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Vaccines for COVID-19: A Systematic Review of Immunogenicity, Current Development, and Future Prospects

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The persistent coronavirus disease 2019 (COVID-19), characterized by severe respiratory syndrome, is caused by coronavirus 2 (SARS-CoV-2), and it poses a major threat to public health all over the world. Currently, optimal COVID-19 management involves effective vaccination. Vaccination is known to greatly enhance immune response against viral infections and reduce public transmission of COVID-19. However, although current vaccines offer some benefits, viral variations and other factors demand the continuous development of vaccines to eliminate this virus from host. Hence, vaccine research and development is crucial and urgent to the elimination of this pandemic. Herein, we summarized the structural and replicatory features of SARS-CoV-2, and focused on vaccine-mediated disease prevention strategies like vaccine antigen selection, vaccine research, and vaccine application. We also evaluated the latest literature on COVID-19 and extensively reviewed action mechanisms, clinical trial (CT) progresses, advantages, as well as disadvantages of various vaccine candidates against SARS-CoV-2. Lastly, we discussed the current viral treatment, prevention trends, and future prospects.

Keywords: COVID-19, SARS-CoV-2, prevention, antigen selection, COVID-19 vaccines

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INTRODUCTION

Recent and ongoing viral diseases, caused by novel coronaviruses, are a significant threat to public health worldwide. Governments and researchers of numerous countries are working vigorously to manage past and ongoing epidemics and carry out etiological research. The current coronavirus outbreak was first reported to the World Health Organization (WHO) on 31 December 2019 (1). On January 12, 2020, WHO named this novel coronavirus "2019-nCoV" (2), and on 11 February 2020, WHO formally named the disease "coronavirus disease 2019" or "COVID-19" (3). The same day this coronavirus was also called "severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)" by the International Committee of classification of viruses (ICTV), due to its similarity with earlier SARS-CoV (3). Globally, as of March 9, 2022, WHO reported over 440 million COVID-19 cases, and the death toll surpassed 6 million deaths (4).

The COVID-19 pandemic prompted an unparalleled worldwide crisis. The coronavirus spread rapidly, destroyed livelihoods of billions of people, and endangered the global economy (5). The reported and confirmed COVID-19 case numbers have not peaked yet and the global condition

remains severe. Hence, the United Nations took lead in the global collaborative efforts to fight this disease. Nevertheless, till now, no efficacious anti-COVID19 treatment has emerged (6). This situation prompted numerous countries and regions worldwide to take part in COVID-19 research to eradicate this disease. In particular, the development of highly efficacious anti-COVID-19 vaccine is key to controlling and preventing this pandemic outbreak (7). Herein, we not only introduced the structural characteristics of 2019-nCoV in detail, but also reviewed the latest vaccine types, research progresses, as well as potential and current challenges in the advancement of vaccine research to eradicate this devastating pandemic.

STRUCTURAL AND REPLICATORY FEATURES OF SARS-COV-2

The SARS-CoV-2 genetic information is packed inside a single-stranded positive-sense RNA, with variable size (29.8 ~ 29.9 kb), and its genomic composition is similar to other coronaviruses (**Figure 1A**). The open reading frames (ORFs) encode 4 structural [namely, spike surface glycoprotein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N)], 16 non-structural (NSP1-16), and some accessory proteins (namely, ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9 and ORF10) (8–10) (**Figure 1B**). The S protein has two subunits: N-terminal S1 and C-terminal S2 subunits (11). The S1 subunit is a receptor-interacting domain, with a relatively high structural divergence, and it interacts with the membrane-bound angiotensin-converting enzyme-2 (ACE2) receptor (**Figure 2**). The S2 subunit contains a fusion peptide, and it is responsible for the viral fusion with the host cellular membrane (12). Upon internalization of the bound ACE2 receptor, the host cell type II transmembranal TMPRSS2 serine proteases cleave the S protein to expose the fusion peptide on the S2 subunit and facilitate viral entry into host cells (13). Therefore, most COVID-19 vaccines were developed, based on some aspects of the S protein, to facilitate the disruption of viral entry (14). Among the structural proteins, the M protein is the most abundant. It is a multi-transmembranal protein, with an N-terminal domain (NTD) that is located outside the viral envelope, and a C-terminal domain (CTD) that remains inside the virus. The E protein is the smallest (76-109 amino acids) membranal protein and it possesses ion channel activity (15, 16). In infected host cells, the E protein undergoes massive replication, and a low copy number of the E protein becomes integrated into the viral envelope (16), whereas the majority of E proteins attach themselves to the endoplasmic reticulum-Golgi intermediate compartment (17). In this regard, the functions of both M and E proteins appear to support assembly, formation, and release of viral particles. During infection, the N protein binds with the viral genome at multiple locations, in a nonspecific manner, to protect the RNA as it enters the infected cell and furthers its replication (18, 19). More importantly, the N protein is highly immunogenic and contains antigenic substances that elicit T and B cell responses (20). Being a viral suppressor of RNA silencing (VSR), the N protein antagonizes the antiviral defense of interferon (IFN) and protein kinase R (PKR) (19), which typically arrests protein synthesis during viral replication and transcription. Thus, the N protein may serve as a potential target for vaccines and drug development.

Approximately two-thirds of the SARS-CoV-2 genome contains ORF1a and ORF1b, which encode non-structural proteins. Non-structural proteins are crucial for viral replication and transcription (**Figure 1**). Two cysteine

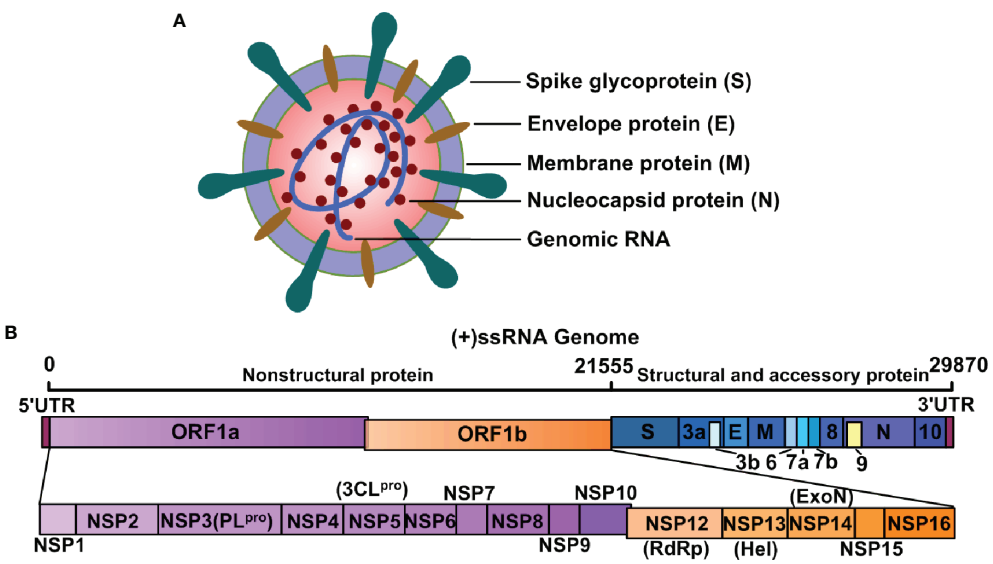

FIGURE 1 | Structure of SARS-CoV-2 and its genomic RNA. **(A)** SARS-CoV-2 is composed of spike glycoprotein (S), envelope protein (E), membrane protein (M), nucleocapsid protein (N), and genomic RNA. These components guide the transcription and translation of its nonstructural, structural, and accessory proteins. **(B)** SARS-CoV-2 is a single-stranded ribonucleic acid (+ssRNA) virus and the genome components encode both structural and nonstructural components of SARS-CoV-2.

