conditions, and damage to existing healthcare infrastructure pose barriers to accessing routine medical services, including vaccination. This creates a conducive environment for outbreaks of vaccine-preventable infections, which under such conditions can spread rapidly and have a high likelihood of sustained transmission due to inadequate supervision, inadequate or even absent treatment, poorly trained or inaccessible medical personnel, as well as challenges associated with outbreak response planning.

The imposition of martial law in Ukraine due to the military aggression of the Russian Federation and subsequent events has led to a significant decline in vaccination coverage and a high likelihood of outbreaks of infectious diseases. In particular, the population is at increased risk of contracting tetanus due to shrapnel wounds and infection with many other vaccine-preventable diseases, considering the unfavorable living conditions, namely poliomyelitis, diphtheria, measles, tuberculosis, and others.

The large-scale armed aggression of the Russian Federation against Ukraine and the military actions initiated by Russian troops on February 24, 2022, have led to the loss of life and injury of civilians in various regions of the country, destruction of many critical infrastructure objects or disruption of their functioning, and mass destruction of civilian objects. All these and other negative consequences of the military invasion, in turn, have caused massive migration. According to EU forecasts, as a result of migration, the population of Ukraine may decrease by 24–33%, depending on the duration of hostilities and the unstable operation of infrastructure. According to official data, since the start of the active phase of the RF armed aggression, the population of Ukraine has decreased by 6.7 million people. There has been a change in the age and gender structure of the population, in particular, a decrease in the proportion of youth under 20 years of age and women of reproductive age.

[10]Genome-wide analysis of polymorphisms associated with cytokine responses in smallpox vaccine recipients / Kennedy R. B., Ovsyannikova I. G., Shane P. V., Haralambieva I. H., Vierkant R. A., Poland G. A. *Hum Genet*. 2012. № 131 (9). P. 1403–1421.

Many of them have already returned home or plan to do so, while others are only planning to leave. The demographic situation in Ukraine during 2022 is rapidly changing both quantitatively and qualitatively. These changes affect the socio-economic sphere, the country's defense capability, its positioning in the world, and lead to consequences that will affect Ukrainian realities in the medium and long term. This also applies to the epidemiological situation in the country and, in particular, to vaccine-preventable infections. The fact that the large-scale Russian-Ukrainian war is still ongoing, the destruction of Ukraine's economic structure, and the complex period of socio-economic post-war recovery of the country are factors that increase the risks of these infections getting out of control in Ukraine. At the same time, the decrease in the number of youth exacerbates the threat of deterioration of the quality of Ukraine's epidemiological potential in the medium and long term.

The dynamics of citizens returning to Ukraine from abroad depends on the security situation. According to sociological surveys, by the end of August 2022, almost 71% of respondents planned to return to Ukraine after the end of the war and in case of improvement in the security situation. During the summer-autumn period of 2022, according to the UN and the EU, nearly 5 million asylum seekers returned to Ukraine from EU countries. Migration and asylum seeking have a pendulum nature. Ukrainian citizens return home for several months, but due to the security situation, they may leave Ukraine again. All this contributes to the deterioration of the country's infectious security.

Significant volumes of internal migration of Ukrainians from conflict zones and temporarily occupied territories have led to a substantial increase in the number of internally displaced persons (IDPs). According to the UN, the number of internally displaced persons (as of November 8, 2022) amounted to 6.243 million people, according to the Ministry of Social Policy of Ukraine – 4.6 million people. According to the Ministry for the Reintegration of Temporarily Occupied Territories of Ukraine, the number of individuals who were forced or obliged to flee or leave their homes or places of habitual residence reached 7.7 million. The internally driven migration in Ukraine, provoked by the large-scale invasion of Russian troops, is considered one of the main factors influencing the current social, economic, and epidemiological situation in recipient regions receiving IDPs. With the increase in the volume of internal migration, problems related not only to temporary accommodation, provision of medical and social protection for internally displaced persons but also employment opportunities have significantly intensified. As a result, the situation with unemployment in Ukraine has worsened, which in turn does not contribute to improving the immunological component of health.

There is a certain uneven distribution of internally displaced persons across regions. The largest number of internally displaced persons who are unemployed is concentrated in regions territorially close to the conflict zone (especially the Kharkiv region), or in relatively safe and remote regions.

