Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Innovations and development of Covid-19 vaccines: A patent review

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ABSTRACT

More than 125 million confirmed cases of COVID-19 have been reported globally with rising cases in all countries since the first case was reported. A vaccine is the best measure for the effective prevention and control of COVID-19. There are more than 292 COVID-19 candidates' vaccines being developed as of July 2021 of which 184 are in human preclinical trials. A patent provides protection and a marketing monopoly to the inventor of an invention for a specified period. Therefore, vaccine developers, including Moderna, BioNTech, Janssen, Inovio, and Gamaleya also filed patent applications for the protection of their vaccines. This review aims to provide an insight into the patent literature of COVID-19 vaccines. The patent search was done using Patentscope and Espacenet databases. The results have revealed that most of the key players have patented their inventive COVID-19 vaccine. Many patent applications related to COVID-19 vaccines developed via different technologies (DNA, RNA, virus, bacteria, and protein subunit) have also been filed. The publication of a normal patent application takes place after 18 months of its filing. Therefore, many patents/patent applications related to the COVID-19 vaccine developed through different technology may come into the public domain in the coming days.

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Introduction

In December 2019, a novel coronavirus associated with cluster pneumonia was identified in Wuhan, China. It spread rapidly, leading to a global pandemic [1]. The disease was named Coronavirus diseases 2019 (COVID-19) by the World Health Organization, and the virus was designated severe acute respiratory syndrome coronavirus two (SARS-CoV-2) [2]. COVID-19 outbreak poses a challenge to the global biomedical community and public health system [3]. The pandemic has now spread to every nation, infected millions, and murdered a considerable number of individuals [4,5]. Because of this unprecedented and earnest health challenge, so many interventions from the use of off-label drugs, stem cell therapy, convalescent patient serum, and drug repurposed were mobilized.

More than 125 million confirmed cases of COVID-19 have been reported globally [6]. Cases have been on the rise in all countries since the first case was reported. However, only a negligible portion of acute infections was diagnosed, thereby underestimated the overall effects of COVID-19. The primary source of infection is infected patients during their prodromal period producing and shedding large quantities of the viruses from their upper respiratory tract [7]. All populations are susceptible to COVID-19 infection, but the most vulnerable are the health care workers, children, elderly and pregnant women [8].

SARS-CoV-2 is an enveloped RNA virus of the β-coronavirus, with a hereditary succession the same as SARS-CoV-1 (80%) and bat coronavirus (96.2%). The viral envelope is covered by spike (S) glycoprotein, envelope (E), and film (M) proteins. Host cell restricting and passage are interceded by the S protein [9]. Practically all SARS-CoV-2 vaccines developed and being developed focused on the spike (S) protein and the viral receptor-binding domain (RBD) [10–12]. This receptor binding domain bind to angiotensin-converting enzyme 2 (ACE2), a receptor on the surface of the host cells, thereby initiating the infection process [13]. SARS-CoV and SARS-CoV-2 share similar host receptor binding sites. However, the latter bind more than ten times higher than the former [14]. This may add to the higher contagiousness and infectiousness of SARS-CoV-2 when contrasted with SARS-CoV. The spike protein is highly immunogenic and capable of inducing neutralizing antibodies and serves as a significant virulence factor of coronaviruses [15,16].

Over 80% of COVID-19 sicknesses are asymptomatic or indicative of gentle side effects like respiratory manifestations, cough, fever, and difficulty breathing. In certain patients, COVID-19 outcomes in severe ailment will present with serious pneumonia, acute respiratory failure, pulmonary edema, acute respiratory syndrome (ARDS), sepsis, and numerous organ disappointment, leading to death [17,18]. However, not every one of these symptoms is available in COVID-19 cases. Pregnant women having COOVId-19 will present with similar symptoms as that of non-pregnant women [19].

