



## Development of SARS-COV-2 vaccines and their mechanisms of action: An approach to change the Africans perspectives on COVID-19 vaccines

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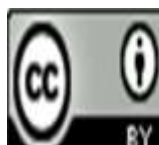


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### Abstract

The sudden outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in late 2019 has necessitated discussions on different facets of the disease. These include its transmission, pathogenesis and vaccine development. The aims of this study were to discuss the SARS-COV-2 vaccines development, mechanisms of action as well as the general acceptance of these vaccines by various countries/or people. Sequel to the outbreak, several vaccines models have been discovered with promising outcomes. Few of these vaccines have been approved for emergency use; but so far, only a small portion of the world's population has been vaccinated, which is a global problem that requires urgent intervention. Knowledge of the immune response associated with SARS-CoV-2 infection is imperative to the understanding of the mechanisms of action of these vaccines. Additional researches on some of these SARS-CoV-2 prominent vaccines have become necessary. The step-to-step development of these vaccines and their effectiveness will clear the air and increase the citizen's trust in these vaccines. Amid SARS-CoV-2 vaccine development; two DNA adenovirus vaccines were developed in the United States (Oxford-AstraZeneca and Johnson and Johnson). In addition, two other mRNA modified lipid nanoparticle vaccines were developed in Europe (Pfizer-BioNTech and Moderna). This review covered the discussion on the basic molecular mechanisms of these vaccines; with particular focus on the *in vivo* responses toward these vaccines recorded by the vaccinated individuals.

**Keywords:** SARS-CoV-2, Immunogenicity, Vaccine, Hesitancy, Acceptance



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## 1. Introduction

Immunogenicity, the molecular response of a living system (often mammalian) to antigenic epitopes presents in an invading infectious agent; is a critical component in vaccine development. Effective vaccine development depends on the ability of the antigen of interest to induce host immune response to produce antibodies that will regulate invasion of the body by the disease pathogens. However, certain viruses such as SARS CoV-2 can evade the host immune system; thereby causing further infection to the neighboring tissues.

Protection of the human system from SARS-CoV-2 viral particle invasion occurs via the synthesis of a double membrane vesicle (DMV). The DMV functions in shielding the invading virus from recognition and detection by the pathogen associated molecular patterns receptors (PAMPSs) ([Muhammed, 2020](#)). This process results in an over-production of viral particles without human immune response, referred to immune docking or viral shielding.

To elaborate, just like the Middle East respiratory syndrome coronavirus (MERS-CoV); the SARS-CoV-2 bypasses the human immune system by blocking the pathways responsible for transportation of the Interferon molecules and down regulation of the major histocompatibility complexes I and II genes ([Yang \*et al.\*, 2013](#)). Astonishingly, in vulnerable individuals with preexisting disease conditions; these viruses can elicit negative pathological consequences when attacked by the human immune system through causing massive production of the inflammatory molecules including; the cytokines and the chemokines. This condition is known as cytokine syndrome; resulting in an organ impairment and death if not treated ([Williams and Chambers, 2014](#); [Huang \*et al.\*, 2020](#); [Xu \*et al.\*, 2020](#)).

The coronavirus family is a single-stranded RNA viruses that were first discovered in animals; basically in birds, in the early 2000s. They were said to be

responsible for 15-30 % of all the common cold cases globally ([Rabi \*et al.\*, 2020](#)), and can also affect humans. Some of these virus strains are capable of initiating human infections including; HCoV-OC43, HCoV-NL63, HCoV-HKU and HCoV229E ([Rabi \*et al.\*, 2020](#)). The most highly recorded infectious strains of these viruses include the earlier Severe acute respiratory syndrome (SARS-CoV); the Middle East respiratory syndrome (MERS-CoV) and the recent Severe acute respiratory syndrome-2 (SARS-CoV-2), as reported in the previous study conducted by [Rabi \*et al.\*, \(2020\)](#). The recent coronavirus; also known as coronavirus disease 2019 (COVID-19) was discovered in late 2019 in the city of Wuhan, Hubei province, China. The common clinical manifestations of this disease include cough; sore throat, nasal congestion, fever, tiredness, loss of taste and smell ([Muhammed, 2020](#)). Recently, [Chiedozie \*et al.\*, \(2021\)](#) reported that severe conditions in patients infected with this virus might present different organ impairments including respiratory; olfactory, gastrointestinal, dermatological, cardiac, neurological, ophthalmic, and rheumatological manifestations.

Since the beginning of the outbreak in late 2019; many SARS-CoV-2 vaccine models have been discovered and some of these vaccines have been proved to be safe with promising outcomes, which led to their approval for emergency use in some countries ([Wouters \*et al.\*, 2021](#)). Notwithstanding, hesitation in taking these vaccines has become a major concern ([Amakiri \*et al.\*, 2021](#); [Wouters \*et al.\*, 2021](#); [Dinga \*et al.\*, 2021](#)). The mechanisms of action of the four SARS-CoV-2 vaccines discussed in this paper were based on knowledge of the human immunological response to SARS-CoV-2 infection ([Pedro \*et al.\*, 2020](#); [Labeau \*et al.\*, 2020](#); [Azkur \*et al.\*, 2020](#)). The actions of these vaccines depend on the ability of the vaccine encoded antigen segment to induce immunity against the SARS-CoV-2 spike protein ([Dicks \*et al.\*, 2012](#); [Knoll and Wonodi, 2021](#); [NHS, 2021](#)). These vaccines

are usually carried by harmless vectors (i.e. viral, bacterial or plasmid) such as the chimpanzee adenovirus for Oxford AstraZeneca; Adenovirus 26 for Johnson and Johnson, and modified lipid nanoparticles (LNP) for Moderna and Pfizer-BioNTech ([Pedro \*et al.\*, 2020](#), [Clinical Protocol Pfizer BioNTech, 2020](#); [Jon, 2021](#)). The molecular fundamentals of the SARS-CoV-2 vaccines are based on the recombinant vaccine technology ([Silveira \*et al.\*, 2021](#)). The recombinant vaccines can be divided into three types; the live attenuated vaccines, death or inactivated vaccines and the genetic vaccines (DNA, RNA vaccines); also called the viral-particle vaccines ([Council for Agricultural Science and Technology, 2008](#)). The live attenuated vaccines are genetically modified versions of the disease-causing viruses or bacteria; with selected gene deletion or insertion. To develop a live attenuated vaccine; one requires a good molecular understanding of the genes associated with virulence of the virus. On the other hand, the death or inactivated vaccines are genetically modified. However, these vaccines only contain a basic subunit of the original virus capable of inducing an immune response. This subunit is usually a segment of the viral peptide or protein; recovered from a cloned copy of the virus. Meanwhile, in an inactivated version of the virus; the whole virus can be used. A good example of this vaccine is the virus-like particles (VLPs). The last category of the recombinant vaccines is the genetic vaccines. These vaccines are usually DNA or RNA vaccines, which contain either a spherical piece of the DNA or a strand of RNA. These genetic materials usually contain genes from the disease-causing agent, in addition to a promoter responsible for initiating protein expression from the genes of interest ([Rodrigues and Whitton, 2000](#)).

