A Review on Approved Vaccines for SARS-CoV-2: Emergency for Fighting the Global Pandemic

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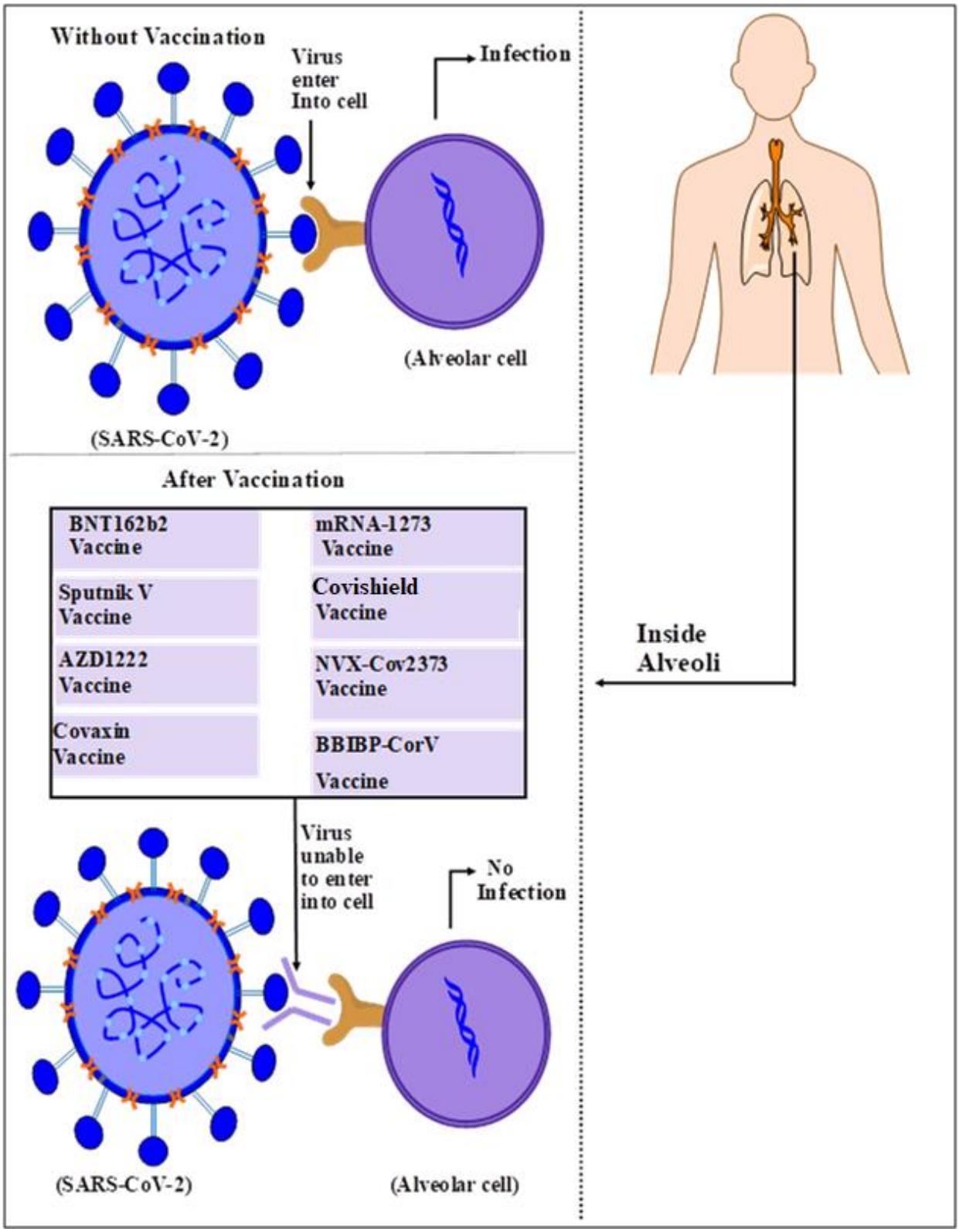
Abstract

To control the COVID-19 pandemic, there is a strong urge for effective and safe vaccines all over the world that triggered global research and development activities to develop a suitable vaccine. Prevention of the disease is possible with an effective vaccine strategy with a successful mass vaccination program. There are rapid efforts made by researchers for the prompt development of an effective and safe vaccine against SARS-CoV-2. The SARA-CoV-2 consists of single-stranded RNA as genetic material and has spike protein (S), an envelope protein (E), membrane glycoprotein (M), and nucleocapsid protein (N) as structural proteins. More than five Pipeline vaccines are under phase III clinical trials. In clinical trials, symptomatic complications are developed in patients after vaccination including fever, chills, headache, muscle pain, joint pain, injection site pain, tenderness as well as Bell's palsy. N501Y is the rapidly mutating variant of SARS-CoV-2 especially in the United Kingdom and South Africa. But BNT162b2 vaccine is a blessing and shows neutralizing capability against SARS-CoV-2 with N501Y spike mutation. Here, we review approved vaccines for SARS-CoV-2, pipeline vaccines to get emergency use approval from regulatory authorities with an ongoing phase III clinical trials, the risk associated with the emergency use of the vaccine, N501Y mutation, and future challenges associated with these vaccines.

Keywords: SARS-CoV-2, alveolar cells, approved vaccines, N501Y mutation, clinical trials, adverse effects, challenges.

Graphical Abstract: Effect of vaccination on SARS- CoV- 2 infection in Alveolar cells.



Educational Aims:

- To understand the design, target, safety, and efficacy of approved SARS-CoV-2 vaccines.
- Examine various vaccines which are in phase III of clinical development.
- Discuss the N501Y mutation in the SARS-CoV-2 virus and its effect on the current pandemic situation.

Future research directions:

- To address the side effect that arises after mass vaccination with approved vaccines.
- Ongoing progress of candidate vaccines against mutated variants of SARS-CoV-2 through preclinical and clinical studies.