The diagnosis of COVID-19 starts with a good clinical evaluation. The clinical diagnosis can be dependent on signs and symptoms, history of exposure, and chest imaging. Even though COVID-19 presents various manifestations, there are no particular signs or symptoms that could be considered diagnostic [20]. Therefore an individual suspected of COVID-19 should be clinically assessed, and a confirmatory test should be done using real-time polymerase chain reaction (RT-PCR). The preferred specimen for this test is the respiratory tract samples like the throat swab. Other specimens that can be used include; cord blood, amniotic fluids in pregnant women [21]. Besides, chest CT may have high symptomatic worth in light of its ordinary pictures of infection contamination, high exactness with a low bogus negative rate, and time productivity.

Globally, researchers are attempting to discover and produce medicines for COVID-19. The optimum supportive patient care incorporates oxygen for seriously sick patients. Such patients are usually extremely sick and need respiratory help, such as ventilation for fundamentally ill patients. Dexamethasone is a corticosteroid that can help lessen the time allotment on a ventilator and save patients' lives with severe and primary disease [22]. WHO doesn't suggest self-prescription with any drugs, including anti-infection agents, as a counteraction or solution for COVID-19. An antiviral medication called remdesivir is the primary medication affirmed by the United States food and drug administration (FDA) to treat hospitalized COVID patients beyond 12 years old [23]. The FDA has also given emergency use approval (EUA) for two medications called monoclonal antibodies to treat COVID-19 [24]. Casirivimab and imdevimab can be given to high-chance patients who have as of late been determined to have gentle to direct ailment to bring down levels of the infection in their bodies and lower the danger of hospitalization [25]. The FDA has repealed its emergency approval to utilize hydroxychloroquine and chloroquine to treat individuals hospitalized with COVID-19 amid genuine worries about their safety and how well they neutralized the infection [26]. However, a vaccine is perhaps the best clinical measure for effective prevention and control, as recommended by WHO [27]. Therefore, making available an effective vaccine will help prevent susceptible populations and provide complex immunity to terminate the COVID-19 pandemic.

Vaccines are biologics that give dynamic, versatile invulnerability against explicit infections and contain drugs that look like the microorganisms that cause infection [28]. They are frequently produced using either killed or attenuated microorganisms, their surface proteins, or toxins, either ingested or inhaled, to stimulate the immune system to produce antibodies that will recognize and neutralize infecting microorganisms [29,30]. There are different types of vaccines, each intended to teach our immune system how to get rid of invading pathogens. These vaccines are of four kinds; subunits, recombinant, live-attenuated, inactivated, toxoid, and conjugated vaccines.

Pfizer-BioNTech COVID-19 vaccine is an mRNA vaccine. It has recently been approved by the U.S. Food and Drug Administration (FDA). However, it has been approved for crisis use by the FDA under an Emergency Use Authorization to forestall Coronavirus Disease 2019 (COVID-19) for use in people from 16 years and above. In light of proof from clinical trials, the Pfizer-BioNTech vaccine was 95% successful at forestalling confirmed cases of COVID-19 without evidence of past infection [31]. The mRNA is formulated in lipid particles to express and deliver the viral spike protein to the host immune system, eliciting an immune response that protects against COVID-19 [32]. Pfizer/BioNTech requires temperature-controlled shippers for transporting vaccines at the recommended storage temperature of $-70 \pm 10\,^{\circ}C$ for up to 15 days. After thawing, the vaccine can only be stored at refrigerated conditions (2–8 °C) for up to 5 days [33].

Moderna vaccine is also a USFDA approved mRNA vaccine recommended for 18 years and above with 94% efficacy with the administration of two doses of the vaccine [34]. It is a modified nucleoside mRNA vaccine. Its formulation is similar to that of the Pfizer-BioNTech vaccine and elicits an immune response to SARS-CoV-2 S antigen, which gives protection against COVID-19 [35]. The mRNA vaccine candidate of Moderna can remain stable at refrigerated conditions (2–8 °C) for 30 days; it can be stored for six months at −20 °C [33].

Johnson & Johnson vaccine, a viral vector vaccine recommended for individuals above 17year and has 66% efficacy [36]. The vaccine was 66.3% viable in clinical trials at forestalling confirmed cases of COVID-19 in individuals who had no proof of earlier infection fourteen days after accepting the vaccine [37]. The vaccine had high adequacy at forestalling hospitalization and demise in individuals who became ill. Nobody who got COVID-19 should be hospitalized

Table 1
Important vaccines under phase III trial.

