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Review Article

Research, Development and Application of COVID-19 Vaccines: Progress, Challenges, and Prospects

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Abstract

The pandemic of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become the most formidable challenge to humanity in this century. The research and development of COVID-19 vaccines, which are believed to be the most effective tools to control this pandemic, has been a topic of critical importance, not only in the field of biomedicine but also in the entire international community. Here, we introduce the concepts related to COVID-19 vaccines, including their development process, clinical trials, designs and types. On this basis, we further summarize the research, development, and application of vaccines in different regions of the world, and describe the vaccines according to their respective regions. Finally, we discuss existing and emerging challenges, strategies and prospects of in the development and application of COVID-19 vaccines.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), occurred in China at the end of 2019 and has become a worldwide pandemic.[1] By March 5, 2021, there were approximately 110 million cumulative cases, with more than 2.4 million deaths globally.[2] Because of the enormous public health, economic, and social impacts of this serious contagious disease, there is an urgent need for safe and effective vaccines to control this pandemic. Speeding up the research, development, and application of COVID-19 vaccines is not only an imminent biomedical issue, but also an essential issue relevant to the economy, social stability, and even politics.[3,4] Therefore, the whole development process of COVID-19 vaccines has been reduced from the conventional 10–15 years to about 1 year,[5] hoping the widespread immunity acquisition from vaccines normalizes the lifestyle of people worldwide.[6]

As of March 5, 2021, according to the data released by the World Health Organization (WHO), 78 candidate vaccines have entered clinical trials, and an additional 182 candidate vaccines have been under pre-clinical investigation.[7] Of the 78 candidates, 21 have been or are being evaluated in phase II/III, III, or IV clinical trials.[7] Moreover, several vaccines have been approved by the authorities of many countries for emergency use in the general population.[8–9] The present review first introduces the general concepts, the categories of COVID-19 vaccines and their underlying mechanisms, then summarizes the progress on the research, development and application of COVID-19 vaccines, and finally provides prospects on the crucial roles of COVID-19 vaccines in preventing and eliminating the disease.

Considerations on COVID-19 vaccine development

Requirement for urgent development of COVID-19 vaccines

The development process of COVID-19 vaccines generally includes vaccine design, preclinical experiments, and phases I, II and III clinical trials.[9] Briefly, preclinical experiments aim to understand whether injection of a vaccine into an animal, such as a

Keywords: SARS-CoV-2; COVID-19; Vaccines; Efficacy; Safety.

Abbreviations: ADE, antibody-dependent enhancement; COVID-19, coronavirus disease 2019; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome-associated coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S protein, spike protein of SARS-CoV-2; VLP, virus-like particle.

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Table 1. Advantages and disadvantages of different types of COVID-19 vaccines

Vaccine type	Advantages	Disadvantages
Inactivated virus[26]	Mature technology and simple preparation	Weak immunogenicity; requirement for multiple immunizations
Attenuated virus[27]	Long-lasting immunity and mature technology	High requirements for storage and transportation; poor safety; toxic reversal risk
Protein subunit[28]	Good safety profile and stability	Weak and short immunity; requirements for adjuvants
Virus-like particle[29]	Induction of humoral and cellular immunity	High requirements for biological fermentation and plasmid purification
Viral vector[30]	Effective induction of humoral and cellular immunity	High requirements for the purity and activity of the viral vector; possibly presenting pre-existing immunity
Nucleic acid (DNA and RNA)[31]	High potency; rapid and cost-efficient development and production	Poor intracellular delivery; potential risk of carcinogenesis for DNA vaccines due to chromosomal integration; poor stability for mRNA vaccines

mouse or monkey, will produce an immune response. Phase I trials involve administering the vaccine candidate to a small number of people (usually fewer than 100) to test its pharmacokinetics, bioavailability, pharmacodynamics and safety, and determine the dose that will activate an adequate immune response.[10] In phase II trials, investigators apply the vaccine to hundreds of people on a representative population to see whether the effects of the vaccine differ among different populations and to further determine the safety, efficacy, vaccination schedule and dose size of the vaccine.[11] In phase III trials, investigators recruit a larger number of people, randomly divide them into the vaccine and placebo groups, and determine whether the vaccine can prevent COVID-19; the safety of the vaccine is further evaluated.[12]

Due to the rapid and widespread transmission of SARS-CoV-2 infection worldwide, there is an urgent need for an expedited development of COVID-19 vaccines.[13] Therefore, combined clinical trials have been designed to accelerate the development of COVID-19 vaccines in phase I/II clinical trials, where hundreds of people are tested, and phase II/III or III trials, where thousands of people are tested.[14] All clinical trial data on the vaccine development need to be reviewed by the regulatory authority of each country to decide whether or not the vaccine is to be approved for use or emergency use in the population. Currently, a few COVID-19 vaccines have been authorized for emergency use in some countries.[15,16]

Vaccine design and underlying mechanisms

IgM and IgG antibodies to SARS-CoV-2 are detectable within 1–2 weeks after the onset of COVID-19 symptoms in most infected individuals.[17] It has been reported that there are high levels of neutralizing antibodies in convalescent individuals,[18] which are associated with T cell responses, particularly those of $CD4^+$ T cells[19] although the associations of neutralizing antibodies with antigen-specific T cells, disease severity, and clinical outcomes remain to be elucidated. According to current immunological knowledge and principles, as well as previous data derived from the similar vaccine platforms, it is assumed that parenteral COVID-19 vaccines that are able to induce a robust and durable response involving both neutralizing antibodies and T cells can provide a significant extent of protection.[5]