For effective induction of viral particles into the human system; different viral vectors have been used, which are responsible for transportation of the genes coding for specific antigenic protein. Some of these viral vectors include alphavirus; retrovirus, herpes virus, adenovirus, adeno-associated virus, vaccinia virus and modified vaccinia virus Ankara (MVA

([Rollier \*et al.\*, 2011](#); [Pérez \*et al.\*, 2012](#)). The cellular introduction of these vaccines into the human body is via intramuscular or intradermal injection ([Yusuf \*et al.\*, 2021](#)). The immunological response usually accompanies the viral injection; as a result of protein expression of the encoded gene of interest ([Azkur \*et al.\*, 2020](#); [Yusuf \*et al.\*, 2021](#)). In Africa, hindrance and unwillingness of the citizens to take the SARS-CoV-2 vaccine have become worrisome ([Dinga \*et al.\*, 2021](#); [Amakiri \*et al.\*, 2021](#); [Ditekemena \*et al.\*, 2021](#)). Therefore, researches on detailed studies of the prominent SARS-CoV-2 vaccines cannot be overstressed. The step-to-step development of the vaccines and their effectiveness will clarify doubts and increase the citizen's trust in these vaccines, thus making citizens willing to take them. The objectives of this review were to cover the detailed delivery systems adopted by the four different SARS-CoV-2 vaccines (i.e. Pfizer BioNTech, Moderna, Oxford-AstraZeneca, and Johnson and Johnson), their mechanisms of action, and how human systems respond to injection with such vaccines.

## 2. Mechanism of SARS-COV-2 infection

### 2.1. Cellular invasion

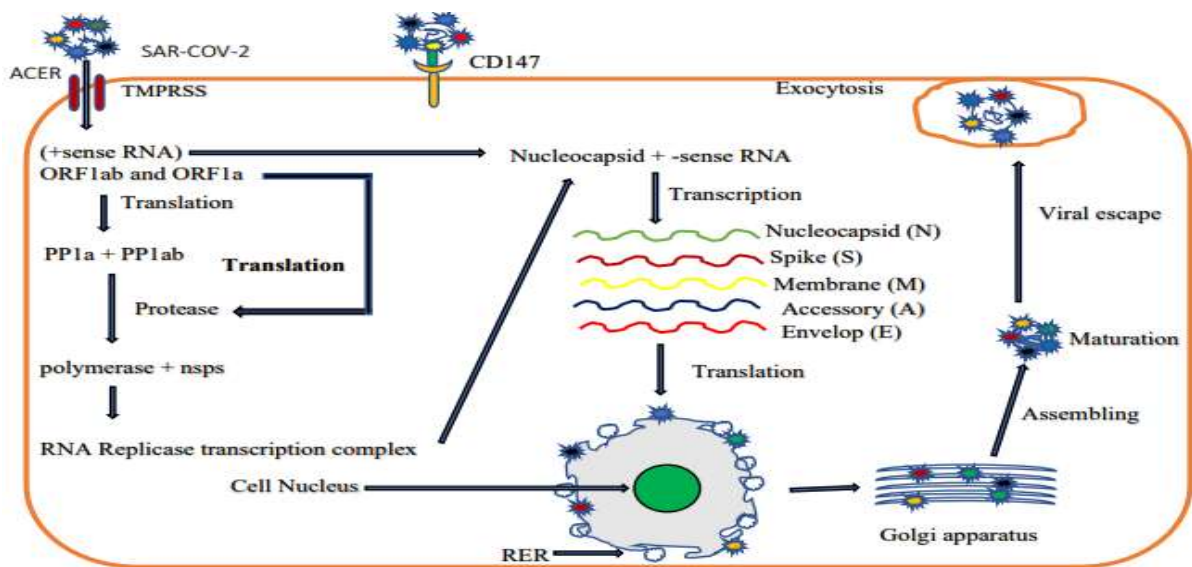
SAR-COV-2 belongs to the *Coronaviridae* family of viruses with a single-stranded positive-sense RNA (+ssRNA) of 27-32 kb in size ([Rabi \*et al.\*, 2020](#)). The capsid of the virus is made up of the nucleocapsid protein (N) with other proteins such as spike proteins; envelope proteins and membrane proteins ([Sunday \*et al.\*, 2021](#)). Viral entry is aided by the spike proteins (S-proteins), which consist of two structural subunits (S1 and S2) ([Muhammed, 2020](#)). The S1 subunit is responsible for binding the virus to the Angiotensin-converting enzymes receptor (ACER) described as interferon-stimulated gene; via the SARS-CoV-2 receptor binding domain (RBD) ([Huang \*et al.\*, 2020](#); [Muhammed, 2020](#)). Meanwhile, viral entry can occur via the CD147 route; as reported in a previous study conducted by [Lebeau \*et al.\*, \(2020\)](#) on SARS-CoV interaction with cyclophilin A. Viral fusion to the host cellular membrane occurs via attachment of the S2

subunit. According to [Rabi \*et al.\*, \(2020\)](#), the S2 subunit consists of the connector domain (CD), trans-membrane domain (TM), heptad repeat 1 and 2 (HR1 and 2), central helix (CH) and cytoplasmic tail (CT). The cleavage binding site; also known as the S1/S2 protease cleavage site, is formed by combining of the S1/S2 subunits. At the point of infection; viral entry occurs through what is known as membrane fusion. The S2 protein binds to the host cell; activating the protein responsible for viral entry via conformational changes mediated by the cellular cathepsin L and the trans-membrane protease serine 2 (TMPRSS2) ([Cevik \*et al.\*, 2020](#)). Proper folding; neutralization of antibodies and trimming of the spike protein take place at this point, with the help of the N-linked glycans.

## 2.2. Viral replication

Replication of the viral particle occurs on entry into the host system, and then the viral genome

(+RNA strand) is released into the host cell. The open reading frames 1a (ORF1a) and 1ab (ORF1ab) are translated to produce the poly-proteins PP1a and PP1ab. The ORF1a encodes for the protease enzyme leading to cleavage of the PP1a and PP1ab proteins; to synthesize the non-structural proteins (NSPS) forming the RNA replicase transcription complex. Thereafter, a (-) RNA strand is generated from the transcription complex, followed by fragmentation through discontinuous transcription ([Bosch \*et al.\*, 2003](#)). The structural proteins are then synthesized including the spike (S); nucleocapsid (N), membrane (M), accessory (A) and the envelope (E) at the endoplasmic reticulum (ER) ([Sunday \*et al.\*, 2021](#)). The structural proteins are passed from the rough endoplasmic reticulum (RER) to the Golgi apparatus for assembly and maturation, which are later released for continuous host cellular infection (Fig. 1).



**Fig. 1:** Stages in the life cycle of SARS CoV-2 in the human cell: Invasion begins with attachment of the viral Spike (S) proteins to the host cellular receptor ACER2, followed by viral entry; replication, translation, maturation and then release of the viral particles for the neighboring cellular invasion and infection (Mechanism adopted with modification by [Sunday \*et al.\*, 2021](#))

### 3. Immunological alteration associated with SARS-CoV-2 infection

#### 3.1. Host immune response via antibodies

SARS-CoV-2 infection, just like any other viral infection; elicits immunological reaction from the host immune system. A previous study of [Akira and Hemmi, \(2003\)](#) revealed that the anti-viral neutralizing immune response against SARS-CoV-2 from the host innate immune cells arises as a result of the viral passage through the CD147 spike protein signal on the surface of T lymphocyte. Later, [Azkur \*et al.\*, \(2020\)](#) reported that CD147 plays important roles in the body, such as the initiation of apoptosis; cell proliferation, tumor cell migration, metastasis and differentiation, in addition to low oxygen state.