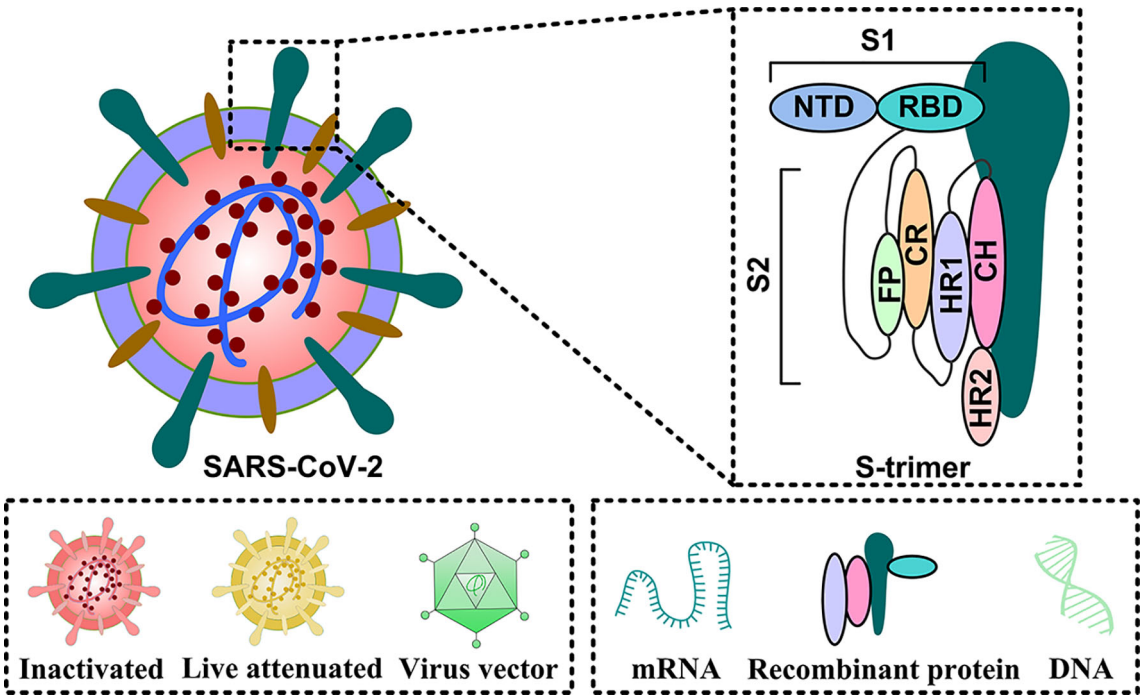

FIGURE 2 | The primary targets of the COVID-19 vaccine candidates. The entire virus can be used as antigen in the following forms: inactivated, live attenuated, and virus vector vaccines. In some cases, functional proteins can also be employed as antigens. These include: mRNA, DNA, and recombinant protein.

proteases, papain-like cysteine protease (PL^{pro}/NSP3) and 3C-like protease ($3CL^{pro}$/NSP5), are indispensable for translated polyprotein processing (21), and can, therefore, be promising targets for antiviral therapy. The RNA-dependent RNA polymerase (RdRp), also known as NSP12, interacts with its co-factors NSP7 and NSP8 to form the replication and transcription complexes (22). NSP13, an NTPase/helicase (Hel), contains a helicase core domain that hydrolyzes all types of NTPs (23), and the zinc-binding and stalk domains are critical for the unwinding of RNA helices, based on the energy released by NTP hydrolysis (24). Another important NSP, NSP14, together with its cofactor NSP10, performs the proofreading of nucleotides by removing nucleotide insertions and mismatches where appropriate (25).

The accessory proteins usually antagonize type I IFN synthesis or IFN-stimulated gene (ISGs) expression in order to resist host antiviral responses. ORF3a downregulates ISG expression *via* suppression of STAT1 phosphorylation (**Figure 3**). One component of the IFN-stimulated gene factor 3 (ISGF3) harbors STAT1, STAT2, and IRF9, while ORF6 directly blocks IFN-β synthesis by interacting with the nuclear import Karyopherin α2 (KPNA2), thereby inhibiting the nuclear translocation of STAT1, IRF3, and ISGF3 (9, 10). Similar to ORF3a, ORF7a and ORF7b repress STAT2 phosphorylation to downregulate ISGs expression (10). Interestingly, ORF8 interaction with MHC class I molecules in lysosomes disrupts antigen presentation *via* downregulation of their surface antigen expression (26). The mitochondrial localization of ORF9b interacts with translocase of the outer membrane 70 (TOM70), and suppresses IFN-β production by negatively regulating mitochondrial antiviral adaptor protein (MAVS)/TRAF3/TRAF6/TOM70 signaling (27). ORF10 is the smallest accessory protein, and surprisingly, it carries the largest number of immunogenic epitopes (28). Thus, ORF10 may be a potential target for vaccines. However, every SARS-CoV-2 ORF10 variant possesses high frequency mutations, and these mutations need to be monitored during the development of anti-viral therapy.

ANTIGEN SELECTION FOR COVID-19 VACCINES

Vaccines play a crucial role in the long history of infectious disease prevention, and it does so *via* induction of human herd immunity. Vaccinal antigen is an active vaccine component capable of inducing a specific immune response in the body. Antigens are not only an essential component of vaccines, but are also critical in determining vaccine efficacy. Thus, vaccine development is accompanied by the evolution of vaccine antigen characters. The COVID-19 vaccine antigen can be an attenuated or inactive form of the entire virus or a part of the virus, such as, a protein or sugar. It can also be an mRNA or DNA that induces the host to self assemble vaccine antigens. Inactivated virus, live attenuated virus, and viral vector can directly act on antigen presenting cells (APC), and stimulate immune cells to produce specific antibodies targeting viral

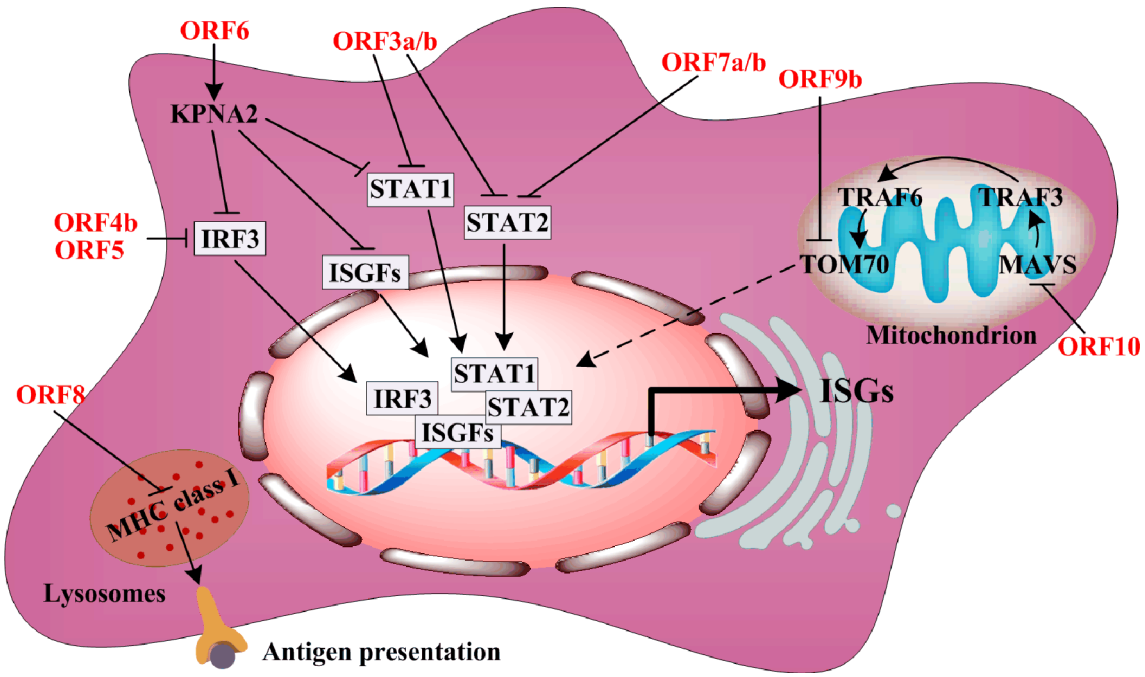

FIGURE 3 | The regulation of ORFs on body immunity.

antigens (**Figure 4**). Other antigen-specific molecules include protein subunits, RNA, and DNA that indirectly act upon APC in the form of antigenic peptides that undergo modification or packaging within host cells. During the development of an efficacious COVID-19 vaccine, selecting effective antigens will enable the human body to produce humoral or/and cellular immunity, and compel the pathogen to lose its pathogenicity, thereby successfully resisting the virus. Moreover, the aforementioned 2019-nCoV structural proteins, as well as the variety of non-structural proteins, can serve as additional antigen candidates for COVID-19 vaccine development.

