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COVID-19 vaccine candidates: A review

Szczepionki przeciwko COVID-19 – aktualny stan wiedzy

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Summary

In December 2019 the first cases of atypical pneumonia caused by a novel coronavirus SARS-CoV-2 were reported in Wuhan, China. This new infection was called coronavirus disease 2019 (COVID-19). SARS-CoV-2 is primarily transmitted human-to-human via direct contact and via the air-respiratory droplets and/or aerosols. The clinical manifestations of COVID-19 could range from asymptomatic or mild non-specific symptoms to severe pneumonia with multiple organ failure and death. The virus spread rapidly to almost all the countries in the world within a few months, and on the 11th of March 2020, the World Health Organization (WHO) announced the COVID-19 pandemic. Since then, a dynamic increase in the number of COVID-19 infections and deaths has been recorded worldwide. The COVID-19 pandemic is accelerating and causing annex tensive impact on the functioning of health care and is also leading to an economic crisis in the world. Today, it is difficult to ultimately assess the long-term effects of the pandemic, although it is known that they will be experienced for decades. Therefore, the most important goal is to stop the pandemic and develop an effective vaccine against SARS-CoV-2. Using the ClinicalTrials.gov and World Health Organization databases, we shed light on the current worldwide clinical and pre-clinical trials in search for a COVID-19 vaccine.

Keywords: **coronavirus, COVID-19, SARS-CoV-2, vaccine**

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Abbreviations: **ACE2** – angiotensin-converting enzyme 2; **ACIP** – Advisory Committee on Immunization Practices, **BARDA** – Biomedical Advanced Research and Development Authority, **CDC** – Centers for Disease Control and Prevention, **COVID-19** – Coronavirus Disease 2019; **DNA** – deoxyribonucleic acid; **DoD** – Department of Defense, **E** – envelope protein; **EMA** – European Medicines Agency, **FDA** – Food and Drug Administration, **HCoVs** – human coronaviruses; **HHS** – Department of Health and Human Services, **M** – membrane protein; **MERS** – Middle East respiratory syndrome; **MERS-CoV** – Middle East respiratory syndrome coronavirus; **mRNA** – messenger RNA; **N** – nucleocapsid protein; **NIH** – National Institutes of Health, **OWS** – Operation Warp Speed, **RBD** – receptor-binding domain; **RNA** – ribonucleic acid; **S** – spike protein; **SARS** – severe acute respiratory syndrome; **SARS-CoV** – severe acute respiratory syndrome coronavirus; **SARS-CoV-2** – severe acute respiratory syndrome coronavirus 2; **TMPRSS2** – human transmembrane protease serine 2.

In December 2019 the first cases of atypical pneumonia caused by a novel coronavirus SARS-CoV-2 were reported in Wuhan, China [14]. The new infection was called coronavirus disease 2019 (COVID-19). SARS-CoV-2 is primarily transmitted human-to-human via direct contact and via the air-respiratory droplets and/or aerosols. The clinical manifestations of COVID-19 could range from asymptomatic or mild non-specific symptoms to severe pneumonia with multiple organ failure and death [50]. The common symptoms are fever, cough, fatigue, dyspnea, myalgia and headache [18, 23, 54]. Studies have shown that sore throat, chest pain, loss of taste or smell, hemoptysis, rhinorrhea, conjunctival congestion, diarrhea, nausea and vomiting are less common among SARS-CoV-2 infected patients [18, 23, 37, 54]. However, some patients might have only gastrointestinal symptoms during the whole course of COVID-19. The systematic review and meta-analysis revealed that approximately 10% of patients with SARS-CoV-2 infection presented with gastrointestinal manifestations without respiratory symptoms [31]. These patients can have delayed diagnosis of COVID-19, which could possibly increase the risk of the virus being transmitted to others. Furthermore, a sudden, severe and isolated loss of smell and/or taste may also be present in infected patients who are otherwise asymptomatic [37]. Data about the frequency of the sensory disorders (smell and/or taste)in affected patients has shown a high variability from 5% to 98%, depending on the country and study [37]. These data indicate that novel coronavirus can cause a wide variety of symptoms.

