Patent Landscape Report

COVID-19-related vaccines and therapeutics

Preliminary insights on related patenting activity during the pandemic

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Further information
Online resources: The electronic version of this report can be accessed at www.wipo.int/publications/en/details.jsp?id=4589. This webpage also includes COVID-19, COVID-19 vaccines and therapeutics datasets.

Contact: patent.information@wipo.int

Key findings

Since the start of the COVID-19 pandemic there have been remarkable research and innovation efforts to fight the SARS-CoV-2 virus and the COVID-19 disease. This report provides early observations on the patenting activity which took place in the field of COVID-19 vaccines and therapeutics, and compares these results with clinical trial data for related candidate vaccines and drugs.

Filing activity related to the pandemic has been extraordinarily active so far

The patent search looked at related patent filings from the beginning of 2020 through the end of September 2021. It revealed 5,293 patent filings on technologies related to COVID-19 in general, including 1,465 patent filings about therapeutics and 417 about vaccine development.

By comparison, from 1941 to 2011 there were just over 500 patent filings related to active ingredients about the influenza vaccines (WIPO, 2012). Even during the SARS outbreak of the early 2000s, fewer than 1,000 related patents were published, with no vaccine candidate emerging.

Early numbers are only a snapshot of actual patent activity

On average, there is an 18-month period between filing a patent application and the time this application becomes published and thus publicly available and known. For this reason, at the time of the data collection (end of September 2021), the information publicly available was not yet complete. The current study should therefore be viewed as a first indication of patenting activity during the pandemic.

Patenting filing activity has been concentrated in three patent offices

As COVID-19 vaccines and therapeutics concern a global market, it is no surprise that already at this stage related applications were filed and published across 31 (therapeutics) and 19 (vaccines) patent offices; numbers which are expected to increase as more patent information becomes available.

In the current dataset the China National Intellectual Property Administration (CNIPA), the World Intellectual Property Organization (WIPO), administering the Patent Cooperation Treaty (PCT) system, and the United States Patent and Trademark Office (USPTO) received most of the patent applications in both these fields.

According to the data available so far, India and the Republic of Korea are offices that have received more filings in the field of therapeutics than vaccines.

Both business and the research community have contributed significantly to the patent landscape

Patent applicants are distributed almost evenly between companies (49 percent of the vaccines and 44 percent of the therapeutics dataset) and universities and research organizations (44 percent of the vaccines and 41 percent of the therapeutics dataset), with companies accounting for a slightly higher proportion of the two datasets.

The research community has played an important role in developing patented technologies

While corporates are typically the producers of final products and hold more patents, universities and research organizations play a significant role in developing patented technologies in this area, as shown by their high contribution to the patent dataset. This is further exemplified by the role of Oxford University in the development of an adenovirus vector COVID-19 vaccine by AstraZeneca, and the number of universities and research organizations which feature among the vaccines and therapeutics developers and manufacturers in the related clinical trial data.

Full information on patent applicants is not yet available, but we see innovators representing different profiles

The present patent analysis does not systematically highlight top patent applicants as the patenting period in question is very short and the full patent data for this period is not yet available. Nevertheless, we already see patenting activity from key innovators and developers of candidate vaccines and therapeutics which feature in the clinical trial data and the news. There are different innovator profiles contributing to patented technologies: pharmaceutical companies, biotechnology startups, universities, research organizations and independent inventors.

China is currently the lead origin of patent filings related to vaccines

The patent applicant's location can provide an indication about the profile and origin of key players in patenting activity.

The top five patent applicant locations in the field of vaccines are China, the United States of America (U.S.), the Russian Federation, the United Kingdom (U.K.) and India. In the field of therapeutics, China, the U.S., India, the Republic of Korea and the Russian Federation are the top applicant locations.

Filing strategies are already focused on international protection through the PCT system

As per the existing data at the time of the patent search, patent filing strategy patterns vary. Applicants in some locations have focused exclusively on protecting their intellectual property (IP) domestically. Others have already expressed an intention to seek patent protection in multiple jurisdictions and related markets, by filing European Patent (EP) and PCT applications: the PCT system has received the second highest number of filings of any office so far, both in the fields of vaccines and therapeutics.

Bearing in mind the increasing availability of patent data over time, the filing strategy picture may change in the coming months, as patent applicants may exercise their right to file for patent protection in additional jurisdictions beyond their national offices, and as PCT applications enter national phase in different jurisdictions.

Development of COVID-19 vaccines has been across both conventional and novel platforms

Multiple vaccine platforms have been explored for COVID-19 vaccine development. These platforms range from the **conventional** ones, such as live attenuated and inactivated/killed whole virus vaccines, protein subunit vaccines and virus-like particles (VLP), to the **novel** ones, including adenovirus-vector-based, DNA-based and mRNA vaccines.

While a patent document may claim different vaccine platforms, there are more patent filings referring to conventional vaccine platforms (protein-based, live attenuated, inactivated, VLP) than to novel vaccine technologies.

The conventional vaccine category of protein subunit vaccines is the largest category in the dataset, with 46 percent of the overall vaccine patent filings referring to it. Novel vaccine technologies have a lower yet notable contribution to the dataset, with 35 percent of the patent filings referring to either viral vector (23 percent) or RNA (12 percent) vaccine technologies.

Looking at the clinical trial data, while protein subunit vaccines are again the biggest category (accounting for 34 percent of vaccines in clinical

trials and preclinical studies), there are nearly double as many RNA vaccines in clinical trials (20 percent) compared to their contribution to the patent dataset (12 percent). This would indicate that the novel platforms are gaining momentum, especially in clinical studies.

Filings related to innovative viral vector and mRNA vaccines are the second biggest categories in patent data and mRNA second biggest in clinical trial data

35 percent of patent filings refer to one of the following novel vaccine platforms: viral vector (23 percent) or mRNA vaccines. Innovative mRNA vaccines account for 20 percent of the vaccines in clinical trials and 12 percent of the vaccines patent dataset. This suggests that the novel vaccine platforms are gaining momentum in clinical studies and their contribution in patenting efforts might be expected to grow, as currently unpublished patent filings become publicly available in the coming months.

COVID-19 therapeutics have developed on multiple fronts

A variety of strategies for developing COVID-19 therapeutics have been explored in a relatively large number of patent documents and clinical trials during the period of January 2020 to September 2021. 63 unique drug candidates have entered Phase 3 (or Phase 2/3) clinical trials based on the analysis of combined WHO, Milken Institute, RAPS COVID-19 tracker data and U.S. clinical trial data as of the end of September 2021 (Milken Institute, n.d.; Craven, 2022; U.S. National Library of Medicine, n.d.), with several of these receiving conditional approval.

Most COVID-19 drug candidates are repurposed

Most drugs (an estimated 80 percent of the candidate drugs listed in the Milken Institute's therapeutic tracker as of September 2021) under evaluation are **repurposed**, i.e., drugs that have been approved for treatment of a different disease. Some new treatments are focused on **disrupting virus replication**, whereas others aim at **modulating the functions of the human immune system to reduce inflammation-associated tissue damage** caused by the over-production and release of pro-inflammatory molecules (i.e., pro-inflammatory cytokines), leading to the so-called cytokine storm. Among these approaches, the **newly developed small-molecule antiviral drugs** that specifically target SARS-CoV-2's proteins and can be taken at home represent another rapid development in bringing patented technologies to potential clinical success.

Small molecule and biologic drugs are the main types of therapeutics

There are two types of therapeutics in general: **small molecules** that include synthetic compounds but may also be natural products extracted and purified from plants; and **biologic drugs** that include antibodies, non-antibody peptides/proteins, cell-based therapies and nucleic-acid-based therapies. Therapeutics for COVID-19 mostly fall into either of these categories. The biggest part of the COVID-19 therapeutics patent filings relates to small molecules and biologics (54 percent and 36 percent of the therapeutics patent dataset, respectively). While the clinical trials data revealed a roughly equal distribution of therapeutic candidates between small molecules and biologics, there is a significantly higher percentage of de novo synthesized drugs in biologics than in small molecules. This may reflect an increasing interest of drug developers in the more sophisticated biologics and in transforming them into clinical success.

Traditional medicine also plays a role in the fight against COVID-19. Among the therapeutics dataset, 17 percent of filings disclose the use of traditional medicines in treating COVID-19.

Antibodies account for nearly half of the biologics, and their newly developed virus-neutralizing form introduces a new class of antiviral

As the fastest growing class of biologics in general, **antibodies** make up close to half (42 percent) of the biologics disclosed in patent documents. These COVID-19 therapeutic antibodies include the newly developed neutralizing antibodies directed against the SARS-CoV-2 spike (S) protein and previously developed antibodies that modulate the host's immune/inflammatory response to the virus. As revealed in both patent and clinical trial data, **virus-neutralizing antibodies**, when given

in a cocktail, are capable of binding to various regions of a crucial segment in the SARS-CoV-2 S protein to effectively block the viral S protein interaction with its receptor on human cells, and **represent a new class of antivirals**. Other antibodies that target human host factors may be used to reduce inflammation and the adverse effects of the cytokine storms seen in some severe cases of COVID-19.

Innovative treatment approaches have been disclosed in the patent dataset

Our dataset also includes information on other potentially new methods for COVID-19 treatment. These new approaches include: the use of **CRISPR-Cas** technology to target viral genes to disrupt the ability of the virus to infect host cells; the **design of nucleic-acid-based drugs** (e.g., small interfering RNA, short hairpin RNA, microRNA, antisense oligonucleotides, aptamers) to attack SARS-CoV-2 at distinct stages of its lifecycle and/or to modulate host dependency factors; and novel delivery vehicles such as engineered exosomes (i.e., membrane-bound extracellular vesicles of human cells).

The advent of biotechnology has enabled the commercial production of exosomes enriched with desired molecules including drugs. Drug or cargo-loaded **exosomes** containing immune-modulating substances in combination with antiviral substances can provide rapid and targeted delivery for disease treatment. The potential application of these innovative strategies for COVID-19 treatment in clinical settings is yet to be determined.

Only one in five patent applications was filed by more than one applicant

Collaboration among organizations has been important to fight COVID-19. Nevertheless, when looking at the available patent data collaboration expressed as filing of patent applications by several applicants, this has not been prominent; only one in every five patent applications either in relation to COVID-19 vaccines or therapeutics (87 out of the 417 vaccines patent families and 289 out of the 1,465 therapeutics) was filed by more than one patent applicant.

Cooperation is higher in drug development, clinical trials and manufacturing

Despite this modest percentage in patent co-filing, and while it is possible that the numbers of patent co-filing will have increased once patent data from 2020–2021 becomes fully available, higher levels of cooperation are happening upstream in the drug development lifecycle, and are already more visible at the clinical trial stage. The analysis of the COVID-19 therapeutic tracker data generated by the Milken Institute and the Regulatory Affairs Professionals Society (RAPS), as well as vaccine information from the World Health Organization (WHO) shows cooperation in the form of licensing, development and marketing agreements used to facilitate the development and distribution of both vaccines and therapeutics.

Collaborations comprise pharmaceutical companies, biotech startups and universities

Such cooperation exists between big pharmaceutical companies and relatively small biotech companies, and between universities and commercial organizations including big pharmaceutical companies and small biotech companies across different regions.

For example, development of the oral antiviral therapeutic molnupiravir involved Emory University, Merck and Ridgeback Biotherapeutics. Merck and the Medicines Patent Pool also have a licensing agreement to provide molnupiravir as a COVID-19 treatment to low- and middle-income countries. Developers of vaccines and therapeutics are also collaborating at the manufacturing stage with different manufacturers (Global Health Center, 2021).

A combination of pandemic preparedness and response allowed for unprecedented accelerated vaccine and drug development

While there was acceleration in the research and innovation efforts during the pandemic, the record times for vaccine and therapeutics development and approvals would not have been possible if it had not been for the decades of scientific breakthroughs and related patenting activity.

Introduction

The COVID-19 pandemic continues to have a far-reaching impact on global public health, the world economy and everyone's daily life. This infectious disease, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 250 million confirmed cases and over 5 million deaths (Johns Hopkins University & Medicine, 2021) across 224 countries/regions and territories as of November 7, 2021 (Worldometer, 2021) making it one of the deadliest pandemics in history. Several variants of concern (VOC), such as the Delta and the Omicron variants, have emerged, resulting in a continued public health risk since late 2020 and adding complexity to combatting COVID-19.

To fight the pandemic and prevent recurrences, scientists around the world have been working tirelessly to understand the SARS-CoV-2 virus and to develop effective therapeutic agents and preventative vaccines, two key components of the health care response to the pandemic. Thanks to decades of research and development on vaccine technologies, a variety of COVID-19 vaccines have been quickly developed and deployed. In addition, new therapeutics have been developed and existing drugs have been repurposed to treat COVID-19. This report presents the global patenting activity from January 2020 to September 2021 associated with COVID-19 vaccines and therapeutics. Due to the very recent patenting activity following the identification of the virus and the time needed between patent filing and publication of the related application (on average 18 months), this work is expected to provide first indications about the patenting activity related to COVID-19 vaccines and therapeutics. It should not be treated as complete information, while the report would need to be updated at a later stage to capture the full patenting activity which will be made publicly available in the meantime.

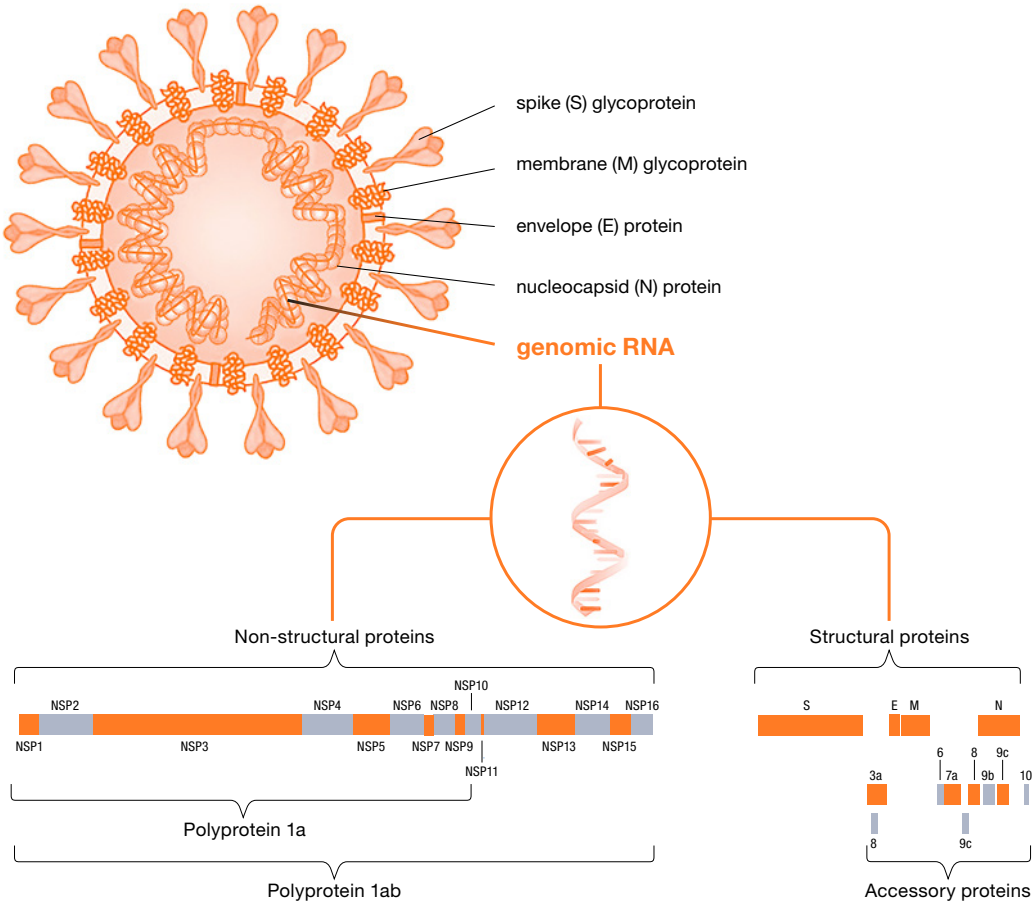
During 2020–2021, there were some early patent analytics and scientific publications aiming to shed some light on technologies related to COVID-19, ranging from *Coronaviridae* families, core technologies such as mRNA vaccines, technologies which could be applied to fighting COVID-19 and some first efforts to track patenting or publishing activity related to COVID-19. A list of these publications can be found in the Further reading section of the Annex, while some patent analytics publications by national IP offices related to COVID-19 can be found in WIPO's compilation of patent landscape reports (WIPO, n.d.). This report identifies first-patenting activity during the pandemic during 2020–2021 – based on information publicly available as of September 21, 2021 – and patent documents specifically referring to SARS-CoV-2 virus or the COVID-19 disease, with a focus on vaccines and treatments. It aims to provide a valuable perspective on the patent landscape with an understanding of the science and technologies behind these vaccines and therapeutics and insights into the innovations that made them possible, even if reviewing the situation in the future would provide a more complete picture.

Background – biology of COVID-19

Understanding the mechanism by which the SARS-CoV-2 virus infects human bodies is crucial to the development of both therapeutics and vaccines. Coronaviruses are a family of relatively large viruses, with a lipid membrane, or envelope, surrounding their RNA-based genetic material. The outer lipid envelope is studded with glycoprotein spikes that give these viruses a crown-like appearance when viewed with a microscope, as illustrated below (Figure 1). These spikes interact with human cells and many vaccine developers have focused on using the spike (S) protein to stimulate a human immune response. The initial steps of coronavirus infection involve the specific binding of the coronavirus S protein to the cellular entry receptor, identified as the angiotensin-converting enzyme 2 (ACE2), leading to endocytosis with the receptor, and subsequently using the host cell's machinery to replicate copies of itself and invade new cells. During the intracellular life cycle, coronaviruses express and replicate their genomic RNA to produce full-length copies that are incorporated into newly-produced viral particles which are secreted from the infected cell by exocytosis. As this report will describe, vaccines and therapeutics can be designed to disrupt many of these steps of infection. The RNA genome of SARS-CoV-2 encodes two large polyproteins – 1a and 1ab, four structural proteins – spike (S), envelope (E), membrane (M) and nucleocapsid (N), and nine accessory proteins (Figure 1). The two polyproteins can be broken apart by viral proteases to generate non-structural proteins (NSPs). Among them, NSP3 and NSP5, commonly called PLpro and 3CLpro, respectively, are two viral proteases (Gordon *et al*., 2020). Some therapeutics are designed to target the 3CLpro protease to disrupt the ability of the virus to produce these non-structural proteins. The interaction and binding of the S protein on the viral surface to the human viral receptor protein ACE2 is crucial for virus invasion into human cells (Yang *et al.*, 2020). This is important because many therapeutics aim to disrupt this interaction, by either mimicking or interfering with the S protein or ACE2, as described in the therapeutics chapter. Certain mutations of the S protein, such as that in the Delta and the Omicron variants, could increase the ability of the virus to bind to human cells, thereby increasing the contagiousness of the virus (Liu *et al.*, 2021; Peacock *et al.*, 2021; Callaway, 2021; Li *et al.*, 2021b). NSP12, also called RNA-dependent RNA polymerase, is responsible for copying the viral genome. Some therapeutics are designed to target this enzyme to prevent the virus from spreading. NSP12 is the target of U.S. Food and Drug Administration (FDA)-approved drug remdesivir, as well as several of the therapeutics in our patent dataset.

Although SARS-CoV-2 is a newly emerged virus, the genome of this virus is considerably similar to some of the known coronaviruses, especially SARS-CoV and MERS-CoV (Zhou *et al.*, 2020). Therefore, the prior research on other human coronavirus diseases may provide insights for research and development of SARS-CoV-2 vaccines and therapeutics. Since the release of SARS-CoV-2 sequence on January 10, 2020 by Yong-Zhen Zhang at Fudan University, China (Virological, 2020), a worldwide race to develop diagnostic agents, vaccines and therapeutics started immediately and intensified day by day. The publication of the sequence enabled among others the German Center for Infection Research (DZIF) at Charité – Universitätsmedizin Berlin to announce on January 16, 2020 the development of a PCR test to detect SARS-CoV-2 that was subsequently made publicly available. Meanwhile, scientists quickly elucidated the structure of the virus as illustrated in Figure 1, while sequencing has continued since then as a means of diagnostics. More recently, sequencing of virus isolates has been used to identify and track mutations and variants and predict whether existing vaccines will combat them. Sequences of viral genes and the proteins they encode provide a basis for vaccine development and for understanding potential therapeutic targets.

Figure 1. The genomic landscape of SARS-CoV-2.



Source: WIPO based on Gordon *et al.*, 2020.

COVID-19 was initially described as a respiratory disease caused by viral infection of the lungs and characterized by lung damage, pneumonia and acute respiratory distress. Observations of the symptoms of COVID-19 survivors (Lopez-Leon *et al.*, 2021) indicate long-term secondary effects in other systems of the body, including the cardiovascular, neuromuscular and endocrine systems. Acute infection may also include symptoms of thrombosis, stroke, hypertension, olfactory and digestive disorders, or an excessive inflammatory response due to cytokine storm. These varied symptoms have led some researchers to characterize COVID-19 as a vascular disorder (Siddiqi *et al.*, 2021). Many of the therapeutics in our patent dataset target one or more of these symptoms as a strategy for treatment.

Substantial efforts have been made to develop vaccines and effective and safe therapeutics for COVID-19. Multiple vaccine platforms have been explored. These platforms include **traditional**, well-established types of vaccines, such as whole-virus vaccines (live attenuated and inactivated), virus-like particles and protein-subunit vaccines, and **novel** vaccines with little pre-existing data on safety and efficacy in humans, such as nucleic acid (DNA- and RNA-based) vaccines, viral-vector-based vaccines and antigen-presenting cells. Additionally, diverse small-molecule drugs and biologics, e.g., peptides and antibodies, are being developed to treat COVID-19.

Overview of patenting activity related to COVID-19

Patent filings during 2020–2021

Since the beginning of 2020 when COVID-19 began to spread quickly around the world, 5,293 patent applications related to COVID-19 have been published across 49 patent offices, including diagnostics, treatments, vaccines and any other references to either the SARS-CoV-2 virus or the COVID-19 infection. Among these, 417 patent applications related to the development of COVID-19 vaccines were filed in 19 patent offices and 1,465 related to COVID-19 therapeutics filed across 31 patent offices (Table 1). To put these numbers in perspective, there were fewer than 1,000 published patent applications related to severe acute respiratory syndrome (SARS) during the 2003–2007 period of the SARS outbreak, 1,173 related to Ebola virus disease, which had several outbreaks from 1976 through 2021 (Centers for Disease Control and Prevention, n.d.), and 1,171 patent filings about Zika virus disease, which was first identified in humans in 1952 and has had several outbreaks from 2007 through 2015 (WHO, 2016). In comparison, related efforts to develop COVID-19-combatting technologies intensified and patenting activities outpaced any previous ones in a given historical period in relation to other human infectious diseases. In addition to 5,293 patent applications published since the beginning of 2020, about 116,000 scientific literature articles, including those in journals, books and meeting proceedings, were published by the end of September 2021, based on the CAS content collection (CAS, n.d.; also STN, n.d.).

Patent filings related to therapeutics considerably outnumber those on vaccines, at an approximate 4:1 ratio. This may be related to the fact that most of the research and development effort on COVID-19 therapeutics was focused on repurposing of drugs, meaning utilizing drugs previously designed/approved for treating other diseases (see Figure 17). For repurposed drugs, the data with respect to drug safety and drug absorption, distribution, metabolism and excretion (ADME) has been collected or is well known. This saves a tremendous amount of time in drug development and could potentially reduce the time to bring a drug to market. On the other hand, COVID-19 vaccines need to be newly developed even with traditional vaccine platforms that use killed/inactivated viruses or activity-attenuated viruses as vaccines (Li *et al.*, 2021b).

Table 1. Number of patent applications related to COVID-19 in general, COVID-19 therapeutics and COVID-19 vaccines, first filed and published in 2020–2021 across different patent offices.
Over one-third of the overall COVID-19 patent dataset concerns COVID-19 vaccines or therapeutics. Patent filings related to COVID-19 therapeutics were over three times higher than for COVID-19 vaccines and were filed for patent protection at nearly twice as many patent offices.

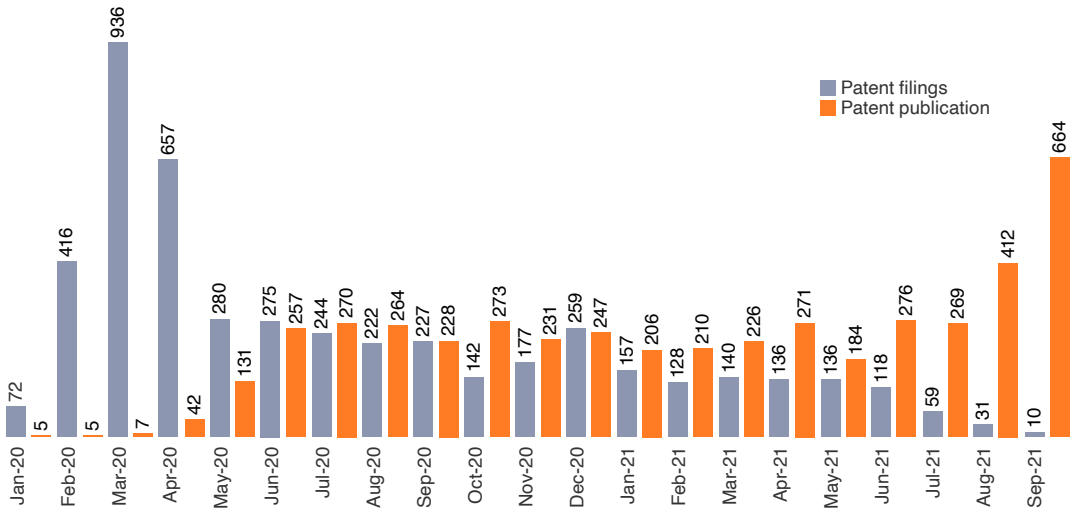
Patent dataset	Number of patent offices of filing	Number of patent applications published in 2020–2021	Number of patent applications first filed in 2020–2021
COVID-19 overall	49	5,293	4,822
COVID-19 therapeutics	31	1,465	1,314
COVID-19 vaccines	19	417	385

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Filing and publication of COVID-19-related patent applications over time

The general patenting activity related to COVID-19 includes patent applications describing inventions of diagnostics, masks and surface disinfectants, vaccines and therapeutics from January 2020 through the end of September 2021 and is shown in Figure 2. There is a delay of approximately 18 months between patent first filing (grey bars) and publication dates (orange bars) for this dataset which is aligned to the general related 18-month average patent publication lag in patent filings.

