# Secondary Publication: COVID-19 Pandemic: Drug Development and Treatment

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**Review**

# Secondary Publication: COVID-19 Pandemic: Drug Development and Treatment

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019. It has been rapidly spreading worldwide ever since. The majority of COVID-19 infections are asymptomatic or mildly symptomatic. However, old age or comorbidities can result in a cytokine storm, which eventually leads to death. To date, no drug has been clinically proven effective to treat COVID-19, and development of effective drugs against SARS-CoV-2 is urgently required. Several drugs used in treating other diseases are being evaluated. Clinical trials on many new antiviral drugs and vaccine candidates are also rapidly ongoing. In this review, we summarized the currently used drugs and newly developed vaccines for the treatment of COVID-19.

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**Keywords**: COVID-19, SARS-CoV-2, drug development, COVID-19 treatment, vaccine

## Introduction

Coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread worldwide since the first case of infection was confirmed in the Wuhan province of China in December 2019, following which the World Health Organization (WHO) declared a pandemic on March 11, 2020. Most of the infected people are asymptomatic or exhibit mild symptoms of the disease; however, adults over 65 years of age and people who have underlying medical conditions, including chronic obstructive pulmonary disease (COPD), chronic kidney disease, diabetes, hypertension, cardiovascular disease, and obesity, are at a higher risk of severe disease progression, leading to the development of an excessive immune response called a cytokine storm, which results in severe respiratory failure (acute respiratory distress syndrome: ARDS), and death in some of these cases.[1] Currently, an effective therapeutic drug for the prevention or treatment of COVID-19 is not available, and thus, the clinical investigations focusing on the approach of so-called drug repositioning/repurposing to develop effective therapeutic agents using existing drugs with established safety norms or those under development. Moreover, the development of new antiviral drugs targeting SARS-CoV-2 and vaccines to prevent the infection are being actively promoted, and the inoculation of approved

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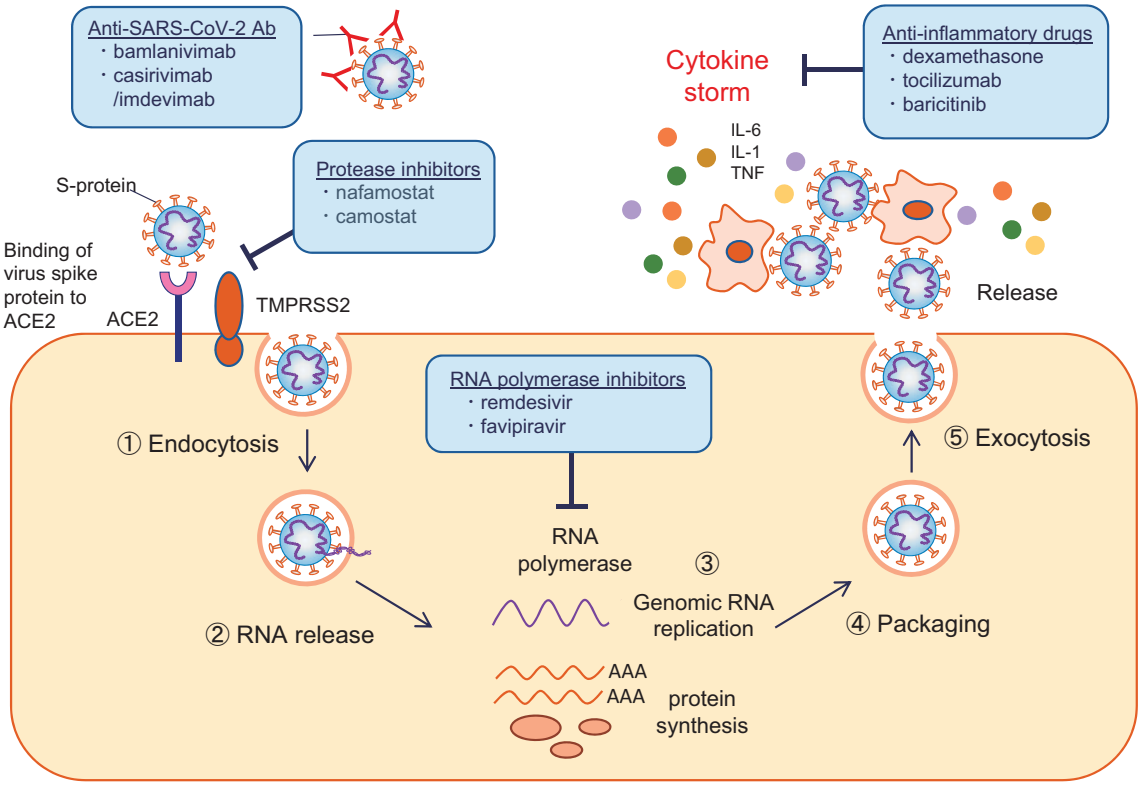


