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Review article

Mechanisms of action and immune response for COVID-19 vaccines: A narrative review

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ABSTRACT

Background: Corona virus disease – 2019 (COVID-19) is the most important topic in this century with consideration of vaccines as the most important protective tools. In this review we aimed to discuss the different types of COVID-19 vaccines as regarding structures, immunological basics, and currently available forms. We reviewed the available literature about recombinant viral vector, mRNA, inactivated, and protein subunit vaccines. And in the review, we covered mechanisms of action, available forms and whether they lead to lifelong immunity or not. We concluded that it is not yet possible to confirm a lifelong immunity by the available COVID-19 vaccines. With the emergence of SARS-CoV2 new mutant strains, no single vaccine can prove to have a lifelong immunity. Further experiments and research work are needed. We need to conduct research to estimate the prevalence and incidence of COVID-19 patients in already vaccinated people, trials to reach the best ways of giving the vaccines to have the longer protection and the effect of these vaccines on the SARS-CoV-2 new variants.

Introduction

Corona virus disease - 2019 (COVID-19) virus is a new strain of coronavirus discovered in China. There were cases found in almost all countries. Globally, as of 26 April 2021, there have been 146,689,258 confirmed cases of COVID-19, with 3,102,410 deaths, reported to WHO. As of 24 April 2021, a total of 900,348,375 vaccine doses have been administered [1].

Besides that, estimating the case fatality rate is difficult as many infected patients have no symptoms. The case fatality rate for patients admitted to the hospital with serious symptoms is

about 15%. Patients who are elderly who have a lot of comorbidities are more likely to die. Children and young adults rarely show signs of the infection, although they may carry it. The COVID-19 vaccine appears an important tool in disease prevention. Corona virus disease - 2019 vaccine is designed to provide acquired immunity against severe acute respiratory syndrome coronavirus 2 (SARS -CoV - 2) [2].

Corona virus disease-2019 vaccine will also help protect you from being severely ill even if you do get COVID-19. At least seven different vaccines across three platforms had been carried out in countries as of February 18, 2021. Vaccination is

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given priority for vulnerable groups in all countries. Concurrently, more than 200 additional vaccine candidates are being developed, with more than 60 of them in clinical trials [3]. Studies claimed people who have been completely vaccinated will resume activities that they had put on hold due to the pandemic. Our review aims to summarize the mechanism of action of different COVID-19 vaccines and the immune response they induce and discuss whether they lead to lifelong immunity or not. Corona virus disease-2019 vaccination helps protect adults and children ages 5 years and older from getting sick or severely ill with COVID-19 and helps protect those around them.

Some people who are vaccinated against COVID-19 will still get sick and have a vaccine breakthrough infection because no vaccine is 100% effective.

Recombinant viral-vectored vaccines (RVVV)

As a modified type of vaccine, viral vector vaccines utilize the vector (not the virus that causes COVID-19 as an adenovirus) to deliver the genomic parts of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) to the cells, then the cells construct a harmless piece of the virus (SARS-CoV-2). Spike protein triggers an immune response, this response includes antibody-producing B-cells, and T-cells which destroy virus-infected cells. Although RVVV is considered safer than the live attenuated vaccine, insufficient immune response to the vectored vaccines, or preexisting antibodies (Ab) to the viral vector can compromise the ability of the vaccine to induce immunity, as seen in adenovirus- and measles virus-based vaccines [4,5]. To date, there are 48 RVVV, 12 of which are in clinical development. eight out of the 12 are based on adenovirus, [4] and the four main vaccines are ChAdOx1 nCoV-19 (AZD-1222), Gam-COVID-Vac, Ad5- nCoV, and Ad26.COV2-S.

In collaboration with AstraZeneca, the University of Oxford developed ChAdOx1nCoV-19, a vaccine based on the chimpanzee adenovirus (ChAd). The vaccine candidate is a nonreplicating viral vector (NRVV), encoding the full-length S protein. Two doses of the vaccine are administered parenterally, and a booster dose follows 28 days after receiving the first dose [3]. Nevertheless, intramuscular (IM) injection decreases viral load in the lungs, but not in the upper respiratory tract [5]. Chimpanzee adenoviruses have been used as viral vectors to overcome pre-existing human adenovirus

immunity and were shown to induce high levels of antibodies and cell-mediated immunity in mice [4].

