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MINI-REVIEW

Tracking the COVID-19 vaccines: The global landscape

Tushar Yadav[a*], Swatantra Kumar[b,c,d*], Gourav Mishra[e], and Shailendra K. Saxena[b,c,d*]

[a]Department of Zoology, Jawaharlal Nehru Smriti Government Post Graduate College, Shujalpur, India; [b]Centre for Advanced Research (CFAR), Faculty of Medicine, King George's Medical University (KGMU), Lucknow, India; [c]World Society for Virology, Northampton, MA, USA; [d]The Indian Virological Society, New Delhi, India; [e]Department of Biotechnology, Meerut Institute of Engineering and Technology, Meerut, India

ABSTRACT

COVID-19, a respiratory infectious disease, occurs due to Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Millions of individuals around the world have been impacted by the illness, which has gravely threatened human health. The development and active involvement of varied vaccines against the COVID-19 have played a great and relieving role in controlling the life-threatening disease. Both the conventional and advanced vaccine platforms are available now to develop vaccines against COVID-19. Therefore, the present systematic review focuses on the global landscape of the COVID-19 vaccines and their current status. Among COVID-19 vaccines, virus like particles (VLPs), subunit vaccines, DNA, RNA-based vaccines, viral vector-based vaccines, inactivated and live-attenuated vaccines are the major contenders and are currently in various phase of clinical trials. Protein subunit, RNA-based and non-replicating viral vector-based platforms have been used majorly. Nevertheless, inactivated virus vaccine has been utilized clinically around the world. The clinical trials revealed that most of the vaccines have local or systemic effects after vaccination and varied efficacy against SARS-CoV-2 and its variants. However, further studies are necessary to refine the technology to minimize adverse effects and improve the safety and efficacy.

Abbreviations: COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; VLPs: Virus like particles; WHO: World Health Organization; E: Envelope; M: Membrane; S: Spike; N: Nucleocapsid; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; FDA: Food and Drug Administration; LNP: lipid-nanoparticle; AZD1222: ChAdOx1 nCoV-19; BNT162b2: Pfizer-BioNTech mRNA vaccine; mRNA-1273: Moderna vaccine; Ad26.COV2.S: Johnson and Johnson – Janssen's vaccine; Gam-COVID-Vac: Sputnik Vaccine; NVX-CoV2373: Novavax vaccine with Matrix-M™ adjuvant.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected a huge population worldwide. During March 2020, the World Health Organization (WHO) specified it as a pandemic, since then it has caused extensive morbidity and mortality around the globe. As of now (December 2022), the disease has caused approximately 6.6 million deaths and infection in more than 651 million people.[1] SARS-CoV-2, produces a variety of health problems, from mild instances to severe ones with significant mortality rates. Among the four most important structural proteins of the coronavirus, three are envelope (E), membrane (M) and spike (S) proteins found on the viral surface envelope, while the fourth one is nucleocapsid (N) protein, present in the ribonucleoprotein core. These are the primary targets for potential vaccines. SARS-CoV-2 like other RNA viruses may undergo mutation very often while passing from one host to another causing emergence of new variants that differ in characteristics with the original strain and responsible for multiple episodes of the pandemic in due time.[2–6]

Many countries are still suffering the multiple waves of disease outbreaks though the disease transmission and death has declined due to several effective measures taken by health providers, communities and concerned governments.[7–9] However, the safe and effective prophylactic vaccines are of immediate necessity to curb the disaster led by pandemic that has already shattered the medical, economic, and social status of the society. Therefore, most of the countries now indulged in the development of effective COVID-19 vaccines through their assessment and manufacture.

Vaccine is a crucial way to restrain the current pandemic and several research activities on COVID-19 therapeutics are going on with an exceptional speed. The vaccine platforms are of two categories one is based on viral components and another is based on the whole virus. Viral components include protein subunit, virus like particle, DNA-based, RNA-based, non-replicating viral vectors and replicating viral vectors. Whereas, the whole virus-based platform includes inactivated and live-attenuated vaccines (Figure 1). Whatever may be the platform, a competent vaccine must be easy to develop, reproduce and administer, safe, thermostable and with low manufacturing cost. Although with several drawbacks presently over 200 vaccine

CONTACT Shailendra K. Saxena shailen@kgmcindia.edu Centre for Advanced Research (CFAR), Faculty of Medicine, King George's Medical University (KGMU), Lucknow 226003, India

*Contributed equally as first author.

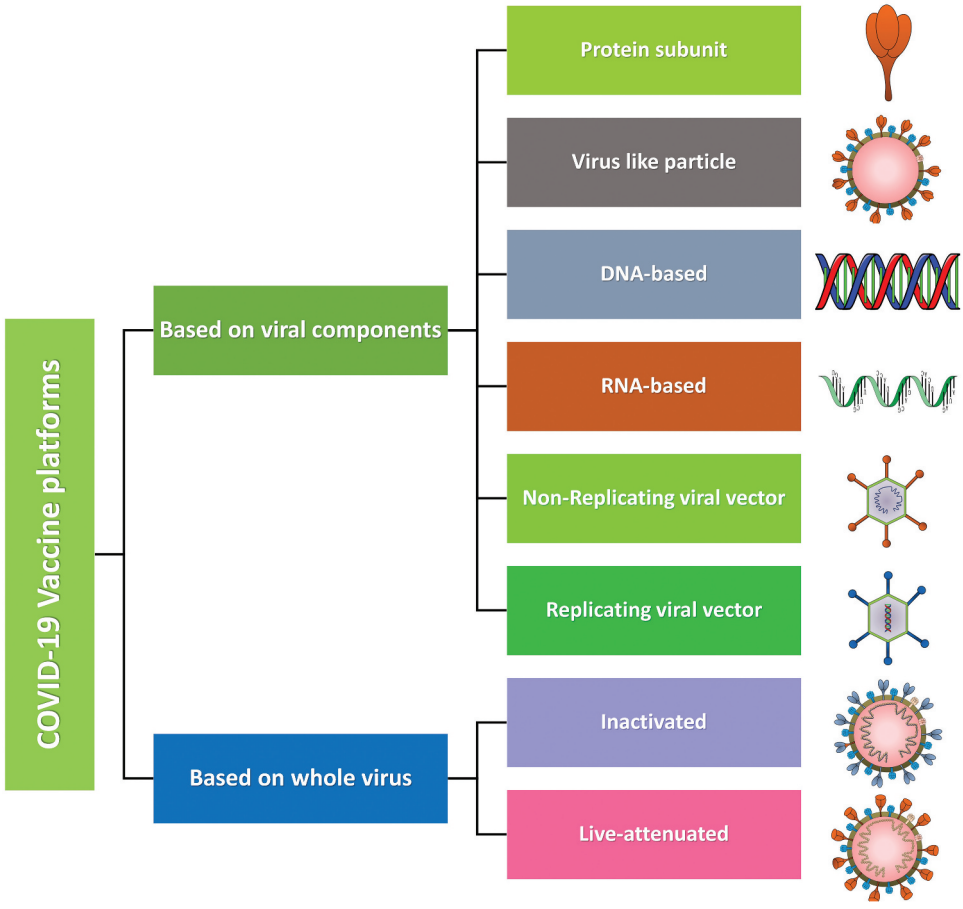

Figure 1. COVID-19 vaccines platforms. Types of various platforms used for the development of COVID-19 vaccines. Platforms based on viral components comprises protein-subunit vaccines which are isolated and purified viral proteins. Virus like particles (VLP) composed of viral proteins that mimic the structure of the virus, but no genetic material. DNA- and RNA-based vaccines are viral genetic material which encodes for viral proteins. Non-replicating viral vectors containing viral genetic material packaged inside viral vectors that cannot replicate. Replicating viral vectors containing viral genetic material packaged inside other viral vectors that can replicate. Whole virus-based vaccines are inactivated that contain copies of the virus that have been killed (inactivated) and live-attenuated which contains copies of the virus that have been weakened (attenuated).

research are in progress among which a large number of vaccines with a variety of platforms have been given approval for clinical trials.[1,10] Pharmaceutical companies and their vaccine contenders like Pfizer-BioNTech's BNT162, Oxford-AstraZeneca's AZD1222, Sinovac's CoronaVac, Moderna's mRNA-1273, Johnson & Johnson's Ad26.COV2.S, Sputnik-V, vector vaccines (Gamaleya National Research Centre for Epidemiology and Microbiology, and adjuvanted recombinant protein nanoparticles (Novavax) are currently leading with their excellent research and development on COVID-19.[11,12]

A recombinant COVID-19 vaccine consists of an antigenic part of the virus that not only minimizes the secondary complications associated with live or attenuated vaccines but also has shown improved efficacy and safety. Till now the performance of the recombinant vaccines has been very promising and going through much detailed evaluation. Several vaccine candidates are under clinical trials and some of them have crossed phase III trials successfully and got administrative approval for further processes. Vaccine studies are mostly designed as individually randomized, placebo-controlled clinical trials (RCTs) and will certainly help to gather the essential information very fast and in an efficient way complying with desired ethical and scientific standards. We have earlier presented the advances in recombinant COVID-19 vaccine research and development and associated issues.[12] Therefore, the present systematic review focuses on the global landscape of the COVID-19 vaccines and their current status.

