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.

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.

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. Briefly, preclinical experiments aim to understand whether injection of a vaccine into an animal, such as a...
Inactivated virus\textsuperscript{26} & Mature technology and simple preparation & Weak immunogenicity; requirement for multiple immunizations

Attenuated virus\textsuperscript{25} & Long-lasting immunity and mature technology & High requirements for storage and transportation; poor safety; toxic reversal risk

Protein subunit\textsuperscript{28} & Good safety profile and stability & Weak and short immunity; requirements for adjuvants

Virus-like particle\textsuperscript{29} & Induction of humoral and cellular immunity & High requirements for biological fermentation and plasmid purification

Viral vector\textsuperscript{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)\textsuperscript{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

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{17} It has been reported that there are high levels of neutralizing antibodies in convalescent individuals,\textsuperscript{18} which are associated with T cell responses, particularly those of CD4\textsuperscript{+} T cells\textsuperscript{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 parental 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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{23} In contrast, the respiratory tract mucosal administration method can more effectively induce antibodies and tissue colonizing T cells.\textsuperscript{24,25}

In general, there are six categories of COVID-19 vaccines, namely, inactivated (killed) virus,\textsuperscript{26} live attenuated (weakened) virus,\textsuperscript{27} protein subunit,\textsuperscript{28} virus-like particle (VLP),\textsuperscript{29} virus vector (non-replicating viral vector or replicating viral vector),\textsuperscript{30} and nucleic acid (DNA or RNA) (Table 1, Fig. 1).\textsuperscript{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).\textsuperscript{33,35,37}

An inactivated vaccine refers to the virus that is cultured and killed \textit{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).\textsuperscript{28} 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).\textsuperscript{37} 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).\textsuperscript{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).\textsuperscript{28} 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).\textsuperscript{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).\textsuperscript{31}
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A 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...
| Continent/Country | Primary developers or research institutions or sponsors | Vaccine platform description | Development stage (refs.) |
|-------------------|------------------------------------------------------|-----------------------------|--------------------------|
| Multiple countries | [Details] | [Details] | [Details] |
| Asia & Oceania | [Details] | [Details] | [Details] |
| China | [Details] | [Details] | [Details] |
| USA + India | [Details] | [Details] | [Details] |
| Netherlands + USA | [Details] | [Details] | [Details] |
| Australia + South Korea | [Details] | [Details] | [Details] |
| China + England + USA | [Details] | [Details] | [Details] |
| China + USA | [Details] | [Details] | [Details] |
| France + England | [Details] | [Details] | [Details] |
| Italy + Belgium | [Details] | [Details] | [Details] |
| USA + Austria + France | [Details] | [Details] | [Details] |
| USA + Indonesia | [Details] | [Details] | [Details] |
| USA + South Korea + China | [Details] | [Details] | [Details] |
| France | [Details] | [Details] | [Details] |
| USA | [Details] | [Details] | [Details] |
| Asia | [Details] | [Details] | [Details] |
| 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                   |
| India             | Bharat Biotech International Limited                   | DNA based vaccine           | Phase II                  |
| India             | Cadila Healthcare Ltd.                                  | Virus vector (Replicating)  | Phase I/II                |
| India             | Israel Institute for Biological Research               | DNA based vaccine           | Phase III                 |
| Japan             | Anes + Takara Bio + Osaka University                    | Protein subunit             | Phase I                   |
| Kazakhstan        | Research Institute for Biological Safety Problems, Rep of Kazakhstan | DNA based vaccine           | Phase II/III              |
| South Korea       | SK Bioscience Co., Ltd.                                 | Protein subunit             | Phase I                   |
| South Korea       | Cellid Co., Ltd.                                        | DNA based vaccine           | Phase III                 |
| South Korea       | GeneOne Life Sciences, Inc.                            | RNA based vaccine           | Phase I                   |
| South Korea       | genomix Consortium                                      | Protein subunit             | Phase I                   |
| Thailand          | Chulalongkorn University                                | DNA based vaccine           | Phase I                   |
| Turkey            | Erciyes University                                     | Protein subunit             | Phase I                   |
| Vietnam           | Nanogen Pharmaceutical Biotechnology                    | DNA based vaccine           | Phase I                   |
| Australia         | The University of Queensland                            | Inactivated virus           | Phase I                   |
| Australia         | Silla Pharmaed Industrial Co                            | Protein subunit             | Phase I                   |
| Australia         | University of Sydney, Bumen Co., Ltd Technovalia       | DNA based vaccine           | Phase I                   |
| Europe            | UK                                                      | RNA based vaccine           | Phase I                   |
| Europe            | University Hospital Tübingen                             | Protein subunit             | Phase I                   |
| Europe            | Imperial College London                                 | DNA based vaccine           | Phase I                   |
| Europe            | University of Munich (Ludwig-Maximilians)               | Virus vector (Non-replicating) | Phase I/II              |
| Europe            | CureVac AG                                              | DNA based vaccine           | Phase I                   |
| Europe            | FSI SRC, Vектор                                        | Protein subunit             | Phase I                   |
| Europe            | Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation | DNA based vaccine           | Phase I                   |

