



## **Recent Advances in Drugs and Vaccines for COVID-19**

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*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Several potential COVID-19 therapeutic approaches and SARS-CoV-2 vaccines have been investigated, and final clinical reports are gradually becoming available. In this mini-review, we discussed the history of selected potential therapeutic drugs and newly designed vaccines, as well as other approaches for the COVID-19 treatment, and made a primary evaluation of their clinical effects. Finally, according to the nature of coronavirus we posed a promising design to against the SARS-CoV-2 by the chemi-physical methods through carbon nano-materials modification.

**Keywords:** Drug; vaccine; COVID-19; SARS-CoV-2.

## 1. INTRODUCTION

The number of confirmed cases of coronavirus infectious disease in 2019 (COVID-19), the illness caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), has drastically increased to more than 100 million worldwide and continues to rise [1] The COVID-19 pandemic has been the largest public health challenge of the 21st century. Scientists and physicians are struggling to develop vaccines and treatments to curb the pandemic and mitigate its effects. Drugs that have been approved for other diseases or that have been tested against other viruses were applied early on after the sudden outbreak of SARS-CoV-2. Researchers continue to investigate whether existing antiviral drugs will be effective, and new drugs are being developed as potential treatments [2] Global efforts have been done to develop a vaccine against SARS-CoV-2 due to the well-known recognition that the vaccines are the most efficient method against viruses. The routine strategy for the vaccine includes mRNA vaccine, inactivated virus vaccine, DNA vaccine recombinant protein vaccine, and viral vector-based vaccine. However the time-consume around 18 months or more makes it even harder to develop an efficacious vaccine timely, though massive-scale efforts are on the way. Then number of drugs used for other diseases have been currently repurposed to tackle the COVID-19 pandemic, maybe it is one of the potentially quickest ways to find treatment for this new viral infection.

We have searched the literature and screened published research articles to further dig-down to list the repurposed drug, vaccines and other methods for COVID-19 treatment by using "Boolean Operators" such as AND, OR and NOT to search relevant research articles/reviews from the PUBMED.

As of May 8, 2020, two drugs had received an emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) for the treatment of COVID-19: the antiviral drug remdesivir and a respiratory sedative drug [3] An EUA allows physicians to use a drug to treat patients even though the drug has not yet undergone the full approval process. In March 2020, the FDA issued an EUA for the antimalarial drugs chloroquine and hydroxychloroquine, but the EUA was later revoked because of the ineffectiveness of these drugs in treating COVID-19 [4,5] These drugs are currently being tested in

clinical trials to evaluate whether they are an effective COVID-19 treatment and to further assess their safety in humans. This research is needed to ensure that these drugs are safe and to define the appropriate dose. It may be some time before an effective COVID-19 treatment is developed, [6] and vaccine development may take longer still [7] Nevertheless, other measures can help to reduce the severity of the pandemic, such as physical distancing, contact-tracing, and self-isolation. (A concise show of main treatment methods to COVID-19 in Table 1)

## 2. A JOURNEY TO FIND EFFECTIVE TREATMENTS

Drug development is sometimes described as a pipeline where compounds flow from early laboratory development, to animal trials, and finally to human clinical trials. It may take 10 years or more from the initial discovery of a new compound to its clinical use, and many compounds never reach clinical trials. That is why many drugs considered as potential candidates for COVID-19 treatment are drugs that have already been developed. In a British Journal of Pharmacology review, scientists from the United Kingdom called for wider screening of existing drugs to investigate their effectiveness against the new coronavirus. The authors identified three stages of infection at which the virus could be targeted: preventing the virus from entering cells, preventing it from replicating in cells, and minimizing organ damage. Many of the drugs being developed to treat COVID-19 are antivirals. These drugs target the virus in people who are already infected. [8] Antiviral drugs should be given before there is considerable virus replication and before significant damage occurs. In general, the earlier the use of antivirals, the better the outcome. Antiviral drugs and vaccines are both valuable tools in the fight against COVID-19. However, antiviral drugs are likely to be developed and approved before vaccines, because vaccine development takes longer [7]