Methods

Literature search strategy and selection criteria

According to the WHO's most recent update, "DRAFT landscape of COVID-19 potential vaccines (December 2022),"[1] was retrieved to ascertain the prospective vaccine contenders. This study was designed according to PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol, a reconstructed guideline for reporting systematic review statements.[13] The concerned literature was searched in PubMed, Google Scholar, Cochrane databases, WHO databases and COVID-19 vaccine tracker[2] till December 30, 2022. The literature available in English language was only considered with search terms such as "COVID-19 Vaccines," "Coronavirus Vaccines," "SARS-CoV-2 vaccine," and individual vaccine names. The literature with vaccines against COVID-19 in phase I to phase IV trials were selected for the study. Only the interventional investigations that evaluated the effectiveness and safety aspects of COVID-19 vaccines in phase III/IV trials among healthy people of all age-groups in both sexes were included and the study that

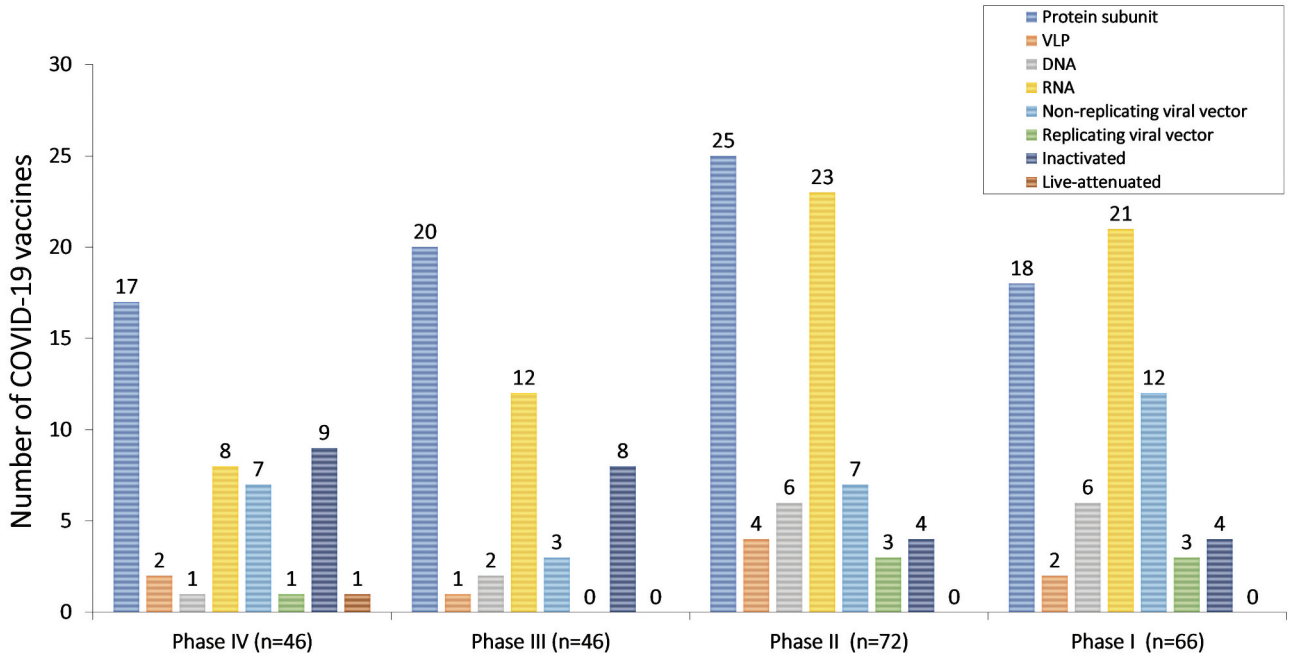

Figure 2. Status of COVID-19 vaccines. Bar graph showing the number of COVID-19 vaccines in different stages of clinical trials. Among the phase IV trials ($n = 46$), 17 are protein subunit vaccines, 2 are VLP vaccines, 1 is DNA vaccine, 8 are RNA vaccines, 7 are non-replicating viral vector vaccines, 1 is replicating viral vector, 9 are inactivated vaccines and 1 is live attenuated vaccine. In phase III trials ($n = 46$), 20 protein subunit vaccines, 1 is VLP vaccine, 2 are DNA vaccines, 12 are RNA vaccines, 3 are non-replicating viral vector vaccines, and 8 inactivated vaccines. In phase II trials ($n = 72$), 25 are protein subunit-based vaccines, 4 VLP based vaccines, 6 DNA based vaccines, 23 are RNA vaccines, 7 are non-replicating viral vector vaccines, 3 are replicating viral vectors, and 4 are inactivated vaccines. In phase I trial ($n = 66$), 18 are protein subunit vaccines, 2 are VLP vaccines, 6 are DNA based vaccines, 21 are RNA vaccines, 12 are non-replicating viral vector vaccines, 3 are replicating viral vector vaccines, and 4 are inactivated vaccines.

showed statistical information on all types of secondary complications. Based on the title and abstract of the articles, those studies and reviews that were not related to the current study or in duplication were rejected. The studies irrelevant to the inclusion criteria were rejected after reading the full text.

Results and discussion

COVID-19 vaccines and their status

Number of COVID-19 vaccines and their status have been summarized in Figure 2. As per the data exhibited in Figure 2 a total of 242 vaccines against COVID-19 are in clinical studies.[1,2] Among which 46 are in phase III clinical trials while 46 in phase IV which have been approved in various countries as on 30 December 2022. Among the phase IV/approved vaccines, 17 are protein subunit vaccines, 2 are VLP vaccines, 1 is DNA vaccine, 8 are RNA vaccines, 7 are non-replicating viral vector vaccines, 1 is replicating viral vector, 9 are inactivated vaccines and 1 is live attenuated vaccine. Whereas, 20 protein subunit vaccines, 1 is VLP vaccine, 2 are DNA vaccines, 12 are RNA vaccines, 3 are non-replicating viral vector vaccines, and 8 inactivated vaccines are in phase III trials (Table 1). In addition, 72 vaccine candidates are in phase II trials among which 25 are protein subunit-based vaccines, 4 VLP-based vaccines, 6 DNA-based vaccines, 23 are RNA vaccines, 7 are non-replicating viral vector vaccines, 3 are replicating viral vectors, and 4 are inactivated vaccines. Importantly, few of the phase II trials related vaccines have been approved in some countries (Table 2). Moreover, 66 vaccine candidates are in phase I trial among which 18 are protein subunit vaccines, 2 are VLP vaccines, 6 are DNA based vaccines, 21 are RNA vaccines, 12 are non-replicating viral vector vaccines, 3 are replicating viral vector vaccines, and 4 are inactivated vaccines (Table 3). Importantly, few of the vaccines have been discontinued even at the stage of phase III trials (Table 4).[2] There are a huge number of publications available on COVID-19 vaccine clinical trials and research, but this still requires a comprehensive analysis on the efficacy and safety. This article reviews and explores the efficacy and various secondary complications observed with COVID-19 vaccines currently in phase III and phase IV clinical trials that may offer assistance to further associated clinical research.

COVID-19 Vaccines in phase III and IV clinical trial

DNA based vaccines

DNA vaccines rely on the *in-situ* production of antigenic proteins. Plasmid containing DNA sequence encoding the antigenic viral protein is injected in the host body against which the host body elicits an immune response that protects from future infections.[14] During August 2021, the Government of India approved Emergency Use Authorization to a DNA-based vaccine against COVID-19.

A pharmaceutical company Zydus Cadila, in association with the Department of Biotechnology, India, came with a 3-dose intradermal vaccine, ZyCov-D, intended to administer in people of age twelve years and above. This was the first case of clinical usage of a DNA-based vaccine among humans. The company claims lack of any severity and mortality in phase I trial and about 1000 youngsters have already registered for phase III trial.[15] Another study on ZyCov-D was conducted.[16] It was a multicenter, double-blind, randomized,

Table 1. Status of COVID-19 vaccines under phase III, and phase IV trials/approved.

