International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Vaccines for Covid-19: Their Preparation and Mechanism

Krishna Bajaj

DPS Sector 19, Faridabad

ABSTRACT

To deal with the COVID-19 pandemic, many types of vaccines have been developed. This paper discusses the mechanism and preparation of three types of vaccines. The paper also focuses on examples of such vaccines, their efficacy and the various advantages and disadvantages that they might have. The review was done using online databases such as GoogleScholar and official websites.

Keywords: COVID-19; vaccines; DNA; mRNA; immune response; SARS-CoV-2

Introduction

In December 2019, a new disease was found which caused pneumonia-like symptoms in patients. After analyzing the respiratory samples of infected patients, the experts of PRC Centre for Disease Control declared that the pneumonia was caused by a novel coronavirus, later known as Novel Coronavirus Pneumonia (NCP). World Health Organization (WHO) officially named the coronavirus disease as 'COVID-19'. The International Committee on Taxonomy of Viruses named the virus 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2). This disease later became a pandemic which has been going on for more than two years. It quickly spread to more than 200 countries and there have been 545,864,232 confirmed cases as of June 22, 2022. The death toll is also at a significant 6,343,813 making it one of the deadliest diseases in the history of humanity. The number of cases and deaths, however, are much higher than this as there has been underreporting of cases by many countries. The most common symptoms of COVID-19 include fever, dry cough, and tiredness, while some less common symptoms are diarrhea, pain, sore throat, headache, skin rashes and discoloration on fingers or toes. The severe symptoms include dyspnea, pain in the chest, and loss of movement or speech. Due to the various lockdowns around the world, people have further been struggling with stress, tension, sleep disorders and other mental issues. This called for an urgent need for vaccines worldwide so people could go about their normal life again. Since 2020, development of more than 200 vaccines both in public and private labs started as listed by WHO. In the third quarter of 2021, vaccines started being administered after being proven effective in their phase III clinical trial.

Mechanism of COVID-19

SARS-CoV-2 is a single stranded RNA virus having a spike S protein having two subsections, S1 and S2. It also has an envelope E protein, Matrix M protein and Nucleocapsid N protein. In addition to this, there are 16 non-structural proteins(nsp1-16). The S spike protein forms homotrimers that protrude from the main envelope. These are essential for the entry of COVID-19. It targets a specific receptor known as Angiotensin converting enzyme 2(ACE2). This receptor is available all around the body, especially in the nose, lungs, guts and brain. Thus, the primary target of COVID-19 is the respiratory system. It also adversely affects the genitourinary system, circulatory and nervous systems. While the S1 protein is responsible for attachment to the ACE2 receptor, the S2 protein is responsible for viral reaction to promote infection. As an essential component of antiviral response, a release of type I interferons is essential for slowing down the virus. However, COVID-19 has the ability to slow down (or in some cases, entirely shut down) this immune response. This causes the cells to release cytokines, leading to inflammation in the respiratory tract and the activation of the immune system. In the case of weak immunity, lack of interferons causes widespread inflammation leading to severe damage to the lungs and alveolar track.

Types of Vaccines

Vaccines can be divided into several subcategories DNA, mRNA, live attenuated, inactivated, viral vector, virion-like particle, recombinant subunit and synthetic peptide. Clinical trials and experiments on animals usually measure the effectiveness of vaccines in fighting off diseases before getting approved. This paper will try to explain and understand the mechanism of three types of vaccines, namely-

1. DNA vaccines
2. mRNA vaccines
3. Viral vector vaccines

1. DNA vaccines:

DNA vaccines can induce both humoral and cellular immune responses and can be easily produced, transported and stored. There has been development of many such vaccines, such as VRC5283 for the Zika virus. Many vaccines against influenza, HIV and malaria are also being developed. In these vaccines, there is a direct injection of fragments of genes which are directly responsible for the production of immunogenic antigens. The genetic material is translocated through the vaccine in the host cell's nucleus. The APCs(Antigen-presenting cells) are responsible for receiving this genetic material. The mammalian promoter present in the structure is activated, which triggers the activation of the gene. After translation of the gene into proteins, it is further converted into peptides which are used to bind to the major histocompatibility complex (MHC class-I and II). All cells with a nucleus use MHC-I for antigen-presenting, while Dendritic cells, macrophages and B cells use MHC-II for presenting the antigen and cross priming to CD4+ and CD8+ T cells.

