

Monograph on COVID-19 Vaccines

Abstract

In this monograph various types of vaccines available in the market and the future of vaccination in relation to COVID-19 will be discussed in detail. The design and production of vaccines to combat SARS-CoV-2 were mostly directed towards the surface exposed spike glycoprotein. Moderna (mRNA-1273) COVID-19 vaccine was approved by the Food and Drug Administration (FDA) on 18 Dec 2020 under Emergency Use Authorization (EUA). BNT162b2 is a lipid nanoparticle encapsulated, nucleoside modified mRNA vaccine that encodes for the surface spike glycoprotein present in SARS-CoV-2. The act of proceeding to approve vaccines before Phase III trials, have installed doubt and vaccine hesitancy. This further impedes the process of vaccination thereby slowing the chance of the entire world getting vaccinated. The only way to protect oneself from being seriously ill and hospitalized is by following social distancing and getting vaccinated as early as possible. Despite, the lack of cold chain storage in certain regions, there are a variety of vaccines available to help negotiate this obstacle. More research and efforts will be poured into COVID-19 pandemic as we work towards a universal vaccine that will be effective against all the variants of SARS-CoV-2 and help eradicate the virus from the face of the earth.

Keywords: COVID 19 vaccines, SARS-CoV-2, health, treatment

1. Introduction

The history of vaccines dates back to the late 18th century and borne out of the necessity to curb the rapid spread of diseases and the ever-growing death toll. It was pioneered by Pasteur and colleagues who worked on the cause of diarrheal disease in chickens [1]. Towards the late 19th century, the development of vaccines began to take place in laboratory where cell cultures revolutionized the creation of vaccines. This assisted in newer and more efficient techniques for vaccine development. Around the 20th century, Thellier and Smith (1937) were successful in

attenuating the yellow fever virus in mice and chicken embryo tissues [2]. The onset of genetic engineering paved way to great strides in vaccine development. The very first progeny was the Hepatitis B vaccine by Hilleman and associates. Despite its failure in the long term, it gave direction for modern vaccine development techniques [3]. The incorporation of decades of knowledge has given rise to fast paced development and more efficacious vaccine. These scientific advances have proven beneficial in the ongoing COVID-19 pandemic, as vaccines were developed and available in the market within 6-9 months from the onset of SARS-CoV2 virus. This rapid development of vaccines has effectively and immensely helped to curb the mortality and infection rates, but the threat has not been completely neutralized. In this monograph various types of vaccines available in the market and the future of vaccination in relation to COVID-19 will be discussed in detail.

2. COVID-19 vaccines

As of September 21th, 2021, WHO reported that there are nearly 319 vaccine candidates were in the development for the prophylaxis of COVID-19 [4]. Out of which 125 were in clinical phase and 194 are in pre-clinical phase. Out of the 121 clinical phase candidates, 38 were in phase 1 clinical development, 34 in phase 1-2 clinical development, 9 in phase 2 clinical development, 11 in phase 2-3 clinical development, 25 in phase 3 clinical development and 8 in phase 4 clinical development [4]. The US FDA has approved the use of two mRNA based (consider mRNA instead of just RNA) vaccines mRNA-1273 (Moderna) and BNT162b2 (BioNTech/Fosun Pharma/Pfizer) for public use. In India, ICMR has approved the use of AZD1222 (University of Oxford/AstraZeneca) also commercially known as Covishield, BBV152 (Bharat Biotech) also known as Covaxin, Gam-COVID-Vac (Gamaleya Research Institute of Epidemiology and Microbiology) known as Sputnik V and most recently ZyCoV-D (Clinical Unit of Zydus Research center, Cadila Healthcare Limited in Ahmedabad, Gujarat, India). Available scientific knowledge on the human immune responses against SARS-CoV and MERS-CoV serves to be a guiding platform in the research and development efforts towards vaccines to combat SARS-CoV-2, this is due to the resemblance of these strains and similar etiology [5].

The design and production of vaccines to combat SARS-CoV-2 were mostly directed towards the surface exposed spike glycoprotein [6]. Based on this design, it is postulated that the utilization of spike protein-based vaccines can induce the manufacturing of antibodies, inhibiting the viral genome uncoating and receptor binding, thereby causing viral transmission to be ineffective [6]. The stimulation of antibody (Ab) response of a vaccine occurs when the targeted antigen contains B cell receptor epitopes. Likewise, cell mediated immune response need T-cell epitope formation [7]. Vaccines are responsible for antigen-specific memory in adaptive immune cells that allows long-lived safety against the targeted pathogen. [8]

2.1 COVID-19 pandemic

SARS-CoV-2 better known as COVID-19, belongs to the beta-coronavirus family, results in severe acute respiratory syndrome (SARS). The virus is believed to have traversed the species barrier and passed onto human beings from bats with subsequent human-to-human transmission. On March 11, 2020 the World Health Organization (WHO) declared COVID-19 a pandemic and as of June 2021, there are about 138 million confirmed cases and 40 million reported deaths as per WHO [9]. The SARS-CoV-2 virus spreads primarily through the inhalation of respiratory aerosols. Direct human contact and fomites have also postulated to be possible routes of transmission. Being a virus born out of mutation, the SARS-CoV-2 virus will continue to evolve despite the various precautionary measures and also due to its rapid multiplication.

Protective solutions such as vaccines that are safe and effective are currently the highest priority to curb spread of COVID-19 in addition to COVID appropriate behavior in paving the way to pre-pandemic normalcy. SARS-CoV-2 presents thru similar features of SARS-CoV and MERS-CoV that had emerged as major pandemics in the 2002 and 2012 respectively. Despite the many similarities, SARS-CoV-2 has shown to have a much greater infectivity, longer incubation period and higher number of undetected asymptomatic cases. [10]. The clinical presentations of SARS-CoV-2 range from mild flu alike symptoms to acute respiratory distress syndrome. Cases of long-standing pulmonary, neurological and cardiological complications are associated with COVID-19 [11]. SARS-CoV-2 has shown to be highly contagious with an approximate reproductive number of 2.2, that is 2.2 new infections per existing COVID-19 case [12]. Spread

of COVID -19 due to asymptomatic patients poses the greatest challenge as they are very hard to identify and effective measures in containing transmission cannot be implemented in a timely manner [13]. Resultantly, COVID-19 has arisen as a major public health crisis of our generation and has massively impacted global economy and geopolitics while at the same time leading to loss of millions of human lives.

The burden of pandemics is based on the rate of transmission, the way it affects people, the timing of peak infectivity and the duration of pandemic. COVID-19 is very similar to Influenza pandemics in the manner it spreads across the globe. The hospitalization rate and fatality are key indicators in evaluating severity. Although both rates are much lesser compared to the other pandemics that we have faced, the threat persists. Modern sanitary methods and equipment to prevent COVID-19 spread are the only things that is stopping COVID-19 from becoming a major global catastrophe.[14]

2.2 Classification of COVID-19 vaccines

The candidates come from various vaccine platforms such as protein based, virus based, gene based and others [Fig. 1]. Protein based vaccines are divided into protein subunit and virus like particles. Virus based vaccines are divided into inactivated virus and live attenuated virus. Gene based vaccines can be further separated into RNA, DNA, non-replicating viral vector and replicating viral vector.[Fig. 1].