1.0 Introduction

To normalize the pandemic situation, which has risen due to SARS-CoV-2, caused an urgency to develop an effective vaccine system. The focused disease primarily transmits via inhalation of respiratory droplets released by the infected person or via asymptomatic carriers, further intensifying the spread of the disease. [1] Till January 15, 2022, a total number of 418,650,474 cases have been confirmed across 220 countries, with 5,856,224 confirmed deaths. [2] Critical populations like elderly patients, patients with immune suppression, and other patients with a history of respiratory and cardiovascular disease are at greater risk apart from patients testing positive for this affliction. These cases become more complicated with the emergence of pneumonia-like conditions and acute respiratory distress syndrome causing fluid to gather in the air sacs of the lungs, and in turn, leading to oxygen deprivation in the body with multiple organ failure and, in some cases, death. [3]

Although the lockdown imposed by the governments of numerous countries for supervision of effective physical distancing and isolation has significantly reduced the spread of disease in the short term, still the scarcity of immunity in the population left them at risk of further waves of infection. The mutated strain of SARS-CoV-2 further accelerates the pandemic in many countries. The absence of effective treatment for SARS-CoV-2 has led to quick action in the development of potential vaccines against the disease. [4] [5]

Since the beginning of the global pandemic, various approaches have been utilized by researchers all over the globe to develop vaccines for COVID-19, using a different type of vaccine platform. These platforms include inactivated, non-Replicating viral vector, protein subunit, RNA, replicating viral vector and DNA platforms so that pre-pandemic normalcy can return to the world. The immediate need for vaccines initiated a prompt response from the international scientific and pharmaceutical communities. This response led to 64 vaccines entering into the clinical evaluation, while 173 vaccines into preclinical evaluation by January 21, 2021(Figure 1). [6]

There are massive side effects associated with these vaccines (as some people believe), due to which suspicious in vaccines has developed in the world with denial and refusal to participate in the vaccination program. The study aims to carry out a review of the literature about various approved vaccines of SARS-CoV-2 for emergency use, pipeline vaccines to get emergency use approval from regulatory authorities with ongoing phase III clinical trial, the risk associated with emergency use of vaccines, N501Y mutation, and future challenges associated with these vaccines.

2.0 Design of approved SARA-CoV-2 Vaccine

The SARA-CoV-2 consists of single-stranded RNA as genetic material and has spike protein (S), an envelope protein (E), membrane glycoprotein (M), and nucleocapsid protein (N) as structural proteins (Figure 2). In the present approved vaccine design, spike protein is the key target because spike proteins enable viral entry into the alveolar cell by ACE 2 receptor. [7-10]

2.1 mRNA-based vaccine

The mRNA vaccine can be manufactured faster and cost-effectively than the conventional protein-based vaccine. [11] Researcher's selected the mRNA that encodes the spike protein of SARS-CoV-2. Spike protein with ACE2 receptor in alveoli form a gateway for virus entry into the human cell [12]. Firstly, RNA is prepared by *in vitro* transcription. [13] mRNA encapsulates lipid nanoparticles, and this layer protects the mRNA and raises a robust immune response (Figure 3). Finally, the vaccine formulation is injectable into the skin or muscle. [14] Once's vaccine enters the cell, it uses the cell translation machinery to produce the viral spike proteins. The spike proteins are recognized as a foreign antigen producing an immune response against it, and antibodies to CD8+ T cells develop in the body against it. In the future, after exposure to the virus, these antibodies will attack the virus, preventing the development of the disease. [15]

2.2 Chimpanzee adenoviral vector-based vaccine (ChAd)

Researchers took the chimpanzee AdV that causes common cold infection for the production of COVID-19 vaccine because 99% of human DNA is similar to these species. Chimpanzee AdV vector has been previously used to control the outbreak of Lassa fever, Nipah, and Middle East respiratory syndrome (MERS). [16] Genetically altered AdV in which genetic material encodes for the spike protein of SARS-CoV-2 is incorporated (Figure 4). Antibodies against the spike proteins produced after vaccination and during a further encounter with COVID 19 protect the body from further encounters. [17]

2.3 AdV serotype 5 vector-based vaccine

Previously, AdV serotype 5 vector were successfully used for the treatment of HIV infection and cancer gene therapy. [18] A piece of mRNA that codes for the SARS-CoV-2 virus are placed inside the non-replicating AdV vector. The vaccine is introduced into the host, and mRNA translates the spike proteins. The body produces antibodies against these spike proteins. On further encounter with the virus, these antibodies prevent the invasion of the virus into the cell by

inhibiting the binding to ACE 2 receptor, which is necessary for entry of the virus into the cell. [19].

2.4 Inactivated vaccine

There are a number of inactivated virus vaccines that are prepared in which infectivity is destroyed in a way by using formalin or β-propiolactone. The immunogenicity should remain in the vaccine. The immunogenicity of inactivated vaccines is enhanced by using adjuvants such as aluminum hydroxide and Algel-IMDG. [4] [20], After vaccination, the person with the vaccine, neutralizing antibodies are produced, which prevent the person from subsequent infection with COVID 19 (Figure 5). Inactivated vaccines require multiple doses of vaccine, as there is a requirement of large amounts of antigen to elicit an adequate antibody response after the primary course of vaccination; further, "booster" doses are required to maintain protective immunity. [21]

2.5 Subunit vaccine

The first gene that encodes for Spike (S) glycoprotein was cloned into baculovirus, and proteins are harvested from a suitable organism, such as Sf9 insect cells. Furthermore, these proteins are used as a vaccine with suitable adjuncts so that a suitable antibody response is elicited in humans and thus neutralizing antibodies are produced (Figure 6). [22] [23]

3.0Approved SARS-CoV-2 Vaccine

3.1 BNT162b2

BNT162b2 vaccine was developed by Pfizer in collaboration with BioNTech and Fosun Pharma. The vaccine is based on an RNA-LNP, which encodes for spike protein. Results of a phase I study suggest that vaccine release dose-dependent neutralizing geometric mean titers, and BNT162b2 are associated with a lower incidence of adverse reactions. [24] [14]. Furthermore, in phase I/II study suggests the strong neutralizing antibody response is produced with activation of CD8+ T cells and cytokines such as IFNγ. [25] Vaccines enter into a phase III studies on April 29, 2020, conducted in the United States, Turkey, South Africa, Germany, and Brazil.[26] On November 20, 2020, Pfizer submitted an Emergency Use Authorization (EUA) application to US FDA and on December 11, 2020 BNT162b2 became the world's first vaccine to get authorization from US FDA for emergency use. [27] The vaccine has to be stored in an ultra-low temperature freezer between -80 to -60 ̊C, and the thawing process is also done at 2 to 8 ̊C. FDA advised patients who are allergic to any ingredient of a vaccine not to take the vaccine. [28] Pfizer's vaccine got emergency use authorization in more than 40 countries worldwide to date. [29]

