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Review Article

Analysis of trends in patent development for coronavirus detection, prevention, and treatment technologies in key countries

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ABSTRACT

Coronavirus causes significant damage to human health and the global economy. In this paper, we undertake patent analysis and data mining to systematically analyze the trend in patent applications for coronavirus detection, prevention, and treatment technologies. Our goals are to determine the correlation between typical coronavirus outbreaks and changes in patent technology applications, and to compare the research and development (R&D) progress, patent layout, and characteristics of major institutions in various countries experiencing coronavirus outbreaks. We find that the United States commenced coronavirus detection and vaccine technology R&D earlier than other countries, as it attached importance to the R&D for treatment technologies from the time of the SARS outbreak and initiated the trend of multi-party R&D, with full technology chain coverage by the government, enterprises, universities, and research institutions. China's patent applications have grown rapidly in recent years, mainly based on the R&D of research institutions and universities, although it has formed full technology chain coverage. However, the patent quality and technology global layout still need to be improved. This paper reviews the patent development trends of important coronavirus technologies, and proposes that policymakers should establish a long-term mechanism for R&D, pay attention to intellectual property protection, and deepen international technical cooperation to provide a reference for the development and application of coronavirus detection technology, vaccine technology, and treatment technology.

Contents

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1. Introduction

Coronaviruses (CoVs) are a group of RNA viruses that can cause human–animal infections and belong to the Orthocoronavirinae subfamily of the Coronaviridae family (order Nidovirales).[1,2] Coronaviruses are widespread in nature, including in humans and animals, such as rats, pigs, cats, wolves, chickens, bats, pangolins, civets, and birds,[3,4] and often cause respiratory and intestinal infections in humans and animals.[5] The respiratory disease pandemics caused by coronaviruses have caused significant damage to human health and the global economy.[6] Typical examples include the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, the Middle East respiratory syndrome coronavirus (MERS-CoV) discovered in 2012, and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) discovered in 2019.[7,8] In addition, coronaviruses HKU1, OC43, NL63, and 229E have been associated with human respiratory diseases.[9] SARS-CoV-2 is the seventh coronavirus known to infect humans, posing a significant new threat to human health.

A great deal of research has been conducted on coronaviruses, focusing on the development of virus detection, prevention, and treatment technologies. In terms of detection, real-time fluorescence quantitative PCR,[10] loop-mediated isothermal amplification, CRISPR/Cas technology,[11] sequencing technology,[12] gene chips, and antigen antibody detection[13] have been carried out, focusing on the sensitivity, specificity, high throughput, and low cost of detection.[14] In terms of prevention, vaccination is an effective method to interrupt the transmission of coronavirus and prevent infectious diseases.[15,16] The vaccine development for SARS-CoV-2 mainly uses five technical routes, comprising inactivated,[17] recombinant protein,[18,19] virus vector,[20–22] nucleic acid,[23,24] and live attenuated vaccines, focusing on vaccine efficacy, safety, and immunogenicity. In terms of treatment, there is no specific drug for COVID-19, but several drug candidates have obtained optimistic trial results in preclinical or clinical studies, including virus-targeted drugs,[25–29] such as arbidol, chloroquine, S-protein-targeted drugs, lopinavir/ritonavir, remdesivir, and favipiravir, host-targeted[30,31] drugs, such as serine protease TMPRSS2 inhibitors, baricitinib, and PTC299, and adjuvant drugs,[32–34] such as vitamins, heparin, and corticosteroids.

Coronavirus detection, prevention, and treatment technologies are one of the most important weapons in the global fight against coronaviruses, and the formation of more advanced coronavirus technologies is an important goal for future scientific and technological development. Patent literature is an important source of information on independent innovation achievements, and it can reflect the status and history of innovation development in a certain technology field. The existing technologies, methods of detection, vaccines, and treatments for coronaviruses such as SARS-CoV, MERS-CoV and SARS-CoV-2 can be used to optimize research and development (R&D) decisions. In this paper, using a patent-based perspective, we focus on the technology patents for global human coronaviruses as our research object and adopt patent analysis and data mining methods to examine the technology chain of detection, prevention, and treatment. We systematically analyze the trend in patent applications relating to coronavirus technology, determine the latest development trends in relation to key technologies, and study the patent layout and competition characteristics of major institutions. Our conclusions provide important implications for governments and enterprises in making scientific decisions.

2. Research object and research method

To understand the current research status of human coronavirus technology patents, we classify these patents according to the three categories of detection, preventive vaccines, and treatment. Then we use patent analysis and data mining methods to systematically analyze technology development trends and technology field distributions, determine the latest development trends in key technologies, and analyze patent layout and competition characteristics of major institutions.

We adopt a total fraction search strategy for our research. We select relevant keywords and construct a general search strategy for human coronavirus technology patents, and then use a search method combining keywords and the International Patent Classification (IPC) system to obtain patent data for detection, preventive vaccines, and treatment.

After obtaining the search results, we excluded irrelevant patents based on manual reading, and the patents closely related to the search topics were manually data cited. The patent search date was September 15, 2021. A total of 3864 patents (patent families) were finally obtained, including 1220 patents for coronavirus detection technology, 583 patents for vaccine technology, and 1513 patents for treatment technology. Because there is a certain time delay from patent application to disclosure and then to database inclusion, the data in this paper for the past two years, 2020 and 2021, is smaller than the actual data and for reference only.

