Special Article

Development of Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-COV-2) Vaccines

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Abstract

The new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) brings about the coronavirus disease 2019 (COVID-19) pandemic. It is a pathogen that causes extreme respiratory tract infection, especially as the world's populations had no previous immunity and there were little or no uniformly acceptable treatment options. The virus may persist to bring about considerable morbidity and mortality except an efficient vaccine is produced. Following erstwhile evidence and experience with SARS and Middle East respiratory syndrome, the major focus to vaccine development was the spike glycoprotein, regarded as the most important target for SARS-CoV-2 immunotherapies. Collaborative efforts were undertaken to ensure that manufacturing occurred as quickly as possible to salvage the situation. Three vaccine candidates were respectively made of one protein-based vaccine, a simian-derived adenovirus vector, and one messenger RNA vaccine. Two of them published their short-term analyses and effective results after their third trial phase. The messenger RNA vaccine was first confirmed in the USA and the adenovirus-derived vaccine in the UK. This paper gives a narrative review of the literature on the present knowledge about this new virus as it concerns the drawn-up plans of COVID-19 vaccines that are not only effective but safe following the new and established approaches to vaccine development.

Keywords: Clinical trials, coronavirus, coronavirus disease 2019, severe acute respiratory syndrome coronavirus-2, vaccination, vaccine safety and efficacy

Introduction

Coronaviruses (CoVs) are club-like positive-sense single strands of RNA viruses. They are the largest group of viruses and are members of the *Coronaviridae* family. They are named "Coronavirus" because they have spike-like projections. These are bulbous spikes like the pointy end of a crown. Three global outbreaks in the last 20 years have been caused by CoVs. The latest is coronavirus disease 2019. This is viral pneumonia with a multisystem disease, which is as a result of contracting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] The COVID-19 pandemic caused by the SARS-CoV-2 virus is having an extraordinary effect on global health. This is due to its rapid spread, which is accredited to (a) its extreme stability in environmental conditions, (b) great mobilisation of the globalised society, and (c) its ability to develop as an asymptomatic disease in some people.[1-3]

SARS-CoV-2, the aetiological agent of COVID-19 belongs to the beta-CoVs (β-CoVs) or alpha-CoVs (α-CoVs) family. Other subfamily members include delta-and gamma-coronavirus.[1] The primary hosts for α-and β-CoVs are bats and rodents, while the primary hosts for γ- and δ-CoVs are birds. Another component is the SARS-CoV-1 which caused SARS-1 and Middle East respiratory syndrome (MERS)-CoV caused MERS. SARS-1-CoV-1 (2002) and MERS (2012) caused ephemeral epidemics which leads to an alarming death rate. MERS is also known to occur at irregular intervals, while there are no reports on the reoccurrence of SARS-CoV-1 since 2008.[2-4] The genetic makeup of SARS-CoV-2 is expressed as follows:

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a. Spike glycoprotein permits entry into the host cells through attaching themselves to their receptors and the coronavirus spike glycoprotein is the main target of antibodies
b. Envelope protein
c. Membrane or matrix protein
d. Nucleocapsid protein which surrounds the genomic RNA
e. Nonstructural proteins.

The shape of the virus is formed by the membrane and nucleocapsid proteins. The spikes glycoproteins appear on the surface of the virus appearing like solar corona or like the pointy end of a crown as stated above. The spike glycoprotein is trimeric and forms the structure through which they bind to the target cells. Angiotensin-converting enzyme 2 (ACE2) which is found on the surficial parts of the cells is the entry receptor for SARS-CoV-2. This is engaged through the receptor-binding domain (RBD) an element of the spike glycoprotein.[1-3] Because the coronavirus spike glycoprotein is superficial and helps the virus to enter with ease into host cells, it is, therefore, the most important target of neutralising antibodies upon infection and the attention of therapeutic and vaccine plan or strategy.