SARS-CoV-2 is a member of the *Coronaviridae*, a large family of viruses that can cause illnesses in animals and humans. Structurally, they are pleomorphic, enveloped, RNA viruses with a characteristic fringe of projections composed of spike (S) protein on their surface [42]. Human coronaviruses (HCoVs) known for causing the common cold were first identified in the mid-1960s. Despite the relatively low pathogenicity for humans, they are responsible for approximately 15-29% of upper respiratory tract infections each year [52]. Therefore, HCoVs have not been the subject of detailed studies of post-infection immunity and the development of an effective vaccine. Studies have shown that a high frequency of recombinations in multiple species of CoVs circulating in the wild is connected with a generation of novel viruses with high genetic diversity and with unpredictable changes in virulence during human infections [52]. It is only a matter of time when the next recombinant CoV will emerge and cause another epidemic in the human population. The history HCoVs, which are highly pathogenic for humans, began in 2002, when a new zoonotic coronavirus appeared - SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and spread rapidly across the world. The virus was highly pathogenic for humans and caused severe acute respiratory syndrome. In the past decades, seven HCoVs that can infect people have been identified including four viruses leading to mild upper respiratory tract infections and gastrointestinal tract infections, such as HCoV-229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus) and three highly pathogenic HCoVs: mentioned SARS-CoV (the beta coronavirus that causes Severe Acute Respiratory Syndrome, or SARS), MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS) and SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19) [11]. Studies have shown that SARS-CoV-2 is genetically similar to the SARS-CoV (about 79.6%) [55]. Furthermore, analysis revealed that SARS-CoV-2 was closely related (with 88% identity) to two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, which suggests the zoonotic origin of the novel virus [30].

The first cases of SARS-CoV infection appeared in November 2002 in the Guangdong Province in southern China. The clinical manifestations of SARS-CoV range from mild infection to sever pneumonia with multiple organ dysfunction and death. The major symptoms include the following: persistent fever, chills/rigor, myalgia, malaise, dry cough, headache, and dyspnoea [25]. Less common symptoms include sore throat, rhinorrhoea, nausea, vomiting, and diarrhea [4, 22]. In 2003 over 8,000 cases of infections and 774 deaths were recorded in a total of 26 countries [20, 47]. Despite efforts from the scientific community, no vaccine for SARS has become commercially available. Since 2004, no known cases of SARS have been reported anywhere in the world. Another highly pathogenic coronavirus, MERS-CoV, was identified in 2012 in Saudi Arabia. The clinical manifestations of MERS-CoV infection range from an asymptomatic course to acute upper respiratory illness and rapidly progressive pneumonitis with respiratory failure, septic shock, multiple organ failure and death [3]. In a symptomatic patient, the most common symptoms include the following: fever, chills, rigors, myalgia, malaise, cough and shortness of breath. Gastrointestinal manifestations may also occur [3]. Cases of MERS infections were recorded in 27 countries (transmitted by people who travelled to the Arabian Peninsula, including the largest epidemic in 2015 in South Korea) and its transmission is still recorded in the Middle East, but analyses have not indicated any ongoing spread of MERS to other regions of the world [29, 34]. Globally, 2,562 MERS-CoV infection cases and 881 deaths have been reported to the WHO [34]. Also in this case, no commercial vaccine for MERS is available. One possible reason that a vaccine has not been produced is because of the low interest in investing in the development of a vaccine for a disease that causes relatively low and geographically centralized cases [39]. Similarly, in the case of SARS, it was considered pointless to continue investing in a vaccine for a disease for which there have been no reported cases since 2004. Unlike SARS and MERS, SARS-CoV-2 spread rapidly to most countries in the world within a few months, and on the 11th of March 2020, the World Health Organization (WHO) announced the COVID-19 pandemic. Since then, a dynamic increase in the number of COVID-19 infections and deaths has been recorded worldwide, especially in the United States, Brazil, India and the current situation in Europe is also very serious. Most of the European countries are declaring more incidences each day now than they were during the first wave earlier this year. The COVID-19 pandemic is accelerating and causing an