**Figure 1.** Potential drugs targeting SARS-CoV-2. The virus enters human cells by binding its spike proteins (S-protein) to the angiotensin-converting enzyme 2 (ACE2) receptor (①). Subsequently, viral genomic RNA is released into the cytoplasm (②), replicated, and translated (③). Finally, the RNA genome is packed (④) and released extracellularly (⑤). Protease inhibitors, such as nafamostat and camostat, block the virus entry through the inhibition of serine protease TMPRSS2 (type 2 transmembrane protease) for S protein priming. RNA polymerase inhibitors, remdesivir and favipiravir, inhibit viral replication by targeting viral RNA-dependent RNA polymerase. Antibodies against the S protein neutralize SARS-CoV-2. Anti-inflammatory drugs attenuate the cytokine storm.

vaccines has begun in some countries. Currently, the organizations, such as the WHO, the Japanese Ministry of Health, Labor and Welfare (MHLW), and the Japanese Association for Infectious Diseases have published the guidelines for the treatment and / or management of COVID-19.[2-5] This review outlines the basic mechanisms of action and development status of major antiviral drugs, therapeutic drugs against cytokine storms, and vaccines, which are expected to exhibit high therapeutic efficacy against COVID-19.

## Antiviral Drugs

### 1. Growth cycle of SARS-CoV-2

SARS-CoV-2 binds to the human cell surface receptor, angiotensin-converting enzyme 2 (ACE2), via its surface spike protein (S protein) and is cleaved by transmembrane protease serine 2 (TMPRSS2), a serine protease on the cell surface, thereby resulting in membrane fusion and entry into the cell.[6,7] Next, SARS-CoV-2 releases viral RNA inside the host cell, following which it replicates using its own enzyme (RNA polymerase), and then translates viral RNA into protein to assemble viral particles and releases the virus extracellularly. Through repetitive cycles of these processes, the virus proliferates inside the host. Currently, the repurposing of existing drugs for the treatment of SARS-CoV-2 is expected to target the viral life cycle through either preventing the viral invasion/entry, replication, or proliferation (**Figure 1**) (**Table 1**).[8-12]

### 2. Drugs to prevent viral entry

Nafamostat (Fusan, Nichi-Iko) and camostat mesilate (Foipan Tablets, Ono Pharmaceutical) are the two serine protease inhibitors that have previously been developed in Japan for the management of chronic pancreatitis. Re-

