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Development of COVID 19 vaccine: A summarized review on global trials, efficacy, and effectiveness on variants

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ABSTRACT

Background and aims: The emergence of SARS CoV2 or COVID 19 pandemic has shocking results on major global public health. This review aims to discuss the nine prominent COVID 19 vaccines with regard to their immunogenicity, efficacy, and effectiveness against the SARS CoV2 variants.
Methods: Electronic databases such as Medline/PubMed, EMBASE, Scopus, science websites, and Google scholar were accessed to retrieve the research published about COVID 19 vaccines.
Results: All the adverse impact ranging from mild to moderate in the clinical trials were analysed, however, there were less reports in which COVID 19 patients either developed severe reactions or died due to the different experimental vaccines. Moreover, SARS CoV2 variants like Delta could escape the immune response.
Conclusion: Overall, the data suggest that the two doses of COVID 19 vaccines are extremely effective against the original SARS CoV2 virus, and also provide well protection against SARS CoV2 variants, especially in severe illnesses. However, a third dose of the COVID 19 vaccine (also said to be the booster dose) will be needed in some immune-compromised people.

1. Introduction

The outbreak and devastating impact of SARS CoV2 or COVID 19 infection was first reported in late 2019 in the city of Wuhan, China [1]. The causative agent, identified as the novel SARS CoV2 (Beta-coronavirus), is closely associated to SARS CoV, which was responsible for SARS outbreak between 2002 and 2004 in Guangdong province, China. SARS CoV2 since have being declared a global pandemic by the WHO, the virus-infected over 445 million people with 6 million deaths till February 2022. The SARS CoV2 are enveloped viruses with a large, positive-sense single-stranded RNA with genomic size approximately 30 kb in length, which is among the largest known RNA genomes [2,3]. The genomic RNA has a 5' — methyl guanosine cap at the starting, and a 3' poly-A tail towards the end, with 6—10 genes in the middle [4]. The genes are usually ordered in a highly conserved manner, with the first one associated with transcription and replication, and the rest are structural in function [4]. The SARS CoV2 virus comprises four different structural proteins, such as spike (S) glycoprotein, membrane (M), envelope (E), and nucleocapsid (N) protein [5], which are key components of mature virus and facilities the viral structural integrity, in the case of SARS CoV2, the spike glycoprotein binds the host cell surface membrane and further endocytosed, as previously in SARS CoV. The Spike (S) protein of SARS CoV2, is composed of two subunits, Subunit 1 (S1) which comprises N terminal membrane, and S2 as C terminal domain proximal. Furthermore, the S1 subunit has four subdivisions $S1^A$, $S1^B$, $S1^C$, and $S1^D$. The $S1^B$ is referred to as Receptor binding domain (RBD) of spike (S) protein of SARS CoV2 virus which docks the angiotensin convertase enzyme-2 (ACE2) receptor for membrane fusion [5]. Likewise in the case of SARS CoV binding, the same ACE2 receptor of host cells play a crucial role in spike protein docking [5]. Based on extensive information by now, seven known human coronavirus (HCoV) species have been identified; four of these belonging to alpha-coronavirus (NL63 and 229E) and beta-coronavirus (OC43 and HKU1) [6]. Conversely, the rest three are SARS CoV, MERS-CoV, and SARS CoV2. Out of the above alpha-coronaviruses (HCoV-NL63 and HCoV-229E) are considered to be highly contagious and to have originated from bats like the SARS CoV and MERS CoV did [6]. Notably, these four (HCoV-OC43, 229E, NL63, and HKU1) of them induce mild to moderate illness in the upper respiratory tract (URT) of the host or might be severe in some elderly patients [6]. Despite this, with the onset of the present COVID 19 outbreak, mucosal immunity has also played a significant role, especially circulating

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antibodies (IgA) and secretory responses [7]. Interestingly mucosal (IgA) immune responses, which is a physical barrier plays the most crucial role against most infection pathogens in the respiratory tract and eventually can neutralize before docking with epithelial cells [8]. It is noteworthy that a naturally infected body triggers both the antibodies responses mucosal (IgA) and systemic (IgG) to provide well protection in the host and the vaccines that are administered intramuscularly (IM) are mainly aiming to induce IgG, and no secretory IgA. Therefore, it is possible that most vaccines at present induce attenuating or disease-preventing immunity, but not necessarily to provide unique sterilizing immunity which is often considered as the gold standard for neutralizing antibodies as they effectively stop and prevent a disease-causing pathogen like COVID 19.

The review aim to discuss COVID 19 vaccines (see Fig. 1) like viral vector, mRNA based, protein-based, and inactivated vaccine. The viral vector vaccines developers like Oxford-ChAdOx1-nCoV-19, Johnson and Johnson, Sputnik-V, Ad-5 Vector from CanSino are recombinant vaccines that uses a modified virus (called a vector) holds extra genetic material that further codes for the SARS CoV2 spike (S) protein [9,10]. The messenger-RNA (m-RNA) vaccines like Pfizer-BioNTech, Moderna-mRNA-1273 encodes a key protein Spike (S) protein of SARS CoV2 [11–14], once the mRNA (is genetic material) get inside our cells, our bodies start producing this protein, and this act as the antigen (same as a foreign molecule) that stimulates our immune response and making antibodies. The protein-based vaccine (NVX-CoV2373/Covovax from Novavax and Corbevax) uses fragments of protein from the disease caused by the virus, to trigger the protective immune response against the infection [15,16]. While inactivated version of vaccine (Covaxin from Bharat BioTech) uses actual version of the virus to trigger protective immunity [17–19], like the way it happens during the natural infection against COVID 19.

