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Sayamov YuN ✉

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The article discusses the global problem of obesity as a socio-ethical phenomenon in the context of UNESCO's program on bioethics, the ethics of science and artificial intelligence. The article also explains the stigma of obesity, or, in other words, the discrediting social identity assigned to an overweight person, and describes the consequences of such stigmatization. The author explores the socio-ethical causes of obesity and points out the link between obesity and some of the challenges addressed by the Sustainable Development goals, including hunger and social inequality.

Keywords: obesity, social and ethical problems, stigmatization, Sustainable Development goals.

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СОЦИАЛЬНО-ЭТИЧЕСКИЕ АСПЕКТЫ ОЖИРЕНИЯ КАК ГЛОБАЛЬНАЯ ПРОБЛЕМА

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Автор рассматривает глобальную проблему ожирения как социально-этический феномен в контексте программы ЮНЕСКО по биоэтике, этике науки и этике искусственного интеллекта. Он останавливается на понятии «стигма ожирения», которое относит человека с избыточным весом к постыдной социальной идентичности, оценивает последствия стигматизации людей, страдающих ожирением. Обращаясь к социально-этическим причинам ожирения, автор указывает на связь ожирения с глобальными проблемами голода и социального неравенства, на преодоление которых направлены соответствующие цели устойчивого развития.

Ключевые слова: ожирение, социально-этические проблемы, стигматизация, цели устойчивого развития.

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INTRODUCTION

Obesity has long become a global concern, and its burden continues to grow. It is one of the most widespread civilization diseases, now affecting one in four people. Both adult and pediatric obesity rates are on the rise everywhere in the world. The World Health Organization (WHO) has recognized obesity as a 21th century epidemic [1][1]. According to expert estimates, 40% of men and 50% of women will be obese in 2025 [2].

In light of the woeful fact that obesity and its complications take 2.8 million lives every year, WHO has called for immediate action to end the epidemic and declared October 11 as the World Obesity Day [3]. Today, about half of the European population are struggling with excess weight. The highest rates of obesity are observed in the Unites States [4], where this condition kills 300,000 people annually. In today's Russia, obesity has too become an important social issue [5].

STIGMA: THE ETHICAL JUDGEMENT OF OBESITY

Obesity is being increasingly recognized not only as a health condition but also as a phenomenon with socio-ethical characteristics and consequences. The bioethics agenda outlined in the UNESCO's program on bioethics, the ethics of science and artificial intelligence addresses obesity-related ethical issues, which, to a greater or lesser extent, affect millions of people worldwide.

Fat stigmatization is one of the most serious social and ethical challenges facing modern society. In Ancient Greece, a stigma was a brand that marked slaves or criminals. Later, this word developed the meaning of a socially shameful, indecent or detestable attribute. According to Erving Gofman, "today, the term… is applied more to the disgrace itself than to the bodily evidence of it" [6].

The stigma of obesity brands an overweight individual with a discrediting social identity and often turns him/her into an object of ridicule and bullying quite common among children and adolescents. Stigmatization is a process of negative stereotyping or marking an individual with a negatively connotated social label. As a socio-ethical phenomenon, stigmatization vilifies obesity as a socially shameful characteristic and shapes a debasing attitude toward overweight people. The latter often develop an inferiority complex, which has a dramatic impact on how they see society and their role in it. Stigmatization can result in derogatory or discriminatory policies toward obese people, foster alienation, frustration and resentfulness, and has social and ethical ramifications, including crime, immoral conduct, aggression, violent assaults, and self-harm.

Obesity stigma can manifest as negative stereotypes entrenched in the sociocultural environment, including claims that overweight people are inferior, inadequate or incapable of self-control. Thus, certain traits shared by some overweight individuals are assigned to all overweight people through unnuanced generalization.

Obesity stigma can be institutional if attempts are made to disenfranchise overweight people from some of their rights by passing discriminatory laws or introduce legal definitions related

[1] WHO measures obesity in kg/m^2. Normal weight: > 25; overweight: 25–29.9; obesity class I — 30–34.9; obesity class II: 35–39.9; obesity class III: 40–44.9; obesity class IV: >45

to obesity. A number of transport service companies have been reported to impose restrictions on passenger weight or force an obese traveler to book 2 tickets instead of one; some of these discriminatory policies have been legalized.

Another type of fat stigmatization is self-stigmatization, i.e. adopting a negative attitude toward oneself and blaming oneself for the inability to control weight. This may have a devastating effect on the mental state of the self-stigmatizing individual and create problems for others. Positive stigmatization and self-excuse are often used as a compensation. This is reflected in sayings like "there is more of me to love", plus-size comedy shows, contests for overweight people, etc.

Stigmatization as such is the manifestation of social and ethical undercurrents and realia. Stigmatized people do not conform with socio-ethical views and expectations that form a virtual social identity perceived as a norm by society. If the actual social identity of a person significantly deviates from the norm in a society where such deviance is frowned upon or not tolerated, stigmatization may be the response. With obese people, the difference from the perceived norm is visible and can trigger stigmatization that will have a socially and ethically devastating effect, creating a divide between "normal" and stigmatized overweight people. This socially and ethically dangerous phenomenon is what Goffman called a spoiled identity [6].

Fat stigmatization may lead to psychological trauma or a disorder, which, in turn, may result in social alienation and discrimination. Those who are prejudiced against obese or overweight members of society sometimes justify their discriminatory attitude by resorting to theories about hazards posed by overweight people to society or the ethical inadequacy of such people. Fat stigmatization can be propagated by accusing overweight people of faults they do not have, like intellectual incapacity, sexual inadequacy, etc.

In turn, people who live with obesity stigma are likely to sink into self-pity and use excess weight as an excuse for all the failures they have ever had in life. They become self-conscious about their own behavior and about how other people see them; they often develop a proclivity for self-stigmatizing, which makes their interaction with society inevitably flawed.

Fat stigmatization is a widespread phenomenon. According to different estimates, as many as half of overweight residents of Europe, which prides itself on tolerance, are stigmatized by their employers, colleagues, educators, healthcare providers, mass media, and even friends and family.

Fat stigmatization deeply affects children and has far-reaching social and ethical implications. Statistically, the chances of falling victim to bullying, abuse and denigration are by 63% higher for overweight children than for their peers with normal weight [3]. Bullying and victimization incite shame in an obese child. This fuels resentment, depression, low self-esteem and despair that often persist into adulthood and may push the person to commit suicide. Overweight children are especially vulnerable to stigmatization from teachers and parents, which may have a dramatic impact on their academic performance, reduce their chances in life, become a bitter disappointment, and promote social and ethical ineptness.

Parents of obese children should realize that they have a profound impact on their child's mindset and are responsible for the psychological comfort of the child in no lesser degree than for the child's health constituted, among other things, by a healthy diet. It is parental responsibility to protect the interests of the child, remember that bullying and victimization can have devastating effects on the child's socio-ethical development and therefore do their best to prevent these malpractices by seeking help with state agencies and members of the community.

According to the Ethical Family Interventions for Childhood Obesity study conducted in 2001, no intervention can be successful if the family, especially parents or caregivers, are not involved [7].

Parents have the right to raise their children as they think fit as long as they abide by the law, but this does not exempt them from being responsible for their child's safety and protection from harm. This gives rise to an ethical dilemma: there are people who believe that pediatric obesity is the result of parental neglect, inadequate parenting style, poor dietary choices and wrong attitude to physical exercise made and formed by the parents. However, experts think that pediatric obesity is a complex physiological phenomenon that cannot be explained by bad parenting alone even if parents make wrong choices or do not meet certain criteria. The socio-ethical controversy surrounding this problem is evident. Parents or caregivers may not always have the means to provide their child with a balanced nutritional diet and buy cheap, affordable foods, including those promoting obesity.

GLOBAL UN GOALS: END HUNGER, OBESITY AND SOCIAL INEQUALITY

There are still regions in the world where access to food and potable water remains a problem. Among the Sustainable Development Goals that were adopted by the United Nations in 2015 and are expected to be achieved by 2030, Goal 2 seeks to end hunger, achieve food security and promote sustainable agriculture. Today, 700 million people worldwide (9% of the planet's population) are affected by hunger. The number of people who do not have sufficient access to food and drinkable water is growing and will have increased by 2 billion by 2050 if the trend continues [8].

Paradoxically as it may sound, there is a close link between hunger and obesity [12]. The primary goal in the battle against hunger is to provide the affected population with food and water for survival. The budget allocated for humanitarian food aid is tight, and the food should be distributed among as many people as possible. This means that the food delivered as humanitarian aid will be very cheap and rich in calories; it will help the person to survive but at the same may cause obesity.

The socio-ethical roots and causes of the global obesity phenomenon are worth a separate discussion. Social inequality, which is in and of itself a global challenge, is a great contributor to obesity. Goal 10 of the Sustainable Development Goals seeks to combat social inequality within and between countries. COVID-19 has aggravated social inequality, taking a terrible toll on the poorest and the most vulnerable populations [10]. The pandemic has substantially increased unemployment rates all over the world and resulted in income loss, widening the gap between the rich and the poor. Because of social inequality and low income, many people have no other choice but to consume cheap, high-calorie foods. Inequality has a stronger impact on socially vulnerable groups. Migrants, refugees, the elderly and the disabled, children and obese people are at high risk. As a socially vulnerable group, overweight people fall the first victim to the consequences of social inequality and economic downturns: they lose their jobs, social status and the money to buy high-quality foods. Caught in this vicious circle, they have only slim hope to break out of it one day.

The socio-ethical aspect of the global obesity phenomenon is tightly linked to the so-called human factor, or, in other words, the social nature of man. Humans satisfy their vital need for nutrients by eating. The most natural eating behavior would be to adequately replenish the body with lost nutrients. However, there is a whole range of socially and ethically determined

individual variations of eating behaviors and habits that fulfill a variety of other needs.

Using food as a self-reward and food cravings are eating behaviors that are often adopted by overweight individuals as a means of relaxation or relief from stress, which in their case often has a socio-ethical nature. Paradoxically, an overweight person resorts to food to relieve stress caused by excess weight; this exacerbates the problem even further.

In times of social catastrophes like revolutions, wars or armed conflicts humans may find solace in food; in the absence of food, this function can be compensated by tea rituals or other attributes of eating behavior of peaceful times.

EATING BEHAVIOR AS A MANIFESTATION OF SOCIAL AND ETHICAL NEEDS

Eating behavior has an obvious socio-ethical function when used to demonstrate and maintain one's social status through dining at expensive restaurants and ordering exquisite dishes in accordance with one's ideas of prestigious foods. Sometimes exotic foods are bought and consumed to demonstrate expertise, unique eating habits and, ultimately, social or ethical superiority over other people.

Many see eating behavior as another opportunity to socialize; for some, it is a socially and ethically significant solution to the problem of loneliness. Overweight people are often very hospitable to the guests they invite to spend time together at the table so as not to feel socially and ethically rejected by society.

Hedonists make up another category of overweight people. They eat for delectation, i.e. the pleasure of senses, which is a goal in itself, both socially and ethically, and in some cases a denial of other pleasures and aspirations.

The process of food consumption and food itself can fulfill the socio-ethical function of maintaining and observing traditions or customs and preserving an ethnic identity, especially in ethnic communities. The UNESCO's list of intangible cultural heritage contains approximately 480 foods and dishes, three national cuisines (Japanese, Mexican and French) and even a Mediterranean diet. On this list, the names of Italian dishes occur next to Armenian lavash and Uzbek pilaw known since the 10th century [11]. This function of food is often used by overweight people as an excuse to justify their unhealthy or extravagant eating habits, which in some cases culminate in polyphagia[2].

The widespread habit of eating in front of TV or a computer only worsens the physical condition of obese individuals. Known as Fernsehkauen in Germany, this habit helps to cope with facts of life and "digest" social anxiety but also results in the continuous growth of obesity rates because, as a rule, the consumed food is rich in calories (nuts, chips, sandwiches, beer etc.).

Food is often used by overweight people to compensate for unsatisfied socio-ethical needs for communication, recognition, acknowledgement of their skills and abilities, including the ability to engage in a sexual relationship. Children with unhealthy eating behavior may be in acute need for the parental love they do not get. Sometimes, food is perceived as a reward or gratification, especially by food addicts[3] in a socially or ethically dependent position. This phenomenon is observed among slaves, prisoners or people who have a strong code of taboos or are ethically controlled by others. Specifically, one of the popular punishments for children is depriving them of food or not allowing them to have sweet treats, ice-cream or delicacies; in the same way, food is often used as a reward. In orthodox Christianity, the end of fasting is celebrated with feasts as a reward for good faith and righteous behavior. There are certain dietary restrictions in other religions, too, including the prohibition of pork in Islam or beef in Hinduism, which morbidly obese people are sometimes exempt from because of their condition.

Among the diversity of socio-ethical manifestations of eating behavior demonstrated by obese individuals, another one is worth mentioning: meals as an aesthetic experience. This is achieved through rituals, beautiful food presentation, etc. It is reported that some people gain weight in order to protect themselves from unwanted socio-ethical changes imposed by the family, like marriage, partnership or employment, or to justify their own failures in life. Often an overweight individual seeks a mystical explanation for their condition, blaming it on supernatural powers, hidden and yet understudied properties of food, etc.

Research into the underlying causes of obesity has uncovered a few implicated social and ethical factors. One of them is psychological trauma caused by society or, more commonly, by family circumstances. Dissatisfaction with family life can result in escapism eating or overeating perceived as a rescue from the unfulfilling reality. Another contributing factor is adherence to social, ethical, ethnical and cultural eating stereotypes consisting in the consumption of profuse amounts of food and alcohol beverages.

The path to obesity can begin with the idea instilled in the child by their parents that chubbiness and good appetite are signs of good health. Another possible cause of obesity is one's own perception of excess weight and overeating as evidence of social success, well-being and prestige. These ideas stem from parenting mistakes and too much parental care that takes the form of giving the child too much food. They are one of the primary social and ethical causes of pediatric obesity usually persisting into adulthood. Similar to excessive love, the total neglect of a child, who is unwanted, can promote obesity; usually such children are victims of the authoritarian parenting style, have frequent confrontations with their parents and develop the feeling of being unwanted in spite of exaggerated care of the child's nutrition or clothing.

Other socio-ethical contributors to obesity include the impact of the social environment on eating habits, advertisement, dissemination of ideas that emphasize the attractiveness of feasts and inadequate consumption of food and beverages. The reality of today makes a person a hostage to food that contains taste enhancers and additives stimulating subconscious craving for such food. Some develop addiction to food and join the ranks of obese people, unable to resist the temptation and adopt a healthy lifestyle.

The ubiquitous feeling of insecurity in the face of multiple threats and challenges, powerlessness and the failure of the state to protect human rights, as was the case during the COVID-19 pandemic, spark an inner socio-ethical conflict. Many try to escape by taking to food and alcohol.

Some use food as a protection from troubles. This behavior was described in the book by the American author Louise Hay *You can heal your life* sold in 50 million copies [12].

Dissatisfied with their appearance or personal life, overweight people sink into depression, and start seeing food as their best friend and the way to cope with inner conflicts. In need of attention or facing a negative attitude from society, they consume more unhealthy foods, trying to satiate the void that stems from the lack of communication [13]. Inability to find a healthy strategy for coping with stress results in seeing a piece of cake or another delicacy as a compensation for negative

[2] Polyphagia: from Ancient Greek: πολύς (many, much) + φάγειν (eating) — an eating disorder manifested as in-creased appetite, excessive hunger and overeating.

[3] Addict – a person who has substance or psychological addiction.

impressions but at the same time aggravates the condition. Oftentimes, overweight people do not know how to control their emotions and seek comfort in food and alcohol. They struggle to prove their worthiness through the adopted eating behavior and recommend this strategy as effective. However, they forget about the consequences. Together or separately, all of these factors can exert their detrimental effect. In the presence of instability, increased stress and information overload, they can cause addiction just like alcohol or narcotic drugs.

