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Review

Coronavirus SARS-CoV-2: Where do we stand?

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Abstract

An outbreak of coronavirus infection named SARS-CoV-2 emerged in December 2019 in Wuhan, a province of China. It caused a worldwide pandemic that led to devastating effects on healthcare systems and the economy. The contagiousness of the infection and the consequences of the disease in everyday life highlighted the great need for a suitable treatment against coronavirus as soon as possible. Therefore, lots of scientists all around the world focused on the discovery of a proper therapy against the virus. The present article explains the main differences in the clinical picture among different patients, the characteristics and concomitant diseases of more vulnerable people, medicines, and vaccines used in mass vaccinations. The first data that concern the effectiveness of vaccines from the countries that have already started mass vaccinations are positive. It is very early to conclude about the efficacy of vaccines in the population. However, the appearance of novel virus mutations raises concerns and forces some countries to impose further restrictions. The latest and the most contagious variant, known as Omicron, seems to decrease the global pandemic significantly.

Keywords: SARS-CoV-2, pathophysiology, diagnosis, symptoms, therapies, vaccines.

Резюме

Огнище на коронавирусна инфекция, наречена КОВИД-19, се появи през декември 2019 г. в Ухан, провинция на Китай. Това предизвика световна пандемия, която доведе до опустошителни ефекти върху здравните системи и икономиката. Заразността на инфекцията и последствията от болестта в ежедневието подчертаха голямата необходимост от подходящо лечение срещу коронавирус възможно най-скоро. Затова много учени по целия свят се фокусираха върху откриването на подходяща терапия срещу вируса. Настоящата статия обяснява основните разлики в клиничната картина при различните пациенти, характеристиките и съпътстващите заболявания при по-уязвимите хора, лекарствата и ваксините, използвани при масовите ваксинации. Първите данни, които касаят ефективността на ваксините от страните, вече са започнали масово ваксиниране са положителни. Много е рано да се правят заключения за ефикасността на ваксините в популацията. Появата на нови вирусни мутации, обаче предизвиква безпокойство и принуждава някои страни да наложат допълнителни ограничения. Най-новият и най-заразният вариант, известен като Омикрон, изглежда намалява значимостта на глобалната пандемия.

Introduction

The coronavirus infection emerged in Wuhan, a China province, and spread rapidly from China to other regions and countries worldwide; thus, the pandemic took over. Europe became the epicenter of the coronavirus pandemic, and the virus spread to the United States. The percentage of active cases of COVID-19 and deaths was very high, especially in Italy and many regions of the United States. Pandemics indicate epidemics that spread globally. An epidemic is an outbreak of a disease that spreads over a large geographic area. Pandemics can result in a significant loss of human life and are considered public threats. During a pandemic, many things that were previously for granted change. There is no doubt that a suitable drug or vaccine that can fight coronavirus infection is the only solution for life to return to the pre-coronavirus state; thus, a vaccine or a cure constitutes one of the most valuable so-

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cial goods nowadays. That is why the research in this field is of great interest, and many scientists focused on it from the beginning of the pandemic. The main aim is the massive protection of the population against infection. Many existing drugs were used to treat patients who suffered from the virus. Although various treatments against the virus and mass vaccinations have already started, all the countries worldwide continue to fight the spread through social distancing, lockdowns, personal protective equipment (PPE), and proper hygiene (Valsamatzi-Panagiotou and Penchovsky, 2022)That is attributed to the fact that new mutations of the virus appeared and that it will take time to vaccinate a satisfactory amount of the population to create immunity (Grennan, 2019; Wang *et al*., 2020; Yuki *et al*., 2020; Valsamatzi-Panagiotou, 2021).

Patients with comorbidities and SARS-CoV-2 infection

The paradox of the infection with the virus is the heterogeneity of the severity of symptoms. There are various reasons why the clinical picture of different patients varies. The person's age who gets infected with the virus is one of the main factors. People after 65 years old are at a higher risk of suffering from a severe infection than younger people who present primarily with mild symptoms. The explanation is that the immune system of the elderly cannot start an effective initial defense. At the same time, children are less affected because their immune system is less likely to progress to a cytokine storm. That is also shown by the data published by Chinese researchers after the SARS-CoV-2 outbreak (Fig. 1).

