# A Brief Introduction and Evaluation of Typical mRNA Vaccine, Inactivated Vaccine, Vectored Vaccine, Sub-unit Vaccine for COVID Protection

Kehan Jiao

*Chongqing NO.2 Foreign Language School, Chongqing, China, 400000*
*kehanjiao70@gmail.com*

**ABSTRACT**
Standing on the shoulders of giants, based on the achievements of previous researchers, scientists and vaccine developers started the most rapid vaccine development process ever since. The central topic of this paper is to introduce and evaluate four kinds of COVID vaccines created to deal with the epidemic situation and contribute to public health globally. The following description will mainly focus on a brief introduction of the working principle and how certain functions of immunity are achieved for four types of mainstream vaccines: mRNA vaccine, inactivated vaccine, vectored vaccine, and sub-unit vaccine. The evaluation of each type of vaccine mainly includes the following: the principle, the protection efficacy, and side effects. The data used in this paper all come from the previous analysis and research results from 2020 to 2022. In addition, this paper will also make some assumptions about future development in the field of COVID vaccine production based on scientific authentic numbers and results, combining the news of economics and policy. The paper finds that mRNA vaccines have high protective efficacy against the coronavirus, but their conservation cost is relatively expensive, needing to be reserved at a very low temperature to be efficient. Because of the low requirements for temperature, inactivated vaccines are easy to transport and restore. Because of this, their production efficacy is merely half that of live vaccines. Vectored vaccines have higher immunogenicity than inactivated vaccines and more readily available storage conditions than mRNA vaccines. The sub-unit vaccines seem to have characteristics of being efficient, safe, and easily achievable.

***Keywords:*** *COVID-19, vaccine evaluation, mRNA vaccine, inactivated vaccine, vectored vaccine, sub-unit vaccine*

## 1. INTRODUCTION

COVID-19, which is also called SARS-CoV-2, is a relatively new coronavirus that was first reported from Wuhan, China, in 2019. This coronavirus pushed all of us into a big challenge, not only in medicine and public health areas but also in political and economic fields. Since it triggered such a huge impact, scientists immediately donated themselves to the development of the COVID-19 vaccine, which is the most rapid vaccine development progress thanks to the accumulation of medical knowledge and an influx of investment [1].

In terms of phylogeny, it has a structure that is similar to MERS-CoV and SARS-CoV, which were discovered by human beings in previous decades. In addition, they invade the organism's cells by a parallel method. [2] Firstly, they pass through the membrane via the natural intermolecular substance exchange between the cell and the ambient environment, endocytosis. Then they will release their genome and translate their viral polymerase protein into ribosomes, initiating the production of protein by the organism. After RNA replication and subgenomic transcription, generating Nucleocapsid (N), Spike (S), Membrane (M), and Envelope (E), the viral structural proteins, only including S, M, and E, will be sent to the Endoplasmic reticulum (ER) and treated as normal proteins to experience further processing. A nucleocapsid always combines with spike, membrane, and envelope in the ERGIC to ultimately form a mature virus virion in the Golgi vesicle, leaving the cell by exocytosis. [3]

Based on the fundamental principle of the parasitism process of SARS-CoV-2, researchers have developed three kinds of vaccines: mRNA vaccines, inactivated

vaccines, vectored vaccines, and subunit vaccines. mRNA vaccines take advantage of recombinant mRNA that is related to spike protein. Inactivated vaccines use inactivated COVID viruses to help B cells produce antibodies. Vectored vaccines transport antigen DNA by Adenovirus into the nest cell and produce spike protein to stimulate the creation of antibodies. Subunit vaccines come from separated parts of the virus, RBD-dimer or chimeric protein, to call for the response of B cells. [4]

Although there is no doubt that all of these vaccines are valuable for the development of a practical strategy for the fight against viruses and modern technology, scholars also need to figure out the development situation of each vaccine and prepare for future development. This paper will focus on a brief introduction of four types of mainstream vaccines and give several assumptions about the future development trends of various vaccines to enhance the function of vaccine products.

