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COVID-19: Vaccines and therapeutics

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a communicable disease triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as leading cause of death from a single infectious agent globally. Despite of rigorous protective measures, availability of multiple vaccines and with few approved therapeutics, the virus effect on the humankind throughout the world is perennial. COVID-19 has become the most urgent health concern with emergence of new challenging variants which outnumbered all other health issues and ensued in overwhelming number of reported deaths. In this unprecedented period of COVID-19 pandemic, scientists work round the clock for rapid development of efficient vaccines for prevention of infection and effective therapeutics for treatment. Here, we report the status of COVID-19 and highlight the ongoing research and development of vaccines and therapeutic strategies. It is necessary to know the present situation and available options to fight against the COVID-19 pandemic.

Background

The coronavirus disease 2019 (COVID-19) outbreak began in Wuhan, Hubei Province, China in December 2019 and rapidly spread throughout the nations worldwide. It was caused by a novel coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1–2] The World Health Organization (WHO) declared COVID-19 as a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and as a global pandemic on March 11, 2020, which is the second one in the 21st century followed by Swine flu in 2009.[3–4] The mankind has already confronted multiple outbreaks of coronavirus such as severe acute respiratory syndrome (SARS) caused by SARS-CoV1 (2003), and Middle Eastern Respiratory Syndrome (MERS) caused by MERS-CoV (2015).[5] Nevertheless, these epidemics were rapidly confined across the world by early development of efficient therapeutics and vaccines.

SARS-CoV-2 virus is being transmitted from person to-person using the same entry portal as SARS-CoV, type 1 transmembrane angiotensin-converting enzyme 2 (ACE2) receptor to enter the host cell.[6–7] ACE2 receptor is abundant in type II alveolar epithelial cells, vascular endothelial cells and enterocytes of the small intestine which makes them more vulnerable target for SARS-CoV-2.[8–9] Diagnosis is mandatory to confirm if an individual was infected with COVID-19. Molecular and serology tests are used for etiologic detection of SARS-CoV-2 infection. However, the test of choice is real-time reverse transcription polymerase chain reaction (RT-PCR) assay for more accuracy. Simultaneously, antibody-based techniques are also being used as supplemental tools.[10–11].

The most common signs of COVID-19 are fever, headache, cough, sore throat, shortness of breath and myalgia. Although the primary target for SARS-CoV-2 in the human body is lungs, disease progression is associated with multi organ injury by severely affecting the heart and kidney. The COVID-19 patients with critical illness may also develop acute respiratory distress syndrome (ARDS), acute cardiac injury, coagulation abnormalities, respiratory failure, traumatized immune system causing amplified cytokines release, and multiple organ breakdown resulting in death.[12–15] The crystal structure analysis and biochemical interactive investigations suggest that higher binding affinity of SARS-CoV-2 spike toward ACE2 receptor is responsible for superior transmissibility and severity than the SARS-CoV.[16–17].

As part of the evolutionary modification, viruses undergo slight genetic changes through mutation and major genetic changes through

Abbreviations: ACE2, Angiotensin-converting enzyme 2; RNA, Ribonucleic acid; DNA, Deoxyribonucleic acid; mRNA, Messenger RNA; CD4-T cells, Cluster of differentiation 4 T-helper cells; CD8-T cells, Cluster of differentiation 8 T-Lymphocytes; CDK-4, Cyclin-dependent kinase 4.

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recombination because they contain less stable RNA than DNA as their nucleic acids. Viruses mutate over the period by altering their genome sequence to create novel virus strains.[18] The same was observed in SARS-CoV-2 virus which accumulated mutations at a rate of about one to two changes per month. Most of the modifications have little to no effect on the virus' properties. Though, some of them may impact the virus's properties, such as transmission rate, the disease severity, or diagnostic tools, therapeutic medicines, the performance of vaccines, or other social measures and public health.[19] Since the discovery of SARS-CoV-2, various new corona virus mutants are identified in the Europe, South Africa, Nigeria, India, Brazil, and the United States of America (USA) and spread across the globe.[19–22] These variants are labelled as Alpha (B.1.1.7),[23–24] Beta (B.1.351),[19,22] Lambda (C.37),[19] Mu (B.1.621),[19] Gamma (P.1),[21] Delta (B.1.617.2),[25–28] and Omicron (B.1.1.529).[29–30] Molecular, serology and antigen tests are impacted with new variant strains differently owing to the inherent design changes of each test.

The SARS-CoV-2 variants such as Alpha, Beta, Gamma, Delta, and Omicron classified as variants of concern (VOCs) by the WHO. The entire world has experienced ferocious waves of COVID-19 infections with these new strains particularly Delta and Omicron which left unprecedented strain on health care systems and resulted in more deaths potentially. These are highly transmissible (~2x), with more severity of disease (increased hospitalizations or deaths), evaded the immune system and confronted with the existing diagnostics, vaccines, or therapeutics. However, the currently circulating variants of concern is Omicron variant and its BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages.[19] At present, studies are underway which include assessments of transmissibility, severity of infection (including symptoms), diagnostic tests, effectiveness of treatments and performance of vaccines.[30] Initially, only few therapeutics and vaccines were available with Emergency Use Authorization (EUA) and had limited access. According to the data available with the WHO, a total of 12,589,972,108 vaccine doses have been administered as of September 10, 2022.[31]

Researchers have been working relentlessly to understand the information about the characteristics of these mutants such as genomic sequence, infection rate, mortality, and their response to the currently authorized vaccines. The current advent of Omicron further highlights the importance of vaccination, boosters, and certain antiviral drugs. Therefore, we present here some glimpses about the accelerating research and development relating to vaccines as well as therapeutics to contain the spread of SARS-CoV-2.

Global strategy to address COVID-19

The impact of the COVID-19 pandemic has been very high not only in terms of public health but as well in the imbalance of social, political, and economic life of public. The total number of confirmed cases across the world touched 606 million mark along with the collective death toll of 64,95,110 as of September 13, 2022.[31] Globally, there are a total of 19,51,870 deaths reported in the year 2020 and 35,14,698 deaths reported in the year 2021.[32] Until recently, the future has been dreadful in view of the number of infections and deaths that have taken place. This led to many clinical trials world over for the development of COVID-19 vaccines as well as therapeutics. In this brief review, we have made some attempts to highlight the major initiatives that took place in this field.

As part of WHO's response to COVID-19, R&D blueprint was activated for initiating 'SOLIDARITY Trial' to accelerate novel diagnostic tools, therapeutics, and vaccines.[33] In an international clinical trial a comparison was carried out for four treatment options (Remdesivir; Ritonavir/ Lopinavir; Chloroquine or Hydroxychloroquine and Lopinavir/Ritonavir with Interferon beta-1a) against standard care by enrolling patients in multiple countries. The Solidarity trial was aimed to rapidly discover whether any of the drugs alleviate disease progression or improve survival of the patients by evaluating drug candidate's efficiency against COVID-19.[33–34].

'Access to COVID-19 Tools' (ACT) accelerator was also launched by WHO with a global collaboration to accelerate development of diagnostics, treatments, and vaccines, and their production to give equitable access for every country in the world. ACT brought together various scientists, philanthropists, governments, civil society, and major global health organizations such as Gavi (the Vaccine Alliance), the Bill & Melinda Gates Foundation, CEPI (The Coalition for Epidemic Preparedness Innovations), FIND (Foundation for Innovative New Diagnostics), Unitaid, The Global Fund, Wellcome, the World Bank and Global Financing Facility and the WHO. More than 150 countries got engaged in COVID-19 vaccine global access facility.[34]

In the global hunt for vaccines, there has been an advancement seen with COVAX initiative which is facilitated by collaboration of global health organizations including the WHO and is targeted to produce 2 billion doses by the end of 2021 that will suffice to vaccinate 20 % of partner countries.[34] Vaccine candidates from various companies such as Moderna, AstraZeneca/University of Oxford, Institut Pasteur/Merck/ Themis, University of Hong Kong, Novavax, CureVac, University of Queensland/CSL, Inovio and Clover Biopharmaceuticals are part of the COVAX initiative. The main goal of the program was to supply low-cost COVID-19 vaccines to as many countries as possible in collaboration with vaccine manufacturers across the globe.[34] The WHO has coordinated these efforts to successfully provide the latest information in the development of drugs and vaccines to control COVID-19.