CONCLUSION

Oversimplification of the obesity problem by reducing it down to physiological or medical factors and personal responsibility, and the lack of attention to its ethical and social aspects make the analysis of this global problem inaccurate and lead to wrong conclusions and solutions. If it were as easy as in the saying "eat less and move more", obesity would have been eradicated long ago. When social and ethical aspects of the problem and its causes are ignored, most serious contributing factors are left out of the equation.

The socio-ethical duty of the state and society is to take effective measures aimed at reducing the prevalence and dangers of obesity and eliminating its causes. Such measures can considerably increase the well-being of the population. Inability to implement them will have a detrimental effect on the social capital and health of generations, promote inequality and multiply troubles.

Strategic mechanisms are needed to fight obesity at the national, regional and international levels and eliminate socio-ethical factors promoting the disease. It is important to bring up the subject of obesity in the context of bioethics discussed in the UNESCO's program on bioethics, the ethics of science and artificial intelligence. International congresses, symposiums or round tables on different aspects of obesity, extensive research into this problem and practical work of bioethics committees of National Commissions for UNESCO would make a great contribution to elaborating strategies to fight obesity.

Obesity affects the lives of millions of people worldwide. Only a comprehensive approach to this social and ethical issue can help in finding the right solution.

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BIOETHICS IN THE 21ST CENTURY: CHALLENGES AND PERSPECTIVES

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In this article, the authors review the role of bioethics in the processes of risk communication and socio-humanistic support for innovative development of technoscience, and analyze its commitment to the concepts of precaution and prevention. More focus is put on certain ethical challenges of the 21st century associated with the development of artificial intelligence, deep learning in medicine, genome editing and 'new parenthood' practices. They have exploited the potential of bioethics in ethical and axiological reflection on the prospects of healthcare far-reaching reforms and in sociohumanistic assessment of transformed ideas about the human nature, family connections and established social order. It is shown that the experience of complex problem discussion and solving alongside with advisory mechanisms and bioethical procedures respond to pressing challenges of biotechnoscience and will be in demand in future.

Key words: bioethics, artificial intelligence technologies, new reproductive technologies, human genome editing, global challenges in bioethics.

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БИОЭТИКА В XXI ВЕКЕ: ВЫЗОВЫ И ПЕРСПЕКТИВЫ

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В статье рассматривается роль биоэтики в процессах коммуникации рисков и социогуманитарного сопровождения инновационного развития технонауки, анализируется её ориентация на идеи предосторожности и превентивные стратегии. Особое внимание уделено этическим вызовам XXI века, связанным с развитием технологий искусственного интеллекта и глубокого обучения в медицине, а также технологий редактирования генома и практик «нового родительства». Раскрыт потенциал биоэтики в этико-аксиологической рефлексии перспектив радикальных преобразований здравоохранения и в социогуманитарной оценке трансформации представлений о природе человека, семейных связях и сложившемся социальном порядке. Показано, что опыт обсуждения и решения сложных проблем, а также совещательные механизмы и процедуры биоэтики отвечают не только актуальным вызовам биотехнонауки, но и будут востребованы в будущем.

Ключевые слова: биоэтика, технологии искусственного интеллекта, новые репродуктивные технологии, редактирование генома человека, глобальные вызовы в биоэтике.

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INTRODUCTION

Bioethics first emerged in the second half of the last century following two basic tendencies. The first tendency was associated with ethical implications in clinical practice, whereas the second one was subject to 'the need of human beings to be well informed about the numerous ethical dilemmas triggering breathtaking progress in biological sciences and their biotechnological applications' [1]. Today, bioethics is an interdisciplinary field of research, academic discipline and social institution of ethical and, in a broader sense, sociohumanistic examination targeted at a comprehensive assessment of biomedical innovations. These comprise ethics committees and commissions, which operate both at the local (ethics committees of research institutions) and national/international levels (as a part of agencies of the United Nations, European Union, European Council, Parliaments, etc.). The Universal Declaration on Bioethics and Human Rights adopted by the General Conference of UNESCO on 19 October 2005 recognized the role of these institutions in universal management mechanisms [2]. In various countries, the nature of these institutions is dependent on sociocultural context such as regulations, values and social attitudes, which are largely explaining why, for instance, a patient's right to refuse life-sustaining treatment is legally justified in some regions (states and countries) and invalid in others.

BIOETHICS AND BIOTECHNOSCIENCE RISK COMMUNICATION

The issues of bioethics are a constant source of *public concern*. This points at a specific role of bioethics in public communication of biomedicine and technoscience risk. Responding to dishonorable things in medical practice and to public concern for how research findings can be used, bioethics is a way and location to accommodate opinions of scientists, doctors, theologists, lawyers, and ethics experts. Many issues are addressed in a *proactive* way, expanding horizons of moral responsibility in the best interests of the future. We can't yet alter the genes of future children or imprint consciousness into an electronic device or replace hospital doctors by robots, but the experience of global disasters and turmoil of the 20th century urged us to reconsider not just the scope and forms of human responsibility amid rapid development of science and technology but also our attitude to remote consequences of irresponsible use of modern technologies.

In terms of theory, Hans Jonas, a German-born American philosopher**,** conceptualized the need of transition from ex post responsibility to ex ante responsibility in the second half of the last century by offering the new 'ethics of anticipation and responsibility' [3]. He assumed that the traditional ethical system was limited to the neighbor effect in the 'here and now'; force and knowledge of modern civilization should, however, make 'heuristics of fear' hold the central place in moral reflection. According to Jonas, the sources of our fear and undesirable scenarios of the future will bring the understanding of what 'we value indeed' steering the technological civilization in the right ethical direction.

Commitment of bioethics to the future is seen in the attempts to deal with cases like wrongful life suits. Children with severe hereditary diseases blame doctors, who could predict that the children would have a bad quality of life, but failed to inform their parents of a possible abortion. The capacity of medicine to predict the risks for the health of future children in such a surprising way turned into an unpredictable reaction of the children, claiming that their 'life is not worth living'. Who should select between a lack of life and life itself, the value of which is compromised from the very beginning? How should this be done and which moral coordinates have to be followed? From the perspective of bioethics, the discussion is deprived of any sense, as it is impossible to estimate the future child's sufferings [4]. The interest hereto is, however, heightened due to the attempt of looking behind the horizon of the present and understanding which risks and rewards are linked to any moral decision or innovation using a thought experiment (an actual bioethical method). At the same time, the research interest is focused both on separate technologies such as editing the human genome, and on ethical and philosophical issues of the 'future human nature'.

Starting from the Human Genome International Project, bioethics and social technical assessment are assigned a key role in *socio-humanistic support for technoscience innovation development*. According to P. D. Tishchenko, 'today, any more or less serious biological and medical project comprises socio-humanistic reflection accompanying and ensuring socialization of innovative achievements' [5]. The programs were responsible for the formation of a language of interdisciplinary and constructive discussion of occurring issues, specific layer of ethical and philosophical knowledge, and evident resource of soft management, which eliminates the gaps in regulatory activity and doesn't require long-term adjustments at the level of national or international legislation.

In this context, it is also important to note the transition from analysis of consequences to the strategies of forward assessment of new technologies. In the first case, bioethical approaches of the Human Genome Project were clearly determined, whereas the Human Brain Project initiated in 2013 was focused on the logic of caution and forward response to possible challenges. This approach is more than just a wish to foresee possible risks and perspectives, it is also an attempt to timely oppose technological inevitability to rational, conscious and responsible choice. However, scientists can't make an independent choice any longer, as interests of the society have to be respected.

Commitment of these programs to social measurements is associated with the so-called turn for a dialogue in science. According to S. Franklin, an investigator from Cambridge, this was the reason why bioethics was similar to the initiatives of public participation in scientific decision-making. 'Politicians, interviewers, and governmental bodies responsible for arrangement of ethics consultation on issues like mitochondrial donation are now making assessments formerly made by experts in bioethics. Journal editors, financial institutions, grant review commissions and politicians are new experts in bioethics' [6]. The author claims that '… everyone has to be an ethicist now' [6].

The article by S. Franklin initiated another discussion devoted to the role of bioethics in social communication of risks associated with new biomedical technologies and in management of science and technologies. However, it played out in fresh colors during the pandemic when shortcomings and ill-preparedness of national healthcare systems updated certain issues that were traditional for clinical ethics and that have remained in the periphery of investigators' interests for a long time. Distribution of scarce healthcare resources was definitely not the only moral issue, though it reminded that searching moral support in this unstable world is difficult and that medical decisions require ethics support. At the same time, there was a widely accepted position. According to it, no decision may be taken by one man only. This can reduce the risk of outrage and 'guarantee sequence, justice and transparency of decisions'. Then the community can comprehend the purpose of any assortment protocol and how it will be used, and be sure that it is used correctly [7].

It is also worth of note that bioethics influenced the formation of nanoethics, neuroethics and IT ethics which determined ethical dimensions of NBIC-convergence and development of complex approaches to ethical reflection of biotechnoscience. Thus, 'accidental findings' of MRI-guided brain research are combined in discussions of neuroethicists and bioethicists. Who and how must inform a volunteer/patient of the finding? How can collaboration between doctors, investigators and patients be built?

An attempt to reveal ethics challenges of **artificial intelligence** (AI) and **deep learning** (DL) **technologies** in medicine results in another complex set of issues. The challenges seem interesting not only because of the issues arising when IT technologies and biotechnologies converge, but also because they show the specific nature of 'grand challenges' in bioethics alongside with **technologies of genome editing and practices of 'new parenthood'**. The interest is not limited by discussions of experts and involved public members, and attracts close attention of international institutions (UNESCO, the Committee on Bioethics of the Council of Europe, etc.).

The issue of grand challenges became part of bioethics under the 'Grand Challenges in Global Health' initiative from the Gates Foundation launched in 2003 in collaboration with the US National Institutes of Health. After that, they turned into the tool, which inspired the international society of scientists to achieve certain predetermined global purposes with social, political and technical aspects [8]. They are associated with a number of socio-humanistic issues which could be settled using the procedures and institutions of bioethics by focusing on the parameters of social and moral acceptability and determining the paths of technoscience stable development.

ETHICAL CHALLENGES OF THE 21ST CENTURY

AI and Deep Learning

Artificial intelligence (AI) and machine learning are capable to fundamentally change healthcare and system of medical services [9] at the institutional, research and clinical levels by, in particular, improving patient care, medical recommendation

compliance control, etc. Utilizing complex algorithms for data processing and based on the experience of numerous specialists, AI systems are superior to any doctor as far as decision making time and scope of the data considered go. Thus, it took 10 minutes for IBM's Watson AI to diagnose a rare form of leukemia in a patient by comparing her genetic changes with the database of 20 million oncological research papers. As a result, doctors from the Tokyo University could make a correct diagnosis and prescribe a necessary treatment [10].

Today, the basic AI advantage is related to the possibility of using deep learning based on a large amount of data for diagnostic and prognostic purposes. Gradual engagement of automated systems into clinical practice, however, results in a set of complicated questions. Will AI implementation result in the loss of competencies and skills, reestimation of clinical thinking as a precondition for high professionalism in medicine? Will the automated systems assist or replace specialists? How can AI development perspectives be applied in medical education?

Specialists in bioethics have to deal with an important task of taking into account a broad range of occurring ethical issues. For instance, high expectations are set for the development of new pharmaceuticals where the use of AI is expected to bring about significant progress [11]. AI can also successfully recruit volunteers and patients for clinical trials. The advantage of using big data by AI can, however, serve as a discriminating factor with rare diseases [12].

The issue of responsibility is equally complicated. Who must be responsible for mistakes: doctors, system developers or clinics? In the majority of cases, it will take time to discover the mistakes, which, as a consequence, can impact more than one patient. At the same time, unrecorded parameters can be the reason for that. This occurred, for example, when a sequence of clinic activities during a machine learning based decision support system (ML-DSS) development was underestimated. The system aimed at a mortality risk prediction in 14199 patients with pneumonia to stratify them according to the risk level. High risk required hospitalization, and low risk meant outpatient care. According to ML-DSS estimation, patients with pneumonia and asthma fell within the low-risk group, whereas for patients with pneumonia only it was quite the opposite. How could asthma be a protective factor? It wasn't the algorithm of decision making that created a problem. The point was that patients with a history of pneumonia and asthma were sent directly to ICUs to prevent complications. Thus, the level of mortality was lower in patients with pneumonia and asthma as compared with those with pneumonia only (5.4% and 11.3%, respectively). The ML-DSS failed to rely on the context and interpreted the presence of asthma as a protective variable [13]. The impossibility to consider all significant facts and parameters during development of similar systems can result in other contextual errors, while overdependence on the ML-DSS will increase the risk of failures. Thus, the use of AI programs with a large potential of human error correction, improving the accuracy of medical diagnosis and quality of healthcare can ultimately lead to a reverse situation, when a large number of imprecisions and errors will have an effect on numerous patients. It is not accidental that, according to some authors, modern medicine may not be developed following the 'or-or' logics (a doctor or an automated system): 'when human and machine intelligence strive to accomplish the same task, we must be ready to use any approach enabling the exact and reliable accomplishment of the task. Ironically, the most difficult task set by the early AI in medicine remains totally human and requires to be aware of itself and its limitations, control any forms of self-confidence, rely upon the assistance of others (even machines) if necessary and always try to do its best' [14].

Another worry is that a constant growth of doctors' dependence on automated machines can result in the lack of experience, loss of important competencies, which make clinical thinking and true professionalism impossible. The last one includes special knowledge, competencies and personal qualities (compassion, patience, etc.) summarized by A. M. Bekhterev as follows: 'If a patient doesn't feel better after chatting with a doctor, then the doctor is failing in his job'. Will patients feel better after their interaction with a machine taking medical decisions? Trust is another problem of a patient-physician relationship. The assertion that 'a robot is better than a doctor' can be based on dissatisfaction with the quality of medical services, unsuccessful experience of interaction with a doctor, and many other factors, but not on trust in new technologies.

Human genome editing

The issues of human genome editing were the center of bioethical discussion in 2015 following the experiment of Chinese scientists in cells from beta-thalassemia patients. They managed to introduce changes in 4 of 86 fertilized eggs using the most effective CRISPR/Cas9 technology of genome editing. This resulted both in hopes to solve numerous medical issues and serious concerns in ethical, social and legal risks. Discussion of the latter in the same year formed the basis of agenda of two international activities such as meetings of the Committee on Bioethics of the Council of Europe and International Summit on Human Genome Editing where the corresponding statements were adopted. The announcement by He Jiankui, the Chinese biochemist, concerning the birth of twin girls with an edited gene, made in autumn 2018, served as a second impulse to the debate between experts and community.

By now, two problematic fields of bioethics are setting the trend for such discussions. The first group of 'technical' questions relates to safety, reliability and clinical appropriateness of using the technologies of genome editing for scientific and medical purposes. The issues will be resolved with their advances. However, the process of innovation development can't be totally deprived of ethical measurements just because no biomedical study may currently be conducted without an approval of the Ethics Committee.

The second group includes numerous ethical challenges concerning the use of genome editing technologies to make edits in somatic and embryonic human cells. Editing somatic cells faces no serious ethical concerns as the changes are not inherited by future generations and are associated with our hopes to get rid of many hereditary diseases; the studies require observance of standard ethical principles and standards. Human germline engineering is the area of greatest concern spawning the fear of using technologies for the 'dual' purpose of treatment and 'human improvement'.

