



## Insight into COVID-19 available Vaccines Authorised for Emergency Use

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### ABSTRACT

In December of 2019, SARS-CoV2, a member of the coronavirus family, started to spread rapidly worldwide. The pandemic known as COVID-19 has resulted in mortality from respiratory disorders in 2,413,912 people to date, according to the World Health Organization. It has also necessitated hospitalization and intensive care for many people around the world, exceeding the capacity of hospitals. The rapid transmission of this virus is an important characteristic that requires individuals to take strict precautions to protect themselves. To date, there is no known treatment for COVID-19, but pharmaceutical companies, collaborating with scientists, have expended huge effort toward developing effective vaccines to prevent this newly emerging coronavirus. Because traditional vaccine development required long periods, genome and vector-based vaccines have helped accelerate this process. From hundreds of candidate vaccines that started undergoing preclinical and clinical trials, 3 have reached the final stage of requesting emergency authorization use from the World Health Organization: the Pfizer/BioNTech, Moderna, and AstraZeneca vaccines and other vaccines had national approval by their countries including Sinovac, Sputnik V, CanSinoBio, Bektap, Sinopharm, and Covaxin. A summary of these candidate vaccines is offered in this review.

**Keywords:** SARS-CoV2, COVID-19, Pfizer/BioNTech, Moderna, AstraZeneca Sinovac, Sputnik V, CanSinoBio, Bektap, Sinopharm, Covaxin vaccines

### INTRODUCTION

Successful prevention of fatal infectious diseases through vaccination has provided a significant transformation in the control of the spread of these diseases. Since the first attempt performed by Edward Jenner in the prevention of smallpox in 1796, scientists have spent much effort in developing vaccines as a powerful tool in the prevention and controlling of many viral and bacterial infections [1]. According to the World Health Organization (WHO), vaccination programs against diseases such as tetanus, diphtheria, influenza, and measles save 2 to 3 million lives every year. Currently, more than 20 vaccines against life-threatening diseases are available [2].

Vaccine technology depends on using the whole attenuated microorganism or parts of it to trigger the immune response in the host to develop adaptive immunity [3]. Although it is an effective methodology in the prevention of the disease before its occurrence, its development requires greater effort, time, and cost compared to the development of traditional medications. The effective development of candidate vaccines that record minimal adverse events on participants in specific periods poses a big challenge to the vaccine industry [4].

One year ago, in December 2019, the first case of Coronavirus Disease 2019 (COVID-19) was recognized in Wuhan, China [5]. That was the start of a global pandemic that would affect 109,217,366 people by February 2021, threatening older people particularly and causing the death of about 2,413,912 people to date, according to the WHO [6]. It is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a member of the coronavirus human COV family that includes these 6 other members: human CoV 229E (HCoV-229E); HCoV-NL63; HCoV-OC43; HCoV-HKU1; SARS-CoV; and MERS-CoV [7]. The symptoms of the disease range from mild respiratory, upper tract cold-like symptoms to more severe, fatal illnesses requiring hospitalization and intensive care [5].

It is known that virus transmission is mostly accomplished through face-to-face contacts, such as coughing, talking, or sneezing, which are all modes of aerosol spread of respiratory droplets. Hence, social distancing is required to manage COVID-19 spread and transmission [8]. At present, there is no antiviral treatment for SARS-CoV2, and several labs

are expending great effort toward the possibility of developing a vaccine. This review will be focused on the up-to-date development of COVID 19 vaccines.

## REVIEW OF LITERATURE

### Vaccine Development Stages

The development of an effective vaccine seems to be the only possible effective procedure against the COVID-19 worldwide pandemic. By the middle of May 2020, around 200 vaccine candidates were under trial as researchers hoped to meet the global demand by the end of 2021 [9]. The traditional process of vaccine development requires the vaccine to pass preclinical and clinical stages, which usually takes around 15 years. The preclinical process starts with vaccine design, cell culture studies, and animal model testing for a couple of years. At the end of that period, the effective dose and administration methodology applicable to humans may be suggested; all possible side effects and immune response to tested vaccines are monitored. Then several years of formal preclinical studies and toxicology testing follows. After that, 3 phases of clinical studies on humans take place over several years; these are listed below [10,11]:

**Phase I** tests the safety and determines the dosage providing an optimal immune response on a small number of volunteers (around 80 participants) who are monitored for the development of any possible side effects.