Overall, these vaccines achieved 62–94% efficacy in Phase III clinical trials against original SARS CoV2. The genetic mutants of SARS CoV2 (Fig. 2) like the Alpha (B.1.1.7, identified in the United Kingdom), Beta (B.1.351, identified in South Africa), Gamma (P.1, identified in Brazil/Japan), and Delta (B.1617, identified in India) had worsen the situation. Evidence confers that some variants like Delta appear to promote rapid transmissibility, and potentially lead to a drop in the neutralization of post-vaccination sera in the individuals. Below a brief overview on nine prominent COVID 19 vaccines development on the fronts of real-world data, vaccine efficacy and its effectiveness has been discussed in detail.

2. Viral vector vaccines

2.1. 1ChAdOx1 nCoV-19 from AstraZeneca and Oxford

ChAdOx1 nCoV-19 (AZD1222) vaccine, a significant development of AstraZeneca and University of Oxford (Oxford, UK) has shown an adequate safety profile. The vaccine comprises the replication-deficient simian adenovirus vector ChAdOx1, that encodes a full-length of (S) spike glycoprotein of SARS CoV2 [20]. The first preliminary Phase I/II trial was conducted on 1077 healthy volunteers (18–55 years randomized controlled) who received 1:1 ratio of ChAdOx1 nCoV-19 vaccine (n = 543) or MenACWY vaccine (n = 534) and (n = 10) of them were assigned in the non-randomized ChAdOx1nCoV-19 prime-boost group [21]. Participants in the ChAdOx1 nCoV-19 group were able to develop a rapid spike-specific T-cell response (peaking at 14 days after vaccination until 28 days onward), antispike IgG responses rose by day 28, and were boosted after a second dose. To determine the neutralizing antibody titers against SARS CoV2, a subgroup of 35 individuals was studied, 32 out of 35 measured in the micro-neutralization assay (MNA80), and reported in all 35 (100%) individuals with 50% plaque

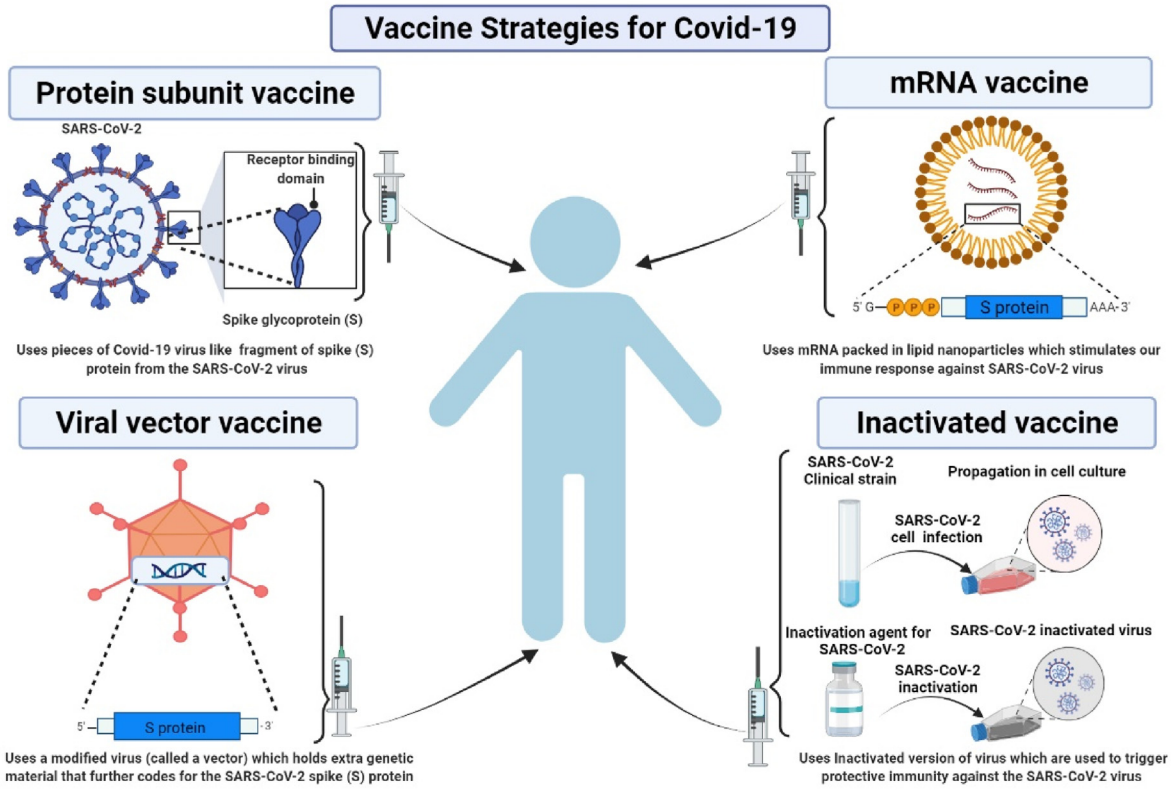

Fig. 1. An illustration representing vaccine strategies against COVID 19 disease.