A boundary between treatment and improvement was set in the report entitled Behind the Therapy: Biotechnologies and Pursuit of Happiness of the President's Council on Bioethics, the USA, where it was asserted, among other issues, that the 'dual use' of biotechnologies for treatment and purposes behind the therapy generates new and complicated problems. Considering therapy as the use of biotechnology derived pharmaceuticals for treatment and correction of disturbances

aimed to restore normal health and working capacity, the authors of the report defined improvement as the use of biotechnologies to ensure direct intervention into 'normal' operation of a human body and mind in order to increase its functional capabilities [15]. The improving technologies include cosmetic surgery, doping in sports, academic doping, adult's and embryo's gene improvement. Thus, the World Anti-Doping Agency has already prohibited using gene doping in elite sports [16]. 'Altering the genes of future children' is yet under discussion as the challenge of the future. It is, however, difficult to ignore B. G. Yudin's opinion who considers the problem from the point of view of humanism: 'In spite of many imperfections inherent to the human race, we, however, must be extremely careful about its biotechnological (or any other) editing. It appears that we stand on the positions of humanism inasmuch as we believe that the human nature is a value and demands protection. If we consider longevity, health, or physical, mental or intellectual traits as the supreme value to achieve which a human being can be edited and a posthuman may be created, we make a step not towards superhumanism, but towards antihumanism' [17]. Thus, according to New Zealand-based bioethicist N. Agar, gene modification can be considered as an improvement if 'it makes a child better than a human being can normally be to a certain significant extent' [18].

Discussions centered around genome editing closely resemble the ones about human cloning which arose at the end of the last century, but quickly came to nothing following banning in the majority of countries. Some scientists believe that future developments of genome editing must be discussed with community. At the same time, in our strive for social consensus, it is necessary to remember that recent discussions concern both ethical context of genetics, and assisted reproductive technologies. The attitude towards a human embryo study and in vitro fertilization (IVF) significantly differs in various countries and can't be assessed with certainty.

Reproductive technologies and new 'parenthood'

Development of assisted reproductive technologies in the second half of the last century gave rise to a number of ethical problems. Their discussion led to a conflict of various moral, religious and legal approaches. Discrepancies were found in the anthropological status of the embryo, determining the moment of life beginning, legitimacy of human germ cell genetic manipulation and preservation.

Moreover, new reproductive technologies left the university rapidly and went to the private sector. In 1980, R. Edwards and P. Steptoe founded Bourn Hall Clinic (Cambridge, United Kingdom). It happened 2 years after the birth of Louise Brown, the first baby to be born as a result of in-vitro fertilization. The global market of reproductive technologies was developed rapidly as well, owing to the interest of potential parents and prohibition in some countries [19]. In this respect, we fear that demand for the birth of a gene-edited child may lead to the technology improvement, and the fear is real, more so that He Jiankui was interested in founding a private clinic of this kind [20]. It is obvious that mechanisms of ethical and legal regulation play a key role under these circumstances as they are taking into account both the requirements of science and technology development and its socio-humanistic measurements

The progress of assisted reproductive technologies did not only allow older reproductive age for women preserving their 'biological material' in biobanks (postponed parenthood) but also launched the practice of 'posthumous reproduction'. Storage of eggs in biobanks leads to no serious ethical objections while used because of health issues (for example, prior to a surgery), but is, however, often critized when social tasks are to be solved.

In case of posthumous reproduction, conception occurs when both parents are alive or when the genetic father or mother or even both would be deceased at the time of conception (IVF or posthumous insemination) [21]. Posthumous reproduction available around the world offers different approaches to biological material sampling in men and in women, consent practice (vital consent, no consent), and transfer of embryos after one or both parents died. For instance, 'in Israel, it is permitted to transfer cryopreserved embryos into the widow's uterus within one year after her husband deceased, even if his consent is lacking. But you can't use the embryos when the wife is dead. The postmortem use and retrieval of sperm of those soldiers died in combat is even possible, and no their preliminary consent is required. In Germany, Italy and France posthumous reproduction is prohibited, no matter whether a written informed consent is lacking or not' [21].

Another aspect of the matter consists in the use of frozen embryos for reproductive purposes after the death of one or both parents. There is no doubt that both parents aimed at a child's birth. But who can assert for one or both of them whether their choice would be the same under new circumstances? If one parent decides to transfer an embryo, the child will be born in a single-parent family, which may be considered as infliction of harm. But an attempt to correlate non-existence with the chance to live, even in a single-parent family, will inevitably generate a discord.

Posthumous reproduction substantially transforms the family institution undermining traditional social values and interrelation models. By acknowledging the right of a human being for a choice, bioethics must play a key role in the development of consent and dissent gaining procedures, and timely and complex estimation of new reproductive technologies which often outrun the possibilities of socio-humanistic expertise.

CONCLUSION

Ethical issues in artificial intelligence and genome editing, intervention in the field of human reproduction and new 'parenthood' are in the center of present public discussions and scientists' attention. In the debate presented, the boundaries of intervention into a human nature, autonomous choice and responsibility are defined, deficiencies in regulatory issues are found, the ways of new technology development in the world of CRISPR twins, autonomous cars and families without a common biological destiny are outlined. The discussions are technically outside the scope of the above problems being ultimately an attempt to answer the question about the kind of world we want to live in. An ultimate answer hereto can hardly be provided. Rapid development of biotechnologies, active implementation of IC technologies in medicine, achievements of neurosciences and synthetic biology, risks of epidemics, etc. will set the agenda of bioethical discussions in the 21st century. However, discussion of the Human Brain Project achievements, resolving regulatory issues of using an artificial uterus for the purpose of reproduction and implantation of chips engaged in health controlling will inevitably require referral to some approved ideas of a human life value, grounds for reasonable intervention into 'the regimen of natural entity' and current social order. That is why a specific expert position of bioethicists, and theory and practice of bioethics, where the academic and publics parts intertwine in a particular way, will be in demand.

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CORRELATION OF NEUROETHICS AND BIOETHICS

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Neuroethics is an interdisciplinary field of study that considers ethical issues raised by increased understanding of how the brain works and development of technologies of research and influence the brain function. In addition, neuroethics is understood as the study of neural processes of moral decision-making. Originally, the problems of neuroethics have developed in bioethical context. With the expansion of the set of questions and the emergence of a separate discussion of the ethics of neuroscience, as well as the development of research on classical issues of ethics using neuroimaging technologies, neuroethics is becoming a separate field of study. In the article, the authors consider two approaches to the relationship between neuroethics and bioethics: (1) neuroethics as a special area of bioethics and (2) neuroethics as an independent discipline that has its specific features. Understanding neuroethics as a part of bioethics predetermines the consideration of its problems as a study of the social consequences of the achievements of neurosciences and the normative regulation of medical and research practice. The approaches that define neuroethics as an independent field emphasize the combination of multidirectional study (ethics of neuroscience and neuroscience of ethics) as a specific feature of the discipline. These studies are related by their common object of research — the brain. The approach of reductionism underlying the dominant research in neuroethics is noted in the article as a factor of a shift of neuroethics from the humanitarian context of bioethics towards neuroscience.

Key words: Neuroethics, Bioethics, Neuroscience, Cognitive Sciences, Medical Ethics, Neurotechnologies, Social and Humanitarian Expertise

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СООТНОШЕНИЕ НЕЙРОЭТИКИ И БИОЭТИКИ

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Нейроэтика является междисциплинарной областью исследования, которая рассматривает этические вопросы, связанные с углублением понимания того, как работает мозг и развитием технологий для исследования мозга и влияния на него. Кроме этого под нейроэтикой понимается исследование нейронных процессов принятия морального решения. Исторически проблематика нейроэтики развивалась в биоэтическом контексте. С расширением набора вопросов и складыванием обособленного обсуждения этики нейронаук, а также развитием исследований классических вопросов этики с применением технологий нейровизуализации, нейроэтика становится отдельной исследовательской областью. В статье авторы рассматривают два подхода к соотношению нейроэтики и биоэтики: (1) нейроэтика как специальное направление биоэтики и (2) нейроэтика как самостоятельная дисциплина, связанная с биоэтикой, но обладающая собственной предметной спецификой. Понимание нейроэтики как части биоэтики предопределяет рассмотрение её проблематики как исследования социальных последствий достижений нейронаук и нормативного регулирования медицинской и исследовательской практики. Подходы, определяющие нейроэтику как независимую область исследования, подчёркивают в качестве специфической особенности дисциплины объединение разнонаправленных исследований (этики нейронауки и нейронауки этики), связанных спецификой объекта исследований — мозга. Редукционистский подход, лежащий в основании господствующих в нейроэтике исследований, отмечен в статье в качестве фактора, отдаляющего нейроэтику от гуманистического контекста биоэтики.

Ключевые слова: нейроэтика, биоэтика, нейронауки, когнитивные науки, медицинская этика, нейротехнологии, социально-гуманитарная экспертиза

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INTRODUCTION

Neuroethics is a young field of study, the conceptual foundations and disciplinary boundaries of which have been determining since the early 2000s. Researchers are still discussing various approaches to understanding the issues of neuroethics, grounds for referring neuroethics to humanitarian or scientific approaches and interdisciplinary classification of questions. Unclear position of neuroethics among novel interdisciplinary areas of concern is also confirmed by various opinions about the correlation of bioethics and neuroethics. Is neuroethics a subdivision of bioethics or should it be developed independently?

It has to be noted that neuroethics is a general term for two different subjects [1]. The first subject is the ethics of neuroscience; it includes ethics in medical research, and social and humanitarian analysis of ethical and legal implications of practices associated with the use of neurotechnologies in different areas of life. The second subject is the neuroscience of ethics, which investigates the neural basis of ethical decisions as well as reconsidering the essence of ethics itself based on empirical data and brain function. There is a close

correlation between the two subjects: neuroscience of ethics provides neuroethics with empirical materials, whereas ethics of neuroscience provides for regulatory research control.

If neuroethics is considered as the ethics of neuroscience, then bioethics and neuroethics must be taken as cognate disciplines with intercrossing problematic fields. For example, the problem of death criteria is one of fundamental issues traditionally developed in bioethics. However, it is currently at the intersection of neuroethics and bioethics as the concept of brain death and criterion of death in the form of brain death are approved [2]. Modern researches of dying processes concentrate on the investigation of attenuated brain activity [3]. Though the criterion of brain death is accepted in medical practice, the validity of using the criterion is still discussed due to medical, philosophical and ethical aspects of uncertain brain death registration in practice and difficult registration of pediatric brain death.

Another common object of interest for bioethics and neuroethics is a possibility to improve a human being. Human enhancement practice is a set of biotechnology-based bodily, genetic, psychoemotional and cognitive transformations necessary to change the physical, cognitive or ethical human attributes [4].

Due to specific issues associated with free will, nature of consciousness, mechanisms of taking an ethical decision and specifics of cognitive processes, neuroethics can be considered as an autonomous research area. To solve specific problems, neuroethics uses the concepts of consciousness philosophy, cognitive neurobiology, neurobiology of emotions and social neurosciences [5, 6].

In this article, we consider two approaches to how to define the relationship between neuroethics and bioethics: neuroethics as subspecialty within the study of bioethics and neuroethics as an independent discipline.

NEUROETHICS AS SUBSPECIALTY WITHIN THE STUDY OF BIOETHICS

According to the first approach, neuroethics is considered as subspecialty within the study of bioethics used for ethical analysis of brain working practices but being an interdisciplinary field. The purpose of bioethics and neuroethics as its domain consists in regulatory control of practices of interacting with the living material. Being a type of applied ethics similar to bioethics, neuroethics is based on bioethical principles. One of them is the concept of Beauchamp and Childress with four principles developed: respect for autonomy, nonmaleficence, beneficence, and justice [7]. Neuroethics is comprehended as a restricted professional medical ethics, applied research ethics, social and humanitarian innovation expertise.

Neuroethical issues and its institutionalization initially occurred in the area of bioethics, and medical ethics of neurology and neurobiology, in particular. According to Illes and Bird, modern neuroethics is rooted in researches devoted to ethical implications of lobotomies, and eugenics programs in Nazi Germany, closely connected with discrimination by mental signs [8]. Since 1960–1980, brain-related ethical issues expanded as neurosciences developed and were discussed in the general context of bioethics. In 1996, the International Bioethics Committee of UNESCO (IBC) presented a special report on ethical implications of neurobiology achievements [9].

During the first conference devoted to neuroethics entitled ‘Neuroethics: Mapping the Field’ and held in 2002, William Safir said that the problems of bioethics and neuroethics were identical. He referred to neuroethics as ‘old wine in a new bottle’ [10]. Wolpe, an American bioethicist, stressed that the problem of neuroethics estimates the ethnicity of brain examination medical techniques associating neuroethics with medical ethics. He stated that ‘the term neuroethics is used by European neurologists to refer to ethical issues in brain disorders, such as stroke or epilepsy, and it had been used at times of ethical concerns in psychiatry, child development, and brain injury rehabilitation’ [11].

Russian neurosurgeon L. B. Likhterman speaks about medical specifics of neuroethics: ‘Neuroethics aims at the development and usage of ethical standards in neurology, neurosurgery and psychiatry’ [12]. According to him, neuroethics is an instrument that humanizes neurosurgery, making the tasks of neuroethics closer to biomedical ethics.

Discussing future purposes and perspectives of neuroethics, researcher Eric Rasin also believes that neuroethics is part of bioethics. The leading directions include an improved interaction between medical staff and patients during treatment, consideration of private problems associated with neurological and mental diseases such as mental patient care, investigating the phenomenon of a mental disturbance, provision of compulsory aid to patients with disturbed consciousness [13]. The important area often falls outside medical bioethics and can be taken under the responsibility of neuroethics. Thus, neuroethics, treated as humanitarian expertise of research practices and techniques, brain therapy and effect, approaches the applied bioethics.

NEUROETHICS AS AN INDEPENDENT AREA OF EXAMINATION

According to the second approach, neuroethics is an independent discipline with its own grounds and problematic boundaries, which are different from those of bioethics. The approach expands the comprehension of bioethics and includes research of the nature of ethics, effect of neurobiological research on human self-understanding and fundamental categories of law and ethics, apart from professional ethics, research ethics and humanitarian expertise [2]. As ethics of neurobiology develops, neuroethics is interpreted as a novel, reconsidered ethics of cognitively improved digital society.

The basic peculiarity of the neuroethics comprehended in such a way is that it discusses ethical issues associated with the unique organ with the functions incompatible with any other organ of a human body. It makes the related problems completely different. Based on the documents of The Human BRAIN Project (USA), it is stated that though ethical issues typical of other areas of biomedicine influence the neuroscience research, there exist special ethical aspects unique for the brain research: ‘as the brain is the source of consciousness, our most inner thought and basic human needs, technological brain studies influenced the occurrence of new social and ethical issues. Can brain development research be used to improve the cognitive development at schools? What are the circumstances when mechanistic understanding of dependance and other neuropsychiatric disorders can be used to determine the liability in the legal system?’ [14].

The project where neuroethics is considered as a discipline is based on the assumption that the brain is an organ, which determines the human personality and is of a paramount importance in interpersonal relations. The approach due to which neuroethics turns into an independent research area makes it closer to the biological direction of the human entity research. In the reductive approach, the thought is expressed as ‘you are your brain’ and ‘brain is a place where the human personality is located’. Neuroethics considered as the birth of

scientific neurorotation tends to examine not just physical but mental issues as well. Considering the disciplinary specifics of neuroethics, Vidal and Ortega state as follows: 'unlike bioethics, neuroethics could gain acceptance as it claims to be exclusive because ontological beliefs are considered as empirical facts' [15]. The reductive grounds for neuroethics are explained by the fact that neuroethics was developed due to expanding possibilities of neurovisualization. The methods of neural process visualization show what direct knowledge looks like: we are more certain that observing the physical processes that take place in the brain makes is possible to comprehend the nature of consciousness, predict human intentions and even read thoughts.

Different approaches to the philosophy of consciousness differently treat the issue of consciousness and cerebral substance correlation: some believe that mental processes result from physical processes (Churchland, Dennet), others only notice the correlation between physical and mental processes (Chalmers, Daniel) [16–19]. However, as far as an empirical aspect of neuropsychology goes, brain damage definitely leads to the change in the personal qualities and type of cognitive processes. Ethical regulation of therapeutic and research intervention to the brain, use of neuroscience potential in various fields of life, and neurobiological research of the interrelation between the brain activity and human behavior turn to be relevant general areas of neuroethics.