**Table 1.** Therapeutic candidates for COVID-19/SARS-CoV-2 by repurposing existing drugs.

| Drug | Trade name | Manufacturer | Mechanism of action | Approved indications |
|---|---|---|---|---|
| Remdesivir | Veklury | Gilead | RNA-dependent RNA polymerase inhibitor | SARS-CoV-2 infection |
| Dexamethasone | Decadron | Nichi-Iko | Cytokine gene expression inhibitor | Anti-inflammatory drug |
| Heparin | | | Anticoagulant | Anticoagulant |
| Approval application completed | | | | |
| Favipiravir | Avigan | Fujifilm | RNA-dependent RNA polymerase inhibitor | Influenza infection |
| Under clinical trial | | | | |
| Tocilizumab | Actemra | Chugai | Cytokine (IL-6) inhibitor | Rheumatoid arthritis |
| Sarilumab | Kevzara | Sanofi | Cytokine (IL-6) inhibitor | Rheumatoid arthritis |
| Camostat | Foipan | Ono | Protease inhibitor | Pancreatitis |
| Nafamostat | Futhan | Nichi-Iko | Protease inhibitor | Pancreatitis |
| Baricitinib | Olumiant | Eli Lilly | JAK inhibitor | Rheumatoid arthritis |
| Tofacitinib | Xeljanz | Pfizer | JAK inhibitor | Rheumatoid arthritis |
| Ruxolitinib | Jakavi | Novartis | JAK inhibitor | Myelofibrosis |
| Ciclesonide | Orbesco | Teijin Pharma | Anti-inflammatory drug | Bronchial asthma |
| Ivermectin | Stromectol | MSD | Inhibition of cell invasion | Intestinal strongyloidiasis |
| Eritoran | - | Eisai | TLR4 inhibitor | Severe sepsis (discontinued) |
| Nelfinavir | Viracept | Japan Tobacco | Protease inhibitor | HIV |

cently, a German research group reported that camostat inhibits the entry of SARS-CoV-2 into cells through inhibiting TMPRSS2 activity.[6] Consequently, a phase 3 clinical trial (jRCT2031200198) for the treatment of COVID-19 patients using the latter agent was initiated in Japan. Additionally, the Institute of Medical Science at the University of Tokyo reported that the required concentration of nafamostat to block the membrane fusion of SARS-CoV-2 is less than one-tenth of that of camostat.[13] However, there is only one case report so far that applied a combination treatment regimen of nafamostat with fabiplavil in 11 patients. Currently, a clinical study (jRCTs 031200026) is ongoing at the University of Tokyo Hospital to evaluate the effectiveness of the combination therapy with nafamostat and fabiplavil for treating COVID-19 patients.[14]

### 3. Drugs to inhibit viral replication and proliferation

Remdesivir (Becklely, Gilead Sciences) and favipiravir (Avigan, FUJIFILM Toyama Chemical) inhibit the viral RNA-dependent RNA polymerase that is involved in viral replication.

Remdesivir was originally developed for the treatment of Ebola virus infections. Remdesivir is a prodrug that metabolizes in the host cell to produce a pharmacologically active metabolite, which is an adenosine triphosphate (ATP) analog. This active metabolite inhibits SARS-CoV-2 replication through preventing the elongation of RNA strand by the viral RNA-dependent RNA polymerase. Remdesivir was granted emergency use authorization for severely ill patients with COVID-19 on May 2, 2020 in the United States of America (USA). Thereafter, the Food and Drug Administration (FDA) formally approved the administration of remdesivir for COVID-19 treatment on October 22, 2020. This decision was a result of significantly shortened recovery periods in patients administered with remdesivir following a randomized double-blind placebo-controlled study [Adaptive COVID-19 Treatment Trial (ACTT)-1 study] involving patients with moderate to severe COVID-19.[15-17] Remdesivir was also granted the approval for emergency treatment of COVID-19 on May 7, 2020 in Japan. "Clinical Management of patients with COVID-19" edited by the MHLW recommends using remdesivir for the treatment of patients with moderate to severe COVID-19 disease symptoms as a standard protocol.[3,5] Meanwhile, the WHO guidelines published on November 20, 2020 stated that remdesivir is not recommended for the treatment of COVID-19 patients. This guideline was issued following a WHO-led open-label, randomized clinical trial, which showed that remdesivir exhibited little or no effect on the mortality or length of hospital stay in COVID-19 patients.[4] However, the FDA and MHLW have announced

no reconsideration of this approval.[18, 19]

Favipiravir has been approved for manufacturing and marketing as an anti-influenza virus drug in Japan. Favipiravir is metabolized into its active form, favipiravir ribosyl triphosphate (RTP), by an intracellular enzyme and selectively inhibits RNA polymerase activity, thereby preventing viral replication.[20] A multicenter, open-label, randomized clinical trial conducted by the Fujita Health University revealed that favipiravir does not exhibit statistically significant efficacy for the treatment of asymptomatic patients and those with mild COVID-19 symptoms.[21] However, a phase 3 clinical trial of favipiravir in COVID-19 patients with non-severe pneumonia (JapicCTI-205238), which started on March 27, 2020, showed an accelerated improvement of symptoms with statistically significant differences, following which an application for the approval of favipiravir in COVID-19 treatment as an additional indication was submitted to the MHLW on October 16, 2020. Since favipiravir is known to be teratogenic, its administration to the women known or suspected to be pregnant is contraindicated.