S. No.	Types of Vaccines	Name of the Vaccines	Status	Approved in number of countries	Status of trials
1	Protein Subunit	**Novavax** (Nuvaxovid)	Approved	40	22 trials in 14 countries
2	Protein Subunit	**Sanofi/GSK** (VidPrevtyn Beta)	Approved	30	3 trials in 2 countries
3	Protein Subunit	**Serum Institute of India** (COVOVAX-Novavax formulation)	Approved	6	7 trials in 3 countries
4	Protein Subunit	**Center for Genetic Engineering and Biotechnology (CIGB)** (Abdala)	Approved	6	5 trials in 1 country
5	Protein Subunit	**Instituto Finlay de Vacunas Cuba** (Soberana 02)	Approved	4	7 trials in 2 countries
6	Protein Subunit	**Medigen** (MVC-COV1901)	Approved	4	15 trials in 4 countries
7	Protein Subunit	**Anhui Zhifei Longcom** (Zifivax)	Approved	4	21 trials in 5 countries
8	Protein Subunit	**Vector State Research Center of Virology and Biotechnology** (EpiVacCorona)	Approved	4	4 trials in 1 country
9	Protein Subunit	**Instituto Finlay de Vacunas Cuba** (Soberana Plus)	Approved	2	5 trials in 1 country
10	Protein Subunit	**Biological E Limited** (Corbevax)	Approved	2	7 trials in 1 country
11	Protein Subunit	**Razi Vaccine and Serum Research Institute** (Razi Cov Pars)	Approved	1	5 trials in 1 country
12	Protein Subunit	**Livzon Mabpharm Inc** (V-01)	Approved	1	7 trials in 3 countries
13	Protein Subunit	**PT Bio Farma** (IndoVac)	Approved	1	4 trials in 1 country
14	Protein Subunit	**Bagheiat-allah University of Medical Sciences** (Noora vaccine)	Approved	1	3 trials in 1 country
15	Protein Subunit	**Vaxine/CinnaGen Co**. (SpikoGen)	Approved	1	8 trials in 2 countries
16	Protein Subunit	**Takeda** (TAK-019-Novavax formulation)	Approved	1	3 trials in 1 country
17	Protein Subunit	**SK Bioscience Co Ltd** (SKYCovione)	Approved	1	7 trials in 6 countries
18	Protein Subunit	**Sanofi/GSK** (SP/GSK subunit D614 vaccine)	Phase III	-	1 trial in 1 country
19	Protein Subunit	**Sanofi/GSK** (Recombinant Protein)	Phase III	-	6 trials in 7 countries
20	Protein Subunit	**Jiangsu Rec-Biotechnology Co Ltd** (ReCOV)	Phase III	-	6 trials in 3 countries
21	Protein Subunit	**Nanogen** (Nanocovax)	Phase III	-	3 trials in 1 country
22	Protein Subunit	**Laboratorios Hipra SA** (COVID-19 vaccine HIPRA)	Phase III	-	10 trials in 4 countries
23	Protein Subunit	**PT Bio Farma** (SARS-CoV-2 Protein Subunit Recombinant Vaccine)	Phase III	-	5 trials in 1 country
24	Protein Subunit	**Novavax** (NVX-CoV2515)	Phase III	-	1 trial in 1 country
25	Protein Subunit	**Novavax** (Bivalent SARS-CoV-2 rS Vaccine)	Phase III	-	1 trial in 1 country
26	Protein Subunit	**Shionogi** (S-268019)	Phase III	-	9 trials in 2 countries
27	Protein Subunit	**EuBiologics Co Ltd** (EuCorVac-19)	Phase III	-	4 trials in 3 countries
28	Protein Subunit	**Sinocelltech** (SCTV01C)	Phase III	-	12 trials in 2 countries
29	Protein Subunit	**COVAXX** (UB-612)	Phase III	-	7 trials in 2 countries
30	Protein Subunit	**Yisheng Biopharma** (PIKA COVID-19 Vaccine)	Phase III	-	3 trials in 1 country
31	Protein Subunit	**Anhui Zhifei Longcom** (Omicron-Delta Recombinant Novel Coronavirus Protein Vaccine-CHO cells)	Phase III	-	1 trial in 1 country
32	Protein Subunit	**West China Hospital** (Recombinant-Sf9 cell)	Phase III	-	9 trials in 5 countries
33	Protein Subunit	**University Medical Center Groningen** (AKS-452)	Phase III	-	4 trials in 2 countries
34	Protein Subunit	**Sinocelltech** (SCTV01E)	Phase III	-	9 trials in 1 country
35	Protein Subunit	**Clover** (SCB-2019)	Phase III	-	15 trials in 13 countries
36	Protein Subunit	**Codagenix Inc** (COVI-VAC)	Phase III	-	3 trials in 1 country
37	Protein Subunit	**Radboud University** (ABNCoV2)	Phase III	-	4 trials in 3 countries
38	VLP	**Medicago** (Covifenz)	Approved	1	6 trials in 6 countries

(*Continued*)

Table 1. (Continued).

S. No.	Types of Vaccines	Name of the Vaccines	Status	Approved in number of countries	Status of trials
39	VLP	**Zydus Cadila** (ZyCoV-D)	Approved	1	6 trials in 1 country
40	VLP	**Yantai Patronus Biotech Co Ltd** (LYB001)	Phase III		6 trials in 1 country
41	DNA	**Moderna** (Spikevax Bivalent Original/Omicron BA.1)	Approved	38	5 trials in 4 countries
42	DNA	**Inovio** (INO-4800)	Phase III		10 trials in 9 countries
43	DNA	**AnGes** (AG0302-COVID19)	Phase III		8 trials in 1 country
44	RNA	**Pfizer/BioNTech** (Comirnaty)	Approved	149	100 trials in 31 countries
45	RNA	**Moderna** (Spikevax)	Approved	88	70 trials in 24 countries
46	RNA	**Pfizer/BioNTech** (Comirnaty Bivalent Original/Omicron BA.1)	Approved	35	3 trials in 5 countries
47	RNA	**Moderna** (Spikevax Bivalent Original/Omicron BA.4/BA.5)	Approved	33	2 trials in 1 country
48	RNA	**Pfizer/BioNTech** (Comirnaty Bivalent Original/Omicron BA.4/BA.5)	Approved	33	4 trials in 1 country
49	RNA	**Gamaleya** (Sputnik Light)	Approved	26	7 trials in 3 countries
50	RNA	**Walvax** (AWcorna)	Approved	1	4 trials in 3 countries
51	RNA	**Gennova Biopharmaceuticals Limited** (GEMCOVAC-19)	Approved	1	2 trials in 1 country
52	RNA	**Providence Therapeutics Holdings Inc**. (PTX-COVID19-B)	Phase III	-	4 trials in 2 countries
53	RNA	**Arcturus Therapeutics Inc** (ARCT-154)	Phase III	-	6 trials in 3 countries
54	RNA	**CanSino Biologics Inc** (COVID-19 mRNA Vaccine)	Phase III	-	3 trials in 1 country
55	RNA	**Stemirna Therapeutics Co Ltd** (SW-BIC-213)	Phase III	-	4 trials in 2 countries
56	RNA	**Daiichi Sankyo Co Ltd** (DS-5670a)	Phase III	-	5 trials in 1 country
57	RNA	**Moderna** (mRNA-1273.211)	Phase III	-	4 trials in 1 country
58	RNA	**AIM Vaccine** (LVRNA009)	Phase III	-	3 trials in 2 countries
59	RNA	**Moderna** (mRNA-1273.617.2)	Phase III	-	2 trials in 1 country
60	RNA	**Moderna** (mRNA-1273.529)	Phase III	-	4 trials in 1 country
61	RNA	**Pfizer/BioNTech** (BNT162b2s01)	Phase III	-	3 trials in 2 countries
62	RNA	**Pfizer/BioNTech (**BNT162b1)	Phase III	-	5 trials in 3 countries
63	RNA	**Moderna** (mRNA-1273.213)	Phase III	-	2 trials in 1 country
64	Non-Replicating Viral Vector	**Oxford/AstraZeneca** (Vaxzevria)	Approved	149	73 trials in 34 countries
65	Non-Replicating Viral Vector	**Janssen (Johnson & Johnson)** (Jcovden)	Approved	113	26 trials in 25 countries
66	Non-Replicating Viral Vector	**Gamaleya** (Sputnik V)	Approved	74	25 trials in 8 countries
67	Non-Replicating Viral Vector	**Serum Institute of India** (Covishield-Oxford/ AstraZeneca formulation)	Approved	49	6 trials in 1 country
68	Non-Replicating Viral Vector	**CanSino** (Convidecia)	Approved	10	14 trials in 6 countries
69	Non-Replicating Viral Vector	**CanSino** (Convidecia Air)	Approved	2	5 trials in 4 countries
70	Non-Replicating Viral Vector	**Bharat Biotech** (iNCOVACC)	Approved	1	4 trials in 1 country
71	Non-Replicating Viral Vector	**Mahidol University** (NDV-HXP-S)	Phase III	-	7 trials in 3 countries
72	Non-Replicating Viral Vector	**ReiThera** (GRAd-COV2)	Phase III	-	5 trials in 12 countries
73	Non-Replicating Viral Vector	**Wantai** (DelNS1–2019-nCoV-RBD-OPT1)	Phase III	-	5 trials in 3 countries
74	Replicating Viral Vector	**Shifa Pharmed Industrial Co** (COVIran Barekat)	Approved	1	6 trials in 1 country

(*Continued*)

Table 1. (Continued).