Russian bioethicist Sidorova suggests that based on the relationship between neuroethics and reductionism related interpretation of psychophysical processes and human nature in general, neuroethics must be considered as part of bioethics or area close to neurobiology [20]. If biological reductionism is behind the neuroethical consideration resulting from neurophysiological determination of neuroscience, neuroethics is taken as an independent discipline.

With such an approach, neuroethics cancels the focus of research and practices on the most important bioethical principles and justifies radical technological interventions into a human organism required to improve its cognitive capacity. The principle of autonomy is at risk; the human integrity is not valued anymore and becomes even more vulnerable. The subject of neuroethical discussion can be not an unacceptability of interference into an individual autonomy, but a measure where the autonomy can be disturbed. If neuroethics is taken as a philosophical project with humanitarian orientation of ethical estimation of neuroscience and neurotechnologies, the author suggests it should be considered as part of bioethics.

The second approach accepts synthesis of various ideas of a human entity to search for perspectives and limitations of the most novel technologies.

CONCLUSION

A problematic field and status of neuroethics can currently be comprehended in different ways. Every comprehension enables various matching of neuroethics and bioethics as a developed research area (the article fails to consider the aspect of institutional designing of social and humanitarian expertise in the area of bioethics and/or neuroethics).

Neuroethics is developed within the projects accompanying the largest global brain research. From the functional point of view, it is closer to bioethics, as neuroethics analyzes ethical and legal implications, limitations and regulatory control of innovations, which result from discovery of neurosciences. Neuroethics becomes alienated from a human bioethical research, as it becomes positivistic, reducing comprehension of a human to description of physical processes in the body.

The relevance of analyzing the effects of novel data about the brain and neurotechnologies on a human being and society is undoubtful. It is impossible to develop criteria estimating safety and ethics of modern practices without a valuable and holistic approach to a human being. It makes neuroethics and bioethics related as problematic fields of philosophical discourse of modernity.

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TRANSPARENCY IN CLINICAL TRIALS

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In the age of information technology development, healthcare professionals around the world have the opportunity to simultaneously access advanced scientific developments, modern achievements, and the results of new clinical trials. The clinical guidelines of the international medical communities are based on the results of meta-analyses of clinical trial data. As new medical challenges emerge, clinical trial data are reviewed and re-analyzed. Unfortunately, to date, the results of not all studies are made public, or are presented selectively, indicating the positive effects of a particular technology (intervention), which makes it difficult to critically evaluate the results of work and makes the task of assessing the true effectiveness of the intervention more difficult. The problem of transparency of research data with the preservation of personal data of participants remains relevant for decades. This article is focused on possible ways of solving this problem and the analysis of the current situation in the world.

Keywords: clinical trials, transparency, openness.

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ТРАНСПАРЕНТНОСТЬ В КЛИНИЧЕСКИХ ИССЛЕДОВАНИЯХ

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В век развития информационных технологий специалисты здравоохранения по всему миру получили возможность одновременного доступа к передовым научным разработкам, современным достижениям, результатам новых клинических исследований. Клинические рекомендации международных медицинских сообществ построены на результатах мета-анализов данных клинических исследований. По мере появления новых медицинских задач проводится пересмотр данных клинических исследований и их повторный анализ. К сожалению, на сегодняшний день результаты не всех исследований предаются огласке, либо представляются выборочно, указывая положительные эффекты той или иной технологии (вмешательства), что затрудняет критическую оценку результатов работы и делает задачу оценки истинной эффективности вмешательства более сложной. Проблема открытости (транспарентности) данных исследований с сохранением персональных данных участников остается актуальной на протяжении десятков лет. Данная статья посвящена возможным путям решения данной проблемы и анализу сложившейся в мире ситуации.

Ключевые слова: клинические исследования, транспарентность, прозрачность.

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PREFACE

In today's world, during the era of evidence-based medicine, the patient-management tactics is selected in accordance with the clinical guidelines, based upon the data of systematic reviews and meta-analyses, which compile the results of randomized clinical trials [1]. Clinical trials, systematic reviews and meta-analyses enable us to assess true benefits and harm of certain intervention, medication or technology. With the high methodological quality of the study, adherence to all scientific principles, as well as the opportunity of free access and analysis of all the participants' individual data, the significance of the data obtained is beyond doubt. Availability of individual data increases the statistical power, allows for subgroup analyses and makes it possible to perform retrospective analysis of new parameters when obtaining new research data.

BACKGROUND

Scientific community, i.e., researchers, editors of medical journals, representatives of pharmaceutical companies, together with representatives of governmental control bodies, have been issuing statements concerning the need for increased research data transparency for many decades. Of particular concern have been the unregistered trials and unpublished research results, which demonstrate adverse effects of the intervention or no effects at all. Increasing competition forced the researchers to publish papers, reporting predominantly positive results, which gave rise

to unfair assessment of the intervention, and gave a false impression of the medication or medical technology efficacy [2]. However, every researcher has to register the clinical trial to be conducted in accordance with the Declaration of Helsinki, which is considered by the WHO as an ethical, moral and scientific responsibility, and to report the research results [3, 4]. That is why FDA changed the requirements for clinical trial registration in 1997. At that time the problems with trial registration transparency were identified, together with the lack of a single platform [5], which resulted in establishment of a single platform ClinicalTrials.gov in 2000 [6]. In 2005, mandatory trial registration as a prerequisite for publication was introduced by the International Committee of Medical Journal Editors (ICMJE) [7]; the WHO defined 20 basic items for trial registration since 2006, and launched the International Clinical Trials Registry Platform (ICTRP) in 2007 [8]. Later, in October 2008, the World Medical Association amended the Declaration of Helsinki by adding the principles for purported registration and public disclosure of the research results. Later the amendments were introduced in 2013: "Researchers are obliged to make the results of their research involving human subjects publicly available, they are responsible for completeness and accuracy of their research. All the parties should adhere to the adopted guidelines for ethical accountability. Negative and inconclusive or positive results should be published or disclosed in a different manner" [9]. Thus, obligation to disclose the results of all studies in a sincere and full manner was postulated. In the same year, 2013, the European Medicines Agency launched the new version of the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), containing information about protocols and results of clinical trials [10]. This register was largely consistent with Clinical Trials gov. A year later, Francis S. Collins, director of the National Institutes of Health (NIH), raised the issue of the need for research transparency, timely correction of errors, and adverse events reporting, referring to the need for maximal use of the knowledge for the greatest benefit to human health, as well as to what society owed to each clinical trial participant [11]. The same association established the time limit of 12 months for publishing the results after the study completion in 2015 [12]. Thus, the rules on timely submission of reports were strengthened annually due to the quest for transparency and extended legal responsibility, as reflected in the final rule issued by U. S. Food and Drug Administration in 2016 [13], and Federal Policy for the Protection of Human Subjects revised in 2017 [14].

Currently, legislative and regulatory framework on biomedical ethics and human rights continues to improve on all continents involving the international community. There are some international initiatives helping to improve the clinical trial transparency: Ottawa Group [15], which proposed a consensus document on global registration of clinical trials, signed by the WHO; Cochrane Community [16], providing accessible and appropriate information, supporting informed decision-making, based on systematic reviews and meta-analyses; UK Medical Research Council [17]; U. S. National Institutes of Health [18]; Institute of Medicine of the U. S. National Academy of Sciences [19]. Many pharmaceutical companies and medical publishing companies have also participated and continue to participate actively in the campaign. They redefined their policy in order to improve access to research data. Thus, the PLoS (Public Library of Science) journal was one of the first to request unrestricted access to data after publication of the article. Later the All Trials campaign was launched All Trials [20], which brought together many publications and scientific communities, as well as Yale University Open Data Access web-site [21], ClinicalStudyDataRequest.com web-site [22], which brought together many pharmaceutical companies, provided unidentified access to data in accordance with the decision of a panel of independent experts with mandatory publishing of data sharing results in refereed journals, and worked with the motto: "Sharing clinical trial data: maximizing benefits, minimizing risk" [23]. Currently, the WHO, UK National Institute for Health Research, USA, European Commission, and editors of many medical journals adhere to this principle.

The Nordic Trial Alliance Working Group on Transparency and Registration has been forged in Europe under the pilot project, involving the Scandinavian countries. The Alliance has embarked on the development of the effective and optimal method for clinical trial registration, raising public awareness on the trials and trial results, and individual participant data depersonalization. Regulations have been established, recommended for consideration and adoption at the statute level by States, in which clinical trials are conducted as amended in accordance with the current legislation. These regulations allow for unification and harmonization of research quality standards, data protection in the era of globalization with preservation of research results transparency [24].

CONCEPT OF TRANSPARENCY

In today's world, clinical trial transparency entails several levels:

1. Mandatory registration of clinical trials

Primary (prospective) registration of the clinical trial on the generally accepted international platforms on a priority basis prior to inclusion of participants. Registration of interventional and non-interventional studies, as well as the studies of medical devices, is mandatory. In addition, principles of transparency also provide for retrospective registration. Commitment to registration may be traced through the increase in the number if registered trials. The annual number of registered clinical trials in 2004 accounted for 3,294 interventional trials, and in 2013 it was 23,384 [25]. In 2013, international register contained information about a total of 186,523 trials, and in 2021 this figure went up to 378,460 trials. (Fig., source: https://clinicaltrials.gov/ct2/resources/trends).

The figure above illustrates the increase in the number of registered trials after the introduction of requirements for clinical trial registration by the International Committee of Medical Journal Editors (ICMJE, 2005) and Food and Drug Administration (FDA, 2007). Registration of trials contributes to effective knowledge sharing due to prevention of overlapping research, as well as the intervention futility and unexpected harm [29].

2. Publishing the clinical trial results and submitting the report regardless of the study results

WHO, World Medical Association (WMA), and European Medical Agency (EMA) request submission of the study results within 12 months after the date of the study completion, i.e. the final date of data acquisition aimed at measuring the initial result. Most of the clinical trial results become open to the public after being published in the peer-reviewed medical journal or on the web-sites where the clinical trials have

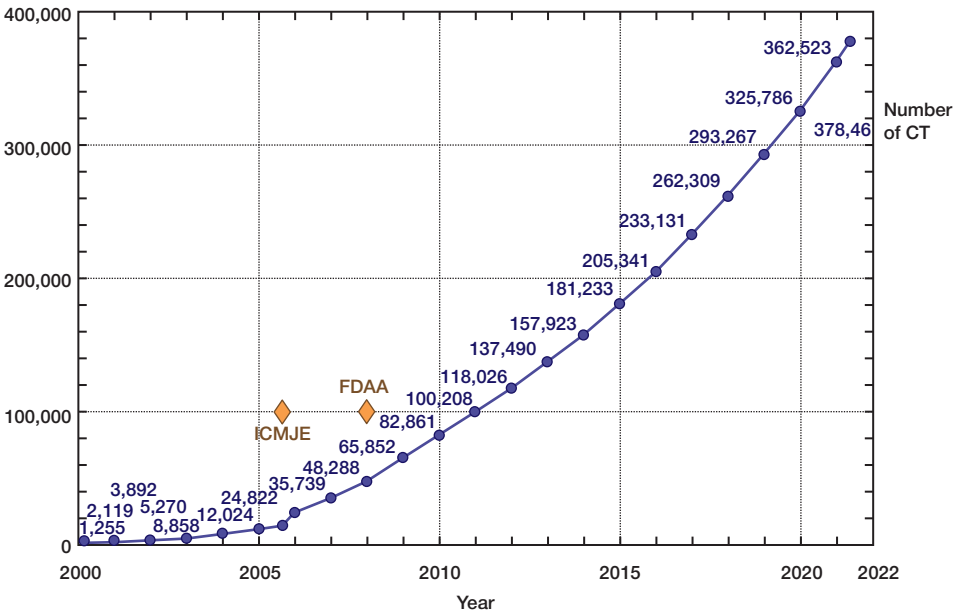

Fig. Dynamic changes in the number of registered CT

been registered. Detailed reports are prepared in accordance with the requirements of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP) [26], and with the CONSORT Statement [27].

FDA has stated (final rule) that in the case of failure to comply with the requirements concerning the time limits for submission of data, penalties would be imposed in the amount of $12,000 thousand per day of delay. Last year the study was published in the Lancet journal, where the authors assessed the average time of submitting the information by the researchers on the ClinicalTrials.gov web-site from March 2018 to September 2019: only 40% of reports were submitted in a timely manner (95% CI 39.4–42.2), the average delay of reporting after the date of the study completion was 424 days (95% CI 412–435), which exceeded the required time limit by 59 days [28]. Moreover, the authors noted, that industry sponsors reported in time, in contrast to state-owned companies and smaller sponsors. Unfortunately, despite the penalties and lawsuit, the compliance remains low. According to some authors, this is due to impossibility of reporting negative study results with limited funding, as well as to attempting to keep the data safe from competitors.

3. Availability of depersonalized (anonymous) participants' data to the scientific community for further analysis.

Clinical study reports are always more complete than publicly available data summaries, published on web-sites. However, such reports are most often available on request. Personal data of the participants are never included in the reports in deference to the personal data confidentiality. Currently, data depersonalization procedure is an extremely important issue, since only anonymized participants' personal data can be shared by the researchers and used for independent review of the clinical trial results and further systematic analysis. The participants' confidence that no re-identification is possible provides full compliance to ethical standards and principles of conducting clinical trials, protecting the interests of the study participant.

To summarize the main principles of the clinical trial transparency, it is worth noting that evidence-based medicine requires complete and thorough reporting, and timely disclosure of information would merely benefit all parties: clinicians, researchers, patients and study participants. This information allows clinicians to use alternative methods of treatment in patients, and contributes to better mutual understanding with the researchers. After gaining accurate insight into up-to-date evaluation of the issue, researchers can make more effective use of data for good planning and research taking into account all possible complications, pharmacoeconomic losses, and avoid the adverse events. The clinical trial participants have the right to know about the study results, to be given full access to the information about the study and all potential risks, and to understand their role and great personal contribution to healthcare promotion. Patients have the opportunity to learn about new technologies and medications, which provides an opportunity for selection of therapy, and increases public confidence in clinical trial data.

To overcome the existing problems with transparency of data, society and industry should understand that clinical trial data cannot be the property of the sponsor. These data are the property of the entire world community, serving to improve the quality of care provided. The system should be upgraded in order to avoid data entry duplication, simplify obtaining the reports for further analysis, ensure better protection of the study participants' personal data, and create a universal digital portal allowing for long-term storage of the data set and simultaneous use of the data set by global health community.

CONCLUSION

Research data transparency is the ongoing challenge and the only way to control safety and efficiency of therapy and vaccination, which is becoming increasingly important during the pandemic of the novel coronavirus infection. Moreover, this is one of the most effective means to motivate and improve vaccination coverage in order to create herd immunity. This would make it possible to prevent the further spread of infection and help the entire world community to return to a normal existence.

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“BIOETHICS: BRIDGE TO THE FUTURE” (1971) BY POTTER VR AS AN INTELLECTUAL MANIFESTO: TO THE 50TH ANNIVERSARY OF THE BOOK RELEASE

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This article analyzes the book “Bioethics: Bridge to the Future” by Potter VR as a personal message, a manifesto of an intellectual, a display of spiritual search against the backdrop of a crisis of ideologies, then looks into the factors that shaped the bioethical concept and establishes the significance this work and the bioethical concept have in the 21st century.

Key words: bioethics, Potter VR, intellectuals, “creative class”, responsibility.

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“BIOETHICS: BRIDGE TO THE FUTURE” (1971 Г.) В. Р. ПОТТЕРА КАК ИНТЕЛЛЕКТУАЛЬНЫЙ МАНИФЕСТ: К 50-ЛЕТИЮ ВЫХОДА КНИГИ

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В статье анализируется книга “Bioethics: Bridge to the Future” В. Р. Поттера как личное послание, манифест интеллектуала, проявление духовного поиска в условиях кризиса идеологий. Рассматриваются факторы формирования биоэтической концепции. Определяется значение работы В. Р. Поттера и биоэтической концепции в XXI в.