**4. Drugs with other mechanisms of action**

The antiparasitic drug, ivermectin (stromectol, MSD), has been shown to suppress the growth of SARS-CoV-2 through inhibiting importin α-mediated nuclear translocation of the viral protein *in vitro*.[22, 23] Although the observational studies have demonstrated that ivermectin reduces the fatality rate in patients with mild to severe COVID-19 symptoms, but still, randomized controlled trials are needed to verify its efficacy.[24] Therefore, investigator at the Kitasato University Hospital initiated the clinical trials of ivermectin (jRCT2031200120) in Japan. The antimalarial drug chloroquine/hydroxychloroquine has been reported to suppress SARS-CoV-2 infection using Vero cells *in vitro*,[25] whereas a report using TMPRSS 2-expressing human lung cell lines failed to demonstrate the suppression of viral infection.[26] Conversely, an open-label, non-randomized controlled trial demonstrated some promising effects;[27] and therefore, the FDA approved the emergency use of chloroquine/hydroxychloroquine. However, another randomized placebo-controlled trial failed to exhibit such therapeutic efficacy, and thus, the authorization was revoked. Moreover, the WHO subsequently announced the discontinuation of chloroquine/hydroxychloroquine clinical trials.[28-30] The anti-human immunodeficiency virus (HIV) therapeutic drug, lopinavir/ritonavir (Kaletra, Abbey), was expected to be a potential drug candidate because it inhibits the protease required for the growth of HIV, but a Chinese research group failed to confirm its therapeutic efficacy in the clinical trials conducted in March 2020.[31]

**5. Convalescent plasma therapy**

The plasma of patients who have recovered from an infectious disease possesses the antibodies against the infectious agent. Therefore, convalescent plasma therapy has been shown to be a low-risk and highly effective treatment regimen for patients with severe COVID-19 symptoms[32-34] and was authorized for emergency application by the FDA in August 2020; however, its effectiveness has not been fully verified yet. In Japan, the clinical trial to scientifically evaluate the effectiveness of convalescent plasma therapy as a treatment option for the treatment of COVID-19 patients is being conducted by the National Center for Global Health and Medicine (jRCTs 031200124).

## Development of New Antiviral Drugs

While the investigation on therapeutic options is rapidly progressing through drug repositioning, the development of new drugs for the treatment of COVID-19 patients is also expanding. Bamlanivimab (LY-CoV555, Eli Lilly), a neutralizing monoclonal antibody, identified in the blood of patients who have recovered from COVID-19, directly works against SARS-CoV-2 to prevent its invasion into the cells. In a phase 2 clinical trial involving patients with mild to moderate COVID-19 symptoms, bamlanivimab reduced the worsening rate of symptoms,[35] and thus, it was authorized for emergency use by the FDA on November 9, 2020. Combination therapy with two types of monoclonal antibodies, casirivimab and imdevimab (VIR-7831 and VIR-7832, Regeneron Pharmaceuticals), was also authorized for emergency use by the FDA on November 25, 2020, as a therapeutic agent for children aged 12 years or older and adults, including elderly patients with mild to moderate COVID-19 symptoms who are at a high risk of developing severe disease symp-

