Review Article

Overview of the Global COVID-19 Vaccines and Review of the Vaccine Technologies

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Abstract

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization in March 2020. Amidst the global lockdown, scientists have worked tirelessly to formulate vaccinations to curb further spread of the disease, in an attempt to restore normalcy in the health of the population as well as the global economy. While healthcare professionals and medical students have sound knowledge regarding the clinical management of COVID-19 patients, there is lesser knowledge regarding the types and exact mechanism of action of different vaccines. This review therefore aims to present an overview of the globally approved COVID-19 vaccines and a brief on the various vaccine technologies. The purpose is to enable members of the medical fraternity obtain the necessary knowledge regarding vaccines in a concise manner.

Keywords:

COVID-19; SARS-CoV-2; Vaccine; Pathogen; Herd immunity; mRNA; Viral vector; Efficacy Introduction

The coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health Organization on March 11, 2020, has called for prompt actions at the global level to control spread of the infection. Since the declaration, the world has witnessed lockdowns, hospitals running full capacity (with waiting period for beds exceeding 2-3 weeks in certain countries), increased mortality rates, and financial hardships. Simultaneously, scientists have been working round the clock to formulate vaccines to minimize the severity of the infection as well as control further spread. Achieving herd immunity, which refers to a significant proportion of the population being immune to an infectious agent (in this pandemic through vaccination), is the global goal to gain an upper hand over the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Amidst rumors and skepticism regarding the vaccines, in December 2020, in what is arguably the world's largest vaccination drive; countries started rolling out one or more of the approved vaccines to the population. A vaccine is a biological preparation that stimulates the immune response to recognize a pathogen or a part of it. Thereafter, in event of the actual infection, the immune system is prepared to recognize and fight-off the organism. Safe and effective vaccines, especially in pandemics such as COVID-19, can be a game changer in the healthcare scenario. In this report, we have provided an overview of the different vaccines approved globally, with a brief on the type of each vaccine [1]. The aim of this review is to provide concise information regarding the mechanism of action and effectiveness of each type of vaccine.

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Literature Review

Herd immunity

The term 'herd immunity' is used to refer to the indirect protection observed in the unimmunized segment of the population in which a large proportion is immunized. The purpose is to ensure mass immunity for a certain period, which would then hinder the spread of the disease. However, it must be understood that a population that is infected and recovers from a disease is capable of acquiring herd immunity naturally. Nonetheless, antibodies developed following the infection may provide protection only for short periods. Moreover, attempting to achieve natural immunity in a pandemic like COVID-19 could lead to extreme burden on hospitals and other healthcare facilities, considering the contagious nature and rapid spread of the disease.

Thus, planned immunization of eligible populations would aid in reducing the extent of transmission of infectious agents as well as severity of the disease. Vaccines permit development of immunity without contracting the disease. The percentage of the population that needs to be immune to achieve herd immunity varies for each disease. Measles is considered a highly contagious disease; therefore, requires more than 95% of the population to be immune to curb spread. In the case of COVID-19, at least 60% of the population needs to be immune. Herd effect is ascertained by quantifying the decline in the incidence of infection in the unimmunized segment of a population in which an immunization program is organized.

Types of vaccines

Advances in immunology have enabled better understanding of the responses of the immune system to different pathogens. As an example, distinct subsets of helper T cells, such as TH1, TH2 and TH17, are effective in protecting the host from different pathogens. Similarly, follicular helper T cells produce interleukin 21 (IL-21) and help with the differentiation of B cells and generation of memory B cells. In addition, differentiating memory CD4+ and CD8+ T cells can be subcategorized into central and effector memory cell subsets, each with a distinct functionality. Based on understanding of these and other mechanisms, it is now possible to harness the ability of the immune system to formulate vaccines against different pathogens.

