Recent Updates on COVID-19 Vaccine Platforms and Its Immunological Aspects: A Review

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ABSTRACT

SARS-CoV-2 firstly emerged in China and sporadically transmitted worldwide. In March 2020, WHO announced that the infection was a pandemic. The outbreak and rapid transmission of COVID-19 have endangered the global health and the economy. This crisis has called for an extensive scientific mobilization of studies on SARS-CoV-2 concerning its clinical aspects, characteristics, and its mechanism of transmission. Although many scientists have published the treatment options against COVID-19, currently, there is not any approved medications against the virus yet. COVID-19 vaccine development has started in many research centers and pharmaceutical industries following the announcement of the agent and the full genome of SARS-CoV-2 recognized. Recently, the collected data described that COVID-19 vaccine candidates grouped into the following types: protein-based, epitope, inactivated or live-attenuated virus, virus-like particle, nucleic acid-based, and viral vectors. Therefore, the present review gives a sneak peek of recent updates on COVID-19 vaccine construction worldwide and COVID-19 vaccine's acceptance in Indonesia.

INTRODUCTION

SARS-CoV-2 firstly occurred in China and then transmitted sporadically worldwide[1]. In March 2020, WHO announced that the infection was a pandemic. COVID-19 outbreak and rapid transmission have endangered the global health and the economy. This crisis has called for extensive scientific mobilization of studies on SARS-CoV-2 focusing its clinical aspects, characteristics, and its mechanism of transmission, with the ultimate aim of counteracting the devastating outcomes[2,3]. At present, the seventh coronavirus has infected approximately 61 million people globally causing more than 1.4 million deaths. Furthermore, there are more than 500,000 cases and around 16,000 people died in Indonesia. These data are based on the Johns Hopkins University online website that tracks COVID-19 cases in real-time[4].

The coronavirus family is classified into four different genera: *Deltacoronavirus*, *Gammacoronavirus*, *Betacoronavirus*, and *Alphacoronavirus*. Animals and humans can be infected by coronaviruses[5]. The SARS-CoV-2 genome is a single-stranded positive-sense RNA of roughly 30,000 nucleotides. There are four structural proteins encoded by the genome: nucleocapsid (N), membrane (M), spike (S), and envelope (E)[6]. The spike protein was the primary target antigen in the SARS-CoV-2 vaccine[7]. Previously, the candidate for a peptide-based vaccine against the virus based on the four structural proteins was identified[8,9]. In addition, the interaction between the host and the virus that causes infection involves a complex response of the immune system[10,11]. On the other hand, we demonstrated the paradoxical phenomenon called antibody-dependent enhancement (ADE) in the Indonesian isolates[12]. Therefore, ADE has become a tipping point in the cultivation of antibody-based therapies and vaccines[10,11].

Currently, scientists are attempting to generate vaccines to fight against SARS-CoV-2 worldwide, with protein-based vaccines becoming the most advanced types and the private sector is at the forefront of this study[13-15]. Even with the recent study publication from Jean *et al.* on the treatment options against COVID-19, currently, there is not any approved medication (drugs or vaccines) against the virus yet[13]. Therefore, the present review gives a sneak peek of recent updates on the development of COVID-19 vaccine worldwide.

