Review Article

Review of COVID-19 Vaccine

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Abstract

Coronavirus disease 2019 (COVID-19) accounts for over 92 million confirmed cases worldwide, with over 2.06 million deaths. In the past year, more than 290 candidate vaccines have been tested; COVID-19 vaccine development was sped up, with shortened timeline, due to the urgent global need in the face of the pandemic. In addition, people with the highest risk of contracting the disease, such as health workers with a high risk of exposure, elderlies, and people with underlying comorbidities, were prioritized with vaccination rollout. The article narratively reviewed original and review articles available on PubMed and Google Scholar related to the theme to provide up-to-date information. The different templates developed and studied for COVID-19 vaccines include the whole-virus vaccine, viral vector vaccine, nucleic acid (deoxyribonucleic acid and ribonucleic acid), and protein subunit vaccine. Myths impede vaccine uptake in this part of the globe. Adopting these myths leads to sharing and spreading, which negatively impacts the prevention of COVID-19 and vaccine uptake. Adverse event following immunizations (AEFIs) is classified based on severity, from minor to severe. The minor ones are common events that pose no potential health risks to the receiver of the vaccine. The type determines the safety profile, severity, and frequency of AEFIs observed with the vaccine administration. Overall, this pandemic has heightened the global level of threat awareness; it has also provided motivation to prepare for future pandemics by developing new vaccines.

Keywords: COVID-19, pandemics, vaccine

Introduction

Coronavirus disease 2019 (COVID-19) is a highly communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the first case of the disease was reported in Wuhan, Peoples Republic of China (PRC), in December 2019.[1] Ninety-two million confirmed cases of COVID-19, with over 2.06 million COVID-19-associated deaths, had been reported globally as of January 23, 2021, and have led to enormous psychological, sociological, demographic, and economic crises around the world.[2,3] Far-reaching measures, such as extensive testing, nationwide lockdown, social distancing, and strict seclusion of infected persons, are necessary to prevent the further spread of SARS-CoV-2. However, employing these preventive measures geared toward containment is not a simple task to achieve.[4] This unremitting CoV spread underscores the significance of global efforts in developing vaccines and therapeutics. Furthermore, the return to normalcy appears to depend on the urgent rollout of an effective vaccine and rapid implementation of the vaccination.

Vaccines are biological agents that humanity usually count on to decrease the death tolls from infectious diseases and their agents. Within a year, immediately after the start of the COVID-19 pandemic, many teams of researchers domiciled in several countries took up the challenge of finding a lasting solution to the pandemic, and they came up with vaccines that can protect humans against SARS-CoV-2.[3] By January 2021, more than 290 candidate vaccines have been developed and tested; 69 candidate vaccines are currently in medical trials, including 43 in Phase one to three trials and 26 in Phase

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Table 1: Coronavirus disease-2019 vaccine categories and important attributes

Types	Subtypes	Efficacy	Storage	Cost
Whole-virus particle (need adjuvant IM vaccine)	Inactivated			
	CoronaVac (China)	CoronaVac (86%)	2-8°C	
	BBIBP-CorV-not yet approved			
	Live attenuated			
	All candidate vaccine. None approved yet			
Viral vector (requires adjuvant addition)	Replicating			
	Candidate vaccines. None approved yet			
	Nonreplicating			
	Johnson and Johnson's (US)	Johnson and Johnson's (70%), two shots	2-8°C	
	Oxford AstraZeneca (UK)	Oxford AstraZeneca (63% revised 73%), two shots	Regular fridge temperature	$4
	Sputnik Gamaleya (Russia)	Sputnik Gamaleya (92%)	Regular fridge temperature (dry form)	$10
Nucleic acid	DNA			
	Candidate vaccines. None approved yet			
	RNA			
	Moderna (US)	Moderna (95%), two shots, 28 days apart	−20°C	$25
	Pfizer BioNtech (US)	Pfizer BioNtech (95%), two shots, 21 days apart	−7°C	$15
Protein subunit	Conjugate subunit			
	EpiVacCorona (Russia)			
	Polysaccharide			

BBIBP-CorV: Beijing Institute of biological products corona vaccine, DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid, CoronaVac: Coronavirus disease-2019 vaccine