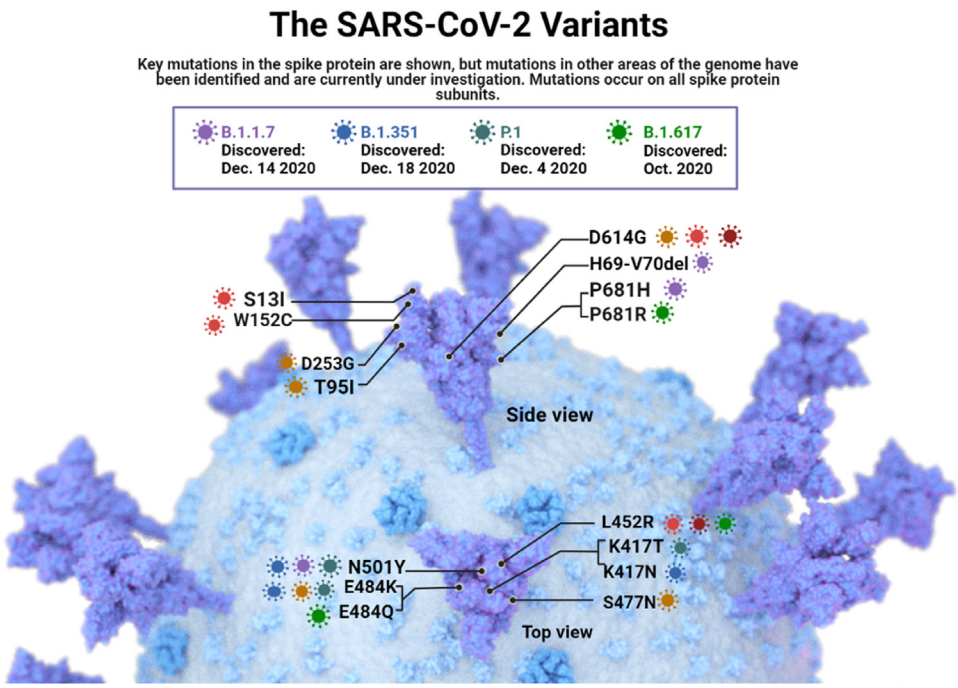

Fig. 2. An illustration representing mutations associated with SARS CoV2 variants under investigation.

reduction neutralization assay (PRNT50) readout (NCT04324606) [21,22]. On day 28 of post-vaccination, all participants had neutralizing activity. In this given trial, a small subset of individuals has also received both doses of prime as well booster. Overall, the ChAdOx1 nCoV-19 vaccine showed homologous boosting antibody response with the same immunogenicity. The local and systemic reaction reported was more common and prophylactic paracetamol was given to reduce the alleviating side effects ($p < 0.05$). However, no serious adverse reactions were reported related to the actual ChAdOx1 nCoV-19 vaccine. The first clinical trial on efficacy was determined by phase II/III which was done in the United Kingdom (UK) and Brazil, although safety primary interim analysis was determined by four advanced trials from the UK, Brazil, and South Africa (SA) [23]. The interim primary efficacy analysis included 23,848 participants enrolled and 11,636 participants (UK-7548 and Brazil-4088), the majority of them were aged (18–55 years) assigned to receive one or two doses regimen [23]. The trial showed two different efficacy results, getting the first dose and second dose after a month apart; the efficacy was 62.1% (95% credibility interval (CI), 41.0%–75.7%) in one group [23,24]. However, decreasing the first dose (initial) followed by the second after a month apart showed higher efficacy with a 90% (95% CI, 67.4%–97.0%) in the second group. Combining both dosing regimens data, the overall average efficacy result was 70.4% (95.8% CI, 54.8%–80.6%) (Table 1) rates in both groups, the severe adverse reaction was also reported in a total of 168 participants (among them 84 were reported in ChAdOx1 nCoV-19 group and 91 in the control group) and 3 were possibly classified under vaccine intervention [23–25]. This vaccine candidate has received an emergency use validation from WHO and multiple countries by their own regulators in January. While the vaccine efficacy tested in the U.K trial was found to be very good at protecting from Alpha variant (U.K with 43–90% higher reproductive rate than pre-existing variants [26]) with 74.5% (Table 2) and 81.5% for non-B.1.1.7 lineages, specifically after both the doses (NCT04400838) [27]. The efficacy trial with two doses on Beta variant offered minimal protection (as low as 10% 95% CI, −76.8-54.8) (Table 2) among the young population with an average age of 30 in (South Africa) against only mild-moderate cases of COVID 19, but still, the vaccine is expected to provide a decrease in severe hospitalization cases and deaths [28]. Meanwhile, this study failed to determine whether it delivered better protection against serious illness or hospitalization because the testing was determined by people who were at low risk from serious COVID 19 illness. The efficacy here on severe COVID 19 patients is undetermined (NCT04444674). Similarly, the lab results on the Gamma variant (P.1) showed less efficacy probably because of resistance to neutralization antibodies by convalescent plasma via 3.4-fold and 3.8–4.8-fold for post-vaccination sera [29]. On Delta variant the vaccine showed reduced effectiveness due to convergent evolution of spike (S) protein which carries multiple mutations (Table 2) on its genes positions may assist in better transmissibility with evading the immune system. However, the latest findings by Public Health of England (PHE) found the effectiveness of ChAdOx1 nCoV-19 vaccine after both doses were 67.0% (95% CI, 61.3–71.8) (Table 2) among persons with the Delta [30]. In addition to this contagious variant, in my opinion, it is highly possible to get reinfection or a significant decline in neutralization antibodies could be possible which was generated through previously COVID 19 infection or post-vaccination. As a result of this, certain recipients here are likely to need a third dose (Booster shot) to get sufficient antibodies if they are immunocompromised condition against these specific variants of infection.

