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REVIEW

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mRNA vaccine-a desirable therapeutic strategy for surmounting COVID-19 pandemic

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ABSTRACT

As an acute respiratory infectious disease, COVID-19 threatens the safety of global public health. Given the current lack of specific treatment against this disease, research and development of vaccines have become sharp weapons for overcoming the pandemic. mRNA vaccines have become the lead in COVID-19 vaccination strategies due to their advantages, such as rapid industrial production and efficacy. A total of 137 COVID-19 vaccines have entered the clinical trial stage, among which 23 are mRNA vaccines, accounting for 17% of the total vaccines. Herein, we summarize the research and developmental processes of mRNA vaccines as well as the approach for protecting the human body against infection. Focusing on the latest clinical trial data of two COVID-19 mRNA vaccines from Pfizer and Modena, we discuss their effectiveness and safety. Finally, we analyze the challenges and problems that mRNA vaccines face in controlling the COVID-19 pandemic.

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1. Introduction

The 2019 coronavirus disease (COVID-19) pandemic caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has exerted a tremendous impact on human beings. Thus, it is particularly important to quickly develop a safe and effective vaccine to prevent coronavirus disease.

Many studies have shown that mRNA vaccines are safe and effective in many infectious diseases such as Acquired Immunodeficiency Syndrome (AIDS),[1] rabies,[2] and in cancer malignancies.[3] Phase I clinical trials of the first mRNA vaccines of H10N8, H7N9 influenza viruses and SARS-CoV-2 showed that the vaccine was well-tolerated and triggered a strong humoral immune response.[4,5] Unlike DNA vaccines, mRNA vaccines are not embedded in the host DNA sequence, so they are safer.[6–8] In addition, the industrial production of mRNA vaccine is very rapid.[9–11] Over one billion doses can be produced by simple amplification technology, and the cost is low; thus, it can address large supply demands in a short period of time.[12] These advantages of mRNA vaccines also allow them to play a leading role in the COVID-19 pandemic.[13]

In the past few decades, mRNA vaccines have evolved from a suspicious idea to a clinical reality. In 2020, the COVID-19 pandemic gave birth to the fastest vaccine development in history, among which mRNA vaccines were one of the earliest types that were urgently applied and popularized.[14] So far, 28 COVID-19 vaccines have been approved in different regions of the world, of which 3 are mRNA vaccines and they are from BioNTech-Pfizer, Moderna and Takeda which are the first to be approved to use. COVID-19 - living NMA initiative collected 461 RCTs and 222 non-randomised studies of vaccines from the International Clinical Trials Registry Platform, of which 170 studies are about mRNA vaccines. Results of many clinical trials exceeded expectations. The research of nano-transport system is very important for stabilizing mRNA, which includes lipid delivery systems (lipid nanoparticles and liposomes), polymer complexes, micelles, cationic peptides and so on.[15] At the same time, research on the mechanism of allergic reactions to mRNA vaccines has also attracted the attention of scientists. Contact system, complement, preexisting antibody and mast cell are gradually considered to be contributors to the allergic reactions.[16] In general, the prospect of mRNA vaccines is worth expectant.

Previous studies and clinical trials have shown that the BNT162b2 vaccine jointly developed by Pfizer and BioNTech and the Moderna vaccine developed by Moderna show high efficacy and good safety profiles,[17,18] having considerable infection prevention againstSARS-CoV-2. This review quotes clinical trial data of BNT162b2 (Pfizer/BioNTech) and Moderna vaccines. While summarizing their efficacy and safety, the challenges and problems faced by mRNA vaccines are also discussed to allow acceptance of mRNA vaccines as an important reference and guide for controlling the pandemic situation of COVID-19.

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2. Research and development of COVID-19 mRNA vaccine

2.1. Antigen selection

SARS-CoV-2 is an enveloped RNA virus. As a member of the coronavirus family, SARS-CoV-2 also has four major structural proteins, respectively called the spike protein S, small molecular envelope protein E, membrane protein M, and the nucleocapsid protein N. Two functional subunits, S1 and S2, are included in the S protein and play different roles. S1 subunit carries the virus's receptor binding domain and is involved in the adhesion of the virus to the host cell membrane surface, while S2 subunit mediates the fusion of the host cell membrane with the virus membrane.[19,20]

Located at the S1 subunit on the S protein of SARS-CoV-2, the receptor binding domain (RBD), possesses a strong affinity with the angiotensin-converting enzyme 2 (ACE2).[21,22] Upon the binding of the S protein to ACE2 on the host cell membrane, ACE2 can be cleaved by proteases in the cell and the S protein be activated at the same time, consequently facilitating the virus membrane to fuse with the host cell membrane and enter the cell.[23] Therefore, the S protein is used as a target spot to develop vaccines.

Additionally, as the RBD is required for receptor docking responsible for the recognition of ACE2,[24] RBD is also a target for vaccine development.

In summary, both the S protein and RBD of the S protein in SARS-CoV-2 can be utilized as antigens for mRNA vaccine development (Figure 1).

2.2. Manufacturing process

At the end of April 2021, Pfizer's messenger RNA vaccine manufacturing process was first introduced. Next, we will take its research and development process as an example to briefly describe the production process of mRNA vaccines (Figure 2). The scientists first obtained the novel coronavirus gene sequence through high-throughput sequencing, and then selected and extracted the target gene sequence. Since novel coronavirus nucleic acid is an RNA fragment with poor stability, the scientists extracted the target fragment sequence and transformed it into a double-stranded DNA loop by reverse transcription, which was stored in the form of plasmid. After that, technicians injected plasmids into the engineered *Escherichia coli* host. During the process of *Escherichia coli* amplification in the culture medium, the plasmids were also replicated at a high speed as the raw material of the vaccine. After replication, the technicians collect the plasmid by means of purification, and then inspect its quality. After confirming that the gene sequence without mutation, the plasmid was cut and the desired DNA linear sequence was purified as well. Under the induction of key enzymes, mRNA was transcribed by using DNA template. It is well known that mRNA fragments could be easily destroyed by human cells, so the transcribed mRNA needed to be combined with lipids to form lipid nanoparticles after quality inspection. Finally, the vaccine particles were packaged in sterile injection vials, and the production of mRNA vaccine was completed.

