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VACCINE STRATEGIES AGAINST COVID19: A REVIEW

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ABSTRACT

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS CoV 2), belonging to the Coronaviridae family, is the main cause of COVID 19. Being a positive single-stranded virus, it spreads primarily through cough and sneeze and exerts its downstream effects by binding to angiotensin-converting enzyme 2 (ACE 2) transmembrane protein that controls the renin - angiotensin system. During the prolonged period of intense lockdown, scientists had been trying to devise various effective vaccine strategies against the virus. One of the most direct consequences of these researches is the development of different types of vaccines like DNA vaccines, mRNA vaccines, Viral Vector Vaccines, Protein Subunit Vaccines, Live attenuated vaccines, Inactivated vaccines, Virus-like particle vaccines just to name a few. Some vaccines have claimed efficacies to be as high as 93.5% in case of COVIran vaccines while others have claimed efficacies to be as low as 45%. Many of the internationally acclaimed and approved vaccines have efficacies in the intermediate ranges of 60%-70% like Oxford Astrazeneca vaccine and the Moderna Vaccine. Clinical trials have been conducted on participants from various parts of the world and different countries have approved various vaccines for emergency usages based on the clinical data. At present, 2 mostly used vaccines in India are Covishield and Covaxin. Our review paper takes into consideration the principal vaccines developed in India and in the rest of the world along with their mode of action, the number of doses required, the storage conditions along with claimed efficacy and clinical trial data. This vaccination strategy must be accelerated as much as possible in order to achieve the goal of 'Herd Immunity' at the earliest.

KEYWORDS: COVID 19 vaccines, vaccination strategy, viral mutants, vaccination dosage, efficacy, clinical trials.

INTRODUCTION

Over the centuries, there have been various kinds of epidemics and pandemics that have affected both mankind and its civilizations alike. The Babylon flu epidemic around 1200 B.C. is considered to be the earliest recorded pandemic. Many other pandemics have also occurred since then. Some of them include the Bubonic Plague of Europe, caused by the bacterium *Yersinia Pestis* which was disastrous and catastrophic and almost turned the entire Europe into a hell during the 14th century and the Spanish Flu pandemic which occurred in 1918 and is said to have killed one-third of the world's population then. Though the ongoing Corona Virus Disease 2019 (COVID-19) pandemic is much less fatal, it still has killed about 6.2 million people in the world, as of now. This pandemic proves the persistence, infectivity, and virulence of the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) which is the pathogen of the disease. The disease is still spreading relentlessly and causing many social, health and economic problems. At this moment, effective vaccines are urgently needed to bring a check to this situation and thus help bring the society back to normalcy. Notably, within a few weeks after the start of the then COVID-19 epidemic in Wuhan, China, Chinese scientists isolated the viral pathogen of the disease which was later named as SARS-CoV-2 by the World Health Organization or WHO and sequenced its genetic code which is an RNA or Ribonucleic Acid and shared it with the entire world. This initiated a neck-to-neck global competition to develop a vaccine against the virus with vaccine producers using novel technical paradigms and next generation vaccine platforms, as well as classical vaccine technology to increase the rate of their production and subsequently win the 'vaccine race'. Since then, many COVID-19 vaccines have been researched, developed, tested and evaluated at an unprecedented speed. As of April 2022, many vaccines have been conditionally approved and others are close to such approval.[1] Here in this review, we are going to look at all the types of COVID-19 vaccines that are

available throughout the world. We will discuss the mode of action of a particular type of vaccine, while shedding light on the manufacturer, dosage, efficacy, clinical trials and authorizations of the vaccines in brief under a particular category.

1. DNA Vaccine: DNA vaccination is a technique that can be used against COVID19 by injecting genetically engineered DNA to produce an immunological response. The mechanism involves fabrication of a circular double stranded plasmid DNA encoding for the S protein of the pathogen. The steps of producing DNA Vaccine against COVID19 are: inserting the genes to be expressed into the S protein of SARS CoV2 into plasmid vectors and expressing the genes in skeletal muscle cells or adipocytes to facilitate an immune response. DNA vaccine provides broad-based humoral, and cell mediated immune response i.e., long lasting CTL response.

1.1 ZyCoV-D: It is the world's first indigenously developed plasmid DNA vaccine manufactured by Zydus Life sciences Limited and Biotechnology Industry Research Assistance Council. It carries the gene encoding SARS CoV2 spike protein, and its effectiveness has been increased by using it as an intradermal injection with a spring-powered jet injector. 3 doses have been recommended for this and the efficacy is 66%.Clinical trials of phases 1 and 2 study revealed that the vaccine was safe, immunogenic and could be well tolerated. Phase 3 trial was a randomized, multicentered, placebo-controlled study to determine its efficacy, safety and immunogenicity. The study was carried out in more than 50 clinical sites throughout India during second wave of COVID19, thus confirming the vaccine's efficacy against new mutant variants, especially the delta variant. It also showed that ZyCoV-D is safe for 12-18 years children and has been authorized for emergency use in India and travel-only use in Malaysia, New Zealand and Turkey.