Table 2. COVID-19 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 III                |
|                   | vakser                                              |                            |                          |
| Italy             | Takis + Rottapharm Biotech                           | Protein subunit            | Phase III                |
|                   |                                      |                            |                          |
| North America     | Novavax                                             | Protein subunit            | Phase III                |
| USA               | Kentucky Bioprocessing Inc.                         |                            |                          |
| USA               | COVAXX + United Biomedical Inc.                     | Protein subunit            | Phase I/II               |
| USA               | VBI Vaccines Inc.                                   | Virus like particle        | Phase III                |
| USA               | Janssen Pharmaceutical                               | Viral vector (Non-replicating) | Phase I/II               |
| USA               | Vaxart                                              | Viral vector (Non-replicating) | Phase III               |
| USA               | City of Hope Medical Center + National Cancer Institute | Viral vector (Non-replicating) | Phase I/II               |
| USA               | Almirall, Inc.                                       | Viral vector (Non-replicating) | Phase I/II               |
| USA               | Gritstone Oncology                                   | Viral vector (Non-replicating) | Phase I/II               |
| USA               | Providence Health & Services                         | DNA based vaccine          | Phase I                  |
| USA               | Moderna + NIAID                                      | RNA based vaccine          | Phase II                 |
| USA               | Arcturus Therapeutics                                | DNA based vaccine          | Phase II                 |
| USA               | ImmunityBio, Inc.                                    | Protein subunit            | Phase I                  |
| USA               | Vaxart                                              | Viral vector (Non-replicating) | Phase III               |
| USA               | Coalition for the National Institutes of Health      | Viral vector (Non-replicating) | Phase I/II               |
| USA               | Providence Therapeutics                              | Viral vector (Non-replicating) | Phase I/II               |
| USA               | University of Saskatchewan                          | Viral vector (Non-replicating) | Phase I/II               |
| USA               | CIGB                                                 | Protein subunit            | Phase I                  |
| USA               | Medicago Inc.                                        | Protein subunit            | Phase I                  |
| USA               | Entos Pharmaceuticals                                | DNA based vaccine          | Phase I                  |
| USA               | Providence Health & Services                         | DNA based vaccine          | Phase I                  |
| Canada            | Symvivo Corporation                                  | Protein subunit            | Phase I/II               |
| Canada            | Providence Therapeutics                              | Virus like particle        | Phase I/II               |
| Cuba              | Instituto Finlay de Vacunas                          | Virus like particle        | Phase I/II               |
| Cuba              | CIGB                                                 | Protein subunit            | Phase I                  |
| Canada            | University of Saskatchewan                          | Protein subunit            | Phase I/II               |
| Canada            | CIGB                                                 | Protein subunit            | Phase I                  |

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 websites (https://www.who.int/publications/m/item/demand-and-supply-of-covid-19-vaccine-9-vaccine-tracker-and-corresponding-references-cited-in-the-table).
being developed in clinical trials, include the United Kingdom of Great Britain (UK), Germany, and Russia. 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. Among them, the USA has 11 vaccines, 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 the WHO. 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%.7 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.8 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 authorized 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.8 This vaccine is reportedly to provide 79.3% protection against the coronavirus which meets the standards of the WHO and NMPA.8 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.8

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-Cov-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 emergency use in the UK, India, Argentina, the Dominican Republic, El Salvador, Mexico, and Morocco,8 and Sputnik V was approved for emergency use in Russia, Belarus, Argentina, Guinea (experimental use), Bolivia, Algeria, Palestine, Venezuela, Paraguay, Turkmenistan, Hungary, UAE, and Serbia.8

