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Review

Comprehensive Review of the Initial 11 WHO Emergency Use Listed COVID-19 Vaccine Candidates: Mechanisms, Efficacy, and Comparative Attributes for Safety and Well-Being

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Abstract

Since December 2019, the world has witnessed a massive outbreak of a novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which prompted cross-national collaboration to establish essential diagnostics, effective treatment protocols, and most importantly the design and development of suitable COVID-19 vaccine candidates. This effort has been fueled by collaborations among academic researchers, funding agencies, companies, and regulatory authorities. As a result, more than 242 vaccine candidates are currently under clinical trial, and nearly 50 vaccines have been approved in different countries. In this study, we conduct a comprehensive review of 11 vaccine candidates that have been granted Emergency Use Listing (EUL) by the World Health Organization (WHO). Our review summarizes the mode of synthesis, mechanism of action, approval authority, target age group, efficacy, merits, and gaps of these vaccine candidates. Additionally, we provide comparative attributes of these vaccine candidates to enhance understanding of safety and well-being.

Introduction

Over the past three years, countries across the globe have been grappling to contain the unprecedented outbreak of Coronavirus Disease 2019 (COVID-19) caused by the novel coronavirus strain Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1-3). Although, the symptoms of COVID-19 are mainly aligned to the respiratory system, but studies have revealed that the symptoms may vary from person to person, making it difficult to diagnose and devise the treatment strategy (4). Considering the death statistics, the World Health Organization (WHO) declared the outbreak a global health emergency which necessitated the development of vaccine candidates that are effective and safe to effectuate herd protection (5). However, recent studies have shown that the newly emerging and contagious variants of coronavirus may be a threat to leading vaccines (6-9). Hence, not only the development but also the periodic amelioration is required to avoid the potential loss of vaccine efficacy.

So far more than 242 vaccine candidates are currently under clinical trial, and nearly 50 vaccines have been approved in different countries (https://covid19.trackvaccines.org/vaccines/7/). Sputnik-V, a non-replicating human adenovirus-based vaccine, became the first registered COVID-19 vaccine in Russia on 11th August 2020 with an efficacy rate of 91.4% (10). In December 2020, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) to two mRNA based vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) (11,12). The BNT162b2 became the first mRNA vaccine against COVID-19 to gain EUA on 2nd December 2020 in UK after showing high efficacy (95%) and safety in Phase III clinical trials (11). BNT162b2 was designed and manufactured by U. S. firm Pfizer Inc. in collaboration with a German Biotechnology company named Biopharmaceutical New Technologies (BioNTech)(11). The WHO also issued Emergency Use Listing (EUL) to BNT162b2 on 31st December 2020 and it is available with the brand name Comirnaty and Tozinameran in Europe (11). FDA issued another EUA to mRNA-1273 on 18th December 2020, when the clinical trials showed rigorous safety, efficacy (95.6% for age group < 65 & 86.4% for age group > 65), and high-quality standards. The mRNA-1273 is a joint venture of Moderna, Inc., a biotechnology company, Cambridge, Massachusetts in association with the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH) (12). After rigorous clinical trials, on 15th March 2022, US FDA granted authorization to Moderna vaccine for active immunization of individuals 18 years of age and older to prevent the spread of COVID-19 (12). Subsequently, several other nations including China, India, UK, *etc.* authorized/approved multiple vaccine candidates (Table 1). On account of the global intent to treat SARS-CoV-2 infection, this review outlines the pros and cons of the 11 initially authorized therapeutic vaccine candidates against COVID-19 and summaries their mode

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of synthesis, mechanism of action, approval authority, target age group, and most importantly their efficacy, merits and gaps. In the light of this review, we aim to provide the comparative attributes of approved vaccine candidates for a better understanding of safety and wellbeing.

Mode of Synthesis: Vaccines authorized against SARS-CoV-2 virus

Four major categories of vaccines are being approved/authorized and several variants are in pipeline to curb the viral transmission and cases of symptomatic or severe COVID-19 (Figure 1). These are nucleic acid (mRNA) vaccines, non-replicating adenoviral vector vaccines, inactivated whole virus, and protein subunit vaccines (Figure 1). In order to meet the urgent need to develop and deliver effective COVID-19 vaccine, mRNA-based vaccines emerged as an innovative platform for the rapid and immediate development of COVID-19 vaccine candidates. Different collaborators teamed up to design mRNA vaccines as soon as the SARS-CoV-2 genome was published by China (13). Merely 66 days later, on 16th March 2020 Moderna Inc. initiated the Phase I clinical trials of mRNA-1273 (Spikevax or Elasomeran) in several countries such as USA, Japan, Taiwan, Netherlands (14,15). Rigorous safety profile and immune response assessment was performed in subsequent Phase II and III trials recruiting hundreds of thousands of participants which yielded promising outcomes with Spikevax showing 94.1% efficacy at preventing COVID-19 illness, including severe disease (12). Another mRNA vaccine Comirnaty was developed by Pfizer/BioNTech and gained FDA approval after completing exhaustive clinical trials. Hence, mRNA vaccines became some of the first candidates to complete Phase III trials and acquire EUL approval in the USA (12,16).

Essentially, mRNA vaccines carry the genetic information for the host cell to synthesize antigen of interest and mimic the infection in a more natural way. The SARS-CoV-2 virus uses spike protein present on its surface to enter the host cell (16). By using the mRNA technology platform, genetic sequence (mRNA) of spike protein is synthesized and encapsulated in carrier vehicles lipid nanoparticles (LNPs). The LNPs protect mRNA from rapid degradation within the body, facilitate its smooth passage across the cell membrane and exert an adjuvant effect by stimulating the host immune response (15,17). Additionally, valuable prior research on SARS and Middle East Coronavirus (MERS) further contributed to enhance the design of mRNA vaccines (14,18). Evidence from SARS and MERS has been exploited to genetically modify the original SARS-CoV-2 spike mRNA sequence and produce a 'pre-fusion' stabilized spike protein configuration, so that the antigen can induce a more robust and protective antibody response (19-21). Furthermore, enhancing the safety profile, mRNA is purified and freed from any form of contaminants and tweaked to reduce their inflammatory nature, therefore mRNA vaccines are available as a potent and safe treatment option against COVID-19.

In subsequent efforts to develop vaccines against SARS-CoV-2, recombinant non-replicating adenoviral vector-based vaccines have emerged as one of the proven and preferred platforms to deliver effective and safe COVID-19 vaccines. Using this approach, few major non-replicating adenovirus vaccines viz. Vaxzevria (AZD1222 or ChAdOx1 nCoV-19 by Oxford/AstraZeneca), Covishield (Oxford/AstraZeneca formulation by Serum Institute of India), Sputnik V, Convidecia (Ad5-nCoV by CanSino) and Jcovden (Ad26.COV2.S or Ad26COVS1 or JNJ-78436735 by Jenssen/Johnson & Johnson) have gained EUL/authorization/approval (Table 1) (22-28). Non-replicating viral vaccines primarily contain genetically altered replication-defective simian or human adenovirus as vectors, carrying double-stranded DNA sequence for the SARS-CoV-2 spike protein (23,29,30). The recombinant viral vectors employed in these vaccines are less virulent common cold viruses with a narrow host range, thus cause negligible pre-existing immune responses against these vectors in the human population (29). Therefore, it becomes easier for the vector to invade human cells and deposit their genetic material (DNA) inside the nucleus. The double-stranded recombinant DNA upon transfer remains stable and does not integrate within the host genome. They are transcribed into single-stranded mRNA molecules in the nucleus which enters the cytoplasm and translate to form spike proteins. These antigens prime the immune system to build cellular response and produce neutralizing antibodies against the SARS-CoV-2 (23,29).