Table 2: Advantages and disadvantages of nucleic acid vaccines

Advantages	Disadvantages
There is no live component, so no risk of the vaccine triggering the disease	Some RNA vaccine requires ultra-cold storage
They are relatively easy to manufacture	A booster shot may be required
The immune response involves B and T cells	Has never been licensed in humans
	Long-term persistence of DNA plasmids upon injection

DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid

two to three trials.[3,4] The speed at which these vaccines were developed was unprecedented in the history of vaccine development compared to other vaccines such as measles and typhoid, among others that took several years.[5,6] Furthermore, many countries where COVID-19 vaccination has commenced have executed phased distribution plans that prioritize those at high risk of exposure and transmission, including health-care workers and those at highest risk of complications and extreme adverse outcome, such as the elderly.[7] The expectation is that additional numbers of companies develop a vaccine for COVID-19, which can be made available for every nation of the world irrespective of their economic strength and race.

Before the COVID-19 pandemic, no available vaccine was shown to be potent against infection with any beta-CoV, the family that includes the SARS-CoV-2-aetiological agent causing COVID-19. The SARS caused by another beta-CoV ended on its own before considerably significant efforts at vaccine developments were commenced, and the fairly small number of the Middle East respiratory syndrome cases have not yet vindicated the huge-scale financings and efforts required to determine whether preclinical vaccine entrants are effective.[8] As more efforts are being geared toward developing more effective vaccines with fewer side effects and increasing the supply of the existing ones to the middle-low-income countries who are not rich enough to afford these vaccines, it is hoped that there would be victory at last.

The article narratively reviewed original and review articles available on PubMed and Google Scholar databases.

Types of COVID-19 Vaccines

Whole-virus vaccine

In general, whole-virus vaccines are derived from inactivated or live-attenuated viral particles, and this technology has been in use for decades. Live-attenuated vaccines are derived by passing disease-causing pathogens through cell culture in a foreign host to strip it of its pathogenic properties, so that it causes a mild infection that the recipient's immune system can eliminate and subsequently develop a robust immunogenic response mechanism.[9] Three live-attenuated COVID-19 vaccine candidates are currently in preclinical trials.[10]

Inactivated COVID-19 vaccines are made by growing the SARS-CoV-2 in Vero cell culture after that chemically inactivating the virus so that the viral particle loses its infectivity

but can still trigger an immunogenic reaction in the recipient.[11] The Sinovac COVID-19 vaccine (CoronaVac) and Beijing Institute of Biological Products corona vaccine (BBIBP-CorV) developed by Chinese company Sinovac Biotech and Beijing Bio-Institute of Biological Products Co Ltd, respectively, are the two COVID-19 candidate vaccines created with the inactivated virus technology [Table 1].[9,12] These vaccines are injected into the body through the intramuscular route and contain adjuvants such as aluminum hydroxide that potentiate their immunogenic capacity. The immune response to these vaccines targets the envelope, spike, matrix, and nuclear proteins of SARS-COV-2 as the virus, as a whole, comes in contact with the recipient's immune system.[10]

Randomized clinical trials for safety and efficacy demonstrated that CoronaVac was well tolerated and induced humoral responses against SARS-CoV-2. This influenced its endorsement for emergency use in PRC and ongoing Phase three clinical trials in three countries with a low dose of three microgram of CoronaVac in 3 and 6 μg in 0.5ml volume of diluent confirmed on a day 0 and 14 vaccination schedule being studied in these trials.[12] The profile of safety of this novel vaccine was outstanding and comparable to that of the placebo. Overall, over 90% of recipients showed seroconversion.[10] The efficacy of this vaccine has yet to be established as the Phase three trials are still in progress at the time of this review.

The inactivated SARS-CoV-2 vaccine BBIBP-CorV clinical trial showed that it has a good safety profile, tolerability, and immunogenicity in apparently healthy people. Two-dose immunizations (with an interval of 28 days in-between the shots) at all doses (two microgram, four microgram, and eight microgram) in two age groups (>17 ≤59 years and >59 years) induced neutralizing antibodies in all of the vaccine recipients.[12] Recipients commonly develop mild adverse reactions in both vaccine trials, including pain and fever, and no serious vaccine-associated adverse events were reported in all groups.[13]

The inactivated COVID-19 vaccines use a killed form of the virus to trigger protective immunity to the organism in the recipient's cells; therefore, it can protect humans without causing an infection. Thus, make it a choice in the vaccination of immunocompromised individuals. Inactivated vaccines are also considered more stable than live attenuated ones; hence, this type of COVID-19 vaccine potency will be better preserved. The challenges of the inactivated COVID-19 vaccine, as with all other vaccines of this type, include induction of a weak or short-lived immune response that diminishes with time, hence the need for booster doses to evoke sufficient immune response.