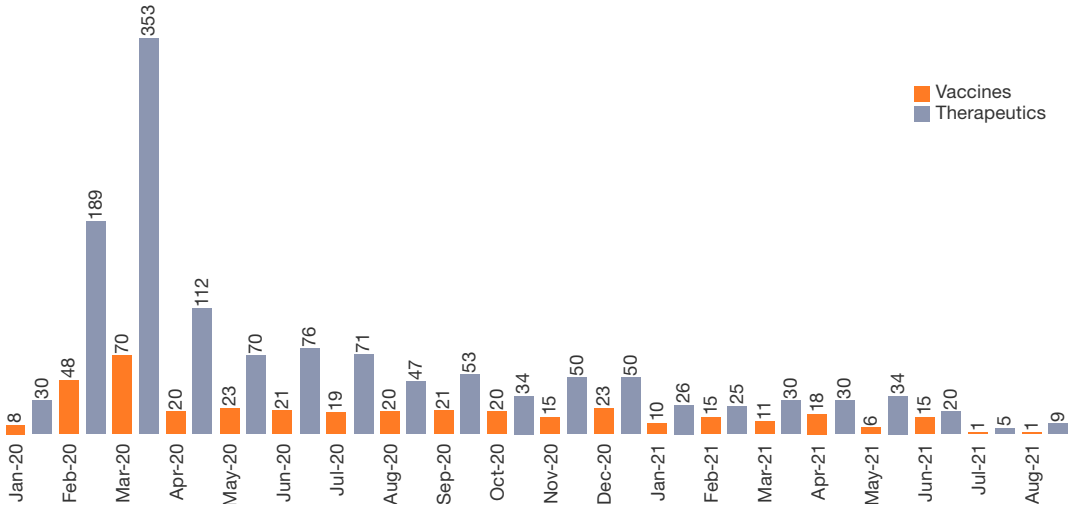
Figure 2. Patent applications related to COVID-19, first filed and published from January 2020 through September 2021 by patent filing and publication month.
There was a peak in COVID-19-related patent applications filed in March 2020.



Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

As shown in Figure 3, the patent filing trend for COVID-19 vaccines and therapeutics is similar to the overall COVID-19 patent filing trend, with March 2020 having marked the peak in patent filings, as per the information publicly available as of the end of September 2021 (date of data collection). As the data collection coincides with the average 18-month period typically involved between patent application and its publication, it is possible that the peak observed here might be related to patent publication delay and thus caution needs to be exercised in drawing a conclusion from the monthly trend.

Figure 3. Patent applications related to COVID-19 vaccines and therapeutics, first filed from January 2020 through September 2021.
Patent filings related to vaccines and therapeutics both peaked in March 2020.



Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18 month delay between patent filing and publication).

Most COVID-19-related patent applications were new filings in the period 2020–2021, with only a limited number based on first filings and related priorities before 2020. One example is a U.S patent application belonging to a COVID-19 patent family about a drug delivery system first filed in 2008.

While the information on patenting activity during 2020–2021 is only partially publicly available and the patent search exercise does not show the complete picture – suggesting a need to be repeated later in 2022 – we nevertheless explored first indications on the use and response of the patent system during the pandemic, and the acceleration in patent prosecution times of COVID-19 related patent filings. In order to do so, we calculated the time from filing a patent application to publication of the patent application (Table 2a), and the time from patent filing to patent grant (Table 2b) for COVID-19-related patent applications across the patent offices with the most patent applications in our dataset. This information was then compared to the same timelines for all chemistry/bioscience filings during 2020–2021. Patent documents were grouped as either patent applications, published patent applications or granted patents based on the codes (known as "kind codes") they are tagged with to mark their stage in the patent lifecycle (more details are available in the Annex).

As can be seen from Table 2a patent publication time (which typically has an average of 18 months) reduces for COVID-19 patent filings in the range of 7–30 percent compared to all patent applications filed during the same period in the field of chemistry/bioscience.

Table 2a. Patent filing to publication time (months) for COVID-19-related applications compared to all chemistry/bioscience applications in top patent offices of filing from January 2020 to September 2021.

COVID-19-related patent applications from the Republic of Korea and Japan were published nearly 30 percent faster than other chemistry or bioscience applications filed during the same period.

Patent office	Average publication time (months) for all chemistry/ bioscience patent applications in 2020–2021	Average publication time (months) for COVID-19 patent applications in 2020–2021	Acceleration
China	7.7	6.1	21%
Japan	18.9	13.8	27%
Republic of Korea	18.7	13.1	30%
U.S.	18.8	17.5	7%

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Calculations were made based on patent documents' kind codes. Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

As revealed by average patent grant lag values in Table 2b, it took fewer months for the listed patent offices to grant a COVID-19-related patent, with related lags ranging from 4.5 to 15.8 months compared to other patents in the field of chemistry and bioscience, with average lag in the range of 10.3 to 35.8 months for the same period. The U.S. and the Russian Federation are the offices which seem to have accelerated the patent grant time the most, by 70 percent and 58 percent respectively, while China and Japan halved their patent grant time. However, many COVID-19 patent applications are still awaiting granted status, and thus this table will need to be revisited and updated at a later stage.

Table 2b. Patent filing to grant time (months) for COVID-19-related patents compared to all chemistry/bioscience patents observed in top patent offices of filing from January 2020 to September 2021.

COVID-19-related patents were granted 70 percent faster compared to other chemistry/bioscience patents in the U.S., and over 50 percent faster in the Russian Federation, China and Japan.

Patent office	Average patent grant time (months) for chemistry/ bioscience patents in 2020–2021	Average patent grant time (months) for COVID-19 patents in 2020–2021	Difference (%)
China	33.6	15.8	53%
U.S.	35.8	10.7	70%
Japan	21.3	10.3	52%
Republic of Korea	10.3	9.7	6%
Russian Federation	10.9	4.5	58%

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Calculations were made based on patent documents' kind codes. Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public.

The differences in publication and grant time may reflect a combination of accelerated patent prosecution times for COVID-19-related patent applications, as well as the use by patent applicants of the option – where applicable – to request expedited patent publication and/or examination. Bearing in mind also that complete information on the use of the patent system across different jurisdictions still remains to become public, further examination is required to draw conclusions, possibly in consultation with national patent authorities on statistics of patent applicants' related requests. As such, the current results should be treated as first observations on the use and reaction of the patent system to COVID-19-related patent filings.

These shorter patent prosecution times for COVID-19-related patents may be partially attributed to the commendable efforts of patent offices to accelerate processing times to assist with the fight against the pandemic. Examples include the United States Patent and Trademark Office (USPTO), which introduced a COVID-19 Prioritized Examination Pilot Program to expedite the examination of applications filed by small and micro enterprises related to COVID-19 (USPTO, n.d.) or a similar accelerated prosecution program for COVID-19-related patent applications which was launched in China (CNIPA, 2020) and in Canada (Government of Canada, n.d.). The Korean Intellectual Property Office (KIPO) also has an expedited program for COVID-19-related patent applications. While the Japan Patent Office (JPO) does not have any separate policies in place for expediting examination of COVID-19-related applications, they may undergo accelerated examination without any additional charge, if they fall into any of the categories for accelerated examination defined by the JPO in general (including among others, working-related applications, internationally-filed applications and applications filed by small-to-medium enterprises, individuals, universities, public research institutes, etc.), with other jurisdictions offering similar possibilities to applicants. A trilateral study devised by the WHO, WIPO and the World Trade Organization (WTO) added a special insert to provide comprehensive information covering a full range of institutional and legal concepts that may be of value to researchers, organizations and government officials (WHO-WIPO-WTO, 2021).

Different strategies were pursued by both applicants and patent offices in patent prosecution of COVID-19-related patent applications. In some jurisdictions, most patents were directly granted (without publication of the application), while in others "classical" grants (with prior publication of the application) were prevalent, as was the case in China. Examples of accelerated prosecution include Regeneron patent US10787501 (3.2 months from filing date to grant/6 months from earliest priority date), Gamaleya Research Institute patent RU2720614 (only 19 days direct filing and grant) and Celltrion/KDCPA patent KR2205028 (2.3 months from application date to grant/10.1 months from earliest priority date).

It should be noted that while there is an average 18-month lag between filing of a patent application and publication of such application, the public may anticipate in some cases and some jurisdictions which entities may have COVID-19-related patent applications published in the following 12 to 18 months. This can be done by searching for early disclosures of related patent applications (e.g., by

looking for COVID-19 or SARS-CoV-2 keywords) in supporting national patent registers or official journals/bulletins of patent offices. These sources may publish some initial information on the title, applicant name and/or inventor for some provisional or other equivalent patent filing format. Examples of this process of partial early disclosure were observed at the Israel, U.K. and Singapore patent offices, for instance, can be found in the Annex.

COVID-19-related vaccine and therapeutic patent applicant profiles

Looking at the applicant profiles, the distribution of the dataset is similar in the vaccines and therapeutics areas (Table 3): corporate applicants account for a slightly larger percentage of the filings (44 percent of therapeutics and 49 percent of vaccine filings). Universities and public research organizations have similar contributions (41 percent of the therapeutics and 44 percent of the vaccine dataset), while independent inventors are more active in the field of therapeutics (15 percent) than vaccines (7 percent), probably because of the complexity of the latter.

Table 3. Contribution of different patent applicant profiles to COVID-19-related vaccine and therapeutic datasets from January 2020 to September 2021.
Patenting activity related to COVID-19 vaccines and therapeutics is nearly equally distributed between companies and universities and research organizations, with companies having a slightly higher contribution.

	COVID-19 vaccines		COVID-19 therapeutics	
Patent applicant profile	Number of patent families	Contribution to the vaccines patent dataset	Number of patent families	Contribution to the therapeutics patent dataset
Companies	222	49%	708	44%
Universities and research organizations	201	44%	665	41%
Independent Inventors	34	7%	237	15%

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers may change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Research collaboration and IP strategies related to technologies important to COVID-19 vaccines and therapeutics

There has been some collaboration among organizations for the development of COVID-19 vaccines and therapeutics, yet this is not so notable at the patenting stage based on the data collected up to the end of September 2021. Most of the patent applications were filed by single applicants, and only one-fifth (21 percent) of both the vaccine dataset (87 out of 417 patent families) and the therapeutics dataset (289 out of 1,465 patent families) involved patent applications filed by more than one applicant. An example of co-filed patent applications is one co-filed by Pfizer and BioNTech published in October 2021 (and thus not included in the patent dataset) disclosing technology related to the packaging, transportation and storage of temperature-sensitive biological and/pharmaceutical products such as mRNA vaccines (WO2021213945). While only a modest percentage of COVID-19 vaccines and therapeutics patent filings reflects collaboration in patent filing, the analysis of the COVID-19 therapeutic tracker data generated by the Milken Institute and RAPS, as well as related vaccine information from the WHO, shows collaboration between different organizations to facilitate development and distribution of both vaccines and therapeutics. These agreements will be discussed in more detail in the following sections.

Some companies followed different approaches to facilitate access to patented technology. AbbVie, for example, voluntarily cancelled six of its patents related to the drugs Kaletra (a mixture of lopinavir and ritonavir) and Norvir (ritonavir) in Chile (INAPI-Chile, 2020), and committed not to enforce its patents on lopinavir/ritonavir in early 2020. Other companies, such as Amazon, Intel and Hewlett Packard Enterprises provided access to thousands of their patents that could help with containing the disease (WIPO, 2020). The Medicines Patent Pool and Merck entered into a license agreement

for the manufacture of molnupiravir, an antiviral COVID-19 medicine, to increase access by low- and middle-income countries (Business Wire, 2021). A license was also signed with Pfizer in November 2021 on nirmatrelvir (PF-07321332 that is administered in combination with lopinavir) to allow additional production and distribution of the drug by qualified generic drug manufacters (Medicines Patent Pool, 2021a; Business Wire, 2021).

Disclosure of sequences within patent documents

Based on the CAS-related sequence indexing, 1,317 out of the overall COVID-19 dataset (5,293 patent families), 210 out of 417 vaccine patent families and 346 out of the 1465 therapeutics patent families refer to biological sequences, these include both amino acid and nucleotide related to vaccine development (such as the antigenic regions of the SARS-CoV-2 proteins as vaccines and their corresponding nucleic acid sequences) or the design of biological drugs such as antibodies. As mentioned above, sequencing the SARS-CoV-2 genome in early 2020 was essential for developing COVID-19 vaccines and identifying targets for therapeutics. Sequences of both the viral genes and the proteins that they encode are important for developing vaccines that effectively stimulate the immune system and treatments that inhibit the virus, while sequencing also continues, also because it plays a role in COVID-19 diagnostics. A number of patent documents have disclosed viral sequences useful for generating immune response, such as Altimmune patent WO2021163536 or Inovio patent WO2021173829, which provide SARS-CoV-2 S protein sequences that can be targeted by antibodies and used as COVID-19 vaccine components. In addition, inventors disclosed sequences of therapeutic antibodies against SARS-CoV-2. For example, Centivax patent WO2021194891 discloses the protein sequences of a variety of antibodies that bind to SARS-CoV-2 and interfere with its ability to cause infection. Some nucleotide sequence listings disclosed by such patent documents are fed into international collaborative platforms and repositories of sequence information, such as the International Nucleotide Sequence Database Collaboration (INSDC), by relevant patent offices or researchers. Such international information sharing arrangements for the rapid exchange of sequences were critical for the successful and swift global pandemic response and facilitated the development of vaccines and therapeutics.

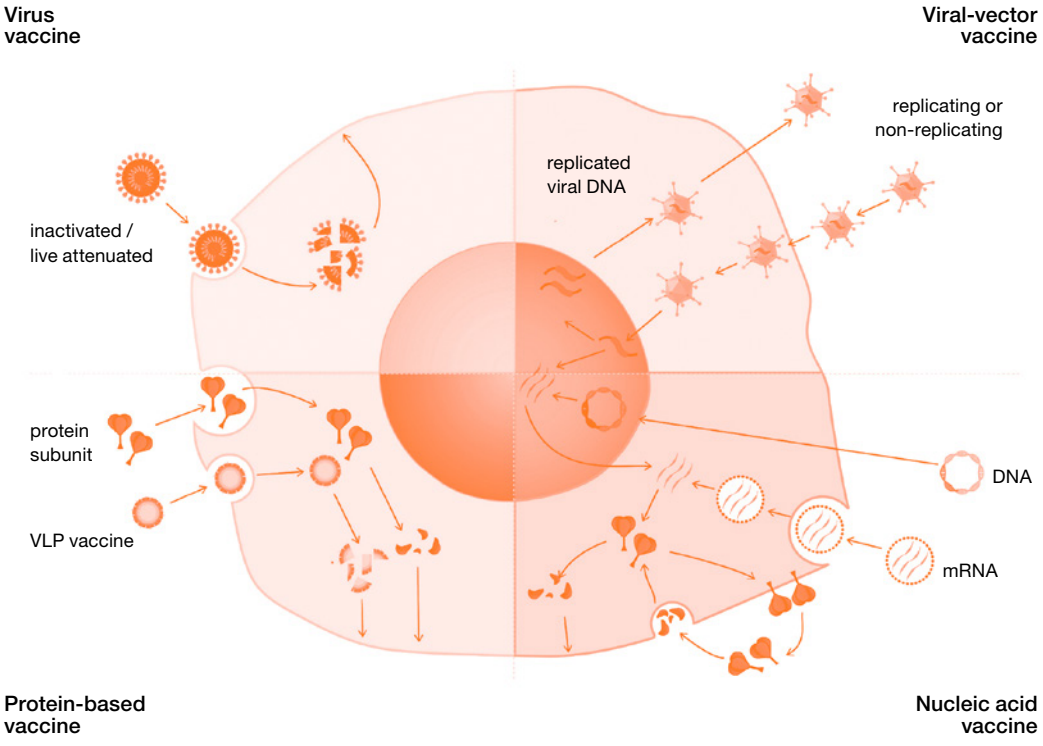
COVID-19 vaccines

Background – vaccine platforms

Multiple vaccine platforms have been explored for COVID-19 vaccine development, with each platform exhibiting unique advantages and disadvantages (Li *et al*., 2021b). Some of them are **conventional**, well-established types of vaccine such as the whole-virus vaccines, including both live attenuated and inactivated vaccines, the virus-like particles and the protein subunit vaccines, while others, such as the nucleic-acid (DNA and RNA)-based vaccines, the viral-vector-based vaccines and the antigen-presenting cells, are **novel**, with little pre-existing data on safety and efficacy in humans. Table 4 provides a summary of all the vaccine platforms.

Different vaccine platforms may produce an immune response in different ways (Figure 4). Inactivated vaccines provide a broad spectrum of protein antigens against which the body can generate protective antibodies. Protein-based vaccines produce a more focused response to a specific antigen. Viral-vector vaccines deliver protein antigen-encoding genes to cells, which the cells then use to produce proteins against which they generate an immune response. Nucleic acid vaccines are packaged in a synthetic coating and deliver protein antigen-encoding genes to cells, which the cells then use to produce proteins and generate immunity.

Figure 4. **Vaccine platforms and the ways they produce immunogens in cells.**



Adapted with-permission (Li *et al*., 2021b).

Conventional vaccine platforms

Live attenuated and **inactivated vaccines** are well-established traditional **whole-virus** vaccine approaches. They contain the structural proteins of SARS-CoV-2 such as the spike, envelope, membrane and nucleocapsid proteins that induce host immune responses. **Live attenuated vaccines** contain a purposefully weakened version of the disease-causing virus. Although these vaccines can elicit strong and lasting humoral (antibody-mediated) and cellular (cell-mediated) immune responses simulating natural infection, they require extensive safety evaluation. A codon de-optimized, single-dose, intranasal live attenuated vaccine candidate from Codagenix/Serum Institute of India entered Phase 1 clinical evaluation (Annex, Table A1). **Inactivated vaccines**, also called "killed vaccines," are produced by growing the virus in culture media, then inactivating it through application of heat, chemicals or radiation. Unlike attenuated vaccines, these vaccines cannot replicate, thus they are safe even for immunocompromised persons. However, inactivated vaccines are less effective since they mainly elicit an antibody-mediated immune response instead of the more effective cell-mediated response (Figure 4), and often require multiple doses of the vaccine to boost immunity. As of October 8, 2021, 18 inactivated vaccine candidates were at the clinical trial stage, of which eight are in Phase 3 trials and two in Phase 4 (Annex, Table A1).

Protein subunit vaccines represent a logical step forward in providing better-characterized and safer vaccines compared to inactivated and live attenuated vaccines. Protein antigens are amenable to established purification methodologies, are scalable for manufacturing, do not require high-level biosafety facilities and eliminate the risk of pathogen-mediated disease. Most of the initial COVID-19 protein subunit vaccines were constructed to direct immune system responses against the SARS-CoV-2 S protein antigen. Vaccines can use either the whole S protein or a fragment of it. The whole protein can be the normal S protein or an engineered form of S protein that is missing a piece that can normally be cut by the furin enzyme and that has mutations (two proline substitutions) that alter the shape of the S protein. These "prefusion stabilized" (2P) S proteins allow for improved antigenicity and antibody accessibility.

Since the initial COVID-19 vaccine rollout, the rise of VOCs has highlighted the importance of establishing correlates of immunity beyond that of neutralizing antibodies. Recent research studies (Hachim *et al*., 2020a, 2020b; Nelde *et al*., 2021) helped in assessing the breadth of antibody and T-cell responses. In this regard, there are multi-antigen vaccines in the clinical pipeline but public results on these vaccines are still limited (OSE Immunotherapeutics, 2021; Dobrovidova, 2021). Protein-based COVID-19 vaccines in clinical trials are listed in Annex Table A2.

Novel vaccine platforms

Virus vectors represent a mechanism to deliver vaccine antigens for stimulation of a host's immune system in a context that mimics that of live attenuated vaccines without allowing the disease associated with the parental pathogen (Ura *et al*., 2014). The vectors may be constructed from viruses whose genomes are either RNA (e.g., myxovirus, alphavirus and vesicular stomatitis virus) or DNA (e.g., adenovirus, poxvirus and herpesvirus) and are derived from viruses of both human (Lasaro and Ertl, 2009) and non-human (Alhashimi *et al*., 2021) origin. The selection criteria for vectors can be complex and dependent on the infectious organism to be targeted. For COVID-19, vaccine vectors have largely been chosen from members of the *Adenoviridae* family and representatives of a few other viral classes. In vaccine applications, the vectors are broadly categorized as replication-competent vs. replication-defective. Here, competency means the ability of the vector to duplicate its genome within a host cell and to assemble virus progeny capable of productive infection. Most COVID-19 vaccines in clinical and preclinical trials are replication-defective. A complete list of such vaccine candidates in clinical trials is presented in Annex Table A3.

DNA virus vectors used for COVID-19 vaccines in our patent dataset include a novel adenoviral single-cycle vector that can amplify the amount of mRNA and antigen produced but is unable to make new viruses (Barry, 2018). This feature of single-cycle adenovirus vectors can lower the effective immunization dose by an order of magnitude. Examples include a modified vaccinia virus Ankara (MVA) encoding the spike, membrane and envelope proteins (WO2021163622A1) and an adeno-associated virus 9 vector created to deliver and express a dimeric SARS-CoV-2 receptor-binding domain (CN112608908 A).

RNA virus vectors used for COVID-19 vaccines in our dataset include: a vesicular stomatitis virus (VSV) in which the VSV envelope glycoprotein (G) was replaced by the SARS-CoV-2 S protein (CN112941038A); a Newcastle Disease virus (NDV) vector, in which the SARS-CoV-2 S protein gene was inserted between the phosphoprotein (P) and the matrix protein (M) genes of the NDV vector (CN112011521A); and a yellow fever virus vector, in which a transgene encoding a stabilized prefusion S protein can be expressed (WO2021170869A1).

Nucleic-acid-based vaccines contain viral genetic material (such as DNA or mRNA) encoding specific viral proteins (antigens), which provides the instructions for making antigens in the host cells. The production of these foreign antigens mimics the natural viral infection that effectively elicits both antibody-mediated and cell-mediated immune responses and prepares the immune system to protect against future infection caused by the same virus. See Annex Table A4 for a complete list of nucleic-acid-based COVID-19 vaccines in clinical trials.

DNA vaccines use plasmid DNA that contains everything needed to express an antigen (such as S protein) in a human cell nucleus. They are easy to produce and very stable at room temperature. Currently, 14 DNA vaccine candidates are in clinical trials, of which four candidates have entered Phase 3 (Annex, Table A4). WO2021173829 by Inovio Pharmaceuticals discloses the DNA vaccine, INO-4800, that encodes the full length of the SARS-CoV-2 S protein. With positive results of safety and immunogenicity (Tebas *et al*., 2021) it entered Phase 3 clinical trials in June 2021 (Clinical Trials Arena, 2021b). AG0301 from AnGes, and GX-19N from Genexine Consortium are also in the late stage of clinical trials.

mRNA vaccines are a new safe, efficient and fast platform. mRNA can be produced in large quantities in a cell-free environment by *in vitro* transcription (IVT) that allows for fast development, a simplified production process and cost-effective manufacturing (Pardi *et al.*, 2018). Indeed, Moderna took just two months from taking a full sequence of SARS-CoV-2 to designing a COVID-19 mRNA vaccine for clinical trials. With outstanding results in clinical trial phase 3, COVID-19 mRNA vaccines BNT162b2 (94.1 percent) (Polack *et al*., 2020) from BioNTech/Pfizer and mRNA-1273 (95 percent) (Baden *et al*., 2021) from Moderna have been approved in many countries. Remarkably, 21 mRNA vaccines are under clinical investigation (Annex, Table A4).

Since the pandemic, a series of patent applications by Moderna relating to COVID-19 vaccine development has been published (WO2021159130, US20210228707, WO2021159040). These patent documents relate to SARS-CoV-2 mRNA vaccines encoding full-length S protein variants, which include two proline substitutions (2P) to stabilize S protein into a configuration that exposes the critical part of the S protein to the immune system. They are formulated with lipid nanoparticles and induce robust immune response against SARS-CoV-2 infection in humans of various ages and disease conditions.

Companies including Moderna, BioNTech and Curvac designed their first generation of COVID vaccines using 2P S protein as antigen, based on the data from other betacorona viruses, SARS and MERS, which resulted in higher protein (antigen) expression and elicited potent immune responses (Pallesen *et al*., 2017). Currently, nine mRNA vaccine candidates encode 2P S protein.

BioNTech patent application WO2021188969 discloses the prediction and immunogenic evaluation of HLA class I- and HLA class II-restricted peptides epitopes derived from SARS-CoV-2 proteins. These are from SARS-CoV-2 genes Orf1ab, M and N, and may be used to either construct multi-epitope protein vaccines directly or delivered as RNA vaccines.

Table 4. Categories of COVID-19 vaccine platforms.

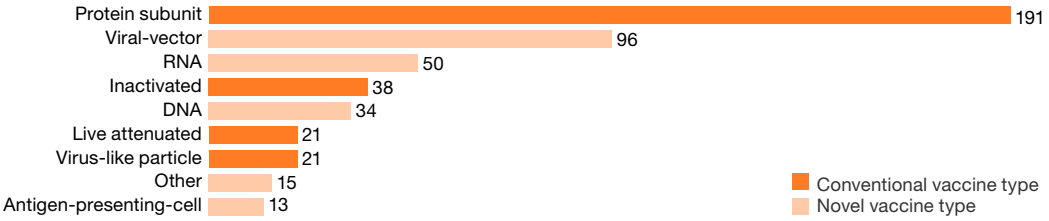
Conventional and novel vaccine platforms are both represented in existing COVID-19 vaccines and vaccine candidates.

Conventional	
Protein-based 	Viral proteins or antigens used to stimulate an immune response *Example*: Novavax vaccine
Virus-like particle 	Protein structures that closely resemble viruses, but are non-infectious because they contain no viral genetic material *Example*: Covifenz (Medicago/GSK)
Inactivated 	Vaccine consisting of pathogens (virus particles, bacteria) grown in culture and then killed to destroy their disease-producing ability *Examples*: Sinovac, Sinopharm, Bharat Biotech vaccines
Live attenuated 	Vaccine comprising a pathogen with reduced virulence (“live”), so that it becomes harmless or less virulent, stimulating a strong and effective, long-lasting immune response
Novel	
Nucleic acids  DNA  RNA	Pieces of DNA or mRNA that encode viral proteins or antigens and depend on the host’s cells to produce the corresponding proteins to stimulate an immune response *Examples*: Pfizer/BioNTech; Moderna vaccines
Virus vector  non-replicating  replicating	Like nucleic acid platforms, viral vectors encode proteins or antigens and depend on the host’s cells to produce these proteins to stimulate an immune response. They are usually based on a modified harmless version of a different virus, such as adenovirus *Examples*: AstraZeneca/Oxford University; Johnson & Johnson; CanSino Biologics; Gamaleya Research Institute vaccines
Antigen-presenting-cell 	Immune cells that mediate the immune response by presenting antigens for recognition by the host’s lymphocytes

Patent and vaccine distribution by vaccine platform and published applicant location

We identified and analyzed 417 patent documents related to COVID-19 vaccine development published by September 30, 2021. These documents included a wide variety of vaccine platforms, ranging from conventional platforms such as live attenuated and inactivated vaccines, protein-based platforms (protein subunit vaccines and VLPs), to more innovative ones such as viral-vector-based platforms, nucleic-acid-based platforms (DNA- and RNA-based vaccines) and antigen-presenting-cell (APC)-based vaccines (Figure 5).

Figure 5. Distribution of COVID-19-related patent filings among vaccine platforms.
Nearly half of the vaccine patent dataset relates to protein subunit vaccines (conventional vaccine platform), followed by patent filings related to novel viral-vector vaccines (novel vaccine platform), which account for one-quarter of the vaccine patent dataset



Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: "Other" include technologies related to nanoparticles, adjuvants, etc. Numbers are indicative and expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication). A patent document may refer to more than one vaccine platform.

