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A Review on Novel Coronavirus (COVID-19) Vaccines: AstraZeneca, Pfizer, Moderna

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Abstract

Rapid progress in vaccine development was prompted by the unprecedented global health challenge posed by the emergence of the novel coronavirus disease (COVID-19) caused by SARS-CoV-2. The current state of COVID-19 vaccines, including their technological platforms, efficacy, safety, and worldwide distribution, is summarized in this review. It discusses the outcomes of clinical trials and the practical efficacy of the main vaccine types, including mRNA-based, viral vector, protein subunit, and inactivated virus vaccines. Challenges like vaccine hesitancy, equitable distribution, and the emergence of variants of concern that could affect vaccine efficacy are also covered in the review. Lastly, it looks at potential future paths, such as ways to improve pandemic preparedness, booster shots, and next-generation vaccines. A thorough grasp of the changing COVID-19 vaccination landscape and its vital role in pandemic control is the goal of this synthesis.

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

Introduction

Reported in December 2019 in Wuhan, the capital of Hubei province in China, the first instances of coronavirus disease 2019 (COVID-19) have been recorded to cause severe respiratory diseases including pneumonia and lung failure. The fast-increasing number of diseases spread throughout China and then over the world. Originally known to as 2019-nCoV or the Wuhan Coronavirus, the sickness COVID-19 was formally identified by the World Health Organisation (WHO). The virus responsible Close proximity of the virus to the severe acute respiratory syndrome coronavirus (SARS-CoV), which started an epidemic in 2002, was found by genetic investigations. As such, the International Committee on Taxonomy of Viruses (ICTV) assigned the virus SARS-CoV-2 [1,2].

SARS-CoV-2 belongs to the Coronaviridae family, characterized by enveloped, positive-sense single-stranded RNA ((+) ssRNA) Viruses. It is believed to have arisen from zoonotic coronaviruses, including SARS-CoV, and has been recognized as the causal agent of COVID-19. Subsequent to its first identification, SARS-CoV-2 swiftly disseminated globally, resulting in a pandemic. As of April 13, 2024, there have been over 704,753,890 crores confirmed cases worldwide and more than 7,010,681 lakh deaths. India recorded approximately 45,035,393 crores cases and 533,570 fatalities, according to statistics from https://www.worldometers.info/coronavirus/#countries [3,4].

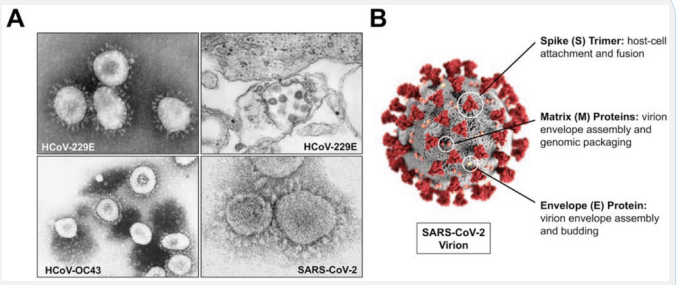

Figure 1: (A) Electron microscopy images of HCoV-229E, HCoV-OC43, and SARS-CoV-2 highlight the structural differences among these coronaviruses. **(B)** A schematic representation of the SARS-CoV-2 virion illustrates its structural proteins, each labeled with its specific function. These visuals were adapted from resources provided by the Centers for Disease Control and Prevention (CDC) through the Public Health Image Library (PHIL) [69].

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The exact origin of the SARS-CoV-2 outbreak remains unclear, but hypotheses suggest bats [5], snakes [6], or pangolins [7,8] may have acted as the virus's vectors. COVID-19 symptoms tend to be more severe in older adults with preexisting conditions, such as asthma, Chronic Obstructive Pulmonary Disease (COPD), and other allergic diseases [9,10]. Given the severe impact of the pandemic on human lives and economies worldwide, understanding the current situation and implementing effective strategies to mitigate the virus's spread are critical. Although various diagnostic kits for COVID-19 are available and some repurposed therapeutic agents have been tested, none have yet demonstrated significant efficacy in clinical trials [64,65].

Vaccines are a more cost-effective solution than treatment and can reduce morbidity and mortality without long-term side effects [11,12]. Preventive and therapeutic vaccines are essential to combating infectious diseases and safeguarding global health [13,14]. In the last two decades, three significant human coronaviruses—SARS-CoV, MERS-CoV, and SARS-CoV-2—have emerged, posing substantial threats to global health [15]. Research teams worldwide are accelerating COVID-19 vaccine development using various strategies. As of Dec 2, 2022, 50 vaccines were approved for limited or emergency use, while 16 vaccines had full approval [16].