Viral vector vaccine

A viral vector as a vaccine technology was initiated in the 1970s. Besides been used as vaccines, it has also been used as gene therapy in cancer treatment.[14] Vaccinia virus, herpes virus, measles virus, adenovirus serotype five, and poxviruses have been developed as vectors for various vaccines whereby these viral vectors are stripped of replicating genes and diseases causing genes; genetic codes for the production of antigen from pathogen are attached into the vector genome.[14,15]

Viral vector vaccine uses a genetically modified form of a different virus (Vector) to deliver genetic materials for antigens into the human cells.[14] There are two types of viral vector vaccines – the replicating and the non-replicating vector vaccines. The non-replicating vector vaccines produce the vaccine antigen when they infect human body cells but cannot retain the capacity to produce new viral particles. The replicating vector vaccines produce new viral particles (vaccine antigen) in the human cells they infect and then infect new human cells to develop new viral particles.[16] The vector is a different virus and harmless virus (it is not the virus that causes COVID-19), and this vector infects the human cells and transform into a piece of harmless virus (the spike protein (S) found on the surface of the virus that causes COVID-19) and make a considerable quantity of the antigen. The immunological system recognizes that the S protein on the COVID-19 virus' surface as a foreign body then triggers the immune system to respond by producing antibodies and initiates the activation of other immune cells to fight the viral infection.[17] This helps develop a strong cellular immunological response by the T-lymphocytes and the production of the memory B-lymphocytes; this memory B-lymphocytes enable the human body to protect against future COVID-19 infection.[18] Some of the challenges of viral vector vaccines are that previous exposure to the virus vector may increase an immunological response against vector vaccine (antivector immunity) and reduce the effect of the vaccine.[19] Non-replicating viral vector vaccines are being authorized for use in the United States of America (USA).[18] An example is the Janssen COVID-19 Vaccine developed by Johnson and Johnson's based in the USA.

Nucleic acid (deoxyribonucleic acid and ribonucleic acid)

Nucleic acid vaccine, a protein subunit, employs an antigen-encoding plasmid ribonucleic acid (RNA), messenger RNA (mRNA), viral replicons, or deoxyribonucleic acid (DNA) [Table 1]. The nucleic acid-encoded antigens can elicit both cell-mediated and humoral immunological responses upon their uptake and expression at the cellular level.[20] The production of antigens in the target cells has the benefit of mimicking protein production during infection.[20]

These DNA vaccines are produced by inserting an eukaryotic expression cassette encoding for the desired antigen (s) into a plasmid derived from bacteria.[20] DNA vaccines are usually injected intramuscularly. However, the problem is getting them to enter the human cell. This is a crucial step because the apparatus which allows the antigen to be translated into protein is situated within the cells. Different methods or technologies are being developed to support this process, such as (i) encapsulation of the DNA in nanoparticles which are devised to undergo fusion with the human cell membrane; (ii) the use of "gene gun," which makes use of helium to propel DNA into skin cells; and (iii) the use of electroporation method, where

short pulses of electrical current are used to generate temporary pores in membranes of human cells.[20]

RNA vaccines encode the desired antigen in mRNA or self-amplifying RNA, which are molecular templates used by cellular factories to make proteins. Because of its transitory nature, there is virtually no risk of it getting incorporated into human genetic material. Instead, the RNA particle can be injected by itself, encapsulated within nanoparticles (as in Pfizer's mRNA-based COVID-19 vaccine), or driven into cells using some of the similar methods being devised for DNA vaccines.

