

## Covid-19 and Its Vaccine Development: A Narrative Review

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### Abstrak

COVID-19 merupakan penyakit saluran pernapasan yang ditetapkan sebagai pandemi pada Maret 2020 dan disebabkan oleh severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Tingginya penyebaran COVID-19 di seluruh dunia menyebabkan pengembangan vaksin mendesak untuk dilakukan. Oleh karena itu, review ini bertujuan untuk mengkaji tentang COVID-19 dan tantangannya dalam pengembangan vaksin serta mengkaji keamanan, efektivitas, dan immunogenisitas dari platform vaksin-vaksin yang telah mendapatkan izin penggunaan di beberapa negara. Berdasarkan pengalaman infeksi yang pernah terjadi di dunia, vaksin mampu mencegah penyebaran penyakit-penyakit infeksi dan menyelamatkan 23,3 juta nyawa. Terdapat beberapa tantangan yang dihadapi dalam pengembangan vaksin untuk COVID-19, diantaranya mudahnya SARS-CoV-2 bermutasi dan potensi terjadinya antibody-dependent enhancement (ADE) setelah vaksinansi. Berbagai macam platform digunakan dalam perkembangan vaksin COVID-19, baik platform teknologi tradisional (inactivated dan live-attenuated vaccine) maupun teknologi baru (viral vector, protein subunit, dan nucleic acid vaccine). Untuk mencegah penyebaran infeksi SARS-CoV-2, terdapat 10 vaksin yang telah mendapatkan izin penggunaan darurat di beberapa negara. Platform yang digunakan antara lain vaksin mRNA, vektor virus, terinaktivasi, dan vaksin peptida. Vaksin-vaksin tersebut dilaporkan efektif, aman dan dapat ditoleransi dengan baik oleh partisipan dengan derajat efek samping yang timbul adalah ringan hingga sedang. Meskipun kejadian ADE tidak ditemukan dalam semua vaksin tersebut, monitoring terhadap kejadian tersebut harus dilakukan karena berdasar pada pengalaman penggunaan platform inactivated vaccine SARS-CoV sebelumnya, diketahui dapat menimbulkan vaccine-associated enhanced respiratory diseases (VAERD).

**Keywords:** COVID-19, SARS-CoV-2, antibody-dependent enhancement (ADE), mutasi, platform vaksin

### Abstract

COVID-19 is a respiratory disease determined as a pandemic in March 2020 and it's caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The high spread of COVID-19 worldwide

lead to vaccine development urgently needed. Therefore, this review aims to examine COVID-19 and its challenges in vaccine development as well as review the safety, effectiveness, and immunogenicity of vaccine platforms that have obtained emergency use authorization (EUA) in several countries. Based on the experience of infections that have occurred in the world, vaccines can prevent the spread of infectious diseases and save 23.3 million lives. There are several challenges faced in vaccine development for COVID-19, including SARS-CoV-2 mutations and the potential for antibody-dependent enhancement (ADE) after vaccination. Various platforms are used in the development of the COVID-19 vaccine, both traditional technology platforms (inactivated and live-attenuated vaccine) and novel technologies (viral vector, protein subunit, and nucleic acid vaccine). To prevent the spread of SARS-CoV-2 infection, 10 vaccines have obtained EUA in several countries. Platforms used include mRNA vaccines, viral vectors, inactivated, and peptide vaccines. The vaccines were reported to be effective, safe, and well-tolerated by participants with mild to moderate adverse events. Although the ADE phenomenon is not found in all of these vaccines, monitoring should always be done, because previous experience shows that the SARS-CoV inactivated vaccine platform, may cause vaccine-related enhanced respiratory disease (VAERD).

**Keywords:** COVID-19, SARS-CoV-2, antibody-dependent enhancement (ADE), mutation, vaccine platforms

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## 1 Introduction

In December 2019, the first case of COVID-19 infection was reported by the Wuhan government in China which was originally known as 'viral pneumonia of unknown cause'. Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 has a high degree of spread and severity, thus in March COVID-19 infection was designated as a pandemic by who [1]. In January 2021, Indonesia has a higher mortality rate of 2.9% than a global mortality rate of 2.2%. In Indonesia, the first case of COVID-19 infection occurred in early March 2020 [2].

