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REVIEW

Diverse vaccine platforms safeguarding against SARS-CoV-2 and its variants

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ABSTRACT

Introduction: Appearances of SARS-CoV-2 variants have created havoc and additional challenges for the ongoing vaccination drive against pandemic COVID-19. Interestingly, several vaccine platforms are showing great potential to produce successful vaccines against SARS-CoV-2 and its variants. Billions of COVID-19 vaccine doses have been administered worldwide. Mix-and-Match COVID-19 vaccines involving the mixing of the same platform vaccines and also two different vaccine platforms may provide greater protection against SARS-CoV-2 and its variants. COVID-19 vaccines have become one of the most important tools to mitigate the ongoing pandemic COVID-19.

Areas covered: We describe SARS-Cov-2 variants, their impact on the population, COVID-19 vaccines, diverse vaccine platforms, doses of vaccines, the efficacy of vaccines against SARS-CoV-2 and its variants, mitigation of the COVID-19 transmission- alternatives to vaccines.

Expert opinion: Diverse vaccine platforms may safeguard against ongoing, deadly SARS-CoV-2 and its infectious variants. The efficacies of COVID-19 vaccines are significantly high after the administration of the second dose. Further, it protects individuals including vulnerable patients with co-morbidities from SARS-CoV-2 and its variants. The hospitalizations and deaths of the individuals may be prevented by COVID-19 vaccines.

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COVID-19; sars-cov-2; vaccines; diverse; variants; platforms

1. Introduction

COVID-19 is a highly infectious, airborne viral disease with a big threat for patients having respiratory, cardiovascular diseases, compromised immune systems, hypertension, diabetes and other diseases [1–3]. It was declared a global pandemic on 11 March 2020 by World Health Organization (WHO). The ongoing SARS-CoV-2 pandemic has challenged human life and the peace of the world. The virus SARS-CoV -2 uses its spike (S) glycoprotein to enter the human body by binding to its angiotensin-converting enzyme 2 (ACE2) receptors [4,5]. SARS-CoV-2 is a positive-sense single-stranded RNA virus and has a greater chance of mutation in its sequence for its survival. The complementary mutations might have evolved to preserve the structural integrity of the virus.

COVID-19 has infected more than billions of humans worldwide and has caused more than a hundred thousand deaths as reported by the World Health Organization (WHO) [6]. This disease has destabilized the health system and economy of the entire world. Notably, the number of infections and mortality rates due to COVID-19 are different worldwide. The global mortality rate is 2.08% [6]. Since the first case of SARS-CoV-2 infection reported in January 2020, its several variants have evolved with changes in the receptor-binding domain of the spike protein [7]. Meanwhile, the structural analysis of the variants has suggested that the mutations change the conformation of the sidechain to reduce the effectiveness of interactions with antibodies [8].

The global pandemic COVID-19 highlighted the importance of the development of safe and effective vaccines with high priority. Therefore, vaccination at a large scale is the need of the hour to control this ongoing pandemic. Vaccination is driven by recent technologies involving the growth of viruses in cell culture, synthetic biology, recombinant DNA, genomics and chemical conjugation [9]. The approval for vaccines is required to go through different stages such as pre-clinical in animals and phase I/II/III/IV in humans. The number of participants, age, doses of vaccines and their response including side effects are key points for the approval of vaccines [10]. Further, infant, neonatal, pregnancy and other severe/chronic diseases are also taken into consideration while approving the vaccines. In most of the clinical trials, the participants' age is between 18 and 55 years while in certain cases it's between 12 and 60 years and between 60 and 80 years. Generally, the number of participants varies from about 30 to 30,000 in number in diverse clinical studies [10,11].

Interestingly, a great achievement in the field of vaccinology was in the development of COVID-19 vaccines which involved design, testing and approval within a year in few countries (Table 1) [12,13]. The S protein of SARS-CoV-2 is the main target for the design of the COVID-19 vaccine as SARS-CoV-2 uses its S protein to bind to host ACE2 receptors [14]. Many vaccines are now available and many vaccine developments are under clinical

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Article highlights

- Resurfacing COVID-19 with new SARS-CoV-2 variants has created panic worldwide. These variants can influence several parameters including transmission, severity, diagnostics, therapeutics, and natural and vaccine-induced immunity.
- COVID-19 vaccines came within a year as the vaccine development program was fast-tracked by several countries/ regulatory authorities. Several COVID-19 vaccines have been globally accepted due to their efficacy and safety thereby overcoming vaccine hesitancy.
- The development of COVID-19 vaccines involved diverse vaccine platforms and is divided into major platforms such as inactivated, viral vector, protein-based, nucleic acids (RNA and DNA) based platform, yeast-based vaccines, and conjugated vaccines with antimicrobial peptides.
- Studies about the effectiveness of different vaccines on the variants of SARS-CoV-2 are developing quickly including several studies about the Mix-and-Match COVID-19 vaccine as it may provide significantly higher protection against SARS-CoV-2 and its variants.
- The vaccine effectiveness was more pronounced after the receipt of the second dose.
- The vaccination will help in preventing hospitalizations and deaths.
- Mitigation of COVID-19 transmission can be achieved by personal, administrative and engineering controls.

trials (Tables 1 and 2). Notably, on 11 August 2020, Russia has approved and registered the first COVID-19 vaccine made by Gamaleya Research Institute and named it 'Sputnik V' and published the result of clinical trial phase 1/2 studies on 4 September 2020 (Clinical Trials No.: NCT04436471 and NCT04437875) [15]. However, vaccination of such a huge population is one of the challenging tasks [16]. The authorized COVID-19 vaccines have shown 65–95% efficacy against non-variant strain [17]. However, the efficacy of authorized COVID-19 vaccines may be affected by SARS-CoV-2 variants.

2. SARS-CoV-2 variants

As SARS-COV-2 is widely circulating in the population and getting more opportunities to spread, there is a high probability of an increase in its mutation. Depending on the location of the mutation in the virus genetic material, the properties of the virus such as transmission or severity are affected [18]. Resurfacing of COVID-19 with new SARS-CoV-2 variants has created panic worldwide [19,20]. These variants can influence the transmission, severity of COVID-19, its diagnostics, therapeutics, and natural and vaccine-induced immunity [21]. The documented variants of SARS-CoV-2 are more than ten in number such as Alpha, Beta, Gamma, Delta, Delta Plus, Epsilon, Eta, Theta, Iota, Kappa, and Lambda and the list will increase by the emergence of new variants (Table 3) [8]. The variants bind more efficiently to ACE2 receptors and have more transmissible ability compared to the original SARS-CoV-2. Unfortunately, variants originated from South Africa and Brazil can easily enter the human lungs [22,23]. Alpha variant (B.1.1.7) was first identified in the UK and the major mutations are on the spike protein of SARS-CoV-2 [24–26].

Several mutations occur in spike proteins including D614G, mutation N501Y in RBD, deletion [69,70, 144] in NTD, mutation P681H near the furin cleavage site. Beta Variant (B.1.351, N501Y. V2) was identified in South Africa and major mutations are on the receptor-binding domain. It has also several mutations in spike proteins including D614G [27,28]. Further, three mutations K417N, E484K, N501Y are found in the RBD region. In addition, deletion (242–244) and mutation R246I are found in NTD, along with the mutation in A701V near the furin cleavage site [19].

Meanwhile, the third Gamma variant (P.1) which is a descendant of variant B.1.1.28 was first identified in Brazil and the major mutations are on the receptor-binding domain including K417T, E484K, N501Y, D614G [29,30]. The major mutant E484K helps the virus to hide and escape easily from monoclonal antibodies and causes hindrance in antibody and plasma-based therapeutics. Notably, D614G is related to an increase in infection due to COVID-19 [31]. Two lineages are identified in India which are the Kappa variant (B.1.617.1) and Delta variant (B.1.617.2). Unfortunately, the Delta variant is one of the reasons for the spreading of the second wave of COVID-19 in India. Delta virus contains mutations K417N, L452R, T478K, D614G (Table 3).

The Delta (B.1.617.2) variant was first identified in India in December 2020 and is related to high transmissibility, virulence, hospitalizations, and deaths [32,33]. Further, the Delta variant affected younger age groups and the risk of hospital admission with the Delta variant is about twice as compared to the Alpha variant [34]. Interestingly, the transmissibility of the Delta variant is 60% more than the Alpha variant and its basic reproduction rate is between 5 and 8 as reported by US Centers for Disease Control and Prevention (CDC) [33]. The Delta Plus variant (AY.1 or B.1.617.2.1) was first detected in India and has spread to the United States through England and Japan. It has ≥20% high-prevalence mutations than in the Delta variant with the exclusive presence of mutations K417N, V70F, and W258L in the Spike region along with mutation of about 58% prevalence in ORF1a (A1146T) [8].

In Japan, the most prevalent variants were 501Y.V1 which was 53% and 452 R.V1 which was 24% according to the collected data from January 2020 to February 2021. A high correlation was found between fatalities and population density (rs = 0.81) and more than 90% fatality was found in patients with an age of more than 60 years [35].

A compartmental mathematical model was constructed to study the impact of the variant VOC-202012/01 of lineage B.1.1.7 (Alpha variant) on the population and it was found that the high transmissibility ability of the variant can infect more people. Further, the studies show health care institutions should involve more non-pharmaceutical interventions and vaccine inoculation to prevent disastrous outcomes in the population due to the high transmissibility ability of the variant [36]. Interestingly, a high reproduction number of 43–90%, compared to the predecessor lineage was estimated by the statistical and dynamic modeling approaches for variant VOC-202012/01 of lineage B.1.1.7 (Alpha variant) in England [37]. The Alpha variant (B.1.1.7) and Gamma (P.1) variants depicted about 66.0% and 5.0% of SARS-CoV-2 infections in the U.S. at the end of April 2021 [21]. The infection with VOC-202012/1 in a population is associated with high mortality [38].

The infection by SARS-CoV-2 also depends upon genetic variation in ACE2 [39]. Another study has shown that the Asian population has a higher expression of ACE2 compared to European, North American, and African populations. The population with lower ACE2 expression is responsible for the

Table 1. Diverse platform vaccines against COVID-19 are in emergency use listing (EUL)/ prequalification evaluation process at WHO.