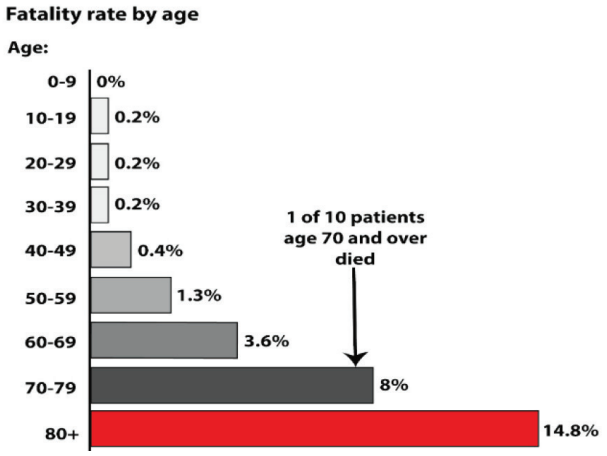

Fig. 1. The age range of the people affected by the SARS-CoV-2

The actual mechanism of action of ACE-2 in the lungs is unknown, although it seems to play a protective role against severe lung injury. A possible scenario for the worse clinical picture of smokers and patients with pulmonary disorders who suffer from Covid-19 is the up-regulation of ACE-2 expression in the lower airways in chronic obstructive pulmonary disease (COPD) and active cigarette smoking (Leung *et al*., 2020). Patients who suffer from chronic diseases such as cardiovascular diseases (CVD), diabetes mellitus (DM), chronic respiratory diseases such as a chronic obstructive pulmonary disease (COPD) and asthma, arterial hypertension (AH), obesity, cancer, and patients who are in medication with immunosuppressive drugs are more vulnerable. If they get infected with the virus, their clinical picture will worsen, and the mortality rate will be higher than those with no comorbidities. A possible explanation may be that the pathogenesis of some chronic diseases may be closely related to the pathogenesis of COVID-19. In detail, there are some standard features between chronic diseases and infectious disorders, such as the proinflammatory state and the attenuation of the innate immune response. In diabetes mellitus, inflammatory mediators such as IL-1β and TNFα are released due to the accumulation of activated innate immune cells in metabolic tissues, leading to systemic insulin resistance and the damage of β-cells. Individuals who suffer from metabolic disorders seem to be more susceptible to the complications of the infection due to their reduced immune function (Bourgonje *et al*., 2020; Hussain *et al*., 2020; Martelli *et al*., 2020; Tadic *et al*., 2020; Yang *et al*., 2020) (Fig 2).

Nevertheless, even though young people infected by SARS-CoV-2 may be asymptomatic or

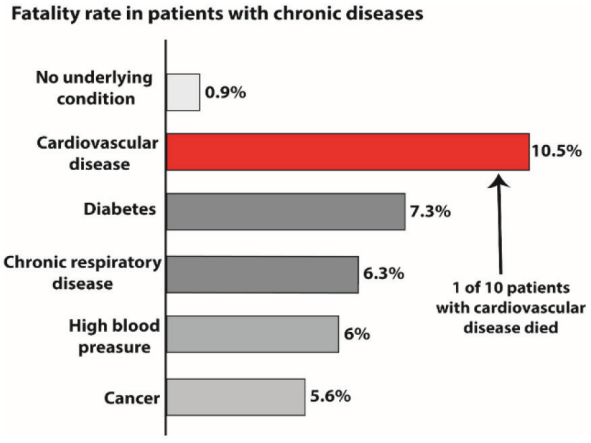

Fig. 2. The fatality rate in COVID-19 patients with concomitant diseases

have mild symptoms, they should also be cautious and avoid a possible infection with the virus. If they get infected, they can be asymptomatic car-

riers and spread the infection to more vulnerable people like the elderly and concomitant diseases. There is no current data on the long-term effects of the virus on the organism, which is also an important reason which highlights the need to reduce the spread of the virus. Indeed, the patients who recover from the infection should be monitored carefully to prevent any possible long-term complications of the virus (Pan *et al.*, 2020; Yu and Yang, 2020) (Fig. 3).