Understanding the precise mechanisms of viral recognition and host interaction is vital for studying host tropism, cross-species transmission, and vaccine development. The spike (S) protein of SARS-CoV-2, which enables viral entrance by binding to host cell receptors, is a pivotal target for vaccine development. This protein interacts with many host receptors, including ACE2 (used by SARS-CoV-2 and SARS-CoV), APN, and DPP4 [17-19]. The Receptor-Binding Domain (RBD) inside the S1 subunit of the spike protein is crucial for receptor recognition, while the S2 subunit enables membrane fusion between the virus and host cells [20-22]. SARS-CoV-2 shares approximately 75% homology in the spike protein RBD with SARS-CoV [20].

Globally, more 200 vaccines are under development, with 38 Indian pharmaceutical companies contributing to these efforts. Currently, 66 vaccines are in phase 1 trials, 72 in phase 2, 93 in phase 3, and 50 have been authorized for use. As of Dec 2, 2022, more than 13.64 billion vaccine doses had been administered worldwide, with 67% of the global population fully vaccinated. In India, over 2.21 billion doses had been given, with 74% of the population fully vaccinated as 31 December 2023 [67,68].

Types of vaccines

Messenger RNA vaccines

The concept behind mRNA vaccines involves introducing mRNA that encodes a viral protein into the host immune system to serve as an antigen, thereby stimulating an immune response and producing neutralizing antibodies. This approach differs fundamentally from traditional vaccines, which typically use inactivated pathogens or protein antigens to elicit immunity [65]. To create the mRNA, an RNA polymerase transcribes it in vitro from a DNA template containing an Open Reading Frame (ORF) that encodes the target protein. Once inside the host, the mRNA leverages the host's translational machinery to synthesize the antigenic protein [23].

mRNA-based vaccines offer several advantages, including their relative safety, reliance on the host's translational machinery, avoidance of genome integration, and the simplicity and scalability of production in laboratory settings. However, challenges such as efficient delivery, maintaining mRNA stability within the host, the potential for unintended immune responses, and storage limitations—requiring freezing to prevent degradation—remain significant hurdles. Despite these obstacles, mRNA vaccines are recognized as the fastest and most effective approach for developing a COVID-19 vaccine, positioning them as one of the most promising solutions for combating the pandemic [70,81].

The spike(S) protein of SARS-CoV-2 has considerable resemblance to the S protein of SARS-CoV, making it a crucial target for RNA vaccine development. This resemblance allows researchers to use established understanding about the S protein to develop viable vaccines for SARS-CoV-2. Neutralizing antibodies directed against the Receptor-Binding Domain (RBD) and the N-terminal domain of the S protein have been detected in a subset of COVID-19 patients, underscoring the potential of the S protein as an antigen and designating these domains as viable targets for vaccine development [24].

RNA vaccines that encode the spike (S) protein are an effective strategy for inducing neutralizing antibodies, which block the virus from binding to the ACE2 receptor and prevent its entry into host cells. However, this approach assumes that SARS-CoV-2 relies solely on ACE2 for cellular entry, leaving a potential vulnerability if alternative entry mechanisms exist. Additional technical challenges include ensuring the stability of the mRNA, its efficient uptake by host cells, and its successful release from encapsulating nanoparticles into the cytoplasm to produce the desired protein. Strategies to enhance mRNA stability often involve protecting it from degradation by host ribonucleases. The mRNA is typically delivered intramuscularly, encapsulated in lipid nanoparticles or similar materials, to ensure effective delivery and stability [25-27].

The mRNA-1273 vaccine, which contains modified viral RNA encapsulated in lipid nanoparticles, was the first mRNA vaccine developed to fight COVID-19. In a Phase 1 trial (NCT04283461), all participants developed neutralizing antibodies following administration of the vaccine, which encodes the stabilized prefusion spike(S) protein. The vaccine requires two doses. However, a considerable number of recipients experienced mild COVID-19-like symptoms as side effects. Since the immunogenicity triggered by mRNA vaccines is temporary, multiple doses are typically necessary to produce a strong and lasting immune response. One promising approach to overcome this limitation is the use of Self-Amplifying mRNA (SAM) constructs, which utilize a replicase to facilitate continuous transcription of viral mRNA, leading to sustained antigen presentation to the immune system.

The SAM strategy allows for the production of a large amount of antigen from a relatively small amount of mRNA. However, the SAM platform faces challenges due to the size limitations of the antigen inserts. Additionally, novel RNA constructs have been developed to maintain persistent antigen expression after a single injection, with one construct encoding the replicase and the other the target antigen. Moreover, transfecting dendritic cells with viral RNA has been shown to induce strong immune responses by activating T cells specific to the antigen [28,29].

Finally, nucleoside-modified mRNA vaccines have proven to be highly effective in presenting antigens and triggering an immune response. Many academic institutions and industry players are actively working to develop mRNA-based vaccines, employing a range of strategies based on the potential effec-

tiveness of this technology. The safety and immunogenicity of several mRNA vaccines, including their ability to generate neutralizing antibodies, have already been assessed in Phase 1 and Phase 2 clinical trials. Large-scale Phase 3 trials assessing the efficacy of these vaccines have also begun enrolling participants [30].