Ключевые слова: биоэтика, В. Р. Поттер, интеллектуалы, «креативный класс», ответственность.

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In 2021, “Bioethics: Bridge to the Future”, a book by Potter VR, turns 50 [1]. Despite the fact that the author himself stated the materials from the book were first published in 1962 (p. 7) [1], and regardless of the debate around the precedence of use of “bioethics”, a key concept, the book of 1971 is undoubtedly one of the keynote works that establishes the idea and conceptual meaning of bioethical categories.

The process of rethinking and updating of bioethical principles in theoretical and applied science, in social practice, including the aspects of economic processes, political decisions, is permanent, focused on the needs of an evolving society that adapt to the current situation. Certain aspects of the bioethical approach undergo critical analysis [2], but in general, its relevance in the real world of the 20th and early 21st centuries is not questioned.

There is obviously every reason to consider the bioethical strategy as a new sociocultural paradigm of its time [3]. Indeed, the fairness and the degree of influence of bioethical principles on the social processes of the 20th and early 21st centuries allow characterizing the V. R. Potter’s concept not only as an important stage in understanding the eternal questions of collation of the nature’s resources and civilization’s capacity, that of the world and the human being, but also view those principles as a socio-cultural phenomenon of that age.

Numerous studies have been published to date [2], but the work of V. R. Potter can be considered in the light of a yet another socio-cultural aspect. This article analyzes the book “Bioethics: Bridge to the Future” as a personal message, a manifesto of an intellectual, a display of spiritual search against the backdrop of a crisis of ideologies.

There are two factors that are rightfully viewed as historical conditions in which the bioethical concept was formed:

1) As a conceptual (in the broadest sense, moral) system, bioethics emerged when the crisis of axiological guidelines, which happened in middle of the 20th century, was gradually subdued, and there was a need for the most critical rethinking of the obvious and dramatic devaluation of what the European community held as its values.

The significance of the dramatic events of the 20th century, as perceived by Potter VR, is reflected in the book. This reflection includes the emotional description of nature in terms typically associated with the post-war chaos, and the didactic connotation of the concept of “dangerous knowledge” linked to the deployment of poisonous gases during World War 1 (pp. 35, 67) [1].

2) Bioethical strategy was formed when the civilization was rapidly advancing technologically, the boundaries of the humanity’s potential were boldly and “futuristically” reassessed, human kind was ready to make smaller steps forward and then leap into the future. Deontological stereotypes of the turn of the 19th and 20th centuries were obviously archaic; they nostalgically reanimated the formal continuity of values in the scientific community, but objectively did not reflect the current trends in the development of science and civilization. Thus, there was a need for a new look at the problem of balance of “facts” and their “meaning”, the dissonance between “goal-driven ethics” and “means-conscious ethics.” The book by V. R. Potter is full of the relevant ideas.

But, in addition to these undoubtedly objective factors, the background against which bioethics was developing contained another influential component that usually escapes the attention of researchers, although it was largely generated by the same historical circumstances. Sixties and seventies of the 20th century were the heyday of European (and Western, in a broad sense) intellectual culture. All the media allowing to express oneself back then, from academic and avant-garde literature to cinema that was mastering new means of expression, were actively used by Western intellectuals as a space for creative self-identification, a platform allowing to manifest the new values: aesthetic, humanistic, ethical [4]. "Future" was one of the most popular topics at that time (p. 7) [1].

V. R. Potter himself saw the book as the result of rethinking of personal and professional ("30 years of cancer research") intellectual experience. The "Bioethical Creed for Individuals" (pp. 5–7, 209) [1], a kind of synopsis of Potter's ideas, highlights the "personal message" side of the book's nature especially strongly (pp. 5–7, 209) [1].

Potter VR formulates his task as an attempt to "understand the nature of man and his relationship to the world." To get this understanding, "humanity urgently needs new wisdom, which would be "knowledge about how to use knowledge" for survival of an individual and improvement of his life" (p. 9) [1]. That is, from a formal point of view, V. R. Potter proposes a universal methodology, a way to support implementation of the progress ethics standard from an epistemological perspective.

But for all the declared universality of bioethical methodology, it is not democratic. "The fate of the world," writes V. R. Potter, "depends on the continued integration and expansion of the knowledge held by a relatively small number of people." This means that bioethical axiology focuses on a special actor of cognition, a type of intellectual Potter calls "survivalists". According to him, they come from academic environments and share the specific trait of being especially concerned with the problem of mankind's survival (pp. 10, 164) [1].

It should be noted that V. R. Potter's description of the community of intellectuals and the specifics of their activity closely resembles the concept of "creative class", which is widespread in the American historical tradition. Generalizing the parameters of this approach, R. Florida (George Mason University Schar School of Policy and Government) stated that the "core of the creative class" includes holders of competencies in various scientific and technological spheres, in "architecture, design, education, art, music and entertainment… the creative class also includes a large group of creative professionals working in business and finance, law and healthcare and the related fields" [5].

The overall socio-economic function of the "creative class" generally seconds the tasks Potter VR saw before the community of intellectuals described in his book. He agrees with D Lilienthal's requirements that are "universal" for all fields of activity: the ability to imagine (creativity as it is), independent thinking, factual perception of the reality, "intellectual independence combined with the ability to accept criticism and analysis of the results by other specialists", scientific universalism, scientific viability. "The path to wisdom," as Potter VR notes, "runs through a consensus reached in interdisciplinary groups." For him, freedom of creativity for is one of the problems of urbanization (pp. 59–61, 76) [1].

The tasks set before the "creative class" are "design" or "creation of new ideas, new technologies and new creative content", "solution of complex problems." The hallmarks of an intellectual here are "significant independence of thought, a high level of education and human capital … creativity, individual characteristics and personal merit." This approach, according to R. Florida's calculation, allows listing 38 million people, which is about 30% of all working Americans, into the "creative class" [5].

It should be noted that the "broad" approach to the reproduction of intellectual environment adopted in the "creative class" theory compensates for the dissonance created by the "exclusivity" and the extended list of tasks set before the community of intellectuals Potter VR appeals to.

The appeal to the need to synthesize the creative and ethical potential of intellectuals and the power resource is also traditional for intellectual manifestation [4]. Stating that "the age-old question of the nature of man and his relationship with the world becomes more and more important in view of the last three decades of our century … when political decisions are made without accounting for biological knowledge", Potter VR develops the idea of the need to influence political processes and power wielded by groups competent in natural science and humanitarian knowledge. According to V. R. Potter, "the attitude of society to a specialist and the attitude of an intellectual to his role in the society" are two current problems (pp. 12, 88, 161) [1].

V. R. Potter characterizes himself as an "adept of the mechanistic theory", "a pragmatic mechanist". At the same time, he finds it important to prevent the premature conclusion that the mechanical explanation of the world cancels teleological meaning of the development [6]. Criticizing teleology of Teilhard de Chardin relying on the "strict sequential mechanicalism" of 12 "paradigms of mechanistic biology," V. R. Potter believes that "a mechanist never doubts that all the facts unknown today will be discovered and explained in the future." In other words, the actuality of mechanistic teleology is not a paradox for him, as is the possibility of combining the concepts of "personality" and "cybernetic machine" in the characteristics of a person (pp. 19, 22–31, 39–49, 126) [1].

From the standpoint of the comparative ideological maturity of the 21st century, it is possible to criticize the sophistic nature of Potter's VR appeal to "wisdom" (regardless of who wields it, be it intellectuals with their "exclusive wisdom", specialists with "competent wisdom or the masses with the wisdom of fatal inevitability) and the path of evolving ideological compromise that it opens. However, it is obvious that the practical value of bioethical appeal to "wisdom" is disavowed by the indication of the possibility of transition ("Bridge") to a new biological and ethical rationality, marking the only productive way to overcome conservatism. In this sense, bioethics is a declaration of humanistic rationalism ("realism") seeking to mobilize a person's spiritual potential and aiming to push this person to his/her moral maximum.

The Creed, which concludes Potter's VR book, is an element of a slightly naive but touching attempt at immortalization: the author hopes that descendants "will remember him with gratitude" (p. 209) [1]. This phrase expresses perhaps the most important thesis of the book — trust in the person of the future. It is the trust in man, his mind and spiritual integrity that ensured the stability of bioethical approach in determining capabilities of science and technology employed to solve urgent problems the society faced in the 20th century. This trust remains as important in the 21st century [7].

Assessing the book by Potter VR, it is important to note that he avoids one of the specific temptations of intellectuals and abstains from condemning imperfections of the world and calling for an individual "fight against evil", which would have represented the vigilante fixation popular in American culture.

Today, bioethics is a reminder that humanistic freedom is ensured by humanistic responsibility. According to Potter VR, “cultural evolution would have been very slow if it were not for the persistent desire of a person to introduce something new into his life and to not follow instructions to the letter.” This “new” is introduced into the soil of bioethics, when in certain areas of science there is a deficit (“crisis”) of methodology that factors in the general ethical aspects of medical research [8]; it is also behind introduction of the new theoretical categories [9], the ways of practical application bioethical principles [7; 10].

Behind its primary significance, Potter’s VR book is the personal message of an intellectual, a declaration that reflects the dialectics of a time of great hopes and equally great threats, when everyone is responsible for the future of the world [1]. This message to humanity continues to gather different assessments, which means that it is still relevant for civilization.

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HISTORY OF BIOMEDICAL RESEARCH IN RUSSIA: ETHICS LESSONS FOR THE FUTURE

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This work is the author's commentary on events and documents that are important for the correct interpretation of the history on bioethics and the search for a moral basis for preventing ethical catastrophes in the future. The historical memory of the Nuremberg trials and the realities of the humanitarian catastrophe of the COVID-19 pandemic certainly give a special impetus to the development of this topic. Important issue is the special editors of the journal's request to write this particular article. The reason is the author's discovery and presentation the unique and forgotten documents of extraordinary importance, as well as the strategic focus of the journal's policy on an objective presentation of the facts of national ethics / bioethics in order to form the integrity of the role and influence of Russia and to improve the quality of education in this area.

Key words: informed voluntary consent, bacteriological weapons, historical responsibility, solidarity, protection of future generations.

Autor contribusions: Kubar O. I. — study of archives and historical documents to analyze the formation and development of research ethics in Russia; comparison of historical documents of Russia on informing patients with the modern standard of ethical regulation; an ethical commentary on the case of former Japanese military personnel accused of preparing and using bacteriological weapons during the trial in the city of Khabarovsk, 1949. Assessment of the importance of the moral inevitability of punishment for the protection of future generations.

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ИСТОРИЯ БИОМЕДИЦИНСКИХ ИССЛЕДОВАНИЙ В РОССИИ: УРОКИ ЭТИКИ ДЛЯ БУДУЩЕГО

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Настоящая работа представляет собой авторский комментарий к событиям и документам, имеющим значение для корректной трактовки истории биоэтики и поиска нравственного основания для того, чтобы избежать этических катастроф в будущем. Особый импульс развитию данной темы, безусловно, предает историческая память Нюрнбергского процесса и реалии гуманитарной катастрофы пандемии COVID-19. Специальный запрос редакции журнала на подготовку этого материла, обусловлен открытием уникальных и забытых документов, представляющихся важными в контексте обсуждаемой проблемы, а также стратегическим фокусом политики журнала на объективное изложение фактов развития отечественной биоэтики с целью осознания роли и влияния России на развитие этики исследований и повышения качества образования в данной сфере.

Ключевые слова: информированное добровольное согласие, бактериологическое оружие, историческая ответственность, солидарность, защита будущих поколений.

Вклад автора: Кубарь О. И. — изучение архивов и исторических документов для анализа становления и развития этики исследований в России; сопоставление исторических документов России по информированию пациентов с современным стандартом этического регулирования; этический комментарий по делу бывших военнослужащих японской армии, обвиняемых в подготовке и применении бактериологического оружия в ходе судебного процесса в г. Хабаровске, 1949 год. Оценка значения нравственной неотвратимости наказания для защиты будущих поколений.

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METHODOLOGY

The methodology is based on a detailed ethical commentary of two phenomena related to the history of biomedical research in Russia. The first is represented by the article by B. V. Dmitriev (B. V. D.) entitled *'A Case of Thyroid Transplantation and Legal Issues Associated with Transplantations of This Kind'* first published in Tsarist Russia in [1]. (Attachment). The second concerns a global historical event associated with the trial against former Japanese soldiers held by the Military Tribunal of the USSR in the city of Khabarovsk in 1949. They were accused of manufacturing and using bacteriological weapons and convicted based on the legislation of the USSR (art. 1 of the Decree of the Presidium of the Supreme Soviet of the Union of the Soviet Socialist Republic dated April 19, 1943) [2, 3].

The historical perspective and scope of the selected facts are obviously ambiguous. However, they have something in common. It's an absolute involvement in comprehension and interpretation of in-depth truth about the epoch-making events accepted by the international society as a beginning of the new era in the history of biomedical research presented by the Nurnberg Code (NC) of 1948 [4]. Our comparative analysis covering a regulatory and social field with different time and scope but having a common ethical resonance of '*crimes against humanity'* during the Second World War and '*ethical medical agony*' of COVID-19 pandemic is based on the conceptual link [5, 6].

It is important that readers examine the content of this article in due sequence. Initial familiarization with the documents presented in the attachment and respective references argues in favor of the topic considered.

RESULTS AND DISCUSSION

Commentary 1

As mentioned above, our attention was initially directed to the article published by B. V. Dmitriev and entitled *'A Case of Thyroid Transplantation and Legal Issues Associated with Transplantations of This Kind'*, 1917 [1]. According to an opinion given in a number of messages previously reported by some authors, the '*receipt'* of a patient presented in the article can be considered as the first sample of a voluntary informed consent (IC) form, and may be not just in Russia [7–9]. The opinion is also important because the review of the recommended handbooks of bioethics in our country contains no reference to such a unique event. In our opinion, this shifts the historical time of an IC formation and its geographical distribution [10–13]. It is widely accepted that data on appearance of the concept of patient rights in world's medicine are controversial. The logics of how the events developed in Russia is unreasonably disadvantaged and limited, even in the works devoted to the topic. Thus, it is announced that '*the necessity of obtaining a patient's consent to a certain treatment regimen was not discussed even in special literature*' or '*in Russia, law-making processes regulating the rights of citizens while obtaining medical assistance were initiated only after the October Revolution of 1917'*; or that '*the issue of patients' right to information and taking a decision on their treatment was first considered in the USA and Western European countries, but not in Russia*' [14, 15]. Thus, it can be asserted that the issue of priority and regulatory status of patients' informing in Russia lies deep and requests principal inclusion into academic heritage, whereof it was justifiably declared in the process of ethical, cultural, philosophical and medical aspects of the issue' [16]. From this perspective, it is possible to reconsider the history of an IC in Russian research practice and shift the traditional idea of implementation of the IC ethical instrument in our country only from the moment when Russia joined the international acts (the Nuremberg Code, 1948, and the Declaration of Helsinki, 1964) to the launching position of domestic ethical and legal regulation in the early XX century (1917) [1, 4, 17]. Herein lies the historical value of the entire publication, and in particular the receipt of patient '*E.P.*' from the article by B. V. Dmitriev, which demonstrate a conjunction of the document with the acting standard of ethically acceptable modern IC elements [1]. We previously analyzed the original text of the mentioned '*receipt*' in detail and line by line compared with a list of requirements and positions set in the accepted ethical canon of biomedical research integrity, i.e., the Declaration of Helsinki [7].

In this article, we can once again confirm the qualitative ethical completeness of the century-old document constituents and their correspondence to the main acts such as the NC and DH in a responsible way without qualifying for matching the moral vigor of effect and authority. It is enough to start the comparison from the determinant thesis of the Nuremberg Code and its main principle which are as follows: '*Those who support human experimentation justify their views stating that the experimentation results are extremely useful for the entire society and can't be achieved using other methods of research. However, we all agree that certain fundamental principles which conform to the moral, ethics and law must be followed'*. According to the first provision of the NC, '*…the voluntary consent of the human subject is absolutely essential for a human experiment'* (NC, 1948) [4].