Operation Warp Speed (OWS) was established by collaboration of several US federal government departments and the private sector.[35] Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) was originated by the collaboration of the National Institutes of Health (NIH) with more than 18 biopharmaceuticals to accelerate COVID-19 research which also comes under OWS. The European Medicines Agency (EMA) has been preparing the necessary protocols to step up the drug and vaccine development activities, assured of swift response pertaining to the scientific queries, regulatory compliance, and market authorizations for COVID-19 related initiatives.[36] Moreover, many national governments are working for the speedy progress of medical interventions. The overarching goal is to manage the COVID-19 pandemic by taking the measures to lessen the transmission and reduce the mortality.[37]

COVID-19 research and development

The COVID-19 is interminable for the last two years since the WHO's declaration as pandemic. Genomic characterization has supported in unfolding various aspects of SARS-CoV-2, however development of specific antiviral drugs and a single vaccine against COVID-19 is still a big challenge for the world. However, each major incident has always led to immense source of progress. Thankfully the existing knowledge that was gained by prior development platforms of vaccines for MERS-CoV and SARS-CoV, thus the initial common discovery stages were skipped and almost immediately phase I/ II trials were planned and initiated.[38] Thereby within a short span of time, the scientists have developed multiple vaccines for COVID-19 with the support of huge funding raised for vaccine research and development, while on a usual mode most vaccines may take about five to ten years for their development. The pipeline itself for SARS-CoV-2 vaccine development has followed an accelerated timeline. As per the data available, there are 2152 drugs and 367 vaccine trials, including 169 candidate vaccines that are in clinical evaluation and 198 candidate vaccines are in preclinical evaluation as of July 30, 2022.[39–40] Vaccination has been the most important strategy indeed to fight this pandemic. It is vital to have equitable access for the safe and effective vaccines to bring an end for this COVID-19 pandemic apart from the reasonable access towards the treatment and diagnostics.[41]

Mechanism of action of COVID-19 vaccines

Most of the current authorized COVID-19 vaccines rely on the viral spike protein (S) as an antigen, either alone/together with other viral proteins or inactivated virus vaccines.[42] The SARS-CoV-2 contains 25–28 proteins, in which the mRNA isolated from the S protein and different strategies have been anticipated to solve the common drawbacks of mRNA-based vaccines, which include the mRNA instability with respect to DNA.[43] A cutting-edge approach was used to generate a protein that itself safely prompts an immune response by using genetically engineered DNA or RNA.

The present COVID-19 vaccines produce the spike protein in various ways to the immune system and perceived into two main categories. The first category named as genetic vaccines consists of mRNA, adenoviral vector (Viral vector) vaccines and DNA vaccines which contain genetic information for the biosynthesis of spike protein in body cells of the vaccine. These vaccines have been designed with certain genetic strings for the precise formation and performance of properly folded spike proteins to B cells. The second category classified as protein-based vaccines entails innovative subunit and classical inactivated whole-virus vaccines. These encompasses protein-based approaches which contain S protein in various forms and combinations with adjuvants that mimic the SAR-COV-2 to safely generate an immune response.[44] The detailed mechanism of action of genetic and protein-based vaccines depicted in Fig.1.

Most prophylactic vaccines block viral entry into the host cells by eliciting antibodies to the viral surface of glycoproteins. These spike proteins have several epitopes that can provoke CD4-T cell responses and some CD8-T cells.[45] Other candidate antigens trigger further *T*-cell responses or boost pre-existing *T*-cell responses are viral proteins like proteases and nucleocapsid. Therefore, the main aim of the SARS-CoV-2 vaccine candidate is to raise robust spike specific humoral responses that prevent viral infection.[46]

Approved COVID-19 vaccines

In response to COVID-19, funds were raised for vaccine research and development and a fast-track vaccine development process was adopted to invent multiple candidates within a year. Extensive efforts by various research teams led to the discovery of few vaccines (Sputnik V, BNT162, mRNA-1273 and AZD1222) that have reached the market at the end of 2020, whereas some others in the middle of 2021.[47] Presently, there are dozens of vaccines that have been approved to be used against COVID-19 (Table 1), but the supply of vaccines to every individual across the globe might take much longer. Especially the LMICs, could not afford and access the vaccine to their people as equal to the developed countries.[48] In many countries, first preference in vaccine distribution is given to frontline warriors (healthcare workers) and people with certain medical conditions such as Cancer, Chronic Kidney disease, Chronic obstructive pulmonary disease, Heart conditions, Obesity, Pregnancy and Type II diabetes mellitus etc.[49]

Several vaccine designs were evaluated by different research groups during the development of a SARS-CoV-2 vaccine. The authorized COVID-19 vaccines currently in use are summarized in the Table 1. The one which was approved first in the vaccine race is Sputnik V, formerly known as Gam-COVID-Vac.[47] It is a heterologous vaccine comprising of two components (rAd26 and rAd5) vector which carries the gene for SARS-CoV-2 spike glycoprotein (rAd26-S and rAd5-S). It was introduced by the Gamaleya Research Institute in Moscow, Russia and approved on 11 August 2020 by the Ministry of Health of the Russian Federation. Scientists and health professionals have raised apprehension on its efficacy and safety globally. However, data from the Phase II clinical trials of the vaccine was published in Lancet, which is supportive to its late-stage evaluation with a good safety profile and "induced strong

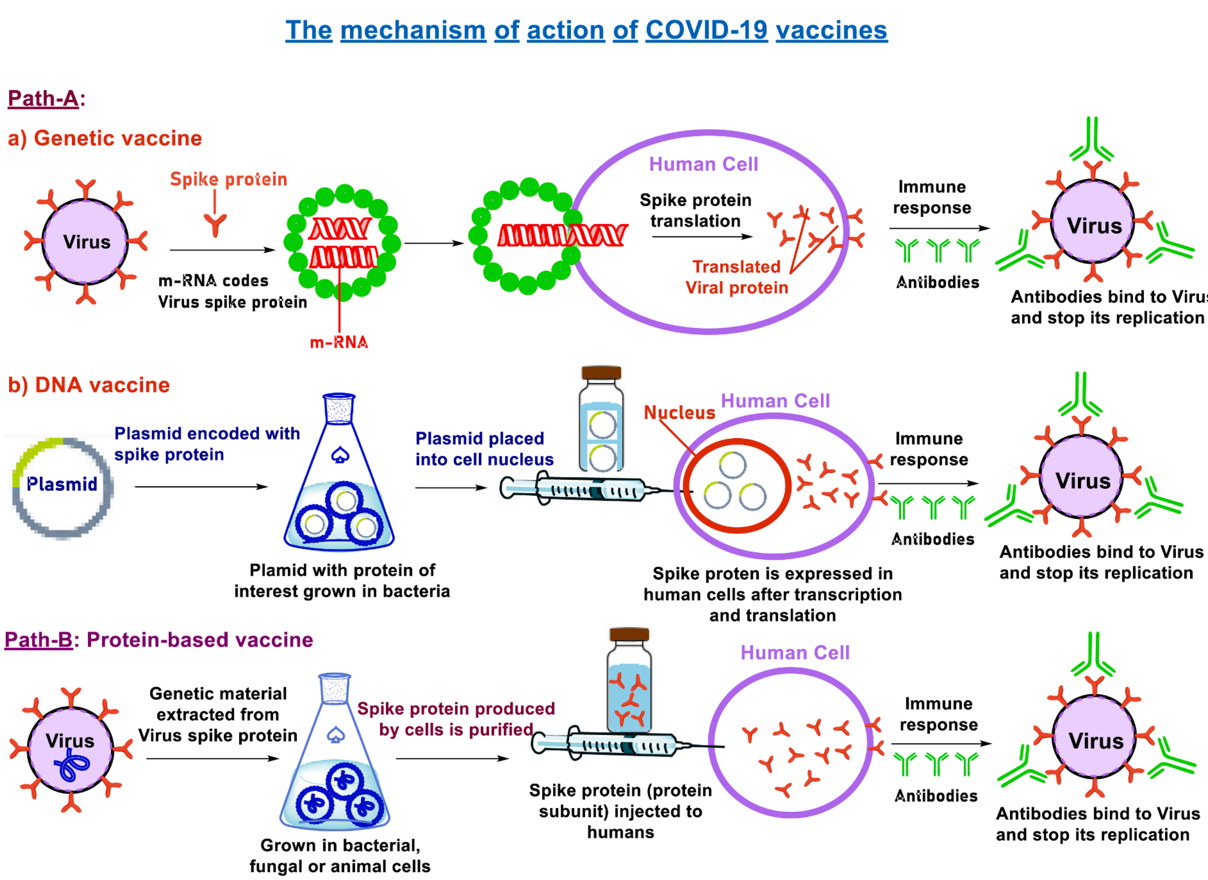

Fig. 1. The mechanism of action of COVID-19 vaccines.