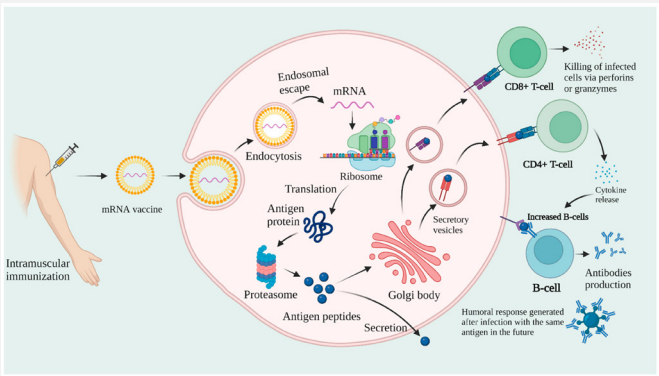

Figure 2: Mechanism of action of mRNA vaccines postvaccination [70].

DNA based vaccines

The approach involves transferring a SARS-CoV-2 gene, typically encoding the spike(S) protein, to induce an immune response through the expression of the viral protein. This is achieved using various vectors, such as plasmids, replication-competent vesicular stomatitis virus, replication-deficient adenoviruses, or lentiviruses. DNA vaccines offer several advantages, including stability at room temperature, good safety profiles, and ease of large-scale production at an affordable cost. These vaccines can be administered through methods such as electroporation, intramuscular injection, or intradermal injection. DNA vaccines have been developed for several infectious diseases and have demonstrated both immunogenicity and favorable safety profiles [42,43].

Investigations are underway to evaluate the immunogenicity and safety of DNA vaccines targeting SARS-CoV-2. Initial research in rhesus macaques has shown that the expression of numerous viral S protein immunogens elicits both humoral and cellular immunological responses, including the generation of neutralizing antibodies and the activation of CD4+ and CD8+ T cells that secrete IFN-g. In response to the SARS-CoV-2 virus, the DNA vaccination markedly decreased viral RNA levels, indicating a robust immune response [32,33]. Vaccinated individuals had dose-dependent antibody and T cell responses, with maximal responses seen about 4 weeks post-vaccination using a recombinant adenovirus that expresses the full-length S protein. Mild to severe side effects were prevalent, although no significant adverse events were documented, and a phase 2 trial of this vaccine has been completed. It is crucial to acknowledge that replication-deficient adenoviruses are immunogenic and might provoke host immunological responses that hinder transgene expression, presenting a hurdle in the first stages of gene therapy [31].

Protein based vaccines: Protein subunits, Virus-Like Particles (VLP) and peptides

Subunit vaccines consist of specific proteins or polysaccharides that are either extracted from natural sources or produced using recombinant DNA technology. These vaccines focus on selected viral antigens, which minimizes the risk of adverse reactions, though it remains essential to identify the most immunogenic antigenic components (Clem, 2011). One example is NVX-CoV2373, a subunit vaccine developed by Novavax, which includes the S protein and the Matrix-M1 adjuvant. Currently in phase III trials, NVX-CoV2373 has shown promise in preclinical and clinical studies [35,36].

Virus-Like Particles (VLPs) consist of the envelope and/or capsid proteins from various viruses, but they do not contain any genetic material. Although their production can be difficult, VLPs offer the advantage of mimicking the virus's structure and antigenicity while being non-infectious. Medicago Inc. has developed a VLP-based vaccine, which is the only one to reach phase I clinical trials. This vaccine is plant-derived, using living plants as bioreactors to produce non-infectious virus-like strains and is adjuvanted to enhance the immune response (Medicago, 2021) [36,38].

Virus-Based vaccines include weekened or inactivated viruses

a. Weakened virus

Attenuated vaccines, using weaker variants of the pathogen, elicit robust humoral and cellular immune responses (Chen et al. 2020). These vaccinations often provide long-lasting protection with just a few numbers of doses. Nonetheless, their primary drawback is the possible hazard presented by the living microorganisms, which might, on infrequent occasions, return to their former, more aggressive state [38].

b. Inactivated virus

Chemical or physical methods are employed to inactivate pathogens, ensuring the vaccine's stability. However, these vaccines often trigger a relatively weak immune response, necessitating multiple doses for optimal efficacy (Clem, 2011; Xia et al., 2020). Sinovac is conducting clinical trials on COVID-19 using various inactivated virus vaccines, including PiCoVacc. This vaccine has shown the ability to generate SARS-CoV-2-specific neutralizing antibodies in multiple preclinical models, such as mice, rats, and nonhuman primates (Gao et al. 2020). It has also demonstrated a favorable safety and immunogenicity profile in phase I/II trials, with phase III trials currently in progress [40,41].