**Phase II** further tests safety, effective doses, immunogenicity, effective administration routes, and schedule of immunization. Hundreds of participants are enrolled in this stage randomly chosen and well-controlled. The trials also involve placebo groups and may involve a group of individuals at risk of acquiring the disease.

**Phase III** aims to monitor immune response development on both the humoral and cellular response level by assessing the immunogenicity of the vaccine. Thousands of participants are involved in the studies at this stage, and protection from disease, known as vaccine efficacy, will be examined [4,12,13].

Once the candidate vaccine proves successful, the regulatory authority will need to approve its manufacture after reviewing all previous results of clinical studies. This stage may also take between 1 and 2 years-except for during this pandemic year when there is an urgent need for the vaccine. For manufacture and surveillance of the vaccine after its release for public use, continuous monitoring of its effectiveness and development of any possible side effects will continue. During the pandemic, the vaccine's developmental stages may be accelerated and phases merged to meet the urgent need, and it may take 12-24 months before the candidate vaccine is released for public use [4,9,12].

### Vaccines Combining Traditional and Modern Techniques

Developing new vaccines requires specific design, depending on the disease type; the behavior of the infectious agent; the type of immunity targeted, whether humoral or cell mediated-all these factors are considered when choosing the appropriate methodology for vaccine manufacture and development [14]. During the past decade, different types of vaccines have been evolved for protection against many threatening diseases, such as live attenuated vaccines, inactivated vaccines, toxoid vaccines, and conjugate vaccines [15].

**Live attenuated vaccines:** In this type of vaccine, infectious agents such as bacteria or viruses undergo multiple passages in a host cell to lose their infectious capabilities while acquiring stronger replication abilities once induced in humans. Another methodology involves inducing mutations during processing and choosing non-virulent strains. The process proves to be effective in protecting against many diseases without the need for adjuvants or inducing humoral and cellular immunity.

**Limitations:** Among the limitations of live attenuated vaccines are the following: the infectious agent may return to its virulent behavior; some microorganisms cannot be cultured effectively; only limited protection against some bacteria and virus strains is offered; undesired inflammatory reactions and autoimmune response may occur [16].

**Inactivated vaccines:** In this type of vaccine, the infectious agents are killed using different methods, including treatment with formaldehyde, glutaraldehyde, heat, and pH, all of which target the virus protein, or with irradiation that targets the virus genome. It is a safe and less expensive type of vaccine that requires adjuvants.

**Limitations:** The process of killing the infectious agent may lead to incomplete inactivation and a resulting outbreak of the virus after administration. Besides, destroying the viral epitope causes a poor immune response [17]. Moreover, long-lasting immunity is not present; booster doses are required owing to the destruction of virus replication [16].

**Toxoid:** A toxoid type of vaccine is based on the exotoxins secreted by bacteria; these become the antigenic determinants that are processed to be administered in humans. Toxins of bacteria, such as tetanus and diphtheria, are inactivated using chemical agents like formaldehyde or physical treatment such as heat so that the immune system evolves a response to bacteria's attacking mechanism that minimizes its virulence.

**Limitations:** Toxins' inactivation may destroy their structures and affect vaccine efficacy [18].

**Subunit Vaccines:** When there is no need for the whole infectious agent to be used, a part of the microorganism is used to produce a subunit vaccine. The part that will be purified from this microorganism could be the surface molecule, the toxin, or a cellular fragment that will act as the antigen. These antigenic parts require adjuvants to act as carriers and help induce the immune response. The T-cells' response generated against protein antigens and the T-cells' independent response against polysaccharides will depend upon the type of purified antigen immune response induced [19].

**Limitations:** Because it has no live particles from the microorganism, memory response is under question. Also, low immunogenicity for this type of vaccine requires good adjuvants [20].

**mRNA/DNA vaccines:** An mRNA/DNA vaccine is a nucleic acid-based vaccine that depends on using the genome of the microorganism to prevent disease. It is effective in inducing both cellular and humoral responses. This time-saving technology of vaccine manufacture appears safe and helpful for an urgent need such as in a pandemic [21]. Moreover, in this type of vaccination processing, there is no need for the growth of a high scale of pathogenic organisms, reducing the danger of contamination.