To design a COVID-19 vaccine, the first consideration is the selection of the target antigens/immunogens of SARS-CoV-2. The structural proteins of SARS-CoV-2 include spike (S), nucleocapsid (N), membrane (M), and envelope (E) proteins. It has been shown that only antibodies directed to the S protein can neutralize SARS-CoV virus,[20] suggesting that only antibodies directed against the S protein of SARS-CoV-2 virus, mainly the receptor-binding domain of the S1 subunit, can neutralize the virus and prevent the virus from infecting the human body. The second consideration is the way that the vaccine is inoculated, which affects its immune protection to the human body.[21,22] At present, most vaccines are administered through the parenteral routes, such as intramuscular injection. The protective IgG antibodies induced by this vaccination can appear on the respiratory mucosa, but cannot induce sufficient mucosal IgA or the tissue-settling T-cells in the lungs.[23] In contrast, the respiratory tract mucosal administration method can more effectively induce antibodies and tissue colonizing T cells.[24,25]

In general, there are six categories of COVID-19 vaccines, namely, inactivated (killed) virus,[26] live attenuated (weakened) virus,[27] protein subunit,[28] virus-like particle (VLP),[29] virus vector (non-replicating viral vector or replicating viral vector),[30] and nucleic acid (DNA or RNA) (Table 1, Fig. 1).[26,31,32] Of these types, inactivated or attenuated virus vaccines belong to the first generation vaccines, protein subunit and VLP vaccines belong to the second generation vaccines, and virus vector and nucleic acid vaccines belong to the third generation vaccines (Fig. 1).[33,27]

An inactivated vaccine refers to the virus that is cultured and killed *in vitro* and used to stimulate the body to produce antibodies. The technology of inactivated vaccine is well established, and its preparation is simple, but its immunogenicity is weak, and thus multiple immunizations are required (Fig. 1a).[26] A live attenuated vaccine mainly refers to a virus with weakened pathogenic virulence through artificially induced mutation but still with the ability to replicate and maintain good immunogenicity (Fig. 1b).[27] However, such vaccines have the potential to recover their virulence, and thus are less commonly considered due to this drawback. Protein subunit vaccines use pieces of the pathogen, usually a fragment of proteins. It has advantage of decreasing side effects, but it may suffer from poor immunogenicity (Fig. 1c).[28] To overcome this weakness, adjuvants are often used to boost the immune response. A VLP vaccine represents a specific subunit vaccine that mimics the structure of authentic virus particle, with dramatic effectiveness (Fig. 1d).[29] A vector vaccine is generally constructed from a carrier virus, such as an adenovirus or a pox virus, and engineered to carry a relevant gene that encodes a target antigen (Fig. 1e).[30] A nucleic acid vaccine refers to a gene encoding a target antigen of the virus (*e.g.* S protein of SARS-Cov-2), which is directly injected into the human body and subsequently induces human cells to produce the target antigen (*e.g.,* the S protein of SARS-Cov-2), which in turn, stimulates the human body to produce antibodies against the virus (Fig. 1f).[31] A