Once the RNA or DNA particle is in the cell and commences antigens production, these are then manifest on its surface, where they can be identified by the immunological system and trigger a response. This response includes killer T-lymphocytes that search for infected cells to destroy such cells, antibody-producing B-lymphocytes, and helper T-lymphocytes that aid the production of antibodies. Once introduced into the host cell, the genetic material is read by the cell's protein and used to produce an antigen, which then triggers an immunological response. This technology is relatively recent, although RNA and DNA vaccines are being developed against diseases such as the human immunodeficiency virus, Zika virus, and now COVID-19. So far, none has been licensed yet for use in humans. However, many DNA vaccines are licensed for animal use, such as an equine vaccine against West Nile Virus. The advantages and disadvantages of nucleic acid vaccines are in Table 2.

Protein subunit vaccine

Subunit vaccines contain a specific part of a pathogen that acts as antigens, eliciting an immune response from the host. They do not contain any genetic material nor live components of the organism: they contain only the antigens capable of causing an immune response.[21] These types of subunit vaccines are grouped protein subunit vaccines, polysaccharide vaccines, and conjugate subunit vaccines.

The protein subunit vaccines contain specific isolated antigen fragments, usually from membrane proteins of pathologic organisms that best stimulate the immune response in the host.[21] Like other types of subunit vaccines, they do not contain viral genetic material and cannot infect or replicate within the host. These proteins, once identified, can be synthesised or produced by recombinant techniques and packaged into vaccines that can be administered.[18,21,22]

The persistence of neutralising antibodies and memory of the immune system against these antigens offer long term protection by preventing the attachment of this viral particle to the host cells when encountered. The receptor-binding domain within the spike (S) protein of SARS-CoV-2 is the most appropriate antigen to stimulate the neutralising antibodies to inhibit COVID-19 infection.[18]

The benefits of the protein subunit vaccines (i) are that they are safe since they do not carry any genetic material, thus no risk of replicating within the host, therefore unable to cause infection in recipients.[18,23] (ii) they are stable product and do not require storage in very low-temperature freezers to preserve their potency as required by other vaccines like the whole virus or live attenuated vaccines.[23] (iii) It can be given to individuals with weakened immune systems due to its inability to replicate or transform to a live form[23] and (iv) there are minimal adverse reactions due to the use of only the specific antigens that best evoke an immune response for the production of the vaccine, and other antigens that increase the risk of adverse reactions are not present.[18,23]

The disadvantages of protein subunit vaccine are (i) there is the risk of generating weak immune responses due to several factors such as the exclusion of other antigens other than the main ones that trigger the immune response, also means the pathogen-associated molecular patterns which contribute to immune response would be excluded[23] and (ii) they have minimal or suboptimal cell-mediated immunity if any,[8] (iii) the production is more complex and more time consuming as the various antigens of the virus has to be examined to determine which ones would be included in the vaccine,[18,23] (iv) It is also more expensive to manufacture,[23] and (v) The long term protection offered by immune memory is not sacrosanct.[18]

The use of adjuncts which are agents that stimulate and/or prolong immune response, and booster doses, which lead to repeated sensitisation and increased immune response, are used to overcome this shortfall of minimal or suboptimal cell-mediated immunity.[18]

Only one protein subunit vaccine (EpiVacCorona) has been approved for vaccination in the human population (only in Russia); however, several vaccine candidates are at different phases of clinical and preclinical trials.[22,24]

Myths Around COVID-19 Vaccines

Myths are stories in the category of folklore, often endorsed in society, traditionally or religiously, and which shape the beliefs and daily lives and attitudes of humans.[25] In the history of man and diseases, there have been several myths, including leprosy and tuberculosis, as well as with vaccines, for instance, the flu vaccine or measle depending on the time or territory. At present, the novel CoV pandemic has necessitated the institution of control and preventive measures and research into vaccination to hinder the spread of the virus among humans and build herd immunity in populations. However, despite the massive awareness efforts to the public on the COVID-19 vaccines, serious criticisms with many myths and conspiracies discouraging its use have arisen among individuals and societies, which has spread quickly in this age of digital and social media, including WhatsApp, Facebook, Twitter leading to a "disinfodemic."[25,26]

The prevailing myths surrounding COVID-19 vaccines, which though false, are generating anxiety about their uptake, include: *"COVID-19 vaccines can give me the disease*;" *"I will test positive for COVID-19 after the vaccination*;" "*I have already*

had and recovered from COVID, I do not need the vaccine;" *"My DNA will be changed by the COVID*-19 vaccine"[27,28] Indeed, many Nigerians still fundamentally hold beliefs suggesting the disease cannot thrive/are easily destroyed in the country such as: "*It is a disease of white people;" "The virus cannot thrive the very hot weather in Nigeria;" "Hot* drinks/local *gins destroy* CoV," and such extreme myth as "*COVID-19 is not real*."[29] These myths further propagate the basis for non-belief in the need for a vaccine and further create challenges for COVID-19 vaccine uptake.