## 2. MRNA VACCINES

mRNA vaccine technology is a sort of newly discovered method to produce vaccines. Developed at a rapid speed and with great attention, it applies lipid nanoparticles (LNP) to the vaccine production process. BioNTech, in collaboration with Pfizer and Fosun Pharma, developed two candidates for effective vaccines, BNT162b1 and BNT162b2. BNT162b1 encodes a trimerized, secreted spike (S) glycoprotein receptor-binding domain (RBD). BNT162b2 encodes a membrane-anchored SARS-CoV-2 full-length spike, which is more stable in prefusion than the previous one.[5] Following their success, the mRNA-1273, which expresses the prefusion-stabilized spike glycoprotein developed by Moderna, has also passed all three phases of testing[6]. mRNA-1273 and Pfizer-Biotech vaccines are both authorized by the Food and Drug Administration (FDA) and vaccinated millions of people. [7]

### *2.1 BNT162b vaccine*

With the proof of three phases of trials and testing, the BNT162b vaccine has become relatively reliable and efficient in immunity to SARS-CoV-2.

BNT162b1 and BNT162b2 elicited dose-dependent SARS-CoV-2–neutralizing geometric mean titers (GMTs) in phase 1. However, BNT162b2 brings less reactogenicity, which partially means that this vaccine is associated with fewer side effects. In that case, BNT162b2 was supported for the further evaluation of phase2/3.[8]: According to WHO data, BNT162b2 maintains its high efficacy in phases 2 and 3. There were no variations in the tria0.ls in Brazil, Germany, Argentina, Turkey, South Africa, and the US, during the 2 separate doses in 21 days. In addition, the efficacy in populations that are relatively easy to infect by COVID-19, including people who are older than 65 years old and people with obesity, is still pretty high. Since there are not so many people infected by severe COVID, its immunogenicity in these people is not certain. There is 1 case of severe symptoms in the BNT162b2 vaccinated group, compared to 9 cases in the placebo group. [9]. Additionally, the WHO mentioned that the most common side effect of this vaccine is pain at the injection site, which happened in 84.1% of the trial population. Also, more than half of the people had fatigue or headache, and less than 40% of the people had muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, or lymphadenopathy. Nevertheless, most adverse events can be healed by simple treatment or recovered spontaneously. Lymphadenopathy, Bell's Palsy, and allergic reactions are adverse events that should be followed in the future. With the vaccine's widespread use, there may be more side effects that affect more people.[10]

Since this vaccine was developed first in the U.S., the test population and trial data are more likely from the U.S. and Germany, which consist mostly of white people. In Asian developing countries, such as China, the relative data is not very sufficient. Fortunately, there is still a phase 1 examination of BNT162b1 on Chinese people for reference, and the result is almost consistent with the research above. A phase 2 test of BNT162b2 is still ongoing in China, but the result is unpublished. [11] For areas in Africa, the statistical data and research are limited and unavailable. In the future, more trials on the patients in the African population are expected to fill the blanks in the research, making the conclusion more believable and comprehensive.

### *2.2 mRNA-1273 vaccine*

In addition, the Moderna vaccine is also authorized by the FDA. [12] The mRNA-1273 vaccine is similar to the BNT162b2 vaccine. Because SARS-CoV-2 affects both adolescents and the elderly, safety and efficacy are both eligible for actual practice in various vulnerable people. According to the phase 3 trials in the U.S., with 30,420 volunteers randomly attending, the vaccine shows excellent immunogenicity and moderate symptoms of side effects. In the testing process, the vaccine efficacy was 94%. Most of the adverse events are local reactions such as pain and swelling, and systemic reactions such as headaches. [13] This result is similar to the side effect of the BNT162b vaccine. For elderly people, the side effects depend on the amount of the dose. The 100-g dose has more severe adverse events than the 25-g dose. However, most of the side effects are mild and moderate, and the binding and neutralizing antibody responses are similar to the responses that happen in people from 18 to 55 years old. [14] For teenagers, pain is the most common side effect, which is within the range of acceptable safety responses. Moreover, the vaccine is pretty effective in preventing infection. After 14 days, there were no cases

of COVID in the mRNA-1273 injected group, but there were four cases of COVID in the placebo group of teenagers. The resultant data is like the response of young adults.[15]