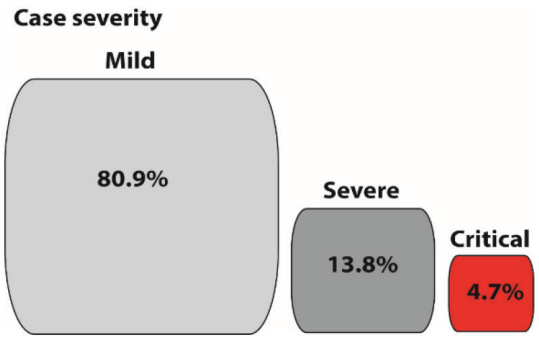

Fig. 3. Case severity of COVID-19 symptoms
The statistics of the patients who were infected with the SARS-CoV-2 reveal that most of the patients experience mild symptoms, some of them severe symptoms, and a few critical.

The nasal mucus contains mucins, electrolytes, IgA and IgG, lysozyme, lactoferrin, and oligosaccharides with antiviral and antibacterial proprieties. Besides, the production of hyaluronic acid is also stimulated, which is responsible for maintaining a good tropism in the nasal mucosa and proper hydration of the mouth. Estrogens also act directly on the bronchial epithelial cells by increasing the production of mucous, which is rich in antiviral agents. All these properties contribute to estrogen's protective role against the virus. In contrast to estrogens, testosterone and progesterone seem to cause an immune suppression of both innate and cell-mediated immune responses. There is a hypothesis that using medications as contraceptives responsible for keeping the female hormones stable and high may have a protective role against the virus. However, using those drugs increases the risk of thromboembolic events in healthy patients, especially those who smoke or suffer from a hematological disease known as thrombophilia.

Another hypothesis involves the potential utility of a local nasal spray with low-dose isoflavones from soya, a natural estrogen suspended in a solution with sodium. This spray could stimulate the nasal receptor by stopping or decreasing the aggressiveness of the virus. The role of estrogens can also explain the clinical picture of children who suffer from the virus and the fact that there are no gender differences. Boys have a prevalence of estrogen until their complete sexual maturity. Even though estrogens seem related to gender differences, some questions cannot be answered. During menopause, the amount of estrogen is decreased, so we expect the severity of the disease between the genders to be the same. Although, gender difference is still present among the elderly (Di Stadio *et al*., 2020; Grandi *et al*., 2020) (Fig. 4).

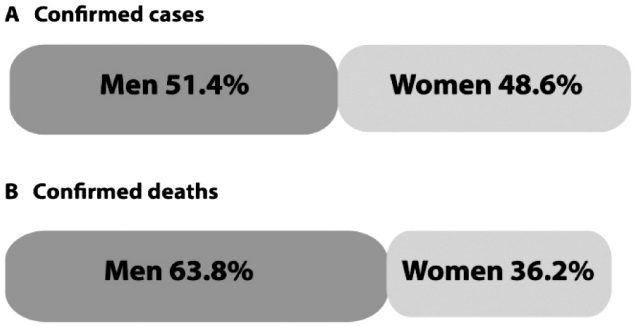

Fig. 4. Confirmed cases vs. confirmed deaths
The figure shows that 28% of the infected men with the virus passed away, while only 1.7% of women infected with the virus passed away.

Symptoms of COVID-19

The most common symptoms of coronavirus infection involve fever, cough, myalgia, fatigue, generalized weakness, sputum production, headache, sore throat, and dyspnea. Less commonly, patients may present with hemoptysis, diarrhea, vomiting, and dizziness. Indeed, some patients present with symptoms like anosmia and ageusia. It is believed that the virus affects the olfactory and gustatory receptors. Some of the symptoms may insist months after the recovery from the virus. The younger patients who suffer from coronavirus mostly have mild symptoms, while the clinical picture of the elderly and people with concomitant diseases is worse. Subsequently, the possibility of mechanical ventilation is higher. There is a high heterogeneity of symptoms between the patients affected by the virus; some may be asymptomatic or present only with mild symptoms.

