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The research progress of the COVID-19 vaccine

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Abstract. The COVID-19 pandemic has been sweeping the world, which has adversely affected both the social and economic sectors. However, there is hope in the development of various vaccines designed to combat the virus. These vaccines come in different forms, including inactivated vaccines, mRNA vaccines and others. When it comes to vaccine safety, attenuated vaccines require special attention. It is important to focus on reducing their toxicity while maintaining their effectiveness. On the other hand, inactivated vaccines are generally considered safe, but it is crucial to ensure that they are effective for the entire population. Recombinant protein vaccines also need to be carefully evaluated for their safety and efficacy. Lastly, mRNA vaccines hold great promise for the future, and it is important to continue developing them to maximize their effectiveness. Overall, vaccine safety is a critical consideration in the development of any new vaccine, and careful attention must be paid to ensure that they are safe and effective for everyone. This article will delve into the structure of the virus before discussing each vaccine type and its respective clinical trials, and also examine the potential prospects of these vaccines, with the ultimate goal of promoting widespread vaccination and achieving full population immunity.

Keywords: COVID-19, Mrna Vaccines, Recombinant Protein Vaccines.

1. Introduction

The symptoms of COVID-19 disease can be chills, muscle pain, headache, throat pain, sudden loss of smell or taste, etc [1]. Corona-virus particles are irregular in shape and have a spike-like surface distribution protein, because of their obvious rod-like particles under the microscope convex, shaped like the crown of medieval European emperors, hence the name crown virus. The diameter is about 60~220nm, this shape can speed up the speed of replication within the host cell. The virus has an envelope structure, and there are three proteins on the surface: spike protein, small envelope protein, membrane protein, and hemagglutinin glycoprotein [2]. It can be spread by respiratory droplet transmission, and the patient does respiration, then the viruses will go into the air, and another person breathe the air, then this person will be infected with COVID-19, and this is the main way for the viruses to spread. It can also spread by close contact transmission because this kind of virus can attach to any item and has a certain amount of in vitro survival time. Then the medium can also be the items in our daily life. The third way is aerosol transmission, viruses can mix with small particles in the air, which can spread with the faeces and urine of infected people. There are three different types of vaccine, including inactivated vaccine, attenuated vaccine, and recombinant protein vaccine. The attenuated vaccine is to decrease the toxicity of the COVID-19 viruses, the inactivated vaccine is to let the viruses

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lose their activity, and the recombinant protein vaccine is to change its structure by artificial technology. These vaccines can protect us against the infection of COVID-19 viruses.

In the previous three years, COVID-19 has been popular throughout the whole world for a long time, and this caused a great deal of mortality. Although the epidemic ban was lifted in most countries, people have started to travel again, and population mobility has increased, outbreaks still occur occasionally in localized areas. Also, the viruses continue to mutate and they become more and more easier to spread. So, we should still focus on COVID-19, and it is still necessary to vaccinate the entire population. So, this paper will introduce the structure of the COVID-19 vaccines, highlight the three different types of vaccines (inactivated vaccine, attenuated vaccine, and recombinant protein vaccine), and focus on arousing people's close attention to COVID-19.

2. Introduction of COVID-19 viruses

2.1. The mutation of COVID-19 viruses

The coronavirus has undergone multiple mutations, resulting in five different variants named alpha, beta, gamma, delta, and Omicron. Three mutations were detected in 2020, with two additional mutations found in 2021. The latest variant, Omicron, is considered more contagious than the Delta variant. Ongoing mutations continue to occur within the Omicron variant, resulting in new strains such as BA.1, BA.2, BA.4, and BA.5. While BA.2 is more transmissible than the previous variant (BA.1), it has not undergone significant changes. The recent surge in BA.2 may be attributed to its higher transmissibility rather than enhanced immune evasion [3].

2.2. Different types of COVID-19 viruses

The diameter of a single coronavirus strand in a positive chain ranges from 80 to 120 nanometers. There are four primary subtypes of RNA viruses: -CoV, -CoV, -CoV, and -CoV [4]. There are now seven different CoV strains that can infect people. There is also the MERS-CoV, CoV-NL63, and CoV-HKU1 virus in addition to SARS-CoV-2. With 29 891 nucleotides in its genome, it can produce 9 860 amino acids [5]. 6,953,743 fatalities and 768,983,095 confirmed COVID-19 cases were reported by August 2, 2023. 13,492,225,267 doses of the vaccine had been given as of August 5, 2023 [6].