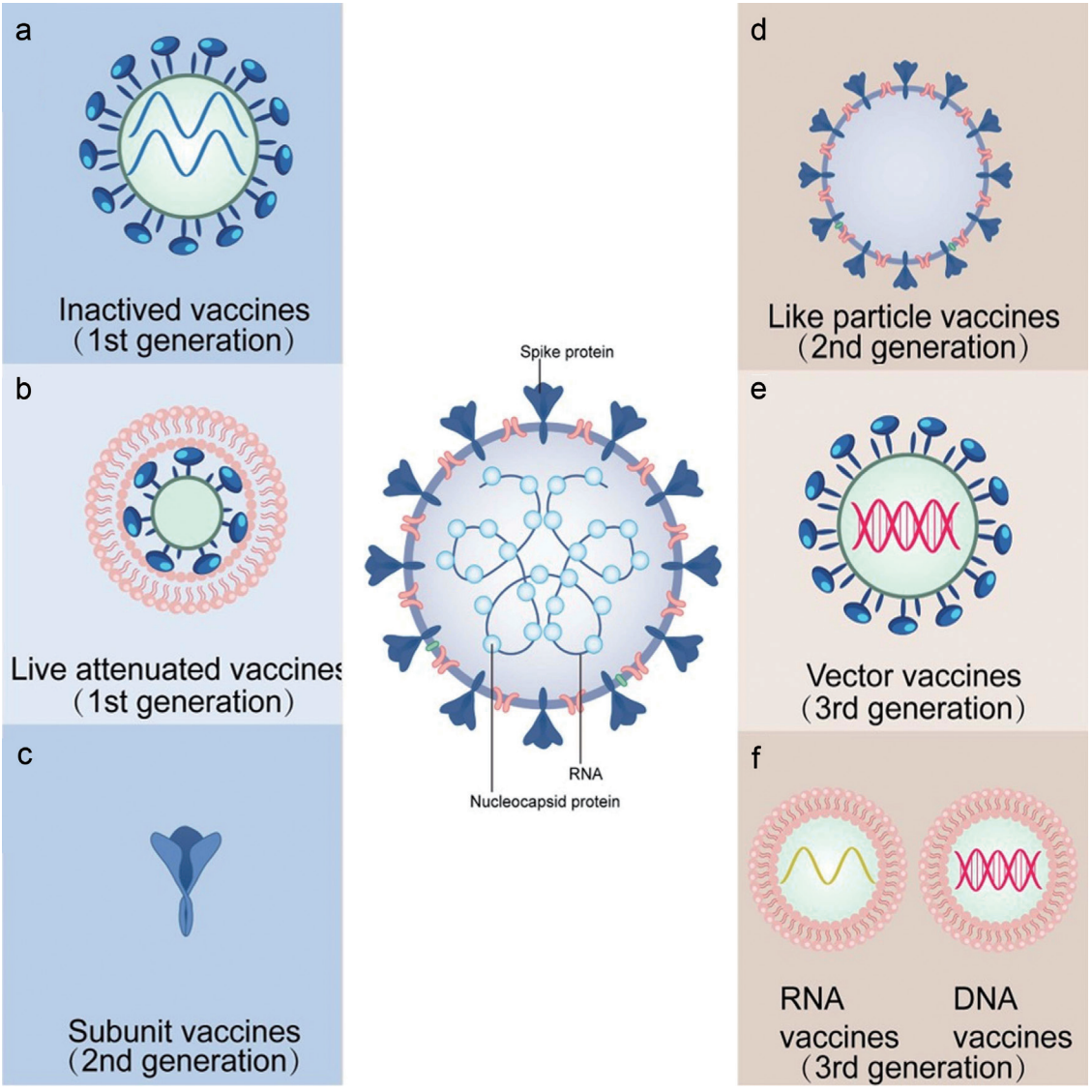

Fig. 1. Illustrations for the six types of COVID-19 vaccines, including inactivated vaccines (a), live attenuated vaccines (b), subunit vaccines (c), virus-like particle vaccines (d), vector vaccine (e), and nucleic acid (DNA or RNA) vaccines (f). The structure of SARS-COV-2 virus is composed of an RNA molecule, surrounded by a series of structural and functional proteins including S protein, N protein, E protein, and M protein. The S protein of SARS-CoV-2, which plays a key role in the receptor recognition and cell membrane fusion process, is the main protein used as a target in COVID-19 vaccine development. In structural biology, a protein subunit is a single protein molecule that assembles with other protein molecules to form a protein complex. Adapted, with modification, from van Riel D and de Wit E. Nat Mater 2020;19(8):810–812.[32]

nucleic acid vaccine can be developed in a short period of time, and its immunogenicity is good. However, it is easily degraded, and its stability is poor. The advantages and disadvantages of the different types of vaccines are summarized in Table 1.[26–31]

Research, development and application of COVID-19 vaccines

COVID-19 vaccines developed in different continents

Currently, at least 78 vaccines are evaluated in the clinical trial phases worldwide.[7] According to the country where the headquarter of the research and development unit is located, these vaccines were either jointly developed by multiple countries, accounting for 13 vaccines, or independently developed by a single country, accounting for 65 vaccines (Table 2).

In Asia and Oceania, countries, where COVID-19 vaccines are currently being developed in clinical trials, include China, South Korea, India, Israel, Japan, Kazakhstan, and Thailand, Turkey, Vietnam and Iran.[7] Among them, China has 15 vaccines, India and South Korea each have three vaccines, Japan has two vaccines, and Israel, Kazakhstan, Thailand, Turkey, Vietnam, and Iran each have one vaccine. Among these vaccines, there are ten inactivated vaccines, six protein subunit vaccines, seven viral vector vaccines, and six nucleic acid vaccines (Table 2).[7,34–36]

In Europe, countries, where COVID-19 vaccines are currently

Table 2. COVID-I9 vaccines developed in different countries as of March 5, 2021

Continent/Country	Primary developers or research institutions or sponsors	Vaccine platform description	Development stage (refs.)
Multiple countries			
USA + India	Codagenix/Serum Institute of India	Live attenuated virus	Phase I[7,25]
Netherlands + USA	University Medical Center Groningen + Akston Biosciences Inc.	Protein subunit	Phase I/II
Australia + South Korea	Vaxine Pty Ltd. + Medytox	Protein subunit	Phase I[7,27]
China + England + USA	Clover Biopharmaceuticals Inc./GSK/Dynavax	Protein subunit	Phase II/III
China + USA	Medigen Vaccine Biologics + Dynavax + NIAID	Protein subunit	Phase I[28]
France + England	Sanofi Pasteur + GlaxoSmithKline	Protein subunit	Phase I/II
India + Australia	Serum Institute of India + Accelagen Pty	Virus like particle	Phase I/II
Italy + Germany + Belgium	ReiThera + Leukocare + Univercells	Viral vector (Non-replicating)	Phase I[7,29]
USA + Austria + France	Merck & Co. + Themis + Sharp & Dohme + Institute Pasteur + University of Pittsburgh	Viral vector (Replicating)	Phase I/II
USA + Indonesia	Aivita Biomedical, Inc. NIHRD, Ministry of Health Republic of Indonesia	Viral vector (Replicating) + APC	Phase I/II
USA + South Korea + China	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	DNA based vaccine	Phase II/III
USA + Germany	Pfizer/BioNTech + Fosun Pharma	RNA based vaccine	Phase IV[30]
USA + Thailand	Mahidol University; The Government Pharmaceutical Organization (GPO); Icahn School of Medicine at Mount Sinai	Viral vector (Replicating)	Phase I/II
Asia & Oceania			
China	Sinovac Research and Development Co., Ltd	Inactivated virus	Phase IV
China	Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products	Inactivated virus	Phase III[7,31]
China	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	Inactivated virus	Phase III
China	Institute of Medical Biology + Chinese Academy of Medical Sciences	Inactivated virus	Phase III
China	Shenzhen Kangtai Biological Products Co., Ltd.	Inactivated virus	Phase II
China	Beijing Minhai Biotechnology Co	Inactivated virus	Phase II
China	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Protein subunit	Phase III
China	West China Hospital + Sichuan University	Protein subunit	Phase II
China	Adimmune Corporation	Protein subunit	Phase I
China	CanSino Biological Inc./Beijing Institute of Biotechnology	Viral vector (Non-replicating)	Phase III
China	Jiangsu Provincial Center for Disease Prevention and Control	Viral vector (Replicating)	Phase II
China	Shenzhen Geno-Immune Medical Institute	Viral vector (Replicating) + APC	Phase I[32]
China	University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy	Viral vector (Replicating)	Phase II
China	Shenzhen Geno-Immune Medical Institute	Viral vector (Non-replicating) + APC	Phase I/II