There is no safe and effective pharmaceutical therapy for COVID-19, thus the development of vaccines to prevent the spread of infection is urgently needed. Studies by Lee et al. show that vaccination can prevent the deaths of 23.3 million people from some infectious diseases [3]. Several outbreaks that have occurred including Zika virus infection, Ebola, HIV, influenza (H5N1, H1N1 dm09, H10N8), SARS, and Middle East Respiratory Syndrome (MERS) encourage the development of the vaccine. Most vaccines are developed using

vaccine technology based on viral vectors and nucleic acids[4].

SARS-CoV-2 is betacoronavirus that is a single strain RNA virus, which has a high prevalence of mutating and adapting to new hosts or environments, thus the immunogenic properties and severity of symptoms that appear, become unpredictable [5]. Its characteristics of SARS-CoV-2 are one of the challenges that should be considered in developing the COVID-19 vaccine. There are 10 vaccines with different platforms (mRNA vaccine, VVnr, IV, PS) that have obtained EUA in several countries. Each vaccine technology has its challenges in the development process. Vaccines that are prioritized as candidates for the COVID-19 vaccine by WHO should meet aspects of safety, effectiveness, stability, implementation of vaccines related to regulated regimens and applicable product profiles, and availability aspects so that they can be produced in large quantities [6]. Therefore, the purpose of this article is to review COVID-19 and challenges in vaccine development and to review the safety, effectiveness, and immunogenicity of vaccine platforms that have obtained EUA in several countries.

## 2 Characteristics of SARS-CoV-2 in the Coronavirus Group

Coronavirus (CoV) is a zoonotic pathogen. SARS-CoV, MERS-CoV, and SARS-CoV-2 are bat origin, but in MERS-CoV, hosts of reservoirs (bat) transmit it to humans through camel dromedaries [7]–[10]. Genome sequence analysis shows that SARS-CoV-2 has a closer similarity to SARS-CoV than MERS-CoV which is 79.6% and 50% respectively [7], [11], [12]. Due to these genetic similarities, SARS-CoV-2 is included in the genus Betacoronavirus that is characterized by an enveloped virus and has a single strand RNA positive sense [13]. Until 2019, there are 7 CoVs infecting humans, including 2  $\alpha$ CoV (HCoV-229E & HKU-NL63) and 5  $\beta$ CoV (HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and most recently is SARS-CoV-2) [14].

Among all CoVs, SARS-CoV, SARS-CoV-2, and MERS-CoV are the most pathogenic strains that may lead to life-threatening respiratory infections and caused the biggest global outbreak [15]. Among the three strains above, The spread of SARS-CoV-2 is the fastest, because of Spike (S) protein structure differences which SARS-CoV-2 has extra nucleotides. It is a furin-like cleavage site that facilitates S protein and can increase the efficiency of SARS-CoV-2 spread compared to other betacoronaviruses [16], [17]. Despite the spread of SARS-CoV-2 is faster than SARS-CoV and MERS-CoV, the fatality rate of SARS-CoV-2 outbreaks is the least (2.08%) compared to SARS-CoV (10.87%) and MERS-CoV (34.77%) [18]–[20].

## 3 Important Proteins of SARS-CoV-2 as Antigen in Vaccine Development

The CoV structure is a spherical and crown-like shape. Among the RNA viruses, CoV has the largest RNA genome, which is about 27 to 32 kb [21]. SARS-CoV-2 has a long polyprotein ORF1ab at the end of 5' which encodes 15 or 16 non-structural proteins, and the end of 3' of the genome encodes 4 major structural proteins including spike protein (S), nucleocapsid protein (N), membrane protein (M), and envelope protein (E) [22]. S protein contains two subunits that are S1 and S2. The S1 subunit includes the N-terminal domain (NTD)

and the receptor-binding domain (RBD) located within the C-terminal domain (CTD). The S2 subunit contains important basic elements for membrane fusion, called a fusion peptide (FP), two 7-peptide repeats (HR), a membrane-proximal external region (MPER), and a transmembrane domain (TM) [23].

S protein is a part of the surface of the virus that is recognized by the host immune system as an antigen and interacts with the host cell through ACE2 receptor binding mediating the entry of the virus, to infect the host cell. Therefore, the protein S becomes a very promising antigen in the formulation of vaccines for COVID-19 [24], [25]. S protein fragments that are potential as antigen include full-length S protein (to maintain protein conformation and provide more epitope for higher immunogenicity), RBD domain, NTD, S1, and FP subunit [22]. N protein is involved in nucleocapsid formation, signal transduction of viral development, RNA replication, and mRNA transcription [26]. M protein is a transmembrane glycoprotein on the SARS-CoV-2 surface and is involved in virus assembly [27]. Protein E allows the virus to escape from the host immune system. In developing the COVID-19 vaccines, among the structural proteins, S, N, and M proteins have a good antigenicity, thus they may induce host immune response [22], [28]–[31], while the E protein is not suitable as an antigen because its immunogenicity depends on the activity of ion channels that can differ in each CoV [22], [32].

