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Review on Vaccine Development on COVID-19

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ABSTRACT

Since the emergence of COVID-19, triggered by the SARS-COV-2 virus at the finish of 2019, there has been an acceleration of vaccine production. By 24 September 2020, a vast number of vaccines had started preclinical development, of which 43 had managed to enter clinical trials, including some approaches that have not previously been licensed for human vaccines. Vaccines have long been considered part of the exit strategy to enable people to return to their previous working, education, and socializing habits. Importantly, if the COVID-19 pandemic is to be effectively regulated, manufacture needs to be increased from a small number of preclinical doses to adequate filled vials to immunize the world's populace, which needs close engagement with manufacturers and regulators. To control the coronavirus, a global initiative will be needed, as will equal access to appropriate vaccines for all countries. This review includes the type of vaccines and their assessment for safety and efficacy. This review article also addresses the vaccine developers and their vaccine types and also the challenges in vaccine development.

INTRODUCTION:

Globally, the "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2)" disease has produced a difficult and dangerous pandemic (COVID-19). This virus is extremely infectious and has wreaked havoc on the global economy and health. SARS-COV-2 prevalence and mortality rates fluctuate regularly. According to the World Health Organization, the COVID-19 pandemic had infected 80.161.578,00 people as of December 25, 2020, with a death rate of 1.756.379,00. (2.19 percent). Since there is no specific medication or vaccine for the COVID-19 pandemic, people around the world are facing significant health care problems, lockdowns, anxiety, and stress. Vaccination will be the main weapon in the fight against the SARS-CoV-2 pandemic, given the lack of specific therapy and the virus's rapid spread. The US Food and Drug Administration recently issued emergency authorization to the Pfizer/BioNTech and Moderna COVID-19 vaccines on December 11, 2020, and 18 December 2020, respectively. These two COVID-19 vaccines were developed rapidly to help humanity and stop the spread of SARS-CoV-2[1]. Clinical trials and evaluations of mass vaccination campaigns have shown that two doses given three to four weeks apart can provide effective protection against symptomatic and severe disease. Despite the remarkable pace of growth, vaccine delivery has proved difficult in many countries due to supply shortages and restricted distribution capacity[2].

1. History of corona vaccine:

Historically, there have been challenges in developing coronavirus vaccines. Covid-19 vaccines have been proven to be immunogenic in animal models that resemble human disease, but they have not been shown to successfully inhibit disease transmission. Furthermore, there is fear that, like normal corona viral infection, vaccination does not have long-term immunity and that re-infection may be possible. Vaccine-associated illness enhancement has become more troubling in several respects. Previous studies in animal models using coronavirus vaccines (SARS-CoV and MERS-CoV) posed safety concerns about Th2-mediated immunopathology. Mice given two inactivated entire virus vaccines, a recombinant DNA spike protein vaccine, or a virus-like particle vaccine developed lung pathology, involving eosinophilic invasion, two days after being challenged with SARS-CoV-2, which was not seen in challenged unvaccinated mice. Several other studies found similar lung immunopathology, especially in older mice compared to younger mice challenged after vaccination. Upon viral challenge, mice immunized with SARSCoVN

protein vaccine experienced extreme pneumonia or lung eosinophilic infiltrate, while mice immunized with viral replicon particles expressing glycoprotein did not, suggesting that the N protein antigen is the antigen related to this immunopathology. When mice vaccinated with inactivated MERS-CoV vaccine were confronted with live virus, they showed similar enhanced immunopathology. Certain vaccine types can pose a greater risk of vaccine-associated disease enhancement. Following the administration of inactivated measles and RSV vaccines, there has been an increase in disease triggered by viral challenge, with potential mechanisms including a Th2 warped response resulting from formalin inactivation, as well as a lack of affinity maturation of the antibodies generated [3].