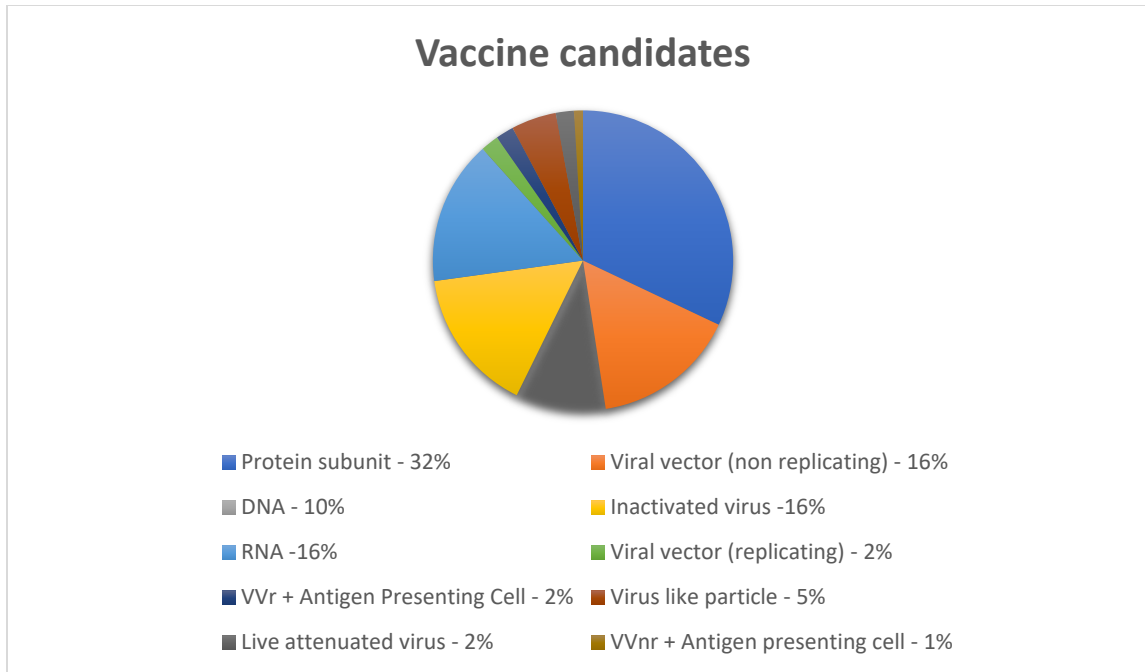


Figure 1 Vaccine candidates

2.3 Gene based vaccines

Gene based vaccine also known as nucleic acid vaccine make use of the genetic material of the disease-causing pathogen to cause an immunological response against it. The genetic material can either be DNA or RNA depending on the type of vaccine. A specific protein from the pathogen is created using the virus genetic material; this is identified by the host immune system as alien material (Antigens) which ultimately trigger an immune response producing antibodies against the antigen. Studies on gene-based vaccine development of MERS-CoV and SARS-CoV pandemics have highlighted the importance of cellular and humoral immunological responses to cause a defensive response within a brief span of time [15,16]. This is used as a guiding tool in the venture of developing a gene-based SARS-CoV-2, thanks to the previous studies and their structural similarity.

2.3.1 mRNA vaccines

mRNA vaccines are widely considered to be the most technologically advanced vaccines available in the market with the US FDA approval of mRNA-1273 (Moderna) and BNT162b2 (BioNTech/Fosun Pharma/Pfizer) further solidifying their status [17-21]. mRNA vaccines have plenty of advantages as compared to other platforms [22, 23]. They are relatively safe, as compared to DNA vaccines; the mRNA does not mix into the host's genome thereby reducing genotoxicity [23]. Manufacture of mRNA is manageable for quality control and there is a lesser chance of contamination during the manufacture phase [24]. mRNA vaccines have also proven their efficacy by producing good humoral and cellular response during clinical trials [24-26]. mRNA vaccines can be both premeditated and manufactured within a small time-frame to achieve the extreme demands of a pandemic. This ability to rapidly scale up production is the key reason for its early success with Moderna and Pfizer [27]. Although there are many benefits certain limitations in the production of mRNA vaccine remain. Due to their unstable nature, mRNA tends to degrade easily by ubiquitous RNases without proper formulation. Secondly, there lies the possibility for it to activate the innate immune system and cause an acute inflammatory response that is potentially toxic or fatal to the individual. Lastly, mRNA vaccines need cold-chain storage conditions for storage and distribution. This must be strictly adhered to as temperature fluctuations can cause it to degenerate [28-29]. Only by overcoming these barriers can sustainable mRNA vaccines be produced, that are, thermally stable, protected from degradation and efficacious.

Currently used delivery mechanism for COVID-19 mRNA vaccines is through lipid nanoparticles (LNP). These LNPs encapsulate the mRNA molecule inside a lipid structure that is made of four different components, cationic lipid for the complexation of mRNA, cholesterol to assist in stabilizing the nanoparticle, helper phospholipids to help the formulation & intercellular release and PEGylated lipids to decrease nonspecific interactions. Overall, mRNA vaccines have immense potential in tackling pandemics, such as COVID-19 but further research is needed/required for effective precautions against newly emerging pathogens and potential threat of mutation or seasonal reoccurrences of SARS-CoV-2. Maximum benefits of mRNA vaccines can be reaped only if they are optimized to pack and guard antigen encoding mRNA, thermostable allowing room temperature storage and shipping/transport, effectively induce

humoral and cellular immune response against a widespread variety of pathogens and achieve quality controlled mass production at affordable price to meet global demands.

Types of mRNA vaccines

2.3.1.1 Pfizer-BioNTech COVID vaccine

Pfizer-BioNTech (BNT162b2) COVID-19 vaccine was approved by the Food and Drug Administration (FDA) on 11 Dec 2020 under Emergency Use Authorization (EUA). BNT162b2 is a lipid nanoparticle formulated, nucleoside modified mRNA vaccine that encodes for the surface spike glycoprotein present in SARS-CoV-2 [30]. The Pfizer-BioNTech vaccine is given in 2 doses (0.3mL each). The vaccine is administered intramuscularly, and two doses are given 3 weeks apart. One large, randomized, double-blind, placebo-controlled Phase II/III clinical trial was conducted involving more than 43000 participants with a median age of 52yrs, ranging between 16 to 91years [31,32]. The findings for this trial with a follow up period of 2 months and 2 doses indicated 95.0% efficient in the prevention of symptomatic COVID-19 in individuals without prior SARS-CoV-2 infection. A high efficacy of $\geq 92\%$ was reported across participants of various age, sex and race. This also held true for participants with underlying medical conditions and previous SARS-CoV-2 infection. Reactogenicity symptoms as local injection site or systemic reactions were frequent and found to vary from mild to moderate during the 7 days period after vaccination. Amongst the vaccine recipients, it was reported that 8.8% individuals had grade ≥ 3 reaction. The most repeated symptom was found to be fatigue (4.2%), followed by headache (2.4%), then muscle pain (1.8%), chills (1.7%) and injection site pain (1.4%) [31,32].

From the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) evidence valuation, the level of certainty for benefits of the vaccine was categorized as type 1 (high certainty) for the prevention of symptomatic COVID-19. The data was categorized as type 3 (low certainty) for the prevention of COVID-19 associated hospitalization and type 4 (very low certainty) for the prevention of death. With regards to troubles after vaccination, data was found to be type 2 (moderate certainty) for very severe adverse events and type 1 (high certainty) for reactogenicity.

Interim estimates of the vaccine efficacy were tested on healthcare personnel, first responders and further essential frontline workers in 8 different US locations between the period of dec 2020 and march 2021 by the CDC. Among the 3950 participants drafted for the study, 2479 (62.8%) had received both the recommended RNA doses and 4 (12.1%) received only one dose. The infection rate in unvaccinated individuals was 1.38 per 1000 person-days as compared to fully vaccinated which as 0.04 infections and 0.19 infections in partially immunized individuals. The adjusted vaccine effectiveness was found to be around 80% in partially vaccinated individuals and 90% in fully vaccinated individuals. This shows that the authorized mRNA vaccines are effective in the prevention of COVID-19 infection [33].

The ACIP has decided that the use of Pfizer-BioNTech COVID-19 vaccine to be reasonable and efficient, despite the great demand for ultracold-chain storage, handling and administration. This issue can limit the availability to certain populations especially in areas without the required storage and transport infrastructure, thereby impacting the health equity in a negative manner. Overall, this vaccine has been a revelation in the battle against COVID-19 and has given optimism for the community that things can return to normal.

2.3.1.2 Moderna COVID-19 vaccine

Moderna (mRNA-1273) COVID-19 vaccine was approved by the Food and Drug Administration (FDA) on 18 Dec 2020 under Emergency Use Authorization (EUA). BNT162b2 is a lipid nanoparticle encapsulated, nucleoside modified mRNA vaccine that encodes for the perfusion spike glycoprotein present in SARS-CoV-2 [34]. This is the second COVID-19 vaccine that has been recognized by the US FDA. Moderna vaccine is administered in 2 doses (0.5mL each). The vaccine is given intramuscularly, 4 weeks apart. One large, randomized, double-blind, placebo-controlled Phase III clinical trial was conducted involving more than 30000 participants with a median age of 52yrs, ranging between 18 to 95yrs assigned in a 1:1 ratio to obtain the vaccine or placebo, with roughly 15000 participants per group. [35-37]. The findings for this trial with a follow up period of 2 months and 2 doses indicated the vaccine is found to be 94.1% effective in the deterrence of symptomatic COVID-19 in individuals without prior SARS-CoV-2 infection. Individuals who had vaccine administered showed serological sign of SARS-CoV-2 infection at baseline. A good efficacy of $\geq 86\%$ was reported across participants of various age,

sex and race. This also held true for participants with underlying medical condition and previous SARS-CoV-2 infection. Initial findings indicate that Moderna COVID-19 vaccine can provide a certain amount of protection against asymptomatic SARS-CoV-2. Reactogenicity symptom also called as local injection site or systemic reactions were frequent and found to vary from mild to moderate during the 7 days period after vaccination. Severe infection of SARS-CoV-2 occurred in 30 participants of the placebo group. Very serious adverse effects were rare and their incidence were found to be similar in both test groups. Amongst the vaccine recipients, it was reported that 21.6% individuals had grade ≥ 3 reaction, among which 9.1% were found to have grade ≥ 3 local injection site reaction and 16.5% were found to have grade ≥ 3 systemic adverse reaction. The incidence of severe adverse event was observed to be less (1.0%) [36].