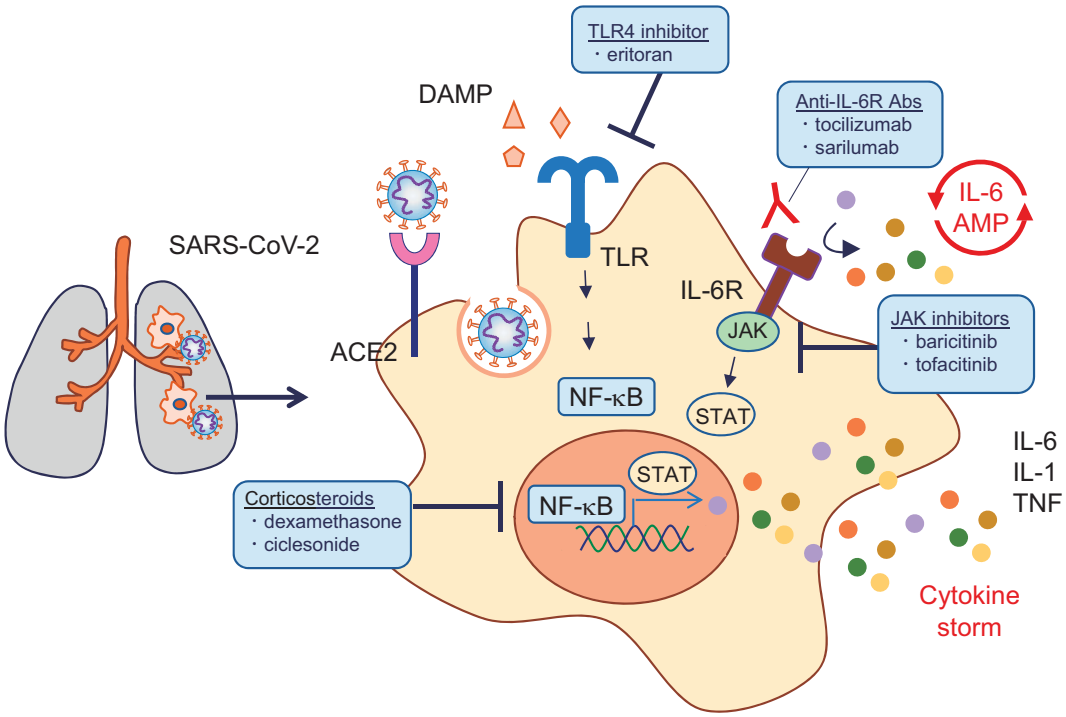


**Figure 2.** Proposed pharmacological treatment strategies for the cytokine storm caused by SARS-CoV-2. Corticosteroids exhibit potent anti-inflammatory and immunosuppressive effects via inhibition of transcription of proinflammatory cytokines and stimulation of transcription of anti-inflammatory molecules. Anti-IL-6 receptor antibodies (Anti-IL-6R Abs) inhibit IL-6-induced synergistic activation of NF-κB and STAT3 (IL-6 amplifier, AMP). Janus kinase (JAK) inhibitors attenuate cytokine-induced activation of JAK-STAT signaling pathway. Toll-like receptor 4 (TLR4) inhibitor inhibits TLR4-mediated inflammatory signaling.
ACE2, angiotensin-converting enzyme 2; DAMP, damage-associated molecular pattern.

toms.[36] These antibody agents are contraindicated in patients with severe COVID-19 symptoms, who require oxygen supplementation because of the worsened disease prognosis.

## Anti-inflammatory Drugs Expected to Be Effective Against Cytokine Storms (Figure 2)

When SARS-CoV-2 infection induces cell death in alveolar epithelial cells, a large number of damage-associated molecular patterns (DAMPs) are released. DAMPs stimulate pattern-recognition receptors (PRRs) represented by innate immune receptors, Toll-like receptors (TLRs), and activate the transcription factor NF-κB, producing various inflammatory cytokines, such as IL-6. Furthermore, the inflammatory cytokine-induced activation of the Janus kinase-signal transducer and the activation of the transcription (JAK-STAT) pathway enhances the transcriptional activation of NF-κB. IL-6 forms an inflammation amplifier circuit (IL-6 amplifier) to further increase the levels of inflammatory cytokines, including IL-1, IL-6, and TNF-α in the blood. Cytokine storms caused by excessive immune responses lead to severe symptoms, such as ARDS and multiple organ failure, through neutrophil activation, the activation of blood coagulation mechanisms, and vasodilation.[37-40]