In contrast, others may suffer the severe infection, which mainly involves pneumonia hypoxia and acute respiratory distress syndrome (ARDS) that may turn into severe respiratory failure. ARDS is a syndrome in which the patients present with hypoxemia, and the X-ray of the lungs shows mostly bilateral effusion. At the same time, computed tomography (CT) may reveal ground glass appear-

ance and patchy shadows. Lymphocytopenia is a common finding in patients who suffer from coronavirus laboratory results. Several types of research indicate that the prognosis of the patients whose laboratory results presented increased rates of D-dimers, fibrinogen, and prolonged thrombin time is worse, and they mostly end up with multi-organ failure (Han *et al.*, 2020; Huang *et al*., 2020; Udugama *et al*., 2020; Vaira *et al*., 2020; Yuki *et al*., 2020; Zhang *et al.*, 2020).

Comparison of existing vaccines

Several vaccines were approved and are used all around the world for mass vaccinations. As we already know, a vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. It typically contains an agent that resembles a disease-causing microorganism, and it is often made from weakened or killed forms of the microbe, toxins, or surface proteins. There are six types of vaccines i) Inactivated, ii) Live attenuated, iii) Subunit, iv) Viral vector, v) Toxoid, and vi) Nucleic acid vaccines (Chung *et al.*, 2020) (Fig. 5).

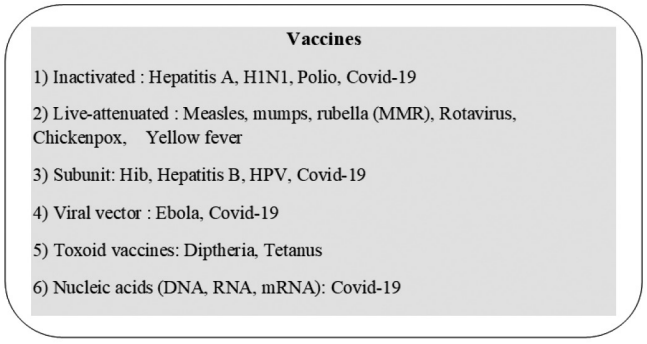

Fig. 5. Types of vaccines and examples

The research for the vaccines for SARS-CoV-2 focused on the S protein, which forms the spikes of the virus. The vaccines currently used for mass vaccinations are mainly based on this mechanism and were created by Pfizer, Moderna, AstraZeneca, The Gamaleya National Centre, Sinovax, and Novavax. However, some vaccines have other targets or multiple antigens, such as N protein or attenuated vaccines, inactivated vaccines, and peptide vaccines (Kalinin *et al.*, 2018; Chung *et al.*, 2020; Le *et al*., 2020).

The Russian vaccine by the Gamaleya National Centre, named Gam-COVID-Vac/ Sputnik V, is a heterologous recombinant adenovirus (rAd)-based vaccine and is the first registered vaccine on the market against Covid-19 (date of registration August 11, 2020). The vaccine seems to provide cellular and humoral immunity even from the first vaccination dose, although the second dose offers a durable and long-lasting immune response (Burki, 2020; Logunov *et al.,* 2020; 2021). Sputnik V seems to be effective and safe. The current data show that the vaccine has an efficacy of 91%, which is very positive (CNN 2021).

Another approved vaccine is from the pharmaceutical company AstraZeneca named ChAdOx1 nCoV-19/ AZD1222, a viral vector vaccine consisting of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen and that a side effect paused its clinical trials. The last stage of the vaccine's clinical trials halted due to a severe adverse reaction observed in a participant known as transverse myelitis (TM). TM is a neurological disorder of the spinal cord caused by inflammation, characterized by acute or subacute spinal cord dysfunction resulting in paresis, a sensory level, and autonomic (bladder, bowel, and sexual) impairment below the level lesion. The clinical trials stopped for a while until the safety board figured out the correlation between the manifestation of the disease with the vaccination and resumed again. Finally, the vaccine was recommended for authorization in European Union on January 29, 2021, by European Medicines Agency (EMA) (Beh *et al*., 2013; West, 2013; Voysey *et al.*, 2021). The average efficacy of the vaccine is 70% (CNN 2021). South Africa stopped its rollout of the AstraZeneca vaccine due to a study that concerns the mild or moderate people infected with the 501Y.V2 variant and shows low efficacy. However, there are no data about the severe cases of the infection and the vaccine's effectiveness.