The antibody dependent enhancement (ADE) is the enhancement of viral infection through an antibody of low efficacy (29). Owing to its confirmation during transmission of other viruses, including SARS-CoV-1, scientists paid much attention to the ADE effect in the early stages of the SARS-CoV-2 outbreak. Patients with severe COVID-19 often exhibited higher IgG responses, and produced higher total antibody titers, both of which were also associated with poorer outcomes, suggesting a possible ADE effect during COVID-19 infections (30). A study involving the ADE effect in SARS-CoV-2, conducted by the Osaka University, confirmed an increase in antibody dependence after COVID-19 infection (31). More importantly, similar effects were observed in numerous mutated strains, due to the recent emergence of a number of mutated viruses, suggesting that it is unreliable to rely on natural infection to achieve mass immunity (32, 33). Therefore, the biggest challenge facing COVID-19 vaccines remains the ADE effect. From the beginning of the COVID-19 vaccine development, scientists and researchers attempted to identify a SARS-CoV-2 protein, which produces the least ADE effect. Thus far, the ADE effect was not observed in animal studies or human clinical trials. However, this factor requires further investigation, as it involves both vaccine development and treatment. After all, if a potential vaccine, instead of producing neutralizing antibodies, induces the body to form ADE, the outcome can be very dangerous.

Whole-Viral Antigen

Whole-viral antigen contains all viral components, including proteins, lipids, polysaccharides, nucleic acids, and other components (34). Viral strain separation and extraction are necessary for the preparation of whole-viral antigen. The key steps include eliminating viral activity *via* physical or chemical methods, or reducing viral toxicity *via* artificial mutagenesis (35). Currently, inactivated and attenuated vaccines make up a large portion of COVID-19 vaccines (36). However, it should be noted that the proteins and nucleic acids contained within the whole-viral antigen possess a certain level of immunogenicity, which may induce the body to produce irrelevant antibodies and, thus, reduce the specificity of antibodies against key proteins (37). As such, people often require multiple inoculations to obtain efficient immunity, so the clinical trials (CTs) of whole-viral antigen COVID-19 vaccines are critical for determining the efficiency of such vaccines.

Spike Protein

The S protein has two subunits S1 and S2 that contribute to viral attachment, fusion, and entry (14). The subunit S1, located at the

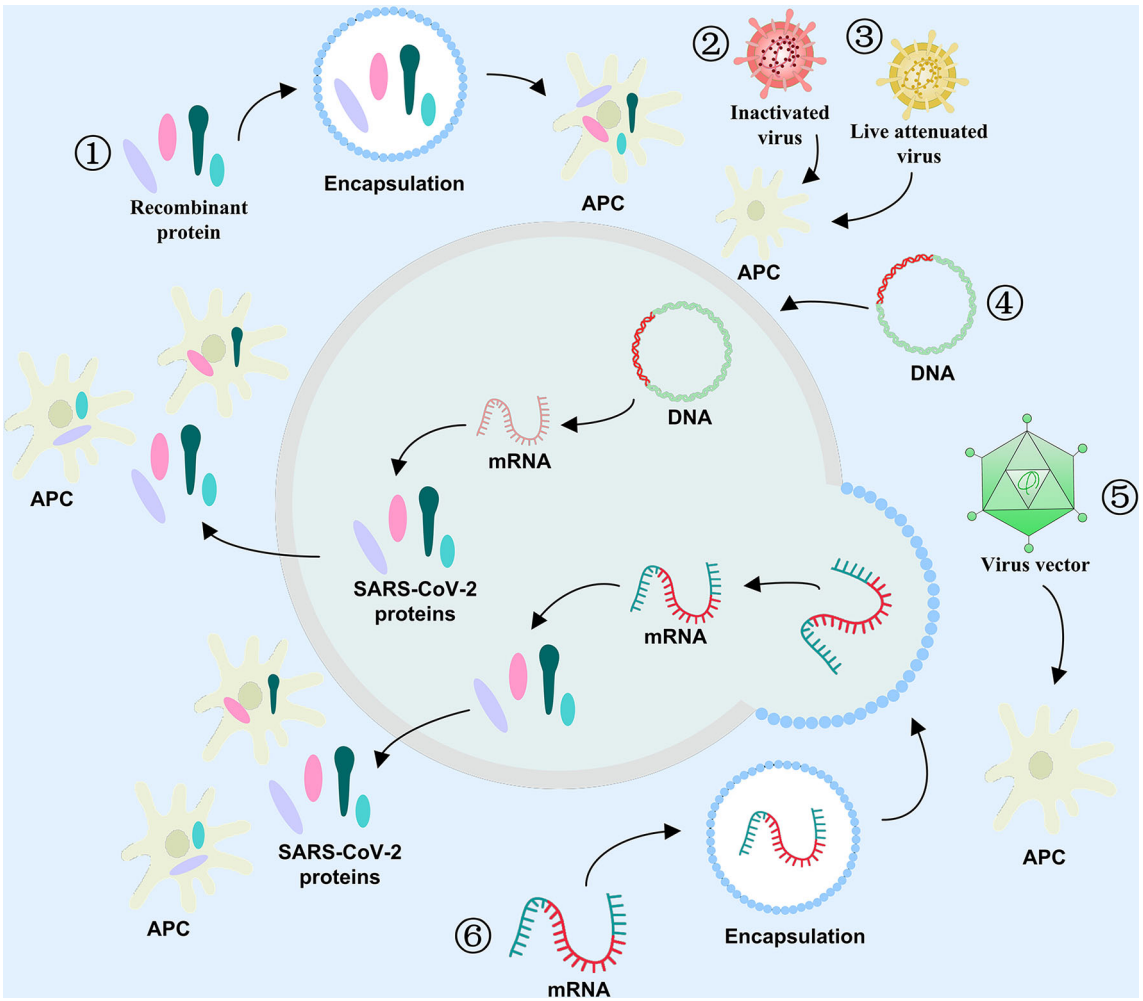

FIGURE 4 | Antigen selection for COVID-19 vaccines. The role of varying antigens in immune response against COVID-19 ① Recombinant protein, ② Inactivated virus, ③ Live attenuated virus, ④ DNA, ⑤ Viral vector, and ⑥ mRNA.

N-terminal of the virus, harbors the N-terminal (NTD) and receptor-binding domains (RBD) (38). RBD interacts with ACE2 on the host cell membrane, and triggers the merging of the viral envelope with the host membrane (39). Therefore, an effective blockage of the RBD-ACE2 interaction can potentially prevent the SARS-CoV-2 invasion of host cells. Thus, the RBD protein is a potential candidate for the COVID-19 vaccine. The subunit S2 resides in the viral C-terminal. It includes the fusion peptide (FP), connecting region (CR), heptad repeat (HR), and central helix (CH), which primarily regulates the S protein attachment to the host cell membrane whilst mediating the merging of the viral envelope with the host membrane such that the encapsulated virus can enter the cell smoothly and complete the infection (37).

While the S protein is an optimal vaccine target-antigen, the natural S protein has unstable properties (37). Therefore, it is not conducive to the research of S protein function and vaccine development. Therefore, scientists processed the S protein to form S protein trimer, which has enhanced stability. Several studies revealed that a proline substitution of two residues (K986 and V987) increases the S protein (S-2P) stability. This approach was used in some vaccine candidates including Ad26.COV2.S viral vector vaccine, mRNA-1273 vaccine, BNT162b2 mRNA vaccine, and NVX-CoV2373 protein subunit vaccine (40–48). Since the S protein trimer structure is relatively stable, it is among the antigens that are optimal for vaccine generation.

Other Proteins

Apart from the S protein, other component proteins can also serve as targets of the COVID-19 vaccine (49). The N protein is a helical folding structure formed by the combination of the viral RNA gene chain, and it plays an essential function in viral replication (50). Relative to the S protein, the N protein was shown to be more conserved and stable, with 90% amino acid homology and fewer observed mutations over time (51). Multiple coronavirus N proteins possess high immunogenicity and are expressed in large quantities during infection (52).

During an immune response, the intermediate or C-terminal region of the N protein induces antibodies against SARS-CoV-2 (53). The M protein is a transmembranal glycoprotein, and it is distributed on the surface of SARS-CoV-2, where it participates in virus replication (54). The M protein plays a critical role in the structural stability and functional expression of other structural proteins (55). Due to its highly conserved nature, the M protein can also be used as a target antigen for developing SARS-CoV-2 vaccine.