The level of assurance for the vaccine's benefits was classified as category 1 (high certainty) for the prevention of symptomatic COVID-19 based on the GRADE evidence assessment. For the prevention of COVID-19-related hospitalization, the evidence was rated as type 2 (moderate certainty) and type 4 (very low certainty) for the prevention of death and asymptomatic SARS-CoV-2 infection. Interim estimates of the vaccine efficacy were tested on healthcare personnel, first responders and other essential frontline workers in 8 different US locations between the period of dec 2020 and march 2021 by the CDC. Among the 3950 participants drafted for the study, 2479 (62.8%) had received both the recommended RNA doses and 4 (12.1%) received only one dose. The infection rate in unvaccinated individuals was 1.38 per 1000 person-days as compared to fully vaccinated which as 0.04 infections and 0.19 infections in partially immunized individuals. The adjusted vaccine effectiveness was found to be around 80% in partially vaccinated individuals and 90% in fully vaccinated individuals. This shows that the authorized mRNA vaccines are effective in the prevention of COVID-19 infection [37].

In the case of vaccine-induced harm, type 2 evidence (moderate certainty) was identified for extremely serious adverse events and type 1 evidence (high certainty) for reactogenicity. Despite the vaccine's requirement for long-term storage in a freezer (-20°C), the ACIP has determined that using Moderna COVID-19 vaccine is reasonable and efficient. It is found to stable at temperature of $2-8^{\circ}\text{C}$ for up to 30 days after thawing. This distinctive nature of the vaccine allows the feasible administration across most of the community settings [38]. Along with Pfizer-

BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine has given the community a greater opportunity to increase the number of people who are vaccinated thanks to its feasible nature.

2.3.2 DNA vaccines

One of the most groundbreaking methods in the field of vaccination is said to be the introduction of DNA vaccines that are based on bacterial plasmids that encode for the viral antigen and delivered to host cells via electroporation that induces an adaptive immunological response [39]. In contrast to protein antigen, the plasmid has to enter into the nucleus of locally transfected cells together with Antigen Presenting Cells. Upon entering the nucleus, synthesis of foreign antigens take place under the expression of these plasmid-encoded genes. They are then subjected to immune surveillance after which humoral and cellular immune responses are initiated [40]. DNA vaccines have plenty of advantages in terms of manufacturing, storage, and safety. The manufacturing of plasmid is very rapid, and one batch can easily be manufactured within 2-4 weeks [41]. Storage is much more convenient as compared to chromosomal DNA as plasmid DNA is capable of renaturing under a host of conditions without any loss in its biological activity [42]. The host of advantages make it seem like DNA vaccines can be developed without much difficulty but there are certain potentially fatal disadvantages as well. DNA vaccines are capable of activating oncogenes thereby eliciting anti-DNA antibodies that may cause an autoimmune response. There is insufficient data and research surrounding DNA vaccines to neutralize the safety concerns of autoimmune responses, allergic reactions and other pathological changes. Another area for concern is the induction of limited immunogenic response due to their inability to spread and amplify in vivo in non-human primates as compared to mice [40]. Another disadvantage is that genomic integration of DNA vaccinations into the host chromosome can result in mutagenesis and cancer [43]. To counteract the negative effects of DNA vaccinations, some methods involve the use of immune modulatory adjuvants. Co-delivery of plasmids encoding cytokines, chemokines, and co-stimulatory molecules with DNA plasmids improves the immunogenicity of otherwise weakly immunogenic antigens and produces tiny proteins important for immune cell communication. [44,45]. Also, the use nanocarriers to package the DNA plasmid prevents the endo/lysosomal degradation [46]. The application of jet injectors allows it to be both safe and easy to administer [47].

Types of DNA vaccines

2.3.2.1 ZyCoV-D COVID-19 vaccine

On 20 August 2021, Drug Controller General of India (DCGI) approved the emergency use authorization (EUA) of ZyCoV-D which is a plasmid DNA vaccine. It consists of 3 doses given on day zero, 28 and 56. It's a needle-free vaccine that's delivered by a needle-free applicator called a Pharma Jet, which ensures a painless intradermal delivery of the vaccine. This vaccine is made up of plasmid DNA that contains the SARS-COV-2 spike-S gene together with a signal peptide gene. Phase I/II of the study began in July 2020, with the goal of determining the effectiveness of ZyCoV-D in fighting SARS-COV-2 in healthy persons aged 18 to 55. Non-randomized, open-label dosage escalation was used to recruit and assign participants. They were divided into 4 treatment arms. The 1st treatment arm consisted of 12 participants receiving 1mg dose via needle. the 2nd treatment arm consisted of 12 participants receiving 1mg dose via needle free injection system (NFIS).The 3rd treatment arm consisted of 12 participants receiving 2mg dose via needle. The 4th treatment arm consisted of 12 participants receiving 2mg dose via NFIS. Participants were ~~were~~ vaccinated intradermally with 3 doses on day zero, 28 and 56 and followed up till day 84 when the study was ended. Participants were placed in the intensive observation unit for 24hrs after the 1st dose and for a duration of 4hrs after the 2nd and 3rd dose. Overall, all participants reported of about 1 adverse event (AE). Most of the AE reported were after the 1st dose. ZyCoV-D was found to generate both humoral and cellular responses in all participants. Humoral responses were found to be lower in participants who received 1mg in both treatment arms. A double-blind placebo-controlled Phase 3 involving about 28000 is currently ongoing and assist in the evaluation of the vaccine efficacy. ZyCoV-D is best stored at 2-8 degrees Celsius; however, it has shown good stability at 25 degrees Celsius for at least three months. The vaccine's room-temperature stability will aid in seamless shipping and storage, as well as reduce any cold-chain breakdown issues that could result in vaccine waste. [48].

2 Other DNA Vaccine candidates

Inovio Pharmaceuticals/International Vaccine Institute (INO-4800) is a prophylactic DNA vaccine used against SARS-CoV-2, using codon optimized S protein sequence. An

immunological response within 7 days of vaccination was seen. This was suggested by functional antibody and T cell responding to it. Trials are being undergone to find out the immune profile, tolerability, and safety of the vaccine in healthy human individuals. Osaka University/ AnGes/ Takara Bio (AG0301-COVID19), Consortium (GX-19), Symvivo (bacTLR-Spike), Providence Health and Services (CORVax12) are still undergoing trials to confirm the effectiveness for all safety parameters.

2.3.3 Viral Vector Vaccines

Viral vector vaccines are very different from conventional vaccines as instead of presenting an antigen, it uses the host own immune cells to produce the antigen. This is done by using a modified virus or vector to deliver a certain specific genetic code for the necessary antigen, with/in regardsto COVID-19 it is the viral surface spike. The role of the viral vector is to deliver the genetic instructions to the host cells via the viral vectors containing nucleic acids to produce large amounts of antigen that the vector codes for. This mimics the action of a natural infection/antigen presentation from a natural infection to which an immune response (antibodies) is produced. The virus itself is harmless and does not develop any disease only acts as vector. There are two main types of viral vector vaccines, non-replicating vector vaccine and replicating vector vaccine. Non replicating vector vaccines are not able to make new viral particles as they are only capable of coding for antigen production. Replicating vector vaccines are capable of producing new viral particles in the host cells that they infect and also code for antigen production. Once the vector is injected into the host cells, they infect the host cell and begin the production of antigen. The immune cells detect these synthesized antigens, to which an immunological response is initiated [49]. This high level and extended period of antigenic protein expression provides a platform for prophylactic use as the mechanism of these vaccines cause the cytotoxic T cells to be primed and triggered leading to the complete destruction of virus infected cells [50]. One major drawback of this approach is that individuals previously exposed to the virus vector, have a reduced effectiveness from the vaccine as they have B cells that code for the virus vector. This sort of anti-vector immunity makes it cumbersome to deliver a second dose of vaccine unless a different viral vector is used.

Types of Viral Vector vaccines

2.3.3.1 Oxford-AstraZenaca COVID-19 vaccine

AstraZeneca-Oxford (AZD1222) The UK Medicines and Healthcare Products Regulatory Agency (MHRA) licensed the COVID-19 vaccine for use in the UK vaccination programme on December 30, 2020. Covishield and Vaxzevria are two brand names for it. It's called ChAdOx1 and it's a modified non-replicating chimpanzee adenovirus vector vaccine that was originally developed as a MERS vaccine. The vaccination from Oxford-Astra Zenaca is given in two doses (0.5mL each). The vaccination is given intramuscularly in two doses, eight to twelve weeks apart. In both the UK and Brazil, a major, randomized, single-blind, controlled Phase III clinical trial including over 11000 people aged 18 to 55 years old was completed. The results of this research, which included a four-month follow-up period and two dosages, showed that it was 90 percent effective against symptomatic COVID-19 disease [51,52]. However, in the second study, which took place in Brazil, the effectiveness dropped to 62%. There were no significant adverse events or deaths connected with the Oxford-Astra Zenaca (AZD1222) COVID-19 vaccination therapy. Primary investigations reported that the vaccine demonstrated a good immunological response which consisted of increased antibodies and T cell responses. The only minor side effects being fatigue and headache. Oxford-AstraZenaca (AZD1222) COVID-19 vaccine can be stored in routine refrigerated cold chain which makes it affordable in many countries [53,54].