2. Viral Vector Vaccines: The mechanism involves inserting SARS CoV2's genetic material into a modified form of a different virus which is used as a vector. When this viral vector enters the body, it distributes COVID19 virus's genetic information that instructs the cells to create copies of S protein. Human immune system responds by producing antibodies and WBCs when the cells exhibit the S protein on their surfaces to protect them from recurrence of the viral infection.[2]

2.1 Oxford AstraZeneca Vaccine: The ChaAdOx1 vaccine was developed by Oxford University in partnership with AstraZeneca and has been introduced in India as Covishield vaccine by Serum Institute in Pune, Maharashtra. SARS CoV2 DNA has been inserted into a modified form of the Chimpanzee Adenovirus vector AZD1222 and administered to humans. The DNA is transcribed into RNA, which is then translated into Spike proteins, which attract antibodies and cause an immune response.[3] 2 doses have been recommended for this vaccine, efficacy is around 70% and can be stored at 2 to 8^0C for 6 months.[4] In April 2020, clinical trials for the COVID-19 vaccine began. The primary goals of the Phase I, II, and III studies were to see if the ChAdOx1 nCoV-19 vaccine would work against COVID-19, if it would cause unacceptable side effects, and if it would induce good immune responses. Researchers looked studied the immune response to vaccination in people of varied ages, to see if there is a difference in how effectively the immune system reacts in elderly people or youngsters.

2.2 Janssen Vaccine: It has been manufactured by Johnson and Johnson and 1 dose has been recommended. The vaccine can be stored at 2 to 8^oC (3 months).[5] According to the information provided by the manufacturer, the Johnson & Johnson vaccine, or Ad26.COV2.S, has been shown to be 66.9% effective in a large-scale clinical investigation.[5] No information on phase I and II clinical trials is available. However, in phase III, a primary analysis of a multicenter, randomized, double-blind, placebo- controlled phase 3 study was conducted in the United States, South Africa, Brazil, Chile, Argentina, Colombia, Peru, and Mexico to assess the efficacy, safety, and immunogenicity of a single-dose of the Janssen COVID-19 Vaccine for the prevention of COVID-19 in adults aged 18 years and older (cut-off date January 22, 2021). The presence or absence of comorbidities associated with a higher risk of progression to severe COVID-19 were used to stratify the randomization. The demographic and baseline characteristics of those who received the Janssen COVID19 Vaccine and those who received placebo were similar.[5] All 108 countries have approved this vaccine including India, Bangladesh and Afghanistan.[5]

2.3 Sputnik V: Russian company Panacea Biotech in partnership with India's Serum Institute. The viral vectors in the Sputnik V COVID-19 vaccination are two distinct adenoviruses. Adenovirus 26 (Ad26) is the viral vector in the first shot, while adenovirus 5 is the viral vector in the second shot (Ad5). The immune response is triggered by the SARS-CoV-2 spike protein gene, which is present in both injections.[6] The dosage is 2 doses and can be stored at -18.5^{o}C (liquid form) and 2 to 8^{o}C (dry form). Vaccine efficacy (VE) against moderate to severeCOVID19 in adults 18 years of age and older was 66.9% at least 14 days after vaccination and 66.1% least 28 days after vaccination in individuals who were seronegative or had an unknown serostatus at baseline in individuals who were seronegative or had an unknown serum.[7] Exploratory subgroup analyses of immunization effectiveness against moderate to severeCOVID-19 were conducted in Brazil, South Africa, and the United States. The subgroup analyses included all COVID- 19 patients who had accumulated data up to the primary effectiveness study data cut-off date, including cases verified by the central laboratory and cases with a reported positive SARS-CoV-2 PCR from a local laboratory pending confirmation by the central

laboratory. Up until the data cut-off date, the PCR results from the local lab and the central lab were 90.3% in agreement.[7] The vaccine went through all levels of pre-clinical testing before entering clinical trials, including research on a range of animals, including two species of primates. On August 1, 2020, the vaccine's phase 1 and 2 clinical trials were completed. There were no unexpected or unfavorable side effects for any of the individuals. The vaccine elicited strong antibody and cellular immunological responses. None of the subjects in the current clinical trials became infected with COVID- 19 after receiving the vaccine. The vaccine has been authorized in Russia, Belarus, Argentina, Bolivia, Serbia, Algeria, Palestine, Venezuela, Paraguay, Turkmenistan, Hungary, UAE, Iran, Republic of Guinea, Tunisia, Armenia, Mexico, Nicaragua, Lebanon, Myanmar, Pakistan, Mongolia, Bahrain etc. India is the 70th country to approve this vaccine.[7]

