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UNDERSTANDING COVID-19 VACCINES: MECHANISMS, EFFICACY, AND SAFETY

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Abstract

It has been over a year since SARS-CoV-2 was first reported in December of 2019 in Wuhan, China. To curb the spread of the virus, many therapies and cures have been tested and developed, most notably mRNA and DNA vaccines. Federal health agencies have approved emergency usage of these S gene-based vaccines with the intention of minimizing any further loss of lives and infections. Unfortunately, SARS-CoV-2 continues to mutate with new strains, such as the delta and omicron variants, which take on different and more contagious forms. Currently, some approved vaccines have shown to be less efficacious against the new variants. Thus, it is crucial to assess which vaccines are the most efficacious by examining their effects on the immune system, and by providing considerations for new technological vaccine strategies in the future.

This paper provides an overview of the current SARS-CoV-2 vaccines with their mechanisms of action, current technologies utilized in manufacturing of the vaccines, and limitations in this new field with emerging data. Currently, there are 19 FDA approved or authorized emergency use vaccines worldwide. Six of these vaccines have been granted emergency use authorization (EUA) by the FDA including three mRNA vaccines, one replication-defective viral vector DNA vaccine, and two inactivated virus vaccines. Each different kind of vaccine utilizes a different approach to induce immune response against the SARS-CoV-2 spike (S) protein. All offered vaccines have demonstrated to be safe and efficacious in preventing severe disease and death. Although the most popular COVID-19 vaccines have been proven effective, time will be the main factor in dictating which vaccine will be able to best address mutations and future infection (Shahid, 2022).

1.2 **Keywords**

COVID-19, SARS-CoV-2, Vaccine, Immunization, Vaccination, mRNA Vaccine, Viral Vector Vaccine, Protein Subunit Vaccine.

1.3 1. Introduction to COVID-19 Vaccines

Since December of 2019, when the first case was reported in Wuhan, China, millions of people have died from Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). After several waves of lockdown and similar public health interventions, the only way to return to "normal" society is by vaccination. Vaccines inoculate antigens from the pathogen to prime the immune system to develop antibodies. As of now, there are several different classes of vaccines currently in use or development, such as mRNA and DNA-based vaccines, S gene-based inactivated virus vaccines, S gene-based protein subunit vaccines, and viral vector-based vaccines. Of these types, mRNA and DNA-based vaccines are the first of its kind to be widely used in public vaccination. These types of vaccines are novel platforms that are faster to develop than traditional vaccines (Zieneldien et al., 2021). Recently approved S gene-based mRNA vaccines contain lipid nanoparticles encapsulating the modified mRNA that encode the receptor binding domain of the Spike protein of SARS-CoV-2. Upon injection, the mRNA is translated into the Spike protein and displayed on the surface of the cells, producing an immune response. The DNA vaccine is a simple circular DNA plasmid that is directly transfected into cells using electrical pulses, which would also produce the Spike protein and a similar immune response. For inactivated virus vaccines, the native SARS-CoV-2 is inactivated, containing the whole viral genome, which is thought to produce the broadest immune response. Currently available protein subunit vaccines use the genetically engineered nanoparticle to present multiple receptor binding domains of the spike protein to elicit a stronger immune response. Similar to the protein subunit vaccines, but using a different platform, viral vector vaccines use a modified and non-replicating adenovirus vector to express the S protein (Shahid, 2022).

1.4 2. Historical Background of Vaccine Development

Since ancient times, contagious diseases have plagued humanity, inducing societal harm ranging from despair and mortality to poverty and conflict. Noting their tendency to reassess psychological and behavioral priorities, some have dubbed them "necessary evils." The choice to invoke the gods for protection, retribution, or understanding is as old as civilization itself. With enlightenment, science replaced mythology, and infectious diseases once again became a focus of inquiry. Charles Nicolle, while pondering the origins of typhus in a Parisian café, asked, "What does a microbe want?" (Hajj Hussein et al., 2015). Descendants of a once-infected individual now sought to eradicate the chain of transmission that doomed the herd. Nevertheless, years of progress could be undone overnight. In a world of interwoven networks, the misfortune of one could easily become the misfortune of all. In the first two decades of the twenty-first century, infectious diseases revisited the prideful inhabitants of Earth.