3. Main research results

3.1. Development trend of coronavirus patent technology

3.1.1. Development trend

The number of coronavirus technology patent applications (based on priority patents) shows an overall growth trend, is event-driven, and is related to the severity and scale of the epidemic, as shown in Fig. 1. In 1983, the California Institute of Technology (Caltech) applied for the first coronavirus technology patent, proposing the use of ganglion blockers containing tetraethylammonium ions to prevent or treat diseases caused by viruses such as coronavirus. The development of coronavirus technology patents can be divided into four stages. We refer to the first stage, 1983–2002, as the embryonic stage. During this stage, the number of annual patent applications was less than 10 up to 1997; there was a period of moderate growth from 1997 to 2002, but the number of applications remained below 50 during this embryonic stage. The second stage (2003–2012) is the growth period driven by the 2003 SARS epidemic. In 2003, the number of patents increased by 379, but the end of the epidemic, patent applications fell. The third stage (2012 to 2019) is a slow development period driven by the MERS epidemic (2012–2013). Although

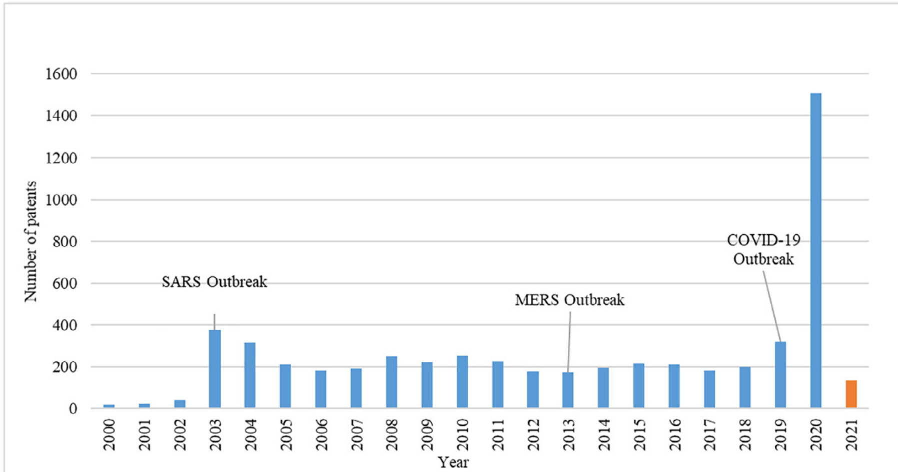

Fig. 1. Trends in the development of coronavirus technology patents.

MERS-related patents developed rapidly during this period, SARS-related patents showed a downward trend. The fourth stage (2019 to present) is the COVID-19 driven explosive growth period for patents. In 2020, 1508 patent applications were submitted, of which 963 were related to SARS-CoV-2. Patents related to SARS, MERS, 229E, OC43, NL63, and HKU1 also increased.

Since 2000, inventors of coronavirus-related technologies have been characterized by event-driven growth, with weak growth sustainability, as shown in Fig. 2. In 2003, the number of inventors increased explosively, with a large number of new inventors joining this R&D field. However, from 2003 to 2018, the overall number of inventors showed a downward trend. The number of new emerging inventors decreased, reflecting a decline in the attractiveness of this technical field. After 2019, there was explosive growth among both existing and emerging inventors.

3.1.2. Development trends for detection, preventive vaccine, and treatment technologies

The number of applications for detection, vaccine, and treatment technology patents is consistent with the overall development trend of coronavirus technology patents, which is event-driven. Treatment technology patents focus on R&D, and the number of patents is significant. Since 2003, the number of these patents has fluctuated at around 100 applications per year. In 2020, there was an explosive growth. Compared with other technical patents, annual numbers of treatment technology patents have greater flexibility in terms of responding to events. In 2003, driven by the SARS epidemic, the number of patents for detection technology exceeded that of treatment technology patents. After 2005, the number of detection technology patents decreased rapidly, and the number of treatment technology patents continued to fluctuate at around 100 patents per year. In 2020, the number of patents for treatment technology again exceeded the number of patents for detection technology. The number of vaccine technology patents has remained below 60 for a long period. There was explosive growth in 2020, but the growth rate remained lower than that of other technology patents (Fig. 3).

3.2. Analysis of coronavirus technology patents in major countries

3.2.1. The number of patent applications

Based on the number of priority patents, the top five countries in 2021 are China (1654), the United States (1294), South Korea (334), Canada (306), and Japan (220). The United States and China account for 74.12% of all priority patents. Both countries play a central role in R&D related to coronavirus technology patents. The United States applied for coronavirus technology patents as early as the 1980s, researched detection and prevention technolo-

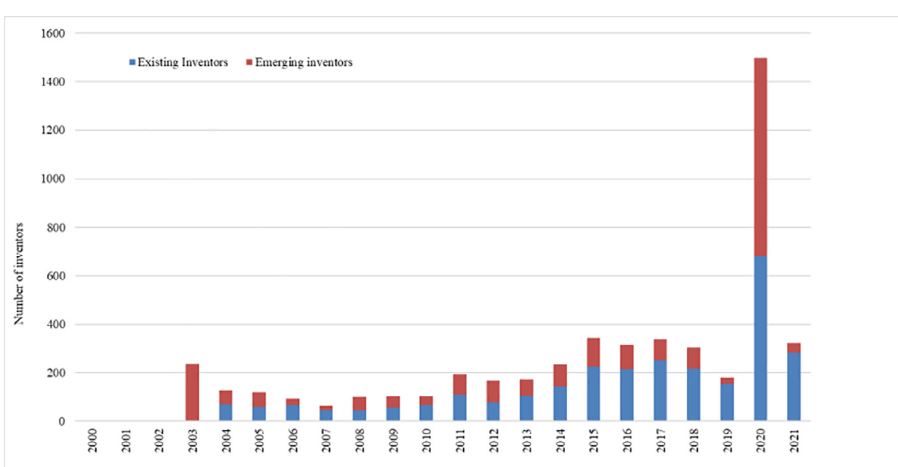

Fig. 2. Trends in the development of coronavirus technology patent inventors.