To make the vaccine, single stranded RNA of SARS-COV-2 is extracted, synthesized into double stranded DNA and cloned into a plasmid. This plasmid is injected through the muscles of the arm along with an electroporation device. Myocytes take up the plasmid within the muscle, leading to activation.

Since S proteins are responsible for the entry of COVID-19 virus using the ACE2 receptor, it is a favourable site for activation of vaccines. Some successful DNA vaccines expressing S, M and N proteins have been developed. The vaccines provided strong humoral and cellular immunity to animals such as mice and macaques. ZyCoV-D, developed by Indian pharmaceutical company Cadila healthcare, developed the first DNA vaccine. It conducted vigorous phase III trials across more than 50 clinical sites around India in January 2021. The results indicated it as a safe and effective vaccine, especially against the delta variant. Although earlier it was devised to be injected in 3 doses, later it was found that two doses of 3mg were just as effective. Hence, ZyCoV-D became the first plasmid DNA vaccine to get DCGI approval for emergency use.

2. mRNA vaccines:

mRNA vaccines are capable of inducing both cellular and humoral responses. Significantly less time is required to manufacture these vaccines as the main principle is to deliver a transcript that encodes a target antigen. These vaccines, unlike DNA vaccines, only need to enter the cytoplasm of target cells to induce the production of antigens. Thus, they possess more biosafety as it is less possible for mRNA to integrate into the genome.

mRNA vaccines are administered intramuscularly under the dermal and subcutaneous layers. The mRNA delivered enters the muscle cells through endocytosis, where it is translated to form metastable trimeric fusion S protein. This translated product contains a signal peptide from amino acids 1-15, which allows the S protein to be transported to the plasma membrane or out of the cytoplasm and presented to CD8+ T cells. Most protein left behind is degraded by endosome-derived proteasome and incorporated in MHC-I, before presenting it to CD4+ T cells. Once B cells interact with CD8+ and CD4+ cells, they get activated. This leads to proliferation of these cells, and they differentiate to either form memory B cells or antibody secreting plasma cells.

For the preparation of vaccine, the S protein was first identified, synthetically manufactured and inserted into a small circular piece of DNA. Researchers then use established in-vitro protocols to create mRNA in a method that mimics our biological processes:

1. They separate the two strands of plasmid DNA.
2. RNA polymerase uses the spike protein gene to create a single mRNA molecule similar to the way our body does it.
3. Other molecules break down the rest of the plasmid to ensure that only the mRNA is packaged as a vaccine.

There has been development of many successful mRNA vaccines against COVID-19, the most popular ones being Moderna, developed by Moderna inc. in collaboration with the US National Institute of Allergy and Infectious Diseases, and Pfizer-BioNTech developed by US-based Pfizer and german company BioNTech. More than 2 billion doses of each have been distributed all over the world.

A disadvantage, however, of mRNA vaccines is that they require ultra-low temperatures to store and transport, making their transfer to countries with a warmer climate a huge financial burden. On the other hand, protein-based vaccines can be stored in less stringent conditions making them more economically viable.

3. Viral vector vaccines:

There are two types of vector vaccines differentiated on the basis of their ability to replicate- replicating and non-replicating. Both use the host cells to make the antigens by sending the code for replication of antigen. This is done by using viral vectors as a delivery system, providing means to invade the cell and inserting the code for the virus trying to get vaccinated against. Many types of viruses are used as vectors including vesicular stomatitis virus, vaccinia virus, retrovirus, lentivirus, and sendai virus. Adenovirus, a double stranded DNA virus, is the main vector used in the development of vaccines for COVID-19. These vectors are stripped of any disease-causing genes, making them harmless. The ability to replicate is also often removed, making them non-replicating vectors.