Smallpox, which killed an estimated 300 million people in the twentieth century alone, is perhaps humanity's most infamous adversary. It was the first disease for which there was a conscious effort to establish an offensive against an infectious disease. In the late 1720s, the approach of inoculation was imported from West Africa to New England and subsequently to Europe. However, this method of vaccination, which involved a "shock" to the immune system, had risks. A safer method was discovered in an experiment that would raise an eyebrow in today's ethical environment: the deliberate transfer of cowpox from diseased heifers to young children. Edward Jenner, a country doctor, reasoned that the milkmaids' cowpox infections spared them from more

serious smallpox infections. Jenner's "vaccine" was an illuminating milestone on the path to the germ theory of infectious diseases. In uncertain times, it is paramount to adhere to knowledge and reason.

1.5 3. Types of COVID-19 Vaccines

Vaccines help develop immunity against a virus, bacteria, or other pathogens. Through vaccination, the immune system is exposed to parts of a pathogen—inoculating a person with these harmless parts allows the immune system to build a defense against the real disease. COVID-19 vaccines provide this learned immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. However, the mechanisms of COVID-19 vaccines vary depending on the vaccine type. There are three types of COVID-19 vaccines approved by the World Health Organization (WHO): mRNA vaccines, adenovirus-vectored vaccines, and inactivated vaccines. All these vaccines target the spike protein of SARS-CoV-2, which binds to human angiotensin-converting enzyme 2 (hACE2) to infect human cells (Park et al., 2022). Since December 2020, COVID-19 vaccines have been distributed globally following emergency use listing (EUL) by the WHO. The time from vaccine development to first vaccine on the market was unprecedentedly short at one year because the vaccine platforms had been previously developed for other diseases. mRNA vaccines had been developed for the Middle East respiratory syndrome (MERS) coronavirus. DNA and inactivated vaccines had been developed for the severe acute respiratory syndrome (SARS) coronavirus. Adenovirus-vectored vaccines had been developed for MERS. Safety assessment of viral vector vaccines had been conducted using other vectors. Nevertheless, several concerns about EUL vaccines have emerged. Although the benefits of the EUL vaccines outweigh their adverse effects, there have been reports of rare but fatal cases associated with vaccinations. For instance, adenovirus-vectored vaccines have been associated with thromboembolic events, particularly in the younger population. mRNA vaccines have been associated with myocarditis and pericarditis (Patel et al., 2022). A reassessment of the immunological rationale underlying EUL vaccines in relation to COVID-19 is required.

3.1. mRNA Vaccines

In the COVID-19 pandemic, mRNA vaccines have emerged as a front line strategy to stop the spread of SARS-CoV-2. mRNA vaccines are a new class of vaccines that were first developed in 1995 for cancer treatment. The COVID-19 pandemic resurrected this dormant technology, and this therapeutic platform has proven to be the most prominent choice to combat infectious diseases, due to its safety, speed of production, stability, and scalability. Currently, 25 different mRNA vaccines against SARS-CoV-2 have advanced to clinical trials. Two of these were found to be approximately 95% efficacious in preventing infection. The design of the COVID-19 mRNA vaccines stems from the attributes of the entry mechanism of the virus into host cells (Zahan Rouf et al., 2022).

3.2. Viral Vector Vaccines

Viral vector vaccines use a modified version of a different virus (vector) to deliver important instructions to our cells. The vector virus has been changed so that it cannot cause disease in the vaccinated person. Once the viral vector is inside the body's cells, it uses the cells' machinery to produce the harmless piece of the target virus. This process triggers an immune response, helping the body defend against the actual disease. An important class of viral vector vaccines is based on

replication-deficient viruses. These vectors can infect cells and express transgene proteins but cannot replicate (Lundstrom, 2020). There are currently two viral vector vaccines against COVID-19 that have been granted marketing authorization in the European Union: Vaxzevria and Johnson & Johnson's Janssen vaccine. These two viral vector vaccines use a human adenoviral vector, while Sputnik V uses two different human adenoviral vectors for the first and second doses. In addition, at least eight other viral vector-based COVID-19 vaccine candidates are in clinical trials (Ura et al., 2014).

Adenoviral vector vaccines against COVID-19 are based on the replication-deficient human serotype Ad26 or simian serotype ChAdOx1 adenoviral vectors, expressing the spike glycoprotein of SARS-CoV-2. Upon exposure to SARS-CoV-2, pre-immunization with Ad26.COV2.S or Ad26.COV2.S plus a boost with the Ad26.COV2.S protein linked to the receptor-binding domain minimized viral RNA detection in the broncho-alveolar lavage fluid and significantly reduced levels of infectivity. These data suggest that adenovirus-vectored SARS-CoV-2 spike glycoprotein vaccines may be effective vaccination strategies against COVID-19. ChAdOx1-SARS-CoV-2 vaccination protected primates from COVID-19 through inhibition of viral replication and reduced pulmonary pathology. Unlike Vaxzevria and Sputnik V, the ZOOmAb monoclonal antibody library did not neutralize any of the Ad5-vectored COVID-19 vaccine candidates in vitro, possibly due to differences in vector design with Ad5 in this study's candidates and Ad26 or ChAdOx1 in approved/vaccine candidates. In cynomolgus macaques, Ad5-anti-HIV-1-gp120 priming followed by Env- and Gag-expressing protein boosting elicited potent systemic immune responses and a significant reduction in viral loads and infection of HIV target cells upon viral challenge.