At the point of viral entry into the cell, the virus glycoproteins attach to the ACE2 receptor; thereby invading the host cell. After evasion, viral particles are recognized by the antigen-presenting cells such as the B-cells; dendritic cells and macrophages through the major histocompatibility complex II (MHCII) through the CD4<sup>+</sup>. Alongside the MHCII; the major histocompatibility complex 1 transmits signals as a result of viral peptide recognition to the CD8<sup>+</sup> cytotoxic T cells ([Jansen \*et al.\*, 2019](#)). These follow the CD8<sup>+</sup>, CD4<sup>+</sup> activation of the T-helper cells. As viral replication spreads across the host cells; the IgM and IgG isotypes viral-specific antibodies are also detected in the blood, thus enhancing the immune response. The T and B cells' immune response to the viral peptide is considered as the central principle behind SARS-CoV-2 vaccine development.

Recently, [Azkur \*et al.\*, \(2020\)](#) stated that identifying the T and B cells conserves epitopes for eliciting an immune response. This could generate host immunity not only for multiple genera of coronavirus, but also can protect against emerging future variants of the virus.

To elaborate in details the host immunological alteration sequential to SARS-CoV-2 infection; the innate immune cells recognize the viral invasion via the pattern recognition receptors (PRRs) such as pulmonary surfactant protein; C-reactive protein, C-Type lectin, NOD and toll-like receptors (i.e. TLR3, TLR7, TR7 and TR8), as revealed by [Akira and Hemmi, \(2003\)](#). The PRRs recognize the pathogen-associated molecular patterns (PAMPs) such as peptidoglycan (cell walls) and double-stranded DNA or single RNA strand (viruses), leading to the release of cytokine molecules ([Clem, 2011](#)).

The dendritic cells and the macrophages are considered as the first point of response in the host innate immune system, sending signals to the adaptive immune system to elicit the viral attack ([Ito \*et al.\*, 2005](#)). Viral particle recognition causes speedy overproduction of Interferon type I (type I IFN 1), which stimulates the antiviral cells to target viral replication in the host cells ([Azkur \*et al.\*, 2020](#); [Muhammed, 2020](#)). The release of type 1 IFN prevents the viral multiplication and production, thereby suppressing viral infection and spread to the other host neighboring cells ([Muhammed, 2020](#)).

Stimulation of the antigen-presenting cells and the cytotoxic T cells induces overproduction of some inflammatory cytokines such as; IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL6, IL-12, IL-18 etc ([Muhammed, 2020](#)). The availability of these cytokines also triggers the plasma cells to produce antibodies to fight the viral invasion ([Chang \*et al.\*, 2020](#)). In the case of vaccine-mediated immunity, the B-cells and plasma cells also stimulate the production of antibodies and memory T-cells. These memory cells are stored in the lymph nodes pending activation by viral particle liked-antigen ([Salerno-Gonçalves and Sztein, 2006](#)).

Likewise, the T helper cells; being one of the essential adaptive immune cells further activate the B-cells and cytotoxic cells towards the production of more antibodies.

### 3.2. Cytokine release syndrome

Amidst SARS-CoV-2 infection; molecular complications include the rapid overproduction of deadly inflammatory molecules by the host immune cells, which is referred to as Cytokine release syndrome (CRS). Cytokines are immune system molecules that create an antiviral state; serving as the non-specific first line of defense in the various viral infections ([Sherwani and Khan, 2020](#)). However, CRS is an immunological disorder associated with excessive cytokine release.

A combined clinical characteristic of CRS is that it is associated with massive inflammatory reaction, which progresses to form an acute respiratory distress syndrome (ARDS). ARDs trigger the host immune system to release dangerous systemic proinflammatory cytokines such as; IFg-g, IFg-a, IL-(1b, 6,12, 18,33), TGFb, TNF-a, CCL-(2, 3,5) and CXCL-(8,9, and 10) ([Williams and Chambers, 2014](#); [Muhammed, 2020](#); [Huang \*et al.\*, 2020](#)). Cytokine release syndrome is reported to be the cause of many severe complications arising from patients infected with SARS-CoV-2 ([Mustafa \*et al.\*, 2020](#)). Moreover, it is also recognized as one of the key causes of multiple organs failure, especially the respiratory organs failure ([Mohammadi \*et al.\*, 2020](#)). The mechanism of ARDS is related to the systemic inflammatory cytokines IFN- $\alpha\beta$  and IFN- $\gamma$ ; stimulating inflammatory cell infiltration through the Fas-Fas ligand (FasL) or the Trail-Death receptors 5 (DR5) ([Muhammed, 2020](#)). This causes the inflammation and apoptosis of cells of the respiratory tract and the epithelial cells of the alveoli, leading to a condition known as alveola edema and oxygen insufficiency (hypoxia). This combined condition is referred to as acute respiratory distress syndrome (ARDS) ([Mustafa \*et al.\*, 2020](#)).

Injury to the renal tubules and the ureter walls also called hypoperfusion has been associated with cytokines systemic attack, as further explained by [Mustafa \*et al.\*, \(2020\)](#). This is accompanied with cardiomyopathy; leading to cardiovascular renal syndrome Type 1.

According to [Cevik \*et al.\*, \(2020\)](#), in the host central nervous system; complications arising from SARS-CoV-2 infection involve invasion of the viral pathogen to the astrocytes, macrophages and microglia. This induce pro-inflammation; accompanied by excessive production of inflammatory mediators such as interleukin-1 $\beta$  (IL-1  $\beta$ ); IL-2 receptor (IL-2R), IL-2, IL-4, IL-6, IL-10, IL-18, IFN- $\gamma$ , TNF- $\alpha$ , monocyte chemo-attractant protein 1 (MCP-1), granulocyte colony-stimulating factor (GCSF), macrophage inflammatory protein 1- $\alpha$  (MIP-1 $\alpha$ ), CXCL10, CCL2, and C-reaction protein (CRP) ([Mohammadi \*et al.\*, 2020](#)). These cytokines cause damage to the blood-brain barrier and also aid in neural death; activation of microglia, disruption of synaptic plasticity and impairment in the neurotransmitter metabolism of the central nervous system ([Muhammed, 2020](#); [Mohammadi \*et al.\*, 2020](#)).

Furthermore, complications can arise from the presence of high serum IL-6 in SARS-CoV-2 patients, which is linked to respiratory failure; acute respiratory syndrome and other adverse clinical conditions.

The immune-mediated complications of the central nervous system by SARS-CoV-2 invasion in some major parts of the brain including the hippocampus and the midbrain region; result in the induction of Alzheimer's disease (AD) and Parkinson's diseases (PD) ([Ritchie \*et al.\* 2020](#)). Interestingly, modulation of the gut microbiome plays a major role in the pathophysiology of AD and PD ([Vogt \*et al.\*, 2017](#)).

[Tang \*et al.\*, \(2020\)](#) suggested that the therapeutical procedures that reliably counteract the effect of CRS in patients infected with SARS-CoV-2 include; cytokine-absorption devices, immunoglobulin and antimalarial drugs, interleukin-6 inhibitor agent (such as tocilizumab), check-point inhibitors, programmed cell death protein (PD-1 /PD-L10) and corticosteroids.