2. SARS-COV-2 virology

Coronaviruses are massive enveloped RNA viruses with a single-stranded, positive-sense RNA genome. A proof-reading replicase ensures the integrity of this lengthy genome. The SARS-CoV-2 gene encodes 11 open reading frames (ORFs), many of which are yet to be identified. ORF1a and ORF1b all code for polyproteins that are cleaved into a variety of nonstructural proteins.ORF4 encodes a viroporin envelope protein, and ORF5 encodes a membrane protein, which works together to organize viral assembly and release. The nucleocapsid (N) protein is encoded by ORF9. ORF2 is the gene that codes for spike surface glycoprotein, a viral entrance protein and key antigenic determinant that binds to the ACE2 receptor on host cells. In the airways, ACE2 is usually present in type II pneumocyte cells. SARS-CoV-2 binds to ACE2 10–20 times more strongly than SARS-CoV-1, the coronavirus that caused the SARS outbreak in 2002–04.SARS-CoV-2 can bind to ACE2 in a variety of mammalian species. After binding ACE2, spike protein is broken by a proteinase on the surface of the host cell, either Furin or TMPRSS2, allowing the viral capsid to come in. There may be a connection between the pathogenesis of disease and the mechanism of viral entry through ACE2.

3. Immune response to SARS-COV-2:

3.1. Protective immunity

Although the precise correlates of immunity for SARS-CoV-2 are unknown since it is a new virus, there are precedents from other respiratory infections in general and covid-19 viruses in particular. There has been speculation that normal immunity to SARS-CoV-2 deteriorates quickly; however, whether this is true remains unknown. Since vaccinations tend to elicit an

immune reaction, we hypothesis that they might be more immunogenic than the virus itself, which may have mechanisms to dampen immune response: if this hypothesis is right or not remains to be seen.

The T cell reaction is crucial in the regulation of other respiratory infections, and it is also likely to be crucial in COVID-19. T cells seem to be defensive in SARS-CoV-1 models. In mouse models, CD4+ T cell depletion slowed viral clearance and improved disease; similarly, T cell transmit resulted in viral clearance and amelioration of disease. In the absence of antibodies, SARS-CoV-1-specific CD8+ T resident memory was protective in a mouse model.SARS-CoV-1 T cells were discovered 4 years after infection, indicating that T cell memory would last a long time.T cell responses to a variety of antigens, including S, M, N, and other ORFs, have been observed in SARSCoV-2.SARS-CoV-2-specific T cells have been found in people with asymptomatic or moderate COVID-19, and SARS-CoV-2-specific T cells have been found in infected people's contacts.COVID-19 patients had a lower number of T cells than healthy controls.

T cells, especially CD4+ T cells, can influence the immune response by producing cytokines, and high levels of cytokines have been linked to exacerbated disease.It's possible that the skewing of the CD4+ T cell response is important. The successful control of SARS-CoV-1 and MERS-CoV relies heavily on T helper type 1 (Th1) responses. Enhanced Th2 cytokines were seen in serious diseases, and Th17 responses were thought to be harmful. COVID-19 patients had higher levels of regulatory T cells, which are critical in the resolution of infection. A small number of people with COVID-19 have circulating follicular T helper cells, which are critical in defining the recall antibody response to infection. It's unclear if the cytokine storm is a cause or a consequence of disease; knowing the difference is crucial for vaccine safety monitoring.

3.2. Antibody response:

The humoral response is essential in the later stages of infection because it helps to prevent reinfection. Antibodies to SARS-CoV-1 and MERS-CoV were found in 80–100% of SARS-CoV-1 and MERS-CoV patients two weeks after onset of symptoms, with slower antibody responses linked to more serious disease. A variety of studies have been conducted to better understand the antibody reaction to SARS-CoV-2; a systematic analysis of studies on coronavirus antibody found that antibody was rarely seen in the first 7 days after infection,

but increased in the second and third weeks. It's uncertain if antibodies are linked to the magnitude of COVID-19.