3.3. Protein Subunit Vaccines

Subunit vaccines comprise proteins from the pathogen of interest that can induce neutralizing immune responses. This category includes (Wong-Arce et al., 2024). Protein subunit vaccines generally have an excellent safety profile, as they carry no live components. However, they often require adjuvants to enhance immunogenicity and generally induce a modest immune response unless delivered in higher doses or via multiple administrations. Besides, other protein vaccine candidates include EpiVacCorona, ZF2001, Covitter, Corbevax, and others in preclinical development. Due to the pandemic nature of the virus, it is crucial to use diverse vaccine technologies to ensure global vaccine coverage. Subunit vaccines are an important platform technology in vaccine development, having successfully been used for several licensed human vaccines. They can be expressed in several biological systems, including yeast, insect cells, mammalian cells, and bacteria.

Although there are concerns with yeast and mammalian systems, subunit vaccines expressed in bacteria have benefited from ongoing COVID-19 research. Bacterial platforms are generally cheaper and faster than other systems and can produce large amounts of vaccine antigens. Protein subunit vaccines often require proper folding and post-translational modifications, including glycosylation, to successfully induce adaptive immune responses. Unfortunately, bacterial systems generally do not provide a range of post-translational modifications most eukaryotic proteins require. Nevertheless, several subunit biopharmaceuticals produced using bacterial systems have been approved. In addition, developments in the rational design and construction of multi-epitope proteins can lead to uncomplicated but effective biopharmaceuticals, and bacterial systems can be adjusted to include built-in adjuvants to enhance protein immunogenicity.

1.6 4. Mechanisms of Action

The COVID-19 pandemic led to extensive efforts to create effective vaccines. As of today, numerous COVID-19 vaccines have been developed with varying technologies, efficacy, and safety profiles. COVID-19 vaccines have been authorized or approved in various regions, including mRNA vaccines, viral vector vaccines, protein subunit vaccines, and inactivated virus vaccines. Meanwhile, some vaccines are still in development using other platforms that have yet to be used in humans, such as DNA plasmid and live-attenuated vaccines (Zieneldien et al., 2021).

A vaccine typically consists of an antigenic component that elicits an adaptive immune response to provide protection against a specific pathogen. COVID-19 vaccines induce immune responses against the SARS-CoV-2 spike (S) protein to provide protection against COVID-19 through various mechanisms. Several protein sequences are involved in cellular attachment, membrane fusion, and entry and are therefore ideal targets for a vaccine. Moreover, the viral S protein mediates the majority of the neutralizing antibody response and is utilized in the vaccine design of most current COVID-19 vaccines (Sadarangani et al., 2021).

Although vaccine efficacy correlates with neutralizing antibody (NAb) levels, other immune mechanisms likely contribute protection against COVID-19. In addition to NAbs, other antibody functions, such as immunoglobulin G (IgG) antibody-dependent cellular phagocytosis (ADCP), have been shown to be associated with protection against COVID-19. Moreover, T cell immunity is also important in vaccine-mediated protection due to the ability to potentiate NAb responses and control infection, preventing the development of severe disease.

4.1. mRNA Vaccines Mechanism

At the core of mRNA vaccines is an mRNA sequence designed to transiently express the antigen of interest, mimicking a key protein of the pathogen targeted for eradication. mRNA vaccines contain an open reading frame (ORF) for the target antigen flanked by untranslated regions (UTRs), an N7-methyl-guanosine cap at the 5’-end, and a 3’-end terminal poly(A) tail. Following in vivo entry and triggering a local inflammatory response at the site of infection, the antigen of interest is generated by translation and presented as peptides on the transfected antigen-presenting cells (APCs). Consequently, a dual-pronged response, consisting of both innate and adaptive immune pathways, is stimulated comprising of humoral and cellular components ((Zahan Rouf et al., 2022)).