Table 1
List of some approved vaccines against COVID-19.

Name of the candidate	Primary developers	Type of vaccine	Country of origin	Authorization/ Approval
Sputnik V	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Recombinant adenovirus vaccine (rAd26 and rAd5)	Russia	Russia and more than 68 countries
EpiVacCorona	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Peptide vaccine	Russia	Belarus, Russia, Turkmenistan
Comirnaty (BNT162b2)	Pfizer, BioNTech; Fosun pharma	mRNA-based vaccine	Multinational	UK, Bahrain, Canada, Mexico, USA, Singapore, Oman, Saudi Arabia, Kuwait, EU, WHO and nearly 65 more nations
Spikevax (mRNA-1273)	Moderna, NIAID, BARDA	mRNA-based vaccine	USA	USA, Canada, EU, UK, WHO and 40 more nations
COVID-19 Vaccine AstraZeneca (AZD1222)/Covishield	The University of Oxford; AstraZeneca; IQVIA; Serum Institute of India; BARDA, OWS	Adenovirus vaccine	UK	UK, EU, India and 110 more nations
WIBP-CorV	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	Inactivated vaccine	China	China and Phillippines
CoronaVac	Sinovac	Inactivated vaccine	China	China, Indonesia, Brazil, Chile, Turkey, WHO and 40 more countries
BBIBP-CorV/NVSI-06–07	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	Inactivated vaccine	China	China, United Arab Emirates, Bahrain, WHO and 72 more nations
Covaxin (BBV152)	Bharat Biotech; ICMR; Ocugen; ViroVax	Whole-Virion Inactivated	India	India, Botswana, Estonia, Finland, Guatemala, Guyana, Hong Kong, WHO and 12 more nations
Convidicea (PakVac, Ad5-nCoV)	CanSino Biologics	Recombinant vaccine	China	China, Chile, Pakistan, Ecuador, Hungary and 6 more nations
COVID-19 Vaccine Janssen (JNJ-78436735)	Janessen Vaccines (Johnson & Johnson), BARDA, NIAID and OWS.	Non-replicating viral vector	The Netherlands, US	US, UK, EU, India, WHO, Saint Vincent and the Grenadines and 37 more nations
Sputnik Light	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Recombinant adenovirus vaccine (rAd26)	Russia	Russia and 21 more nations
CoviVac	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Inactivated vaccine	Russia	Russia and Belarus
NVX-CoV2373	Novavax, CEPI, Serum Institute of India	Recombinant nanoparticle vaccine	US	Australia, Canada, European Union, South Korea, Philippines, India, Indonesia, Philippines, Singapore, Switzerland, UK, and WHO
ZyCoV-D	Zydus Cadila	DNA vaccine (Plasmid)	India	India
Spikogen (COVAX-19)	Vaxine Pty ltd.; CinnaGen	Monovalent recombinant protein vaccine	Iran	Iran
ZF2001 (ZIFIVAX)	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	Recombinant vaccine	China, Uzbekistan	China, Uzbekistan, Pakistan, and Indonesia,
Abdala (CIGB 66)	Center for Genetic Engineering and Biotechnology	Protein subunit vaccine	Cuba	Cuba, Vietnam, St. Vincent & Grenadines, Venezuela, Vietnam, and Nicaragua
COVIran Barekat	Shifa Pharmed Industrial Group	Inactivated vaccine	Iran	Iran
QazVac (QazCovid-in)	Research Institute for Biological Safety Problems	Inactivated vaccine	Kazakhstan	Kazakhstan
Soberana 02/Soberana Plus	Finlay Institute of Vaccines; Pasteur Institute	Conjugate vaccine	Cuba, Iran	Cuba, Iran, Nicaragua, and Venezuela
MVC-COV1901	Medigen Vaccine Biologics Corp.; Dynavax	Protein subunit vaccine	Taiwan	Taiwan and Paraguay
Turkovac (ERUCOV-VAC)	Health Institutes of Turkey	Inactivated vaccine	Turkey	Turkey
Corbevax	Biological E, Baylor College of Medicine, Dynavax, CEPI	Adjuvanted protein subunit vaccine	India, United States	India and Botswana
Noora	Baqiyatallah University of Medical Sciences	Recombinant protein vaccine	Iran	Iran
Covifenz (CoVLP)	Medicago; GSK; Dynavax	Plant-based adjuvant vaccine	Canada	Canada
VLA2001	Valneva; UK National Institute for Health Research	Inactivated vaccine	France, United States	Bahrain; UK

Source: Regulatory Affairs Professional Society. Craven J, Therapeutic Tracker. https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-therapeutics-tracker[47].

humoral and cellular immune response".[50,51] Sputhnik V's efficacy is found to be 91.6% when tested on a large group of participants in the Phase 3 trials.[52] While the second one is EpiVacCorona, which was also granted regulatory approval by the Russian Authorities without undergoing Phase III clinical trials and also received authorization in Belarus, and Turkmenistan.[47,53,54] Well-known candidates in the vaccine race, named AZD1222 (the University of Oxford and AstraZeneca), mRNA-1273 (Moderna), and BNT162 (Pfizer and BioNTech) have successfully completed Phase III clinical studies and have reached the market. These candidates were funded by the US government under OWS.[35,47]

As per the United States Food and Drug Administration (USFDA) guidelines released on June 30, 2021, a vaccine needs to show a minimum of 50 % activity against COVID-19 in the placebo-controlled clinical trials to be authorized for its usage.[55] In the recently released guidelines on COVID-19 vaccines, EUAs, FDA entailed an interim analysis report evaluated from a clinical endpoint in Phase III trial for a minimum period of two months in more than 3000 volunteers along with relevant efficacy and safety results from Phase I and Phase II trials.[56]

Pfizer and BioNtech are collaboratively developed BNT162, a series of vaccine candidates for the COVID-19. Initially, four candidates were developed and tested in the first stage trials. Out of these, only one candidate Comirnaty (BNT162b2, a nucleoside modified mRNA-based vaccine) was advanced to Phases II/III safety study and got the first regulatory approval from the UK authorities on the recommendation of its Medicines and Healthcare products Regulatory Agency (MHRA) followed by Bahrain, Canada, USA, European Union (EU), Singapore, India, Australia and about another sixty countries.[47,57] Comirnaty is the first one to receive emergency validation for a COVID-19 vaccine from the WHO.[58] Based on prior studies of SARS and MERS, Moderna developed mRNA-1273 vaccine candidate which has shown promising results in Phase I/II trial. Recently, it has shown a 94.5 % efficacy rate in an interim analysis in Phase III trial and got approved by the authorities of USA, Canada, UK, WHO followed by many countries worldwide.[47,59–62] The Oxford Vaccine Group's candidate, AZD1222 with the name of Covishield (previously ChAdOx1, a chimpanzee adenovirus vaccine vector) entered the market with collaboration of AstraZeneca and produced by the Serum Institute of India. It has shown strong immune response in Phases I/II trials. OWS and Biomedical Advanced Research and Development Authority (BARDA) co-funded to late-stage Phase II/III clinical trials in various countries with more than 30,000 people. Recently, it has completed Phase III clinical evaluation and got the first regulatory approval by the UK authorities followed by WHO, EU, India, and many others.[47, 63-65]

Indian origin Covaxin, which is an inactivated vaccine, developed by Bharat Biotech and National Institute of Virology was evaluated in Phase III clinical trials with 25,800 volunteers across the India and showed the results with an efficacy of 77.8 % and is 93.4 % effective in preventing the severe disease. It got restricted emergency approval from Drugs Controller General of India (DCGI) and very recently from the WHO.[47,66–68] Covaxin has shown "robust immune memory" in opposition to multiple variants for at least six months after the vaccination.[69]

Three potential vaccine candidates from China, an inactivated vaccine WIBP-CorV (Wuhan Institute of Biological Products & Sinopharm),[47,70] BBIBP-CorV (Inactivated vaccine, Beijing Institute of Biological Products & Sinopharm),[47,71] and CoronaVac (a formalin-inactivated and alum-adjuvanted candidate vaccine, Sinovac Research and Development Co., ltd. were approved by the authorities of China.[47,72] Recently, another prominent recombinant vaccine is named Convidicea (formerly Ad5-nCoV, CanSino Biologics),[73–74] got approval from the authorities of China followed by Mexico and Pakisthan.[47] Another important candidate named JNJ-78436735 (non-replicating viral vector, Johnson & Johnson, Phase III) has got first authorization from Saint Vincent and the Grenadines, followed by many countries.[47,75,76].