Higher antibody levels are associated with safety in human challenge trials using non-COVID-19 coronavirus strains. Reinfection has also been proposed by these challenge studies, but the dosage in challenge studies could be greater than that experienced during normal infection. Natural reinfections of SARS-CoV-2 have been found in two recent studies, one asymptomatic and the other symptomatic, but this is in the sense of more than 25 million confirmed cases worldwide, implying that it is a rare occurrence. Since the spike proteins of SARS-CoV-1 and SARS-CoV-2 overlap, antibodies may be cross-neutralizing. The most potent specific, neutralizing monoclonal antibodies against SARS-receptor CoV-1's binding domain (RBD) did not bind to SARS-spike CoV-2's protein. One encouraging finding is that isolated neutralizing antibodies have minimally mutated VDJ genes, allowing for faster induction with fewer vaccine rounds.

While neutralizing IgG antibodies in the serum have received the most recognition, other antibody-mediated pathways may also play a role in disease pathogenesis. The interactions between fragment crystallizable (Fc) and Fc receptor (FcR) will control the inflammatory response, and the SARS-CoV-2 virus–antibody complex could theoretically cause FcR-mediated inflammatory responses, resulting in acute lung injury. The IgA response may be significant in deciding the seriousness of COVID-19 patients' illness, but it has received little attention thus far[4].

4. Covid 19 and coronavirus

COVID-19 is a novel respiratory infection that has the potential to cause fulminant pneumonia, similar to extreme acute respiratory syndrome (SARS), which is caused by a novel coronavirus, which is spread by inhaling respiratory droplets from the nose and mouth. Notably, 80 percent of patients who are exposed or sick do not contract the active disease and instead have minor effects of seasonal flu, which they rebound from without requiring further medication. However, the approximate rate of occurrence is significantly higher, in the range of 20–60%, compared to 8% for flu, and preliminary observations suggest that those who experience serious illness need hospitalization for twice as long as those who develop acute flu. It began in late 2019 in China's Hubei province and quickly spread across the world through human-to-human transmission via international air travel networks. At the time of publication, the case fatality rate for COVID-19 was ten times higher than the seasonal flu's

estimated rate of 0.1 percent. After SARS-CoV and MERS-CoV, SARS-CoV-2 is the third member of the pathogenic coronavirus family to exhibit serious pathology in humans, among the others that only cause moderate clinical effects like the flu. In the lack of a scientifically validated successful treatment regimen, COVID-19 patients are currently treated with a mixture of supportive care and antiretroviral medications. A few FDA-approved medications and immune therapies are being repurposed and are now in various phases of clinical trials, with only compassionate access. They are effective in regulating the replication of SARS, influenza, HIV, and the Ebola virus by attacking the viral RNA polymerase or the polyprotein protease, or by improving host immunity as an adjunct therapy. Convalescent plasma from healed people is being produced, as are monoclonal antibody treatments, which were effective during the Ebola epidemic in Western Africa. These antibodies will also form the base for diagnosing asymptomatic spreaders, who are currently undiagnosed. However, we will limit our discussion to the various SARS-CoV-2 vaccines currently being produced [5].

5. Vaccine

To manage the COVID-19 pandemic, eradicate its dissemination, and eventually avoid its recurrence, it is critical to producing secure and reliable vaccines. Since the SARS-CoV-2 virus shares important sequence homology with two other deadly coronaviruses, SARS and MERS, the vaccines listed in these patents for SARS and MERS viruses can help with the development of anti-SARS-CoV-2 vaccines.

5.1. Attenuated Virus Vaccines.

Live attenuated coronavirus or torovirus vaccines are defined in patent application US20060039926. The virulence of mouse coronavirus was reduced when a mutation (Y6398H) was introduced into the Orf1a/b polyprotein (p59/nsp14/ExoN) (MHV-A59). At five days after intracerebral inoculation, the attenuated MHV virus showed decreased replication in mice.