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.43,44 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...
| 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 | NCT04565955 | E1, E2 |
| Inactivated virus | Vero cell | 2 | Day 0 + 21 | Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products | NCT04560881 | E1, E2 |
| Inactivated virus | BBIBP-CorV | 2 | Day 0 + 21 | Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products | NCT045691908 | 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 |
| Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) | Bharat Biotech International Limited | 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 or Day 0 + 28 or Day 0 + 28 + 56 | Anhui Zhifei Longcom Biopharmaceutical Inc + Chinese Academy of Sciences | NCT04646590 | E1, E2 |
| Protein subunit | BBV152 (Whole-Virion Inactivated SARS-CoV-2 Vaccine) | 2 | Day 0 + 14 | Berlin Bioteck International Limited | NCT04672395 | E1, E2 |
| Protein subunit | UB-612 (Multitope peptide based S1-RBD-protein based vaccine) | 2 | Day 0 + 28 | COVAX + 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 or Day 0 + 28 + 56 | AstraZeneca + University of Oxford | NCT04649151; NCT04470427 | E1, E2 |
| Viral vector (Non-replicating) | Ad5-nCoV | 1 | Day 0 | CanSino Biological Inc + Beijing Institute of Biotechnology + Chinese Academy of Sciences | NCT04636977 | E1, E2 |
| Virus like particle | Coronavirus-Like Particle COVID-19 (CoVLP) | 2 | Day 0 + 21 | Medicago Inc. | NCT046367189 | E1, E2 |
| RNA based vaccine | mRNA-1273 (Moderna COVID-19 Vaccine) | 2 | Day 0 + 28 | Moderna + NIAID | NCT04646515 | E1, E2 |
| RNA based vaccine | BNT162b2 (Comirnaty) | 2 | Day 0 + 21 | Pfizer/BioNTech + Fosun Pharma | NCT046367289 | E1, E2 |
| RNA based vaccine | CVnCoV Vaccine | 2 | Day 0 + 28 | CureVac AG | NCT046467189 | E1, E2 |
### Table 3. COVID-19 vaccines developed in phase II/III, and IV clinical trials as of March 5, 2021 - (continued)

| Vaccine type               | Vaccine name* | Dose | Dosing schedule | Primary developers or research institutions or sponsors | Registration number | Endpoint | Approval status |
|----------------------------|---------------|------|-----------------|--------------------------------------------------------|---------------------|----------|----------------|
| DNA based vaccine          | INO-4800-electroporation | 2    | Day 0 + 28      | Inovio Pharmaceuticals + International Vaccine Institute (Dubai) BioPharmaceutical Co., Ltd. | NCT04645838**       | E1, E2   | Preclinical    |
| DNA based vaccine          | AG8012-COVID19 | 2    | Day 0 + 14      | Aeges + Takeda Bio + Osaka University                   | NCT04656552**       | E1, E2   | Preclinical    |
| DNA based vaccine          | nCov vaccine  | 3    | Day 0 + 28 + 56 | Cadila Healthcare Ltd.                                  | CTRI/2020/07/026352 | E1, E2   | Preclinical    |

** Endpoint:
- E1, E2: efficacy for prevention of SARS-CoV-2 infection; E1, E2: safety and immunogenicity of a booster dose. **Note**: some endpoints may be different from those reported in the table. **Reference**: World Health Organization website (https://www.who.int/docs/default-source/blue-print/20201217-novel-coronavirus-novel-coronavirus-vaccine-tracker-landscape_covid-19.xlsx.zip?sfvrsn=a5dc3b8d_34&download=true), COVID-19 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 emergency use as of February 12, 2021