The innate immune response is triggered via pathogen-associated molecular pattern recognition on non-self RNA, mediated by pattern recognition receptors (PRRs) such as MDA-5, NOD2, RIG-I, or toll-like receptors (TLRs), resulting in type I interferon release, activation of the Th1 pathway and APC activation. The internalised mRNA can be translated to generate the antigen, which is presented on the major histocompatibility complexes (MHC) on the APCs, initiating the adaptive response. Antigens secreted exogenously can be internalised by other APCs, degraded into peptides within lysosomal endosomes, and presented on MHC II complexes on the cell surface. The adaptive immune response requires the manifestation of the antigen translated from the mRNA, which has to be presented on major histocompatibility complexes (MHCs) on APCs after degradation by intracellular proteasomes. If the antigen epitopes are presented on MHC I complex, a cytotoxic cellular response is initiated when the antigen interacts with CD8+ T lymphocytes.

Conversely, exogenously secreted antigens can be endocytosed, degraded by other circulating APCs and consequently presented on MHC II complexes, fostering CD4+ T-helper lymphocyte- and B lymphocyte-mediated response.

4.2. Viral Vector Vaccines Mechanism

COVID-19 Vaccine Mechanisms Understanding the mechanisms of the COVID-19 vaccines is crucial for addressing vaccine-related concerns. COVID-19 vaccines fall into three main categories: mRNA, protein subunit, and viral vector. Each category has a unique mechanism of delivering the SARS-CoV-2 spike protein (S protein) to elicit an immune response. The spike protein allows SARS-CoV-2 to bind to human angiotensin-converting enzyme 2 (ACE2) for cell entry, making it an ideal target for vaccines.

Viral vector vaccines use non-replicating viral vectors to deliver the S protein gene. There are two types of viral vectors: adenovirus-based and vesicular stomatitis virus (VSV)-based. Viral vector technology has been utilized in the development of various vaccines against infectious diseases and cancers. In the context of COVID-19, viral vector vaccines have shown promise in preclinical and clinical studies (Lundstrom, 2020). Viral Vector Vaccines MechanismStarting with the Oxford/AstraZeneca vaccine, it uses a replication-incompetent simian adenovirus vector (ChAdOx1) to express the SARS-CoV-2 S protein. The vaccine demonstrated safety and immunogenicity in nonhuman primates and induced a robust immune response in humans, leading to protection from severe symptoms in infected macaques. Phase III trials showed 62-90% efficacy. The vaccine was granted emergency use in several countries. The Johnson & Johnson vaccine employs a non-replicating human adenoviral vector (Ad26) to express the S protein. Preclinical studies in mice and NHPs showed robust immune responses and protection against challenges. Phase III trials reported 66.9% efficacy in preventing moderate to severe illness. The FDA granted emergency use authorization (Ura et al., 2014). The Gamaleya Research Institute developed the Sputnik V vaccine, which consists of two heterologous adenovirus vectors (rAd26-S and rAd5-S) carrying the S protein gene. Preclinical studies showed protection against severe disease. Phase III trials reported 91.6% efficacy. The vaccine was granted emergency use in several countries. The CanSino Biologics vaccine uses a replication-incompetent human adenovirus type 5 vector (Ad5) to deliver the S gene. Phase II trials showed safety and immunogenicity (seroconversion in all participants).

1.7 5. Clinical Trials and Regulatory Approval

Before any vaccine can be made available for widespread use, it must go through several phases of clinical trials, followed by regulatory review and approval. In the U.S., the Food and Drug Administration (FDA) is responsible for this process. Typically, this process takes years, if not decades. However, in response to the COVID-19 pandemic, efforts were made to rapidly develop and roll out effective vaccines in a safe manner. Thankfully, these efforts were met with great success.

Clinical Trials Phases

Once a vaccine candidate has been shown to be safe in preclinical studies and can be manufactured in sufficient quantities, it can move on to clinical trials in humans. Clinical trials consist of three phases. A vaccine candidate must be shown to be safe and produce an adequate immune response

in a small number of people during Phase 1 trials. If the results of Phase 1 trials are promising, the vaccine candidate can move on to Phase 2 trials, which involve a larger number of people and are meant to further assess safety as well as optimal dosage. If a vaccine candidate is shown to be safe and effective at a given dose after Phase 2 trials, it can move on to Phase 3 trials, which involve tens of thousands of people and are designed to determine efficacy, or how well the vaccine protects against disease (J. Mena Lora et al., 2023). Unfortunately, due to complications in finding subjects who had not been exposed to SARS-CoV-2, the virus that causes COVID-19, it took months longer than expected to start randomized Phase 3 clinical trials for the vaccine candidates that eventually received Emergency Use Authorization in the U.S.