### *2.3 Discussion*

In contrast, the reaction of mRNA-1273 vaccines and BNT162b2 vaccines to certain variants in Qatar has a significant difference. After nearly 2 weeks after the injection of both vaccines, the SARS-CoV-2 incidence of mRNA-1273 vaccines started to be lower than that of BNT162b2 vaccines. With the accumulation of incidence, the difference between mRNA-1273 vaccines and BNT162b2 vaccines becomes more obvious, and the mRNA-1273 vaccines have a stronger capability to control the amount of incidence population in front of Qatar. Nevertheless, both of these mRNA vaccines are pretty effective in protecting people against COVID-19-related deaths and hospitalization. [16]

## 3. INACTIVATED VACCINES

### *3.1 CoronaVac COVID-19 Vaccine*

The CoronaVac COVID-19 Vaccine was developed by a Chinese company called Sinovac Life Sciences. This type of inactivated vaccine consists of two doses. The second dose should be injected after a time interval of 14 days.[17] Another notable feature of this vaccine is that it has been used on a large number of people all over the world, including Chile, Brazil, and China. The CoronaVac COVID-19 Vaccine is easily imported into some developing, relatively low-income countries because it can be preserved at fridge temperature, which means it can be used under an easily-reachable apparatus, bringing hope of a pandemic. In terms of efficiency, it has immunogenicity of 51% and 100% to prevent death and serious infection. The adverse effects are mild to moderate as well. [18]

In phases 1 and 2, the trials have shown that the CoronaVac COVID-19 Vaccine has a high rate of seroconversion and moderate side effects. According to the testing data in Renqiu (Hebei, China), with the cooperation of healthy adults who are older than 60 years old, the seroconversion rate after the second dose is 100% in phase 1. In phase 2, it is approximately 90.7% in the 1.5g group, 98% in the 3.0g group, and 99.0% in the 6.0g group. In addition, the adverse reaction happened in 20% of the trial population, but injection site pain is most commonly found, which means generally this vaccine is safe and acceptable. Conclusively, the 3.0 g group has been chosen to enter the phase 3 test because this group, with slight side effects, shows a seroconversion rate that is much higher than the 1.5 g group and, similarly, the 6.0 g group. [19] For teenagers and children aged 3–17 years old, the result is parallel. [20]

In the phase 3 test in Turkey, the researchers concluded that CoronaVac, with great safety, is very effective in decreasing the number of PCR-confirmed symptomatic COVID-19. A total of 11,303 volunteers, ranging from 18 years old to 59 years old, participated in the experiment, which proved the vaccine efficacy of 83.5%. The level of immunogenicity in this report is higher than the information provided by WHO. This difference might be caused by the population age: in this phase 3 test, children and elderly adults are excluded. For safety, the density of side effects is 18.9%, with no grade 4 adverse events or fatalities reported. The most adverse event is injection site pain, which is consistent with the result of phases 1-2. [21]

### *3.2 Discussion*

Compared to mRNA vaccines, inactivated vaccines, such as the CoronaVac COVID-19 Vaccine, obviously have lower vaccine efficacy and a higher rate of adverse effects. Although it is much easier to apply in less developed countries, scientists still want to develop a stronger vaccine and take advantage of both the low cost and high efficacy. Thus, a booster dose was created. The study in phases 1 and 2 shows that the booster dose increases the immune response dramatically when the trail population experiences a decline in neutralizing antibody titres six weeks after the previous two doses were taken among old adults. Therefore, the conclusion is that the third dose should be applied to preserve the continuity of herd immunity. [22]

## 4. VECTORED VACCINES

### *4.1 Johnson & Johnson-vaccine*

Johnson & Johnson-vaccine was developed by Johnson & Johnson Company in the United States. This type of vaccine works differently from the previous two vaccines mentioned before. mRNA vaccines are protected by lipid nanoparticles, which break down quickly when they are injected into the human body and cause the human cells to make a part of the virus. Since the genetic material breaks down rapidly, it cannot remain in the human body for a long time. Thus, mRNA has to be conserved at a pretty low temperature, which increases the cost and barriers to widely applying it. In contrast, the vectored vaccines, such as Johnson & Johnson vaccines, are protected by respiratory viruses. Johnson & Johnson vaccines use adenovirus 26, which is modified by doctors so that it will not cause any illness. After Johnson & Johnson vaccines enter the normal human cells, the viral DNA is released and the spike protein is going to be recognized by the immune system. [23] Eventually, the antibody is produced spontaneously, and people can prevent being infected by COVID-19.