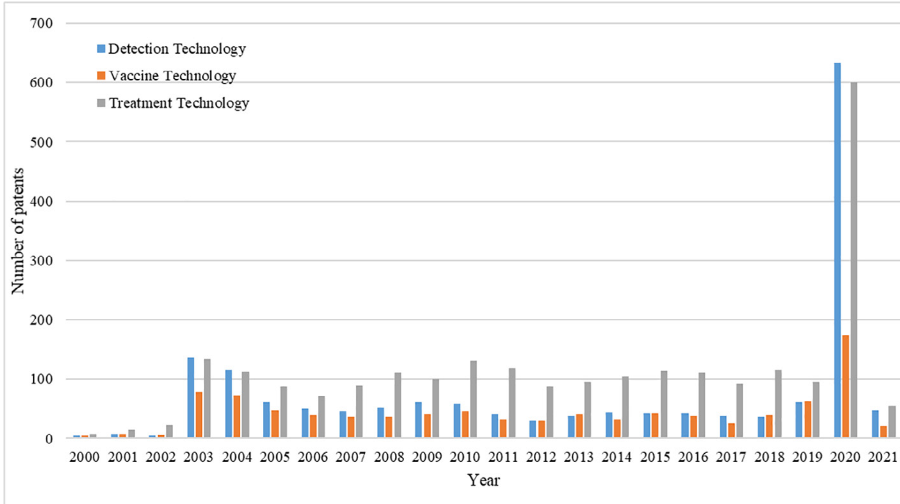

Fig. 3. Trends in detection, vaccine, and treatment technology patents for coronavirus.

gies, and began to pay attention to treatment technologies after 2003. For decades, the United States was leading the world in terms of number of the patents. The development of patents and changes in patents in the United States are consistent with the global trend because the US is a vital driving force promoting relevant technologies worldwide. China began applying for more patents from 2003, when it was affected by the SARS epidemic. Between 2004 and 2012, the number of patents from China remained around 30. From 2013, China was affected by the MERS epidemic and there was an increase in patents related to MERS and SARS. In 2020, COVID-19 influenced China's patent applications, which rose to 1094. The number of patent applications in South Korea, Canada, and Japan was also significant. In South Korea, there was an increase in patents from 2001 to 2010, followed by a downward trend. In Japan, the SARS epidemic drove more patent applications in 2003 and 2004, but growth then gradually slowed (Fig. 4).

3.2.2. Distribution of patented technologies

Compared with other countries, China has more patents relating to testing and treatment technologies, number of such patents reaching 787 and 715, respectively. China has fewer patents in vaccine technology (187), less than the number in the United States. The United States has 463 patents in detection technology, 313 in treatment technology, and 241 patents in vaccine technology. Considering all three types of coronavirus technology patents, China and the United States have considerable patent reserves in detection, vaccine, and treatment, much higher than the reserves of other countries.

3.3. Analysis of key patents

Coronavirus detection, prevention, and treatment technologies are the main links in the coronavirus technology chain. In this subsection, we analyze critical patents relevant to these technologies (Fig. 5).

3.3.1. Critical patents for coronavirus detection technology

Table 1 presents an analysis of coronavirus detection technology patents based on the internationally recognized IPC method of classifying disciplines, technologies, and patents, the technical characteristics of coronavirus, the technical fields, patent numbers, and hot spots (i.e. proportion of applications in the last 3 years). The lar-

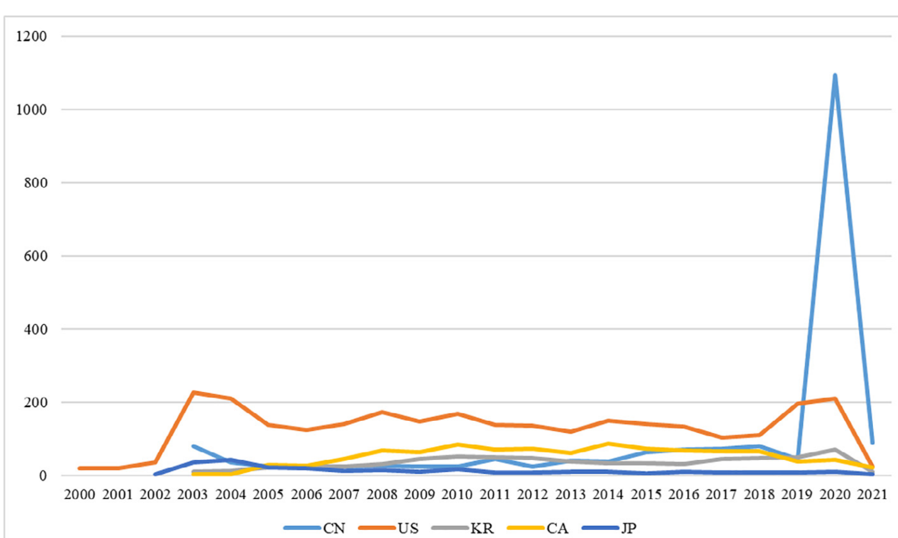

Fig. 4. Developments in the number of patent applications in major countries, 2000–2021.

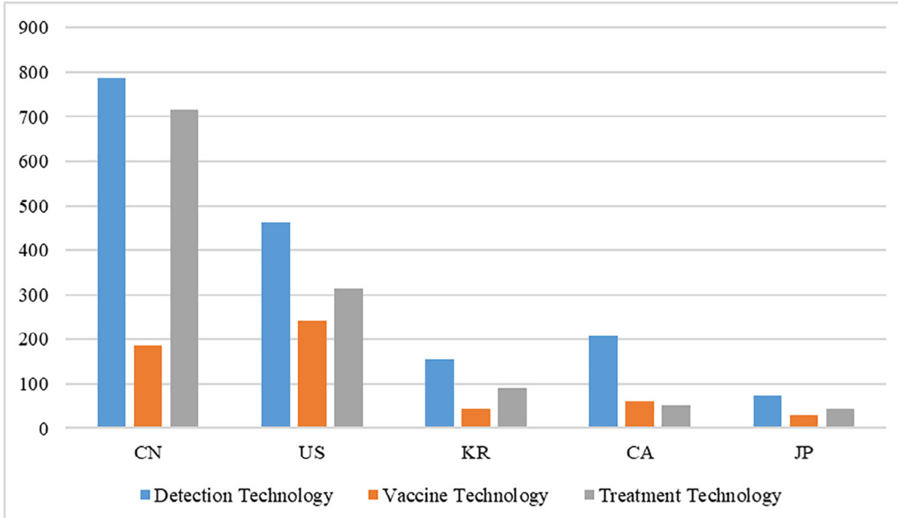

Fig. 5. Distribution of patent technologies in major countries.