Name of vaccine	Manufacturer	Type of vaccine	Reference
CoronaVac (PiCoVacc)	Sinovac	Purified whole SARS-CoV-2 components	[46]
New Crown COVID-19	Wuhan Institute of Biological Products/Sinopharm	Purified whole SARS-CoV-2 components	[47]
BBIBP-CorV	Beijing Institute of Biological Products/Sinopharm	Purified whole SARS-CoV-2 components	[48]
mRNA1273	Moderna/NIAID	Lipid-encapsulated mRNA	[32,49–51]
BNT162b2	BioNTech/Fosun Pharma/Pfizer	Lipid-encapsulated mRNA	[52,53]
Ad5-nCoV	CanSino Biological Inc./Beijing Institute of Biotechnology	Human adenovirus type5 (Ad5)	[54]
ChAdOx1 nCoV-19	AstraZeneca/University of Oxford	Chimpanzee adenovirus (ChAd)	[55,56]
Ad26.COV2-S	Janssen Pharmaceutical companies	Human adenovirus type 26 (Ad26)	[57–59]

after 4week of vaccination. Early proof proposes that the vaccine may protect against asymptomatic infection, which is the point at which an individual is infected by the virus that causes COVID-19 yet doesn't become ill [38]. Un-punctured vials of Janssen COVID-19 Vaccine may be stored between 9 and 25 °C for up to 12 h [33].

AstraZeneca/Oxford vaccine against COVID-19 is a replication-defective viral vector vaccine with an average efficacy of 70.4% on a clinical trial. The effectiveness of the AstraZeneca/Oxford vaccine was evaluated in participants aged 18 years and older and confirmed its safety and efficacy against symptomatic COVID-19 [39]. The vaccine was found to possess similar immunogenicity across all age groups following the booster dose [40]. Although the average efficacy of the vaccine is lower than those produced by Moderna and Pfizer/BioNTech, its recommended storage conditions are worth consideration, most especially by scarce resource countries. The vaccine can be transported, stored, and distributed at refrigerated conditions (2–8 °C) for a minimum of six months using existing healthcare settings [33].

As of July 2021, there are more than 292 candidates' vaccines being developed for COVID-19. Of these, about 184 are in human preclinical trials while the remaining are in the clinical trials of which the majority of them are protein subunit vaccines [41–43]. There are many others in clinical trial phase I/II, which will soon enter phase III clinical trials [44,45]. Many of these vaccines will be assessed for safety and effectiveness before considering the human clinical trial. Only one in five is booming after the clinical trial. Therefore, having bunches of various vaccines being developed builds the odds that there will be at least one effective vaccine that will be demonstrated to be effective and safe to the population (Table 1).

The global race to develop an effective and safe vaccine against COVID-19 is ongoing, and it involved many strategies and approaches which include but are not limited to: Live attenuated vaccine strategies that involved the use of live pathogen after long cell culture passaging in non-human cell lines to decreases its virulence [60]. This sort of vaccine typically evokes strong and long-haul memory invulnerable reactions after a single dosage. Inactivated vaccine strategies involved using the entire microbe that has been weakened by chemicals or heat to the level that it cannot cause diseases [46]. Sub-unit vaccine strategies involved using purification of antigens of pathogens from recombinant expressed antigens or replicated via cell culture [61]. However, this type of vaccine needs an adjuvant to signal antigen-presenting cells and incite vigorous immune reactions. Virus-like particle strategies involved using recombinant yeast and an expression system. Viral vector strategies involved genetically modifying the virus to serves as a platform for expressing antigen of interest leading to stimulation of powerful cell and humoral reaction [62]. Finally, nucleic acid (mRNA and DNA) vaccine strategies are swift to produce but untested as successful human vaccine systems. The immunogenic protein of the pathogen is being corded in mRNA or DNA upon administration. It is captured antigen-presenting cells that expressed and presented the antigen to the immune system to produce neutralizing antibodies [63]. This type of vaccine has been predicted to be safe and has little or no safety as the nucleic acid is immediately degraded in the body.