As of today, threats and risks associated with the massive influx of labor immigrants from developing countries are considered purely hypothetical, as there is no relatively clear understanding of the deadlines for the end of hostilities, mechanisms for economic recovery, and the volume of investments in the Ukrainian economy. However, there is no doubt that after the end of the war and thanks to international assistance, there will be a demand for labor in Ukraine, which can be satisfied by attracting labor immigrants from developing countries. Therefore, it is advisable to identify potential threats and problems in advance, including those related to the vaccination status of such individuals, with whom it will be necessary to deal when shaping state policies for the adaptation and integration of labor immigrants into Ukrainian society during the economic recovery of Ukraine. Therefore, it is quite likely that we will face a paradox where, in conditions of acute labor shortages, millions of Ukrainians will work abroad, while international recruiting agencies will attract a large number of labor immigrants from developing countries to Ukraine.

The war has led to disruptions in obtaining comprehensive information on the population's disease burden from infectious diseases and conducting objective analysis. Reduced statistical indicators have been observed in the territories of most administrative regions of the country. Bombed hospitals, killings and kidnappings of doctors, looting of medical equipment, shortage of medicines and medical personnel, lack of clean water and electricity, thousands of unburied and decaying bodies polluting the environment – the war has dealt a severe blow to Ukraine's healthcare system.

Due to the destroyed infrastructure and lack of normal access to medical care in many regions, Ukrainians may be at risk of many diseases. For example, diphtheria and tetanus, against which only every fifth adult in Ukraine is vaccinated. According to official data, only 20% of people in Ukraine are currently vaccinated. That is, only every fifth adult has protection. During the war, the risks of contracting diphtheria and tetanus increase because the risk of injury increases. Therefore, it is important to continue mandatory and recommended vaccinations according to the National Immunization Schedule, considering how feasible it is in the conditions of martial law. Obtaining all necessary vaccinations among newborns and children in the first two years of life is crucial. In case of disruption of the immunization schedule among any age group of the population, vaccination should be resumed as soon as possible. Timely vaccination is the key to protecting children, adults, and the elderly from serious and life-threatening

infectious diseases. In times of war, vaccination is perhaps the most effective method to protect oneself and one's children from severe illnesses and their consequences. The health of Ukrainians remains the country's top priority, and adherence to the Vaccination Schedule is no exception.

Interrupting routine vaccination – according to the national schedule of preventive vaccinations – even for a short period increases the likelihood of outbreaks of infections and diseases prevented by vaccination. Therefore, in our opinion, a personalized approach to vaccination during the period of martial law is extremely relevant for preserving the health of both military personnel and the civilian population.

3. The paradigm of personalized vaccinology

The beginning of the third millennium was marked by the emergence of a new paradigm in medicine – predictive and preventive personalized medicine (PPPM). One of the main prerequisites for the emergence of personalized medicine (PM) was the successful implementation of the international project "Human Genome"[11]. As it is known, each (or almost each) organism is unique in its set of genes. Thus, knowing the genetic characteristics of a specific organism, we can subject it to individually oriented therapeutic interventions that take into account not only the nature of the disease but also the specific genetic characteristics of the patient, according to the principle of "treating the patient, not the disease," taking into account the genetic uniqueness of the organism. It is believed that the prospects of personalized medicine are primarily associated with two biomedical technologies: single-nucleotide polymorphism (SNP) genotyping, which allows detecting a patient's predisposition to various diseases and their response to specific drug therapy, and microchips that allow storing and rapidly analyzing a patient's genome. These technologies facilitate the rapid development of diagnostics and therapy based on the use of proteins[12].

Predictive-preventive and personalized medicine is defined as a "rapidly evolving field of healthcare based on an integrated, coordinated individual approach to the analysis of the onset and course of disease (or as "integrated medicine that includes the development of a personalized treatment based on genomics, susceptibility testing, prevention, combining diagnosis with treatment, and treatment monitoring." From the perspective of genetics, two

[11] Personalized medicines fact sheet. Genes to personalized medicines. Progress from the National Institute of General Medical Sciences. National Institute of Health. https://www.nih.gov/about-nih/what-wedo/nih-turning-discovery-into-health/personalizedmedicine (29 August 2021)

[12] Mediouni M, Schlatterer DR, Madry H, et al. A review of translational medicine. The future paradigm: how can we connect the orthopedic dots better? Curr Med Res Opin. 2018;34(7):1217–1229. DOI: 10.1080/03007995.2017.1385450.

characteristic foundations of modern medicine are determined: the individual approach to the patient (prevention, treatment, and diagnosis of any disease are based on the genetic characteristics of each subject, and their genetic uniqueness) – the preventive (predictive) nature of medicine.

