EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 11
110-120
Year: 2022

A REVIEW ON MEDICINES, VACCINES AND FUTURE PROSPECTIVES FOR THE TREATMENT OF COVID DISEASE

Prashanth M. E.[1]*, Dr. Basavaraj H.[1], Dr. Mallappa Shalavadi[2] and Leela J.[1]

[1]Department of Pharmacology, Government College of Pharmacy, Bengaluru, Karnataka,India.
[2]Department of Pharmacology, BVVS Hanagal Shri Kumareshwar College of Pharmacy, Bagalkot, Karnataka, India.

***Corresponding Author: Prashanth M. E.**
Department of Pharmacology, Government College of Pharmacy, Bengaluru, Karnataka, India.

Article Received on 29/08/2022 **Article Revised on 19/09/2022** **Article Accepted on 09/10/2022**

ABSTRACT
The Covid pandemic caused a serious issue all over the world in the last few years affecting health, economy and progress of all the countries and it was necessary to develop a medicine against the virus with immediate effect. Initially, the disease was treated by available drugs which targeted different structures of virus inhibiting their normal phenomenon for binding, release, replication of viral particles in host cells. However, these drugs did not guarantee complete cure of Covid disease. Like all other virus there was development of Vaccines for SARS-CoV-2 from the pharma giants all over the world. The vaccines were developed based on different vectors but all the vaccines had its own side effects with range of effectiveness among different populations. Few other pharma companies are in search of development of vaccines which can be given by different routes other than intramuscular to ease the vaccine intake by the patients. This article briefs out the different vaccines, their mechanism, effectiveness and future of vaccines against covid disease.

KEYWORDS: SARS-CoV-2, Covid, Vaccines, Covaxin. Covishield, Sputnik, ZyCoV-D.

1. INTRODUCTION

The Covid outbreak notified in Dec 2019 at Wuhan, China was declared as health emergency by WHO in Jan 30 2020. The covid disease is caused by SARS-CoV-2 virus that mainly affects lower respiratory affect. Given the chaos wrought by SARS-CoV-2 on human health and life at the initial phase of its origin, it was critical to develop drugs or to use already available drugs that avert the virus from intruding and amplifying within host cells. Since the SARS-CoV-2 virus damages host cells in several ways, a combination of drugs or a drug with multiple targets effective in inhibiting both virus incursion and propagation would be required. The following drugs, however, are used as antimicrobials, antivirals, other treatments, etc., and were only preliminary options prescribed to reduce the severity of the disease, and these drugs do not guarantee complete cure from SARS-CoV-2 infection. (Table no.1)

I.) Classification of drugs for SARS-CoV-2 based on the targets.

DRUGS WITH ANTI-VIRAL PROPERTY		
TARGETS	**DRUG**	**MECHANISM**
S- Protein	Umifenovir (Arbidol)	Exerts its effects by interrupting the hydrogen bonds of phospholipid molecules in the cell membrane, preventing virus-host cell contact or virus-endosome fusion into the cell membrane, and thus preventing virus entry into host cells.[1][3]
	Chloroquine/ Hydroxychloroquine	It interferes with ACE2 glycosylation, restricting it from adhesion to the S-protein and thereby hindering virus replication, assembly, and release.[4] Chloroquine can elevate the pH of acidic vesicles like endosomes and lysosomes, which prevents viral envelope uncoating and RNA release into the host cell cytoplasm.[5-6] Chloroquine has also been proposed to restrict the production and release of TNF and IL-6, minimizing cytokine storms.[7]
TMPRSS2	Nafamostat	By aiming for TMPRSS2, it forbids SARS-CoV-2 entry and stifles S- protein initiated fusion to the host cell membrane. Plasmin has been shown to boost virus pathogenicity and infectivity by slicing the S protein and Nafamostat inhibits plasmin activity.[8]

RNA-dependent RNA polymerase (RdRp)	Remdesivir	Remdesivir is a monophosphoramidate prodrug of remdesivir- triphosphate (RDVTP), an adenosine analog that acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). Remdesivir-TP competes with adenosine-triphosphate for incorporation into nascent viral RNA chains.[2][9]
	Ribavirin	It is a nucleoside analogof guanosine, inhibits RNA polymerase, and acts as a chain terminator, it gets incorporated into the genome and causes mutations resultingin defective viral progeny - called "error catastrophe"[10]
	Molnupiravir	Molnupiravir is converted to the active nucleoside analog in plasma by host esterases, which then diffuses to various tissues and converts to triphosphate form. Instead of cytidine-triphosphate and uridine-triphosphate, RdRp uses this triphosphate form of Molnupiravir as a substrate, resulting in the production of mutated RNA.[11]
	Favipiravir	Favipiravir is a prodrug that, upon entering the cell, is phosphorylated and converted to an active antiviral form, Favipiravir-RTP. Which is then used in the synthesis of mRNA strands by RNA-dependent RNA- polymerase (RdRp) due to its similarity to the purine nucleotide, which can stop viral protein synthesis by suppressing the translation process.[2]
Cytokines	Azithromycin (in combination with other antivirals)	Upregulates the production of type 1 interferons which play a role inreducing viral load and organ damage by a cytokine storm.[13] It is hypothesized that an acidic condition is required for the uncoating of coronavirus. Azithromycin being a weak base increases the pH thereby preventing the uncoating and release of the viral gene.[15]
	Ulinastatin	Cytokine storms are thought to play an important role in the pathogenesisof Covid19 and may be linked to disease severity and fatality. Ulinastatin inhibits the production of inflammatory cytokines and adhesion molecules. It also increases the stability of the lysosomal membrane and decreases the synthesis and delivery of lysosomal enzymes, scavenging oxygen or hydroxyl radicals.[12]
	Dexamethasone	Inhibition of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, TNF, IFN gamma, VEGF, and prostaglandins which have been linked to the severity of SARSCoV-2. It also activates the synthesis of anti- inflammatory cytokines such as IL-10 and lipocortin-1 by inducing the synthesis of glucocorticoid response elements.[14]

2. VACCINATION AGAINST SARS-CoV-2

The immune system is composed of cells, tissues, and organs that collaborate to boost the immune system to produce antibodies against hazardous bacteria or viruses also known as an **antigen**. When an antigen enters the body, our immune system identifies it as threatening and launches an invasion to destroy it by producing large proteins known as antibodies. These antibodies serve as scouts, tracking down the antigen and tagging it for obliteration by the immune response. Vaccination is the most pervasive and healthiest way to gain immunity to an antigen that our bodies have not yet confronted. A vaccine is a biological component that could be used to securely stimulate an immune reaction that protects against infectious disease and/or disease when revealed to a pathogen in the future. With vaccines, the bacteria or virus will be killed, severely weakened, or broken down into small pieces so that they can elicit an immune response without making people sick.