**Limitations:** RNA vaccine instability and low immunogenicity are limits that need to be overcome. For DNA vaccines, the possibility of integration into the human genome and low immunogenicity are limits that need addressing [22].

**Vector vaccines:** One of the most promising and advanced technologies in the manufacture of vaccines is the use of viral vectors. Many viruses are characterized as vectors for the delivery of parts of pathogenic genomes. These vectors are first engineered to not cause disease once administered to the host, either by replicating viral vectors that are attenuated or by not replicating at all. Once these vectors reach host cells, they deliver the pathogenic genomic material to the body, initiating an immune response [23].

**Limitations:** There is the possibility for integration with the host genome, leading to the development of cancer. The presence of pre-existing antibodies for the vector from previous exposure may reduce the vaccine's efficacy [24].

### COVID-19 Approved and Available Vaccines

The development of a vaccine effective against COVID-19 is a challenging process because time is a huge obstacle to be overcome. A successful candidate vaccine must demonstrate safety and efficacy as well as both humoral and cellular responses [25]. Several vaccine candidates have been tested since the start of the pandemic, relying on information from previous trials of SARS-CoV and MERS-CoV that helped shorten the required preclinical and clinical phases [26]. These efforts include different strategies of vaccine development, such as live attenuated, inactivated, and nucleic acid-based, subunit, and viral vector-based vaccines; they are variously at Phase I and Phase II, and some are at Phase III trials [25]. According to the WHO, 3 vaccines have been authorized by national regulatory authorities for use against COVID-19-those developed by Pfizer-BioNTech, Moderna, and AstraZeneca. Besides, other vaccines have been authorized by national authorities but not WHO including Sinovac, Sputnik V, CanSinoBio, Bektop, Sinopharm, and Covaxin-which will be summarized herein (Table 1).

**Table 1 Approved vaccines by WHO and other national authorities**

Developing Company	Vaccine Name	Type of the Vaccine	Route of Administration	Number of Doses	Efficacy Rate	Approval Authorities
Pfizer-BioNTech	BNT162b2	mRNA	Muscle injection	2	95	USFAD and WHO
Moderna	mRNA-1273	mRNA	Muscle injection	2	91.4	USFAD, European Medicines Agency, and WHO
AstraZeneca	AZD1222	Adenoviral vector	Muscle injection	2	82.4	European Union and WHO

Sinovac	CoronaVac	inactivated vaccine	Muscle injection	2	50.38	Chinese authorities
Sputnik V	Gam-Covid-Vac	Adenoviral vector	Muscle injection	2	91.6	Russia national authority
CanSinoBio	Ad5-nCoV	Adenoviral vector	Muscle injection	1	65.7	Chinese authorities
Bektop	EpiVacCorona	Protein	Muscle injection	2	Not none	Russia national authorities
Sinopharm	BBIBP-CorV	Inactivate vaccine	Muscle injection	2	79.34	Chinese authorities
Covaxin	BBV152	Inactivate vaccine	Muscle injection	2	Not none	Indian authorities

**Pfizer-BioNTech vaccine:** On April 23, 2020, Pfizer and BioNTech started the first clinical studies on their candidate vaccine, BNT162b1, in a trial with 200 volunteers between 18 and 55 years old in Germany. The study was also applied to 360 US volunteers aged 18-85 years beginning in May of 2020, and collaboration with Fusion Pharma to start the trial in China was agreed upon. These were Phases I and II of the vaccine's development. The candidate vaccine BNT162b1 is an mRNA vaccine that uses lipid nanoparticles to carry antigenic genomic material to the host [27]. The Pfizer vaccine was first tested in 3 doses (0 µg, 30 µg, and 100 µg), using a poster-boost strategy where vaccines were given in 2 doses, separated by 3 weeks, except the 100 µg, which was given in a single dose, for safety reasons. After each boost of neutralizing antibodies, titers were examined using ELISA. The highest titers reached for the 10 µg and 30 µg vaccines 14 days after the second booster were 1:180 and 1:437, respectively. Some of the side effects recorded included fever, headache, fatigue, and chills, reported in 50% of the participants who received the 100 µg booster, while 70% of the 30 µg group reported fever after the second dose.