Today, the idea of a personalized approach to the patient has become especially relevant due to the mandatory introduction of standardization in medicine[13]. An individual approach to the patient is more effective compared to a standardized approach envisaged by the standardization project. Applying the same methodologies to a large number of patients reduces the effectiveness of treatment. According to many studies, most widely used drugs are effective for only 25-60% of patients[14].

Personalized medicine envisions that molecular disease classification based on genomic analysis will replace symptom-based classification. Molecular diagnostics for predicting treatment outcomes will be based on patients' genomic profiles.

The approach to treatment should focus not on diseases and syndromes but on individual patients, each of whom is unique, hence the treatment approach must be individualized. Standards can be considered necessary only for the development of standardized organizational, material-technical, and staffing conditions for the provision of medical care in each region of the country, i.e., only the standardization of healthcare organization can be discussed, without extending it to the individual patient.

Personalization of medicine is one of the key trends in the development of global healthcare, associated with the transition from a reactive model to a proactive, predictive, and preventive one. Viewing modern medicine as "expensive, reactive, inefficient, and focused mainly on one format that fits all and in all cases," proponents of the new approach also emphasize increasing patient involvement in healthcare and advocating for "patient-centric" strategies. The expected outcomes of the new medical paradigm include effective population screening, early childhood prevention, health risk identification, patient stratification for optimal therapy planning, forecasting and reducing adverse treatment effects and drug interactions, and creating individual disease profiles – all of which allow personalized medicine to be seen as the medicine of the future. However, expectations and new perspectives raise concerns and new opportunities for the intensification of the medicalization of society.

The main obstacle to the development of personalized medicine, along with the still high cost of necessary research, is the insufficient readiness of

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[14] Meadows M. Genomics and personalized medicine. FDA Consum. November-December 2005;39(6):12–17.

specialists, the large gap between the new valuable diagnostic and therapeutic capabilities provided by personalized medicine and the ability of practicing physicians to evaluate and apply them in practice, as well as the deficit of objective data proving the usefulness for the patient of presymptomatic testing for hereditary predisposition to multifactorial diseases. Moreover, there is no information about how and which environmental factors specifically trigger the development of the disease in a particular individual.

The task of personalized medicine is to identify, describe, mark, and create a comprehensive picture of the patient's condition. But even if the doctor has all the information about the patient's health, informing the patient about their existing and predicted condition will be of paramount importance. This process includes the possibility of incorrect (inadequate understanding by the doctor) interpretation of information, multiplied by the necessity of making decisions regarding changes in the patient's usual lifestyle. Technologies can work clearly and accurately, the doctor's recommendations will be comprehensive, but whether to follow them or not will depend on the decision of each patient[15]. What motivates a patient to follow a doctor's recommendations? External and/or internal motivation: internal motivation will prevail if a person understands and accepts the seriousness of the danger to their health, for maintaining/changing their usual way of life, meaning the person is ill and seeks to alleviate, change, or correct their condition. External motivation comes from external pressure. The doctor's activity is quite strictly regulated by legal and ethical norms. The patient, on the other hand, is mostly free in their behavior and protected in their freedom by the principles of bioethics, such as the principle of respect for patient autonomy and current legal norms, including the doctor's obligation to obtain voluntary informed consent. The doctor may act according to a regulated normative procedure, but the patient will act more in line with their social and spiritual beliefs, which are adequate to their health condition. However, since the patient also participates in making decisions regarding their treatment and, among other things, takes on part of the responsibility for medical intervention, it is worth considering changing the traditional doctor-patient interaction dynamic[16].