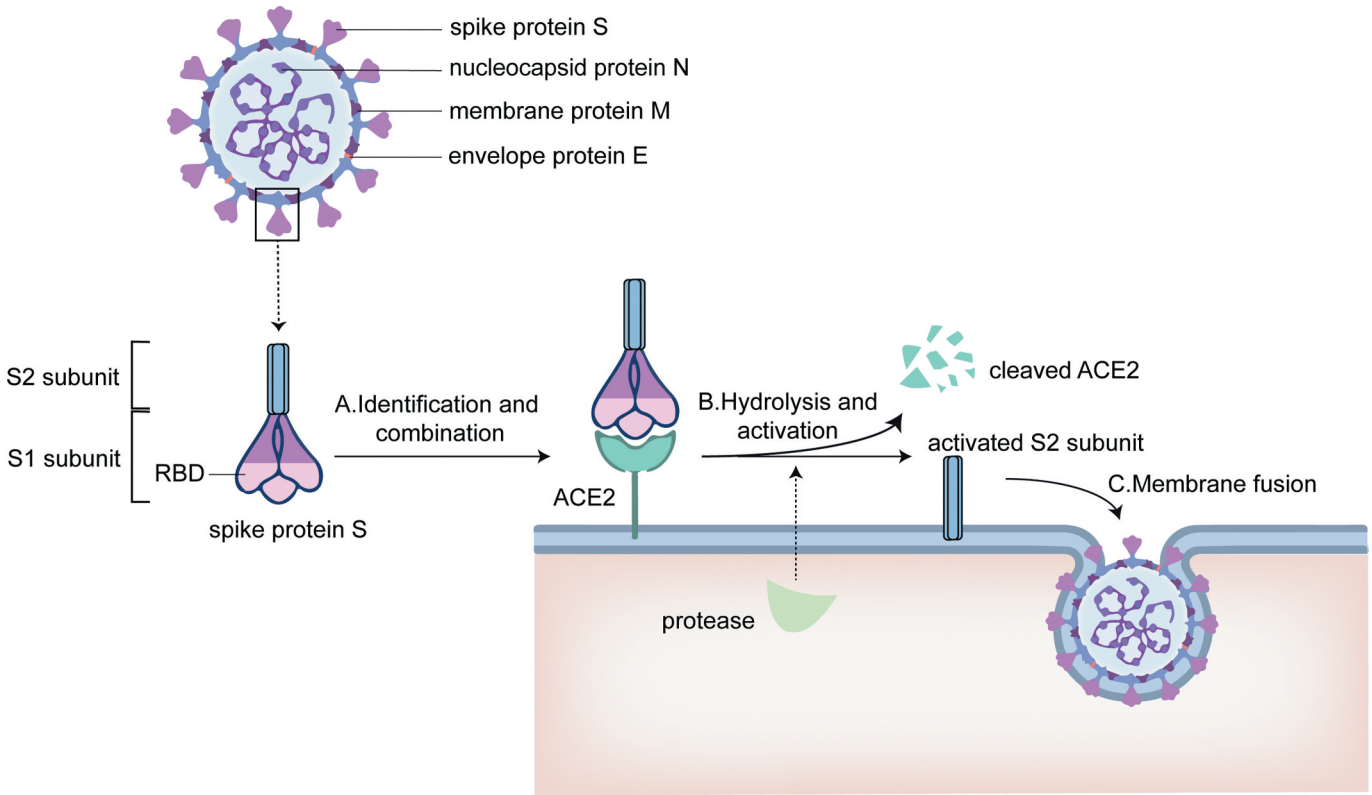

Figure 1. Membrane surface protein of SARS-CoV-2 and the mechanism of SARS-CoV-2 invading cells. A. S1 subunit recognizes and binds ACE2 on host cell membrane. B. Proteases from host cells disassemble ACE2 and activate S2 subunit C. Activated S2 subunit mediates the fusion of virus envelope and host cell membrane, and then the virus invades the cell.