3.2 mRNA-1273

This vaccine was developed by an American biotechnology company Moderna, a lipid nanoparticle encapsulated mRNA vaccine and encoded for the spike protein of SARS-CoV-2. Dose-dependent production of neutralizing antibodies occurs after two weeks of vaccination, further with a different intra- muscular dose of vaccines such as two 25μg or 100μg and one 250μg, no serious adverse effects were observed in the phase I study. [12] Further, in the Phase II study, two doses of 100μg were found to be appropriate for the prevention of disease. Phase 3 study started on July 27, 2020. [30] On November 30, 2020, Moderna submitted an Emergency Use Authorization (EUA) request to FDA and obtained authorization on December 18, 2020. [31]

mRNA-based vaccines are safe compared to another type of vaccine because it does not cross the cell nucleus, translates only precise proteins, and are expressed transiently. The Vaccine efficacy was 95.6% for subjects 18 to <65 years of age and 86.4% for ≥65 years of age. The vaccine has to be stored frozen between -25 to -15 ℃. [32] [33], Moderna has also received authorization for its COVID-19 vaccine from regulatory authorities in the United States, Canada, Israel, the European Union, and the United Kingdom. [34]

3.3 **Sputnik V (rAd26-S+rAd5-S)**

This vaccine developed by Gamaleya Research has two components, the first is a recombinant AdV type 26 (rAd26) vector, and the second is a recombinant AdV type 5 (rAd5) vector, both containing the gene for spike protein. [35] Phase I/II studies were conducted in Russia suggesting that the vaccine has a better safety profile and produces a strong immune response in participants at both cellular and humoral. [36] The vaccine efficacy is reported to be 100% against severe cases of coronavirus. [37] On September 7, 2020, the vaccine entered into phase III trials in Russian Federation, Belarus, and then in Venezuela. [30] [38] Vaccine got emergency use authorization in Argentina, Bolivia and Serbia, and Algeria. [39] [40]

3.4 AZD1222

AZD1222 were developed by the University of Oxford with AstraZeneca by using a non-Replicating Viral Vector. It is a recombinant protein vaccine along S Trimer. AstraZeneca's vaccine is a simian (ape), replication-deficient antiviral vaccine. [41] In a phase 1/2 study, the vaccine showed a tolerable safety profile, increasing antibody responses with 91% seroconversion rate with humoral and cellular immune response. The vaccine is now in Phase III clinical trials which are conducted in the United States, Peru, Brazil, and Russia. [43] [44], During September all trials are suspended when a participant reports transverse myelitis, but FDA reviewed the safety data again and in October gave permission to restart trials again. [45] In the UK, the vaccine is authorized for emergency on December 30, 2020. The vaccine can be handled and stored at normal refrigerated conditions at 2-8. [46]

3.5 COVAXIN

COVAXIN is a whole-virion inactivated SARS-CoV-2 vaccine formulated with Algel (alum), and Algel-IMDG adjuvant is being developed by Bharat Biotech international limited in collaboration with ICMR. [47] In a phase I study, it was observed that BBV152 is capable of inducing neutralizing antibody responses and was the first inactivated vaccine that induces a Th1-biased response and is well tolerated in all dose groups without any serious adverse reaction. Vaccines can be stored between 2 and 8 ̊C, so there are no requirements for ultra-deep freezers, and mass vaccination can be done easily. [48] Bharat Biotech started the phase III study on November 16, 2020, which is ongoing in several locations in India. [49] On January 03, 2021, Bharat Biotech's COVAXIN attained the emergency Use Authorization approval by DCGI-CDSCO MoH&FW. [49] [50]

3.6 NVX-CoV2373

NVX-CoV2373 is a nanoparticle-based recombinant SARS-CoV-2 vaccine with an adjuvant to intensify the immune response, which is developed by Novavax. [51] Phase 1 trial of the vaccine is conducted in Australia, suggesting that the candidate vaccine is safe, single-dose produce anti-spike IgG antibodies, after second dose wild-type virus-neutralizing antibody responses are produced in all participants. Storage of the vaccine can be done from 2°C to 8°C. Vaccines produce CD4+ T-cell responses that were biased for the Th1 phenotype without any serious adverse effects. [23] After completing the phase 2 study on September 23, 2020 the vaccine entered into a phase 3 study, which is conducted in the United Kingdom, the United States, and Mexico. [52]

3.7 BBIBP-CorV

BBIBP-CorV is being prepared by China-based pharmaceutical group, Sinopharm, and the Beijing Institute of Biological Products. In phase I study, 8 μg dose of vaccine results in earlier seroconversion compared to 2 μg and 4 μg, and further in phase II study, there is 86 percent efficacy against COVID-19 virus with 99% seroconversion rate and the vaccine is found 100% effective in preventing moderate and severe cases of SARS-CoV-2 without any serious adverse effects. [53] [29] On September 2020, the vaccine was authorized by the UAE's Ministry of Health and Prevention (MOHAP) to protect frontline workers from the risk of COVID-19. [54] Ongoing phase III clinical trials are conducted in UAE and Argentina. [55] [35]

3.8 Covishield

Serum Institute of India collaborated with Oxford University and pharmaceutical company Astra Zeneca for making the vaccine. On August 15, 2020, the vaccine is registered for phase three trials in India. Phase III trials are conducted to compare the efficacy of Covishield with the AZ-ChAdOx1 nCoV-19 vaccine. [56] The vaccine is authorized in India for emergency use to prevent SARS-CoV-2. [50]

4.0Pipeline Vaccines with ongoing phase III clinical trial

4.1 Ad5-nCo'V

Ad5-nCo'V is being developed by CanSino Biological Inc and Beijing Institute of Biotechnology using a non-replicating Viral Vector platform containing defective Human AdV Ad5 and the SARS-CoV-2 Spike gene. [57] The phase 1 study suggests that Ad5 vectored vaccine is tolerable in maximum participants, and after 14 days of vaccination, rapid specific T-cells were observed, and peak humoral responses against the virus were observed on day 28 after vaccination. [3] The results of the phase II study suggested that a vaccine at 5 × 1010 viral particles was found to be safe, and after a single dose of vaccine significant immune response was induced in the majority of participants. [58] Phase III Trial of Vaccine started from September 15, 2020, which is conducted in Argentina, Chile, Mexico, Pakistan, followed by trials in several locations in Russian Federation. [59] [60].