The phase 3 test of the Johnson & Johnson vaccine shows that this type of vaccine has relatively high efficacy and reliable safety. 39,321 participants attended the international, randomized, and double-blind trial. In 14 days, the immunogenicity is 66.9% to prevent the moderate infection of SARS-CoV-2 and 66.1% in 28 days. For critical or severe infections, the efficacy is 84%, and there is no cause of death or hospitalization for all of the participants. In addition, scientists find that the efficacy remains almost the same for elderly people and young people. In terms of safety, the side effects are different for adults aged 18 to 59 years old and older people aged over 60 years old. For the younger adults, the major adverse effects are injection site pain, which happened to 58.6% of the attendants, and headache, which occurred to 44.4% of the participants. For the elderly, the major side effects are injection site pain (33.3%), headache (30.4%), and fatigue (29.7%). [24]

However, the Johnson & Johnson vaccine was halted for a safety problem on April 13, 2021. The cause is that there are six cases of women between 18 and 48 who got cerebral venous sinus thromboses (CVST) after the injection of the Johnson & Johnson vaccines. The FDA suggested pausing the application of the Johnson & Johnson vaccine until April 13, after their judgment for the conclusion decision on the widely spread of Johnson & Johnson vaccine injections. Finally, the FDA and CDC announced that the Johnson & Johnson vaccine is very effective in preventing SARS-CoV-2 infection. However, the application of this vaccine might lead to a low risk of CVST and thrombosis-thrombocytopenia syndrome. [24]

### *4.2 Oxford-AstraZeneca*

The Oxford-AstraZeneca vaccine, also known as ChAdOx1, is a vaccine developed by the University of Oxford in the United Kingdom. The principle is almost the same as with the Johnson & Johnson vaccine: using the adenovirus virus to protect genetic materials.

During the trial of phase 3, the efficacy is pretty similar to that of the Johnson & Johnson vaccine, and the side effects are much more slight. The approximated efficacy is 64.3% in 32451 participants to prevent SARS-CoV-2 infection. This data is extremely close to the efficacy of the Johnson & Johnson vaccine, which is estimated to be 66.1%. However, adverse events happen much less frequently. Injection-site pain is 6.8% in the vaccine group and 2.0% in the placebo group. Headache is 6.2% in the vaccine group and 4.6% in the placebo group. Overall, the side effect occurred in 37.0% of the ChAdOx1 group and 40.6% of the placebo group. In particular, the thrombosis-thrombocytopenia syndrome, just like the research data of the Johnson & Johnson vaccine, is still an adverse event in the trial. [25]

### *4.3 Discussion*

The phenomenon of thrombosis-thrombocytopenia syndrome that happened as a side effect of both vector vaccines has been named vaccine-induced immune thrombotic thrombocytopenia (VITT). Since Oxford-AstraZeneca and Johnson & Johnson-vaccine are both made from adenovirus, the possible reason for the occurrence of headache and VITT is the material both used by these two vaccines to protect the genetic information of the COVID virus, the spike protein creator. So, the experts suggested avoiding the use of heparin and platelet transfusions, which are the coagulating causes. They advised using anticoagulants (DOACs). Furthermore, the rapid and large amount of injection dose could be one of the causes of VITT.[26] Consequently, scientists are focusing on the prevention of VITT and CVST to increase the safety of vector vaccines through multiple methods.

## 5. SUB-UNIT VACCINES

As part of the promotion of the great need to develop an effective and safe vaccine globally, scientists also applied a part of the virus to vaccine production. The vaccines produced by this method are termed "sub-unit vaccines."