Table 2. COVID-I9 vaccines developed in different countries as of March 5, 2021 - *(continued)*

Continent/Country	Primary developers or research institutions or sponsors	Vaccine platform description	Development stage (refs.)
China	Shulan (Hangzhou) Hospital + Center for Disease Control and Prevention of Guangxi Zhuang Autonomous Region	RNA based vaccine	Phase I
India	Bharat Biotech International Limited	Inactivated virus	Phase III
India	Biological E Limited	Protein subunit	Phase I/II
India	Bharat Biotech International Limited		
India	Cadila Healthcare Ltd.	DNA based vaccine	Phase III
Israel	Israel Institute for Biological Research	Viral vector (Replicating)	Phase I/II
Japan	Shionogi	Protein subunit	Phase I/II
Japan	AnGes + Takara Bio + Osaka University	DNA based vaccine	Phase II/III
Kazakhstan	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Inactivated virus	Phase III
South Korea	SK Bioscience Co., Ltd.	Protein subunit	Phase I
South Korea	Cellid Co., Ltd.	Viral vector (Replicating)	Phase I/II
South Korea	GeneOne Life Science, Inc.	DNA based vaccine	Phase I/II
South Korea	Genexine Consortium	DNA based vaccine	Phase I/II
Thailand	Chulalongkorn University	RNA based vaccine	Phase I
Turkey	Erciyes University	Inactivated virus	Phase I
Vietnam	Nanogen Pharmaceutical Biotechnology	Protein subunit	Phase I/II
Iran	Shifa Pharmed Industrial Co	Inactivated virus	Phase I
Australia	The University of Queensland	Protein subunit	Phase I
Australia	University of Sydney, Bionet Co., Ltd Technovalia	DNA based vaccine	Phase I
Europe			
UK	Valneva, National Institute for Health Research, United Kingdom	Inactivated Virus	Phase I/II
UK	AstraZeneca + University of Oxford	Viral vector (Non-replicating)	Phase IV[33]
UK	Imperial College London	RNA based vaccine	Phase I
UK	GlaxoSmithKline	RNA based vaccine	Phase I
Germany	University Hospital Tuebingen	Protein subunit	Phase I
Germany	University of Munich (Ludwig-Maximilians)	Viral vector (Non-replicating)	Phase I
Germany	CureVac AG	RNA based vaccine	Phase III
Russia	FSRI SRC VB VECTOR	Protein subunit	Phase I/II
Russia	Gamaleya Research Institute of Epidemiology and Microbiology; Health Ministry of the Russian Federation	Viral vector (Non-replicating)	Phase III

Table 2. COVID-I9 vaccines developed in different countries as of March 5, 2021 - *(continued)*

Continent/Country	Primary developers or research institutions or sponsors	Vaccine platform description	Development stage (refs.)
Russia	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Protein subunit	Phase I/II
Italy	Takis + Rottapharm Biotech	DNA based vaccine	Phase I/II
North America			
USA	Novavax	Protein subunit	Phase III
USA	Kentucky Bioprocessing Inc.	Protein subunit	Phase I/II
USA	COVAXX + United Biomedical Inc	Protein subunit	Phase II/III
USA	VBI Vaccines Inc.	Virus like particle	Phase I/II
USA	Janssen Pharmaceutical	Viral vector (Non-replicating)	Phase III
USA	Vaxart	Viral vector (Non-replicating)	Phase I
USA	ImmunityBio, Inc.	Viral vector (Non-replicating)	Phase I
USA	City of Hope Medical Center + National Cancer Institute	Viral vector (Non-replicating)	Phase I
USA	Altimmune, Inc.	Viral vector (Non-replicating)	Phase I
USA	Gritstone Oncology	Viral vector (Non-replicating)	Phase I
USA	Providence Health & Services	DNA based vaccine	Phase I
USA	Moderna + NIAID	RNA based vaccine	Phase IV[34,35]
USA	Arcturus Therapeutics	RNA based vaccine	Phase II
Canada	Symvivo Corporation	DNA based vaccine	Phase I
Canada	Providence Therapeutics	RNA based vaccine	Phase I
Canada	University of Saskatchewan	Protein subunit	Phase I/II
Cuba	Instituto Finlay de Vacunas	Protein subunit	Phase II
Cuba	CIGB	Protein subunit	Phase I/II
Cuba	CIGB	Protein subunit	Phase I/II
Canada	Medicago Inc.	Virus like particle	Phase II/III[7,36]
Canada	Entos Pharmaceuticals Inc.	DNA based vaccine	Phase I

USA, the United States of America; UK, The United Kingdom of Great Britain; FSRI SRC VB VECTOR, State Research Center of Virology and Biotechnology VECTOR of the Federal Service for Surveillance in Consumer Rights Protection and Human Well-being; NIHRD, National Institute of Health Research and Development; NIAID, National Institute of Allergy and Infectious Diseases; CIGB, Center for Genetic Engineering and Biotechnology; APC, antigen presenting cells. According to the country and region where the headquarters of the vaccine research and development unit is located, we divide these vaccines into two categories, including those jointly participated by multiple countries, and those independently developed by a single country. Data in the table are derived from World Health Organization website (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines), COVIDI9 vaccine tracker (https://www.raps.org/news-and-articles/news-articles/II0II0/III/covid-I9-vaccine-tracker) and corresponding refences cited in the table.