Russia has developed and approved two more vaccine candidates named as Sputnik Light (a heterologic recombinant adenovirus (rAd)-based vaccine),[77] and CoviVac (inactivated COVID-19 vaccine candidate)[78] and were authorized while still being evaluated in clinical trials. One of the other prominent vaccine candidates named NVX-CoV2373 (Nanoparticle vaccine) was developed by Novavax, CEPI and Serum Institute of India. It was authorized by India, Indonesia; South Korea, Philippines, European Union, and WHO.[79–80] Zydus Cadila (an Indian company) developed ZyCoV-D (a plasmid DNA vaccine candidate) that has been approved in India.[81–82] Many other new vaccines such as ZF2001 (China, Uzbekistan),[83] MVC-COV1901 (Taiwan),[84] Spikogen (COVAX-19), COVIran Barekat (Iran), Soberana 02/Soberana Plus (Cuba, Iran) Abdala (Cuba), Turkovac (Turkey), Corbevax (India, USA), QazVac (Cuba, Iran), Noora (Iran), Covifenz (Canada), and VLA2001 (France and United States) have been developed and authorised by at least one or two countries.[47]

COVID-19 vaccine-candidates under consideration

At present, there are one hundred and sixty-nine vaccine candidates in clinical trials and one hundred and ninety-eight are in pre-clinical evaluation to contain COVID-19 worldwide.[40] Percentage of vaccine candidates from various platforms in clinical phases is illustrated as a Pie Chart in Fig. 2. Some of the efficient vaccine candidates which are under late stage of clinical evaluation are listed in Table 2. BCG-vaccine, one of the oldest vaccines that is being given to babies to combat Tuberculosis, could also protect us against novel corona virus.[85–86] It is evident that besides the protection from *Mycobacterium Tuberculosis*, BCG vaccine also protects against other infections by boosting the immune system which encouraged scientists to investigate the vaccine's efficacy against the corona virus.[47,87] INO-4800 (DNA vaccine, Inovio Pharmaceuticals, Phase II/III),[82,88] Vidprevtyn (Protein subunit vaccine, Sanofi; Glaxo Smith Kline (GSK), Phase I/II),[89] GBP510 (Nanoparticle vaccine, SK bioscience Co., ltd.; GSK; University of Washington; CEPI; Phase 3),[47] ARCoV (mRNA-based vaccine, Walvax Biotechnology Co., ltd.; Abogen Biosciences Co. ltd.; Yuxi Walvax Biotechnology Co., ltd.), Unnamed vaccine candidate (Recombinant vaccine, WestVac Biopharma Co., ltd.; West China Hospital; Sichuan University) and CVnCoV (mRNA-based vaccine, CureVac, Phase IIb/III)[90] are being evaluated in various phases with large number of participants (greater than10,000).[47] V-01 (Recombinant protein vaccine, Zhuhai Livzonumab Biotechnology Co., ltd; Phase III),[91] COVI-VAC (intranasal live attenuated vaccine candidate, Novavax, Codagenix and the Serum Institute of India using Codagenix's Synthetic Attenuated Virus Engineering (SAVE) platform),[92] BNT162 (mRNA-based vaccine, Pfizer, BioNTech, Phase I/II/III) and BBV154 (Intranasal vaccine, Bharat Biotech, Phase II/III) are being studied in various phases.[47]

Many other potential vaccine candidates such as Nanocovax (Recombinant vaccine, Spike protein, Phase III), Razi Cov Pars (Recombinant vaccine, Spike protein, Phase III), S-268019 (Recombinant protein vaccine, Phase III), Unnamed vaccine candidate (Recombinant vaccine, Sf9 cells), GBP510 (Nanoparticle vaccine, Phase III), and SCB-2019 (Protein subunit vaccine, Phase III) are being evaluated in various international trials.[40,47] We assume that some of them may find clinical usage for COVID-19 in the coming years.

COVID-19 drug targets and development of drugs

SARS-CoV-2 is enveloped, positive-sense, single-stranded RNA genome virus (30 kb) and consists of 14 open reading frames (ORFs). The most important ORF1ab encodes for two overlapping polyproteins named as pp1a and pp1ab, which further cleaves into 16 non-structural proteins (nsp1-16) including the RNA-dependent RNA polymerase (RdRp, nsp12) by the main protease M^{pro}/$3CL^{pro}$ and the papain-like protease PL^{pro}. The remainder of the genome encodes for structural and accessory proteins such as the S protein, envelope protein (E), matrix/membrane protein (M) and the nucleocapsid phosphoprotein (N).[93] The M^{pro} and PL^{pro} are essential for the cleavage of polypeptides into functional proteins. Hence, these viral proteases are attractive drug targets for antiviral drug discovery against SARS-CoV-2. Especially, M^{pro} is the ideal viral target as it exclusively cleaves polypeptide sequences after a glutamine residue which is a critical step during viral replication.[94–95].

The S protein is a surface-located trimeric glycoprotein that promotes the attachment of viruses to the host cells through binding to ACE2 and virus-cell membrane fusion during the viral infection. Thus, the S protein considered as a significant target for developing therapeutics against SARS-CoV-2.[45,96] The E protein also identified as drug target which involves in viral assembly and localizing to the endoplasmic reticulum (ER) and Golgi body membranes. The E protein also participates in activating the host inflammasome by regulation of pumping Ca^{2+} out of the endoplasmic reticulum.[93]

The most vital role of the M protein is to maintain the shape of the viral envelope that achieves by incorporating Golgi complex into new virions, interacting with other virus proteins, and stabilizing nucleocapsid protein. The M protein is also important in viral intracellular homeostasis through multiple protein–protein interactions such as M−M, M−N, and M−S proteins takes a particular part in viral assembly. Therefore, it is a good target for the development of new drugs for

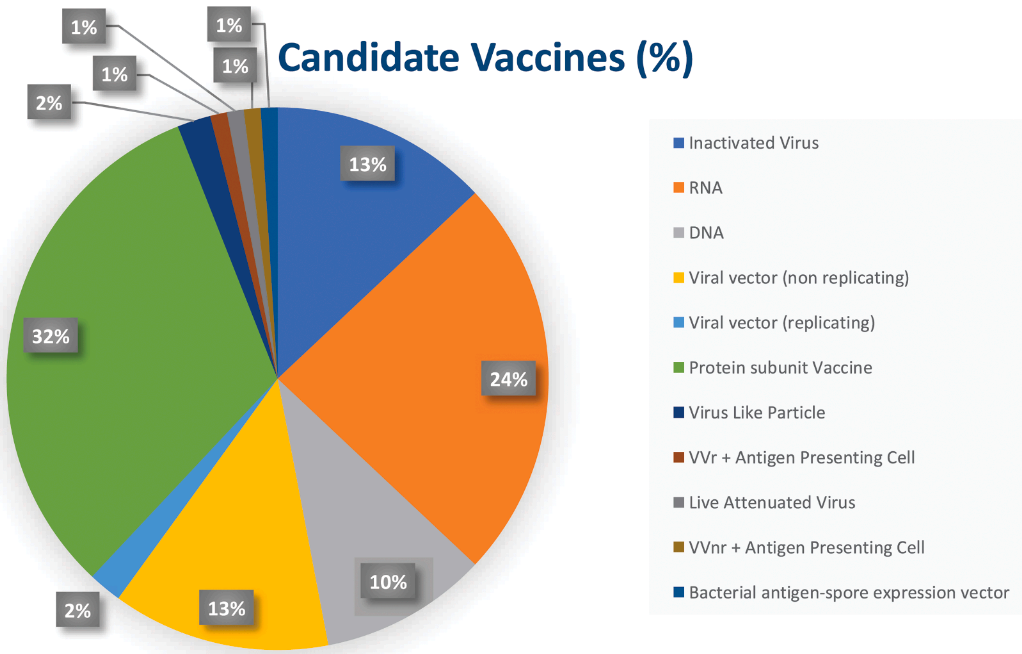

Fig. 2. Pie Chart of vaccine candidates from various platforms in clinical phases. Source: The WHO. COVID-19 vaccine tracker and landscape, as of 29 July 2022.[38.]