Regulatory Approval Once all clinical trials for a vaccine candidate have been completed, the data from these trials are compiled into a document called a Biologics License Application (BLA) or New Drug Application (NDA) and submitted to a regulatory agency for review. In the U.S., the BLA or NDA is reviewed by the FDA, which has five major divisions, called offices, that review clinical trial data: the Office of Biostatistics, the Office of Epidemiology, the Office of New Drugs, the Office of Scientific Investigations, and the Office of Policy. In addition, the Office of Vaccines Research and Review, which is part of the Center for Biologics Evaluation and Research (CBER), is responsible for regulating the safety and efficacy of vaccines.

5.1. Phase 1-3 Clinical Trials

The mechanism of actions and types of COVID-19 Vaccines. At the beginning of 2023, about 13 billion of COVID-19 vaccines have been injected globally with an average of 1.51 doses per person (Jiang et al., 2020). To halt the COVID-19 pandemic and control the SARS-CoV-2 virus that causes such disease, several COVID-19 vaccines have been developed and distributed in emergency use authorization and regular use. Vaccines that are designed to expose the immune system to harmless components of the viral pathogen will elicit adaptive immunity and develop immunological memory to prepare for subsequent attacks by the actual viral pathogen.

There are five COVID-19 vaccines that were mechanistically categorized as different types. 1. DNA vaccines DNA vaccine utilizes plasmid DNA that encodes a portion of SARS-CoV-2 viral antigen proteins to be transcribed and translated into antigen proteins in host cells, similar to mRNA vaccine. With the help of electroporation device, naked plasmid DNA is delivered directly into the cytoplasm of host cells and a cellular immune response is induced. 2. RNA vaccines mRNA vaccine is composed of a portion of SARS-CoV-2 viral RNA encoding the spike protein in a lipid nanoparticle. Once injected into host cells, the mRNA is translated into spike proteins that are presented on the surface of the host cells, and a humoral immune response is induced against the spike protein. 3. Inactivated vaccines Inactivated vaccine utilizes SARS-CoV-2 viral particles that are killed or inactivated. Pre-existing humoral immunity to coronaviruses can cross-neutralize COVID-19 infection. 4. Protein subunit vaccines Protein subunit vaccine employs recombinant SARS-CoV-2 spike proteins or receptor binding domain protein to induce the production of neutralizing antibodies against the virus. 5. Viral-vectored vaccines Viral-vectored vaccine uses an innocuous replication-incompetent viral vector to deliver SARS-CoV-2 genes, typically the spike protein genes, to host cells to induce both humoral immunity and T-cell immunity.

5.2. Emergency Use Authorization

The three types of approved COVID-19 vaccines that have been emergency-use listed are mRNA vaccines, adenovirus-vectored vaccines, and inactivated vaccines. The EUL vaccines being used in the current situation comprise several COVID-19 vaccine candidates applied in studies and clinical settings across the world. The extraordinary circumstances of the COVID-19 pandemic have necessitated the emergency authorization of these vaccines, which have been rapidly developed. Vaccines are generally biopharmaceutical products that deliberately introduce an immunogenic material into the body to activate an immunological memory, preventing future pathogenic insults. Although the benefits of the EUL vaccines outweigh their adverse effects, there have been reports of rare but fatal cases directly associated with COVID-19 vaccinations (Park et al., 2022). Thus, a reassessment of the immunological rationale underlying EUL vaccines in relation to COVID-19 caused by SARS-CoV-2 virus infection is now required.

Given the enormous effort of the developers, the vaccines approved by the United States Food and Drug Administration or World Health Organization as emergency-use listed vaccines appear to reduce the rate of fatality in countries in which a large proportion of the population has been vaccinated. Notably, vaccine shortages and vaccine avoidance have occurred together because infrequent but fatal adverse effects of the vaccines have been reported. Mitigating vaccine avoidance by providing a better understanding of the vaccine mechanisms may be as critical as mitigating vaccine shortages by scaling-up production (Amir Singh & E G Upshur, 2021). Both mRNA vaccines and adenovirus-vectored vaccines have been under development for decades but have never been approved for use before this pandemic.

1.8 6. Efficacy of COVID-19 Vaccines

The coronavirus disease 2019 (COVID-19) pandemic has had a colossal impact on health, society, and economies globally. Vaccines are critical to ending the pandemic through the rapid reduction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission and disease burden. The development of COVID-19 vaccines has been an astounding feat of science. Within 1-year time from detecting the first outbreak of COVID-19 in Wuhan, Hubei province, China, there were multiple vaccine candidates entering human clinical trials and several vaccines Emergency Use Authorized (EUA) or licensed by regulatory agencies (M Higdon et al., 2022). As of March 2022, over 11 billion vaccine doses have been administered globally, with over 60% of the world's population receiving at least one dose.