COVID 19 infection incubation period in infected individuals ranges from 2 to 14 days with an average of five days. Viral replication could be rapid in the first few days of infection causing many of the clinical manifestations. This has been shown to be affected by the distribution of ACE2. The initial clinical manifestations may include fever, headache, dry cough, sore throat, running nose, joint pain, dyspnea, and anosmia (absence of the sense of smell) among others.[3] Infections in the elderly and those with significant comorbidities tend to be more severe and they are more prone to die of COVID-19 infection.[1-3] SARS-CoV-2 infection can also be asymptomatic. Most patients are often asymptomatic while others may only be infected with a slight respiratory tract infection.[3] SARS-CoV-2 (including its variants) can be very infectious before and soon after symptoms commencement. Thus, this has helped force rapid global spread (the Delta variant is causing a surge in cases globally and more recently, the Omicron variant). The only morally conventional path to achieving an elevated degree of immunity is increased coverage with effective vaccines.[4] Because the COVID-19 outbreak was declared a pandemic by the World Health Organization in March 2020, more than 100 million cases and almost 3 million confirmed deaths as a result of SARS-CoV-2 infection have been reported globally.[5] Currently, there is no known effective treatment for COVID-19 or SARS-CoV-2.[3] Thus, the present pandemic has drawn attention to the importance of useful preventive measures to decrease the problem and spread of the virus and its infection. If COVID-19 should breakout in a particular place, then there is a possibility of contracting the virus elsewhere. Immunisation may both protect persons induce resistance to limit the viral spread and decrease infection and death throughout the world.

In response to this, many vaccines are being rapidly developed to stop the further spread of COVID-19 disease. This has suddenly developed into a battle between man and this virus[6] and a race against time. Vaccines enable the body to build immunity without experiencing illness. Many countries around the world have stepped up the procedure of laboratory trials to produce a vaccine that can be both effective and safe to fight the spread of SARS-2 COVID-19 and salvage the new pandemic.[7,8] The effectiveness of the different COVID-19 potential vaccines will rely on their efficacy to decrease contagiousness as well as prevent severe infection. Starting with about 250 candidates of vaccines such as messenger ribonucleic acid (mRNA), viral vector, autologous dendritic cell-based vaccines, deoxyribonucleic acid (DNA), and inactive virus vaccines against SARS-CoV-2 that were developed globally [Table 1].[9,10]

The six main types of vaccine methods to develop immunity against the SARS-CoV-2 include:

a. Live diminished virus – This is constructed by changing the original virus. Attenuation is the process of reducing the disease-producing ability of a virus (the production of a weaker virus). It can be achieved by serial passage through another organism or other processes
b. Inactivated virus – The inactivated vaccine is developed by disabling a virus through radiation, chemicals, or heat. The inactivated virus cannot cause disease, because it cannot enter cells and replicate
c. Viral protein subunit – The viral protein subunit vaccine has a subunit of a SARS-CoV-2 antigen. The vaccine contains no other part of the SARS-CoV-2, that can possibly cause replication toward a clinical condition
d. Virus-like particles – These vaccines are closely like the SARS-CoV-2 in formation but contain none of its genetic material. Although this is similar to the coronavirus it cannot cause disease
e. DNA and RNA – These consist of mRNA or DNA code for synthesise a form of a SARS-CoV-2 protein. The code is transported into a cell which then applies the genetic instructions to produce this antigen. The immune system can then generate antibodies that will identify that antigen and repel or ward off the virus
f. Viral vector – This is like the DNA and RNA vaccines which consist of instructions for generating or synthesise a SARS-CoV-2 antigen. The instructions are transported into a cell by a risk-free or safe virus.

Although these six vaccine types differ in technique, but they all present an antigen into the body, which the immune system can use to develop antibodies against the genuine SARS-CoV-2. Each one technique comes with its own merits and demerits, and variable or adjustable instance to advance, cost, and strength, including expected safety and immunogenicity profiles. All techniques are characterise by preclinical and clinical trials. To date, some well-known of these vaccine candidates are being used in most countries around the world or globally [Table 1]. This narrative

Table 1: Severe acute respiratory syndrome coronavirus-2 coronavirus disease 2019 vaccines currently in use