Ad5-nCoV is being developed in China, and it is administered IM. In clinical trials, recipients who received larger and higher doses than normal levels developed toxicity, while smaller doses provided immunity in 50% of the recipients [6]. The decline in antibody titer in phase II due to developing immunity against adenovirus put the vaccine in a questionable position. Animal studies show that intranasal administration of Ad5-nCoV induces memory of alveolar macrophages more effectively than IM administration [5]. Another study revealed that nasal delivery (respiratory mucosal vaccination, RMV) of Ad5nCoV and ChAdOx1nCoV-19 is safe and highly effective [3].

In general, Ad5-nCoV and ChAdOx1nCoV-19 need to be administered once to maintain their immunogenicity, because of the possibility of developing immunity against the vector that could reduce the immunogenicity of the vectored antigen when a booster dose is administered, this shifted the development toward single-dose vaccines [3].

Gam-COVID-Vac, the vaccine consists of two doses, the first of which contains a recombinant adenovirus type 26 (rAd26-S) and the second of which contains a recombinant adenovirus type 5 (rAd5-S), both with full-length spike (S) proteins. Gam-COVID-Vac overcame the Ad-5 immunity issue by using the Ad-5 virus as a vector in the first dose, then Ad-26 in the second dose [7].

Ad26.COV2-S is an adenovirus-based vaccine developed in the USA by Johnson & Johnson. In phase 1 trials, a single dose has induced rapid binding and cellular immune response [8]. To extend the protease resistance of Ad26.COV2-S, a mutation at the S1-S2 polybasic cleavage site provides further stabilization of S protein [9].

Merck developed the replicating viral-vectored VSV-S vaccine (rVSV-ΔG-spike). This vaccine was designed after three mutations on the S protein; mutation at 507 position, mutation at R685G position, and mutation at C1250 position; elimination of the G gene and presenting the S protein; restricting the entry only to ACE2-expressing cells, thus improving its safety, replication control, and overall stability [10,11].

Infection of mice with VSV-S generates stronger neutralizing antibodies (humoral immunity) than normal infection with SARS-CoV

[12]. A single parenteral dose of the VSV-S vaccine can provide immunity against SARS-CoV-2 as detected in hamsters [11].

- Can RVVV provide long-term immunity?

Naturally, SARS-CoV-2 enters the cell using mainly by angiotensin-converting enzyme 2 (ACE2) receptor, followed by the translation of viral polymerase protein then RNA replication and transcription, and with the help of endoplasmic reticulum and Golgi apparatus, formation of the virus and exocytosis occur. The replicating viruses cause cell lysis of the epithelial cells. The epithelium presents viral antigens to CD8⁺ T-cells, then CD8⁺ T-cells and natural killer (NK) cells induce apoptosis to the virus-infected cells. Macrophages and dendritic cells (DCs) phagocytose the antigen and present it in the form of peptides to T-helper cells by MHC II. leading to differentiation of them to Th1, Th17, and memory T follicular helper (FH) cells. T follicular helper cells help B cells to differentiate to plasma cells to promote the production of virus-specific antibodies (IgM, IgA, and IgG).

Similarly, RVVVs are expected to develop the same type of immune response as active infection, with T and B cells along with specific neutralizing Abs. but RVVV only provides immunity against a specific type or strain, regardless of the variations that may occur in the future as B.1.1.7 (UK variant), and B. 1.1529 (Omicron variant). RVVVs are known to trigger strong immune responses by T-cells, as well as the production of antibodies by B-cells, which mimic natural infection and provide lifelong immunity. for example: chAdOx1 sCHIKV, a vaccine designed to protect against the chikungunya virus, was successful in providing a lasting immunity [11]. The rMVEZ-HPV vaccine provides lifelong protection against human papillomavirus 16 and 18 [8].

Multiple elements must work together to produce long-lasting immunity, antibodies, different types of T cells, and memory B cells. Researchers studied 254 samples from 188 COVID-19 cases, including 43 samples at 6 to 8 months after infection, for 8 months after SARS-CoV-2 infection. kinetics of adaptive immunity was illustrated in this study, specifically CD4⁺ T cells specific to SARS-CoV-2, CD8⁺ T cells specific to SARS-CoV-2, spike IgA, receptor-binding domain (RBD) IgG, and RBD memory B cells. After one to two months post-symptom onset, 64 % of COVID-19 cases were positive for all five compartments. After a five-to-

eight-month period, the percentage drops to 43%, with 95% of participants still displaying positive results for at least three compartments, emphasizing the heterogeneity of immune memory, which differs between individuals [13]. A study published in the New England journal of medicine found that IgG levels declined by half every 36 days in those who recovered from COVID-19, raising concerns that humoral immunity may not be long lasting in patients with mild illness, who constitute the majority of the cases, in other words, we may be losing our immunological memory [14]. Another study on rhesus macaques showed primary infection with SARS-CoV-2 elicited short-term protection [15].