2.2. Johnson and Johnson

Johnson and Johnson (Ad26.COV2. S or JNJ-78436735) vaccine developed by Janssen Pharmaceutica, a Belgium-based subsidiary of the American company Johnson and Johnson (J&J). The vaccine, Ad26.COV2. S has a replication-incompetent adenovirus seroaccine for human adenovirus type 26 (Ad26) vector which encodes a full-length and stabilized spike (S) protein of SARS CoV2. Previously the J&J had already used this technique Ad26 adenovirus to design the Ebola vaccine and other infectious diseases too. In the phase of the 1-2a trial enrolled 805 participants (18–55 years) in cohort 1 and

Table 1
An overview of different types of prominent COVID 19 vaccines with efficacy achieved in differing Phase III clinical trials at different geographical areas. Vaccines like Moderna, Pfizer/BioNTech, and J&J are fully FDA-approved licensed vaccines and others have received emergency authorization from the WHO usage and regional regulators too.

Ref	Name of Vaccines	Type of Vaccines	Vaccines Developer	Clinical dose regimen	Efficacy on original variants of SARS CoV2	Country
(Voysey et al., 2021) (Knoll and Wonodi, 2021) [23,24]	(University of Oxford/ AstraZeneca) AZD1222	Viral vector (ChAdOx1-5)	University of Oxford/ AstraZeneca	2 Doses (4 weeks apart)	Overall, 70.4% (95% CI 54.8−80.6) 2-standard dose: 62.1% (95% CI 41.0−75.7) Low dose + standard dose: 90.0% (95% CI 67.4 −97.0)	UK
(Tehrani and Sajadi, 2021) [32]	(Johnson and Johnson) Ad26.COV2. S	Viral vector-based (Ad26)	Johnson and Johnson (J&J)	1 Dose	66.9% (95% CI 59.0−73.4) ≥60 years old 76.3% (95% CI, 61.6−86.0)	USA
(Logunov et al., 2021) [41]	Gamaleya (Sputnik V)	Adeno based rAd26+rAd5 (Viral vector) (Genetically modified virus)	Gamaleya Research Institute, Russia	2 Doses (3 weeks apart)	91.6% (95% CI 85.6−95.2)	Russia
[45]	CanSino (Convidecia)	recombinant adenovirus type-5 (Ad5) vector	Beijing Institute of Biotech and CanSino Biological	1 Dose	65.7% (As per company own claim) Full data Unpublished	China
(Polack et al., 2020) [48]	Pfizer (BNT162b2)	mRNA	Pfizer and BioNTech	2 Doses (3 weeks apart)	94.6% (95% CI 89.9−97.3)	USA and Germany
(Baden et al., 2021) [54]	Moderna (mRNA-1273)	Encapsulated mRNA (Part of virus genetic code)	Moderna and NIAID	2 Doses (4 weeks apart)	94.1% (95% CI 89.3−96.8; $p < 0.001$)	USA
(Heath et al., 2021) [60]	Novavax/ Covovax (NVX-CoV2373)	Protein subunit	Novavax (Gaithersburg, USA)	2 doses (3 weeks apart)	89.7% (95% CI 80.2−94.6)	USA
[64]	Corbevax	Protein subunit	Texas Children's Hospital and Baylor College of Medicine	2 Doses (4 weeks apart)	Over 90% effective (As per company own claim) Full data Unpublished	USA
(Ella et al., 2021) [68]	Covaxin	Inactivated	Bharat BioTech	2 Doses (4 weeks apart)	77.8% (95%CI 65.2−86.4)	India

Table 2
An overview of COVID 19 vaccines against SARS CoV2 variants under investigation. Importantly, a head-to-head comparison is impossible due to the study trials conducted at different times and circumstances. Data in * showing the effectiveness of vaccines and rest for the vaccine efficacy.

S. No	(Genetic Variants of SARS CoV2)	First Identified	Spike protein substitutions (Mutations)	(University of Oxford/AstraZeneca) AZD1222	(Johnson and Johnson) Ad26.COV2. S	Pfizer (BNT162b2)	Gamaleya (Sputnik V)	Novavax NVX-CoV2373	Covaxin (Bharat Biotech)
1	Original Wuhan reference strain	China, December 2019	References strain	55−81% (Voysey et al., 2021) [23]	66% (Tehrani and Sajadi, 2021) [32]	95% (Polack et al., 2020) [48]	91.6% (Logunov et al., 2021) [41]	89.7% (Heath et al., 2021) [60]	77.8% (Ella et al., 2021) [68]
2	B.1.1.7 (Detected in UK) 20I/501. Y. V1 (Alpha)	United Kingdom	69del,70del,144del N501Y, A570D, D614G, S982A, D1118H, K1191 N, P681H, T716I	74.5% (Davies et al., 2021) [26]	Unknown	*93.7% effectiveness (Lopez Bernal et al., 2021) [30]	Unknown	85.6% efficacy (Heath et al., 2021) [60]	Unknown
3	B.1.351 (Detected in SA) 20H/ 501.V2 (Beta)	South Africa	D80A, D215G, 241del, 242del, 243del, N501Y, D614G, A701V, K417 N, E484K	10 (Madhi et al., 2021) % [28]	64−66% in USA (Shrestha, 2021) [33]	*95% effective against severe disease and death [34]	Virus-neutralizing activity with 3.1-fold (Gushchin et al., 2021) [42]	60.1% (Mahase, 2021b) [61]	Unknown
4	B.1.617.2 Delta Variants 21A/ S:478K (Delta)	India	L452R, D614G, P681R, D950 N, T478K,	*67.0% effectiveness after two doses (Lopez Bernal et al., 2021) [30]	*71% effectiveness against hospitalization, 95% effective against death [34]	*On 2 dose 88% effectiveness (Lopez Bernal et al., 2021) [30]	*83.1% effective [43]	6-fold higher in cross-reactive functional antibodies [62]	65.2% (Ella et al., 2021) [68]
5	P.1 (Gamma) 20J/ 501Y.V3	Brazil/ Japan	E484K, K417T, N501Y D614G, H655Y, T1027I	Unknown	69% (Sadoff et al., 2021) [35]	Unknown	*Effectiveness of 78.6−83.7% after 2 doses [43]	Unknown	Unknown