COVID-19.[93]

The N protein is a crucial part that protects the viral RNA genome and regulates the replication and transcription of viral RNA. It as well hinders the protein translation through EF1α-mediated action, modification of host cell metabolism and host cell cycle (N proteins are reported to inhibit CDK4) further leads to apoptosis. Consequently, it plays an important role in antagonizing the host immune response and binds with the double-stranded RNA to counter cellular RNAi-mediated antiviral activities.[97] The structural proteins are responsible for virion assembly participate in the suppression of the host immune response. Hence, these are considered as important drug targets for SARS-CoV-2.

Approved COVID-19 drugs

To reduce the severity and mortality rates of coronavirus disease, researchers have worked round the clock to find the treatment/drug candidates. The trials were initiated based on the three categories: Drugs already approved and available for treatment of other diseases; Drugs that have shown promise in animal studies for treating SARS and MERS; New research: from design and discovery to development of new drugs that includes pre-clinical to clinical trial studies, and this could take many years.[98] In the first category, drugs such as lopinavir/ritonavir (anti-HIV drugs); chloroquine and hydroxychloroquine (anti-malarial); favipiravir (an oral antiviral for the treatment of influenza) and systemic interferons: particularly, interferon beta (used for multiple sclerosis) were selected for clinical trials. The second category comprises of remdesivir (an investigational, anti-viral compound) and dexamethasone. The last category (new research/pre-clinical trials) includes the use of antibodies. These can be used to develop recombinant monoclonal antibodies or harvested to use in a plasma treatment (usage of convalescent plasma) which are present in the blood plasma of already infected persons and who have later recovered. For the evaluation of convalescent plasma, FDA granted an emergency use authorization (EUA) to the program led by the Mayo Clinic.[99–100] It has strong evidence (history of effectiveness in other corona viruses) that it can be used in the COVID-19 treatment. Based on several studies, it may consider that the most promising one is the cocktail approach of Regeneron.[101]

In the early days of pandemic, only three drug candidates were approved to treat COVID-19 with trade names: Veklury (remdesivir) in Japan and Australia; Avigan (favipiravir) in China, Italy, and Russia; and dexamethasone in the United Kingdom and Japan.[98] In combination to these drugs, a handful of therapeutics such as Lagevrio (molnupiravir), Olumiant (baricitinib), Regkirona (regdanvimab), Xevudy (sotrovimab), Ronapreve (imdevimab and casirivimab), romlusevimab and amubarvimab (formerly BRII-198 and BRII-196), RoActemra/Actemra (tocilizumab), Kineret (anakinra) and Paxlovid (nirmatrelvir + ritonavir) have been authorized specifically to treat COVID-19 in various countries. Especially, Evusheld (tixagevimab and cilgavimab; AZD7442) has been approved in multiple countries for use as pre-exposure prophylaxis.[99] The chemical structures of some approved drugs are given in Fig. 3.

Remdesivir and favipiravir have been approved by the various governments to give critically ill patients.[99] These two are antiviral agents which act by inhibiting viral replication. Remdesivir with the trade name Velkury has become the first drug to be approved to treat COVID-19 in Europe, Japan, and Australia. Remdesivir has been shown to be effective in severely ill adults as per the guidelines of National Institutes of Health.[102–103] Intravenous remdesivir got emergency use authorization from the USFDA and many countries. However, after numerous case studies, it was understood that Remdesivir was not as effective as anticipated. Hence, the WHO has issued a conditional recommendation against the use of remdesivir in hospitalized patients.[104] Nevertheless, it is being assessed in various high-profile trials.[105] One more antiviral compound named Avigan (favipiravir) which was primarily developed for the treatment of Ebola has also been approved in many countries for COVID-19 treatment. It is an intravenous drug which inhibits viral replication and has shown good *in vitro* and *in vivo* activity against SARS-CoV-2. Favipiravir is mainly given for mild/moderate COVID-19 disease as an oral medication.[106] On the other hand, dexamethasone in low-dose has also been approved to treat severe COVID-19. Dexamethasone, an inexpensive steroid, which can be administered both orally and intravenously, has now been approved in the UK and Japan for patients who require oxygen, including those on ventilators. Dexamethasone is being tested as a treatment arm of the RECOVERY trial (The national clinical trial aspires to recognize better treatments for people hospitalised with

Table 2
List of few vaccine candidates against COVID-19 currently in Phase I-III trials.

Name of the candidate	Sponsor	Institute	Funding agency	Trial phase
Bacillus Calmette-Guerin (BCG) live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	Murdoch Children's Research Institute; UMC Utrecht	II/III
INO-4800 (DNA vaccine, plasmid)	Inovio Pharmaceuticals; Advaccine	University of Pennsylvania, Center for Pharmaceutical Research, Kansas City. Mo. & the Korea National Institute of Health (KNIH)	Inovio Pharmaceuticals, CEPI & the International Vaccine Institute (IVI)	II/III
ARCoV (mRNA-based vaccine)	Walvax Biotechnology Co., ltd.; Abogen Biosciences Co. ltd.; Yuxi Walvax Biotechnology Co., ltd.	Xiangfen CDC	Walvax Biotechnology Co., ltd.; Abogen Biosciences Co. ltd.; Yuxi Walvax Biotechnology Co., ltd.	III
Vidprevtyn (Recombinant protein vaccine)	Sanofi; GlaxoSmithKline	Various	OWS and the U.S. Department of Defense	III
Unnamed vaccine candidate (Recombinant vaccine, Sf9 cells)	WestVac Biopharma Co., ltd.; West China Hospital; Sichuan University;	Jiangsu Province Centers for Disease Control and Prevention	WestVac Biopharma Co., ltd.; West China Hospital; Sichuan University;	III
GBP510 (Nanoparticle vaccine)	SK bioscience Co., ltd.; GSK; University of Washington; CEPI	Multiple	SK bioscience Co., ltd.; GSK; University of Washington; CEPI	III
CVnCoV (mRNA-based vaccine)	CureVac; GSK	CureVac (Various study sites in Europe)	The German federal government	IIb/III
V-01 (Recombinant protein vaccine)	Guangdong Provincial Center for Disease Control and Prevention; Gaozhou Municipal Center for Disease Control and Prevention; Zhuhai Livzonumab Biotechnology Co., ltd.	Livzon Mabpharm Inc.	Zhuhai Livzonumab Biotechnology Co.	III
COVI-VAC (Intranasal vaccine)	Codagenix; Serum Institute of India	Codagenix; Serum Institute of India	Codagenix; Serum Institute of India	I
BBV154 (Intranasal vaccine)	Bharat Biotech	Various	Bharat Biotech	II/III
BNT162 (mRNA-based vaccine)	Pfizer, BioNTech	Multiple study sites in Europe, North America, and China	Pfizer, BioNTech	I/ II/ III
Nanocovax (Recombinant vaccine, Spike protein)	Nanogen Biopharmaceuticals	Military Medical Academy (Vietnam)	Nanogen Biopharmaceutical	III
Razi Cov Pars (Recombinant vaccine, Spike protein)	Razi Vaccine and Serum Research Institute	Tehran Rasoul Akram Hospital; Karaj, Hesarak, Razi Vaccine and Serum Research Institute	Razi Vaccine and Serum Research Institute	III
S-268019 (Recombinant protein vaccine)	Shionogi & Co., ltd; Japan Agency for Medical Research and Development	–	Shionogi & Co., ltd; Japan Agency for Medical Research and Development	II/III
Unnamed vaccine candidate (Recombinant vaccine, Sf9 cells)	WestVac Biopharma Co., ltd.; West China Hospital; Sichuan University;	Jiangsu Province Centers for Disease Control and Prevention	WestVac Biopharma Co., ltd.	III
GBP510 (Nanoparticle vaccine)	SK bioscience Co., ltd.; GSK; University of Washington; CEPI	Various	GSK; CEPI	III
SCB-2019 (Protein subunit vaccine)	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	Linear Clinical Research (Australia)	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	III

Source: Regulatory Affairs Professional Society. Craven J, Vaccine Tracker. https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker[47].

suspected or confirmed COVID-19).[107–109].