4.2 Ad26.COV2.S

Janssen Pharmaceutical Company is on the way to develop a non-replicating viral vector-based vaccine. Phase 1/2a study of the vaccine suggested that a single dose of vaccine produces a safe and moderate immunogenic response with 92% of the candidates having neutralizing antibodies to 5×1010 or 1×1011 viral particles. [71] On September 7, 2020, the vaccine entered into a phase 3 study which is under progress in the United States, Peru, South Africa. [61]

4.3 Recombinant Novel Coronavirus Vaccine (Adjuvanted recombinant protein (RBD-Dimer) expressed in CHO cells)

The vaccine is being developed by Anhui Zhifei Longcom Biopharmaceutical. The company started the phase III study in china from 2020-11-06. [62]

4.4 CoronaVac

CoronaVac is being developed by Sinovac Biotech, which combines a SARS-CoV-2 sample from a patient with an aluminum additive. [57] Phase II study shows that the vaccine induces neutralizing antibodies with a 90% seroconversion rate. The seroconversion rate with the medium-dose vaccine was found to be 98% in elder participants and 97% in healthy adults. The 3 μg suggested dose for efficacy assessment in phase 3 trials. [4] Phase III trials are conducted in Brazil, Turkey, and China. [63] [64]

4.5 Inactivated novel coronavirus pneumonia (COVID-19) (Vero cells) Vaccine

CNBG subsidiary Sinopharm and Wuhan Institute of Biological Products produced the world's first inactivated COVID-19 vaccine. After 28 days of vaccination, antibodies against the virus emerged in all participant's and during phase I and II studies, there were no serious adverse reactions observed, and the neutralizing antibody-positive conversion rate was 100%. (Sinopharm) [53]. From July 26, 2020, the phase 3 study started, currently in ongoing status in UAE, then in Morocco, and lastly in Peru. [65]

4.6 Coronavirus-Like Particle Covid-19 Vaccine

The vaccine is being developed by Medicago, a plant-derived VLP adjuvant with AS03 based vaccine under a phase 3 study from November 19, 2020, in Canada. [38]

5.0 Risk associated with emergency use of SARS- CoV-2 vaccine.

Several ADR has been reported in the initial stage of the vaccine trials. The associated symptomatology with the BNT162b2 mRNA vaccine is fever, chills, headache, muscle pain, joint pain, injection site pain, and tenderness. It was also reported that four participants developed Bell's palsy after receiving the vaccine. [24] The most common symptom in the phase 1 trial of CoronaVac was injection-site pain (17%) and one case of acute hypersensitivity with the manifestation of urticaria. [1]. In phase I and II clinical studies of BBIBP-CorV, the most common adverse reaction was pain with swelling on the injection site, itching, fatigue, inappetence, nausea, constipation, mucocutaneous abnormalities, headache, and muscle pain. Less than 14% of participants of 60 years aged group recipients had mild to moderate abnormal white blood cells, blood urea nitrogen, alanine aminotransferase, blood urea nitrogen, serum total bilirubin, urinary protein. [53]

In the clinical study of the ChAdOx1 nCoV-19 vaccine, myalgia, Injection-site pain, tenderness, fatigue, and headache were observed. [17] Adverse reactions to rAd26 and rAd5 were pain at the injection site, hyperthermia, headache, asthenia, and muscle and joint pain [36]. In the clinical study of recombinant AdV type-5-vectored COVID-19 vaccine: fatigue, fever, injection site pain, and the headache were the major adverse effects that were pronounced. [3]

6.0N501Y mutation

In the United Kingdom and South Africa, the rapid spread of SARS-CoV-2 variants with N501Y spike mutation was prominent. N501Y mutation was responsible for the more formed binding of spike proteins to the ACE-2 receptor. These variants have multiple mutations in their spike glycoproteins, which are the main targets of virus-neutralizing antibodies. [5] [66]. The BNT162b2 vaccine was a blessing and showed neutralizing capability against SARS-CoV-2 with N501Y spike mutation. [67]

7.0Future challenge

There is a need for high-tech research laboratories and infrastructure for developing vaccine, which is challenging for developing countries. Some developing countries are unable to buy developed vaccines due to financial drawbacks. Furthermore, if these countries buy these vaccines from developed countries, there is also a need for effective mass vaccination, a difficult task. Infrastructure to store vaccines is another hurdle because vaccine-like Pfizer's required to store in an ultra-low temperature freezer between -80ºC to -60ºC, while that process is also done at 2 ºC to 8 ºC. Vaccines are associated with adverse effects, some of them were investigated during the clinical study, whereas some of them appear after mass vaccination because the phase

III study is not completed by most of the vaccines, and they had taken the emergency use authorization from regularity authorities. [67] [28] The mutated variant of SARS-CoV-2 has a high spreading rate, and the effectiveness of this vaccine is yet to be assured after clinical studies. [5] [66]

8.0 Conclusion

This review focuses on various advancements that occurred in the safe and effective development of the COVID-19 vaccine, normalizing the current pandemic situation. Currently, eight vaccines are approved for emergency use preventing SARS-CoV-2, with considerable vaccines in the pipeline for approval by regulatory bodies (Table 1). Effective global vaccination drives are the possible solution to cope with the COVID-19. The effect of rapid mutations in SARS-CoV-2 has already accelerated the pandemic worldwide several times. Another key point that we must understand is that vaccination alone is not the solution, and we people have to mend our ways by maintaining proper protocols for eradication. Unless these points are not assessed, the normalization of life to pre-COVID-19 times is impossible.