Among these platforms, protein subunit vaccine-related patent filings constitute the largest category (191, 46 percent), followed by viral-vector (96, 23 percent), RNA (50, 12 percent), inactivated (38, 9 percent), DNA (34, 8 percent), live attenuated vaccines (21, 5 percent) and VLPs (21, 5 percent). In addition, 13 patent filings relate to APC-based vaccine development and 15 patent documents classified as "other" include technologies related to nanoparticles, adjuvants, etc. We observed that some patent documents claim more than one type of platform and as a result are counted in all the related platforms they cover in Figure 5. While conventional vaccine platforms such as protein subunit vaccines still account for the largest portion of the patent dataset, novel approaches such as viral vectors and nucleic acid platforms (RNA and DNA) gain momentum. Such achievements can be attributed to decades of advanced research, as illustrated, for example, in the mRNA research advancement timeline, which resulted in the invention of the most promising mRNA vaccine formulations, arising from intense collaboration among various research organizations including universities and pharmaceutical/biotech companies, and the tireless efforts of vaccine scientists.

All the COVID-19 vaccines approved so far need to be given via intramuscular injection. Interestingly, since the generation of the patent dataset for the development of this report, a few patent applications on the development of inhalable COVID-19 vaccines have been published (WO2021244120, WO2021216467, WO2021207213). This represents a new alternative method for COVID-19 vaccination, which may boost immune defense in the upper respiratory system. However, the effectiveness of such a vaccination method is yet to be determined in clinical trials, although intranasal viral vaccination has been applied to influenza (Oran, 2021). From an IP perspective, such vaccines may raise additional issues with delivery devices (WHO–WIPO–WTO, 2021, box 3.14).

Table 5. Distribution of COVID-19-related patent filings from January 2020 to September 2021 among vaccine platforms by top patent applicant locations.
While China-based applicants filed patent applications across different vaccine platforms, U.S.-based applicants focused on protein subunit, viral-vector and RNA vaccines, and Russian Federation applicants filed mainly in the fields of viral-vector and protein subunit vaccines.

Vaccine platforms									
Patent applicant location	Protein subunit	Viral-vector	RNA	Inactivated	DNA	Live attenuated	Virus-like particle	Antigen-presenting-cell	Other
China	132	61	28	25	22	15	12	9	9
U.S.	36	14	14	7	5	4	4	–	5
Russian Federation	5	13	1	1	2	1	–	–	–
U.K.	4	2	2	–	–	–	3	–	–
Germany	1	1	3	1	–	–	–	–	–
India	1	1	–	2	–	–	1	1	–
Republic of Korea	1	1	1	–	–	1	–	1	–

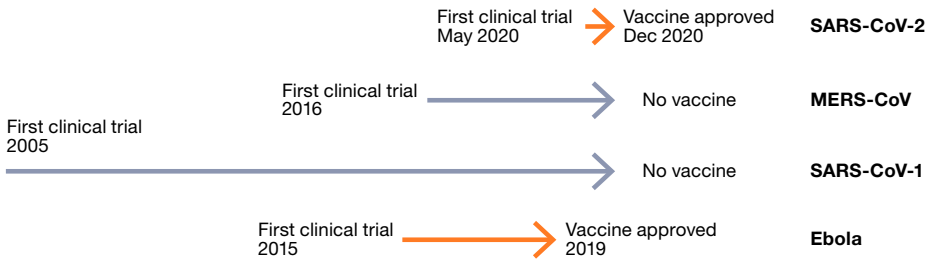
Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

The applicants for these SARS-CoV-2 vaccine patent filings were from 21 published applicant locations, an indication of a global effort by public and private institutions over the past 21 months. Nevertheless, China, the U.S., the Russian Federation, the Republic of Korea, the U.K., India and Germany account for over 95 percent of the COVID-19 vaccine patent dataset. Applicants based in China have filed 313 patents across a wide range of vaccine platforms. U.S.-based applicants filed 89 patent applications largely focusing on protein subunit, viral-vector-based and RNA vaccines. Applicants based in the Russian Federation had filed 23 patent applications at the time of data collection, mainly for viral-vector-based and protein subunit vaccines (Table 5).

Speed of vaccine development

Some COVID-19 vaccine candidates entered clinical trials in less than 6 months and were conditionally approved 10 months after the beginning of the COVID-19 outbreak (FDA, 2021a, 2021f), which was a record-breaking speed in vaccine development history. Undoubtedly, the emergency use authorization (EUA), which FDA issued for several COVID-19 vaccines, substantially contributed to their prompt application in public health protection. As a comparison, a vaccine for Ebola disease took at least 15 years of development, including four years of clinical trials, for authorized clinical use (Figure 6). As for the other coronavirus disease-causing outbreaks (SARS and MERS), there was a strong momentum to develop vaccines initially, but the effort significantly reduced when the outbreaks ended. Although vaccine research for SARS-CoV-1 and MERS-CoV is still ongoing (de Wit *et al*., 2016; Song *et al*., 2019) there is no approved vaccine for either disease, probably because there are now too few real cases for a clinical trial (Figure 6).

Figure 6. Timelines for the development of vaccines for Ebola virus and three beta-coronaviruses (SARS-CoV-1, MERS-CoV and SARS-CoV-2).
The seven months it took from the first clinical trial to the first COVID-19 vaccine approval is a record time compared to similar timelines for other viruses.



Source: Funk *et al*., 2020.

By the end of September 2021, many countries were working on developing COVID-19 vaccines. According to the WHO's vaccine development data, over 330 vaccine candidates were in various stages of development and more than 100 in clinical trials (WHO, 2021a). Several vaccines have demonstrated efficacy as high as 95 percent in preventing COVID-19 infections (Li *et al*., 2021b).

COVID-19 vaccine patent landscape

As patent protection is territorial and the same invention may be filed for patent protection in multiple jurisdictions, we looked at all related filings related to COVID-19 vaccines, considering for each simple patent family every patent jurisdiction where patent protection was sought and counting it once for each family (for a wider discussion of patent families see Annex). The analysis by patent office revealed (Table 6) that China received the most COVID-19-related vaccine patent applications, followed by WIPO administering the PCT System, the U.S., the Russian Federation and the European Patent Office (EPO) administering the European Patent Convention (EPC).

The high ranking of WIPO and thus the strong use of the PCT System allowing for easier filings across several national patent offices is an indication of the intention of patent applicants to seek patent protection for their inventions across multiple jurisdictions, similar to European Patent (EP) filings, which are as yet much lower. It is also worth noting that the country coverage is bound to increase once many PCT applications currently in the international phase enter the national phase in 2022.

China, the U.S., the Russian Federation and the U.K. also form the top four applicant locations (Table 7). Germany, India and the Republic of Korea are jointly 5th in the ranking. Australia, Austria and Switzerland are joint 6th, with an equal number of patent applications. Filings from applicants based in these ten countries account for over 90 percent of the total number of patent applications in vaccines.

Table 6. Top patent offices by number of COVID-19 vaccine-related patent applications filed for patent protection from January 2020 to September 2021.

As per September 2021 patent applications related to COVID-19 vaccines were filed in 19 patent offices. Most applications were filed in China, WIPO and the U.S., with these three offices accounting for 84 percent of all COVID-19 vaccine patent applications.

Patent offices of filing for COVID-19 vaccines	Number of patent families
China	274
WIPO	130
U.S.	96
Russian Federation	21
EPO	21
U.K.	14
Canada	7
Republic of Korea	6
India	6
Australia	4

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: WIPO represents PCT applications, the European Patent Office (EPO) EP applications. EAPO is the Eurasian patent office. Numbers are indicative and expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Table 7. Top applicant locations for patent filings related to COVID-19 vaccine development filed for patent protection from January 2020 to September 2021.

Most patent applications were filed by patent applicants based in China, the U.S. and the Russian Federation.

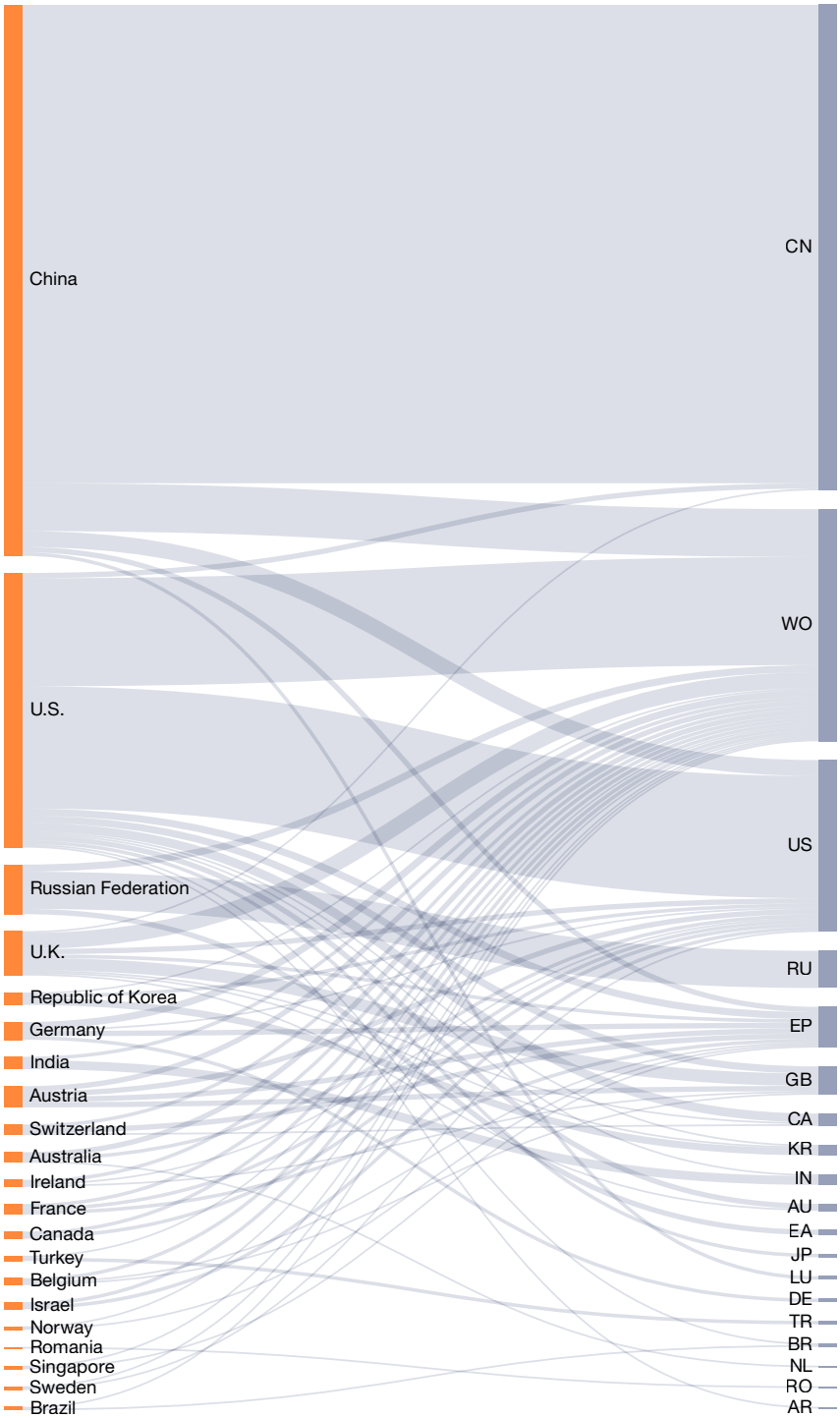
Patent applicant location (vaccines)	Number of patent families (vaccines)
China	276
U.S.	72
Russian Federation	21
U.K.	9
Republic of Korea	5
Germany	5
India	5
Australia	3
Austria	3
Switzerland	3

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Comparing the offices of filing to the origin of the applicants, we see similar trends in the top locations, with differentiations further down the ranking, which may indicate different applicant filing strategies. Figure 7 illustrates where applicants from different origins filed their applications.

Figure 7. Flow of patent filings related to COVID-19 vaccines from different applicant locations (left) to various patent offices of filing (right).

There are diverse patent filing strategies: many applicants file foremost in their home country, with a smaller proportion filing PCT applications or in other jurisdictions, while others, for instance U.S.-based applicants, have a nearly equal number of U.S. and PCT filings.



Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: The figure was prepared based on patent applicant location and patent offices of filing of patent family members. The two-digit codes used follow the WIPO Standard ST.3. The patent applicant filing strategy represented in this figure may change over time as patent applicants file subsequent patent applications in different jurisdictions.

Most patent applicants based in China almost exclusively filed their patent applications in China, with only a few exceptions in the U.S. and EP filings, while U.S.-based applicants filed mainly PCT and U.S. applications. Such a trend reflects the interest of U.S. patent applicants in seeking patent protection for their inventions across multiple jurisdictions and their interest in several markets. Applicants based in other countries showed diverse filing strategies. Russian Federation applicants filed their vaccine patent applications mainly in the Russian Federation, at WIPO/PCT and in the Eurasian Patent Office. German applicants filed PCT and EP applications, while Republic of Korea applicants filed home office, U.S. and PCT applications.

As revealed earlier in the report, patenting activity related to vaccines is nearly equally shared between corporate and academic players. To reveal the major players in the vaccine patent dataset, we initially investigated the overall rankings of top patent applicants, even if the patent portfolios in such a short period of filing and with the publication lag are quite small. The results led to a list of China-based universities and research organizations. To gain a more representative picture of activity around the world, we further examined the applicant data by continent/region and the result is presented in Tables 8a–c. While in an area with such recent patenting activity the patent portfolios are smaller and it is difficult to talk about top players, the approach taken in this report is to address the general trends, and to point out some patent applicants with very few patent applications yet which feature both in the patent data as well in the vaccines clinical trial lists (see Tables A2–A5). As such, they should be considered as examples meant to illustrate either geographical distribution or links to vaccine candidates.

The Russian Gamaleya National Center of Epidemiology and Microbiology and the State Research Center of Virology and Biotechnology VECTOR filed more vaccine-related patent applications (eight and nine, respectively) than other universities and research organizations in Europe, while the French Institut Pasteur filed two patent applications (Table 8a). Oxford University Innovation Limited – as all other European academic patent applicants – filed only one patent directly related to COVID-19 vaccines (as per the information available at the time the patent search was carried out). Nevertheless, it has applied its previously patented work (WO2017221031) on using a chimpanzee adenovirus as the vector (or Trojan horse) for its viral-vector-based COVID-19 vaccine design and through collaboration with AstraZeneca, successfully brought this previously patented technology onto the COVID-19 vaccine market. Therefore, other factors beyond patent counts, such as collaboration after the patent filing stage, may also play a significant role in the commercialization of patented technologies. Looking at European corporate applicants, the German company CureVac, with two patent applications, initially devoted its effort to the first generation of mRNA COVID-19 vaccines and has now shifted its effort to the second generation in collaboration with GSK.

Table 8a. Examples of COVID-19 vaccines patent applicants (companies, universities and research organizations) based in Europe and the Russian Federation selected by number of filings and/or presence in clinical trial data.

Developers or manufacturers of COVID-19 vaccines as per the clinical trial data from different European countries start featuring in the patent data as it starts becoming publicly available.

Patent applicant	Patent family count	Applicant profile	Applicant location
State Research Center of Virology and Biotechnology VECTOR	9	University or research organization	Russian Federation
Gamaleya National Center of Epidemiology and Microbiology	8	Universities or research organization	Russian Federation
Valneva	3	Company	Austria/France
Institut Pasteur	2	University or research organization	France
CureVac	2	Company	Germany
Imperial College Innovations	2	Company	U.K.
Oxford University Innovation Limited	1	University or research organization	U.K.
PepTC Vaccines	1	Company	U.K.
RocketVax	1	Company	Switzerland
Svenska Vaccinfabriken Produktion	1	Company	Sweden

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Looking at some corporate applicants in Europe, Valneva is a French biotechnology company. Its Austrian and French R&D teams developed the candidate vaccine VLA2001 using adjuvant from the American company Dynavax Technology. It is a whole-virus inactivated vaccine that contains two adjuvants, alum and CpG 1018. On November 10, 2021 the European Commission approved a contract with Valneva providing the possibility to purchase almost 27 million doses of its vaccine in 2022. This also includes the possibility to adapt the vaccine to new variants, as well as the order of an additional 33 million vaccine doses in 2023. The Imperial College Innovations vaccine is mRNA, like other vaccines from BioNTech/Pfizer and Moderna. It uses self-amplifying RNA (saRNA) technology and began human trials in June 2020.

It should be noted that some companies have a presence across different jurisdictions and they may file with different subsidiaries. BioNTech in Germany for example is a known player, yet the first published patent directly related to COVID-19 by this company was filed by BioNTech U.S.

Both Russian applicants Gamaleya and State Research Center of Virology and Biotechnology VECTOR feature in the list with candidate vaccines in clinical trials (see Annex).

Table 8b shows Moderna – one of the major mRNA vaccine suppliers – which features in the current dataset and in several vaccine candidates in clinical trials (see Annex). Although Pfizer is a major mRNA vaccine contributor, it got its foot-hold in this area through collaboration with BioNTech with its vaccine production capability rather than patenting activity. Novavax (Table 8b) collaborated with the Serum Institute of India in clinical trials (see Table A2 in Annex). The U.S.-based Soligenix featured in the patent dataset with a patent application co-filed with the University of Hawaii and have a candidate vaccine (CiVax), while the Oswaldo Cruz Foundation from Brazil (Fiocruz) also represented in the patent dataset works on the development on several COVID-19 vaccines and collaborated with Oxford/AstraZeneca in COVID-19 vaccine production (Fiocruz, 2021).

Table 8b. Examples of COVID-19 vaccine patent applicants (companies and universities and research organizations) based in the U.S. selected by number of filings and/or presence in clinical trial data.

Patent applicant	Vaccines patent family count	Applicant profile
Altimmune	2	Company
Mead Johnson Nutrition Company	2	Company
Moderna Therapeutics	2	Company
The Corporation of Mercer University	2	University or research organization
University of Pittsburgh	2	University or research organization
Wisconsin Alumni Research Foundation	2	University or research organization
Arcturus Therapeutics	1	Company
BioNTech US	1	Company
Codagenix	1	Company
Elixirgen Therapeutics	1	Company
Gritstone Oncology	1	Company
Janssen Pharmaceuticals	1	Company
Novavax	1	Company

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Table 8c and the analysis of the patent dataset shows that in Asia patenting activity related to COVID-19 vaccine development stems mainly from patent applicants from China, regardless of the applicant profile. Several of the patent applicants featuring in the patent dataset have candidate vaccines in clinical trials (see Tables A1 to A4 in the Annex), such as the Institute of Medical Biology.

Table 8c. Examples COVID-19 vaccine patent applicants (companies and universities and research organizations) in Asia selected by number of patent filings and/or presence in the clinical trial data.

Patent Applicant	Number of COVID-19 vaccine patent families	Applicant profile	Applicant Location
Institute of Microbiology, Chinese Academy of Sciences	8	University or research organization	China
Sun Yat-Sen University	6	University or research organization	China
Chongqing University of Medical Sciences	6	University or research organization	China
Academy of Military Sciences Military Medical Research Institute Military Veterinary Institute	6	University or research organization	China
Wuhan University	5	University or research organization	China
Beijing Huaren Biotechnology	4	Company	China
Kunming Medical University	4	University or research organization	China
Beijing Dingcheng Taiyuan Biotechnology	4	Company	China
Academy of Military Medical Science	4	University or research organization	China
Premas Biotech	1	Company	India
Enzychem Lifesciences Corporation	1	Company	Republic of Korea
ACM Biolabs	1	Company	Singapore

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

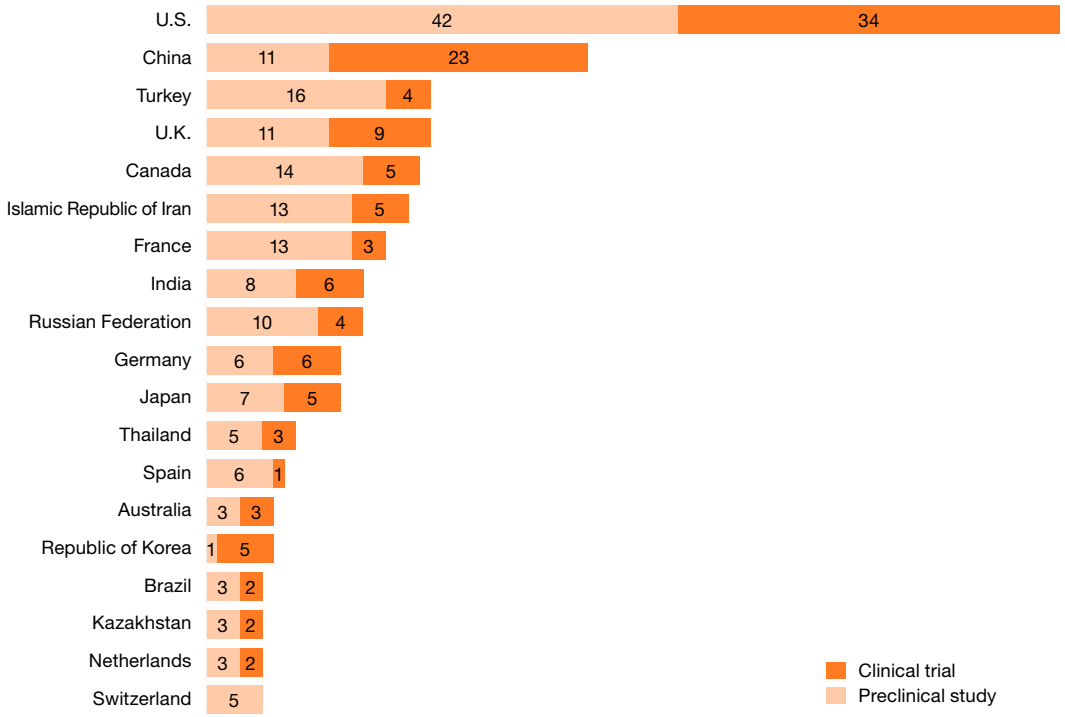
Core vaccine technologies, collaboration and licensing

Collaborations and licensing agreements were key to facilitating rapid COVID-19 mRNA vaccine development. However, patent applications for the underlying technologies were, for the most part, filed prior to 2020. These technologies centered on the mRNA itself and the lipid nanoparticle capsule that is used to deliver the mRNA to human cells, both of which make possible today's mRNA vaccines. In the early 2000s, researchers at the University of Pennsylvania published their groundbreaking study that showed mRNA could be modified to allow it to induce protective immune response while not eliciting undesired response upon delivery into the body (Kariko et al., 2005). Their pioneering work led to the development of recent mRNA-based therapies and vaccines. The University of Pennsylvania sublicensed these mRNA-related patents to Moderna and BioNTech through RiboTherapeutics and its affiliate CellScript. The University of British Columbia and Arbutus Biopharmaceuticals collaborated on lipid nanoparticle research in the late 1990s, which also proved to be key to development of mRNA-based therapies and vaccines. The University of British Columbia holds the patents and licensed the work back to Arbutus which now holds the IP of lipid nanoparticles (LNP) for a wide range of applications. Through a series of sublicenses accompanied by legal disputes, Moderna obtained some sublicenses for its use of the technology in certain viral vaccines (Nature Biotechnology, 2020; JDSUPRA, 2021a.) Through licensing agreement, BioNTech also obtained Arbutus LNP technology for delivery of its mRNA vaccines and drug candidates (JDSUPRA, 2021b). An interesting example patent application (WO2021163365) filed during the pandemic time frame was a collaboration among the U.S. National Institutes of Health, The University of Texas and Dartmouth College. They patented a stabilized, modified version of SARS-CoV-2 S protein that was then encoded by the mRNAs used by the companies Moderna, CureVac, Pfizer and BioNTech when constructing mRNA vaccines (Gaviria and Kilic, 2021).

Analysis of WHO data on COVID-19 vaccines

To achieve a more comprehensive overview of the global COVID-19 vaccine development landscape, we also analyzed candidate vaccines in the development pipeline based on WHO data. In Figures 8–9 and Table 9, we examine the geographical location of the developer, stage of study and vaccine platform. As of October 8, 2021, there were 320 COVID-19 vaccine candidates, of which 194 were in preclinical studies and 126 in clinical trials (WHO, 2021a).

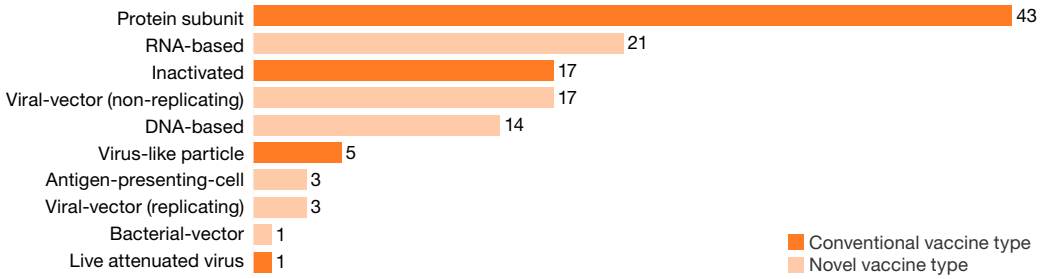
Figure 8. Top 19 locations based on number of COVID-19 vaccines in the development pipeline. *The U.S., China, Turkey and the U.K. have the highest number of vaccines at the clinical and preclinical stage.*



Source: WHO COVID-19 vaccine tracker and landscape data as of October 8, 2021.
Note: COVID-19 vaccine development is a dynamic area and vaccine tracker information changes over time, affecting numbers and the locations in question.

Since the COVID-19 outbreak, many regions have devoted significant resources toward vaccine development against SARS-CoV-2. As shown in Figure 8, the U.S. leads in both the numbers of clinical and preclinical vaccine candidates, with 34 and 42 respectively, followed by China (with 23 and 11), Turkey (4 and 16) and the U.K. (9 and 11). It is also noteworthy that India has six candidates in clinical trials and eight in preclinical studies, while Germany has 12 vaccine candidates with six under clinical evaluation. This trend analysis demonstrates a more diversified array of countries (34) involved in clinical trials of COVID-19 vaccine designs compared to COVID-19-related vaccine patent publications (21) (Table 5), so one could anticipate more patent applications related to COVID-19 from other regions to be filed and/or be published soon, as they may not yet feature in the current published information.

Figure 9. Landscape of COVID-19 vaccine candidates in clinical trials among various vaccine platforms.
While most vaccines in clinical trials concern traditional vaccine platforms, the two largest categories are the conventional protein subunit vaccine and the novel RNA vaccine platform.



Source: WHO COVID-19 vaccine tracker and landscape data as of October 8, 2021.
Note: COVID-19 vaccine development is a dynamic area and related information changes over time.

Figure 9 illustrates the distribution of COVID-19 vaccine candidates in clinical trials across various platforms. The largest category in clinical trials is protein-based (subunit) – vaccines with 43 vaccines. A substantial global effort in RNA vaccine development is indicated by 21 RNA candidate vaccines under clinical evaluation. These top two platforms are followed by live and attenuated (LA=1) and inactivated virus vaccines (17), non-replicating viral-vector vaccines (17), DNA vaccines (14), VLP (5), replicating viral-vector vaccine (3), and APC and bacterial-vector-based (1).