The vaccine started to be used for massive vaccinations worldwide since the appearance of some cases of cerebral venous sinus thrombosis (CVST), which were correlated with the vaccination, according to the European Medicines Agency (EMA). However, their pathophysiology is still unknown, and the cases are rare. The EMA highlights that the benefits of the vaccination outweigh the risks and reports 44 cases of CVST out of 9,2 million vaccinations in Europe. According to the current vaccination status, Robert Koch Institute reported 31 cases out of 2.7 million from the first and 767 patients from the second dose. Indeed, in an amount of 19 people, platelet deficiency has been observed. In Germany, from the end of March, the vaccine of Astra Zeneca is not administered to people under 60 years old because the cases of thrombosis occur mainly in younger people. Those who have already been vaccinated should watch out for

symptoms like severe headaches after 2-3 weeks of vaccination. In case of such symptoms, they should get further evaluated by physicians. Countries like France and the Netherlands also ceased vaccine administration in younger people (Reuters, 2021; Sterzik, 2021).

Jannsen, Johnson & Johnson created a vaccine named JNJ-78436735/ Ad26.COV2.S., a viral vector vaccine, a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding the SARS-CoV-2 spike protein (Sadoff *et al*., 2021). The difference with the other vaccines is that only a single shot is needed to prevent the manifestation of severe infection caused by the virus and hospitalization. In January 2021, the company announced the vaccine's safety and efficacy results, which came up from Phase 3 clinical trial ENSEMBLE. The positive results show that the vaccine is 85% effective in preventing severe disease manifestation. In Phase 3 of the clinical trial of ENSEMBLE 2, the immune response after a two-dose regimen is investigated (Johnson, 2021).

There is data about the vaccines based on replication-incompetent Ad26 viral vectors. Their safety and features are under investigation. The first Ad26-based vaccine which was created was against the Ebola virus. Sputnik V also uses a heterologous recombinant adenovirus approach using adenovirus 26 (Ad26) and adenovirus 5 (Ad5) as vectors for the expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein. Jannsen, Johnson & Johnson also uses a replication-incompetent adenovirus serotype 26 (Ad26) vector encoding the SARS-CoV-2 spike protein. The immunogenicity of Ad26-based vaccines was evaluated in humans, and the results show strong, durable humoral and cellular immune responses. The clinical trials have not revealed the impact of pre-existing immunity to Ad26 on vaccine immunogenicity. That happens even in the presence of Ad26 neutralizing antibody titers or Ad26-targeting T cell responses at baseline. This data may raise concerns about using the adenovirus in vaccines against COVID-19, and the immune response should be investigated carefully (Jerome Custers, 2020; Jones and Roy, 2021; Sadoff *et al.*, 2021).

Sinovac Biotech is a Chinese biopharmaceutical company that developed an inactivated virus vaccine named CoronaVac (PiCoVacc). This vaccine development technology has been traditionally used and is safe and effective (Gao *et al*., 2020). This vaccine was approved by the National Medical Products Administration (NMPA) for a clinical trial in adolescents and children on August 10, 2020 (Sinovax, 2020). The study conducted in Brazil showed that the efficacy is 50.38% for those who suffered very mild cases of Covid-19 and 78% for mild to severe cases (CNN, 2021).

Novavax developed a subunit vaccine named NVX-CoV2373, a recombinant nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant (Keech *et al*., 2020). In January 2021, Novavax published the results of Phase 3 clinical trials conducted in the U.K., which show that the vaccine's efficacy is 89.3% (Novavax, 2021).

Pfizer and Moderna used a novel technology for the development of vaccines. The vaccine which Pfizer developed is named BNT16b2, while the name of Moderna's vaccine is mRNA-1273. They are mRNA vaccines. Both companies used similar techniques for the development of vaccines. In detail, they utilized mRNA that encodes for subunits of the SARS-CoV-2 S protein. The mRNA is modified. These vaccines are encapsulated in lipid nanoparticles (LNPs) which can enter cells and enable the expression of antigens from delivered nucleic acids. Thus, they allow cytoplasmic delivery. Some specific receptors in the cell's endosome are called toll-like receptors (TLRs), such as TLR 3, 7, and 8. RNA acts by activating these receptors. Indeed, TLRs 7 and 8 recognize single-stranded RNA and participate in recognizing the virus, making them very important for mRNA vaccines.