Viral vectors vaccines

Utilize altered and non-related viruses that express one or more antigens. This method employs either living vectors, which are often attenuated, or non-replicating vectors. Adenovirus, measles virus, and Vesicular Stomatitis Virus (VSV) are among the most often used viral vectors (Rauch et al., 2018) [39]. The Ad5 vectored COVID-19 vaccine demonstrated substantial immunogenicity and tolerability in phase I trials (Zhu FC et al. 2020). Additionally, various phase III COVID-19 vaccines utilize adenoviral vectors that express the S glycoprotein, such as ChAdOx1, which yielded significant outcomes regarding T-cell response and neutralizing antibody generation (Folegatti et al. 2020) [44].

Status of vaccines

Status of various vaccines under development/ investigation for the Novel Coronavirus

Table 1: Status of various vaccines in under development.

S. No	Vaccine candidates	Technology	Manufacturers/Sponsors/Trials location	Generic name	Ref
1	**mRNA-1273, The Moderna vaccine**	mRNA-containing lipid nanoparticle dispersion	BARDA (U.S.), NIAID, and Moderna	The COVID-19 Moderna Vaccine	[63]
2	**BNT162b2**	mRNA	Fosun Pharma, Pfizer, and BioNTech (Germany, U.S.)	Tozinameran	[53]
3	**(ChAdOx1 nCoV-19) or Astra-Zeneca (AZD1222) (Vaxzevria, Covishield)**	Adenovirus vector modified in chimpanzees (ChAdOx1)	Oxford University, AstraZeneca (United Kingdom)	AstraZeneca The COVID-19 vaccine	[44]
4	**Vac Gam-COVID (Sputnik V))**	Non-replicating vector for viruses	Russian Gamaleya Research Institute	COVID-Vac Gam	[76]
5	**Convidecia (Ad5-nCOV)**	Vector of recombinant adenovirus type 5	Beijing Institute of Biotechnology, CanSinoBIO (China, Russia)	Ad5-nCOV	[5]
6	**BBV152 (Covaxin)**	The SARS-CoV-2 inactivated	Bharat Biotech, ICMR (India)	BBV152	[79]
7	**Ad26.COV2 (JNJ-78436735; Ad26.COV2.S)**	Non-replicating vector of infection	Janssen Vaccines, Belgium, U.S, Brazil, South Africa	Ad26.COV2	[33]
8	**NVX-CoV2373 (Novavax, TAK-019)**	Recombinant spike protein nanoparticle with adjuvant	Novavax, Serum Institute of India, Takeda Pharmaceutical (U.K, Japan)	SARS-CoV-2 Vaccine	[49]
9	**CoronaVac**	Inactivated SARS-CoV-2	Sinovac Biotech (China, Brazil, Indonesia)	COVID-19 Vaccine (Vero Cell)	[33]
10	**BBIBP-CorV Sinopharm**	The SARS-CoV-2 inactivated	China, Argentina, and the United Arab Emirates' Beijing Institute of Biological Products.	Vero Cell, a Sinopharm COVID-19 vaccine	[26]
11	**EpiVacCorona**	Peptide vaccine	Virology and Biotechnology State Research Center (Russia)	The EpiVakKorona	[27]
12	**CoviVac**	The Inactivated vaccine	Russian Chumakov Federal Scientific Center	The Chumakov COVID-19 virus	[27]
13	**ZF2001 (ZIFIVAX)**	Vaccine recombinant for virus	Chinese Academy of Sciences (China) Zhifei Longcom Biopharmaceutical	Dimer RBD	[24]
14	**ARCoV**	vaccine based on mRNA	Abogen Biosciences Co. and Walvax Biotechnology Co. (China)	The COVID-19 vaccine, Walvax	[24]
15	**ZyCoV-D**	Plasmid DNA vaccine	India's Zydus Biotech	The ZyCoV-D	[33]
16	**Abdala (CIGB 66)**	Vaccine using protein subunits	Center for Biotechnology and Genetic Engineering (Cuba)	Unknown	[65]
17	**VLA2001**	Vaccine that has been inactivated	National Institute for Health Research, Valneva (France, UK)	Vaccine for Valneva COVID-19	[41]
18	**CVnCoV (CureVac)**	mRNA-based vaccine	Curevac, GSK (Austria)	CVnCoV	[23]
19	**Bacillus Calmette-Guerin (BCG) vaccine**	Live-attenuated vaccine	University of Melbourne, Radboud University (Australia, Netherlands)	BCG Vaccine	[5]
20	**INOVIO-4800**	Plasmid DNA vaccine	U.S.-based Inovio Pharmaceuticals	COVID-19 Inovio Vaccine	[23]
21	**COVAXX UB-612**	vaccination based on multitope peptides	Brazil's Vaxxinity United Biomedical Inc.	Covid-19 UB-612	[39].
22	**Gorrilla Adenovirus GRAd-COV2**	vaccine based on adenovirus	Leukocare, Univercells (Italy), and ReiThera	GRAd-COV2	[39]
23	**Trimer vaccine SCB-2019**	Vaccine using protein subunits	Sanofi, Clover Biopharmaceuticals, and GlaxoSmithKline (Australia)	SCB-2019	[67]
24	**V-01**	vaccine made of recombinant proteins	Center for Disease Prevention and Control in Guangdong Province, China	COVID-19 Vaccine V-01	[5]
25	**Razi Cov Pars**	Spike protein-based recombinant vaccination	Iran's Razi Vaccine Institute	Unknown	[41]
26	**Nanocovax**	Recombinant vaccine (Spike protein)	Vietnam's Military Medical Academy, Nanogen Biopharmaceutical	Unknown	[39]
27	**Soberana 1 and 2**	Conjugated/monovalent vaccine	Finlay Institute of Vaccines (Cuba)	FINLAY-FR-1, FINLAY-FR-2	[41]