The company also has trials on another vaccine candidate known as BNT162b2. It is similar to BNT162b1, although it is based on using full spike protein and it showed a beneficial safety profile, for which it was advanced to Phase III [28]. A study published by Pfizer on December 10, 2020, reported that its candidate vaccine, BNT162b2, comprising 30 µg given in 2 doses separated by 21 days, proved to be safe and 95% effective as an immunization against COVID-19. The side effects reported were mild or moderate and less common in older adults, remaining only for a couple of days. According to the report, some groups have still not been included in the studies: pregnant women, adolescents, and children. These groups will require additional separate studies. The company also highlighted the importance of cold storage of the vaccine [29]. The US Food and Drug Administration (USFDA) has already given emergency authorization for the use of BNT162b2 in people 16 years and older, and the vaccine is authorized for use in several other countries.

**Moderna vaccine:** On March 16, 2020, the first Phase I trial of the candidate vaccine developed by the American company Moderna started in the US. This is also an mRNA-based vaccine coding for SARS-CoV2 spike protein S-2P, like the vaccine known as mRNA-1273 and designed in the same methodology of Pfizer's, where the virus mRNA genome is carried in a lipid nanoparticle. The Phase I trial involved 45 healthy participants from 18-55 years of age who received 2 doses of the vaccine separated by 28 days in 3 different concentrations (25 µg, 100 µg, and 250 µg) [30]. During this trial, the participants reported no serious side effects after the first dose. The participants reported some moderate to mild side effects on the second dose report, specifically the 250 µg group, including headache, pain at the site of injection, chill, fatigue, and myalgia. The vaccine was found to be immunogenic, causing both antibody response and cellular response. The degree of immunogenicity and safety encouraged the transfer of the vaccine to Phase II and Phase III [30]. Efficacy of the mRNA-1273 vaccine was confirmed by the company after Phase III results, which involved 30,000 volunteers enrolled in the study using 100 µg of the vaccine in 2 doses. A report published on the Moderna website listed 94.1% efficacy of the mRNA-1273 vaccine against COVID-19. The company started the process of applying for emergency authorization approval from the USFDA and the European Medicines Agency [31]. By December 18, Moderna announced USFDA approval for emergency use of its candidate vaccine, with 20 million doses to be delivered to the US government by the end of December 2020 [32].

**AstraZeneca vaccine:** AstraZeneca, a British biopharmaceutical company located in Cambridge, UK, developed a candidate COVID-19 vaccine known as (AZD1222) ChAdOx1 nCoV-19 in collaboration with Oxford University. This is a vector-based vaccine that uses the replication-deficient chimpanzee adenoviral vector ChAdOx1 to carry the surface glycoprotein spike protein of SARS-CoV2 (nCoV-19). Vaccine trials were carried out in different locations

around the world, including the UK, Brazil, Kenya, and South Africa [33]. A Phase I trial on AZD1222 started at 5 different locations within the UK involving 1,077 healthy adults aged 18-55 years on April 23, 2020. The participants were given  $5 \times 10^{10}$  viral particles, which is the standard dose for vector vaccines, similar to a single dose. After giving their approval, 10 of the participants received a second dose on day 28. No serious adverse effects were recorded; only moderate to mild side effects, including headache, fever, muscular ache, chill, and malaise in some participants, who tolerated the effects by using paracetamol. Participants generated both humoral responses (day 28) and cellular responses (day 14). After the second dose, neutralizing antibodies were higher on day 42. The safety records and immunogenicity of the vaccine encouraged its transfer to Phase III trials, which took place in Brazil and the UK [34]. The Phase III trial of AZD1222 took place between April 23 and November 4, with 10,673 participants enrolled in the UK study and 10,002 enrolled in Brazil. The participant groups were aged 18-55 years, each receiving 2 doses of the vaccine, but in different dose concentrations and intervals. In the UK study, participants received  $2.2 \times 10^{10}$  viral particles in 2 doses separated by 12 weeks. The Brazilian participants received  $(3.5-6.5) \times 10^{10}$  viral particles in 2 doses separated by 6 weeks. Data from both studies showed the same vaccine efficacy 82.4% in addition to tolerated local and systemic reactogenicity. Although some serious side effects were reported by the company, they were only reported among 0.7% of the total volunteers. Three cases of transverse myelitis were recorded; according to their records, it appears that 2 cases were not related to study intervention, while 1 is still possibly related. The company has clarified that safety follow-up in the vaccine trials must continue [33], as AstraZeneca posted on its website because it has started to seek emergency use licenses from the WHO. Also, it has made progress toward its goal of producing 3 billion doses in 2021 [35].