Sl. No.	Vaccine Name	Platform/Type of Vaccine	Manufacturer Industry/Academy	NRA of Record	EOI accepted at WHO	Status of assessment of WHO
1	BNT162b2/COMIRNATY Tozinameran (INN)	Nucleoside modified mNRA	Pfizer, BioNTech Manufacturing GmbH	EMA USFDA	Yes	Finalized
2	AZD1222 Vaxzevria, Covishield (ChAdOx1_nCoV-19)	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	AstraZeneca, AB, University of Oxford	EMA, MFDS KOREA, Japan MHLW/PMDA, Australia TGA, DCGI	Yes	Finalized
3	Ad26.COV2.S	Recombinant, replicationincompetent adenovirus type 26 (Ad26) vectored vaccine encoding the (SARS-CoV-2) Spike (S) protein	Janssen–Cilag International NV	EMA	Yes	Finalized
4	mRNA-1273	mNRA-based vaccine encapsulated in lipid nanoparticle (LNP)	Moderna Biotech	EMA, USFDA	Yes	Finalized
5	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	Inactivated, produced in Vero cells	Sinopharm/Beijing Institute of Biological Products Co., Ltd. (BIBP)	NMPA	Yes	Finalized
6	COVID-19 Vaccine (Vero Cell), Inactivated/ CoronavacTM	Inactivated, produced in Vero cells	Sinovac Life Sciences Co., Ltd.	NMPA	Yes	Finalized
7	Sputnik V	Human Adenovirus Vector-based Covid-19 vaccine	The Gamaleya National Center	Russian NRA	Yes	Ongoing
8	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)/ COVAXIN	Whole-Virion Inactivated Vero Cell	Bharat Biotech, India	DCGI	Yes	Ongoing
9	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	Inactivated, produced in Vero cells	Sinopharm/WIBP	NMPA	Yes	Ongoing
10	Ad5-nCoV	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)	CanSinoBio	NMPA	Yes	-
11	NVX-CoV2373/Covovax	Recombinant nanoparticle prefusion spike protein formulated with Matrix-M™ adjuvant	Novavax, Serum Institute of India	EMA, DCGI	Yes	-
12	CoV2 preS dTM-AS03 vaccine	Recombinant, adjuvanted	Sanofi	EMA	Yes	-
13	SCB-2019	Novel recombinant SARS-CoV-2 Spike (S)-Trimer fusion protein	Clover Biopharmaceuticals	NMPA	Yes	-
14	Zorecimeran (INN) concentrate and solvent for dispersion for injection; Company code: CVnCoV/ CV07050101	mNRA-based vaccine encapsulated in lipid nanoparticle (LNP)	Curevac	EMA	Yes	-
15	EpiVacCorona	Peptide antigen	Vector State Research Center of Viralogy and Biotechnology	Russian NRA	Letter Received	-
16	Recombinant Novel Coronavirus Vaccine (CHO Cell)	Recombinant protein subunit	Zhifei Longcom, China	NMPA	in process	-
17	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	Inactivated	IMBCAMS, China	NMPA	in process	-
18	Soberana 01, Soberana 02 Soberana Plus Abdala	SARS-CoV-2 spike protein conjugated chemically to meningococcal B or tetanus toxoid or Aluminum	BioCubaFarma – Cuba	CECMED	in process	-

Table 2. Diverse platform vaccines are under clinical trial against COVID-19.

Sl. No.	Vaccine Platform	Type/Name of COVID-19 Vaccine	Manufacturer Industry/Academy	2Phase Dose Day of Dose Route	References/Clinical Trial
Phase 4					
1	Inactivated virus	CoronaVac; inactivated SARS-CoV-2 vaccine (vero cell)	Sinovac Research and Development Co., Ltd	Phase 4 2 Dose Day 0 + 14 IM	NCT04756830 NCT04747821 NCT04775069 NCT04789356 NCT04754698 NCT04801888 NCT04894227 NCT04892459 NCT04911790 NCT04953325 NCT04962308 NCT04993365
2	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell), vaccine name BBIBP-CorV	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	Phase 4 2 Dose Day 0 + 21 IM	NCT04863638
3	Viral vector (Non-replicating)	ChAdOx1-S – (AZD1222) (Covishield) (Vaxzevria)	AstraZeneca + University of Oxford	Phase 4 1–2Dose Day 0 + 28 IM	NCT04760132 NCT04775069 EUCTR2021-002327-38-NL NCT04914832 ACTRN12621000661875
4	Viral vector (Non-replicating)	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector) Ad5-nCoV	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 3 1Dose Day 0 IM	NCT04892459
5	Viral vector (Non-replicating)	Ad26.COV2.S	Janssen Pharmaceutical, Johnson & Johnson	Phase 4 1–2Dose Day 0 or Day 0 + 56 IM	EUCTR2021-002327-38-NL
6	RNA based vaccine	mRNA −1273	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4 2Dose Day 0 + 28 IM	NCT04760132 NCT04792567 NCT04885907 EUCTR2021-002327-38-NL EUCTR2021-003388-90-NL NCT04952402 EUCTR2021-003618-37-NO NCT04969250
7	RNA based vaccine	BNT162b2 (3 LNP-mRNAs), also known as 'Comirnaty'	Pfizer/BioNTech + Fosun Pharma	Phase 4 2Dose Day 0 + 21 IM	NCT04760132 ACTRN12621000661875 EUCTR2021-000412-28-BE EUCTR2021-002327-38-NL NCT04780659 NCT04961229 NCT04775069 EUCTR2021-000893-27-BE EUCTR2021-000930-32-BE NCT04852861 NCT04878211 EUCTR2021-003388-90-NL EUCTR2021-003618-37-NO NCT04955626 NCT04952766 NCT04969250
8	RNA based vaccine	mRNA-1273.351. A lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized S protein of the SARS-CoV-2 B.1.351 variant.	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4 1 or 2 Dose Day 0 or Day 0 + 28 or 56 IM	EUCTR2021-000930-32 NCT04878211 NCT04869358
Phase 3					
9	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products	Phase 3 2Dose Day 0 + 21 IM	ChiCTR2000034780 ChiCTR2000039000 NCT04510207 NCT04612972

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Table 2. (Continued).

Sl. No.	Vaccine Platform	Type/Name of COVID-19 Vaccine	Manufacturer Industry/Academy	2Phase Dose Day of Dose Route	References/Clinical Trial
10	Viral vector (Non-replicating)	Gam-COVID-Vac Adeno-based (rAd26-S+ rAd5-S) Sputnik V COVID-19 vaccine	Gamaleya Research Institute; Health Ministry of the Russian Federation	Phase 3 2Dose Day 0 + 21 IM	NCT04530396 NCT04564716 NCT04642339 NCT04656613 NCT04741061
11	Protein subunit	SARS-CoV-2 rS/Matrix M1-Adjuvant (Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M) NVX-CoV2373	Novavax	Phase 3 2Dose Day 0 + 21 IM	NCT04611802 EUCTR2020-004123-16-GB NCT04583995
12	Protein subunit	Recombinant SARS-CoV-2 vaccine (CHO Cell)	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Phase 3 2–3Dose Day 0 + 28 or Day 0 + 28 + 56 IM	NCT04646590
13	RNA based vaccine	CVnCoV Vaccine	CureVac AG	Phase 3 2 Day 0 + 28 IM	NCT04674189 NCT04838847 NCT04838847
14	Inactivated virus	SARS-CoV-2 vaccine (vero cells)	Institute of Medical Biology + Chinese Academy of Medical Sciences	Phase 3 2Dose Day 0 + 28 IM	NCT04659239
15	Inactivated virus	QazCovid-in® – COVID-19 inactivated vaccine	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Phase 3 2Dose Day 0 + 21 IM	NCT04691908
16	DNA based vaccine	nCov vaccine	Zydus Cadila	Phase 3 3Dose Day 0 + 28 + 56 IM	CTRI/2020/07/026352
17	Inactivated virus	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)	Bharat Biotech International Limited	Phase 3 2Dose Day 0 + 14 IM	NCT04641481; CTRI/2020/11/028976
18	Protein subunit	VAT00002: SARS-CoV-2 S protein with adjuvant	Sanofi Pasteur + GSK	Phase 3 2Dose Day 0 + 21 IM	PACTR202011523101903 NCT04904549
19	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	Shenzhen Kangtai Biological Products Co., Ltd.	Phase 3 2 Dose Day 0 + 28 IM	NCT04852705
20	Protein subunit	COVAX-19® Recombinant spike protein + adjuvant	Vaxine Pty Ltd.	Phase 3 2 Dose Day 0 + 21 IM	IRCT20150303021315N24
21	Protein subunit	FINLAY-FR-2 anti-SARS-CoV-2 Vaccine (RBD chemically conjugated to tetanus toxoid plus adjuvant)	Instituto Finlay de Vacunas	Phase 3 2 Dose Day 0 + 28 IM	RPCEC00000354
22	Protein subunit	EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology 'Vector'	Phase 3 2 Dose Day 0 + 21 IM	NCT04780035
23	Protein subunit	RBD (baculovirus production expressed in Sf9 cells) Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	West China Hospital + Sichuan University	Phase 3 2 Dose Day 0 + 28 IM	NCT04887207 NCT04904471
24	RNA based vaccine	SARS-CoV-2 mRNA vaccine (ARCoV)	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences	Phase 3 2 Dose Day 0 + 14 Or Day 0 + 28 IM	NCT04847102

(*Continued*)

Table 2. (Continued).