28	**AdCLD-CoV19**	vaccine based on adenovirus	Cellid, LG Chem (Korea)	AdCLD-COVID19 Vaccine	[67]
29	**KD-414**	vaccine that has been inactivated	Japan Agency for Medical Research and Development, KM Biologics	Unknown	[39]
30	**VBI-2902a**	vaccine with virus-like particles (enveloped)	VBI Vaccines Inc. (U.S)	Unknown	[41]
31	**COVID-eVax**	Plasmid DNA vaccine	Takis, Rottapharm Biotech (Italy)	Unknown	[23]
32	**S-268019**	vaccine made of recombinant proteins	Agency for Medical Research and Development of Japan; Shionogi & Co., Ltd.	Unknown	[67]
33	**GLS-5310**	Plasmid-based DNA vaccine	Korea's GeneOne Life Science, Inc.	Unknown	[65]
34	**Covigenix VAX-001**	Plasmid-based DNA vaccine	Aegis Life, Inc. and Entos Pharmaceuticals Inc. (Canada)	Unknown	[67]
35	**EXG-5003**	Intradermal vaccine candidate	Fujita Health University, Elixirgen Therapeutics, Inc. (Japan)	Elixirgen (EXG-5003)	[66]
36	**AKS-452**	Vaccine using protein subunits	Netherlands: Akston Biosciences, University Medical Center Groningen	Unknown	[40]
37	**DS-5670a**	Recombinant protein vaccine	Dong-A Pharmaceutical, Korea Institute of Science and Technology	Unknown	[23]
38.	**ABNCoV2**	vaccine based on cVLP	Nordic A/S Bavarian ExpreS2ion Biotech	IMVANEX®	[24]
39.	**EuCorVac-19**	vaccine using nanoparticles	EuBiologics; Hospital of Eunpyeong St. Mary's	Unknown	[23]
40.	**Mambisa (CIGB 669)**	Vaccine using protein subunits	Genetic Engineering and Biotechnology Center	CIGB 669 Mambisa	[76]
41.	**IIBR-100**	vaccine against the recombinant vesicular stomatitis virus (rVSV)	Hadassah Medical Center, Sheba Medical Center Hospital, and Israel Institute for Biological Research	Brilife	[24]
42.	**AG0301-COVID19**	DNA vaccine	Agency for Medical Research and Development of Japan; AnGes, Inc.	AG0301-COVID19	[76]
43.	**GX-19N**	DNA vaccine	Genexine	Unknown	[33]
44.	**LUNAR VACCINE (CoV19)**	RNA vaccination that replicates itself	Duke-NUS Medical School and Arcturus Therapeutics	LUNAR-COV19	[53]
45.	**MCTI-CIMATEC- HDT Vaccine**	The RNA vaccine	Gennova Biopharmaceuticals, HDT Bio Corp, the National Institutes of Health, and the University of Washington	HGCO19	[40]
46.	**MRT5500**	mRNA-based vaccine	Sanofi; Translate Bio	Unknown	[53]
47.	**AV-COVID-19**	vaccine using dendritic cells.	Dr. Kariadi's residence; Aivita Biomedical, Inc.	AV-COVID-19	[24]
48.	**FAKHRAVAC (MIVAC)**	Based on Inactivated vaccines	Research Center for Stem Cell Technology; Fakhra Clinical Trial Center; Defensive Innovation and Research Organization	Unknown	[49]
49.	**NBP2001**	vaccine made of recombinant proteins	Seoul National University Bundang Hospital; Seoul National University Hospital; SK Bioscience Co., Ltd.	Unknown	[40]
50.	**SpFN**	vaccine using spike ferritin nanoparticles	Walter Reed Army Institute of Research; United States Army Medical Research and Development Command.	Unknown	[33]
51.	**KBP-201**	Vaccine using protein subunits	Velocity Clinical Research, PMG Research of Winston-Salem, ICON, DM Clinical Research, and Kentucky BioProcessing, Inc.	COVID-19 KBP	[49]
52.	**MEISSA MV-014-212 Vaccine**	Recombinant live Intranasal vaccines	Meridian Clinical Research; Johnson County ClinTrials; Meissa Vaccines, Inc.	Unknown	[24]
53.	**BRAD -T PTX COV19-B**	vaccine based on mRNA	The Canadian government and Providence Therapeutics	Unknown	[33]
54.	**AdimrSC-2F**	vaccine using protein subunits	Ad Immune	AdimrSC-2f	[23]
55.	**bacTRL-Spike vaccine**	Bifidobacteria-based monovalent oral vaccination	Symvivo Company	Spike BacTRL	[41]
56.	**COVAXX-19**	Immunization with monovalent recombinant proteins	Royal Adelaide Hospital; CinnaGen; Vaccine Pty Ltd.	Covax-19™	[33]