Next-Generation COVID-19 Vaccine Platforms

COVID-19 vaccine development has started in many research centers and pharmaceutical industries following the announcement of SARS-CoV-2 agent and its full genome recognized. Recently, the available assemble data stated that COVID-19 vaccine candidates were grouped into the following types: protein-based, epitope, inactivated or live-attenuated virus, virus-like particle, nucleic acid-based, and viral vectors[15,16] (Figure 1). Today, approximately nine months after the prevalence of novel coronavirus, vaccine and antiviral products are still in progress due to the pandemic paradigm development with several medication options and vaccines are in clinical trials globally[9,15,17]. In regard to this matter, we considered traversing the new concepts and latest cultivation in each type of vaccine to formularize a potent vaccine contrary to COVID-19.
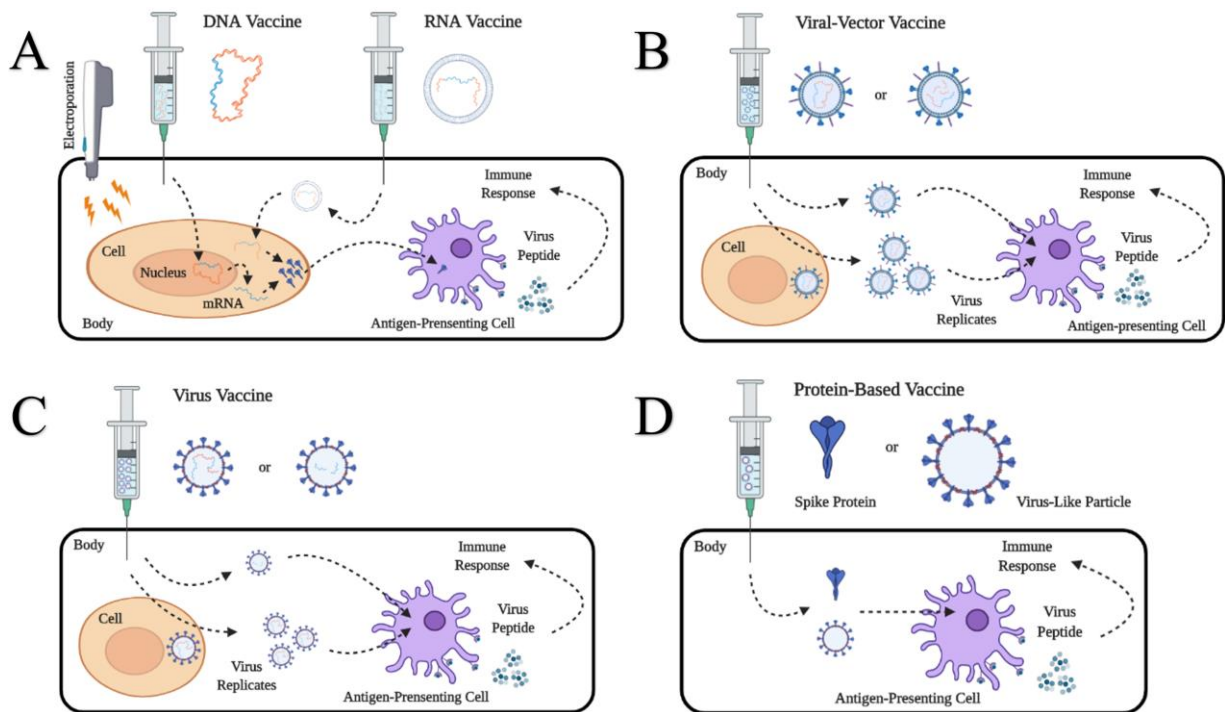
Figure 1. The schematic diagrams of COVID-19 vaccine platforms (illustrated and assembled using BioRender). A. DNA and RNA vaccines; B. Viral-vector vaccine; C. Virus vaccine; and D. Protein-based vaccine.

Inactivated and live attenuated vaccines

Whole killed virus, also called as the inactivated vaccine, is a notable vaccine that has the potency to discontinue the virus replication and directly overcome the virus via heating or radiation, and formaldehyde (chemicals). In addition, the inactivated vaccine is promoted as the effective and safe vaccine, which is trippingly available with much less expensive price compared to DNA/RNA vaccines[18]. The whole killed virus vaccine might importantly quarry the subunits of viruses from the envelope and spike proteins, matrix, and open reading frames, and encourage the immune system[19]. The whole killed virus vaccine has achieved the distinct concern over decades in consequence of its benefits against the viruses, that might easily counteract the virus[18].

Moreover, a research was conducted on non-human primates, rats, and mice at various doses focusing on the immunogenicity and protective potential of inactivated vaccine candidate (PiCoVacc). The group invented that PiCoVacc neutralized the novel virus significantly and established the preservative potency against the novel virus in non-human primates. The PiCoVacc might be established as a novel vaccine candidate[20]. Additionally, the inactivated virus vaccine demonstrated a preservative behavior challenging SARS-CoV that might be a potent against COVID-19[21,22].

The inactivated and live attenuated vaccines (LAV) demonstrated as one of the effective and safest vaccines against influenza based on the data[23]. The LAV might be developed via a fewer feasible chance of pathogenesis, such as lung infection, neutrophil influx, and anti-inflammatory cytokines[24]. A research which examined LAV suggested the replication reduction of the virus by initiating alteration into nsp14 in animal model[25]. Likewise, current research proposed that the progress of oral LAV vaccine might decrease the lung infections rendered by SARS-CoV-2 and is correlated with the immune tract throughout the reaction against COVID-19[26]. Furthermore, the LAV might be administered and

presented as a society deployment to quickly promote the herd immunity to cure SARS-CoV-2[27].

Today, as LAV might be the first licensed COVID-19 vaccine, currently, many research centers and universities in China invented the SARS-CoV-2 viral strains successfully and began an activity on the formularization of LAV. Moreover, Serum Institute of India, Ltd. also promoted LAV in collaboration of Codagenix, Inc. to fight against SARS-CoV-2[28]. In any case, several limitations might be represented during the LAV or inactivated vaccine extensions to fight against SARS-CoV-2[29].

Protein-based vaccine

The construction of vaccines obtained exclusive concerns throughout the last twenty years, such as the establishment of nucleic acids- and protein-based vaccines contrary to many viruses (dengue, Zika virus, or HIV). Furthermore, proteins are the notable elements in structural actions of the virus and brought in replication, contagion, and inlet of the viruses. The study indicated that proteins might be magnificent quarries for the construction of vaccines[23].

Protein-based vaccine (spike protein) exhibits higher neutralizing titers in fighting SARS-CoV than any other vaccine candidates based on the emerging evidence. Meanwhile, the spike protein is the important vaccine establishment contrary to SARS-CoV and MERS-CoV since spike protein might be easily examined and allow the immune reaction more streamlined than other proteins based on the accumulated data[21,22]. Moreover, the potency sections of spike protein used as antigens in immunization refinement fuse the whole level of spike protein and vaccine construction[29]. Further research on spike protein is urgently needed to reveal its potential as a promising vaccine candidate. However, the structure-based design of the virus might be a more prospective solution for vaccine formulations[30].