## 4 Genomic Variations of SARS-CoV-2: Challenges in Vaccine Development

SARS-CoV-2 is an RNA virus that mutates easily, resulting in a lot of viral genome variations. They have spread throughout the world causing specific etiological effects in each geographic area. There are at least three clades based on geography and genomic specificity i.e. the G (GH & GR), S, and V clades. The S protein mutation named D614G (aspartate [D] to glycine [G] in protein 614), which is commonly found in Europe [33]–[35] and likewise in Indonesia [36], originated from clade G. In the D614G mutation there is a replacement of large aspartic acid residues with small hydrophobic G residues [37], while mutations in RBD there are

changes in the antigenic epitope of positively charged amino acids to uncharged (R→I, H→Q), and negatively charged amino acids to uncharged (D→N, D→G, D→Y) [38]. Differences in size and charge can loosen the binding affinity of antibodies to spike proteins [37] and can affect the tertiary structure of the protein [39] so that the virus can escape from the host immune system [39]–[41] as a result of increased virulence [39], [42], [43].

The vaccine that uses glycoproteins as a target, requires some adjustment [37]. These adjustments have been occurring for seasonal flu vaccines that continue to mutate each year. However SARS-CoV-2 does not mutate as quickly as the flu virus, and the result of the clinical trial showed that the COVID-19 vaccine used a platform that could be easily adjusted was effective. Besides, vaccines produce antibodies against many areas of the spike protein, thus it is impossible if only a change can make the vaccine less effective [44]. A study by McAuley et al. showed that the D614G mutation had a slight effect on the vaccine neutralization efficiency and a log of neutralizing antibodies did not significantly differ against two different mutants (G614 and D614G variants) [45]. A study by Dearlove et al. found that the diversity of the SARS-CoV-2 genome is limited and there is no evidence showed that mutations can affect bonds in ACE2 receptors. It is due to the spread of SARS-CoV-2 is faster than its evolution, thus the virus population becomes more homogeneous. Therefore, the limited diversity of SARS-CoV-2 should not obstruct the development of vaccines [46].

If the D614G mutation affects the sensitivity of antibodies, it can result in an antibody-dependent enhancement (ADE) phenomenon. ADE enables viruses to enter the host cells for replication and escape from the host immune system, thus an individual is more likely to encounter worsen disease and re-infection [41]. ADE is a phenomenon that produces interactions between the complex of antibody-viruses with Fcγ receptors (FcγR) and/or complements in host cells. It leads to viral fusion and viral entry to immune cells (monocytes, B cells, and macrophages) even though they do not have ACE-2 receptors,

consequently increasing virus formation and lowering viral clearance [47], as well as producing pro-inflammatory cytokines such as IL-6, TNFα, IL-10 which can trigger cytokine storms [48]–[51]. Importantly, SARS-CoV-2 does not show productively infecting macrophages [48], [52]. The potential risk of ADE increases with mutations in the Spike Glycoprotein of SARS-CoV-2, which weakens the host antibody response [53]. Cases of ADE enhanced by the vaccine have been reported after vaccination with a formalin-inactivated vaccine against the respiratory syncytial virus (RSV), measles virus, dengue virus [54]–[56]. Modification of Fc area in antibodies, e.g. mutant F241A, not only removes the bond against FcγR but also produces antibodies with a stronger endogenous immune response through the efficiency of the CD23 uptake and stronger immunogen formations [57].