COVID-19 VACCINES

The optimal strategy to ending this pandemic is the development of a highly efficacious anti-COVID-19 vaccine. Therefore, currently, global scientists are actively tackling the research and development of COVID-19 vaccines. The accelerated scientific research and CTs, along with the government-approved emergency use of life-saving COVID-19 vaccines are the main current efforts in combating this pandemic. So far, multiple vaccines have either completed CTs or are in CTs. Compared to other vaccines, the time spent in pre-CT and CT research in developing the COVID-19 vaccine was significantly less. However, this was a tradeoff on the premise of ensuring safety and effectiveness (**Figure 5**).

Currently, scientists all over the world are exploring all possible strategies to develop a highly efficacious vaccine against COVID-19. As mentioned before, the S protein is an optimal candidate protein for vaccine development, since it is the main target of host immune defense (49). Therefore, specific and effective neutralizing antibodies against COVID-19 can be produced that specifically target this early stage of infection. COVID-19 vaccines broke the record in the laboratory experimentation to first-in-human trials timeline (56). As of October 27, 2021, the International CTs Registry Platform (ICTRP) and COVID-NMA, an international initiative working in conjunction with WHO, reported more than 600 CTs examining COVID-19 vaccines (57). Among all CTs, the top vaccine types include traditional vaccines like inactivated and recombinant protein vaccines, as well as some novel vaccines like RNA-based, DNA-based, and non replicating viral vector vaccines, the percentages of which account for 84% of the total CTs (57) (**Figure 6**).

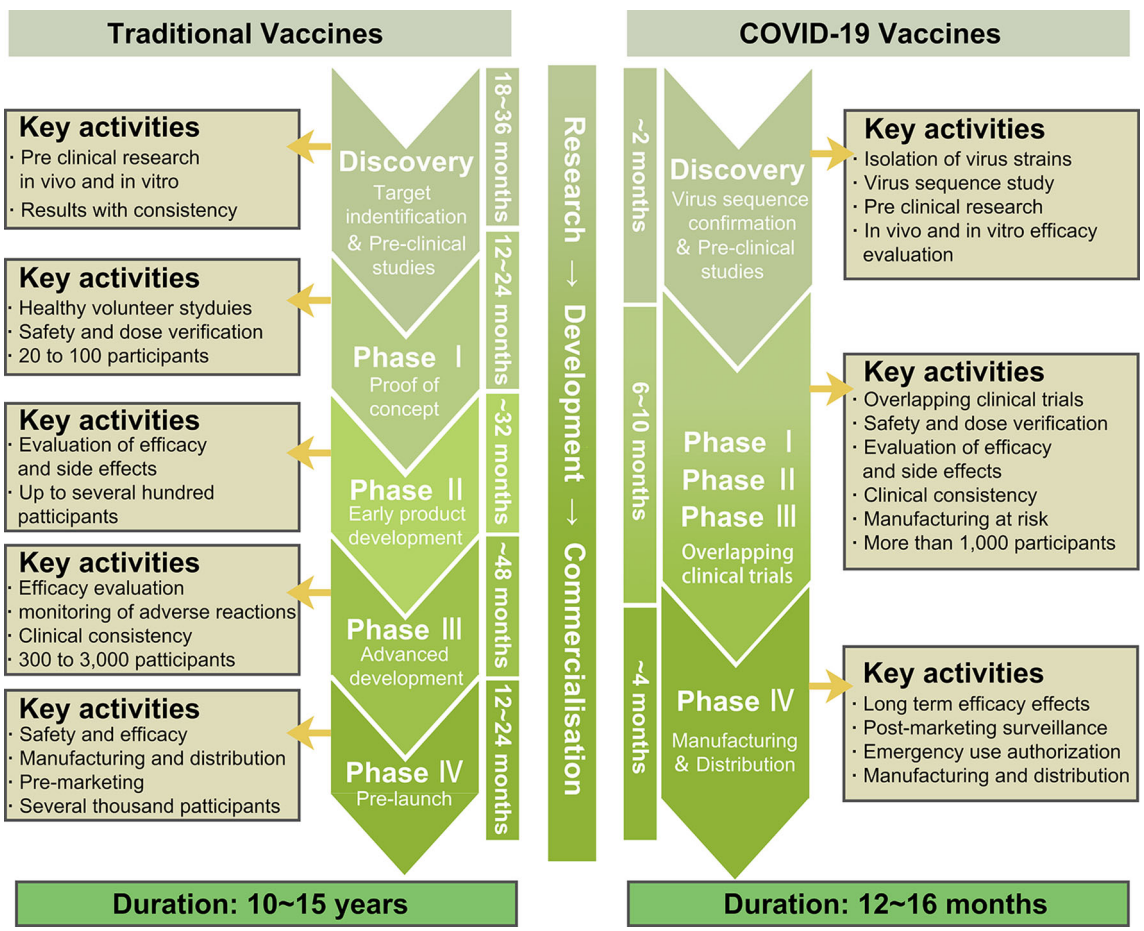

FIGURE 5 | The rapid development of COVID-19 vaccines.

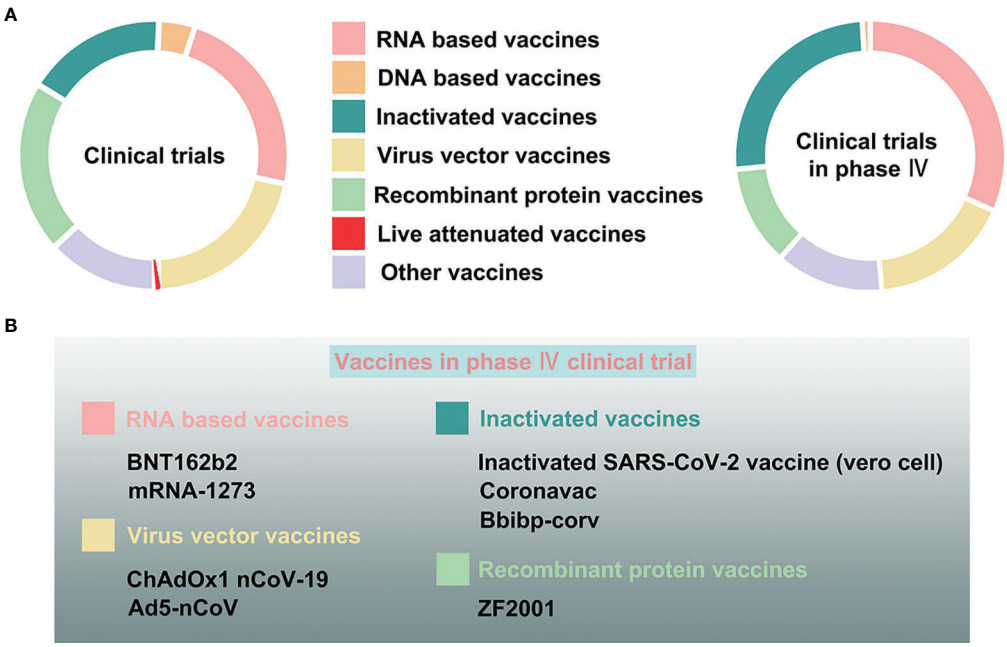

FIGURE 6 | The clinical trials assessing COVID-19 vaccines. **(A)** The proportion of varying vaccine types, namely, RNA-based, DNA-based, inactivated, live attenuated, virus vector, recombinant protein, and other vaccines, in all clinical trials, and especially in phase IV clinical trials. **(B)** The COVID-19 vaccines in phase IV clinical trials.

Inactivated Vaccines

Inactivated viral vaccines are developed by culturing the viruses first, and then inactivating them with heat or chemical agents (6). These vaccines are typically composed of the entire virus, or split viral fragments. Whole virus inactivated vaccine is a classic vaccine technology route (7). Put simply, the virus itself is killed whereas its shell is retained. Therefore, it is unable to induce host cell interference, but it does elicit a strong immune response, based on humoral immunity (58). In response to inactivated vaccines, host immune system can boost antibody production that neutralize and remove pathogenic microbes as well as their toxins so they do not bind target cell receptors and initiate infection. The production of inactivated vaccines is relatively easy. However, their yield depends on *in vitro* viral productivity and need for bio-safe viral production facilities (7).