2.3.3.2 Gamaleya Research Institute (Gam-COVID-Vac/Sputnik V)

The COVID-19 vaccine developed by Gamaleya Research Institute (Gam-COVID-Vac) was licenced by the Russian Federation's Ministry of Health (MHRF) in August 2020 [55] under an emergency use of authorisation (EUA) [56]. It's known as **Sputnik V**, with **the V signifying for victory over COVID-19**. It's a mixed vaccine made up of recombinant rAD26 and rAD5 viral vectors (origin of the vector as stated for astra-zeneca). The **Sputnik V vaccination is given in two doses (0.5ml) separated by 21 days**. The MHRF gave its permission for the vaccine's usage even before Phase III trials were completed. According to the interim study, Sputnik V had a 91.4 percent efficacy in the 18794 volunteers in Russia 7 days after taking the second dose. Following these findings, more than 50 countries requested 1.2 billion vaccination doses [57].

Headache, heat, soreness at the injection site, and asthenia are the only adverse effects. There were no major side effects or deaths connected with the use of the Sputnik V vaccination during the study. Gam-COVID-Vac has a formulation comparable to smallpox vaccine and can be stored between 2-8 degrees Celsius, making it easier to deliver vaccines to remote locations with reduced chance of vaccine spoiling.

3 Cansino Biological Inc./Beijing Institute of Bio-technology (Ad5-nCov-19/Covidecia)

Cansino Biological Inc./Beijing Institute of Bio-technology (Ad5-nCov-19/Covidecia) is a non-replicative recombinant adenovirus vector type 5 (Ad5) constructed by Microbix system using Adamax [58]. Phase 2 trial was conducted in April 2021, 508 participants were selected for a randomised, double blind, placebo-controlled trial, the mean age being 39.7 years. An injection of either 1×10^{11} or 5×10^{10} viral particle or placebo was given to the participants intramuscularly (253 assigned to 1×10^{11} vp, 129 assigned to 5×10^{10} vp and 126 placebo). Post immunization, the participants were monitored for a period of 30mins and then followed up for any injection site reaction or adverse reaction and any adverse events within 28days post vaccination. Out of the 508 participants, 266 were found to have high preexisting immunity and 242 participants had low preexisting immunity. Both vaccine doses caused significant antibody responses to live SARS-CoV-2. 95% of the participants showed either cellular or humoral immunity by the end of 28days after vaccination. The most common side effect was found to be pain at injection site seen in 228 participants. The most common adverse effect was grade 3 fever seen in 21 participants. On the whole, 196 participants in 1×10^{11} vp dose group, 98 participants in 5×10^{10} vp dose group and 61 in placebo group had encountered at least one or more adverse event by the 28th day of vaccination. In this particular study, most of the reactions post vaccination was found to be moderate or mild. The safety profile of the vaccine candidate is relatively good and in line with the phase 1 trail [59].

4 Janssen Pharmaceuticals Companies (Ad26Cov2-S) COVID-19 vaccine

Janssen Pharmaceuticals Companies (Ad26Cov2-S) use Ad26 vector viral technology to develop the Ad26Cov2-S vaccine which encodes for stabilized S immunogen and two proline stabilizing mutation. In the month of Feb 2021, US FDA approved the use of Janssen COVID-19 vaccine for public use under EUA for individuals 18years and older. The US FDA has reviewed the safety and efficacy based on the ongoing phase 3 trial which had more than 43000 participants

over the age of 18 that were randomized to receive either the Janssen COVID-19 vaccine or saline control as placebo. Follow-up was done up to 8 weeks post vaccination and there were no safety concerns highlighted by the FDA's review. Efficacy was found to be 66.9% in seronegative individuals and 66.1% in individuals who had unknown serostatus in preventing moderate to severe COVID-19 infection. The most common side effect was found to be pain at the injection site, headache and fatigue. The vaccine was 77% effective in preventing severe/critical COVID-19 which occurred 14 days after vaccination and 85% effectiveness in the same individuals after 28 days after vaccination. It has good immunological response and was approved by the European Commission by March 2021. It has **single dose** (0.5ml). Vaccine Efficacy against hospitalization was found to be 71% as compared to mRNA vaccines Moderna and Pfizer that have 93% and 88% respectively. This was based on a study based on the serum antibody levels to the SARS-CoV-2 among about 100 healthy volunteers who were enrolled from 3 different hospitals for a period of 2-6 weeks after the vaccination of the above mentioned 3 vaccines. The vaccine efficacy was based on logistic regression. There were also lower post vaccination anti SARS-CoV-2 antibody levels as compared to the mRNA vaccines. This suggests that both mRNA vaccines provide greater protection than the single dose Janssen viral vector vaccine.

2.4 Protein based vaccine

The design of protein subunit vaccine is based on the isolated, synthetic, recombinant, antigenic protein base subunits with a short antigen segment [60]. Protein subunit-based vaccines differ from other conventional vaccines as rather than injecting the entire pathogen to initiate an immune response, a protein subunit containing purified pieces of the specific pathogen structures are inserted. These pieces have been identified for their **ability to stimulate the immune cells similar to that of a pathogen. They are generally considered safe as they are not capable of causing disease. There are different types of such as protein subunit vaccines containing specific proteins from the bacterial/viral pathogens, polysaccharide vaccines that contains certain chains of sugar molecules present in cell walls of specific bacteria or conjugate vaccines that binds to a polysaccharide chain of a carrier protein thereby stimulating the immune response [61].** With regards to COVID-19, protein subunit vaccines containing specific SARS-CoV2 proteins are the only applicable vaccine type that contain specific proteins of the viral pathogens. The benefits of

using this platform are that it is suitable for immuno-compromised individuals and the lack of live viral components helps eliminate the risk of an actual disease (COVID-19) being triggered. The downside being the determination of best antigen combination is time consuming and requires the use of adjuvants booster shots due to low immunogenicity.

2.4.1 Protein subunit vaccines

EpiVacCorona is a protein-based peptide vaccine developed to fight against COVID-19. The protein is the combined product of viral nucleocapsid protein and MBP bacterial protein. In recent studies, the vaccine was effective in causing the production of protective antibodies. The Russian government authorized the use of EpiVac Corona for emergency use in October 2020. It is delivered intramuscularly and has aluminum hydroxide as an additional immunological adjuvant to boost antibody production. ZF2001 also known commercially as ZIFIVAX is an adjuvanted protein subunit vaccine developed by the Institute of Microbiology at Chinese Academy of Sciences in association with Anhui Zhifei Longcom. It was first approved by Uzbekistan on March 2021. There are more studies that are required to better evaluate the efficiency of the vaccine for public use.

2.5 Whole virus-based vaccine

Whole virus vaccine make use of a weakened or attenuated /deactivated form of the virus to induce a disease like state and trigger immunity against it. There are two types of whole virus vaccine, live attenuated and inactivated vaccine. Live attenuated vaccine makes use of a weakened form of the vaccine that grows and multiplies but does not cause any disease. In the case of inactivated vaccine, the genetic material of virus present in the vaccine is destroyed by chemicals or radiation so that it does not infect the host cells and replicates yet still induce an immunogenic response without causing disease.

2.5.1 Live attenuated vaccine

The live attenuated vaccines are created from viruses that have been debilitated under laboratory conditions through heat, chemicals, and radiation. When injected to the host, the vaccine will infect host cells and duplicate but does not causedisease or causes a slight reaction. This makes it unsuitable for immuno-compromised individuals and pregnant women as a weakened virus can

still trigger the disease to a very bad state. In some sporadic cases, the live attenuated vaccine can return to its infective form, causing disease in the vaccinated individual.

As mentioned earlier, the live attenuated vaccines are lesser versions of natural pathogens. Therefore, the immune system of the host responds in the similar way it would react to any other foreign invader. This initiates the body to ready its defense mechanism by mobilizing helper T cells which is responsible for anti-body production by stimulating B cells, killer T cells which recognize infected cells and destroys them and present their antigen to B cells which produces antibody targeting pathogens. This kind of immunogenic response continues until the virus is completely erased from the system. This shows a great advantage of live attenuated vaccines as they trigger a very strong immunogenic response which is as good as being exposed and acquiring immunity from the live pathogen itself.

2.5.2 Inactivated virus vaccine

Inactivated virus vaccines carry Parts of disease carrying virus or the genetic material that is destroyed by ~~destroyed by~~ heat, chemicals or radiation in laboratory conditions. This accounts for the better safety and stability as compared to live attenuated vaccines making it safer to be administered to immuno-compromised individuals. This is because the viral genetic material is degraded and deactivated, yet it still contains many proteins that our immune system will recognize and respond to. As inactivated virus vaccines are unable to infect cells, they rouse an antibody-mediated response causing the response to be much weaker and short lived as compared to live attenuated vaccines. Adjuvants and booster doses can be administered along with the vaccine to address this issue and illicit a desired response.