2.3. The mechanism of immune response to Covid-19

The innate immune response starts work when the body is infected with Covid-19. Macrophages will first start to fight against those viruses and swallow and ingest them as well. Then enzymes will break them into several pieces and form the antigens on the surface of the macrophages. Next T cells and macrophages will react according to the lock and key model, in which substrates and active sites will be together. And T helper cells will help other T cells become more active and B cells will start to produce the specific antigens for the Covid-19 viruses. T cells will find the human body cells which are infected and kill them to prevent the COVID-19 viruses from producing offspring. B cells will join with the COVID-19 viruses and let it lose activity.

When the person is infected with a disease for the first time, lymphocytes will retain the memory of their antigens, and the memory may last for many years. When the COVID-19 virus infects the person again, memory cells can reproduce more antibodies, and the secondary immune response will be faster than the first one. So, the person can kill the viruses before they produce multiple generations. In addition, the person will recover quickly.

3. Current vaccine progress

3.1. Attenuate vaccine

A pathogen's pathogenicity is decreased while keeping its vitality to create an attenuated vaccine (Figure 1). The ultimate goal of vaccine design is attenuation, which is the absorption of an infectious agent and alteration to make it harmless or less dangerous. Vaccines that have been attenuated have the potential

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to produce a powerful and durable immune response. When compared to inactivated vaccines, attenuated vaccines work faster and better in eliciting an immune response.

Further investigation into the security and effectiveness of intranasal vaccinations is required because the study was unable to identify whether the live-attenuated influenza virus vector-based SARS-CoV-2 vaccine (dNS1-RBD) was appropriate for the general public. The vaccine can be administered via intranasal spray to healthy people. At a single Jiangsu, China, location, phase 1 and phase 2 investigations, as well as a phase 2 extension trial, were conducted. The data suggested that adult use of dNS1-RBD was safe. The mucosal and humoral immune responses to SARS-CoV-2 in those who received the vaccination, as well as the levels of peripheral blood T-cell immunity, were, however, less potent [7]. The effect of those vaccines on the inflammatory response to SARS-CoV-2 was investigated in a hamster experiment. dNS1-RBD has been the subject of research. In the respiratory tracts, it was discovered that the dNS1-RBD vaccination induced tissue-resident memory T cells, and trained immunity responses. By lowering levels of pro-inflammatory cytokine in comparison to the control group, it was able to minimize the excessive immune-induced tissue damage and restrict the early phase virus load following the SARS-CoV-2 challenge. The NS1-deleted influenza virus vector vaccine is administered intravenously as a COVID-19 immunization technique [8]. It is not known whether intranasal vaccines are suitable for the entire population, thus more study is needed to evaluate the safety and efficacy of these treatments. A top focus for research must be the creation of all-inclusive, easily accessible vaccinations.

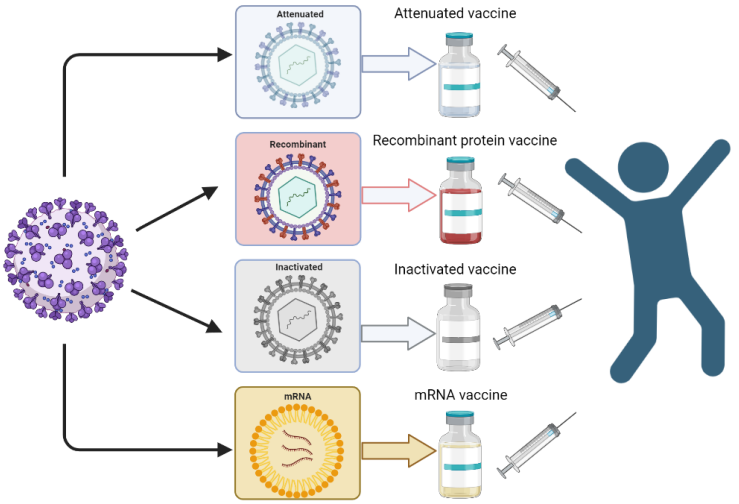

Figure 1. Illustration of the different COVID-19 vaccines.