| Name*                      | Vaccine Type                  | Developer/Sponsor                        | Country of Origin | Authorization/Approval |
|----------------------------|-------------------------------|------------------------------------------|-------------------|------------------------|
| Vero cell vaccine          | Inactivated vaccine           | Wuhan Institute of Biological Products   | China             | China                  |
| BBIBP-CorV                 | Inactivated vaccine           | Beijing Institute of Biological Products | China             | China, Bahrain, United Arab Emirates, Egypt, Jordan, Iraq, Pakistan, Russia, Serbia | Country of origin: China; Authorization/Approval: Russia |
| CoronaVac                  | Inactivated vaccine (formalin with adjuvant) | Bharat Biotech, ICMR                     | India             | India                  |
| EpivacCorona               | Protein subunit               | Federal Bureaucratic Research Institution, Center of Vector Vigor and Biotechnology | Russia            | Russia                |
| AZD1222                    | Non-replicating viral vector  | AstraZeneca, University of Oxford, BARDA, ONS | UK                | UK, Argentina, El Salvador, Dominican Republic, India, Bangladesh, Brazil, China, Malaysia, Pakistan, Saudi Arabia, South Africa, South Korea, Taiwan, Thailand, United Arab Emirates, United Kingdom, United States, Vietnam, Zambia, Zimbabwe | Country of origin: UK; Authorization/Approval: United Kingdom; Brazil; China; Singapore; South Africa; Malaysia; Thailand; United Arab Emirates; United States; Russia; United Kingdom; South Africa; Zambia; Zimbabwe |
| mRNA-1273                  | mRNA-based vaccine            | Moderna, BNT1621, Pfizer, BioNTech, Fosun Pharma | USA               | USA, Argentina, Australia, Canada, China, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Japan, South Korea, Luxembourg, Monaco, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Saudi Arabia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States | Country of origin: USA; Authorization/Approval: USA, Argentina, Australia, Canada, China, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Japan, South Korea, Luxembourg, Monaco, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Saudi Arabia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States |

** Endpoint:**
- E1, E2: efficacy for prevention of SARS-CoV-2 infection; E1, E2: safety and immunogenicity of a booster dose. **Note**: some endpoints may be different from those reported in the table. **Reference**: World Health Organization website (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines), COVID-19 vaccine tracker (https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker) and corresponding references cited in the table.

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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. 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.

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. 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. 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-mediated 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. 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. 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. 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. 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 titer to three variants of SARS-CoV-2 that were similar to their parental virus.

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. 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 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. 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, 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. 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. Therefore, the US National Academies of Sciences, Engineering, and Medicine prioritize these patients in the allocation of vaccines. However, patients with these underlying physical conditions should be carefully monitored during and a few days after vaccination due to safety concerns. 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. 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. 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. Additionally, in addition to ensuring the funding, development, production, supply, transportation, and distribution of vaccines, world leaders should continue the 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. 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. 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). 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. 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.

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.

References

[1] Kamel Boulos MN, Geraghty EM. Geographical tracking and mapping of coronavirus disease COVID-19/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic and associated events around the world: how 21st century GIS technologies are supporting the global fight against outbreaks and epidemics. Int J Health Geogr 2020;19(1):8. doi:10.1186/s12942-020-00202-8.
[2] WHO. COVID-19 Weekly Epidemiological Update. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed March 5, 2021.
[3] Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med 2020;382(21):1969–1973. doi:10.1056/NEJMmp2005630.
[4] O’Callaghan KP, Blatz AM, Offit PA. Developing a SARS-CoV-2 vaccine at warp speed. JAMA 2020;324(5):437–438. doi:10.1001/jama.2020.12190.
[5] Jeyanathan M, Afkhami S, Smalll F, Miller MS, Lichy BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol 2020;20(10):615–632. doi:10.1038/s41577-020-00434-6.
[6] Meisner HC. A viral pandemic, vaccine safety, and compensation for adverse events. JAMA 2021;325(8):711–722. doi:10.1001/jama.2020.26792.
[7] WHO. Draft landscape and tracker of COVID-19 candidate vaccines. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed March 5, 2021.
[8] Craven J. COVID-19 vaccine tracker. Available from: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker. Accessed February 12, 2021.
[9] Calina D, Docea AO, Petракis D, Egorov AM, Ishmukhametov AA, Gaibov AG, et al. Towards effective COVID19 vaccines: updates, perspectives and challenges (Review). Int J Mol Med 2020;46(1):3–16. doi:10.3892/ijmm.2020.4596.
[10] Goetz KB, Pfleiderer M, Schneider CK. First-in-human clinical trials with vaccines—what regulators want. Nat Biotechnol 2010;28(9):910–916. doi:10.1038/nbt0910-910.
[11] Overton ET, Stapleton J, Frank J, Hassler S, Goepfert PA, Barker D, et al. Safety and immunogenicity of Modified Vaccinia Ankara-Bavarian Nordic smallpox vaccine in vaccinia-naive and experienced Human Immunodeficiency Virus-infected individuals: An open-label, controlled clinical phase II trial. Open Forum Infect Dis 2015;2(2):ofv040. doi:10.1093/ofid/ofv040.
[12] Palacios R, Patino EG, de Oliveira Piorelli R, Conde M, Batista AP, Zeng G, et al. Double-blind, randomized, placebo-controlled phase III clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac-PROFISCOV-Astructuredsummaryofastudyprotocol for a randomised controlled trial. Trials 2020;20(1):853. doi:10.1186/s13063-020-04775-4.
[13] Funk CD, Laferriere C, Aradkan A. A snapshot of the global race for
and national estimates of target population sizes for COVID-19 vaccination: descriptive study. BMJ 2020;371:m4704. doi:10.1136/bmj.m4704.