The antigen in the case of SARS-CoV-2 is the spike protein that encloses the outer surface. SARS-CoV-2 vaccines infuse an antigen and use our cellular machinery to establish a strong immune system. Whenever the immune system is subjected to the spike protein, it commences organizing antigen-specific antibodies. When a coronavirus invades, these antibodies wait for the chance to target the actual spike protein. Since antibodies decline over the period, a boosterdose is essential to sustain a solid defense system.

a. Whole virion inactivated vaccine

The vaccines in which the virulence properties of live viruses are reduced by heat, UV rays, and chemical treatment are known as inactivated vaccines. This vaccine contains a dormant pathogen that does not cause disease, but can trigger an immune response in response to a possible infection. The inactivated form of the organism creates a safe vaccine, especially for immunocom promised individuals. It is not as dangerous as a live attenuated vaccine (LAVs). Adjuvants must be included in vaccine formulations to improve vaccination efficacy.[18]

II.) Whole Virion Inactivated Vaccine

WHOLE VIRION INACTIVATED VACCINE			
	COVAXIN[16,17]	**CORONAVAC**[19,20]	**SINOPHARM**[21,22]
Code Name	BBV152	Sinovac COVID-19	BBIBP-CorV or covilo
Manufacturer	Bharat Biotech International Limited in collaboration with the Indian Council of Medical Research & National Institute of Virology (NIV), India	Sinovac Biotech, China	Sinopharm and the Beijing Institute of Biological ProductsCo., China
Dose & Duration	2 dose and 28 days duration	2 doses and after 28 days	2 dose and 3 weeks
Ingredients	6µg of whole-virion inactivated SARS-CoV-2 antigen (Strain: NIV-2020- 770), and the other inactive ingredients such as aluminum hydroxide gel (250 µg), Toll Like Receptor 7/8 agonist (15 µg), 2-phenoxyethanol (2.5 mg), and phosphate buffer saline up to 0.5 ml.	Inactivated SARS-CoV-2 Virus (CZ02 strain), Aluminum hydroxide, Disodium hydrogen phosphate dodecahydrate, Sodium dihydrogen phosphate monohydrate, Sodium chloride.	**Active ingredient**: inactivated antigen of SARS-CoV-2 WIV04 strain. **Adjuvant:** aluminumhydroxide. **Auxiliary materials**: sodium chloride, disodium hydrogen phosphate, sodium dihydrogen phosphate
Mode ofAction	COVAXIN is an inactivated vaccine obtained from the SARS-CoV-2 strain. The vaccine is used along with immune stimulants, commonly known as vaccine adjuvants (Alhydroxiquim-II), to improve immune response and longer-lasting immunity. This is the first inactivated SARS-CoV-2 vaccine that has been reported to induce a Th1- biased response	Part of the coronavirus genetic code is injected into the body, triggering the body to begin making viral proteins, but not the whole virus, which is enough to train the immune system to attack and hence, immunity is developed.	It works by exposing the immune system to the inactivated (incapable of disease-producing) virus particulate which leads to the development of antibodiesagainst the virus.
Efficacy	About 81% following seconddose	About 50.65% to 83.5% differing in different countries	79%
Side Effects	Injection site pain, swelling, redness, itching, stiffness in the upper arm, weakness in injection arm, body ache, headache, fever, malaise, Dizziness & weakness, rashes, nausea, vomiting, Allergic reactions, Swelling of face and throat, fast heartbeat.	Blood Pressure Increase; Headache; Vaccination site pain; Dizziness; Rash	Pain at the injection site, fatigue, headache, lethargy, swelling and redness, muscle pain (non-injection site), diarrhea, cough, oropharyngeal pain, fever, runny nose, dyspnea, arthralgia, pruritus (non-injection site), nausea, dizziness, and constipation.

b. Protein subunit-based vaccine

Protein subunit vaccines are composed of viral antigenic fragments created using recombinant protein techniques. It makes use of one or more purified antigens to boostthe immune system, does not introduce the entire pathogen, and does not require the use of a safe viral vector. The reduced immunogenicity of protein subunit vaccines is a barrier. As a result, adjuvants are typically used in conjunction with subunit vaccines to strengthen immunogenicity.[23,24]

III.) Protein Subunit Based Vaccine

PROTEIN SUBUNIT-BASED VACCINE	
	EPIVAC CORONA[23][27]
Manufacturer	Federal Budgetary Research Institution State Biotechnology, Russia Research Center of Virology
Dose & Duration	2 dose and 21 days duration
Ingredients	The vaccine is based on chemically synthesised SARS-CoV-2 protein peptide antigens inflected to a carrier protein and adsorbed on an aluminum-containing adjuvant (aluminium hydroxide).
Mode Action of	The vaccine contains no live virus and generates immunity through the use of artificially synthesised peptides. EpiVacCorona is comprised of three synthetic spike fragments tethered to a carrier protein, which is made up of synthetic fragments of the virus's nucleocapsid protein, known as N. One peptide is anticipated to evoke antibodies to the spike's receptor binding domain, which is the portion that attaches to a human cell protein. The remaining spike peptides are designed to elicit antibodies that prevent the virus from entering the cell.
Efficacy	proven to be 100% based on phase II & III

c. DNA-based vaccine

Using DNA plasmids as a vector, it delivers genes or fragments of genes that encode immunogenic antigens to host cells. The vaccine formulation is designed in such a way that the genetic material is translocated to the nucleus of the host cell. Once there, the mammalian

promoter in the vector structure is activated, triggering the transcription ofthe vaccine gene via the host's cellular machinery. The antigen-presenting cells (APCs) are the primary target cells for genetic material delivery. Following translation of the translocated gene into a protein or protein fragment, it is further processed into peptidesthat bind to MHC class I or II. Other cells, such as myocytes, use MHC-I for antigen presentation, whereas APC, such as dendritic cells (DCs), can use MHC-II, resulting in cross-priming and antigen presentation to both CD4+ and CD8+ cells.[28]