The dangers in the belief and adoption of these myths and conspiracy theories are that such individuals are more likely to share and spread these myths; they connect to other forms of distrust, exhibit low compliance with governmental guidelines, and show increased hesitancy towards the uptake of vaccines.[30] Thus, there is a need for in-depth study of the prevailing myths and conspiracy theories to address them to pave the way for improved acceptance and uptake of the COVID-19 vaccines. Finally, it is worth emphasising as a deterrent to the vaccine theorists that such myths are detrimental to societies and can be punishable through cyber policing.[31]

Adverse Events following Immunisation with COVID-19 Vaccine

According to the World Health Organization (WHO), the term "adverse event following immunisation" (AEFI) is referred to as "any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine."[32,33] Furthermore, this event can be an anomalous lab finding, an unfavourable or unintended sign, a symptom, or a disease.[32]

Based on severity, AEFIs can be classified into minor or serious.[34] The minor AEFIs are common events, and they pose no potential health risk to the receiver of a vaccine dose;[3,4] they include rash, fever, malaise, loss of appetite, reactions at the injection site (such as redness, tenderness and swelling), and other mild reactions.[34,35] The serious AEFIs are rare events. An AEFI is considered a serious AEFI if it is life-threatening or results in hospitalisation, persistent or major disability/incapacity, birth defect (if the receiver of the vaccine dose is a pregnant woman), or death of the vaccine dose receiver.[34,35]

All vaccines, when received, have the potential to cause an AEFI.[32-35] The level of severity (minor or severe) of AEFIs associated with a vaccine, as well as the frequency of the AEFIs observed with such a vaccine, is one of the major determinants used in assessing the safety profile of the vaccine.[36,37] Before a vaccine can be certified to be safe by the vaccine regulatory body/agency of a nation, it must have satisfactory reports on AEFI at the preclinical and clinical phases of its development. Postcertification, AEFI data collection, analysis and monitoring also continue from the day its use begins in the general population.[38]

Traditionally, it takes many years to develop a vaccine. However, the COVID-19 vaccine development timeline was an exception; the period spent in the trial of the COVID-19 vaccine was quite very short due to the urgent need for the vaccine globally.[38] As a result, the AEFIs associated with the vaccine may still not be fully known and deeply studied to a conclusive point. Available data has shown that AEFIs occurred in 0.015% of the COVID-19 vaccine doses administered, of which two-thirds of these AEFIs were minor ones.[39] Incidence of (0.03%) adverse events after receipt of Moderna COVID-19 vaccine were submitted to Vaccine Adverse Event Reporting System.[40]

Close surveillance of COVID-19 vaccine-related AEFIs during the rollout of the vaccine for use in the general population needs to be taken very seriously. The surveillance of this vaccine's AEFIs will help understand the vaccine deeper, guide public health laws, policies, and strategies regarding COVID-19 vaccination; in preparation for public health emergencies, and build public trust about the vaccine.[41]

Conclusion

Pandemics have raised the awareness of global threats caused by newly emerging pathogens and has provided the motivation to prepare against future pandemics through the development of new vaccines to provide viable solutions. Some have demonstrated a high level of effectiveness with the use of adjuncts with good safety profiles. The COVID-19 vaccine distribution to every part of the world is being worked towards by many health agencies in the world, especially WHO, UNICEF and other partners, and every head of state should continue to sensitise its people on the vaccine, its importance and the need to take it once it is made available. According to the WHO, the COVID-19 vaccine goal is for it to be a global public good, although it is also important to note that taking the vaccine should not stop essential public actions such as physical distancing, use of face masks, and sanitisation of hands to reduce the rate of transmission and subsequently reduce mortality.

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Conflicts of interest

There are no conflicts of interest.

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