Speeding up vaccine development by merging typical clinical trial phases being done on smaller populations [64]. This is a massive worry since when the vaccine is delivered for public use internationally, obscure results may show up in the bigger populace, which was already not seen inside the smaller population. Moreover, if all young and old and those with comorbidities are not properly viewed as in the plan of the clinical trials, entirely possibly unjustifiable results might be seen in those populations when the vaccine is made available for public use [65]. Similarly, this type of vaccine's long-term side effect is unknown and cannot be predicted due to the shortening of the clinical trial period [66].

The vaccine developer, including Moderna, BioNTech, Janssen, Inovio, and Gamaleya filed patent applications for the protection of their vaccines. A patent grants protection and marketing exclusivity to the inventor of an invention for a predetermined period. This review aims to provide an insight into the patent literature of COVID-19 vaccines.

Patent searching

The patent search was performed on September 30, 2021. A combination search of "vaccine and COVID-19" in the Espacenet database revealed 722 hits, whereas the "vaccine and SARS-CoV-2" combination provided 1601 hits. Similarly, a combination search of "vaccine and COVID-19" in the Patentscope database yielded 331 hits, whereas the "vaccine and SARS-CoV-2" combination provided 2657 hits. The Sci-finder search afforded 207 and 174 hits, respectively for the combination search. According to the WHO website (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines; Accessed on September 30, 2021), about 121 COVID-19 vaccines based on different platforms (protein subunit, viral vector, DNA, inactivated virus, RNA, viral vector, virus-like particle, and live attenuated virus) are in clinical development, and about 194 are in preclinical development. The resultant patents/patent applications were segregated based on the platform technology and the names of the key developers. The duplicate references were removed and patent families were separated. The websites of the vaccine marketers were also searched to know about vaccine patents assigned to them.

Analysis

Several reputed pharmaceutical companies are using innovative technologies to manufacture safe and effective COVID-19vaccines. China, the US, Russia, Europe, and India have leaped in this race of conducting trials for their vaccines. Due to the pandemic, increased

cooperation was seen among the healthcare coordinators including the research centers in sharing the knowledge to tackle the spread of infection [11]. Moderna Inc has collaborated with the US National Institute of Health (NIH) for conducting their mRNA-based vaccine. Clover Biopharmaceuticals in China has partnered with GlaxoSmithKline for manufacturing the potential protein-based vaccine. Similarly, AstraZeneca has collaborated with Oxford, Pfizer with BioNTech [35].

Discovering a new drug requires huge expenditure and time, and considering the bleak success rate, the pharmaceutical companies usually patent their products to recover the cost. Chinese firms have registered a maximum number of COVID-19 vaccine patents followed by the US, Russia, South Korea, Switzerland, etc. [22]. However, the present pandemic created a situation wherein nations understood the need to remove stringent patent rules on COVID-19 vaccines and medications. European countries already declared that they would be glad to share their innovations. Chile, Cannada, Ecuador, and Germany have approved a 'compulsory license' for all medications that are useful in COVID-19, to improve their accessibility [41].

Following the sequencing of the SARS-CoV-2 genome in January 2020, the scientific community worked overtime to design and develop the COVID-19 vaccine. If desired results were achieved in record time, then this could be one of the fastest discoveries in modern history [35,43]. Several vaccines developed for COVID-19 have been patented. Among them, the maximum numbers were found for the protein subunit vaccines followed by viral vector, inactivated, and RNA vaccines [67]. Following are some of the important COVID-19 vaccines that were granted the regulatory authorization; EpiVacCorona (Protein Subunit) by FBRI, mRNA-1273 (RNA based) by Moderna, BNT162b2 (RNA) by Pfizer/BioNTech, Ad5-nCoV (Viral Vector) by CanSino, Sputnik V (Viral Vector) by Gamaleya, Ad26CoV2.S (Viral Vector) by Janssen (Johnson and Johnson). AZD1222 (Viral Vector) by Oxford/AstraZeneca, Covishield (Viral Vector) by Serum Institute of India, Covaxin (Inactivated) by Bharat Biotech, BBIBP-CorV (Inactivated) by Sinopharm (China), CoronaVac (Inactivated) by SinoVac, China, CoviVac (Inactivated) by Chumakov Federal Scientific Centre for Research and Development [68]. These vaccines have some interesting characteristics, such as Protein subunit vaccines are considered to be safer, peptide-based vaccines are relatively easy to manufacture in bulk quantities, viral vector vaccines are cheap to make, inactivated vaccines can be freeze-dried convenient for transportation and long-term storage, and mRNA vaccines are manufactured in shorter time but have challenges in the supply chain due to special storage condition [69].