## 3. ANTIVIRAL DRUGS

### 3.1 Remdesivir

Remdesivir was developed 10 years ago and failed in a clinical trial against Ebola in 2014, but it is generally considered to be safe [9] A study of Middle East respiratory syndrome (a disease caused by a different coronavirus) showed that remdesivir could prevent viral replication [10]

This drug is being tested in many COVID-19 clinical trials, including in combination with other drugs, such as the anti-inflammatory drug baricitinib [11,12] The clinical trials have been expanded to include children with moderate to severe COVID-19 [13-15] However, the manufacturer of remdesivir announced that one of the trials had been terminated because of the low number of applicants; therefore, the outcome of that trial is unknown. Shortly after that announcement, the company stated that preliminary data from another trial, supervised by the US National Institute of Allergy and Infectious Diseases, had reached its primary end point [14] There was a clear, positive effect in reducing the recovery time from 15 days to 11 days. However, another clinical trial reported that participants who received remdesivir had no benefit compared with those who received a placebo [16] While a clinical trial has demonstrated that among 86 pregnant and postpartum women with severe COVID-19 who received compassionate use remdesivir, recovery rates were high, with a low rate of serious adverse events [17] Despite these conflicting results, the FDA issued an EUA on May 1, 2020 for the use of remdesivir [18] Federal officials announced they would shortly run out of supplies and recommended the manufacturer to increase production to meet the emerging need.

### 3.2 Arbidol Hydrochloride

Arbidol hydrochloride is an antiviral drug and was tested along with Kaletra (lopinavir/ritonavir) as a treatment for COVID-19. Neither drug improved the clinical outcomes of hospitalized patients with mild to moderate COVID-19 [19]

### 3.3 EIDD-2801

EIDD-2801 was developed by scientists at a nonprofit biotechnology company owned by Emory University. Mouse studies showed that it reduces the replication of many coronaviruses, including SARS-CoV-2. EIDD-2801 was tested in a UK clinical trial under an agreement issued by Merck and Ridgeback Biotherapeutics. Different from remdesivir, EIDD-2801 can be taken orally; this would allow more people who are at risk of infection to take this drug [20] Lopinavir has been approved as a flu treatment in many countries. [21] Several reports from China have shown that it may be a useful therapeutic for COVID-19 [22-24] The drug is produced in Japan, and it is undergoing clinical trials in 43 countries as a treatment for mild or moderate COVID-19.

Canadian researchers have investigated whether this drug is effective for use in nursing homes that have experienced COVID-19 outbreaks.[25]

### 3.4 Lopinavir/ritonavir

The two-drug combination of lopinavir and ritonavir is an effective HIV treatment. Clinical trials are underway to assess whether it is also effective against SARS-CoV-2. A cohort study reported that lopinavir/ritonavir did not improve outcomes in patients with mild or moderate COVID-19 compared with those receiving standard care; furthermore, this drug combination was ineffective in patients with severe COVID-19 [26].

However, another study found that patients who received  $\beta$ -1b, lopinavir/ritonavir, and two other drugs, ribavirin and interferon, had a reduced viral clearance time [27] Merimepodib (vx-497), a drug developed by ViralClear Pharmaceuticals, has previously been identified as an antiviral and immunosuppressive compound [28] A phase II trial of this drug is underway for people with advanced COVID-19; patients are randomly allocated to receive merimepodib with remdesivir or placebo.

### 3.5 Favipiravir

Favipiravir is a type of RNA-dependent RNA polymerase (RdRp) inhibitor. It is presumably acts as a nucleotide analog that selectively inhibits the viral RNA dependent RNA polymerase or causes lethal mutagenesis upon embedding into the virus RNA [29-33]. Favipiravir used for the treatment of influenza is dosed at 1600 mg twice daily on Day 1, followed by 600 mg twice daily on Days 2-5. Besides influenza virus [34], favipiravir has shown potent antiviral activity against other segmented negative-strand RNA viruses in vitro and in vivo [35,36]. Furthermore, some positive-strand RNA viruses are also can be inactivated by favipiravir [37,38], and the virus replication can be interfered by competing with the purine nucleosides, and consequently inhibits the viral RdRp of SARS-CoV-2 [39]. Studies have shown that favipiravir administration has better prognosis in COVID-19 patients in terms of disease progression and viral clearance [40].