2.4 Sputnik Light: Panacea Biotech Company in Russia, in partnership with India's Serum Institute. The first component of Sputnik V, the world's first licensed coronavirus vaccine, is Sputnik Light (recombinant human adenovirus serotype number 26 (rAd26). Sputnik Light, like Sputnik V, is built on a well-studied human adenovirus vector platform; these vectors cause the common cold and have coexisted peacefully with humans for millennia.[7] The dosage and storage conditions of this vaccine are same as that of Sputnik V. Sputnik Light is a one-shot vaccination that is both safe and effective. As a stand-alone vaccination, Sputnik Light is very effective against Delta and other mutations. The effectiveness of Sputnik Light as a booster will be comparable to that of two Sputnik V blasts against Delta. Efficacy was found to be around 80%.[7] The clinical trial data of Sputnik Light is same as that of Sputnik V as per the official website.[7]

3. Inactivated Vaccines: Inactivated COVID-19 vaccines contain SARS-CoV-2, which is either killed or modified in such a way that it is unable to replicate within the host body. Due to the presence of the whole virus along with its multiple surface antigenic components, these vaccines induce a diverse immunogenic response.[9] In this way immunization with inactivated pathogens can provide protection against infectious diseases like COVID-19. Inactivated vaccines have a higher safety profile as compared to the live attenuated vaccines because they are less reactogenic and give rise to a weaker immune response and are, therefore, suitable for those with a compromised immune system. They have a similar method of production like all other inactivated vaccines in which viruses are first cultivated on a suitable substrate for production of large amounts of antigen. Once propagated the viruses are purified and concentrated prior to inactivation. Then they are inactivated using physical or chemical methods or combination of these two.[9] A wide range of well-established inactivation agents or methods have been proven successful to inactivate viruses for vaccine production. Examples are UV treatment,[10] heat,[11] gamma irradiation,[12,13] psoralens.[14] hydrogen peroxide.[15] and many more. Though only formaldehyde and β-Propiolactone (BPL) have been widely used for inactivation of licensed human viral vaccines for decades.[9] Inactivation of a virus destroys its genetic material which stops it from replicating. Inactivated vaccines can trigger immune response but that is not as strong as live attenuated virus vaccines. Therefore, booster doses are needed to ensure ongoing protection.

3.1 Sinopharm BIBP COVID-19 Vaccine: The COVID-19 vaccine BIBP, is an aluminum hydroxide-adjuvanted, inactivated whole virus vaccine developed by Sinopharm's Beijing Institute of Biological Products in China. The trade name of the vaccine is Covilo and is also known as BBIBP-CorV.[16] The WHO Strategic Advisory Group of Experts (SAGE) has recommended the use of BIBP vaccine as 2 doses of 0.5 ml given intramuscularly. Also, an additional dose should be offered to persons aged 60 and above and persons who are severe or moderately immunocompromised, as part of an extension of the primary series.[16] WHO has recommended an interval of 3–4 weeks between the first and second dose of primary series? A large international phase III trial has shown that 2 doses of BIBP VACCINE, administered at an interval of 21 days, have an efficacy of 79% against symptomatic SARS-CoV-2 infection, after 14 days or more from the second dose. Vaccine efficacy against hospitalization was 79%.[17] A large multi-country (conducted in Bahrain, Egypt, Jordan and United Arab Emirates) double blind, randomized, phase III clinical trial, designed by the Wuhan Institute of Biological Products Co, Ltd, and the Beijing Institute of Biological Products Co, Ltd, both of which belong to the China National Biotec Group Company Limited (CNBG), was performed on a large number of participants. As of April 10, 2022, the Sinopharm BIBP COVID-19 vaccine is authorized in 90 countries including Algeria, Argentina, Bolivia, Brazil, Bangladesh, Cambodia, China, Egypt, and United Arab Emirates. WHO added the vaccine to the list of vaccines authorized for emergency use for COVID-19 Vaccines Global Access (COVAX) ON 7 May 2021.[18] UK and Australia also approved and authorized it for international visitors.

3.2 Covaxin: Covaxin (codenamed as BBV152) is developed by Bharat Biotech of India in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). It is a whole virion inactivated SARS-CoV-2 vaccine formulated with an imidazoquinolinone(IMDG) class molecule adsorbed to alum.[19] SAGE recommended use of Covaxin as a 2-dose series, 4 weeks apart, into the deltoid muscle of the upper arm.A booster dose may be offered 4-6 months after completing the primary series for the highest- risk groups, for example, older adults, health workers or persons with comorbidities.[20] From phase III trial, the vaccine efficacy was found to be 78% against severe