those over 65 years of age were assigned in cohort 3. Both the groups either received a low dose of Ad26.COV2. S vaccine (5×10^{10} viral particles) or high dose of Ad26.COV2. S vaccine (1×10^{11} viral particles) per milliliter or placebo was administered in a single or

two-dose schedule [31]. The long-term effects of a single-dose regimen or a double-dose regimen were studied in cohort 2. Systemic adverse events were more uncommon in cohort 3 as compared to cohort 1 and in those participants, who received the low viral dose of vaccine than for those who received the higher viral dose [31]. In this trial, more than 90% of entire participants were detected Neutralizing-antibody titers readout against the wild-type virus on day 29 after the first dose of vaccine (Geometric mean titers (GMT) 224 to 354). These results were obtained regardless of vaccine or age group and further reached up to 100% by day 57 (GMT 288 to 488) in cohort 1a. Until day 71, titers continued to be stable, further, a second dose was given which resulted in titers increment 2.6–2.9 (GMT, 827 to 1266). The neutralizing-antibody response was similar, $CD4^+$ T cell responses were also distinguished in 76–83% in participants in cohort 1 and of those in cohort 3 it was reported in 60–67% of participants, with a reasonable skewing towards type 1 helper cells, likewise, $CD8^+$ T-cell response was vigorous in overall yet lesser was observed in cohort 3. The Phase 3 trial results with 40,000 enrolled participants from multi-national, double-blind, and placebo-controlled for a single dose of (5×10^{10}vp) of Ad26.COV2. S vaccine suggested overall efficacy was 66.9% (95% CI 59.0–73.4) at least 14 days after the single-dose and was 66.1% (55.0–74.8) (Table 1) at least 28 days after post-vaccination considering moderate to severe COVID 19 disease [32]. While the post-analysis of all COVID 19 related hospitalization cases was 29 in the placebo group (with near 16 hospitalizations after 28 days of vaccination) and there were 7 deaths (placebo) in the trial, whereas the vaccine group has no COVID 19 related deaths. However, the efficacy for preventing mild to moderate or critical and severe COVID 19 patients was 72% in the United States (US), 64% in South Africa (SA) [32]. For South Africa dominated Beta variant (B.1.3.5.1) was reported to have 64% (Table 2) protection against moderate to severe or critical COVID 19 disease, and over 66% (Table 2) showed protection against moderate to severe disease in the USA (primarily the Wuhan-1 variants with mutation D614G), at least 29 days after vaccine intervention [33]. In July J&J was reported to be effective against the highly contagious Delta variant but had only a small decrease in potency compared with the original SARS CoV2 strain, nevertheless, the first evaluation of the Ad26.COV2-S vaccine against Delta in real life was 71% Table 2 effective against hospitalization and 95% effective against death according to data released from J&J [34]. The overall Ad26.COV2-S vaccine efficacy remained 85.4% [adjusted 95% CI, 54.2–96.9] in preventing severe COVID 19 all across the geographical regions [35]. Although one study suggested to have less effectiveness against Delta [36]. This vaccine candidate is currently became fully licensed by the US FDA for usage, additionally with emergency use validation from WHO including multiple countries by their own regulators. Meanwhile, the FDA recommends an extra J&J dose (Second booster dose) for emergency use authorization in all individuals (people 19 or older) at least 2 months after the first J&J vaccination.

2.3. Sputnik V from Gamaleya

The Gamaleya Research Institute in Moscow, Russia, developed Gam-COVID-Vac trade (Sputnik V), the world's first vaccine against SARS CoV2. The vaccine involves vector segments, recombinant adenovirus serotype 26 (rAd26), and recombinant adenovirus type 5 (rAd5) vector segments, both vectors are very promising for design vaccines that carries the gene for SARS-2 full-length surface (S) spike protein [37]. Adenovirus Ad26 is used in the first dose and adenovirus Ad5 in the second, both of them expressing spike (S) glycoprotein of SARS CoV2 in separate doses within 21 days of the interval [37–39]. Its phase I/II of the clinical trial, non-randomized on just 76 participants separated into Phase I and II (38 in each phase) for evaluating safety and immunogenicity for over 28 days and over. In phase I, 9 participants received rAd26-S, and another 9 participants received rAd5-S and in phase II 20 out of 38 were received rAd26-S and rAd5-S showed both the vaccine was found to have high safety and well-tolerated profile with no serious adverse events reported, suggesting that the vaccine would deliver a strong immune response against SARS CoV2, at day 42, IgG titers readout was 14,703 for the frozen formulation, and neutralizing antibodies was 49.25, with the lyophilized formulation titers was 11,143 and 45.95, with a seroconversion rate of 100%, during the clinical trial, all the participants were also detected cell-mediated response at day 28 against spike (S) glycoprotein against SARS CoV2 [40]. Interim phase III trial based on over 21,977 participants (18 years or older) randomly assigned to received vaccine dose in 16,501 participants group and 5476 in the placebo group. Demonstrated the vaccine efficacy was 91·6% (95% CI 85·6–95·2) (Table 1) against COVID 19 [41]. With no mild or severe events were reported. There were four deaths recorded during the study. However, none of them were related to the vaccine. Virus-neutralizing activity (VNA) of sera in individuals who received the two doses of Sputnik V vaccine statically significant VNA reduction were observed for Beta (3.1), Gamma (2.8-), and Delta (2.5-fold), respectively [42]. Notably, for effectiveness against contagious Delta variant, showed to have 83.1% efficacy Table 2 with 6x reduction in infection risk in addition to 94.4% efficacy against hospitalization with an 18x reduction in hospitalization risk, also confirmed the neutralization effectiveness with 78.6–83.7% against Manaus (P.1) variant Table 2 in Argentine after receiving two doses of Sputnik V [43]. To date, this vaccine has been authorized in nearly 70 countries and territories.