extensive impact on the functioning of health care and is also leading to a worldwide economic crisis. Today, it is difficult to ultimately assess the long-term effects of the pandemic, although it is known that they will be experienced for decades. Therefore, the most important goal is to stop the pandemic. The current methods of prevention have not achieved a satisfactory effect, which is why all hopes are placed on the development of effective vaccines. The whole world is waiting for the mass production of potent vaccines, which is why scientists and pharmaceutical companies are significantly intensifying their work on them. The search for vaccines against SARS-CoV-2 is accelerated by advances in technology based on the experiences of researchers. The United States government announced Operation Warp Speed (OWS) to accelerate development, production, and distribution of COVID-19 vaccines. Operation Warp Speed (OWS) includes the following components: the Department of Health and Human Services (HHS), the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense (DoD) [16]. OWS is providing support for the expeditious, parallel procedures necessary for the approval of safe and effective vaccine candidates. It allows for faster distribution than is allowed by typical timelines. BioNTech companies announced *Project Lightspeed* to accelerate the rapid development of a COVID-19 vaccine [44].

Knowing precisely the structure of pathogens, their paths getting into the cell and how they replicate can be crucial in further investigations.

SARS-CoV-2 is a novel enveloped, positive-sense, single-stranded RNA beta coronavirus consisting of genome encoded structural and non-structural proteins, which perform numerous roles in the replication and virus assembly processes [45]. The structural proteins include spike (S) consist of two subunits: S1 and S2, nucleocapsid (N), membrane (M), and envelope (E) proteins. The envelope of SARS-CoV-2 contains crown-shaped projections called spike proteins. These projections are responsible for recognizing the host's receptor followed by its binding to it and fusing with its membrane [48]. Spike protein comprises two functional subunits: S1 and S2 [51]. The S1 subunit is responsible for binding to the host cell receptor. Angiotensin converting enzyme-2 (ACE2) receptors mediate the entry of SARS-CoV-2 into the cell. The S1 subunit of S protein facilitates ACE2 mediated virus attachment; then after structural receptor changes S2 subunit promotes membrane fusion [45]. After attachment, the human transmembrane protease serine 2 (TMPRSS2) cleaves and activates the spike protein in an event that allows SARS-CoV-2 to enter the cells by endocytosis or direct fusion of the viral envelope with the host membrane [45]. The N protein has multiple functions including viral assembly, budding, RNA replication and host cellular response [33]. The coronavirus E protein is implicated in viral assembly, release and viral pathogenesis [46, 49]. The M protein forms the shape of the viral envelope and organizes viral assembly through interaction with all major coronaviral structural proteins [32, 38]. Analysis revealed that the S protein is highly immunogenic with the receptor-binding domain (RBD) and is the primary target for neutralizing antibodies [1]. Therefore, it seems that antibodies against S protein may play a key role in COVID-19 immunity. These data offer hope that a highly immunogenic vaccine will elicit the adequate magnitude and quality of antibody responses required for protection against SARS-CoV-2 [10]. The vaccine formulation and delivery can also be crafted to influence T cell functions and response patterns [19]. However, it is difficult to assess whether specific antibodies against SARS-CoV-2 will fulfill a protective function for many years. Seroprotection rate could be influenced by many factors. Hence, if the new coronavirus mutates frequently with attendant changes in the spike protein, the antibodies produced by a vaccine will indeed be out of date and might not bind the virus effectively enough to prevent infection. The ideal vaccine should meet the following conditions: is effective in preventing infectious disease (or reducing the severity of the disease), provides long-lasting protection against the disease, stimulates an effective immune response with a minimum number of administrations, provides as much antigen as possible to provide extensive protection against infections, does not cause clinically significant side effects, is stable under storage conditions, can be produced on a large scale and it is financially accessible to the populations [6]. Development of the new vaccine takes an average of 10 years [36]. Due to the epidemiological situation and the global crisis related to the COVID-19 pandemic, everyone is hoping that a vaccine against SARS-CoV-2 is developed quickly. The acceleration of this process may be obtained in two ways: by large financial support for research and infrastructure (almost all countries are involved in the development of the vaccine) and parallel research.

According to the ClinicalTrials.gov database, over 200 clinical and preclinical studies on the COVID-19 vaccine are currently registered [9].