The technology for designing a COVID-19 vaccine is mostly invented in the academic lab setting or start-up research firms. The Jenner Institute at Oxford University is the place where the first positive report about a vaccine for COVID-19 came. The institute later collaborated with AstraZeneca to develop, manufacture and distribute worldwide the vaccine on a no-profit basis. Jenner institute is famous for innovations in topics related to infectious diseases, emerging pathogens, and non-communicable diseases [70]. The innovation for designing the vaccine is named Chimpanzee Adenovirus Oxford (ChAdOx) viral vector technology. The patented technique allows artificially selected genetic information to be transported into human cells and instructs the cells to produce biological materials. These substances are essentially harmless and must trigger the immune system to produce antibodies and T-cells [45]. The concept was based on the earlier design of the ChAdOx-based MERS (Middle Eastern Respiratory Syndrome) vaccine, which was found to be safe, well-tolerated, and induced satisfactory immunological responses in the host system. The MERS vaccine studies are conducted in collaboration with Saudi Arabia's King Abdullah International Medical Research Centre. Jenner Institute is also collaborated with Janssen in developing vaccines against Nipah and Lassa virus. In addition, the institute has collaborated with several manufacturing units across the globe to scale up the production of COVID-19vaccines [70].

The following sections summarize the important innovations in the development of COVID-19vaccines. AstraZeneca vaccine patent information number W02012-1722777 (PCT Publication number: 2014-516536), the title of innovation-Simian adenovirus and hybrid adenovirus vector. The patent description is as follows; the COVID-19 vaccine is an adenovirus vector comprised of a capsid. The proteins derived from wild-type Chimpanzee adenovirus (AdY25) are present in the capsid. An exogenous nucleotide sequence of interest is encapsidated to the nucleus of the vector. The sequence contains the code for translation, transcription, and/or expression of the viral component in the animal cells [71].

The techniques adopted by Pfizer, Moderna, CureVac are based on mRNA. In this, the degradation of artificially synthesized mRNA in the body is avoided by using lipid nanoparticles (LNP). Once the mRNA is delivered into the host cells, it instructs the host cells to produce SARS-CoV2 spike proteins, which are then recognized by immune cells. LNP is an innovative technology that was first demonstrated jointly by the University of British Columbia and Arbutus Biopharmaceuticals in 1998. This technology has now been sublicensed to various pharmaceuticals companies such as BioNTech, Pfizer, and Moderna. The technology of development of mRNA, synthesis, and incorporation into LNP are all patented. The rapid designing, development, and success of mRNA-based COVID-19 vaccines need to be credited to different organizations including academic labs, small biotech firms, and drug-manufacturing companies [31,71].

Moderna vaccine is RNA-based. Patent information number 10702600 (US patent registration), the innovation was titled 'Beta coronavirus in RNA vaccine'. The description mentioned in the patent is that the vaccine is a lipid nanoparticle (LNP) encapsulated mRNA. An artificial mRNA strand an open reading frame encoding a coronavirus S-gene protein subunit was synthesized and encapsulated with lipids as nanoparticles. The components when injected into a living organism will get translated into viral protein (spike proteins), which are then recognized by the immunological system to produce the antibodies. The vaccines can be manufactured with less cumbersome tasks and are tested for the first time in the history of medicine [34,71]. Loyola University, Chicago vaccine patent information number W02018-160977 with PCT Publication number: 2020-513845, title 'A live attenuated coronavirus vaccine'. The information mentioned in the patent is that vaccine contains a live but attenuated coronavirus consisting of a variant gene coding polyproteins called non-structural proteins (nsp-15). The proteins are one of the important components of a virus. The administration of the vaccine triggers the host cells to produce harmless/unstable nsp-15, identified by immune cells [71,72].