IV.) DNA based Vaccine

DNA-BASED VACCINE	
	ZYCOV-D[23][29][30] It is a needle free intra dermal vaccine
Manufacturer	Cadila Healthcare Limited, Ahmedabad, India
Dose & Duration	3 doses and 28 days apart i.e., at 0th, 28th & 56th day
Ingredients	It comprises of a DNA plasmid Vector pVAX1 carrying gene expressing spike-S protein of SARS-CoV-2 and IgE signal peptide. Each 0.5 mL of ZyCoV-D vaccine contains–5 mg of DNA plasmid with spike protein gene region inserts from SARS-CoV-2 Virus suspended in phosphate buffer saline.
Mode ofAction	This vaccine delivers a specific set of instructions to our cells. This allows them to make thespecific protein that the immune system recognize and respond.
Efficacy	66.6%
Side effects	Tenderness at the site of injection

d. RNA-based vaccine

The antigen of interest is encoded in a messenger RNA (mRNA) or self-amplifying RNA, which is a molecular template used by cellular factories to synthesize proteins. The RNA, encapsulated inside nanoparticles, can be injected on its own. Once the RNA enters the cell and begins producing antigens, these are showcased on the surface of thecell, where they'll be sensed by the immune system, culminating in a reaction. This response involves killer T cells (which seek out and kill infected cells), antibody- producing B cells, and helper T cells (which assist in antibody production).[24]

V.) RNA based Vaccine

RNA-BASED VACCINE		
	COMINARTY[31-33]	**mRNA- 1273**[23][34][35]
Codename	BNT162B2	-
Manufacturer	Pfizer, BioNTech, Fosun Pharma, German	Moderna and National Institute of Allergy and Infectious Diseases (NIAID)
Dose & Duration	2 doses and 21 days apart	2 doses and 28 days apart
Ingredients	It contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients: lipids ((4-hydroxybutyl) azanediyl) bis(hexane-6,1-diyl) bis (2-hexyldecanoate), 2- [(polyethylene glycol)- 2000]- N,N - itetradecylacetamide, 1,2- distearoyl-snglycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.	The vaccine contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero3- methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-snglycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.
Mode of Action	It is made of nucleoside-modified mRNA which has been formulated in lipid nanoparticles. The mRNA encrypts the membrane-anchored, full-length SARS-CoV-19 spike proteinand includes mutations that maintain the spike protein in an antigenically preferred, prefusion conformation. Upon intramuscular injection, the lipid nanoparticles safeguard the non-replicating RNA from deterioration and allow it to be conveyed into host cells. Insidethe host cell, the mRNA is translated into theSARS-CoV-2 spike protein, which is expressed on the cell's surface. Transient expression of this spike antigen instils neutralising antibody and cellular immune responses, which may impart protection against COVID-19.	The Moderna COVID19 Vaccine utilizes mRNA as a template for cells to construct body's protection against the virus. The nucleoside-modified mRNA is formulated in lipid particles, allowing delivery of the nucleoside-modified mRNA into host cells and expression of the SARSCoV2 Spike antigen. The vaccine stimulates an immune response to the Spike antigen, which provides protection against COVID19

Efficacy	95%	94.1%
Side effects	Pain, redness, and swelling at the site of injection. Other effect includes tiredness, headache, muscle pain, chills, fever and nausea can be the few side effects that can be felt throughout the body.	Local reactions, fever, fatigue, headache, tenderness and swelling of the lymph nodes in the same arm of the injection, swelling (hardness).

e. viral vector

The virus endures and reproduces by subverting and interrupting the host cell's protein synthesis mechanism. The host cells then read the viral genetic code and synthesise viral protein, infecting the individual. A similar concept upholds viral vector vaccines, in which host cells are only given a code to produce specific antigens. The viral vector serves as a delivery system, allowing the virus to enter the cell and insert the SARS-CoV-2 antigen code. The virus used as a vector has been chemically weakened, making it incapable of causing disease. Adenovirus, measles virus, and vaccinia virus are beenused as vectors.[24]

VI.) Viral vector Vaccines

VIRAL VECTOR			
	Astra Zeneca Covid-19 Vaccine(Azd1222)[23],[36],[37]	**Sputnik V**[23],[37],[38]	**Janssen Covid-19 Vaccine**[23],[37],[39]
Code Name	ChAdOx1_nCoV-19, Vaxzevria, Covishield	Gam-COVID-Vac, rAd26, rAd5	Ad26.COV2. S
Manufacturer	University of Oxford, Astra Zeneca Serum Institute of India (for Covishield)	Gamaleya research institute, Russia	Janssen Pharmaceutical Companies (Johnson & Johnson)
Dose & Duration	2 doses and 12 weeks apart	2 doses and 21 days apart	1
Ingredients	One dose (0.5ml) contains$5x10^{10}$ ChAdOx1-S viral particles & the excipients L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate and water for injection.	recombinant serotype 5 or 26 adenoviral particles, containing the SARS-CoV-2 protein S gene, in the amount of (1.0±0.5) x 10^{11} particles per dose and excipients such as tris-(hydroxymethyl)aminomethane, sodium chloride, sucrose, magnesium chloride hexahydrate, EDTA-disodium salt dihydrate, polysorbate, ethanol, water for injections.	The vaccine consists of a replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the SARS- CoV-2 spike (S) protein in a stabilized conformation & inactive ingredient: citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β- cyclodextrin (HBCD), polysorbate 80, sodium chloride.
	Mode of Action It is a solitary recombinant, replication- deficient chimp adenovirus vector encoding the S glycoprotein of SARS-CoV-2. In the vaccine, the SARS-CoV-2 S immunogen is expressed in a trimeric conformation. To preserve the expressed S-protein in the conformation, the coding sequence has not been altered. Post vaccination, the adenovirus vector enters cells and releases its genes, which are transported to the cell nucleus; the cell's machinery then transcribes the mRNA and translates it into proteins. The protein of interest i.e., the spike protein, allows SARS-type coronaviruses to enter cells via the ACE2 enzymatic domain. This stimulates the immune system to attack the coronavirus via antibodies and T-cells if it later infects the body	It employs a debilitated virus to deliver viral fragments and induce an immune response. It is an adenovirus-based vector vaccine with the SARS-CoV-2 coronavirus gene integrated. Adenovirus is used as a vehicle to deliver the coronavirus gene to cells and activate the synthesis of the new coronavirus envelope proteins, effectively activating the immune system against it.	This employs double- stranded DNA. The coronavirus spike protein gene is incorporated to the viral vector, which serves as a delivery system, allowing the virus to enter the cell and introduce the targeted antigen code. Themodified virus enters the cell and enters the nucleus, where the spike protein gene is copied intomRNA and then translated to proteins outside the nucleus. The spike proteins migrate to the cell surface and activate the immune system. B cells, helper T cells, and cytotoxic T cells are all activated.
Efficacy	70.4%	91.6%	66%
Side Effects	Headache, nausea, myalgia, arthralgia, fatigue, malaise, feverishness, chills and swelling, erythema, tenderness, pain, warmth,pruritus at the site of injection.	Injection site pain, hyperthermia, headache, asthenia, muscle and joint pain	Pain at the injection site, headache, fatigue, muscleaches and nausea.