As mentioned above, the vaccines are encapsulated in LNPs, improving RNA phagocytosis by antigen-presenting cells (APCs). Nuclease degradation and weak immune stimulation are the results of the unsuccessful endocytosis of the RNA. The mRNA is translated into the cytoplasm inside the cell, leading to a higher amount of antigen in smaller doses. However, mRNA expression is shorter-lived (Chung *et al.*, 2020; Wang *et al*., 2020; Harky *et al*., 2021). The data from utilizing the vaccines developed by Pfizer-BioNTech and Moderna are very positive and show an efficacy rate of about 95% (Mahase, 2020a, b; Baden *et al*., 2021; CNN, 2021). The development of an adequate safety database is significant for a novel vaccine to be approved and accepted by the public. Immunization programs and the population's education are necessary to lessen the concerns about the vaccine's safety (Table 1) (Le *et al*., 2020; Wang *et al*., 2020).

Mutations of SARS-Cov-2 and evolution

It is believed that SARS-CoV-2 is capable of recognizing and binding the ACE-2 receptors very

Table 1. Comparison of the vaccines available on the market

Company	Name	Type of vaccine	Efficacy	Doses	Period between doses
Pfizer BioNTech	BNT162b2	mRNA	92% from first data Israel	2	3 weeks
Moderna NIAID	mRNA-1273	mRNA	94.1%	2	4 weeks
AstraZeneca Oxford	ChAdOx1 nCoV-19/ AZD1222	Viral vector	59.5% (2 doses)	2	4-12 weeks
The Gamaleya National Centre	Sputnik V/ Gam-COVID-Vac	Viral vector	92% (2 doses)	2	3 weeks
Jannsen Johnson & Johnson	JNJ-78436735/ Ad26.COV2.S.	Viral vector	66% but 85% in the appearance of serious cases	1	-
Sinovac Biotech	CoronaVac (PiCoVacc)	Inactivated virus	50.6% (data from Brazil)	2	2 weeks
Novavax	NVX-CoV2373	Subunit	95.6% (7 d after the second dose)	2	4 weeks

strongly due to a mutation that made the virus capable of infecting humans. Although the odds of a random bat virus having the right traits to infect people were low, this is the most reasonable explanation of the virus's origin. Since the beginning of the pandemic, the virus has not changed a lot. Still, it mutated in a standard way that all viruses do due to evolution and adaptation processes. Most of the mutations did not have a significant impact.

More specifically, the D614G variant was the first one found in Australia and India in May 2020. It was followed by a variant known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7, which appeared in December 2020 in the United Kingdom. This variant has a mutation- N501Y in the receptor-binding domain (RBD) of the spike protein used by the virus to attach to human cells. Except for this, several other mutations, such as 69/70 deletion and P681H. Another variant known as 20H/501Y.V2 or B.1.351 was found in South Africa, and the P.1 variant was identified in Brazil and Japan. The South African variant has multiple mutations in the spike protein as K417N, E484K, and N501Y. The P.1 variant has three mutations in the spike protein and, more specifically, in the RBD, which are the following K417T, E484K, and N501Y. The effectiveness of the Pfizer vaccine against E484K mutation present in B.1.351 and P.1 lineages was evaluated in a study. The results presented that the serum neutralization efficacy was lower but not absent against this mutation, which means that the mutation in the RBD of the spike protein affects antibodies binding from convalescent and vaccinated donors. Thus, highest titers of antibodies are needed to increase the possibilities of protection even in cases of antigenic drift.

Although there is no such reliable data yet, the results from the first researchers show that B.1.1.7 variant is more contagious and may increase the mortality rate. In detail, the data from three regions of England showed that the variant is 56% more transmissible than previously identified variants. In contrast, the data available from Danish studies showed that this variant is 36% more infectious than the others. The novel variants create conflicts for the efficacy of the vaccines against the variants. According to the U.N. health agency, the B.1.617 variant of the SARS-CoV-2, also known as the Indian strain, is increased transmissibility and reduced neutralization.