When a steroidal anti-inflammatory drug binds to the glucocorticoid receptor (GR), which is a transcription factor, the GR translocates into the nucleus, which leads to the induction of the transcriptional inhibition or activation of the genes encoding pro-inflammatory molecules (inflammatory cytokines) or anti-inflammatory molecules, respectively, thereby exhibiting anti-inflammatory and immunosuppressive effects.[41] The anti-inflammatory glucocorticoid, dexamethasone, reduced the mortality in patients who required mechanical ventilation; however, the mortality was not reduced in patients who did not need respiratory support as per a multicenter randomized, open-label study conducted in the United Kingdom.[42] Dexamethasone is listed as a standard treatment agent for

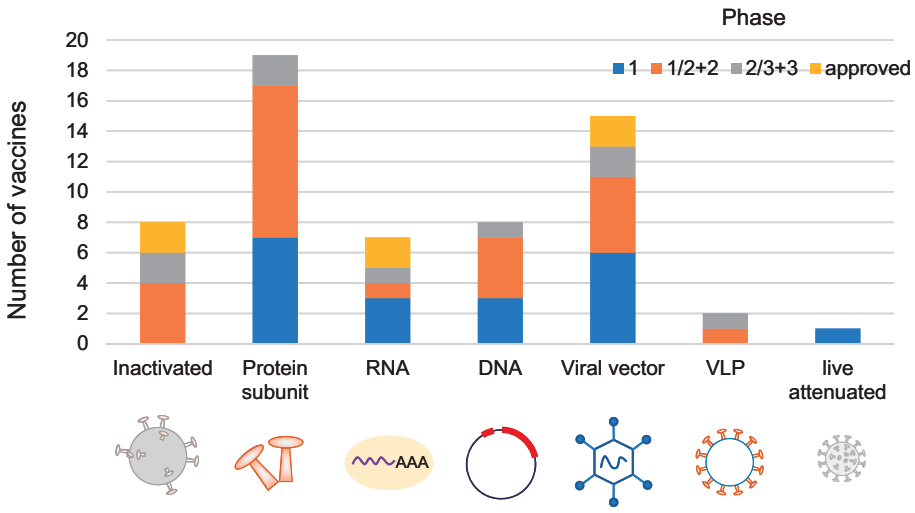


**Figure 3.** Current development status of vaccines. Modified from "Landscape of candidate vaccines in clinical development-29 December 2020".[55] The mentioned development status is as of January 5, 2021. Approved drugs include those granted emergency use authorization.

the "Clinical management of patients with COVID-19," edited by the MHLW. "The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG2020) Special Edition: COVID-19 Rapid/Living recommendations on drug treatment" recommends the administration of dexamethasone in patients with moderate to severe, and not mild COVID-19 symptoms.[3,5] In Japan, there are case reports on the use of other steroidal anti-inflammatory drugs, such as prednisolone.[43] A research group from the National Institute of Infectious Diseases reported that the inhaled steroid, ciclesonide (Orbesco, Teijin Pharma), which is prescribed for bronchial asthma, exhibited an anti-inflammatory effect as well as a specific growth inhibitory effect against SARS-CoV-2 in culture cells *in vitro*.[44] However, the detailed mechanism of action of ciclesonide has not been elucidated yet. Moreover, a specific clinical trial of ciclesonide in asymptomatic patients and those with mild COVID-19 symptoms conducted by the National Center for Global Health and Medicine (jRCTs031190269) has shown that the ciclesonide-treated group exhibited significantly more pneumonia exacerbations than the control group. Based on these results, the use of ciclesonide inhalers in asymptomatic patients and those with mild COVID-19 symptoms is not recommended.[45]

The anti-IL-6 receptor antibody, tocilizumab (Actemra, Chugai Pharmaceutical), and the JAK inhibitor, baricitinib (Olumiant, Eli Lilly), are both used as antirheumatic drugs. The efficacy of tocilizumab has only been reported in the observational studies of patients with COVID-19.[46,47] Combination therapy using baricitinib and remdesivir was approved for the emergency use by the FDA on November 19, 2020, but only for patients with COVID-19 who require artificial respiration.[48-50] The clinical trials for a TLR4 antagonist (Eritoran, Eisai), an unapproved drug developed for the treatment of severe sepsis, which is expected to suppress the cytokine storm upon COVID-19 infection, have been initiated in October 2020.[51]