2.4. Convidecia from CanSino

Conavidecia is a vaccine that relies on a recombinant adenovirus type-5 vector (Ad5) that expresses the SARS CoV2 strain of surface spike (S) protein, which jointly developed by the Beijing Institute, China of Biotech and CanSino Biological. In a randomized, double-blind, placebo-controlled clinical trial of phase II on 508 participants (18 years and above) divided into three groups received the vaccine at a dose of (5×10^{10} viral particle dose group n = 129), (1×10^{11} viral particle dose group n = 253) and 126 in placebo group (NCT04341389) [44]. Cellular and neutralizing antibody both the responses were readout with GMTs of 19.5 (95% Cl 16.8–22.7) and 18.3 (14.4–23.3) in both the groups who received 1×10^{11} and 5×10^{10} viral particles per ml, respectively after 28 days of SARS CoV2 vaccination. In addition, flow cytometry assays revealed rapid high and specific T-cell responses 14 days after post-vaccination [44]. Specific anti-SARS CoV2 (S) IgG antibodies were measured in 227 of 253 and 113 of 129 participants in the 1×10^{11} viral particle dose group and 5×10^{10} viral particle dose groups through ELISA (enzyme-linked immunosorbent assay) on 28 days of post-vaccination [44]. No severe adverse reactions were reported. In the advanced multicenter phase III trial to determine the efficacy and safety profile enrolled 30,000 individuals globally (18 years and above) and 101 COVID 19 cases were reported during the study, full data is yet to be published (NCT04526990). The company claimed to have an efficacy of 65.7% (Table 1) with one dose at preventing all symptomatic COVID 19 cases and 90.98% at preventing severe COVID 19 cases [45]. This vaccine candidate has got general approval for use in China and an Emergency authorization permit in Chile, Hungary, and Mexico yet still under evaluation by the WHO. Efficacies on the concern variants like Alpha, Beta, and Delta are unknown.

3. mRNA based vaccines

3.1. BNT162 from Pfizer

The BNT162 vaccine is an mRNA-based vaccine candidate, a collaboration of Pfizer and BioNTech company. The vaccine is a nucleotide-modified RNA encapsulated in lipid or polyethylene glycol lipid nanoparticles formulated and encodes the trimerized (RBD) of SARS CoV2 spike (S) protein antigen. These vaccines BNT162 have four different variants which were undertaken in the clinical evaluation (BNT162a1, BNT162b1, BNT162b2, and BNT162c2), among these variants, BNT162b1 and BNT162b2 variants emerged as two strong candidates based on immune response and safety profile. In the phase, I/II trial among 45 healthy adults (18−55 years) randomized received two doses of shots (10 μg and 30 μg/100 μg) of BNT162b1 vaccine, separated by 3 weeks of the interval [46]. No severe reaction was reported (NCT04368728). However, the second dose of 100 μg was not administered due to a high level of reactogenicity and unfavourable increased immunogenicity [46]. SARS CoV2 neutralizing titers and RBD-binding IgG concentrations in sera both levels got increased after receiving the first dose followed by the second dose. On day 35 (2 weeks after the second dose) the neutralizing geometric mean concentrations (GMCs) titers reached 1.9−4.6-fold of the COVID 19 convalescent human sera obtained after the two weeks after a positive RT-PCR quantitative confirmed in patients with COVID 19 infection [46]. An unblinded reactogenicity data achieved in phase II/III trial with advanced nucleoside-mRNA candidate BNT162b2 similar to BNT162b1 encodes of full-length spike glycoprotein on 8,000 participants (18 years and older) were evaluated for safety demonstrates that the vaccine was acceptably endured with the most adverse event decline after the vaccination. The only grade 3 adverse events reported was 2% in frequency after the first or second dose and 3.8% at were fatigue, 2.0% at headache followed after the second dose of vaccination [47]. In the final Phase III trial over 43,000 participants (16 years or older) were enrolled and underwent randomization into two separated groups assigned to receive either two doses of BNT162b2 vaccine (30 μg per dose) or placebo 21 days apart. There primary analysis from the phase III trial demonstrated a 94.6% efficacy (95% (CI) 89.9−97.3%) (Table 1) in preventing against COVID 19, this conclusion was based on 170 cases of COVID 19 study, 8 cases were reported positive for COVID 19 after a week of the second dose in BNT162b2 group and 162 cases from among those receiving the placebo (NCT04368728) [48]. Data released by (PHE) found to prevent symptomatic cases of Alpha variant with 93.7% (95% CI, 91.6−95.3) (Table 2) effectiveness within two weeks after the second dose and 88% (95% CI, 85.3−90.1) (Table 2) effectiveness rate against the symptomatic COVID 19 diseases with Delta variant, two weeks after the second dose [30]. Overall, the vaccine protection was better in Alpha compared to the Delta variant. Unsurprisingly, a trial study conducted in Israel suggested that Pfizer/BioNTech vaccines were less potent against the Beta B.1.351 than non-B.1.351 variants based on a small investigation of breakthrough cases that were observed for Beta [49,50], notably Beta variant having multiple mutations (Table 2) in RBD which may affect the vaccine protection. But still, the vaccine able to shows 95% (Table 2) effectiveness against severe disease and death [34]. This vaccine candidate received full licensed by US FDA for usage, additionally with emergency usage from WHO including multiple countries by their own regulators. Meanwhile, Pfizer/BioNTech also received FDA authorization for third dose (single booster shot), to profit certain individuals (16 years of age and older >65 years) who are immune-compromised and at very high risk of severe COVID 19 with at least 6 months after receiving both the doses of primary series of vaccination.