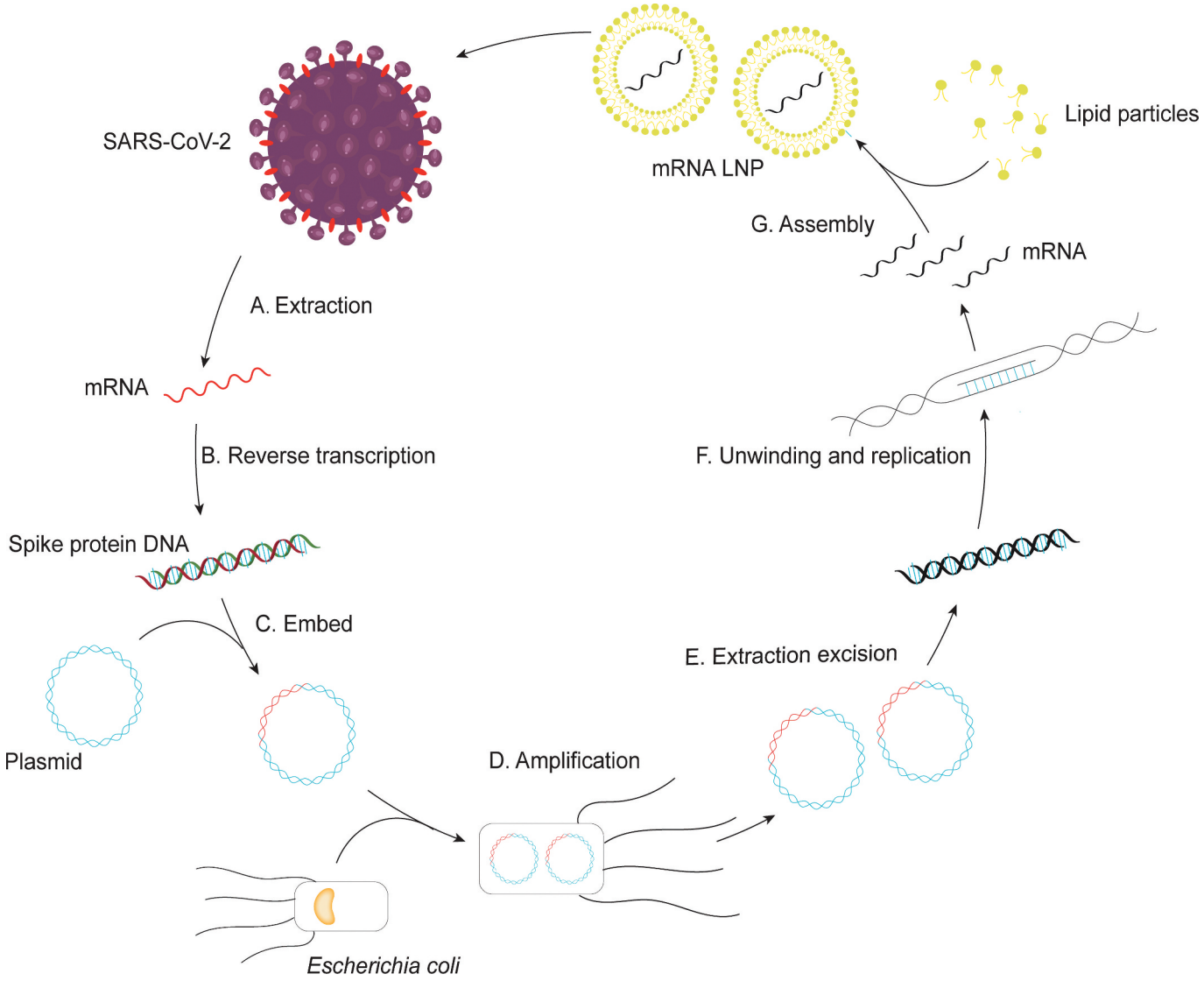

Figure 2. Synthesis of the mRNA vaccine. A. mRNA of target protein is extracted from SARS-CoV-2. B. Targeted mRNA is transcribed into double-helix DNA through reverse transcription; C. DNA strands combine with plasmid. D. Plasmid incorporating fragments of DNA are amplified in *Escherichia coli;* E. the target DNA is sheared from many cloned plasmids and purified; F. the double stranded DNA (dsDNA) template is unwound by enzymes and transcribe into mRNA; G. the final assembly of the vaccine is achieved by enclosing mRNA with liposomes. LNP: Lipid nanoparticles

3. Mechanism of activity of COVID-19 mRNA vaccine

As early as the nineties of the 20th century, mRNA vaccines were proposed and studied by researchers. The theory, technology, and economic investment of mRNA vaccines have constantly accumulated and improved. Their underlying mechanism have increasingly been clarified and better understood by scientists. The breakthrough in the mechanism of action has allowed the novel coronavirus mRNA vaccines, which are a third-generation vaccine technology, to achieve a prominent role during this pandemic.[25]

Currently, mRNA vaccines not only activate the exogenous immune response pathway of CD4+T cells like the inactivated vaccines, but also activates a large number of endogenous immune response pathways involving CD8+T cells, resulting in the activation of numerous of effector and memory CD8+T cells (Figure 3).[26] In addition, the mRNA vaccine complex can activate antigen presenting cells (APCs) to transcribe many viral S protein fragments after entering the APC cytoplasm. mRNA vaccine can be synthesized in the human body, so it has several unique advantages, which are listed as follow. First, it can reduce the adverse reactions of direct injection of viral protein. Furthermore, mRNA vaccines can be fordized quickly through PCR and induce spike antigen in vivo instead in vitro, which can save time and money.

The exogenous immune response pathway of the mRNA vaccine is as follows: The mRNA vaccine is taken up by muscle cells after injection into the human body. Muscle cells translate many S protein fragments and transport them out of cells in a short time, which allows them to bind to different types of APCs, such as macrophages, and dendritic cells (DCs), to activate human immunity. Immature DC cells phagocytose S protein fragments and activate mature DC cells. At the same time, macrophages can process synthetic protein antigen information, release cytokines, and promote the maturation of DC cells. Mature DC cells splice S protein fragments and present them to CD4+T cells for recognition and binding