### 3.3. Immune system ducking by the SARS-CoV-2

Studies on MERS CoV and SARS-CoV have shed more light on how SARS-CoV-2 has protective mechanism against the host immune responses. Upon

viral invasion, the pathogen-associated molecular patterns (PAMPs) receptors are responsible for viral particle recognition, but in the case of MER-CoV and SARS-CoV infections; the viruses induce the production of double-membrane vesicle, shielding away from the PAMPs recognition receptors. This facilitates replication and multiplication of the viral load without any host immunological response, which is believed to be similar to SARS-CoV-2 ([Huang \*et al.\*, 2020](#); [Muhammed, 2020](#)). In addition, several pathways including the inhibition of IFN-1a and b via activation of the melanoma differentiation association proteins genes -5 (MDA5) utilized by MERS-CoV and SARS-CoV are also deployed by the recent SARS-CoV-2 ([Niemeyer \*et al.\*, 2013](#), [Yang \*et al.\*, 2013](#); [Channappanavar \*et al.\*, 2016](#); [Muhammed, 2020](#)).

Interestingly, the ORF4a, ORF4b, ORF5 and membrane proteins of MERS-CoV block the transportation of IFN regulatory proteins and activation of the IFN promoter ([Chang \*et al.\*, 2020](#)). Moreover, SARS-CoV also down regulates MHC I and MHC II in the infected antigen-presenting cells such as the macrophages and the dendritic cells; resulting in decreased antigen-presentation and T cell stimulation ([Clem, 2011](#)). Therefore, understanding of immune ducking of the virus is very important for drug development; especially in designing drugs that will block viral immune invasion by the SARS-CoV-2 infection.

## 4. SARS- CoV-2 vaccine development

### 4.1. Development of vaccine-mediated immunity

Hindrance and unwillingness of citizens of African countries to take the SARS-CoV-2 vaccine has become a serious issue. Researches on the detailed studies of some SARS-CoV-2 prominent vaccines cannot be overemphasized. Accordingly, a step-by-step development of these vaccines and the effectiveness of the vaccines will clarify doubts and increase citizen trust in these vaccines. This section discusses the immune response accompanying vaccination of SARS-CoV-2 infected individuals, and

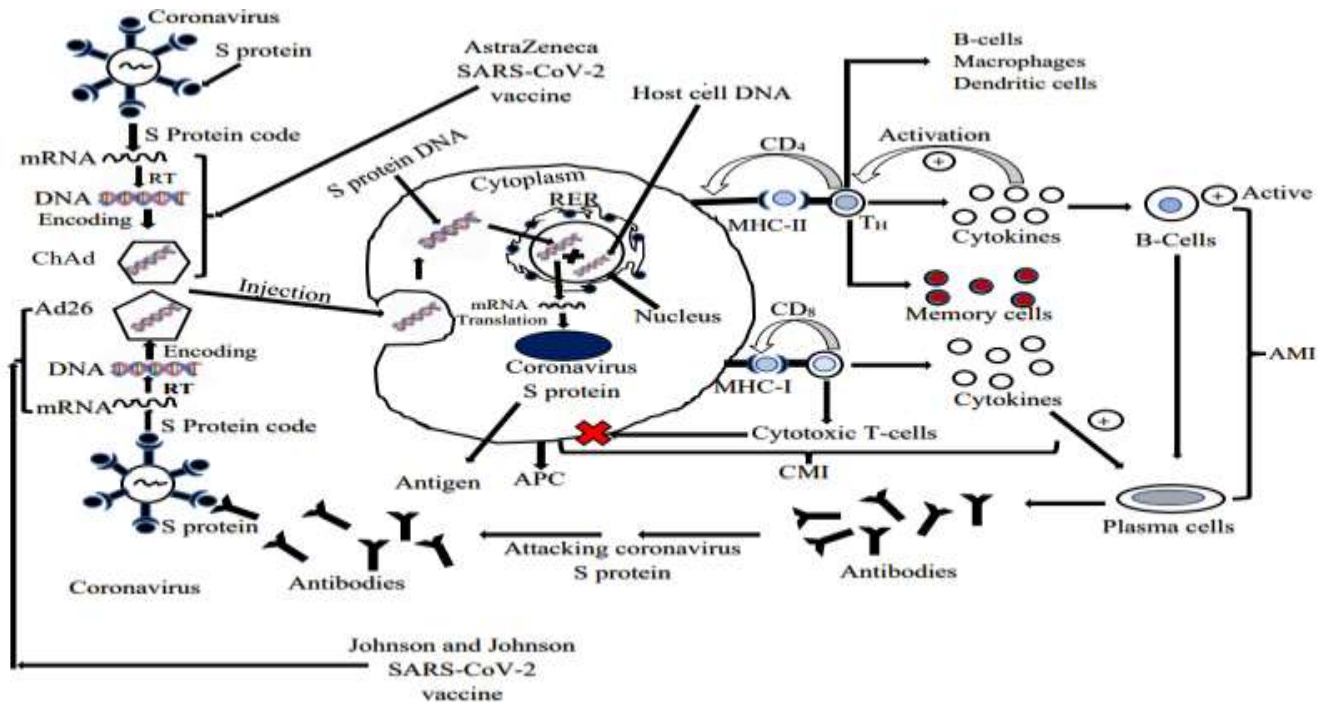
detailed mechanisms of action of four prominent SARS-CoV-2 vaccines such as; Oxford-AstraZeneca, Johnson and Johnson, Pfizer BioNTech and Moderna.

The mechanism of vaccination involves the exposure of an unvaccinated individual to a pathogenic-like agent ([Nascimento and Leite, 2012](#)). The SARS-CoV-2 vaccines discussed in this study use the spike protein viral genomic material as the antigenic agent. Upon introduction of the viral-like particle through an intramuscular injection, the host immune system of the vaccinated individual stimulates the immune response ([Yusuf \*et al.\*, 2021](#)). Noteworthy, the active immunity triggered by vaccination produces long-time immunity than the passive immunity ([Clem, 2011](#)). Meanwhile, the host active immunity can also come naturally without vaccine stimulation ([Azkur \*et al.\*, 2020](#)). Firstly, the host immune system; specifically the innate immune system and the B-cells will have to verify the pathogenic agent or the vaccine particle through the PAMPs by the PRRs. These will initiate multiple immune responses by the antigen-presenting cells, as described by [Jansen \*et al.\*, \(2019\)](#). In the case of SARS-CoV-2, MHC I binds to the antigen and presents it to the CD8<sup>+</sup> cells via the APC; eliciting cell-mediated immunity and antigen mediated immunity (Fig. 2), as reported by ([Muhammed, 2020](#)). Although in several types of antigens such as the bacterial antigens; the MHC II performs this function by presenting the antigens to the CD4<sup>+</sup> cells for antibody-mediated immune response ([Goldsby \*et al.\*, 2003](#)). In addition, the memory cells are developed for future invasion by the same viral antigen.