According to the previous results we conclude, vaccination provides immunity that lasts for at least 6 to 8 months without the guarantee to prevent reinfection by future strains of SARS-Cov-2. ChAdOx1nCoV-19 and VSV-S vaccines have the most outstanding results, but can they compete with future strains and provide long-term immunity? Indeed, more research and studies are needed, with the current studies the best vaccines can do is be administered multiple times throughout a human's life against different futuristic strains of CoVs. The challenge remains to develop a vaccine administered only once, without developing immunity against the vector, and provide long-term immunity against not only the present but also future strains.

Messenger RNA (mRNA) vaccines

This type of vaccine uses genetically engineered mRNA to give your cells instructions to make the S protein found on the surface of the COVID-19 virus. After taking the vaccine, your muscle cells begin making the S protein and showing all them on cell surfaces. This causes your body to create antibodies. If you are infected with the COVID-19 virus after that, these antibodies will fight the virus.

After delivering instructions, the mRNA is immediately broken down. It never enters the nucleus of your cells, where your DNA is kept. Both the Pfizer-BioNTech and the Moderna COVID-19 vaccines use mRNA. Like all vaccines in the United States, mRNA vaccines require authorization or approval from the Food and Drug Administration (FDA) before they can be used. Currently vaccines for COVID-19, the disease caused by the SARS-CoV-2 coronavirus, are the only authorized or approved mRNA vaccines. These vaccines use mRNA that directs cells to produce copies of a

protein on the outside of the coronavirus known as the “spike protein”. Researchers are studying how mRNA might be used to develop vaccines for additional infectious diseases.

There are only two mRNA vaccines that have been authorized for regular and emergency use: the Pfizer/BioNTech (BNT162B2) and Moderna (mRNA 1273) Vaccines, while a third (CVnCoV) is in phase III clinical trials and pending authorization by the Committee for Medicinal Products for Human Use (CHMP), and nine others are in phase I-II clinical trials. Both Moderna and Pfizer/BioNTech vaccines use nucleoside-modified RNA enveloped in lipids that together with the modified mRNA form nanoparticles that prevent mRNA degradation, facilitate endocytosis and endosomal escape. The former uses a PEGylated lipid nanoparticle (LNP) composition that contains polyethylene glycol (PEG) 2000-dimyristoyl glycerol [DMG], SM102 (a proprietary lipid by Moderna), cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), while the latter contains proprietary ALC-0315 and ALC-0159 lipids in addition to cholesterol and DSPC. Meanwhile, CVnCoV uses unmodified mRNA encoding a minimal part of the viral S antigen. The Moderna (mRNA 1273) and Pfizer/BioNTech Vaccine (BNT162B2) encode a membrane-anchored full-length SARS-CoV2 S protein, and their mRNA sequences contain two proline substitutes originally designed for a MERS vaccine (K986P and V987P) that are necessary for stabilization of the protein spike in the perfusion conformation, which was demonstrated to induce higher immunogenicity of the S protein at lower doses than the wild type. The two vaccines elicit a humoral response of rapid increase in IgG and IgM antiSars-CoV-2 S protein and receptor-binding domain (RBD) geometric mean titers (GMTs) after the first vaccination and another significant increase after the second dose, with both vaccines showing similar levels of plasma neutralizing activity [15]. Furthermore, it was demonstrated that SARS-CoV-2 RBD-specific B-memory cells undergo notable increase in mRNA vaccinated individuals in comparison to naturally infected individuals after 1.3 months but similar after 6.2 months which indicates a robust B-cell memory response resembling the natural infection [16-18] However, a one- to threefold decrease in neutralizing activity against the E484K, N501Y and K417N/E484K/N501Y emerging variants of SARS-

CoV-2 that carry RBD mutations was noted. Similarly, plasma obtained from patients who had recovered from COVID-19 show less effectiveness in neutralizing the K417N/E484K/N501Y mutant [19,20] The mRNA vaccines developed for SARS-CoV-2 are regarded as a new class of vaccine which have an advantage in efficacy over other classes currently authorized for use, with Pfizer/BioNTech and Moderna vaccines respectively showing 95% and 94.1% 2 efficacy in preventing mild and moderate infection and near 100% prevention of severe disease, hospitalization, and death. In addition, they have a better safety profile than viral vaccines, since they are not made with an actual pathogen and do not integrate into host DNA, meaning that while they can still be less effective in immunocompromised patients, they will never induce an infection as attenuated vaccines might. However, studies showing that the efficacy of the neutralizing activity falls over time against some of the rising serotypes are concerning and call for further investigation. In addition, rare cases of anaphylaxis potentially in response to the PEG-based lipid nanoparticles used in mRNA vaccines have been reported.