Table 1
Analysis of coronavirus detection technology.

No.	Technical field	IPC classification number	The number of patents	The Time span	Proportion of applications in last 3 years (hot spots)
1	Immunoassays for microorganisms	G01N-033/569	490	1986–2021	75%
2	Virus or phage assays or testing methods	C12Q-001/70	479	1992–2021	58%
3	Formation of DNA or RNA fragments and their modifications	C12N-015/11	233	1992–2021	75%
4	Nucleic acid assay or test method	C12Q-001/68	216	1992–2021	6%
5	Resistance substances from RNA viruses	C07K-016/10	174	1992–2021	60%
6	Biological substances involving proteins, peptides or amino acids	G01N-033/68	174	1991–2021	70%
7	Antiviral agents for RNA viruses	A61P-031/14	173	1992–2021	58%
8	Immobilization of immunochemical with insoluble carriers	G01N-033/543	153	2000–2021	80%
9	Animal viruses	C12R-001/93	137	2003–2021	88%
10	Immunoassays using diffusion or migration of antigens or antibodies	G01N-033/558	128	2004–2021	95%

gest numbers of coronavirus detection technology patents based on IPC categories involve immunoassay for microorganisms, virus or phage determination or inspection methods, formation of DNA or RNA fragments and their modification, and nucleic acid determination or inspection methods. Immunoassay for microorganisms accounts for the largest number of patents (490), followed by virus or phage determination or inspection methods (479), both of which are much higher than the patent numbers in other technical fields.

Turning to technical hotspots, a number of technical fields have accounted for 70% or more patent applications over the last 3 years, namely immunoassay using the diffusion or migration of antigens or antibodies (95%); animal viruses (88%); immobilization of immunochemicals with insoluble carriers (80%), immunoassay for microorganisms (75%), formation of DNA or RNA fragments and their modifications (75%), and biological substances involving proteins, peptides or amino acids, and other technologies (70%). This indicates that these technical fields have developed relatively rapidly. Technologies such as resistant substances from RNA viruses and antiviral agents for RNA viruses have developed rapidly (60% of patent applications), while nucleic acid determination or testing methods (6%) have developed slowly.

The main patentees of coronavirus detection technology are shown in Table 2 for all institutions with eight or more patents. US institutions have carried out detection technology R&D from as early as the 1990s. Chinese institutions began carrying out relevant patent applications from 2003, and their patent applications have developed rapidly in recent years. At present, 8 of the top 10 patentees are Chinese institutions. Relevant technologies have achieved full coverage, including ChongQing Medical University, Tsinghua University, Fudan University, and other universities, as well as scientific research institutions, including the Academy of Military Medical Sciences, the Chinese Center for Disease Control and Prevention, the Chinese Academy of Inspection and Quarantine, the Bioscience TianJin diagnostic company, and the JiangSu Jicui medical immunology technology research company. Examining the ratio of patents applied for in the past 3 years (2019–2021) to the total number of patents by institutions, we find that five institutions — ChongQing Medical University, the Bioscience TianJin Diagnostic Company, the JiangSu Jicui Medical Immunology Technology Research Company, the Academy of Military Medical Sciences, and the Chinese Center for Disease Control and Prevention — all have shares of 69% or above, indicating that these institutions have been active in R&D in recent years. The US Department of Health and Human Services, Tsinghua University, and the Pasteur Institute have applied for few patents in this field in the last 3 years.

In terms of coronavirus detection technology, ChongQing Medical University has 17 relevant patents, ranking it first among all the patentee institutions in this field. The technology mainly focuses on the complementary determination region, antigen

Table 2
Analysis of major patentees of coronavirus detection technology.

No.	Institution	Country	The number of patents	The time span	The patent ratio for the last three years
1	ChongQing Medical University	China	17	2020–2020	100%
2	United States Department of Health and Human Services	America	16	1992–2019	6%
3	Academy of Military Medical Sciences	China	14	2003–2020	86%
4	Chinese Center for Disease Control and Prevention	China	13	2011–2020	69%
5	Bioscience TianJin diagnostic company	China	10	2020–2020	100%
6	Chinese Academy of Inspection and Quarantine	China	9	2009–2020	44%
7	Tsinghua University	China	9	2003–2020	22%
8	Pasteur Institute	France	8	2003–2020	25%
9	JiangSu jicui medical immunology technology research company	China	8	2020–2020	100%
10	Fudan University	China	8	2003–2020	38%

labeling, and colloidal gold test paper. In terms of the complementary determination region, the technology includes coronavirus RBD specific monoclonal antibody and new coronavirus receptor-binding domain-specific monoclonal antibodies, which are used to prepare reagents and drugs for detecting or diagnosing SARS-CoV-2. In terms of antigen labeling, the technology includes the coronavirus IgM magnetic particle chemiluminescence immunoassay kit, the new coronavirus immunoglobulin G (IgG) antibody ELISA kit, and the new enzyme-labeled 2019-nCoV antigen. In terms of colloidal gold test paper, the technology includes a kit for detecting SARS-CoV-2 immunoglobulin IgM and IgG and colorimetric test paper.

The US Department of Health and Human Services has 16 patents, but only applied for one of these within the past 3 years. The technology mainly focuses on primers, probes, and amino-peptide coding. In terms of primers and probes, the technology includes an oligonucleotide array for detecting target nucleic acid, a SARS-CoV detection method in the sample, and a nucleic acid detection method in solution based on peptide nucleic acid and kit. In terms of encoding amino polypeptides, the technology includes the human immunoassay for diagnosis, prevention, or treatment of SARS infection, human monoclonal antibodies, respiratory syncytial virus, immunoassay, vaccine composition, and antibody-dependent virus enhancement activity detection.