Recently, University of Oxford and AstraZeneca have started out a collaborative attempt to construct a spike protein vaccine, such as AZD1222 contrary to SARS-CoV-

2. *In vivo* study suggested that the spike protein might be robust B- and T-cell reactions to reveal the preferable prevention with a low dose[31]. Furthermore, spike protein subunits, such as the N-terminal domain (NTD), C-terminal domain (CTD), and receptor-binding domain (RBD), reflect as the crucial results to generate a vaccine (Figure 2). Jiaming and the team stated that S1-NTD of the virus is useable related in stability to construct a vaccine. Their study examined the reaction of recombinant NTD (rNTD) to analyze the immunogenicity in mice within two doses and constructed a vaccine (aluminum and CpG adjuvant). It also demonstrated that high dose lowered the infection in lungs and strengthened T-cell immune reaction in vaccinated mice[32].
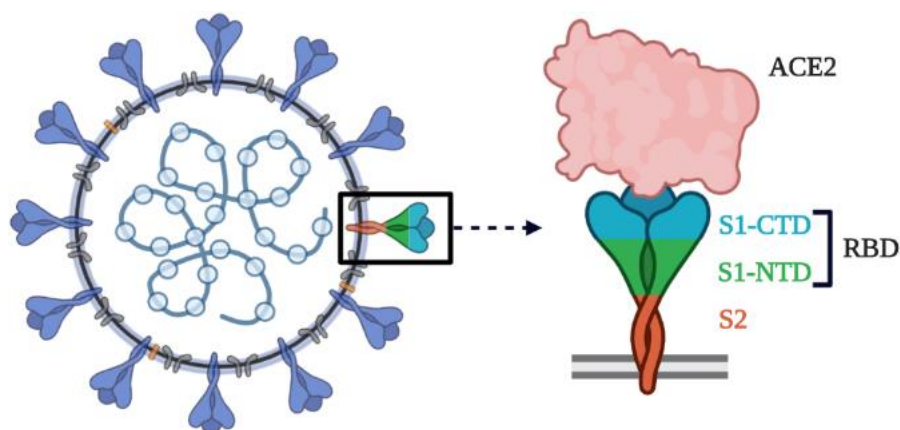
Figure 2. Diagram of spike-receptor binding apparatus in SARS-CoV-2 (illustrated and assembled using BioRender).

mRNA-based vaccine

Recently, various mRNA-based vaccines are also undergone the clinical trial phase. Because of the rapid construction process related to the manufacturing of the COVID-19 vaccine, the mRNA-based vaccines become the first vaccine in the phase of clinical trials[33]. Several elements that affect the mRNA immunization are safety evaluation, immune reaction evaluation, transmission establishment, preservation of newly promoted nucleotides, sequence regulations, and foreign particles[23]. Moreover, there are two methods that are utilized to establish an antibody of the virus based on the accumulated data; they are the application of the mRNA to convey the infection and the application of mRNA to deliver within the region of spike protein and RBD of the virus[34,35]. Therefore, mRNA-based vaccine construction is one of the most successful vaccine development methods so far.

Subunit-based vaccine

The immunization of subunit-based vaccines comprises at the minimum of one protein with the strong immunogenicity available to be an effective vaccine that drives the immune tract. This variety of antibodies is more straightforward and safer to develop because it does not have any substance of live virus for the vaccine establishment. Nevertheless, it often needs the adjuvants' generation to instigate a strong protective secure response. On the other hand, the subunit vaccine is not so effective immunogenic that are able to elevate by adding on the appropriate adjuvants[36,37]. Up until today, many principles have commenced employing the subunit-based vaccine formulation to fight the virus. Furthermore, the University of Queensland has started developing the subunit-based vaccine[38].

Recombinant vaccine

There are several basic reasons that make recombinant protein known as a vaccine platform against viruses[38]. For example, it increases the antigenicity against the virus, improves antibody-dependent viral entry, triggers the immune protection against viral infections, and its tight binding to definite ACE-2 receptors[25]. The recombinant ACE-2 receptor employs the possibility of results toward the preservation of various illnesses based on the accumulated data, as well as severe lung injury and acute angiotensin 2-induced hypertension[39,40]. Moreover, recombinant ACE-2 indicated a quick heal rapidity in mice[41]. Besides, the recombinant protein demonstrated significantly neutralized SARS-CoV-2 and might be a prospective indication for the vaccine development against SARS-CoV-2[42]. Similarly, another group of scientists also established a recombinant adenovirus contrary to SARS-CoV as a platform. The type of vaccine indicated an astounding humoral response and antigen-specific cellular toward SARS-CoV in non-human primates and was assumed that it might be a hope to cure SARS-CoV-2[43].