Whole pathogen vaccines

One of the well-known methods of vaccine development is based on the use of whole disease-causing pathogens. Using the whole pathogen could cause disease in an otherwise healthy individual and increase the risk of spread of disease; therefore, the pathogens are either weakened (attenuated) or killed during development. The former type of vaccine is known as 'live attenuated' and the latter 'inactivated' vaccine. Attenuation or weakening is commonly achieved by genetic alteration of the pathogen. Such vaccines elicit a robust and long-lasting immune response after minimal number of doses. The measles-mumps-rubella vaccine is a prime example of live attenuated vaccine. However, these vaccines may exhibit increased virulence in immunocompromised individuals; therefore must be used with caution to reduce the risk of development of the disease [2]. Moreover, production of live attenuated vaccines is relatively easier for viruses, but not for complex pathogens such as bacteria and parasites.

Inactivated vaccines on the other hand contain whole viruses or bacteria that have been killed to prevent their replication. This is accomplished with the use of chemicals, heat, or radiation. Since they do not contain any living pathogen components, inactivated vaccines can be used safely in immunocompromised individuals. As a drawback, the immune response elicited may not be as strong as live attenuated vaccines. The polio, rabies, and hepatitis A vaccines are examples of inactivated (killed) vaccines.

Toxoid vaccines

Certain pathogens release toxins (poisonous substances) that are responsible for their deleterious effects on the body. Toxoids are inactivated bacterial or viral toxic elements, similar to killed vaccines, which trigger a strong immune response. Vaccination with toxoids induces anti-toxoid antibodies that bind with the toxin and neutralize its deleterious effects. However, procedures for the production of toxoid vaccines must be strictly controlled to achieve detoxification/inactivation without excessive modification of the antigenic epitope structure. Tetanus and diphtheria vaccines are examples of toxoids.

Subunit vaccines

Subunit vaccines contain one or more specific antigens (proteins or sugars) from the surface of the pathogen. This is done to facilitate recognition of lesser number of target antigens by the immune system compared to whole pathogen vaccines. These vaccines need to be repeatedly administered (as booster doses) and are also manufactured in combination with adjuvants in order to strengthen and lengthen the immune responses. Considering the requirement of multiple doses, local reactions such as soreness may be noticed frequently.

Recombinant protein vaccines

These vaccines are produced by recombinant DNA technology. Recombinant protein vaccines use specific protein antigens taken from organisms such as yeasts or insect cells, among others (manufacturing cells). A small piece of DNA is taken from the virus or bacterium against which protection is desired and is inserted into the manufacturing cells [3]. A classic example of this type is the hepatitis B vaccine, wherein part of the DNA from the hepatitis B virus is inserted into the DNA of yeast cells. These yeast cells are then able to produce one of the surface proteins from the hepatitis B virus, which is purified and used as the active ingredient in the vaccine.

Conjugate vaccines

A conjugate vaccine is composed of a polysaccharide antigen fused (conjugated) to a carrier molecule, which enhances the stability and the effectiveness of the vaccine. The need for conjugate vaccines arose due to the existence of a polysaccharide capsule that protects certain organisms (Neisseria meningitides, Streptococcus pneumonia, among others) from human host defenses. In the majority of the conjugate vaccines, the polysaccharide is attached to a toxoid protein, which is readily recognized by the immune system. Thus, a stronger response is generated to the polysaccharide. The Hemophilus influenza type B vaccine is an example of a conjugate vaccine.

Virus-like particles (VLPs)

VLPs closely resemble viruses, but do not contain the genetic material; therefore, are non-infectious. Compared to other vaccine types, VLPs are easy to produce using stable cell lines; therefore, mass production is facilitated. Considering the absence of replication ability, these molecules can be safely used in immunocompromised individuals. Multivalent VLPs provide repetitive antigens on their surface; therefore, ensure enhanced immunogenicity. The human papilloma virus vaccine is an example of VLP.

Nucleic acid vaccines

Messenger RNA (mRNA) vaccines have strands of genetic material (mRNA) inside a special coating (lipid/fat membrane). The coating protects the mRNA from enzymes in the body that would otherwise result in its breakdown. Considering that mRNA is a non-integrating platform, there is no risk of insertional mutagenesis. The lipid membrane also helps the mRNA enter the cells by fusing with their cell membranes. Early stage clinical trials using mRNA vaccines have been performed for influenza, Zika, rabies, and cytomegalovirus. The limitations observed in these trials include instability of free RNA in the body, unintended inflammatory outcomes, and modest immune responses. Nonetheless, recent technological advancements in RNA biology and chemistry, as well as delivery systems, have mitigated these challenges and improved their stability, safety, and effectiveness.