Non-replicating vector vaccines are unable to produce new virus particles and only produce the antigens, whereas replicating vector vaccines use the host cells to form new viral particles as well. These new virus particles go on to other host cells to form more antigens. This is the reason that vector vaccines are the most effective vaccines and can induce a strong immune response.

Most of the vaccines developed are non-replicating vaccines. Deletion of the E1 gene terminates replication of virus. Since Adenovirus has a compact nucleic structure, it is a suitable contender for use as a vector. Genes encoding the SARS-CoV-2 spike protein are introduced in the adenovirus vector using gene sequencing. These viruses then grow in specialized medium to form functional cells that, upon further purification, become vaccines. These

vaccines are injected intramuscularly, triggering both cellular and humoral immune responses. They develop neutralizing antibodies, which results in the destruction of COVID-19 virus on future exposure to an actual replicating COVID-19 virus.

Many adenovirus vector-based vaccines have been developed to fight against the pandemic. These include JNJ-78435735(Janssen) by Johnson along with Beth Israel Deaconess Medical Center, AZD1222 by Oxford-AstraZeneca and Covishield by SII, among many others. AstraZeneca has a high efficacy of 70.4% after two doses and has more than 4 billion doses shipped worldwide.

Some limitations of vector vaccines are that people previously immune to Adenovirus showed decreased efficacy, especially in the case of hemorrhagic immune response. Such immunity against the vector also made delivering the second dose more challenging. It has also been found to be ineffective against people with recessive infectious diseases.

References

1. *Han, X., Xu, P., & Ye, Q. (2021). Analysis of COVID-19 vaccines: Types, thoughts, and application. Journal of Clinical Laboratory Analysis, 35(9). https://doi.org/10.1002/jcla.23937*
2. *The different types of COVID-19 vaccines. (2021, January 12). The Different Types of COVID-19 Vaccines. https://www.who.int/news-room/feature-stories/detail/the-race-for-a-covid-19-vaccine-explained*
3. *Dettmer, P. (2021). Immune. In A Journey into the Mysterious System That Keeps You Alive.*
4. *Silveira, M. M., Schmidt Garcia Moreira, G. M., & Mendonça, M. (2020, December 19). DNA vaccines against COVID-19: Perspectives and challenges - PMC. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7749647/*
5. *Chavda, V. P., Pandya, R., & Apostolopoulos, V. (2021). DNA vaccines for SARS-CoV-2: toward third-generation vaccination era. Expert Review of Vaccines, 20(12), 1549–1560. https://doi.org/10.1080/14760584.2021.1987223*
6. *Schlake, T., Thess, A., Fotin-Mleczek, M., & Kallen, K. J. (n.d.). Developing mRNA-vaccine technologies - PMC. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597572/*
7. *Park, J. W., Lagniton, P. N., Liu, Y., & Xu, R. H. (2021, April 10). mRNA vaccines for COVID-19: what, why and how - PMC. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8071766/*
8. *COVID-19 mRNA Vaccine Production. (2021, August 31). Genome.Gov. https://www.genome.gov/about-genomics/fact-sheets/COVID-19-mRNA-Vaccine-Production*
9. *Vanaparthy, R., Mohan, G., Vasireddy, D., & Atluri, P. (2021, September 10). Review of COVID-19 viral vector-based vaccines and COVID-19 variants - PMC. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8805485/*
10. *What are viral vector-based vaccines and how could they be used against COVID-19? | Gavi, the Vaccine Alliance. (2001, September 2). What Are Viral Vector-Based Vaccines and How Could They Be Used against COVID-19? | Gavi, the Vaccine Alliance. https://www.gavi.org/vaccineswork/what-are-viral-vector-based-vaccines-and-how-could-they-be-used-against-covid-19*