Table 9. Distribution of COVID-19 vaccine candidates in clinical trials among various platforms by country.
Almost all listed countries have protein subunit and DNA vaccines in clinical trials. The U.S. has the highest number in most vaccine platforms apart from China which has the highest number of inactivated and antigen-presenting-cell vaccine candidates.

Vaccine platform type									
Country	Protein subunit	RNA	Non-replicating viral-vector	DNA	Inactivated	Antigen-presenting-cell & Bacterial-vector	Virus-like particle	Replicating viral-vector	Live attenuated virus
U.S.	12	10	7	2	1	1	1	1	–
China	9	3	2	1	5	3	–	1	–
U.K.	2	3	2	1	1	–	–	–	–
Germany	1	2	3	–	–	–	–	–	–
India	1	–	1	1	1	–	1	–	1
Canada	1	1	–	2	–	–	1	–	–
Islamic Republic of Iran	3	–	–	–	2	–	–	–	–
Japan	1	1	–	2	1	–	–	–	–
Republic of Korea	2	–	–	2	–	–	1	–	–

Source: WHO COVID-19 vaccine tracker and landscape data as of October 8, 2021.
Note: the field of COVID-19 vaccine development is dynamic and related information changes over time, affecting numbers and locations in question.

While the different vaccine platforms are distributed in a similar way across patents and clinical trials, for example, the protein subunit vaccines dominate in both patents and clinical trials, some differences are worth noting. In the patent, data traditional platforms (protein-based, live attenuated, inactivated, VLP) account for nearly two-thirds (65 percent) of the patent filings, with a lower contribution from novel approaches to the dataset (especially the innovative RNA vaccines which account for 12 percent of the dataset). RNA vaccines account for almost double in the clinical trial vaccines (20 percent), while traditional vaccines account for 48 percent of the vaccines in clinical trial. This perhaps can be taken as an indication that the novel platforms are gaining momentum, especially in clinical studies as part of the strong ongoing effort to translate innovative vaccine technology into clinical success. Some of the RNA features allow quick adjustments and large-scale production in a cell-free environment, for which reason there may be growth of mRNA-related patents to be expected in the vaccine area and even beyond in the future.

Table 9 presents the top nine countries/regions based on the number of COVID-19 vaccine candidates in clinical trials. All regions show protein subunit vaccine activity, while only India features a live attenuated COVID-19 vaccine. The U.S. (35) and China (24) hold the largest numbers of vaccines in clinical trials and have most vaccine platforms represented, with the exception of VLP for China and live attenuated for both. Tables A2–A5 in the Annex contain additional information related to these candidate vaccines in the clinical trials and associated patent documents.

Comparing the contributions of countries worldwide with respect to patenting and clinical trials, a distinct tendency is evident – while the patent area is clearly dominated by China, the U.S. and, to some extent, the Russian Federation, in clinical trials, the set of countries with substantial contributions is much more diverse, including at least the top nine countries shown in Table 9. Thus, the combined vaccine development efforts in terms of both patenting activity and clinical trials are not limited to only two or three countries but instead are becoming global, reflecting the expectations about global markets and related impact. As more filed patent applications become publicly available over the coming months and patent information becomes complete, this may change.

Timelines on key technologies for COVID-19 vaccine development

Vaccines often involve multiple patents, some of which relate to enabling technologies. In addition to the patent documents we identified in our dataset, other inventions are also needed to manufacture and deliver a vaccine. An example of this, from the VaxPal COVID-19 vaccines patent database (Medicines Patent Pool, 2021b), is a series of patents from Janssen covering technologies related to adenovirus vectors (PCT/NL9600244), gene switch technology (PCT/US9810907), methods for nucleic acid transfer (PCT/NL0000263), virus particle production methods (PCT/NL0100892), SARS antigenic peptides (PCT/EP2004051102), adenovirus nucleic acid sequences (PCT/IB2020069289) and more. These technologies were filed for patent protection over a 24-year span and all necessary for development of the Janssen Ad26.COV-2-S vaccine. As per a WTO report's calculations, 83 percent of the patent families identified as relevant to the vaccines included in the MPP VaxPal were filed before the pandemic (WTO, 2022).

Technologies relevant to mRNA vaccine

Decades of innovation and research, as documented in Table 10 have laid foundational work for the mRNA vaccine and enabled it to become a highly successful COVID-19 vaccine platform with a promising potential in the development of other vaccines. The use of mRNA has several significant advantages over other vaccines in terms of efficacy and production despite its need for storage at freezing temperature. Since mRNA is a non-infectious, non-cell platform, there is no potential risk of insertional mutagenesis. Also, mRNA is degraded by normal cellular processes and its half-life in the human body can be regulated using various modifications. A variety of modifications make mRNA stable and highly translatable and thus highly efficient. Moreover, mRNA vaccines can be rapidly produced, and their manufacturing can be much more easily scaled up. Currently, two COVID-19 mRNA vaccines, one from Pfizer/BioNTech (BNT162b2) and one from Moderna (mRNA-1273), have been approved in multiple countries after showing excellent clinical trial results. Both vaccines are formulated in lipid nanoparticles, which significantly augment their successful delivery.

Lipid nanoparticle (LNP)-formulated mRNA vaccines are currently considered the most promising and innovative COVID-19 vaccine approach. Tables 10 and 11 below summarize the timelines of the technology advancements in the development of mRNA and LNPs, respectively.

Table 10. Timeline of mRNA technology and vaccine development.

Year	mRNA
1961	Discovery of mRNA (Brenner *et al.*, 1961)
1969	First protein produced via *in vitro* translation (Lockard and Lingrel, 1969; Gurdon *et al.*, 1971)
1975	Discovery of mRNA cap (Muthukrishnan *et al.*, 1975; Furuichi and Miura, 1975)
1984	mRNA synthesized in lab (Krieg and Melton, 1984)
1992	First mRNA therapeutics tested in rats (diabetes insipidus) (Jirikowski *et al.*, 1992)
1993	First mRNA vaccine for infectious disease tested in mice (influenza) (Martinon *et al.*, 1993)
1995	First mRNA cancer vaccine tested in mice (Conry *et al.*, 1995) (WO2003051401, WO2006008154, WO2009046738, WO2015024666)
2005	Discovery of pseudouridine modification (Kariko *et al.*, 2005) (WO2007024708)
2012	First LNP-formulated mRNA vaccine tested in mice (Geall *et al.*, 2012) (US10703789)
2013	First mRNA vaccine for infectious disease in clinical trial (rabies) (Alberer *et al.*, 2017) (WO2015024665)
2015	First LNP-formulated mRNA vaccine in clinical trial (influenza) (Bahl *et al.*, 2017; NIH, 2017) (WO2017191258)
2020	COVID-19 mRNA vaccines approved for emergency use authorization (FDA, 2020a, 2020b) (US10702600, US10577403)

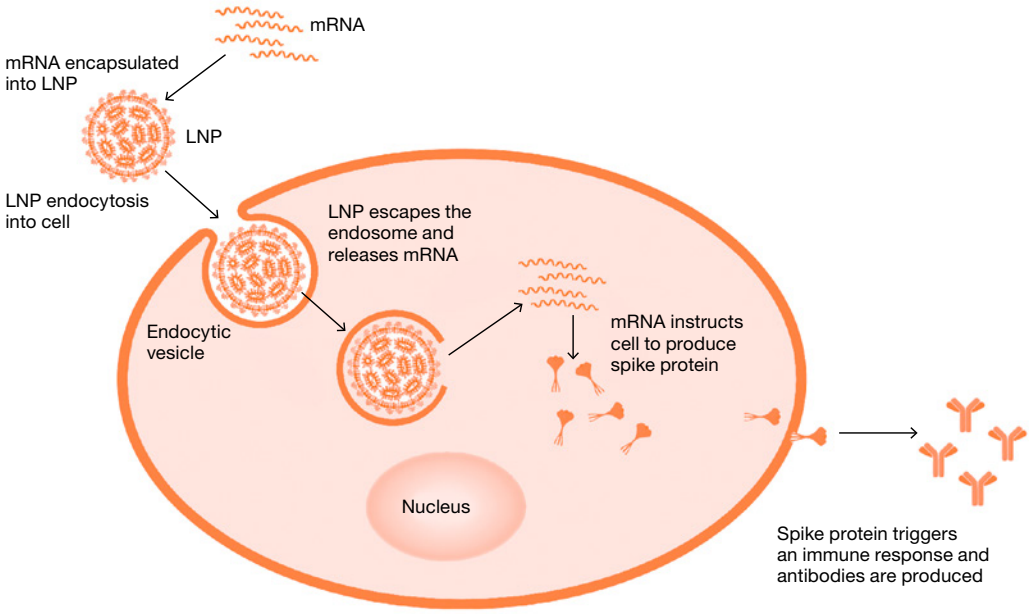
Table 11. Timeline of lipid nanoparticle development.

Year	Lipid nanoparticle
1965	The discovery of liposomes (Bangham *et al.*, 1965)
1971	Liposomes in drug delivery – enzyme entrapment into liposomes (Gregoriadis *et al.*, 1971; Weissmann *et al.*, 1975) (WO8102344)
1976	Liposomes in vaccine delivery (Allison and Gregoriadis, 1976)
1976–78	Development of fundamental procedures for liposome formation (Szoka and Papahadjopoulos, 1978; Deamer and Bangham, 1976)
1987	First cationic lipid synthesized, potential for gene delivery recognized (Felgner *et al.*, 1987) (US4897355)
1990	Polyethylene glycol (PEG)-lipid conjugates synthesized; long-circulating ("stealth") liposomes developed (Klibanov *et al.*, 1990; Blume and Cevc, 1990; Allen *et al.*, 1994) (WO9420073)
1994	Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) (Muller *et al.*, 1995; Schwarz *et al.*, 1994)
1995	First FDA-approved liposomal drug Doxil (liposomal doxorubicin) (Working and Dayan, 1996) (DE3001842, WO8809168, US4797285, US4898735A)
1997	Deciphering the structure of DNA-cationic liposome complexes (Radler *et al.*, 1997; Lasic *et al.*, 1997; Boukhnikachvili *et al.*, 1997)
2000	Lipid nanoparticles for nucleic acid delivery (WO9816202, WO9603977 WO2009127060, WO2013086373, WO2020077007)
2005	Correlation between lipid phase behavior and nucleic acid delivery efficiency (Zuhorn and Hoekstra, 2002; Koynova *et al.*, 2005)
2012	Lipid nanoparticles for delivery of RNA vaccines (Geall *et al.*, 2012) (WO2015164674, WO2017218704, WO2019152557, WO2016118725, US10442756, US10576146, US10703789)
2014	Scalable microfluidic method for LNP production (Walsh *et al.*, 2014; Shepherd *et al.*, 2021)
2018	First FDA-approved LNP-based nucleic acid (siRNA) drug Onpattro (Akinc *et al.*, 2019) (US8168775B2)
2020	LNP-based mRNA vaccines for COVID-19 approved (FDA, 2020a, 2020b) (US10702600, US10577403)

LNPs are essential to the mRNA vaccines. The groundwork for lipid-based drug delivery systems was laid more than 50 years ago with the discovery of liposomes. In fact, the early LNPs – the liposomes – were the first nanomedicine delivery platform to successfully proceed from concept to clinical application, with a number of approved pharmaceutical preparations.

The latest successful use of LNPs is as the delivery vehicle in the two recently approved COVID-19 mRNA vaccines by Pfizer/BioNTech and Moderna, which have been developed with unparalleled speed and shown notable effectiveness in disease prevention (FDA, 2020a, 2020b; Li *et al*., 2021b; Loh, 2021; Cross, 2021) The vaccines deliver mRNA encoding for the SARS-CoV-2 spike protein into the cytoplasm of host cells; the mRNA is translated into the spike protein, which acts as an antigen and leads to the development of an immune response to the virus (Figure 10).

Figure 10. Mechanism of action of mRNA-mediated vaccination.



The compositions of the lipid nanoparticles used in the two mRNA vaccines are very similar. Both use proprietary cationic lipids: ALC-0315 (Pfizer) and SM-102 (Moderna). The negatively charged mRNA and the positively charged lipids are rapidly mixed under acidic conditions, using a microfluidic device. They self-assemble into nanoparticles with mRNA at the center and lipids on the outside (Schoenmaker *et al*., 2021). In the more neutral pH conditions of the human body, these nanoparticles have no charge (Sealy, 2021; Chen *et al*., 2012) (WO2018081480). The lipids themselves have structures that are optimized for efficient mRNA delivery (DailyMed, 2020; Miller, 2020; FDA, 2020a, 2020b; Zhang *et al*., 2020).

Timeline details for adenovirus vaccine development

Adenoviruses have been utilized as delivery vectors for both human and non-human vaccines. As shown in Table 12, the initial adenoviral vectors developed in the late 1980s were replication-competent (RC), meaning they were able to reproduce themselves in the host's body, but complications and side effects led to the adoption of replication-defective (RD) vectors, which are unable to reproduce. Both types of vectors typically carry a piece of genetic material encoding the vaccine antigen inserted in their viral genomes. Since these viruses are natural pathogens for humans, less common types are used for vaccine applications to reduce the chance that the host's own antibodies would recognize and neutralize the vector before the vaccine could be delivered.

Table 12. Timeline of adenovirus-based vaccine development.

Year	Adenovirus type	RC/RD/SC	Gene therapy/vaccine
1986	Human adenovirus Ad2 (GB2166349)	RC	Antiviral vaccine
1988	Human adenovirus Ad5 (EP185573)	RD	Antiviral vaccine
1991	Canine adenovirus 2 (WO9111525)	RD	Antiviral vaccine
1994	Chimpanzee adenovirus AdC6, AdC7 (WO9410322)	RD	Gene therapy
1994	Fowl adenovirus CFA20 (WO9424268)	RC	Antiviral vaccine
1997	Ovine adenovirus OAv205 (Rothel *et al.*, 1997)	RC	Antiparasitic vaccine
1998	Chimpanzee adenovirus AdC1, AdC68 (WO9810087)	RD	Gene/vaccine therapy
1998	Fowl adenovirus 10 (Sheppard *et al.*, 1998)	RC	Antiviral vaccine
2003	Human adenovirus Ad6 (WO2003031588)	RC	Antiviral vaccine
2003	Porcine adenovirus 3 (WO2003040305)	RD	Antiviral vaccine
2004	Human adenovirus Ad11, Ad26, Ad34, Ad35, Ad46, Ad49 (WO2004037294)	RC	Antiviral vaccine
2005	Chimpanzee adenovirus ChAd3 (WO2005071093)	RD	Antitumor/antiviral vaccine
2006	Bonobo adenovirus Pan-5, Pan-6, Pan-7 or Pan-9 (WO2006120034)	RD	Antiviral vaccine
2009	Simian adenovirus SAd36, SAd42, SAd43 and SAd44 (WO2009136977)	RD	Antiviral vaccine
2012	Chimpanzee adenovirus ChAdOx1 (WO2012172277)	RC	Antibacterial vaccine
2013	Bonobo adenovirus PanAd3 (Vitelli *et al.*, 2013)	RD	Antiviral vaccine
2014	Human adenovirus Ad6 (Crosby and Barry, 2014)	SC	Vaccine
2015	Bovine adenovirus 3 (Brownlie *et al.*, 2015)	RC	Antiviral vaccine
2017	Chimpanzee adenovirus ChAdOx2 (WO2017221031)	RD	Gene/vaccine therapy
2017	Chimpanzee adenovirus ChAd155 (WO2017017049)	RD	Antiviral vaccine
2018	Bovine adenovirus 1 (Ren *et al.*, 2018)	RC	Antiviral vaccine
2020	Gorilla adenovirus GRAd32 (Capone *et al.*, 2020)	RD	Antiviral vaccine

Note: RD: replication-defective; RC: replication-competent; SC: single cycle.

Timeline details for vaccine adjuvant development

Adjuvants represent traditional and well-established agents that contribute to the prophylactic and therapeutic efficacy of vaccines. These agents are structurally quite diverse but generally seen to enhance immune responses to vaccines through mechanisms that include:

- decreasing the amount of antigen required for eliciting immunity;
- cytokine and chemokine helping to recruit white blood cells;
- activation of helper T-cells (a special type of immune cell) to assist in antibody production.

As shown in Table 13, the earliest application (1926) of adjuvants involved aluminum salts, which act as a depot to prevent rapid clearance of adsorbed antigen. These were the most prominent adjuvants for six decades.

Following this, natural products (e.g., plant polysaccharides and saponins, bacterial toxins), endogenous cytokines (e.g., interleukins, interferons, GM-CSF) and synthetic stimulants (e.g., CpG oligonucleotides) have been examined in clinical and experimental settings. Many of these agents invoke mixed mechanisms (depot, immunostimulation, particulate uptake) to affect their application as adjuvants.

Most COVID-19 vaccines employ adjuvants that have clinical approval (i.e., aluminum salts, MP59, saponin mixtures and CpG oligonucleotides). However, more recent research has recognized that the host receptors for pathogen-associated molecular patterns (PAMPs) and host danger-associated molecular patterns (DAMPs) mediate many of the effects of adjuvants. As a result, synthetic agents targeting these receptors are being developed. Some interesting examples include:

- cannabinoid receptor agonists as adjuvants to enhance mucosal immunity (US20210213129 A1);
- anionic and cationic nanoparticles of poly(lactic-co-glycolic acid) (PLGA) as vaccine adjuvants (WO2021123430 A1);
- betulin for use as an adjuvant in vaccines against SARS-CoV-2 (RU2749193 C1);
- metabolic reprogramming of immune cells to enhance the efficacy of prophylactic and therapeutic vaccines (WO2021092471 A1).

Table 13. Timeline of adjuvant development.

Year	Adjuvant	Type
1926	AlK(SO4)2 (Marrack *et al.*, 2009)	Alum, antigen depot
1974	Al(OH)3 (Thomson *et al.*, 1971)	Alhydrogel, antigen depot
1978	Montanide (NL7704555)	Emulsion, antigen depot
1978	Quil-A (Houdayer *et al.*, 1978)	Saponin
1988	IL-2 (Melchionda *et al.*, 2005)	Cytokine, immunostimulant
1989	MPL (Tomai and Johnson, 1989)	Polysaccharide, TLR4 agonist
1990	TNF (US4963354)	Cytokine, immunostimulant
1991	AlOH(PO4) (Hem and White, 1995)	Adju-Phos, antigen depot
1991	Algammulin (Cooper *et al.*, 1991)	Polysaccharide, TLR4 agonist
1991	QS-21 (Kensil *et al.*, 1991)	Saponin
1991	Pertussis toxin B (JP3135923)	Toxin B oligomers
1994	IL-12 (Melchionda *et al.*, 2005)	Cytokine, immunostimulant
1995	MF59 (Ott *et al.*, 1995)	Emulsion, antigen depot
1996	AL(OH)3 + Mg(OH)2 (Gomez *et al.*, 1995)	Imject alum, antigen depot
1997	CpG 1018 (Roman *et al.*, 1997)	Nanoparticles
1997	ISCOMATRIX (Bates *et al.*, 1996)	Nanoparticles
1997	AS02 (Stoute *et al.*, 1997)	Mixed
1999	IL-18 (Afonso *et al.*, 1994)	Cytokine, immunostimulant
1999	GM-CSF (WO9956775)	Cytokine, immunostimulant
2002	Flagellin (McSorley *et al.*, 2002)	Protein, TLR5 agonist
2002	Cholera toxin (WO200264162)	Immunostimulant
2002	Heat-labile enterotoxin (WO200264162)	Enterotoxin
2003	CpG 7909 (Paul, 2003)	ISS/CpG oligos, TLR9 agonist
2005	IL-7/IL-15 (WO9401133)	Cytokine, immunostimulant
2005	AS03 (Stoute *et al.*, 1997)	Mixed
2006	AS01 (WO2016054003)	Mixed
2006	AS04 (Garçon *et al.*, 2011)	Mixed
2010	Matrix-M (Magnusson *et al.*, 2018)	Nanoparticles
2011	Delta inulin (Layton *et al.*, 2011)	Polysaccharide, TLR4 agonist
2011	3M-052 (Smirnov *et al.*, 2011)	Organic small molecule
2012	GLA (WO2008153541)	Polysaccharide, TLR4 agonist
2015	ALFQ (Beck *et al.*, 2015)	Nanoparticles
2016	IL-21 (WO2016054003)	Cytokine, immunostimulant
2021	Essai O/W 1849101 (Arunachalam *et al.*, 2021)	Emulsion, antigen depot

COVID-19 therapeutics

Background

There are two major categories of therapeutics: small molecules and biologics. **Small-molecule drugs** are usually organic chemical compounds with a molecular weight less than 1,000 daltons (Da). While most small-molecule drugs are chemically synthesized, there are also some that are extracted and purified from a natural source such as plants (these are called "natural products"). Small-molecule drugs may be cheaper as compared to biologic drugs, but their interaction with molecular target may not be as specific as some biologic drugs such as antibodies. Their development process from identifying lead compounds to full approval may take 10 and 15 years (Corr and Williams, 2009; Deore *et al.*, 2019).

Biologic drugs, also known as biologics, biopharmaceuticals or biotherapeutic products (WHO–WIPO–WTO, 2021, p. 56) are either derived from a biological system such as living cells or blood or are produced with biotechnologies such as recombinant DNA technology. The technologies used in developing and producing biologic drugs have been propelled by dramatic advances in molecular biology and bioengineering over the past few decades. Biologics are usually large molecules (greater than 1,000 Da) and are relatively complex in structure. They can be proteins, nucleic acids (DNA or RNA), cells, tissues or combinations thereof. Major subclasses of biologics include antibodies, non-antibody peptides/proteins, cell-based therapies and nucleic-acid-based therapies. These are explained further in later sections. The research and development cost for both small-molecule and biologic drugs collectively range from less than USD 1 billion to more than USD 2 billion (Congressional Budget Office, 2021).

In general, small-molecule drugs and biologics for potential use in treating COVID-19 can be designed to do one or two of the following (Zhou *et al*., 2020; Khavinson *et al*., 2020; *SciTechDaily*, 2021; Liu *et al*., 2020; Mao *et al*., 2021; WHO–WIPO–WTO, 2021):

- inhibit SARS-CoV-2 entry into a host (human) cell by targeting factors involved in viral entry;
- inhibit the virus from replicating once in a host cell;
- enhance the immune system's ability to fight the virus;
- modify the host's immune response to alleviate the cytokine storm;
- impact other physiological processes that may disarm/weaken the virus.

Some of these strategies have been well characterized and studied, whereas others (such as drug-loaded exosomes) represent more novel approaches with little preexisting data on safety and efficacy (Gurunathan *et al*., 2021; *SciTechDaily*, 2021).

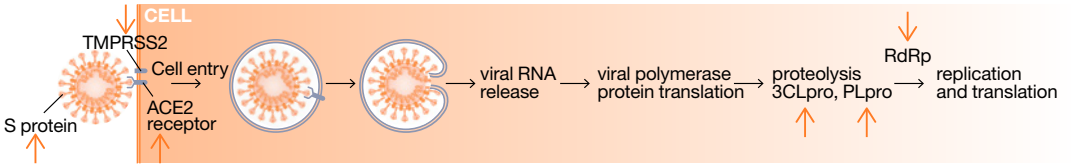
As with the development of other drugs, selection of COVID-19 treatment targets is a critical step. In principle, all SARS-CoV-2 enzymes and proteins involved in viral replication as well as the host proteins that mediate inflammation and tissue damage are potential drug targets. Our analysis of the Milken/RAPS data shows that all the anti-SARS-CoV-2 drug candidates in clinical trials aim at one of four targets (Figure 11):

- viral S protein, responsible for binding to ACE2 and mediating virus entry into host cells;
- viral 3CLpro protease, responsible for converting the non-functional viral polyprotein into functional viral proteins;

– viral RdRp, responsible for mediating viral replication in human cells;
– human ACE2, the receptor protein for SARS-CoV-2 at the surface of human cells.

Our patent dataset, however, shows a wider variety of potential therapeutic targets being explored, including TMPRSS2, RIG-I, RNAse L and various cytokines. The viral S protein has received the greatest attention in COVID-19 drug development and most drugs targeting this viral protein are biologics, or more specifically, virus-neutralizing antibodies. The development of small-molecule antiviral drugs has been exclusively focused on viral RdRp polymerase and 3CLpro protease.

Figure 11. **Illustration of the COVID-19 drug targets.**
The ACE2 receptor and the TMPRSS2 in the host cells are a major host target, while the spike (S) protein and the viral enzymes 3CLpro, PLpro and RdRp represent viral targets.



Analysis of COVID-19 therapeutics-related patent applications by substances type

The 1,465 patent families identified relating to COVID-19 therapeutic development were first categorized by types of potential therapeutics (Table 14). As shown in Figure 12, 54 percent (786 of 1,465) of them have a type of **small molecule**. **Biologics** account for 36 percent of the therapeutics patent dataset, of which antibodies make up the largest subset (221, 15 percent), followed by peptides/proteins (177, 12 percent), nucleic-acid-based (83, 6 percent), cell-based therapy (79, 5 percent) and other biologics (13, 1 percent), such as exosomes, CRISPR and probiotics. In addition, 17 percent of patent documents (249) describe the use of traditional medicines and a very limited number of patent documents (15, 1 percent describe the use of miscellaneous potential therapeutics, such as polymers and nanoparticles. It is worth noting that some patent applications describe the use of more than one category of therapeutics. For example, 7 percent of patent applications claim the use of both biologics and small molecules. These documents are classified as both biologics and small molecules in analysis. As a result, the total percentage value of all the high-level classes is more than 100 percent.

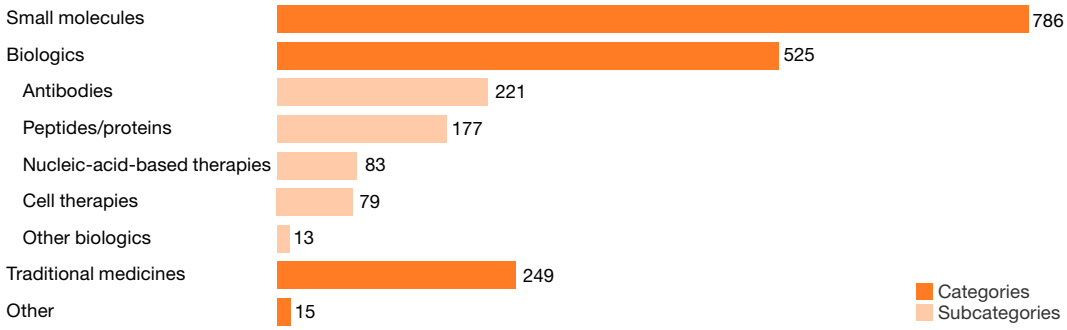
Table 14. **Categories of COVID-19 therapeutics.**

Small molecules	A broad category of organic chemical compounds with a molecule size smaller than 1,000 Da. These molecules can be synthesized chemically or extracted from natural sources (natural products)
Traditional medicines	Crude preparations of medicines that are produced according to the principle of traditional medicinal practice. These preparations usually are composed of a mixture of natural plant parts boiled in a liquid (decoction) or made into small balls or granules
Biologics	A broad category of large molecules produced from living systems or with the use of advanced biotechnologies such as recombinant DNA technology. Biologics are usually large molecules (>1,000 Da) and complex in structure. Subclasses of biologics in the context of this report are listed below
Antibodies	Proteins that constitute part of the human immune system for identifying and neutralizing pathogens. Antibody biologics for COVID-19 treatment may be either obtained from patients who have recovered from COVID-19 or manufactured in large quantities using recombinant DNA technologies with the assistance of other biotechnologies
Cell therapy	Viable cells with or without modification, which can be placed into the human body to produce a beneficial effect
Peptides and proteins	Large molecules (or biopolymers) made of chains of amino acids. They occur naturally in organisms but can also be produced synthetically (for some peptides) or with the use of recombinant DNA technology
Nucleic acids	Biopolymers, essential to all forms of life, which store genetic information. These include DNA and RNA. Nucleic acid biologics in the context of this report include small interfering RNA, antisense nucleotides, etc.
Other biologics	CRISPR-related, probiotics, exosomes, etc.