### 3.6 Nitazoxanide

Nitazoxanide has shown efficacy in vitro against coronavirus infections (MERS, SARS, SARS-

CoV-2). A study of treating COVID-19 positive patients with nitazoxanide in three clinical settings: pregnancy/puerperium, hospitalized patients in an Internal Medicine Service and in an ambulatory setting. Nitazoxanide seems to be useful against SARS-CoV-2, not only in an early intervention but also in critical condition as well as in pregnancy without undesired effects for the babies. As an adjunctive therapy budesonide was used that seems to contribute to the clinical improvement. Nitazoxanide could be useful against COVID-19 as a safe and available regimen to be tested in a massive way immediately [41].

### 3.7 Lenzilumab

In high-risk COVID-19 patients with severe pneumonia, granulocyte-macrophage colony-stimulating factor neutralization with lenzilumab was safe and associated with faster improvement in clinical outcomes, including oxygenation, and greater reductions in inflammatory markers compared with a matched control cohort of patients hospitalized with severe COVID-19 pneumonia. A randomized, placebo-controlled clinical trial to validate these findings is ongoing (NCT04351152) [42]

## 4. OTHER TREATMENT METHODS

Scientists are also looking for other ways to target viruses and treat COVID-19 complications.

### 4.1 Ibuprofen

Physicians began a clinical trial to investigate whether this painkiller could be used to treat COVID-19 patients. [43] It is theorized that the anti-inflammatory properties of ibuprofen can help relieve disease-related dyspnea.

### 4.2 Monoclonal Antibodies (mAbs)

Monoclonal antibodies can trigger the immune system to attack viruses. As with antibodies made by the body's immune system, lab-made mAbs target specific antigens, such as those on SARS-CoV-2. mAbs could potentially be used to treat COVID-19 patients and prevent infection [44-46] Based on this information and a theoretical foundation, many biotechnology companies have begun to urgently investigate this therapeutic route. AbCellera has isolated 500 unique antibodies from a COVID-19 rehabitee and is currently testing them. Regeneron Pharmaceuticals is testing a double antibody combination in four groups: people hospitalized

with COVID-19; people with COVID-19 symptoms but who are not hospitalized; healthy people at high risk of COVID-19 illness; and healthy people who have close contact with COVID-19 patients. The company is expecting promising results. In collaboration with Chinese companies, Vir Biotechnology has isolated antibodies from people who recovered from SARS and has tested their ability to treat COVID-19.

### 4.3 Convalescent Serum

Inspired by mAbs, several countries have allowed medical institutions to use plasma from recovered COVID-19 patients as an experimental treatment. In theory, plasma from recovered patients contains antibodies against SARS-CoV-2.

Researchers at the Methodist Hospital in Houston, Texas reported that 19 of 25 COVID-19 patients who received plasma treatment had improved. Of these, 11 patients have been discharged [47] Another study undergone in Argentina has tried to treat COVID-19 with hyperimmune plasma found that the equine polyclonal antibodies (EpAbs) put forward a sound alternative. The new generation of processed and purified EpAbs containing highly purified F(ab')<sub>2</sub> fragments demonstrated to be safe and well tolerated [48]

### 4.4 Immunoregulators

In some COVID-19 patients, the immune system enters a hyperactive state, releasing large amounts of small proteins called cytokines. Scientists believe that this 'cytokine storm' may be responsible for the development of acute respiratory distress syndrome (ARDS), causing some people with severe COVID-19 to require ventilation. Several immunosuppressants are in clinical trials to assess whether they can inhibit cytokine storm and reduce ARDS severity.[49,50] Researchers have announced that a low-cost corticosteroid, dexamethasone, reduced the number of deaths of severe COVID-19 patients who required mechanical ventilation by approximately one-third and of those requiring oxygen support by one-fifth, although these results have not yet been published in a peer-reviewed journal. However, dexamethasone has been approved for other conditions and can be administered orally or intravenously [51,52] Other drugs being tested include baricitinib [53] a treatment for rheumatoid arthritis, and IL-6 inhibitors [54]