5.2. DNA-Based Vaccines.

Compositions and methods for inducing/enhancing immune responses are disclosed in patent application WO2005081716. Antigen-specific CD8+ T cell-mediated responses to SARS coronavirus antigens, in particular. Chimeric nucleic acids that encode an endoplasmic reticulum chaperone polypeptide linked to at least one antigenic polypeptide or peptide from SARS-CoV induce an enhanced immune response in vivo, especially cytotoxic T cell

immune responses. Vaccination of mice next to a calreticulin-nucleocapsid fusion protein using gene gun distribution of DNA-coated gold particles show potent nucleocapsid-specific humoral and T cell-mediated immune responses. Vaccinated animals were able to significantly lower the titer of difficult vaccinia vector expressing the SARS virus's N protein. Immunogens, which are consensus proteins originating from the MERSCoV Spike antigen, are disclosed in patent application WO2015081155 for use in DNA-based vaccines targeting MERS-CoV. Both humoral and cellular immune responses were greatly induced by the consensus spike protein, including elevated IgG titers and neutralizing antibodies. The induced cellular immune reaction involved increased CD3+CD4+ and CD3+CD8+ T cell responses that created IFN-γ, TNF-α, IL-2, or both IFN-γ and TNF-α. On March 3, 2020, Inovio Pharmaceutical, Inc. declared they had designed the DNA vaccine known as INO-4800 to be planned for human trials in the United States in April.

5.3. Protein-Based Vaccines.

GlaxoSmithKline (GSK) has filed a patent application WO2010063685 for a vaccine that can cause a safe immune reaction to SARS. An S protein immunogen and an oil-in-water emulsion adjuvant are used in the vaccine. In animal models, an engineered ectodomain immunogen combined with the emulsion adjuvant GSK2 produced high levels of anti-SARS-CoV IgG2a or IgG2b antibody responses as well as neutralizing antibody responses. GSK announced a partnership with Chinese company Clover Biopharmaceuticals in late February 2020 to evaluate a coronavirus vaccine candidate. Clover's protein-based coronavirus vaccine candidate (COVID-19 S-Trimer) will be combined with GSK's adjuvant method in this collaboration. Clover has developed an S-Trimer subunit vaccine using their Trimer-Tag technology and a rapid mammalian cell culture-based expression mechanism. The Trimer-Tag is an advanced drug improvement platform, which enables the invention of the novel, covalently trimerized fusion proteins that can better target previous undruggable pathways. Patent application US20070003577 discloses immunogenic compositions and vaccines related to the S protein of SARS coronavirus. A recombinant full-length trimeric S protein was used to make a TriSpike SARS coronavirus vaccine. Antigen Express, Inc., a Generex subsidiary, has filed a patent application for hybrid peptides that include (a) an invariant chain (Ii) main peptide for antigen presentation enhancing action, (b) a chemical structure connecting the Ii to the antigenic epitope, and (c) an antigenic epitope that binds to an MHC type II molecule. Ii Key/ MHC II SARS hybrids were created using this approach. Following a contractual arrangement with a Chinese consortium consisting of China Technology

Exchange, Beijing Zhonghua Investment Fund Management, Biology Institute of Shandong Academy of Sciences, and Sinotek- Advocates International Industry Growth, Generex recently announced that it is producing a COVID-19 vaccine. The organization will develop a COVID-19 viral peptide for human clinical trials using its Ii-Key immune system activation technology.

5.4. mRNA-Based Vaccines.