DNA-based vaccine

Antibodies which are synthetic of DNA considered more preferable as compared to the other antibodies. This circular DNA molecules encode at the minimum one foreign gene[44,45]. The DNA-based vaccine might successfully overcome many various of coronavirus family including the transmembrane domain, RBD, spike protein, cytoplasmic tail, and S1 domain[46,47]. The DNA-based vaccine configuration is an up-to-date technique and considered as an expensive one. This technique is composed of plasmids which are generally constructed with a smart device that helps to reveal an immune system to defeat the virus. Additionally, various institutions have kick-started the study to develop a vaccine to cure the novel virus. Uniquely, Cellectra®, a precise tool, is applied to reveal the electric pulse to accompany the DNA-based vaccine[48,49].

Peptide or epitope-based vaccine

Previous research stated that *in silico* study is promoted as a useful method to generate vaccine against various diseases, such as dengue, zika, cancer, and HIV[23]. This method is employed by identifying MHC 1 and 2, B-cell and T-cell epitopes correlated with antigen

presentation[50,51]. This type of vaccine consists of antibodies associated with the regions of foreign particles. These antibodies are straightforward and considered as the effective control. Based on the available data, the epitope-based virus might be a significant alternative vaccine formulation to fight SARS-CoV-2. Recently, there are various programs on vaccine developments[23]. Moreover, our previous projects revealed the potency of four structural proteins of Indonesian SARS-CoV-2 as promising vaccine candidates[8,9]. Nevertheless, both *in vitro* and *in vivo* researches are further required for the advanced explanation of epitopes for the invention of SARS-CoV-2 vaccine.
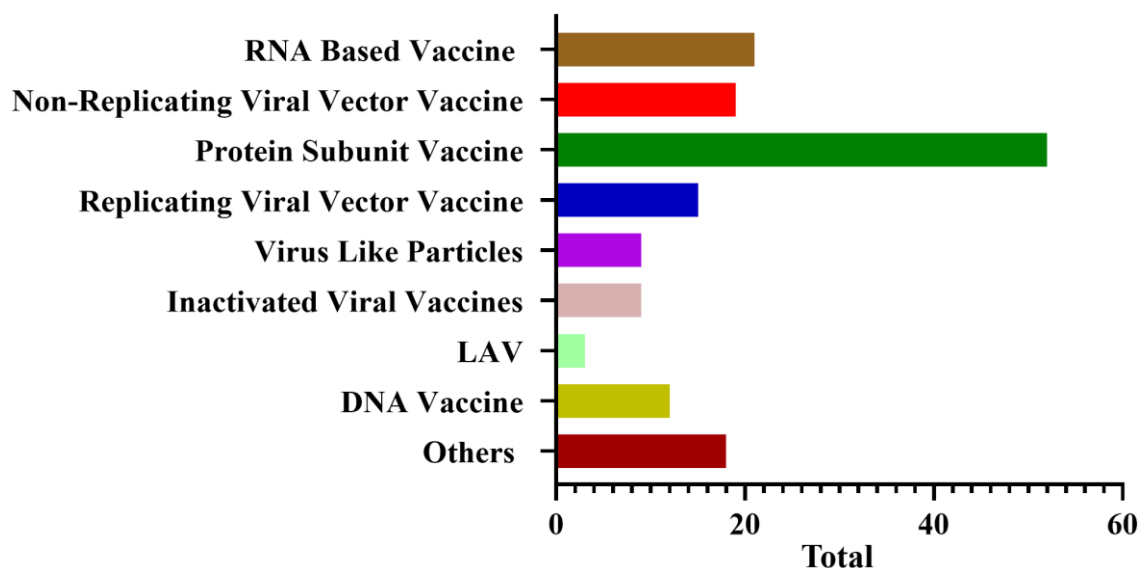

Figure 3. SARS-CoV-2 vaccine developments according to Kaur and Gupta[52].

Virus-like particles vaccine
Meanwhile, virus-like particles (VLPs) are the protein capsids (noninfectious) conjugated with virus' structural proteins that are engineered to be utilized in nanotechnology. The VLPs structure is conformable to natural viruses without a viral genome[53]. Besides, VLPs have particle sizes ranging from 20 to 100 nm[54]. VLPs are biologically active, robustly immunogenic, and adequate for rendering both humoral and cellular immune systems[55,56]. VLPs might be more easily generated at a low-cost and safer when compared to conventional virus vaccines, such as live-attenuated or inactive vaccines. VLPs have more various immunogenicity than nucleic acid or subunit vaccines[53]. The assembled data from various studies demonstrated that VLPs encourage robust immunity contrary to infectious agents, such as hepatitis[57], influenza[58,59], and human papillomavirus[60]. A previous study revealed that the immunogenicity of hepatitis B vaccine based on the VLP has notably higher than the recombinant vaccine. Furthermore, an *in vivo* study stated that the hepatitis B vaccine based on the VLP reveals neutralizing antibodies and adequate in restorative specific CD4+ and CD8+ T cell retorts[61]. Because of their capable result on the immunity generation against the virus, VLPs can be used as a prospective therapeutic vaccine[53]. Nowadays, there are various commercially obtainable VLP vaccines against human papillomavirus and hepatitis B virus, such as Sci-B-Vac™, Cervarix®, and Gardasil®[62,63]. Additionally, VLPs can be produced in yeast-, insect-, and cell-based expression systems. Therefore, we can reveal a protein of the virus on a large scale for various benefits[53,64]. Today, VLP vaccines are highly regarded as an effective candidate in order to stop the COVID-19 pandemic[53]. Previously, VLP-based coronavirus vaccines have been constructed by applying various expression systems or antigen combinations. These products demonstrate adequately in preventing coronavirus taint and show very promising in clinical uses[65]. Moreover, various studies explored the adjuvants to enhance the efficacy of VLP-based vaccines. Meanwhile, a recent study also revealed that the recombinant protein with a nanotechnology platform might be utilized to generate a COVID-19 vaccine candidate. Matrix-M™ adjuvant in the vaccine was reported to elevate any immune retorts during the vaccination. Currently, there is a COVID-19 vaccine candidate under the VLP platform and enters the clinical trial phase (Table 1 and Table 2).