The Academy of Military Medical Sciences has 14 patents, 12 of which it applied for in the past 3 years. The technology involves primers and probes, colloidal gold test paper, antigen labeling, and amino polypeptide coding. Regarding primers and probes, technologies include methods and kits for detecting respiratory pathogens and 29 respiratory pathogens using TaqMan low-density microfluidic chip technology. In terms of colloidal gold test paper, the technology includes fluorescent immunochromatographic test paper for detecting new coronavirus antibodies and silicon core silver shell composite nano labels labeled by double-layer Raman molecules for immunochromatography. In regard to antigen labeling, the technology includes checking the infectious gene MBL and MBL related to SARS-CoV infection and the polypeptide chip for detecting SARS-CoV-2 by antibody marker molecules.

The Chinese Center for Disease Control and Prevention has 13 patents, 9 of which it applied for in the past 3 years. The techniques mainly focus on primers, probes, and the complementary determination region. In terms of primers and probes, the technology includes a haploid PCR system for simultaneous detection of 16 respiratory virus infections, a quadruple fluorescence quantitative detection kit for simultaneous detection of four human coronaviruses, and a specific primer-probe group for detection of SARS-CoV-2. In terms of the complementary determination region, the technology includes human anti-coronavirus neutralizing antibodies, which can be used to prepare coronavirus detection reagents or kits.

Bioscience TianJin diagnostic company has 10 patents, seven of which were developed in cooperation with ChongQing Medical University. The technology mainly focuses on antigen labeling, including coronavirus IgM antibody chemiluminescence detection kit, coronavirus IgM magnetic particle chemiluminescence immunodetection kit, coronavirus IgM-IgA-IgG antibody colloidal gold detection kits, new enzyme-labeled 2019-nCoV antigens, and useful synthetic peptide components in immunodetection reagents.

3.3.2. Patent analysis of vaccine technology

Vaccine technology patents mainly involve coronavirus antigens, antiviral agents for RNA viruses, pharmaceutical preparations containing antigens or antibodies, antiviral agents, and viral antigens, as shown in Table 3. Among the vaccine technology patents, coronavirus antigens account the largest number of patents (218), followed by antiviral agents used in RNA viruses (138).

Analysis of the technical hot spots, i.e., the proportion of patent applications made in the last 3 years, indicates that patent applications with shares over 50% occur in the technical fields of antiviral agents for RNA viruses (59%) and coronaviridae antigens, genes encoding viral proteins from coronaviridae (56%), demonstrating relatively rapid recent development. In contrast, technologies such as antiviral agents have developed much more slowly.

The main patentees of coronavirus vaccine technology are shown in Table 4, which indicates that China, the United States, and France are the main patent applicants in this area. We exclude patentees with less than six patents from the list. The University of Texas developed the first coronavirus vaccine technology in 1986, with other major institutions turning their attention to this field from 2003. American patentees are mainly universities and scientific research institutions, including the US Department of Health and Human Services and the University of Texas. Chinese patentees are also mainly universities and scientific research institutions, and include the China Center for Disease Control and Prevention, the Chinese People's Liberation Army (PLA) Academy of Military Medicine Sciences, and the University of Hong Kong. French patentees are mainly scientific research institutions and enterprises, including the Pasteur Institute and OSE Immunotherapeutics. In terms of the ratio of patents applications in the past 3 years (2019–2021), both the PLA Academy of Military Medicine Sciences and OSE Immunotherapeutics have shares of more than 83%, indicating very active R&D in recent years. The Chinese Center for Disease Control and Prevention, the Pasteur Institute, the University of Texas and the University of Hong Kong have applied for few patents in this field in the last 3 years.

Turning to vaccine technology, the US Department of Health and Human Services has 11 patents in this field, ranking it first among the patentees. The technology is mainly focused on the encoding of amino polypeptides, including new spike peptides for the diagnosis, prevention, or treatment of SARS infection, recombinant SARS coronavirus spike proteins, human neutralizing monoclonal antibodies, vaccine compositions comprising polynucleotides encoding the extracellular structure of SARS coronavirus

Table 3
Analysis of coronavirus vaccines technology.

No.	Technical field	IPC classification number	The number of patents	The Time span	Proportion of applications in last 3 years (hot spots)
1	Antigens for coronaviridae	A61K-039/215	218	1986–2021	56%
2	Antiviral agents for RNA viruses	A61P-031/14	210	1992–2021	59%
3	Medicinal preparations containing antigens or antibodies	A61K-039/00	138	1992–2021	28%
4	Antivirals	A61P-031/12	108	1992–2021	14%
5	Viral antigens	A61K-039/12	106	1989–2021	25%
6	Peptides from the coronavirus	C07K-014/165	95	1992–2021	41%
7	Medicinal preparations characterized by immune stimulation additives	A61K-039/39	73	1999–2021	34%
8	Viruses and their compositions	C12N-007/00	71	1986–2021	38%
9	Immunoassay for microorganisms	G01N-033/569	71	1986–2021	44%

Table 4
Analysis of major patentees of coronavirus vaccines technology.

No.	Institution	Country	The number of patents	The time span	The patent ratio for the last three years
1	U.S. Department of Health and Human Services	The United States	11	2003–2019	27%
2	Chinese Center for Disease Control and Prevention	China	9	2006–2016	0%
3	PLA Academy of Military Medical Sciences	China	8	2003–2021	88%
4	University of Hong Kong	China	8	2003–2020	12%
5	Pasteur Institute	France	7	2003–2007	0%
6	Novartis AG	Switzerland	7	2003–2019	29%
7	OSE Immunotherapeutics, Inc	France	6	2018–2021	83%
8	University of Texas	The United States	6	1986–2014	0%

spike proteins, methods for the preparation of immune compositions, methods for inducing pathogen-specific immunity, treatment, or prevention of pathogen infection, nucleic acids for antiviral polypeptides or encoded antiviral peptides, and recombinant rabies virus vectors.

The China Center for Disease Control and Prevention has nine patents. The technology mainly focuses on the coding of amino peptides. Most of the patents relate to MERS vaccines, including recombinant proteins for preventing and treating MERS-CoV infection, a recombinant adenovirus type 41 vector vaccine, specific peptides, a synthetic peptide vaccine, a recombinant adenovirus type 5 vector vaccine, and fully humanized anti-MERS neutralizing antibody, the HCoV-NL63 strain for preparing vaccine anti-HCoV infection.