**Table 1. Main treatment methods to COVID-19**

Strategy	Developer	cell responses	Clinical stage	Clinical trial identifier	References
<b>Drugs</b>					
Remdesivir	Veklury®; Gilead Sciences	RNA replicase inhibitors	Phase III	NCT04431453 ,NCT04292730 ,NCT04292899 ,NCT04280705,NCT04409262	9-18
Arbidol hydrochloride	Ruijin Hospital	SARS-CoV-2 RNA replicase inhibitors	Phase II	NCT04260594	19
EIDD-2801	Emory University	reduces SARS-CoV-2 RNA replication	Phase III	/	20-25
Lopinavir/ritonavir	Tongji Hospital	/	Phase III	NCT04255017	26-28
Favipiravir	Gilead Sciences	RNA-dependent RNA polymerase (RdRp) inhibitor	Phase III	NCT04358549	39-40
Nitazoxanide	/	Regulating autophagy and inhibiting mTORC1 signaling	Phase III		41
Lenzilumab	Mayo Clinic, Rochester, MN	potential immunomodulatory activity, high binding affinity in the picomolar range	Phase II	NCT04351152	42
<b>other treatment methods</b>					
Ibuprofen	ShamirMedical Centre, Israel	/	/	/	43
Monoclonal antibodies	AbCellera/Eli Lilly/NIH, Vir biotechnology/GSK	neutralizing mAbs targeted against the SARS-CoV-2 spike protein	Phase I-III	NCT04411628 ,NCT04545060	44-46
Convalescent serum	Houston Methodist hospitals	neutralizing mAbs targeted against the SARS-CoV-2 spike protein	Phase III	<a href="https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations">https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations</a>	47,48
Immunoregulators	University of Toronto, Toronto, Canada	changes the pulmonary and systemic inflammatory response and thereby reduces mortality	Phase III	NCT04325061	49-54

Hydroxychloroquine and chloroquine	Shanghai Public Health Clinical Center	/	Phase III	NCT04261517	55,56
<b>Vaccines</b>					
BNT162b2	BioNTech/Pfizer	Induction of S1-specific IgG and mAbs in humans, with mAb titres higher than convalescent plasma	Phase III	NCT04368728	57-62
ChAdOx1	University of Oxford, with AstraZeneca, UK	Induction of S-specific IgG and nAbs in mice and NHPs; induction of high TH1 cell responses but low TH2 cell responses in mice; induction of S-specific IgG and nAbs in humans, with nAb titres similar to convalescent plasma	Phase III	ISRCTN89951424, NCT04516746, NCT04540393, CTRI/2020/08/027170	57-62
Gam-COVID-Vac	Gamaleya	Induction of RBD-specific IgG and nAbs in humans, with nAb titres similar to convalescent plasma; induction of IFN $\gamma$ -associated T cell responses	Phase III	NCT04530396, NCT04564716, NCT04642339	65
CoronaVac	Sinovac	Induction of S-specific, RBD-specific and N-specific IgG, and nAbs in mice, rats and NHPs; no induction of either TH1 or TH2 cell responses in NHPs; induction of RBD-specific IgG and nAbs in humans; no obvious vaccine-induced T cell responses in humans	Phase III	NCT04456595, 669/UN6. KEP/EC/2020, NCT04582344, NCT04617483	66

Abbreviations: mAbs: mono-clonal antibodies RBD: receptor binding domain

#### 4.5 Hydroxychloroquine and Chloroquine

Hydroxychloroquine and chloroquine have also received much interest from physicians as a treatment for COVID-19. These compounds have undergone clinical trials as COVID-19 therapeutics [55,56] however, their effectiveness remains questionable.