Recent Update on COVID-19 Vaccine Development
Various attempts have emerged in COVID-19 vaccine development. However, most of the evolving vaccine possibilities apply the spike protein of SARS-CoV-2 (Table 1). Currently, based on the available data, there are 158 vaccine candidates worldwide, there are 135 candidates in the investigational phase of cultivation or in the preclinical phase[66] (Figure 3). This section reports the construction progress of vaccines in Table 2 and Figure 4.

Table 1. Immunological characteristics of COVID-19 vaccine candidate platforms.

Platform	Antigens	Immunogenicity	Neutralizing Antibody Retort
VSV (replicating)	Spike protein	Good with a single delivery	Not hampered owing to shortage of prevailing anti-vector immunity
Virus-like particle	Various viral proteins	Requires reiterated vaccination; weak, but stronger than subunit proteins	Strong induction

Protein subunit vaccine	Spike protein or RBD	Weak; requires repeated vaccination	Strong induction
Inactivated virus	Various viral proteins	Weak; requires repeated vaccination	Strong induction
DNA-based vaccine	Spike protein	Requires reiterated delivery; poor than the mRNA-based platform	Retort not as robust as for some of the viral vectors
mRNA-based vaccine	Spike protein or RBD encapsulated with nanoparticle	Requires repeated delivery	Hinges on options of formulation and adjuvant
Chimpanzee adenovirus (non-replicating; viral-vectored vaccines)	Spike protein	Not hampered owing to the shortage of prevailing antivector immunity	Robust with single delivery
Human serotype 26 adenovirus (non-replicating; viral-vectored vaccines)	Spike protein	Durability and quality affected by pre-existing antivector immunity	Needs repeated vaccination; weak
Live attenuated virus	Various viral proteins	Needs only a single dispatch	Strong induction
Human serotype 5 adenovirus (non-replicating; viral-vectored vaccines)	Spike protein	Durability and quality affected by pre-existing antivector immunity	Strong with a single delivery

Note: This table is assembled according to Jeyanathan *et al*[67].

Table 2. Recent developments of COVID-19 vaccine candidates

Clinical Trial Registrations	Developer	Vaccine	Platform	Preclinical/Clinical Data	Clinical Trial Phase
NCT04487210	Dynavax, Biologics, Medigen Vaccine	MVC-COV1901	Protein subunit	NA	Phases I (Taiwan)
NCT04453852	Central Adelaide Local Health Network, Medytox, Vaxine Pty Ltd	COVAX19	Protein subunit	NA	Phases I (Australia)
NCT04473690	Kentucky Bioprocessing Inc.	KBP-COVID-19	Protein subunit	NA	Phases I and II (USA)
NCT04436276	Johnson & Johnson	Ad26.COV2- S	Ad26-vectored	Initiation of effective neutralizing antibodies by a single dose	Phases I and II (Belgium, USA)
ACTRN12620000674932p	University of Queensland	COVID-19 vaccine	Protein subunit	Information issued to exhibit safety	Phases I (Australia)
CTRI/2020/07/026352	Zydus Cadila	ZyCov- D	Plasmid DNA	NA	Phases I and II (India)
NCT04471519, CTRI/2020/07/026300	Covaxin	National Institute of Virology, Bharat Biotech, Indian Council of Medical Research	Inactivated SARS- CoV-2	NA	Phases I and II (India)
NCT04480957	Lunar-COV19	Duke-National University of Singapore, Arcturus Therapeutics	Self-replicating mRNA	Elevate titers of neutralizing antibodies after a single injection	Phases I and II (Singapore)
NCT04450004	COVID-19 vaccine	Medicago, Laval University	Virus-like particle	Exhibit antibody responses in mice	Phase I (Canada)