In the article by B. V. Dmitriev, we come across similar thoughts: '*Is a doctor entitled to do at least negligible and temporary harm to one healthy person for the benefit of the other?*' B. V. Dmitriev further expands the borders of responsibility which coincides with par. 4 and 5 of the Nuremberg Code describing a doctor's rights as follows: '*Is he competent to decide in every particular case whether benefit for one can compensate harm to the other when harm and benefit are considered in a broad sense, i.e., not just in relation to bodily health of these individuals but also taking into account an integrity of emotions and bodily forces of the both?*'. The author's response is totally concordant with the NC, as he states that the decisive factor for a doctor's decision is '*… law and human consciousness*'. The first lines of the 'receipt' taken from the article by V. B. Dmitriev are compliant with the fundamental NC condition on voluntary participation in the research: '*I, the undersigned E.K., willingly and with no outside influence… offered for transplantation …*' [1].

In the '*receipt by E. K.*' and the entire article by B. V. Dmitriev, we come across specific issues which are relevant not only to the Nuremberg Code, but also to the modern international and national standard of biomedical research, protocol of ethical, social and scientific requirements. The issues include research justification based on scientific data and medical indications, respect for individual autonomy, risk awareness and liability for data completeness and objectivity, compliance with freedom and voluntary choice, confidentiality, taking into account social and mental maturity of a clinical trial participant [1, 18, 19].

B. V. Dmitriev's thoughts about the legal aspect of a patient's informed consent, its accessibility and objectivity, compensation for voluntary participation and proving the lack of interest, conflict of interests and doctors acting independently are of special integrity. In particular, it is stated as follows: '*A doctor must explain to the donor (volunteer/ donor — explanation provided by the author — O. I. K.) every potential incident and danger of the future operation and obtain the donor's consent subsequently. To avoid any possible future complaints, it is better to provide the explanation and consent in writing in the presence of and signed by witnesses*' [1].

The mandatory condition of validity is a legally arranged agreement between a donor and a receiver which excludes the possibility of participation of '*the minor, weak-minded or those artificially excited'*; '*moreover, it is stated that the decision on participation must not result from 'mental constraint, deception, seducement, profit or authoritative advice'*, i.e., it must be voluntary and informed. The entire legal concept of informed participation in medical research, described in the article analyzed, lies on the acting regulatory basis interpreted by A. F. Koni, a highly-respected lawyer of Tsarist Russia in the beginning of the XX century. A. F. Koni mentions a lack of legally punished criminal activity associated with a sale of organs in therapeutic purposes, provides for a legal recommendation and evaluates the necessity to terminate trials [1]. The latter is an essential condition reflected in point 10 of the Nurnberg Code: '*During an experiment, a responsible investigator must be ready for its termination at any stage if professional considerations, good faith and cautious judgements… make it think that continuation of the experiment may result in an injury, disability or death of the one examined'* [4].

There is no doubt that it is possible to match conceptual characteristics of all messages from the analyzed article with monumental and acting documents developed in the XX and XXI centuries in a clear and deliberate way. However, the task of the present comparative analysis doesn't mean to define the superiority and equality, as the practice of patients' information was obviously present in the medical environment of various countries of the last century, though its hierarchy wasn't our interest. The primary objective of this part of the article has two constituents. First, one more page in national and world's history of bioethics is turned. It determines a just relation to the rich ethical heritage and potential of Russia in the area of bioethics, making the knowledge accessible for education.

Second, it is stated in a clear and persuasive way that no pseudo-justifying factors exist by the moment of barbarian and antihuman '*death experiment'* in the ideology of a state crime against the humanity during the Second World War. The factors include a lack of knowledge, standards/practice/conditions of ethical requirements for the research process.

The truth gives the result and conclusions of our first ethical commentary a global and civilized meaning. Intentional violation of all universal moral, professional regulatory norms and those available at the moment of crime commitment, deepens the abyss of guilt, inevitability of punishment and approaches the moral force of effect produced by the Nurnberg Code to the manifest '*on behalf of the insulted humanity consciousness'* [4, 5].

Commentary 2

Unlike the subject of our first ethical commentary, the events associated with the Military Tribunal of the USSR and legal trial against former Japanese soldiers accused of manufacturing and using bacteriological weapons in the city of Khabarovsk (1949) had a unique destiny. Due to political and ideological reasons, the Khabarovsk trial was initially almost in the wilderness or definitely in the shadow of the Nurnberg trial against Nazi doctors who performed sadistic medical human experiments. In the subsequent years, the Khabarovsk trial revealed to the world terrible archives of unhuman experiments on prisoners of unit 731 of Nazi Japan [2, 3, 20, 21]. Materials and facts from the publications and movies above show us a frightful record of a '*Japanese apocalypse'*. It was all left in the past. 70 years have passed since the Khabarovsk trial in 1949 and the world is dealing with a virologic disaster again. Thus, the article faces a specific task which is to discuss the ethical part of experiments over people perpetrated by Nazi Japan and their threatening echo heard during the COVID-19 pandemic.

B. G. Yudin, a Russian brilliant scientist in bioethics, devoted a deep philosophical and historical research to the issue of understanding an ethical constituent of the Khabarovsk trial [22]. In his article, B. G. Yudin states as follows: '*…the entire history of mankind puts at not so many cruelties compared with the 'trials' held not far from Harbin*'. Sheer cynicism of Nazi philosophy was revealed with an inevitable clarity, reducing to a minimum the effect of moral restraints on researchers, trial sponsors and potential users of the '*death laboratory'* results.

In his analytics, B. G. Yudin tries to answer the following question: '*How was is possible to conduct the sadistic experiments from the ethical point of view?*' [22].

We are using the ethical commentary to realize *why it was possible to forget the lessons taught by the sadistic experiments from the ethical point of view*. Unfortunately, the answer can be found in those events, which occurred soon after the Second World War. They accepted the compatibility of '*a genius and an evil-doer'* and justified the acceptability of using the results of the '*evil deed of genius'*. It is enough to look back at the fate of Shirō Ishii. He was the main '*scientific demon'* of 'unit 731'. He was given not just immunity to legal prosecution and ethical redemption, but also political patronage to continue bacteriological weapon trials in the leading centers of the USA [2, 3, 21]. Today, bioterrorism geopolitics covers all countries of the world and definitely exists in reality, originating from non-punishability/misprison of crime in Nazi Japan in spite of international limitation and prohibition law instruments [23].

The humanitarian, legal, social, economic and ecological crisis of COVID-19 pandemic demonstrates the destiny of a human civilization in the uncontrolled and inevitable reflection of a bacteriological/virological catastrophe, even in case of its natural development. Not to miss another lesson of global bioethics, it is necessary to refer to the humanitarian agenda of UNESCO, one of the most respected international structures in this sphere. By implementing the entire intellectual resource, experience and authority in drafting ethical recommendations on the most delicate issues of scientific ethics, UNESCO determined the strategy of actions in relation to COVID-19 as '*Protection of health and human dignity while respecting universal values'* [24].

Adherence to universal ethical principles and sequence of steps related to the ethical concept achievement and observance revealed a format and results of joint statements made by the leading structures of UNESCO in the area of bioethics such as the International Bioethics Committee (IBC), Intergovernmental Bioethics Committee (IGBC) and the World Commission on the Ethics of Scientific Knowledge and Technology (COMEST). An opinion about a special significance of issues to struggle the pandemic was expressed during the first joint meeting in the headquarters of UNESCO in Paris on April 6, 2020. The topic was as follows: '*Ethical aspects to be considered during the global struggle with COVID-19 pandemic*'. They include *'exacerbation of mental stress among vulnerable and marginalized individuals and groups; collective recognition of growing vulnerability factors to produce response measures in healthcare and social politics in the world; interdependence of states providing the accessibility of protection measures, development of politics in public healthcare and stimulation of research: international cooperation in view of solidarity and responsibility of rich countries providing help to poor countries'* [24].

Even a cursory look at the list and concerns of UNESCO suggests a dramatic unacceptability of injustice and moral use of some people for the assumed benefit of others. This is the lesson provided by the Nurnberg and Khabarovsk trials. Audrey Azoulay, Director-General of UNESCO, makes the ethical appeal obvious stating that '*this crisis encourages the best traits of humanity with ethical principles serving as a compass*' [24]. She also mentions here that political decisions must be based on scientific knowledge and follow ethical standards. An important point is that UNESCO lays the entire responsibility for rational ethics on itself and national bioethics committees.

Social and ethical maturity of the strategy is undoubtful. However, these principles are not continuously followed everywhere and always. The author's attempt to carry out an ethical monitoring of the pandemic resulted in a '*sad truth*' of disturbed autonomy, discrimination, dysbalanced justice, cascade disturbances of medical aid accessibility and development of humanitarian disasters [25].

The most vivid contradiction between ethical solidarity and adequate conclusion made from the lessons of the past was '*vaccine egocentrism'*. This looks especially bad under the conditions of a panhuman disaster and panhuman dependence to leave the pandemic. UNESCO reacted to the moral crisis with the second joint announcement of IBC, IGBC and COMEST treating COVID-19 vaccines as a global common good (Paris, February 24, 2021) [26].

To understand the scope of ethical anti-solidarity, it is enough to provide some principal ideas the announcement is based on. '*When vaccination campaigns were announced worldwide, everyone was relieved. We are far from the goal achievement without solidarity, as over 130 countries failed to get a vaccine yet, and the most vulnerable layers of population are still not protected'* (Audrey Azoulay, Director-General of UNESCO) [26].

'We won't come over the pandemic wherever it takes until it is over everywhere. In the end, the justice of vaccination is not just a correct choice but the best way to control the pandemic, restore trust and reactivate world economy…' (D-r Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization).

CONCLUSION

The basic and enlightening conclusion for the activity designed to formulate ethical commentaries to two events of various scope but with the same moral force of effect should be an absolute and indisputable moral association of human decisions and deeds of the present, past and future. The axiom requires responsible thoughts about the heritage prepared by the current generation of scientists and doctors for their descendants. Humanistic wealth of mankind formulated by V. R. Potter should be considered as a standard in bioethics determination: '… A science of survival must be more than science alone, *it must be the new wisdom, which could unite two most important and essential ingredients such as bacteriological knowledge and universal human values*' [27].

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Attachment

EXTRACTS FROM THE ARTICLE BY DMITRIEV BV *‘A CASE OF THYROID TRANSPLANTATION AND LEGAL ISSUES ASSOCIATED WITH TRANSPLANTATIONS OF THIS KIND’. MEDIZINSKOYE OBOZRENIYE*, 1917; LXXXVII (13–16): 618–619, 626–628 P. RUSSIAN.

SURGERY. A CASE OF THYROID TRANSPLANTATION AND LEGAL ISSUES ASSOCIATED WITH TRANSPLANTATIONS OF THIS KIND

Written by Dmitriev BD, Chief Physician of the Machinery Plant in Kolomna

In December 1909, a student NN, 26 y.o., presented with complaints of severe forms of hypothyroidism and asked for thyroid transplantation.

‘In 1907, she read that Prof. Christiani from Geneva successfully treated cretinism with thyroid transplantation. She went there at once, and Christiani transplanted freshly cut pieces of goiter under her skin (at eight sites). According to NN, the surgical outcomes were very good. There was no need to take thyroidin for almost a year. She felt especially well during the first month after the injection. However, by the end of the year she began taking thyroidin again due to a worsened well-being. She was in Paris that time. In summer 1908, she requested transplantation from Walther. Walther injected thyroidal parts taken from a healthy man under her skin (at seven sites). This made her feel satisfactory for about three months only. Christiani assured that the second operation was not successful due to an insufficient implant amount and advised to repeat the transplantation using a healthy gland. For this purpose, NN referred to me in the end of 1909 stating that her maidservant was ready to sacrifice her gland for 50 rubles (!)

The right of a doctor for human-to-human transplantation of tissues and organs is of a keen interest from the legal point of view. Does a doctor have a right for harming a healthy person for the benefit of someone else, even if the harm is insignificant and transitory? Is he competent enough to decide whether benefit of one person can compensate for harm to the other one? Benefit and harm are comprehended in the broadest sense here: not only as the physical health, but also as an entity of physical and mental health of the individuals. During the practice, a doctor will have to come across similar issues, and their resolution is not that simple. For instance,

producing a miscarriage, embryotomy, selection of wet nurses. Law and consciousness place a high value on a human life, even at the embryonal level, and allow to destroy it only when there is an evident risk for a maternal health. As far as the embryotomy goes, a maternal life is obviously more valuable than the life of a mature fetus. However, a doctor often places a mother at risk to preserve the fetus. These provisions can be considered as generally accepted — though with some exceptions. Unfortunately, neither society, not doctors have one opinion about wet-nursing. Wet nurses usually deprive their own children of breast feeding in favor of formula feeding, exposing them to all related dangers.

The client requests a doctor just to estimate a wet nurse's health and her milk quality, sanctioning the deal. Meanwhile, a child is entitled to breastfeeding, not capable to maintain his own rights and demands protection. The doctor who examines the wet nurse's health must protect the child. A doctor performing transplantation occupies a similar position. The analogy is more perfect when a donor donates a body part in return for a fee and becomes absolutely perfect when the donor is a minor, insane or of little culture. In the first case, the doctor should use the strength of words and persuade the mother not to deprive her own child of milk; in the second case, the doctor must refuse from using body parts of minors and those insane for the purpose of transplantation. Specimen of homologous grafts can be taken from a responsible adult only. It is necessary that the harm provided by a body part removal be transient and based on precise scientific data. The doctor must provide for an exhaustive explanation of all possible accidents and dangers of the coming surgery and make the patient explain the consent provided. To avoid possible problems in the future, the explanation and consent must be given in writing in the presence of and under the signature of witnesses.

What should a doctor do, when a person donates a body part at a charge? It seems to me that a doctor must not act as a mediator or advisor for the financial part of the agreement; there is absolutely no way he should link an amount of a transplanted organ to the money paid.

I have already mentioned that my patient paid 50 rubles for the gland. The amount was offered by the donor. Though I found out later in the context of skin transplantation that the donor had already been paid for the skin provided, I should acknowledge that the sales procedure seemed confusing to me. Explaining the consequences of the action to the donor and entering the record I didn't mention the financial part of the deal following the advice of a Moscow lawyer'.

Let me cite the full text of the document: 'I, the undersigned EP, offered a part of my thyroid gland with the size necessary for successful transplantation (approximately, one eighth part hereof) without any irrelevant influence. I was explained in detail and I understand well all the possible related dangers. Thus, an unsuccessful surgery may result in a life-threatening bleeding, neck suppuration or even sepsis that may be fatal. I was explained that the effect of the future surgery on a human health was not known yet, as the surgery was rarely performed, and experience of those people who underwent the surgery was not reported. However, it is proved that removal of two thirds of the thyroid in animals won't do any harm. So, the conclusions can be applied to humans as well, as the glands of animals and people have much in common. It is enough to leave a small portion of the thyroid in a person with a thyroid tumor and the person will continue living without suffering from the gland deficiency. I am aware of the consequences that occur in case of gland deficiency. I was also explained that in spite of anesthetics given I will still feel some pain during and after the surgery. I was also told that in case of success or suppuration, I would get a scar on my neck that would be 2.6–3.5 inches long. Notwithstanding the above, I still agree to have the surgery. I shall under no circumstances hold a demand against the doctors performing the surgery and the patient who needs the transplantation. I am signing the paper in the presence of doctors Dmitrieva BV, Vinokurova EK, Alekseeva MP and nurse Schevchenko EV (signature). We witnessed the reading and signing of the paper and certify that E.P. is an adult and mentally healthy person' (signatures of the doctors and nurse).