In December 2020, the United Kingdom (UK) reported a new SARS-Cov-2 variant. It called SARS-CoV-2 VOC 202012/01 (Variant of Concern, 2020, month 12, variant 01) derived from 20B/GR clade and contains a combination of the N501Y mutation (substitution of amino acid asparagine to tyrosine at position 501 in the S gene virus) and mutation 69-70del (deletion of 6 bases encoded histidine and valine at position 69 and 70 in the S gene virus) both of which had been circulating, separately, freely and globally over the previous few months [58], [59]. Based on preliminary epidemiological, modeling, phylogenetic studies and clinical findings showed that SARS-CoV-2 VOC 202012/01 may increase transmission, but there is no change in the severity of disease or the incidence of re-infection between the new variant cases compared to other SARS-CoV-2 viruses circulating in the UK [60]. In South Africa, a new variant of SARS-CoV-2 was found called 501Y. V2. It is also related to the mutation N501Y. The new variant quickly replaced the other derivatives that currently circulating in South Africa. An ongoing study was conducted to find out if the variant affects the vaccine effectivity by investigating the neutralization activity of antibodies from the serum of patients who have been cured and vaccinated against the new variant virus [61].

Table 1 List of COVID-19 Vaccines that Have Had Emergency Use Authorization

Name of Vaccine	Vaccine Type	Primary Developers	Country of Origin	Status (Authorization/Approval)
Comirnaty (also known as Tozinameran or BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech	Multi-national	Early, Limited/ Emergency Use: UK, US, Argentina, Chile, Costa Rica, Ecuador, Kuwait, Mexico, Panama, Singapore, EU Full Approval: Bahrain, Canada, Oman, Saudi Arabia, Switzerland
mRNA-1273	mRNA-based vaccine	Moderna	US	Early, Limited/ Emergency Use: US, Israel, Canada
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	China
No name announced	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	Limited use in China, United Arab Emirates
Sputnik V	Non-replicating viral vector	Gamaleya Research Institute; Acellena Contract Drug Research and Development	Russia	Early, Limited/ Emergency Use: Russia, Belarus, Argentina
BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	Early, Limited/ Emergency Use: Egypt Full Approval: China, United Arab Emirates, Bahrain
EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	Early use in Russia
ChAdOx1/AZD1222 (also known as Covishield in India)	Viral vector	University of Oxford; AstraZeneca	UK	Early, Limited/ Emergency Use: Britain, India, Argentina
Convidecia (also known as Ad5-nCoV)	Viral vector	CanSinoBIO	China	Limited Use in China
Covaxin (also known as BBV152 A, B, C)	Inactivated vaccine	Indian Council of Medical Research; National Institute of Virology; Bharat Biotech	India	Emergency use in India

## 5 Safety, Immunogenicity, and Efficacy of Emergency Use Authorized (EUA) Covid-19 Vaccine

In January 2021, WHO noted that there are 64 vaccine candidates in clinical trials and 173 are in preclinical development. Platforms used include protein subunits (PS), viral vector replicating/non-replicating (VVR/nr) either without or with an antigen-presenting cell (APC), nucleic acid-based (DNA or RNA), inactivated virus (IV), virus-like particle (VLP), and live attenuated virus (LAV). Whereas 10 COVID-19 vaccines already had EUA from several countries. The vaccine platforms used by the 10 COVID-19 are two mRNA-based vaccines, four inactivated vaccines, three viral vector vaccines, dan one peptide vaccine.

### 5.1 Nucleic Acid-Based Vaccine (mRNA Vaccine)

There are two types of the nucleic acid-based vaccine including DNA and mRNA vaccines. The mRNA vaccine works by delivering mRNA that encodes the antigen into the ribosome to produce viral antigens that will be expressed on the surface of the host cell, thus it will induce host-specific immune responses. mRNA is an intermediate molecule between DNA and protein [62]–[65]. The mRNA vaccine is a new promising platform that has advantages including multifunction, safe, effective, practical, scalable, inexpensive, and has the potential to be free of cold chains [65]–[67]. Multifunctional is the most important advantage for vaccine development in this pandemic period because it is related to the promptness in producing effective vaccines and the inexpensive cost of developing vaccines [68], [69].

BNT162b2 developed by Pfizer (New York, USA) together with BioNTech (Germany) and mRNA-1273 developed by Moderna (Boston, USA) are mRNA-based vaccines that have obtained EUA in several countries around the world. In November 2020, for the first time in the world, BNT162b2 published the results of phase 3 clinical trial which explained that two doses of the 30µg vaccine administered 21 days apart were safe and provided short-term protection of 95% (95% CI, 90.3-97.6%;  $P < 0.001$ ) against symptomatic COVID-19 in  $\geq 16$  years old of participants [70]. Strong humoral immune (neutralizing antibodies titer) and cellular (CD8+ and Th1 CD4+ T cells) responses occur at the second dose of the vaccine. Geometric mean titers (GMTs) neutralization inflicted on both older and younger adults has exceeded the GMT of the convalescent human panel, although the neutralization response is lower in older adults than younger adults [71], [72].