being developed in clinical trials, include the United Kingdom of Great Britain (UK), Germany, and Russia.[7] Among them, there are three vaccines in the UK, three vaccines in Germany, and two in Russia. Among these vaccines, there are one inactivated vaccine, two protein subunit vaccines, three viral vector vaccines, and two nucleic acid vaccines (Table 2).[7]

In North America, countries, where COVID-19 vaccines are currently being developed in clinical trials, include the United States of America (USA), Canada and Cuba.[7] Among them, the USA has 11vaccines, and Canada and Cuba each have three vaccines. Among these vaccines, there are six protein subunit vaccines, one virus-like particle vaccine, five viral vector vaccines, and five nucleic acid vaccines (Table 2).[7]

COVID-19 vaccines developed in phase II/III, III or IV clinical trials

As of March 5, 2021, 21 COVID-19 vaccines worldwide have entered the phase II/III, III or IV of clinical trials according to data released by WHO.[7] These include six inactivated vaccines, four viral vector vaccines, four protein subunit vaccines, one VLP vaccine, and six nucleic acid vaccines (Table 3).[7] Most vaccines require two doses; three may require one dose only, and the one developed by Cadila Healthcare Limited (Ahmedabad, India) requires three doses. These vaccines provide a pipeline for the potential approval by the regulatory authorities of the different countries for emergency use in the general population as more clinical data become publicly available. For example, on January 28, 2021, Novavax (Gaithersburg, USA) announced that its recombinant protein COVID-19 vaccine, NVX-CoV2373, reached the primary endpoint in a phase III clinical trial conducted in the UK, with a vaccine effectiveness of 89.3%.[37] This study evaluated the effectiveness of the vaccine during the period when SARS-Cov-2 infection was spread quickly, with the emergence of new variants of the virus in the country. NVX-CoV2373 is stable under refrigerated conditions at 2–8 °C and can be distributed using existing vaccine supply chain channels.[38] This vaccine is currently undergoing multiple phase II and III clinical trials in South Africa, the UK, the USA and Mexico.

COVID-19 vaccines approved for application in the general population

To our knowledge, at least nine vaccines, including four inactivated vaccines, one protein subunit vaccine, two viral vector vaccines, and two nucleic acid vaccines, have been authored or approved by authorities of many countries for emergency use in general population at present (Table 4).[8]

The four approved inactivated vaccines were developed by Wuhan Institute of Biological Products (Wuhan, China), Beijing Institute of Biological Products (Beijing, China), Sinovac (Beijing, China) and Bharat Biotech (Hyderabad, India), respectively.[8] On December 30, 2020, the COVID-19 vaccine, BBIBP-CorV, from Beijing Institute of Biological Products was approved by the National Medical Products Administration (NMPA) for marketing in China.[39] This vaccine is reportedly to provide 79.3% protection against the coronavirus which meets the standards of the WHO and NMPA.[39] Adverse events, which are mainly local pain and induration, have been reported in a proportion of people who have been inoculated with this vaccine. Mild fever occurs in less than 0.1% of cases, and the incidence of more severe adverse events such as allergic reactions is about two per million. These adverse events are improved or disappear over time with or without treatment.[39]

The approved protein subunit vaccine, EpiVacCorona, was developed by the Federal Budgetary Research Institution State Research Center of Virology and Biotechnology (Koltsovo, Russia). The unique feature of EpiVacCorona is that it contains the fragment of synthetic peptide antigen of the virus. According to consumer health watchdog, EpiVacCorona has proved to be 100% effective in early-stage trials.[40]

The two approved viral vector vaccines, AZD1222 (formerly ChAdOx1 nCoV-19) and Sputnik V (or Gam-Covid-Vac), were developed by AstraZeneca (Cambridge, UK), in collaboration with University of Oxford, UK, and Gamaleya Research Institute of Epidemiology and Microbiology (Moscow, Russia), respectively.[8] An interim analysis of four ongoing randomized controlled trials in Brazil, South Africa, and the UK showed that AZD1222 had an acceptable safety profile and was efficacious against symptomatic COVID-19.[41] So far, AZD1222, or Covishield (the Serum Institute of India version), has been authorized for emergence use in the UK, India, Argentina, the Dominican Republic, El Salvador, Mexico, and Morocco,[7] and Sputnik V was approved for emergence use in Russia, Belarus, Argentina, Guinea (experimental use), Bolivia, Algeria, Palestine, Venezuela, Paraguay, Turkmenistan, Hungary, UAE, and Serbia.[42]

The two approved mRNA vaccines, mRNA-1273 and BNT162b2, were developed by Moderna (Cambridge, MA, USA) and Pfizer (New York, USA) in collaboration with BioNTech's (Mainz, Germany) respectively.[43,44] It has been reported that the two vaccines have efficacy rates of 95.0% and 94.1%, respectively.[44,45] The local reactions to mRNA-1273 vaccination are mild; however, moderate-to-severe systemic adverse events, such as fatigue, myalgia, arthralgia, and headache, have been noted in approximately 50% of recipients of mRNA-1273 after the second dose. These adverse events are transient; they usually start about 15 hours after vaccination and are resolved on day 2 without severe consequences.[46] The preliminary data on the safety of BNT162b2 have also been reported. Among the 1,893,360 first doses of BNT162b2 administered from December 14 to 23, 2020 in the USA, 21 case reports submitted to Vaccine Adverse Event Reporting System (VAERS) met the Brighton Collaboration case definition criteria for anaphylaxis, corresponding to an estimated rate of 11.1 cases per million doses administered.[47] Four (19%) of these cases were hospitalized, with three being treated in the intensive care unit, and 17 (81%) were treated in the emergency department. In addition, 20 (95%) were discharged or had recovered at the time of the report to VAERS. There were no deaths from anaphylaxis.[47] Therefore, both vaccines appear to be safe without serious adverse events; however, considering that mRNA vaccines are relatively new, their safety must be closely monitored in phase IV clinical trials in the future (Table 3).[48] Currently, mRNA-1273 has also been approved in the USA, Canada, Israel, Saudi Arabia, Switzerland, the UK, the European Union, Faroe Islands, Greenland, Iceland, and Norway.[7,41] BNT162b2 has been approved for emergency use in the USA, the UK, Bahrain, Canada, Mexico, Singapore, Costa Rica, Ecuador, Jordan, Panama, Chile, Oman, Saudi Arabia, *etc.*[8,42]