Sl. No.	Vaccine Platform	Type/Name of COVID-19 Vaccine	Manufacturer Industry/Academy	2Phase Dose Day of Dose Route	References/Clinical Trial
25	Protein subunit	CIGB-66 (RBD+aluminum hydroxide)	Center for Genetic Engineering and Biotechnology (CIGB)	Phase 3 3 Dose Day 0 + 14 + 28 or Day 0 + 28 + 56 IM	RPCEC00000359
26	Inactivated Virus	VLA2001	Valneva, National Institute for Health Research, United Kingdom	Phase 3 2 Dose Day 0 + 21, IM	NCT04864561 NCT04956224
27	Protein subunit	Recombinant Sars-CoV-2 Spike protein, Aluminum adjuvanted (Nanocovax)	Nanogen Pharmaceutical Biotechnology	Phase 3 2 Dose Day 0 + 21, IM	NCT04922788
28	Inactivated Virus	ERUCOV-VAC, inactivated virus	Erciyes University	Phase 3 2 Dose Day 0 + 21, IM	NCT04942405
Phase 2/3					
29	DNA based vaccine	INO-4800+ electroporation	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	Phase 2/3 2 Dose Day 0 + 28 IM	NCT04642638
30	DNA based vaccine	AG0301-COVID19	AnGes + Takara Bio + Osaka University	Phase 2/3 2 Dose Day 0 + 14 IM	NCT04655625
31	Viral vector (Non-replicating)	GRAd-COV2 (Replication defective Simian Adenovirus (GRAd) encoding S)	ReiThera + Leukocare + Univercells	Phase 2/3 1 Dose 0 IM	NCT04791423
32	Protein subunit	SCB-2019 + AS03 or CpG 1018 adjuvant plus Alum adjuvant (Native like Trimeric subunit Spike Protein vaccine)	Clover Biopharmaceuticals Inc./GSK/Dynavax	Phase 2/3 2 Dose Day 0 + 21 IM	NCT04672395
33	Protein subunit	UB-612 (Multitope peptide based S1-RBD-protein based vaccine)	Vaxxinity	Phase 2/3 2 Dose Day 0 + 28, IM	NCT04683224
34	Virus like particle	Coronavirus-Like Particle COVID-19 (CoVLP)	Medicago Inc.	Phase 2/3 2 Dose Day 0 + 21 IM	NCT04636697
35	Viral vector (Replicating)	rVSV-SARS-CoV-2-S Vaccine (IIBR-100)	Israel Institute for Biological Research	Phase 2/3 1 Dose Day 0 IM	NCT04990466
36	Inactivated Virus	COVID-19 inactivated vaccine	Shifa Pharmed Industrial Co	Phase 2/3 2 Dose Day 0 + 14, IM	IRCT20201202049567N3
37	RNA based vaccine	mRNA-1273.211. A multivalent booster candidate combining mRNA-1273 plus mRNA-1273.351.	ModernaTX, Inc.	Phase 2/3 1 Dose Day 0 IM	NCT04927065
38	Viral vector (Non-replicating)	AZD2816; adenoviral vector ChAdOx platform and based on the Beta (B.1.351) variant	AstraZeneca + University of Oxford	Phase 2/3 2 Dose Day 0, 28 IM	NCT04973449
Phase 2					
39	RNA based vaccine	ARCT-021	Arcturus Therapeutics	Phase 2 ND ND IM	NCT04668339 NCT04728347
40	Protein subunit Protein subunit	MVC-COV1901 (S-2P protein + CpG 1018)	Medigen Vaccine Biologics + Dynavax + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 2 2 Dose Day 0 + 28 IM	NCT04695652 NCT04822025 NCT04951388

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Table 2. (Continued).

Sl. No.	Vaccine Platform	Type/Name of COVID-19 Vaccine	Manufacturer Industry/Academy	2Phase Dose Day of Dose Route	References/Clinical Trial
41	Protein subunit	FINLAY-FR1 anti-SARS-CoV-2 Vaccine (RBD + adjuvant)	Instituto Finlay de Vacunas	Phase 2 2 Dose Day 0 + 28 IM	RPCEC00000366
42	Viral vector (Replicating)	DelNS1–2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD)	University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy	Phase 2 2 Dose Day 0 + 28 IN	ChiCTR2000039715
43	Protein subunit	Razi Cov Pars, recombinant spike protein	Razi Vaccine and Serum Research Institute	Phase 2 3 Dose Day 0 + 21 + 51 IM or IN	IRCT20201214049709N2
44	RNA based vaccine	MRT5500, an mRNA vaccine candidate	Sanofi Pasteur and Translate Bio	Phase 2, 2 Dose Day 0 + 21, IM	IRCT20210206050259N2
45	Virus like particle	SARS-CoV-2 VLP Vaccine Vaccine-Wuhan; Vaccine-Alpha variant; Vaccine-Wuhan +Alpha variant	The Scientific and Technological Research Council of Turkey	Phase 2, 2 Dose Day 0 and later, SC	NCT04962893
46	Protein subunit	Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01)	Guangdong Provincial Center for Disease Control and Prevention/Gaozhou Center for Disease Control and Prevention	Phase 2 2 Dose Day 0 + 21 IM	ChiCTR2100045107
47	Protein subunit	SCB-2020S, an adjuvanted recombinant SARS-CoV-2 trimeric S-protein (from B.1.351 variant)	Clover Biopharmaceuticals AUS Pty Ltd	Phase 2 2 Dose Day 0 + 21 IM	NCT04950751
Phase1/2					
48	DNA based vaccine	GX-19 N	Genexine Consortium	Phase 1/2 2 Dose Day 0 + 28 IM	NCT04445389 NCT04715997
49	Protein subunit	KBP-COVID-19 (RBD-based)	Kentucky Bioprocessing Inc.	Phase 1/2 2 Dose Day 0 + 21 IM	NCT04473690
50	Virus like particle	RBD SARS-CoV-2 HBsAg VLP vaccine	Serum Institute of India + Accelagen Pty + SpyBiotech	Phase 1/2 2 Dose Day 0 + 28 IM	ACTRN12620000817943 ACTRN12620001308987
51	Protein subunit	IMP CoVac-1 (SARS-CoV-2 HLA-DR peptides)	University Hospital Tuebingen	Phase 1/2 1 Dose Day 0 SC	NCT04954469
52	Viral vector (Non-replicating) + APC	LV-SMENP-DC vaccine. Dendritic cells are modified with lentivirus vectors expressing Covid-19 minigene SMENP and immune modulatory genes. CTLs are activated by LV-DC presenting Covid-19 specific antigens.	Shenzhen Geno-Immune Medical Institute	Phase 1/2 1 Dose Day 0 SC & IV	NCT04276896
53	Viral vector (Non-replicating)	Human Adenovirus Type 5: hAd5 S + N vaccine (S-Fusion + N-ETSD). E2b-Deleted Adeno.	ImmunityBio, Inc	Phase 1/2 1–2 Dose Day 0 + 21 SC or Oral	NCT04843722 NCT04845191
54	Viral vector (Replicating) + APC	Dendritic cell vaccine AV-COVID-19. A vaccine consisting of autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CSF	Aivita Biomedical, Inc. National Institute of Health Research and Development, Ministry of Health Republic of Indonesia	Phase 1/2 1 Dose Day 0 IM	NCT04386252
55	Protein subunit	CIGB-669 (RBD+AgnHB)	Center for Genetic Engineering and Biotechnology (CIGB)	Phase 1/2 3 Dose Day 0 + 14 + 28 or Day 0 + 28 + 56 IN	RPCEC00000345

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Table 2. (Continued).

Sl. No.	Vaccine Platform	Type/Name of COVID-19 Vaccine	Manufacturer Industry/Academy	2Phase Dose Day of Dose Route	References/Clinical Trial
56	Protein subunit	BECOV2	Biological E. Limited	Phase 1/2 2 Dose Day 0 + 28, IM	CTRI/2020/11/029032
57	Viral vector (Replicating)	AdCLD-CoV19 (adenovirus vector)	Cellid Co., Ltd.	Phase 1/2 1 Dose Day 0 IM	NCT04666012
58	DNA based vaccine	GLS-5310	GeneOne Life Science, Inc.	Phase 1/2 2 Dose Day 0 + 56, Day 0 + 84, IM	NCT04673149
59	Protein subunit	Recombinant protein vaccine S-268019 (using Baculovirus expression vector system)	Shionogi	Phase 1/2 2 Dose Day 0 + 21, IM	jRCT2051200092
60	Protein subunit	SARS-CoV-2-RBD-Fc fusion protein	University Medical Center Groningen + Akston Biosciences Inc.	Phase 1/2 SC or IM	NCT04681092
61	Protein subunit	COVAC-1 and COVAC-2 subunit vaccine (spike protein) + SWE adjuvant	University of Saskatchewan	Phase 1/2 2 Dose Day 0 + 28, IM	NCT04702178
62	Protein subunit	GBP510, a recombinant surface protein vaccine with adjuvant AS03 (aluminum hydroxide)	SK Bioscience Co., Ltd. and CEPI	Phase 1/2 2 Dose Day 0 + 28, IM	NCT04742738 NCT04750343
63	DNA based vaccine	COVID-eVax, a candidate plasmid DNA vaccine of the Spike protein	Takis + Rottapharm Biotech	Phase 1/2 IM or IM + electroporation	NCT04788459 EUCTR2020-003734-20-IT
64	Inactivated virus	Inactivated (NDV-based) chimeric vaccine with or without the adjuvant CpG 1018	The Government Pharmaceutical Organization (GPO); PATH; Dynavax	Phase 1/2 2 Dose Day 0 + 28 IM	NCT04764422
65	Virus like particle	VBI-2902a. An enveloped virus-like particle (eVLP) of SARS-CoV-2 spike (S) glycoprotein and aluminum phosphate adjuvant.	VBI Vaccines Inc.	Phase 1/2, 2 Dose Day 0 + 28, IM	NCT04773665
66	Protein subunit	EuCorVac-19; A spike protein using the recombinant protein technology and with an adjuvant.	POP Biotechnologies and EuBiologics Co.,Ltd	Phase 1/2, 2 Dose Day 0 + 21, IM	NCT04783311
67	RNA based vaccine	DS-5670a, mRNA vaccine	Daiichi Sankyo Co., Ltd.	Phase 1/2, 2 Dose IM	NCT04821674
68	Viral vector (Non-replicating)	COVIVAC. Newcastle Disease Virus (NDV) expressing membrane-anchored pre-fusion-stabilized trimeric SARS-CoV-2 S protein ± adjuvant CpG 1018	Institute of Vaccines and Medical Biologicals, Vietnam	Phase 1/2, 2 Dose Day 0 + 28, IM	NCT04830800
69	Protein subunit	Recombinant SARS-CoV-2 Vaccine (CHO cell)	National Vaccine and Serum Institute, China	Phase 1/2, 2 Dose Day 0, IM	NCT04869592
70	RNA based vaccine	EXG-5003; a temperature-sensitive self-replicating RNA vaccine expressing the receptor binding domain of the SARS-CoV-2 spike protein.	Elixirgen Therapeutics, Inc	Phase 1/2, 1 Dose Day 0, ID	NCT04863131
71	Inactivated Virus	Inactivated COVID-19 vaccine	KM Biologics Co., Ltd.	Phase 1/2, 2 Dose Day 0, 28 IM	jRCT2071200106

(*Continued*)

Table 2. (Continued).