In context of COVID-19, mRNA vaccines take advantage of the process that cells use to make proteins in order to trigger immune response and build immunity to SARS-CoV-2. The vaccine only induces production of a piece of the "spike protein" that is unique to SARS-CoV-2. Following production of the spike protein, the cell breaks the mRNA strand and eliminates it from the body, thereby negating the possibility of any genetic alteration. On being displayed on the cell surface, the protein or antigen causes the immune system to begin producing antibodies and activating T-cells to fight off the presumed infection.

DNA vaccines

DNA vaccines are a radical new approach, wherein a plasmid containing the DNA sequence encoding the antigen (s) against which the immune response is desired is directly introduced into the appropriate tissues. The technique is based on in situ production of the target antigen. The advantages of these vaccines over the other types are the stimulation of B- and T-cell responses, enhanced stability, scalability, and absence of any infectious agent. DNA vaccines have been proposed to be used in conjunction with electroporation to enable the cells to take up the molecule [4]. There are no commercial DNA vaccines currently; however, several proof of principle studies/research is being conducted (for SARS-CoV-2, influenza virus, hepatitis virus, HIV, among others).

Viral vector vaccines

These vaccines use a modified form of a different virus (vector) than the target to trigger an immune response. The modified virus delivers the genetic code for the antigen (for example, the spike protein found on the SARS-CoV-2) into human cells. The advantage of this approach is that a strong immune response, which mimics the body's natural response to infection, is triggered (based on T cells as well as antibody production by B cells). However, an inherent disadvantage of this type of vaccine is that a history exposure to the vector can reduce the effectiveness. Although these vaccines are difficult to develop, they trigger a strong immune response without the need for adjuvants. A classic example of viral vector vaccine is the Ebola vaccine (rVSV-ZEBOV), which is a recombinant vesicular stomatitis virus-Zaire Ebola virus.

Discussion

There is ongoing discussion regarding the best type of vaccine for COVID-19. While historically, whole pathogen vaccines have been used and considered most effective, nucleic acid vaccines are now being researched to trigger a more effective and longer-lasting immune response. However, in the current COVID-19 scenario, the disadvantage of the nucleic acid mRNA vaccines is the requirement for cold storage (-20°C to -70°C) as opposed to regular fridge temperatures for the viral vector vaccines. This aspect might be problematic in developing and underdeveloped countries, due to the need for added infrastructure to transport and store the vaccines.

Currently, inactivated and recombinant viral vector vaccines are being used and researched predominantly for immunization against SARS-CoV-2. Irrespective of the type of vaccine administered, the body takes approximately 2 weeks to develop immunity against the pathogen. Based on this, currently, the single dose non-replicating viral vector vaccine developed by Johnson and Johnson provides the fastest immune response against SARS-CoV-2.

The advantages of non-replicating viral vector vaccines are well known. Particularly, a single type of vector can be used to deliver codes for a range of antigens [5]. This facilitates

rapid development of the vaccine and may be advantageous in immunization against the mutating strains of COVID-19. However, the process is challenging, can complicate production lines, and increase cost, without a possible increase in efficacy.

Theoretically, inactivated vaccines would have an upper hand in cases of SARS-CoV-2 mutations, considering the broader immune response induced by them. This could be attributed to the fact that these are whole pathogen vaccines; therefore, remain unaffected by mutations in the surface proteins of SARS-CoV-2. Moreover, relatively rapid re-engineering of inactivated vaccines is possible. However, certain scientists oppose this view by stating that while a broader immune response is ideal, an increase in neutralizing antibodies appears more relevant in context of COVID-19 vaccine efficacy. A targeted immune response is required, which may be elicited by a vaccine featuring a specific antigen as opposed to whole pathogen vaccines. Development of neutralizing antibodies following inactivated virus vaccination is not as high as that following other vaccine types. Thus, the long-term efficacy of inactivated vaccines, especially against the mutated variants remains debatable.