Another vaccine reported to have used innovative technology to develop the COVID-19 vaccine is the Russian-made Sputnik V vaccine. The vaccine is developed by Gamaleya National Research Centre of Epidemiology and Microbiology and the technology is patented WO2021002776A1. The description given for the vaccine is that it is vector-based and contains two adenovirus serotypes 5 and 26. The viral component genes are integrated into the adenovirus and when it delivers the genes to host cells, it triggers the synthesis of coronavirus envelop proteins. The first dose of vaccine is reported to develop humoral cell immunity, while the second dose assists in memory formation [73].

CanSinoBio, a Chinese vaccine maker has patented their COVID-19 vaccine (CN202010193587.8). The details mentioned are that; it is a 'New recombinant coronavirus vaccine using human replication-deficient adenovirus as a vector. It also includes

Table 2
COVID-19 vaccines patents/applications filed by key players.

Patent/application number (Date of patent/publication)	Summary of claims	Ref. No.
Moderna		
US10703789B2 (July 7, 2020)	A pharmaceutical composition (vaccine) comprising lipid nanoparticles containing an mRNA encoding a polypeptide that can be used as a vaccine.	[78]
US10702600B1 (July 7, 2020)	A vaccine composition comprising a mRNA containing an open reading frame encoding a beta-coronavirus (Beta-CoV) S protein or S protein subunit formulated in a lipid nanoparticle.	[79]
US10064959B2 (September 4, 2018)	A synthetic mRNA, which is effective as a vaccine when administered to a mammalian subject.	[80]
US10933127B2 (March 2, 2021)	A method of inducing an immune response to the Beta-CoV S protein or S protein subunit in a mammal using a mRNA containing an open reading frame encoding a Beta-CoV S protein or S protein subunit formulated in a lipid nanoparticle in an effective amount.	[81]
BioNTech		
US20190321458A1 (October 24, 2019)	A vaccine composition comprising a single-stranded RNA containing an open reading frame encoding a peptide or protein of interest, and polyalkyleneimine (polyethylenimine and/or polypropylenimine).	[82]
US10729785B2 (August 4, 2020)	A method of immunity stimulation against an infectious disease using a vaccine composition comprising protamine 1000/5000, a mRNA, and at least one endosome destabilizing agent.	[83]
Curevac		
WO2021123332A1 (June 24, 2021)	A method of treatment or prophylaxis of infectious diseases (COVID-19) using a vaccine of mRNA.	[84]
US20210023199A1 (January 28, 2021)	A method of stimulating an antigen-specific immune response in a human subject comprising administering to the subject an effective amount of a vaccine composition containing a mRNA encoding a spike protein (S) from a SARS-CoV.	[85]
US20210060175A1 (March 4, 2021)	A method of stimulating an immune response in a subject comprising administering an effective amount of a vaccine composition comprising a purified mRNA encoding a SARS-CoV antigen to the subject.	[86]
Janssen Pharmaceuticals		
WO2021155323A1 (August 5, 2021)	A vaccine against COVID-19 to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older, comprising a recombinant human adenovirus of serotype 26 that contains nucleic acid encoding a SARS-CoV-2 S protein or fragment thereof.	[87]
CA3101131A1 (July 31, 2021)	A vaccine comprising a recombinant human adenovirus of serotype 26 that comprises a nucleic acid encoding a SARS-CoV-2 S protein.	[88]
Inovio Pharmaceuticals		
US10548971B2 (February 4, 2020)	An immunogenic vaccine composition comprising a nucleic acid molecule of a specific sequence for inducing an immune response against a coronavirus infection.	[89]
Gamaleya		
EA037297B1 (March 5, 2021)	A pharmaceutical agent of specific sequence ID for the induction of specific immunity against SARS-CoV-2.	[90]
EA037291B1 (March 5, 2021)	An expression vector containing the genome of the recombinant human adenovirus to create an immunobiological agent for the induction of specific immunity against SARS-CoV-2.	[91]
RU2731342C1 (September 1, 2020)	A pharmaceutical agent of specified sequence ID for the induction of specific immunity against SARS-CoV-2.	[92]
Novavax		
WO2021154812A1 (August 5, 2021)	A vaccine composition comprising coronavirus Spike glycoprotein of specific sequence ID to stimulate an immune response against SAR.S-CoV-2 in a subject.	[93]
US10953089B1 (March 23, 2021)	An immunogenic vaccine composition comprising a nanoparticle containing a coronavirus S glycoprotein having a specific amino acid sequence.	[94]