Inactivated vaccine

The virus is destroyed using methods such as heating or using formaldehyde. The pathogen particles are demolished and lose the capacity of division, but the pathogens keep some of their integrity, thus the immune system recognizes and tracks the pathogens inducing the immune response of the adaptive system. When a vaccine is made correctly, it can't be infectious, but inappropriate inactivation can result in integral particles which could be infectious. Since the killed pathogens in a vaccine which is produced appropriately do not replicate, booster doses are needed every period of time to reinforce the immune response [21].

World Health Organization has classified the inactivated vaccines according to the technique used to inactivate the virus. The vaccines that use the whole virus particle are called “whole virus vaccines”. They are destroyed completely using heat, radiation or chemicals. Some vaccines are produced by using a cleansing agent to disrupt the virus which are called “split virus vaccines”. Other vaccines use the best stimulant antigens in the virus by purifying them out, so they stimulate immunity to induce the best immune response against the virus, while the other components of the virus are removed such as components needed for

reproduction, surviving in the hard environment or that can cause adverse reactions. This type of inactivated vaccines is called “subunit vaccines” [22].

As killed vaccines are known to produce a weaker immune response than live attenuated ones, Immunologic adjuvants and several “booster” shots may be needed to provide a more effective immune response against the infectious microbes [23].

Many inactivated vaccines against SARS-CoV-2 are being experienced at different clinical stages. Most of these vaccines are formulated with one adjuvant such as aluminum hydroxide, however two adjuvants are added to VLA-2001, CpG oligodeoxynucleotides and aluminum hydroxide (Nikolai). Considering the studies on innate immunity from the coronavirus, experts assume that protective immunity acquired from the vaccines will last at least six to eight months. And if immunity from SARS-CoV-2 ends up being like other seasonal coronaviruses, such as “common colds,” it is even possible the vaccines could provide protective immunity for up to a year or two before a booster dose is required. So, the scientific guess is that inactivated COVID-19 vaccine will not produce a lifelong immunity.

Most of the inactivated vaccines have no or mild adverse effects such as BBIBP-CorV (Sinofarm), CoronaVac (Sinovac) and CoviVac which induce mild pain at the site of injection and mild fever for one or two days [24].

Protein subunit vaccines

A type of vaccines contains antigenic part of pathogen that provide recognition of human immune system to antigen as a residue 319-545 of the SARS-COV-2 RBD [25].

The subunit vaccines considered the most common platform, this is because there are seven vaccines of this type in clinical trials, and 50 more candidates in the preclinical developmental stage, However, none is intended for treatment of COVID-19 yet. Full-length SARS-Cov-2 S protein or proteins are used in the subunit vaccines. So, it induces CD4⁺ TH cell and the response of antibody as neutralizing antibody [5].

The subunit vaccines concentrate the immune response against neutralizing epitopes, but it prevents the production of non-neutralizing antibody that may promote Antibody-dependent enhancement (ADE) of disease [5].

This vaccine doesn't provide lifelong immunity, because it is not making a full antigenic complex, so protective efficacy may be limited [26] which makes the vaccine need an adjuvant or repeated administration. It also has a limited ability to stimulate CD8⁺ T cell responses. In fact, this vaccine cannot be used with SARS-CoV-2 [27]. and may have a role in ADE of disease [17,28].

The ASO3 and Matrix M adjuvants are used for subunit COVID-19. The viruses contain a number of proteins and they are S Protein, N Protein, Matrix M and envelope E protein, the N Protein surrounds the large positive stranded RNA genome, coated with a layer of lipid from the host cell membrane, which contains the rest of the protein. At least SARSCov-2 vaccines include protein of S Protein, either S2 domain or RBD. The S Protein vaccines can neutralize the virus [29].

Novavax (NVX-COV2373) is a type of recombinant spike protein vaccines which contains full-length SARS-COV-2 spike (s) glycoprotein and a saponin-based Matrix-M adjuvant. It was tested on *Cynomolgus* macaques (*Macaca fascicularis*), and the results showed protection from upper and lower respiratory infections and pulmonary disease. Antibodies to protein S contain saponin based matrix – M adjuvant elicit high titer anti S IgG, which are neutralizing and blocked binding to human angiotensin- converting enzyme 2(hACE2) receptor to prevent bronchospasm resulting from vasoconstriction effect of angiotensin 1. Initial trials proved the effectiveness of the vaccine in the United Kingdom by 89.3%, but on the contrary, its effectiveness in South Africa did not exceed 60%. NVX-COV2373 activated multifunctional CD4⁺ T, CD8⁺ T, CD4⁺ follicular helper T cells, and antigen specific germinal center B cells in the spleen in phase I and II clinical trials [5].