3. DIFFERENT DELIVERY ROUTES FOR COVID VACCINES

To achieve a systemic effect, the majority of vaccines are administered intramuscularly or subcutaneously. The above-mentioned vaccines, as well as others developed for Covid-19, are typically administered intramuscularly. When administered subcutaneously, the majority of Covid19 vaccines contain aluminum salt as an adjuvant, which has serious side effects.[40]

Although the i.m route is beneficial at introducing antigens systemically for an immunogenic response, it has several obstacles, including needlestick pain and fear, constrained thermostability, a need for qualified healthcare workers for vaccine administration, contamination of multidose vials, the transmission of blood-borne disease via needle stick injury. As a result, there is a need for vaccines that could be administered through various routes, that may be advantageous in overcoming the aforementioned limitations.

3.1 ORAL ROUTE

Oral vaccines may not only be the most patient-friendly route, but they may also strengthen vaccine outcomes by improving accessibility and adherence. It also drastically reduces administration costs and encourages a larger proportion of the population to get vaccinated.

Advantages

- It eliminates the need for freezing equipment for transportation and storage.
- Better population coverage results from easy accessibility (especially for those who fearneedles)
- Reduces the cost of training and mobilising health-care workers.
- Prevents occupational needle-stick injuries
- Removes the problem of biohazardous waste.

a. ORAVAX

Oravax Medical, a collaboration between Premas Biotech and Oramed, is working on an oral COVID-19 vaccine. Premas Biotech is a forward-thinking biotherapeutic and vaccine candidate developer and manufacturer. Oramed Pharmaceuticals is a platform technology innovator in the field of oral delivery solutions for drugs that are currently administered via injection. Oramed's proprietary Protein Oral Delivery (POD™) technology enables therapeutic proteins and vaccines to be delivered orally. Premas Biotech's D-Crypt™ technology is used in the Oravax technology, which combines a novel vaccine approach with an oral delivery platform from Oramed Pharmaceuticals' proprietary POD™ delivery technology. This vaccine targets three SARS CoV-2 virus surface proteins, including proteins that are less susceptible to mutation, making it an excellent candidate for protecting against evolving mutated viruses. It is safe, effective, and welltolerated at low to high doses, and it produces high serum levels of neutralizing antibodies.

In a pilot animal study, the oral COVID-19 vaccine stimulated systemic immunity via Immunoglobulin G (IgG), the most common antibody in blood and bodily fluids that protects against viral infections, as well as Immunoglobulin A (IgA), which protects the respiratory and gastrointestinal tracts from infection.[41]

b. VXA-CoV2-1[42]-[45]

Vaxart is working on a tablet formulation of a non-replicating adenovirus type 5 (Ad5)- based COVID-19 vaccine using its patented VAAST™ (Vector-Adjuvant-Antigen Standardized Technology) platform. The oral recombinant vaccines are formulated as enterically coated tablets for delivery to the small bowel. The enteric coating shields the active ingredient from the acidic environment of the stomach. The vaccines engage the gut's finely tuned immune system to generate broad systemic and mucosal immune responses for robust, long-lasting immunity by targeting the small bowel. Vaxart is also working on a liquid formulation for young children and adults who are unable to swallowtablets. In terms of immunity, the vaccine candidate has been shown in animal models to elicit a very high titer of neutralizing antibodies in the lungs, a dose dependent increase in IgG levels, and the production of antigen-dependent CD4+ and CD8+ cells. The vaccine induces a significant CD8+ T-cell response and was found to be significantly protective against the new strains of SARS-CoV-2. The vaccine candidate (VXA-CoV2-1) employs both the outer spike protein (S) and the nucleocapsid protein (NP) (N). Because the N protein is more conserved, it is less prone to mutation. As a result, it may be able to provideimmunity to various strains. Second, N protein is said to be a better T-cell response target. According to the official press release, the primary immune responses observed are CD8+ cytotoxic T-cell responses against S and N antigens (responsible for long-lasting cross- reactive immunity). In all subjects, an increase in plasma B-cells and an upregulation of mucosal homing receptor on these cells indicated B-cell activation, an increase in pro- inflammatory Th1 cytokine (essential for an anti-viral response), and an IgA response.

According to a public statement from Vaxart (dated February 24th, 2022), the effect of three various candidates was investigated on animals, each of which was assigned a code,and the results were as follows.

VXA-CoV2-1.1-S or ED90 (that includes the S protein from the parental strain (Wuhan variant)) Cross-reactive serum and nasal antibodies were induced to multiple variants, with the Wuhan and delta variants eliciting the highest neutralizing antibody responses.