At the time of this review, no assessment has been carried out to determine the optimum level of induced memory T cells in response to these vaccines. In addition, there are no findings on the half-life of the antibodies produced against the SARS-CoV-2 virus in the human body. However, these challenges are preeminent in vaccine development ([Salerno-Gonçalves and Szein, 2006](#)). To meet the current challenges in vaccine development; the level of antigen exposure that is high enough to stimulate the

antigen mediated immunity, the cell mediated immunity and precise protection from the infection were among the key features in the coherent approach-based study reported by [Salerno-Gonçalves and Szein, \(2006\)](#).

Therefore, more researches to improve the current SARS-CoV-2 vaccines for effective host immunity are urgently needed.



**Fig. 2:** An overview of the mechanisms of action of DNA SARS-CoV-19 vaccines (Oxford-AstraZeneca and Johnson and Johnson). The AstraZeneca vaccine encode spike protein viral particle in a weakened Chimpanzee Adenovirus (ChAd). The Johnson and Johnson vaccine encodes viral spike protein particle in an Adenovirus serotype 26 (Ad26). Vaccine entry into the host cell is accompanied by replication and translation of the viral genome via the rough endoplasmic reticulum (RER), to synthesize the SARS-CoV-2 spike(s) proteins. The S proteins recognition by the antigen presenting cells (APC) stimulates the immune response from the cell-mediated immunity (CMI) and the Antigen-mediated Immunity (AMI), leading to the production of antibodies by the plasma cells of the host organism ([Mohammadi, 2020](#); [Yusuf \*et al.\*, 2021](#))

#### 4.2. Recombinant vaccine

Knowledge of the mechanism of infection by a disease-causing pathogen and the immunological response of the host immune system has been the guiding principle behind recombinant vaccines. These vaccines depend on the ability of the antigen or group of antigens to induce immunity against itself

([Nascimento and Leite, 2012](#)). The recombinant vaccines are usually carried by harmless vectors such as the plasmids or viral vectors. Generally, three types of recombinant vaccines exist; the life attenuated vaccines, the death or inactivated vaccines and the genetic vaccines ([Council for Agricultural Science and Technology, 2008](#)). The life attenuated vaccines are genetically modified version of the disease causing



bacteria or virus with a selected gene deletion or insertion. Developing a life attenuated vaccine requires molecular understanding of the genes associated with pathogenicity of the pathogen. Similarly, the death or inactivated vaccines are usually also genetically modified. However, these vaccines contain only a basic subunit of the original pathogen capable of inducing an immune response. This subunit is usually a segment of the pathogen peptide or protein from a cloned copy of the pathogen. Notwithstanding, an inactivated version of the whole pathogen can be used. A good example of this vaccine is the virus-like particles (VLPs). VLPs are immunogenic cloned viral particles that lack the genetic instruction for viral replication; thereby eliciting a similar immunological response as the original viral pathogen. The genetic vaccines categories usually contain either a spherical piece of the DNA or of the RNA strand. These genetic materials usually carry genes from the disease-causing pathogen and a promoter responsible for initiating protein expression from the gene of interest ([Rodriguez and Whitton, 2000](#)).

Vectors utilized in vaccine development are in the form of a purified plasmid encoded with the DNA or the RNA of interest. These vectors are responsible for transportation of the genes coding for specific antigenic proteins. Some of these viral vectors include alphavirus; retrovirus, herpes virus, adenovirus, adeno-associated virus, vaccinia virus and modified vaccinia virus Ankara (MVA) ([Rollier \*et al.\*, 2011](#); [Pérez \*et al.\*, 2012](#)).

Cellular introduction of these vaccines to the humans is via intramuscular or intradermal injection ([Yusuf \*et al.\*, 2021](#)). Immunological response usually accompanies the viral injection; as a result of protein expression of the gene of interest encoded in the carrier vector ([Knoll and Wonodi, 2021](#); [Yusuf \*et al.\*, 2021](#)).

Importantly, the substantial efforts exerted by scientists all over the world toward SARS-CoV-2 vaccine development are recommendable, especially on using the SARS-CoV-2 spike protein to induce

immune response in uninfected individuals. However, the discovery of vaccines for a novel disease requires combination of different strategies. In spite of the promising results generated from using the viral vectors and the lipid nanoparticles in SARS-CoV-2 vaccines discussed in this study; however, combination in heterologous prime boost or simply prime boost vaccine development might be more promising.

### 4.3. SARS-CoV-2 DNA vaccine

With the current determination of safe guide for public health, there is an urgent need for mass production, distribution and administration of SARS-CoV-2 vaccines across the world. Direct administration of naked DNA incorporated in a plasmid vector into a host organism via inhalation or muscular injection; to elicit an immune response and future protection against the same pathogen has been fully explored. Several promising outcomes had been generated from DNA vaccine developments in the past ([Wolff \*et al.\*, 1990](#); [Ulmer \*et al.\*, 1993](#)). A DNA vaccine; also referred to as genetic vaccines consists of several components including a plasmid (vector); origin of replication, a promoter, multiple cloning sites and the antigen of interest ([Wolff \*et al.\*, 1990](#); [Ulmer \*et al.\*, 1993](#); [Oliveira \*et al.\*, 1999](#)). The mechanism of action of the DNA vaccine is similar to that occurring during an actual viral infection. The DNA expresses itself in cells of the host to release the antigen proteins, which are then presented to the immune system by the MHC Type I molecules and the MCH Type II molecules, thus inducing a specific antibody immune response ([Mohammadi \*et al.\*, 2020](#); [Silveira \*et al.\*, 2021](#)). Interestingly, memory cells are also developed specifically for the antigen of interest ([Belakova \*et al.\*, 2007](#)). Some of the advantages associated with DNA vaccines include lower risk of infection; compared to the life attenuated vaccines, and also induction of both the humoral immunity and the cell-mediated immunity, alongside with the cytotoxic T cells immunogenicity ([Salerno-Gonçalves and Szein, 2006](#); [Jansen \*et al.\*, 2019](#)). Furthermore, these vaccines are very cheap compared to the recombinant protein

vaccines; due to the high cost of protein purification in the latter ([Wolff \*et al.\*, 1990](#)). In addition, the DNA vaccines have been proven to be very safe ([Medjitna \*et al.\*, 2006](#); [Silveira \*et al.\*, 2021](#)).

Several DNA vaccines have been effectively used in deploying protection against infectious diseases such as; influenza, malaria and tuberculosis TB in animal models ([Nascimento and Leife, 2012](#)). However, not all DNA vaccines have been proven to be very effective in inducing immunogenicity in human host ([Belakova \*et al.\*, 2007](#)). Therefore, several approaches have been employed to enhance the efficacy of these vaccines. Previous studies conducted by [Belakova \*et al.\*, \(2007\)](#); [Saade and Petrovsky, \(2012\)](#) revealed that molecules such as Toll-like receptors (TLRs) genes that induce apoptosis have been utilized for maximum immunogenicity.

Furthermore, the use of a plasmid and peptide particles with the ability to increase the expression of genes and regulate the cytokine release have been also captured. With all these available data on vaccine development; we recommend a multiple prime boost strategy with the capacity to enhance the immune response in the host cellular environment.