2.5.2.1 Sinovac (CoronaVac) COVID-19 vaccine

Sinovac (Coronavac) COVID-19 is an inactivated vaccine was approved by the Chinese authorities on August 2020 for emergency use, particularly in high-risk individuals such as the front-line healthcare workers. It is commercially sold under the name of Coronavac. [62,63]. It is very similar to Covaxin (Bharath Biotech) in terms of the technology used to develop the vaccine. The vaccination of Cornovac is divided into 2 doses (0.5ml each). The vaccine is administered intramuscularly and the given 4 weeks apart. In the phase III trials conducted in

Brazil, 12,396 participants took part and were divided into two main groups, vaccine group and placebo group [64]. Based on the interim study, Coronavac showed an efficacy of 51% against all symptomatic cases, 84% against cases that required additional medical treatment and more than 95% against severe or hospitalized individuals. Similarly, a phase III trial report in Turkey showed an efficacy of 84%. Most of the reported adverse effects were found to be of Grade 1 nature. This was mainly concerning the placebo group individuals. Coronavac was found to be safe and induced both cell-mediated and humoral immunity. The side effects were minimal and mostly local, limited to pain in the site of injection [65, 66]. Coronavac can be transported and refrigerated at 2-8 C like that of flu vaccines. Coronavac has been reported to remain stable up to 3 years storage which is very helpful for regions where the use of cold-chain is not feasible due to its cost, making Coronavac very cost-effective in many developing/underdeveloped countries.

2.5.2.2 Bharat Biotech (Covaxin) COVID-19 vaccine

Bharat Biotech along with Indian Council of Medical Research (ICMR) developed Covaxin and was approved by the Central Drugs and Standards Committee (CDSCO) on January 2021. Its mechanism is similar to Sinovac, it uses an infective SARS-CoV-2 virus that is modified to make it unable to replicate. In phase I trials, safety and immunogenicity was evaluated and notable elevated antibody response was identified. All participants had cytokine responses to BBV152. In BBV152 elicited antibody binding and neutralising antibody responses similar to other SARS-CoV-2 inactivated vaccine candidates in phase 1 studies. There were demonstrable humoral and cell-mediated responses to SARS-CoV-2 3 months after the second injection. The neutralizing antibodies were similar to those found in a panel of convalescent serum samples, confirming Moderna's findings. Improved immune response and tolerable safety limits were found in phase II trials. Clinical efficacy was shown to be 81 percent in interim efficacy data. BBV152 boosted the number of antigen-specific CD4 T cells in the body. Pain at the injection site was the most prevalent adverse event, followed by fever, headache, and exhaustion [67]. Despite the vaccine's many benefits, the absence of evidence that it is effective against new SARS-CoV-2 strains is the only drawback. 2 doses (0.5ml) are given intramuscularly with a duration of 28 days apart. It does not require sub-zero temperature storage and is stable between 2 and 8 degrees which ordinary refrigeration can provide. Due to the emergency approval of the

vaccine before the completion of Phase III trials, there has been some widespread criticism in the medical community.

2.6 Others

Virus-like particles (VLPs) are multiprotein supramolecular preparations having molecular structures that are similar to those of viruses. They are engineered to express authentic virus surface proteins or nucleic acid sequences without the risk of infection or reproduction. Because of their adaptable immunological properties, including as appropriate size and stimulation of innate and adaptive immune responses, they are a useful platform for vaccine development. VLP vaccines target B lymphocytes, eliciting a strong antibody response that aids in the activation of helper T cells and MHC class II molecules via antigen-presenting cells (APCs) [68, 69]. A VLP-based vaccination against SARS-CoV-2 was created by Medicago Inc, a Canadian pharmaceutical company, utilising a plant-based technique in which a lab-made synthetic gene carrying a component of the virus was transmitted to the tobacco plant via a bacterial vector. Strong cellular and humoral responses have been shown in phase II and III trials.

2.7 Adjuvant administration

Adjuvants are chemicals that assist the body's immune system respond more effectively. They aid in the activation of pattern recognition receptors (PRR) on adaptive immune cells, which can promote a variety of immunological responses depending on the kind of PRR. As a result, adding an effective and well-designed adjuvant to a vaccine can dramatically boost its efficacy [70-72]. Adjuvants like TL3, 7, 8, RIG-I, PKR, OAS, and MDA5 have been demonstrated to increase innate immune system activation, generation of proinflammatory cytokines, and type 1 interferon activation in mRNA vaccines. But, the activation of these receptors can cause a natural anti-viral mechanism which is harmful for the translation of mRNA. This helps to balance the activation of innate immunity through mRNA and the translation of mRNA. Because many DNA plasmids contain unmethylated CpG patterns, DNA vaccines have a lot of promise in combination with adjuvants [73]. CpG motifs have been purposefully inserted to DNA plasmids in order to improve DNA vaccination efficacy by enhancing the antigen specific T cell mediated immune response [74]. Another area that merits additional investigation is the use of adjuvants in protein-based vaccines, which has enormous potential to increase immunological responses in immunologically sensitive populations, particularly infants and the elderly [75,76].

3. Vaccine hesitation

The delay, refusal or perusal of vaccine with doubts with regards to the usefulness, effectiveness and safety is termed as vaccine hesitancy [77]. Vaccine hesitancy has been classified as one of the top 10 most important health threats by the WHO [78]. A large proportion of the population are not confident about the idea of vaccination despite high risks associated with pandemic. A survey in France stated that 25% of the people across 5 different surveys stated that they would refuse the idea of getting vaccinated if it was available as they have safety concern regarding a vaccine that is developed hastily for emergency use [79]. The fear of adverse reactions is the main determining factor for people to incline towards acceptance or disapproval of vaccination. The determinants of vaccine hesitancy vary between countries and are found to be multiple and complex. Among them, there three very significant determinants. These include confidence, complacency due to the perceived usefulness of the vaccine and lastly convenience due to the challenges in access to health services [80].

Confidence is built on public trust on healthcare professionals, healthcare system, scientific research, and the socio-political scenario of the country. The greater the trust in these fields, the greater the confidence and acceptance of the vaccines produced. Healthcare professionals play an important role in boosting confidence in vaccines as their recommendation or professional advice are key to acceptance of vaccines by the public [80]. In certain regions of the world, healthcare professionals are also equally affected by vaccine hesitancy which is generally due to lack of confidence in the health officials and persistent bureaucracy. As health professionals are not experts in the field of vaccination, their uncertainty might foster doubts in normal people and push them towards adopting a negative attitude towards vaccination of preventable disease [81].

Vaccine hesitancy is also attributed with the crisis of confidence in science and technology, this is due to the incomplete information which are conditional, partial, provisional and in certain situations contradictory [82]. The knowledge of SARS-CoV-2 and COVID-19 pandemic has been affected by balkanization that is scrutinized by every accumulating new information. The leap of faith or reluctant trust as mentioned by sociologist Anthony Giddens is very much necessary not only by the public but equally by healthcare professionals [82,83]. This reluctant trust is the belief that despite uncertainty in benefits and risks, people still recommend the usage of vaccines. This kind of trust is very brittle and targeted by anti-vaccine activist who through

criticism and misinformation induce emotional reactions and sow doubt in the minds of the general public [84].

As the thought of vaccine hesitancy persists, the balance between persuasive and coercive measures are in constant debate. Most countries have adopted the idea of coerciveness by making vaccination mandatory and aggressively advertising its benefits. This does not nip the root cause of vaccine hesitancy but tends to trigger greater resistance as it instigates the issue of state intruding into individual freedom of choice. [85].

The identification of effective measure and public education at both individual and state level can restore the trust of the public in vaccination and is a key factor that must be pursued by scientific researchers. The facilitation of knowledge sharing and proper explanation of adverse reactions and their possibilities will help improve acceptance among people. The acceptance of vaccination and elimination of vaccine hesitancy is the road towards protecting everyone from possible existing and future pathogen outbreaks.

4. Effect of vaccines on Delta variant of SARS-CoV-2

The use of COVID-19 vaccines has been used for about 9 months in the UK. Real world data has shown the effectiveness of high-level protection against the disease based on the hospitalization and mortality index. There are various concerns with regards to the effectiveness of these vaccines against the delta variant, this has aroused doubts in the hearts of normal people to its high infective rate. A recent test was conducted between the period of December 2020 and August 2021 to estimate the vaccine efficacy. The inclusion criteria included individuals who had symptoms and people who underwent the test within 10 days of the onset of the symptoms. People who had previously tested positive for the virus before the vaccination were excluded from the study. The study revealed that the vaccine efficacy was waning off over the Delta variant. It was reported that vaccine efficacy was found to be 50% in Oxford AstraZeneca, and 70% in Pfizer after 10 weeks. Data for Moderna was not available at the time of the release of data. Vaccine efficacy was less waning in terms of hospitalization, Pfizer was very effective showcasing 95% vaccine efficacy and AstraZeneca showing 80% which was slightly waning. Very similar to the hospitalization data, mortality had very minimal waning and follow-up study past 20 weeks is undergoing. Based on stratification of age group, Oxford AstraZeneca had significant waning in older age groups (>65 years). Also, waning is much greater in clinically

vulnerable group individuals such as immunocompromised people in both Oxford AstraZeneca and Pfizer [86]. On the whole, the Delta variant is a very big risk to the society as the older population seems to be affected. This creates doubt in prospective individuals who are intending to get vaccinated due to the fear of lack of vaccine efficacy. More studies have to be done to learn and analyze more about the Delta variant and its waning effect across all vaccines. The need for a universal vaccine that is capable of combating the rapidly mutating virus.