3.2. Inactivated vaccine

Inactivated vaccines are safer than attenuated vaccines because there is no toxicity. The inactivated vaccine breeds viruses or bacteria and then uses special physical or chemical methods to destroy infectious pathogens, but it can retain the integrity of the pathogen's antigen particles so that the pathogen loses its pathogenic ability to retain antigenicity. Patients can produce an immune response based on humoral immunity in the body after receiving inactivated vaccine, and the antibodies induced by it can neutralize or remove toxins produced by pathogens to prevent diseases. Chemical inactivation is the use of chemicals to destroy the protein structure of pathogens so that they cannot replicate and infect cells. Commonly used chemicals include highly concentrated ethanol, trypsin solution, and so on. Physical inactivation is to destroy the protein structure of the pathogens by using physical methods such as high temperature, ultrasound, or ultraviolet so that it cannot replicate and infect cells. Bio-inactivation is the use of special bacteria or yeasts to destroy the protein structure of a virus so that it also cannot replicate and infect cells.

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The principle of an inactivated vaccine is that after vaccination, it will cause an immune response based on humoral immunity, which can neutralize or remove toxins. When the real virus invades, it will have a specific immune reaction with the previously produced antibodies to achieve the purpose of resisting the virus, just like the immune response after the vaccination. Inactivating pathogens does not cause infection and disease, but it still stimulates the body's immune system to produce an immune response to prevent disease. So, the mechanism is just like we first infect the COVID-19 viruses (without the symptoms caused by the viruses, but maybe we'll have some symptoms caused by the immune system).

Recently, the security of inactivated vaccinations with food or medication sensitivities was investigated. A week following each treatment, 150 trial participants received questionnaires to assess any potential local or systemic effects. Fatigue (16%) and pain (30%) were the common adverse reactions following the initial dose. Surprisingly, after the second dose, both local and systemic side effects decreased in frequency. People with a history of food or drug sensitivities also saw this inclination. The phase III clinical trials showed a comparable rate of side effects. These results imply that individuals who have a history of allergies have a safety profile for immunization [9].

A phase 3 immunological cross-linkage trial that compares the immunogenicity and safety of an inactivated whole virus COVID-19 vaccine (VLA2001) is presently underway. Adults in the UK are using the adenovirus vector vaccination ChAdOx1-S (COV comparison). VLA2001 has developed an immune response as a primary immunization against the virus in comparison to the ChAdOx1-S. Its safety and pathogenicity were assessed. According to the research, ChAdOx1-S and VLA2001 performed better than each other when it came to neutralizing antibodies and seroconversion rates, respectively. The tolerability profile of VLA2001 was also determined to be quite good. These findings have led to the European Union, the United Kingdom, Bahrain, and the UAE successfully approving the use of VLA2001 for primary vaccination [10]. Inactivated vaccines are still fairly safe because the virus loses its capacity to cause disease. In the future, safer and more thorough methods will need to be the main emphasis of vaccination research and development.

3.3. Recombinant protein vaccine

The recombinant protein vaccine requires three shots. This vaccine works by extracting the S protein from the virus, replicating it in large quantities, and injecting it into the human body. This process induces an immune response and generates the necessary antibodies to fight the virus [11]. Phase I and II trials were taken to evaluate the safety and immunogenicity of Tandmer dimer RBD protein (ZF2001) for COVID-19 in adults. Based on the available data, the protein subunit vaccine identified by ZF2001 appears to be a safe and effective way to generate an immune response. Early safety and immune response results from phase 1 and 2 trials have led to the implementation of a three-dose schedule, with each dose consisting of a 25μg quantity, in a phase 3 trial [11].

A phase 2/3 trial tested the immunogenicity of the S protein subunit vaccine (SCB-2019). The SPECTRA experiment, which was conducted in five different nations, recruited participants who were under the age of 18. Then, at random, they received two intramuscular injections of either SCB-2019 or a placebo. On days 1, 22, and 36 of the Phase II study, researchers evaluated participants for the presence of neutralizing antibodies using pseudoviruses and wild-type viruses using detection methods against SARS-CoV-2 prototypes and mutants. In addition, ACE2 receptor-binding antibodies and SCB-2019-binding antibodies were evaluated using enzyme-linked immunosorbent assay (ELISA), and intracellular cytokine labelling was performed using flow cytometry to assess cellular immunity. A single dose of it is immunogenic for people who have been exposed to the virus, but for people infected with SARS-CoV-2, two doses of SCB-2019 are required to elicit an immune response. In addition, SCB-2019 showed a cross-neutralization response to recently identified mutations, with antibody levels correlated with clinical defences, suggesting that it has the potential to act as a synergist [12]. The possibility for immunizations to be given to everyone, in addition to their safety and effectiveness, must now be considered when developing new vaccines.