The emerging COVID-19 variants of concern (VOCs) have brought unexpected challenges to public health systems and vaccine strategies around the world. The data evaluation and collection methods define the outcomes, note study characteristics, and systematically collect efficacy and effectiveness values by vaccine platform and disease outcome. The findings demonstrate robust evidence for the high efficacy of COVID-19 vaccines in clinical trials and high effectiveness in real-world settings (Mohammed et al., 2022). Protection against severe infection or death in the general population was at least 60% and most often close to 100%. Efficacy and effectiveness against symptomatic disease was heterogeneous but was almost always greater than 50% and often greater than 90%. Most vaccines retained high levels of protection for most SARS-CoV-2 variants, especially against severe outcomes. Some studies provided evidence of slight reductions in efficacy and effectiveness for the Beta and Delta strains. A recent meta-analysis of 10 efficacy and

effectiveness studies found larger reductions in protection against both mild and severe infection for the Omicron variant. Nevertheless, fully vaccinated individuals were at least 41% and usually well over 70% protected from symptomatic infection with Omicron.

6.1. Real-World Effectiveness Studies

Real-world vaccine effectiveness (VE) studies are essential to confirm and expand upon findings from randomized clinical trials. Many factors can affect the outcome of VE studies, including study design, population characteristics such as age and comorbidities, the definition of endpoints, and the severity of circulating variants of the virus. These factors should be considered when interpreting real-world VE results (Kherabi et al., 2022). However, all COVID-19 vaccines authorized for emergency use by the FDA have been shown to be highly effective against symptomatic infection and even more effective against severe infection and hospitalization. Real-world data on VE may lead to a comprehensive re-evaluation of vaccination recommendations, just as updated information from randomized clinical trials had led to the initial recommendations (Panahi et al., 2022).

The essential epidemiological characteristics of the COVID-19 pandemic (high infectivity, rapid propagation, and severe forms) required a quick vaccine deployment strategy. A massive worldwide vaccine campaign implementation immediately raised multiple questions regarding COVID-19 vaccines safety, efficacy, and effectiveness. Phase III studies provided data regarding safety and efficacy in preventing severe forms of COVID-19, but real-world data were needed to evaluate that efficacy and safety at a larger scale. Safety questions included consideration of the vaccinated population's characteristics (age, comorbidities, health status), the treatments they were undergoing, the mRNA and viral vector platforms used, and the number of vaccinated doses. Efficacy questions included the exact definitions of endpoints and needed clarification on VE with regard to asymptomatic infections and transmission.

1.9 **7. Safety Profile**

Most recently authorized COVID-19 vaccines demonstrate acceptable safety profiles. A total of 83 million doses of mRNA-based BNT162b2 and mRNA-1273 COVID-19 vaccines have been administered in the USA, and clinical trial data from >107,000 randomly selected participants from Phase 1–3 studies of these vaccines are available for analysis (Wu et al., 2021). Due to the large populations receiving vaccination, the publicly accessible Vaccine Adverse Events Reporting System (VAERS) can be a tool to analyze vaccine safety. Concerns regarding COVID-19 vaccines focus on possible safety issues. With decades of vaccine research and development, signaling detection methods are well established to evaluate the safety profiles of vaccines.

mRNA-based vaccines are a new class of vaccines never previously authorized for widespread human use. mRNA vaccines consist of nucleoside-modified mRNA encoding a pathogen protein, typically packaged with lipid nanoparticles to facilitate cellular uptake. Upon parenteral administration, mRNA is taken up by antigen-presenting cells that express the encoded protein and secrete cytokines. Importantly, mRNA also acts as a danger signal, activating toll-like receptors and triggering type I interferon production, inflammation, and APC maturation that enhance adaptive immune responses but may lead to adverse events.

7.1. Common Side Effects

In general, COVID-19 vaccines, like any other vaccine, are associated with side effects and adverse events. Most post-vaccination effects are mild and self-limiting. They generally include injection site pain, fever, fatigue, myalgia, headache, and nausea (Van Nguyen et al., 2023). Common side effects of COVID-19 vaccinations reported by the recipients include pain at the injection site, fatigue, headache, muscle pain, fever, and chills. Side effects are usually mild and occur within a short time after vaccination. People with prior COVID-19 infection seem to have a higher chance of developing side effects following vaccination. Most side effects go away within a few days.