CLINICAL TRIALS OF COVID-19 VACCINES AND VACCINATION CAMPAIGN: ETHICAL ISSUES

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For many centuries, infectious diseases have posed a serious threat: epidemics and pandemics claim lives and multiply the burden on health systems and countries' economies. Humanity managed to defeat a number of infections only thanks to specific preventive measures, i.e., vaccination. In 2020, society faced the new COVID-19 virus that has swept the whole world. The situation required swift and decisive action, including in what concerned vaccine development. It has also raised a number of ethical issues. The article analyzes ethical issues related to clinical trials and vaccination against COVID-19 by studying the regulations, literary sources and bioethical incidents. The key problems identified are: human participation in clinical trials during a pandemic, availability and, simultaneously, voluntariness of vaccination, public confidence in the SARS-Cov-2 vaccines approved for clinical practice. The study showed that the basic principles of clinical trials, voluntariness and awareness, are violated. It was revealed that despite all the efforts of public organizations and WHO initiatives in the world, there is a pronounced imbalance in the availability of the developed vaccines, while the vaccination voluntariness principle is violated by application of various mechanisms to put pressure on people, and public confidence in the developed vaccines can be called insufficient. In general, the problem of vaccination against COVID-19 remains relevant and requires comprehensive discussion.

Keywords: COVID-19 vaccination, clinical trials of vaccines, voluntary vaccination, COVID-19 vaccine availability, SARS-Cov-2 specific prevention

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ЭТИЧЕСКИЕ ВОПРОСЫ ПРОВЕДЕНИЯ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ И ВАКЦИНАЦИИ ПРОТИВ COVID-19

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Инфекционные заболевания на протяжении многих столетий представляли серьезную угрозу: эпидемии и пандемии уносят жизни, многократно повышают нагрузку на системы здравоохранения и экономики стран. Человечество смогло победить ряд инфекций только благодаря мерам специфической профилактики — вакцинации. В 2020 году общество столкнулось с новым вирусом COVID-19, охватившем весь мир. Ситуация требовала быстрых и решительных действий, в том числе и в аспекте разработки вакцин и породила ряд этических проблем. В статье проанализированы этические вопросы, связанные с проведением клинических исследований и вакцинации против COVID-19. Основой выступили нормативные правовые акты, литературные источники и биоэтические казусы. Обозначены ключевые проблемы: участие человека в клиническом исследовании в условиях пандемии, доступность и одновременно добровольность вакцинации, доверие общества к допущенным к клинической практике вакцинам от SARS-Cov-2. Проведенное исследование продемонстрировало, что имеет место нарушение базовых принципов проведения клинических исследований: добровольности и информированности. Выявлено, что, несмотря на все усилия общественных организаций и инициативы ВОЗ, в мире имеется выраженный дисбаланс в доступности разработанных вакцин, одновременно с этим, отмечено нарушение добровольности вакцинации и факт использования различных механизмов давления на человека, в то время как доверие общества к разработанным вакцинам можно назвать недостаточным. В целом проблема вакцинации COVID-19 остается актуальной и требует всестороннего обсуждения.

Ключевые слова: вакцинация COVID-19, клинические исследования вакцин, добровольность вакцинации, доступность вакцины COVID-19, специфическая профилактика SARS-Cov-2

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COVID-19 pandemic continues its march across the planet. The current challenge is to find effective, safe and affordable ways of specific prevention, which keeps the problem of developing and conducting clinical trials (CT) of COVID-19 vaccines urgent.

From the ethical perspective, organization of human clinical trials is a multifaceted matter: there are rights of the patient-participants, guarantees of their safety, limits of responsibility of the researchers, control of quality of the activities carried out. The current pandemic makes everything even more complicated because the trials need to be conducted in difficult epidemiological conditions.

The problem of availability of the vaccines allowed on the pharmacological market is equally important. WHO has suggested a number of initiatives as solutions thereto: COVAX (ensuring equitable access to COVID-19 vaccines), 100 days (ensuring vaccination of all health care workers and the elderly at greatest

risk, worldwide, within the first 100 days of the year), Declaration on Equitable Global Access to COVID-19 Vaccines [1].

This study aimed to analyze ethical issues arising in connection with clinical trials and COVID-19 vaccination campaign.

Currently, the researchers pay greatest attention to the issues of the voluntariness principle observance and protection of the patients' rights in the context of both CTs and the mass vaccination. There is also a number of articles covering ethical issues of vaccine development in the current pandemic. Some authors considered the possibility of infecting a human being with SARS-Cov-2 deliberately, for a research purpose of assessing the effectiveness of vaccination, substantiating the benefits this approach offers society (reliable data, new information, accelerated development of an effective vaccine), emphasizing ethical issues (high health risks the volunteers are exposed to, uncertainty about the consequences of the infection), highlighting the fact that a pandemic is a significant threat to society and, under such conditions, the risk can be justified [2]. Other researchers focused on the safety of the developed vaccines both for volunteers and those who will be vaccinated later during the mass vaccination campaign, highlighting such problems as the reduced duration of the first phase of studies, decision to forego animal testing made by some companies, launch of CTs without convincing data on the safety of the drug. Most authors arrive at the conclusion stating the importance of strict adherence to all ethical requirements for conducting a clinical trial, protecting the rights and safety of the volunteers, especially vulnerable groups [3]. In any case, the need for a vaccine CT in the pandemic era only exacerbates unresolved ethical issues and introduces new ones that require discussion.

As for the equity of access to vaccines, the commonly discussed issues are those of vaccination of the most vulnerable groups of the population, vaccines distribution criteria, availability of the vaccines to countries of the world and their capability to buy them [4]. The religious and legal aspects of the vaccination are also analyzed [5].

STUDY RESULTS AND DISCUSSION

Ethical considerations concerning clinical trials of the COVID-19 vaccines

Human trials have been practiced in medicine since the 18th century [6], but it was not until the middle of the 20th century that the documents regulating them were developed, stating rights of the patients and obligations of the researcher, as well as touching upon ethical issues [7]. Everyone is well aware of the horrific experiments carried out by medical workers in Nazi Germany on the concentration camp prisoners [8], as well as what was done by Unit 731 of the Japanese armed forces [9] and a number of other researchers whose studies involved human participation. The first document that outlined the rules for conducting studies was the Nuremberg Code of 1947 [10]. Later, in 1964, there appeared the Declaration of Helsinki, which was subsequently revised seven times, with the current revision being that of 2013. The Declaration was developed by the World Medical Association; it is a set of ethical principles developed for the medical community and governing research with involvement of people. The Declaration expands the provisions outlined in the Nuremberg Code and updates them. The Principles of Good Clinical Practice, which were adopted in 1974, are the standard document regulating CTs today, with no experimental protocol organized and implemented without observance thereof [11]. The Principles form the basis of the Russian Federation Research Execution Standard. The above documents underscore the importance and role of the informed voluntary consent given by the research subjects, the need for a permission from the Ethics Committee, for consideration of the specific interests of vulnerable categories of patients, observance of the ethical principles of confidentiality, as well as balance of benefits and risks for the subjects, fairness, etc.

In the context of the COVID-19 pandemic, the principles discussed have not changed. Despite the complexity of the situation with the spread of the new coronavirus infection, the requirements organizing and conducting CT must be strictly observed and conform to all international standards. In the Russian Federation, research activities are regulated by the Federal Law "On Circulation of Medicines" [12], the Russian Federation National Standard (GOST R 52379–2005 of 2005) and a number of explanatory letters from the Federal Service for Surveillance in Healthcare. The analysis of expert opinions about the possibility of making requirements for vaccine clinical trials less strict in order to accelerate development of the vaccines and have them introduced to the daily practice faster yielded a conclusion that vaccine safety is prioritized and health of volunteers participating in the vaccine tests is paid much attention to. In summer of 2020, A. L. Gintsburg, director of the Gamaleya Research Institute, pointed out that vaccine development cannot be compared to a run, research takes time and must be carried out at the highest level [13]. Along similar lines, European Medicines Agency has published an official statement to its website noting the need for exceptional transparency of the COVID-19 vaccine CTs [14].

The problem of public confidence in the results of tests comes to the fore, since this confidence greatly affects people's readiness to be vaccinated and their sense of security in the context of the current pandemic. The traditional issues of voluntary participation in the research, proper information campaigns for the patients, safety of their life and health also remain as relevant as they were.

Ethical issues of COVID-19 vaccination

There is an official definition of preventive vaccinations in the Federal Law 157-FZ of September 17, 1998 "On Immunoprophylaxis of Infectious Diseases", which enshrines vaccination as introduction of immunobiological drugs into the human body with the aim to create specific immunity to infectious diseases. The same law enshrines the concept of the National Vaccination Calendar, which lists the preventive vaccination types, terms and procedures. Introduction of the National Vaccination Calendars, routinely revised and updated and adjusted to the epidemiological situation, enabled the human race to overcome many infectious diseases, reduce morbidity and mortality [15].

Vaccine safety became an investigated topic in the middle of the 20th century, but the first regulations making vaccine testing mandatory were not adopted until the 1990s, and WHO launched its Global Vaccine Safety Initiative only in 2012. These documents emphasize the importance of all stages of a study, point out lack of a legal way to leave out any of them, prescribe much attention to the protocols and results of the clinical stage, highlight the importance of vaccination as an effective method of prevention of the spread of infectious diseases [16].

The idea of how effective vaccines are in terms of prevention took shape in the 19th century, and the 20th century saw mass vaccination campaigns organized throughout the world, including the developing countries [17]. Currently, public vaccine hesitancy is gaining momentum: in 2019, WHO included lack of confidence in vaccination in the list of ten global threats to public health. The roots of the anti-vaccination movement date back to the 19th century, when, shortly after the development of the first smallpox vaccine, first anti-vaccination organizations

began to emerge. At the beginning, the protests were mostly religious in nature, but towards the end of the 19th century their focus was shifted to the vaccines' insufficient efficacy and safety and human rights violations when vaccination was declared mandatory [18]. Today, the anti-vaccination movement also focuses on the problem of safety of immunoprophylaxis drugs. According to a study conducted in 2012 jointly by scientists from the UK and Australia, over 20% of parents do not fully trust vaccine prevention campaigns [19], and in Russia, as of 2016, 28% of the public exhibited vaccine hesitancy [20]. The new coronavirus infection has exacerbated this problem significantly: the extraordinary need for a vaccine, the short time between CT launch and public release of the drug, fears about the compulsory nature of COVID-19 vaccination — all these factors may add to a person's decision to refuse vaccination.

On the other hand, when some countries struggle to motivate their citizens to get the COVID-19 vaccine shots, other states cannot afford purchasing them even for medical workers and the most vulnerable groups of their population. This is the problem that WHO is focusing on with COVAX, a mechanism developed as part of the initiative to accelerate access to the SARS-CoV-2 remedies [1], which is designed to enable cooperation in the interests of equitable access to COVID-19 vaccines throughout the world. COVAX aims to provide vaccine to at least 20% of the population, end the acute phase of the pandemic, restore the economies of the most severely affected countries. The first country to receive the vaccine through COVAX was Ghana (on February 24, 2021), and overall, there were over 38 million vaccine doses delivered to more than 100 countries worldwide.

Thus, the availability of the drug for all categories of the population and the voluntariness of both vaccination and participation in the CTs can be singled out as urgent ethical problems associated with vaccination against COVID-19. Officially, Russian Federation declares strict adherence to the principle of voluntariness, but the real situation has somewhat different features.

Cases of ethical violations in the context of CTs and the vaccination campaign

Here are some examples of how CTs and mass vaccination are handled with the current COVID-19 pandemic in the background. On October 6, 2020, Elizabeth Focht, a BBC Russia journalist, published an article with a telling title of "Some learn where they came to only upon arrival: the who and the why of Russian coronavirus vaccine testing" [21]. The author conducted her own investigation and interviewed people who came to the volunteer center recruiting coronavirus vaccine CT participants in Moscow. One of the main goals of the investigation was to learn motivation of the volunteers. According to the survey, some of the respondents were sent by their employer to undergo a mandatory screening with the aim to subsequently enroll them in a CT. Also, as mentioned by the respondents, some experienced certain pressure from the employer, like threats of dismissal, bonus deprivation, "a promise of problems at work." Some were asked to "just check in" at the center to increase the footfall numbers. In this case, the key ethical problem is non-adherence to the principle of voluntariness in recruiting CT participants, which is a gross violation of the GCP principles that may add to the public distrust towards the results of such a CT. We believe that recruiting volunteers when there is a need to accelerate transition into the clinical phase of trials generates a serious ethical, legal and social problem that cannot be solved only with administrative measures and material incentives encouraging participation, which are simply a wrong tool in some cases.

Here is another case (from our own practice) related to the voluntariness of vaccination against COVID-19. A large company purchased a certain number of COVID-19 vaccine doses and offered its employees vaccination. Managers of the company's units received plans stating the required number of vaccinated employees, and the implementation of these plans was linked to the amount of bonus paid at the end of the quarter. The managers resorted to various measures aiming to influence their subordinates and to motivate them to get the vaccine shots. Some of the employees who did not want to be vaccinated had to either confront their immediate superiors or look for reasons to avoid immunization against COVID-19: contraindications, imitation of illness, pregnancy, etc. The analysis of this situation raises a number of questions. First, why has the company not attempted other ways to motivate its employees, e.g., campaigns to increase confidence in the vaccine, outreach events, meetings or conversations with a vaccine or infectious disease specialist? Secondly, can it be considered justified to force a person to vaccinate against his/her will, even for good purposes? Does this stance of the employer not violate the law, which establishes strict voluntariness of vaccination?

Sharing the burdens and the benefits: the challenge of vaccine availability

According to WHO, developed countries show the largest coverage of the population with preventive vaccinations against the new coronavirus infection, while most developing countries cannot afford to purchase the vaccines. At the same time, experts emphasize the extraordinary importance the widest possible vaccination has in the matter of reducing the virus spread and mutation. Only a joint effort by the entire world community can ensure provision of the poorest countries with a safe and effective vaccine. A number of WHO initiatives discussed above and designed to solve this task, of course, requires further development and implementation, because cooperation is the only way to stop the pandemic, and access to what medicine has to offer must be equal and fair.

Besides, there is another fairness-related factor associated with SARS-CoV-2 vaccine CTs: the distribution of burdens and benefits. The so-called third world countries have traditionally been used by pharmaceutical companies as testing grounds for their new drugs, including vaccines, and the interests of the populations of those countries were not always taken into account. Currently, when the very participation in vaccine trials could be beneficial, third world is not the place to host CTs, which leaves the countries thereof without priority access to the vaccines [22].

Safety and efficacy of COVID-19 vaccination

As indicated above, the main priorities in vaccination are the efficacy and safety of the drug for human beings. Preclinical and clinical studies serve to establish the former and the latter, and the results obtained form the basis for use of the drug in routine practice, factoring in contraindications and possible adverse events. A good example is the safety-related situation around the AstraZeneca COVID-19 vaccine: the registered adverse side effects thereof are thrombosis and thromboembolism, with death being the possible ultimate outcome. A series of studies enabled EMA to conclude that the benefits of vaccination outweigh its risks, and rare side effects are to be expected when vaccinating on the scale of millions. Nevertheless, some countries have withdrawn the approval for use of this vaccine [23]. This is when an ethical question arises: how justified is it to expose a healthy person to the risk of a severe outcome, minimal as it may be, in order

to specifically prevent COVID-19? What should be the relation between personal risks and interests of the public? Is it possible to maintain public confidence in vaccine-based prevention after publication of the results of such post-marketing research efforts? In our opinion, given the pandemic, the objective need for vaccination and the proven efficacy of the drug, it is necessary to study the complications that have occurred in more detail, identify the risk groups, develop preventive measures, provide patients with exhaustive information and give them the choice of taking the shot of the drug in question or refusing the vaccine.