## Vaccines

### 1. Type of vaccine

Currently, various vaccines, including inactivated virus, peptide, recombinant protein, messenger RNA (mRNA), DNA, and recombinant viral vector vaccines, are being developed in Japan and in other countries (**Figure 3**).[52-55] Inactivated virus vaccines are generated through incapacitating the virus itself, and these vaccines have proven to be effective so far. Since the virus grown using cultured cells is inactivated and purified, the development of inactivated virus vaccines is time consuming due to the examination of culture conditions and inactivation techniques. Recombinant protein vaccines, generated using recombinant DNA technology, generally have low

**Table 2.** Development status of major vaccines in Japan and overseas.

| Vaccine platform | Type of candidate vaccine | Producer | Current stage of development * |
|---|---|---|---|
| Overseas | | | |
| RNA | BNT162 (3 LNP-mRNAs) | Pfizer/BioNTech | Approved in U.K., U.S., etc. |
| Non-replicating viral vector | Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S) | Gamaleya Research Institute; Health Ministry of the Russian Federation | Approved in Russia |
| RNA | mRNA-1273 | Moderna/NIAID | Approved in U.S. |
| Non-replicating viral vector | ChAdOx1-S- (AZD1222) (Covishield) | AstraZeneca/University of Oxford | Approved in U.K., India |
| Non-replicating viral vector | Ad26.COV2.S | Janssen Pharmaceuticals | Phase 3 |
| Protein subunit | Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M | Novavax | Phase 3 |
| Inactivated | SARS CoV-2 vaccine (inactivated) | Sinovac Research and Development Co., Ltd | Phase 3 |
| Inactivated | Inactivated CoV-2 vaccine (Vero cell) | Sinopharm/Wuhan Institute of Biological Products | Phase 3 |
| Inactivated | Inactivated CoV-2 vaccine (Vero cell) | Sinopharm/Beijing Institute of Biological Products | Approved in China |
| Inactivated | Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) | Bharat Biotech | Approved in India |
| Non-replicating viral vector | Recombinant novel coronavirus vaccine (Adenovirus Type 5 Vector) | CanSino Biological Inc./Beijing Institute of Biotechnology | Phase 3 |
| Protein subunit | Recombinant SARS-CoV-2 vaccine (CHO cells) | Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences | Phase 3 |
| VLP | Coronavirus-Like Particle COVID-19 (CoVLP) | Medicago Inc. | Phase 2/3 |
| DNA | INO-4800+electroporation | Inovio Pharmaceutical/International Vaccine Institute | Phase 2/3 |
| RNA | CVnCoV Vaccine | CureVac AG | Phase 2/3 |
| Japan | | | |
| DNA | AG0301-COVID-19 (DNA plasmid vaccine + adjuvant) | AnGes/ Takara Bio/Osaka University | Phase 1/2 |
| Protein subunit | Recombinant protein vaccine S-268019 (Baculovirus expression system) | Shionogi | Phase 1/2 |
| Inactivated | Inactivated + alum | KM Biologics | Pre-clinical |
| Non-replicating viral vector | Sendai virus vector | ID Pharma | Pre-clinical |
| RNA | LNP-encapsulated mRNA | Daiichi-Sankyo/University of Tokyo | Pre-clinical |

Modified from "Landscape of candidate vaccines in clinical development-29 December 2020".[55] *The mentioned development stage is as of January 5, 2021. Approved drugs include those granted emergency use authorization.