ED94 (includes only S protein from the beta variant) It was less cross-reactive against other variants than VXA-CoV2-1.1-S and generated the highest IgG responses to the matched beta variant.

ED88 (includes a combination of parental S and N proteins) Produced weaker IgG and IgA responses than the other adenoviral strains.

c. OraPro

iosBio Pharma, a UK-based company, is using the OraPro™ platform to create an oral capsulebased COVID-19 vaccine. The powder in OraPro Capsule is encased in a capsule with an enteric coating that prevents it from being dissolved by stomach acid. When the capsule enters the small intestine, the pH changes from acid to alkaline, and the enteric coating dissolves, releasing the viral vector to the GI tract's mucosal cells.

The main objective of iosBio Pharma, in collaboration with Therm-SB technology and ImmunityBio (a biopharmaceutical company based in the United States), is to develop a human Adenoviral (hAd5) vector-based COVID-19 vaccine. A modified spike protein gene (S-fusion) and a nucleocapsid protein gene with an enhanced T-cell stimulation domain (N-ETSD) are used in the vaccine candidate.

As per the study, it was indicated to have a defensive antibody response and formed a Th1dominant T-cell response after a subcutaneous and an oral boost that illustrated protection in Rhesus monkeys challenged with SARS-CoV-2. Substantial immunity was noted in the animal's lower and upper respiratory tracts. Another notable feature of the hAd5 vector (as a delivery vehicle) is its ability to be used even in pre-formed immunity against adenoviruses. [46]

d. BacTRL Spike vaccine

Developed by Canada based company Symvivo corporation. Symvivo's bacTRL platform was developed to deliver orally administered, genetically modified probiotic bacteria that colonize the gut, directly bind to intestinal epithelial cells, and constitutively replicate, secrete, and deliver plasmid DNA encoding antigenic transgenes and neutralizing nanobodies. Each oral dose of bacTRL-Spike contains a bacterial medium containing 1 billion (Group 1A), 3 billion (Group 2A), or 10 billion (Group 3A) colony-forming units of live Bifidobacterium longum engineered to deliver plasmids containing synthetic DNA encoding SARS-CoV-2 spike protein. Both cellular and humoral immunity against Spike Protein is induced by bacTRL-Spike.[54,55]

3.2 INTRANASAL ROUTE

IM vaccines appear to be ineffective at limiting viral replication and nasal shedding in the upper respiratory tract. The IM vaccines offer better systemic immunity but lack mucosal immunity, enabling the virus to accumulate in the nasal pathway and be easily transmitted to others. As a result, mucosal immunity is required to trigger antibodies to clear or fight infection at the nasal pathway itself. Intra Nasal vaccines expose the antigens at the entry site of the virus and stimulate potent immune responses at local mucosa. IN vaccine can also elicit pan-reactive antibodies, which is enticing given the rise in COVID-19 variants. The innovation of IN vaccines has quite a significant socioeconomic impact. IN vaccines could vaccinate entire populations as early as possible in a global pandemic, such as COVID-19, since they do not need to be administered by health care providers, resulting in greater patient comfort. The foremost challenge in IN vaccines is to deliver the antigens to the respiratory tract while avoiding nasal clearing. The epithelial layer, baits and eliminates pathogens from the body. The antigen used in the vaccine should stay in the respiratory tract for a good length of time to enable antigen absorption, which incites immune responses for an extended period. Furthermore, the antigen should be sufficiently stable to endure enzymatic depletion in the mucous membrane, like azoreductase-mediated depletion. To address such issues in vaccine formulations, adjuvants and delivery systems, are commonly used to extend the period of the antigen to stay in the mucosal lining while improving its stability.

a. Ad5-nCoV

CanSino Biologics Inc. created it. It is a replication-deficient type 5 human adenovirus vector (Ad5) encoding the SARS-CoV-2 spike protein gene, more specifically antigen for RBD of S protein. [48] In non-human primate models, the vaccine formulated as inhaled aerosols was found to be safe and immunogenic against Sars-CoV-2 and its variants. It also induced solid mucosal and systemic immunity, which aids in the prevention of SARS-CoV-2 transmission. [47]

b. BBV154

BBV 154 is an intranasal replication-deficient adenoviral vectored vaccine that spurs a broad immune reaction such as mucosal IgA, neutralising IgG, and T cell responses. Washington University School of Medicine developed it in collaboration with Bharat Biotech and Precision Virologics.[50] COVID-19 transmission and infection can be avoidedby evoking immune responses at the site of infection (in the nasal mucosa).[49]

On January 28th, 2022, it was reported that Bharat Biotech had received approval from the Drug Controller General of India (DCGI) to conduct phase 3 clinical trials at nine differentsites.

c. AdCOVID

Altimmune, Inc. (Gaithersburg, USA), a biopharmaceutical company, is partnering with the University of Alabama (Birmingham, USA) to develop a promising vaccine named as AdCOVID to prevent COVID-19 disease. It is based on NasoVAX™, Altimmune's specialised intranasal vaccine technology. The NasoVAX™ vaccine is a recombinant intranasal vaccine designed for both recurring and pandemic use. The vaccine is a single- dose, intranasal adenovirus type-5 vectored vaccine that induces a strong and focused immune response against the RBD of the SARS-CoV-2 spike protein by inducing mucosal IgA, serum neutralising antibodies, and CD4+ and CD8+ T cells with a Th1-like cytokine expression profile.[51,52]

d. COROFLU

FluGen (US) and Bharat Biotech (India), in collaboration with the University of Wisconsin- Madison (US), have begun research and refinement of a novel intranasal vaccine (CoroFlu) against SARS-CoV-2. Gene sequences from SARS-CoV-2 will be inserted into M2SR (A vaccine against influenza strain) to create a vaccine against COVID-19. The spike protein, which the coronavirus uses to attach to human cells and infect them, will be pinned into M2SR. The Kawaoka group (University of Wisconsin-Madison) will insert SARS-CoV-2 genetic sequences into M2SR and then test CoroFlu's safety and efficacy in animal models. FluGen will also transfer its existing manufacturing technique to Bharat Biotech, allowing the company to expand and produce the CoroFlu vaccine for clinical trials.[51]

e. COVI-VAC

It is been developed by Codagenix in partnership with Serum Institute of India. COVI- VAC™ is an intra-nasal live-attenuated SARS-COV-2 synthetic viral vaccine under development for COVID-19 mitigation. COVI-VAC is attenuated by removing the furin cleavage site and incorporating 283 silent deoptimizing mutations, which sustain the viral amino acid sequence but lead to significant attenuation due to slow translation in the humanhost cell. COVI-VAC, in particular, would include all viral antigens and is not restricted to spike. COVI-VAC has been shown to have attenuation, immunogenicity, and single dose protection in both Syrian golden hamster and nonhuman primate models.[52,53]