SARS-CoV-2 (COVID-19) vaccine	Applied vaccine technology/method	Developer(s)/Country	Dose plan
BNT162b2	mRNA (lipid nanoparticle)	BioNTech/Pfizer (Germany and USA)	2 doses
ChAdO×1-S	Viral vector (Chimpanzee adenovirus vector carrying the gene for SARS-CoV-2 spike protein)	University of Oxford/AstraZeneca (United Kingdom)	2 doses
mRNA-1273	mRNA that encodes SARS-CoV-2 spike protein is encapsulated in ionizable lipid (i.e., a lipid nanoparticle)	Moderna/NIAID (USA)	2 doses
Ad26.CoV2.S	Viral vector (nonreplicating human adenovirus type 26 carrying undisclosed genetic material of SARS-CoV-2)	Janssen/Johnson and Johnson (USA)	1 dose
NVX-CoV2373	Protein lipid nanoparticle that contains antigen derived from SARS-CoV-2 spike protein (with Matrix M adjuvant)	Novavax (Australia and South Africa)	2 doses
Gam-COVID-Vac	Viral vector (human adenovirus type 26 and 5, sequentially administered)	Gamaleya Research Institute (Russia and the United Arab Emirates)	2 doses
Ad5-nCoV	Viral vector (human adenovirus type 5 vector which expresses spike protein)	CanSino Biologics (China)	2 doses
CoronaVac	Inactivated SARS-CoV-2	Sinovac Biotech (China, Brazil, Bangladesh, and Indonesia)	2 doses
Not named (Sinopharm)	Inactivated SARS-CoV-2	Beijing Institute of Biological Products/Sinopharm (China)	2 doses
BBV152B/Covaxin	Inactivated SARS-CoV-2	Bharat Biotech International (India)	2 doses
Not named (Sinopharm)	Inactivated SARS-CoV-2	Wuhan Institute of Biological Products and China National Pharmaceutical Group (Sinopharm) (China and the United Arab Emirates)	2 doses

NIAID: National Institute of Allergy and Infectious Diseases, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, COVID-19: Coronavirus disease 2019, mRNA: Messenger ribonucleic acid

review, therefore, aims to look into the global effort to contain the pandemic, especially the development of effective vaccines.

Methods

This study is a narrative review and the articles used were selected after a careful search of PubMed, SCOPUS, Google Scholar, and African Journals Online databases. The inclusion criteria were that the article should be a recent study (preferably within the past 1–2 years) and should contain information relating to the manufacturing of SARS-CoV-2 vaccines. Search terms include "clinical trials," "coronavirus vaccines," "COVID-19 vaccines," "SARS-CoV-2," "vaccination," and "vaccine safety and efficacy." The Boolean operators "AND," "OR," and "NOT" were employed to enhance the results of the literature search. The authors independently reviewed all selected articles and recommended each for inclusion based on the set inclusion criteria.

The Preparedness for Pandemic

On the basis of prior evidence and testimonies on the outbreak of diseases for more than 20 years now, that includes the 2009 outbreak of SARS and MERS, influenza, the 2014 outbreak of Ebola,[11] and the occurrence of the Zika viral disease have strengthened the speedy development of COVID-19 vaccine. These have also led to noteworthy advances in basic vaccine research and development.[4,6] Thus, studies are now on not just to put an end to COVID-19 infections, but also to ward off reinfection and deal with emerging variants too.

The Development of Vaccines

A variety of vaccine design approaches and programs have been used. Immunisation is said to be effective if the developed vaccine has been endorsed for application and is circulated to the intended populace. The process of which vaccines are developed is a series of distinct phases, pyramidal and discriminating or thorough.[4,12] It initially begins in the laboratory and experimented with cell lines and whole animals (i.e., preclinical phase). If these give positive results, then the trials have qualified for phase 1. The phase 1 stage evaluates the safe dosage and immunity in a few healthy individuals. Usually, just an insignificant percentage of trials advanced to phase 2. The phase 2 trials are planned to detect or distinguish the best possible formulations, dosages, and intervals for administration. The phase 2 requires between 100 and 1000 test individuals for the trials. Phase 3 assesses drug safety and the effectiveness of protection against disease within the ambient clinical conditions. The phase 3 trials depend on the likely number of test individuals but generally involve many hundreds that round up to thousands of cases. Advancement through all clinical trials generally takes not <10–15 years. However, the enormity of the COVID-19 pandemic requires huge intervention in terms of funding toward the speedy development of vaccines by running parallel phases.[4,6] A lot of studies have merged phase 1 and 2 trials and only some have merged phase 2 and 3 trials to reduce time plans or designs. The development process then takes about two years or less. This has not conceded or compromised scientific strictness or thoroughness. But the following: (a) safety, (b)