#### 4.3.1. Oxford-AstraZeneca vaccine

The Oxford AstraZeneca SARS-CoV-2 vaccine is one of the most promising vaccines developed for treatment of the SARS-CoV-2 ([Yusuf \*et al.\*, 2021](#)). It is usually called the Chimpanzee adenovirus-vectorized Oxford/AstraZeneca vaccine (ChAdOx1). This vaccine is produced by AstraZeneca in collaboration with Oxford University, to ensure global accessibility of the vaccine ([Knoll and Wonodi, 2021](#)). The vaccine encodes for a genomic DNA segment of the SARS-CoV-2 spike protein encoded in a non-replicating weakened chimpanzee adenovirus vector; hence the name CghAdOx1 ([Yusuf \*et al.\*, 2021](#)). The principle behind this vaccine is based on the immunological response stimulated by the viral particle invasion and replication as shown in Fig. (1), in addition to how efficacious and safety of the vaccine are ([Wouters \*et\*](#)

[al., 2021](#); [Yusuf \*et al.\*, 2021](#)). This vaccine has been reported to stimulate the humoral and the cell-mediated immune response; via the T-helper activation through overproduction of the IgG subclass and the cytokines. Stimulation of the humoral and cellular responses is experienced in CghAdOx1 injected individuals ([Van \*et al.\*, 2020](#)).

Fascinatingly, the chimpanzee adenovirus was used as a carrier because of its inability to alter the pre-existing host immunity ([Dicks \*et al.\*, 2012](#)). The vaccine is preservative free and is presented in 5 ml containing  $5 \times 10^{10}$  viral particles. The vaccine has 62 % efficacy recorded from an initial trial in Brazil, and 90 % in a later trial in the United Kingdom ([Yusuf \*et al.\*, 2021](#)). Vaccine administration is done in 2 doses regime at day 0 and day 28; via intramuscular injection (0.5 ml) after storing for 6 months at 2-8°C. This vaccine tends to strongly induce the host immune response; especially the B and T cells responses in a single dose ([Pedro \*et al.\*, 2020](#)). Moreover, an additional good feature of this vaccine is that no serious adverse effects and/or deaths have been recorded yet in individuals who received this vaccine ([Knoll and Wonodi, 2021](#)).

#### 4.3.2. Johnson and Johnson vaccine

In recent times, the Johnson and Johnson vaccine (JNJ-78436735) is one of the unique SARS-CoV-2 vaccines developed in the United States, as described by the Center for Disease Control and Prevention ([U.S. News, 2021](#)). Although Johnson and Johnson vaccine is a DNA vaccine and utilizes similar vector as the Oxford-AstraZeneca (Adenovirus serotype 26); however, this vaccine is administered in a single dose. Johnson and Johnson vaccine can be stored in a normal refrigerator ([Schoenmaker \*et al.\*, 2021](#); [Yusuf \*et al.\*, 2021](#)). The vaccine has an efficacy of about 66.3 % against the confirmed SARS-CoV-2 patients ([Yusuf \*et al.\*, 2021](#)). It was earlier postulated to provide protection for even asymptomatic individuals ([Medjitna \*et al.\*, 2006](#)). Unfortunately, this vaccine has lower efficacy against the South Africa variants (B.1.3.5.1); expressing an efficacy of about 57 %.

Thus, the vaccine is not highly effective against the South African variant (B.1.351). In April, 2021, the United State Food and Drug Administration (FDA) recommended a hold-on with the use of this vaccine; due to reports of individuals developing severe complications such as headache; abdominal pain, leg pain and shortness of breath, as described by the Center for Disease Control and Prevention ([U.S. News. 2021](#)). Interestingly, further complications such as cerebral venous sinus thrombosis (CVST) and low levels of blood platelets (thrombocytopenia) were reported among women aged 18-48; 6 to 8 days after vaccination with the Johnson and Johnson SARS-CoV-2 vaccine. Notwithstanding, about 30,000 participants were used to investigate the co-morbidities and molecular confirmation of using this vaccine. Interestingly; the US (100 million doses) and EU (400 million doses) have signed a contract for production of the Johnson Johnsons vaccine ([Prüß \*et al.\*, 2021](#)).