[56] Kreps S, Prasad S, Brownstein JS, Hswen Y, Garibaldi BT, Zhang B, et al. Factors associated with US adults’ likelihood of accepting COVID-19 vaccination. JAMA Netw Open 2020;3(10):e2025594. doi:10.1001/jamanetworkopen.2020.25594.

[57] Wang J, Jing R, Lai X, Zhang H, Lyu Y, Knoll MD, et al. Acceptance of COVID-19 vaccination during the COVID-19 pandemic in China. Vaccines (Basel) 2020;8(3):482. doi:10.3390/vaccines8030482.

[58] Rasmussen SA, Jamieson DJ. Pregnancy, postpartum care, and COVID-19 vaccination in 2021. JAMA 2021;325(11):1099–1100. doi:10.1001/jama.2021.1683.

[59] Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020;109(6):1088–1095. doi:10.1111/apa.15270.

[60] Eberhardt CS, Siegrist CA. Is there a role for childhood vaccination against COVID-19? Pediatr Allergy Immunol 2021;32(1):9–16. doi:10.1111/pai.13401.

[61] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020;36(7):e3319. doi:10.1002/dmrr.3319.

[62] De Hert M, Mazereel V, Detraux J, Van Assche K. Prioritizing COVID-19 vaccination for people with severe mental illness. World Psychiatry 2021;20(1):54–55. doi:10.1002/wps.20826.

[63] Ma XF. People with chronic diseases in Beijing have no obvious discomfort after being vaccinated with domestic vaccines (in Chinese). Available from: https://m.tkww.hk/s/202102/20/AP60309B24e4b0661d55719115.html. Accessed February 20, 2021.

[64] CCTV News. How to vaccinate the COVID-19 vaccine? Available from: https://baijiahao.baidu.com/s?id=1688378614088013094&wfr=spider&for=pc. Accessed January 9, 2021.

[65] Fix OK, Blumberg EA, Chang KM, Chu J, Chung RT, Goacher EK, et al. AASLD expert panel consensus statement: vaccines to prevent COVID-19 infection in patients with liver disease. Hepatology 2021. doi:10.1002/hep.31751.

[66] Callaghan T, Moghtaderi A, Lueck JA, Hotez P, Strych U, Dor A, et al. Correlates and disparities of intention to vaccinate against COVID-19. Soc Sci Med 2021;272:113638. doi:10.1016/j.socscimed.2020.113638.

[67] De Francesco L. Whither COVID-19 vaccines? Nat Biotechnol 2020;38(10):1132–1145. doi:10.1038/s41587-020-0697-7.

[68] Dube T, Ghosh A, Mishra J, Kompella UB, Panda JJ. Repurposed drugs, molecular vaccines, immune-modulators, and nanotherapeutics to treat and prevent COVID-19 associated with SARS-CoV-2, a deadly nanovector. Adv Ther (Weinh) 2020;4(2):2000172. doi:10.1002/adtp.202000172.

[69] Doshi P. Pfizer and Moderna’s “95% effective” vaccines—we need more details and the raw data. Available from: https://blogs.bmj.com/bmj/2021/01/04/peter-doshi-pfizer-and-modernas-95-effective-vaccines-we-need-more-details-and-the-raw-data/. Accessed January 4, 2021.

[70] Nature News. Looking ahead to the most noteworthy scientific events of 2021. Available from: https://www.nature.com/articles/d41586-020-03651-0. Accessed December 22, 2020.

[71] WHO. Public statement for collaboration on COVID-19 vaccine development. Available from: https://www.who.int/news/item/13-04-2020-public-statement-for-collaboration-on-covid-19-vaccine-development. Accessed April 16, 2020.

[72] Bakken S. Informatics is a critical strategy in combating the COVID-19 pandemic. J Am Med Inform Assoc 2020;27(6):843–844. doi:10.1093/jamia/ocaa101.