Sl. No.	Vaccine Platform	Type/Name of COVID-19 Vaccine	Manufacturer Industry/Academy	2Phase Dose Day of Dose Route	References/Clinical Trial
72	Viral vector (Non-replicating)	Modified Vaccinia Virus Ankara (MVA) vector expressing a stabilized SARS-CoV-2 spike protein	German Center for Infection Research	Phase 1/2, 2 Dose Day 0, 28 IM	NCT04895449
73	Protein subunit	QazCoVac-P – COVID-19 Subunit Vaccine	Research Institute for Biological Safety Problems	Phase 1/2, 2 Dose Day 0, 21 IM	NCT04930003
74	DNA based vaccine	AG0302-COVID19	AnGes, Inc	Phase 1/2, 2–3 Dose Day 0,14,28 IM	NCT04993586
75	Protein subunit	Recombinant protein RBD fusion dimer adjuvanted vaccine (COVID-19 Vaccine Hipra)	Laboratorios Hipra, S.A.	Phase 1/2, 2 Dose Day 0, 21 IM	NCT05007509
Phase 1					
76	Viral vector (Non-replicating)	ChAdOx1-S – (AZD1222) (Covishield) (Vaxzevria)	University of Oxford	Phase 1 1–2 Dose Day 0 + 28 IN	NCT04816019
77	Viral vector (Non-replicating)	VXA-CoV2-1 Ad5 adjuvanted Oral Vaccine platform	Vaxart	Phase 1 2 Dose Day 0 + 28 Oral	NCT04563702
78	Viral vector (Non-replicating)	MVA-SARS-2-S	University of Munich (Ludwig-Maximilians)	Phase 1 2 Dose Day 0 + 28 IM	NCT04569383
79	RNA based vaccine	LNP-nCoVsaRNA	Imperial College London	Phase 1 2 Dose ND IM	ISRCTN17072692
80	Viral vector (Replicating) + APC	Covid-19/aAPC vaccine. The Covid-19/aAPC vaccine is prepared by applying lentivirus modification with immune modulatory genes and the viral minigenes to the artificial antigen presenting cells (aAPCs).	Shenzhen Geno-Immune Medical Institute	Phase 1 3 Dose Day 0 + 14 + 28 SC	NCT04299724
81	Protein subunit	AdimrSC-2 f (recombinant RBD ± Aluminum)	Adimmune Corporation	Phase 1 ND ND ND	NCT04522089
82	DNA based vaccine	Covigenix VAX-001 – DNA vaccines + proteo-lipid vehicle (PLV) formulation	Entos Pharmaceuticals Inc.	Phase 1 2 Dose Day 0 + 14 IM	NCT04591184
83	DNA based vaccine	CORVax – Spike (S) Protein Plasmid DNA Vaccine	Providence Health & Services	Phase 1 2 Dose Day 0 + 14 ID	NCT04627675
84	RNA based vaccine	ChulaCov19 mRNA vaccine	Chulalongkorn University	Phase 1 2 Dose Day 0 + 21 IM	NCT04566276
85	DNA based vaccine	bacTRL-Spike oral DNA vaccine	Symvivo Corporation	Phase 1 1 Dose Day 0 Oral	NCT04334980
86	Viral vector (Non-replicating)	COH04S1 (MVA-SARS-2-S) – Modified vaccinia ankara (sMVA) platform + synthetic SARS-CoV-2	City of Hope Medical Center + National Cancer Institute	Phase 1 1–2 Dose Day 0, + 28 IM	NCT04639466
87	Live attenuated virus	COVI-VAC	Codagenix/Serum Institute of India	Phase 1 1–2 Dose Day 0 or Day 0 + 28 IN	NCT04619628

(*Continued*)

Table 2. (Continued).

Sl. No.	Vaccine Platform	Type/Name of COVID-19 Vaccine	Manufacturer Industry/Academy	2Phase Dose Day of Dose Route	References/Clinical Trial
88	Protein subunit	MF59 adjuvanted SARS-CoV-2 Sclamp vaccine	The University of Queensland	Phase 1 2 Dose Day 0 + 28, IM	NCT04495933
89	DNA based vaccine	COVIGEN	University of Sydney, Bionet Co., Ltd Technovalia	Phase 1 2 Dose Day 0 + 28, ID or IM	NCT04742842
90	Viral vector (Non-replicating)	BBV154, Adenoviral vector COVID-19 vaccine	Bharat Biotech International Limited	Phase 1 1 Dose Day 0, IN	NCT04751682
91	RNA based vaccine	PTX-COVID19-B, mRNA vaccine	Providence Therapeutics	Phase 1, 2 Dose Day 0 + 28, IM	NCT04765436
92	RNA based vaccine	CoV2 SAM (LNP) vaccine. A self-amplifying mRNA (SAM) lipid nanoparticle (LNP) platform + Spike antigen	GlaxoSmithKline	Phase 1, 2 Dose Day 0 + 28, IM	NCT04758962
93	Protein subunit	SK SARS-CoV-2 recombinant surface antigen protein subunit (NBP2001) + adjuvanted with alum.	SK Bioscience Co., Ltd.	Phase 1, 2 Dose Day 0 + 28, IM	NCT04760743
94	Viral vector (Non-replicating)	Chimpanzee Adenovirus serotype 68 (ChAd) and self-amplifying mRNA (SAM) vectors expressing spike alone, or spike plus Gritstone Oncology additional SARS-CoV-2 T cell epitopes.	Gritstone Oncology	Phase 1, 3, Dose Day 0 + 14 + 28 or Day 0 + 28 + 56 or Day 0 + 112, IM	NCT04776317
95	Protein subunit	SpFN (spike ferritin nanoparticle) uses spike proteins with a liposomal formulation QS21 (ALFQ) adjuvant.	Walter Reed Army Institute of Research (WRAIR)	Phase 1, 2–3 Dose Day 0 + 28 + 180, IM	NCT04784767
96	Inactivated virus	Inactivated SARS-CoV-2 vaccine FAKHRAVAC (MIVAC)	Organization of Defensive Innovation and Research	Phase 1, 2 Dose Day 0 + 14 ± 21, IM	IRCT20210206050259N1
97	Live attenuated virus	MV-014-212, a live attenuated vaccine that expresses the spike (S) protein of SARS-CoV-2	Meissa Vaccines, Inc.	Phase 1, 3 Dose Day 0 ± 35, IN	NCT04798001
98	Protein subunit	ReCOV: Recombinant two-component spike and RBD protein COVID-19 vaccine (CHO cell).	Jiangsu Rec-Biotechnology	Phase 1, 2 Dose Day 0 + 21, IM	NCT04818801
99	Inactivated Virus	Inactivated COVID-19 vaccine	Kocak Farma	Phase 1, 2 Dose Day 0 + 21, IM	NCT04838080
100	Viral vector (Non-replicating)	SC-Ad6-1, Adneviral vector vaccine	Tetherex Pharmaceuticals Corporation	Phase 1, 1–2 Dose Day 0 ±21, IM	NCT04839042
101	Virus like particle	ABNCoV2 capsid virus-like particle (cVLP) ± adjuvant MF59	Radboud University	Phase 1, 2 Dose Day 0, Day 28, IM	NCT04839146
102	RNA based vaccine	HDT-301: Self-replicating mRNA vaccine formulated as a lipid nanoparticle.	SENAI CIMATEC	Phase 1, 2 Dose Day 0, Day 28, IM	NCT04844268
103	Inactivated Virus	Adjuvanted inactivated vaccine against SARS-CoV-2	The Scientific and Technological Research Council of Turkey (TÜBITAK)	Phase 1, 2 Dose Day 0, Day 21, SC	NCT04866069

(*Continued*)

Table 2. (Continued).

Sl. No.	Vaccine Platform	Type/Name of COVID-19 Vaccine	Manufacturer Industry/Academy	2Phase Dose Day of Dose Route	References/Clinical Trial
104	RNA based vaccine	mRNA-1283	ModernaTX, Inc.	Phase 1, 2 Dose Day 0, Day 28, IM	NCT04813796
105	Inactivated Virus	Live recombinant Newcastle Disease Virus (rNDV) vector vaccine	Laboratorio Avi-Mex	Phase 1, 2 Dose Day 0, Day 21, IM or IN	NCT04871737
106	mRNA vaccine	mRNA COVID-19 vaccine	Shanghai East Hospital and Stemirna Therapeutics	Phase 1, 2 Dose TBD IM	ChiCTR2100045984
107	Protein subunit	CoVepiT vaccine: SARS-CoV-2 multi-target peptide vaccine (targeting Spike, M, N, and several non-structural proteins)	OSE Immunotherapeutics	Phase 1 1-2 Day 0 ± 21 SC	NCT04885361
108	Protein subunit	CoV2-OGEN1, protein-based vaccine	USSF/Vaxform	Phase 1 1–2 Dose Day 0 ± 14 Oral	NCT04893512
109	RNA based vaccine	LNP-nCOV saRNA-02 vaccine; Self-amplifying RNA (saRNA) encapsulated in lipid nanoparticles (LNP)	MRC/UVRI and LSHTM Uganda Research Unit	Phase 1 2 Dose Day 0, + 28, IM	NCT04934111
110	Protein subunit	RBD protein recombinant SARS-CoV-2 vaccine	Bagheiat-allah University of Medical Sciences	Phase 1 3 Dose Day 0 + 21 + 35 IM	IRCT20210620051639N1
111	Protein subunit	Baiya SARS-CoV-2 VAX1, a plant-based subunit vaccine (RBD-Fc + adjuvant)	Baiya Phytopharm Co., Ltd.	Phase 1 2 Dose Day 0 + 21 IM	NCT04953078
112	Viral vector (Non-replicating)	PIV5 vector that encodes the SARS-CoV-2 spike protein	CyanVac LLC	Phase 1 1 Dose Day 0 IN	NCT04954287
113	Protein subunit	202-CoV; SARS-CoV-2 spike trimer protein + adjuvant, CpG7909.	Shanghai Zerun Biotechnology + Walvax Biotechnology + CEPI	Phase 1 2 Dose Day 0, + 28, IM	NCT04982068

selection of D614G mutation and is associated with an increased transmission efficiency of D614G mutation. The variations in human population genetics are responsible for viral evolution [40].

3. COVID-19 Vaccines

Already, there are about 18 vaccines against COVID-19 that are in emergency use listing (EUL)/ prequalification evaluation process at WHO (Table 1, Figures 1 – 2). According to WHO, more than 112 candidate vaccines are in clinical trial evaluation while more than 183 candidate vaccines are in pre-clinical evaluation [41]. Notably, eight vaccines are in phase 4 clinical trial including ChAdOx1-S from University of Oxford/AstraZeneca, UK; Inactivated from Sinovac, China; LNP-encapsulated mRNA from Moderna/NIAID, USA; and LNP-mRNAs from BioNTech/Fosun Pharma/Pfizer, Germany (Table 2). In addition, 20 vaccines are in phase 3 clinical trials and 10 vaccines are in phase 2/3 clinical trials. Further, 9 vaccines are in phase 2 clinical trials, 28 vaccines are in phase 1/2 clinical trial and 38 vaccines are in clinical trial phase 1 (Table 2) (Figure 3).