3.2. mRNA-1273-from Moderna

Moderna's mRNA-1273 is a messenger RNA (mRNA) vaccine jointly developed by the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Centre against COVID 19 encoded with prefusion stabilized for viral spike (S) protein [51]. The mRNA vaccine encoded with viral antigen has been a promising approach for COVID 19 [52]. During the Phase I trial findings on 45 healthy adults who received two doses of mRNA vaccination (18−55 years with 15 participants in each group) 25 μg, 100 μg, or 250 μg doses resulted in strong S-specific antibody response by increased higher ACE2 binding inhibition and neutralizing activity against SARS CoV2. On day 29 the geometric mean titer (GMT) readout in the low 25-μg group was 40,227, 109,209 in the 100-μg group, and the higher dose group readout was 213, 526 [53]. After day 57 followed the second dose the titers reached 299,751, 782,719, and 1,192,154, respectively. The most common side effects in the participants were reported was fatigue, headache, myalgia, and pain at the site of injection. However, systemic adverse events were dose-dependent and reported after the second higher dose of vaccination in the 3 participants (21%) of the higher dose group of 250 μg [53]. The phase III randomized, double-blind COVE study evaluation involving 30,420 participants assigned to receive 100 μg of two-dose regime either experimental vaccine or placebo was given 28 days apart via intramuscular showed well tolerated with around 94.1% efficacy (95% CI 89.3−96.8%) (Table 1) results in preventing at COVID 19 illness in 18 or over [54]. Based on 196 cases, out of which 185 were reported in the placebo group and 11 cases from the Moderna vaccine group. Most importantly, participants from the phase I study retained sufficient levels of neutralizing antibodies reported through 119 days followed the first dose of vaccination (90 days followed the second dose) [54]. Based on these promising results this vaccine was fully licensed by US FDA, emergency usage from WHO, and multiple countries by their own regulators. For effectiveness studies against variants like Alpha and Beta a trial conducted in Qatar showed that vaccine is highly effective against both the variants, with 88.1% after the first dose and 100% after the second dose against Alpha, meanwhile, the effectiveness against Beta was 63.3% after the first dose and exceeded to 96.4% with the second [55]. Similarly, for other variants a booster dose of Moderna suggests to provoke a well immune response against the Beta (B.1.351) variant and Gamma (P.1), which were spreaded in the US and other countries too. With regard to single-dose booster candidate of mRNA-1273.351 (Beta variant, B.1.351) and multivalent booster dose mRNA-1273.211 (Beta variant + Wild Type) with each of (50 μg of each dose) found to achieve strong antibody responses against ancestral (D614G mutation) strain including with Gamma, Beta and, Delta variants in the in participants [56,57]. Additionally, data from the Canadian trial suggest to having 72% effectiveness (Table 2) in a single dose against Delta from preventing symptomatic and 96% effective in preventing severe illness against COVID 19 [58]. Based on EUA-FDA authorization in recent, CDC recommends the booster dose (50 μg) of vaccine at least 6 months after completing their two doses of Moderna vaccine in certain individuals (18 years of age and older >64 years) who are immunocompromised or suppressed immune system or while having any certain medical condition to benefit them against severe illness or dying from COVID 19.

4. Protein-based vaccine

4.1. NVX-CoV2373 from Novavax (Covovax)

NVX-CoV2373 (Covovax) is a vaccine candidate developed by Novavax a U.S based biotech company is a recombinant spike

protein nanoparticle vaccine (rSARS CoV-2), comprising a full trimeric length for SARS CoV2 spike (S) proteins with saponin based Matrix-M1 adjuvant. In the rSARS CoV2 vaccine, the polybasic cleavage site is removed from the spike protein, but the remaining stabilizing residues are present, which are expressed in insect cells and then further extracted and purified with a membrane extraction [59]. Published phase I/II initial trial data from the randomized, placebo-controlled to determine the safety and immunogenicity analyses on 131 healthy participants (between 18 and 59 age group) vaccination comprised 2 doses of intramuscular administration (5 μg and 25 μg first dose of rSARS CoV2 with or without Matrix-M1 adjuvant and placebo) and a second dose at 21 days no severe adverse event was reported. The two doses of 5 μg and 25 μg regimens with Matrix-M1 adjuvant develops anti-spike IgG (measured in ELISA) and neutralizing antibodies which enhanced the level of immune response (measured in convalescent serum samples), additionally, CD4 + and $CD8^+$ polyfunctional T-cell response were also induced toward a T helper 1 (Th1-phenotype) in mostly symptomatic COVID 19 patients (NCT04368988) [59,60]. The phase III final trial enrolled more than 15,000 participants (group 18−84 of ages with 27% of them over the age of 65). Here the full interim analysis data was based on 106 COVID 19 cases, of which 96 cases were reported in the placebo group and 10 cases in vaccine group, with no severe event reported except 1 in the placebo group. The vaccine efficacy based on the original strain was demonstrated around 89.7% (Table 1) against the SARS CoV2 infection (NCT04611802). A post hoc analysis showed an 86.3% efficacy rate (Table 2) against the variant Alpha and less effective at preventing infection by Beta variant with approximately 60.1% (95% CI, 19.9−80.1) efficacy (Table 2) profile in preventing mild to moderate with severe COVID 19 [60,61]. Meanwhile, Novavax single booster dose administered 6 months after the two-dose regimen, observed functional antibody titers increased by 4.6-fold, addition to effectiveness on Delta variant was 6-fold higher in cross-reactive functional antibodies in comparative to initial vaccination series observation [62].