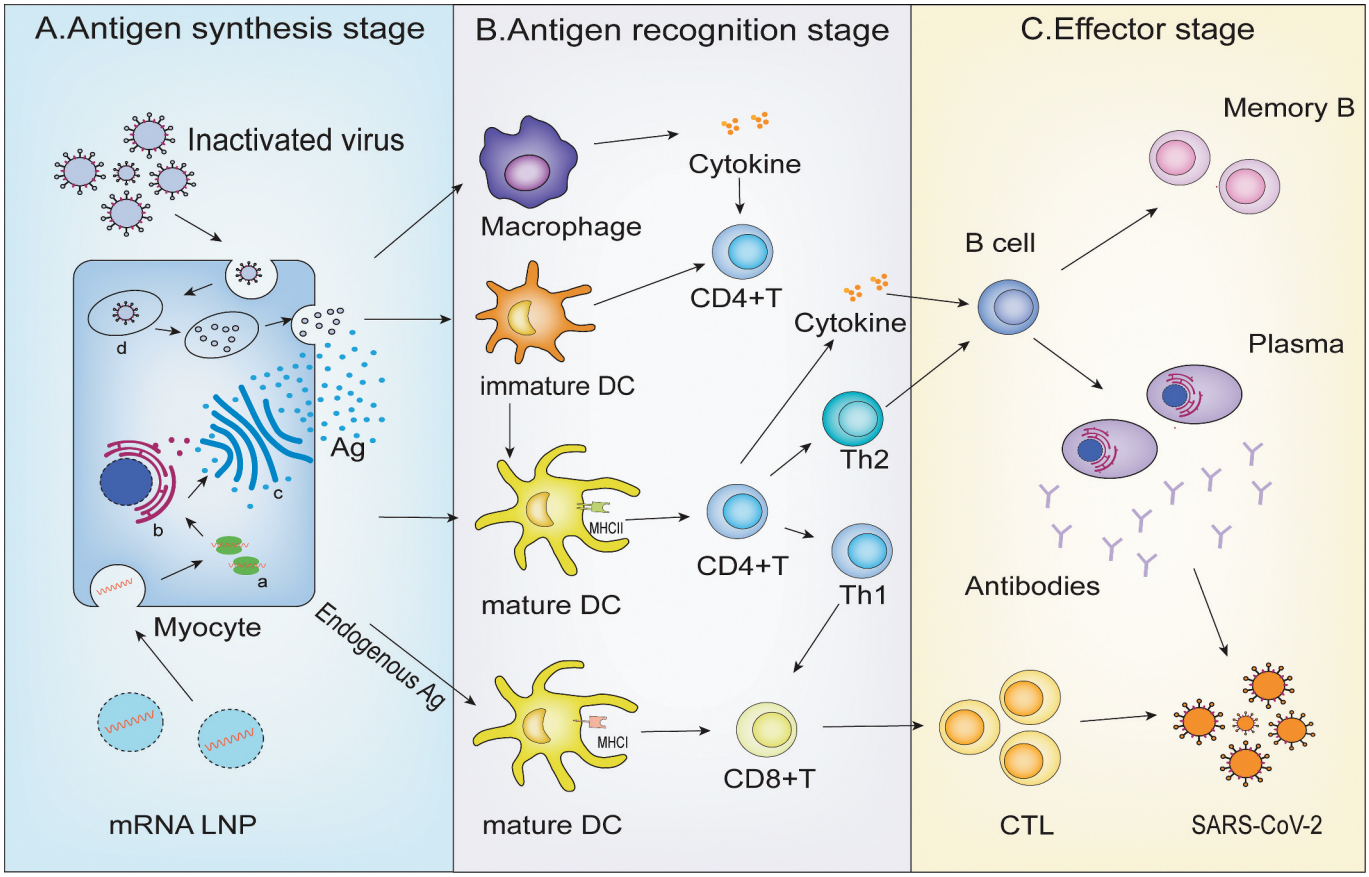

Figure 3. Mechanism of inactivated vaccine and mRNA vaccine. A. Antigen synthesis stage: Myocytes capture inactivated virus from inactivated vaccine and target mRNA LNP from the mRNA vaccine; B. Antigen recognition stage: (1) Antigen presenting cell including DC cells and macrophages recognize the antigen phagocytosed from muscle cells and present it to DC cells; (2) Common features: Both vaccines activate CD4+T cell immunity through the MHC class II pathway; (3) mRNA vaccine advantages: mRNA LNP can activate more CD8+T cells because of the presence of the MHC class I pathway; C. Effector stage: CTL and B cells are activated and destroy the virus. a. Ribosome b. endoplasmic reticulum c. golgiapparatus d. lysosome.

through MHC class II molecules.[27] CD4+T cells activate B cells and produce plasma cells and memory B cells by directly binding and secreting cytokines, resulting in a series of downstream humoral immune effects dominated by antibodies. The mRNA vaccine can also activate the endogenous immune response pathway: both APC cells and other nucleated tissue cells can splice the S protein constituted in mRNA vaccine and then present it to CD8+T cells through MHC class I molecules on the membrane surface, thus activating CD8+T cells and producing memory and effector T cells. When reinfected with SARS-CoV-2, cellular immunity and humoral immunity are activated at the same time.[28–30] The memory immune cells produced by the body, such as memory B cells and antigen-specific cytotoxic T cells, can quickly recognize the virus, produce additional antibodies, accurately kill the infected cells, eliminate the virus, and prevent the continuation of infection.

4. Efficacy of COVID-19 mRNA vaccine

As a vaccine product of the latest technology, mRNA vaccines have made a historic breakthrough in the fight against COVID-19. Its clinical trial outcomes have been far beyond the public expectation. The vaccines not only exhibit a low incidence of adverse reactions, but they also hold a prominent position in clinical efficacy among all existing vaccines. The latest clinical trial data evaluating these two vaccines which highlight the superior clinical efficacy of mRNA vaccines will be briefly summarized below.

4.1. Phase III clinical trials of BNT162b2 and mRNA-1237

First, we will describe the phase III clinical trials of the BNT162b2 and mRNA-1237 vaccines. All the volunteers in this phase III trial were over age 16 years, while volunteers in mRNA-1237 trial were over 18 years.

The phase III trial of the BNT162b2 vaccine enrolled 43,548 volunteers who were randomly assigned. Compared to placebo group, BNT162B2 was 95% effective in preventing COVID-19 overall. In addition, as for prevention of severe COVID-19 infection, the preventive rate was 95% over all ages, and 94% in the elders over 65 years of age.[17] Moreover, the trial classified different age groups including 16–55 years, over 65 years and over 75 years. From the survey analysis mentioned in the trial, according to confidence interval (CI), we cannot clearly judge that the efficacy of the vaccine differs in different age groups. As a result, we have reasons to believe that BNT162b2 have considerable efficacy in all age group which is over 16 years.

The efficacy of the mRNA-1237 vaccine during phase III clinical trials also exceeded researchers' expectations. Researchers carried out III trial, which involved 30,000 people,

and found that vaccination reduced the rate of infection by 94.5%. In other words, individuals who were inoculated had a 94.5% lower risk of infection than those who were not.[18] We compare the efficacy classified in two age subgroups. One group which individuals aged from 18 to 65 years reached vaccine efficacy of 95.6% (90.6%-97.9%). The efficacy of another group which individuals aged over 65 years was 86.4% (61.4%-95%). From the data listed above, we can draw a conclusion that even the efficacy of two vaccines differ in different groups, the protective reaction of mRNA vaccine is quite receptable over all ages.

4.2. Clinical efficiency for specific populations

4.2.1. Medical staff

As the main physical force in the fight against COVID-19, the safety of medical staff must be guaranteed. Many countries and institutions are investigating the efficacy of mRNA vaccination among medical staff. Only by effectively protecting the safety of health care workers we can continue the fight against the virus.

In a survey conducted at the largest medical center in Israel, a total of 11,453 medical personnel received two doses of mRNA vaccine from 9 December 2020 to 28 April 2021 throughout the medical center. Thirty-nine SARS-CoV-2 breakthrough infections were detected among healthcare personnel with access to RT-PCR testing. As a result of survey, we found that the breakthrough infection rate among medical personnel was very low, and most symptoms were mild to absent, albeit persistent.[31]

Three studies published on the same day by the New England Journal of Medicine included real-world data from four medical institutions across different countries. The results of the three studies showed that the mRNA vaccine could significantly reduce the risk of Novel coronavirus infection in first-line medical staff, especially after two doses of injection. We can reach a conclusion that according to data mentioned above, after two doses of mRNA vaccines, positive infection rate of people decreases to .05% or so compared to 2.6% of unvaccinated people. After the completion of two doses of vaccine, it still could not achieve “zero risk”. Thus, researchers suggest that front-line medical staff should continue to take necessary precautions even after vaccination is completed.[32–35]

4.2.2. Teenagers

At present, the number of teenagers infected is also increasing, and the issue of whether teenagers should be vaccinated has attracted increasing attention in various countries, especially in America.[36] Majority of Children and adolescents infected with SARS-COV-2 have mild symptoms, but they are prone to suffer from long-term complications that affect their growth and development. Adolescents currently spend most of their time at school or at home, although school life is relatively shut-down. However, if the number of cases among adolescents continues to rise, the pandemic will inevitably worsen.[37] If the age of vaccination can be widened, it will contribute to an earlier return to normal school life among children.