Most of the countries/ regulatory authorities have treated the vaccine development with topmost priority and also fast-tracked the vaccine development process and maybe this is the reason the world got some vaccines within a year. Further, most of the vaccines were approved for emergency use without completing all the phases of clinical trials except a few. Interestingly, a total of several billion COVID-19 vaccine doses have been administered worldwide mostly through intramuscular [6]. Notably, 86 candidates of vaccines will be delivered intramuscular (IM), 8 candidates of vaccines will be administered intranasal, 4 candidates of vaccines will be delivered intradermal (ID), 5 candidates of vaccines will be delivered subcutaneous and other 3 candidates of vaccines will be delivered orally (Figure 4) [41]. The success in nasal or oral vaccines will have great benefits as it will save syringes and plastic wastes and therefore will be environment friendly. The nasal or oral vaccines will be liked by young children and neonatal in the future.

4. Diverse vaccine platforms

The diverse vaccine platforms have been used for the development of COVID-19 vaccines. It can be divided into major platforms

Table 3. SARS-CoV-2: Variants of concern and interest (classified according to WHO).

Sl. No.	WHO Label	Pango lineages	Spike Protein Substitutions:	Earliest documented samples
Variants of concern				
1	Alpha	B.1.1.7	69del, 70del, 144del, E484K, S494P, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H K1191N	United Kingdom, Sep-2020
2	Beta	B.1.351, B.1.351.2, B.1.351.3	D80A, D215G, 241del, 242del, 243del, K417N, E484K, N501Y, D614G, A701V	South Africa, May 2020,
3	Gamma	P.1 P.1.1 P.1.2 P.1.4 P.1.6 P.1.7	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	Brazil, Nov 2020
4	Delta	B.1.617.2 AY.1 AY.2 AY.3 AY.3.1	T19R, V70F, T95I, G142D, E156-, F157-, R158G, A222V, W258L, K417N, L452R, T478K, D614G, P681R, D950N	India, Oct2020
Variants of interest				
5	Eta	B.1.525	A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888	Multiple countries, Dec-2020
6	Iota	B.1.526	L5F, D80G, T95I, Y144-, F157S, D253G, L452R, S477N, E484K, D614G, A701V, T859N, D950H, Q957R	United States of America Nov 2020
7	Kappa	B.1.617.1	T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	India, Oct-2020
8	Lambda	C.37	G75V, T76I, RSYLTPGD246-253 N, L452Q, F490S, T859N	Peru, Dec 2020

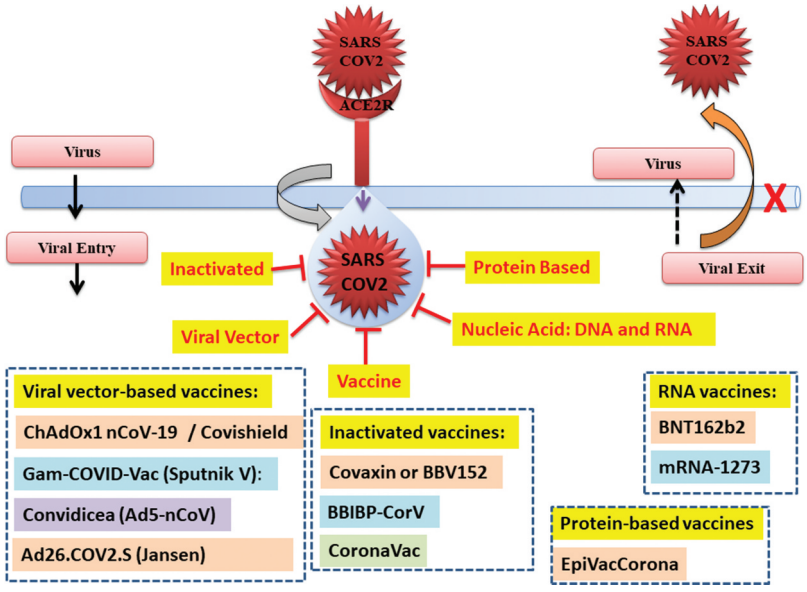

Figure 1. Vaccine against SARS-CoV-2.

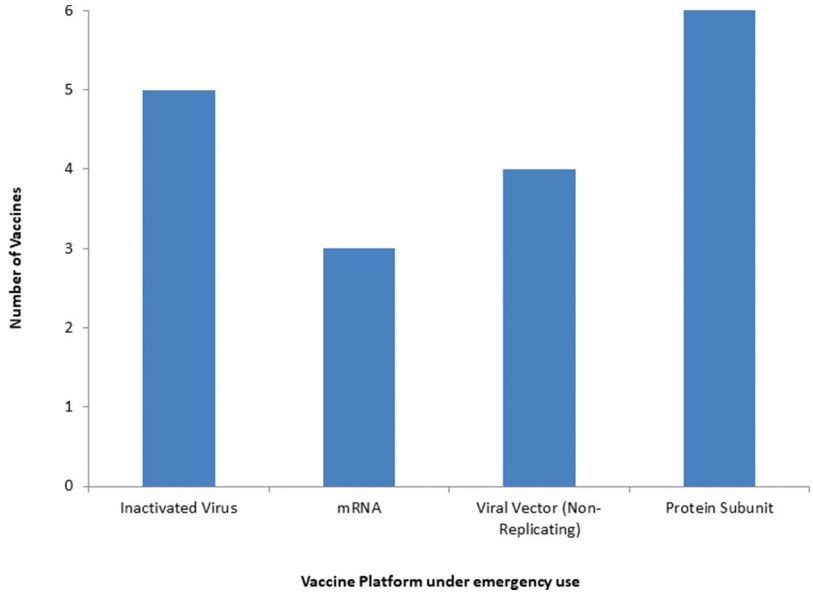

Figure 2. Vaccines for COVID-19 are in the emergency use listing (EUL)/ prequalification evaluation process at WHO.

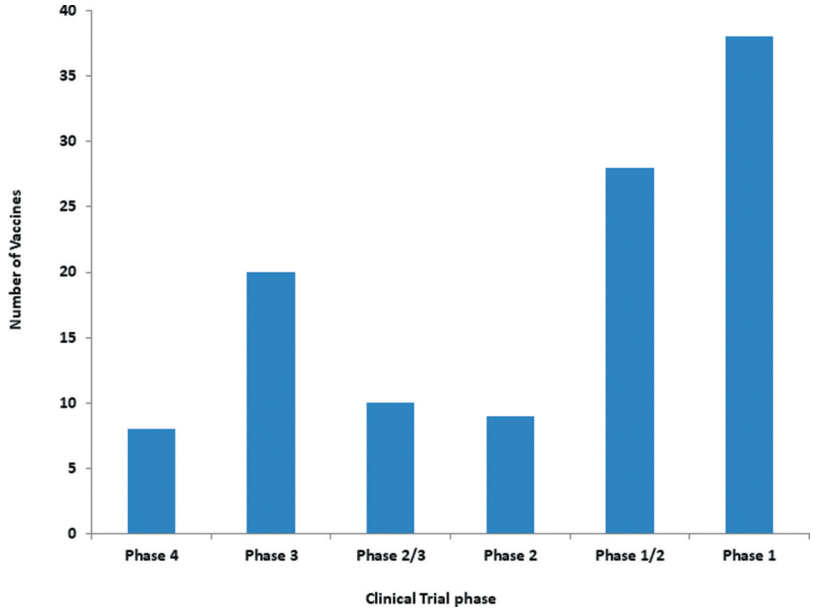

Figure 3. Vaccines for COVID-19 under the different phases of the clinical trial.

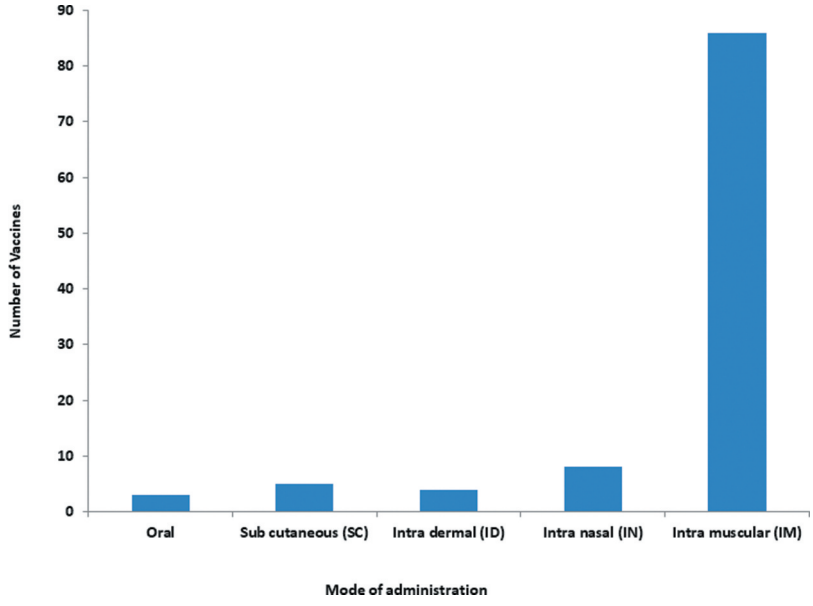

Figure 4. Mode of administration of COVID-19 vaccines.

such as inactivated, viral vector, protein-based, nucleic acids (RNA and DNA) based platform, yeast-based vaccines, and conjugated vaccines with antimicrobial peptides. A total of about 18 vaccines for COVID-19 are in emergency use listing (EUL)/prequalification evaluation process at WHO with different platforms such as mRNA, inactivated virus vaccine, non-replicating viral vector and protein subunit-based vaccine (Table 1) (Figure 2).