immunogenicity, and (c) efficacy results are stringently evaluated and safety monitoring has been maintained even after registration by the regulatory board.

In or after the middle of December 2020, there have been reports from four COVID-19 vaccine candidates on improvement during the third trial phase in press publications.[13] However, only two of them did publish interim effectiveness results by that time; one of which was an adenovirus-vectored vaccine (University of Oxford/AstraZeneca), and the other a ([mRNA], BioNTech/Pfizer).[14,15] About the same time Russia and China had approved for using the vaccines developed and produced by them [Table 1]. COVID-19 vaccine trials were applying both regular and new techniques to develop an effective vaccine. All the vaccines produce resistance against the glycoprotein needed by the virus to enter into its host as stated earlier. The goal or purpose of the vaccine to generate antigens against the viral glycoprotein is to stop their multiplication and or neutralise them, thus preventing cell invasion. Apart from the direct neutralisation of the virus through denying access to the host cell, other antigenic properties to destabilise the actions of SARS-CoV-2 are probably essential determinants of the route of infection.[4,16]

Conventional or Regular Approaches of Vaccines Development

The SARS-CoV-2 (COVID-2) vaccines development may be time-consuming to manufacture if the regular approaches were applied for the vaccine development as mentioned above ([i.e., about 10–15 years], see the various phases involved listed below). The regular approaches employed to develop a vaccine have the benefits of being common and properly analysed. SARS-CoV-2 (COVID-19) clinical trials that have been developed through these approaches, which are currently in use throughout the world, include inactivated viral vaccines, protein subunit vaccines virus-semblance particles, and live-soothed viral vaccines.

At present at least one live-soothed SARS-CoV-2 (COVID-19) vaccine has been developed; others of this type may progress to human studies. In summary, the development of vaccines by conventional or regular approach involves the following phases:

a. Laboratory – Laboratory trials on the development of safe vaccine candidate start. It is usually carried out sometimes in laboratory animals or cells as mentioned above. The laboratory animal tests are applied so as to be informed on the workability of the vaccine and the likeliness of its efficacy. This is a preclinical phase. Before studies in humans, laboratory results (i.e., preclinical data) are compiled together with reports to guide the manufacturers on the quality of vaccines to be produced following the guidelines as stipulated by regulating bodies such as Food and Drug Administration (FDA) in the United States or the National Agency for FDA and Control (NAFDAC) in Nigeria. These are evaluated to see if the laboratory procedures followed good laboratory practices. The product is also assessed to see if it is safe to a reasonable extent before carrying out the test on humans. At this time, the clinical trial has gotten to the next stage referred to as clinical development stage. This stage is made up of three phases supervised by the regulating body (i.e., FDA in the USA or NAFDAC in Nigeria). Clinical trials are carried out in accordance to FDA or NAFDAC plans or protocols. The phases may progress one after the other or they may overlap
b. Phase 1 – These are initial clinical trials carried out on a few subjects, for example, a few dozen of those who have not been exposed to the disease that is being studied. The phase 1 trial is to induce an immune response to the vaccine and observe whether there are adverse reactions with increasing doses
c. Phase 2 – These involve a few hundred individuals. The trials inform their effectiveness and the range of dose that proves to be safest
d. Phase 3 – These trials involve a few thousand individuals. The trials provide information about the efficacy and safety in a larger group. This phase informs the level at which the immune system responds to treatment and compares between vaccinated and controlled individuals, for example, a placebo. This comparison is carried so as to ascertain if the vaccine lowers the incidence of disease or not.