3.3 INTRADERMAL ROUTE

The intradermal route can stimulate both systemic and mucosal immunity; the antigen is conveyed through the skin using self-administrable gadgets. The use of microneedle technology, in particular, helps to overcome the stratum corneum's skin permeation barrier andenables antigen delivery. The availability of several types of immune cells (such as DCs, T lymphocytes, NK cells, macrophages, and mast cells) in the epithelium contributes to the efficacy of this new microneedle-based immunisation approach.

a. INO-4800

It is a DNA vaccine developed by INOVIO Pharmaceuticals. It consists of a concisely designed DNA plasmid injected intradermally, pursued by electroporation with a proprietary smart device, which delivers the DNA plasmid directly into body cells and is intended to elicit a well-tolerated immune response. INO-4800 contains the plasmid pGX9501, which expresses a synthetic, full-length sequence of the SARS-CoV-2 Spike glycoprotein from the original Wuhan strain, which was created using Inovio's proprietary in silico Gene Optimization Algorithm to boost expression. Following INO-4800 ID administration, electroporation is performed using the CELLECTRA® 2000 device, whichgenerates a controlled electric field at the injection site to enhance cellular uptake and expression of the DNA plasmid. The device generates four electrical pulses per EP, each of which lasts 52 milliseconds and has a current strength of 0.2 amps and a voltage of 40-200 volts. INO-4800 is expected to be well-positioned for both primary series and booster immunisation because it is one of the only nucleic-acid-based vaccines that is stable at roomtemperature for more than a year, at 37°C for more than a month, has a five-year projected shelf life at normal refrigeration temperatures, and does not require freezing during transport or storage. According to INOVIO Pharmaceuticals' most recent news, dated November 9th, 2021, INOVIO is colluding with Advaccine Biopharmaceuticals to conduct phase 3 trials in multiple countries to assess the efficacy of INO-4800 in a two-dose regimen (2.0mg per dose) given one month apart.[56,57]

b. CORVax 12

Developed by OncoSec Immunotherapies, consists of DNA that encodes for both the spike protein and Interleukin (IL)-12, allowing the body to generate extra IL-12, optimising the immune system's potential to deliver antibodies to the spike protein. The CORVax vaccine strategy combines OncoSec's immuno-stimulant IL-12 expression platform, Tavo (plasmid IL-12) with a DNA-encodable trimeric SARS-CoV-2 spike glycoprotein developed by scientists at the NIAID Vaccine Research Center to boost immunogenicity of the component.[58]

c. GLS-5310

It is a DNA vaccine developed by GeneOne Life Science that encodes the spike (S) protein and a second antigenic target of SARS-CoV-2. GLS-5310 is being developed as part of a national project to develop COVID-19 vaccines with funding from the Korean government via the Centers for Disease Control and Prevention.[58]

CONCLUSION

The SARS pandemic served as a stark reminder that animal coronaviruses can pose a risk to the general public, even though it is still uncertain how the coronavirus transmits from one species to another. A substantial threat to the health of both humans and animals, coronaviruses frequently appear. The majority of existing medications, in particular antivirals and antibiotics, were repurposed or provisionally permitted for the prophylaxis ofCovid-19, but they did not ensure a full recovery from the illness or its symptoms. Meanwhile, other pharmaceutical entrants from across the world stepped up to formulate a vaccine that may protect against the deadly virus by focusing on various viral structural or critical components that are necessary for viral transmission and multiplication in host cells. Although none of the vaccines offers 100% efficacy, the majority of them are approved and were given to the public as a preventative strategy to ward off infection. The booster dose of vaccines is advised for the public's health due to changing mutations in the genetic

framework of SARS-CoV-2 and with the elevated danger of various evolving stains of SARS-CoV-2. The goal of the ongoing research is to create a vaccine that might be delivered via several routes, be adaptable, painless, and accessible to the general people. This novel method of vaccine administration has the potential to completely revolutionise the field of vaccination.