**Sputnik vaccine:** Gamaleya Research Institute developed this vaccine, also known as Gam-COVID-Vac. It is a heterologous adenoviral vector-based vaccine consisting of 2 components: recombinant Adenoviral type 26 vector (rAd26) and recombinant Adenoviral type 5 vector (rAd5). It can be used in 2 formulations: frozen or lyophilized. The Phase I and Phase II trials occurred in Russia between June 18 and August 3, 2020, with a total of 76 participants aged 18-60 years old. Participants received one of the 2 formulations-rAd26 or rAd5. According to the published data for these trials, both formulations proved safe and were tolerated with mild side effects, including hyperthermia, pain at the site of injection, headache, asthenia, and muscle and joint pain. Besides, participants produced a strong humoral response of IgG titers-they detected 14,703 titers for the frozen vaccine formulation and 11,143 titers for the lyophilized vaccine formulation at Day 42. They also determined strong cellular response generated in participants at Day 28 [36].

Between September 7 and November 24, 2020, Phase III trials occurred in Moscow, Russia, with 21,977 participants enrolled in the study in 2 groups: 16,501 in the vaccine group and 5,476 in the placebo group. In the vaccine group, participants received 2 doses (0.5 ml/dose)-the first dose of rAd26 and a second dose of rAd5-at 21 days between the first and second dose. Serious adverse effects in the 2 groups stood at 0.3% in the vaccine group and 0.4% in the placebo group, with 4 deaths reported but not linked to vaccination. The published data reported 91.6% efficacy for this vaccine [37]. The vaccine is approved for use in Russia and several other countries, including Argentina, the United Arab Emirates (UAE), Iran, Venezuela, Hungary, and Palestine [38].

**CanSinoBio vaccine:** The Chinese company CanSino Biologics developed Convidecia, also known as Ad5-nCoV, in partnership with the Institute of Biology at China's Academy of Military Medical Sciences. The vaccine is designed using the recombinant adenoviral vector type rAd5. The first trial of the vaccine in Phase I involved 108 participants aged 18-60 years old. Participants were divided to receive a low dose, a moderate dose, or a high dose ( $5 \times 10^{10}$ ,  $1 \times 10^{11}$ , and  $1.5 \times 10^{11}$  viral particles, respectively). This vaccine is dependent on a single dose, and both humoral and cellular response had generated at the 28-day follow-up. Mild adverse effects reported included fever, pain at the site of injection, fatigue, headache, and muscle pain [39].

The Phase II trial occurred in Wuhan, China, involving 603 participants aged 18 years and older between April 11 and April 16, 2020. The participants were divided into 3 groups to receive  $1 \times 10^{11}$  viral particles per ml,  $5 \times 10^{10}$  viral particles per ml or a placebo. No participants reported serious adverse events, and the results showed a good immune response determined with high neutralizing antibodies and a high concentration of interferon. The published data indicated that the single dose of rAd5  $5 \times 10^{10}$  viral particles per ml was safe and effective [40]. The Phase III trial started on September 15, 2020, and ended on January 30, 2021. It involved 40,000 participants, divided into a vaccine group and a placebo group. The trials occurred in several countries, including Pakistan, Russia, Mexico, and Chile, the vaccine showed 65.7% efficacy [41].

**Becktop vaccine:** Russia's Vector Institute started Phase I and Phase II trials of the vaccine known as EpiVacCorona

on August 26, 2020. It is a protein-based vaccine containing peptides of the virus. On Phase III of the vaccine trials, 1,438 participants enrolled in November 2020 to receive 2 doses of vaccination with an interval of 3 weeks. Although data were not published regarding the efficacy of the vaccine, starting this February, Russia has used it following its early approval [42].