S. No.	Types of Vaccines	Name of the Vaccines	Status	Approved in number of countries	Status of trials
75	Inactivated	**Sinopharm (Beijing)** (Covilo)	Approved	93	39 trials in 18 countries
76	Inactivated	**Sinovac** (CoronaVac)	Approved	56	42 trials in 10 countries
77	Inactivated	**Valneva** (VLA2001)	Approved	33	9 trials in 4 countries
78	Inactivated	**Bharat Biotech** (Covaxin)	Approved	14	16 trials in 2 countries
79	Inactivated	**Research Institute for Biological Safety Problems (RIBSP)** (QazVac)	Approved	2	3 trials in 1 country
80	Inactivated	**Shenzhen Kangtai Biological Products Co** (KCONVAC)	Approved	2	7 trials in 1 country
81	Inactivated	**Sinopharm (Wuhan)** (Inactivated-Vero Cells)	Approved	2	9 trials in 7 countries
82	Inactivated	**Health Institutes of Turkey** (Turkovac)	Approved	1	8 trials in 1 country
83	Inactivated	**Organization of Defensive Innovation and Research** (FAKHRAVAC-MIVAC)	Approved	1	3 trials in 1 country
84	Inactivated	**KM Biologics Co Ltd** (KD-414)	Phase III	-	7 trials in 2 countries
85	Inactivated	**Airlangga University** (UNAIR Inactivated COVID-19 Vaccine)	Phase III	-	3 trials in 1 country
86	Inactivated	**Valneva** (VLA2101)	Phase III	-	1 trial in 1 country
87	Inactivated	**China National Biotec Group Company Limited** (Omicron COVID-19 Vaccine-Vero Cell)	Phase III	-	3 trials in 1 country
88	Inactivated	**Sinovac** (Trivalent COVID-19 Vaccine-Vero Cell), Inactivated	Phase III	-	1 trial in 1 country
89	Inactivated	**Sinovac** (COVID-19 Vaccine-Vero cell), (Inactivated-Omicron variant)	Phase III	-	1 trial in 1 country
90	Inactivated	**Sinovac** (COVID-19 Vaccine-Vero cell), Inactivated (CZ strain)	Phase III	-	1 trial in 1 country
91	Inactivated	**Chinese Academy of Medical Sciences** (Inactivated-Vero Cells)	Phase III	-	8 trials in 4 countries
92	Live-Attenuated	**National Vaccine and Serum Institute** (Recombinant SARS-CoV-2 Vaccine-CHO Cell)	Approved	1	3 trials in 2 countries

placebo-controlled phase III clinical study conducted at 49 sites in India among subjects of age twelve years and above predominantly males. A needle-free vaccine shot was used to inoculate 3 doses of vaccine or placebo intradermally keeping the distance of 28 days in-between each dose. The ZyCoV-D vaccine was able to promote neutralizing antibodies and cellular immune responses in the recipients making the vaccine about 66·6% efficient with some cases of mild adverse events. The safety profile of ZyCoV-D was equivalent to other DNA-based vaccines in development. Overall, the analysis demonstrates the immunogenicity, efficacy and the safety aspects of ZyCoV-D vaccine in phase III clinical trials. Since the ZyCoV-D vaccine has been constructed on a plasmid DNA platform, the development of new constructs could be fast and therefore will be easy to handle the upcoming new mutant strains.[16,17]

Pennsylvania-based INOVIO has recently got FDA approval for the phase III trial of INO-4800. It is a SARS-CoV-2 Spike DNA-based vaccine administered intradermally with subsequent electroporation with the help of CELLECTRA® 2000. Andrade et al. (2021)[18] evaluated post-vaccination functional antibodies and T cell responses in hosts against SARS-CoV-2 B.1.1.7, B.1.351, and P.1 variants. In agreement to the previous trial results, INO-4800 was found to provoke a satisfactory immune response characterized by the appearance of counteracting antibodies as well as T cell responses. Further, the vaccine was well tolerated and safe for young and elderly people.[14–18–20]

There are few other DNA-based vaccines that are in phase II/III trial. One is AG0302-COVID19 [NCT04655625], a two-dose DNA plasmid vaccine that codes for SARS-CoV-2 S protein administered via intramuscular inoculation designed by AnGes in association with Osaka University and Japan Agency for Medical Research and Development. Another in pipeline is GX-19N [NCT05067946], a two-dose DNA plasmid vaccine expressing SARS-CoV-2 antigenic S protein together with the antigenic nucleocapsid protein (N) developed by Genexine.[21] Even with few limitations, the recent development in DNA vaccine technology and the availability of molecular adjuvants has improved the immunogenicity of these vaccines. The cost-effective production and ease to store are some characteristics that will make them popular especially in third-world countries.

mRNA based vaccines

This platform uses genetically engineered mRNA to train the host cells to express antigenic viral proteins against which the immune system produces antibodies that protect the host body in case of later infections with the same virus. The use of mRNA in the development of a vaccine against COVID-19 is a novel approach. The major advantage of mRNA vaccine platform is its flexibility and effectiveness. Therefore, several RNA vaccine contenders in different developmental stages are under evaluation for their effectiveness against COVID-19. The Food and Drug Administration (FDA) currently endorsed the three mRNA-based vaccinations against COVID-19, these are Pfizer – BioNTech's BNT162b2, Moderna' mRNA-1273 and Johnson and Johnson – Janssen's Ad26.COV2.S. These vaccines have shown high efficacy of about 72% to 95% in trials

Table 2. Status of COVID-19 vaccines under phase II trials/approved.