The efficacy and safety of inactivated vaccines often hold significant advantages. Furthermore, compared to other vaccines, the development cycle of inactivated vaccines is relatively short. Therefore, numerous COVID-19 inactivated vaccines entered into CTs in different countries, including China, India, Turkey, Brazil, Thailand, and Pakistan (3, 9, 10). In particular, about half of the inactivated vaccines entered phase III or IV CTs, and several were approved for marketing, including Sinopharm Beijing Biological Vaccine in China, Sinopharm Wuhan Biological Vaccine in China, and Sinovac Biotech inactivated vaccine in China (**Table 1**) (57). The simultaneous research and development of different inactivated vaccines and CTs provides guarantee for faster production of effective vaccines. Two inactivated vaccines developed in China, namely, the inactivated sars-cov-2 vaccine (vero cell) and the Coronavac, can effectively produce a strong immune response, and significantly lower symptomatic COVID-19 risk (59, 60, 72–75). Since the inactivated vaccine is suitable for long-term preservation and transportation, the China-based vaccine was supplied to multiple countries all over the world (205, 206). However, serum neutralizing activity against multiple SARS-CoV-2 variants of concern (VOCs), including Delta, Beta, and Omicron variants, elicited by the inactivated vaccines is decreased, suggesting that inactivated vaccine protection against mutant strains is weakened and further immunization is needed to deal with the VOCs (61, 76, 207).

Covaxin is the first indigenous anti-COVID-19 vaccine developed in India (208), where the epidemic is still very serious. Coupled with various COVID-19 mutations, it is difficult for some regions to cope with the impact of the epidemic (209). However, India made considerable contributions to the prevention and control of the epidemic (210). Studies revealed that the inactivated vaccine Covaxin effectively neutralizes a variety of recently emerging variants of SARS-CoV-2 (89, 90). In addition, Covaxin Booster could effectively protect against VOCs, including Delta and Omicron variants (91, 92). Covaxin promotes and enhances the response of cytokines and chemokines (211). Following vaccination, the innate and adaptive immune responses of vaccine recipients are also strongly activated (211). In a large phase III CTs, the vaccine was found to have a 77.8% protective effect against symptomatic COVID-19, with no major side effects (93). However, it is worrying that the Covaxin vaccine lacks some reports on the

TABLE 1 | SARS-CoV-2 vaccine candidates in clinical phase III and IV.

Vaccine Type	Vaccine Name	Country/ Organization	Targets	Phase	Safety	Efficacy	Reference
Inactivated virus	Inactivated sars-cov-2 vaccine (vero cell)	China	Whole inactivated SARS-CoV-2 with aluminum hydroxide adjuvant	**Phase III** ChiCTR2000034780 ChiCTR2000039000 NCT04510207 NCT04612972 NCT04659239 NCT04852705 PER-051-20 **Phase IV** ChiCTR2100043907 ChiCTR2100046174 ChiCTR2100046227 ChiCTR2100050589 NCT05065892 NCT05065879	Serious adverse events were rare.	Treatment of adults with the inactivated SARS-CoV-2 vaccines significantly reduced the risk of symptomatic COVID-19. Protection against VOCs is weakened.	(59–71)
Inactivated virus	Coronavac	China	Whole inactivated SARS-CoV-2 with aluminum hydroxide adjuvant	**Phase III** NCT04456595 NCT04582344 NCT04651790 NCT04942405 **Phase IV** NCT04747821 NCT04756830 NCT04775069 NCT04789356 NCT04911790 NCT04953325 NCT04962308 RBR-9ksh5f4 TCTR20210308003 NCT04801667	Immunization with Coronavac in a 0-14 schedule in adults is safe, induces anti-S1-RBD IgG with neutralizing capacity, activates T cells, and promotes the secretion of IFN-γ upon stimulation with SARS-CoV-2 antigens.	The vaccine exhibited a over 60% efficacy on average at preventing COVID-19 illness with favorable safety and immunogenicity profiles. Protection against VOCs is weakened and further immunization is needed.	(72–88)
Inactivated virus	Covaxin	India	Whole inactivated SARS-CoV-2 with Algel-IMDG adjuvant	**Phase III** NCT04641481 **Phase IV** CTRI/2021/08/035648	Vaccination was well tolerated with no safety concerns raised.	A protective effect of 77.8% against symptomatic COVID-19. Effectively protect against VOCs.	(89–95)
Inactivated virus	Bbibp-corv	China	Whole Inactivated SARS-CoV-2	**Phase III** NCT04560881 NCT04917523 NCT04984408 TCTR20210923013 **Phase IV** NCT04863638 TCTR20210910002 NCT05079152 NCT05105295 NCT05104216	BBIBP-CorV is tolerable and immunogenic in healthy people.	More than 75% of the vaccinators had seroconversion after the first vaccination.	(60, 63, 96–106)
Inactivated virus	QazCovid-in	Kazakhstan	Whole Inactivated SARS-CoV-2	**Phase III** NCT04691908	High safety and potency.	Preliminary results of studies demonstrate efficacy of the vaccine at 96%.	(107, 108)
Inactivated virus	VLA2001	Cooperation between France and Britain	Whole inactivated SARS-CoV-2 with high S-protein density, in combination with two adjuvants, alum and CpG 1018	**Phase III** NCT04864561 NCT04956224	Not reported.	Not reported.	(109, 110)
RNA based vaccines	BNT162b2	Germany	Full-length S protein with proline substitutions	**Phase III** NCT04713553 NCT04754594 NCT04800133 NCT04816669 NCT04955626 **Phase IV** NCT04852861 NCT04951323	High safety.	It was well tolerated and could induce neutralizing antibodies. Better protection for VOCs.	(111–122)

(Continued)

TABLE 1 | Continued

Vaccine Type	Vaccine Name	Country/ Organization	Targets	Phase	Safety	Efficacy	Reference
RNA based vaccines	mRNA-1273	America	Full-length S-2P protein	**Phase III** NCT04470427 NCT04805125 NCT04806113 NCT04811664 NCT04860297 **Phase IV** NCT04885907 NCT04952402	No safety concerns were identified.	The vaccine showed 94.1% efficacy in preventing SARS-CoV-2. Better protection for VOCs.	(42, 112, 123–133)
RNA based vaccines	CVnCoV	Germany	Full-length S-2P protein	**Phase III** NCT04674189 NCT04838847 NCT04860258	Two doses of vaccine were safe.	The vaccine could effectively induce immune response. CVnCoV exists immune escape for VOCs.	(134–139)
RNA based vaccines	ARCoV	China	Encoding the RBD of S protein	**Phase III** NCT04847102	Not reported.	Not reported.	(140, 141)
DNA based vaccines	ZyCov-D	India	S protein	**Phase III** CTRI/2021/01/03041-6	Not reported.	The vaccine has 66.6% efficacy from Clinical trials.	(142–144)
DNA based vaccines	Electroporation +ino-4800	America	S1 and S2 subunits	**Phase III** PACTR20211062694-4896	The vaccine showed excellent safety and tolerability.	The vaccine induced a protective immune response.	(145–147)
Recombinant protein vaccines	Recombinant SARS-CoV-2 vaccine (CHO Cell) (ZF2001)	China	RBD-Dimer with alum adjuvant	**Phase III** ChiCTR2000040153 NCT04646590 NCT05091411 ChiCTR2100050849	Not reported.	Have good tolerance and immunogenicityand be effective effect on neutralization of VOCs.	(148–154)
Recombinant protein vaccines	Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	China	RBD with alum adjuvant	**Phase III** NCT04887207 NCT04904471 PACTR20210384538-1761	Not reported.	Not reported.	(155, 156)
Recombinant protein vaccines	NVX-CoV2373	America	S protein with Matrix-M adjuvant	**Phase III** NCT04583995 NCT04611802	High safety.	The overall effectiveness of the vaccine is more than 80%.	(41, 157–160)
Recombinant protein vaccines	Nanocovax	Vietnam	Recombinant S protein with alum adjuvant	**Phase III** NCT04922788	Not reported.	Not reported.	(161)
Recombinant protein vaccines	MVC-COV1901	America	Recombinant S protein with CpG 1018 and alum adjuvants	**Phase III** NCT05011526 **Phase IV** NCT05097053	MVC-COV1901 has a good safety profile.	The vaccine could elicit promising immunogenicity responses.	(162–165)
Recombinant protein vaccines	EpiVacCorona	Russia	Peptide antigens of SARS-CoV-2 proteins with alum adjuvant	**Phase III** NCT04780035	Not reported.	Not reported.	(166)
Recombinant protein vaccines	CIGB-66 (RBD/ aluminium hydroxide)	ICGEB	RBD with aluminum hydroxide adjuvant	**Phase III** RPCEC00000359	High safety.	High efficiency.	(167)
Recombinant protein vaccines	Razi Cov Pars	Razi Vaccine and Serum Research Institute	Recombinant S protein	**Phase III** IRCT2020121404970-9N3	Not reported.	Not reported.	(168)
Recombinant protein vaccines	FINLAY-FR-2 anti-SARS-CoV-2 Vaccine	Instituto Finlay de Vacunas	RBD with adjuvant	**Phase III** RPCEC00000354 IRCT2021030305055-8N1	Not reported.	Not reported.	(169, 170)
Virus vector vaccines	ChAdOx1 nCoV-19	Britain	Chimpanzee adenovirusvectored vaccine (ChAdOx1)	**Phase III** ISRCTN89951424 NCT04516746 NCT04536051 NCT04540393 **Phase IV**	ChAdOx1 nCoV-19 has an acceptable safety profile.	ChAdOx1 nCoV-19 is efficacious against	(171–179)