5. Conclusion

In this monograph, the various types of COVID-19 vaccines and the one that have been sold commercially and approved by many countries have been discussed in detail. In general, the goal of vaccination is to artificially stimulate the immune system to provide necessary antibodies to prevent COVID-19 infection. The vaccines that have been approved by various governments is based on the needs, affordability, and ability to be stored in a cold chain or refrigerated storage. The adverse drug reaction immediately after the vaccination and up to 4 weeks after vaccination have been found to be similar in most vaccines, that include pain at the site of injection, mild malaise, body pain, etc. There have been many other platforms that are undergoing research aimed at bringing out vaccines that are most appropriate and effective to combat the current crisis. As, the spread of COVID-19 has been rampant and the rate of mutations increasing, there are plenty of studies that are evaluating the effectiveness of the currently approved vaccines against the various variants. The act of proceeding to approve vaccines before Phase III trials, has installed doubt and vaccine hesitancy. This further impedes the process of vaccination thereby slowing the chance of the entire world getting vaccinated. The only way to protect oneself from being seriously ill and hospitalized is by following social distancing and getting vaccinated as early as possible. Despite, the lack of cold chain storage in certain regions, there are a variety of vaccines available to help negotiate this obstacle. More research and efforts will be poured into COVID-19 pandemic as we work towards a universal vaccine that will be effective against all the variants of SARS-CoV-2 and help eradicate the virus from the face of the earth.

References:

1. Pasteur L (1880) De l'attenuation du virus du choléra des poules. C R Acad Sci Paris 91:673–680.
2. Theiler M, Smith HH (1937) Effect of prolonged cultivation invitro upon pathogenicity of yellow fever. J Exp Med 65(6):767–786.
3. Hilleman MR, McAleer WJ, Buynak EB, McLean AA (1983) The preparation and safety of hepatitis B vaccine. J Infect 7(Suppl 1):3–8.
4. Draft Landscape of COVID-19 Candidate Vaccines, <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines> 2021, Accessed date: 24 September 2021.
5. R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet Lond. Engl. 395 (2020) 565–574, [https://doi.org/10.1016/S01406736\(20\)30251-8](https://doi.org/10.1016/S01406736(20)30251-8).
6. Dhama K, Sharun K, Tiwari R, et al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Hum Vaccin 2020;16:1232e1238
7. C. Rueckert, C.A. Guzmán, Vaccines: from empirical development to rational design, PLoS Pathog. 8 (2012) <https://doi.org/10.1371/journal.ppat.1003001>.
8. Messina NL, Zimmermann P, Curtis N. The impact of vaccines on heterologous adaptive immunity. Clin Microbiol Infect. 2019 Dec;25(12):1484-1493. doi: 10.1016/j.cmi.2019.02.016. Epub 2019 Feb 20. PMID: 30797062.
9. WHO Coronavirus Disease (COVID-19) Dashboard, <https://covid19.who.int> 2020, Accessed date: 29 June 2021.
10. Del Rio C, Collins LF, Malani P. Long-term health consequences of COVID-19. JAMA. 2020. <https://doi.org/10.1001/jama.2020.19719>.
11. E. Petersen, M. Koopmans, U. Go, D.H. Hamer, N. Petrosillo, F. Castelli, et al., Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics, Lancet Infect. Dis. 20 (2020) e238–e244, [https://doi.org/10.1016/S1473-3099\(20\)30484-9](https://doi.org/10.1016/S1473-3099(20)30484-9).
12. . Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C,

- Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early transmission dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med.* 2020;382(13):1199–207.
13. Akin L, Gözel MG. Understanding dynamics of pandemics. *Turk J Med Sci.* 2020;50(SI-1):515-519. Published 2020 Apr 21. doi:10.3906/sag-2004-133
 14. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic transmission, the Achilles' Heel of current strategies to control covid-19. *N Engl J Med.* 2020;382(22):2158–60.
 15. A. Mubarak, W. Alturaiki, M.G. Hemida, Middle East Respiratory Syndrome Coronavirus (MERS-CoV): infection, immunological response, and vaccine development, *J. Immunol. Res.* 2019 (2019), e6491738. <https://doi.org/10.1155/2019/6491738>.
 16. X. Xu, X. Gao, Immunological responses against SARS-coronavirus infection in humans, *Cell. Mol. Immunol.* 1 (2004) 119–122.
 17. K.S. Corbett, B. Flynn, K.E. Foulds, J.R. Francica, S. Boyoglu-Barnum, A.P. Werner, B. Flach, S. O'Connell, K.W. Bock, M. Minai, B.M. Nagata, H. Andersen, D.R. Martinez, A.T. Noe, N. Douek, M.M. Donaldson, N.N. Nji, G.S. Alvarado, D.K. Edwards, D.R. Flebbe, E. Lamb, N.A. Doria-Rose, B.C. Lin, M.K. Louder, S. O'Dell, S.D. Schmidt, E. Phung, L.A. Chang, C. Yap, J.M. Todd, L. Pessaint, A. Van Ry, S. Browne, J. Greenhouse, T. Putman-Taylor, A. Strasbaugh, T.A. Campbell, A. Cook, A. Dodson, K. Steingrebe, W. Shi, Y. Zhang, O.M. Abiona, L. Wang, A. Pegu, E.S. Yang, K. Leung, T. Zhou, I.T. Teng, A. Widge, I. Gordon, L. Novik, R.A. Gillespie, R.J. Loomis, J.I. Moliva, G. Stewart-Jones, S. Himansu, W.P. Kong, M.C. Nason, K.M. Morabito, T.J. Ruckwardt, J.E. Ledgerwood, M.R. Gaudinski, P.D. Kwong, J.R. Mascola, A. Carfi, M.G. Lewis, R.S. Baric, A. McDermott, I.N. Moore, N.J. Sullivan, M. Roederer, R.A. Seder, B.S. Graham, Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in Nonhuman Primates, *N. Engl. J. Med.* 383 (2020) 1544–1555.
 18. Lisa A. Jackson, Evan J. Anderson, Nadine G. Rouphael, Paul C. Roberts, Mamodikoe Makhene, Rhea N. Coler, Michele P. McCullough, James D. Chappell, Mark R. Denison, Laura J. Stevens, Andrea J. Pruijssers, Adrian McDermott, Britta Flach, Nicole A. Doria-Rose, Kizzmekia S. Corbett, Kaitlyn M. Morabito, Sijy O'Dell, Stephen D. Schmidt, Phillip A. Swanson, Marcelino Padilla, John R. Mascola,

- ~~Kathleen M. Neuzil, Hamilton Bennett, Wellington Sun, Etza Peters, Mat Makowski, Jim Albert, Kaitlyn Cross, Wendy Buchanan, Rhonda Pikaart Tautges, Julie E. Ledgerwood, Barney S. Graham, John H. Beigel, An mRNA vaccine against SARSCoV-2 - preliminary report, N. Engl. J. Med. 383 (2020) 1920–1931.~~
19. M.J. Mulligan, K.E. Lyke, N. Kitchin, J. Absalon, A. Gurtman, S.P. Lockhart, K. Neuzil, V. Raabe, R. Bailey, K.A.J.M. Swanson, Phase 1/2 study to describe the safety and immunogenicity of a COVID-19 RNA vaccine candidate (BNT162b1) in adults 18 to 55 years of age: interim report, *Nature* 586 (2020) 589–593.
 20. N.-N. Zhang, X.-F. Li, Y.-Q. Deng, H. Zhao, Y.-J. Huang, G. Yang, W.-J. Huang, P. Gao, C. Zhou, R.-R.J.C. Zhang, A thermostable mRNA vaccine against COVID-19, *Cell* 182(2020) 1271–1283.e16.
 21. U. Sahin, A. Muik, E. Derhovanessian, I. Vogler, L.M. Kranz, M. Vormehr, A. Baum, K. Pascal, J. Quandt, D.J.M. Maurus, Concurrent human antibody and TH1 type T-cell responses elicited by a COVID-19 RNA vaccine, *MedRxiv* (2020) <https://doi.org/10.1101/2020.07.17.20140533>.
 22. K.A. Hajj, K.A. Whitehead, Tools for translation: non-viral materials for therapeutic mRNA delivery, *Nat. Rev. Mater.* 2 (2017) 1–17.
 23. N. Pardi, M.J. Hogan, F.W. Porter, D. Weissman, mRNA vaccines - a new era in vaccinology, *Nat. Rev. Drug Discov.* 17 (2018) 261–279.
 24. N. Pardi, H. Muramatsu, D. Weissman, K. Kariko, In vitro transcription of long RNA containing modified nucleosides, *Methods Mol. Biol.* 969 (2013) 29–42.
 25. N. Pardi, M.J. Hogan, R.S. Pelc, H. Muramatsu, H. Andersen, C.R. DeMaso, K.A. Dowd, L.L. Sutherland, R.M. Scarce, R. Parks, W. Wagner, A. Granados, J. Greenhouse, M. Walker, E. Willis, J.S. Yu, C.E. McGee, G.D. Sempowski, B.L. Mui, Y.K. Tam, Y.J. Huang, D. Vanlandingham, V.M. Holmes, H. Balachandran, S. Sahu, M. Lifton, S. Higgs, S.E. Hensley, T.D. Madden, M.J. Hope, K. Kariko, S. Santra, B.S. Graham, M.G. Lewis, T.C. Pierson, B.F. Haynes, D. Weissman, Zika virus protection by a single low-dose nucleoside-modified mRNA vaccination, *Nature* 543 (2017) 248–251.
 26. B. Petsch, M. Schnee, A.B. Vogel, E. Lange, B. Hoffmann, D. Voss, T. Schlake, A. Thess, K.J. Kallen, L. Stitz, T. Kramps, Protective efficacy of in vitro synthesized,