NCT04463472, JapicCTI-205328	COVID-19 vaccine	Takara Bio, Osaka University, AnGes Inc.	Plasmid DNA	NA	Phases I and II (Japan)
ChiCTR2000034112	ARCoV	Suzhou Abogen Biosciences, Walvax Biotechnology, Academy of Military Medical Sciences	mRNA	Initiation of neutralizing antibodies in non-human primates and mice	Phase I (China)
NCT04445194, NCT04466085	COVID-19 vaccine	Chinese Academy of Medical Sciences, Anhui Zhifei Longcom Biologic Pharmacy	Protein subunit	NA	Phases I and II (China)
NCT04405908	SCB-2019	Dynavax, GlaxoSmithKline, Clover Pharmaceuticals	Protein subunit	Initiation of neutralizing antibodies in various animal models	Phase I (Australia)
NCT04445389	GX-19	Genexine Consortium	Plasmid DNA	NA	Phases I and II (South Korea)
NCT04449276	CVnCoV	CureVac	Lipid nanoparticle (mRNA)	Indicating protection in animal models	Phase I (Germany, Belgium)
NCT04412538, NCT04470609	COVID-19 vaccine	Chinese Academy of Medical Sciences	Inactivated virus	NA	Phases I and II (China)
NCT04437875, NCT04436471	Gam-COVID- Vac Lyo	Gameleya Research Institute	Ad26- or Ad5-vectored, non-replicating	NA	Phases I and II (Russia)
ISRCTN17072692	LNP-nCoVsaRNA	Morningside Ventures, Imperial College London	Lipid Nanoparticle (saRNA)	Initiation of neutralizing antibodies and TH1 cell responses in animal models	Phases I and II (UK)
NCT04336410, NCT04447781	INO-4800	International Vaccine Institute, Inovio Pharmaceuticals	Plasmid DNA	Immunogenicity in guinea pigs and mice, exhibit safety and immune responses	Phases I, II, III (USA)
ChiCTR2000034780, ChiCTR2000031809	COVID-19 vaccine	Wuhan Institute of Biological Products Co. Ltd, Sinopharm	Inactivated virus	News released to indicate safety	Phases I, II, III (China)
ChiCTR2000032459, ChiCTR2000034780	BBIBP-CorV	Beijing Institute of Biological Products Co. Ltd, Sinopharm	Inactivated virus	Neutralizing antibodies and protection in non-human primate models, rabbits, and rodents; elevate antibody and exhibit safety in the vaccines	Phases I, II, III (United Arab Emirates, China)
Eudra CT 020-001038-36, NCT04368728, ChiCTR2000034825	BNT162b1	Fosun Pharma, Pfizer, BioNTech	Lipid nanoparticle (mRNA)	Robust antibody and T cell retorts in animal models; indicating safety and high neutralizing antibody titers	Phases I, II, III

NCT04368988	NVX-CoV2373	Novavax	Protein subunit	Elevated levels of spike specific neutralizing antibodies	Phases I and II (Australia)
NCT04352608, NCT04456595, NCT04383574	PiCoVacc	Sinovac Biotech	Inactivated virus	Showing protection in non-human primate models; data delivered to exhibit immunogenicity and safety	Phases I, II, III
NCT04470427, NCT04405076, NCT04283461	mRNA-1273	NIAID, Moderna	Lipid nanoparticle (mRNA)	Induction of neutralizing antibodies in mouse models; initiation of neutralizing antibodies in all vaccines; exhibits safety, but highest dose causes severe adverse events	Phases I, II, and III (USA)
NCT04341389, ChiCTR2000030906, ChiCTR2000031781	Ad5- nCoV	Beijing Institute of Biotechnology, CanSino Biologics Inc.	Ad5-vectored, non-replicating	High dose unsafe; antibody levels negatively correlated with pre- existing antivector immunity and age (>55 years); low and medium doses acquire neutralizing antibodies	Phases I and II
NCT04324606, ISRCTN89951424, EudraCT 2020-001072-15, EudraCT 2020-001228-32, PACTR202006922165132	AZD-1222	AstraZeneca, University of Oxford	ChAd-vectored, non-replicating	Prevention of pneumonia in non-human primates; safety, T cell activation, and initiation of neutralizing antibodies	Phases I, II, and III (South Africa, Brazil, USA, and UK)