57.	**2019-nCoV-RBD-OPT1 DelNS1**	The viral vector that replicates	Jiangsu Provincial Center for Disease Control and Prevention, Beijing Wantai Biological Pharmacy, and Xiamen University	As of 2019, DelNS1-nCoV-RBD-OPT1	[41]
58.	**V451 UQ-CSL**	vaccine using protein subunits	University of Queensland (CSL)	Sclamping SARS-CoV-2	[49]
59.	**CoV2-1 VXA**	Adenovirus type 5 vector recombinant vaccine	Vaxart company	The VXA-CoV2-1	[24]
60.	**Ad-COVID**	vaccine administered intranasally	Summit Biosciences, Altimmune, and the University of Alabama at Birmingham	Unknown	[26]
61.	**COVAC-2**	Based on Protein subunit vaccines	Vaccine and Infectious Disease Organization-International Vaccine Center; University of Saskatchewan	Unknown	[40]
62.	**AAVCOVID**	vaccine based on genes	University of Pennsylvania; Massachusetts Eye and Ear; Massachusetts General Hospital	Unknown	[49]
63.	**SARS-CoV-2-S-ChAd**	vaccine based on adenovirus	St. Louis's Washington University School of Medicine	SARS-ChAd-CoV-2-S	[40]
64.	**HaloVax Vccine**	Vaccine that assembles itself	MGH Vaccine and Immunotherapy Center; Hoth Therapeutics, Inc.; Voltron Therapeutics, Inc.	HaloVax trademark	[26]
65.	**LineaDNA**	DNA vaccine	Takis Biotech	Linear DNA Vaccine	[53]
66.	**PittCoVacc**	Microneedle array recombinant protein subunit vaccine	School of Medicine at the University of Pittsburgh (UPMC)	Unknown	[76]
67.	**T-COVID™**	Intranasal vaccine	Autoimmune	Unknown	[53]
68.	**LNP-nCoVsaRNA**	The RNA vaccine that amplifies itself	Imperial College London	Unknown	[24]
69.	**V590**	Vesicular stomatitis virus recombinant vaccine	Merck; IAVI	Unknown	[49]

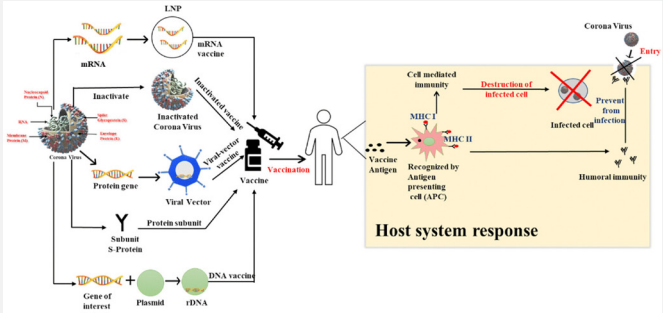

Figure 3: Vaccine strategies and immune response [71].