Participants in Pfizer/Biotech‘s vaccine trial included 2260 U.S. adolescents aged 12 to 15, 50% of whom received placebo. In the placebo group, 18 participants were later infected with COVID-19, while none of the participants who received the actual vaccine were infected, achieving 100% immunity and experiencing no serious side effects.[38] On 10 May 2021, the United States Food and Drug Administration (FDA) approved Pfizer‘s COVID-19 vaccine BNT162b2 for emergency use authorization (EUA) in the United States for children aged 12 to 15 years. The follow-up surveys indicated that the vaccine sustains the efficacy of 91% against SARS-COV-2.[39] At the same time, clinical trials under 12 years of age are gradually being carried out, and clinical results currently shown in 5–11 years of age are similar in both safety and immunogenicity to other age groups which is over 16 years.[40,41]

4.2.3. Elders

It is particularly important to develop a vaccine for the elderly, who suffer from weakened body functions and inferior immune systems. It can effectively reduce the number of critically severe cases and reduce the spread of disease. 42% of participants in the BNT162b2 phase III trial who received two consecutive doses were over 55 years of age, suggesting that the vaccine is also highly effective in elder individuals.[17] The phase III trial of mRNA-1237 also encounter similar result.[18] A clinical trial of mRNA-1273 in people aged 56 and older found that the immune response of those aged 56 and older after the vaccine was similar to that of those aged 18–55.[42] A clinical test conducted in China found that the elderly (65–85) could produce robust interferon-γ T cell responses. Although one analysis found lower levels of antibody production in people over 80 years of age after vaccination, in particular B.1.1.7 (Alpha), B.1.351 (Beta) and P.1 were less potent neutralizing agents.[43] However, the elders, a high-risk group of virus infection, it is necessary to inoculate vaccine as vaccine protection is still acceptable.[44]

4.2.4. Individuals with a history of SARS-CoV-2 infection

The COVID-19 pandemic is rapidly spreading around the world beyond our imagination. Although many vaccines have currently become industrialized, the supply of vaccines is unable to meet the high demand for vaccines in a short time. Therefore, in the face of insufficient supply, individuals questioned whether a single dose of vaccination could effectively improve the body‘s immunity. Scientists first investigated individuals with previous infections.[45] Could the immunity of previously infected patients be fully enhanced after vaccination with a single dose? It is observed that a single dose of BNT162B2 mRNA vaccine was sufficient for individuals with a history of SARS-CoV-2 infection, according to clinical researches.[46–48] The researchers found that at all time points, individuals previously infected with SARS-CoV-2 presented higher antibody levels for both IgG (N) and IgG (s-RBD). Both of them represented the immune reaction to prior infection. In addition, IgG (s-RBD) also represented the immune reaction to prior infection or vaccine. Furthermore, there was no significant discrepancy in IgG (s-RBD) levels between individuals who previously infected and revived only a single dose and individuals who were uninfected before and received two doses. According to serum antibody analysis of COVID-19 patients, we found that serum-associated antibodies are closely associated with the prognosis and severity of the disease. High titers of neutralizing antibodies can help patients recover more quickly and ward off a reinfection.[49] Scientists are starting to

develop neutralizing antibodies to prevent and treat COVID-19 infections.[50] Therefore, serum neutralizing antibodies highly predict that only one dose of vaccine is needed to achieve the effect of two doses of vaccine for persons previously inflected.

4.3. Neutralizing effects in the real world

As the time goes by, mRNA vaccines are being promoted in more and more countries, providing rich data support for efficient statistics of mRNA vaccines in the real world. The first two mRNA vaccines approved for use are Moderna mRNA-1273 and Pfizer-BioNTech BNT162b2, which still show excellent effectiveness in the environment of large-scale vaccination.

In 2020, studies have begun to try to count the effectiveness of mRNA vaccines in population vaccination. In a large-scale study on the effectiveness of mRNA COVID-19 vaccine among U.S. veterans from May to July 2020 (n = 6 647 733), the overall vaccine effectiveness (VE) was 95% (95% CI, 93%-96%) for complete vaccination (≥14 days after the second dose) and 64% (95% CI, 59%-68%) for partial vaccination (≥14 days after the first dose) and the estimated VE for two doses of vaccination against COVID-19-related hospitalizations is 91% (95% CI 83%-95%).[51] In the same study of American veterans, a case-control study (n = 108 720) from 15 December 2020 to 4 March 2021 showed that the overall vaccine effectiveness was 97.1% (95% CI, 96.6% to 97.5%) injected with the second dose after 7 days or more.[52] This study also reached a more detailed conclusion that the VE of Moderna mRNA-1273 and Pfizer-BioNTech BNT162b2 were 96.2% (CI, 95.5% to 96.9%) and 98.2% (CI, 97.5% to 98.6%), respectively.[52]

It is worth celebrating that by the end of 2021, similar results have been obtained in the vaccine effectiveness studies in the context of extensive mRNA vaccination in many regions and countries such as the United Kingdom, Italy, and Israel.[46,53,54]

In addition, the number of inoculation doses and the time after inoculation are very important influencing factors for VE. Studies have shown that the more doses of Pfizer-BioNTech BNT162b2 are administered, the more effective the vaccine is; and as the time of inoculation of Pfizer-BioNTech BNT162b2 increases, the VE will gradually decrease.[55–58] In particular, the interim results of a prospective observational cohort study indicate that in individuals with a history of COVID-19, vaccination with Moderna mRNA-1273 may provide additional protection beyond the immunity gained from previous infections, with a VE range of 8.2%-33.6%.[59]

4.4. Mutant virus variants

Over time, novel Coronavirus variants have spread throughout the world. To escape the attack of the human immune system in different environments, the virus has evolved different mutant variants, which have greatly altered the pathogenic potential of the virus and have enhanced concern regarding the development of effective vaccines. As of December 2021, more than 10 mutant variants have been identified by the World Health Organization (WHO),[60] which four are highly virulent, widely diffused, and have attracted widespread public attention, namely variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2).[61] Here are some clinical trials testing the efficacy of mRNA vaccines defending mutants.