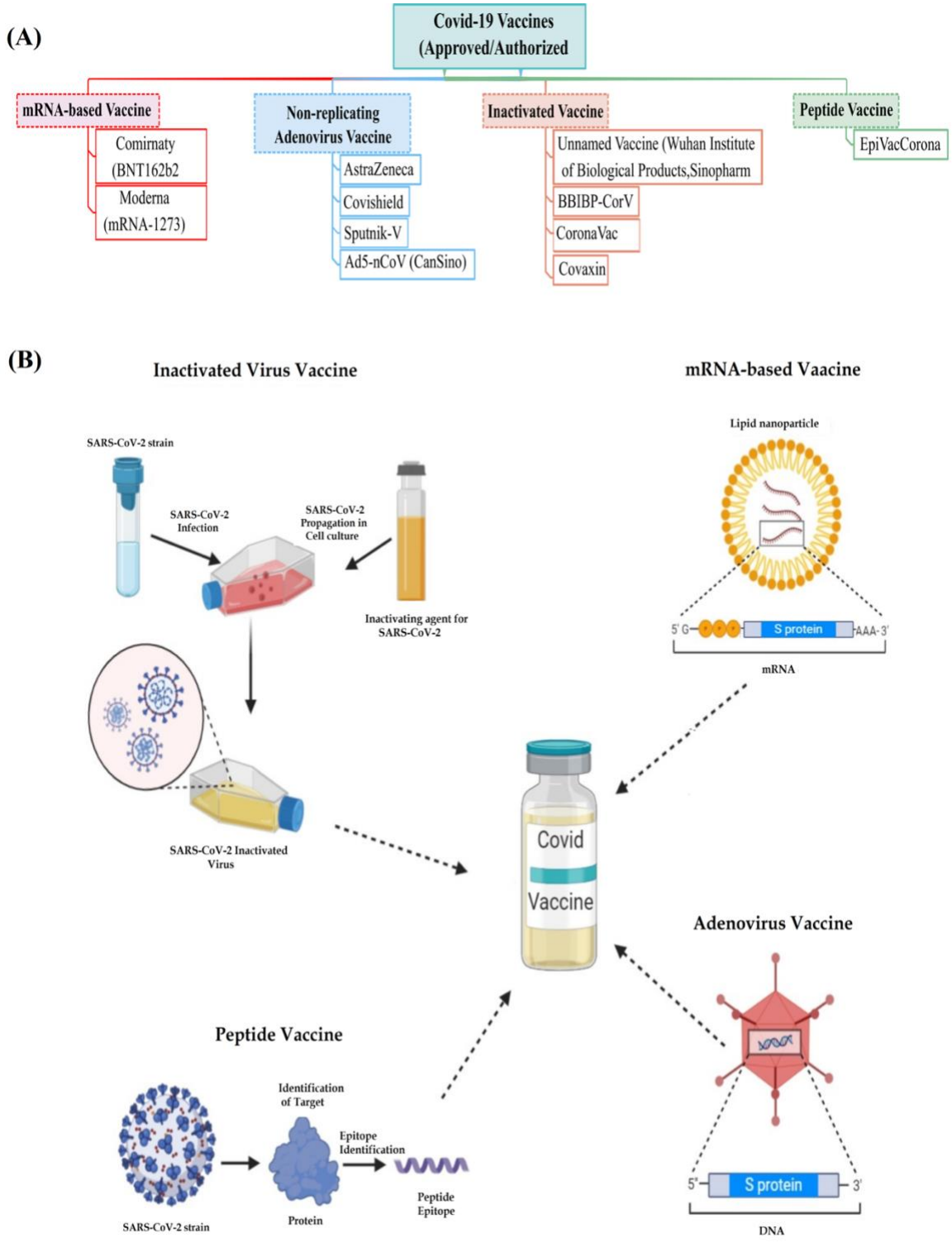

Figure 1: The schematic representation showing the mode of synthesis of different COVID-19 vaccines authorized/approved by different countries. A) The flowchart describes four different methods opted to generate 11 approved/authorized vaccine candidates, while (B) the diagram represents the overall methodology used for designing these vaccine candidates. This figure was generated with BioRender.com

Among other EUL/approved/authorized vaccine candidates (Figure 1; Table 1), four belong to the category of inactivated vaccines (Figure 1). The mode of synthesis of inactivated vaccines relies on inactivating the pathogen using physical or chemical methods. In most cases, a suitable cell line with infinite growth properties along with suppressed antiviral tendency is used to grow the viruses (31). This is followed by inactivating the virus using chemicals (β-propiolactone) or physical methods (32). Upon inactivation, vaccination is performed on model organisms to assess their immunogenicity and sometimes adjuvants are used to enhance the immunogenicity (32). Covaxin or BBV152 developed by Bharat Biotech, Covilo or BBIBP-CorV (Vero Cells) developed by Sinopharm (Beijing) and CoronaVac by Sinovac are few inactivated vaccines which are approved.

The fourth category among authorized vaccines is the peptide vaccine which utilizes the minimum microbial component which is sufficient to induce long-lasting immune responses against the pathogen (33). The peptide-based vaccines are customized to induce a protective immune response in a naïve host by exposing the host immune system to specific epitopes present on the pathogen (34). Most importantly these customized peptides are free from other biological antigen contaminants to enhance safety (33). The major challenge remains the identification of non-immunodominant epitopes which are highly conserved as well as susceptible to neutralization (34). Additionally, these peptide-vaccines are poor immunogens and to overcome this limitation, either multiple immunizations are required or they need assistance from adjuvants (such as alum, monophosphoryl lipid-A containing AS04 and squalene-based emulsions AF03, etc.) or delivery system (such as liposomes) to improve the immunogenicity (33,34). The Nuvaxovid or NVX-CoV2373 vaccine developed by Novavax, Covovax by Serum Institute of India and EpiVacCorona are few peptide vaccines to get EUL or regulatory approval for the development of immunogenicity against the SARS-CoV-2 viruses (35-39). In the next section of this review, we begin by describing each vaccine candidate that received EUL/authorization/approval.