Phase 3 clinical trial results of the mRNA-1273 vaccine showed that two doses of 100 µg administered 28 days apart were safe and had an effectiveness of 94% (95% CI, 89.3–96.8%;  $P < 0.001$ ) against symptomatic COVID-19 in  $\geq 18$  years old of participants [73]. Although the GMT of IgG antibody to S-2P antigens binding increases rapidly after the first dose, the GMT value remains equal with the serum convalescent specimen. GMT of vaccine exceeds GMT of convalescent serum specimen at the second dose. Strong cellular immune response increase at the second dose, in which the response of CD4+ T cells biased by Th1 cytokine expression ( $TNF \alpha > IL-2 > INF \gamma$ ) is stronger than Th2 cytokine expression (IL-4 and IL-13). While at the second dose, CD8+ T cell response to S-2P was detected at low levels [74].

There were one in 10 severe cases of COVID-19 after the first dose of BNT162b2 that was associated with vaccine-mediated disease enhancement theory [75]. Both vaccines BNT162b2 and mRNA-1273 have similar safety profiles. Participants who receive the vaccine experience mild to moderate local reactions (pain, erythema, swelling) and systemic reactions (headache, fatigue, myalgia) that could be resolved in 1-3 days. Such local and systemic reactions are most common in younger adults (16 - <65 years old) and at the second dose of vaccine. In both mRNA vaccines, an

interesting finding occurred, that is bell's palsy. We should be cautious for the possibility that it was not coincidental and required close monitoring. The protection duration of vaccines remains not known, but to ensure it, the long-term safety observation is planned for 2 years after the second dose of the vaccines. It is not yet known the efficacy and safety of vaccines in children, adolescents, and pregnant women populations [70], [73].

## 5.2 Inactivated Virus (IV) Vaccine

Inactivated vaccines use whole parts of the viral particle then it is killed by radiation or chemicals. This type of vaccine can induce a strong immune response and has various epitopes on the surface of the virus [76]. Previously, the inactivated SARS-CoV vaccine was able to induce the production of high-level neutralizing antibodies in animal models, including antibodies against the S, N, and M proteins of the virus [77]–[79]. However, historically, compared to the inactivated vaccine, live attenuated vaccine is more capable to provide effective protection against viral infections and diseases, due to its ability to replicate [80].

CoronaVac (Sinovac, China), Covaxin/BBV152 (Bharat Biotech, India), BBIBP-CorV (Sinopharm, China), and an anonymous vaccine (Wuhan Institute of Biological Products & Sinopharm, China), are inactivated vaccines that have obtained EUA for COVID-19 in several countries. In their clinical trials, BBIBP-CorV involved two age groups of 18-59 and  $\geq 60$  years old, CoronaVac, and an anonymous vaccine from Sinopharm involved the aged group of 18-59 years old and Covaxin involved the aged group of 18-55 years old. The vaccines were using prime-boost regimen doses via the intramuscular route. The doses and intervals of administration used by the four inactivated vaccines were CoronaVac (3 µg in 14/28 days apart), Covaxin (6 µg in 14 days apart), BBIBP-CorV (4/8 µg in 14/21/28 days apart), anonymous Sinopharm vaccine (5 µg in 14/21 days apart). The Neutralizing antibodies at a single dose were lower than two doses of the vaccine as well as longer administration intervals (21 and 28 days apart) had stronger, persistent and longer antibody response than short administration intervals (14 days apart) [81]–[84].