S. No.	Types of Vaccines	Name of the Vaccines	Status	Approved in number of countries	Status of trials
1	Protein Subunit	**Vector State Research Center of Virology and Biotechnology** (Aurora-CoV)	Approved	1	2 trials in 1 country
2	Protein Subunit	**Adimmune Corporation** (AdimrSC-2f)	Phase II	-	3 trials in 2 countries
3	Protein Subunit	**Novavax** (SII Bivalent)	Phase II	-	2 trials in 1 country
4	Protein Subunit	**Kentucky Bioprocessing** (KBP-201)	Phase II	-	2 trials in 1 country
5	Protein Subunit	**Livzon Pharmaceutical Group Inc** (V-01-351/V-01D)	Phase II	-	2 trials in 1 country
6	Protein Subunit	**Medigen** (MVC-COV1901-Beta)	Phase II	-	1 trial in 1 country
7	Protein Subunit	**Novavax** (ICC Vaccine)	Phase II	-	3 trials in 2 countries
8	Protein Subunit	**Novavax** (SII B.1.351)	Phase II	-	2 trials in 1 country
9	Protein Subunit	**Novavax** (SII B.1.617.2)	Phase II	-	2 trials in 1 country
10	Protein Subunit	**Research Institute for Biological Safety Problems** (QazCoVac-P)	Phase II	-	2 trials in 1 country
11	Protein Subunit	**Human Stem Cell Institute Russia** (Betuvax-CoV-2)	Phase II	-	2 trials in 1 country
12	Protein Subunit	**Shanghai Zerun Biotechnology, Walvax Biotechnology** (202-CoV)	Phase II	-	6 trials in 2 countries
13	Protein Subunit	**Shanghai Zerun Biotechnology, Walvax Biotechnology** (202a-CoV)	Phase II	-	2 trials in 1 country
14	Protein Subunit	**Sinocelltech** (SCTV01E–1)	Phase II	-	1 trial in 0 countries
15	Protein Subunit	**St. Petersburg Research Institute of Vaccines and Sera** (Recombinant subunit vaccine)	Phase II	-	2 trials in 1 country
16	Protein Subunit	**Tuebingen** (CoVac-1)	Phase II	-	3 trials in 1 country
17	Protein Subunit	**University Medical Center Groningen** (AKS-452×)	Phase II	-	1 trial in 1 country
18	Protein Subunit	**University of Saskatchewan** (COVAC-2)	Phase II	-	5 trials in 2 countries
19	Protein Subunit	**Instituto Finlay de Vacunas Cuba** (Soberana 01)	Phase II	-	3 trials in 1 country
20	Protein Subunit	**Clover** (SCB-2020S)	Phase II	-	2 trials in 1 country
21	Protein Subunit	**Center for Genetic Engineering and Biotechnology (CIGB)** (CIGB-669)	Phase II	-	2 trials in 1 country
22	Protein Subunit	**Biological E Limited** (BECOV2D)	Phase II	-	2 trials in 1 country
23	Protein Subunit	**Biological E Limited** (BECOV2C)	Phase II	-	2 trials in 1 country
24	Protein Subunit	**Biological E Limited** (BECOV2B)	Phase II	-	2 trials in 1 country
25	Protein Subunit	**SpyBiotech** (RBD SARS-CoV-2 HBsAg VLP)	Phase II	-	2 trials in 1 country
26	VLP	**VBI Vaccines Inc** (VBI-2902a)	Phase II	-	2 trials in 1 country
27	VLP	**The Scientific and Technological Research Council of Turkey** (SARS-CoV-2 VLP Vaccine Alpha Variant)	Phase II	-	1 trial in 1 country
28	VLP	**The Scientific and Technological Research Council of Turkey** (SARS-CoV-2 VLP Vaccine)	Phase II	-	2 trials in 1 country
29	VLP	**Nykode Therapeutics** (VB10.2129)	Phase II	-	2 trials in 1 country
30	DNA	**Takeda** (TAK-919-Moderna formulation)	Approved	1	2 trials in 1 country
31	DNA	**Nykode Therapeutics (VB10.2129)**	Phase II	-	2 trials in 1 country
32	DNA	**Takis** (COVID-eVax)	Phase II	-	2 trials in 1 country
33	DNA	**Entos Pharmaceuticals Inc** (Covigenix VAX-001)	Phase II	-	2 trials in 1 country
34	DNA	**AnGes** (AG0301-COVID19)	Phase II	-	2 trials in 1 country
35	DNA	**GeneOne Life Science, Inc**. (GLS-5310)	Phase II	-	4 trials in 2 countries
36	RNA	**Pfizer/BioNTech** (BNT162b2-B.1.617.2)	Phase II	-	1 trial in 4 countries

(*Continued*)

Table 2. (Continued).

S. No.	Types of Vaccines	Name of the Vaccines	Status	Approved in number of countries	Status of trials
37	RNA	**Arcturus Therapeutics Inc** (LUNAR-COV19/ARCT-021)	Phase II	-	6 trials in 2 countries
38	RNA	**Arcturus Therapeutics Inc** (ARCT-165)	Phase II	-	2 trials in 2 countries
39	RNA	**SENAI CIMATEC** (HDT-301)	Phase II	-	2 trials in 1 country
40	RNA	**Pfizer/BioNTech** (BNT162c2)	Phase II	-	2 trials in 1 country
41	RNA	**Pfizer/BioNTech** (BNT162b5 Bivalent-WT/OMI BA.2)	Phase II	-	2 trials in 1 country
42	RNA	**Pfizer/BioNTech** (BNT162b3)	Phase II	-	2 trials in 1 country
43	RNA	**EyeGene Inc** (EG-COVID-003)	Phase II	-	2 trials in 1 country
44	RNA	**Pfizer/BioNTech** (BNT162b2-B.1.1.7)	Phase II	-	1 trial in 4 countries
45	RNA	**Pfizer/BioNTech** (BNT162b2-B.1.1.7 + B.1.617.2)	Phase II	-	1 trial in 4 countries
46	RNA	**Moderna** (mRNA-1073)	Phase II	-	2 trials in 1 country
47	RNA	**Gennova Biopharmaceuticals Limited** (HGCO19)	Phase II	-	2 trials in 1 country
48	RNA	**GreenLight Biosciences, Inc**. (GLB-COV2-043)	Phase II	-	2 trials in 0 countries
49	RNA	**ImmunityBio Inc** (AAHI-SC2 Vaccine)	Phase II	-	2 trials in 1 country
50	RNA	**ImmunityBio Inc** (AAHI-SC3 Vaccine)	Phase II	-	2 trials in 1 country
51	RNA	**Elixirgen Therapeutics Inc** (EXG-5003)	Phase II	-	2 trials in 1 country
52	RNA	**CSPC ZhongQi Pharmaceutical Technology** (SYS6006)	Phase II	-	3 trials in 1 country
53	RNA	**Moderna** (mRNA-1283.211)	Phase II	-	1 trial in 1 country
54	RNA	**Moderna** (mRNA-1283)	Phase II	-	2 trials in 1 country
55	RNA	**Pfizer/BioNTech** (BNT162a1)	Phase II	-	2 trials in 1 country
56	RNA	**Chulalongkorn University** (ChulaCov19)	Phase II	-	5 trials in 2 countries
57	RNA	**Chulalongkorn University** (ChulaCov19-BNA159 mRNA Vaccine)	Phase II	-	2 trials in 1 country
58	RNA	**ImmunityBio Inc** (hAd5-Covid-19)	Phase II	-	7 trials in 2 countries
59	Non-Replicating Viral Vector	**Gamaleya** (Gam-COVID-Vac)	Approved	1	2 trials in 0 countries
60	Non-Replicating Viral Vector	**Vaxart** (VXA-CoV2–1.1-S)	Phase II	-	1 trial in 1 country
61	Non-Replicating Viral Vector	**Biocad** (BCD-250)	Phase II	-	2 trials in 1 country
62	Non-Replicating Viral Vector	**Universitätsklinikum Hamburg-Eppendorf** (MVA-SARS-2-ST)	Phase II	-	3 trials in 1 country
63	Non-Replicating Viral Vector	**Shenzhen Geno-Immune Medical Institute** (LV-SMENP)	Phase II	-	2 trials in 1 country
64	Non-Replicating Viral Vector	**Institute of Vaccines and Medical Biologicals** (COVIVAC)	Phase II	-	4 trials in 2 countries
65	Non-Replicating Viral Vector	**Cellid Co (AdCLD-CoV19)**	Phase II	-	5 trials in 1 country
66	Replicating Viral Vector	**Chumakov Center** (KoviVac)	Approved	3	3 trials in 1 country
67	Replicating Viral Vector	**Aivita Biomedical Inc** (AV-COVID-19)	Phase II	-	4 trials in 2 countries
68	Replicating Viral Vector	**City of Hope Medical Center** (COH04S1)	Phase II	-	2 trials in 1 country
69	Inactivated	**Laboratorio Avi-Mex** (Recombinant NDV Vectored Vaccine)	Phase II	-	2 trials in 1 country
70	Inactivated	**Sinovac** (CoronaVac Omicron Vaccine)	Phase II	-	1 trial in 1 country
71	Inactivated	**Sinovac Biotech (Hong Kong) Limited** (COVID-19 Vaccine-Vero Cell), Inactivated, Omicron Strain	Phase II	-	1 trial in 1 country
72	Inactivated	**Sinovac** (CoronaVac Trivalent Vaccine)	Phase II	-	1 trial in 1 country

against moderate-to-severe COVID-19 among adults.[22] The WHO Strategic Advisory Group of Experts on Immunization (SAGE) has recommended the immunization with Pfizer BioNTech (BNT162b2) vaccine against COVID-19. BNT162b2 is a lipid nanoparticle-based nucleoside-modified RNA vaccine encoding a prefusion stabilized, membrane-bound SARS-CoV-2 complete S protein. Polack et al.[23] have investigated the safe use and effectiveness of the BNT162b2 vaccine. The mRNA vaccine was found to cause a brief, mild-to-moderate pain at the inoculation site, tiredness, and headache with minimal cases of severity. The effects were alike in the vaccinated and placebo groups. The two-dose regime of the vaccine offered about 95% safety against the COVID-19 in individuals aged 16 years or above. The study outcomes strengthened the potential of RNA-based vaccines as an efficient protective measure against the disease.