4.2. Corbevax from Texas Children's Hospital Centre and Baylor College of Medicine

Corbevax is a protein subunit COVID 19 vaccine developed by Texas Children's Hospital Centre for Vaccine development at Baylor College of Medicine partnered with integrated commercialization team Biological E. (BioE) Limited. BioE uses a harmless piece of spike protein from the coronavirus causing COVID 19 [63]. The researchers obtain genetic information from a portion of the SARS CoV1 virus spike protein to produce large amounts of this protein in yeast with adding the CpG 1018 adjuvant alum to trigger immune response. This technology made this vaccine so cheaper to use. In Phase I/II trial carried out to evaluated the safety and immunogenicity on 360 participants (Between 18 and 65 aged), 0.5 ml each two doses 28 days apart [63]. Induces high level of antibodies response with longer-lasting immunity. In Phase III trial on 1268 participants (between 18 and 80 years) conducted in India as part of global study trial, produced only mild adverse events, which was reported half compared the AstraZeneca vaccine participants making it one of safe COVID 19 vaccine in market [63]. As per company claim, Corbevax showed over 90% effective (Table 1) against the original SARS CoV2 variant based on antibodies produced by the people who received the vaccine [64]. The effectiveness against Delta and Beta variants was also found with high amount of neutralizing antibodies with durable protection so far, the data is unavailable [65]. On December 2021, based on its promising phase III trial the Drugs Controller General of India (DCGI) granted emergency use authorization for restricted use in India.

5. Inactivated vaccines

5.1. Covaxin (BBV152) from Bharat Biotech

Covaxin developed by Bharat Biotech and National Institute of Virology is a whole-virion inactivated COVID 19 vaccine (BBV152) (3 μg or 6 μg) formulated with a toll-like receptor 7/8 agonist adsorbed to alum (Algel-IMDG). In Phase I/II randomized, double-blind, with placebo-controlled trial on 827 participants (Between 18 and 55 years of age) out of which 375 were enrolled. Among the enrolled participants, three vaccine groups with 100 each participant were randomly assigned, and 75 in controlled group. Participants in both groups reported solicited and adverse reactions in the 3 μg with Algel-IMDG group by 17 participants, in the 6 μg doses with Algel-IMDG group by 21 participants, followed by 14 in 6 μg with Algel-IMDG, and 10 in Algel-IMDG group respectively [66]. Both the Algel-IMDG groups with 16 participants were showed the $CD4^+$ and $CD8^+$ T-Cell responses against the COVID 19. With these promising findings, both the Algel-IMDG were selected for immunogenicity trials. In Phase II trials to evaluate the safety and immunogenicity were conducted on 921 participants, of whom 380 were randomly assigned in 3 μg (n = 190) or 6 μg (n = 190) with Algel-IMDG group. At day 56 (GMT; $PRNT_{50}$) were significantly higher in the 6 μg with Algel-IMDG group in compared with the 3 μg with Algel-IMDG group. The $PRNT_{50}$ seroconversion at day 56 were reported in 171 of 184 participants with the 3 μg Algel-IMDG group and 174 of 177 in the 6 μg with Algel-IMDG group. The GMT (MNT_{50}) was also obtained at day 56 in 3 μg Algel-IMDG group were 92.5% and 160.1% in 6 μg Algel-IMDG group [67]. The 3 and 6 μg with Algel-IMDG group induced T-cell responses biased towards the Th1 phenotype at day 42. No serious adverse reactions were reported while the study [67]. The final Phase III trial recruited 25798 participants assigned randomly to receive the BBV152 vaccine or placebo. Out of 25798 participants, 24410 received two doses of BBV152 vaccine (n = 12221) or placebo (n = 12198) group. In this trial a total 130 cases were reported with symptomatic COVID 19 at least 14 days of post-vaccination, of which 24 cases reported in vaccine recipients and 106 among placebo group, overall, the vaccine efficacy was 77.8% (95%CI 65.2−86.4) (Table 1), and 93.4% (57.1−99.8) for severe COVID 19 (NCT04641481). In addition to delta variants the estimated efficacy was found to have 65.2% (95% CI 33.1−83.0) (Table 2) [68]. Meanwhile, the data for other VOCs are under investigation. This vaccine candidate receives full licensed with Indian regulators, and EUA use from WHO later followed by many other African, Asia, South American countries too.

6. Conclusion remark

Based on aspects we concluded that vaccines are very much safe and effective against COVID 19 especially preventing hospitalization and severe illness (eg: death and hospitalization). Variants like Delta are more likely to reinfect or escape the immune response either provoked by COVID 19 infection or post-vaccination. As a result, a third dose (Booster dose) will be needed in some immunocompromised individuals to restore the immunity level. Meanwhile, possibly more variants are likely to emerge within different populations across the affected countries and territories. Therefore, increasing the mass vaccination globally will surely increase the protection level against a wide variety of coronaviruses and will make it harder for the infection to spread further. As of final note now 07, March over 63.2% of the world population so far had received at least one dose of COVID 19 vaccine, and over 10.85 billion doses had been administered globally so far with only 13% of individuals having received at least a single dose belonging to Low-income countries.

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Declaration of competing interest

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