Status of these vaccines during different phases of clinical trials

a. Preclinical phase

- In vitro testing and animal models to evaluate safety and immunogenicity.
- Variant-specific new-generation mRNA vaccines.
- Innovative delivery techniques (electroporation for DNA vaccines, nanoparticles) [46,47].

b. Phase I: Safety and dose escalation

- Evaluate the initial immune response, safety, and tolerability in small groups (20-100 participants)
- **mRNA vaccines:** Moderna's mRNA-1273 started in Phase I in March 2020.
- **Inactivated vaccines:** Early trials of Sinopharm and Sinovac [72,73].

c. Phase II: Immunogenicity and dosage optimization

- Verify immunological response, adjust dosage, and assess immediate safety in larger cohorts (hundreds of participants).[45]
- **Novavax (NVX-CoV2373):** Showed strong immune responses with adjuvant in Phase II trials.
- **ZyCoV-D:** DNA vaccine by Zydus Cadila demonstrated safety and immunogenicity in Phase II [74].

d. Phase III: Large-scale efficacy trials

- Evaluate efficacy and rare side effects across diverse populations (thousands of participants).
- **Pfizer-BioNTech (BNT162b2):** Completed Phase III with >95% efficacy against symptomatic COVID-19.
- **AstraZeneca (ChAdOx1-S):** Reported ~70% efficacy, varying with dosing regimens.
- **Johnson & Johnson (Ad26.COV2.S):** Demonstrated 66% efficacy against moderate to severe disease in Phase III [48,49].

e. Post-approval (Phase IV): Long-term monitoring

- Assess long-term safety and effectiveness in real-world setting.

1. Booster studies: Pfizer and Moderna evaluating third and bivalent doses against Omicron and other variants.

2. Mix-and-Match trials: Research into heterologous vaccine schedules (e.g., AstraZeneca followed by mRNA vaccines) [74,75,76].

Table 2: Comparative analysis by trial phase [74,75].

Vaccine Platform	Vaccine Name(s)	Phase I	Phase II	Phase III	Post-Approval Studies
mRNA	Pfizer-BioNTech, Moderna	Completed	Completed	Completed; high efficacy	Boosters, variant updates
Viral Vector	AstraZeneca, Sputnik V	Completed	Completed	Efficacy varies (70%-91.6%)	Real-world effectiveness
Protein Subunit	Novavax	Completed	Completed	~90% efficacy	Pending wider approval
Inactivated Virus	Sinopharm, Sinovac	Completed	Completed	Efficacy 50%-79%	Global usage monitoring
DNA	ZyCoV-D	Completed	Completed	~66% efficacy in Phase III	Early rollout

Outcomes of these trials if any during the completion of the study/interim analysis

1. Interim analyses

- In order to help inform public health decisions and emergency use authorizations, interim analyses are carried out throughout a trial to evaluate initial safety and efficacy.

2. Outcomes of completed studies

- During trials, vaccines demonstrated good overall safety profiles, with the majority of side effects (such as fever, fatigue, and injection site pain) being mild to moderate.
- Although they were discovered after the product was put on the market, rare side effects like myocarditis (mRNA vaccines) and thrombosis (AstraZeneca, Johnson & Johnson) are still extremely uncommon [76].

Table 3: Outcomes of SARS-CoV-2 vaccine trials [77,78].

Vaccine name	Platform	Interim efficacy results	Final outcomes	Real-world effectiveness	Notable findings
Pfizer-BioNTech	mRNA	95% efficacy (Phase III)	Confirmed 95% efficacy; mild to moderate side effects	High protection against severe disease; reduced efficacy for Omicron	Approved globally; recommended boosters for waning immunity
Moderna	mRNA	94% efficacy (Phase III)	Similar to Pfizer; strong protection against severe disease	Similar real-world effectiveness as Pfizer	Long-lasting T-cell response; booster doses effective
AstraZeneca	Viral vector	~70% efficacy (varies by dose)	Effective but lower efficacy than mRNA vaccines	~70% effective in real-world studies; significant in low-resource settings	Rare blood clotting cases observed
Johnson & Johnson	Viral vector	66% efficacy (Phase III)	85% effective against severe disease; one-dose regimen	Effective against severe disease; lower efficacy vs variants	Single-dose convenience for low-resource areas
Novavax	Protein subunit	90% efficacy overall	Effective against Alpha; reduced efficacy for Beta	Pending real-world data; likely similar to trial results	Adjuvant boosts immune response significantly
Sinopharm	Inactivated virus	~79% efficacy (Phase III)	Safe and effective; efficacy lower than mRNA vaccines	Effective at preventing severe disease; used widely in LMICs	Lower immunogenicity in elderly; booster shots recommended
Sinovac	Inactivated virus	~50%-78% efficacy (varied by trial)	Effective but less robust immune response than others	Moderate real-world efficacy; good safety profile	Widely used; key in global vaccination campaigns
Sputnik V	Viral vector (heterologous)	~91.6% efficacy (Phase III)	High efficacy and protection against severe disease	Effective in real-world studies; widely used in some regions	Two different adenoviral vectors reduce resistance risks
ZyCoV-D	DNA	~66% efficacy (Phase III)	Safe and effective; first approved DNA vaccine	Early data promising; pending broader real-world analysis	Needle-free delivery technology (jet injector)

Various adverse effects related to the vaccines during these trials

1. Mild-to-Moderate effects:

- All vaccines frequently resulted in temporary systemic and local side effects, including fever, exhaustion, and injection site pain. Usually, these effects were self-limiting [57,58].