Source: CAS, National Science Library, n.d.

Figure 12. Distribution of patent applications relating to COVID-19 therapeutics among different categories and subcategories of therapeutics.

Over half (54 percent) of the COVID-19 therapeutics patent dataset refers to small molecules, while the biggest subcategory of biologics is the one of antibodies which accounts for 15 percent of the dataset.



Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: "Other biologics" includes exosomes, cytokines and general biologics. "Other" include nanoparticles, surfactants and polymers. Total counts and percentages of different categories and subcategories exceed the total number of therapeutics patent families because some documents address more than one category or subcategory and are thus counted more than once. Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Top locations of patent applicants for COVID-19 therapeutics and their filing strategies

The top patent offices of filing for COVID-19 therapeutics are China, WIPO, the U.S., India and the EPO (Table 15). Looking at the origin of the filings based on the applicants' locations (Table 15), China, the U.S., India, the Republic of Korea and the Russian Federation are the top five applicant locations. The patent applications filed by applicants based in these countries account for about 90 percent of the total number of patent filings in therapeutics. The fact that there are substantial numbers of China-based applicants – three times more than the ones based in the U.S. – may be attributed to both the large numbers of patent applications stemming from China that are common across most technology areas, and the relatively faster processing by the Chinese patent office (CNIPA) of patent applications related to COVID-19 (see Table 2a).

Table 15. Top patent offices of filing and applicant locations by number of COVID-19 therapeutics-related patent filings.

Most patent applicants in the field of COVID-19 therapeutics are based in China, the U.S. and India. These three locations also coincide with three of the top patent offices of filing.

Top patent offices of filing – therapeutics	Therapeutics patent filings count
China	885
WIPO	548
U.S.	368
India	65
EPO	60
Republic of Korea	42
Canada	28
Russian Federation	28
Australia	27
U.K.	24
Japan	20
Turkey	14
Italy	5
Israel	5
Colombia	4

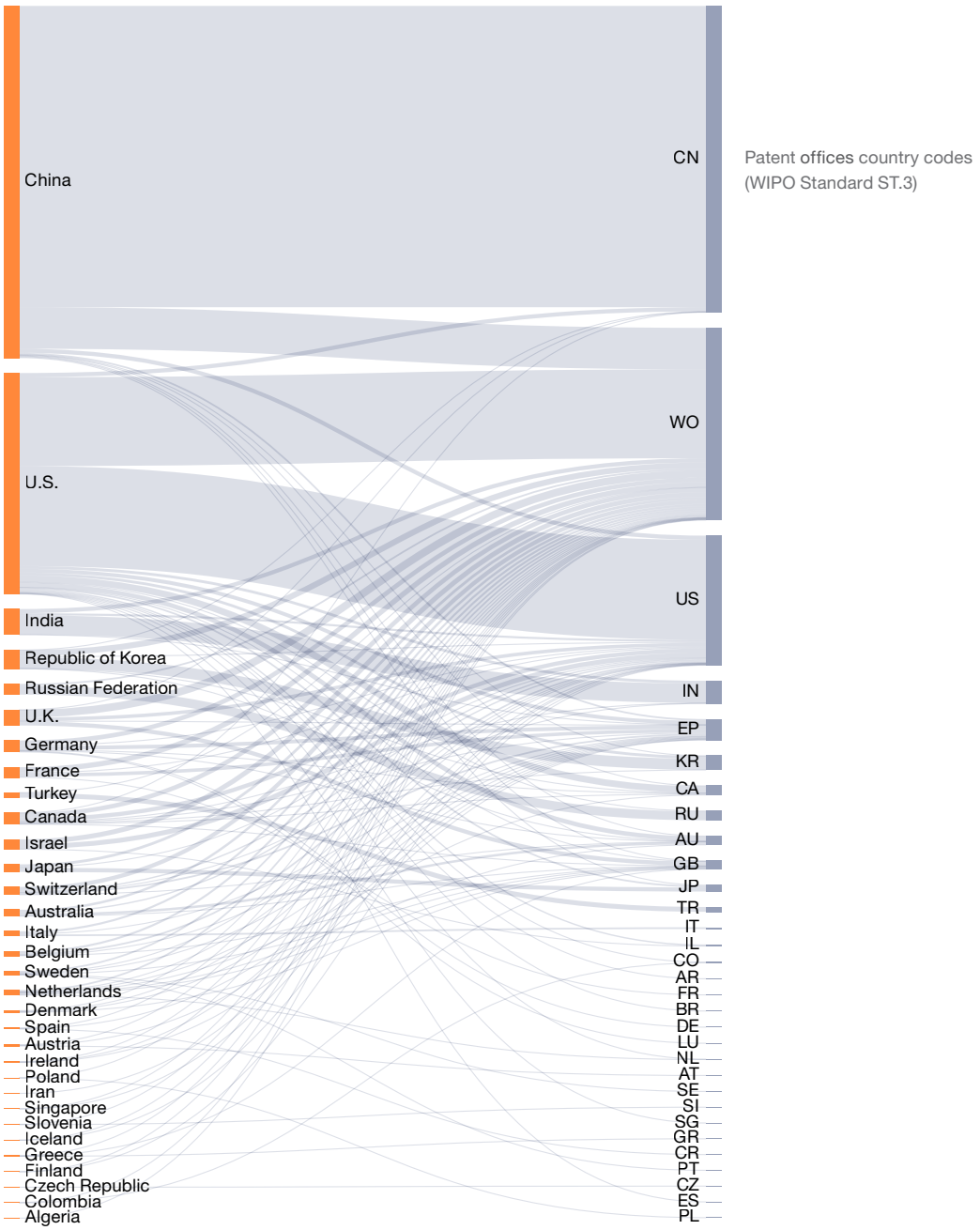
Applicant location – therapeutics	Therapeutics patent filings count
China	887
U.S.	292
India	60
Republic of Korea	35
Russian Federation	26
U.K.	22
Germany	15
France	15
Turkey	15
Canada	14
Israel	14
Japan	13
Switzerland	12
Australia	10
Italy	7
Belgium	6

Source: WIPO, based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

The patent filing strategy of the COVID-19 therapeutic patent applicants, as reflected in the choice of patent offices of filing made by the applicants grouped by their location (Figure 13) shows that most China-based applicants filed their patents exclusively in China, filing only a few other applications with the PCT System and in locations such as the U.S. Russian applicants would also appear to have filed their COVID-19 therapeutic patent applications exclusively in the Russian Federation. U.S. applicants, on the other hand, filed mostly PCT and U.S. patent applications. This trend reflects the interest of U.S. patent applicants in seeking patent protection for their inventions across multiple jurisdictions and thus their interest in several markets. Observations on patent filing strategies are not yet conclusive, as subsequent filings may still take place, and as PCT applications enter into the national phase.

Figure 13. Flow of patent filings in the field of COVID-19 therapeutics from different applicant locations (left) to various jurisdictions (right).

While in general applicants of COVID-19 therapeutics tend to file in their local jurisdiction, there are some profiles, such as U.S. and to a lesser extent China applicants who file PCT (WO) applications.



Source: WIPO based on patent data from the CAS Content Collection, September 2021.
Note: The figure was prepared based on patent applicant location and patent offices of filing for patent family members. The two-digit codes used follow the WIPO Standard ST.3. The patent applicant filing strategy represented in this figure may change over time as patent applicants file subsequent patent applications in different jurisdictions.

Tables 16a–16c list examples of patent applicants from Europe and the Russian Federation, the U.S. and Asia by number of patent filings and/or presence in the clinical trial data. It is worth mentioning that due to the very short time period in question (January 2020 through September 2021) and unlike other patent analytics exercises, these tables provide no ranking of top patent applicants or a conclusive picture of the top players in this area. Moreover, the information included in the tables should be viewed together with the clinical trial data included in the Annex of this report. There are some patent applicants that can be linked to the companies and organizations behind specific vaccine and therapeutic candidates.

As can be seen in the tables, both companies and universities and research organizations are contributors of patents related to COVID-19 therapeutic development. The top three contributors in Europe and the Russian Federation come from France (INSERM), Belgium (Softhale) and the Russian Federation (VECTOR) with one being a corporate applicant and two being a university or research organization applicant. It is interesting to note that some organizations who have developed approved COVID-19 therapeutics, such as Pfizer, Emory University and Regeneron do not feature among the top three patent applicants in North America in terms of patent count. Thus, caution needs to be exercised in drawing conclusions from patent count only, also bearing in mind that at the time of the research not all patent data reflecting patenting activity during the pandemic was publicly available. Though not listed in a table, Latin America is also represented in our dataset with a few filings from Colombia and Brazil.

Table 16a. Examples of COVID-19 therapeutics patent applicants (companies, universities and research organizations) based in Europe and the Russian Federation selected by number of filings and/or presence in the clinical trial data.

Patenting activity from companies and universities and research organizations based in different European countries reflects the diversity in the research location and the applicants' profile. Selected examples feature also in the clinical trials and preclinical studies dataset.

Patent applicant	Number of therapeutics patent families	Applicant profile	Applicant location
INSERM (National Institute of Health and Medical Research)	4	University or research organization	France
Softhale	3	Company	Belgium
State Research Center of Virology and Biotechnology VECTOR	3	University or research organization	Russian Federation
Tonix Pharma Holdings	2	Company	U.K.
SOFAR	2	Company	Italy
Dompe Pharmaceutici	2	Company	Italy
Harbour Antibodies	2	Company	Netherlands
Institute of Immunology	2	University or research organization	Russian Federation
Idorsia Pharmaceuticals	2	Company	Switzerland
ProQR Therapeutics	2	Company	Netherlands
Aviron	2	Company	Russian Federation
ABIVAX	2	Company	France
Sanofi Biotechnology	1	Company	France
Roche	1	Company	Switzerland
GlaxoSmithkline IP Development	1	Company	U.K.
Glenmark Specialty	1	Company	Switzerland
Institut Pasteur	1	University or research organization	France
Imperial College Innovations	1	Company	U.K.

Source: WIPO based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Table 16b. Examples of COVID-19 therapeutics patent applicants (companies, universities and research organizations) based in the U.S. selected by number of filings and/or presence in the clinical trial data.

A combination of companies, universities and research organizations based in the U.S. feature in the patent and clinical trial data.

Patent applicant	Number of therapeutcics patent filings	Applicant profile
University of California	5	University or research organization
Baylor College of Medicine	4	University or research organization
Board of Regents, The University of Texas System	4	University or research organization
Vanderbilt University	4	University or research organization
Prelude Therapeutics	3	Corporate
Duke University	3	Universities and Research Organization
Natural Extraction Systems	3	Corporate
Emory University	3	Universities and Research Organization
Stanford University	3	Universities and Research Organization
Massachusetts Institute of Technology	3	Universities and Research Organization
Regeneron Pharmaceuticals	2	Company
City of Hope	2	Universities and Research Organization
Oncotelic	1	Company
Gilead Sciences	1	Company

Source: WIPO based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Similar to the landscape of the COVID-19 vaccine patents, China showed the highest patenting activity related to COVID-19 therapeutic development in Asia, with most Asian applicants being from China, and mainly representing universities and research organizations. Examples of such applicants and some other Asian applicants who also feature in the clinical trial data are shown in Table 16c.

Table 16c. Examples of COVID-19 therapeutics patent applicants (companies, universities and research organizations) based in Asia selected by number of filings and/or presence in the clinical trial data.

Most Asian patent applicants in the COVID-19 therapeutics patent dataset are Chinese universities and research organizations, while there are some corporate players from other Asian countries who also feature in the COVID-19 therapeutics clinical trial dataset.

Patent applicant	COVID-19 therapeutics patent family count	Applicant profile	Applicant location
Academy of Military Medical Sciences	30	University or research organization	China
Chinese Academy of Sciences	23	University or research organization	China
Chongqing University of Medical Sciences	13	University or research organization	China
Sun Yat-Sen University	12	University or research organization	China
Peking University	8	University or research organization	China
Huazhong Agricultural University	8	University or research organization	China
The Fifth Affiliated Hospital of Sun Yat-Sen University	7	University or research organization	China
West China Hospital, Sichuan University	7	University or research organization	China
Fudan University	7	University or research organization	China
Wuhan Frasergen Genomic Medicine	6	Company	China
Sun Pharmaceutical Industries	1	Company	India
Enzychem Lifesciences Corporation	1	Company	Republic of Korea
Celltrion	1	Company	Republic of Korea

Source: WIPO based on patent data from the CAS Content Collection, September 2021.
Note: Numbers are indicative and are expected to change over time as patent applications filed in 2020–2021 become public (there is an average 18-month delay between patent filing and publication).

Highlights of patent filings related to COVID-19 therapeutic development

Patent filings related to development of small-molecule drugs for COVID-19

Small-molecule therapeutics represent the largest category of COVID-19 therapeutics in the patent dataset (Figure 15). Many patents claimed small molecules are existing drugs approved for other diseases that are being investigated as repurposed drugs for use against SARS-CoV-2 infection. As these drugs are already approved for treating other diseases and in production, they can be assessed/evaluated and approved for COVID-19 treatment much faster than new therapeutics (WHO–WIPO–WTO, 2021).

COVID-19 therapeutics may exert their effects by different mechanisms of action. Some directly act on the virus to block its entry to human cells or stop it from replicating inside human cells. Others either enhance the immune system's ability to fight the virus or attenuate the over-reaction of the immune system as in the case of the cytokine storm seen in many severe COVID-19 patents. Some anti-inflammatory agents would serve the latter function and may be used as COVID-19 therapeutics.

Examples of patent applications claiming repurposed anti-COVID-19 small-molecule drugs include WO2021101902, describing the use of the anti-cancer drug pazopanib to treat lung injury related to a coronavirus infection, and CN112451534, claiming that the existing natural product drug corilagin effectively inhibits the replication of SARS-CoV-2 virus. PCT applications WO2021176369 and WO2021250648 (Pfizer) describe a series of new small-molecule compounds that target directly SARS-CoV-2 3CL protease (3CLpro) and act as 3CLpro inhibitors. The antiviral PF-07321332/Paxlovid (see also below) has received conditional approval (see Feature summary of examples of anti-COVID-19 drug candidates in clinical trials). Further claimed treatments aim to stimulate a patient's immune system so as to strengthen their response to the virus, for example WO2021130195. A further example includes a patent application claiming the use of a natural

product extract from the *Menispermaceae* plant family to successfully treat patients infected with SARS-CoV-2 virus (WO2021053651).

Some patents focus on developing drug delivery systems or antiviral drug packaging methods, like WO2021055467, disclosing the development of controlled-release polymeric nanoparticles which may be administered orally to treat infection by RNA viruses, specifically Zika and coronavirus.

Patent filings related to the development of biologics for COVID-19

This section addresses patenting activity in the subclasses of biologics, namely:

- antibodies;
- non-antibody peptides/proteins;
- cell-based therapies;
- nucleic-acid-based therapies;
- others, such as CRISPR and exosomes.

Table A6 in the Annex summarizes selected patents that illustrate different strategies using various biologics.

Patents related to antibodies for COVID-19 treatment

Antibody drugs are the fastest growing class of biologics for various diseases over the past two decades and have now become a mainstay in disease treatment. In general, therapeutic antibodies for COVID-19 treatment fall into two categories: virus-neutralizing antibodies directed against the SARS-CoV-2 proteins (e.g., the S protein); and antibodies that modulate the human immune system's response to the virus.

Neutralizing antibodies can be obtained from patients recovered from COVID-19 or manufactured in large quantities using recombinant DNA technologies. Patent application WO2021045836 by Regeneron describes the development of SARS-CoV-2 S protein-neutralizing antibodies, especially the cocktail REGN-COV2 (a combination of casivirimab and imdevimab) which received emergency approval (Deeks, 2021).

Patent applications KR2205028 by Celltrion and CN112390879 by Shanghai Tech University disclose the creation of a collection of neutralizing antibodies that bind to the SARS-CoV-2 S protein. In addition, Shenzhen Yinnuosai Biotechnology Co. Ltd (patent application CN112513076) and Shanghai Novamab Biopharmaceuticals Co. Ltd (patent application CN112500480) have disclosed a special type of small neutralizing antibodies, called nanobodies, that also target the viral S protein and are highly stable and less expensive to produce than traditional polyclonal antibodies.

Instead of designing antibodies that target viral proteins, some patents evaluated antibodies that target the host (human) proteins involved in the infection process. Patent application CN111420048, by the Fourth Military Medical University in China, claimed an antibody targeting human basigin/CD147, which may function as a co-receptor for the SARS-CoV-2 S protein. Patent application US20210246226 by Regeneron Pharmaceuticals discloses a human antibody targeting TMPRSS2 to inhibit the function of this protease in S protein activation.

Published/patented antibodies and nanobodies that bind to coronaviruses, including SARS-CoV-2, are available in the Coronavirus-Binding Antibody Sequences & Structures database released by the Oxford Protein Informatics Group, Department of Statistics, University of Oxford (Raybould *et al.*, 2021).

Peptide and protein therapies

Peptide-mediated therapy

Recent patent publications included in this report disclose therapeutic peptides (very short proteins usually with a chain length of less than about 20 amino acids) that specifically inhibit viral proteins,

or host cell proteins. An example of this strategy is the invention from the Institute of Pathogen Biology, Chinese Academy of Medical Sciences (CN111643656) showing that peptide EK1 and lipopeptide EK1M (modified with cholesterol) bind to specific regions of the SARS-CoV-2 S protein and affect the ability of the virus to fuse with a host cell membrane and enter the cell.

Protein-mediated therapy

Non-antibody proteins (> approx. 50 amino acids), including fusion proteins, cytokines such as interferons and interleukins, and other proteins (e.g., TFF2, TAFA4 or SLAMF7), are also being explored as potential anti-COVID-19 therapeutics.

Patent application WO2021160170 (OncoImmune) presents the use of fusion protein CD24Fc (made of CD24 and the Fc fragment of immunoglobulin G1) to inhibit the production of inflammatory cytokines that can cause damage to host cells.

Patent application WO2021160163 by Evive Biotechnology discloses the use of F-652 (a fusion protein made of interleukin 22 and immunoglobulin G2 Fc fragment) along with an antiviral agent. F-652 may inhibit inflammation and promote tissue repair. A phase 2 clinical trial is underway to evaluate the effect of F-652 in patients with moderate to severe COVID-19 (NIH, 2020b).

Patent applications CN112220913 and WO2021195883 disclose the use of interferon-ϰ (IFN-ϰ) and Trefoil factor 2 (TFF2) in treating SARS-CoV-2 infections by inhibiting inflammation while enhancing anti-inflammatory immune response, representing an interesting situation with the use of two different approaches. Patent applications WO2021170113 by Nanjing Genscript Biotech and Nanjing Legend Biotech and WO2021183717 by NantCell, Inc. present a therapeutic and potentially prophylactic approach by disclosing the use of ACE2-Fc fusion proteins, expected to have a higher affinity to the S protein compared to human ACE2. By binding to the viral S protein, ACE2-Fc fusion protein prevents the viral S protein interacting with ACE2 on the surface of human host cells.

Nucleic-acid-based therapies

The use of nucleic-acid-based molecules, such as small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), double-stranded RNAs (dsRNAs), microRNAs, antisense oligonucleotides and nucleic acid aptamers (Liu *et al*., 2020; Mao *et al*., 2021) to fight SARS-CoV-2 was addressed in a number of patent applications. These types of nucleic acids can be used to bind specific viral or host targets and disrupt infection.

Examples for the use of siRNAs in our dataset include patent application RU2746362A by FGBU GNTs Institute of Immunology, which describes their use to target the RdRp gene to suppress SARS-CoV-2 viral reproduction. Patent application WO2021130537 discloses siRNA-based antiviral compounds that target a number of viral genes (e.g., ORF1ab, spike, nucleocapsid, Nsp12 and Nsp13) and host genes (e.g., ACE2, IL-6 and IL-6 receptor).

Patent application US20210102209 describes the use of small hairpin RNAs that target RIG-I, a host sensor protein that recognizes viral RNA and helps to initiate host anti-viral immune response (Mao *et al*., 2021).

Our dataset also contains patents claiming the use of anti-sense oligonucleotides for targeting both SARS-CoV-2 and human targets to treat COVID-19. Patent application RU2750584 (Russian Federation) reports the use of a modified antisense oligonucleotide, targeting the 5' end region of the SARS-CoV-2 genome to decrease the number of viruses in infected cells. Patent application CN113249380 (Peking University) discloses the use of modified antisense oligonucleotides in combination with an activator of ribonuclease L (RNase L), a host enzyme that can degrade SARS-CoV-2 RNA during immune response. Patent application WO2021186396 (Oncotelic Inc.) discloses a new strategy that uses an antisense oligonucleotide that inhibits a host cytokine, transforming growth factor β2 (TGF-β2), in combination with the immune system stimulant, Artemisinin. Oncotelic is currently supporting a clinical trial in patients hospitalized with COVID-19 (NIH, 2021). Patent application WO2020201144 (ProQR Therapeutics II B.V.) presents an antisense oligonucleotide that targets a different host protein in the human CD274 (PD-L1) gene, leading to a more robust immune response to viral infection.

Aptamer-mediated therapy

While patents disclosing the use of nucleic acid aptamers to target viral proteins for treating COVID-19 are less common, this strategy offers benefits such as lower production costs and relatively scalable production (Keefe *et al.*, 2010). For example, patent application CN111849994 (Xiamen University) discloses a receptor-binding domain (RBD)-specific aptamer targeting the SARS-CoV-2 S protein.

Cell-based therapies

Cell-based therapies use immune cells (such as T-cells, innate lymphoid cells, or natural killer cells) or stem cells (cells that can develop into other cell types) to induce, regulate and/or repair damage in parts of the body impacted by a viral infection. One type of cell-based therapy is CAR T-cell immunotherapy, which has been mostly used so far for treating blood cancers. In this therapy, a patient's own immune T-cells are taken from the patient's blood, transformed with insertion of a chimeric antigen receptor (CAR) in a lab to allow these cells to recognize a desired antigen molecule, and then given back to the patient. This breakthrough immunotherapy approach first succeeded in treating some blood cancers (Grisham, 2013). While the use of cell-based therapy in treating COVID-19 is theoretically possible, with 120 clinical trials underway as of the end of October 2021), their final approval for COVID-19 treatment, cost-effectiveness and practicality are yet to be seen (Zaki *et al.*, 2021).

Patent application CN111675765 (Nanjing KAEDI Biotech Inc.) discloses the use of CAR-T-mediated therapy for COVID-19, using an engineered immune cell targeting the viral S protein and the RdRp enzyme, to inhibit viral invasion and replication while also, it claims, effectively inhibiting cytokine storm.

Patent application WO2021155312 claims the use of natural killer immune cells and ILC3 (type 3 innate lymphoid cells) in treating coronavirus infections. This work is currently in clinical trial (NCT04365101; NIH, 2020a) to determine its efficacy in treating COVID-19 patients.

Other biologic-based therapies

CRISPR-Cas

CRISPR is a gene-targeting system that uses a guide RNA and a nuclease enzyme (such as Cas9, Csm or Cas13d) to cut a gene in a specific location. Therapies based on this technology are being developed for various diseases (WHO–WIPO–WTO, 2021). This approach has been devised for the diagnosis of COVID-19 with emergency use authorization (EUA) from the U.S. FDA (Sherlock Biosciences, 2021; UCSF Health Clinical Laboratories, n.d.). Several patents have explored the use of this Nobel Prize-winning technology as a potential new method for COVID-19 treatment. For example, patent application CN112143731 by Guangzhou Reforgene Biotechnology Co. discloses a CRISPR-Cas13d system designed to target the S gene region of SARS-CoV-2, whereas patent application CN112852817 by a Chinese PLA Army Specialized Medical Center discloses a CRISPR-Csm system that targets the SARS-CoV-2 RdRp gene. Targeting the S gene disrupts the ability of the virus to infect a host cell, and targeting the RdRp gene interferes with the virus's ability to reproduce in the host cell.

Exosome-mediated therapy

Exosomes are membrane-bound extracellular vesicles produced by human cells. The advent of biotechnology has enabled production of exosomes enriched with desired molecules, including drugs. Drug or cargo-loaded exosomes containing immune-modulating substances in combination with antiviral substances can provide a rapid and targeted delivery of substances in disease treatment. The exosomes derived from certain stem cells have been explored as cell-free therapeutic agents for treating COVID-19 (Gurunathan *et al.*, 2021).

Patent applications US20200362052 by Physis Biotechnologies and US20200362052 by Souvie Biodelivery both describe a method for generating exosomes. Some of the exosomes may contain anti-SARS-CoV-2 small molecules or neutralizing antibodies (US20200362052), whereas other exosomes may contain a fusion protein drug used to inhibit inflammation and cytokine storm (US20200362052).

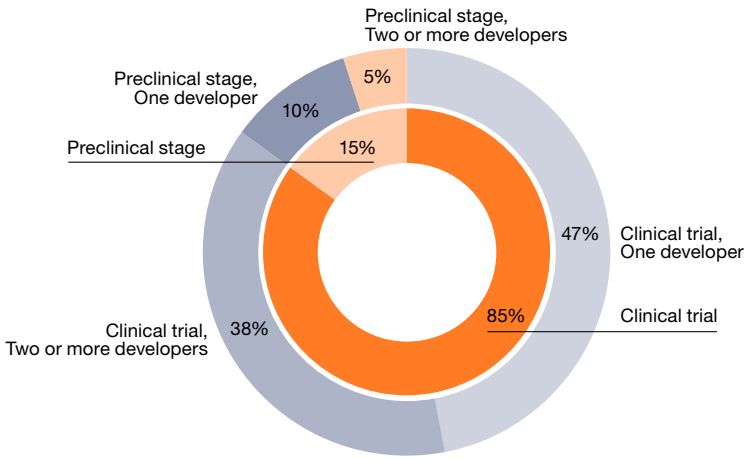
Analysis of COVID-19 therapeutics in clinical trials

There have been several COVID-19 therapeutics conditionally approved, some of which are included in our patent dataset. The antiviral drug remdesivir (Imran, 2021) was the first drug to be approved by the U.S. FDA to be given to hospitalized patients (FDA, 2020c). REGEN-COV, a monoclonal antibody therapy, was granted EUA by the U.S. FDA for the treatment of COVID-19 (FDA, 2021b). The WHO is conducting an international collaboration to test three therapies, artesunate, imatinib and infliximab, to reduce COVID-19 mortality (WHO, 2021d). This collaboration represents the largest therapeutic trial among WHO member states (WHO, n.d.). Clinical trials are currently ongoing for many additional therapeutics to help fight this disease.