Based on phase 2 clinical trials, humoral immune responses (neutralizing antibodies) of CoronaVac increase on day 28 (after the second dose), however, the GMT (23.8-65.4) was lower than the GMT (163.7) of convalescent serum patients. Nevertheless, CoronaVac was considered to be effective for three reasons, first, the enterovirus 71 and varicella vaccines were previously effective with a range of neutralizing antibodies titer of 8-24 [85], [86], second, the preclinical trial showed that 1/24 of the neutralizing antibodies appeared in the macaque model provided complete protection against SARS-CoV-2 [87], third, previous SARS and MERS vaccine studies in which the antibody response against natural infections decreased over time [88]–[90], however, re-infection rarely reported [91]–[93], it can be concluded that antibody levels are not the key to COVID-19 vaccine success, but rather building a recallable memory immune response against SARS-CoV-2 [84]. BBIBP-CorV clinical trials showed the older adult had a longer seroconversion time (day 28) and lower magnitude of neutralizing antibodies than younger adults which was the seroconversion already appeared on day 14. Neutralizing antibodies stimulated by BBIBP-CorV could neutralize various strains of SARS-CoV-2, thus it could provide cross-protection against other SARS-CoV-2 strains [83]. In the study of the Sinopharm's anonymous vaccine, no cytokines that related to Th2 cells (IL-4, IL-5, IL-10) were found in the vaccine group or alum group only (placebo). Its observation was conducted because the previous vaccines that use alum as adjuvant were instead inducing a Th2-biased cell response associated with vaccine-associated enhanced respiratory diseases (VAERD) [81]. Different from CoronaVac and BBIBP-CorV which did not report a cellular immune response, Covaxin reported a significant increase in the Th1-biased response characterized by an increase in the number of CD4<sup>+</sup> INF- $\gamma$ <sup>+</sup> T cells. The cellular immune response is related to the use of Algel-IMDG in Covaxin formulations [82].

Generally, the COVID-19 inactivated vaccines have a lighter safety profile than other vaccine platforms. All clinical trials of inactivated vaccines have mild to moderate adverse events. The most common adverse events are injection area pain and fever [81]–[84]. An inactivated vaccine that uses Algel

(alum) as an adjuvant may form Th2-biased cells and strong humoral responses [94]. It can increase the side effect of eosinophilic pro-inflammatory pulmonary response which previously occurred in SARS-CoV inactivated vaccines [95]–[97]. This side effect can be attributed to the ADE phenomenon. Therefore, it is necessary to develop a SARS-CoV-2 vaccine that can induce Th1 CD4<sup>+</sup> response with minimal Th2 response [47], [98], [99].

### 5.3 Viral Vector (Vv) Vaccine

Viral vector vaccines use live recombinant viruses to deliver DNA into human cells. DNA strands are loaded into viral vectors that encode one or more antigens. The antigens carried is expressed on the surface of the host cells after the viral vector vaccine infects the host cell, then the antigen can be recognized and subsequently activate the host immune responses [68]. Viral vectors that available in two forms both replicating and non-replicating are adenovirus (Ad) and poxvirus. Vectors specifically designed as non-replicating include Ad, alphavirus, and herpesvirus while replicating vectors include measles virus and vesicular stomatitis virus. Ad Vector is widely used in gene therapy, vaccination, cancer therapy and is one of the best candidates for vaccine development. Therefore, The high prevalence of Ad5 seropositive individuals was found worldwide, and was hypothesized that individuals who had had immunity against Ad5 previously would reduce the effectiveness of the vaccine. Therefore repeated administration or higher doses were required [80]. Ad vectors have advantages such as low pathogenicity, genetically safe, a low stage of genome integration to hosts in the replication cycle, induce humoral and cellular immune responses strongly, and establish long-term immune memory [100].

Sputnik V (Gamaleya, Russia), ChAdOx1/AZD1222/Covishield (AstraZeneca, UK), and Convidecia/Ad5-nCoV (CanSinoBIO, China) are viral vector vaccines that have obtained EUA in several countries to prevent the spread of COVID-19. All vaccines use full-length spike glycoprotein of SARS-CoV-2 as antigen. In phases 1 and 2 clinical trials of Sputnik V showed that neutralizing antibodies against rAd26 did not neutralize rAd5, therefore prime-boost doses could be delivered by that

two different viral vectors, hence Sputnik V is called a heterologous vaccine. A total of  $10^{11}$  virus particles per dose are delivered by the Ad26 recombinant viral vector (rAd26) for prime dose and rAd5 for boost dose administered 21 days apart in aged group of 18-60 year old. Covishield uses the AdY25 viral vector to deliver doses administered 28 days apart. Two types of doses may be given, i.e. low doses ( $2.2 \times 10^{10}$  virus particles) or standard doses ( $3.5-6.5 \times 10^{10}$  virus particles). The vaccine has been tested in 3 different age groups of 18-55, 56-69, and  $\geq 70$  years old. Convidecia uses rAd5 viral vectors to deliver a single dose of  $5 \times 10^{10}$  virus particles in the aged group of  $\geq 18$  years old [101]–[103].