information about a polynucleotide for coding an S protein of 2019 novel coronavirus is recombined with a vector. The human replication-deficient adenovirus capable of recombination with the polynucleotide is used. The technique describes the steps for synthesis of the polynucleotide, transfection with the shuttle plasmid, and then recombination with adenovirus, culturing it, and purification for obtaining the recombinant adenovirus. The administration of the recombined adenovirus is expected to generate the immunological response [68,74].

Currently, intramuscular is the recommended route for administering the COVID-19 vaccine. However, considering the pathway through which the SARS-CoV2 enters the body, innovations have been trialed for the inhalation route of vaccine delivery [75]. Since, the approved COVID-19 vaccines are demonstrated to provide mostly the activation of T cells and serum neutralizing antibodies, without altering the mucosal immunity in the nasal cavity or lung tissue, the intra-nasal route was tested for this purpose. Moreover, drugs used to treat respiratory diseases are preferred to be given by the intra-nasal route; the COVID-19 vaccine is also tried by this route [76]. Various pharmaceutical companies such as CanSino Biologics, Bharat Biotech, AstraZeneca, and Codagenix are testing their COVID-19 vaccines for the intra-nasal route of delivery [75,77].

Many patents/patent applications on COVID-19 vaccines have been published. The summary of vaccines developed by the key players is provided in Table 2.

The cause of COVID-19 was described in the second week of January 2020. The publication of a normal patent application takes place after 18 months of its filing. Therefore, it is not possible to know exactly how many patent applications have been filed? How many have been published? and How many will be published in the coming days?. Accordingly, the list of some patents/patent applications related to the COVID-19 vaccine developed through different technology is provided in Table 3.

Conclusion

The most effective means of infectious disease prevention and control is through the use of a vaccine. Most COVID-19 vaccines have been developed, while some are being evaluated in experimental animals and clinical trials. Hastening the development of vaccines by combining phases of the trial involved within a smaller group is of more significant concern when the vaccine is used globally due to unknown, unwanted effects in a larger population. Additional critical challenges consist of finding the immunogenic

Table 3
List of some COVID-19 vaccine patents/applications related to platform technology.

Patent/patent application number	Publication date	Assignee/applicant	Ref. No.
DNA based vaccines			
RU2745626C1	March 29, 2021	IP Suvorov Aleksandr Nikolaevich	[95]
CN112048445A	December 8, 2020	Tianjin Hemujianmin Biotechnology	[96]
CN111588843A	August 28, 2020	Sichuan Chengyu Biological Products	[97]
CN111569057A	August 25, 2020	Jilin Zhongke Bio-Engineering	[98]
RNA based vaccines			
CN112168958A	January 5, 2021	Shanghai Jiao Tong University	[99]
CN111647053A	September 11, 2020	Academy Of Military Sciences Physiome Institute	[100]
WO2021000968A2	January 7, 2021	Guangzhou N Biomed Ltd.	[101]
CN111330003A	June 26, 2020	Weng Binghuan	[102]
CN111218458B	November 20, 2020	Zhuhai Livanda Biotechnology	[103]
Inactivated/attenuated vaccines			
US11020475B1	June 1, 2021	The Industry & Academic Cooperation in Chungnam National University	[104]
CN111437384A	July 24, 2020	Sichuan Chengyu Biological Products	[105]
WO2021092392A1	May 14, 2021	Cornell University	[106]
CN112175913A	January 5, 2021	Institute Of Military Medicine, Academy Of Military Sciences Of PLA	[107]
Bacterial vector-based vaccine			
US10973908B1	April 13, 2021	Bermudes David Gordon	[108]
CN111944837A	November 17, 2020	Henan Normal University	[109]
Virus-Like particles based vaccine			
CN112300290A	February 2, 2021	Beijing Health-Guard Biotechnology	[110]
Protein subunit based vaccines			
CN112480268A	March 12, 2021	Beijing Health-Guard Biotechnology	[111]
CN111603556A	September 1, 2020	Sun Yat-Sen University	[112]
Virus vector-based vaccine			
CN110974950B	August 7, 2020	Guangzhou Enbao Biomedical Technology	[113]
CN111778264A	October 16, 2020	Guangzhou Bairuikang Biological Technology	[114]