Abbreviation's

SARS-CoV 2 - Sevare acute respiratory syndrome, coronavirus 2

COVID - Coronavirus disease

ACE 2 – Angiotensin converting enzyme 2

EUA - Emergency Use Authorization

MERS-Middle East respiratory syndrome (MERS)

MoH&FW - Ministry of health and family welfare

DNA - Deoxyribonucleic acid

SARS-CoV-2 - Severe acute respiratory syndrome, coronavirus2

ACE-2 - Angiotensin-converting Enzyme 2

rAD26 - Recombinant AdV 26

rAD5 - Recombinant AdV 5

VLP - Virus like particle

Ad - AdV

mRNA - Messenger Ribonucleic Acid

EUA - Emergency Use Authorization

USFDA - United state- Food and Drug Administration

IFN_{Υ} - Interferon Gamma

RNA-LNP- Ribonucleic acid Lipid Nanoparticles

Algel-IMDG - Aluminium hydroxide-Imidazoquinoline

ChAD - Chimpanzee AdV

RNA - Ribonucleic acid

Consent for Publication
All authors have given their consent to publish this work.

Conflict of Interest
There is no conflict of interest with respect to the content of this article.

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Table 1 Characteristics of Approved Vaccine of SARS-CoV-2 for emergency use

Vaccine	Efficacy	No of Participants	Storage (−℃)	Reference
BNT16b2	95%	44,000	80- 60	[67] [28]
mRNA-1273	94.1%	30,000	25-15	[32] [49]
Sputnik V	91.4%	22 714	2-8	[37] [68]
AZD 1222	70.4%	11,636	2-8	[46] [69]
BBIBP-CovrV	70%	60,000	2-8	[70]
COVAXIN	-	26,000	2-8	[48] [49]
NVX-CoV2373	-	30,000	2-8	[23] [71]
Covishield	-	1600	2-8	[56]