Note: This table is arranged according to Jeyanathan *et al*[67].
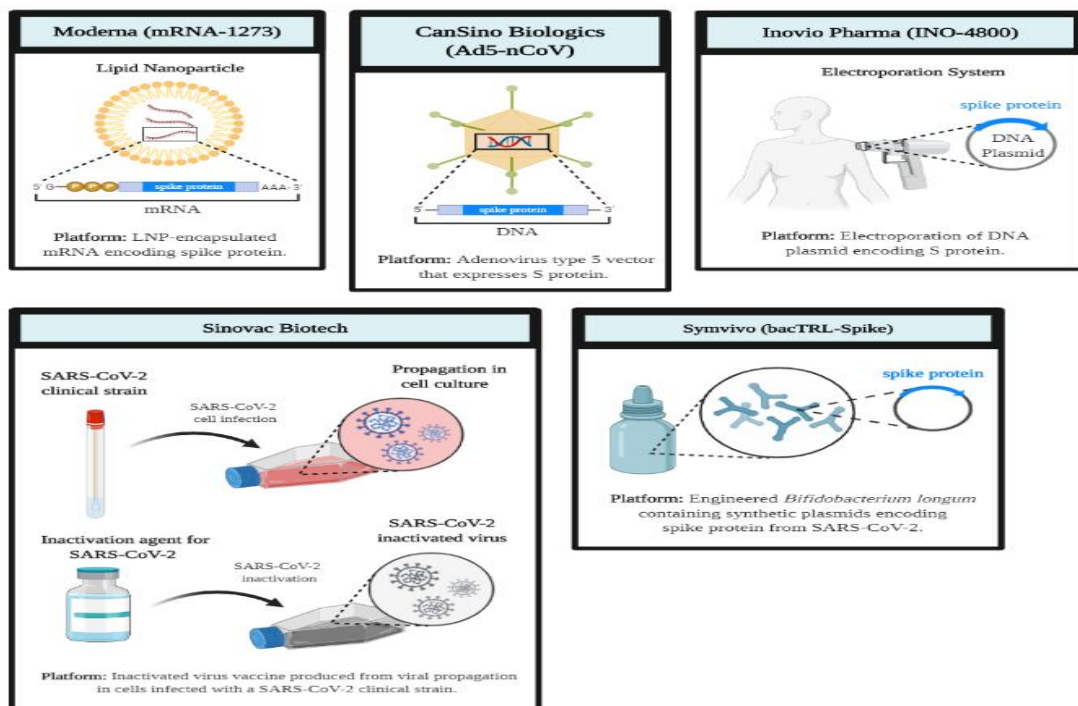

Figure 4. Several clinical phased vaccine candidates for COVID-19 (illustrated and assembled using BioRender).

Immune Response towards Vaccine Administration: An Overview of Various Vaccine Platforms

The urgent need for an effective and safe vaccine against COVID-19 has driven the development of vaccine candidates in a number of countries[8,9,12]. Some of these vaccine candidates are designed using different vaccine platforms including the conventional platforms. The trial results of several vaccine candidate platforms have also been published which include recombinant adenovirus type-5 (Ad5)–vectored vaccine, a chimpanzee

adenovirus-vectored vaccine (ChAdOx1 nCoV-19), mRNA vaccine, and inactivated vaccine[68-74] (Figure 4).

The natural mechanisms in which SARS-CoV-2 modulates the immune response have been extensively studied, particularly for vaccine development. In short, it can be concluded that this mechanism is highly dependent on the inhibition of innate immunity, especially in terms of the recognition and activation of type 1 interferons. Viral proteins which include membrane proteins (M) and nonstructural proteins (NS) are the key molecules in modulating the body's immune response. In adaptive immunity to viral infections, Th1 plays a dominant role. Helper T cells regulate the overall adaptive immune response, while cytotoxic T cells play a role in destroying virus-infected cells. Neutralizing antibodies as a result of the humoral immune response process will provide protection by inhibiting the further development of infection and preventing any re-infection. In SARS-CoV-2 infection, specific IgG and neutralizing antibodies are reported to be present in the body for 2 years after infection[75]. SARS-CoV-2 IgM and IgG are detected within 1-2 weeks after the onset of symptoms in the majority of infected individuals[76]. High levels of neutralizing antibodies were observed in a number of recovered individuals who were correlated with T cells, especially CD4+ T cells[77]. Recent studies have shown that the level of neutralizing antibody is positively correlated with disease severity[78], however, in contrast neutralizing antibody in asymptomatic individuals is relatively small and decreases faster than symptomatic individuals. The main target of neutralizing antibody is spike protein which consists of S1 and S2 subunits. S1 is the distal membrane and contains RBD which binds to the ACE2 receptor, while S2 is the proximal membrane that plays a role in membrane fusion[79]. In the case of SARS-CoV, only antibodies targeting protein S can neutralize the virus. Therefore, most of the developing SARS-CoV-2 vaccine candidates involve at least part of the spike protein. The induction of neutralizing antibodies has been the main target of several SARS-CoV-2 vaccine candidates, one of which is As5-nCOV that is a recombinant viral-vectored vaccine from CanSino Biologics China using the route of administration by intramuscular injection. In several previous vaccine studies, viral-vectored recombinants were known to have a high level of safety and ability to induce a T cell response without the need for vaccine adjuvants[80-83] and this method is the second most widely used platform for the development of the COVID-19 vaccine[19]. The opposite occurs with the inactivated viral vaccine and the protein subunit vaccine platforms, both of which have a weakness in inducing a CD8+ cytotoxic T cell response. To increase the effectiveness of the inactivated viral vaccine platform, it requires the addition of an adjuvant and the repeated frequency of vaccinations[66].