REFERENCES

1. Bolarin JA, Oluwatoyosi MA, Orege JI, Ayeni EA, Ibrahim YA, Adeyemi SB, Tiamiyu BB, Gbadegesin LA, Akinyemi TO, Odoh CK, Umeobi HI. Therapeutic drugs for SARS-CoV-2 treatment: Current state and perspective. International Immunopharmacology, 2021 Jan 1; 90: 107228.
2. Rommasi F, Nasiri MJ, Mirsaiedi M. Antiviral drugs proposed for COVID-19: action mechanism and pharmacological data. Eur Rev Med Pharmacol Sci, 2021 Jan 1; 25(11): 4163-73.
3. Nojomi M, Yassin Z, Keyvani H, Makiani MJ, Roham M, Laali A, Dehghan N, Navaei M, Ranjbar M. Effect of Arbidol (Umifenovir) on COVID-19: a randomizedcontrolled trial. BMC infectious diseases, 2020 Dec; 20(1): 1-0.
4. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. International journal of antimicrobial agents, 2020 May 1; 55(5): 105938.
5. Gorshkov K, Chen CZ, Bostwick R, Rasmussen L, Tran BN, Cheng YS, Xu M, Pradhan M, Henderson M, Zhu W, Oh E. The SARS-CoV-2 cytopathic effect is blocked by lysosome alkalizing small molecules. ACS infectious diseases, 2020 Dec 21; 7(6): 1389-408.
6. Shetty R, Ghosh A, Honavar SG, Khamar P, Sethu S. Therapeutic opportunities to manage COVID-19/SARS-CoV-2 infection: Present and future. Indian journal of ophthalmology, 2020 May; 68(5): 693.
7. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the Cytokine Storm'in COVID-19. Journal of infection, 2020 Jun 1; 80(6): 607-13.
8. Takahashi W, Yoneda T, Koba H, Ueda T, Tsuji N, Ogawa H, Asakura H. Potential mechanisms of nafamostat therapy for severe COVID-19 pneumonia with disseminated intravascular coagulation. International Journal of Infectious Diseases, 2021 Jan 1; 102: 529-31.
9. Malin JJ, Suárez I, Priesner V, Fätkenheuer G, Rybniker J. Remdesivir against COVID-19 and other viral diseases. Clinical microbiology reviews, 2020 Oct 14; 34(1): e00162-20.
10. Ali MJ, Hanif M, Haider MA, Ahmed MU, Sundas FN, Hirani A, Khan IA, Anis K, Karim AH. Treatment options for COVID-19: a review. Frontiers in medicine, 2020; 480.
11. Pourkarim F, Pourtaghi- Anvarian S, Rezaee H. Molnupiravir: A new candidate for COVID- 19 treatment. Pharmacology research & perspectives, 2022 Feb; 10(1): e00909.
12. Huang H, Hu PF, Sun LL, Guo YB, Wang Q, Liu ZM, Yin JZ, Shi PM, Yuan ZL, Xie WF. Treatment of patients with Covid-19 with a high dose of ulinastatin. Experimental and Therapeutic Medicine, 2022 Feb 1; 23(2): 1-8.
13. Venditto VJ, Haydar D, Abdel-Latif A, Gensel J, Anstead MI, Pitts MG, CreameansJW, Kopper TJ, Peng C, Feola DJ. Immunomodulatory effects of azithromycin revisited: potential applications to COVID-19. Frontiers in Immunology, 2021; 12: 285.
14. Ahmed MH, Hassan A. Dexamethasone for the treatment of coronavirus disease (COVID-19): a review. SN comprehensive clinical medicine, 2020 Dec; 2(12): 2637-46.
15. Khezri MR, Zolbanin NM, Ghasemnejad-Berenji M, Jafari R. Azithromycin: Immunomodulatory and antiviral properties for SARS-CoV-2 infection. European journal of pharmacology, 2021 Aug 15; 905: 174191.
16. Restricted Use of COVAXIN™ Under Clinical Trial Mode. 2021 Jan. Available from: https: //www.mohfw.gov.in/pdf/Version4PDFCOVAXINImplementationPlan11Jan 2021.pdf
17. Darbar S, Agarwal S, Saha S. COVID19 Vaccine: COVAXIN®-India's First Indigenous Effective Weapon to Fight against Coronavirus (A Review). Parana Journal of Science and Education, 2021; 7(3): 1-9.
18. Das S, Kar SS, Samanta S, Banerjee J, Giri B, Dash SK. Immunogenic and reactogenic efficacy of Covaxin and Covishield: a comparative review. ImmunologicResearch, 2022 Feb 22: 1-27.
19. Ghasemiyeh P, Mohammadi-Samani S, Firouzabadi N, Dehshahri A, Vazin A. A focused review on technologies, mechanisms, safety, and efficacy of available COVID-19 vaccines. International immunopharmacology, 2021 Nov 1; 100: 108162.
20. COVID-19 Vaccine (Vero cell), Inactivated (Brief Edition). [Internet]. 2021. Available from: https: //www. covidvaccine.gov.hk/pdf/CoronaVac_ENG_PI_brief . pdf. (Accessed: 12.07.2021)
21. Shuja SH, Asad D, Parekh AS. Sinopharm! An Unavoidable Contender in the Struggle Against COVID. Infection and Drug Resistance, 2021; 14: 3899.
22. https: //www.fda.gov.ph/wp-content/uploads/2021/08/Product-Information-of-SinoPharm-Covid-19-Vaccine-Covilo.pdf
23. Hadj Hassine I. Covid- 19 vaccines and variants of concern: A review. Reviews in medical virology. 2021: e2313.
24. Ndwandwe D, Wiysonge CS. COVID-19 vaccines. Current Opinion in Immunology, 2021 Aug 1; 71: 111-6.
25. precisionvaccinations.com/vaccines/epivaccorona-vaccine. EpiVacCorona Vaccine. EpiVacCorona (Aurora-CoV) Vaccine Description. Available from:

https: //www.precisionvaccinations.com/vaccines/epivaccorona-vaccine
26. raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker. Covid-19 Vaccine tracker. Jun 2022. Available from: https: //www.raps.org/news-and- articles/news-articles/2020/3/covid-19-vaccine-tracker
27. reuters.com/article. Healthcare & Pharmaceuticals. Jan 2021. Available from: https: //www.reuters.com/article/us-health-coronavirus-russia-vaccine-vec/russias- second-vaccine-100-effective-watchdog-tells-media-idUSKBN29O151.
28. Silveira MM, Moreira GM, Mendonça M. DNA vaccines against COVID-19: Perspectives and challenges. Life sciences, 2021 Feb 15; 267: 118919.
29. Samal KC, Sahoo JP, Yadav NS, Pradhan P. ZyCoV-D: World's First Needle-Free DNA Vaccine's Emergency Approval in India. Biotica Research Today, 2021 Aug 30; 3(8): 714-6.
30. A. Narendranath, V.N. Vamsi Krishna, J. Akhila. A Brief Review on Covid-19 Vaccines. J Cli Pharm Res [Internet]. 2022Jan.31 [cited 2022Mar.4]; : 1-3. Available from: https: //jcpr.in/index.php/journal/article/view/48
31. fda.gov/media. Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020. Available from: https: //www.fda.gov/media/144245/download
32. Lamb YN. BNT162b2 mRNA COVID-19 vaccine: First approval. Drugs, 2021 Mar; 81(4): 495-501.
33. Bhattacharyya P, Das S, Aich S, Sarkar J. COVID-19: morphology and mechanism of the SARS-CoV-2, global outbreak, medication, vaccines and future of the virus. Front Biosci (Elite Ed), 2021 Dec 1: 272-90.
34. fda.gov/media. Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020. Available from: https: //www.fda.gov/media/144434/download.
35. modernatx.com/covid19vaccine-eua/providers. Available from: https: //www.modernatx.com/covid19vaccine-eua/providers/about-vaccine.
36. Sharma K, Koirala A, Nicolopoulos K, Chiu C, Wood N, Britton PN. Vaccines for COVID-19: Where do we stand in 2021?. Paediatric respiratory reviews, 2021 Sep 1; 39: 22-31.
37. Gharate JS, Daitkar SA, Aher KA. APPROVED COVID 19 VACCINES: AREVIEW.
38. fda.gov.ph MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION Gam- COVID-Vac, combined vector vaccine for the prevention of coronaviral infection caused by the SARS-CoV-2 virus Available from: https: //www.fda.gov.ph/wp-content/uploads/2021/03/12.-Proposed-Philippine-package-insert-Instruction- Eng.pdf
39. fda.gov/media. Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum. Feb 2021. Available from: https: //www.fda.gov/media/146338/download.
40. Cook IF. Evidence based route of administration of vaccines. Human vaccines, 2008Jan 1; 4(1): 67-73.
41. ora-vax.com available from: https: //ora-vax.com/
42. precisionvaccinations.com/vaccines/vaxart-covid-19-oral-vaccine. Vaxart Covid-19 Oral Vaccine May2022. Available from: https: //www.precisionvaccinations.com/vaccines/vaxart-covid-19-oral-vaccine
43. Moore AC, Dora EG, Peinovich N, Tucker KP, Lin K, Cortese M, Tucker SN. Pre- clinical studies of a recombinant adenoviral mucosal vaccine to prevent SARS-CoV-2 infection. BioRxiv. 2020 Jan 1.
44. Vaxart, Inc.. Vaxart Announces Positive Preliminary Data from Phase 1 ClinicalTrial Evaluating Its Oral COVID-19 Tablet Vaccine Candidate. Feb 2021. Available from: https: //www.globenewswire.com/en/news-release/2021/02/03/2169091/0/en/Vaxart-Announces-Positive-Preliminary-Data- from-Phase-1-Clinical-Trial-Evaluating-Its-Oral-COVID-19-Tablet-Vaccine- Candidate.html
45. Vaxart's S-Only COVID-19 Vaccine Candidate Produces Strong-Cross Reactive Mucosal and Systemic Immune Responses in Non-Human Primates. Feb 2022. Available from: https: //investors.vaxart.com/node/16766/pdf
46. Gabitzsch E, Safrit JT, Verma M, Rice A, Sieling P, Zakin L, Shin A, Morimoto B, Adisetiyo H, Wong R, Bezawada A. Complete protection of nasal and lung airways against SARS-CoV-2 challenge by antibody plus Th1 dominant N-and S-specific T-cell responses to subcutaneous prime and thermally-stable oral boost bivalent hAd5 vaccination in an NHP study. bioRxiv, 2021 Jan 1: 2020-12.
47. Xu F, Wu S, Yi L, Peng S, Wang F, Si W, Hou L, Zhu T. Safety, mucosal and systemic immunopotency of an aerosolized adenovirus-vectored vaccine against SARS-CoV-2 in rhesus macaques. Emerging microbes & infections, 2022 Dec 31; 11(1): 438-41.
48. Dhama K, Dhawan M, Tiwari R, Emran TB, Mitra S, Rabaan AA, Alhumaid S, Alawi ZA, Al Mutair A. COVID-19 intranasal vaccines: current progress, advantages, prospects, and challenges. Human Vaccines & Immunotherapeutics, 2022 Mar 6: 1- 1.
49. Pawar HA, Pawar AH, Pawar SA, Pawar PA. COVID-19 Vaccines approved for use and under development in India: An overview.
50. Khan Sharun M, Dhama K. Indias role in COVID-19 vaccine diplomacy.
51. Mehta PP, Dhapte-Pawar VS. Novel and Evolving Therapies for COVID-19 Related Pulmonary Complications. The American journal of the medical sciences, 2021 May1; 361(5): 557-66.
52. Shah SS, Patel CM, Patel DH, Vadgama PH, Patel M, Trivedi R. A Review on Modern Use of Intranasal Vaccination in the Treatment of SARS-COV-2. Journal of Drug Delivery and Therapeutics, 2021 Aug 15; 11(4-S): 263-70.

53. Tasker S, Bendel D, Bevan M, Mueller S, Kushnir A, Londt B, Coleman R. 584. Phase 1 Placebo-Controlled Trial of COVI-VAC™, an Intranasal, Live Attenuated COVID-19 Vaccine. InOpen Forum Infectious Diseases, 2021 Nov 1 (Vol. 8, No. Suppl 1, pp. S394-S394).
54. Ye T, Zhong Z, García- Sastre A, Schotsaert M, De Geest BG. Current status of COVID- 19 (pre) clinical vaccine development. Angewandte Chemie International Edition, 2020 Oct 19; 59(43): 18885-97.
55. clinicaltrials.gov Evaluating the Safety, Tolerability, and immunogenicity of bacTRL-Spike Vaccine for Prevention of COVID-19 Apr 2020. Available from: https: //clinicaltrials.gov/ct2/show/NCT04334980
56. prnewswire.com INOVIO Receives U.S. FDA Authorization to Proceed with INNOVATE Phase 3 Segment for its COVID-19 Vaccine Candidate, INO-4800, in the U.S. Nov 2021. Available from: https: //www.prnewswire.com/news-releases/inovio-receives-us-fda-authorization-to-proceed-with-innovate-phase-3- segment-for-its-covid-19-vaccine-candidate-ino-4800-in-the-us-301419117.html
57. Mammen MP, Tebas P, Agnes J, Giffear M, Kraynyak KA, Blackwood E, Amante D, Reuschel EL, Purwar M, Christensen-Quick A, Liu N. Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: a preliminary report of a randomized, blinded, placebo-controlled, Phase 2 clinical trial in adults at high risk of viral exposure. medRxiv. 2021 Jan 1.
58. GURAJALA S. A Sneak Peek into COVID-19 Vaccines-Present Status. Journal of Clinical & Diagnostic Research, 2021 Mar 1; 15(3).