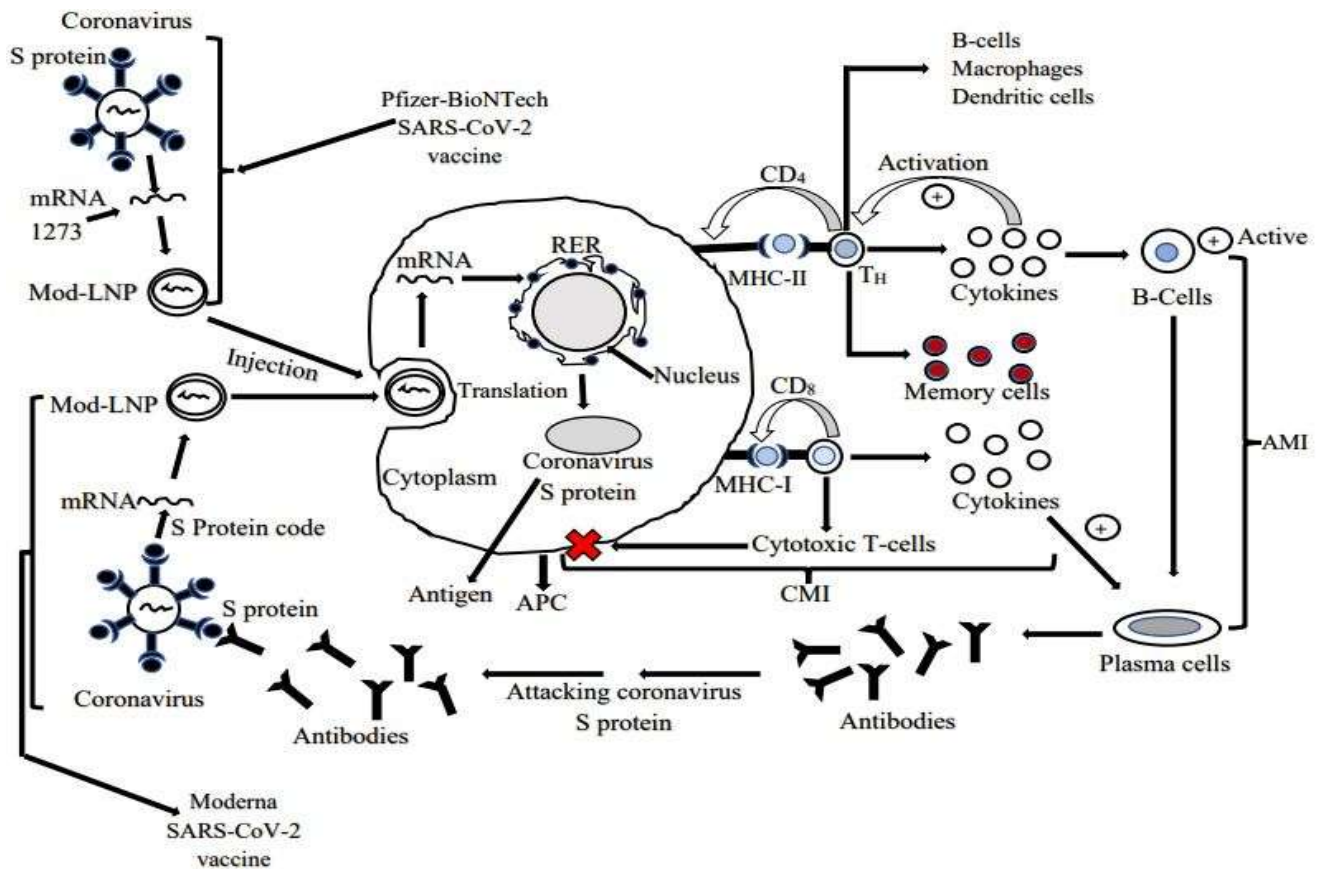
#### 4.4. SARS-CoV-2 mRNA vaccines

The mechanism of action of mRNA SARS-CoV-2 vaccine is similar to the SARS-CoV-2 DNA vaccine in stimulation of immune response ([Schoenmaker \*et al.\*, 2021](#)). The SARS-CoV-2 mRNA vaccines as well as several other mRNA vaccines use a lipid nanoparticle (LNP) vector, due to its suitability in bypassing the human cellular membrane lipid bilayer and successfully delivering the mRNA of interest to the cytosol ([Mendonça \*et al.\*, 2021](#)). Introduction of the vaccine takes place via intramuscular injection ([Yusuf \*et al.\*, 2021](#)). Upon recognition of the antigen of interest that belong to the disease-causing pathogen; the gene of spike protein becomes sequenced and transcript to mRNA ([Kowalzik \*et al.\*, 2021](#)). The process involves translation of the mRNA by the host organism into the target antigen (spike protein); thereby imitating the actual viral infection ([John \*et al.\*, 2018](#)). This process induces the host immune system; leading to humoral and cellular immunogenicity, as described by ([Nicholas \*et al.\*, 2020](#)). Transportation of the viral mRNA occurs via a lipid capsule vector; to bypass the degradation of the ubiquitous extracellular ribonucleases enzymes by the host organisms ([Kose \*et\*](#)

[al., 2019](#); [Pardi \*et al.\*, 2018](#)). However, no genetic alteration to the host genome is performed by the mRNA because the mRNA never enters the nucleus of the host cell ([Cheng \*et al.\*, 2001](#); [Pardi \*et al.\*, 2018](#)). Here, we explicitly explained the mechanism of action of Pfizer-BioNTech and Moderna SARS-CoV-2 vaccines (Fig. 3). The detailed description of these vaccines has become necessary, due to the misleading information in the media; thereby serving as a hindrance to the citizens' willingness to take these vaccines. However, the short-lasting viral half-life and the short-lasting memory T-cells are setbacks associated with the mRNA vaccines ([Rodriguez and Whitton, 2000](#)).

##### 4.4.1. Pfizer-BioNTech vaccine

The Pfizer BioNTech SARS-CoV-2 vaccine model employs a modified-nucleoside mRNA (mod-RNA) ([Clinical Protocol Pfizer BioNTech. 2020](#)). Capped methylation of the 5'prime end of the single stranded mod-RNA is done to protect the mod-RNA from degradation by the nucleosidase enzymes in the host cellular system ([Kose \*et al.\*, 2019](#); [Yusuf \*et al.\*, 2021](#)). The single stranded mRNA is produced via cell-free in vitro transcription of the original SARS-CoV-2 DNA templates, which is then encoded in a lipid nanoparticle vector ([Yusuf \*et al.\*, 2021](#)). After introduction of the vaccine into the host system via intramuscular injection; the mRNA is translated by the host cellular ribosome or the endoplasmic reticulum into the target antigen. The presence of these antigens will imitate the actual viral infection; leading to an immune system response and subsequent production of antibodies by the host immune system. The Pfizer BioNTech SARS-CoV-2 vaccine is usually white to off-white in color at a specific pH of 6.9-7.9 and is stored at -70°C; with a record efficacy of about 95 % against the disease and 87 % against the severe disease. The vaccine comes in a multi-viral dose and requires dilution with normal saline before use. The Pfizer-BioNTech vaccine is used in two doses (day 0 and day 21); with 1 dose containing 30 µg of the mRNA molecules, and an age indication of 16 years and older ([Yusuf \*et al.\*, 2021](#)).



**Fig. 3:** An overview of the mechanisms of action of the mRNA SARS-CoV-19 vaccines (Pfizer BioNTech and Moderna). The mRNAs are encoded in a modified lipid nanoparticle (Mod-LNP) vector ([Kose \*et al.\*, 2019](#); [Schoenmaker \*et al.\*, 2021](#)). Vaccine entry into the host cell is accompanied with translation of the mRNA by the rough endoplasmic reticulum (RER) to synthesize the SARS-CoV-2 spike (s) proteins. Detection of the spike proteins by the antigen presenting cells (APC) stimulates both the cellular mediated and the antigen mediated immune response. This immunological response causes antibodies production by the cellular plasma molecules ([Mohammadi, 2020](#); [Yusuf \*et al.\*, 2021](#))

#### 4.4.2. Moderna vaccine

In December 18, (2020), the United States Food and Drug Administration (FDA) issued an authorization for the emergency use of the Moderna (mRNA-1273) SARS-CoV-2 vaccine as a mean to curtail the spread and mortality from the novel coronavirus. Similar to the Pfizer BioNTech SARS-CoV-2 vaccine, the mRNA is translated by the host cellular ribosome endoplasmic reticulum into viral

spike proteins. The spike proteins then elicit an immune system response, and afterward; the production of antibodies by the host immune system. The vaccine is also available in two doses of 0.5 ml each (days 0 and 28), with an age limit of 18 years and older. Recently, in August, 2021, the FDA approved a booster dose for the specific immuno-suppressant individuals ([Jaimie, 2021](#)). This vaccine is administered intramuscularly; specifically at the deltoid muscle. The Moderna SARS-CoV-2 vaccines

are normally stored frozen at about -25°C- 15°C in the darkness. The side effects of this vaccine include; headache, fatigue, myalgia, arthralgia, nausea/vomiting, axillary swelling/tenderness, fever, pains, swelling and erythema at the injection site ([Vaccine Recipient Fact Sheet, 2020](#)).

## 5. The Prime-boost Regimen in SARS-CoV-2 vaccine development: A promising approach

The last decade has recorded tremendous success in vaccines development. Vaccines efficacies have been enhanced through different approaches such as; the combination of genes of interest, enhancer molecules and vector-carriers; to stimulate maximum immunological response.

Molecules such as genes that induce apoptosis and genes for Toll-like receptors (TLRs) have been utilized for maximum immunogenicity ([Belakova \*et al.\*, 2007](#); [Saade and Petrovsky, 2012](#)). In the current study, we discuss the detailed combined strategy used for the development of SARS-CoV-2 vaccines, specifically Oxford-AstraZeneca and Johnson and Johnson vaccines.

Current vaccine development involves the formulation and sequential use of double strategic approaches in a single administration. This regime is referred to as "Prime-boost Regimen", and involves administration of the same antigen or recombinant protein in appropriate adjuvants. This has proven to induce a stronger and more efficient immune response against the intracellular pathogens ([Nascimento and Leite, 2012](#)). The rationale behind this vaccine is to induce both humoral and cellular immunity; in an attempt to maximize the induced immune response against the antigen, as further explained by [Nascimento and Leite, \(2012\)](#). Although the SARS-CoV-2 vaccine development utilizes the same approach; however, it is very imperative to incorporate more than two different approaches for the development of an effective vaccine. Such a vaccine should contain more than one subunit of the antigen; combined with a live vector and possibly a molecular

enhancer such as a DNA segment from the pathogen of interest. While subunit particles usually induce humoral immune response; the vector and DNA segment will in turn complement the immunogenicity by eliciting cell mediated immunity (CMI), as described by [Radosevic \*et al.\*, \(2009\)](#).