Challenges and strategies in vaccine development and application

There are challenges that need to be overcome in the development of COVID-19 vaccines. The first one is the clinical trial design. In a conventional clinical trial, an accurate estimate of the background incidence rate of the primary endpoint in the placebo

Table 3. COVID-19 vaccines developed in phase II/III, III and IV clinical trials as of March 5, 2021

Vaccine type	Vaccine name*	Dose number	Dosing schedule	Primary developers or research institutions or sponsors	Registration number	Endpoint
Inactivated virus#	Coronavac (PiCo Vacc)	2	Day 0 + 14	Sinovac Research and Development Co., Ltd	NCT04456595[37]	E1, E2
Inactivated virus#	Vero cell	2	Day 0 + 21	Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products	ChiCTR2000034780	E1, E2
Inactivated virus#	BBIBP-CorV	2	Day 0 + 21	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	NCT04560881	E1, E2
Inactivated virus	–	2	Day 0 + 28	Institute of Medical Biology + Chinese Academy of Medical Sciences	NCT04659239	E1, E2
Inactivated virus	QazCovid-in® - COVID-19 inactivated vaccine	2	Day 0 + 21	Research Institute for Biological Safety Problems, Rep of Kazakhstan	NCT04691908	E1, E2
Inactivated virus#	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)	2	Day 0 + 14	Bharat Biotech International Limited	NCT04641481; CTRI/2020/11/028976	E1, E2
Protein subunit	Recombinant SARS-CoV-2 vaccine (CHO Cell)	2–3	Day 0 + 28 or Day 0 + 28 + 56	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	NCT04646590[38]	E1, E2
Protein subunit	BBV152 (Whole-Virion Inactivated SARS-CoV-2 Vaccine)	2	Day 0 + 21	Clover Biopharmaceuticals Inc./ GlaxoSmithKline/Dynavax	NCT04672395**	E1, E2
Protein subunit	UB-612 (Multitope peptide based S1-RBD-protein based vaccine)	2	Day 0 + 28	COVAXX + United Biomedical Inc	NCT04683224**	E1, E2
Protein subunit	NVX-CoV2373	2	Day 0 + 21	Novavax	NCT04611802	E1, E2
Viral vector# (Non-replicating)	AZD1222 (ChAdOx1 nCoV-19, Covishield)	1–2	Day 0 + 28	AstraZeneca + University of Oxford	NCT04400838**, ISRCTN89951424	E2
Viral vector (Non-replicating)	Ad5-nCoV	1	Day 0	CanSino Biological Inc./Beijing Institute of Biotechnology	NCT04526990[39]	E1
Viral vector# (Non-replicating)	Sputnik V	2	Day 0 + 21	Gamaleya Research Institute of Epidemiology and Microbiology; Health Ministry of the Russian Federation	NCT04530396	E2
Viral vector (Non-replicating)	Ad26.COV2.S	1–2	Day 0 or Day 0 +56	Johnson & Johnson	NCT04505722	E1, E2
Virus like particle	Coronavirus-Like Particle COVID-19 (CoVLP)	2	Day 0 + 21	Medicago Inc.	NCT04636697**	E1, E2
RNA based vaccine#	mRNA-1273 (Moderna COVID 19 Vaccine)#	2	Day 0 + 28	Moderna + NIAID	NCT04649151**, NCT04470427	E1, E2
RNA based vaccine#	BNT162b2 (Comirnaty)#	2	Day 0 + 21	Pfizer/BioNTech + Fosun Pharma	NCT04368728**	E1, E2
RNA based vaccine	CVnCoV Vaccine	2	Day 0 + 28	CureVac AG	NCT04652102**, NCT04674189	E1, E2

Table 3. COVID-19 vaccines developed in phase II/III, III and IV clinical trials as of March 5, 2021 - *(continued)*

Vaccine type	Vaccine name*	Dose number	Dosing schedule	Primary developers or research institutions or sponsors	Registration number	Endpoint
DNA based vaccine	INO-4800+electroporation	2	Day 0 + 28	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	NCT04642638**	E1, E2
DNA based vaccine	AG0301-COVID19	2	Day 0 + 14	AnGes + Takara Bio + Osaka University	NCT04655625**	E1, E2
DNA based vaccine	nCov vaccine	3	Day 0 + 28 + 56	Cadila Healthcare Ltd.	CTRI/2020/07/026352	E1, E2

S1-RBD, t the receptor binding domain (RBD) of the S1 subunit of S protein; Sinopharm, China National Pharmaceutical NIAID, Group; National Institute of Allergy and Infectious Diseases; E1, efficacy for prevention of SARS-CoV-2 infection; E2, safety and immunogenicity of a booster dose; NA, not available. *, currently used or generic name with former, brand, or any alternative name in parentheses; **, phase II/III trials; #, vaccines approved for emergence use; –, no name or name not publicly disclosed. Data in the table are derived from World Health Organization website (https://www.who.int/docs/default-source/blue-print/20201217-novel-coronavirus_landscape_covid-19.xlsx.zip?sfvrsn=a5dc3b8d_34&download=true), COVID19 vaccine tracker (https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker).