Before moving to phase 4 clinical trials, a government regulatory body will evaluate phase 3 data and then make a decision to use the vaccine on the general populace

e. Phase 4 – These clinical trials are carried out after the approval of the vaccine following extensive testimonies on the broad-spectrum safety and effectiveness. In Nigeria, the NAFDAC is responsible for carrying out these trials. The National Centre for Disease Control may also be involved.[4,6,16]

New Approaches for Vaccine Development

The new approaches for vaccine development have possible or prospective benefits in the effectiveness of immune reactions and the speed at which manufacturing takes place but are not properly studied. The latest approach applied for SARS-CoV-2 vaccine development includes (a) viral vector vaccines, (b) mRNA vaccines, and (c) DNA vaccines. Human adenoviruses or nonhuman primate viruses are used for viral vector vaccines. These viruses can invade cells and produce the genetic cryptogram for the SARS-CoV-2 spike protein antibody. They are harmless and nonreplicating viruses. For DNA-based vaccines, specific methods may be needed to transfer the DNA into cells through the cytoplasm to the nucleus. This is known as electroporation. On the other hand, mRNA vaccines allow the mRNA to blend into the cell wall without being broken down. This is so because the mRNA vaccines have already been encapsulated with nanoparticles of lipid which aid in the process. This technology was applied by Moderna and

BioNTech/Pfizer to develop their SARS-CoV-2 vaccines. The DNA and mRNA vaccines stimulate the receiver's cells to make or turn out SARS-CoV-2 spike protein.[4,16]

Clinical Trials of Coronavirus Disease 2019 Vaccines

The characteristics of some vaccine candidates produced by early December 2020 are shown in Table 1.[10,14-22] Some countries have signed an agreement with authorities to locally produce a vaccine, for example, the University of Oxford/AstraZeneca. This is a viral vector vaccine as earlier mentioned. This was in phase 3 trials, with interim efficacy results.[14]

Registration of Vaccine

COVID-19 vaccines used in Nigeria will be required for approval by the NAFDAC. As of early 2021, the ChAdOx1 nCoV-19/AZD1222 a viral vector vaccine has been granted authorisation for use in Nigeria. To register any medicine or vaccine, the manufacturer must be able to provide preliminary clinical data showing that such drug is safe, effective, and of high quality.[4]

Safety of Vaccines

From the first to the last stage of the clinical development process of vaccines, their safety is vital or supreme. Safety is an integral part of vaccine development following laid down principles from the initial stages, (which is in keeping to safe laboratory ethics) to clinical tests (i.e., according to good clinical practice). In most of the developed countries, during clinical trials, vaccine safety is evaluated by a body or board that does not depend on the manufacturer. Vaccine safety evaluation becomes a routine process once vaccines are in circulation. The regulator (e.g., NAFDAC in Nigeria) reviews the vaccine for approval and also evaluates or assesses it for vaccination or immunisation by the country. This is to guarantee that the safety of any SARS-CoV-2 (COVID-19) vaccine applied in the country is comprehensively monitored. Studies showed that an efficacious SARS-CoV-2 vaccine (e.g., Oxford/AstraZeneca COVID-19 vaccine) as stated earlier stimulates the production of high concentrations of antigens which are brought about by activated B-cells. These are very important in antiviral immunity through various routes. These include viral destabilisation, and antibody-dependent activities such as cellular cytotoxicity, cellular phagocytosis, and complement activation.

The production of increased concentrations of neutralising antibodies against SARS-CoV-2 is needed for a successful human vaccine.[23] These antibodies prevent viruses from infecting cells by binding to viral antigens (i.e., antibodies to the spike glycoprotein block attachment of RBD or RBD to ACE2 or ACE2 receptor on host cell), as mentioned earlier. T-cell responses are not associated with allergy.[24] Stronger antibody responses were produced by a booster dose of the vaccine than one dose, although the magnitude of T cell responses was not higher with the boost dose.[25] Hence, the two-dose vaccine method is used.