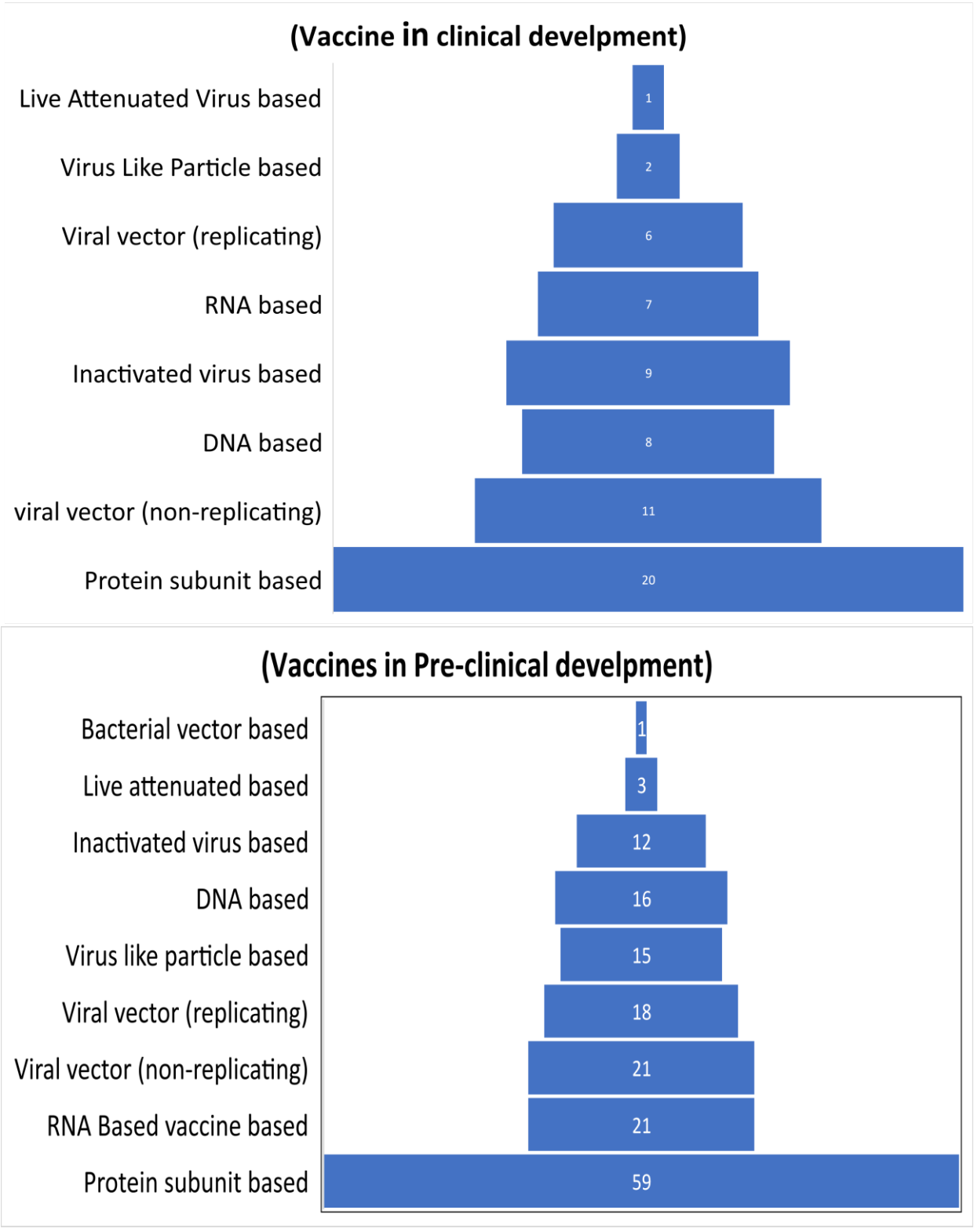

Figure 1 Types of vaccines in clinical and pre-clinical development phase

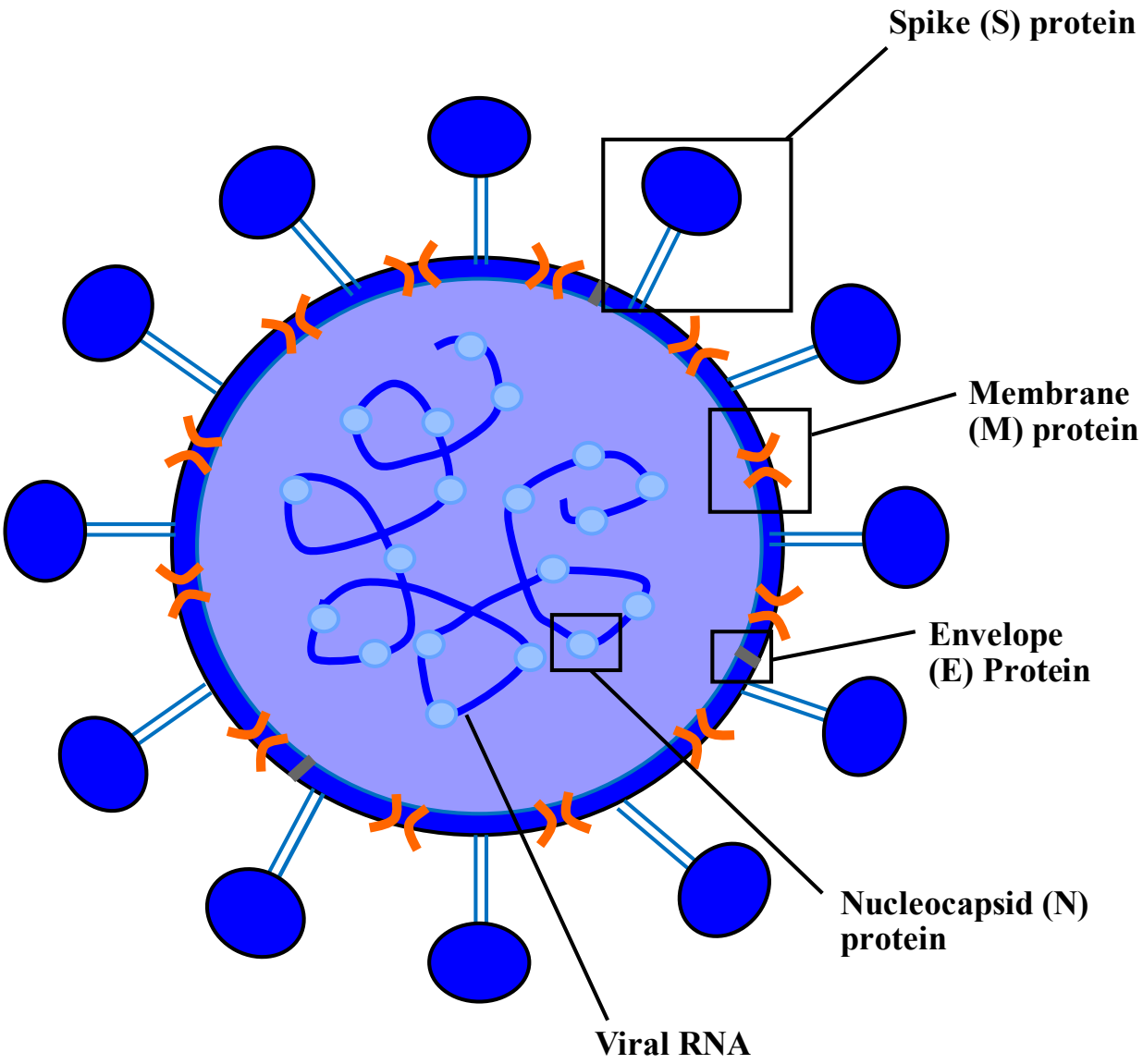

Figure 2 Schematic diagram of SARS-CoV-2 virus structure [9]