Analysis of COVID-19 therapeutics data in the Milken Institute and Regulatory Affairs Professionals Society (RAPS) tracker data

In addition to patent analysis, this report also examined therapeutic candidates for COVID-19 using combined data derived from the COVID-19 therapeutic tracker data by the Milken Institute and RAPS, both as of the end of September 2021. In this combined set, there are 314 drug candidates determined by their drug uniqueness. If a drug cocktail contains two or more active components, this drug candidate is regarded as distinct from those individual drugs making up the cocktail. If any of the drugs have a patent related to COVID-19, the corresponding patent is also included in our patent analysis dataset discussed earlier. As can be seen in Figure 14, 85 percent and 15 percent of COVID-19 drug candidates are in clinical trials and preclinical studies, respectively. Of all the candidates, more than half (57 percent) were developed by one organization, whereas 43 percent involved two or more organizations, a cooperation level higher than observed in the patent data, where co-applications are less prevalent. Further collaboration can be observed at the manufacturing phase between developers and manufacturers which can be a public research organization or an other facility (Global Health Centre, 2021).

Figure 14. Distribution of COVID-19 drug candidates between the clinical trial stage and preclinical stage and cooperation during this development stage.
Of COVID-19 drug candidates, 85 percent were in clinical trials and 15 percent in preclinical studies, while 43 percent of the therapeutic candidates listed in the dataset were developed by two or more organizations.

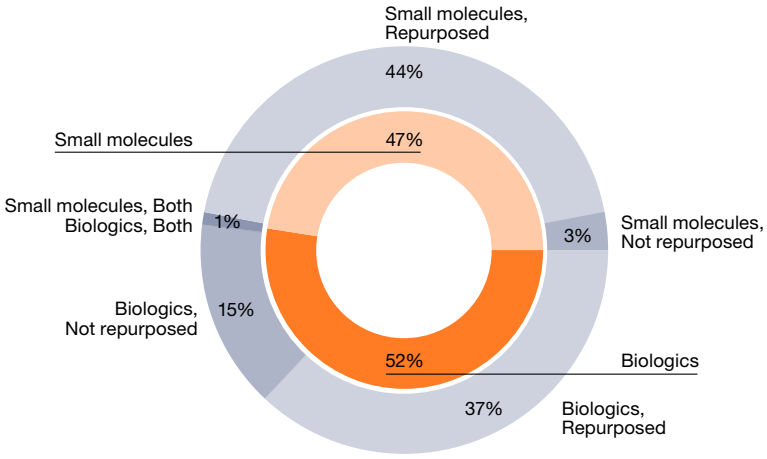


Source: WIPO based on Milken Institute and Regulatory Affairs Professionals Society (RAPS) COVID-19 therapeutics tracker data, September 2021.
Note: COVID-19 drug development is a dynamic area and related information changes over time.

Distribution of COVID-19 drug candidates across small molecules and biologics, repurposed drugs and *de novo* synthesized drugs

As seen in the Milken/RAPS clinical trial data, 52 percent of the COVID-19 drugs in the development pipeline are biologics and 47 percent are small molecules (Figure 15). The remaining 1 percent is drug combination containing a small molecule and biologics. Interestingly, 81 percent (44 percent for small molecules plus 37 percent for biologics) of all the drugs are repurposed/redirected drugs, meaning they have been approved (or initially developed) for treating other diseases. Only 18 percent (3 percent for small molecules plus 15 percent for biologics) of these drugs are not repurposed drugs for COVID-19 or related coronavirus diseases.

Figure 15. Distribution of COVID-19 drug candidates in the categories of small molecules and biologics.
A total 81 percent (44 percent for small molecules plus 37 percent for biologics) of all the COVID-19 therapeutic candidates were repurposed and only 18 percent newly and specifically developed to treat COVID-19.



Source: WIPO based on Milken Institute and Regulatory Affairs Professionals Society (RAPS) COVID-19 therapeutics tracker data, September 2021.
Note: COVID-19 drug development is a dynamic area and related information changes over time.

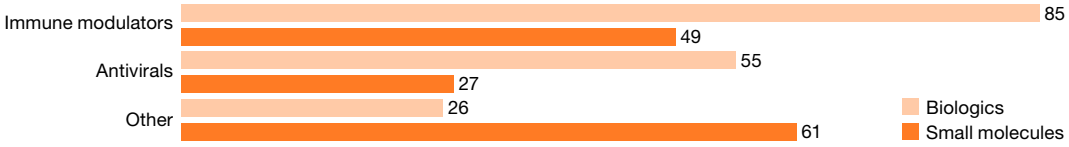
Classification of COVID-19 drug candidates in clinical trials by molecular nature and function

The COVID-19 drug candidates may also be classified by function into:

- antivirals, including viral neutralizing antibodies;
- immune modulators;
- others that function via various mechanisms without direct effects on viral invasion into or replication inside human host cells.

The immune modulators may either stimulate the human immune response to viral infection or suppress the immune response to prevent/reduce the over-reaction (cytokine storm) to virus invasion, which may be harmful or even life-threatening. As shown in Figure 16, for both biologics and small-molecule COVID-19 drug candidates in clinical trials, most candidates are immune modulators or have other functions. Relatively speaking, the number of drug candidates that directly act on the virus is small, especially for small molecules. Modulation of immune response is not only a therapy strategy for coronavirus infection treatment, but also a viable approach for treating other diseases such as cancer and inflammatory diseases. Almost all the immune modulators reported here are repurposed drugs that either have been approved for clinical use or initially designed for treating various inflammatory diseases related to over-reaction of the immune system or for cancer in which the immune system's ability to recognize and destroy cancerous cells needs to be stimulated.

Figure 16. Classification of small-molecule COVID-19 drugs in clinical trials by function.
Most COVID-19 therapeutics in clinical trials aim to either stimulate or suppress human immune response to the SARS-CoV-2 virus, or have other functions, while only a few act directly on the virus.



Source: WIPO based on Milken Institute and Regulatory Affairs Professionals Society (RAPS) COVID-19 therapeutics tracker data, September 2021.
Note: "Other" refers to therapeutics that function via various mechanisms without direct effects on viral invasion into or replication inside human host cells. COVID-19 drug development is a dynamic area and related information changes over time.

Feature summary of examples of anti-COVID-19 drug candidates in clinical trials

Table 17 lists 11 example drug and drug combination candidates for COVID-19. The selection of these candidates is based on a combination of the following factors:

- whether the drug has received EUA in certain countries or is at least in a Phase 2 clinical trial and has generated promising trial results;
- whether it acts on a specific molecular target that plays an important role in COVID-19 development;
- whether the drug represents a novel design or is a repurposed one;
- whether the drug can be administered conveniently (e.g., oral drug that can be taken at home).

The key/pioneering patents for each therapeutic are those patents filed earliest in relation to the technology by one of the drug developers. These patents may not directly relate to coronavirus or COVID-19 and could be filed prior to 2020, but they provided the technology groundwork needed for the development of anti-COVID-19 drugs. As can be seen, some of the listed drugs have received either full approval or EUA in at least one country.

Table 17. Example of small-molecule and biologic anti-COVID-19 drugs and drug combinations in clinical trials and related patent documents.
The examples list some drugs which obtained full or emergency use approval in one or more countries, some private–private and private–public cooperation and cases where existing patenting activity set the ground for developing COVID-19 treatments.

Drug name, CAS Registry Number(R)	Developer	Drug type	Target	Delivery method	Repur-posed	Key pioneering patents**
Molnupiravir* (EIDD-2801, MK-4482), 2492423-29-5	Emory University (Drug Innovation Ventures at Emory), Merck, & Ridgeback Biotherapeutics	Antiviral ribonucleoside analogue (SM)	Viral RdRp	Oral	Yes	WO2019113462, WO2019173602, WO2021137913
Paxlovid (PF-07321332), 2628280-40-8	Pfizer	Antiviral ribonucleoside analogue (SM)	Viral 3CLpro	Oral	No	WO2004093860, WO2006061714
AT-527 (RG-6422), 2241337-84-6	Atea Pharmaceuticals and Roche	Antiviral ribonucleoside analogue (SM)	Viral RdRp	Oral	Yes	WO2018144640, WO2019200005, WO2020117966, WO2021173713
Favilavir* (favipiravir, T-705, Avigan), 259793-96-9	Fujifilm Toyama Chemical, Zhejiang Hisun Pharmaceuticals, Glenmark Pharmaceuticals and various global research sponsors, Brigham and Women's Hospital, Massachusetts General Hospital and Univ. of Massachusetts Medical School	Antiviral (SM)	Viral RdRp	Oral	Yes	WO2012063931, WO2020138067

Drug name, CAS Registry Number(R)	Developer	Drug type	Target	Delivery method	Repur-posed	Key pioneering patents**
Remdesivir,* 1809249-37-3	Gilead, WHO Solidarity trial, NIAID (U.S.), Feinstein Institutes, I-SPY COVID	Antiviral ribonucleoside analogue (SM)	Viral RdRp	IV	Yes	WO2017049060, WO2017184668, WO2018204198, WO2021154687
REGN-COV2* (REGN10933 and REGN10987, casirivimab and imdevimab), 2489257-47-6	Regeneron and NIAID (Regeneron; Cipla in India, which approved it)	Neutralizing antibodies (BLG)	Viral S protein	IV	No	WO2021045836
Bamlanivimab (LY-CoV555) and etesevimab (JS016, LY-CoV016) cocktail,* 2423943-37-5 and 2423948-94-9	Eli Lilly, Junshi Bioscience, Lonza and AbCellera	Neutralizing monoclonal antibodies (BLG)	Viral S protein	IV	No	WO2021183195
Kevzara (sarilumab), 1189541-98-7	Sanofi and Regeneron	Immune-modulating monoclonal antibody (BLG)	IL-6R	SC	Yes	WO2013053751, WO2015077582, WO2016044343, WO2013053751
AZD7442 (AZD8895+AZD1061), 2603443-62-3	AstraZeneca and Vanderbilt Univ. Med. Ctr.	Neutralizing monoclonal antibodies (BLG)	Viral S protein	IV, IM	No	WO2021163265
BMS-986414+BMS-986413 (C135-LS and C144-LS), 2691785-24-5+2691785-23-4	Rockefeller University and Bristol Myers Squibb	Neutralizing monoclonal antibodies (BLG)	Viral S protein	SC	No	WO2013016468, WO2021195326
BRII-196 and BRII-198, 2509447-07-6 and 2509447-07-6	Brii Biosciences, Tsinghua University and Third People's Hospital of Shenzhen, China	Neutralizing monoclonal antibodies (BLG) that effectively suppress MERS-CoV entry into human cells	Viral S protein	IV	No	CN104628848

Source: WIPO based on Milken Institute and Regulatory Affairs Professionals Society (RAPS) COVID-19 therapeutics tracker and patent data from the CAS Content Collection, September 2021.
Notes: BLG: biologic drug; SM: small-molecule drug; IV: intravenous; IM: intramuscular; SC: subcutaneous. COVID-19 drug development is a dynamic area and related information changes over time.
* The drug has obtained full approval or EUA in at least one country.
** The first filing patents related to the technology for the development of the drug are listed. Some of these patents may not directly relate to coronavirus or COVID-19 and could have been filed prior to 2020, but they provided the technology groundwork needed for the development of anti-COVID-19 drugs.

Molnupiravir is an orally available antiviral therapeutic that can be given to non-hospitalized patients. This drug was initially invented for treatment of influenza by Drug Innovation at Emory (DRIVE), a non-profit biotechnology company owned by Emory University. After the COVID-19 outbreak, the further development of this drug was largely carried out by Merck and Ridgeback Biotherapeutics. This drug is structurally similar to, but different from, a crucial viral RNA-building block. This feature of the molecule introduces errors during the process of RNA replication mediated by the viral enzyme, RdRp, and thus inhibits viral replication. Based on the clinical trial result showing this drug reduces the risk of hospitalization or death to some extent, the U.K. Medicines and Healthcare products Regulatory Agency authorized its use in the treatment of mild-to-moderate COVID-19 in adults in November 2021. Later the U.S. FDA also granted EUA to this drug (O'Shaughnessy, 2021). It is thus the first oral anti-coronavirus drug to be authorized in the world. It is worth mentioning that this drug needs to be taken within a few days of the onset of symptoms, is not suitable during pregnancy and requires breastfeeding to stop for a number of days (FDA, 2022a; European Medicines Agency, 2021). As mentioned above, molnupiravir is the focus of a licensing agreement between Merck and the Medicines Patent Pool to provide COVID treatment to low- and middle-income countries.

Paxlovid (containing PF-07321332/nirmatrelvir and ritonavir) is also an oral antiviral drug that can be given to non-hospitalized patients. This drug was developed by Pfizer during the pandemic to inhibit specifically the activity of SARS-CoV-2 3CLpro, a protein-hydrolyzing enzyme critical for the formation of functional coronavirus proteins and viral function. Its related form (PF-00835231 with the same mechanism of action) was developed earlier for combating SARS (Owen *et al.*, 2021) but

needs to be administered intravenously. It has been reported recently that paxlovid may reduce the risk of hospitalization and death of COVID-19 patients by 89 percent based on the interim result of a Phase 2/3 clinical trial (Pfizer, 2021). As a result, this drug has received conditional recommendations for treating COVID-19 from the European Medicine Agency and EUA from the U.S. FDA. This drug is not authorized for use for longer than five days, for post-exposure prophylaxis purpose or for patients in a severe/critical condition (FDA, 2022b).

AT-527/RG-6422 is another oral antiviral initially being co-developed by Roche and Atea Pharmaceuticals, a clinical stage biopharmaceutical company started in 2012 in the U.S. This drug is similar to molnupiravir in that it is also an analogue of a building block needed for viral RNA replication and, with this structural feature, inhibits RdRp in all single-stranded RNA viruses, including coronavirus, to prevent viral replication. While it has been shown to be well tolerated and safe, as well as to reduce viral replication in hospitalized COVID-19 patents, it has failed to meet the primary goal of reducing SARS-CoV-2 RNA level, according to a recent report (Clinical Trials Arena, 2021a).

Also listed in Table 17 are several virus-neutralizing monoclonal antibodies that bind to SARS-CoV-2 to neutralize the virus in infected patients. These biologic drugs may be produced from the antibody-producing cells of convalescent plasma from patients who have recovered from COVID-19, or humanized mice (i.e., mice which were genetically modified to be carriers of the COVID-19 disease). They represent a new class of antivirals (Taylor *et al.*, 2021; Asdaq *et al.*, 2021). Because these monoclonal antibodies may bind to different regions of a crucial segment in SARS-CoV-2 S protein to block the viral S protein interacting with its receptor on human cells effectively, combining them into a cocktail to strengthen the neutralizing effects has proven to be an effective strategy for treatment of COVID-19, especially in the presence of SARS-CoV-2 variants. Examples of antibody cocktails include REGN-COV2 by Regeneron, AZD7442 by AstraZeneca and Vanderbilt University Medical Center, the combination of bamlanivimab (LY-CoV555 co-developed by Eli Lilly and AbCellera) and etesevimab (JS016/LY-CoV016 co-developed by Eli Lilly, Junshi Biosciences, Lonza, AbCellera), the combination of BMS-986414 and BMS-986413 by Rockefeller University and Bristol Myers Squibb, and BRII-196 plus BRII-198 by Brii Biosciences, Ltd., Tsinghua University and Third People's Hospital of Shenzhen in China. Most of the listed antibody cocktails have either received EUA from the U.S. FDA (FDA, 2021c, 2021d, 2021e), or are in the process of EUA review (AstraZeneca, 2021). Important patents that are either directly related to or laid the critical foundation for the development of these antibody drugs are also listed in the table. Finally, it needs to be pointed out that due to their high specificity and affinity to their molecular targets and low toxicity, neutralizing antibodies have also been used for treating other infections caused by other viruses such as Ebola virus, cytomegalovirus, influenza virus, human immunodeficiency virus (HIV), and respiratory syncytial virus (Jiang *et al.*, 2020).

Perspectives

This report provides an overview of patent documents published as at end of September 2021 related to the development of vaccines and therapeutics for COVID-19. As this is a very recent patenting activity, the picture we see in published patent data at the time of drafting the present report is not complete and serves more as a first indication about patenting activity during the pandemic trying to combat the SARS-CoV-2 virus and the related COVID-19 disease through prophylactic (vaccines) or therapeutic (medical treatments) approaches. Patent data is complemented by WHO data related to COVID-19 vaccines and COVID-19 drug candidates listed in the COVID-19 therapeutic tracker data generated by the Milken Institute and the Regulatory Affairs Professionals Society (RAPS). The report identifies first trends on patenting activity over time, patent distribution among patent applicants and their location, as well as their choice of patent offices when filing applications, indicating related markets of interest. It also discusses the role of previously patented foundational technologies in facilitating the unprecedentedly rapid vaccine development in response to the pandemic. In some cases, these technologies were patented decades earlier. The report further identifies the distribution of vaccines and therapeutics patents, as well as COVID-19 drug candidates among different vaccine platforms and drug classes, and highlights some notable examples. The information provided in this report can serve as a valuable resource on patenting activity related to COVID-19 vaccine and therapeutic development in the ongoing fight against the COVID-19 pandemic. Moreover, patented technology beyond those developed during the pandemic may be of relevance for vaccine development (see also VaxPal (Medicines Patent Pool, 2021b) for a number of related examples) and even helpful for the development of further therapeutics or vaccines related to other diseases.

The abrupt outbreak and fast spread of the COVID-19 pandemic has had a devastating impact on public health and the global economy. This impact in turn has catalyzed an unprecedented effort in the development of therapeutics and vaccines. The development of a vaccine or therapeutic is a complex and long process which usually takes 10 and 15 years or longer. Yet within one-and-a-half years of the outbreak of this pandemic, several COVID-19 vaccines of different types have been conditionally approved and deployed in many countries with some of them receiving full approval as of the end of October 2021. This remarkable progress may be attributed to:

- decades of persistent and innovative research and enabling breakthrough developments marked by scientists and business leaders, who endorse visionary thinking and do not give up in the face of many hurdles and setbacks;
- wide availability of scientific knowledge about the disease;
- intensified collaboration between various organizations, including large biopharmaceutical companies, medium/small biotech companies, universities and government entities and their willingness to risk investment;
- an integrated health, trade and IP approach to respond to the COVID-19 pandemic (WHO–WIPO–WTO, 2021);
- excellence in the execution of both innovation and operation (McKinsey & Company, 2021);
- policies/measures installed by governments of various countries to facilitate cooperation and delivery of vaccines (WTO, n.d.);
- a disease responsible for a pandemic with a global impact creating a global market for COVID-19 vaccines and therapeutics.

As of February 2, 2022, over 10 billion COVID-19 vaccine doses had been administered worldwide, 4.79 billion people (61.2 percent of the world's population) had received at least one dose of vaccine, and 4.13 billion people were fully vaccinated (Our World in Data, n.d., WHO, 2021c).

COVID-19 therapeutics are equally critical to the effort to end this pandemic even in the presence of vaccines. However, even though there have been significantly more patents related to the development of COVID-19 therapeutics than vaccines, to date there has not been such remarkable success in this area as in vaccine development. Nevertheless, 63 unique drug candidates have entered Phase 3 (or Phase 2/3) clinical trials based on the analysis of combined Milken Institute, RAPS COVID-19 tracker data and U.S. clinical trial data as of the end of September 2021 (Milken Institute, n.d.; Craven, 2022; U.S. National Library of Medicine, n.d.) with several of these receiving conditional approval.

The biologic and small-molecule drug classes each account for roughly 50 percent in development based on our analysis of individual drug candidates and most of these are repurposed drugs (approximately 80 percent). Particularly promising are a few oral antiviral drugs in the late stage of clinical trials, which target specifically certain coronavirus proteins and can be conveniently given to patents outside hospitals. Among these, molnupiravir by Merck & Co. and its partners, which was developed as the result of efforts by three organizations, was authorized for use in the U.K. and is under review for approval by other regulatory agencies around the world (Francis and Parker, 2021) as of early November. Paxlovid, developed by Pfizer, has also shown promising clinical trial results and been granted EUA by the U.S. FDA. Also encouraging is the ongoing development of several virus-neutralizing antibodies, a new class of antivirals that has been shown to effectively reduce viral load and/or alleviate disease symptoms (Li *et al.*, 2021a). Some of these neutralizing antibodies have been deployed clinically upon receiving approval from regulatory agencies. All this rapid progress highlights the immense importance of persistent research and collaboration among different organizations.

Despite significant progress in the development of COVID-19 vaccines and therapeutics during this pandemic, major challenges remain. One of these is the SARS-CoV-2 variants that may evade human body immunity and the protection offered by the currently available vaccines and recognition by viral neutralizing antibodies. In particular, the appearance of the Omicron variant identified at the end of November 2021, with an unusually high number of mutations within the crucial segment of the viral S protein important for viral infection of human cells and critical for recognition by various vaccines and antibody drugs on the market, could potentially lead to a significant reduction in the effectiveness of some vaccines and therapeutics targeting this segment of the original S protein. Most COVID-19 vaccines developed so far are based on the viral S protein. It may also be desirable to develop vaccines based on other viral genes/proteins that do not mutate as often as the viral S protein. The fact that a small percentage of vaccinated people may still get breakthrough infection and transmit the virus is also raising doubts about how quickly the world can leave the coronavirus pandemic behind (Dyer, 2021). In the therapeutic area, incorporation of artificial intelligence and other enabling technologies to quickly identify molecules that may specifically bind to viral target proteins and the development of a mechanism that may speed up clinical trials would be highly desirable. Although quite a few

virus-neutralizing antibodies have shown promising results with some gaining conditional approval, the expensive and complex production process for these drugs has meant such drugs are not yet readily available for all COVID-19 patients.

The world is still waiting for the widespread availability of further highly efficacious and yet cheaper drugs that can be easily taken by patients. Despite all of these challenges, the high level of patenting activity related to COVID-19 vaccines and therapeutics, as revealed in this report, along with the abundance of scientific literature reported in other resources (and the unforeseen speed in the development of both COVID-19 vaccines and therapeutics) offer us a hope that this pandemic will be defeated. The breakthroughs in some technologies such as mRNA vaccine design that the world has witnessed during this pandemic and the use of the underlying lipid nanoparticle technology for mRNA vaccine delivery not only have profoundly benefited the fight against this pandemic but may also have enormous potential in vaccine development for other infectious diseases and even the therapeutic strategies using RNA molecules for treatment of diseases beyond COVID-19.

Annex

Data sources and methods

Having a representative or complete picture of the patenting activity during the pandemic is not yet possible, due to the very recent related activity, the time needed for this information to become publicly available through publication of the patent application, and the different practices across jurisdictions during the pandemic. As a result, this report should be seen as an indicator of the patenting activity and help with a first understanding of the situation. Repeating the exercise at a later stage would provide a more complete picture and allow conclusions to be drawn.

This report focuses on the analysis of patents related to vaccines and therapeutics for COVID-19. In order to develop a patent search strategy a project team was put together consisting of WIPO staff members, scientific information specialists from CAS (a division of the American Chemical Society), and a patent information professional and subject matter expert.

The patent information was extracted from the CAS Content Collection (CAS, n.d.), which includes patents published by 65 patent offices around the world up to September 30, 2021. First, a broad COVID-19 patent dataset was created by searching for patent documents related to COVID-19 or SARS-CoV-2 and keyword variations thereof. At the next stage, two search strategies were developed for the creation of the sub-datasets related to vaccines and therapeutics. These involved title–abstract search queries using keywords (used in patent documents or assigned to documents by CAS), patent classification symbols, CAS indexing and concept approaches (based on full-text content), and role indicators, such as THU for therapeutic use, PAC for pharmacological activity and PKT for pharmacokinetics, to identify substances with potential as therapeutic agents. Obvious noise, i.e., irrelevant search results, was removed by further search refinements, and the search results were further intellectually reviewed to remove noise, as well as to cluster the patent documents across different categories. The patent search strategy and the patent datasets (broad COVID-19, vaccines and therapeutics dataset) are available on the WIPO website (https://www.wipo.int/patentscope/en/programs/patent_landscapes). A further patent search was carried out in parallel using public databases, and related documentation will be made available separately.

Many COVID-19 drug candidates in development are repurposed or redirected drugs without a recently published, corresponding patent in our datasets. Furthermore, we observe variable delays in publishing patents by different patent offices. For these reasons, this report also used other data sources for COVID-19 vaccines and therapeutics, such as the WHO's COVID-19 vaccine data (as of October 8, 2021), the WHO's living guidelines for COVID-19 therapeutics, the Milken Institute's COVID-19 therapeutic tracker data (as of the end of September 2021), and Regulatory Affairs Professionals Society (RAPS) COVID-19 therapeutic tracker data (as of the end of September 2021). The external data was analyzed in combination with substance information extracted from the CAS Content Collection. In order to identify the prior-art patents for this report, patent applicants' information and names of organizations that developed certain COVID-19 therapeutics were also searched along with drug names independently from the search for COVID-19/SARS-CoV-2. Through this process, 5,293 patent families were identified related to COVID-19. Among them, 417 related to vaccine development, and 1,465 to therapeutics.

Various analyses were then performed on these datasets to reveal trends and insights. In this

report, all counts of records and most of the analysis refer to patent families or inventions, unless stated otherwise. Patent families consist of the earliest patent application filed for patent protection, and the subsequent patent applications related to the same invention. Where patents for the same invention are filed in numerous jurisdictions, they are described as patent applications corresponding to the same invention or as members of the same patent family. The filings themselves may claim zero, one, or multiple priorities. There are different definitions of patent families; for this report, the CAS patent family approach was followed, based on grouping patent documents that share the novel scientific content. The filings themselves may claim zero, one, or multiple priorities. CAS intellectually evaluates each patent family and will create additional connections (links) to include domestically-related applications, countries that have not ratified the Paris Convention, or applications filed too late to claim priority.

A combination of technology and human intelligence is used to evaluate each patent family and verify similar content within families. For each patent document, CAS has identified other closely related patent family members that tend to have priority relationships with the representative patents, such as claiming the same priority applications (or same set of priority applications) as well as priorities claimed by this patent and other patent documents that claim priorities to this patent. The patent family members may not have exactly the same priorities but all family members are linked through at least one priority. Continuations-in-part are placed in separate families, as are some divisions, depending on whether patent law in the jurisdiction allows new content. While most patent families consist of closely related patents, there are some cases where more than one patent within a patent family is curated separately. This may happen when related patents have somewhat different technical content or when family members have more complex relationships such as multiple priorities from different countries or relationships resulting from division, continuation, or continuation-in-part (CIP) patents.

The analysis refers to patent families (which in some cases may include a single patent family member). In most graphs and analysis, each patent family is represented by a single patent document. This ensures that even where there are several members of a patent family it is only counted once – in this way we refer to invention numbers – giving a more accurate picture of the actual innovative activity. The patent families are broken down into individual patent applications (counting one per jurisdiction) only in the analysis relating to the geographical distribution of the patent protection. Here, the numbers refer to patent applications, and the percentages refer to the proportion of patent families that include a patent application in the jurisdiction in question, reflecting the IP strategy of the patent applicants and their choice of jurisdiction and related markets.