More serious side effects, like anaphylaxis after mRNA vaccinations, have been observed but are extremely rare (Seida et al., 2023). Other serious adverse events post-vaccination have been reported as well, including thrombotic events, thrombocytopenia, Guillain–Barré syndrome, and myocarditis. However, these serious adverse events are also very rare. The risk of adverse events due to COVID-19 vaccinations is much lower compared to those associated with COVID-19 infection.

7.2. Rare Adverse Events

Rare adverse events have been reported after COVID-19 vaccinations, including myocarditis, pericarditis, thrombosis with thrombocytopenia syndrome, and Guillain-Barré syndrome. Most events occurred within days after vaccination, were more frequent after the second dose and in males, and resulted in good outcomes after monitoring and treatment. Causality is established for some events, but not for others (Yong et al., 2022). Myocarditis (or myopericarditis) is the only condition with sufficient evidence for causality among the rare adverse events examined in this review, which are associated with BNT162b2. On the other hand, other conditions, such as anaphylaxis and thrombosis with thrombocytopenia syndrome, have been classified as “likely” to be caused by BNT162b2. For the remaining conditions, the evidence is considered insufficient or inappropriate. It was concluded that the risk of BNT162b2 is extremely minimal and the benefits of vaccination far exceed its risks.

1.10 **8. Vaccine Distribution and Administration**

Vaccination has been proven as the most effective method to control contagious disease pandemics. The emergence of SARS-CoV-2 has seriously affected the health and lives of people worldwide. The development of COVID-19 vaccines is of great importance in tackling the pandemic. Compared to traditional vaccine technology, COVID-19 vaccine research is using new technologies with current evidence in a rapid time (Gannon et al., 2021). As of May 8, 2021, there are 96 candidate COVID-19 vaccines that have progressed to human clinical trials, and 23 established vaccines have received market authorization. The COVID-19 vaccine national rollout plans include nine regions: European Union, United Kingdom, United States, Ghana, India, Japan, Mexico, Russia, and China. National plans include coordination, prioritization, public information, prevention of imbalance in access and delivery, and monitoring safety and effectiveness. Safety monitoring plans comprise setting up independent advisory committees, pharmacovigilance plans, and public transparency (Tavilani et al., 2021). COVID-19 vaccines can prevent SARS-CoV-2 infection and control the COVID-19 pandemic. There are various types of new vaccines that are based on different technology platforms in clinical development. Understanding these vaccine

platforms and mechanisms is warranted as they play critical roles in public health. Vaccine candidate clinical trials and published data were accessed to provide information about the various available vaccines, their mechanisms of action, and the evidence supporting their efficacy and safety.

1.11 9. Herd Immunity and Vaccine Coverage

Introduction of a COVID-19 vaccine in a population will first create immunity in vaccine recipients and then result in decreasing susceptibility to infection in non-vaccinated individuals through the herd effect, if the vaccine is sufficiently effective against transmission. Here, a deterministic mathematical model is formulated to quantify the vaccination-induced herd immunity effect considering the emergence of a new variant. This model is fitted to the daily numbers of new COVID-19 cases, deaths, and hospitalizations across the US states and New York City. The results demonstrate that Delta vaccination programs will create sufficient herd immunity and suppress Delta epidemics if the vaccination coverage exceeds the critical coverage of 73%. However, even with 100% coverage of fully vaccinated individuals, Omicron vaccination is estimated to only induce 49% herd immunity, which would not be sufficient to control the epidemic spread of a new Vo. The model also suggests that more than 80% coverage of boosted vaccinations or at least 93% coverage of primary vaccinations in conjunction with second-dose and boosted vaccinations are needed to effectively control the Omicron spread in the presence of Vo (Liu et al., 2021).

1.12 10. Vaccine Hesitancy and Misinformation

Vaccines are known to be one of the most robust tools against the transmission of infectious diseases. Global vaccine coverage is crucial to ensure the success of vaccination programmes during a pandemic. However, high levels of background population immunity or indirect protection are hindered by factors such as the emergence of highly transmissible virus variants, waning immunity, or insufficient vaccine uptake. Although vaccination reduces hospitalizations and severe disease, a substantial proportion of the population is undecided about or unwilling to vaccinate. COVID-19 vaccine hesitancy ranges from 4% to 28% across EU member states and was estimated at 22% in the United States. Likewise, the intent to receive a COVID-19 vaccine is substantially lower among racial/ethnic minorities compared to non-Hispanic whites. Vaccine hesitancy is multifactorial and may be due to confidence, complacency, convenience, fear, cultural or political factors. Lack of information or misinformation is one of the most influential causes and has contributed to a decrease in vaccination intent. Misinformation and conspiracy beliefs have been associated with lower intent to vaccinate against COVID-19. Inadequate and insufficient information from governments may further enhance fears and anxieties, promoting the spread of misinterpretations and conspiracy beliefs. Social media, as a major source of information, can either prevent the spread of conspiracy theories or fan the flames by becoming echo chambers (Hughes et al., 2021).