COVID19 disease. For those with severe COVID-19, infected with a non-Delta variant of SARS CoV-2 virus, the vaccine efficacy was 84%. Also, efficiency of the vaccine against asymptomatic COVID-19 was 64%.[21] A phase I trial was conducted on 375 adults which showed seroconversion rates of 92% in the 6 mcg with Algel-IMDG, 14 days after dose 2.[22] In phase II safety and immunogenicity trial, conducted on 380 adolescent and adult participants neutralization response of the vaccine was found significantly higher than phase I.[23] Phase III trialwas conducted on 25798 participants, of whom 24419 were vaccinated with either 2 doses of Covaxin or placebo. The participants were adults (≥18 years) among whom 11% were aged >60 years, 33% were women and 28.6% had comorbidities. Primary analysis included the vaccine efficacyto be 78%.[21] Covaxin received full authorization in India. The vaccine was also approved for emergency use in Iran, Zimbabwe, Nepal, Mexico, Philippines, Guatemala, Nicaragua, Guyana, Venezuela and Botswana. It was also approved in Mauritius, Paraguay and Argentina. On 3 November 2021, the World Health Organization (WHO) validated the vaccine for emergency use.[24] but after a subsequent inspection of manufacturing facilities WHO suspended procurement of Covaxin through UN agencies in April 2022.[25]

3.3 CoviVac Vaccine: The vaccine was manufactured by Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products, Russia and was approved on 20th February, 2021.[26] The CoviVac shot is given by intramuscular injection in two doses, 14 days apart and is recommended for use from 18 to 60 years old.[27] One dose of 0.5 ml is composed only of 3 μg or more of SARS-CoV-2 strain AYDAR-1 antigen inactivated by betapropiolactone and the following excipients: 0.3–0.5 mg of aluminum hydroxide (adjuvant) 0.5 ml or less of phosphate buffer solution composed of disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, and water for injection.[28] It is Russia's 3rd vaccine against COVID-19 and has shown approximately 80% efficacy after preliminary trial results.[29]

The phase I /II trialsstarted on 21st September2020, and it continued till 15th October, 2020 [30]. Phase III trials started in early 2021 and are still ongoing and are expected to end on 30th December 2022 so efficacy has not yet been established in Phase III trials.[31] Presently third (booster) dose of the anti-COVID vaccineCoviVac is fully potent to enhance the immunity against novel coronavirus.[32] As the phase III trial is not complete so CoviVac is not fully authorized. On an emergency basis it is authorized in Belarus, Cambodia, Russia and has travel permission only in Malaysia, New Zealand, Turkey.[29]

4. mRNA Vaccines: mRNA vaccines contain mRNA molecules that encode protein antigen.[33] The mRNA molecules contain informationfor the synthesis of stabilized prefusion form of SARS-CoV-2 spike(S) protein encapsulated in a lipid nanoparticle (LNP) vector that enhances uptake by the host immune cells.[34] This LNPs acts as adjuvants and induce B-cell and T follicular helper immune response. In this type of vaccine, mRNA is directly inserted and in the host they are translated into target protein.[34] The overall design of mRNA contains an open reading frame (ORF) with a 3'-polyadenylated tail that induces cellular and humoral responses.[33] mRNA vaccines introduce a short-lived.[35] synthetically created fragment of the RNA sequence of a virus into the individual being vaccinated. These mRNA fragments are taken up by dendritic cells through phagocytosis.[36] The dendritic cells use their internal machinery (ribosomes) to read the mRNA and produce the viral antigens that the mRNA encodes.[37] The body degrades the mRNA fragments within a few days of introduction.[38] Although non-immune cells can potentially also absorb vaccine mRNA, produce antigens, and display the antigens on their surfaces, dendritic cells absorb the mRNA globules much more readily.[39] The mRNA fragments are translated in the cytoplasm and do not affect the body's genomic DNA, located separately in the cell nucleus.[40]

4.1 Pfizer-BioNTech COVID-19 Vaccine: It is sold under the brand name of "Comirnaty" it was manufactured by Pfizer, of America in collaboration with BioNTech of Germany.[41] The vaccine usually delivered in vial once diluted contains 2.25 mL of vaccine, comprising 0.45 mL frozen and 1.8 mL of diluents. Each and every individual should be administered 0.3 mL of dose.[42] The initial course consists of two doses.[43] The doses must be in an interval of three to four weeks. Later the interval of 12 weeks between two doses showed improved immunogenicity among patients. An additional 3rd or 4th dose can also be given in some countries according to their requirement.[42] A test negative case study published in august 2021 found duel doses of BNT162b2 had 93.7% effectiveness against symptomatic disease caused by alpha variant and 88% against symptomatic delta variant.[44,45] In Preclinical Trials**,** BNT162b1 and BNT162b2 emerged as strong prospects based on the safety and immune response data obtained and assessed on four BNT162RNA candidates. In preclinical trials, the BNT162b1 and BNT162b2 vaccine candidates were given prophylactically to rhesus macaques and mice, respectively. COVID-19 was not found in any of the animals that took part in the preclinical experiments. Two intramuscular (I.M.) injections of 100 g BNT162b2 or 100 g saline were given to macaques at random during the trial. On day 1, the first injection was administered, and on day 21, the second injection was given. Macaques immunized with 100 g of BNT162b2 had positive CD4+ and CD8+ responses, high levels of neutralizing antibodies, and no signs of viral SARS-CoV-2 RNA or lung infection.[46] In phase 1 and 2 Trial**,** between April 23, 2020, and May 22, 2020, 60 healthy male and nonpregnant female participants (96.7% Caucasian, one African American, and one Asian) between the ages of 18 and 55 years were