Calculations of patent publication lags in months were performed using the difference between patent publication and filing dates for office-specific patent kind codes. For documents from the patent offices of China (CN), Japan (JP) and the Republic of Korea (KR), the kind code “A” was used. For U.S. publications generated by USPTO, kind code A1 was selected. For PCT (WO) publications, A1, A2 and A3 kind codes were used. Calculations of patent grant lags include Chinese (CN) documents with kind codes B and Y; U.S. (US) and Japanese (JP) patent documents with kind codes B1 and B2; Republic of Korea (KR) patent documents with kind codes B1 and Y1; and Russian Federation patent documents (RU) with kind codes C, C1 and C2.

Tables of vaccine types and candidates currently in clinical trials

Table A1. Live attenuated and inactivated COVID-19 vaccine candidates in clinical trials, based on WHO data.

Vaccine platform	Developer/manufacturer	Vaccine (CAS Registry Number)	Antigen	Phase
Live attenuated virus (1)	Codagenix/Serum Institute of India (India)	COVI-VAC (2695472-84-3)	N/A	Phase 1
Inactivated virus (18)	Sinovac Research and Development (China)	CoronaVac (2480309-93-9)	N/A (inactivated virus)	Phase 4
	Sinopharm + China National Biotec Group Wuhan Institute of Biological Products (China)	WIBP-CorV (2699874-55-8)	N/A (inactivated virus)	Phase 3
	Sinopharm + China National Biotec Group + Beijing Institute of Biological Products (China)	BBIBP-CorV (2503126-65-4)	N/A (inactivated virus)	Phase 4
	Institute of Medical Biology + Chinese Academy of Medical Sciences (China)	KMS 1 (2699688-05-4)	N/A (inactivated virus)	Phase 3
	Research Institute for Biological Safety Problems (Kazakhstan)	QazCovid-in (2541708-50-1)	N/A (inactivated virus)	Phase 3
	Bharat Biotech International Limited (India)	Covaxin/BBV152 (2501889-19-4)	N/A (inactivated virus)	Phase 3
	Shenzhen Kangtai Biological Products (China)	KCONVAC (2698355-03-0)	N/A (inactivated virus)	Phase 3
	Valneva, National Institute for Health Research (U.K.)	VLA 2001 (2695500-31-1)	N/A (inactivated virus)	Phase 3
	Erciyes University (Turkey)	Erucov-Vac (2695585-27-2)	N/A (inactivated virus)	Phase 3
	Shifa Pharmed Industrial (Islamic Republic of Iran)	COVIran Barekat (2698354-65-1)	N/A (inactivated virus)	Phase 2/3
	The Government Pharmaceutical Organization (Thailand); PATH (U.S.); Dynavax (U.S.)	NDV-HXP-S (2698357-82-1)	Prefusion stabilized spike (HexaPro) in NDV vector	Phase 1/2
	Organization of Defensive Innovation and Research (Islamic Republic of Iran)	Fakhravac (2695587-69-8)	N/A (inactivated virus)	Phase 1
	Kocak Farma (Turkey)	Kocak 19 (2699009-33-9)	N/A (inactivated virus)	Phase 2
	The Scientific and Technological Research Council of Turkey (TÜBITAK) (Turkey)	Adjuvanted inactivated vaccine against SARS-CoV-2	N/A (inactivated virus)	Phase 1
	KM Biologics (Japan)	KD 414 (2699012-28-5)	N/A (inactivated virus)	Phase 1/2
	Laboratorio Avi-Mex (Mexico)	Patria (2699009-20-4)	Prefusion stabilized spike (HexaPro) in NDV vector	Phase 1
	Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products (Russian Federation)	CoviVac (inactivated SARS-CoV-2 vaccine) (2714563-97-8)	N/A (inactivated virus)	Phase 1/2
	Institute of Vaccines and Medical Biologicals (Vietnam)	COVIVAC	Prefusion stabilized spike (HexaPro) in NDV vector	Phase 1/2

Note: NDV: Newcastle disease virus.

Table A2. Protein-based COVID-19 vaccine candidates in clinical trials, based on WHO data.

Vaccine platform	Developer/manufacturer	Vaccine (CAS registry number)	Antigen	Phase
Protein subunit (43)	Novavax (U.S.)	NVX-CoV2373 (2502099-58-1)	Spike protein nanoparticle (Sf9 cell)	Phase 3
	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences (China)	ZF 2001 (2609662-31-7)	RBD dimer	Phase 3
	Kentucky Bioprocessing (U.S.)	KBP-COVID-19/KBP-201 (2543206-35-3)	RBD linked to TMV VLP	Phase 1/2
	Sanofi Pasteur (France) + GSK (U.K.)	VAT 00002 (2696235-99-9)	Spike protein nanoparticle (Sf900 cell)	Phase 3
	Clover Biopharmaceuticals (China)/ GSK/Dynavax (U.S.)	SCB-2019 (2541906-99-2)	Stabilized trimer of spike	Phase 3
	Vaxine (Australia)/CinnaGen (Islamic Republic of Iran)	COVAX-19/Spikogen (2543231-22-5)	Spike (insect cell)	Phase 3
	Medigen Vaccine Biologics (Taiwan, Province of China) + Dynavax (U.S.) + National Institute of Allergy and Infectious Diseases (NIAID) (U.S.)	MVC-COV1901 (2565776-92-1)	Prefusion stabilized (2P) trimer of spike	Phase 3
	Instituto Finlay de Vacunas (Cuba)	FINLAY-FR1 (2695520-51-3)	RBD-dimer	Phase 2
	Instituto Finlay de Vacunas (Cuba)	FINLAY-FR-2 (2543416-58-4)	RBD conjugate with tetanus toxoid	Phase 3
	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "VECTOR" (Russian Federation)	EpiVacCorona (2695474-42-9)	Spike-derived peptides conjugated to nucleoprotein-maltose-binding protein fusion protein	Phase 3
	West China Hospital + Sichuan University (China)	N/A	RBD	Phase 3
	University Hospital Tuebingen (Germany)	IMP CoVac-1 (2696246-74-7)	Multi-peptide cocktail of HLA–DR peptides	Phase 1/2
	Vaxxinity (U.S.)	UB-612 (2543531-06-0)	Multi-peptide vaccine targeting RBD plus viral structural proteins	Phase 2/3
	Adimmune Corporation (Taiwan, Province of China)	AdimrSC-2f (2696236-00-5)	RBD-Fc fusion protein	Phase 1
	Center for Genetic Engineering and Biotechnology (CIGB) (Cuba)	CIGB-669 (2696238-03-4)	RBD	Phase 1/2
	Center for Genetic Engineering and Biotechnology (CIGB) (Cuba)	CIGB-66 (2696238-04-5)	RBD + AlOH	Phase 3
	Biological E. Limited (India)	BECOV 2 (2696240-61-4)	RBD + HBcAg	Phase 3
	Nanogen Pharmaceutical Biotechnology (Vietnam)	Nanocovax (2695523-49-8)	Prefusion stabilized (protease + 2P) spike	Phase 3
	Shionogi (Japan)	S 268019 (2696247-53-5)	Spike	Phase 1/2
	University Medical Center Groningen (Netherlands) + Akston Biosciences (U.S.)	AKS 452 (2699015-60-4)	RBD-Fc fusion protein	Phase 1/2
	University of Saskatchewan (Canada)	COVAC 2 (2696294-15-0)	Spike protein S1	Phase 1/2
	SK Bioscience C and CEPI (Republic of Korea)	GBP 510 (2696258-34-9)	RBD linked to I53-50 nanoparticles	Phase 3
	Razi Vaccine and Serum Research Institute (Islamic Republic of Iran)	Cov Pars (2696315-86-1)	Spike protein S1	Phase 3
	The University of Queensland (Australia)	SARS-CoV-2 Sclamp (2696323-20-1)	Prefusion stabilized trimer of spike using gp41env fragment	Phase 1

Table A2. *(Continued)*

Vaccine platform	Developer/manufacturer	Vaccine (CAS registry number)	Antigen	Phase
Protein subunit (43) *Continued*	SK Bioscience (Republic of Korea)	NBP 2001 (2696258-42-9)	RBD fused to tetanus toxoid epitope	Phase 1
	Walter Reed Army Institute of Research (WRAIR) (U.S.)	SpFN (2696325-76-3)	Eight prefusion stabilized spike glycoprotein trimers in an ordered array on a ferritin nanoparticle	Phase 1
	POP Biotechnologies and EuBiologics (U.S.)	EuCorVac 19 (2696268-42-3)	RBD linked to cobalt porphyrin-phospholipid (PoP) nanoliposome	Phase 1/2
	Jiangsu Rec-Biotechnology (China)	ReCOV (2696273-05-7).	NTD + RBD of spike	Phase 1
	Guangdong Provincial Center for Disease Control and Prevention/ Gaozhou Center for Disease Control and Prevention (China)	V 01 (2699080-34-5)	INFalpha-PADRE-RBD-Fc fusion protein	Phase 2
	National Vaccine and Serum Institute (China)	N/A	N/A	Phase 1/2
	OSE Immunotherapeutics (France)	CoVepiT (2698316-94-6)	Peptide cocktail from spike, M, N, non-structural proteins	Phase 1
	USSF/Vaxform (U.S.)	CoV2-OGEN1 (2698316-95-7)	RBD for oral delivery	Phase 1
	Research Institute for Biological Safety Problems (Kazakhstan)	QazCoVac-P (2699021-46-8)	RBD + N	Phase 1/2
	Bagheiat-allah University of Medical Sciences (Islamic Republic of Iran)	Noora (2699609-20-4)	RBD	Phase 1
	Baiya Phytopharm (Thailand)	Baiya SARS-CoV-2 VAX 1 (2699023-86-2)	RBD-Fc	Phase 1
	Clover Biopharmaceuticals AUS (China)	SCB 2020S (2698364-51-9)	Trimeric S protein (from B.1.351 variant)	Phase 2
	Shanghai Zerun Biotechnology + Walvax Biotechnology + CEPI (China)	202CoV (2699024-52-5)	Spike trimer	Phase 1
	Laboratorios Hipra (Spain)	Hipra SARS-CoV 2 (2699003-75-1)	RBD	Phase 1/2
	Hospital do Coracao (Brazil)	Versamune-CoV 2FC (2699028-16-3)	Spike protein S1	Phase 1/2
	Novavax (U.S.)/Serum Institute of India (SII)	SII B.1.351 + Matrix-M1 adjuvant, a monovalent SII SARS-CoV-2 B.1.351 (Beta) variant vaccine	Prefusion stabilized S protein of beta variant	Phase 1/2
	Novavax (U.S.)/Serum Institute of India (SII)	SII Bivalent + Matrix-M1 adjuvant, a bivalent SII vaccine containing antigen for both the ancestral strain and B.1.351 (Beta) variant of SARS-CoV-2	Prefusion stabilized S proteins of alpha and beta variants	Phase 1/2
	Novavax (U.S.)/Serum Institute of India (SII)	SII B.1.617.2 + Matrix-M1 adjuvant, a monovalent SII SARS-CoV-2 B.1.617.2 (Delta) variant vaccine	Prefusion stabilized S protein of delta variant	Phase 1/2
	Sinocelltech (China)	SCTV01C (2714576-04-0)	Trimeric S protein	Phase 2/3

Table A2. *(Continued)*

Vaccine platform	Developer/manufacturer	Vaccine (CAS registry number)	Antigen	Phase
Virus like particle (5)	Serum Institute of India + Accelagen Pty + SpyBiotech (India)	RBD SARS-CoV-2 HBsAg (2699603-12-6)	RBD linked to HBsAg via SpyTag/ SpyCatcher tags	Phase 1/2
	Medicago (Canada)	CoVLP (2698316-96-8)	Prefusion stabilized (2P) protease-resistant S protein fused to transmembrane domain and cytoplasmic tail of influenza A virus H5	Phase 3
	VBI Vaccines (U.S.)	VBI-2902a (2695526-51-1)	Prefusion stabilized (2P) protease-resistant S protein fused to transmembrane domain and cytoplasmic tail of VSV G glycoprotein + MLV Gag to form VLPs	Phase 1/2
	The Scientific and Technological Research Council of Turkey (Turkey)	SARS-CoV-2 VLP (2699603-41-1)	M, N, E and prefusion stabilized (6P) S protein form SARS-like VLP	Phase 2
	Radboud University (Netherlands)	ABNCoV 2 (2698316-97-9)	RBD linked to capsid protein VLP	Phase 1

Notes: TMV VLP: tobacco mosaic virus virus-like particle; HLA-DR: human leukocyte antigen DR isotype; RBD: receptor-binding domain of viral S (spike) protein; AlOH: aluminum hydroxide; HBcAg: Hepatitis B core antigen; Fc: "fragment crystallizable" region of antibody; NTD: N-terminal domain; VSV: vesicular stomatitis virus; MLV: murine leukemia virus.

Table A3. Viral-vector- and bacterial-vector-based COVID-19 vaccines in clinical trials, based on WHO data.

Vaccine platform	Developer/manufacturer	Vaccine (CAS registry number)	Antigen	Phase
Viral-vector (replicating) (3)	University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy (China)	DelNS1-2019-nCoV-RBD-OPT1 (2696350–29-3)	RBD (LAIV for IN administration)	Phase 2
	Israel Institute for Biological Research (Israel)	IIBR-100 (2699603-14-8)	Spike protein in VSV delta G	Phase 2/3
	Meissa Vaccines, Inc. (U.S.)	MV-014-212 (2695491-34-8)	Spike fused to VSV F protein	Phase 1
Viral-vector (replicating) + APC (2)	Aivita Biomedical, Inc. (U.S.) National Institute of Health Research and Development, Ministry of Health Republic of Indonesia	AV-COVID 19 (2698316-98-0)	Spike protein-loaded autologous DC	Phase 1
	Shenzhen Geno-Immune Medical Institute (China)	Covid-19/aAPC (2699603-15-9)	Lentivirus vector minigene LV-SMENP transduced inactivated artificial APC	Phase 2
Viral-vector (non-replicating) (17)	AstraZeneca + University of Oxford (U.K.)	AZD1222; ChAdOx1-S; ChAdOx1 nCoV-19; Covishield; Vaxzevria (2499737-08-3)	Spike	Phase 4/ Phase 1
	CanSino Biological Inc./Beijing Institute of Biotechnology (China)	Ad5 nCoV (2540656-88-8)	Spike	Phase 4
	Gamaleya Research Institute; Health Ministry of the Russian Federation (Russian Federation)	rAd26-S+rAd5-S/Gam-COVID-Vac/Sputnik V (2541629-85-8)	Spike	Phase 3
	Janssen Pharmaceutical; Johnson & Johnson (U.S.)	Ad2626.COV2-S/JNJ-78436735 (2541607-46-7)	Prefusion stabilized spike	Phase 4
	ReiThera (Italy)+ Leukocare (Germany)+ Univercells (Belgium)	GRAd-CoV2 (2543636-44-6)	Prefusion stabilized spike	Phase 2/3
	Vaxart (U.S.)	VXA-CoV2-1 (2543668-36-4)	Spike + nucleoprotein + TLR3 agonist (dsRNA)	Phase 2
	University of Munich (Ludwig-Maximilians) (Germany)	MVA-SARS-2-S (2543700-32-7)	Spike	Phase 1
	ImmunityBio, Inc (U.S.)	hAd 5S-Fusion+N-ETSD (2698362-05-7)	Spike + nucleocapsid-enhanced T-cell stimulation domain fusion protein in hAd5 vector	Phase 1/2
	City of Hope Medical Center + National Cancer Institute (U.S.)	COH 04S1 (2716897-29-7)	Spike	Phase 1
	Cellid Co. Ltd (Republic of Korea)	AdCLD-CoV19 (2698316-99-1)	Spike	Phase 1/2
	Bharat Biotech International Limited (India)	BBV 154 (2698317-00-7)	Prefusion stabilized spike in simian Ad36 for IN administration	Phase 1
	Gritstone Oncology (U.S.)	ChAdV 68S (2699094-02-3); ChAdV 68S-TCE (2699094-03-4)	Spike +/- T-cell epitopes in ChAD68 vector	Phase 1
	Tetherex Pharmaceuticals Corporation (U.S.)	SC-Ad 6-1 (2698317-01-8)	Spike	Phase 1
	German Center for Infection Research (Germany)	MVA-SARS-2-S (2543700-32-7)	Spike	Phase 1/2
	CyanVac LLC (U.S.)	CVXGA 1 (2698357-98-9)	Spike protein in PVI5 vector	Phase 1
	AstraZeneca + University of Oxford (U.K.)	AZD 2816 (2695526-74-8)	Spike beta (B.1.351) variant in ChAdOx1 vector	Phase 2/3
	Biocad (Russian Federation)	AAV5-RBD-S vaccine (BCD-250)	Optimized spike RBD in nrAAV5 vector	Phase 1/2
Viral-vector (non-replicating) + APC (1)	Shenzhen Geno-Immune Medical Institute (China)	LV-SMENP-DC (2696360-97-9)	Lentiviral vector SMENP minigene in DC	Phase 1/2
Bacterial-vector (1)	DreamTec Research Limited (China)	COVID19 Oral Vaccine Consisting of Bacillus Subtilis Spores	RBD fused to spore coat protein	N/A

Notes: LAIV: live attenuated influenza vaccine; IN: intranasal; RBD: receptor-binding domain of viral S (spike) protein; VSV: vesicular stomatitis virus.

Table A4. Nucleic-acid-based COVID-19 vaccines in clinical trials, based on WHO data.

Vaccine platform	Developer/manufacturer	Vaccine (CAS registry number)	Antigen	Phase
DNA-based vaccine (14)	Inovio Pharmaceuticals (U.S.) + International Vaccine Institute (U.S.) + Advaccine (Suzhou) Biopharmaceutical (China)	INO-4800 (2535490-43-6)	Optimized spike	Phase 2/3
	AnGes + Takara Bio + Osaka University (Japan)	AG0301-COVID19 (2541593-92-2)	Spike	Phase 2/3
	Zydus Cadila (India)	ZyCoV-D (2541524-47-2)	Spike	Phase 3
	Genexine Consortium (Republic of Korea)	GX-19N (2695527-94-5)	Spike + nucleocapsid protein	Phase 2/3
	Entos Pharmaceuticals Inc. (Canada)	Covigenix VAX-001(2696365-40-7)	Spike encapsulated in a proprietary Fusogenix proteo-lipid vehicle (PLV)	Phase 1
	Providence Health & Services (U.S.)	CORVax (2696366-75-1)	Prefusion stabilized spike	Phase 1
	Symvivo Corporation (Canada)	bacTRL-Spike (2696368-59-7)	Plasmid-encoded spike protein for oral delivery via *Bifidobacterium longum*	Phase 1
	GeneOne Life Science, Inc. (Republic of Korea)	GLS-5310 (2696371-11-4)	Spike	Phase 1/2
	University of Sydney, Bionet Co., Ltd Technovalia (Australia)	COVIGEN (2696378-52-4)	Spike	Phase 1
	Takis + Rottapharm Biotech (Italy)	COVID-eVax (2695568-16-0)	RBD	Phase 1/2
	AnGes, Inc (Japan)	AG0302-COVID19 (2541593-93-3)	Optimized spike	Phase 1/2
	Scancell Ltd (U.K.)	COVIDITY	Trimeric RBD plus nucleoprotein	Phase 1
	Vaccibody AS (Norway)	VB10.2129 (2714576-17-5)	RBD of beta variant fused to dimerization domain and APC-targeting agent (MIP-1alpha)	Phase 1/2
	Vaccibody AS (Norway)	VB10.2210 (2714576-24-4)	T-cell epitopes of SARS-CoV-2 antigens	Phase 1/2
RNA-based vaccine (21)	Moderna + National Institute of Allergy and Infectious Diseases (NIAID) (U.S.)	mRNA-1273 (2457298-05-2)	Prefusion stabilized spike	Phase 4
	Pfizer (U.S.)/BioNTech + Fosun Pharma (China)	BNT162b2; Comirnaty (2417899-77-3)	Prefusion stabilized spike	Phase 4
	CureVac AG (Germany)	CVNCOV (2541470-90-8)	Prefusion stabilized spike	Phase 3
	Arcturus Therapeutics (Singapore)	ARCT-021 (2541451-24-3)	Spike expression via saRNA	Phase 2
	Imperial College London (U.K.)	LNP-nCoVsaRNA (2545641-90-3)	Prefusion stabilized spike via saRNA	Phase 1
	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences (China)	ARCoV (2543878-98-2)	RBD	Phase 3
	Chulalongkorn University (Thailand)	ChulaCov 19 (2696385-07-4)	Spike protein	Phase 1
	Providence Therapeutics (Canada)	PTX-COVID 19B (2695572-65-5)	Spike protein	Phase 1
	GlaxoSmithKline (U.K.)	CoV2 SAM (2698317-02-9)	Prefusion stabilized spike via saRNA	Phase 1
	Moderna + National Institute of Allergy and Infectious Diseases (NIAID) (U.S.)	mRNA-1273.351 (2695574-78-6)	Full-length, prefusion stabilized spike of the SARS-CoV-2 B.1.351 variant	Phase 4
	Sanofi Pasteur and Translate Bio (France)	MRT 5500 (2541853-30-7)	Prefusion stabilized protease-resistant spike protein	Phase 2

Table A4. *(Continued)*

Vaccine platform	Developer/manufacturer	Vaccine (CAS registry number)	Antigen	Phase
RNA-based vaccine (21) *Continued*	Daiichi Sankyo Co. Ltd (Japan)	DS 5670a (2696391-55-4)	RBD	Phase 1/2
	SENAI CIMATEC (Brazil)	HDT 301 (2437182-02-8)	Spike protein in saRNA	Phase 1
	ModernaTX, Inc. (U.S.)	mRNA-1283 (2696398-77-1)	Spike N-terminal domain + RBD	Phase 1
	Elixirgen Therapeutics, Inc (U.S.)	EXG 5003 (2698317-03-0)	RBD in saRNA	Phase 1/2
	Shanghai East Hospital (China) and Stemirna Therapeutics (U.S.)	SW 0123 (2699076-70-3)	Spike protein	Phase 1
	MRC/UVRI (U.K.) and LSHTM Uganda Research Unit (Uganda)	LNP-nCOV saRNA 02 (2698334-91-5)	Prefusion stabilized spike	Phase 1
	ModernaTX, Inc. (U.S.)	mRNA-1273.211	Prefusion stabilized spike (Wuhan + beta variant)	Phase 2/3
	Arcturus Therapeutics, Inc. (U.S.)	ARCT-154 (2698334-90-4)	Spike of VOCs alpha, beta, gamma, delta in saRNA	Phase 2/3
	Arcturus Therapeutics, Inc. (U.S.)	ARCT-165 (2714576-70-0)	VEEV replicon for S of VOCs alpha, beta, gamma, delta	Phase 1/2
	Arcturus Therapeutics, Inc. (U.S.)	ARCT-021 (2541451-24-3)	Full length spike protein in VEEV replicon	Phase 1/2

Notes: RBD: receptor-binding domain of viral S (spike) protein; saRNA: self-amplifying RNA; VOC: variant of concern; VEEV: Venezuelan equine encephalitis virus.

Table A5. Example patents related to small-molecule candidates, including natural products, for treating COVID-19.

Patent application number and filing date	Title	Patent applicant	Key statement
CN113018306 March 5, 2021	Application of nicotinamide mononucleotide in preparation of drugs for inhibiting susceptibility of SARS-CoV-2 virus	Academy of Military Medical Science (China)	Application of NMN in preparation of drugs for inhibiting the susceptibility of SARS-CoV-2 virus
WO2021101902 November 17, 2020	Compounds, compositions, and methods for treating ischemia-reperfusion injury and/or lung injury comprising pazopanib	Yale University (U.S.)	Methods of treating ischemia-reperfusion injury using a MAP3K2/MAP3K3 inhibitor
WO2021055467 September 16, 2020	Orally administrable nano-medicine for viral diseases	University of Miami (U.S.)	Nanoparticles for treating viral infection, specifically Zika and coronavirus infections
WO2021053651 September 30, 2020	Extract of *Cocculus hirsutus* for treatment of COVID-19	Sun Pharm. Industries (India)	Extract of *Cocculus hirsutus* for treatment of infection caused by SARS-CoV-2 virus
US20210085619 September 23, 2020	Nanoencapsulated combination drug formulations	Northeastern University (U.S.)	Pharmaceutical nano-cocktails of nano-particulate including active agent to provide overlapping therapeutic windows and pharmacokinetic and pharmacodynamic profiles
CN112516149 July 21, 2020	Application of estradiol benzoate or pharmaceutically acceptable salt thereof in preparing medicine for resisting coronavirus	South Med. Univ., Wuhan Inst. Virology, Chinese Acad. Sci.; Guangzhou Inst. Respiratory Health (China)	Application of estradiol benzoate in preparing medicine for resisting the entrance of coronavirus into target cells
US20210079008 September 16, 2020	Benzimidazoles and their use for the treatment of hepatitis and RNA virus infections	University of Utah (U.S.)	Benzimidazoles for treatment of hepatitis, RNA virus infections, Rift Valley fever, influenza, Tacaribe virus, Mayaro virus, West Nile virus, yellow fever virus and coronavirus
CN112451534 October 12, 2020	Application of corilagin in inhibiting replication of coronavirus to exert anti-coronavirus drug function	Inst. Med. Biotechnol., Chinese Acad. Med. Sci. (China)	Application of corilagin for preparation of an inhibitor of the replication of SARS-CoV-2, for treating SARS-CoV-2 infection

Table A5. *(Continued)*

Patent application number and filing date	Title	Patent applicant	Key statement
CN112402402 November 20, 2020	Application of xanthohumol in preparation of novel coronavirus inhibitor	Qingdao Natl. Lab. Marine Sci. Technol.; Marine Biomed. Res. Inst. Qingdao (China)	Application of xanthohumol to inhibit the activity of Mpro protease and to inhibit the transcription and replication of viruses
CN112137991 September 27, 2020	Application of diselenide as inhibitor of coronavirus 3C like protease and anti-coronavirus drug	Shandong University (China)	Application of diselenide as inhibitor of coronavirus 3C-like protease and anti-coronavirus drug (IG1)
WO2020247665 June 4, 2020	Preparation of peptidomimetics for the treatment of norovirus infection	Emory University (U.S.)	Peptidomimetic compounds for curing a coronavirus, picornavirus and/or *Hepeviridae* virus infections, multiple sclerosis, SARS, MERS, or COVID-19
IN202041020573 May 15, 2020	Process of synthesizing quinoline and rhein derived chiral molecules effective against COVID-19	India	Synthesis of quinoline and rhein chiral molecules effective against COVID-19, comprising multi-receptors targeting protein complex drugs for SARS-CoV-2 pandemic infection
WO2021160768 February 11, 2021	Compounds useful as antiviral agents	Nature Crete Pharmaceut. PC (Greece)	Compounds useful as anti-viral agents in treatment of diseases caused by RNA viruses, such as SARS-CoV-2, Ebola, rabies or influenza
WO2021160220 February 9, 2021	Preparation of 1-substituted pyridin-2-ones as antiviral agents with broad activity	Univ. Luebeck (Germany)	Substituted pyridin-2-ones as antiviral agents in treating viral infections
WO2021130195 December 22, 2020	Method of treating virus infection using a TLR-7 agonist	F. Hoffmann-La Roche AG (Switzerland)	Methods of treating HBV, COVID-19 or SARS-CoV-2 infection comprising TLR7 agonist
WO2021181368 March 15, 2021	Methods of treating respiratory disease with deupirfenidone	PureTech LYT 100, Inc. (U.S.)	Method of treating viral, e.g., SARS-CoV-2, respiratory disease, COVID-19 related pneumonia, incl. deuterium-enriched pirfenidone
WO2021176369 March 3, 2021	Methods of inhibiting SARS-CoV-2 replication and treating coronavirus disease 2019	Pfizer Inc. (U.S.)	Use of SARS-CoV-2 protease inhibitor, such as a SARS-CoV-2 3CL protease inhibitor for treating COVID-19
WO2021161283 February 15, 2021	Pharmaceutical compositions comprising naphthoquinone compds for treating coronavirus infections	NLC Pharma Ltd. (Israel)	Naphthoquinone compounds for treatment of a coronavirus infection by inhibiting coronavirus proteinase 3CLpro, combined with phospholipid
WO2021155119 January 29, 2021	Therapeutics for COVID-19	Columbia University (U.S.)	Nucleoside, nucleotide and other inhibitors of viral RdRp or inhibitors of exonucleases as antiviral agents to treat viral infections such as SARS-CoV-2
WO2021041852 August 28, 2020	Glycosylated diphyllin as a broad-spectrum antiviral agent against Zika virus and COVID-19	Albert Einstein College of Medicine (U.S.)	Treating a viral infection caused by a flavivirus, a filovirus, a SARS-CoV-1 virus, a SARS-CoV-2 virus, or a MERS-CoV virus by administering a glycosylated diphyllin as a broad-spectrum antiviral agent
WO2021018786 July 24, 2020	Use of free fatty acid receptor FFAR2 agonists for the treatment of bacterial superinfections post-viral infection	INSERM, Univ. Lille; Inst. Pasteur Lille; CNRS, France; Univ. Copenhagen	Synthetic free fatty acid receptor 2 (FFAR2) agonist for the treatment of bacterial superinfections post-viral infection (eg post-influenza)
WO2021176088 March 5, 2021	Compounds for the treatment of COVID-19	Dompe Farmaceutici SpA (Italy)	Inhibitors of SARS-CoV-2 virus proteins, selected from: 3CLpro, PLpro, N-protein, NSP3, NSP6, NSP9, NSP12, NSP13, NSP14, NSP15, NSP16 and spike-ACE2 for use in the treatment of COVID-19

Note: NMN: nicotinamide mononucleotide.