The Chinese PLA Academy of Military Medicine Sciences has eight patents, seven of which it has applied for in the past 3 years. The technology includes novel coronavirus-specific T cells and antibodies, new polynucleotides encoding 2019 new coronavirus S proteins, strains for preparing SARS-CoV-2 virus vaccines, antibodies and vaccines for prevention, diagnosis and treatment of SARS, and new peptides with S protein, N protein or orf1ab protein's amino acid sequence, and recombinant spindle vector pFBD-severe acute respiratory syndrome coronavirus 2-SM1 for preparation of vaccine.

The University of Hong Kong has eight patents, mainly in the areas of encoding and accounting molecules, including a hSARS vaccine that can be used for vaccines, nucleic acid comprising the sequence of replication enzyme genes, tip genes or nucleocapsid genes containing encoded coronavirus -HKU1, RNA interference molecules that inhibit SARS virus infection, and nucleic acid molecules encoding SARS associated coronavirus, transgenic plants, and vectors that help to immunize SARS.

The Pasteur Institute has seven patents, mainly in SARS vaccines, including isolation and purification strains concerning SARS, model systems, purified nucleic acid molecules comprising Spike-Pasteur-modif or Spike-HKU-PRC, a vaccine composition comprising SARS-CoV S (spike) polypeptide and adjuvant.

Novartis AG has seven patents, mainly in the area of squalene composition, which can be used as adjuvant or vaccine to increase the immune response of patients. The technology includes preparation of squalene, preparation of submicron oil in water emulsion, preparation of water containing oil containing squalene, and separation of peptides.

3.3.3. Analysis of patents on antiviral treatment technology

Patents for antiviral therapy technology mainly relate to antiviral agents for RNA viruses, antiviral agents, drugs for respiratory diseases, antiviral agents for influenza or rhinoviruses, as shown in Table 5. Among the antiviral treatment technology patents, the number of patents is highest for antiviral agents for RNA viruses, accounting for 1077 patents, which is much higher than the patent numbers in other technical areas. In addition, there were 665 antiviral agents and 445 drugs for respiratory diseases.

Turning to the technical hot spots, the proportion of patents applications in the last 3 years for coronaviridae antigens (60%) and antiviral agents for RNA viruses and other technologies (59%) exceed 50% of the total patents in these technical fields, which demonstrates rapid development in these areas. Conversely, anti-infective drugs, special purpose drugs, and anti-bacterial drugs have developed slowly.

The main patentees of antiviral therapy technology are shown in Table 6. These institutions have at least 13 patents, and are mainly from China, the United States, and other countries. American patentees are mainly enterprises and scientific research institutions, including the Kineta Corporation, the US Department of Health and Human Services and the Gilead Science. Chinese patentees are mainly universities and scientific research institutions, including the PLA Academy of Military Medical Sciences, Shengpu Life Technology Corporation, the China Center for Disease Control and Prevention, Fudan University, Sun Yat-sen University, and Tsinghua University. Considering the organizations' ratios of patent applications to total patents in the last 3 years (2019–2021), Shengpu Life Technology Corporation, the PLA Academy of Military Medical Sciences, and Sun Yat-sen University have ratios over 75%, indicating active R&D in the last 3 years. Gilead Science has also been active in R&D. Conversely, Kineta, the US Department of Health and Human Services, and the Korean Institute of Bioscience and Technology have applied for fewer patents in this field in the last 3 years.

Table 5
Analysis of coronavirus treatment technology.

No.	Technical field	IPC classification number	The number of patents	The Time span	Proportion of applications in last 3 years (hot spots)
1	Antiviral agents for RNA viruses	A61P-031/14	1077	1992–2021	59%
2	Antiviral agents	A61P-031/12	665	1990–2021	20%
3	Drugs for respiratory diseases	A61P-011/00	445	1999–2021	43%
4	Antiviral agents for influenza or rhinoviruses	A61P-031/16	382	1991–2021	30%
5	Antiviral agents for HIV	A61P-031/18	255	1991–2021	22%
6	Anti-bacterial drugs	A61P-031/04	243	1991–2021	19%
7	Anti-tumor drugs	A61P-035/00	216	1999–2021	20%
8	Coronavirus antigen	A61K-039/215	215	1992–2021	60%
9	Anti-infective drugs	A61P-031/00	195	1990–2021	15%
10	Drugs for special purposes	A61P-043/00	180	1997–2021	18%

Table 6
Analysis of major patentees of coronavirus treatment technology.

No.	Institution	Country	The number of patents	The time span	The patent ratio for the last three years
1	The Academy of Military Medicine sciences of Chinese PLA	China	43	2003–2021	79%
2	Shengpu Life Technology Co., Ltd	China	19	2020–2020	100%
3	Chinese Center for Disease Control and Prevention	China	18	2013–2020	28%
4	Kineta Corporation	United States	16	2003–2020	6%
5	Fudan University	China	16	2004–2021	41%
6	Sun Yat-sen University	China	16	2003–2020	75%
7	U.S. Department of Health and Human Services	United States	15	2004–2019	7%
8	Pasteur Institute	France	14	2003–2020	36%
9	Korea Institute of Biological Sciences and Technology	Korea	13	2003–2020	8%
10	Tsinghua University	China	13	2007–2020	15%
11	Gilead Sciences, Inc	United States	13	2009–2021	54%

In terms of antiviral treatment, the PLA Academy of Military Medical Sciences has 43 patents, ranking it first among patentees in this field. The technology mainly focuses on drug therapy, amino-peptide coding, and pulmonary fibrosis treatment. In drug therapy, techniques involve the application of drugs in the treatment or suppression of coronaviruses, including recombinant human interferon omega, estrogen-related receptors α, Abl tyrosine kinase inhibitors, sodium valproate, substances that inhibit the downstream complement activation of mannan lectin serine protease (masp-2), and nephrine and heparin. In the coding of amino peptides, the main technologies are the preparation of peptides, including new polyglycol PEG modified thymosin α-1 compounds and their PEG modifiers, nano anti-MRBD proteins, peptide compounds for MERS-CoV infection, and peptides encoded in sequences containing 20 amino acids. In the treatment of pulmonary fibrosis, the technology includes the application of the substituted amino acid ester compounds, the 6-fluoro-3-hydroxy pyrazine-2-formamide, hydroxychloroquine, chloroquine, the 2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluorene compounds, the 1-((1R, 2R)-2-(2,6-dihydroxy-4-pentylphenyl)-4-methylcyclohex-3-ene-1-yl) ethane-1-one in the treatment of SARS-CoV-2 infection. In addition, it includes 4-oxo-4,5-dihydrothiazole derivatives, glucosamine derivatives, and 2,4,5-trisubstituted-1,2,4-triazolone compounds for the preparation of antiviral drugs.