In United States, a phase III trial [NCT04470427] was carried out at various centers for mRNA-1273 vaccine, a lipid-nanoparticle (LNP)–encapsulated mRNA vaccine that expresses the prefusion-stabilized antigenic S protein of SARS-CoV-2, developed by Moderna in collaboration with Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). The vaccine was about 94.1% effective against COVID-19 along with better ability to prevent the severe conditions too. Further, the minimal secondary complications make the vaccine safe and appealing for the mass application.[24] Stamatatos et al. (2021)[25] collected pre- and post-immunization sera from individuals recovered from COVID-19 and from those who were naive and investigated whether the vaccination with BNT162b2 and mRNA-1273 may effective against Wuhan-Hu-1 and B.1.351 strains. The neutralization of Wuhan-Hu-1 strain with pre-immunization sera from recovered individuals were reported while it also counteracted B.1.351 up to certain extent. Moreover, a single shot of vaccines heightened the antibody titer upto 1000 times against both the variants although the second dose of vaccination did not cause any considerable enhancement of neutralization reaction. Upon vaccination the neutralization reaction was also observed in naive individuals, but the magnitude was comparatively low. This study justifies the significance of mRNA vaccines in both COVID-19 affected and naive populations. In one study[22] evaluated the efficacy of three RNA vaccines, Ad26.COV2.S, BNT162b2, and mRNA-1273 in COVID-19 infected patients. They found that the appearance and predominance of delta variants in circulation reduced the efficacy of these vaccines. However, the patients of age 65 years or above showed good response with BNT162b2 and mRNA-1273.

World Health Organization[1] has standardized the doses of BNT162b2 mRNA vaccine that has to be administered 3 to 4 weeks apart. A study was outlined to check the effectiveness of the vaccine if the distance between two doses increases.[26] Worked with the longitudinal data on generation of humoral immunity against the D614G strain and other SARS-CoV-2 variants in a group of previously affected people with SARS-CoV-2 and naive ones who were vaccinated with two doses 16 weeks apart. The distantly administered doses were found to produce much stronger responses especially among naive individuals suggesting that this strategy not only improved the efficacy of doses but also makes the vaccination regime flexible. However, the recognition of all variants and Omicron was found to decline speedily among naive individuals as compared to the previously infected individuals.[26] A similar investigation was led by Chatterjee et al, [27]who have evaluated the host immune response against the Omicron variant in a cohort of previously infected and naive individuals who underwent BNT162b2 mRNA vaccination with a gap of 16 weeks. As compared to the D614G, Alpha, Beta, Gamma, and Delta Spikes the Omicron Spike antigen was not recognized much proficiently. Moreover, those who received two vaccination doses with larger gaps had better antigen recognition and neutralization than the individuals whose two doses were four weeks apart. Most of the studies suggest that the immune system of previously infected individuals was able to recognize and respond more well against all Spike antigens than the naive individuals as observed after 3 weeks and 16 weeks of second dose.[25–27]

Narowski et al.[6] investigated longitudinal immunogenic activity induced by Pfizer-BioNTech mRNA vaccine (BNT162b2), and Moderna mRNA-1273 vaccine against the reference Wuhan strain (WIV04), Delta variant, seven other variants, and four endemic corona viruses in 168 health workers among which 20 were previously infected while 148 were naive at three different stages, prior to vaccination, post first vaccination, and post second vaccination. Following full vaccine doses both the recipients developed a prominent immune response against SARS-CoV-2 spike and varied magnitude of cross-reactive antibodies to seasonal variants. Though the intensity and rate of SARS-CoV-2 counterbalancing antibody response in naive were observed lesser as compared to the previously infected participants. The study also found weaker immune reactions against the Alpha and Delta variants as compared to the reference strain in all participants. The results recommend the development of custom-made vaccines against evolving SARSCoV-2 variants since the current mRNA-vaccine induces inconstant neutralizing antibodies among individuals.

A study was conducted to test the sera obtained from 51 participants inoculated with 2 or 3 doses of mRNA vaccine BNT162b2 against Wuhan-Hu-1 reference strain, Beta (B.1.351), Delta (B.1.617.2), or Omicron pseudo-viruses. Next to the second dose the Omicron neutralizing titers were found to decline by more than 22-fold in comparison to those concentrations found with Wuhan reference strain. Although, a month afterward the third dose, immune response against Omicron showed 23-fold amplification in comparison to their level after the second dose and was equivalent to the concentrations of reference strain neutralizing titers in the second dose afterward. The necessity of a third vaccine dose for effective neutralization of Omicron was defined with sera obtained from a population employing live SARS-CoV-2. The outcomes support the use of the mRNA vaccine in a three-dosage regimen to counteract Omicron infection.[28,29] BNT162b2 mRNA vaccination has been found to be effective against Omicron subvariants including BA.4 and BA.5.[30] In addition, two doses of BNT162b2 have been found to provide 54.9% efficacy in children and adolescents against SARS-CoV

Table 3. Status of COVID-19 vaccines under phase I trials.