Molnupiravir (Lagevrio) is an oral broad-spectrum antiviral drug prevents replication of the virus by inhibiting RNA dependent RNA polymerase. It has received EUA from USA, UK, EU, India, and authorization process initiated by many countries.[99] By administering the drug to the non-hospitalized patients with mild to moderate COVID-19, a 50 % reduction in the hospitalization was reported.[110–112] Olumiant (baricitinib), a Janus kinase (JAK) inhibitor is also being evaluated as a therapeutic for COVID-19 alone as well as in combination with other drugs.[113] It received EUA from USA, EU, Japan, Brazil, India and strongly recommended by the WHO for COVID-19 treatment.[99,114]

Regkirona (regdanvimab) is a monoclonal antibody and has been found to neutralize SARS-CoV-2 and emergent variants.[115] It has been approved by Australia, Brazil, EU, Indonesia, and South Korea.[99] Xevudy (sotrovimab) is another monoclonal antibody, developed by GSK and Vir Biotechnology, Inc. to treat COVID-19.[116] It has been approved by Australia, Bahrain, Canada, EU, Italy, Japan, UK, and USA.[99] Ronapreve (Casirivimab/REGEN-COV and imdevimab/REGN-COV2) is monoclonal antibody cocktail to target the spike protein of SARS-CoV-2.[117] It has been permitted by Australia, Bahrain, Canada, EU, India, Japan, Singapore, Sri Lanka, UK, and USA and recommended by the WHO for COVID-19 treatment.[99]

Romlusevimab and amubarvimab (formerly BRII-198 and BRII-196) are monoclonal antibodies, used to neutralise SARS-CoV-2. The therapy was approved by China and authorisation process initiated for FDA to treat mild and moderate COVID-19 at high risk of progression to severe disease.[99] RoActemra/Actemra (tocilizumab) is an Interleukin 6 (IL-6) receptor agonist used to treat autoimmune diseases like rheumatoid arthritis and cytokine release syndrome, which is now used to neutralize SARS-CoV-2. It has shown a beneficial outcome in some hospitalised

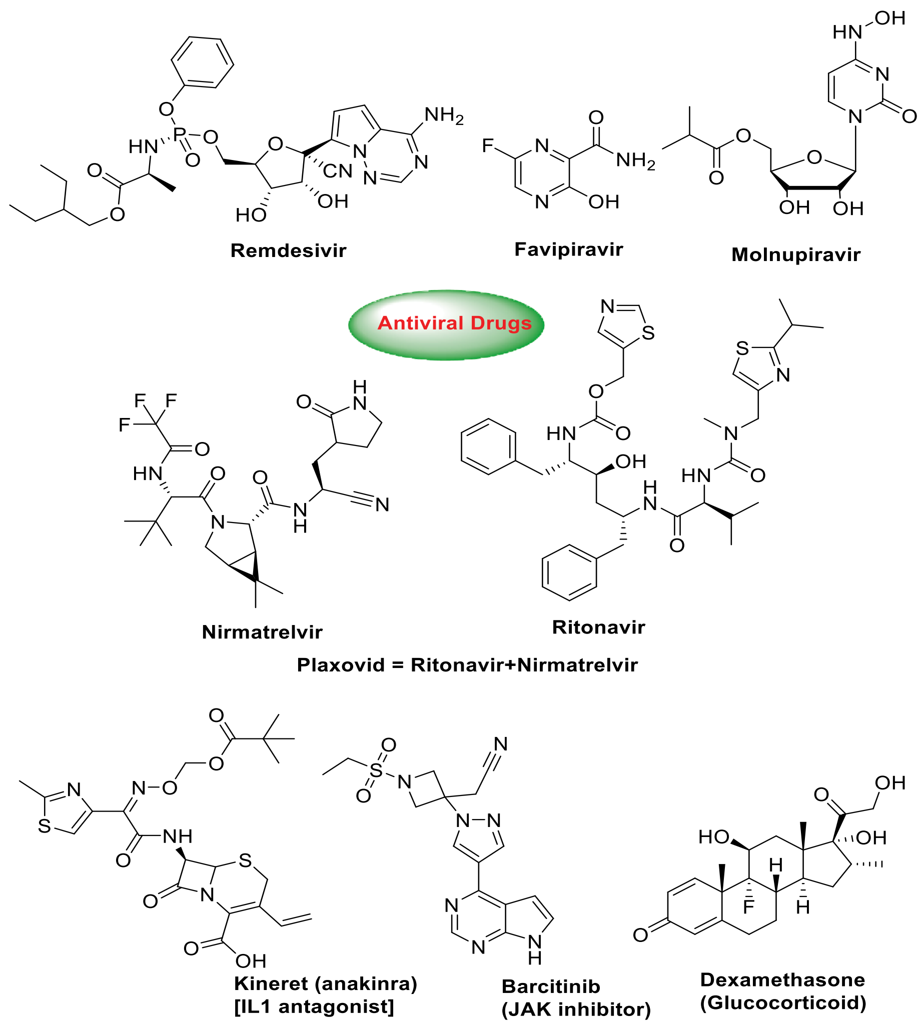

Fig. 3. The chemical structures of various approved COVID-19 drugs.

COVID-19 patients and recommended to use in only severe/critical COVID-19 cases by the WHO.[118] It has received EUA status from FDA, India, EU, and Australia.[99]

Kineret (anakinra) is an interleukin-1 (IL-1) receptor agonist used in rheumatoid arthritis, cryopyrin-associated periodic syndromes, etc. It is being repurposed as a COVID-19 therapeutics candidate and be part of various international trials. Kineret has authorized by European Medicines Agency (EMA) to use as a treatment option for patients with COVID-19 associated pneumonia and listed it in the top ten promising COVID-19 therapeutics as of October 2021 by The European Commission.[99,119] Paxlovid (nirmatrelvir + ritonavir) is an antiviral therapeutic combination for COVID-19 which inhibits replication of virus by blocking protease enzyme in SARS-CoV-2.[120] It has shown promising results in clinical trials with 89 % reduction in death or hospitalization compared with placebo (if the treatment started within 3 days of developing symptoms).[121] Paxlovid has received emergency authorized usage from South Korea, UK, USA, EU and Australia.[99] Evusheld (tixagevimab and cilgavimab; AZD7442) is a combination of two monoclonal antibodies to treat COVID-19 which exhibited promising results in early stages and reduced the risk of progression to severe disease or death was 88 % (the 600-mg group) as compared with placebo.[122] It is being part of many international trials and received EUA from FDA and Australia as pre-exposure prophylaxis for immunocompromised individuals. The authorization process initiated in UK, EU, and Canada.[99]

COVID-19 drug-candidates under consideration

Meanwhile, some of the antiviral, antimalarial drug candidates and the drugs from other therapeutic areas, are being examined for COVID-19 in many international trials (Table 3). These studies have entered final stages of evaluation (Phase II & III) and the details are provided in Table 3.,[99,101 105] Especially, antivirals like Bemnifosbuvir (AT-527), Galidesivir, Xocova (Ensitrelvir), Kaletra (Lopinavir + Retonavir), and TEMPOL take the lead role in COVID-19 therapeutic hunt shown in Fig. 4. Besides, few antimalarial drugs such as Artesunate and Pyronaridine are also being evaluated (Fig. 4). Other repurposed drug candidates like Famotidine (Histamine H_2 receptor antagonist), Bucillamine (Antirheumatic), Metformic (Biguanide), Vascepa (Lipid lowering agent), Colchicine (Anti gout agent), Heparin (anti-coagulant), Abivertinib (Tyrosine kinase inhibitor), Imatinib (Tyrosine kinase inhibitor), Opaganib (Sphingosine kinase inhibitor), and Proxalutamide (Non-steroidal antagonist) that are under consideration are depicted in Fig. 5. Monoclonal antibodies (Infliximab, Bamlanivimab, Etesevimab, AGD20, Lenzilumab, Mavrilimumab and Sarilumab) also take a vital part in the therapeutic research of COVID-19.[99] We expect some of these might soon be developed as potential COVID-19 therapeutics for their future usage.