In order for the vaccine to work effectively and on target, it is important to induce an immune response that produces a long-term memory. Generally, any stimulation of immune response to vaccines begins with the body's reaction to the first detection of the incoming agent, whether it is recognized as a threat or an immunization. Then, the innate immune system carries out any initiation stage. The process of initiation and detection begins when the immune system recognizes the epitope of antigen. The components of innate immune system will form opsonization or bind to antigens and help to be recognized by APCs such as macrophages or monocytes. APC will process and insert the antigen that has been processed together with MHC class 1 protein onto the APC surface and carried to CD8+ cells which will then trigger the cell-mediated immune system. The different receptors play an important role in sending the different signals to the host cell. The activated APC correctly translates the nature of the threat, then transmits this information to secondary lymphoid organs, and promotes the relevant adaptive immune response[79].

In the design and development of vaccine candidates, several key factors determine the effectiveness of vaccines in inducing a specific immune response which includes the density of antigen protein and its distribution in a particle. The high density and orderly arrangement of antigens in a particle will make it easy to bond between the immunoglobulin on the surface of the host B cell and the particle, which is an important step in inducing an immune response[80].

The ability to induce antibodies is also a determining factor for vaccine success. In the case of SARS-CoV-2, antibody- and T-cell-mediated immunities are the most effective protection[84]. Immunologically, there are two components that must be present in a vaccine to cause the desired immune response, namely the antigen from the target virus and an infection signal (PAMP or DAMP) which will warn the body to activate the immune system. These components are both an advantage and a weakness of several vaccine platforms. Live attenuated vaccines can provide these two components, in contrast to the non-viral vaccine platform which can only provide antigens but often requires artificial signals to activate the body's immune response, usually known as adjuvant forms[67]. Live attenuated vaccines are known as platform vaccines capable of providing long-term memory to the immune system, whereas nonliving vaccines provide shorter-term protection[85].

Several factors inhibiting the induction of immune response through vaccines have become the main focus in developing SARS-CoV-2 vaccine candidates. These obstacles can be in the form of a viral strategy to avoid the body's immune mechanism or the presence of ADE. In some cases, ADE has become a tipping point for vaccine development. Several *in silico* studies have shown that the presence of an ADE motif in the SARS-CoV-2 virus sequence[86]. In this case, the subunit vaccine platform is designed to focus on the immune response to the neutralizing epitope, thus, it can prevent non-neutralizing antibodies that can increase the risk of ADE[12]. The weakness of the subunit vaccine is the presence of recombinant protein S, which can have an incorrect epitope shape if it is not produced in mammalian cells[67,87].

In the VLP platform, the presence of the spike protein on the surface of VLP makes it easier to bind ACE2 and enter the cells. However, unlike the subunit vaccine, the spike protein arrays on the VLP surface cross-links with B cell receptors and can directly activate B cells. This is expected to increase the effectiveness of the vaccine in inducing an immune response. VLP, subunit, and inactivated viral vaccine platforms require the repeated adjuvant and vaccination[88]. So far, there is only one SARS-CoV-2 vaccine candidate using the VLP platform and it just enters the clinical trial phase in Canada (Table 2).

The Acceptance of COVID-19 Vaccine in Indonesia

The recent COVID-19 pandemic is a crucial health problem in Southeast Asia countries, especially Indonesia[89]. Based on the accumulated data, the mortality increases significantly in the elderly with comorbidities, such as the ones with prior condition of chronic

obstructive pulmonary disease, chronic kidney disease, and cardiovascular disease[90,91]. On the other hand, various remedies are used to manage COVID-19 patients. Up until today, there is not any specific treatments approved by the United States Food and Drug Administration as a benchmark for the Government of Indonesia. The cultivation and dissemination of a vaccine are one of the most optimistic methods in the COVID-19 pandemic[92].

Additionally, the vaccine construction has started in various pharmaceutical industries and research institutes worldwide. The first vaccine candidate announced is by Moderna Inc. in March 2020 using the mRNA platform (Table 2). Unluckily, the vaccine efficacy is still unclear and the issue on the vaccine safety will be affected by vaccine acceptance.

Lastly, vaccination might be needed to stop the pandemic. Nevertheless, vaccine requests in low-, middle-, and high-income countries are different[92]. Indonesia is one of the middle-income countries with elevated vaccine doubt[93]. Various research demonstrated the acceptance of vaccines against many diseases in Southeast Asia, for example, Ebola[94], COVID-19[92], and dengue[95].

On a side note, the political situation in terms of the government's response to this pandemic in a country plays a major role in shaping the acceptance of COVID-19 vaccines among its citizens like in the U.S. these days[96]. Indeed, in some countries, the situations are exacerbated as these governments have been indicated as less responsive in dealing with this pandemic as a result of democratic decline marked by the rising of anti-vaccine and religious conservatism movements, religious-political polarization, corruption, and clientelism[97]. In a cross-sectional study, it believed that the effectiveness of the COVID-19 vaccine also affects the acceptance of the vaccine in Indonesia. If the vaccine has high effectiveness, the acceptance is high. However, the government needs to establish several methods to convince its communities to be vaccinated[92].

CONCLUSION
In summary, this study demonstrated that the next-generation vaccine platforms play an important role in stopping the global COVID-19 pandemic. In addition, further study is needed on the safety issue of vaccines associated with the community's acceptance of the vaccine.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

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