#### 5. NEXT-STEP THERAPIES

Although there has been intense focus on developing new treatments for COVID-19, it is also crucial to improve existing technologies to care for these patients. SARS-CoV-2 can cause pneumonia and ARDS. Doctors are applying the existing methods used to treat these conditions and reduce their impact. Companies cannot provide a timetable for when their products may become available to treat COVID-19 because this is difficult to estimate. After laboratory and animal experiments, drugs must go through several stages of clinical trials before they can be approved for widespread use in patients.

It is also difficult to speed up the progression of clinical trials because a sufficient number of people must be recruited into each stage to obtain useful data. Additionally, the trials must be sufficiently long to assess whether the drug has harmful side effects. However, through the FDA "compassionate use" pathway, experimental drugs can sometimes be administered to patients outside of a clinical trial. To receive an experimental drug through this pathway, the patient must have an immediate life-threatening condition or serious disease or condition. If the patient improves, it could be taken as a sign of the drug's effectiveness; however, because the drug was administered to only one person outside of a clinical trial, firm conclusions cannot be drawn. Moreover, other people may react differently to the drug. Improved virus detection can also reduce the number of COVID-19 deaths by slowing the spread of the virus.

On May 8, 2020, the FDA authorized the first at-home saliva collection test for COVID-19. Designed by the Rutgers Clinical Genomics Laboratory, a person takes a sample of their saliva at home and mails it to the Rutgers laboratory for testing. This was the first approved COVID-19 test that used a saliva sample—all other approved at-home tests used nasal swab samples.

A test developed by European scientists can reveal whether someone is infected within 15

minutes. The test uses a sample collected from a nasopharyngeal swab that is inserted into the nasal cavity. An analysis of this test found that it could detect six out of 10 infections. This test is more accurate for identifying non-infected people. Although the test is not 100% effective, it does not require special reagents or trained laboratory personnel to operate. This will make it an ideal choice for low- and middle-income countries with limited clinical and laboratory capacity, but it must be used as part of a broader detection strategy.

#### 6. VACCINES

A vaccine is designed to protect people from a virus, such as SARS-CoV-2. Vaccines train the immune system to recognize and attack a virus when it is subsequently encountered. In this way, vaccines can protect people and communities. Viruses are less likely to infect people who have been vaccinated. This means that vaccinated people are less likely to pass the virus to others, a phenomenon known as herd immunity. Several groups are studying potential COVID-19 vaccines. Some of these efforts are supported by the nonprofit Coalition for Epidemic Preparedness Innovations, which is a global partnership. More than 100 projects around the world are focusing on COVID-19 vaccine development. As of May 11, 2020, there were eight candidate vaccines in clinical trials, and some have been tested through phase III clinical trials and have been authorized for clinical use in various countries [57,58].

Moderna began testing its mRNA vaccine in a phase I clinical trial in Seattle, Washington. In mid-May 2020, the company announced that all 45 phase I participants produced antibodies. The study included 45 healthy volunteers aged 18 to 55. They received two doses, with the second dose given 28 days after the first [59] This early study showed that the vaccine platform was safe, and allowed the company to skip certain animal tests for this particular vaccine [60,61] The FDA allowed Moderna to begin the second phase of the vaccine study, and they started the phase III clinical trial soon thereafter. The FDA also agreed that if the phase III trial results were promising, the vaccine would undergo a rapid regulatory review.

In late April 2020, Inovio Pharmaceuticals began a clinical trial involving more than 500 participants. They stated that the potential vaccine had an 80% chance of success and that

it could be available to the public as early as September. The vaccine uses a modified virus to trigger the immune system. Another vaccine is being developed by Oxford University and the pharmaceutical company AstraZeneca. The company reported that the vaccine was effective against SARS-CoV-2 after testing it in six macaques [62,63].