As for the alpha variant, the results of the recently published vaccine's efficacy tracking displayed a 93.7% prevention rate against the mutant strain after two doses of Pfizer vaccine.[62] As for Beta mutant strain, two real-world studies in Qatar determined that two doses of the Pfizer and Modena vaccines were 75% and 96.4% effective against the mutant strain, respectively.[62,63] However, over 95% of severe cases were averted, and the Pfizer vaccine even achieved a 100% protection rate.[63] Thus, it is not difficult to conclude that despite the obvious immune escape potential of the mutant strain, the currently developed mRNA vaccines still present good preventive and protective effects. As for Gamma, investigations showed that the Gamma strain spread 1.7 to 2.4 times faster than the non-Gamma strain, and that prior (non- Gamma) infection did not provide 100% protection against Gamma infection, with immune escape rates ranging from 21% to 46%.[64] In a recent real-world study in Chile, the Pfizer's vaccine was 92.6% effective. As for Delta, with regard to the strongest mutant strain Delta, the BNT162b2 vaccine also holds a certain effective defense against it. A clinical trial compared patients infected with Alpha and Delta mutants who were inoculated with the BNT162b2 vaccine. The results of the trial showed that the efficacy of the vaccine was significantly lower in those infected with the Delta variant than in those infected with the Alpha variant when only one dose was administered. After two doses, however, the efficacy was almost identical.[65]

In addition to the statistical analysis of cases, researchers have also measured the efficacy of the mRNA vaccine by measuring antibody levels in the serum of vaccinated individuals. An experimental study by Pfizer and the Texas University School of Medicine revealed that antibodies produced by mRNA coronavirus vaccine against the three mutant strains: Alpha（B.1.1.7）, Beta（B.1.351）and Gamma（P.1）, still present great neutralization efficacy.[66] One study assessed the neutralization ability of serum from human subjects or non-human primates (NHP) inoculated with mRNA-1273 against strains Alpha and Beta. The results showed that the neutralization ability of the immune serum to the virus strain Alpha and Gamma did not decrease, while the neutralization ability of the immune serum to the virus strain Beta decreased, but remained constant at a high level.[67]

In general, although several highly infectious variants have emerged, such as Omicron (B.1.1.529), studies have confirmed that the currently developed mRNA vaccines have considerable efficacy against virus mutants. While there are concerns about the vaccine's reduced protection against mutant strains, we should not ignore the fact that immunity decreases over time after vaccination.[68] As a result, the decrease in vaccine efficacy should not be entirely due to the mutation avoiding immune protection, but may be due to the time. To effectively deal with mutations, in addition to reducing the spread of the virus and ensure personal protection, individuals should actively advocate vaccination, control the pandemic as early as possible, and avoid the generation of mutant strains. Furthermore, it is also necessary to inoculate the third dose of vaccine to reach the purpose above.[56,69]

4.5. Retransmission inhibition

The BNT162b2 mRNA vaccine not only provides protection to the vaccinees, but also effectively reduces the viral load in infection regions characterized by Coronavirus outbreaks, which allows to further inhibit the retransmission of the virus. In an analysis of data sets that tested positive for SARS-CoV-2 after vaccination with the BNT162b2 mRNA vaccine, researchers found a significant reduction in viral load in infections that occurred 12 to 37 days after the initial vaccination. These reductions in viral loads suggest that vaccinated individuals are less infectious after re-infection with coronavirus compared to non-vaccinated individuals, further illustrating the impact of the vaccine on viral transmission.[70]

5. Safety of COVID-19 mRNA vaccine

5.1. Adverse reaction of the vaccine

The *Journal of the American Medical Association* of the Center for Disease Control and Prevention (CDC) analyzed local and systemic response data voluntarily reported by 3.644 million people vaccinated with mRNA coronavirus vaccines from 14 December 2020, to 28 February 2021. Statistical data indicated that adverse events of varying severity may occur after vaccination with mRNA vaccine for COVID-19. As with vaccines for other diseases, pain at the injection site after vaccination is common and generally lasts up to 2 days.[71–74] In addition, the main systemic reactions are fatigue, headache, muscle pain, fever, while other adverse events are less frequent, such as chills, fever, joint pain, nausea, vomiting, local redness and swelling of the skin.[18,75–77] Moreover, some common non-allergic symptoms such as pruritus, rash, scratchy throat and mild respiratory symptoms have also been reported.[78] But in general, most of these adverse reactions are temporary and will disappear within a short time.

Besides, some clinical studies have found that the occurrence of adverse events (AEs) in different groups is different. For example, AEs is more common in young adults, women, and people who received the second dose than in older adults, men, and people who received the first dose.[53,79–82] In contrast, since the immune response of young people and women is generally more active, and the response will be more reactive after the second dose of the mRNA vaccine, we consider that the stronger the immune response in the human body, the greater the possibility of adverse reactions after vaccination.

In addition, the CDC's Vaccine Adverse Event Reporting System found that the incidence of severe anaphylaxis was 5 cases per million population and 2.8 cases per million population after the first injection of Pfizer vaccine and mRNA-1273 vaccine, suggesting that serious adverse reactions were rarer with the mRNA-1273 vaccine.

Reports of hypersensitivity reactions to COVID-19 vaccines can be divided into immediate and delayed reactions. Among them, the former is equivalent to anaphylaxis. Most of these patients have a history of allergic reaction, which usually occurs within the observation window of 30 minutes after inoculation and may be life-threatening, requiring immediate treatment.[83] Delayed large local reactions were most common after administration of mRNA-1273 vaccine.[78,84] At the same time, further analysis of the components of the mRNA vaccine showed that the active components will not cause allergic reactions of the vaccine, but the excipient is the allergic sources, such as polyethylene glycol (PEG) and polysorbate. However, these excipients are essential to stabilize the lipid nanoparticles containing the mRNA, stimulate stronger immune response, and prevent bacterial contamination.[83,85] In the future, the development of excipients with weak sensitization may become one of the important research directions of vaccine research and development institutions.