More and more frequently, mass media voice questions about the EpiVacCorona vaccine developed at the State Research Center of Virology and Biotechnology VECTOR. For example, participants of the 3rd phase of the CT sent an open letter to the Ministry of Health of the Russian Federation, Roszdravnadzor (Federal Service for Surveillance in Healthcare) and VECTOR, stating lack of antibodies to SARS-Cov-2 in more than half of the volunteers, while earlier VECTOR has reported that all (100%) of participants had them [24]. At a meeting with the volunteers, VECTOR representatives pointed out the complex mechanisms behind vaccine-induced development of the immune response, noted that vaccination does not guarantee protection against infection but helps avoid severe course of the disease. Many questions also arise because of the lack of publications covering the CT results in peer-reviewed journals. To date, not a single peptide vaccine against the new coronavirus infection has been registered for practical use in the world, mainly due to insufficient immunogenicity, i.e., efficacy. The discrepancy between VECTOR's statements and the results that CT participants present as an efficacy descriptor raises public doubts about the effectiveness of the vaccine and the "transparency" of the trials. Of course, development of the SARS-CoV-2 vaccines is accompanied with a very large number of purely scientific questions revolving around the real efficacy of the protection mechanisms set up by the vaccine, and whether it is possible to eradicate the new plague of the 21st century relying on the traditionally used immunization methods. However, these situations, which imply vulnerability from the point of view of science and health, will be better resolved if the population is worked with competently and openly.

The issue of vaccination efficacy enormously important, especially in the current pandemic. To implement the principle of awareness in the context of the vaccination campaign, it is necessary to make the research results accessible, heard and read, as any lack of information and alarming messages in the media only exacerbate vaccine hesitancy. The limited choice of vaccines gives rise to an ethical problem: if a vaccine's efficacy was not confirmed by the generally accepted methods, how well-protected from the infection can a person that received this vaccine should feel himself/herself? In case of EpiVacCorona, this problem becomes even more important, since it is marketed as the safest vaccine for the vulnerable categories of citizens, i.e., the elderly and people with severe chronic diseases.

CONCLUSIONS

Analysis of the literature, expert and public opinions yields a conclusion that the key ethical problems associated with the COVID-19 CTs and vaccination are compliance with the principles of awareness and voluntariness, patient safety, vaccine availability for the population, priority of vaccination, public confidence in the CT results. In our opinion, with the current pandemic in the background, it is very important to disclose the results of all the CTs and make their protocols transparent for experts and understandable by the public. At the same time, regardless of how complex the epidemiological situation is, it should be considered unacceptable to violate the GCP principles, neglect the ethical foundations of the CTs and disregard the principles of voluntariness and awareness of trial participants. As for the vaccination campaign, the matters of vaccine efficacy and safety should be prioritized, and the world community should tirelessly cooperate to ensure equitable access to the vaccines, thus helping stop the pandemic and normalize epidemiological situation in the world.

A comprehensive analysis of the cases considered allowed noting violations of the principles of voluntariness and awareness peculiar to both the CTs and the vaccination effort. Such messages could undermine public confidence in vaccination against the new coronavirus infection. The principle of voluntariness is a fundamental one in medicine, its violation is completely unacceptable; it is necessary to form a conscious attitude of citizens to the prevention campaign with vaccines and increase the level of awareness and trust of the population. The most effective way is to provide reliable information about benefits and risks, as well as the possible adverse events, thus enabling people to independently make the vaccination decision.

The analysis of statistical data describing current situation in the world showed that despite all the efforts of WHO and the initiative group, COVID-19 vaccines remain partly unavailable to poor countries, while the world community, nevertheless, continues with its effort to provide the most vulnerable population groups and medical personnel with the vaccines. Both national governments and pharmaceutical companies are joining the program, which allows hoping for a higher level of vaccine availability in the future and, consequently, decreased mortality and improved epidemiological situation. Also, despite the current CT requirements and WHO calling for their transparency and reliability, as well as compliance with the key principles, there are messages that challenge the basics: safety and efficacy of the vaccines. This state of affairs can aggravate public mistrust in vaccine-based prevention and requires additional attention from the governments, the expert community and the public.

In general, this work allows stating that the COVID-19 pandemic, the CT and vaccination problems are the topics that are complex and discussed on all platforms used by the world community for the purpose, and that efforts are being made to address the issues of safety, vaccine accessibility and respect for human rights.

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VACCINATION AGAINST COVID-19: CONTRIBUTION TO THERAPY AND PROGNOSIS

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The article elaborates on the principles and modern methodology of evaluating vaccine safety, efficacy and effectiveness. The main parameters and criteria of successful immunization are described in plain and concise language. Special attention is paid to the analysis of clinical and epidemiological aspects of vaccination against Covid-19. The article provides the most recent epidemiological statistics on this disease. A report of the efficacy and safety of the BNT162b2 vaccine is given as an example.

Keywords: vaccine efficacy, vaccine safety, COVID-19, immunization

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ВАКЦИНОПРОФИЛАКТИКА COVID-19: ОЦЕНКА ВКЛАДА В СХЕМАХ ТЕРАПИИ И ПРОГНОЗА ИНФЕКЦИИ

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В статье подробно освещены принципы и современная методология оценки эффективности и безопасности применения вакцин. В доступной форме, коротко и лаконично характеризованы основные показатели и критерии оценки вакцинопрофилактики. Особое внимание удалено анализу клинических и эпидемиологических особенностей вакцинопрофилактики COVID-19. В тексте приводятся последние статистические данные заболеваемости инфекцией COVID-19. В качестве примера представлена оценка эффективности конкретного препарата (BNT162b2), который применяется, с целью вакцинопрофилактики инфекции COVID-19.

Ключевые слова: эффективность вакцины, безопасность вакцины, COVID-19, вакцинопрофилактика.

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INTRODUCTION

The first reports of the novel coronavirus disease, which is known as Covid-19 and is caused by SARS-CoV-2, came from Wuhan, China, in December 2019. In only a matter of months, the infection spread to other continents and sparked a pandemic. By June 2021, there were over 183 million reported cases of Covid-19 worldwide, with the total death toll of 3.9 million [1].

The course of Covid-19 varies from asymptomatic infection to severe pneumonia and death. Risk factors predisposing to severe SARS-CoV-2 infection remain understudied [2]. Today, one of the top public health priorities is vaccination against the disease because there has been no steady decline in Covid-19 morbidity and mortality in the past year [1]. To this day, there are no consensus approaches to the pathogenetic therapy of the infection [3]. Since the beginning of the pandemic, Covid-19 treatment guidelines have been revised a few times to take into account the accumulated data about the pathogenesis of the disease and its course in different subpopulations. At the outset of the pandemic, treatment regimens for Covid-19 included drugs that had been previously approved to fight other infection: chloroquine, hydroxychloroquine, remdesivir, favipiravir and some others [4, 5]. Today, the focus has shifted to anti-inflammatory drugs, anticoagulants, convalescent plasma, and symptomatic therapy [6]. With Covid-19, the outcome and survival are difficult to predict, and the disease has long-term sequelae, including post-Covid syndrome manifested as neurological symptoms, pulmonary fibrosis, renal failure, myocarditis, gastrointestinal disorders, etc. [7–9]. Given that the pathogenesis of the disease is not fully understood and treatment options are limited, vaccination remains the only solution that could prevent the infection and its complications [6].

The discovery of vaccines is a crucial milestone in the history of medical science. Vaccination has significantly increased life expectancy and had a positive effect on human health. The history of contemporary vaccines began in the late 18th century when Edward Jenner invented a vaccine against small pox. Since then, there has been a tremendous progress in vaccinology; due to successful vaccination programs, many dangerous infections are now under control, including small pox, polio, rabbis, tetanus, pertussis, measles, mumps and rubella. Technological advancements in vaccine manufacturing have facilitated their mass production, leading to a significant reduction in morbidity and mortality from infectious diseases in the 21st century. As more knowledge is accrued about microbiology and immunology, indications for immunization against infections continue to expand [11].

According to WHO, the BCG vaccine against tuberculosis prevents TB-associated deaths in 65% of cases, deaths from tuberculous meningitis in 64% of cases and deaths from disseminated TB in 78% of cases. A report from the 1920s reveals that BCG vaccination of Norwegian nursing students led to an over 80% reduction in pulmonary TB incidence in this subpopulation during a 3-year-long follow-up period [12].

WHO reports that by July 2021, there were 13 registered vaccines against Covid-19. Three of them were designed in Russia [13].The most discussed aspects of vaccination are the efficacy and safety of vaccines in different groups of patients, including severely ill individuals or those with pre-existing conditions, who are at greater risk for severe Covid-19 and death [7].

IMPORTANCE OF IMMUNIZATION AGAINST COVID-19

Today the efficacy and safety of vaccines against Covid-19 are high on the public health agenda [14]. Before a vaccine is approved for use, its efficacy and safety need to be proved in a clinical trial. Knowledge of basic vaccine efficacy criteria plays the crucial role in decision making about mass immunization in the general population and medical communities. One of the key steps toward promoting vaccination and building confidence in vaccines is dissemination of knowledge about vaccine epidemiology among clinicians, public health experts, politicians, and the general population [15]. Raising awareness about the basic principles of vaccine testing may help to bridge the gap between public health, fundamental sciences and clinical practice [16].

The aim of this article was to analyze the main criteria of vaccine efficacy. The article also discusses the role of immunization in therapeutic regimens for Covid-19 and the outcomes of the disease.

MEASURING VACCINE EFFICACY

Studies investigating the efficacy and safety of vaccines against Covid-19 are intended to answer the question which of the many vaccines, whose number is continuously growing, is the right one. Below we describe the main terms used in qualitative vaccine analysis.

In the formulas below “a” and “b” represent the number of vaccinated individuals who have or have not contracted the infection (which is Covid-19 in our case), respectively; “c” and “d” represent the number of unvaccinated individuals who have or have not contracted the infection, respectively.

Absolute risk reduction (ARR) is the absolute difference in the risk of infection between the vaccinated and unvaccinated groups; it is calculated by the formula:

$$ARR = \left[\frac{c}{(c+d)} - \frac{a}{(a+b)} \right] = [n_{unv} - n_v],$$

where $n_{unv} = \frac{c}{(c+d)}$ and $n_v = \frac{a}{(a+b)}$ are the incidence rates of the infection in the unvaccinated and vaccinated groups, respectively.

The mathematic difference in the rate of infection between the groups $n_{unv} - n_v$ is also known as vaccine preventable disease incidence (VPDI).

Number needed to treat (NNT) is the number of individuals that need to be vaccinated in order to prevent one case of infection:

$$NTT = \frac{1}{ARR}$$

Relative risk (RR) compares the probability of infection between the vaccinated and unvaccinated groups:

$$RR = \frac{n_v}{n_{unv}} = \frac{(a / (a / b)))}{(c / (c - d)))}$$

Odds ratio (OR) is the ratio of the probability of contracting the infection for a vaccinated individual to the probability of contracting the infection for an unvaccinated individual:

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

VACCINE EFFICACY

Vaccine efficacy is tested in randomized placebo-controlled clinical trials (RCT). It is essentially a percent reduction in the rate of infection in the vaccinated group vs. the control group. This parameter is tested during phase II and III trials.

Relative risk reduction (RRR), or vaccine efficacy (VE):

$$RRR = VE = 1 - RR = 1 - \frac{n_v}{n_{unv}}$$

Vaccine efficacy is also known as a rate fraction, etiologic fraction and attributable fraction. It describes the proportion of infection incidents prevented by the vaccine. Unlike VE, VPDI is not a proportion but a frequency. Mathematically, VPDI equals $n_{unv} \times VE$. This definition shows that VPDI takes into account both VE and the background rate of infection. Vaccine efficacy may not always reflect the full epidemiological picture and can be relatively low, with the burden of the disease remaining high. VPDI may a more appropriate measure of the epidemiological situation and can play a considerable role in vaccine approval and development of guidelines for vaccine use.

Vaccine effectiveness (VEF)

Vaccine effectiveness is measured as a percent reduction in the number of infections in the vaccinated vs. unvaccinated groups of the unselected population in real-world conditions during the actual immunization campaign [17].

$$VEF = 1 - \frac{n_n}{n_{unv}},$$

where n_n is the rate of random infections in the population. This parameter relates to VE as shown in the formula:

$$VEF = VE \times PPV,$$

where PPV is the vaccinated proportion of the population, also known as coverage.

Basic reproductive number (R0) is the average number of secondary cases generated by a single primary case in a susceptible population. This parameter can be measured by means of serological tests.

In order for an epidemic to unfold in a susceptible population, R0 needs to be >1. By contrast, if R0 is <1, the epidemic subsides because the pool of infected individuals shrinks.

Effective reproductive rate (Re) is the average number of secondary cases per one primary case in a population consisting of both susceptible and unsusceptible individuals.

$$Re = R0 \times x,$$

where x is the susceptible proportion of the population.

Herd immunity threshold (HIT): herd immunity occurs when a substantial proportion of the population has been vaccinated, ensuring that susceptible individuals are protected against the infection. HIT is the proportion of the population that needs to have immunity against the infection in order to contain its spread. If HIT is achieved through, say, immunization, then every administered vaccine dose reduces the risk of new transmission (i.e., Re=1) and the infection becomes stable in this population [16].

Below, we provide an example of a clinical trial conducted by Polack et al. [17] evaluating the efficacy and safety of the BNT162b2 vaccine against Covid-19. A double-blind placebo-controlled trial was conducted among individuals aged 16 years and above from 152 centers around the world (USA: 130 centers, Argentina: 1; Brazil: 2; South Africa: 4; Germany: 6; Turkey: 9). The allocation ratio was 1:1. A total of 43,548 participants underwent randomization; of them 21, 720 received 2 doses of BNT162b2 (30 μg per dose) with a 21-day interval and 21,728 received 2 doses of a placebo.

The safety of the vaccine was analyzed on a sample of 37,706 participants. The follow-up period was at least 2 months after the administration of the second dose. Of 37,706 participants 49% were women, 83% were Caucasian, 9% were Black or African Americans, 28% were Hispanic, 35% were obese (BMI ≥30.0), and 21% had at least one preexisting condition. The mean age was 52 years; 42% of the participants were older than 55 years [18].

The following parameters were evaluated: pain at the injection site and asthenic syndrome. Among severe adverse events were shoulder injury caused by the injection, axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and limb paresthesia. There were 2 deaths in the vaccinated group (one from acute coronary syndrome, the other one from cardiac arrest). Four participants died in the placebo group (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction). The frequency of adverse events was low and did not differ between the groups [18].

The efficacy of the BNT162b2 vaccine was computed as (100×(1–IRR), where IRR is the calculated ratio of confirmed Covid-19 cases per 1,000 person-years of follow-up in the vaccinated group to the rate of infection in the placebo group. BNT162b2 was found to be 95% effective in preventing Covid-19 (95% CI: 90.3–98.6). The 95.0% CI for vaccine efficacy and the probability of vaccine efficacy of over 30% were calculated using a Bayesian beta-binomial model. In the final analysis, the success threshold for the probability of vaccine efficacy over 30% was set to 98.6% to compensate for the interim analysis and control the overall type 1 error rate at 2.5%. Primary and secondary efficacy end points were evaluated sequentially in order to control type 1 family-wise error rate at 2.5%. In the vaccinated group, there were 8 cases of infection 7 days after the administration of the second dose. There were 162 cases of Covid-19 in the placebo group. Vaccine efficacy was very similar (90 to 100%) in all the subgroups by age, sex, race, ethnicity, BMI, and preexisting conditions [18].

CONCLUSION

The use of adequate methods for vaccine evaluation and timely dissemination of data generated by the clinical trials of anti-Covid-19 vaccines are a crucial contributor to the successful fight against this infection, helping to promote the idea of vaccination in the population. The methods for evaluating vaccine efficacy, effectiveness and safety described in this article might improve immunization coverage, especially in susceptible populations at risk for severe Covid –19 and death from this infection. These goals can be achieved through the use of modern technologies for vaccine manufacturing and by providing accurate statistics on Covid-19 epidemiology, vaccine efficacy, safety and immunogenicity. In the absence of a consensus view on immunization, society needs more information about methods for vaccine evaluation and their role in preventing the risks associated with Covid-19 [19].

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