The double approaches strategy has long been used in vaccine development; interestingly, in the development of Malaria, HIV, influenza and TB vaccines ([Leong \*et al.\*, 1994](#)). However, combination of three different approaches might be more promising; especially for the development of effective memory T cells.

## 6. Arising issues regarding COVID-19 vaccines in Africa

Although the World Health Organization (WHO) has approved several SARS-CoV-2 vaccines for emergency use due to the deadly effect of the novel coronavirus; however, the citizen's hesitance in accepting these vaccines is a major global issue ([Jaimie, 2021](#)). According to [Wouters \*et al.\*, \(2021\)](#), hesitance in vaccine intake is prevalent in both high and low income countries; with skeptics from different backgrounds (socioeconomic, religious and ethnicity). However, a recent study conducted by [Dinga \*et al.\*, \(2021\)](#) expressed modest acceptance of about 54 % of people's reported in high income countries. In Nigeria, [Amakiri \*et al.\*, \(2021\)](#) reported that about 51.1 % of Nigerians are willing to take the SARS-CoV-2 vaccine, while 30.5 % are unwilling; with 18.4 % indecisive. In Cameroon, about 84.6 % of adults were reported to be unwilling to accept the novel vaccine ([Dinga \*et al.\*, 2021](#)). Although the number of people willing to take the vaccine in Nigeria is higher than those unwilling to take it; the unwillingness of the latter can be attributed to conspiracy theories about the vaccines, safety doubts and/or lack of confidence in these vaccines ([Ditekemena \*et al.\*, 2021](#)). Compared to the other African countries, the willingness to take the SARS-CoV-2 vaccine in Australia is recorded in 85.8 %, in Europe in 73.9 %, in Canada in 57.5 % and 54 % in

the United States ([Nachega \*et al.\*, 2021](#)). Although Canada and the United States fall under the same range as some of the African countries in their willingness to take the vaccine; the high numbers of citizen's willingness to take the SARS-CoV-2 vaccine in these countries could be due attributed to the higher literacy level; availability of genuine and adequate information.

Further studies have suggested that the unwillingness of Africans to take the new novel SARS-CoV-2 vaccines is a result of confusing information; anti-vaccine campaigns in some African countries, warning Africans to refuse the COVID-19 vaccines on the social media, negative perceptions of the pharmaceutical industry, concerns about the reliability or sources of these vaccines and cost to the individuals ([Duru \*et al.\*, 2020](#); [NHS, 2021](#); [Conti \*et al.\*, 2021](#)). Some theories even described the African continent to be "immune" to the SARS-CoV-2 virus; stating that the climatic conditions act as combating factors ([Jon, 2021](#); [Nachega \*et al.\*, 2021](#)).

Other major concerns are the increased detection of new viral variants and effectiveness of the COVID-19 vaccines against these variants. Since the virus was discovered till now; several accessible databases were able to share more than 414,575 complete viral genomic sequences, in addition to mutations discovered within the public (Pan American Health Organization, 2021)

Sequel to the SARS-CoV-2 pandemic; different researchers across the globe have conducted various studies on the mutations arising from the novel coronavirus ([Sunday \*et al.\*, 2021](#)). These studies generated different variants such as the British variant also known as the Alpha variant (B.1.1.7), which caused about 70 % of the new COVID 19 cases in December, 2020. The Alpha variant was followed by the prevalent variant in Africa; called the South African variant, and was also known as the Beta variant (B.1.351). This variant has the ability to re-infect people who have hitherto recovered from the earlier variants ([Amakiri \*et al.\*, 2021](#)). The Beta

variant has received more attention from the researchers; as individuals who received the Oxford-AstraZeneca vaccine had weaker protection from this variant, which led the South African government to discontinue its use ([Jon, 2021](#)). Another variant of concern that attracted the global attention was the Brazilian variant, also known as the Gamma variant (P.1). Similar to the Beta variant; the Gamma variant also possesses increased transmission rate, although less than the alpha variant. Moreover, this Gamma variant rendered the SARS-CoV-2 monoclonal antibody vaccines less effective when administered to individuals infected by it.

Lately in July, (2021), the SARS-CoV-2 Indian variant (B.1.617.2) was discovered, officially known as the Delta variant. This variant is considered to be more transmissible than the other variants discovered earlier, and was most prevalent in India and in the United States of America. Complications related to this variant have not yet been discovered ([Lauring and Malani, 2021](#)). As the Delta variant has high rate of transmission; unvaccinated individuals are at higher risk of infection. Likewise, a single dose vaccinated individuals in a 2-dose vaccine regimen like AstraZeneca have been reported to have lesser immunity against the Delta variant, as described recently by [Lauring and Malani, \(2021\)](#).

Although there have been many doubts about the efficacies of vaccines against this variant; however, there is no available data to express that these mutations will impact the efficacy of the vaccines already approved by the FDA ([Conti \*et al.\*, 2021](#)).

[Wouters \*et al.\*, \(2021\)](#) related the imperative issues arising from development of SARS-CoV-2 vaccines to the velocity of the vaccine's discoveries and productions; in line with the global pressure to find a cure for this disease. Therefore, passage of time and the detailed studies on the effectiveness of the various vaccines will enable the clarification of questions; clearing of doubts and increasing trust in these vaccines. Moreover, research work must be conducted on the new variants and the ones yet to appear in the

future; for better understanding of the effectiveness of the existing vaccines against these variants. Policy makers should engage effective education of their various communities; in order to fight misinformation and conspiracy theories; thereby, increasing confidence in the vaccines. Likewise, the African government must participate in the role of enlightening the Africans about these vaccines, and to further debunk the fallacious theories in the social and traditional media about the immunity of Africans to the SARS-CoV-2 virus. In addition, implementing the novel vaccines in the primary healthcare routine immunization scheme will enhance the healthcare delivery, and also increases the public acceptance of these vaccines.

## Conclusion

The development of efficient and successful vaccines against SARS-CoV-2 infection is truly remarkable. SARS-CoV-2 vaccines are crucial in evading the ravaging pandemic that has affected the global community since December, 2019. The most common current circulating vaccines include Oxford AstraZeneca; Johnson and Johnson, Pfizer BioNTech and Moderna vaccine. Despite the proved efficacy of these vaccines and their emergency use approval, the citizen's hesitance in accepting these vaccines is bothersome. Other major concern is the increased detection of new variants and effectiveness of the COVID-19 vaccines against these variants. However, good understanding of the host immune response against SARS-CoV-2 and detailed studies on the mechanisms of action of these vaccines will aid in increasing the public acceptance of these vaccines, and improve the citizens' willingness to take the vaccine.

## Future recommendations

As scientists are working hard to stabilize the already overwhelming global health care system due to the current pandemic; citizen's hindrance and unwillingness to take these vaccines are a global concern. It is important for the diverse strategies to

incorporate the basic knowledge about the vaccines to the citizens. In this study, we recommend public awareness about these vaccines to the communities by policy makers; religious leaders and health workers, in order to fight the misinformation and conspiracy theories about these vaccines. The African government must work to enlighten the Africans and debunk the fallacious theories prevalent in the social and traditional media about immunity of the Africans to this SARS-CoV-2 virus.

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