The investigated formulas for COVID-19 vaccine include:

- Genetic, nucleic-acid vaccines, which are obtained by inserting mRNA and DNA acids into some cells of vaccinated individuals, forcing them to manufacture immunogenic viral proteins;
- Viral vector vaccines that use a non-replicating viral vector (animal adenovirus) as a way of delivering SARS-CoV-2 antigens to the body;
- Live attenuated viruses;
- Inactivated viruses;
- Recombinant protein based virus-like particle vaccines, which contain an antigen or an antigenic fraction with a major role in triggering the production of antibodies.

Optimistic results have been observed in genetic mRNA vaccines. The mRNA encodes proteins that are identical or resemble those of the pathogen. Upon the delivery of the vaccine into the body, this sequence is translated by the host cells to produce the encoded antigens, which then stimulate the immune system to produce antibodies

against the pathogen [40]. The mechanism of action of mRNA vaccines is similar to that used by replicating viruses. The example of this vaccine, known as mRNA-1273, was co-developed by the Cambridge, Massachusetts-based biotechnology company Moderna, Inc., and the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. The vaccine mRNA-1273 is a lipid nanoparticle–encapsulated, nucleoside-modified messenger RNA (mRNA)–based vaccine that encodes the SARS-CoV-2 spike (S) glycoprotein stabilized in its prefusion conformation [27].

Another possibility is a DNA vaccine. This type of vaccine is based on plasmid containing DNA sequence encoding the antigen (SARS-CoV-2 spike protein) against which an immune response is sought. Human cells detect the DNA fragment and transcribe it into an RNA fragment capable of inducing production of the spike protein. Potential advantages of this strategy, including the stimulation of both B- and T-cell responses, improved vaccine stability and the relative ease of large-scale manufacture [5, 12]. The main disadvantages of DNA vaccine include the following: limitation to protein immunogens, activation of oncogenes as a result of genomic incorporation of immunising DNA, possibility of inducing antibody production against DNA [21]. Results of preclinical trials have been promising regarding immune response in several animal models. The clinical trials for a new DNA vaccine against COVID-19 are in Phase 2. An example is a clinical trial evaluating the safety, tolerability and immunogenicity of INO-4800, a prophylactic vaccine against SARS-CoV-2 led by the Inovio Pharmaceuticals. The product is administered intradermally, followed by electroporation as a vaccine delivery system.

Another promising candidate is viral vector vaccine. The Lancet published preliminary results of a single-blind randomized controlled trial (Phase 1/2), which assessed the immunogenicity, tolerability and preliminary safety of the "ChAdOx1 nCoV-19" - vaccine based on a non-replicating adenoviral vector (chimpanzee adenovirus) as a way of delivering SARS-CoV-2 antigens to human cells [17]. ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses. The vaccine encodes the spike protein of SARS-CoV-2 closed in an adenovirus molecule, upon the delivery of the vaccine into the body, this sequence is translated by the host cells to produce the encoded S antigens, which then stimulate the immune system to produce antibodies against the pathogen [17]. The latest results of the Phase 3 clinical trial led by Astra Zeneca and University of Oxford indicate that vaccine efficacy was on average 70% [2].

Another possible vaccine involves using SARS-CoV-2 with diminished virulence achieved by genetic engineering. Live attenuated vaccines are the most potent immunogenic vaccines [24]. However, it is important to avoid the restoration of virulence in these vaccines. The main disadvantage is the potential reversion to natural virulence via back mutations of the attenuated vaccine-organism and the possibility of causing a symptomatic affection similar to wild-virus infection. In the case of coronaviruses it is difficult to use an attenuated strain of the pathogen as a vaccine, because coronaviruses are known to undergo recombinations in nature, and an attenuated vaccine strain could theoretically recombine with wild-type coronaviruses to restore the pathogenic strain [28, 53]. Preclinical trials on live attenuated SARS-CoV-2 vaccine are conducted by Mehmet Ali Aydinlar University in Turkey, Codagenix and Serum Institute of India and Indian Immunologicals Ltd and Griffith University [13].

The possibility of using the inactivated vaccines is also considered. Such vaccines consist of whole bacterial/viral particles killed by heat or formaldehyde. Inactivated vaccines are more stable and safer than live vaccines, as they cannot revert to a more pathogenic phenotype and are unlikely to interfere with each other in combination. Research on the development of an inactivated vaccine is being carried out, among others, by the Chinese company Sino Vac [13].