Summary and future perspective

SARS-CoV-2 is a highly contagious virus which may become severe

Table 3
Some of the promising drug candidates against COVID-19 currently in Phase I-III trials.

Trade Name (Generic Name)	Medication class	Treatment strategy/Mechanism of action	Researcher/Developer	Trial Phase
Veklury (remdesivir)	Antiviral	RNA dependent RNA polymerase inhibition	Gilead Sciences	II/III
Avigan (favipiravir/avifavir/favilavir)	Antiviral	RNA dependent RNA polymerase inhibition	Fujifilm Toyama Chemical (as Avigan); Zhejiang Hisun Pharmaceutical	II/III
Dexamethasone (many brands and generics)	Glucocorticoid	Reduces the inflammation associated with cytokine release syndrome by inhibiting pro-inflammatory gene	Multiple	II/III
Lagevrio (Molnupiravir)	Antiviral	RNA dependent RNA polymerase inhibition	Ridgeback Biotherapeutics; Merck	III
Olumiant, Baricinix (baricitinib)	JAK inhibitor	Receptor mediated endocytosis inhibition Suppress disease progression	Eli Lilly/NIAID	III/IV
Regkirona (regdanvimab, CT-P59)	Monoclonal antibody	Targets spike protein of SARS-CoV-2	Celltrion	III
Xevudy (Sotrovimab) also known as (VIR-7831, GSK4182136)	Monoclonal antibody	Targets spike protein of SARS-CoV-2	GSK, Vir Biotechnology	II/III
Ronapreve (Casirivimab/imdevimab) (REGEN-COV, REGN-COV2)	Antibody cocktail	Targets spike protein of SARS-CoV-2	Regeneron; Cipla; Roche	II/III
Amubarvimab and romlusevimab (formerly BRII-196 and BRII-198)	Monoclonal antibody	Targets spike protein of SARS-CoV-2	Brii Biosciences Limited; NIAID	III
Actemra/RoActemra (Tocilizumab)	Humanized monoclonal antibody	IL-6 receptor agonist	Roche	III
Kineret (anakinra)	Interleukin-1 receptor antagonist	It works by blocking the activity of interleukin, a substance in the body that causes inflammation.	Sobi, Inc.	Various
Paxlovid (Nirmatrelvir + ritonavir)	Antiviral	a protease inhibitor Inhibition of virus replication	Pfizer	III
Evusheld (tixagevimab and cilgavimab; AZD7442)	Monoclonal antibody	Targets the spike protein of SARS-CoV-2	AstraZeneca; Vanderbilt University Medical Cente; BARDA	III
Remicade (infliximab)	Monoclonal antibody	Targets the spike protein of SARS-CoV-2	UHB; Birmingham National Institute for Health Research Biomedical Research Centre (NIHR BRC); NCATS; BARDA	II/III
Pepcid (famotidine)	histamine H_2 receptor antagonist	Reduces acid secretion in the stomach by blocking the action of histamine on the parietal cells.	Yamanouchi Pharmaceutical Co.; J&J; Merck; US Department of Defense	III
Bamlanivimab + etesevimab	Monoclonal antibodies	Targets the spike protein of SARS-CoV-2	Lilly; Junshi Biosciences; OWS	II/III
Proxalutamide (GT-0918)	Nonsteroidal antiandrogen	Second generation AR antagonist	Suzhou Kintor Pharmaceutical Inc.	III
Bucillamine	Antirheumatic agent	Loose the thick mucus in individuals with chronic bronchopulmonary disorders like pneumonia and bronchitis	Revive Therapeutics ltd.	III
Orencia (abatacept)	Selective costimulation modulator	Binds to the CD80 and CD86, thereby blocking interaction with CD28 which on further leads to inhibition of *T*-cell (*T*-lymphocyte) activation	Bristol Myers Squibb; National Center for Advancing Translational Science (NCATS); BARDA	III
Ivermectin	Antihelmintic	Targets the Importin α (IMP α) component of the IMP α/β1 heterodimer and prevents interaction with IMP β1, resultantly blocking the nuclear transport of viral proteins	Various	II/III
Gleevec/Glivec (Imatinib)	Tyrosine kinase inhibitor	Works by binding close to the ATP binding site of bcr-abl which further results in inhibition of enzyme activity of protien	Novartis	II/III
AGD20	Monoclonal antibody	Targeting the spike protein of SARS-CoV-2	Adagio Therapeutics, Inc.	II/III
SNG001	interferon-beta-1a	Activates multiple (~100) immunomodulatory and antiviral proteins by binding to type I interferon receptors	Synairgen	II/III
Opaganib	Sphingosine kinase 2 (SK2) inhibitor	Targets the SK2 human host cell factor	RedHill Biopharma	II/III
Xocova (ensitrelvir, S-217622)	Oral antiviral	3C-like protease inhibitor Prevents viral transcription and replication	Shionogi, Hokkaido University	III
Galidesivir	Antiviral	Prevents viral transcription and replication by inhibition of RNA dependent RNA polymerase	BioCryst Pharmaceuticals; NIAID	Ib
Vascepa	Lipid-lowering agent	Reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion	Amarin Pharma Inc.; Estudios Clínicos Latino América; Kaiser Permanente; Canadian Medical and Surgical Knowledge Translation Research Group	II/III/IV
Pyramax (artesunate/pyronaridine)	Antimalarial	Decrease the viral load by inhibiting the formation of β-haematin	Shin Poong Pharmaceutical Co., ltd	II/III
Colchicine (Mitigare, Colcrys)	Antigout agent	Modulates multiple pro- and anti-inflammatory pathways in turn stops cytokine storm	NHLBI; Bill and Melinda Gates Foundation; Government of Quebec; Montreal Heart Institute	II/III
Metformin (Glucophage, Glumetza, Riomet)	Biguanide	It improves the microbiome and can contribute to better mucosal health and overall lowered inflammation.	University of Minnesota	II/III
Lenzilumab	Monoclonal antibody	Targeting the spike protein of SARS-CoV-2	NIAID; Humanigen; Catalent	III
Heparin (UF and LMW)	Anticoagulant	Prevents the formation of blood clots	NHLB under Operation Warp Speed; University of Pittsburgh	II/III/IV
Mavrilimumab	Monoclonal antibody	Targeting the spike protein of SARS-CoV-2	Kiniksa Pharmaceuticals; The Cleveland Clinic	II
Kaletra (lopinavir-ritonavir)	HIV protease inhibitor		AbbVie	II/IV

(*continued on next page*)

Table 3 (*continued*)

Trade Name (Generic Name)	Medication class	Treatment strategy/Mechanism of action	Researcher/Developer	Trial Phase
		Inhibits the HIV protease enzyme by forming an inhibitor-enzyme complex thereby preventing cleavage of the gag-pol polyproteins.		
Kevzara (sarilumab)	IL-6 receptor agonist	Binds to IL-6 receptors by inhibiting IL-6–mediated signaling. The IL-6 cytokine plays a role in the body's inflammatory process and response.	Sanofi; Regeneron	II/III
Ensovibep (MP0420)	designed ankyrin repeat protein (DARPin) Antiviral	Binds to three different locations on the spike protein on the surface of SARS-CoV-2.	Molecular Partners; Novartis	II/III
STI-5656 (abivertinib)	Tyrosine kinase inhibitor	Selectively targets both mutant forms of the epidermal growth factor receptor (EGFR) and Bruton's tyrosine kinase (BTK)	Sorrento Therapeutics	II
Convalescent plasma	Immunoglobulin	Direct neutralization of the virus, control of an overactive immune system (i.e., cytokine storm, Th1/Th17 ratio, complement activation) and immunomodulation of a hypercoagulable state.	Multiple	I/II
TEMPOL (4-Hydroxy-TEMPO)	Oral antiviral/ antioxidant	Prevents cytokine storms, inactive free radicals and reduce clumping of platelets	Adamis Pharmaceuticals Corporation; NIH/ Eunice Kennedy Shriver National Institute of Child Health and Human Development	II/III
Artesunate	Artemisinin derivative acts as antimalarial	Metabolized to DHA, which generates free radicals to inhibit normal function of Plasmodium parasites.	Liu Xu	II