(Continued)

TABLE 1 | Continued

Vaccine Type	Vaccine Name	Country/ Organization	Targets	Phase	Safety	Efficacy	Reference
			expressing S protein	NCT04760132		symptomatic COVID-19.	
Virus vector vaccines	Ad5-ncov	China	Recombinant replicationdefective human type 5 adenovirus (Ad5) expressing S protein	**Phase III** ChiCTR2100044249NCT04526990 NCT04540419 **Phase IV** NCT04892459 NCT04952727	High safety.	Ad5-nCoV was well tolerated and could elicit neutralizing antibody responses.	(180–187)
Virus vector vaccines	Ad26.COV2.S	America	Recombinant replication-incompetent adenovirus serotype 26 (Ad26) vector encoding full-length S protein	**Phase III** NCT04505722 NCT04614948 NCT04838795 NCT05028257 **Phase IV** NCT05030974	High safety.	The vaccine protected against symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection.	(44, 45, 188–193)
Virus vector vaccines	Gam-COVID-Vac	Russia	Recombinant Ad26 and recombinant Ad5 encoding full-length S protein	**Phase III** NCT04530396 NCT04564716 NCT04642339 NCT04656613	High safety.	Well tolerated 91.6% efficacy against COVID-19.	(194–201)
Virus vector vaccines	Sputnik light vaccine	Russia	Recombinant Ad26 vector carrying the gene for SARS-CoV-2 S glycoprotein	**Phase III** NCT04741061 PACTR20210460157-2565	Sputnik light vaccine has a good safety profile.	Strong humoral and cellular immune responses both in seronegative and seropositive participants.	(202–204)

detailed analysis of vaccine development and any potential limitations in research design (208).

Inactivated vaccines do not cause disease, even in immunosuppressed individuals, but because they do not have a durable and long-lasting immune responses, they usually require repeat or enhanced doses, as well as adjuvants, such as, aluminum salt to be added to the vaccine.

Live Attenuated Vaccines

Live attenuated vaccine employs viruses that undergo multiple treatments or mutations to reduce pathogenecity, without diminishing immunogenicity (11). As a result, inoculation with live attenuated vaccine will not result in disease. Instead, the attenuated pathogen will continue to grow and replicate within the host body, and trigger host immune response. This aids in the acquisition of long-term or life-long protection (12). Compared to inactivated vaccines, live attenuated vaccines elicit stronger immunity and longer action time (212). However, these vaccines may not be suitable for people with compromised immune systems. Therefore, safety can be a major issue with potential risk of disease. The TMV-083 vaccine employs the measles pathogen as a vector and expresses the SARS-CoV-2 S protein antigen (13). Thus far, three live attenuated vaccine candidates, namely COVI-VAC, MV-014-212, and DelNS1-nCoV-RBD LAIV, completed phase I CTs examining safety and immunogenicity (57).

RNA-Based Vaccines

Although traditional vaccines have successfully prevented multiple diseases, in face of acute outbreaks like this new coronavirus, the development and production cycle of traditional vaccines are too time consuming to meet the needs of epidemic control (213, 214). Therefore, we urgently need a more effective and universal vaccine development platform, and mRNA vaccines are a potential solution to circumventing long vaccine production time.

The mRNA vaccine is a nucleic acid sequence that encodes a specific antigen protein synthesized *in vitro* prior to injection into the human body. Once injected, the specific protein is synthesized within the body, and induces a strong cellular and humoral immune response. This, in turn, produces specific antibodies and exerts immune protection (215). For mRNA vaccines, there is no need to inject pathogenic proteins into the body. Instead, the mRNA is introduced for translation and expression of pathogenic proteins by the vaccine recipient. This approach greatly reduces the body's adverse reactions and achieves high-efficiency immune effects. Currently, two primary mRNA vaccines are employed against infectious pathogens, including self-amplifying or replicon RNA and non-replicating RNA vaccines (216). Both vaccines produce antigen targets using the body's own translation mechanism, and then trigger an adaptive immune response within the body (217). Self-amplifying mRNA (SAM) vaccines employ an alpha viral genome, with intact RNA replication machinery, and structural information substituted with mRNA encoding the antigenic protein (218). Since the antigen-encoding RNA can replicate inside the body, the SAM platform facilitates massive antigen synthesis from a relatively small dose of vaccine. Non-replicating mRNA vaccines are artificially transcribed regions of whole mRNA encoding antigenic proteins. This includes the 5' and 3' untranslated regions, and the poly(A) tail that adds stability to

the mRNA and aids in transcription (219, 220). Other non-replicating mRNA vaccines include plasmid DNA or other DNA fragments that contain the open reading frame of target protein, and are synthesized *in vitro* (221, 222).

Pre-CT research on anti-COVID-19 mRNA vaccines has rapidly increased in recent times, and some have entered human CTs. Once Chinese scholars revealed the COVID-19 gene sequence for the first time, the first COVID-19 vaccine candidates were mRNA-1273, developed by National Institutes of Health (NIH), and Moderna, funded by the Coalition for Epidemic Preparedness Innovations (CEPI) (223). mRNA-1273 is a newly developed nanoparticle (LNP)-encapsulated mRNA vaccine encoding the prefusion stabilized full-length S protein of SARS-CoV-2 (36). In an mRNA-1273 phase I trial, the vaccine exerted a powerful neutralizing antibody titer after two vaccinations (42). On day 43, the SARS-CoV-2 neutralizing activity was observed in all assessed participants, and the antibody levels were comparable to a patient who recuperated from a new crown. Moderna recently published data on an ongoing phase III CT of the mRNA-1273 vaccine. The aforementioned trial included 30,000 subjects of varying ages (between 18 and 85 years old) (123). All participants were arbitrarily separated into two groups receiving two doses of either 100 μg mRNA-1273 or saline placebo, 28 days apart. The protective effect rate of the mRNA-1273 vaccine was 94.1%. They reported only 11 COVID-19 cases among the vaccinated participants, and 185 cases among the placebo cohort. Based on this study, this vaccine not only exerted a good protective effect, but was also relatively safe, with minimal complications (123). In a phase IV CT, involving 120 samples, the immunogenicity of a third dose of the mRNA-1273 vaccine in transplant recipients was shown to be significantly higher than the placebo (224).