- specific mRNA vaccines against influenza A virus infection, *Nat. Biotechnol.* 30 (2012) 1210–1216.
27. A.M. Reichmuth, M.A. Oberli, A. Jaklenec, R. Langer, D. Blankschtein, mRNA vaccine delivery using lipid nanoparticles, *Ther. Deliv.* 7 (2016) 319–334.
 28. Lisa A. Jackson, Evan J. Anderson, Nadine G. Roupheal, Paul C. Roberts, Mamodikoe Makhene, Rhea N. Coler, Michele P. McCullough, James D. Chappell, Mark R. Denison, Laura J. Stevens, Andrea J. Pruijssers, Adrian McDermott, Britta Flach, Nicole A. Doria-Rose, Kizzmekia S. Corbett, Kaitlyn M. Morabito, Sijy O'Dell, Stephen D. Schmidt, Phillip A. Swanson, Marcelino Padilla, John R. Mascola, Kathleen M. Neuzil, Hamilton Bennett, Wellington Sun, Etza Peters, Mat Makowski, Jim Albert, Kaitlyn Cross, Wendy Buchanan, Rhonda Pikaart-Tautges, Julie E. Ledgerwood, Barney S. Graham, John H. Beigel, An mRNA vaccine against SARS-CoV-2 - preliminary report, *N. Engl. J. Med.* 383 (2020) 1920–1931.
 29. M.J. Mulligan, K.E. Lyke, N. Kitchin, J. Absalon, A. Gurtman, S.P. Lockhart, K. Neuzil, V. Raabe, R. Bailey, K.A.J.M. Swanson, Phase 1/2 study to describe the safety and immunogenicity of a COVID-19 RNA vaccine candidate (BNT162b1) in adults 18 to 55 years of age: interim report, *Nature* 586 (2020) 589–593.
 30. Food and Drug Administration. Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. <https://www.fda.gov/emergency-preparedness-and-response/coronavirusdisease-2019-covid-19/pfizer-biontech-covid-19-vaccine>.
 31. Vaccines and Related Biological Products Advisory Committee. Vaccines and Related Biological Products Advisory Committee December 10, 2020, meeting: sponsor briefing document. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. <https://www.fda.gov/media/144246/download>
 32. Vaccines and Related Biological Products Advisory Committee. Vaccines and Related Biological Products Advisory Committee December 10, 2020, meeting: FDA briefing document. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. <https://www.fda.gov/media/144245/download>
 33. Thompson MG, Burgess JL, Naleway AL, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-

CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:495–500. DOI: <http://dx.doi.org/10.15585/mmwr.mm7013e3>external icon.

34. Food and Drug Administration. Moderna COVID-19 vaccine Emergency Use Authorization. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/Moderna-covid-19-vaccine>
35. Vaccines and Related Biological Products Advisory Committee. Vaccines and Related Biological Products Advisory Committee December 17, 2020, meeting: sponsor briefing document. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. <https://www.fda.gov/media/144452/download>
36. Vaccines and Related Biological Products Advisory Committee. Vaccines and Related Biological Products Advisory Committee December 17, 2020, meeting: sponsor briefing document addendum. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. <https://www.fda.gov/media/144453/download>
37. Vaccines and Related Biological Products Advisory Committee. Vaccines and Related Biological Products Advisory Committee December 17, 2020, meeting: FDA briefing document. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. <https://www.fda.gov/media/144434/download>
38. Vaccines and Related Biological Products Advisory Committee December 17, 2020 meeting presentation: FDA review of efficacy and safety of Moderna COVID-19 vaccine EUA. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. <https://www.fda.gov/media/144585/download>
39. McClung N, Chamberland M, Kinlaw K, et al. The Advisory Committee on Immunization Practices' ethical principles for allocating initial supplies of COVID-19 vaccine—United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1782–6. PMID:33237895 <https://doi.org/10.15585/mmwr.mm6947e3>
40. Li, N. Petrovsky, Molecular mechanisms for enhanced DNA vaccine immunogenicity, *Expert. Rev. Vaccines* 15 (2016) 313–329.

41. M.A. Kutzler, D.B. Weiner, DNA vaccines: ready for prime time? *Nat. Rev. Genet.* 9 (2008) 776–788.
42. Rauch S, Jasny E, Schmidt KE, Petsch B. New vaccine technologies to combat outbreak situations. *Front Immunol.* 2018;9:1963.
43. Y. Cai, S. Rodriguez, H. Hebel, DNA vaccine manufacture: scale and quality, *Expert.Rev. Vaccines* 8 (2009) 1277–1291.
44. C.R. Middaugh, R.K. Evans, D.L. Montgomery, D.R. Casimiro, Analysis of plasmid DNA from a pharmaceutical perspective, *J. Pharm. Sci.* 87 (1998) 130–146.
45. R. Garg, M. Kaur, A. Saxena, R. Prasad, R. Bhatnagar, Alum adjuvanted rabies DNA vaccine confers 80% protection against lethal 50 LD, *Mol. Immunol.* 85 (2017) 166–173.
46. H. Hemmi, O. Takeuchi, T. Kawai, T. Kaisho, S. Sato, H. Sanjo, M. Matsumoto, K. Hoshino, H. Wagner, K. Takeda, S. Akira, A toll-like receptor recognizes bacterial DNA, *Nature* 408 (2000) 740–745.
47. D. Hobernik, M. Bros, DNA vaccines-how far from clinical use? *Int. J. Mol. Sci.* 19(2018).
48. J.B. Ulmer, J.J. Donnelly, S.E. Parker, G.H. Rhodes, P.L. Felgner, V.J. Dwarki, S.H. Gromkowski, R.R. Deck, C.M. DeWitt, A. Friedman, Heterologous protection against influenza by injection of DNA encoding a viral protein, *Science* 259 (1993) 1745–1749.
- 47a. Momin, Taufik et al. “Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): Results of an open-label, non-randomized phase I part of phase I/II clinical study by intradermal route in healthy subjects in India.” *EClinicalMedicine* vol. 38 (2021): 101020. doi:10.1016/j.eclinm.2021.101020
49. Ura T, Okuda K, Shimada M. Developments in viral vector-based vaccines. *Vaccines.* 2014;2(3):624–41. doi:10.3390/ vaccines2030624.
50. Le, Tung Thanh, Andreadakis, Zacharias, Kumar, Arun, Román, Raúl Gómez, Tollefsen, Stig, Saville, Melanie, Mayhew, Stephen, 2020. The COVID-19 vaccine development landscape. *Nature Reviews Drug Discovery* 19 (5), 305–306.
51. Zimmer C, Corum J, Wee S. Coronavirus vaccine tracker. *New York Times.* 2020. <https://www.nytimes.com/interactive/2020/science/coronavirusvaccine-tracker.html> (accessed Jun 5, 2021).