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3.4. mRNA vaccine

mRNA is a molecule that occurs naturally and contains instructions for producing certain proteins or activating an immune response against pathogens in human cells. mRNA vaccines use the genetic code of a virus instead of the actual virus, making them safe from infection. Additionally, mRNA vaccines have a short research and development cycle, which means that new vaccine candidates can be quickly developed to combat virus mutations. These vaccines provide humoral and T-cell immunity, are effective, do not require adjuvants, are easy to produce at scale, and are important tools in global health.

Phase 1 research showed that each of the five immunization doses was well tolerated. The vaccination generated potent immune responses while maintaining a tolerable safety profile, highlighting the need for additional, in-depth clinical studies with ARCoV. Initial testing has been completed, but further testing of ARCoV mRNA vaccines containing the RBD is needed [13].

A study was conducted to ascertain the neutralizing antibody response against the variants following the administration of the mRNA COVID-19 vaccine in two to three doses. The SARS-CoV-2 pandemic vaccine has received the second and third doses, but it is still unclear how much immunity these additional shots provide. This study examined the development of SARS-CoV-2 Omicron variant neutralizing antibodies in BNT162b2 messenger RNA (mRNA) inoculation recipients following doses 2 and 3. Kobe University Hospital conducted a cohort study of 82 physicians who received 2 doses of the vaccine between June 1, 2021, and January 12, 2022. After two and three doses of the vaccine, positive test results and neutralizing antibody titers against the omicron variant were tested. In this study, two doses of the BNT162b2 mRNA vaccine did not produce enough neutralizing antibodies. Regardless of the age of the subject, the booster produces high levels of neutralizing antibodies against the Omicro strain. The next goal is to develop a BNT162b2 mRNA vaccine that can generate enough neutralizing antibodies against the omicron variant for 2 doses [14].

3.5. Current vaccine challenges and dilemmas

Not safe enough for children: It is important to thoroughly review regulations regarding COVID-19 vaccination for children and to ensure that vaccines would not injure their growth and development [15]. The short duration of prevention: COVID-19 immunization must be given to halt and reduce the virus's spread. Nevertheless, there is currently no vaccine in clinical development that confers lifelong immunity. Most COVID-19 vaccines afford protection for approximately six months, after which a booster dose is necessary to maintain immunity. High cost: Despite China's current policy of providing free vaccinations to all, it should be noted that the development of the COVID-19 vaccine requires a significant amount of manpower and financial resources. National medical insurance also invests a lot of money in this endeavor, resulting in higher costs.

Mutation: The aetiology of pneumonia caused by the novel coronavirus stems from a viral strain hitherto unknown to the human immune system. During the process of replication, the virus undergoes a continual sequence of mutations, which enables it to adapt to its host. Such mutations can influence a range of factors, such as the virus's transmissibility, its degree of pathogenicity, and the response of the immune system to it. Hence, there is an urgent need to enhance the efficacy of the vaccine to ensure protection against these variants.

4. Conclusion

With the ongoing COVID-19 pandemic claiming numerous lives worldwide, the importance of vaccine research cannot be overstated. The goal of this essay is to evaluate current COVID-19 vaccination research trends. The efficiency of the current vaccines has been somewhat poor, and it is still unclear if they will protect against new strains. This review focuses on four types of vaccines: attenuated, inactivated, recombinant protein, and mRNA vaccines. Attenuated vaccines require measures to reduce their toxicity to enhance safety. Inactivated vaccines are relatively safe, but efficacy needs to be improved across all demographics. Recombinant protein vaccines require further development to increase both safety and efficacy. mRNA vaccines show promise and require further study to improve efficacy. In conclusion, developing vaccines targeting specific structures of COVID-19, such as

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polysaccharides or mRNA vaccines, to provide more comprehensive protection against new variants was important.

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