All vaccines above were capable to elicit humoral immune responses (IgG antibodies against Spike glycoproteins, neutralizing antibodies) and IFN $\gamma$  T cell responses regardless of age group and vaccine dosage. Sputnik V was producing IgG antibodies and neutralizing antibodies on day 14 onwards, while the T cell response was elicited on day 28 after vaccination [101]. Although Covishield was inducing immune response after the first dose, IgG antibodies began to increase and maintained on day 28 after the second dose, while T cell response peaked on day 14 after the first dose [103]. Convidecia used single dose was able to attain immune response onset rapidly within 14 days, where a significant increase of it on day 28 [102], [104]. Not only neutralizing antibodies, but the specific T cells response was also essential to directly attack and kill virus-infected cells [105].

All of the above viral vector vaccines have mild to moderate and no serious adverse events detected. The most common adverse events of Sputnik V include injection site pain, hyperthermia, headache, asthenia, joint and muscle aches, furthermore no ADE phenomenon [101]. The effectiveness and safety of Sputnik V have been concerned due to the use approval of it, announced by the Russian president even before the phase 3 clinical trials were conducted [106]. Covishield was reported that had adverse events lower in booster than prime dose and the reactogenicity decreased with increased age. Local and systemic reactions that had occurred were injection site pain, fever, cold, muscle aches, headaches, and malaise [103]. Increased age ( $\geq 55$  years) and high pre-

existing anti-Ad5 immunity can significantly reduce the immune response by a vaccine, therefore a single dose may not be adequate to induce high levels of humoral immune responses. Older adults are more likely to have a history of Ad5 exposure, thus they may have a higher baseline of neutralizing antibodies against Ad5. Therefore, older adults are more tolerant of higher vaccine dose regimens or booster doses than younger adults [102].

#### 5.4 Peptide Vaccine

Peptide vaccine is a peptide-based vaccine synthesized in vitro and consists of 20-30 amino acids, highly immunogenic and able to stimulate specific immune responses. Peptide vaccine can reduce the potential allergenic and/or reactogenic complications. However, naturally, oligopeptides have a low molecular weight resulting in low efficiency. Therefore, carrier and adjuvant are required. [107]. For example, the efficiency of cytotoxic T cell activation and anti-tumor immune response may increase when peptides are encapsulated in liposomes or covalently conjugated with adjuvant [108], [109]. Such modifications can optimize the uptake of antigenic peptides from the vaccination area by APC with an efficient proteolytic process for major histocompatibility complex (MHC) class I against cytotoxic CD8+ and MHC class II against CD4+ Th cells [110].

The advantage of peptide vaccine both in terms of immunology and chemistry is its versatility. Because of the efficient translocation of peptides from the endosome into the cytoplasm, peptide vaccines are better at inducing T cell responses, endocytosed efficiently, processed, and presented on MHC molecules compared to whole protein vaccines. Chemically, peptide antigens are easier to produce than proteins because the peptide antigens do not need to be assembled into tertiary structures [111]–[113].

EviVacCorona is a SARS-CoV-2 antigen peptide-based vaccine that is chemically synthesized and then adsorbed into aluminum hydroxide as an adjuvant. The clinical trial was conducted in the aged group of 18-60 years old and two doses were administered by comparing the administration interval of 21 and 28 days apart [114]. In October 2020, EpivacCorona was the second vaccine that obtained EUA in Russia after Sputnik V, even though phase 1 and 2



clinical trials results have not been published and phase 3 has not been started. The phase 3 clinical trial conducted in November 2020 involved 30,000 participants. However, until now, the results of clinical trials in phases 1, 2, and 3 have not been published.

## 6 Conclusion

There are several challenges faced in COVID-19 vaccine development, including the ease of SARS-CoV-2 mutating and the potential for ADE after vaccination. To prevent the spread of SARS-CoV-2 infection, 10 vaccines have obtained emergency use authorization in several countries. Platforms used include mRNA, viral vectors, inactivated, and peptide vaccines. The vaccines were reported to be safe and well-tolerated by participants with mild to moderate adverse events. Although ADE is not found in all vaccines tested, monitoring against such events should be done because of the experience of using the SARS-CoV inactivated vaccine platform before, it is known to cause vaccine-associated enhanced respiratory diseases (VAERD). Clinical trial's result of the ten COVID-19 vaccines showed that the vaccines were effective and had adequate immunogenicity to prevent the spread of SARS-CoV-2 infection

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