protein and viral virulence capability, experimental model, route of admiration, clinical trials, and safety and efficacy of the vaccine. Most of the key players have patented their inventive COVID-19 vaccine. Many patent applications related to COVID-19 vaccines developed via different technologies (DNA, RNA, virus, bacteria, and protein subunit) have also been filed. Many patents/patent applications related to the COVID-19 vaccine are foreseeable in the future.

Expert opinion

The advancement of a viable and effective COVID-19 vaccine is a significant priority worldwide and is a sure way of finishing the COVID-19 pandemic. Astoundingly, in under one year, vaccines have been created and demonstrated to be solid and are now being sent worldwide. Vaccines are preventive or remedial mediations that significantly diminish morbidity and mortality brought about by infectious diseases. They are clinically straightforward yet immunologically unpredictable. The strain to build up a COVID-19 vaccine is immense. However, vaccine development without completely understanding the immune system's response to infections and vaccine safety could bring unjustifiable mishaps now and later on.

Furthermore, SARS-CoV-2 may transform in manners that would make beforehand viable vaccines futile. A considerable number of advances must be made in developing any vaccine. There are added intricacies with COVID-19, given that its seriousness shows up be diverse across sexual orientation and age. There's additionally proof that it has the captivity of having mutant strains.

Coronaviruses have a Spike protein or S-protein, which they use to append to receptors in human cells. A significant number of the vaccine developed or under development focuses on the S proteins, which are antigenic proteins recognized by the immune system. This is valid for all strains of coronaviruses, including SARS-CoV, MERS-CoV, and SARS-CoV-2, accountable for COVID-19. Mainstream researchers have taken in a great deal about COVID-19, thinking that the infection and the sickness just arose in mid-2020; however, the insusceptible instrument is as yet not surely knew especially on how the immune system responds to the infection even though seriousness comes from the wrong, inordinate and additionally insufficient immune response. A significant test of these vaccines will be immune enhancement found during the 1960s when a vaccine contender for the respiratory syncytial virus (RSV) was tried which showed that the illness deteriorated after inoculated kids were presented to the virus, with two mortalities. Previous animal vaccines created against other coronaviruses, the feline peritonitis virus, expanded cats' danger of building up the sickness brought about by the virus. Comparative marvels have been found in animal research for coronaviruses and other viruses that cause severe acute respiratory syndrome (SARS). The mechanism that causes this isn't wholly perceived and is one of the challenges of the effective advancement of a Coronaviruses vaccine.

Several other challenges and troubles in the fastening of successful vaccines for SARS-CoV-2 include discovering explicit highlights and virulence capacities of this viral pandemic. It is also challenging, choosing the appropriate experimental model and the route of admiration for practical vaccine efficacy. Selecting a suitable vaccine adjuvant that will enhance the immunogenicity of the COVID-19 vaccine is also challenging. These challenges, as well as clinical trials, are significant for vaccine safety and efficacy. Likewise, there is a worry in the field of the inactivated and live attenuated vaccine of which the virus can regain its virulence, most especially in immune-suppressed individuals. Consequently, safety is considered a very significant challenge in fast-tracking vaccine development.

Many patents have been granted and several patent applications on COVID-19 vaccines developed via different technologies (DNA, RNA, virus, bacteria, and protein subunit) have also been filed. A conventional patent application takes 18 months to be published after it is filed. As a result, several COVID-19 vaccine patents/patent

applications developed using various technologies may become publicly available in the coming future.

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