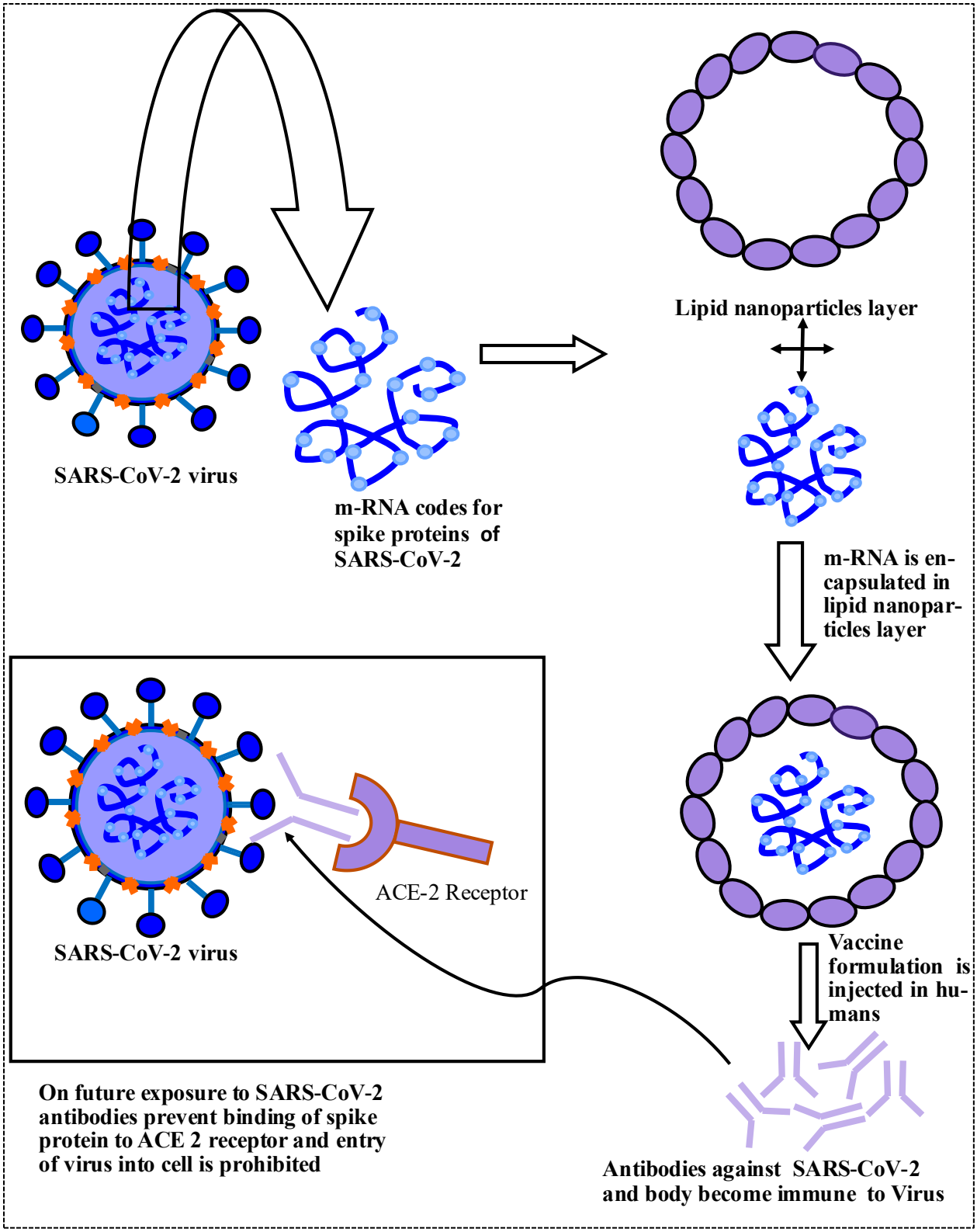

Figure 3 Design of m-RNA based vaccines

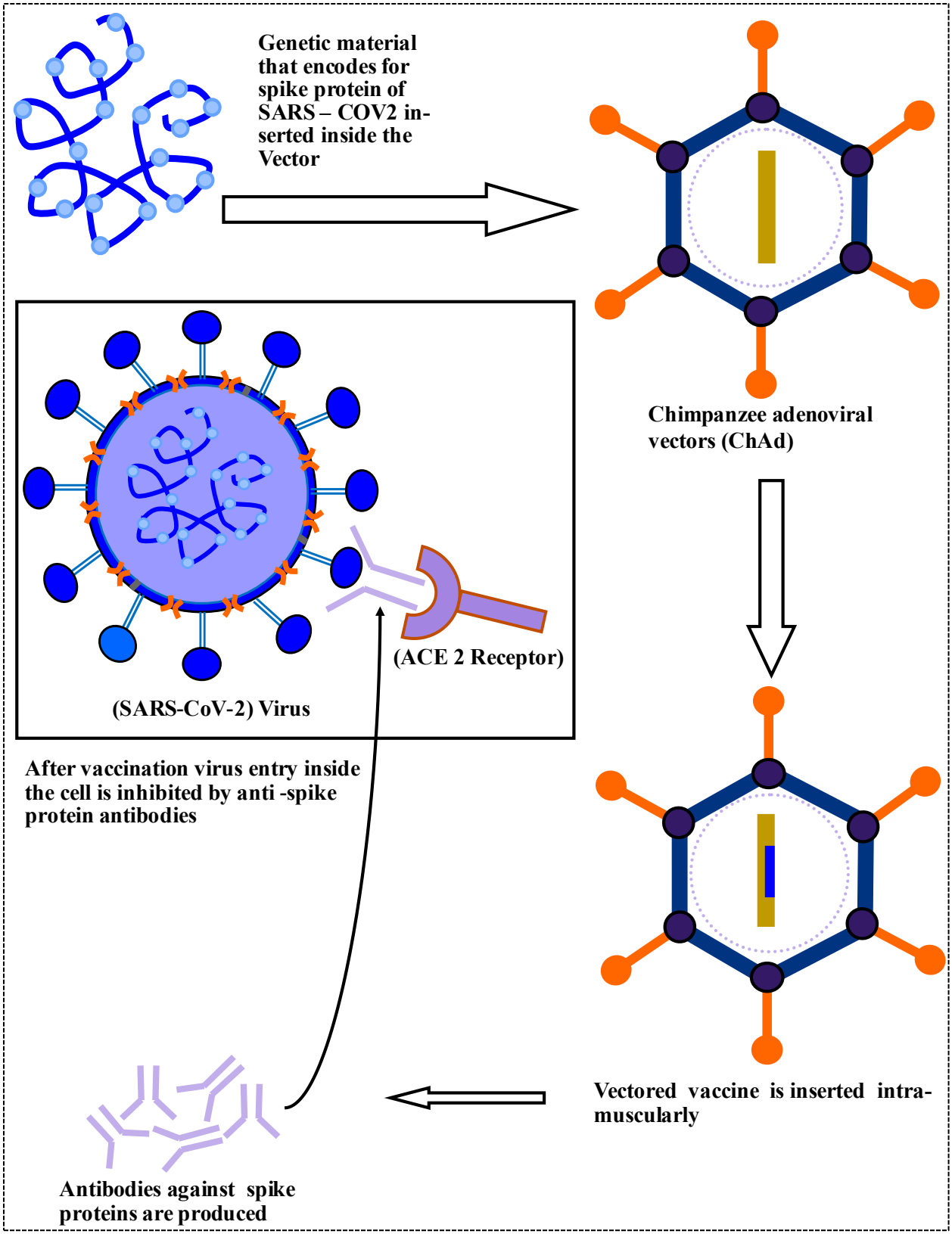

Figure 4 Design of chimpanzee adenoviral vector-based vaccines