enrolled in phase 1/2 of the study in Germany. They were divided into 1 g, 10 g, 30 g, and 50 g dose groups. In the beginning, each dose group had twelve participants who were injected intramuscularly on day 1 and day 22. One participant from the 10 g dose group and one participant from the 50 g dose group withdrew from the trial due to unforeseen circumstances unrelated to the phase ½ clinical trials. Another group of twelve participants in the 60 g dose group received only a placebo. Mild to moderate side effects were observed in the 10 g and 30 g dose groups on day one, as expected. Symptoms such as fever, chills, headache, joint pain, muscle pain, and pain at the injection site were common within 7 days of each vaccination. In both the initial (day 1) and booster (day 22) immunizations, pain and tenderness at the injection site were common complaints. There were no serious side effects in any of the dose groups, and thus no one dropped out of the study due to serious side effects.[46] BNT162b2's Phase 3 clinical trial began on July 27 and has so far enrolled 43,661 people, with 41,135 of them receiving a second dose of the vaccine candidate as of November 13, 2020. Around42 percent of global participants and 30 percent of U.S. participants come from racially and ethnically diverse backgrounds, and 41 percent of global and 45 percent ofU.S. participants are between the ages of 56 and 85, representing approximately 150 clinical trial sites across the United States, Germany, Turkey, South Africa, Brazil, and Argentina. For the next two years, the trial will collect efficacy and safety data from participants.[47] Pfizer BioNTech vaccine got full authorization from 10 countries that include Australia, Brazil, Canada, USA, Switzerland, Saudi-Arabia, Palau, New Zealand, Micronesia, Marshall Island and got emergency authorization from almost 140 countries across the world.[48]

4.2 Moderna Vaccine: Moderna COVID-19 vaccine, sold under the brand name Spikevax. developed by American company Moderna, the United States National Institute of Allergy and Infectious Diseases (NIAID), and the Biomedical Advanced Research and Development Authority (BARDA).[49] Moderna COVID19 vaccine is administered at an interval of 1 months in two doses each of 0.5 mL to 18 years old or above. A third dose can also be given to 18 years old or above having undergone any organ transplant. A booster dose of 0.25 mL is eligible to be given to 18 years or above after 5 months from the last dose administered.[50] The mRNA-1273 or moderna vaccine has a 94.1 percent overall efficacy (89.3- 96.8). People between the ages of 18 and 65 have an efficacy of 95.6 percent (90.6-97.9), while those over 65 have an efficacy of 86.4 percent (61.4-95.2). This was discovered in a data analysis of 14134 candidates.[51] The Phase 1 trial began with an open-label trial in which 45 healthy adults aged 18 to 55 received two vaccinations with mRNA-1273 in doses of 25 g, 100 g, or 250 g, 28 days apart. Each dose group had a total of 15 participants. Antibody responses were higher with higher doses following the first vaccination (day 29 enzyme-linked immunosorbent assay anti–S-2P antibody geometric mean titer [GMT], 40,227 in the 25-g group, 109,209 in the 100-g group, and 213,526 in the 250g group). The titers increased after the second vaccination (day 57 GMT, 299,751, 782,719, and 1,192,154, respectively).[52] After phase 1 trial, the mRNA-1273 vaccine induced anti–SARS CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified. The US Food and Drug Administration has approved plans for a Phase II dosing and efficacy trial to begin in May.[50,53] Moderna began recruiting 600 adult participants for a Phase II-a clinical trial on May 25, 2020, to assess the safety and differences in antibody response to two doses of its candidate vaccine, mRNA-1273. On July 27, Moderna and the National Institute of Allergy and Infectious Diseases launched a Phase III trial in the United States, with the goal of enrolling and randomly assigning 30,000 volunteers to one of two groups: one receiving two 100-g doses of mRNA-1273 vaccine and the other receiving a 0.9 percent sodium chloride placebo.[54] Moderna had completed the enrollment of 30,000 participants for its Phase III trial as of October 2020.[55] The US National Institutes of Health announced on 15 November 2020, that overall trial results were positive.[56] Moderna vaccine got full authorization from 5 countries that include Australia, Canada, USA, Switzerland, United Kingdom and got emergency authorization from almost 104 countries across the world.[57]