Authorized/Approved Vaccine Candidates Against SARS-CoV-2

A. Pfizer/BioNTech mRNA vaccine (Comirnaty/ BNT162b2) for COVID-19

Comirnaty or Pfizer-BioNTech COVID-19 vaccine (BNT162b2) is a nucleic acid vaccine that consists of Lipid Nanoparticle (LNP) encapsulating single-stranded, 5'-capped nucleoside-modified RNA or modRNA encoding full-length, stable, and membrane anchoring surface spike (S) glycoprotein of SARS-CoV-2 (19,20). The LNP contains four different types of lipids *e.g.*, cholesterol, 1, 2-distearoyl-glycero-3-phosphocholine (DSPC), ALC-0315 and ALC-0159 (40). The S protein of SARS-CoV-2 is the prime target of most of the vaccines or therapies under trial. The mRNA sequence in BNT162b2 is modified to generate two proline (P2) amino acid mutations in the spike (P2 S) protein (19). This causes the spike glycoprotein conformation to become locked in a pre-fused state *i.e.*, they are unable to modify their receptor-binding domain (RBD) for binding to Angiotensin-Converting Enzyme 2 (ACE2) receptors (21). This modified design mimics the intact virus before they infect the human cells and thus allows the immune system to generate antibodies for neutralizing SARS-CoV-2 effectively (20). Interestingly, the mRNA vaccines have no risk of integration in the host genome and produce a pure form of protein.

Pharmacology/Mechanism of Action

The lipid nanoparticle encapsulation in Comirnaty vaccine allows easy transfection of the mRNA sequence in the human cells when injected intramuscularly (IM) (20). The mRNA is released into the cytoplasm and it gets translated into the encoded mutant spike protein P2S using the host translation machinery (19,20). The mRNA is degraded rapidly within the cells and the resulting peptide chain (antigen) is presented onto the cell membrane. The antigen triggers specific humoral and T-cell-mediated immune responses against the viral protein. During clinical trials neutralizing antibodies against the spike protein have been detected in the participants and more investigation is being carried out to assess the cellular immunization imparted by mRNA vaccines (19,20). In general, the newly synthesized spike proteins are presented by Major Histocompatibility Complex (MHC) I and II molecules onto the cell membrane of all body cells and Antigen Presenting Cells (APCs), respectively. These MHC molecules will be recognized by T-Cytotoxic Cells (T_C) via T-cell receptors (TCRs) and $CD4^+$ or $CD8^+$ molecules. Activation of cell-mediated immunity generates T-Memory cells for recognition of viral particles and profound immune response upon subsequent exposures with SARS-CoV-2. Interleukins further attune both cellular and humoral immunity and facilitates the production of neutralizing antibodies against the viral particles (20).

Phase III clinical trial analysis

The multinational Phase III clinical trial of Comirnaty mRNA vaccine was conducted in 43,448 participants in the USA (76.7%), Argentina (15.3%), Brazil (6.1%), and South Africa (2%) representing diversity in race, ethnic groups, and gender *i. e.* White (82.9%), Black or African American (9.2%), Asian (4.2%), Hispanic or Latinx (27.9%), women (49%) *etc* (19). Participants ≥ 16 years of age were selected for the trial and it excluded individuals with a history of COVID-19 or SARS-CoV-2 infection, immunocompromised individuals, those receiving immunosuppressive treatment, children, and pregnant women (19,41). Comirnaty vaccine when administered in a two-dose regimen with an interval of 21 days showed very high efficacy of 95.1% which remained the same across all tested age-groups, race, ethnic groups,

gender, obese, or those with hypertension (19,41). Only eight individuals in the vaccine group contracted COVID-19 as compared to 162 individuals in the placebo group. Initially, there was 52% efficacy within 12 days after the first dose against the symptomatic COVID-19, but it increased to 91% within 7 days after the second dose. Also, the severity of COVID-19 was found to be significantly reduced in the vaccinated candidates seven days post-administration of the second dose and there was no COVID-19 induced fatality (19,41).

Reactivity and Safety

Comirnaty vaccine shows no major safety concerns in its clinical trials. No severe adverse incidents were seen over a follow-up period of two months after giving the vaccine. Although, fatigue was reported by a significant number of vaccines within the next day. Other local side effects such as redness, swelling, or pain at the site of injection can occur apart from headache, chills, fever, nausea, vomiting, muscle pain, or myalgia (19). Two deaths were observed in the placebo and vaccine group each, however, the investigations concluded that they were not associated with either the placebo or the vaccine (19). The long-term safety of these mRNA vaccines is being extensively investigated and there are no major concerns reported yet.

B. Spikevax vaccine (mRNA-1273) for COVID-19

The Spikevax or mRNA-1273 vaccine is a joint venture of Moderna, Inc., a biotechnology company, Cambridge, Massachusetts with the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH). This is the second successful vaccine developed using the mRNA technology platform (12). Spikevax vaccines have modified mRNA sequence encased in lipid bilayer capsule encoding spike glycoprotein of SARS-CoV-2, altered via replacement of two proline inside the domain one (S-2P) of heptad reiteration, that strengthens the glycoprotein of the spike into a prefusion configuration, which is delivered directly to the host cells (14,42).

Structurally, the trimeric spike protein is 1273 amino acids long and possesses a signal peptide (1-13aa) located at the N-terminus followed by two subunits named S1 (14-685aa) and S2 (686-1273aa), accountable for association with host receptor and mediates viral cell membrane fusion, respectively (43). S1 subunit has a fragment stretch (319-541 residues) referred to as receptor-binding domain (RBD) which potentially binds with angiotensin-converting enzyme receptor (ACE2) of the host cell (44,45). This binding of S1 and ACE 2 triggers conformational changes subsequently directing the S protein from a prefusion to a postfusion conformation, suggesting a plausible approach of the virus to evade the host immune system (46). The RBD region plays a critical target for neutralizing antibodies (nAbs) and T-cell immune response activation. Hence, Spike protein is preferably the potential target molecule for SARS-CoV-2 vaccine development (47). The vaccine also consists of the other components like: cholesterol, 1,2-distearoyl-snglycero-3-phosphocholine (DSPC)), tromethamine, tromethamine hydrochloride, lipids (SM-102, 1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000 [PEG2000-DMG], sodium acetate, sucrose and acetic acid (48). This lipid-encased mRNA-1273 vaccine candidate is potentially immunogenic which induces antibody generation and activates T-cell ($CD8^+$) responses against SARS CoV-2 (14).

Pharmacology/Mechanism of Action

Post-vaccination, cells surrounding the site of injection and the nearby draining lymph nodes take over the lipid nanoparticles and permits efficient transportation of mRNA inside the host cell compartments for the synthesis of virion spike glycoproteins (49). The internalized mRNA neither goes inside the nucleus of the cell nor associates with host cell genetic material as it is non-replicating, rather expressed by dendritic cells and sub capsular sinus macrophages (42,50). These antigen-presenting cells (APCs) express SARS-CoV-2 spike protein using its translation machinery, which in turn will stimulate the host immune response and initiate the production of antibodies (51). These mRNA vaccines generate immune responses by activating both humoral and cell-mediated immunity. The foreign spike proteins presented by MHC I and MHC II of APCs and non-Antigen-presenting cells are therefore recognized by the T-Cytotoxic Cells (T_C) via T-cell receptors (TCRs) and $CD4^+/8^+$ T cells resulting in the activation of cell-mediated immunity by generating-Memory Cells (Tm) for recognition of viral particles on subsequent exposure (52). Simultaneously, the cascade of interleukins will attune the humoral immunity which will produce neutralizing antibodies against the SARS-CoV-2 spike protein (14), hence will provide protective immunity against SARS-CoV-2.