S. No.	Types of Vaccines	Name of the Vaccines	Status	Status of trials
1	Protein Subunit	**ACM Biolabs** (ACM-001)	Phase I	1 trial in 1 country
2	Protein Subunit	**University of Melbourne** (DoCo-Pro-RBD-1)	Phase I	1 trial in 1 country
3	Protein Subunit	**Livzon Pharmaceutical Group Inc** (V-01/V-01-B5)	Phase I	1 trial in 1 country
4	Protein Subunit	**Livzon Pharmaceutical Group Inc** (V-01-351/V-01-B5)	Phase I	1 trial in 1 country
5	Protein Subunit	**Livzon Pharmaceutical Group Inc** (V-01)	Phase I	1 trial in 1 country
6	Protein Subunit	**SK Bioscience Co Ltd** (NBP2001)	Phase I	1 trial in 1 country
7	Protein Subunit	**Intravacc B.V**. (Avacc 10)	Phase I	1 trial in 1 country
8	Protein Subunit	**HK inno.N Corporation** (IN-B009)	Phase I	1 trial in 1 country
9	Protein Subunit	**Speransa Therapeutics** (PRIME-2-CoV_Beta)	Phase I	1 trial in 2 countries
10	Protein Subunit	**National Vaccine and Serum Institute** (GEN2-Recombinant COVID-19 Vaccine-CHO Cells)	Phase I	1 trial in 1 country
11	Protein Subunit	**OSE Immunotherapeutics** (CoVepiT)	Phase I	1 trial in 1 country
12	Protein Subunit	**University of Saskatchewan** (COVAC-1)	Phase I	1 trial in 3 countries
13	Protein Subunit	**Emergex Vaccines Holding Ltd** (PepGNP-SARSCoV2)	Phase I	1 trial in 1 country
14	Protein Subunit	**Baiya Phytopharm Co Ltd** (Baiya SARS-CoV-2 Vax 1 Vaccine)	Phase I	1 trial in 1 country
15	Protein Subunit	**Baiya Phytopharm Co Ltd** (Baiya SARS-CoV-2 Vax 2)	Phase I	1 trial in 1 country
16	Protein Subunit	**US Army Medical Research and Development Command** (SpFN COVID-19 Vaccine)	Phase I	1 trial in 1 country
17	Protein Subunit	**VaxForm** (CoV2-OGEN1)	Phase I	1 trial in 1 country
18	Protein Subunit	**VBI Vaccines Inc**. (VBI-2901e)	Phase I	1 trial in 1 country
19	VLP	**VBI Vaccines Inc** (VBI-2901a)	Phase I	1 trial in 1 country
20	VLP	**Imam Abdulrahman Bin Faisal University** (Almansour-001)	Phase I	1 trial in 0 countries
21	DNA	**Symvivo** (bacTRL-Spike)	Phase I	1 trial in 1 country
22	DNA	**Scancell** (COVIDITY)	Phase I	1 trial in 1 country
23	DNA	**The University of Hong Kong** (SARS-CoV-2 DNA Vaccine)	Phase I	1 trial in 1 country
24	DNA	**University of Sydney** (COVIGEN)	Phase I	1 trial in 1 country
25	DNA	**Providence Health & Services** (CORVax12)	Phase I	1 trial in 1 country
26	DNA	**Suzhou Abogen Biosciences** (ABO-CoV.617.2)	Phase I	1 trial in 1 country
27	RNA	**University of Melbourne** (MIPSCo-mRNA-RBD-1)	Phase I	1 trial in 1 country
28	RNA	**VLP Therapeutics Japan** (VLPCOV-01)	Phase I	1 trial in 1 country
29	RNA	**RVAC Medicines** (RVM-V001)	Phase I	1 trial in 1 country
30	RNA	**Pfizer/BioNTech** (qIRV + bivalent BNT162b2 (original/Omi BA.4/BA.5)	Phase I	1 trial in 0 countries
31	RNA	**Pfizer/BioNTech** (BNT162b4)	Phase I	1 trial in 0 countries
32	RNA	**Suzhou Abogen Biosciences** (ABO1009-DP)	Phase I	2 trials in 2 countries
33	RNA	**Walvax Biotechnology** (RQ3013)	Phase I	2 trials in 0 countries
34	RNA	**AIM Vaccine Co., Ltd**. (LVRNA010)	Phase I	1 trial in 0 countries
35	RNA	**Jiangsu Rec-Biotechnology** (RH109)	Phase I	3 trials in 0 countries
36	RNA	**GlaxoSmithKline** (CoV2 SAM-LNP)	Phase I	1 trial in 1 country
37	RNA	**GlaxoSmithKline** (CV0501)	Phase I	1 trial in 3 countries
38	RNA	**GlaxoSmithKline** (CV2CoV)	Phase I	1 trial in 1 country
39	RNA	**Gritstone Bio, Inc**. (GRT-R910)	Phase I	1 trial in 1 country
40	RNA	**MRC/UVRI and LSHTM Uganda Research Unit** (LNP-nCOV saRNA-02 Vaccine)	Phase I	1 trial in 1 country
41	RNA	**Gritstone bio, Inc**. (GRT-R914)	Phase I	1 trial in 1 country
42	RNA	**Gritstone bio, Inc**. (GRT-R918)	Phase I	1 trial in 1 country
43	RNA	**HDT Bio** (HDT-301)	Phase I	1 trial in 1 country
44	RNA	**Gritstone bio, Inc**. (GRT-R912)	Phase I	1 trial in 1 country
45	RNA	**Moderna** (mRNA-1273.351)	Phase I	1 trial in 1 country
46	RNA	**Moderna** (mRNA-1230)	Phase I	1 trial in 3 countries
47	RNA	**EnGeneIC** (COVID-19-EDV)	Phase I	1 trial in 1 country
48	Non-Replicating Viral Vector	**McMaster University** (Ad5-triCoV/Mac)	Phase I	1 trial in 1 country
49	Non-Replicating Viral Vector	**McMaster University** (ChAd-triCoV/Mac)	Phase I	1 trial in 1 country
50	Non-Replicating Viral Vector	**AMMS** (Ad5-nCoV)	Phase I	1 trial in 1 country
51	Non-Replicating Viral Vector	**Tetherex Pharmaceuticals Corporation** (SC-Ad6–1)	Phase I	1 trial in 1 country
52	Non-Replicating Viral Vector	**Ankara City Hospital Bilkent** (CoVacHGMix)	Phase I	1 trial in 1 country
53	Non-Replicating Viral Vector	**Cellid Co** (AdCLD-CoV19–1)	Phase I	1 trial in 1 country
54	Non-Replicating Viral Vector	**CyanVac LLC** (CVXGA1)	Phase I	1 trial in 1 country
55	Non-Replicating Viral Vector	**Universitatsklinikum Hamburg-Eppendorf** (MVA-SARS-2-S)	Phase I	1 trial in 1 country
56	Non-Replicating Viral Vector	**Vaxart** (VXA-CoV2–1)	Phase I	1 trial in 1 country
57	Non-Replicating Viral Vector	**NIAID** (SAM-LNP-S)	Phase I	1 trial in 1 country
58	Non-Replicating Viral Vector	**NIAID** (ChAdV68-S)	Phase I	1 trial in 1 country
59	Non-Replicating Viral Vector	**Shenzhen Geno-Immune Medical Institute** (Covid-19/aAPC)	Phase I	1 trial in 1 country
60	Replicating Viral Vector	**The University of Hong Kong** (DelNS1-nCoV-RBD LAIV)	Phase I	1 trial in 1 country
61	Replicating Viral Vector	**Meissa Vaccines Inc** (MV-014-212)	Phase I	1 trial in 1 country
62	Replicating Viral Vector	**Eva Pharma** (EgyVax Vaccine Candidate)	Phase I	1 trial in 1 country

(*Continued*)

Table 3. (Continued).

S. No.	Types of Vaccines	Name of the Vaccines	Status	Status of trials
63	Inactivated	**Kocak Farma** (Koçak-19 Inaktif Adjuvanlı COVID-19 Vaccine)	Phase I	1 trial in 1 country
64	Inactivated	**Osve Pharmaceutical Company** (OSVID-19)	Phase I	1 trial in 1 country
65	Inactivated	**The Scientific and Technological Research Council of Turkey** (Adjuvanted Inactivated Vaccine)	Phase I	1 trial in 1 country
66	Inactivated	**National Research Centre Egypt** (Covi Vax)	Phase I	1 trial in 1 country

-2 subvariant BA.2 infection in Hong Kong over the past 6 months.[31]

Anti-nucleocapsid antibody (anti-NAb) seropositivity in mRNA-1273 (Moderna) vaccinated individuals have been evaluated who have had severe COVID-19. Out of 700 PCR-confirmed COVID-19 positive participants, 52 were vaccinated with mRNA-1273 in which 21 (40%) showed seroconversion to anti-N Abs. On the other hand, 605 out of 648 placebo recipients exhibited the seroconversion which was about 93%. Each 1-log rise in SARS-CoV-2 copy number at the time of analysis was correlated with 90% higher odds of anti-NAb seroconversion (odds ratio, 1.90). mRNA-1273 vaccination has been found to provide moderate and short-lived (~90 days) protection against several of the Omicron subvariants including BA.1, BA.2, BA.2.12.1, BA.4 and BA.5.[32] Currently three candidate mRNA vaccines including mRNA-1273 and BNT162 (3 LNP-mRNAs) are in phase IV clinical trials although the final data is yet to come.[1,12] Overall, the mRNA vaccination programme appears to be quite effective at reducing the number of COVID-19 variations in circulation, although more study is required to improve its specificity and efficacy.

Vector-based vaccines

A viral vector-based vaccine utilizes a viral vector to carry genetic material that codes for a sought-after antigenic protein inside the recipient's host cells. The adenoviral vector-based vaccines have long been studied for their safe and effective use. These vaccines have the ability to stimulate cellular as well as humoral immune response.[11] Ramasamy et al.[33] reported the immunogenicity of ChAdOx1 nCoV-19 (AZD1222), a chimpanzee adenovirus-vectored vaccine with defective replication that express the full-length SARS-CoV-2 antigenic S protein gene. The safety and efficacy of this vaccine were tested on a widespread population including young adults as well as those with age 70 years or more. This single-blind, randomized, controlled, phase II/III trial (COV002) recruited healthy adults of age 18 years and above in two clinical research facilities in the United Kingdom (UK). The study was conducted in a hierarchical manner by grouping participants into various subgroups; first with age between 18 to 55 years, second with age 56 to 69 years, and third subgroup with 70 years and above. ChAdOx1 nCoV-19 was found to be tolerated well among old adult subgroups as compared to the younger adult subgroup with equivalent immune response following a booster dose. Further evaluation of the vaccine among all age groups and people with comorbidities is necessary regarding its safe and effective application. AZD1222 vaccine with hybrid immunity has been found effective after 6 months of the vaccination (COV005) against Omicron BA.1 and BA.4 variants.[34]

Another phase III clinical trial of rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine Gam-COVID-Vac (Sputnik V) developed by Gamaleya Research Institute of Epidemiology and Microbiology was conducted at 25 clinical setups in Moscow, Russia. The vaccine was reported as a very safe and potent immune stimulator during phase I/II clinical trials. The vaccine exhibited about 91.6% efficacy against COVID-19 and was well tolerated among a large group as exhibited in the preliminary analysis of phase III trial.[11] As of June 2021, the Sputnik V vaccine has been approved in 68 countries, though the efficacy of the vaccine needs more analysis on large samples.[35]