Table 4. COVID-19 vaccines authorized/approved for emergence use as of February 12, 2021[8]

Name*	Vaccine Type	Developer/sponsor	Country of Origin	Authorization/Approval
Vero cell	Inactivated vaccine	Wuhan Institute of Biological Products; Sinopharm	China	China
BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; Sinopharm	China	China, Bahrain, United Arab Emirates, Egypt, Jordan, Iraq, Pakistan, Serbia[35]
Covaxin	Inactivated vaccine	Bharat Biotech, ICMR	India	India
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	China, Bolivia, Turkey, Indonesia, Brazil
EpiVacCorona	Protein subunit	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology “Vector”	Russia	Russia[36]
AZD1222 (Covishield)	Non-replicating viral vector	AstraZeneca, University of Oxford, BARDA, OWS	UK	UK, Argentina, El Salvador, Dominican Republic, India, Bangladesh, Mexico, Nepal, Pakistan, Brazil, Saudi Arabia, Iraq, Hungary, Thailand[37]
Sputnik V	Non-replicating viral vector	Gamaleya Research Institute of Epidemiology and Microbiology, Acellena Contract Drug Research and Development	Russia	Russia, Belarus, Argentina, Guinea (experimental use), Bolivia, Algeria, Palestine, Venezuela, Paraguay, Turkmenistan, Hungary, UAE, Serbia[38]
mRNA-1273	mRNA-based vaccine	Moderna, BARDA, NIAID	USA	Canada, Israel, Saudi Arabia, Switzerland, United Kingdom, United States, EU, Faroe Islands, Greenland, Iceland, Norway[37]
Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational	United Kingdom, Bahrain, Canada, Mexico, USA, Singapore, Costa Rica, Ecuador, Jordan, Panama, Chile, Oman, Saudi Arabia, Argentina, Switzerland, Kuwait, EU, Philippines, Pakistan, Colombia, Iraq, Israel, Qatar, Singapore, United Arab Emirates, Faroe Islands, Greenland, Iceland, Malaysia, Norway, Serbia[38]

Sinopharm, China National Pharmaceutical Group; ICMR, The Indian Council of Medical Research BARDA, Biomedical Advanced Research and Development Authority; NIAID, The National Institute of Allergy and Infectious Diseases. *, currently used or generic name with former, brand, or any alternative name in parentheses. Data in the table are derived from World Health Organization website (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines), COVID19 vaccine tracker (https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker) and corresponding refences cited in the table.

arm is required for a robust sample size calculation. However, the rapid changes in the COVID-19 pandemic indicate that predicting the incidence of SARS-Cov-2 infection in the general population without vaccination is challenging, and public health interventions such as masking and social distancing to control the spread of the virus further complicates the prediction. Therefore, investigators should carefully consider appropriate clinical trial design options.[49] For example, an adaptive case-driven trial design, in which the power and precision are not determined by the size of the trial but rather by the overall number of COVID-19 cases identified for the primary endpoint, is worth considering.[49]

The second one is safety, which is a critical issue. The development of an adequate safety database is essential for the regulatory approval and public acceptance of any new vaccines.[50] In addition to serious adverse events, the phenomenon of disease enhancement after vaccine immunization also requires attention. Antibody-dependent enhancement (ADE) of a viral infection has always been a major concern of vaccine development and antibody-based therapeutic modalities.[51] Previous studies on the development of vaccines against severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have shown that if animals are exposed to the respective live virus after vaccination, the vaccinated animals may develop more severe disease. Therefore, COVID-19 vaccines should be rationally designed to only induce both neutralized antibodies and robust T cell-medicated immunity, which may minimize the possibility of ADE. The potential of any vaccines to result in ADE should be fully evaluated in animal models prior to clinical trials.

The third one is the emergence of variants of SARS-Cov-2 virus, which may compromise the vaccine efficacy.[52] Alterations in the S-protein that increase viral shedding from an infected individual or the binding affinity to the human angiotensin-converting enzyme 2 receptor would increase the transmission of the virus. Such alterations can also change the shape of the S-protein and impair or even destroy the binding sites of virus-neutralizing antibodies.[52] These alterations may occur when the virus is under a selective pressure by the neutralizing antibodies that can inhibit replication of the virus but cannot eliminate it. The virus would escape the pressure and restore its replication capacity through the alterations. Thus, viral evolution under such a suboptimal immunity condition is one of the major concerns for the development of a SARS-CoV-2 vaccine.[52] Therefore, a few measures have been recommended to prevent or minimize the potential effects of the emergence of variants on the vaccine efficacy. First, SARS-CoV-2 virus must be immediately isolated and characterized from individuals who have been fully vaccinated but are later diagnosed with COVID-19, which can help understand the signs that a variant is becoming resistant to vaccine-induced immunity. Second, it has been recommended to create a central repository of serum samples from people immunized with SARS-CoV-2 vaccines, which would allow to test their neutralizing capacities against any potential new variants as soon as they are identified.[52] Third, it is essential to establish international cooperation in order to create and maintain active and efficient sequencing and surveillance systems that identify the variants as soon as they occur. Fourth, SARS-CoV-2 vaccines, especially mRNA and replication-defective adenovirus vaccines, should be designed to accommodate the major sequence alterations in the new variants, so the vaccines are effective against the variants. Recently, Xie *et al.* engineered three SARS-CoV-2 variants containing key spike mutations, including N501Y, spike 69/70 deletion, E484K, and demonstrated that the mRNA-based COVID-19 vaccine BNT162b2 had neutralizing titers to three variants of SARS-CoV-2 that were similar to their parental virus.[53,54] These findings indicate that these mutations may have small effects on neutralization by sera elicited by two BNT162b2 doses. However, vaccines may need to be redesigned and adjusted to be a better match for the new variants.