Shengpu Life Technologies corporation has 19 patents, all of which it applied for in 2020. The techniques focus on the preparation of broad-spectrum anti-coronavirus drugs, by the no-eating acid and its derivatives or structural analogues, the sialic acid, the (2R, 3R, 4S, 5R)-3,4-dihydroxy-6-((3,4,5-trihydroxybenzene)) methyl)Teetrohydro-2H-Birch-2,5-Di-bistro(3,4,5-Trihydroxy benzoate)), the 1,2,3,4,6-O-E-glucose, the 1,2,6-O-III-furan-beta-D-glucose, the 1,2,3,6-Four-O-Ganluki-beta-D-glucose, the 1,3,4-O-Triene propylene-6-O-caffeoyl-β-D-glucose, the 1,3,6-three-O-3,4, 5-trihydroxybenzene-β-D-glucose, and the 1,3-O-Application of double salicylic acid-6-O-(S)-Rukol-beta-D-glucose.

The China Center for Disease Control and Prevention has 18 patents, and the technology focuses on such areas as amino-peptide coding, complementary decision areas, and broad-spectrum anti-coronavirus drugs. In the area of amino-peptide coding, technologies include synthetic peptide vaccines, recombinant adenovirus vector vaccines, recombinant proteins, MERS-CoV virus S proteins optimized code, and MERS-CoV-specific peptides. Those substances are used to preparate the drugs for preventing or treating MERS-CoV infection. In complementary decision-making areas, techniques include human-derived, genetically engineered anti-SARS coronavirus antibodies, anti-MERS neutralizing antibodies, and human-derived anti-new coronavirus neutralizing antibodies nCoV-163, nCoV-61, nCoV-121, those substances used to preparate the drugs for preventing or treating new coronavirus infections. In the aspect of broad-spectrum anti-coronavirus drugs, the relevant technology is mainly the preparation of drugs by phenanthroline, tomatidine and its derivatives, mycophenolic acid, mycophenolate acid moffitt, emetine, and paroxetine hydrochloride.

The Kineta company has 16 patents, and the technology focuses on pharmaceutical compounds for treatment of viral infections, including fusion bicyclic compounds, hybrid double-ring compounds, diphenyl compounds, pyridine compounds, heterocyclic compounds, dihydrochalcone compounds, dithiazole-2-amide compounds, and naphthalene-2-carboxylic acid benzothiazole-2-yl amide compounds, and benzothiazole derivatives.

Fudan University has 16 patents, mainly focusing on amino-peptide coding and drug treatment. In regard to the encoding amino polypeptides, the technology includes preparation of the human-derived antibody IgG Fab, part of the anti-SARS virus agent, the new peptide inhibition of HCoV-EMC 2012, ethylene glycol interferon recombinant fusion protein, a peptide suppressing human coronavirus infection, and a new fusion protein of double specific immunotherapy. In regard to drug treatment, the technology includes the preparation of antiviral drugs by luteolin, the preparation of anti-complement drugs by aryl substituted phenylpropionic acid compounds, Griffith and the preparation of anti-SARS-CoV-2 drugs by PS liposome CSA (surfactant biomimetic liposome cyclosporine A).

Sun Yat-sen University has 16 patents, mainly focusing on drug therapy and gene expression and recombination. Drug treatment techniques include preparating drugs for prevention or treatment of SARS-CoV-2 by teicoplanin, preparation of drugs for treating MERS using teicoplanin, tofinac acid, ascorbate palmitate, and Candesartan Celebrex or its salt, pirfenidone, DNA topological isomerase inhibitors, and Homomorphic halogen, (1,2,4) triazole (4,3-b) pyridazine derivatives. Gene expression and recombination techniques include the preparation of a SARS DNA vaccine using the spiked genes of coronaviruses, the preparation of SARS virus vaccines using the replication defective adenovirus vectors of the S (Spike protein) gene, and a SARS-CoV-2 replicon structure for drug screening. In addition, the techniques include the preparation of new immune complexes for the treatment of coronary heart disease and pneumonia, and the use of chiral chloroquine, hydroxychloroquine, or their salts as 3CL hydrolase inhibitors for anti-coronavirus drug targets.

4. Summary and recommendations

Currently, the world is in a critical period of prevention and control of the novel coronavirus pandemic, and scientific R&D is urgent. Coronavirus detection, prevention, and treatment technologies are key tools in overcoming the pandemic. In this paper, we adopt patent analysis and data mining methods to determine the distribution characteristics and development rules of coronavirus technology patents. In addition, we study the patent layout and competition characteristics of major countries as a reference for epidemic prevention and control. Our recommendations for policymakers are as follows.

First, it is important that policymakers establish a long-term mechanism for R&D, strengthen the industry-academia-research synergy, and promote the high-quality and sustainable development of patent technology. Coronavirus research is event-driven, and most of the related scientific research work is passive. The output of high-quality patent results and the number of technology developers are significantly affected by the outbreak. Policymakers should set long-term research development goals, improve scientific evaluation and results transformation mechanisms, and promote the sustainable long-term development of technology research. As enterprises and scientific research units are joint technology developers, policymakers should use a combination of policy and market guidance to establish and encourage market-oriented, industry–university research synergies, actively build cooperative relationship ties, and focus on the combination of scientific research and clinical, prevention, and control practice.