There is a belief that the vaccines are still adequate; nevertheless, some companies as Moderna, made a third booster dose of the vaccine called mRNA-1273.351, which is in Phase I studies in the U.S.A. to test if it can increase the immunological effect against variant B.1.351 that raised the most concerns about the efficacy of the vaccines. Research about the effectiveness of the Moderna vaccine was published, and the results show reduced but still significant neutralization against the full B.1.351 variant following mRNA-1273. More effective measures should be taken to restrict the spread of the variants. These include the proper diagnostic tools as next-generation sequencing technologies are needed to find novel variants and increase surveillance levels. Personal protective equipment is still inevitable. Indeed in some states of Germany as Bayern,

it is suggested only the use of FFP2-N95-KN95 masks from the population, which filter about 95% of aerosol-containing particles compared to standard surgical masks, to decrease the possibility of variants transfer between the people (Plante *et al*., 2020; Kai Wu, 2021; Prevention, 2021; Regli *et al*., 2021; Sonia Jangra, 2021; Tanne, 2021).

Unfortunately, all vaccines developed for the time being express the spike protein of SARS-CoV-2. Suppose some of them had expressed a different SARS-CoV-2 protein. In that case, combining two vaccines could have induced two different types of antibodies to tackle various variants of the SARS-CoV-2 more efficiently.

The latest known variant of SARS-CoV-2, Omicron BA.2.12.1, is more transmissible than other variants. Thus, it is more likely to cause reinfections than other variants. Omicron may sometimes cause severe conditions and death; however, it is generally milder than infections caused by the Delta variant. Now, there are vaccines specific against the omicron variant.

Discussion

An effective vaccine or medication is the only possibility to return to pre-COVID-19 societal behavior. Global cooperation and teamwork are very significant in the fight against the virus. Mass vaccinations have already started, although the appearance of new variants raises concerns about the efficacy of the vaccines against them. The immunization of the population results in the production of antibodies against the spike protein of the virus. Although some of the mutations which came up concern the spike protein as the mutations in RBD. That is the main reason why the effectiveness of vaccines may be reduced against these new variants. More specifically, the South African variant seems to be the one that threatens the vaccine's efficacy. It is generally believed that vaccination is more efficient than adaptive immunity due to the high titers of antibodies. The vaccines work based on protective antibody responses, neutralizing antibodies as the most common mechanism of action, although there is an additional elicitation of CD4+ or CD8+ T cells. Nevertheless, the antibodies produced because of vaccination act against only one protein, the spike protein, the leading region where the novel mutations appeared.

On the other hand, when a person has been infected with the virus, the adaptive immunity (humoral and cellular) is activated, which consists of B cells (antibody-producing cells), CD4+ T cells (helper T cells), and CD8+ T cells (cytotoxic, or killer, T cells) which are very important for the protection against viral infections. Therefore, there is a great need to develop poly mRNA vaccines with different antigens to produce more antibodies. In addition, it is believed that using poly mRNA vaccines will reduce the appearance of mutations.

Conclusion

There is no specific drug that is effective against coronavirus. The treatment for patients who suffer a severe infection includes mechanical ventilation and a combination of medications. Although mass vaccinations have already started, the most successful ways to protect ourselves from the disease are social distancing, isolation, lockdowns, and PPE. That is because many of the population should be vaccinated to achieve herd immunity. Many drugs were tested and used as possible treatments against coronavirus, and some seem to play an essential role in reducing the mortality rate. The use of vaccines massively is promising for the future. However, the appearance of new variants of the virus, which seem more contagious, raises conflicts about the efficacy of some vaccines against them. The new-sequencing technologies are powerful diagnostic tools for detecting new variants. The first data available from countries that have already managed to vaccinate a substantial amount of the population is very positive, which raises hope that eventually, the quality of life will start to improve. Globally, as of June 10th, 2022, there have been 532,201,219 confirmed cases of COVID-19, including 6,305,358 deaths, reported to WHO. As of June 6th, 2022, 11,854,673,610 vaccine doses have been administered (https://covid19.who.int/). However, the COVID-19 spread by less than 10% compared to its peak worldwide due to vaccination and the Omicron variant, which seems to decrease the global pandemic significantly. However, we must stay vigilant and develop novel drugs against SARS-CoV-2 that are easily adaptive to its mutations, such as ASOs.

Acknowledgments

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