Source: Regulatory Affairs Professional Society. Craven J, Therapeutic Tracker. https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-therapeutics-tracker.[99]

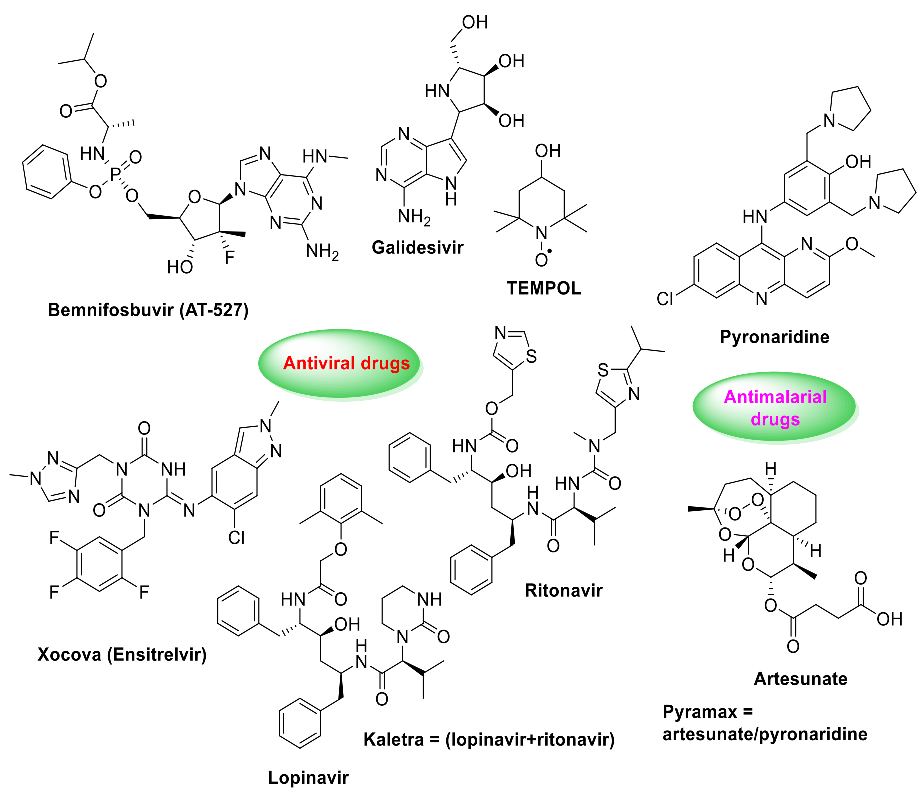

Fig. 4. Some of the antiviral and antimalarial drugs under investigation for COVID-19.

mainly by affecting the respiratory system with consequent maladjusted immune functions and overactive inflammatory system originating multiple organ failure. The studies to understand the virus pathogenesis are ongoing and the genomic characterization has assisted in unfolding various aspects of SARS-CoV-2 to some extent. Nevertheless, with constant mutations, development of specific antiviral drugs and vaccines against the virus is still a challenge. Most of the existing drugs and few vaccine candidates have been repurposed to fight COVID-19. With the accelerating research and development, a few vaccines and therapeutics are made available on emergency use. In this review, we have provided a glance at the expeditious research and development that has taken place to fight COVID-19 pandemic. It continues to be a significant health crisis with the recurring emergence of new variants, we believe a broadly neutralizing therapy that might be given for both prevention and treatment will be essential. A key focus in 2022 will be the speedy development of effective vaccine and novel therapeutic strategies against emergent as well as the current SARS-CoV-2 variants. It is possible that SARS-CoV-2 may not be the last human coronavirus emerging from animals. Therefore, close monitoring of virus populations to understand their replication mechanism early on and to

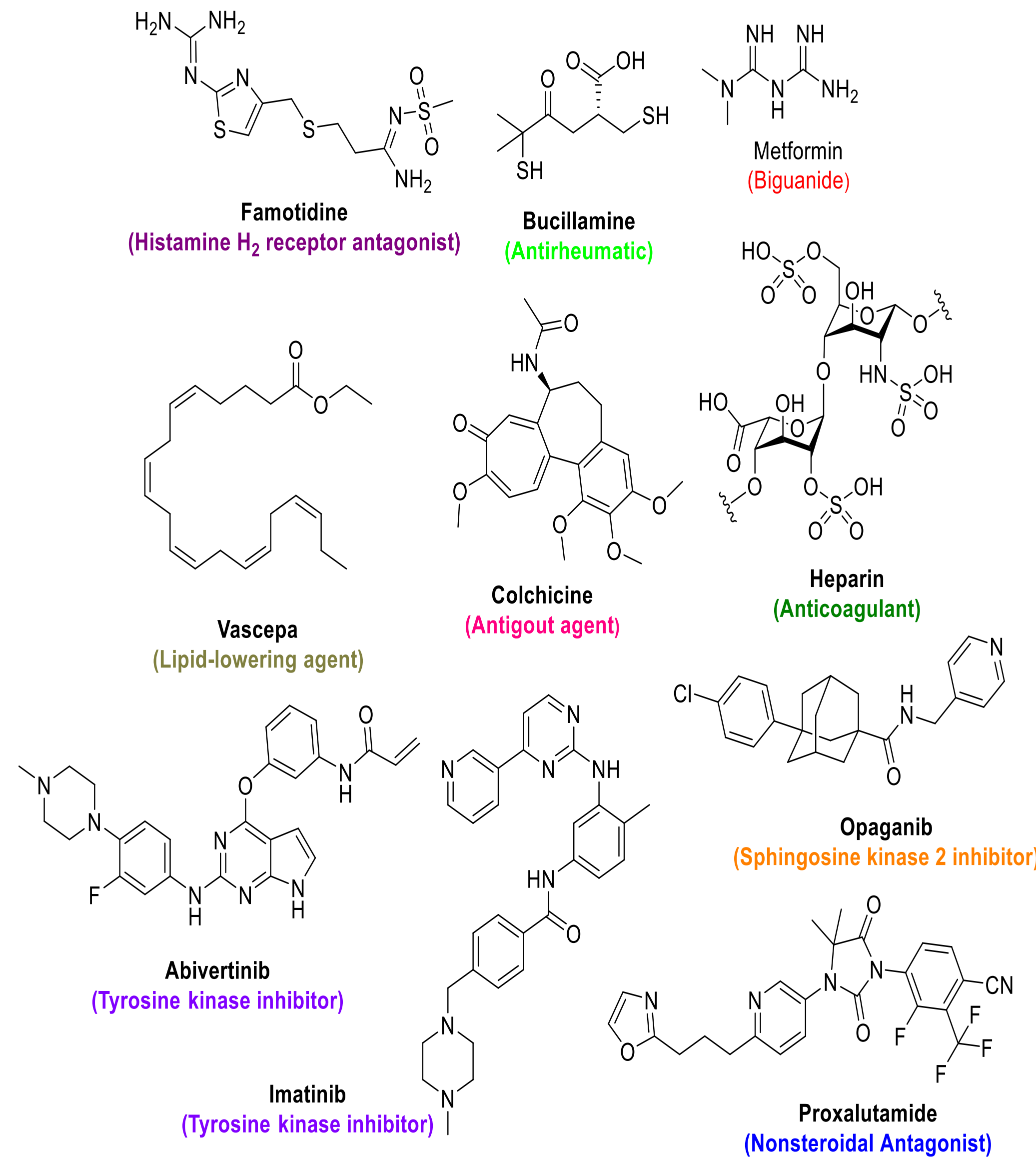

Fig. 5. Various repurposed drugs under investigation for COVID-19.

investigate the druggable targets are the important optimistic strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Author contributions

These authors contributed equally.

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