52. Gavi, the Vaccine Alliance. New collaboration makes further 100 million doses of COVID-19 vaccine available to low- and middle-income countries. Sept 29, 2020. <https://www.gavi.org/news/media-room/newcollaboration-makes-further-100-million-doses-covid-19-vaccineavailable-low> (accessed Jun 5, 2021).
53. Amnesty International. COVID-19: Oxford/AstraZeneca vaccine a boost for global access, but huge inequality remains. Nov 23, 2020. <https://www.amnesty.org/en/latest/news/2020/11/oxford-astrazeneca-vaccine-a-boostfor-global-access-but-huge-inequality-remains> (accessed Jun 5, 2021).
54. McCarthy N. The cost per jab of Covid-19 vaccine candidates. Statista. Dec 1, 2020. <https://www.statista.com/chart/23658/reported-cost-perdose-of-covid-19-vaccines> (accessed Jun 5, 2021).
55. E. Mahase, Covid-19: where are we on immunity and vaccines? *BMJ* (2020), m3096. <https://doi.org/10.1136/bmj.m3096>.
56. Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, Hou LH, Li JX, Yang BF, Wang L, Wang WJ, Wu SP, Wang Z, Wu XH, Xu JJ, Zhang Z, Jia SY, Wang BS, Hu Y, Liu JJ, Zhang J, Qian XA, Li Q, Pan HX, Jiang HD, Deng P, Gou JB, Wang XW, Wang XH, Chen W. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2020 Aug 15;396(10249):479-488. doi: 10.1016/S0140-6736(20)31605-6. Epub 2020 Jul 20. PMID: 32702299; PMCID: PMC7836858.
57. The First Interim Data Analysis of the Sputnik V Vaccine Against COVID-19 Phase III Clinical Trials in the Russian Federation Demonstrated 92% Efficacy, <http://sputnikvaccine.com/newsroom/pressreleases/the-first-interim-data-analysis-ofthe-sputnik-v-vaccine-against-covid-19-phase-iii-clinical-trials/> 2020, Accesseddate: 30June 2021.
58. Second InterimAnalysis of Clinical Trial Data Showed a 91.4% Efficacy for the Sputnik V Vaccine on Day 28 After the First Dose; Vaccine Efficacy is Over 95% 42 Days After the First Dose, <http://sputnikvaccine.com/newsroom/pressreleases/secondinterim-analysis-of-clinical-trial-data-showed-a-91-4-efficacy-for-the-sputnik-vvaccine-on-d/> 2020, Accessed date: 15 December 2020

59. Zhu, Feng-Cai et al. "Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomized , double-blind, placebo-controlled, phase 2 trial." *Lancet* (London, England) vol. 396,10249 (2020): 479-488. doi:10.1016/S0140-6736(20)31605-6
60. Vartak A, Sucheck SJ. Recent advances in subunit vaccine carriers. *Vaccines* (Basel). 2016;4(2):12.
61. Guo Y, Sun S, Wang K, et al. Elicitation of immunity in mice after immunization with the S2 subunit of the severe acute respiratory syndrome coronavirus. *DNA Cell Biol.* 2005;24(8):510–515.106
62. Zhang, Y.; Zeng, G.; Pan, H.; Li, C.; Hu, Y.; Chu, K.; Han, W.; Chen, Z.; Tang, R.; Yin, W.; et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: A randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect. Dis.* 2021, 21, 181–192. [CrossRef]
63. Wu, Z.; Hu, Y.; Xu, M.; Chen, Z.; Yang, W.; Jiang, Z.; Li, M.; Jin, H.; Cui, G.; Chen, P.; et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: A randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect. Dis.* 2021. [CrossRef]
64. Costa, Anna (11 April 2021). "Estudoclínico que comprovamaioreficácia da Coronavac é enviado para Lancet" [Clinical study proving greater efficacy of Coronavac is submitted to The Lancet]. *CNN Brasil* (in Portuguese). São Paulo. Retrieved 12 April 2021.
65. Pontificia Universidad Catolica de Chile (25 February 2021). "Multicenter, Phase 3, Randomized Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of Two Vaccination Schedules of an Inactivated Vaccine Against SARS-CoV-2 Infection in Adults". Ministry of Health, Chile, Sinovac Biotech Co., Ltd.
66. Bueno, Susan; Abarca, Katia; González, Pablo; Gálvez, Nicolás; Soto, Jorge; Duarte, Luisa; et al. (1 April 2021). "Interim report: Safety and immunogenicity of an inactivated vaccine against SARS-CoV-2 in healthy Chilean adults in a phase 3 clinical trial". *medRxiv* (Preprint): 2021.03.31.21254494. doi:10.1101/2021.03.31.21254494. S2CID 232448335
67. Ella, Raches et al. "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and

- 3-month follow-up of a double-blind, randomised phase 1 trial.” *The Lancet. Infectious diseases* vol. 21,7 (2021): 950-961. doi:10.1016/S1473-3099(21)00070-0
68. Kushnir N, Streatfield SJ, Virus-like YV. Particles as a highly efficient vaccine platform: diversity of targets and production systems and advances in clinical development. *Vaccine*. 2012;31(1):58–83. doi:10.1016/j.vaccine.2012.10.083.
69. Mohsen MO, Zha L, Cabral-Miranda G, Bachmann MF. Major findings and recent advances in virus-like particle (VLP)-based vaccines. *Semin Immunol*. 2017;34:123–32. doi:10.1016/j. smim.2017.08.014.46.
70. N. Garçon, D.W. Vaughn, A.M. Didierlaurent, Development and evaluation of AS03, an Adjuvant System containing α -tocopherol and squalene in an oil-in-water emulsion, *Expert. Rev. Vaccines* 11 (2012) 349–366.
71. D.T. O'Hagan, G.S. Ott, G.V. Nest, R. Rappuoli, G.D. Giudice, The history of MF59(®) adjuvant: a phoenix that arose from the ashes, *Expert. Rev. Vaccines* 12 (2013) 13–30.
72. J.D. Campbell, Development of the CpG adjuvant 1018: a case study, *Methods Mol. Biol.* 1494 (2017) 15–27
73. T. Grunwald, S. Ulbert, Improvement of DNA vaccination by adjuvants and sophisticated delivery devices: vaccine-platforms for the battle against infectious diseases, *Clin. Exp. Vaccine Res.* 4 (2015) 1–10.
74. A. Schneeberger, C. Wagner, A. Zemann, P. Lührs, R. Kutil, M. Goos, G. Stingl, S.N. Wagner, CpG motifs are efficient adjuvants for DNA cancer vaccines, *J. Invest. Dermatol.* 123 (2004) 371–379.
75. S.P. Kasturi, M.A.U. Rasheed, C. Havenar-Daughton, M. Pham, T. Legere, Z.J. Sher, Y. Kovalenkov, S. Gumber, J.Y. Huang, R. Gottardo, W. Fulp, A. Sato, S. Sawant, S. Stanfield-Oakley, N. Yates, C. LaBranche, S.M. Alam, G. Tomaras, G. Ferrari, D. Montefiori, J. Wrammert, F. Villinger, M. Tomai, J. Vasilakos, C.B. Fox, S.G. Reed, B.F. Haynes, S. Crotty, R. Ahmed, B. Pulendran, 3M-052, a synthetic TLR-7/8 agonist, induces durable HIV-1 envelope-specific plasma cells and humoral immunity in nonhuman primates, *Sci. Immunol.* (2020) 5.
76. D.J. Dowling, Recent advances in the discovery and delivery of TLR7/8 agonists as vaccine adjuvants, *Immunohorizons* 2 (2018) 185–197.

77. Dubé E, Gagnon D, MacDonald NE, et al. Strategies intended to address vaccine hesitancy: review of published reviews. *Vaccine*. 2015;33(34):4191–4203.
78. World Health Organization. Ten threats to global health in 2019 [Internet]. [cited 2021 Jun 28]. Available from: <https://www.who.int/news-room/feature-stories/ten-threats-to-global-health-in-2019>
79. Ward JK, Peretti-Watel P, Bocquier A, et al. Vaccine hesitancy and coercion: all eyes on France. *Nat Immunol*. 2019;20(10): 1257–1259. •• Analysis of determinants and challenges of vaccine hesitancy in France.
80. Manca T. “One of the greatest medical success stories:” Physicians and nurses’ small stories about vaccine knowledge and anxieties. *Soc Sci Med*. 2018;196:182–189.
81. Wilson RJI, Vergélys C, Ward J, et al. Vaccine hesitancy among general practitioners in Southern France and their reluctant trust in the health authorities. *Int J Qual Stud Health Well-Being*. 2020;15 (1):1757336. •• Qualitative analysis of the reasons for vaccine hesitancy among general practitioners.
82. Riphagen-Dalhuisen J, Gefenaite G, Hak E. Predictors of seasonal influenza vaccination among healthcare workers in hospitals: a descriptive meta-analysis. *Occup Environ Med*. 2012;69 (4):230–235.
83. Peretti-Watel P, Ward JK, Schulz WS, et al. Vaccine hesitancy: clarifying a theoretical framework for an ambiguous notion. *PLoS Curr*. 2015 Feb 25;7:eurrents.outbreaks.6844c80ff9f5b273f34c91f71b7fc289. •• Article putting vaccine hesitancy into perspective from a sociologic point of view.
84. Ward JK, Crépin L, Bocquier C, et al. “I don’t know if I’m making the right decision”: french mothers and HPV vaccination in a context of controversy. *Health Risk Soc*. 2017;19(1–2):38–57.
85. Colgrove J. Vaccine refusal revisited — the limits of public health persuasion and coercion. *N Engl J Med*. 2016;375(14):1316–1317.
86. Duration of protection of covid-19 vaccines against clinical disease. *Public health England* 2021 September. Accessed on 29 September 2021