The ability to replicate natural infection to induce a more potent immune response, as well as the ability to incorporate multiple mRNAs into single vaccines, are two possible benefits of an mRNA approach to prophylactic vaccinations. Moderna's patent application WO2017070626 describes mRNA vaccines developed in cationic lipid nanoparticles that contain mRNAs encoding antigenic viral full-length S, S1, or S2 proteins from SARS-CoV and MERS-CoV viruses. They discovered that mice vaccinated with mRNA encoding the full-length S protein of the coronavirus generated significantly higher neutralizing antibody titers than mice vaccinated with mRNA encoding the S protein's S2 subunit. MERS-CoV mRNA vaccine encoding the full-length S protein decreased viral load in rabbits' lungs by more than 90% and caused a considerable amount of neutralizing antibody against MERS-CoV in New Zealand white rabbits. On February 24, 2020, Moderna announced the publication of the first lot of mRNA-1273 against SARS-CoV-2 for human use, which was made using methods and strategies described in previous patents. The National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health (NIH), has received mRNA-1273 vials for use in the proposed Phase 1 trial in the United States. Moderna states that mRNA-1273 is an mRNA vaccine targeting a prefusion stabilized version of S protein associated with SARS-CoV-2 that was chosen in cooperation with NIAID Vaccine Research Center investigators. The Coalition for Epidemic Preparedness Innovations financed the production of this batch [6].

6. Models to assess vaccine safety and efficacy

6.1. Animal models:

Since coronaviruses have been linked to immunopathogenesis in the past, the vaccine-enhanced disease is a possible concern for SARS-CoV-2 vaccine development. Models may help in interpretation and may also be able to forecast disease or safety correlations. The perfect animal model is receptive to virus infection and mimics the pathology and clinical

course seen in humans. Since the SARS-CoV-1 epidemic in 2002–04, a variety of animals have been used to research coronavirus pathogenesis, including hamsters, cats, ferrets, and non-human primates. Despite effective infection in a variety of laboratory animals, only a handful showed overt clinical illness.

Several inbred mouse strains, including BALB/c, C57BL/6, RAG1/, and 129SvEv mice, have been used to model SARS-CoV-1. About the fact that young adult mice infected with various doses of SARS-CoV-1 display signs of infection, the inbred strains do not adequately represent the alveolar damage observed in humans. Aged mice, exhibit symptoms of clinical illness in the lack of lung lesions found in humans in many cases, and have therefore been used more frequently than younger mice. Disease incidence in transgenic mice was largely associated with the degree of hACE2 expression, and when challenged with SARS-CoV-1, they experienced extreme infection and achieved 100% mortality by day 7. Except for certain primate species and camelids, MERS-CoV tends to be much more difficult to model, with most species immune to infection.

SARS-CoV-2 is being studied using the same models. SARS-CoV-2 infection in human ACE2 transgenic mice resulted in weight loss, viral RNA detection in the lungs, and lung pathology. Hamsters have shown symptomatic infection and spread of SARS-CoV-2 between animals, while ferrets have shown asymptomatic infection and transmission of SARS-CoV-2.In laboratory conditions, SARS-CoV-2 is also contagious in cats, but not in dogs, pigs, chickens, or ducks. Nonhuman primates, such as rhesus or cynomologous macaques, have been useful for testing immune protection in the case of SARS-CoV-1.

6.2. Human challenge:

Alternative solutions may be necessary because animal models do not completely mimic human disease. Controlled human infection models (CHIM) are trials in which patients are deliberately exposed to an infectious organism. CHIM trials of SARS-CoV-2 vaccine participants may be especially useful in vaccine and drug effectiveness tests, particularly if the community infection speed has decreased as a result of epidemiological interventions. The intentional inoculation of safe people with SARS-CoV-2 necessitates a stringent ethical and regulatory structure. The main issues are that we do not have a full understanding of the long-term effect of SARS-CoV-2 infection and that there is no rescue treatment to allow for the resolution of serious infection, despite recent studies suggesting that dexamethasone can reduce mortality in severe disease and Remdesivir may boost clinical status. SARS-CoV-2

CHIMs aren't the only ones who don't have access to rescue therapy. Rhinovirus and RSV CHIM have no specific antiviral treatment and resolve on their own, which could be the case with SARS-CoV-2 in healthy young adults. There are also difficulties in creating challenge virus stock, which necessitates the use of a high-containment [biosafety level III (BSLIII)] laboratory. Infecting young, low-risk individuals to build herd immunity and thus protect the unvaccinated, immunocompromised, and immunologically naive has been proposed as another use of human infection. However, because the risk factors for severe disease are not well understood, this strategy is unappealing: There are also ethical concerns about infecting groups of people for the greater good, particularly if there is a financial incentive [7].