immunogenicity, and thus, the enhancement of immunogenicity using adjuvants is needed. mRNA vaccines induce immunity through inoculating the mRNA and expressing the protein encoded by the mRNA in the host. Since mRNA vaccines are unstable, lipid nanoparticles (LNPs) or polymer particles are being used as the carriers. mRNA vaccines are considered as safe because there is no risk of mRNA insertion or mutation in the host genome. DNA vaccines induce immunity in the body following the injection of a DNA plasmid encoding an antigenic protein. Since DNA vaccines can be produced easily using *Escherichia coli*, the DNA of several candidate antigens can be immediately investigated for the development of these vaccines. Viral vector vaccines that incorporate the antigen protein gene into a non-pathogenic viral vector are directly inoculated into the host. Antigenic viral proteins produced in the body induce sustained immunity. To date, no mRNA, DNA, or viral vector vaccines have been approved in Japan. The virus-like particle (VLP) vaccine is the one obtained through isolating and purifying an outer protein shell that does not contain a viral genome using organisms, such as *Escherichia coli* and plants, who production can be scaled up in a short duration. Since this type of vaccine does not possess a viral gene, there is no viral proliferation in the host, and high immune effects can be expected.

### 2. Vaccine development

As of December 29, 2020, according to the WHO reports, 60 vaccines were in different phases of clinical trials worldwide, and 172 were undergoing preclinical trials (**Table 2**).[55]

LNP-mRNA vaccine (BNT162b2) developed by Pfizer (USA) and BioNTech (Germany), encodes the receptor binding site of the S protein of SARS-CoV-2 and has been shown to be 95% effective in preventing COVID-19 infection, which is based on the data analyzed during the final stage of the clinical trials.[56, 57] The British government authorized BNT162b2 vaccine for the emergency use on December 2, 2020, and thereafter, it has been approved for use in several countries. LNP-mRNA vaccine (mRNA-1273) developed by Moderna (USA) encodes the S protein of SARS-CoV-2 and was shown to be 94.5% effective in preventing COVID-19[58] following an interim analysis of clinical trial data on December 18, 2020. Consequently, the emergency use of this vaccine was authorized in the United States. Both vaccines are administered intramuscularly in two doses separated by an interval of 21-28 days.

Adverse reactions to vaccination, including pain and swelling at the injection site, fatigue, headache, myalgia, arthralgia, fever, chills, nausea, and vomiting have been reported.[59, 60] More than 270,000 people have already received their first shot of Pfizer-BioNTech vaccine by December 19, 2020, and only six cases of anaphylaxis-like symptoms were identified and recorded by the Centers for Disease Control and Prevention (CDC) in the USA. It is possible that the reason for the allergic reaction could be attributed to polyethylene glycol contained in the vaccine, and thus, further investigations are ongoing. Since mRNA is unstable due to the presence of RNA-degrading enzymes, Pfizer-BioNTech vaccine must be stored at −60 to −80°C and Moderna vaccine at −15 to −25°C.[61] The vaccine (AZD1222) developed by AstraZeneca and Oxford University uses the replication-deficient simian adenovirus vector (ChAdOx1), which contains a genetic sequence of SARS-CoV-2. When AZD1222 vaccine is inoculated into the host, the resulting S protein induces an immune response.[62, 63] The phase 3 trials of AZD1222 vaccine resulted in an average efficacy of 70%, and thereafter, the UK government authorized it for emergency use on December 30, 2020. In contrast to the aforementioned vaccines, AZD1222 vaccine can be transported easily because it can be stored under normal refrigeration conditions (2-8°C).

In Japan, phase 2 clinical trials of a DNA-based COVID-19 vaccine developed by AnGes are underway. Also, Shionogi has initiated the clinical trials of a recombinant protein vaccine.

## Conclusion

As SARS-CoV-2 infection continues to spread worldwide, there is an urgent need to develop the therapeutic and prophylactic agents. Although the medical care provision system is under immense pressure because of the rapid spread of COVID-19 pandemic, it is important to scientifically and appropriately verify the effectiveness of all the preventative and therapeutic agents through conducting randomized controlled trials. We are hopeful that effective vaccines and therapeutic agents will be developed in the near future to eradicate COVID-19.

**Remarks**: This is a secondary publication of "COVID-19 Pandemic: Drug Development and Drug Treatment" published in the Journal of Tokyo Women's Medical University (in Japanese) 91(1): 19-28, 2021.

**Conflicts of Interest**: The authors have no conflict of interests to declare.

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