5. Virus-like Particle Vaccine: Virus-like particles are the assemblies of supra- molecular particles.[58] They consist of one or more than one viral proteins that are self- assembled into various nanoparticles. They lack the pathogen's genetic material. VLP vaccines are a kind of subunit vaccine which contains specific supra-molecular particles that are taken up by cells through non- specific pathways such as phagocytosis and macropinocytosis.[59] VLPs are internalized into antigen presenting cells(APCs) , controlled within phagolysosome and the resulting antigen peptides are presented to $CD4^+$helper T cells by loading on MHC II molecules. Helper T cell receptors identify epitopes presented on MHC II and activate themselves in additional signaling through costimulatory receptors and cytokines depending upon the strength of interaction. Because of their high stability, immunogenicity, diversity, and production versatility, VLPs are a promising technology for vaccine design.[60] VLP technology offers an alternative platform for developing effective vaccines against serious infectious diseases, and it is progressing in tandem with mRNA and viral-vector-based vaccine.[61] VLPs are also far more immunogenic than other subunit vaccines because they have repetitive antigenic epitopes on their surface, which the immune system can detect.[62]

5.1 CoVLP Vaccine: CoVLP in the brand name of *Covifenz* has been developed by Medicago of Canada and GlaxoSmithK line.[63] It is authorized as a two-dose

regimen of 3.75 micrograms per dose, to be administered 21 days apart.[64] A preliminary analysis by Medicago and GSK on December 2021 found an overall efficacy of 71%, with 75% against the Delta variant and 89% efficacy against Gamma variant.[64] In phase I results of clinical trials, 180 adults (18–55 years) were randomized to receive two intramuscular doses of CoVLP (3.75 g,7.5 g, and 15 g) 21 days apart, either alone or adjuvanted with AS03 or CpG1018 at two sites in Quebec, Canada, beginning in August 2020. All well-tolerated formulations and post-vaccination adverse events were mild to moderate, transient, and more common in the adjuvanted groups. There was no effect of CoVLP dose on serum NAbs, but both adjuvants significantly increased titers. NAbs in the CoVLP + AS03 groups were more than tenfold higher than titers in Coronavirus 2019 convalescent sera after the second dose. Cellular responses to spike protein-specific interferon and interleukin-4 were also induced. This prespecified interim analysis supports the CoVLP's further evaluation.[65,66] Medicago-GSK began a Phase II clinical trial for CoVLP with 588 participants in November 2020. Researchers published interim safety and immunogenicity data from a Phase II, randomized, placebo-controlled trial in adults aged 18 and up who were immunized with a virus-like particle vaccine candidate produced in plants displaying 19 SARS-CoV-2 spike glycoprotein (CoVLP) adjuvanted with AS03 on day 42. (NCT04636697). This report focused on presenting safety, tolerability, and immunogenicity as measured by 21 neutralizing antibody (NAb) and cell mediated immunity (IFN- and IL-4 ELISpot) responses in adults aged 18-64 (Adults) and Older Adults aged 65+ (Older Adults) (Older Adults).[65,66] Medicago-GSK began a Phase III clinical trial for CoVLP in April 2021, enrolling 30,918 participants. (Medicago) CoVLP exhibited 69.5 percent efficacy against laboratory-confirmed, symptomatic SARS-CoV-2 infection starting at least 7 days after the second dose of the vaccine in the intention-to-treat analysis, even though the trial included some participants who had previously been infected with the virus when the trial began, according to the data presented by Health Canada's National Advisory Committee on Immunization (NACI). In the per-protocol analysis, it showed efficacy of 100.0 percent against the Alpha variant, 75.3 percent against the Delta variant, and 88.6 percent against the Gamma variant, with "similar" results in the intention-to-treat analysis.[64] The only country to authorize this vaccine on 24th of February, to be used among 18-64 years old in Canada.[63]

6. Protein Subunit Vaccine: These are generated through recombinant synthesis of protein antigens and purification method after cultivating large amounts of pathogens. In case of COVID19 all protein subunit vaccines target a specific viral protein called spike protein, one which seems to trigger a robust immune response. When the immune system encounters the spike protein it responds like it would as if seeing the active virus itself. But this vaccine can’t cause infection because they only contain a viral protein or group of proteins, not the complete viral machinery needed for this virus to replicate. One disadvantage of this precision vaccine is that the antigens used to elicit an immune response may lack pathogen-associated molecular patterns, which are shared by a group of pathogens. Immune cells can read these structures and recognize them as danger signals, so their absence could result in a weakened immune response. Protein subunit vaccines also elicit antibody-mediated immune responses because the antigens do not infect cells. This means that the immune response with this vaccine may be weaker than with other vaccines. Protein subunit vaccines are sometimes given with adjuvants (agents that stimulate the immune system) to overcome this problem, and booster doses may be required.[67]