7. Vaccine developers:

7.1. Pfizer/BioNTech mRNA-based vaccine

BNT162b2, a lipid nanoparticle (LNP)–formulated, nucleoside–modified mRNA–based vaccine developed by Pfizer/BioNTech, encodes the S glycoprotein captured in its prefusion conformation. In phase three clinical trial with over 40,000 patients, this vaccine confirmed safety and 95 percent effective in preventing COVID-19 illness, with comparable efficacy through sex, race, ethnicity, and the prevalence of coexisting conditions. Pregnant or lactating mothers were not screened for the vaccine. The researchers compared two 30-µg doses of BNT162b2 given intramuscularly 21 days apart to a placebo. The safety of the vaccine was comparable to that of other viral vaccines after a median of two months, and participants would be treated for two years. Nine of the ten serious COVID-19 cases of study participants happened in the placebo community. The preliminary results did not discuss whether vaccination stopped the asymptomatic infection, nor did it address defense longevity or immune correlations. Immunogenicity results from phase 1 trials of this vaccine showed that geometric mean titer (GMT) of neutralizing antibodies in older adults aged 65 to 85 years was 41% of titers in younger adults aged 18 to 55 years, which could impact the longevity of safety in aging populations. The US FDA and regulatory authorities in the United Kingdom and the European Union recently granted emergency use authorization (EUA) to the Pfizer/BioNTech COVID-19 vaccine.

7.2. Moderna mRNA-based vaccine

Moderna produced mRNA-1273, an mRNA-based vaccine encoding a stabilized prefusion S protein of SARS-CoV-2 encased in LNPs, in partnership with the US National Institute of

Allergy and Infectious Diseases (NIAID). In March 2020, this was the first new COVID-19 vaccine to undergo clinical trials. GMT for neutralizing antibodies was 63.8 percent lower in elderly adults >71 years compared to younger adults in initial protection and immunogenicity studies. The durability of reactions to two 100 µg mRNA-1273 vaccines was tested up to 90 days after the second vaccination. The 80 percent inhibitory dilution GMT in participants aged 56 to 70 years fell from 878 on day 43 to 269 on day 119 using a live-virus plaque-reduction neutralization testing assay. In participants aged >71 years, the GMT declined from 317 on day 43 to 165 on day 119. Moderna recently announced the findings of a 30,000-person phase 3 experiment, showing protection and 94.1 percent effectiveness, with 30 extreme cases of COVID-19 arising exclusively in the placebo population. The FDA, the United Kingdom, and other regulatory authorities recently granted the Moderna COVID-19 vaccine EUA.

7.3. AstraZeneca/University of Oxford adenovirus vector-based vaccine

The vaccine chAdOx1 nCoV-19 encoding the SARS-CoV-2 S protein was invented by the University of Oxford and AstraZeneca using a chimpanzee adenovirus vector. The vaccine was tested in healthy volunteers aged 18 to 55 years in phase 1/2 trials as a single-dose and two-dose regimen, with the two-dose regimen inducing mild neutralizing antibody responses and cell-mediated immune responses as determined by the interferon- γ enzyme-linked immunospot (ELISpot) assay. Further testing of the vaccine in 560 volunteers, classified by age groups 18 to 55, 56 to 70, and >70 years, revealed median neutralizing antibody titers of 193, 144, and 161 and median T cell responses of 1187, 797, and 977 spot-forming cells per million peripheral blood mononuclear cells at 14 days after immunization, respectively. Interim study of phase 2/3 efficacy trials in participants 18 to 55 years conducted across Brazil, South Africa, and United Kingdom display the chAdOx1 nCoV-19 vaccine to have a suitable safety profile and 62.1% efficacy in participants who got the two-dose regimen of 5 × 1010 viral particles. A subset of participants in the U.K. trial got a half dose (2.5 × 1010) for the first vaccination and a full dose for the second vaccination. The vaccine was 90 percent effective in this subset of participants. The United Kingdom and other regulatory authorities recently issued EUA to the AstraZeneca/University of Oxford COVID-19 vaccine.