Routes of Immunisation

Most vaccines approved for human immunisation are administered through the intramuscular (i.m.) route (i.e., parenteral, a conventional approach). These lead to the stimulation of immune responses that cover, to some degree, the protection of mucosal surfaces. These vaccines include the current SARS-CoV-2 (COVID-19) vaccines. Because infection of SARS-CoV-2 is through the respiratory tract, the vaccine that is directed at the mucosal immune system may be more advantageous.[26] The mucosal vaccines will be needle-free, which is advantageous and hence possible for mass immunisation. The immune tolerance stimulation may be a problem or concern. The application of mucosal adjuvants so that adequate local and systemic immunity can be stimulated while other formulations are still being studied.[27] The mucosal SARS-CoV-2 vaccines have been brought about by some study groups. Intranasal immunisation or vaccination is done with a live soothed type vaccine. Some adenovirus-based vaccines have also been developed to be given or administered through the intranasal route. There is also a plan of clinical trials for oral probiotic pill-based SARS-CoV-2 DNA vaccine. Furthermore, being considered is the administration of the SARS-CoV-2 vaccine through the sublingual route to induce mucosal immunity.[26] Another alternative approach is the combination of parenteral vaccines with adjuvants, for example, retinoic acid and CAF01 that can stimulate responses due to protective IgA mucosal.[28-30] Self-administration mechanisms for SARS-CoV-2 vaccines to overcome the necessity for a health-care worker to carry out the vaccination are being studied.[23] A new handheld CELLECTRA R2000 intradermal (skin) delivery gadget that applies a momentary or short-lived electrical pulse to open skin cell pores at the opposite end so as to permit the access of their INO-4800 DNA plasmid vaccine has been developed by InovioTM (Inovio Pharmaceuticals, the USA and South Korea)[23,31] This administers spike protein-encoding DNA molecules through the dermis.[23,31]

Method of Application of the Severe Acute Respiratory Syndrome Coronavirus-2 Vaccines

There is a consensus that the following should be prioritised to receive the COVID-19 vaccines:

a. Frontline workers, for example:
   i. Health-care staff
b. Individuals at the highest risk of severe disease:
   i. The elderly
   ii. Immunocompromised and others with significant risk factors such as those with comorbidities.[32-34]

Major doubt is whether COVID-19 vaccination will decrease

transmission of SARS-CoV-2 and create indirect herd immunity which might protect individuals who are not able to respond to vaccines. This is still being studied and may delay while waiting for such data and the period of immunity and the need to repeat dosages.[23] A major question now is how vaccines will work in individuals with chronic clinical cases or who are immunocompromised and in elderly subjects, especially the weak ones or accommodated in non-health facilities. Still to be studied is the effect of the vaccine on pregnant women and the effect on the neonates of vaccinated pregnant women. Additional in-depth concerns for particular target individuals will change with the accessibility of vaccines and their detailed properties.[34] As experience with SARS-CoV-2 (COVID-19) increases, vaccine recommendations, along with other control counsels will be advancing. Even if sufficient SARS-CoV-2 vaccine doses can be produced, global delivery offers a key logistic and financial challenge. Storage conditions will be great, for example in developing countries, such as Nigeria. The vaccine may be required to be either frozen or refrigerated, thus presenting cold-chain issues. Preparation of vaccine in single- or multi-dose vials will influence production and storage, delivery, and possible risk of infection. Proper distribution and administration of vaccines will require infrastructure and workforce. Well-to-do countries can buy the vaccine for their citizens, while poor countries may not be able to afford it.

Conclusion

Assuring or certifying public trust in both the safety and effectiveness of SARS-CoV-2 (COVID-19) vaccines will be decisive to realising increased vaccination among target populations in the present vaccination or immunisation program in Nigeria. It is still to be clarified if repeated or annual vaccination is needed. A great deal is still required to be done globally to ensure that the extraordinary scientific effort that has permitted prompt development of SARS-CoV-2 (COVID-19) vaccines transforms into increased vaccination desired to quickly prevail over this major global pandemic observed in more than a century. An immense logistic challenge is also the increased production of billions of doses of the different vaccines and their distribution to all areas of the world.

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Conflicts of interest

There are no conflicts of interest.

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