Finally, the application of COVID-19 vaccines in the general population is an unprecedented challenge. It is widely accepted that safe and efficacious vaccines are considered the "ultimate weapon" to defeat the COVID-19 pandemic. At present, some countries have begun or plan to carry out COVID-19 vaccination in the general population.[55–57] However, the critical issue is how to vaccinate the whole population in the world, as quickly as possible. WHO has called for giving priority to vaccinating for those who need it most, including health workers with a higher risk of infection and people suffering from serious diseases. Moreover, particular attention should be paid to specific population groups. For example, currently, there are insufficient data on the effects of COVID-19 vaccines on pregnant women, lactating mothers and breastfed infants. However, the Centers for Disease Control and Prevention (CDC), American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine of the USA state that pregnant individuals who meet the criteria for receiving a COVID-19 vaccine may wish to choose to be vaccinated. They all reassure about initiating or continuing breastfeeding in a recently vaccinated individual, considering the benefits of breastfeeding to the infant and the safety profiles of other vaccines given during lactation.[58] Currently, almost all candidates tested are in the adult population, and whether COVID-19 vaccination should be implemented in children is a question. Although the incidence of SARS-CoV-2 infection is lower and the severity of COVID-19 is much milder in children than in adults,[59] the role of SARS-CoV-2 infection in children in the transmission of the infection among the population cannot be ignored. Therefore, COVID-19 vaccination in children would significantly help prevent SARS-CoV-2 transmission. However, the vaccines must demonstrate their safety and efficacy in children before implementation of childhood vaccination.[60] It has been shown that people with COVID-19 are at high risk for morbidity and mortality when they have underlying physical conditions, such as chronic obstructive pulmonary disease, cardiovascular diseases, type 2 diabetes mellitus, obesity, chronic kidney disease, immunodeficiency, and cancer.[61] Therefore, the US National Academies of Sciences, Engineering, and Medicine prioritize these patients in the allocation of vaccines.[62] However, patients with these underlying physical conditions should be carefully monitored during and a few days after vaccination due to safety concerns.[63] In addition, it has been reported that people with acute exacerbation of chronic diseases such as high blood pressure, chronic hepatitis, and chronic nephritis, and those with weakened immune systems are unsuitable for getting vaccine shots.[64] Although patients with hepatocellular carcinoma undergoing locoregional or systemic therapy should also be considered for vaccination without interruption of their treatment, patients with recent infections or fever should not receive the COVID-19 vaccine until they are medically stable.[65] Currently, convincing the public that the COVID-19 vaccine is safe and effective is challenging, as recently reported in the USA, where a large proportion (31.1%) of the American public do not intend to pursue a vaccine against COVID-19 even if it becomes available, due to concerns about safety, effectiveness, and a lack of resources.[66,67] Therefore, in addition to ensuring the funding, development, production, supply, transportation, and distribution of vaccines, world leaders should strengthen advocacy and communication to further educate the population on the importance of vaccination; even the most effective vaccine cannot protect the public if people are afraid to or do not

take it. Particularly, stop the anti-vaccination fake news and anti-vaccination movement!

Prospects

Now that COVID-19 vaccines have advanced to the later stages of clinical development and application at an extraordinary rate, it is expected that clinical data on more candidate vaccines with promising efficacy and good safety profiles as evaluated in phase III trials will be reported in the next few months.[68] Given the regulatory bodies' first-in-class and best-in-class drug-approval philosophy, some of the vaccines may have difficulty in obtaining approval in certain counties or markets due to existing vaccines in the same class. The two mRNA vaccines, BNT162b2 and mRNA-1273, developed by Pfizer/BioNTech and Moderna, respectively, are expected to be used in more countries although the efficacy of BNT162b2 has been recently questioned.[69] Moreover, the vaccine (a protein subunit vaccine) developed by Novavax and the one (a viral vector) by Johnson & Johnson, which are more convenient to store and distribute than the two mRNA vaccines, are anticipated to produce promising results in the phase III clinical trials (Table 3).[70] However, it should be mentioned that clinical trials of vaccines may be restricted by limited cases if the pandemic is under control, as demonstrated in China. Moreover, the potential short protection duration of a COVID-19 vaccine is also a challenging issue at present, and thus vaccines with long-term protection are anticipated.

Over the past year, governments of various countries have invested heavily in the research and development of COVID-19 vaccines, and some have initiated emergency vaccine approval. WHO has also established a special team to coordinate global COVID-19 vaccine development.[71] It is believed that with the reference of SARS-CoV and MERS-CoV vaccine development experience and lessons, as well as the concerted cooperation of global scientists and the policy support of various governments, the process of the development and application of COVID-19 vaccines will be greatly shortened and eventually matured. Practically, international cooperation is essential with the leadership and coordination of WHO and CDCs of participating countries in order to accelerate and optimize the production and vaccination of approved vaccines, and educate and convince the population to receive vaccination. Informatics is also a critical strategy in combating the COVID-19 pandemic.[72]

Conclusions

The pace of vaccines development and application is accelerating, and the number of vaccines entering phase IV clinical trials is increasing. Although there will be difficulties and challenges in the development of the vaccine, with the accumulation of our experience, we will eventually overcome the disease.

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Conflict of interest

None.

Author contributions

GF and HHXX designed the review outline. GF collected information and data from literature and online, summarized and analyzed the data and drafted the manuscript. KW helped collect the data. HHXX, LZ and BC advised on the structure and content of the manuscript, figure and tables, and revised and finalized the manuscript.

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