According to WHO, more than 112 candidate vaccines are in a clinical trial including 16 Inactivated Virus, 17 Viral Vector Non-Replicating (VVnr), 38 Protein Subunit, 18 RNA, 11 DNA, 2 Viral Vector Replicating (VVr), 5 Virus-like particles, 2 VVr Antigen Presenting Cell, 2 Live Attenuated Virus and 1 VVnr Antigen Presenting Cell (Table 2, Figure 5) [41]. Notably, 183 potential candidate vaccines against SARS-CoV-2 are under pre-clinical evaluation using different vaccine platforms including 70 Protein Subunit, 21 Non-Replicating Viral Vector, 9 Inactivated, 24 RNA based vaccines, 16 DNA based vaccines, 19 Replicating Viral vectors, 2 Live attenuated Virus, 18 virus-like particles and 1 cellular-based vaccine (Figure 6).

4.1. Viral vector-based vaccines: The harmless virus that is unable to cause disease was used as a platform to produce proteins coronavirus which successfully generated an immune response in the body. The viral-based vaccines belong to two categories such as non-replicating vaccines and replicating vaccines. The COVID-19 Vaccine-AstraZeneca (AZD1222) popularly known as Covishield [ChAdOx1-S-(AZD1222)] from Oxford/AstraZeneca [42–46], Sputnik V of Gamaleya Research Institute [15,47], Convidicea (Ad5-nCoV) from CanSino Biologics,

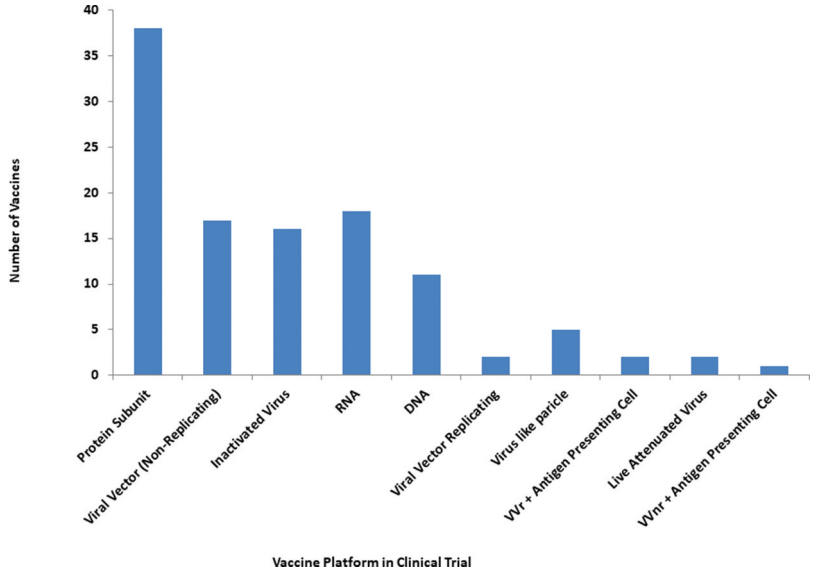

Figure 5. Diverse platform vaccines under clinical trial for COVID-19.

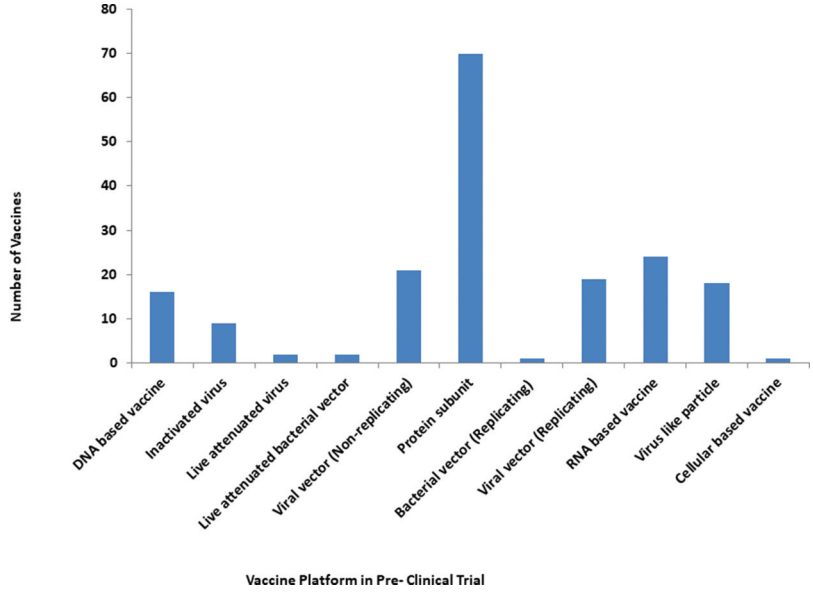

Figure 6. Diverse platform vaccines in Pre-clinical trial for COVID-19.

recombinant vaccine (adenovirus type 5 vector) from China belongs to non-replicating viral vector-based vaccines [48,49].

4.1.1. ChAdOx1 nCoV-19/Covishield: Folegattiet *et al* from the University of Oxford/AstraZeneca, have selected 1077 healthy participants in the age group of 18 to 55 years and administered 5×10^{10} viral particles of chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) [42]. This vaccine expresses SARS-CoV-2 spike proteins in 543 participants. Further, the meningococcal conjugate vaccine (MenACWY) was used as a control in 534 participants. Notably, there were no adverse side effects, while common symptoms have been minimized by paracetamol. Significantly, spike-specific T-cell responses peaked on day 14 and Anti-spike IgG responses rose by day 28 and further the booster dose was given. Neutralizing antibody response was detected in more than 90% of participants after the first dose while it was detected in 100% of participants after the second dose [42]. The vaccine did not have any adverse side effects. Furthermore, this study may be extended to patients with chronic diseases, old age, neonatal and pediatrics thereby giving protection from SARS-CoV-2 infection and recovered SARS-CoV-2 individuals from re-infection. Notably, the efficacy of this vaccine should be tested against different recent circulating strains of SARS-CoV-2. Moreover, further studies are required to unearth the long duration of immunity caused by this vaccine and the requirement for booster doses in the future. The need to extend the suitability of this vaccine to different ethnic groups and persons with rare diseases such as blood clotting complications might be helpful.

Notably, Voysey *et al* have reported that ChAdOx1 nCoV-19 is efficacious for symptomatic COVID-19 and safe [43]. Further, Ramasamy *et al* have reported ChAdOx1 nCoV-19 (AZD1222) a chimpanzee adenovirus-vectored vaccine is well tolerated in older people above 70 years and has good immunogenicity after the booster dose [44]. Ewer *et al* have reported that the ChAdOx1 nCoV-19 vaccine was inducing a favorable immune profile in age groups of 18–55 years [45]. The booster dose of ChAdOx1 nCoV-19 vaccines induced stronger antibody responses and is safe and well-tolerated. Further, this vaccine substantially enhances anti-spike neutralizing antibody titers, Fc-mediated functional antibody responses, antibody-dependent neutrophil/monocyte phagocytosis, natural killer cell activation and complement activation [46].

4.1.2. Gam-COVID-Vac (Sputnik V): Sputnik V of Gamaleya Research Institute is a recombinant adenovirus (rAd26 and rAd5). Logunov *et al* [15] have reported a heterologous vaccine against SARS-CoV-2 using recombinant adenovirus platform containing rAd26 vector and rAd5 vector that has successfully induced humoral and cellular response with safety profile [15]. They have established that both frozen and lyophilized formulations of vaccines are safe and immunogenic during non-randomized clinical trial phases 1 and 2 against COVID-19. The studies involved 76 participants between 18 to 60 age groups including both genders in both phase 1 and 2 studies and measured successfully their antigen-specific humoral immunity, antigen-specific cellular immunity, and changes in neutralizing antibodies. In Phase 1, they have administered one dose either rAd26-S or rAd5-S in participants on day 0, while in Phase 2, rAd26-S was administered on day 0 and rAd5-S was administered on day 21 through intramuscularly as prime-boost vaccination [15]. Phase 3 trial of sputnik V reported immunogenicity, high efficacy as 91.6% against SARS-CoV-2 and well-tolerated in large clinical trial studies in 18 years and above [47].

4.1.3. Convidicea (Ad5-nCoV): Zhu *et al* from CanSino Biological Inc with Beijing Institute of Biotechnology have studied 108 participants during Phase 1 clinical trial and reported that the administration of AD5 vectored COVID-19 vaccine in healthy participants have been tolerable and immunogenic after 28 days of vaccination while the rapid specific T-cell response was observed after 14 days of vaccination [48]. Thereafter, Zhu *et al*. have studied 508 participants [1×10^{11} viral particles n = 253; 5×10^{10} viral particles n = 129; placebo n = 126) in Phase 2 clinical trial [49]. They reported AD5 vectored COVID-19 vaccine was safe and single immunization had successfully induced immune response in the majority of participants at the dose of 5×10^{10} viral particles. However, 1×10^{11} viral particle dose had shown adverse reactions in 24 (9%) participants while 5×10^{10} viral particle dose had shown adverse effect only in 1 (1%) participants. Notably, 1×10^{11} viral particle dose showed solicited adverse reactions in 183 (72%) of 253 participants while 5×10^{10} viral particle dose had shown solicited adverse reactions in 96 (74%) of 129 participants.

4.2. Inactivated or weakened virus vaccines: Notably, 16 vaccines in clinical trials of COVID-19 belonged to inactivated or weakened virus vaccines. The desired strain of the virus can be inactivated by using heat or chemicals including formalin/formaldehyde/Beta propiolactone (BPL). Hence the virus loses the ability to replicate and cannot cause the related disease. Thus, after injecting the inactivated virus into the human body, it generates an immune response. An Inactivated-based vaccine is safe as there is no live virus in the vaccine. Several vaccines have been made earlier using an inactivated platform such as Influenza, Hepatitis A, Polio, and Rabies.

Notably, there are three well-known inactivated virus-based vaccines for COVID-19. One such inactivated virus-based vaccine is Covaxin that was produced by Bharat Biotech International Limited and ICMR-India [50,51]. The other is BBIBP-CorV produced by Sinopharm with China National Biotec Group Co. and Beijing Institute of Biological Products [52,53]. Another is CoronaVac produced by Sinovac Research and Development Co Ltd respectively [54].

4.2.1 Covaxin: Covaxin or BBV152 is made in India as the SARS-CoV-2 vaccine. It has inactivated whole-virion and toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG). Ella *et al* [50,51] have reported that BBV152 is safe, well tolerable with enhanced immune responses, inducing both cell-mediated and humoral neutralizing responses based on Phase 1 clinical trial. Notably, both the doses of 3-µg and 6-µg Algel-IMDG vaccines were successfully able to induce T-cell responses and it was biased to T-helper-1 cells [50]. In the phase 2 trial, BBV152 has shown better reactogenicity and immune response in the expected line of phase 1 trial and suggested 6 µg with Algel-IMDG formulation for further clinical studies [51]. Further, the observation of humoral and cell-mediated response and neutralizing of antibody response was reported in different age groups and gender without any serious adverse events. Two doses of vaccine were needed to be administered with the first dose on day 0 and the second dose on day 28. Notably, the vaccine is immunogenic that persists for three months and preferable the storage temperature for the vaccine is 2–8°C.