Phase III clinical trial analysis

The crucial phase III study of Spikevax vaccine i.e., mRNA 1273, referred as the COVE study, which was performed to analyze the efficacy of mRNA-1273 randomly in a 1:1 placebo-controlled test of 100-µg dose level in around 30,000 participants in the U.S. at 100 clinical research sites of age group 18 or older (12). This trial analysis was being executed in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services and the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The major and key secondary endpoints analysis consists of inhibition of symptomatic COVID-19 disease, prevention of acute form of COVID-19, and deterrence of contamination by SARS-CoV-2. In an interim analysis, the preliminary efficacy evaluation of phase 3 COVE Study of mRNA-1273 against COVID-19 was observed to be 94.1% (95% CI (confidence interval):

89.3-96.8); whereas, vaccine efficacy against severe COVID-19 was 100% (NCT04470427) (12).

Reactivity and Safety

Among the young and elderly individuals, adverse responses related to the administration of the mRNA-1273 vaccine were found to be either mild or moderate for a 100-µg dose (53,54). The most common risk factors associated with the Spikevax vaccine were found to be solicited adverse reactions (SARs) such as ache at the site of administration of vaccine among 91.6%, tiredness among 68.5%, headache in 63.0%, muscle ache in 59.6%, joint ache in 44.8%, and shivering in 43.4% vaccinees. While, serious adverse events observed to be uncommon i.e., 1.0% in both treatment groups (55).

C. Vaxzevria (AZD1222/ ChAdOx1 nCoV-19)

Vaxzevria is a non-replicating adenoviral vector-based vaccine, which consists of genetically altered replication-defective simian adenovirus (ChAdOx-1) as a vector carrying DNA sequence that codes for full-length SARS-CoV-2 surface spike glycoprotein (56). This viral vector is a less virulent form of the common cold virus that infects chimpanzees (56). Normally, the human population does not have any pre-existing immunity towards the non-human adenoviral vector, so it is easier for ChAdOx-1 to invade human cells and transfer the recombinant genetic material inside cells. The recombinant DNA used in vaccines is stable as compared to RNA of mRNA vaccines.

This vaccine was originally co-invented and developed by Jenner Institute and Oxford Vaccine Group at the University of Oxford and its spin-off company Vaccitech (57). It was formerly known as AZD1222 and is synonymous with ChAdOx1 nCoV-19 or Oxford vaccine (56). University of Oxford and Vaccitech collaborated with the British-Swedish biopharma company AstraZeneca for large-scale production which is later responsible for the development, manufacturing, and distribution of Vaxzevria vaccine worldwide (57). AstraZeneca emphasizes making the vaccine accessible and available for middle or low-income group countries (57).

Pharmacology/Mechanism of Action

Vaxzevria vaccine is designed using a recombinant chimpanzee adenoviral vector ChAdOx-1 harboring DNA fragment encoding SARS-CoV-2 spike protein (56). When injected intramuscularly, the ChAdOx-1 vector can enter human cells and transfer its DNA sequence to the cells (29). The recombinant DNA enters the host nucleus but does not integrate with the host genetic material, as claimed by the investigators (23,29). The foreign DNA is transcribed into single-stranded mRNA molecules within the nucleus and moved to the cytoplasm where they are translated to form spike glycoproteins or antigens (29). The viral spike protein is presented on the cell membrane by MHC molecules (I or II) and primes the immune system by activating T cells, generating antibodies against SARS-CoV-2 surface glycoproteins, *etc* (56,58,59). They provide active immunization by recognizing and destroying the SARS-CoV-2 virus particles in case of re-infection (23,29).

Phase III clinical trial analysis

The Phase III clinical trial of AZD1222 vaccine was conducted on approximately 24,000 individuals representing diverse racial and geographic distribution from the UK, Brazil, and South Africa (23,29,60). Phase III clinical trial data from UK, Brazil, and South Africa (n=8,895) showed that administration of two standard doses (~5×10^{10} viral particles) of the vaccine with one month gap has 62.1% efficacy in preventing severe COVID-19 and no hospitalization even in cases of infection. Interestingly, clinical trial in the UK on another small sub-group (n=2,741) aged 18-55 years showed that administration of half dose (~2.5×10^{10} viral particles) of AZD1222 vaccine followed by another standard dose (~5×10^{10} viral particles) at one month gap proved better with 90% efficacy in preventing COVID-19 (23). The primary efficacy endpoint of the vaccine from the pooled analysis was 70.4% (n=11,636). The results from these data were found to be statistically significant ($p <= 0.0001$) (23). Overall, the AZD1222 vaccine gave an early indication of reducing viral transmission as well after observing a decline in asymptomatic infection cases and is also effective in preventing symptomatic COVID-19.

Reactivity and Safety

AstraZeneca vaccine can be tolerated well among the tested participants. There were only 0.7% serious adverse incidents in the clinical trials (58,59). Arm pain (67%), muscle aches (60%), joint pain (31%), chills (51%), fever (18%), fatigue (70%), and headaches (68%) are some common side effects associated with this vaccine (58,59).

D. Covishield (Oxford/AstraZeneca formulation)

The Serum Institute of India (SII), Pune has developed a recombinant adenoviral vector vaccine Covishield (Oxford/AstraZeneca formulation), originally based on the AstraZeneca and Oxford vaccine (24,61). Covishield contains a non-replicating, weakened, chimpanzee adenovirus vector carrying DNA sequence encoding the full-length SARS-CoV-2 spike protein with technology transfer from the AstraZeneca and Oxford University (56,62).

Pharmacology/Mechanism of action

Covishield vaccine is composed of recombinant chimpanzee ChAdOx1 viral vector with the genetic sequence for spike protein of SARS-CoV-2. Once the vaccine is administered, the spike protein is expressed and they stimulate the production of neutralizing antibodies and initiate cellular immune response (46,47).

Phase III clinical trial analysis

The safety and efficacy of Covishield were determined overseas in randomized Phase III clinical trials conducted in the UK, Brazil, and South Africa with over 23,745 participants, aged 18 years and above (23). The participants received either AstraZeneca vaccine or control, and were followed-up for 105 days after the first dose and 62 days after the second dose. The administered doses were found to be immunogenic, safe, and showed an overall efficacy of 73.43% (47).

Reactivity and Safety

Some of the local and systemic adverse reactions associated with Covishield vaccination are tenderness and pain at the injection site, headache, muscle pain, fatigue, chills, nausea, joint pain, and fever (47). The majority of these effects can be mild to moderate in nature and subside within a few days. After 7 days of receiving the first dose, local or systemic side effects were seen in 4% and 13% of vaccinees, respectively. However, these side-effects became mild and less frequent after the second dose (47). Individuals ≥ 65 years experienced lesser and mild adverse reactions (47).