**Sinopharm vaccine:** Sinopharm developed 2 candidate vaccines. Beijing Institute of Biological Products developed the first vaccine, known as BBIBP-CorV, as a whole inactivated vaccine. Phases I and II occurred in Henan, China, where 192 participants enrolled in Phase I, grouped either 18-59 years old or  $\geq 60$  years old. Participants received 2  $\mu\text{g}$ , 4  $\mu\text{g}$ , or 8  $\mu\text{g}$ /dose or placebo in 2 doses at days 0 and 28. By contrast, Phase II trials involved 448 participants who received doses as 8  $\mu\text{g}$  at Day 1 or 4  $\mu\text{g}$  at Day 1 and Day 14, Day 1 and Day 21, or Day 1 and Day 28, in addition to the placebo group. The trials recorded no serious adverse events and a common side effect of fever. The company data pointed to the effective humoral response generated on Day 42 shown by an increase of antibody titers, and the company recommended the 4  $\mu\text{g}$  dose on Days 0 and 21 or Days 0 and 28 as their best-tested doses [43]. Phase III trials of the vaccine occurred in several countries, including the UAE, Bahrain, and Egypt, with 45,000 participants enrolled [44]. Although Sinopharm announced 79.34% efficacy, on December 9, 2020, the UAE gave full approval for the use of the vaccine because their efficacy rate was 86%. Also, in January 2021, Hungary became the first European country to permit the use of this vaccine [42,45].

A second version of the whole inactivated Sinopharm vaccine saw development by the Wuhan Institute of Biological Products. On April 12, 2020, phases I and II of the Sinopharm vaccine trials started in Henan, China, where 96 participants enrolled in Phase I and 224 enrolled in Phase II. At Phase I, they tested 3 doses of the vaccine (2.5  $\mu\text{g}$ /dose, 5  $\mu\text{g}$ /dose, and 10  $\mu\text{g}$ /dose) in addition to a placebo. These doses occurred in 3 injections at Days 0, 28, and 56. In phase II, the trials tested the 5  $\mu\text{g}$ /dose with 2 injections given either at Days 0 and 14 or Days 0 and 21 in addition to a placebo. The published data showed no serious adverse events in both phases, with only mild side effects, including fever and pain at the site of injection. Besides, good immune responses and neutralizing antibody titers characterized an encouraging third phase of the study [46]. Limited use of the vaccine in China and the UAE means no clear results are available for this version [42].

**Bharat Biotech Vaccine:** Bharat Biotech of India developed Covaxin as an inactivated vaccine, which is also known as BBV152. The Phase I trial of the vaccine involved 375 participants who received 2 doses of 3  $\mu\text{g}$  with Algel-IMDG, 6  $\mu\text{g}$  with Algel-IMDG, or 6  $\mu\text{g}$  with Algel. The control group received doses at Days 0 and 14. They recorded no serious adverse events, with only mild to moderate effects, including fever, headache, and pain at the site of injection, fatigue, and nausea. The study data showed vaccine safety and good immune response, encouraging further trials [47]. In November 2020, a Phase III trial started in India with 25,800 participants. Although the efficacy rate of the vaccine remains unpublished, on January 3, 2021, the Indian government approved its emergency use. The company claimed that the efficacy rate would be published in February 2021 [48].

## CONCLUSION

The rapid spread of SARS-Cov2, starting in December of 2019 and continuing to date, concludes a pandemic year that affected the lives of millions around the world and emphasizes the urgent need for the development of an effective vaccine against COVID-19. It is a respiratory disorder characterized by its rapid transmission between individuals, which requires many protective considerations from governments to reduce its dangerous impact on human health, life, and economics. Many countries underwent strict lockdown for months, which affected them in many ways. Pharmaceutical companies started immediately to develop vaccine candidates for this virus, hoping to secure a protective method to help minimize this pandemic spread. From around 200 vaccine candidates, 3 reached the final stage of obtaining reduce its dangerous impact on human health, life, and economics. Many countries underwent strict lockdown for months, which affected them in many ways. Pharmaceutical companies started immediately to develop vaccine candidates for this virus, hoping to secure a protective method to help minimize this pandemic spread. From around 200 vaccine candidates, 3 reached the final stage of obtaining other vaccines gained national authorized approval for early use including Sinovac, Sputnik V, CanSinoBio, Bektop, Sinopharm, and Covaxin vaccines. While highly aware of the importance of assuring the safety of these vaccines, nevertheless researchers are hopeful for the vaccines' success because it may help to stop this pandemic and allow people to return to normal life.

## DECLARATIONS

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### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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