Now, WHO recommends Novavax (NVX-COV2373) for high-risk patients with chronic diseases, but there are not enough data about effects of this vaccine on HIV or immunocompromised patients. So, however, we can say that protein subunit Vaccines are a promising type

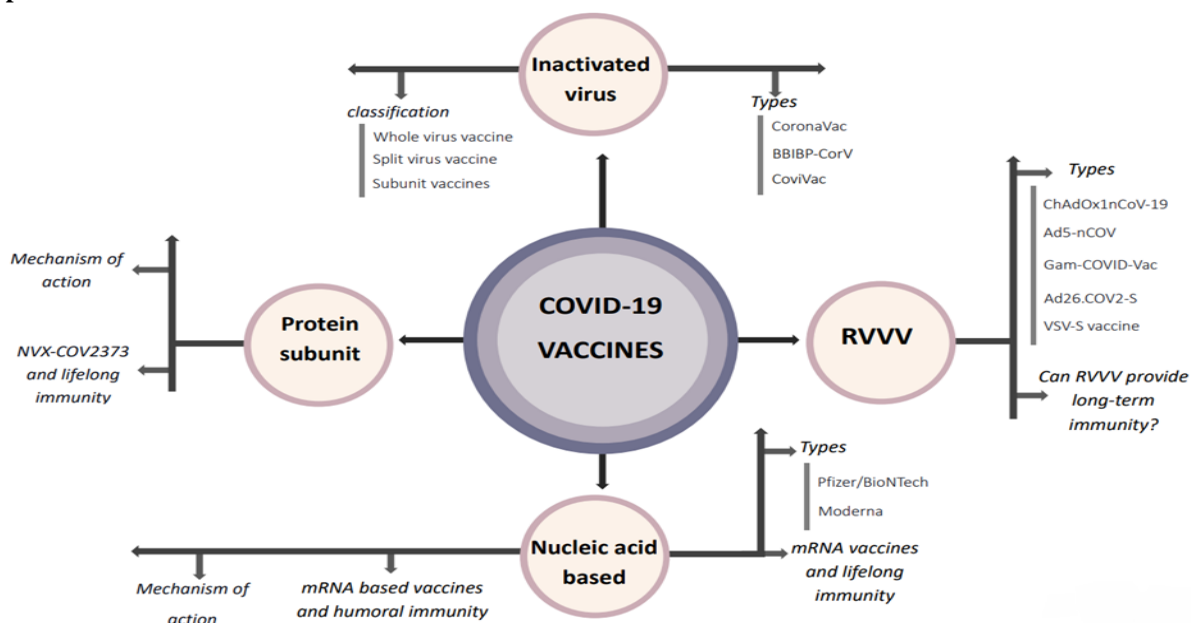
Conclusion

To sum up, COVID-19 is a major health challenge facing the whole world. The unique, unexpected pathological and epidemiological natures of COVID-19 require unprecedented efforts and resources, particularly in the development of effective and safe vaccines. At this level, RVVV has

been known to trigger a strong immune response providing a lifelong immunity by involving elements as antibodies, T-cells and memory B-cell, while inactivated one protective immunity may last six to eight months and if COVID-19 ends as a seasonal coronaviruses it can provide up to one or two years of protection. On the other hand the, mRNA vaccine efficacy falls over time against some of the rising serotypes, Lastly the protein subunit vaccine doesn't also provide a lifelong immunity. The recommended vaccine now is the mRNA vaccine as being not made with an actual pathogen,

so they won't induce an infection in immunocompromised patients, and it shows high efficacy in preventing mild and moderate infection. However, with the emergence of the new mutant COVID-19 strain named B.1.1.7, no single vaccine can prove to have lifelong immunity as long as new mutants emerge. To overcome this challenge, further studies and more literature are needed to be able to provide an efficient vaccine that will put an end to the pandemic.

Mind map shows the content of the review.



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The authors report no conflicts of interest.

Authors contribution

All authors have made substantial contributions to all of the following: (1) the conception and design of the review (2) drafting the article or revising it critically for important

intellectual content, (3) final approval of the version to be submitted.

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