E. Ad5-nCoV vaccine (Convidicea/CanSino)

The Ad5-nCoV covid vaccine is yet another non-replicating adenovirus vaccine with the trade name Convidicea and it was the first vaccine candidate to be used for clinical trials in China (30). Convidicea is a joint venture of Can Sino Biologics Inc. and Beijing Institute of Biotechnology, China (28). The Ad5-nCoV covid vaccine contain a cloned spike gene Wuhan-Hu-1 (GenBank: YP_009724390) strains of the SARS-CoV-2 virus, which causes COVID-19. This gene was inserted into an adenovirus vector that has been modified to remove the E1 and E3 which are responsible for virus replication evasion of the host immune system, respectively (30). The Ad5-nCoV vaccine was produced as a liquid formulation containing 5×10^{10} viral particles per 0.5 mL. This vaccine is administered as a single intramuscular dose, is characteristically well-tolerated, and capable of induction of potentially neutralizing antibodies against covid virus (30).

Pharmacology/Mechanism of Action

Both humoral and cellular immunity holds the potential key to treat COVID-19 disease. The Ad5-nCoV vaccine was reported to increase the affinity of antibodies against the receptor-binding domain (RBD) (30). Post-vaccination, the activation of both $CD4^+$ and $CD8^+$ T cells was observed, primarily generating antigen-specific $CD4^+$ T cells and $CD8^+$ T cells (30). However, this response was partially reduced due to the pre-existing anti-AD5 immunity (30). Altogether, humoral response peaked at day 28, while specific T-cell responses were noted from day 14, post-vaccination (30).

Phase III clinical trial analysis

The Phase III clinical trial of the Ad5-nCoV vaccine **(**NCT04526990) was initiated on 15th September 2020 with approximately 40,000 individuals representing diverse geographic and racial distribution (Chile, Argentina, Pakistan, Mexico, Russia, and Saudi Arabia) using a single dose administration (63). One dose of the Ad5-nCoV vaccine showed a 57.5% efficacy against symptomatic, PCR-confirmed COVID-19 infection at least 28 days after vaccination. The study included 21,250 participants, and the median duration of follow-up was 45 days. Additionally, no serious adverse events related to the study product were reported in either group. However, the Ad5-nCoV vaccine did show a higher incidence of solicited systemic adverse events and injection-site adverse events compared to the placebo group. The most common solicited systemic adverse event was headache, reported by 44% of Ad5-nCoV recipients and 30.6% of placebo recipients. The most frequent injection-site adverse event was pain at the injection site, reported by 59% of Ad5-nCoV recipients and 19% of placebo recipients (63).

Post-vaccination, the reactions reported were mild or moderate. The study also reported that the proportions of participants with adverse reactions such as fever, injection site pain, and fatigue, were significantly higher in vaccine recipients in comparison to the placebo recipients (30). But the adverse reactions were generally not severe and thus resolved within the period of 48 h (30). The Ad5-vectored COVID-19 vaccine recipients with 1×10^{11} viral particles, all grade 3 adverse symptoms were reported (30). Although this study captured common adverse events post-immunization, the results suggest that this vaccine has a good safety profile.

F. Sputnik V or Gam-COVID-Vac Vaccine

Sputnik V is the world's first registered vaccine against SARS-CoV-2 to be approved on 11th August 2020 by the Russian Ministry of Health after reviewing clinical data from the Phase I/II trial involving 76 participants which were published later (64). Sputnik V was developed by Gamaleya National Center of Epidemiology and Microbiology, Moscow, and is named after Soviet-era popular space satellite (10). Sputnik V is based on an adenoviral vector platform which is proven for its safety, generation of strong cellular and humoral immune response, and conferring protective immunity usually after one or two doses (65-67).

Pharmacology/Mechanism of action

Sputnik V vaccine comprises of two recombinant, replication-deficient adenovirus vectors type 26 (rAd26) and type 5 (rAd5) which are weakened human adenoviruses carrying the gene for full-length SARS-CoV-2 surface spike glycoprotein (64). The first dose of Sputnik V contains Ad26 as a viral vector and the second dose contains Ad5 as a vector (68). The presence of heterologous viral vectors (Ad26 and Ad5) in Sputnik V ensures that there is an added prime-boost in the immune response after vaccination (68).

In phase 1/2 clinical trials, Sputnik V was developed as two formulations, one as frozen form (Gam-COVID-Vac) and another as lyophilized form (Gam-COVID-Vac-Lyo) (64). The components of the vaccine and varying formulations were evaluated for their safety and immunogenicity in the phase 1/2 trial.

Phase III clinical trial analysis

The multinational Phase II/III clinical trial of Sputnik V began in Russia, India, UAE, Philippines, Brazil, and Saudi Arabia with around 40,000 participants (64, 69). As per the Phase III clinical trials analysis, 21,977 adults were randomly assigned to administered either the vaccine or placebo. Out of these 19,866 received two doses of vaccine or placebo and were included in the primary outcome analysis. After 21 days from the first dose, 16 (0.1%) of 14,964 participants in the vaccine group and 62 (1.3%) of 4,902 in the placebo group were confirmed to have COVID-19. The vaccine demonstrated an efficacy of 91.6% (95% CI 85.6-95.2). Phase III clinical trials show high efficacy, immunogenicity and a good tolerability profile in participants aged 18 years or older (69).

Reactivity and Safety

As per the Phase III clinical analysis most reported adverse event were grade one, that means they were mild and did not require medical attention. A total of 7,485 (94.0%) of 7,966 reported were grade one. Additionally, 45 (0.3%) of 16,427 participants in the vaccine group and 23 (0.4%) of 5,435 participants in the placebo group had serious adverse effects, but none of these events were considered associated with vaccination, as confirmed by independent data monitoring committee (69).

G. Inactivated Novel Coronavirus Pneumonia (COVID-19) Vaccine-Wuhan or β-propiolactone-inactivated-whole-virus vaccine

This vaccine was designed based on Vero cell technology for the rapid development of the COVID-19 whole virus vaccine in a joint adventure of Wuhan Institute of Biological Products and China National Pharmaceutical Group Corporation (Sinopharm). Vero cell technology uses the Vero cell line, a continuous cell line with infinite growth properties (70). This cell line was established from African green monkey kidneys and is available at the American Type Culture Collection (ATCC) (71). The most obvious reason for using this cell line is its inability to produce antiviral molecules such as interferon and thus it sustains the growth of a large number of different viruses (72). The low passage level Vero cells have been known for extensive use for the development of polio and Rabies vaccines for a long, together with excellent downstream purification (31).

This inactive COVID-19 vaccine was created using the Vero cells along with viral inactivation by chemical treatment using β-propiolactone (BPL) (Figure 1). BPL is widely used for the inactivation of infectious pathogens such as viruses and bacteria (73,74). Not only this, but it is also used as a disinfectant in plasma sterilization and tissue transplants (75). This chemical agent has the potential to alter different biomolecules including proteins (especially methionine, cysteine, and histidine) and nucleic acids (adenosine, guanosine, and cytidine moieties of viral RNA) (76,77). It has been reported to alter the capability of DNA to be used as a template by DNA dependent DNA polymerases (74). However, a better fine-tuning of the BPL dose is required to obtain the loss of infectivity while keeping the antigenicity. During virus infection, the fusion of the virus with the endosome is a critical step during the onset of the infection. In the H3N2 influenza virus, it was reported that the cell infectivity (membrane fusion) by the virus was entirely abolished after the treatment with 1mM BPL through altering the properties of proteins involved in the fusion (75).