1.13 11. Global Vaccine Equity

Adequate and equal access to vaccines concerns the entire world population. The protection of the global population from SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) transmission, as well as from COVID-19 (coronavirus disease 2019) disease, is directly influenced by the development and implementation of effective vaccines. Therefore, vaccines should be made

available to, and accessible by, every country, in particular by those that are less developed and less economically powerful (Bolcato et al., 2021). Unfortunately, in light of COVID-19, governments of many rich and powerful countries turned towards vaccine nationalism, which means prioritizing and guaranteeing access to vaccines only for their population instead of adopting a global perspective. In response to this, several action plans have been made to protect the global population from COVID-19 and ensure equal access to vaccines for every country. In September 2020, the World Health Organization devised the COVAX equitable vaccine access plan, co-led by GAVI, WHO, and CEPI. The aim is to develop and distribute vaccines against COVID-19 in order to mitigate the pandemic. To achieve this aim, COVAX should ensure that, once available, vaccines are fairly distributed to all participating countries, regardless of their economic situation. For this purpose, the plan offers initial vaccine doses for 92 countries, most of them being poor, in proportion to their population size, thus ensuring that they, at least, get something. After doses are provided to reach the coverage of 20% of each population, the next stage will make new doses available considering the order of priority defined by the epidemiological and risk profiles of each country.

1.14 12. Future Developments and Variants

The worldwide prevalence of the causative agent of COVID-19, SARS-CoV-2, leads to an increased viral burden in populations, thereby increasing the likelihood of new mutations emergence. New variants of SARS-CoV-2 have been reported since the January 2020 Pangolin lineage was first recorded. Amidst the global challenges posed by the COVID-19 pandemic, various strains of the SARS-CoV-2 virus have surfaced and disseminated globally. While these new variants are inevitable in viral evolution, most of them exhibit minimal impact on the virus's mutations. Nevertheless, certain mutations may result in phenotypic changes (S Kumar et al., 2024). The emergence of new variants poses a challenge to the efficacy of vaccines and monoclonal antibody therapies. Several candidate vaccines are already undergoing clinical trials to ensure public health safety against new variants. To understand the potential risk posed by newly recognized variants of concern (VOCs), in-depth studies on the virus's transmissibility, pathogenicity, and effectiveness of current countermeasure approaches are essential. Since the global prevalence of COVID-19, novel variants of SARS-CoV-2 have been discovered. Some variants exhibit mutations in the spike (S) protein that have been associated with increased infectivity and resistance against neutralizing antibodies. In an alarming fashion, several VOCs have emerged, leading to a heightened global public health risk. Meanwhile, the emergence of these mutated strains presents novel obstacles in the prevention and management of COVID-19. Recently identified VOCs have caused an increase in hospitalization, infectivity, mortality, and transmissibility. Additional concerns stemming from the discovery of these variants include increased viral shedding in ferrets, higher respiratory infection rates in minks, increased ACE2 receptor binding, and transmissibility in humans. There have been reports of reduced protective effectiveness of current vaccines against VOCs. Variants containing combinations of critical mutations pose significant challenges in developing antiviral therapeutics and effective vaccine designs.

1.15 13.Conclustion

Research and development of COVID-19 vaccines have made remarkable success. In this review, the mechanisms of representative COVID-19 vaccines were comprehensively discussed. The free

RBD protein based COVID-19 vaccines showed effective protection against SARS-CoV-2 challenge. Well-designed preclinical studies are urgently needed to better investigate the safety and efficacy of attenuated SARS-CoV-2 based vaccines. The representative COVID-19 vaccines developed worldwide, including inactivated virus, viral vector, mRNA, protein subunit, D-variant virus and RBD protein, have been summarized. Currently applied methods for assessment of safety and immunogenicity of COVID-19 vaccines have been discussed. Vaccine efficacy is determined by multiple factors including vaccine platforms, dosing time-intervals, study population characteristics and assessment methodologies, which need to be carefully considered in relevant studies (Liu et al., 2022).

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