As for the nucleic acid vaccines, the efficacy of the available mRNA vaccines is the highest against the original SARS-CoV-2 compared to other vaccine types. Furthermore, the developers Modern and Pfizer have announced a three-dose strategy with their respective mRNA vaccines to tackle the B. 1.351 variant of SARS-CoV-2. In addition, Modern has proposed a two-dose approach as well, wherein the booster dose would include mRNA-1273.211 that combines the original and new vaccine permutations.

The optimal time interval between the two doses of the COVID-19 vaccines is another aspect to be considered. The majority of the developers have suggested a 28-day interval between the two doses in order to achieve effective protection against SARS-CoV-2. These are based on Phase 3 clinical trials conducted on various populations globally. For instance, Modern and Pfizer have reported an efficacy of 95% following the two doses of their respective mRNA vaccines, while the Oxford University-AstraZeneca genetically modified adenovirus vaccine is 62-90% effective. Russia's Sputnik V vaccine on the other hand has demonstrated 92% effectiveness in Phase 3 trials, and the Chinese inactivated vaccines are 50-79% effective (based on phase 2 and 3 trials on Asian, Middle-Eastern, and South American populations). In March 2021, Bharat Biotech, India announced their Phase 3 results pertaining to the interim clinical efficacy of the inactivated coronavirus vaccine, Covaxin as 81%.

Future trends

Considering the global presence and rapidly evolving strains of SARS-CoV-2, the GAVI vaccine alliance recommends a mixture of approaches to control spread of the infection and end the pandemic. Developers are now also focusing on alternative routes of vaccination to speed up the process and reach a wider population in a short period. For example, an intranasal vaccine is being co-developed by Codagenix (USA) and the Serum Institute of India, as well as by Meissa Vaccines, Inc., and Altimmune that are in Phase 1 trials currently. The vaccines are live attenuated SARS-CoV-2, which have been designed to produce immunity against all proteins of the virus, thereby making it a promising candidate against the mutating strains as well. The chief advantage is that, being non-invasive, the requirement for trained professionals to administer the vaccine will be reduced. A dendritic cell vaccine is also in Phase 1 trials (AV-COVID-19; Aivita Biomedical, Inc., Indonesia). Autologous dendritic cells (cells of the innate immune system) are loaded ex-vivo with the SARS-CoV-2 spike protein, which will then be injected into the patient's body. The optimal dosing regimen for the vaccine has not yet been established.

The COVID-19 pandemic has increased the need for novel vaccine development technologies. Novavax (among other developers) has used one such technology, known as recombinant nanoparticle vaccine engineering, based on a Sf9/Baculovirus insect cell platform to produce a candidate vaccine against SARS-CoV-2. The advantage of the recombinant nanoparticle technology is the ability to produce appropriately folded and modified proteins, which are critical for functional, protective immunity. The candidate vaccine NVX-CoV2373 has demonstrated 89.3% efficacy in a UK phase 3 trial, including responses against the UK and South African variants of SARS-CoV-2.

Interestingly, considering that the complete genome of SARS-CoV-2 was recently published, as many as six DNA vaccines are in the pipeline against the virus (Zydus Cadila, Inovio Pharmaceuticals, AnGes, Inc., Genexine, OncoSec/ Providence Cancer Institute, Takis Biotech). DNA vaccines deliver genes or its fragments encoding immunogenic antigens to the host cells, and efficiently induce both humoral and cell-mediated immunity. The vaccines are formulated in a manner that the genetic material is translocated into the nucleus of the host cell. All candidate DNA vaccines currently under research use the S (spike) protein as the antigen.

Scientists have stated that immune responses against SARS-CoV-2 could lead to antibody-dependent enhancement. This refers to the phenomenon where antibodies facilitate entry of the virus into the host cells and enhance the infection [6]. While currently SARS-CoV-2 and its variants have not shown this phenomenon, in event of such an occurrence, the nucleic acid vaccines (both mRNA and DNA) could have an upper hand as regions or motifs of the antigen causing such an effect can be engineered or removed easily.

Conclusion

Currently, there are around 181 candidate vaccines being explored in preclinical stages, 28 each in phase 1 and 2 trials, and 21 vaccines in phase 3 trials. Research must focus on the vaccine type and optimal dosing regimen in order to plan subsequent booster doses, as/if required, to ensure a sustained

immune response against SARS-CoV-2 and possibly against other related viruses.

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