Reactivity and Safety

The datasets in the public domain are limited and thus not much can be inferred regarding the reactivity and safety of this vaccine candidate.

H. BBIBP-CorV

The BBIBP-CorV is the second inactivated vaccine developed by the Wuhan Institute of Biological Products and China National Pharmaceutical Group Corporation (Sinopharm) (78). Strain 19nCoV-CDC-Tan-HB02 (HB02) was isolated from the bronchoalveolar lavage sample and upon isolation, this isolate was used to generate the inactivated vaccine using the Vero cell line (32). The HB02 strain was purified and successively cultured in Vero cell lines from P1 to P10 stocks. The HB02 strain from both the stocks was found 99.95% identical suggesting the high genetic stability (32). The growth kinetics revealed that the P7 stock could replicate more efficiently and reach a peak titer after 48-72h post-infection at multiplicities of infection (MOI) (this represents the ratio of the numbers of virus particles to the numbers of the host cells) of 0.01-0.03 (32). This was followed by inactivation of the virus using β-propionolactone in a ratio of 1:4,000 at 2-8^{o}C (32). A liquid formulation of vaccine was prepared to contain 2µg, 4µg, or 8µg total protein with aluminum hydroxide adjuvant (0.45mg/ml) per 0.5ml (32). To measure the immunogenicity of this vaccine, it was administered on various animal models like rabbits, guinea pigs, rats, mice, and non -human primates (32). Later on, it was considered for clinical trials (78).

Pharmacology/Mechanism of action

The secondary humoral immunogenicity outcomes were measured using an infectious SARS-CoV-2 neutralizing assay and expressed as neutralizing antibody geometric mean titer (GMT) (78). Seroconversion was defined as an increase in post-vaccination titer of four-fold or more from baseline (78). To directly demonstrate antibody neutralizing efficacy and avoid the situation in which antibody binds to the receptor-binding domain, but fails to neutralize SARS-CoV-2 infection, IgG binding to specific

virus protein (e.g., S protein) assay was not included in the trial (78).

The phase III clinical trials have been conducted in numerous countries with 15,000 participants in the United Arab Emirates, 6,000 participants in Peru, and 45,000 participants enrolled in Bahrain, Egypt, Jordan, United Arab Emirates (79). It has been observed that participants (18-59 years of age) were immunized with two doses of BBIBP-CorV (4μg/dose) at day 0 and day 21 (78). The two 4μg BBIBP-CorV doses (within three weeks) emit higher neutralizing geometric mean antibody titers compared to the same-dose immunization at two-week intervals (78). Thus, it was the most recommended dose.

Reactivity and Safety

From the phase I/II trail, in the majority of cases, the adverse reactions include pain at the injection site, swelling, and itching, which subsequently increased in the age group 60 years and above (78). According to the phase III analysis, BBIBP-CoV COVID-19 vaccine had most adverse effects associated were mild to moderate, and the most commonly reported adverse events were pain at the injection site, headache and fatigue. Furthermore, it seems that there was no significant difference in the number of serious adverse events, adverse events of special interest (such as neurological diseases), or Grade 3+ adverse events between the BBIBP-CorV and placebo groups. However, there were two serious adverse events that were assessed to be possibly linked to vaccination, which were serious nausea and inflammatory demyelination syndrome/acute disseminated encephalomyelitis. It is important to note that these adverse events were rare and further investigation is needed to confirm any causal link with the vaccine. Overall, it appears that BBIBP-CorV has a generally favorable safety profile, with most adverse effects being mild to moderate, and no significant safety concerns identified in clinical trials.

I. CoronaVac

CoronaVac is an inactivated vaccine developed by Sinovac Biotech Ltd., Beijing, China which has shown promising immunogenicity in rats, mice, and non-human primates (80). The CN2 strain selected for inactivated SARS-CoV-2 virus vaccine (PiCoVacc) development was isolated from the bronchoalveolar lavage fluid sample (80). The CN2 strain was purified and successively passaged in Vero cell lines to generate five stocks (P1-P5). The growth kinetics revealed that the P5 stock replicates efficiently and reach a peak titer by 3-4 days post-infection with MOI of 0.0001-0.01 at a temperature between 33°C-37°C (80). This was followed by inactivation using β-propiolactone and subsequent purification.

Pharmacology/Mechanism of action

When the inactivated vaccine PiCoVacc is combined with alum adjuvant, immunogenicity increases multiple folds. Initially, the immunogenicity of inactivated vaccine was tested in BALB/c mice models (80). The results suggested that the S- and RBD-specific IgG developed quickly in the serum and the concentration was maximum at week 6 (80). It was reported that this vaccine could elicit approximately 10 folds higher S-specific antibody titer in the serum of mice as compared to the titer in recovered COVID-19 patients (80).

Phase III clinical trial analysis

Phase 1/2 studies of CoronaVac demonstrated a good safety and tolerability profile, with a dosage of 3 μg resulting in seroconversion rates of 92.0% with a 14-day immunization schedule and 97.0% with a 28-day schedule in participants aged 18–59 years (81). Similarly, in participants aged 60 years and older in phase 2 trials, a 28-day schedule produced seroconversion rates of 98.0%. Interim data from late-stage clinical trials of phase III in Turkey and Indonesia have shown that the vaccine is 91.25% and 65.3% effective, respectively (82). However, the overall efficacy, including asymptomatic cases and symptomatic cases not requiring medical assistance was 50.38% (82,83).

The vaccine can be administered in two doses (0.5 mL/dose) intramuscularly at an interval of 14 days, and each prefilled vaccine syringe contains 600 SU of SARS-CoV-2 virus antigen. The overall efficacy of CoronaVac is 78% as seen in clinical trials. The vaccine has been shown to be safe, with no symptoms such as fever, weight loss, appetite loss, or any clinical sign of mental deterioration observed in macaques during systematic safety evaluation. Additionally, the vaccine remains stable in storage and can be refrigerated at 2–8 °C without the need for freezing, making it easy to transport.

J. BBV152 (Covaxin)

Like CoronaVac and Sinopharm's vaccine, BBV152 is another inactivated vaccine with the trade name Covaxin. It was India's first indigenous COVID-19 vaccine which has been developed by Bharat Biotech in collaboration with the Indian Council of Medical Research and National Institute of Virology (84). A double-blind randomized multicenter study was conducted at 11 hospitals across India to evaluate the safety and immunogenicity of BBV152 (84). In this study, the SARS-CoV-2 strain NIV-2020-770 containing the Asp614Gly mutation, isolated from a COVID-19 patient was selected and subsequently inactivated using β-propiolactone (84). This inactivated vaccine is unique in the sense that it has used Algel-IMDG (an imidazoquinoline molecule chemisorbed on alum [Algel *i.e.*, Aluminium hydroxide gel]) as adjuvant (84). This IMDG molecule; a toll-like receptor (TLR) 7/8 agonist, is sufficient to induce cell-mediated responses (85, 86). Algel-IMDG has been shown to traffic vaccine antigen in draining lymph nodes directly without diffusing into the systemic circulation (84). Suitable safety profiles and humoral and cell-mediated responses have been recorded during preclinical trials in mice, rats, rabbits, and non-human primates (84,87).