Meanwhile, Biotech and Pfizer developed two COVID-19 lipid nanoparticle-formulated, nucleoside-modified RNA vaccination candidates: BNT162b1 and BNT162b2. In the pre-CT and CTs, BNT162B1 and BNT162B2 demonstrated significant safety and immune response advantages (48, 225). Upon extensive review of the phase I/II pre-CT and CT data, including consultations with the US Food and Drug Administration Center for Biologics Evaluation and Research (CBER) and other global regulatory agencies, the vaccine manufacturers selected 30 μg BNT162b2 in a two-dose immunization regimen to proceed to the crucial phase III safety and efficacy assessment. In the phase III CT, 43,448 healthy individuals were arbitrarily selected to receive injections: 21,720 with BNT162b2 and 21,728 with placebo (111). In the sample population, a total of 170 COVID-19 cases emerged, after at least 7 days of booster immunization. Among these, only 8 cases were among vaccinated individuals, and 162 cases among the placebo cohort. Therefore, the BNT162b2 protection rate was 95.0%. A survey of nearly 600,000 vaccinators further revealed that the two doses of the BNT162b2 vaccine prevented 92% of infections and 94% of symptomatic COVID-19 (226). Vaccination with mRNA-1273 or BNT162b2 vaccine provided better protection, but the effect of mrNA-1273 vaccine seemed to be better for α and δ variants (112). Due to the urgent need of the epidemic, two COVID-19 mRNA vaccines (mRNA-1273 and BNT162b2) were approved by the FDA for their versatility and rapid development advantages.

CV2CoV, an enhanced mRNA-driven SARS-CoV-2 vaccine candidate, accelerates virus neutralizing antibody production, and positively regulates immune protection in rodents (227). Research demonstrated that CV2CoV supports elevated protein levels and enhanced immunogenicity in a rat pre-CT (228). In a pre-clinical study, CV2CoV was also able to achieve a stronger antibody neutralization of variants, including the beta, delta, and lambda variants (229). According to a recent phase III CT assessing the efficacy and safety of the CVnCoV SARS-CoV-2 mRNA candidate vaccine, CVnCoV effectively prevents COVID-19 of any severity and has an acceptable safety profile (230). However, CVnCoV exists immune escape for SARS-CoV-2 variant (134, 135). Therefore, vaccination needs to be strengthened to deal with the weakened immune response and the emerging SARS-CoV-2 variants.

Compared to traditional vaccines, the difficulty and key technology of the mRNA vaccine development mostly lies in its modification and delivery system (217, 231). In fact, mRNA synthesis and modification can vastly improve its molecular stability, while preventing degradation. The delivery system selection can also improve the efficiency of mRNA entry into human cells, to produce antigen, and stimulate an immune response within the host. Both Moderna and BioNTech chemically modified their mRNA vaccines, replacing Uridine (U) with Pseudouridine (ψ), which reduced immunogenicity and increased stability of the mRNA (232). In contrast, CureVac, one of the three giants in mRNA vaccine research and development, employed unmodified uridine to enhance mRNA translation through sequence optimization and selection of untranslated regions (UTRs), perhaps to circumvent patent issues related to mRNA molecular modification, thus, resulting in high immunogenicity, low dose, and poor effect (233, 234). In addition, lipid nanoparticles (LNPs) are the current most advanced and mainstream mRNA delivery system (235). Their high entrapment efficiency protects mRNA from degradation, and the easy fusion of liposomes with recipient cells improves delivery efficiency. The delivery mechanism of LNPs is mainly through the combination of cationic liposomes with negatively charged mRNA to form complexes with particle size less than 200nm, and then enter cells through endocytosis (236). LNPs delivery system was used for all COVID-19 mRNA vaccines. BioNTech and Moderna's COVID-19 mRNA vaccines use ionizable lipids ALC-0315 and SM102, respectively (237). The common auxiliary lipids were DSPC and cholesterol. Due to the complex relationship between patent protection and license transaction of COVID-19 mRNA vaccines, the LNP delivery system is a major focus of competition. However, none of these technologies have been commercialized thus far.

The biggest advantage of such vaccines is that they can be produced completely *in vitro*. However, it is unclear what challenges may surface during large-scale production, long-term frozen storage, and in vaccine stability. In addition, since the drug is administered by injection, it is unlikely to induce a strong mucosal immune response.

DNA-Based Vaccines

DNA vaccine, yet another type of nucleic acid vaccine, is made from DNA encoding antigen protein. Unlike traditional vaccines, DNA vaccines are designed to inject a specific naked DNA code of the pathogen directly into the human body (219, 238). Once inside, it can be transcribed into mRNA in the nucleus and translated into antigen in the cytoplasm, thereby inducing the body to produce an immune response (239). Thus, vaccinated individuals obtain corresponding immune protection and disease prevention capabilities (240). Interestingly, its rapid technological development may create a whole new generation of immunologic tools. Multiple DNA vaccines are currently under development, including malaria, influenza, rotavirus, HIV, and so on. Furthermore, many of them have already entered CTs (241–243). DNA vaccination offers more potential advantages, compared to traditional vaccines, including stimulation of the B and T cell immune responses, stabilization of the vaccine, avoidance of any infectious agents, and ease of large scale production (244). More importantly, a large-scale COVID-19 vaccination is under rapid execution around the world, and the "stability" that determines whether a vaccine is convenient for transportation, and storage is a major indicator of vaccine feasibility (245). Compared to RNA vaccines, DNA vaccines can be stored for a longer period of time at the same refrigeration temperature, or even for a longer time at room temperature (246). Once successfully developed and put into use, this will likely bring great convenience to the mass production of vaccines. However, DNA vaccines usually exhibit low immunogenicity, and must be inoculated through delivery devices (such as, electric perforators) to be effective, which also limits their use.

Due to the COVID-19 pandemic outbreak, numerous DNA vaccine candidates entered CTs. According to the information from ICTRP, three of them entered phase III CTs, namely INO-4800, AG0302-COVID19, and, ZyCoV-D. INO-4800, developed by INOVIO Pharmaceuticals, is a DNA vaccine candidate for the prevention of the new coronavirus (243, 247). After the new coronavirus gene sequence was released, INOVIO employed a proprietary DNA drug platform to quickly design the INO-4800 vaccine (247). Pre-CT revealed that INO-4800 strongly induces SARS-CoV-2 specific antibody and T cell responses in mice and guinea pigs, hence, it was quickly approved for CTs (248). Based on the phase I CT results, INO-4800 is immunogenic in all subjects, and effectively produces humoral immune and/or cellular responses (145). Currently, the INO-4800 vaccine is simultaneously in both phase II/III CTs, and its safety and effectiveness reports are worthy of attention. AG0301-COVID19, a DNA vaccine developed by Osaka University/AnGes/Takara Bio, expresses the full-length S protein upon host cell entry. In a pre-CT, AG0301-COVID19, with an aluminium-containing adjuvant, strongly stimulated neutralizing antibody production, and enhanced T cell responses in rats, with no toxic response to body organs. Yet another COVID-19 DNA vaccine candidate is AG0301-COVID19, also developed by the Osaka University/AnGes/Takara Bio. The safety and effectiveness of the AG0301-COVID19 vaccine was examined in phase I/II CTs, but the results are not yet reported (243). It is worth noting that the phase III CTs are in progress at the present time. Recently, India urgently authorized and approved the listing of a DNA COVID-19 vaccine ZyCov-D that consists of a DNA plasmid vector harboring the S protein genetic code. A pre-CT study revealed that ZyCov-D elicits marked antibody and Th-1 responses, as demonstrated by augmented IFN-c expression (249). In a phase I CT, the ZyCov-D vaccine, which is administered by pressing a needle-free device on the skin, was reported to be safe, well tolerated, and immunogenic (142). The device creates a tiny stream of high-pressure liquid that pierces the skin surface, thus causing less pain for the recipient. ZycoV-D is currently conducting a large-scale phase III CT in India, involving tens of thousands of subjects, but the data is not public yet. However, due to its high efficiency and safety, India urgently authorized the application of ZycoV-D. Thus far, this is not only the first DNA vaccine for COVID-19, but also the first DNA vaccine in the world. Till date, no DNA vaccine completed phase III trials or received approval.

Recombinant Protein Vaccines

Recombinant vaccine is a virus or protein, produced by modern genetic engineering technology, which can induce immune response in human or animal host to achieve disease prevention or treatment (12). There are two types of vectors: bacteria and virus. The primary mechanism of this vaccine is to employ genetic engineering to introduce and express pathogenic antigen encoding genes in adenoviruses (46). The first step is to identify the gene that encodes the target antigenic protein, for example, the viral S protein (5, 12). The following step involves fusion of this gene with the adenovirus, prior to introduction into human body. Once inside, the encoded gene synthesizes the S protein and induces a strong humoral and cellular immunity that encourages the body to produce target-specific antibodies (3, 5).