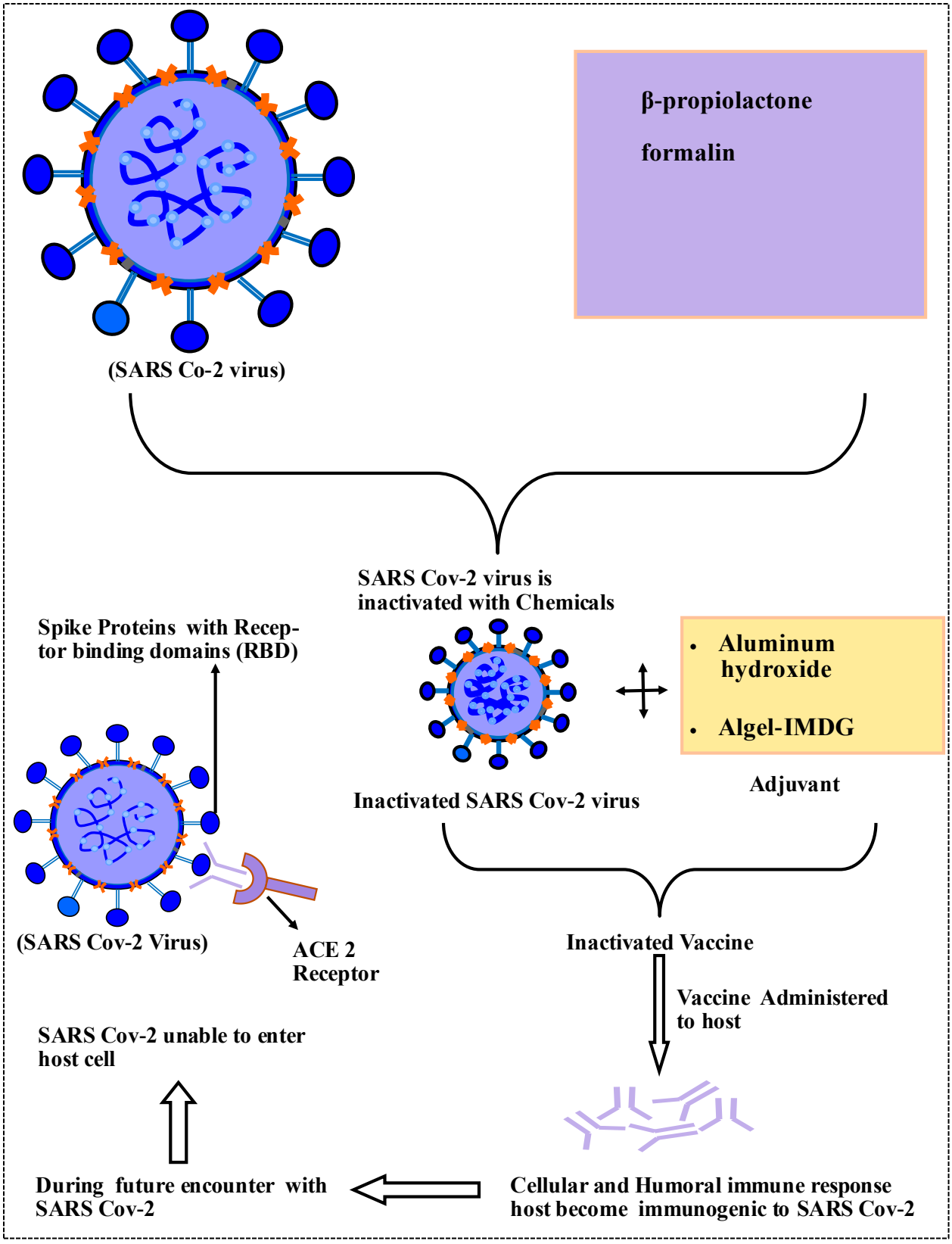

Figure 5 Design of inactivated vaccines

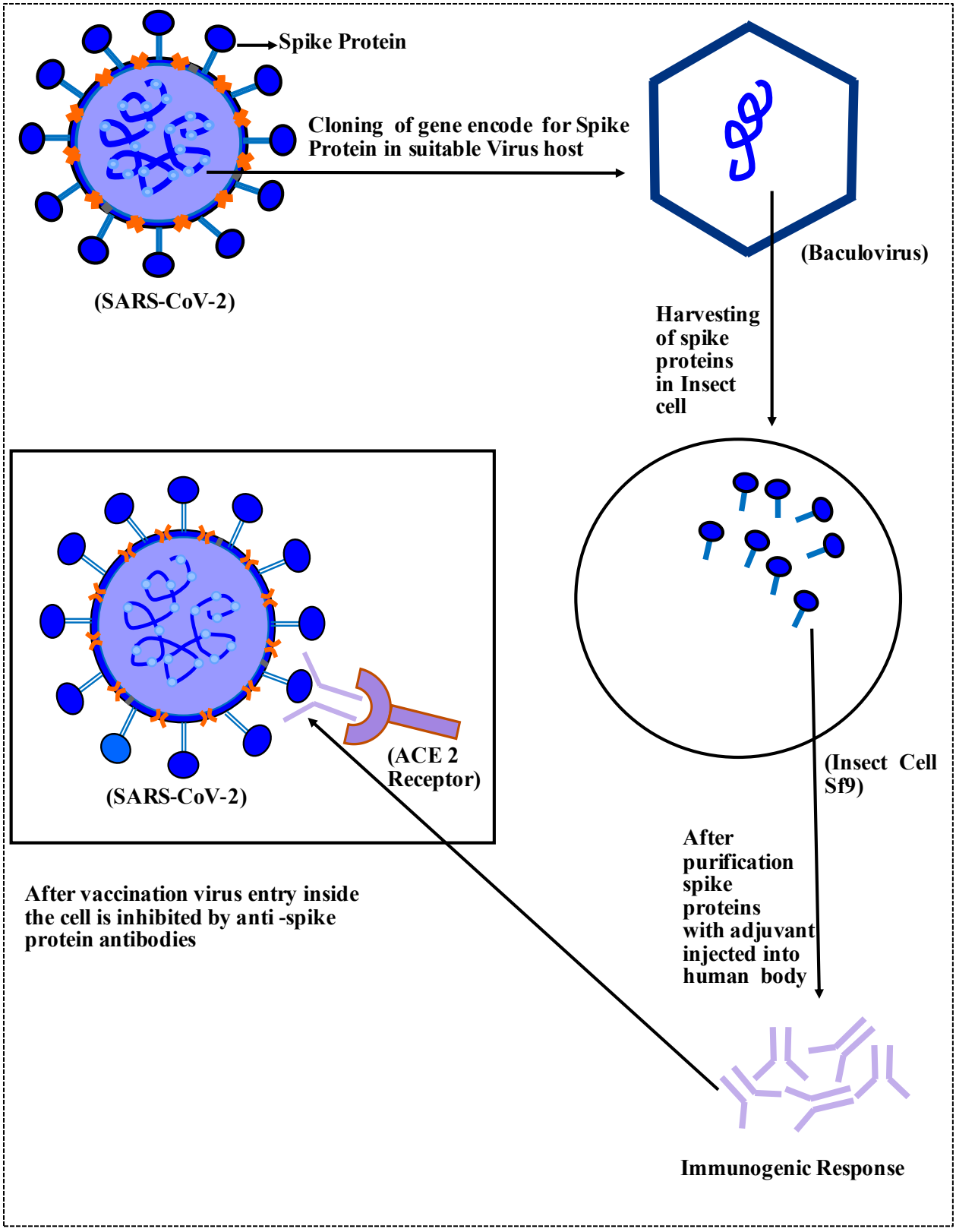

Figure 6 Design of subunit-based vaccines