Pharmacology/Mechanism of action

Like other inactivated vaccines, after the administration of both doses, the IgG titers to all available epitopes viz. receptor-binding domain, spike protein, and nucleocapsid protein increased rapidly leading to BBV152 induced binding and neutralizing antibody responses (84).

Phase III clinical trial analysis

The sale and distribution of Covaxin was initially granted permission by the Central Licensing Authority for restricted use in emergency only with abundant precautions. The Phase III clinical trial of BBV152 demonstrated an estimated vaccine efficacy of 77.8% against symptomatic COVID-19 disease, with a higher efficacy of 93.4% against severe COVID-19 (88). The efficacy against symptomatic COVID-19 was also high in subgroups categorized by age or the presence of pre-existing comorbid conditions, with the lower limits of the respective 95% confidence intervals being higher than 30% in all cases except for the older age group (≥60 years) (88). The study was not powered to definitively assess efficacy in subgroups, but the number of older participants included in the efficacy analysis was meaningful according to FDA guidance.

K. "EpiVacCorona" peptide Vaccine

EpiVacCorona is developed by the Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector", Russia, and is designed on a promising synthetic platform by utilizing synthetic peptide of SARS-CoV-2 proteins as antigen (38, 39). As mentioned above, these peptide vaccines are developed using chemically synthesized target specific epitopes/antigens of SARS-CoV-2 proteins and thus it is free from any biological contaminants (33). To increase the immunogenicity, the synthetic peptides are coupled with a carrier protein and allowed to be adsorbed on alum (aluminium hydroxide) (38,39).

Pharmacology/Mechanism of Action

The vaccines which are designed on synthetic peptide-based platform targets either epitopes of B-lymphocytes or T-lymphocytes (class I or class II) or joint epitope complex of the B- or T- cells (89). Antigen-presenting cells (APCs) present these peptide sequences multifaceted by MHC class I or class II complex, that is identified by T-lymphocytes. $CD4^+$ T helper cells recognize the epitope complex of MHC II and stimulate the activity of cytotoxic T lymphocytes ($CD8^+$ cells) for the efficient killing of cells that are infected with the pathogen. Further, $CD4^+$ T helper cells trigger the B-lymphocytes to produce specialized antibodies against the microorganism (32).

Phase III clinical trial analysis

The synthetic peptide vaccine EpiVacCorona, containing chemically synthesized peptide immunogens of the S protein of SARS-CoV-2 conjugated to a carrier protein and adsorbed on aluminum hydroxide, has shown positive results in Phase I-II clinical trials (90). The two-dose vaccination scheme induced the production of antibodies specific to the antigens in 100% of the volunteers with no signs of adverse reactions. Seroconversion with a neutralizing antibody titer ≥1:20 was reported in 100% of the volunteers 21 days after the second immunization dose. The vaccine is considered safe and has low reactogenicity.

Conclusion

The COVID-19 pandemic has had significant medical and socio-economic impacts globally, pushing millions of lives to the brink of crisis. To control the spread of the virus and achieve immunity to SARS-CoV-2, several vaccine candidates have rapidly progressed to clinical trials. After evaluating the initial authorized/approved COVID-19 vaccines, we emphasize that three vaccines, including the Pfizer-BioNTech and Moderna mRNA vaccines and the AstraZeneca adenoviral vector vaccine, have adhered to strict safety standards, development protocols, and standard demographic representations required for vaccine approval. These vaccines have demonstrated efficacy above 90% and can prevent symptomatic or severe COVID-19 cases. Phase III clinical trial results for these vaccines have clearly outlined their immunogenicity, reactogenicity, dosage, and safety. The Covishield vaccine, a recombinant adenoviral vector vaccine with a weakened chimpanzee adenovirus vector carrying the DNA sequence for the full-length SARS-CoV-2 spike protein, demonstrated an overall efficacy of 73.43% in Phase III clinical trials, with mild to moderate adverse reactions that generally resolved within a few days. The Ad5-nCoV vaccine, a non-replicating adenovirus vaccine containing a cloned spike gene of the SARS-CoV-2 virus, showed a 57.5% efficacy against symptomatic, PCR-confirmed COVID-19 infection and mild to moderate adverse reactions in Phase III clinical trials, with a higher incidence of solicited systemic adverse events and injection-site adverse events compared to the placebo group. The BBIBP-CorV and CoronaVac vaccines, two inactivated vaccines developed in China, have shown promising results in preclinical and clinical trials. BBIBP-CorV has been shown to elicit higher neutralizing antibody titers when administered in a two-dose schedule of 4μg/dose within three weeks. Both vaccines have demonstrated mild to moderate adverse reactions in clinical trials, and no significant safety concerns have been identified. These vaccines are important tools in the fight against COVID-19 and have been approved for emergency use in several countries. However, further studies are necessary to determine the long-term efficacy and safety of these vaccines. The data collected from COVID-19 vaccines will not only provide useful insights to tackle future pandemic situations but will also improve treatment strategies for such devastating diseases.

Conflict of Interest

The authors declare no conflict of interest.

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Table 1: The detailed description of 11 initially authorized/approved vaccine candidates for SARS-CoV-2.

Vaccine Name	Developer	Participants enrolled in the phase 3 trial	Approvals	No of doses	Dose interval	Vaccine technology platform	Phase 3 Efficacy	Target age group	Adjuvants/ Vector	Storage temperature	Registered trials	Approved in countries
Comirnaty (Tozinameran/BNT162b2)	Pfizer Inc. USA and BioNTech, Germany	~ 43,400 Study number: NCT04368728	Caribbean Regulatory System, Emergency Use Recommendation, WHO Emergency Use Listing, EUA by FDA on 11th December, 2020	Two doses (0.3 mL each, 30 µg/dose) to be administered intramuscularly	21 days	Modified mRNA encoding full-length SARS-CoV-2 spike protein	95%	≥ 16 years	Lipid Nanoparticle (LNP)	-70 ºC ± 10 ºC for up to 6 months 2-8 ºC for up to 5 days	Phase I: 17 trials Phase II: 54 trials Phase III: 29 trials	149 countries
Spikevax (mRNA-1273, Elasomeran)	Moderna Inc. and National Institute of Allergy and Infectious Diseases (NIAID), USA Also manufactured by Takeda (TAK-919)	30,000 Study number: NCT04470427 NCT04400838	Caribbean Regulatory System, Emergency Use Recommendation, WHO Emergency Use Listing, EUA by FDA on 18th December, 2020	Two doses (0.5 mL each, 100 µg/dose) to be administered intramuscularly	28 days	Modified mRNA encoding full-length SARS-CoV-2 spike protein	94.1% (95.6% for age group < 65 & 86.4% for age group > 65)	≥ 18 years	Lipid Nanoparticle (LNP)	-25 ºC to -15 ºC for up to 7 months 2-8 ºC for up to 30 days 8-25°C for 12 hours	Phase I: 10 trials Phase II: 36 trials Phase III: 24 trials	88 countries
Vaxzevria (AZD1222, ChAdOx1 nCoV-19)	University of Oxford and AstraZeneca, UK	~24,000 Study number: NCT04516746 NCT04540393 ISRCTN89951424	Africa Regulatory Taskforce Endorsed, Caribbean Regulatory System, Emergency Use Recommendation, WHO Emergency Use Listing, Emergency approval by UK	Two doses (0.5 mL each with ~5×10^{10} or ~3.5-6.5× 10^{10} viral particles, to be administered intramuscularly	28 days (Max. 84 days)	Adenoviral vector carrying DNA for full-length SARS-CoV-2 spike protein	70.4%	≥ 18 years	Chimpanzee adenoviral vector (ChAdOx-1)	2-8 ºC	Phase I: 10 trials Phase II: 39 trials Phase III: 24 trials	149 countries