Overall, the advantages and disadvantages of the sub-unit vaccine are pretty obvious. They contain pure antigens with high safety and an easy production process. These critical advantages can help the popularity of COVID vaccines and control the spread of the epidemic globally. However, this type of vaccine requires adjuvants and multiple doses to ensure its efficacy of protection. In that case, people might have to spend more time and investment in the progress of the injection.[31]

ZIFIVAX, ZF2001, is based on RBD-dimer. Researchers found that the recombinant RBD protein, a fragment of the virus, can form a strong bond with the human ACE2 and bat ACE2 receptors. In that case, this reaction will be a barrier to the combination of SARS-CoV-2 and its counterpart receptors in the animal cells. Additionally, doctors discovered a specific antibody that cross-reacted with the RBD protein, preventing SARS-CoV-2 infection.[27] On this principle, the ZIFIVAX vaccines came to a realization.

In phase 1 and phase 2 trials, the ZF2001 exhibits 93%–97% of the antibody neutralizing rate, which is relatively high. And for safety reasons, the systemic advent events are absent or mild for the majority of the participants in the trials. [28] In the phase 3 trial, the ZF2001 provided a vaccine efficacy of 81.76% at any degree of severity. Also, the conservation and transmission method of ZF2001 is much easier to achieve than the ones to protect the efficacy of mRNA vaccines. Thus, ZF2001 has been authorized for emergency use

authorization (EUA) in China.[29] This vaccine might be widely applied in developing countries where advanced protection devices are not commonly available.

In addition, some scholars also discovered that the milk of cows and goats injected with ZIFIVAX still contains neutralizing antibodies and remains active after standard milk pasteurization. This phenomenon infers that human beings who consume the milk or the offspring of the ZIFIVAX-injected animals might passively gain the antibody. However, this hypothesis has not been peer-reviewed, so it cannot be a certain conclusion. [30]

## 6. CONCLUSION

Four types of vaccines have both merits and defects in vaccine production. mRNA vaccines have high protective efficacy against the coronavirus, but their conservation cost is relatively expensive, needing to be reserved at a very low temperature to be efficient. Because of the low requirements for temperature, inactivated vaccines are easy to transport and restore. Because of this, their production efficacy is merely half that of live vaccines. Vectored vaccines have higher immunogenicity than inactivated vaccines and more readily available storage conditions than mRNA vaccines. However, the risk of VITT and CVST caused by the side effects of this vaccine has not been eliminated to assure the safety of vectored vaccines. The subunit vaccines seem to have characteristics of being efficient, safe, and easily achievable. Nevertheless, they need adjuvants and multiple doses.

Although the principle and results have differences between various kinds of vaccine products, scientists in each research field are still trying to come up with more safe, more efficient, more available, and more convenient vaccines through multiple creative methods.

To produce a higher quality vaccine, scientists might choose different ways to improve different vaccines. For mRNA vaccines, the scholars would increase the tolerance of protein under more accessible conditions by making the S protein more stable. Scientists may develop more doses of inactivated vaccines to improve protection efficacy against COVID. Furthermore, because inactivated vaccines require a large number of inactivated viruses, increasing the risk of epidemic, scientists may be able to create an inert version of the COVID virus for vaccine production. For vectored vaccines, doctors can decrease the possibility of VITT by reducing the coagulating causer contained in the virus protein used in the vaccine production or by lowering the amount of injection for each dose. Additionally, scientists can advise people who are injected with vectored vaccines to have appropriate food or drugs to avoid thrombus. For subunit vaccines, the vaccine developer could try to combine different functions of different doses to make them more convenient for injection.

With the rapid development of vaccines, the virus variants have also become stronger and stronger, such as Omicron. The facts show that the vaccines mentioned at present can be effective for different types of COVID variants, but a huge breakout or creative way that is relatively reliable to protect people from worrying about the variants is still expected. In that case, there will be more improvements in the vaccine production method or new types of vaccines will be discovered in the future.

People in the developing countries in Asia and Africa are still facing the risk of vaccine shortages and are short of the mindset to be injected with an immune vaccine for COVID. More focus and research are needed to promote public health worldwide.

As for the limitations, this introduction to the four mainstream types of COVID vaccines gives some basic specialty of different vaccines, narrating the differences in vaccine principles and trial results. Nonetheless, the data mentioned in this paper come from different countries and researchers, which leads to a high chance of unpredictability. Also, the several inaccessible trial results form a great barrier to the extent of comprehensive It would be more scientific and precise if the information about the four vaccines in the phase 3 trials all came from the same country with the same number of participants and the same ratio of young and elderly people.

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