Furthermore, a number of rare serious untoward reactions, which were thought to be possibly related to the immunizations COVID-19 vaccine, were reported by different countries in succession in 2021, such as thrombosis with thrombocytopenia syndrome [TTS], Guillain-Barré syndrome [GBS], myocarditis, pericarditis, and myocardial infarction.[84,86,87] The above adverse reactions have aroused great concern and need to be confirmed by further studies. The occurrence of myocarditis has attracted much attention. According to the Advisory Committee on Immunization Practices (ACIP) statistical data, as of 11 June 2021, 1226 cases of possible myocarditis/pericarditis had been reported after about 300 million doses of COVID – 19 mRNA vaccine.[88] Clinical observation found that the incidence of myocarditis was concentrated in young men, aged between 16 and 29 years old.[82,89,90] Additionally, the latest study found an increased risk of myocarditis events in three cases: within 1 week after receiving the first dose of mRNA or adenovirus vaccine, after SARS-COV-2 infection in the same population, and after vaccination for people under 40 years old.[91] Concerns about these adverse events have led several countries to suspend mRNA vaccination for young people, limiting the popularization of vaccines.[92]

Nevertheless, as more clinical trials were completed, the results show that the mRNA vaccine's safety is still satisfactory[93]and the mRNA vaccine has a good safety profile in terms of the response of recipients.[17,94] Since 26 May 2021, the Global Advisory Committee on Vaccine Safety (GACVS) has declared that although myocarditis and pericarditis may be causally related, severe cases are rare and most cases are mild after all.[82] Meanwhile, at the ACIP meeting in July 2021, after assessing the balance of benefits and risks of the mRNA vaccine for COVID-19 in adolescents and young adults, it was concluded that the benefits of vaccination with mRNA vaccine significantly outweigh the risk of rare serious adverse events following vaccination, and that all eligible individuals were recommended to be actively vaccinated against COVID-19.[82,86]

According to the latest vaccination schedule, Pfizer BioNTech's BNT162b2 mRNA vaccine showed excellent safety and efficacy in phase 2/3 clinical trials in children aged 5–11 years. Therefore, people over the age of five are encouraged to vaccinate COVID-19 vaccine as soon as possible. In the context of the current global pandemic, COVID-19 vaccines are advantageous in preventing the occurrence and mortality of COVID-19 globally, as well as preventing the occurrence of COVID 19-related complications such as ARDS and myocarditis. Thus, vaccination should continue to be actively promoted around the world to jointly promote rapid global vaccine deployment.

5.2. Safety of the vaccine for pregnant women

There has been a long and heated debate about whether pregnant women should be vaccinated. Determining whether to vaccinate pregnant women should take into consideration not only the impact of the vaccine on woman's own health, but also the potential danger to the fetus.[95] Several recent experimental studies have shed light on whether advantages of mRNA vaccines outweigh the disadvantages in pregnant women. A mouse experiment showed that mice injected with the BNT162b2 vaccine induced a significant immune response, and the presence of neutralizing antibodies was also detected in fetuses and progeny. No effect of BNT162b2 on female fertility was observed. Local side effects were also similar to those found in clinical trials.[96] The results also enabled clinical trials to include pregnant women to be inoculated with COVID-19 mRNA vaccine and to proceed smoothly. A clinical trial enrolled total of 35,691 pregnant volunteers, and the outcomes of pregnancies of participants enrolled in the V-SAFE pregnancy registry were similar to those in the pre-pandemic study. Compared with non-pregnant women, pregnant women reported more pronounced local pain, while headaches, muscle aches, chills, and high fever seemed to be weaker. Therefore, based on the results of this study, we did not find any evidence that mRNA produced serious adverse reactions in pregnant women.[97] Of course, participants will still need to be followed longitudinally to obtain more accurate data and results.

5.3. Safety of the vaccine for teenagers

By the end of December 2021 in the United States, more than 21 million adolescents under the age of 18 had received the mRNA vaccines at least one dose. The injection number of adolescents under 18 years is expected to increase further as children aged 5–11 years are also approved for vaccination in November. As a result, concerns about the safety of mRNA vaccines in adolescents are raised sequentially. Many clinical trials and surveys have been carried out to reveal the safety of mRNA vaccines in adolescents. The Vaccine Adverse Event Reporting System (VAERS) which administered by the CDC and FDA, collected 9,246 data reports from 12 to 17 years. The conclusion is that majority of adverse reactions (90.7%) are mild, and only 9.3% are considered serious, including 4.3% for myocarditis.[98] This means that, with the exception of myocarditis, multiple serious adverse reactions are considered rare. Two representative mRNA vaccines, BNT162b2 and mrnA-1273, also implemented placebo-controlled trials researching for adverse effects in adolescents.[99,100] The results showed that all adverse reactions are common. Among them, injection-site pain, fatigue, and headache are most accessible. Furthermore, both trials found no serious adverse events associated with the mRNA vaccine.[99,100] All studies indicate that mRNA vaccines may not bring serious adverse reactions to teenagers, and also reduce the hospitalization rate of severe infection and promote recovery.[101]

5.4. Safety data from long-term monitoring

The long-term safety of the mRNA vaccine is worth expectation. Safety data from a phase 3 clinical trial with a median follow-up of two months after vaccination with the BNT162b2 mRNA vaccine showed that both local reactions and systemic reactions to the BNT162b2 mRNA vaccine were predominantly mild to moderate, with no grade four local reactions. The percentage of participants reporting local adverse events did not increase after vaccinating the second dose. Meanwhile, apart from fatigue and headache, the frequency of reported serious systemic events after vaccinating any one dose was less than 2%. Additionally, in the vaccine group and the placebo group, the incidence of serious adverse events was similar.[17] Researchers followed 12,006 participants in this clinical trial after the second dose of vaccination with the BNT162b2 mRNA vaccine for at least six months. The results of the follow-up showed that the safety data obtained from six months after vaccination were similar to those obtained from two months of previous follow-up; at the same time, none of the cases of myocarditis were identified.[39] The current study results suggest that the mRNA vaccine has a good long-term safety profile. Before the outbreak of COVID-19, no vaccines have been approved for human trials. Therefore, whether there are some potential adverse reactions after injection is indistinct. The excitement is that serious adverse reactions reported so far are rare, sporadic, and unrepresentative. As the follow-up period extends, more data will be available to demonstrate the safety of mRNA vaccines. But in the background of COVID-19 pandemic, the popularization of mRNA vaccines should not be affected by this concern.