4.2.2. BBIBP-CorV: It is an inactivated vaccine with the potential to prevent COVID-19. Wang *et al* have reported BBIBP-CorV was successfully able to induce significant neutralizing antibodies titers in several animals including mice, guinea pigs, rabbits and monkeys. The 2 mg/dose of BBIBP-CorV has shown better results in rhesus macaques with two-dose immunizations [52]. Further, Xia *et al* have reported that BBIBP-CorV is safe in humans and suggested that the two doses of immunization are better as compared to a single dose against COVID-19. Notably, 4 µg dose of BBIBP-CorV with double dose has shown that immunization on day 0 and day 21 or day 0 and day 28 both gave better results with significant neutralizing antibody titer as compared to a single dose of the different amount [53].

4.2.3. CoronaVac: Zhang *et al* have reported that inactivated vaccine with two doses of CoronaVac is safe and immunogenic. They recommended 3ug doses for phase 3 clinical trial based on phase 1/2 clinical trial study in 18–59 age groups [54]. Further Wu *et al* recommended CoronaVac for older people above the age of 60 years. They further found that in the phase 3 clinical trial, the 3 µg dose of the vaccine was successfully able to induce neutralizing antibodies [55].

4.3. Nucleic acid-RNA and DNA-based platform vaccines: The genetically engineered nucleic acids such as RNA and DNA were used to generate immune responses safely.

Comirnaty (BNT162b2) of Pfizer-BioNTech [56–61] and COVID 19 Vaccine mRNA-1273 of Moderna/NIAID belongs to mRNA-based vaccines [62–68].

4.3.1. BNT162b2: A lipid nanoparticle-formulated nucleoside-modified mRNA vaccine, BNT162b1 has significant potential to protect from SARS-CoV-2 from Pfizer-BioNTech. It encodes the receptor-binding domain (RBD) of the spike protein1 of SARS-CoV-2 [61]. BNT162b2 can be used as a COVID-19 vaccine for 16 years and older. It is administered in two doses and provides remarkably 95% protection in COVID-19. Clinical trials have been done in a large population of 43,448 individuals that included 21,720 people receiving BNT162b2 injection while 21,728 people receiving placebo [56]. Monin *et al* have reported that BNT162b2 is safe and beneficial also in cancer patients especially when the second dose was given on 21 days after the first dose increased immunogenicity significantly, while single-dose alone yielded poor efficacy [59]. Dagan *et al* have reported mass vaccination by BNT162b2 that is effective in COVID-19 and protects from most of the COVID-19 outcomes including severe conditions [58]. Notably, BNT162b2 is also very effective after 14 days of the second dose against the Covid-19 and its variants Alpha (B.1.1.7) and Beta (B.1.351). It has been reported it is effective in the case of 89.5% infection from Alpha variant (B.1.1.7) and 75% infection from Beta variant (B.1.351), however, it is still effective in cases of severe and critical conditions [60].

4.3.2. mRNA-1273: The mRNA-1273 vaccine has successfully induced anti-SARS-CoV-2 immune response in all participants and notably no trial limiting safety issues had been observed during phase 1 human clinical trial in 45 healthy adults between the ages of 18 to 55 years without any adverse side effects [62]. This vaccine is successfully able to stabilize spike protein S-2P (prefusion spike trimer). Notably, structural rearrangement of fusion (S2) subunit can be prevented by substitution of two prolines on top of heptad repeat 1 that results in stabilization of coronavirus spike protein [62]. These studies have shown that the majority of the participants are from one ethnic group and place, therefore it would be helpful to expand these studies to the wider range of human populations including different ethnic groups and geographical areas. It is necessary to extend the clinical trials to different age groups, especially those below the age of 18 and above 55 years, and to the patients having preexisting chronic diseases and ethnicity to make this vaccine universal.

Anderson *et al* reported that 100-µg dose of mRNA-1273 vaccine on day 0 and day 28 had performed better as compared to a 25-µg dose based on neutralizing-antibody titers. Notably, the mRNA-1273 vaccine is safe and adverse events were either mainly mild or moderate in older adult people [66]. Baden *et al* have reported the phase 3 clinical trial of mRNA-1273 vaccine suggesting 94.1% efficacy in preventing Covid-19 related complications based on 30,420 volunteers. This lipid nanoparticle–encapsulated mRNA vaccine is safe and no safety concerns were observed, while it has only transient local and systemic reactions. Further, it suggests that mRNA-1273 vaccines are safe for a person with chronic diseases [65].

Widge *et al* have reported that administration of two doses of 100-µg dose of mRNA-1273 vaccine induces a high level of binding and neutralizing antibodies and remains elevated for 90 days after a booster dose of vaccination [64]. Doria-Rose *et al* have reported that 100-µg dose of mRNA-1273 vaccine induces antibody activity and remarkably it remains high at 180 days after the second dose of vaccination in all the age groups [68]. Corbett *et al* have reported mRNA-1273 to induce significant neutralizing activity, quick protection in upper and lower airways and does not cause pathological changes [63]. Notably, mRNA-1273 induces potent neutralizing antibody responses to D614G mutant SARS-CoV-2 and wild type D614 along with CD8 + T cell responses and protects against SARS-CoV-2 infection in the upper respiratory tract (nose) and lower respiratory tract (lungs) [67].

4.4. Protein-based vaccines: The harmless fragments of proteins or their shells that mimic the COVID-19 disease virus have been used to generate an immune response. Interestingly, EpiVacCorona from Federal Budgetary Research Institution State Research Center of Virology and Biotechnology, Russia is a protein subunit vaccine [69].

4.5. Yeast-based vaccines: The availability of yeast expression technology provides significant benefits for the manufacture of inexpensive yeast-based SARS-CoV-2 vaccines [70]. The yeast-based vaccine such as the yeast *Pichia pastoris* expressed SARS-CoV-2 receptor-binding domain (RBD) combined with 3 M-052-alum adjuvants provided immunogenicity and protective efficacy in rhesus macaques suggesting promising SARS-CoV-2 vaccine candidate eligible for human trials as it is cost-effective, thermostable and scalable [71]. Another finding of yeast-based vaccine which yielded significant immune response in mice was by using oral administration of yeast S. cerevisiae-based SARS-CoV-2 vaccine EBY100/pYD1-RBD without any adjuvants [72]. Further, Zang J *et al*. found that the immunized mice with yeast (*Pichia pastoris*) derived RBD (either monomeric or dimeric) based recombinant SARS-CoV-2 vaccines effectively protects and neutralize SARS-COV-2 variants Alpha (B.1.1.7) and Beta (B.1.351) [73].

4.6. Conjugated vaccines with antimicrobial peptides: The mice immunized with the conjugates resulting from the synthesized peptide epitopes from the spike protein of SARS-CoV-2 attached covalently to cross-reactive material (CRM197) neutralized SARS-CoV-2 pseudovirus suggesting these conjugates as a potential COVID-19 vaccine candidate [74]. A Study by Outlaw et al., found that SARS-CoV-2 HRC-derived cholesterol conjugate inhibits Coronavirus Entry i*n vitro* and *ex vivo*, therefore acting like a potential candidate for the COVID-19 vaccine [75].

5. Doses of vaccines

The majority of approved vaccines are working in two doses and 64 vaccines are under clinical trial for two doses (Figure 7). FDA has approved the Janssen COVID-19 vaccine that is working in a single dose against SARS-CoV-2. Earlier approved Pfizer-BioNTech COVID-19 vaccine and Moderna COVID-19 vaccine was working in two doses. Further, the AstraZeneca vaccine produced by the Serum Institute of India and Covaxin from Bharat Biotech is working in two doses. Furthermore, Sputnik V with two doses has been approved for emergency use in India (Table 2).

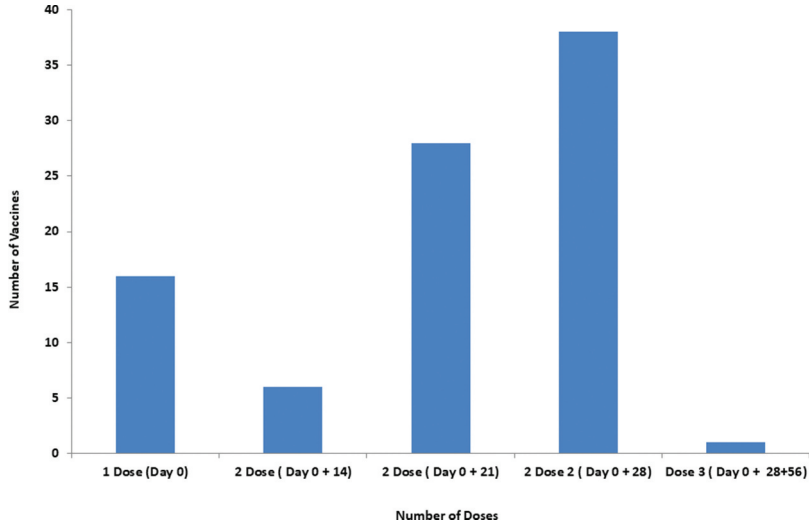

Figure 7. Doses of COVID-19 vaccines for immunization against SARS-CoV-2.

The benefits of the single-dose vaccine are it does not require follow-up and hence saves extra doses. The majority of vaccines have two doses. Notably, the time required for the second dose differs from vaccine to vaccine. Few vaccines need to be administered in 3 doses with the first dose on day 0, the second dose on 28 days, the third dose on 180 days for longer immunity. This is the longest time duration for three doses while some vaccine that requires shortest time duration for three doses involves the first dose on day 0, the second dose on 14 days and the third dose on 28 days (Figure 7).

Mix-and-Match or heterologous prime and boost of COVID-19 vaccine approaches are showing a bright future. Recently, the Spanish CombivacS trial enrolled with more than 600 people have presented promising trial results. The first dose administered was of Oxford–AstraZeneca vaccine with harmless chimpanzee adenovirus platform while the booster dose was of mRNA-based Pfizer-BioNTech. This combination produces a significantly higher level of antibodies compared to without booster dose and with the booster dose having the same adenovirus vaccine. Further, no severe adverse effects were observed [76]. Notably, Oxford–AstraZeneca vaccine induces significant T-cell responses and the Pfizer-BioNTech vaccine induce significantly high levels of antibodies [77]. Several studies are going on about the Mix-and-Match COVID-19 vaccine including mixing of same platform vaccine and also two different platform vaccines [78–80]. The Mix-and-Match approach of COVID-19 vaccines may provide significantly higher protection against SARS-CoV-2 and its variants.