The preventive function of vaccination is likely to be maximally effective when a population-based approach is complemented by an individualized approach, and in the future, with the help of genetic research in integrative medicine, which will help significantly reduce the risks of vaccination side effects. Today, in the conditions of constant transportation migration of people

[15] Bunnik EM, Schermer MHN, Janssens AC. Personal genome testing: test characteristics to clarify the discourse on ethical, legal and societal issues. BMC Med Ethics. 2011;12:11. DOI: 10.1186/1472-6939-12-11.

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within the country and around the world, it is more necessary than ever to establish a dialogue between these two approaches – the deontological approach from the side of the doctor and the mythologized fear from the side of parents. Ethically, it is not only appropriate to explain to parents all the risks of both vaccination refusal and vaccination itself but also to conduct medical examinations of each specific child at the parents' request. In the era of widespread media and the Internet, former methods of one-sided persuasion and propaganda seem ineffective and questionable from an ethical point of view. It is desirable to prevent mass vaccination refusals in such a way that parents are confident that the risks of vaccination for their children are minimized. Vaccination personalization is the creation of safe and effective immunity in each vaccinated individual. When discussing issues of immunological vaccination individualization and the development of vaccination principles, it is important to agree on the concept of immunological vaccination individualization. One possible definition could be: immunological vaccination individualization is the correction of the immune response to vaccines using various vaccination means and methods to create sufficient immunity in each vaccinated person. For such correction, various vaccination doses and schedules, as well as additional means of immune response modulation, can be used.

All measures of specific prevention of controlled infections are aimed at creating herd immunity. To assess the effectiveness of such measures and the state of herd immunity, serological monitoring is conducted. The main task of the complex of methods proposed at the post-vaccination stage is to analyze the effectiveness of vaccination by determining the intensity of immunity to each administered vaccine. Ideally, it is desirable to have an idea of a person's immunity to a specific infection before vaccination.

The solution to the problem of vaccination individualization would be significantly accelerated if we knew the degree of sensitivity of each person to specific infections. Reliable methods for determining such sensitivity do not yet exist, although ideally, it would be desirable to know a person's immunity to a specific infection before vaccination. It is also advisable to conduct additional scientific research on the following aspects of the discussed problem:

– development of methods for predicting the strength of the immune response to vaccines;

– establishment of the upper level of sufficient immunization for specific infections;

– study of the genetic characteristics of groups of individuals differing in their ability to respond to specific types of vaccines;

– determination and evaluation of cellular defense indicators for vaccines that induce cellular immunity;

– development of methods to overcome immunological refractoriness;

– creation of vaccine variants for selective immunization of low– and high-reacting individuals;

– development of new, safe methods of vaccine administration;

– creation of special diagnostic test systems for simultaneous determination of antibody titers to antigens of several types of vaccines (for example, vaccines in the vaccination schedule).

To implement the new paradigm of vaccination, it is necessary to consider the influence of various factors (gender, age, epidemiological situation, etc.) and at the same time take into account the possibility of a wider range of protection resulting from previous immunization with multiple vaccines. We need to learn to predict the relative likelihood of developing a protective response and the likelihood of adverse side effects in specific individuals. This is the further development of systemic vaccinology and vaccination prevention. The path to vaccination individualization is not an easy one, and it has no finish line. But no matter how difficult it may be, we must constantly move forward on this path.

CONCLUSIONS

Vaccination personalization can be achieved by selecting vaccines among similar vaccines, choice of doses, vaccination schedules, use of adjuvants, and other immunomodulations. Naturally, each vaccine has its own characteristics, and for each vaccine preparation, its own tactics of immunological correction are necessary. At the same time, general methods and means of correction of the immune response to various types of vaccines can be recommended. The problem of immunological individualization applies not only to vaccines but also to other immunobiological preparations, primarily various immunomodulators, which are widely used for the prevention and treatment of many types of human pathology.

SUMMARY

To implement the new vaccination paradigm, it is necessary to consider the influence of various factors while taking into account the possibility of a broader spectrum of protection, resulting from previous immunization with multiple vaccines. It is necessary to learn to predict the relative probability of developing a protective response and the probability of adverse side effects in specific individuals. Vaccination personalization can be achieved through the selection of vaccines among similar vaccines, choice of doses, vaccination schedules, use of adjuvants, and other immunomodulations. At the same time, general methods and means of correcting the immune response to various

types of vaccines can be recommended. This is a further development of systemic vaccinology and vaccination prophylaxis.

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