Another promising candidate is a vaccine containing recombinant structural proteins of the virus without genetic material. An example of such a vaccine contains antigenic fragments of the S protein, developed by Novavax [13]. The formulation is based on nanoparticle trimers of complete S glycoprotein with the Matrix M adjuvant system to enhance the immune response against SARS-CoV-2 spike protein by the induction of high levels of neutralizing antibodies. [13]. Novavax is currently leading the Phase 3 of clinical trials.

According to the currently available scientific knowledge, it seems that genetic and vector preparations containing recombinant structural proteins of the virus have the greatest chance of success as a safe and effective vaccine. The vaccine should stimulate an effective immune response to induce the long-term vaccine protection.

Assuming that the COVID-19 vaccine will generate an effective immune response in a sufficient number of vaccinated people, it is necessary to establish how long the protective levels of antibody will persist [41]. Limited data of coronaviruses are available. Studies show that after 229E coronavirus infection, immunity was maintained for only 2 years [7], and in the case of SARS-CoV infection, people who had been infected after 3 years lost their protective antibody titers [8]. Therefore, it is crucial to establish how long the protective antibody titers will persist after vaccination. In August 2020 Russia had announced that they developed an effective COVID-19 vaccine called Gam-COVID-Vac Sputnik V (adenoviral-based vaccine). It was approved for distribution in Russia, despite having been tested in only a small number of people in early-stage clinical trials. Scientists from the international community have signed an open letter questioning the published results into Russia's Sputnik V vaccine. On November 9, 2020, the companies Pfizer and BioNTech announced that their vaccine candidate against COVID-19 achieved success in first interim analysis from Phase 3 of clinical trial [43]. Early data suggests that this vaccine is more than 90% effective in preventing

COVID-19. The Pfizer used mRNA-based vaccine to produce an immune response in people who are vaccinated. The Phase 3 clinical trial of BNT162b2 began on July 27 and has enrolled 43,538 participants. An interim analysis included 94 participants who developed SARS-CoV-2 infection after receiving either the vaccine or the placebo. It found that fewer than 10% of COVID-19 cases included participants who had been given the second dose of new vaccine candidate. These data indicate the vaccine efficacy rate above 90% at 7 days after the second dose and suggest that protection is achieved 28 days after the initiation of the vaccination, which consists of a 2-dose schedule. Pfizer said in a statement that this percentage may vary as the trial continues. The companies Pfizer and BioNTech expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses in 2021. In December 2020 the United Kingdom became the first Western nation to approve the COVID-19 vaccine developed by Pfizer and BioNTech for public use. The vaccines are recommend for individuals 16 years of age and older and require two doses 21 days apart. Also, other countries started the approval process for the new vaccine. On December 18, 2020, the Food and Drug Administration (FDA) approved another mRNA-based vaccine made by Moderna, which showed a 94.1% efficacy rate in its Phase 3 trial [35]. This vaccine is intended for individuals 18 years of age and older and requires a 2-dose series separated by 28 days. On January 6, 2021, the European Medicines Agency (EMA) approved the Moderna vaccine [15]. Now, the world must wait for the full data on the new vaccine candidates.

CONCLUSIONS

The efforts of scientists from around the world to obtain vaccines against SARS-CoV-2 are unprecedented in terms of the scale and speed. These data bring optimism that a safe and effective vaccine will be available quickly for all countries in the world to stop the COVID-19 pandemic. Currently, the Pfizer and BioNTech COVID-19 vaccine has been introduced for widespread use in the world. Poland launched its immunization program with this vaccine on December 27, 2020. On January 6,2021, *Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States* were published [26]. These recommendations focus on the use of Pfizer-BioNTech and Moderna COVID-19 vaccines and concerned, among others, the vaccination of pregnant and lactating women, people who had COVID-19 infection in the past or suffered from COVID-19 after the first dose of mRNA vaccine. It also concerned the contraindications and co-administration with other vaccines, etc. These considerations complete the previously obtained data and more information is expected in the nearest future. It seems we can also expect that another COVID-19 vaccine candidates will be available in the near future.

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