6.1 Nuxavoid: Nuvaxovid is a subunit COVID-19 vaccine developed by the American Biotech company Novavax and the Coalition for Epidemic Preparedness Innovations (CEPI).[68] It is administered intramuscularly as a course of 2 doses of 0.5 mL each. and is recommended to administer the second dose 3 weeks after the first dose in 18 years or above adults (ema.europa.eu). The overall efficacy was 90.4% and efficacy against moderate -to -severe disease was 100%.[69] On January 28, 2021, According to Novavax's report, preliminary results from its clinical trial in the United Kingdom showed that it was more than 89% effective.[70] The vaccine has an overall efficacy of 83.4 % two weeks after the first dose and 89.7% one week after the second dose, according to a primary Novavax-funded study published in The New England Journal of Medicine on June 30, 2021.[71] Phase I and II human trials Novavax's NVX-CoV2373, began in Melbourne on May 26, 2020. It enlisted the help of about 130 volunteers, ranging in age from 18 to 59.[72] In December 2021, Novavax announced that the vaccine had met its primary endpoint of preventing infection for at least seven days after the second dose in a phase III trial. Novavax began a pediatric expansion for the phase III clinical trial on May 3, 2021, with 3,000 adolescents aged 12 to 17, yet no further documented report came out.[73] Three countries have fully authorized this vaccine that include Australia, Canada & South Korea and almost 36 countries have given authorization for using it in emergency situation.[74]

6.2 Corbevax: It was developed by the Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine, in Texas. It was licensed to Biological E. Ltd.,of India, For production and further development.[75] The vaccine is given using intramuscular injections in 2 doses, which are 28 days apart.0.5 ml of this vaccine is used for each dose.[76] nAB GMT against ancestral Wuhan strain indicates the vaccine effectiveness of >90%. Vaccine effectiveness of >80% for the prevention of symptomatic infection is indicated by the nABGMT against Delta strain. During the continuous monitoring of the phase 2 trial, the

effectiveness of this vaccine was indicated by <30% drop of nAB GMT over a period of 6 months after the second dose.[76] Phase 1 study was uninterruptedly followed by Phase 2 study. Healthy volunteers from both the genders, between ages 18 and 65(both inclusive) were enlisted for the trials.360 volunteers were there and they were divided into random groups.4 formulations namely, ECOV2D, BECOV2C, BECOV2B and BECOV2A were introduced. Administration of the vaccine was performed via intramuscular injections, 28 days apart, with 0.5 ml of the vaccine in every dose. Registration ID is CTRI/2020/11/029032.[77] Phase 2 trial was uninterruptedly followed by Phase 3 trial (CTRI/2021/06/034014). Healthy volunteers from both the sexes, between ages 18 and 80 were enlisted for the trials. The total sample size was 1268. 0.5 ml of the vaccine was administered via intramuscular injections. 2 doses were administered, 28 days apart. Anti-RBD IgG concentrations, neutralizing antibody titer, proportion of candidates with solicited adverse reactions, SAEs and MAAEs were checked during the trials at various intervals. Safety follow up visits were performed between 6-12 months after 2nd dose.[78] India has approved this vaccine for emergency usage.[79]

6.3 Soberana 02: Soberana 02 which has the technical name of FINLAY FR-2 is produced by the Finlay Institute in Cuba and the Pasteur institute of Iran. Intramuscular injection of 0.5 ml is required in 2 individual doses(28 days apart). On the 56th day 0.5ml of FINLAY-FR- 1A(Soberana Plus) can be given as a booster dose. The 3 dose combination had a VE of 92.4%, adjusted(CI 95% 86.9-95.6%). While the 2 dose schedule(without the booster dose) had an efficacy of 71.0%. Phase 3 trial was a double blind randomized trial with 24,00 adults, aged between 18 and 80 years. They were divided into vaccine and placebo groups in 4:1 ratio. They were further divided into 3 sub-groups. Sub-Group 1 received 25 µg of the vaccine in individual doses on day 0 and day 28. Sub group 2 received 25 µg of the vaccine in individual doses on day 0 and day 28 and on the 56 th day received a booster dose of SOBERANA PLUS along with the normal dose. SOBERANA 02 is a conjugate vaccine so 25 µg of it contains RBD conjugated with Tetanus toxin. The Placebo group received 0.5 ml of Aluminium hydroxide in a 3 dose regime (28th day and 56th day). The outcomes that were studied are-the effectiveness of the vaccine in preventing symptomatic Covid-19 infection, humoral safety (under 2-dose + booster regimen), the frequency of local and systemic events and mild, moderate, severe, critical adverse events and death, cellular safety and SARS- CoV-2 virus neutralization assay. On June 29, 2021, Iran approved the use of SOBERANA 02 in an emergency. Cuba authorized the emergency use of SOBERANA 02.[79]