6. Efficacy of vaccines against SARS-CoV-2 and variants

The reports about the effectiveness of different vaccines on the variants of SARS-CoV-2 are developing quickly. Different vaccines have different efficacies against SARS-CoV-2 such as Pfizer-BioNTech has 95% efficacy, Moderna has 94% efficacy, J&J has 72% efficacy, Astrazeneca has 62 to 90% efficacy and Sinovac has 50% efficacy. As SARS-CoV-2 has a high tendency of mutation, therefore it is difficult to predict, which vaccine will work for which variants. Notably, all these vaccines have some efficacy against Alpha variant (B.1.1.7, first detected in UK strain). Unfortunately, these vaccines have fewer efficacies against Beta Variant (B.1.351) (first detected in South Africa). Pfizer-BioNTech and Astrazeneca have the same efficacy against the Gamma variant (P.1, first detected in Brazil). Other vaccines have also reported different efficacies against SARS-CoV-2 such as sputnik V has 92% efficacy, Novavax has 96% efficacy, Sinopharm has 79 to 86% efficacy, Covaxin has 80% efficacy and CanSinoBIO has 66% efficacy [81–83].

The D614G substitution helps in virus replication in airway tissue and epithelial lung cells and causes higher infectivity and stability of the virus. Therefore, D614G mutation increases the transmission and viral load. Notably, D614G produces more infectious titer in the upper respiratory tract (Nasal, trachea) compare to the lower tract (lung) [81]. This indicates that further mutation in SARS-CoV-2 especially in spike protein will make it more infectious and lethal.

The ChAdOx1 nCoV-19 showed neutralization activity in the Alpha (B.1.1.7) variant, while it has shown better neutralization activity in non-B.1.1.7 (Alpha) variant. Efficacy for B.1.1.7 lineage was 70 · 4% compared to 81 · 5% for non-B.1.1.7 lineages [83]. The two doses of the ChAdOx1 nCoV-19 vaccine are unable to protect against the Beta (B.1.351) variant in mild to moderate COVID-19 [84]. Notably, the single dose of non-replicating adenovirus type 26 vaccine (Ad26.COV2.S from Janssen) has shown efficacy against Beta (B.1.351) variant such as 89% against severe COVID-19 and 57% against moderate to severe COVID-19 [84]. A single dose of Ad26.COV2.S has great efficacy against variants originated in South Africa and Brazil [85]. The NVX-CoV2373 vaccine has significant efficacy and cross-protection against the Beta (B.1.351) variant that originated in South Africa. Further, it has shown higher efficacy in HIV-negative groups [86]. Beta Variant (B.1.351) is more resistant compare to wild-type SARS-CoV-2. Mutation E484K in spike protein has made several variants more transmissible, tough and lethal including Alpha (B.1.1.7) and B.1.351 [19]. E484K mutation in B.1.1.7

makes the BNT162b2 vaccine less effective compared to wild type [87]. The mRNA-1273 vaccine may protect against COVID-19 from the Beta (B.1.351) variant as humoral immunity can be retained, despite the reduction in the efficacy of mRNA-1273 against the Beta (B.1.351) variant [88]. BBV152/COVAXIN significantly neutralizes the Alpha (B.1.1.7) variant that originated in the UK and sera of BBV152 is also protective against Delta (B.1.617) variant that originated in India [89,90].

SARS-CoV-2 dynamic multiple mutation ability has made the recent variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Kappa (B.1.617.1) and Delta (B.1.617.2) indicating SARS-CoV-2 antigenic drift has helped these to escape current prophylactics including some vaccines and therapeutics. Interestingly, all the individuals responded to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Epsilon (B.1.429), Iota (B.1.526), and Delta (B.1.617.2) on the second dose of mRNA-1273 vaccine. However, Beta (B.1.351) had the lowest recognition by the antibody [91]. The Pfizer–BioNTech vaccine appeared to be more effective than Oxford–AstraZeneca vaccine in preventing Delta variant infection [34].

Two doses of Pfizer or the AstraZeneca vaccine have been found to produce a neutralizing response in 95% of individuals with three to five times lower effect against the Delta variant as compared to the Alpha variant while one dose of this vaccine had an even less inhibitory effect on the Delta variant. The Delta variant spreadability is related to getting away from antibodies that target receptor-binding domain (RBD) and non-RBD of the SARS-CoV-2 spike protein [92]. The two-dose vaccination scheme among the Guangzhou participants in the age group of 40–59 years with inactivated SARS-CoV-2 vaccine has the vaccine efficacy of 72.5% against the Delta variant infection and has been found to be more effective in females compared to the males [32].

In South Korea, the vaccination program using AstraZeneca-Oxford and Pfizer COVID-19 vaccines brought down the virus attack rate from 6.9% (without vaccination) to 3.9% over 150 days with a 50% reduction observed among 50–59 years individuals during the fourth wave of the COVID-19 using an age-structured, two-strain model of SARS-CoV-2 transmission and vaccination. Further, the vaccination has been thought to decrease the attack rate from 26.9% to 11.9% for the Delta variant [7].

7. Mitigation of the COVID-19 transmission-alternatives to vaccines

Mitigation of COVID-19 transmission can be achieved by personal, administrative and engineering controls. Personal controls include masking, physical distancing, and ensuring proper ventilation, while administrative and engineering controls include proper guidance, educational information, access to clean water and policies for implementing masking and physical distances in dense population and market areas [93]. Further, preventive measures such as appropriate mask-wearing, hand hygiene, physical distancing, promoting respiratory etiquette and frequent cleaning of high touch surfaces in crowded areas can help to mitigate the transmission of COVID-19. Notably, reducing the crowd at public places following occupational safety/health measures, avoiding unnecessary visits, possible remote work, proper ventilation and maximum open-air stay/circulation can help to minimize the exposure and spread of COVID-19. Routine screening, monitoring of the symptom, early diagnosis and quick proper treatments are important to mitigate the COVID-19 [93, 94].

8. Conclusions

Systematic clinical trial studies of COVID-19 vaccines have provided trust and confidence among clinicians and the general public. Several COVID-19 vaccines have been globally accepted due to their efficacy and safety that has helped to overcome vaccine hesitancy. Notably, COVID-19 vaccines protect vulnerable patients with co-morbidities. It can also be administered in pregnant ladies for the safety of the mother and the newborn.

Emerging of SARS-CoV-2 variants has challenged the ongoing vaccine drive against pandemic COVID-19. The diverse vaccine platforms have opened new avenues for quick and cost-effective production of COVID-19 vaccines to attain immunization globally. The vaccine effectiveness was more pronounced after the receipt of second dose. The vaccination will help in preventing hospitalizations and deaths. Further, if the vaccinated individuals get infected with COVID-19, they will recover without serious illness.

There is a potential requirement for additional boost vaccinations as the SARS-CoV-2 variants decrease the vaccine-induced protective immune response over time especially in individuals with medical co-morbidities. Mix-and-Match COVID-19 vaccines including mixing of same vaccine platform and also two different vaccines platform may provide higher protection against SARS-CoV-2 and its variants. The vaccines for the COVID-19 pandemic will help in preserving health care infrastructure, economy and may eventually end this pandemic.

9. Expert Opinion

The world is going through the havoc of an airborne coronavirus disease (COVID-19) pandemic caused by SARS-CoV-2 infection. The passage of the corona virus into the human body is through the upper respiratory tract (nose, mouth) to the lower respiratory tract (lung). This virus has infected more than billions of humans worldwide and has caused several thousand deaths. The multiple COVID-19 infection waves have created an increased demand for medical oxygen, hospitalization, ventilator and the usage of emergency drugs. The subsequent waves of COVID-19 have taught the value for continued usage of masks, avoidance of public gatherings and application of vaccines. This may be continued for months to years, to overcome the damage from the future wave of the COVID-19 pandemic as we know that SARS-CoV-2 has a high ability to mutate and form dangerous variants. Interestingly, the vaccination of the human population may help to overcome the infections from the emergence of new mutant strains of SARS-CoV-2.

To vaccinate billion of the population worldwide, there is an urgent requirement for resources and funds. Ongoing vaccination drive has administered several billion vaccine doses as reported by the World Health Organization (WHO). The worldwide vaccination, if completed simultaneously may lead to herd

immunity and help in the eradication of COVID-19. If some groups of human populations are left unvaccinated, again there are chances for the emergence of new mutant strains of SARS-CoV-2 that may again start a new chain of infections.

Though intramuscular vaccines protect the lungs including protection from the severity of COVID-19 condition with the help of IgG1, however, they are unable to provide complete protection from SARS-CoV-2 infection and its transmission including breaking the chain of COVID-19 infection. Notably, intranasal or oral vaccines can protect the upper respiratory tract with the help of IgA1 thus preventing SARS-CoV-2 transmission. Therefore in this extraordinary pandemic situation, both intranasal and intramuscular COVID-19 vaccines provide better protection from infection, transmission and severe condition of COVID-19. Notably, the majority of vaccines that are under clinical trial are intramuscular while some as intranasal, and a few are oral. Besides, nasal and oral vaccines are environmentally friendly and may be a preferable candidate for vaccination to young children and neonatal in the future.

Interestingly, industry and academia have been the torchbearer in this pandemic and have provided several vaccines worldwide for adults and notably, the studies on vaccines for children are in process. In the ongoing pandemic situation, vaccines from diverse platforms may help to deal with the infection from SARS-CoV-2 and its variants. In the future, it may be possible to use diverse platforms to produce several vaccine doses to protect humans worldwide. The administration of two vaccine doses belonging to different platforms may play an important role in the handling of the ongoing SARS-CoV-2 and its variants. There is a potential need for additional boost vaccinations especially in individuals with medical co-morbidities. Additionally, more studies are required to be done for the mixing of vaccine doses belonging to the same and different platforms. These may provide better immunity against SARS-CoV-2 and its variants. Further, this may cope with the vaccine scarcity in low and middle-income nations and also in nations having large populations. However, patients' side effects must be studied. The vaccination will help in preventing hospitalizations and deaths to the individuals.

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