The phase III clinical trial of Ad26.COV2.S, a non-replicating adenovirus vector-based vaccine revealed that even one dose (5×10^{10} viral particles) have capability to induce 73.1% and 81.7% efficacy in critically infected subjects on 14 and 28 days, respectively, presenting its safer side.[36] Another phase III clinical trial [NCT04516746] funded by AstraZeneca and others was conducted by Falsey et al..[37] They inspected the safety, effectiveness, and immunogenic potential of two dose regimes of AZD1222 vaccine in blocking the commencement of symptomatic and severe COVID-19 within 15 days or more following second dose in young and older adults, in the United States, Chile, and Peru. There were few local and systemic effects but largely mild or moderate was reported in both cohorts although the vaccine was found about 74.0% effective. The first dose of vaccine escalated the neutralizing antibodies that further increased on 28th day following the second dose. So far AZD1222 was found safe and effective against symptomatic and severe COVID-19 cases among different populations including older adults. Viral vector-based vaccines are among the most studied platforms and currently 4 candidate vaccines are in phase IV clinical trials including ChAdOx1-S (AZD1222), Ad5-nCoV and Ad26.COV2.S.[1,12]

Subunit vaccines

Heath et al.[38] recently completed a Phase III clinical trial for the comparison of immunogenic potential and safety of 3 distinct sets of Novavax vaccine with Matrix-M™ adjuvant (NVX-CoV2373). It is a recombinant nanoparticle-based vaccine containing complete S glycoprotein of the prototype SARSCoV-2 strain with Matrix-M adjuvant. The NVX-CoV2373 vaccine imparted about 89.7% protection to the adult participants against SARS-CoV-2 infection who received two doses. The vaccine had substantial ability to restrain the B.1.1.7 variant. The trial was sponsored by Novavax and was carried out at 33 locations in the UK [EudraCT number 2020–004123–16]. One more observer-blinded phase III trial was

Table 4. Discontinued COVID-19 vaccines.

S. No.	Types of Vaccines	Name of the Vaccines	Status	Status of trials
1	Protein Subunit	**Merck Sharp & Dohme Corp** (V591)	Phase II	2 trials in 3 countries
2	DNA	**Genexine** (GX-19)	Phase III	7 trials in 1 country
3	DNA	**Israel Institute for Biological Research (IIBR)** (Brilife)	Phase III	4 trials in 1 country
4	RNA	**Curevac** (CVnCoV)	Phase III	9 trials in 12 countries
5	RNA	**Altimmune Inc** (AdCOVID)	Phase I	1 trial in 1 country
6	RNA	**Institut Pasteur** (COVID-19-101)	Phase I	1 trial in 2 countries
7	Non-Replicating Viral Vector	**Icosavax** (IVX-411)	Phase II	2 trials in 1 country
8	Non-Replicating Viral Vector	**Imperial** (LNP-nCoVsaRNA)	Phase I	1 trial in 1 country
9	Replicating Viral Vector	**Oxford/AstraZeneca** (AZD2816)	Phase III	2 trials in 2 countries
10	Replicating Viral Vector	**Sanofi Pasteur** (MRT5500)	Phase II	2 trials in 1 country
11	Replicating Viral Vector	**Merck Sharp & Dohme Corp** (V590)	Phase I	1 trial in 1 country
12	Replicating Viral Vector	**Queensland** (Sclamp)	Phase I	1 trial in 1 country

conducted in the United States and Mexico during the initial phase of the year 2021 to assess the safety and effectiveness of NVX-CoV2373 in grown-ups. The clinical study involved 29,949 participants and was funded by Novavax and others [NCT04611802]. The study reported mild to moderate immune response after the first dose that became more prominent after the second dose. The vaccine was found about 92.6% (95% CI, 83.6 to 96.7) efficient against the variant under examination. Further analysis is underway to prove the NVX-CoV2373 vaccine safer and effective against COVID-19.[39] Recently, Novavax has been found to provide neutralization of Omicron subvariants including BA.1, BA.4, and BA.5 after three doses of NVX-CoV2373 vaccine.[40]

COVID-19 vaccines and emerging SARS-CoV-2 variants

Since the past few years COVID-19 has imposed a huge issue not only regarding human health but also affected the social and economic status of the society. Even after several strategies made mandatory by the administrative bodies and practicing personal hygiene and maintaining social distance the endemic has caused a huge morbidity and mortality worldwide. Even the administration of antiviral drugs couldn't be able to curb the dissemination of COVID-19 and prevention of endemic. Vaccines were found as an indispensable tool to fight against the hazardous disease. Currently varied platforms are available for development of vaccines against COVID-19, each with their associated pros and cons. Since the last two years numerous vaccines have been given approval to curtail morbidity and mortality linked to COVID-19, regardless of the potential risks accompanying newly permitted vaccines. The quick licensing of COVID-19 vaccinations could potentially be very important in managing the dangerous disease.[41] Several of the crucial factors which may determine efficacy of vaccines are route of vaccination, its dose and frequency. Most of the current vaccines are designed to induced immune response via targeting systemic immune system and generating weak mucosal immunity. Importantly, mucosal immunity is crucial to achieve for robust immune response due to its microenvironment comprising of integrated network of lymphoid, nonlymphoid, tissue, and effector molecules. In case of COVID-19, vaccines targeting mucosal immunity is crucial to achieve since it may prevent the spread of SARS-CoV-2 in the lower airways and lungs and therefore important as a preventive measures to reduce the transmission. AZD1222 has been shown to induce durable nasal anti-spike IgG response.[42] Importantly, BNT162b2 has been shown to induce robust systemic immune response. However, it has failed to provide mucosal immunity.[43,44]

Systemic mRNA vaccination has been shown to induce weak mucosal immunity. Interestingly, combination of mucosal adenovirus-S along with mRNA immunization has been found to induce robust neutralizing antibody response not only toward previous variants but also against Omicron subvariant BA.1.1.[45] Importantly, recurrent emerging variants of SARS-CoV-2 are continuously challenging the efficacy of COVID-19 vaccines. Recent emergence of Omicron and its subvariants has transmitted throughout the globe as a VOCs. Therefore, it is crucial to address the efficacy of the vaccines against emerging variants. Interestingly, BNT162b2 mRNA vaccine has been found to be effective against Omicron subvariants including BA.4 and BA.5.[30] In addition, it has been found to provide 54.9% efficacy after two doses of BNT162b2.[31] Importantly, mRNA 1273 has been found to be effective against several of the Omicron subvariants including BA.1, BA.2, and BA.4/BA.5.[32] AZD1222 has been recently found to provide hybrid immunity against Omicron subvariants including BA.1 and BA.4.[34] Recently, Novavax has been found to provide neutralization of Omicron subvariants including BA.1, BA.4/BA.5 after three doses of NVX-CoV2373 vaccine.[40] Several of the vaccines have been administered as a booster dose to combat the newly emerging SARS-CoV-2 variants.

Conclusions

However, the vaccines developed in rush without suitable time-taking clinical trials may generate some long-lasting or life-threatening health hazards as most of these vaccines have mild to moderate local and systemic adverse effects. Studies have reported pain in the injection site, erythema, headache, fatigue, malaise, etc.[24–48] One major threat is Vaccine-associated enhanced disease (VAED) or antibody-dependent enhancement (ADE) although an uncommon secondary complication, it may give rise to some life-threatening adverse consequences developed due to pathogen-specific antibodies generated either by vaccination or primary infection.[41] The current phase III and phase IV vaccines seem promising, and the study will help to find a better option and strategy to manage the disease. To halt the pandemic spread it is essential to speed up the current vaccination drives. The earlier studies

on COVID-19 have generated a large quantity of data on virus as well as vaccine mediated immune responses that will certainly improve the vaccine development strategy. We have recently discussed the progress and challenges toward generation and maintenance of long-lived memory T lymphocyte responses during COVID-19 in detail.[49]

Future perspectives

The phase III and phase IV clinical trial will pave a path to clear substantial uncertainties about the developed COVID-19 vaccines and their application. It is crucial to thoroughly assess the COVID-19 vaccines' safety and effectiveness in a sizable population. Waning immunity following COVID-19 vaccination is a big concern, and millions of vaccinated individuals have opted out of booster vaccination. There is an absolute need for a long-term follow-up strategy to uncover any underlying adverse events post vaccination. However, the novel vaccines may contribute a lot in minimizing the devastating effect of the COVID-19 pandemic. Most of the vaccines are designed to induce an antibody mediated protection against SARS-CoV-2 infection. However, due to vaccine breakthrough cases and antibody escape mechanisms attained by the newer emerging strains of SARS-CoV-2, it is imperative to look for the robust T memory cell response for long-term protection against COVID-19.

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ORCID

Shailendra K. Saxena http://orcid.org/0000-0003-2856-4185

Author contributions statement

SKS conceived the idea and planned the study. TY, SK, and SKS collected the data, devised the initial draft, reviewed the final draft, and contributed equally to this study as the first author. TY, SK, GM, and SKS finalized the draft for submission. All authors read and approved the final version of the manuscript.

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