2. Serious adverse events:

- There was a slight risk of myocarditis with mRNA vaccines, particularly in younger males.
- Very uncommon cases of TTS and GBS have been linked to viral vector vaccines (AstraZeneca and Johnson & Johnson).
- Inactivated vaccines had the mildest profiles overall, while other platforms displayed fewer systemic or uncommon side effects [52-54].

Post-trial monitoring insights

- Rare adverse effects were detected by enhanced pharmacovigilance, guaranteeing continued safety;
- Booster doses were generally well-tolerated, with no appreciable rise in rare adverse events.

Risk-benefit ratio

- For all vaccines, the advantages of vaccination (such as preventing serious illness, hospitalization, and death) greatly exceeded the risks, even in the case of uncommon side effects [78-80].

Table 4: Adverse effects observed during vaccine trials [78,79].

Vaccine Name	Platform	Common Adverse Effects	Rare Adverse Effects	Severity and Frequency	Post-Trial Monitoring Insights
Pfizer-BioNTech	mRNA	Fatigue, fever, headache, injection site pain	Myocarditis (more in younger males, 1:50,000), anaphylaxis	Mild to moderate; rare AEs very infrequent	Booster doses well-tolerated with similar AE profile
Moderna	mRNA	Fatigue, chills, headache, injection site pain	Myocarditis (younger males), anaphylaxis	Slightly higher rates of systemic AEs vs Pfizer	Similar safety for boosters; myocarditis cases manageable
AstraZeneca	Viral vector	Fatigue, fever, injection site pain, muscle aches	Thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré Syndrome	Very rare TTS (~1:100,000); higher in younger women	Risk-benefit ratio favorable, with continued usage
Johnson & Johnson	Viral vector	Fatigue, fever, injection site pain, headache	TTS, Guillain-Barré Syndrome	Rare TTS (~1:500,000); lower frequency vs AstraZeneca	Safety monitoring led to targeted age-group advisories
Novavax	Protein subunit	Fatigue, fever, headache, injection site reactions	Myocarditis (rare), hypersensitivity reactions	Lower systemic AEs compared to mRNA vaccines	Awaiting real-world AE data; promising safety profile
Sinopharm	Inactivated virus	Injection site pain, fatigue, headache, fever	Rare allergic reactions	Generally mild and less frequent systemic AEs	High safety in real-world studies, including elderly
Sinovac	Inactivated virus	Injection site pain, fatigue, headache, fever	Rare allergic reactions	Lower rate of AEs vs mRNA and viral vector vaccines	Similar safety profile globally
Sputnik V	Viral vector	Fatigue, fever, headache, muscle pain	No notable rare AEs reported	Mild to moderate AEs; good tolerability	Long-term safety data limited
ZyCoV-D	DNA	Fatigue, fever, headache, injection site redness	No major rare AEs reported	Mild AEs; injection site reactions common	Needle-free delivery reduced injection pain

Discussion

In addition to being effective at preventing serious illness and death, the COVID-19 vaccines are anticipated to offer at least some protection against novel virus variants [61]. This is due to the fact that these vaccines elicit a wide-ranging immune response, so any modifications or mutations in the virus shouldn't render them totally ineffective. It will be feasible to alter the vaccines' composition to provide protection against these variants if any of them lose their effectiveness against one or more of them. Data on novel COVID-19 virus variations is still being gathered and examined.

In order to prevent mutations that could lessen the effectiveness of current vaccines, we must take all reasonable steps to stop the virus's spread while we learn more. This entails keeping a minimum of one meter between you and other people, covering your elbow when you cough or sneeze, washing your hands often, donning a mask, avoiding poorly ventilated spaces, and opening windows.

Conclusion

The baseline effectiveness of a COVID-19 vaccine had a significant impact on its acceptance. It might be challenging to get the general public to accept a vaccine with comparatively low efficacy [55,56].

Therefore, creating a COVID-19 vaccine that is suitable for use everywhere is a top priority. The process of developing a vaccine is time-consuming and costly [59,60]. Preclinical testing concurrent with phase 1 clinical trials, platform development, and simple licensing are some of the new strategies that have been introduced to speed up the development of an appropriate COVID-19 vaccine. Gaining more knowledge about SARS-CoV-2's traits can aid in directing the creation of more targeted vaccinations. 115 of the more than 200 vaccine candidates that have been reported so far have advanced to phase 1, 2, or even 3 clinical trials. A COVID-19 vaccine's demonstrated safety and effectiveness are crucial factors to take into account before approving it. To guarantee that everyone has equal access to resources, careful and comprehensive planning must. Priority should be given to administering vaccines to high-risk individuals and medical personnel. Issues pertaining to supply chains, ownership of vaccines, and funding large-scale production need to be fixed [62,63].

Declarations

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