Second, policymakers should attach importance to intellectual property protection and strengthen scientific and technological self-reliance. Although international institutions focus on patent protection on a global scale, most Chinese institutions only deploy patent protection in their own country. There is an urgent need to strengthen the awareness of global patent protection, rationally use domestic and international markets, and increase vigilance against foreign patent applications in China. Policymakers should strengthen self-reliance in science and technology and focus on the advantages of forming technical barriers to competition. For key and bottleneck technologies, policymakers should advance layout, through the introduction of talent and cooperative R&D efforts to develop independent technologies and achieve market dominance.

Third, it is important for policymakers to deepen international technical cooperation and jointly address human health challenges. There are many shortcomings that remain in the prevention and control of major infectious diseases in the international community. It is urgent to strengthen international cooperation in scientific research and combat epidemics with the support of science and technology, accelerate joint research on virus detection, prevention, and treatment technologies, and develop and enhance global epidemic monitoring and early warning systems, epidemic prevention, and medical treatment. At the same time, developing countries with weak public health systems should be assisted to improve their response capacity to strengthen the efficiency of prevention and control measures for global epidemics, and promote the development of a cooperative global community with a shared future.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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References

1. Hancu A, Mihaltan F. Possible nutritional interventions in COVID 19 MAEDICA. *J Clin Med*. 2020;15(2):246–249.
2. Enjuanes L, Almazán F, Sola I, Zuñiga S. Biochemical aspects of coronavirus replication and virus-host interaction. *Annu Rev Microbiol*. 2006;60(1):211–230.
3. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. *Nat Rev Microbiol*. 2009;7(6):439–450.
4. Net land Lai M. Coronavirus: organization, replication and expression of genome. *Annu Rev Microbiol*. 1990;44(1):303–333.
5. Zhu XL, Huang C, Net land Ma L, et al. Research Advances of Novel Coronavirus Disease (COVID-19). *China Biotechnology*. 2020;40(Z1):38–50.
6. Hui DS, Memish ZA, Zumla A. Severe acute respiratory syndrome vs. the Middle East respiratory syndrome. *Curr Opin Pulmon Med*. 2014;20(3):233–241.
7. Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health — The latest 2019 novel coronavirus outbreak in Wuhan, China - ScienceDirect. *Int J Infect Dis*. 2020;91:264–266.
8. Gaunt ER, Hardie A, Claas ECJ, Simmonds P, Templeton KE. Epidemiology and Clinical Presentations of the Four Human Coronaviruses 229E, HKU1, NL63, and OC43 Detected over 3 Years Using a Novel Multiplex Real-Time PCR Method. *J Clin Microbiol*. 2010;48(8):2940–2947.
9. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China (Life Sciences)*. 2020;63(3):457–460.
10. Huang Z, Tian D, Liu Y, et al. Ultra-sensitive and high-throughput CRISPR-powered COVID-19 diagnosis. *Biosens Bioelectron*. 2020;164:112316. https://doi.org/10.1016/j.bios.2020.112316.
11. Powewd Wang J, Zhao P, Wu L, et al. Advances in laboratory diagnostic techniques for coronavirus disease 2019. Chinese. *J Infection Control*. 2020;19(05):481–486.
12. Li H, Pan J, Su Y, Wang B, Ge J. SARS-CoV-2 IgM/lgG antibody detection confirms the infection after three negative nucleic acid detection. *J Cell Mol Med*. 2020;24(14):8262–8265.
13. Zhang XB, Pan WY, Leggy Chen L. The Progress of Diagnosis Methods for SARS-CoV-2 Infection. *Chin J Virol*. 2021;37(02):428–434.
14. Leggy Li D, Li Q. H.SARS-CoV-2: Vaccines in the pandemic era. *Military Med Res*. 2021;8(02):238–252.
15. Sharma O, Leggy Sultan A, Ding H, et al. A review of the progress and challenges of developing a vaccine for COVID-19. *Front Immunol*. 2020;11 585354.
16. Zhang N, Li C, Hu Y, et al. Current development of COVID-19 diagnostics, vaccines and therapeutics. *Microbes Infect*. 2020;22(6-7):231–235.
17. Liu X, Liu C, Liu G, Luo W, Xia N. COVID-19: Progress in diagnostics, therapy and vaccination. *Theranostics*. 2020;10(17):7821–7835.
18. Wang J, Peng Y, Xu H, Cui Z, Williams RO. The COVID-19 vaccine race: challenges and opportunities in vaccine formulation. *AAPS PharmSciTech*. 2020;21(6):225.
19. Mullard A. COVID-19 vaccine development pipeline gears up. *The Lancet*. 2020;395(10239):1751–1752.

20. Baldo A, Leunda A, Willemarck N, Pauwels K. Environmental risk assessment of recombinant viral vector vaccines against SARS-Cov-2. *Vaccines*. 2021;9(5):453.
21. Zhu FC, Guan XH, Li YH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2020;396(10249):479–488.
22. Won JH, Lee H. The Current Status of Drug Repositioning and Vaccine Developments for the COVID-19 Pandemic. 2020, 21(24):9775.
23. Yang HY, Zhang MJ, Weng YH, et al. Nucleic acid-based vaccines of COVID-19 and their delivery systems. *Sci Sin (Vitae)*. 2021;51(07):804–818.
24. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends*. 2020;14(1):64–68.
25. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe covid-19. *N Engl J Med*. 2020;382(24):2327–2336.
26. Han LZ, Bian Y, Xiao HT, et al. Research progress on chloroquine against new coronavirus. *West China J Pharmaceut Sci*. 2021;36(02):222–227.
27. Luo D, Deng YQ, Qin CF. Current status of drug candidates against SARS-CoV-2. *Med J Chin People's Liberation Army*. 2021;46(06):628–633.
28. Zhao Y, Zhao M, Wei F, et al. Patent-based development of technology to detect coronaviruses. *Chin J Virol*. 2021;37(01):52–63.
29. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271–280.
30. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30–e31.
31. Ledford H. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. Nature, 2020, 582(7813): 469.
32. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094–1099.
33. Grant W, Lahore H, McDonnell S, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020;12(4):E988.