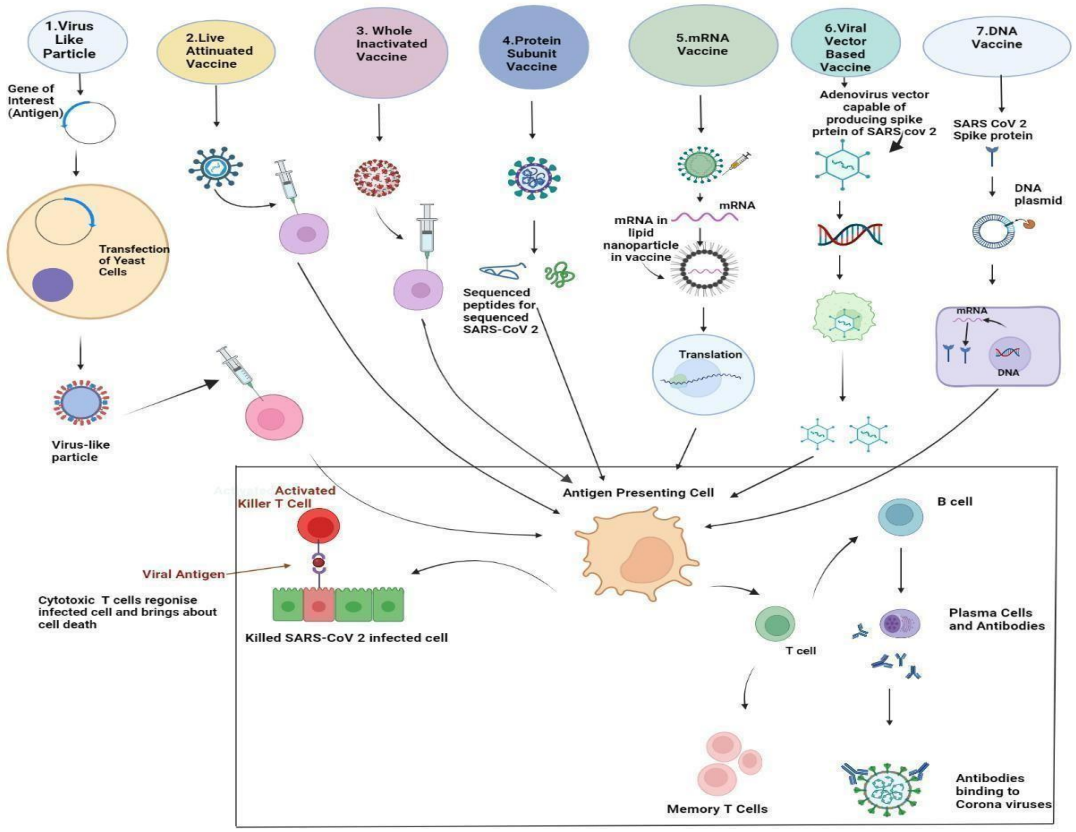

Figure 1: Mode of action of all majorly available COVID-19 Vaccines: 1)Virus-like particles can be self assembled in and released from recombinant yeast cells or other expression systems such as the vaccinia virus expression system or even tobacco mosaic virus.2) Attenuated live pathogen vaccine strategies consist in administering a debilitated form of live pathogen. Lengthy cell culture passaging in non-human cell lines or

animals decreases the virulence of the pathogen. This type of vaccines usually elicits robust and long-term memory immune responses after a single dose.3) Inactivated pathogen vaccines contain whole pathogen that has been submitted to heat or chemical treatment inactivation.4) Subunit vaccines are prepared either from antigen purification of pathogens replicated in cell cultures or from recombinantly expressed antigens. These vaccines commonly require adjuvant addition in order to deliver danger signals to antigen presenting cells and provoke robust immune responses.5)mRNA vaccines are very quick to produce, yet were untested as successful human vaccine strategies.6) Viral vector vaccines use a genetically manipulated measles or adenoviral platform to express a foreign antigen commonly resulting in robust cellular and humoral response.7)Lastly, in DNA vaccines the nucleic acid codifying for an immunogenic protein of the pathogen once administered is captured by antigen-presenting cells that use it to express and present the antigen. These vaccines are predicted to have minor safety issues as nucleic acid is swiftly degraded within the human body.

CONCLUSION

Since their approval, COVID-19 vaccines have protected vaccinated individuals from the infection of COVID-19. There are also data that strongly support the fact that certain vaccines can also prevent asymptomatic cases of COVID-19 in most instances. Despite such remarkable progress in COVID-19 vaccine development, there remain many questions that need to be answered. Though clinical trial data shows that the approved COVID-19 vaccines are efficient, it is not yet known how long the immunity will persist. A study predicts the decay of neutralization titre over the first 250 days after immunization with seven conditionally approved vaccines although protection from severe diseases may be retained. Finally, mutations of the S protein have been reported in the SARS-CoV-2 virus. The variants having these mutations may be more infectious and/or resistant to the neutralizing antibodies. Therefore, how mutations and its resultant.

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