Compared to traditional vaccines, recombinant vaccines are not only easier to produce, but also more effective or widespread. Since the pandemic outbreak, the viral recombinant subunit protein vaccine is, for the first time, being jointly developed by cooperative enterprises. The recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) is a recombinant protein vaccine, made from a prefusion-stabilized spike trimer of SARS-CoV-2, and combined with aluminium hydroxide and CpG 7909, prior to expression and purification in Chinese hamster ovary (CHO) cells (151). Immunogenicity studies revealed that the recombinant new coronavirus vaccine (CHO cell) triggered a strong neutralizing antibody response and considerable $CD4^+$ T cell responses in both mice and non-human subjects (151). Importantly, the candidate vaccine significantly lowered viral loads and lung inflammation in SARS-CoV-2-infected golden Syrian hamsters (22). According to the phase I and II CT data, the protein subunit vaccine ZF2001 has good tolerance and immunogenicity (148). Importantly, ZF2001 presented effective effect on neutralization of the antisera to SARS-CoV-2 variants including Delta (149, 150). At present, a large-scale phase III CT was launched in China,

Uzbekistan, Pakistan, Ecuador, Indonesia and other countries to evaluate the safety and effectiveness of ZF2001. Since the ZF2001 phase III CT is progressing smoothly, it has already received approval for emergency use in China. This makes this vaccine the first virus recombinant subunit protein vaccine to be approved for clinical use in the world.

In conclusion, the key advantage of these vaccines is that they can be produced without employing live viruses, and they possess considerable market production value. However, this kind of vaccine also has certain disadvantages. The S protein is relatively difficult to express, which may affect the yield. In addition, the selection of a purification method may affect the vaccine-triggered immune response.

Virus Vector Vaccines

Virus vector vaccine, another kind of nucleic acid vaccine, uses non-toxic viruses as vectors. Genes that encode pathogenic antigens are cloned into non-replicating or replicating viral vectors (such as, adenoviruses). The injected pathogenic gene produces corresponding pathogenic protein fragment that induces an immune response to the target pathogen. Since the viral vector itself promotes an immune response, it produces a stronger response than a simple nucleic acid sequence from the target pathogen. Due to the advantages of high titer, reduced pathogenicity, enhanced transduction efficiency, widely infected tissues, and no host cell genome integration, adenovirus vectors are commonly used in experimental and clinical research, including fields of gene transduction, gene therapy, vaccination, and oncolytic therapy.

Being a non-replicating viral vector, a replication-defective human type 5 adenovirus, encoding the SARS-CoV-2 S protein (Ad5-nCoV), developed by the Chinese People's Liberation Army Academy of Military Sciences and CanSino Biologics, is the first vaccine candidate to enter CT for COVID-19 vaccination in the world. Pre-CT research revealed that a single dose of Ad5-nCoV offers full protection to murine upper and lower respiratory tracts against the SARS-CoV-2 infection (180). It was also confirmed that a single dose of Ad5-nCoV protects ferret upper respiratory tracts against wild-type SARS-CoV-2 infection (180). In a phase I CT, an aerosolized booster vaccination with Ad5-nCoV at 28 days after the first intramuscular injection induces strong IgG and neutralizing antibody responses (181). Single-peripheral blood mononuclear cell RNA sequencing of samples from the COVID-19 vaccine trial participants revealed that the cellular immunity, cell type-specific IFN, and humoral immunity responses with SARS-CoV-2-specific antibodies were enhanced. This indicates that Ad5-nCoV is a promising vaccine candidate for COVID-19 (250). In addition, the percentage of neutralizing antibodies induced by the Ad5-nCoV vaccine in individuals with COVID -19 was higher than in individuals without COVID -19 (251). Phase II CT revealed that Ad5-nCoV was safe and generated a massive immune response in most recipients following a single dose of vaccine (252). At present, Ad5-nCoV is in phase III CTs and received approval for emergency use in multiple countries.

ChAdOx1 nCoV-19, co-developed by the Oxford University and AstraZeneca, also demonstrated satisfactory safety profile and efficacy, and homologous booster shots enhanced antibody responses in phase I/II CTs (253, 254). The ChAdOx1 nCoV-19 vaccine not only possesses immunogenicity, and induces strong humoral and cell-mediated responses in mice, but also effectively prevents SARS-CoV-2 pneumonia in rhesus monkeys (255). Additionally, the vaccine is tolerant and promotes neutralizing antibody and antigen-specific T cell production against the SARS-CoV-2 S protein (256). Based on the phase III CT study, ChAdOx1 nCoV-19 tolerance is enhanced in older adults, relative to younger adults. In addition, a booster shot induces comparable immunogenicity in all age groups (171).

In addition, the Ad26 vector-based COVID-19 vaccine (Ad26.COV2.S) is a non replicating viral vector vaccine that encodes a prefusion-stabilized SARS-CoV-2 spike immunogen, and it induces effective humoral and cellular immune responses (257), and enhances immunogenicity and reactivity of booster vaccinations (258). Pre-CT revealed that Ad26.COV2.S protects against SARS-CoV-2, and develops better immunogenicity in rats, as well as adult and elderly rhesus monkeys, suggesting that it may be a potential vaccine candidate for COVID-19 (43, 46, 259). In multiple CTs, the candidate vaccine Ad26.COV2.S was found to be both safe and immunogenic in both younger and older adults (44, 260, 261). Considering the safety and effectiveness of pre-CT, several phase III CTs involving Ad26.COV2.S are currently underway. The outcome of Ad26.COV2.S on infection and transmission is yet to be released. Gam-COVID-Vac and Sputnik light vaccine, two additional non-replicating viral vector vaccines, employ the recombinant adenovirus type 26 (rAd26) vector harboring the SARS-CoV-2 S protein genetic code, and were developed by Russia. Single immunization with the Ad26 vector vaccine expressing the stable SARS-CoV-2 spike protein elicits interaction and neutralizing antibody reactions. The Ad26 vaccine safeguards against severe clinical disease of SARS-CoV-2 in hamsters. This indicates that the vaccine protects against the SARS-CoV-2 infection (46). According to the CT analysis, Gam-COVID-Vac and Sputnik light vaccine demonstrated good efficacy, safety, and tolerance against COVID-19 infection (194–196, 202, 262, 263). Thus, based on the proven efficacy and safety of these vaccinations, both Gam-COVID-Vac and Sputnik light vaccines received approval for emergency use in Russia and numerous other countries (264).

The approval and emergency usage authorization of several COVID-19 vaccines worldwide have made significant progress in fighting against SARS-CoV-2. However, the emergence of mutant strains, which can re-infect a large number of previously immunized individuals, has renewed concerns about potential vaccine vulnerability. Therefore, a comprehensive analysis of the current development status of vaccines provides a theoretical basis for guiding the design and deployment of vaccines in the future.

CONCLUSIONS

The COVID-19 pandemic brought severe challenges to the global economic burden, medical institutions, and medical infrastructure. It is time-consuming to collaborate with a wide

range of expertise to achieve innovative and effective solutions. Vaccines are an important strategy in the management of viral transmission. One of challenges of COVID-19 vaccines is the ADE effect. From the beginning of the COVID-19 vaccine development, scientists and researchers attempted to identify a SARS-CoV-2 protein, which elicited the least ADE effect. Thus far, no ADE effect was observed in the animal studies and human clinical trials. However, the ADE effect requires additional investigation, as it involves both vaccine development and treatment.

In addition, vaccines must be used effectively, and in combination with other evidence-based public health measures, in order to play a decisive role. Furthermore, the efficacy of SARS-CoV-2 novel vaccines must be critically evaluated, with a scientific and rigorous attitude, in order to understand its universality and clinical significance. Considering the nature of SARS-CoV-2, the vaccine may require regular modifications, and other scientific questions regarding novel vaccines will need to be answered, particularly, in terms of vaccine design and improvement of vaccine effectiveness, including antigen screening, administration route, clinical trials, vaccine safety, effectiveness, dose enhancement, optimization of vaccination regimens, strengthening of post-vaccination monitoring, and so on. Timely and coordinated implementation of these post-vaccination tasks will effectively and efficiently bring the pandemic to an end.

AUTHOR CONTRIBUTIONS

ZZ and QS prepared the initial drafts of the manuscript and contributed equally to this work. HC was mainly responsible for revising the manuscript. All of the authors approved the final version of the manuscript.

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