7.4. Janssen adenovirus vector-based vaccine

In healthy people aged 18 to 55 years and >65 years, Janssen's Ad26.COV2. S vaccine, a nonreplicating human adenovirus 26 vector producing the stabilised prefusion S protein of

SARS-CoV-2, was given at doses of 5 1010 or 1 1011 viral particles per injection, either as a single dose or as a two-dose schedule separated by 56 days. The vaccine was shown to be healthy and immunogenic in preliminary studies, eliciting neutralizing antibody responses as well as CD4+ T helper cell & CD8+ T cell immune responses. GMT of neutralizing antibody responses in vaccine users, as determined by a replicating virus neutralization assay at 50percent inhibitory concentration, is decreased by around 50% for adults >65 years old as compared to younger older people at the 1 1011 dose (243 versus 127, respectively). There were no discrepancies between older people and younger people among those who were vaccinated with 5 1010 viral particles, the dosage chosen for further growth (GMT 196 versus 214, respectively). The investigational Janssen Ad26.COV2.S COVID-19 single-dose vaccine applicant is now completely enrolled in a large-scale, multicountry phase 3 trial, with preliminary analyses scheduled for the end of January 2021. A separate phase 3 clinical trial of the vaccine is currently underway, to determine the safety and effectiveness of a two-dose dosage of 5 1010 viral particles.

7.5. CanSino adenovirus vector-based vaccine

In participants 18 years and older, CanSino's adenovirus 5 vector-based COVID-19 vaccine (Ad5- nCoV) was provided as a single immunization. It was found to be healthy, with only minor neutralizing antibody and cellular immune responses. In this phase 1/2 clinical trial, it was discovered that the age (>55 years) and having a high level of preexisting adenovirus 5 immunity reduced immune responses to the vaccine. The Ad5-nCoV vaccine was launched in a phase three trial by CanSino, with findings anticipated in the first quarter of 2021.

7.6. Sinovac inactivated vaccine

Sinovac produced an inactivated COVID-19 vaccine with an alum adjuvant that was given in a two-dose schedule to 600 people aged 18 to 59 years on days 0 and 14 or days 0 and 28. The vaccine was shown to be both healthy and immunogenic as neutralizing antibodies were induced. Among young adults (18 to 29 years) and older adults, data gathered during the trial revealed 30 to 40% decrease in neutralizing antibody titers (50 to 59 years). The neutralizing antibody titers of recovery patients who had previously had COVID-19 ranged from 23.8 to 65.4 GMT, based on the vaccine schedule. They were less than those seen in COVID-19-positive convalescent patients. Sinovac's inactivated COVID-19 vaccine has progressed to phase 3 trials, which are still underway. In Brazilian clinical trials, the Sinovac vaccine was found to be 50.4 percent effective.

7.7. Sinopharm inactivated vaccine

Sinopharm has also invented an inactivated COVID-19 vaccine in cooperation with the China National Biotec Group, which uses β-propriolactone as an inactivating agent and alum as an adjuvant. With 96 patients in phase 1 and 224 in phase 2, phase 1/2 trials comparing various dosages and regimens of the vaccine demonstrated protection and immunogenicity in participants aged 18 to 59 years, with neutralizing antibody titers equal to those seen with other leading COVID-19 vaccines. Phase three clinical trials for this new vaccine are currently underway.