Table A6. Example patents related to development of biologics for treating COVID-19.

Patent application number and filing date	Title	Patent applicant	Description	Type of treatment
CN112552399 February 24, 2021	Anti-SARS-CoV-2 neutralizing antibodies and conjugates for diagnosis, prevention and treatment of COVID-19	Hengyi Biomedical Technology (China)	The invention provides neutralizing antibodies from recovered COVID-19 patients	Antibody
CN112513076021 September 23, 2020	Spike protein binding molecule of SARS-COV-2 and its application	Shenzhen Yinnuosai Biotechnology Co. Ltd (China)	The invention provides alpaca anti-RBD single-domain antibodies and sd-Fc fusion proteins that neutralize infection	Antibody
CN11250048 July 17, 2020	Nano antibody for SARS-CoV-2 and application thereof	Shanghai Novamab Biopharmaceuticals Co. Ltd (China)	The invention provides a camel VHH antibody cocktail for nebulization that shows activity against SARS-CoV-2 variants	Antibody
CN112390879 January 21, 2021	Preparation of anti-SARS-CoV-2 spike protein RBD domain antibodies, chimeric antigen receptor and CAR-modified immune cells for diagnosis, prevention and therapy of COVID-19	ShanghaiTech University (China)	The invention discloses a phage display isolation of human anti-RBD neutralizing antibody	Antibody
CN112076316 September 21, 2020	Double-antibody composition and application thereof in preparation of covid-19 therapeutic medicine	Academy of Military Medical Sciences, PLA Academy of Military Science (China)	The invention discloses a two non-competitive antibody cocktail targeting RBD and the N-terminal domain of spike protein	Antibody
CN111420048 March 11, 2020	Application of anti-basigin humanized antibody in preparing medicament for treating novel coronavirus pneumonia	Fourth Military Medical University (China)	The invention provides a humanized anti-basigin antibody that inhibits infection via CD147 co-receptor for SARS-CoV-2	Antibody
US20210246226 February 9, 2021	Engineering of anti-TMPRSS2 antibodies and antigen-binding fragments for treating or preventing viral infections and cancer	Regeneron Pharmaceuticals, Inc. (U.S.)	The invention provides transgenic mouse-derived human anti-TMPRSS2 antibodies for inhibiting viral infection	Antibody
KR2205028 November 13, 2020	Binding molecule having neutralizing activity against SARS-coronavirus-2	Celltrion, Inc. KDCA (Republic of Korea)	The invention provides neutralizing human antibodies using phage display able to bind SARS-CoV-2 variants	Antibody
RU2750584 October 14, 2020	Modified antisense oligonucleotide against SARS-CoV-2	Russia	The invention discloses an antisense oligonucleotide specific for SARS-CoV-2, which is shown in examples to significantly inhibit replication of viral RNA	Antisense oligonucle-otide
WO2020201144 March 27, 2020	Preparation of antisense oligonucleotides specific to CD274 and their use for treatment of virus infection	ProQR Therapeutics II B.V. (Netherlands)	The invention discloses an antisense oligonucleotide specific for exon 3 of the CD274 pre-mRNA that can induce exon skipping. Sequences for AON1-AON12 are found in the patent, with examples showing optimized AON9 and AON12 oligonucleotides display good exon skipping ability. The optimizations included creating 2'-OMe and 2'-MOE variants	Antisense oligonucle-otide
CN113249380 March 1, 2021	Preparation of antisense oligonucleotide and NATAC chimeric molecules specific to SARS-CoV-2 S and N gene and their uses for treatment of coronaviral infection	Peking University (China)	The invention discloses chemically modified antisense oligonucleotide targeting the spike or E genes. The invention also discloses an NATAC (nucleic acid hydrolysis targeting chimeras) chimeric molecule also targeting the S or E genes that appears to be an oligonucleotide conjugated to PEG. The examples show that Chimeria-S4 reduced the expression of SARS-CoV-2 S protein in Vero cells	Antisense oligonucle-otide
WO2021186396 A2 March 18, 2021	TGF-β inhibition, agents such as Artemisinin and antisense oligonucleotides and composition therefore treating various viral diseases	Oncotelic Inc. (U.S.)	The invention discloses the use of a TGF-β antisense oligonucleotide (OT-101), in combination with Artemisinin in treating viral infections	Antisense oligonucle-otide

Table A6. *(Continued)*

Patent application number and filing date	Title	Patent applicant	Description	Type of treatment
CN111849994 March 31, 2020	Nucleic acid aptamer of SARS-CoV-2 S protein or RBD protein	Xiamen University (China)	The invention discloses sequences for nucleic acid aptamers that can bind the spike protein or RBD domain of the spike protein. The examples show that aptamer CoV2-RBD-4C has a binding affinity	Aptamer
CN111748558 June 17, 2020	Aptamers capable of binding nucleocapsid protein of coronavirus SARS-CoV-2 and application	Anhui Angpu Tuomai Biotechnology Co. Ltd (China)	The invention discloses aptamer that binds to nucleocapsid protein and presents the sequences for these aptamers	Aptamer
CN111675765 June 2, 2020	Preparation of SARS-CoV-2 spike protein targeting scFv, chimeric antigen receptor and CAR immune cells for treatment of SARS, MERS or COVID-19	Nanjing KAEDI Biotech Inc. (China)	The invention discloses chimeric antigen receptors (CARs) targeting the spike protein, including the components and sequences used to make the CAR. The invention also discloses the use of CARs in construction of immune cells that can be used to inhibit the virus. The CAR appears to help to knock out the RNA polymerase of SARS-CoV-2	Cell therapy
CN113355288 March 6, 2020	Preparation of general chimeric antigen receptor T cell for treatment of COVID-19	Hebei Senlang Biotechnology Co. Ltd (China)	The invention discloses chimeric antigen receptors and their use in making CAR-T cells with ACE2 or ACE2 fragment on the outside of the cells able to bind to SARS-CoV-2	Cell therapy
WO2021155312 January 29, 2021	Placental derived natural killer cells for treatment of coronavirus infections	Celularity Inc. (U.S.)	The invention discloses the use of natural killer cells and/or ILC3 cells in treating viral infection	Cell therapy
CN112852817 March 4, 2021	Composition and application for RNA editing in type III-A CRISPR-Csm system	Chinese PLA Army Specialized Medical Center (China)	The invention discloses a type III-A CRISPR-Csm system composed of more than one enzyme able to reduce the expression of SARS-CoV-2 RdRp gene	CRISPR-Cas system
CN112143731 September 14, 2020	Preparation of gRNA targeting SARS-CoV-2 virus S gene and its use for treatment of coronavirus infection	Guangzhou Reforgene Biotechnology Co. (China)	The invention discloses a CRISRP-Cas13d mRNA-gRNA molecule integrated into a lipid nanoparticle for use in treating viral infections, able to target the spike gene	CRISPR-Cas system
CN112220913 March 30, 2020	Application of combination of TFF2 protein and IFN-kappa protein in treating corona virus 2019 infection	Shandong Ruiying Pioneer Pharmaceutical Co. Ltd (China)	The invention discloses the use of IFN-κ and TFF2 protein administered together in treating disorders and infections caused by coronavirus	Cytokine; Protein
US20210102209 December 9, 2020	Compositions and methods for treating, ameliorating, and/or preventing viral infections	Yale University (U.S.)	The invention discloses the use of small hairpin tri- or-phosphorylated double-stranded RNAs that can activate the immune response to viruses. Specifically, the invention provides dsRNAs that are agonists of RIG-I which can stimulate interferon production	dsRNA
US20210260201 February 10, 2021	Extracellular vesicles for the treatment and prevention of infections and other diseases	Physis Biotechnologies, LLC (U.S.)	The invention discloses the use of bioactive-loaded (drug) extracellular vesicles or surface modified extracellular vesicles in treatment of infections and other diseases. The drug can be a biologic (e.g., casirivimab, imdevimab, ACE2 receptor antibodies or peptides) or could be a small molecule (e.g., remdesivir)	Extra-cellular vesicle
US20200362052 August 5, 2020	Compositions comprising engineered extracellular vesicle comprising anti-TLR antibody fusion protein with tetraspanin for use in treatment of inflammatory diseases	Souvie Biodelivery, LLC (U.S.)	The invention discloses engineered extracellular vesicles comprising a fusion protein that has tetraspanin fused to anti-TLR antibody for use in treating inflammatory diseases	Extra-cellular vesicle
WO2021160170 February 10, 2021	Methods of use of soluble CD24 for treating coronavirus infection, particularly, SARS-CoV-2	OncoImmune, Inc. (U.S.)	The invention discloses the use of CD24-Fc protein to turn off inflammation, specifically by inhibiting CD24	Fusion protein

Table A6. *(Continued)*

Patent application number and filing date	Title	Patent applicant	Description	Type of treatment
WO2021183717 March 11, 2021	Engineering of antibodies and fusion proteins for preventing and treating SARS-CoV-2 infection	NANTCELL, Inc. (U.S.)	The invention discloses antibodies specific for the spike protein of SARS-CoV-2 and ACE2-Ig fusion proteins that can be used ACE2 decoy peptides. ACE2(WT2)-IgG1Fc and ACE2(T27Y/H34A/H374N)-IgG1-Fc fusion proteins generated shown to bind to RBD domains of spike proteins	Fusion protein
WO2021170113 February 26, 2021	Method for treating coronavirus by using ace-2-fc fusion protein	Nanjing Genscript Biotech Co. Ltd Nanjing Legend Biotech Co. Ltd (China)	The invention discusses the use of ACE-2 fused to Ig Fc region as a decoy to bind to the virus and hence reduce viral replication. Examples show that lungs of mice injected with ACE2-hFc did not show pulmonary fibrosis and immune cell infiltration caused by the virus infection	Fusion protein
WO2021160163 February 10, 2021	Methods for prevention and treatment of virus-induced organ injury or organ failure with interleukin 22 (IL-22) dimer (F-652)	Evive Biotechnology (Shanghai) Ltd. (China)	The invention discloses the use of interleukin 22 (IL-22) dimer (F-652) to inhibit inflammation. The IL-22 dimer down-regulates TLR4 signaling and/or regenerating endothelial glycocalyx	Fusion protein
CN111494416 July 1, 2020	Application of NK cell exosomes and related miRNAs in the preparation of COVID-19 virus inhibitors	Shanghai Jiakang Bioengineering Co. Ltd (China)	The invention discloses miRNA targeting the spike gene RNA using exosomes secreted by NK cells activated by IL-21	miRNA
CN113292638 February 21, 2020	Polypeptide medicament for resisting corona virus and method and application thereof	Sichuan Kelun-Biotech Biopharmaceutical Co. Ltd (China)	The invention discloses peptides that change the spike protein's secondary structure can be used to treat viral infections. Peptides ACV01 and ACV03 shown to inhibit fusion of S protein in cells expressing ACE2 protein, with IC50 0.0456μM and 0.9353μM respectively	Peptide
CN113264990 February 14, 2020	Heptapeptide repeat-2 inhibitory polypeptide inhibiting novel SARS-CoV-2, and its application	Shenzhen University (China)	The invention discloses the use of peptides that impact the spike protein's secondary structure and their use in treating viral infections	Peptide
CN111643656 May 14, 2020	Broad-spectrum coronavirus membrane fusion inhibitor, and application thereof in resisting AIDS virus	Institute of Pathogen Biology, Chinese Academy of Medical Sciences (China)	The invention relates that peptides EK1 and EK1M can inhibit the SARS-CoV-2S protein-mediated cell fusion activity, with IC50 values of 0.53 μM and 0.34 μM, respectively. The peptides bind to the HR1 region of the S2 subunit of the spike protein	Peptide
CN111354420 March 8, 2020	A siRNA development method for COVID-19 virus drug treatment	Jilin University (China)	This invention discloses siRNAs specific for spike protein gene and their use in treating COVID-19	siRNA
WO2021130537	Compositions and methods for simultaneously modulating expression of genes	Versameb AG (Switzerland)	The invention discloses siRNA targeting different genes/proteins including genes/proteins that are part of the cytokine storm, as well as viral proteins (spike, ORF1ab, N genes)	siRNA
RU2746362 December 21, 2020	Combination antiviral formulation against SARS-CoV-2 comprising SARS-CoV-2 genome-targeting siRNAs and transfection-enhancing cationic peptide dendrimer	FGBU "GNTs Institut Immunologii" FMBA Rossii (Russian Federation)	The invention discloses siRNA targeting viral genes/proteins with SEQ IDs claimed for the two strands that make up the siRNAs. Examples show siRK-12-EM plus a dendrimeric peptide KK-46 as a potential combination for treating infections caused by SARS-CoV-2	siRNA
CN111518809 May 12, 2020	siRNA for interfering expression of neocoronavirus COVID-19 gene and application thereof in preparing anti-neocoronavirus COVID-19 drug	Hangzhou Yongchengrui Biotechnology Co. Ltd (China)	The invention discloses the sense and antisense strands of siRNA that target the spike protein and RdRp genes/mRNA and test these siRNAs in decreasing viral proteins in Vero E6 cells	siRNA

Examples of partial, early disclosure observed at the Israeli, U.K. and Singapore patent offices

At the Israeli patent office, a series of still unpublished, relevant IL patent applications were filed by Israeli research institutions between May and December 2020.

Table A7. Examples of unpublished Israeli patent applications.

Application no. (IL)	Title	Filing date	Applicants	Current status
274678	Anti SARS Cov-2 antibodies	May 13, 2020	The Israel Institute of Biological Research (IIBR)	Pending examination
275128	A SARS-CoV-2 Vaccine	June 3, 2020		
276627	Compositions for diagnosis and treatment of coronavirus infections	August 9, 2020	Yeda Research and Development Co. Ltd.	Examination in process
276741	A SARS-CoV-2 multi-epitope vaccine	August 15, 2020	The Israel Institute of Biological Research (IIBR)	Pending examination
278955	Anti SARS-CoV-2 antibodies	November 23, 2020		
279463	Coronavirus derived peptides and uses thereof	December 14, 2020	Yeda Research and Development Co. Ltd.	Examination in process

The same search approach may be tested in the Singapore patent office patent register, where some local companies and research institutions have filed a number of patent applications that are indicated as having the status of *pending (not published), abandoned*, or *withdrawn*, but are still available for claiming priority rights.

Table A8. Examples of patent applications in the Singapore patent register with pending, abandoned or withdrawn status.

Application no. (SG)	Title	Filing date	Applicants	Current status
10202002784P	Detection of antibodies to SARS-CoV	March 25, 2020	National University of Singapore	Abandoned
10202002981P	Antibody-binding linear b cell epitopes of SARS-CoV and SARS-CoV-2	March 30, 2020	Agency for Science, Technology and Research	Abandoned
10202009830R	Guide RNAs Targeting Sars-cov-2	October. 2, 2020		Abandoned
10202010008W	SARS-CoV-2 spike protein antigen-binding molecules	October 8, 2020	Hummingbird Bioscience Holdings Ltd; DSO National Lab.; Agency for science, technology and research	Abandoned
10202108612Y		August 6, 2021		Pending (not published)

It is worth observing that even if patent applications filed together by Hummingbird Bioscience and Singapore research institutions are still unpublished, the following information about the other cited patent applications is available:

- The SG applications filed by National University of Singapore, together with some other subsequent filings, have been claimed as priority documents for at least three patent applications (and then published together with them) filed in China, Europe and the U.S. between July and August 2020 (i.e., well before the usual 12-month deadline) and published between November and September 2021 (with two U.S. patents already granted), then followed by the publication of regular PCT applications in September 2021.

- The SG applications filed by the Agency for Science, Technology and Research in March 2020 have been regularly published together with the PCT application claiming this application in September 2021, so we may expect that the one filed by this entity in October 2020 may be published in April 2022.

The official journal of patents of the Intellectual Property Office of the United Kingdom (UKIPO) can be similarly searched, and more than 150 potentially relevant U.K. patent applications are identified as having been filed between February 27 and September 8, 2021, and then notified within this

publication 6–7 weeks later. The list of applicants having filed such U.K. applications includes not only U.K.-based applicants but also Belgian, Dutch and U.S. applicants that took advantage of the U.K. patent system.

Table A9. A selection of patent applications filed and notified to UKIPO.

Application no. (U.K.)	Title	Filing date	Applicants	UKIPO public notification
2002766.0	Coronavirus vaccines	February 27, 2020	Katholieke Universiteit, Leuven	April 15, 2020
2003632.3	SARS-CoV-2 (SARS2, COVID-19) antibodies	March 12, 2020	Harbour Antibodies; Utrecht University; Erasmus University Medical Center, Rotterdam	April 29, 2020
2003980.0	Coronavirus antibody	March 19, 2020	Imperial College Innovations Ltd	May 6, 2020
2004007.7	Coronavirus	March 19, 2020	Immodulon Therapeutics Ltd	May 6, 2020
2004826.0	Coronavirus vaccines	April 1, 2020	DIOSynVax Ltd; University of Cambridge	May 13, 2020
2105465.5 2105481.2	Coronavirus vaccines	April 16, 2021	BioNTech RNA Pharmaceuticals GmbH	June 2, 2021

Each of the U.K. patent applications filed from February to April 2020 cited above has been used as a priority application for a least for a PCT application covering antibodies or vaccines directed against SARS-CoV-2 regularly published between August and October 2021. The last example represents a different situation determined by the filing of U.K. applications on the basis of 23 patent applications filed between April 2020 and February 2021 and actually published with a PCT application (WO2021/213924) on October 28, 2021.

Glossary

Adenoviruses
A group of non-enveloped viruses that cause a wide range of diseases such as cold and cold-like symptoms. They are named as such because they were first isolated from human adenoid tissue. These viruses have an icosahedral nucleocapsid containing a double stranded DNA genome. Modified adenoviruses have been used as viral vectors for delivery of targeted gene therapy and vaccines

Adjuvant
Substance which enhances or modulates the immune response to an antigen

ADME
Abbreviation in pharmacokinetics and pharmacology for Absorption, Distribution, Metabolism and Excretion. These four processes are considered the four steps of pharmacokinetics. ADME studies are designed to investigate how a chemical compound (e.g., a drug) is processed by a living organism. Characterization of ADME properties helps to explore and explain how pharmacokinetic processes happen, so as to provide safety considerations for a new drug on which risk-based assessments can be made

Antibody
Protein that constitutes part of the human immune system for identifying and neutralizing pathogens. Antibody biologics for COVID-19 treatment may be either obtained from patients who have recovered from COVID-19 or manufactured in large quantities using recombinant DNA technologies with the assistance of other biotechnologies

Antigen
Foreign substance inducing an immune response in the body, especially the production of antibodies

Antigen-presenting cells
Immune cells such as dendritic cells, macrophages, Langerhans cells and B cells that mediate the cellular immune response by presenting antigens for recognition by lymphocytes such as T-cells

Biologic drugs (biologics)
Broad category of large molecules produced from living systems, containing components of living organisms, or produced with the use of advanced biotechnologies such as recombinant DNA technology. Biologics are usually large molecules (>1,000 Da) and complex in structure. Subclasses of biologics include, but are not limited to, antibodies, non-antibody proteins such as recombinant fusion proteins, gene/cell therapy products and nucleic-acid-based therapy products in the context of this report

Cell therapy
Placement of viable cells, with or without modification, into the human body to produce a beneficial effect

Clinical trial
Clinical research designed to explore specific issues about biomedical interventions, including new treatments such as novel drugs, vaccines or medical procedures

COVID-19
Viral infection caused by a coronavirus called SARS-CoV-2

Cytokine
Small cell-signaling protein important in regulating host immune response to infection and inflammation. These proteins influence the growth and activity of other immune system cells and blood cells

DNA
Deoxyribonucleic acid, a molecule that carries genetic information and is formed from two chains of polynucleotides wound around each other, with backbones made of alternating sugar (deoxyribose) and phosphate groups

DNA-based vaccine
Vaccine that transfects specific antigen-coding DNA sequence into the cells as a mechanism to induce an immune response

Enveloped virus
Virus exhibiting outer wrapping/envelope made of lipids. This envelope originates from the host cell, where newly formed virus nucleic acid becomes wrapped in an outer coat made from the cell's plasma membrane and studded with viral proteins

Exosome
Membrane-bound extracellular vesicles produced in the endosomal compartment of the cells and released from cells into the extracellular environment. Exosomes may be engineered to serve as drug-containing vehicles for targeted drug delivery

Fc fragment
Tail region of an antibody that interacts with cell surface receptors

Fusion protein
Protein made up of parts from two or more other proteins joined together. Therapeutic fusion proteins are usually created artificially by recombinant DNA technology

Inactivated vaccine
Vaccine consisting of whole pathogens (virus particles, bacteria) grown in culture and then killed to destroy their disease-producing ability

Lipid nanoparticle
Nanoparticle composed of lipids used as a pharmaceutical drug and gene delivery system

Live attenuated vaccine
Vaccine comprising a pathogen with reduced virulence ("live"), so that it becomes harmless or less virulent and yet can stimulate a strong and effective, long-lasting immune response

MERS-CoV
Middle East respiratory syndrome coronavirus, or EMC/2012, a virus transferred to humans from infected dromedary camels

mRNA
Messenger ribonucleic acid, a single-stranded RNA that is complementary to one of the DNA strands of a gene; it is read by a ribosome throughout protein synthesis

Natural product
Chemical compound or substance produced by living organisms such as plants

Neutralizing antibody
Antibody that protects a host cell from a virus. These are part of the normal human immune response but can also be commercially produced using recombinant DNA technology

Non-structural protein (NSP)
Protein encoded by a virus that is not part of the viral particle. Typically, nonstructural proteins include enzymes and transcription factors for virus replication, such as viral protease (3CL/nsp5, etc.), RNA replicate or other template-directed polymerases. The SARS-CoV-2 virus contains 16 nonstructural proteins (NSP1–NSP16)

Pandemic
Epidemic of an infectious disease spread across multiple continents or worldwide, affecting a sizable number of individuals

Patent
Legal title that gives inventors the right, for a limited period (usually 20 years), to prevent others from making, using or selling their invention without their permission in the countries for which the patent has been granted

Patent application/filing
Request for patent protection for an invention in a given jurisdiction filed with a patent office

Patent Cooperation Treaty (PCT)
International treaty, administered by the World Intellectual Property Organization (WIPO), under which a single international patent application can be filed for patent protection in up to 154 countries

Patent family
Set of interrelated patent applications filed in one or more countries to protect the same or a similar invention by a common inventor and linked by one or several common priority data. For this report's search and analysis, the CAS family approach was used, in which patent documents sharing similar content are grouped in a family following priority rules and manual review and validation

Patent publication
Patent document published at different stages of the patent life cycle, including patent applications and granted patents. For the purposes of this report, "patent publication" is used interchangeably with "patent filing" or "patent application"

Protease
Enzyme that breaks apart proteins. The SARS-CoV-2 virus contains two proteases: NSP3 and NSP5, which are commonly called PLpro and 3CLpro

RNA
Ribonucleic acid, a single-stranded chain of nucleotides, with a backbone made of alternating sugar (ribose) and phosphate groups. It plays a vital role in the essential biological processes of coding, decoding, regulation and expression of genes

RNA-based vaccine
Vaccine using antigen-encoding messenger RNA (mRNA) to produce immune response

SARS
Severe acute respiratory syndrome, a viral respiratory illness caused by a coronavirus SARS-CoV-1 or SARS-CoV

SARS-CoV-1
Strain of coronavirus responsible for the 2002–2004 SARS outbreak

SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2, the virus that caused COVID-19 (coronavirus disease 2019)

Small-molecule drug
Broad category of organic chemical compounds with a molecule size smaller than 1,000 Da. These molecules can be synthesized by chemical synthesis or extracted from natural sources (natural products)

Structural protein
Proteins playing an important role in shaping the skeletons and structures of cells, tissues and organisms. The amino acid sequences of structural proteins often show characteristic features that are notably different from those of functional proteins such as enzymes and antibodies

Subunit vaccine
Vaccine containing fragments of a pathogen (protein or polysaccharide) that are antigenic, or required on order to induce an effective immune response

Therapeutic drug
Substance used to treat or prevent disease

Traditional medicine
Crude preparation of medication that is produced according to the principles of traditional medicinal practice. These preparations usually are composed of a mixture of natural plant parts boiled in a liquid (decoction) or made into balls or granules

Vaccine
Substance intended to stimulate the production of antibodies and provide immunity against infectious diseases. It typically contains the agent causing the disease or a synthetic substitute that acts as an antigen without inducing the disease

Viral vector
Modified virus used to deliver antigen-encoding genetic material into cells

Virus
Infectious pathogenic agent that cannot reproduce by itself but replicates inside the living cells of another organism (human, animal, plant or bacteria)

Virus-like particle
Protein nanoparticle structure similar to wild-type virus, but has neither a viral genome nor infectious ability, producing safer vaccine candidates

WHO
World Health Organization, a specialized agency of the United Nations responsible for international public health

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