6. Stability of COVID-19 mRNA vaccination

In addition to the vaccine's efficacy, many people are also concerned about how long the effect of the vaccine lasts and when revaccination will be required. If the duration of the vaccine effect is too short, efficacy cannot be maintained over a substantial period, even if the efficacy is strong, the clinical significance is not extensive. It is of interest that Moderna has recently released phase III data, showing that six months after completing the second dose, the vaccine was still more than 90% effective against the virus. The Pfizer vaccine has also been investigated and follow-up data from a trial of 46,307 participants showed that the vaccine was still 91.3% effective six months after one week of the second dose. In the United States, the efficacy rate was 92.6%.[102]

Previously, the timeliness of vaccines was mostly evaluated by monitoring antibody levels in the peripheral blood. Recently, Jackson et al. focused their research on germinal center (GC), the birthplace of immune responses. The GC is the region where the immune memory is formed. Compared with the antibody, as the final product of the immune response, monitoring the GC can more effectively evaluate whether the human body effectively produces lasting immunity. The GC is the key to a lasting immune response, and the longer it exists, the longer the immune response lasts. This study shows that mRNA vaccines can induce a sustained GC B cell response,

which continues to produce strong humoral immunity. This further demonstrates that mRNA vaccine can provide long-term protection to humans.[103]

7. Discussion

7.1. Clinical efficiency

Due to the rapid spread of the COVID-19 pandemic, vaccines are urgently being developed and have been approved for use. Vaccine efficiency is currently based on results of phase III clinical trials. Phase III clinical trials involving the Pfizer and Moderna vaccines have revealed that the effective vaccine protection rate is approximately 95%. Currently, the efficacy rate of mRNA vaccine is much higher than that of inactive vaccines. However, at present, there is a lack of a standardized evaluation system for evaluating infection or vaccine efficiency in the world. For example, the symptoms that can be diagnosed as infection, are defined differently in different vaccine studies. In addition, the diagnosis generally depends on nucleic acid positive results, but if individuals in the trial do not undergo nucleic acid testing, despite the high likelihood of an infection, this will affect the accuracy of the trial. At the same time, in addition to paying attention to confirmed cases, suspected cases are also worthy of our attention. If there are too many suspected cases, this will introduce significant uncertainty to the trial results. Further, the number of individuals enrolled in trials are still limited compared to target population around the world, and with the current increase in the number of vaccinated individuals, vaccine efficiency will inevitably begin to fluctuate. Moreover, we need to consider differences in the efficacy of the vaccine in different trial groups, and whether the vaccine can prevent the transmission of coronavirus in COVID-19 patients with only mild symptoms.[104,105]

7.2. Transportation and storage

The stringent conditions required for the transport and storage of currently available vaccines is a central problem to be overcome in the promotion of mRNA vaccines. According to the temperature of storage conditions and shelf life of the mRNA COVID-19 vaccine published by the vaccine manufacturers, Pfizer vaccines are valid for six months when stored between −80 and −60°C but only for five days at 2 to 8°C At room temperature, its shelf life is greatly shortened to only two hours. The Moderna vaccine has made a breakthrough in the research and development of preparations, and its product can be stored at 2–8°C for 30 days, but only for 12 hours at room temperature.[106] Yet for economic constraints, it is tough to achieve such low-temperature preservation conditions in many countries, which hinders the promotion of the mRNA vaccine. How to improve the stability of mRNA vaccine has become an urgent problem due to scientists. Some researchers have determined that purified mRNA can maintain its activity at 4°C for up to 10 months after freeze-drying in trehalose, and its stability is similar to that of the traditional vaccines. Moreover, others have proposed to enhance the stability of the mRNA vaccine by modifying the preparation.[107] Relevant studies have found that various chemical modifications of mRNA through sequences and/or structural engineering contribute to enhance the stability of mRNA, such as extension of poly (A) tail, modification of the 5'cap, editing of UTRs, increasing the G-C fraction of mRNA, and so on.[108–111]

Currently, sufficient progress has been made in the application of mRNA vaccine in influenza and rabies. The mRNA vaccine of influenza virus HA maintains its protective effect after being stored at 37°C for 3 weeks.[12] Scientists found that the mRNA vaccine encoding rabies virus glycoprotein (RABV-G) still retained immunogenicity after long-term storage at 2–8°C 25°C and 37°C in the phase I trial of mRNA rabies virus vaccine CV7201. At the same time, it can also be used as a lyophilized preparation, which can be stored for 3 years at 5°C to 25°C and 6 months at 40°C without significant loss of activity.[29,112] Thus, we have reason to believe that in the future, it will not be too difficult to resolve problems related to transportation and storage.

7.3. Facing the mutant

Although the mRNA COVID-19 vaccine has a certain neutralizing effect against mutant novel coronavirus, it is particularly important to significantly improve the neutralizing ability. A clinical trial conducted by Moderna Company showed that among volunteers who had received two doses of mRNA-1273 vaccine, the third dose of COVID-19 vaccine could significantly improve the neutralization ability against COVID-19 mutant strains B.1.351 and P.1. Fifteen days after inoculation with mRNA- 1273. 35,115 designed for B.1.351 mutant virus, the Geometric mean titer (GMT) of the inoculant serum to B.1.351 was 1400, while the value for inoculated mRNA-1273 was 864. These preliminary data suggest that mRNA-1273.351 may more effectively enhance the neutralization ability of B.1.351 strain. In addition, local and systemic adverse reactions after the third dose of the vaccine were similar to those after the second dose of the vaccine in phase II and phase III clinical trials. Thus, mRNA vaccines exhibit a larger breakthrough space and better protective efficacy in the face of mutant strains. Due to the more rapid industrial preparation of mRNA vaccines, it can be produced in large quantities in a short time. By splicing and synthesizing the gene sequences of different mutant strains, we can prevent multiple mutant strains by inoculating only a single vaccine. Nonetheless, new vaccines require to undergo a series of clinical trials. It remains to be seen whether the optimization of the mRNA COVID-19 vaccine can catch up with the speed of virus mutation and defeat the virus.

8. Conclusions

As a new technology vaccine, mRNA vaccines present good prospects for more widespread application. In this COVID-19 pandemic, the data of existing clinical trials has proved that compared with other COVID-19 vaccines, the COVID-19 mRNA vaccine has a higher protection rate and safety, less side effects, and good defense against mutated viruses. Thus, it is reasonable to propose that mRNA vaccines will become an effective weapon to defeat novel coronaviruses. In addition, the emergence of the COVID-19mRNA vaccine has promoted rapid progress in the field of vaccine research and development, and mRNA technology platform is likely to provide novel formulations for the development

of vaccines for other infectious disease, which is expected to exert a positive "subversive" impact on vaccine development.

Author contributions

P.D. Zhang and H.L. Wang conceptualized and designed the study. Peixian Chen and Xiaoye Shi performed the literature search, drafted the manuscript and contributed equally to this manuscript. Weixin He and Yan Tang participated in manuscript writing and data collecting. Guowei Zhong were responsible for the formatting and image editing. All authors critically revised the manuscript and approved the final version.

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