			MHRA on 30th December, 2020									
Covishield (Oxford/AstraZeneca formulation)	Serum Institute of India (SII), India	~24,000 (Overseas) 1600 (India) Study number: CTRI/2020/08/027170 NCT04516746 NCT04540393 ISRCTN89951424	Africa Regulatory Taskforce Endorsed, Caribbean Regulatory System, Emergency Use Recommendation, WHO Emergency Use Listing, Restricted emergency use by CDSCO, India on 1st January, 2021	Two doses (0.5 mL each with $5x10^5$ viral particles to be administered intramuscularly	28-42 days (Max. 84 days)	Adenoviral vector with DNA encoding full-length SARS-CoV-2 spike protein	70.4%	≥ 18 years	Chimpanzee adenoviral vector (ChAdOx-1)	2-8 ºC	Phase I: 0 trials Phase II: 2 trials Phase III: 4 trials	49 countries
Sputnik V	Gamaleya National Center of Epidemiology and Microbiology, Moscow, Russia	40,000	EUA by Russian Ministry of Health on 11th August, 2020	Two doses (0.5 mL each)	21 days	Adenoviral vector containing DNA for full-length SARS-CoV-2 spike protein	91.6%	≥ 18 years	Human adenoviral vector (rAd26 and rAd5)	2-8 ºC (for lyophilized form)	6 Trials **NCT04954092** Russian Federation **NCT04530396** Russian Federation **NCT04564716** Belarus **NCT04640233** India **NCT04642339** Venezuela (Bolivarian Republic of) **NCT04656613** United Arab Emirates	74 countries
Ad5-nCoV (Convidicea/CanSino)	Can Sino Biologics Inc. and Beijing Institute of Biotechnology, China	40,000	China approved the EUA of Ad5-nCoV June 25 ,2020, WHO Emergency Use Listing (EUL) in May 2022	Single dose (0.5 mL, 5×10^{10} viral particles/dose)	Not Applicable	Adenoviral vector carrying DNA for full-length SARS-CoV-2	70%	≥ 18 years	Adenoviral vector	2-8 ºC	NCT04526990 NCT04540419 **NCT05517642**	China, Latin American, Asian, and 5 European countries (Argentina, Chile,

						spike protein						China, Ecuador, Hungary, Indonesia, Malaysia, Mexico, Pakistan, 6 and Republic of Moldova)
Unnamed vaccine Inactivated Novel Coronavirus Pneumonia (COVID-19) Vaccine-Wuhan	Wuhan Institute of Biological Products and China National Pharmaceutical Group Corporation (Sinopharm), China	60,000	The National Medical Products Administration of China (conditional approval) on December 30, 2020.	Two doses	21 days	Inactivated SARS-CoV-2 (developed with Vero cell technology)	86% in UAE and 79.34% in China	≥ 18 years	(Inactivated SARS-CoV-2, strainWIV04, / aluminium hydroxide adjuvant)	2–8 ºC	NCT04510207 ChiCTR2000031809 Phase 3 ictrp-ChiCTR2000034780	United Arab Emirates
BBIBP-CorV	Wuhan Institute of Biological Products and China National Pharmaceutical Group Corporation (Sinopharm), China	50,000	NMPA of China, WHO approved BBIBP-CorV for emergency use listing on 5 May, 2021	Two doses	21 days	Inactivated virus	79.34 (China) 86%(UAE)	18-80 years	Inactivated SARS-CoV-2 strain HB02, in aluminium hydroxide adjuvant	2-8 ºC	NCT04510207 NCT04560881 Phase 3: ChiCTR2000034780	Bahrain, China, Egypt, Jordan, Seychelles, United Arab Emirates
CoronaVac	Sinovac Biotech Ltd., Beijing, China	17 Trials NCT05433272 NCT05428592 NCT05308576 NCT05204589 NCT04942405 NCT05077176 NCT05225285 NCT04992260 PHRR210210-003308 NCT05137418 NCT05156632	Approvals Africa Regulatory Taskforce Endorsed Caribbean Regulatory System Emergency Use Recommendation	Two doses 0.5 mL/dose) To be administered intramuscularly	14-days	Inactivated virus	78%	≥ 18 years	Inactivated SARS-CoV-2 in aluminium hydroxide adjuvant	2-8 ºC	Phase I: 8 trials Phase II: 17 trials Phase III: 17 trials	56 Countries

		NCT04800133 NCT04456595 NCT04508075, 669/UN6.KEP/EC/2020 NCT04582344 NCT04617483 NCT04651790	WHO Emergency Use Listing									
BBV152 (Covaxin)	Bharat Biotech in collaboration with the Indian Council of Medical Research and National Institute of Virology, India	33947 Study number NCT0464148 NCT05567471 NCT05522335 CTRI/2022/02/040065 CTRI/2022/04/041792 CTRI/2022/04/042017	Restricted emergency use by CDSCO, India on 1st January 2021 Caribbean Regulatory System Emergency Use Recommendation WHO Emergency Use Listing	Two doses (0·5 mL/dose) to be administered intramuscularly	28 days 21 days	Inactivated vaccine	-- 70-90%	18-55 years ≥ 18 years	Inactivated SARS-CoV-2 in aluminum hydroxide gel—imidazoquinoline adjuvant	2-8 ºC	Phase I: 2 trials Phase II: 5 trials Phase III: 9 trials	14 Countries Bahrain Botswana Guyana India Iran (Islamic Republic of) Malaysia Mauritius Mexico Nepal Paraguay Philippines Trinidad and Tobago Viet Nam Zimbabwe
EpiVacCorona Peptide Vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector", Russia	3,000 Study Number NCT04780035 NCT05021016	Early use regulatory approbal on Oct 14 2020 by Russian authority Tukmenistan gave approval in march 2021	Two doses (0.5 ml) to be administered intramuscularly	21-28 days	A synthetic peptide of SARS-CoV-2 proteins as antigen	No protection	18 to 60 years of age	Alum	2-8 ºC	Phase I: 1 trials Phase II: 1 trials Phase III: 2 trials	4 Countries Cambodia Russian Federation Turkmenistan Venezuela (Bolivarian Republic of)