7.8. Novavax recombinant VLP–based vaccine

The NVX-CoV2373 vaccine from Novavax is a recombinant SARS-CoV-2 nanoparticle vaccine made up of trimeric full-length SARS-CoV-2 S glycoprotein and Matrix-M1, a saponin-based adjuvant. VLPs are formed when the vaccine's S protein component is expressed in a baculovirus insect cell expression system. The structure of the full-length S protein, trapped in the antigenically desired prefusion conformation, was discovered by cryo-electron microscopy and site-specific glycan evaluation of the S protein from this candidate vaccine.NVX-CoV2373 proved to be secure in phase 1/2 clinical trials in adults aged 18 to 59 years, with two intramuscular injections at days 0 and 21. The two-dose 5-µg adjuvanted regimen elicited a strong neutralizing antibody response by day 35, which surpassed neutralising antibody responses in COVID-19 convalescent serum. Data on older adults, on the other hand, is currently unavailable. Novavax has enrolled 15,000 people in phase three clinical trial in the United Kingdom, with 25% of the patients being over 65 years old, to assess the safety and effectiveness of NVX-CoV2373, with preliminary results anticipated in Q1 2021.A new phase 3 experiment has recently begun in the USA and Mexico, intending to enroll 30,000 participants [8].

8. Vaccines developed in India:

Covid-19 virus is single-stranded RNA viruses with an enveloped surface glycoprotein spike that mediates receptor attachment and cell entrance during infection. Because of its functions in receptor binding and membrane fusion, the spike protein is a capable vaccine antigen. Apart from whole virion inactivated vaccines, almost all manufacturers are selecting spike protein as an antigen. For the manufacture of this vaccine, a variety of approaches and platforms are being used. Vaccines are traditionally made as inactivated, live attenuated, or

subunit vaccines, but different organizations and manufacturers are experimenting with next-generation techniques. COVAXIN (Bharat Biotech-ICMR) and CoviShield (Serum Institute-ICMR) are two locally produced vaccines that have been licensed for commercial use in India, though ZyCov-D (Zydus Cadilla) is still in clinical trials. As a result, the Indian government and companies must form license agreements with those companies to import vaccines for use in India. India now manufactures nearly 120 million vaccine doses every month. This ability is being used to produce several vaccines to combat a variety of diseases for both domestic and global distribution. This capability cannot be transferred completely to the production of COVID-19 vaccines, since a decline in the supply of other vaccines will result in a rise in the burden of disease. A COVID-19 vaccine cannot be developed at the risk of a potential epidemic outbreak. To satisfy the vaccine demand, an increase in vaccine manufacturing ability is needed. Regulatory acceptance of vaccines for use in India, collaboration with vaccine testing agencies, and increased production capacity to meet market requirements are all part of securing vaccine supply.

9. Challenges in vaccine development:

The advancement of any new vaccine, including the SARS-CoV2 vaccine, faces several obstacles. The novel SARS-CoV2 virus is rapidly drifting, with many genomic modifications discovered. The most reliable way to validate a vaccine's effectiveness is to infect subjects with the offending organism and compare the disease incidence of vaccine recipients to the control community. In Covid-19, though, this experiment will be immoral since the disorder is still developing and there is no successful cure. It's impossible to say much about the vaccines in development's safety and effectiveness before Phase three clinical trial evidence was thoroughly analyzed. It's still up for debate whether neutralizing antibodies are enough, and what amount of antibodies is needed to be protected. The vaccine's T cell response and cell-mediated immunity could be needed for effectiveness, which is another question that needs to be addressed in clinical trials. It is necessary to determine the amount of antigen dosage, the number of doses, the length of immunity, and the need for boosters. All of the experiments are currently being conducted on healthier people, but they will need to be replicated in people who are at high risks, such as infants, immunocompromised people, senior citizens, people with asthma, people with heart disease, and so on. Only a sufficient number of subjects from various racial and regional backgrounds can be tested to determine the vaccine's safety. Given the availability of a secure and reliable vaccine, ensuring fair access to the most marginalized would be a significant challenge. Procurement, delivery,

distribution, cold chain, and government logistics at the city level would be a massive undertaking. It's possible that by the time a safe and reliable vaccine against Covid-19 disease is available and logistics are worked out, the pandemic will have already started to fade and be over [9].

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