Johnson & Johnson and Sanofi are also developing their own vaccines. Johnson & Johnson announced that phase I clinical trials would begin in July. Furthermore, Pfizer has partnered with the German biotechnology company BioNTech to develop a vaccine. At the end of April, a phase I clinical trial involving 200 participants was allowed to begin. Clinical testing in the United States began in early May, and the final report of this trial has been published [64]. A heterologous recombinant adenovirus (rAd)-based vaccine, Gam-COVID-Vac (Sputnik V), showed a good safety profile and induced strong humoral and cellular immune responses in participants in phase 1/2 clinical trials, and the preliminary results on the efficacy and safety of Gam-COVID-Vac from the interim analysis of the phase 3 trial showed 91.6% efficacy against COVID-19 and was well tolerated in a large cohort [65]. CoronaVac (Sinovac Life Sciences, Beijing, China), an inactivated vaccine candidate against COVID-19, containing inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also was investigated for its safety, tolerability and immunogenicity showed that the 3µg dose of CoronaVac is the suggested dose for efficacy assessment in future phase 3 trials [66].

Advances in gene sequencing and other technologies have accelerated the laboratory work involved in early vaccine development. However, a variety of successful vaccines may be needed in order to vaccinate billions of people around the world. Even if a vaccine is developed and distributed, it is unlikely to be fully effective. Measles, mumps, and rubella (MMR) vaccines are 97% effective, while seasonal influenza vaccines are approximately 60% effective. However, vaccines with even lower efficacy may still reduce the severity of COVID-19 symptoms. Some experts worry that those who are vaccinated may stop taking other measures that will still be necessary to control the COVID-19 pandemic, such as hand washing and staying home when sick.

## 7. ACCELERATING VACCINE DEVELOPMENT

Some scientists believe that "human challenge trials" can speed up clinical trials for new vaccines by up to a few months. In this type of trial, healthy volunteers are given a potential vaccine and then deliberately infected with the virus. In typical vaccine trials, researchers must wait for the participants to become naturally infected before they can assess the vaccine's efficacy. Nearly 30,000 people from more than 140 countries have signed up for a human challenge trial. However, these trials raise many ethical issues. Much is still unknown about SARS-CoV-2 and COVID-19, including who will become seriously ill or even die of this disease. This means that people cannot know their true risk of participating in a challenge trial; thus, they cannot give fully informed consent. Informed consent is an important aspect of modern clinical trials. Nevertheless, given the extent of the pandemic, some experts believe this type of trial will eventually be conducted. In preparation, the World Health Organization has recently issued ethical guidelines regarding human challenge trials. Meanwhile, clinical trials are underway in Israel, the Netherlands, and Australia to determine whether existing TB vaccines can also prevent SARS-CoV-2 infection. The polio vaccine is another possible option. Some scientists believe these vaccines may strengthen the immune system enough to fight SARS-CoV-2, although there is no evidence to support this theory. Two US researchers suggested that the MMR vaccines may protect against inflammation and sepsis in COVID-19 patients. Clinical trials of MMR vaccines in health care workers has been recommended.

Vaccine development is uncertain, and there is no guarantee that any given vaccine candidate will be effective. It is essential that a vaccine is safe and that it elicits a sufficient immune response. Vaccine candidates must undergo the various phases of clinical trials; this is particularly important to ensure their safety, even during pandemics. The public's willingness to support quarantines and other public health measures to slow virus transmission is often linked to the level of trust in government, and the rush to authorize potentially risky vaccines and treatments would decrease this trust and hamper public health efforts.

In an effort to further advance vaccine technology, our group has developed a nano-



intermediate based on carbon nanotubes and expect it to enter preclinical trials in the near future [67].

## 8. PERSPECTIVE

The pandemic caused by SARS-CoV-2 has changed many aspects of our world. Much effort has been expended to find COVID-19 treatments, and this research continues. However, from existing antiviral drugs to newly designed vaccines, there has been limited positive clinical effect. Among the methods discussed herein, we believe that vaccines and mAbs are the most promising [68]. Further clinical trials should investigate the combination of three or more mAbs because of SARS-CoV-2 antigen heterogeneity.

## 9. CONCLUSION

Among various methods for COVID-19 treatment, vaccines monoclonal-antibody are the most promising ones, but the uncertainty and long time-consuming make them infeasible under emergent status. Some old drugs repurposed have the significance, and should be widely improved.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## DATA AVAILABILITY STATEMENT

Previously reported data were used to support this perspective and are available in PubMed. These studies (and datasets) are cited at relevant places within the text as references 1–56.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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