

COVID-19 vaccine research focusses on safety, efficacy, immunoinformatics, and vaccine production and delivery: a bibliometric analysis based on VOSviewer

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SUMMARY Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected tens of millions of people globally since it was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. There is an urgent need for safe and effective preventive vaccines to curb this pandemic. A growing amount of related research has been published. This study aimed to provide the current status of COVID-19 vaccine using bibliometric analysis. We searched Embase.com and MEDLINE comprehensively and included articles, articles in press, reviews, short surveys, conference abstracts and conference papers about COVID-19 vaccine. VOSviewer1.6.11 (Leiden University, Leiden, Netherlands) was applied to perform the bibliometric analysis of these papers. A total of 1,312 papers were finally included. The BMJ has been the most popular journal in this field. The United States maintained a top position worldwide and has provided a pivotal influence, followed by China, India and United Kingdom. Among all the institutions, Harvard University was regarded as a leader for research collaboration. We analyzed the keywords and identified seven COVID-19 vaccine research hotspot clusters. COVID-19 vaccine research hotspots focus on clinical trials on vaccine safety and efficacy, research on vaccine immunology and immunoinformatics, and vaccine hesitancy. Our analysis results demonstrated that cooperation between countries, institutions, and authors were insufficient. The results suggested that clinical trials on vaccine safety, efficacy, immunology, immunoinformatics, production and delivery are research hotspots. Furthermore, we can predict that there will be a lot of research focusing on vaccine adverse reactions.

Keywords COVID-19, vaccine, bibliometric analysis, VOSviewer

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected tens of millions of people globally since it was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (1). The clinical manifestations of COVID-19 usually include fever, dry cough and fatigue, often accompanied by lung infections (2). As of 28 February 2021, the number of confirmed cases has exceeded 110 million, with 2,512,272 reported deaths, indicating this pandemic's significant global impact (3). The high transmission rate of the COVID-19 has led to the current heavy burden on public health and the global economy, highlighting the need for a fast and effective method to prevent or treat deadly infections

(4). An effective treatment strategy is to reduce the symptoms of patients (4). Simultaneously, many therapeutic treatments such as antiviral drugs (nucleotide analogue) (5,6), antimalarial drugs (those inhibit viral cell entry and its replication) (7,8), immunomodulators (9), and cell and plasma-based therapy (10) have shown therapeutic effects. Despite the various treatment approaches, there are no potential drugs available to treat COVID-19. Some studies reported reinfection in patients who have been declared clinically recovered (11). Thus, there is an urgent need for safe and effective preventive vaccines to curb this pandemic. More and more research teams, and pharmaceutical companies are committed to vaccine research and development, which has led to numerous articles about vaccines published in a short time. However, the status of COVID-19 vaccine research

is still unclear.

Bibliometric analysis is a quantitative analysis combining mathematics and statistics, which focuses on the bibliometric characteristics of research in a particular field, and helps investigators grasp the development priorities and trends in the field and guides their follow-up work (12,13). Bibliometric methods have expanded the focus on topics, publications, countries, authors, institutions and journals in many research fields (14,15). Bibliometrics can assess the research reputation of a large number of units, because individual experts are not capable of handling so much information in a single evaluation procedure (16). To a certain degree, bibliometric analysis can systematically estimate the trend of future research hotspots (17). A large number of studies have applied bibliometric analyses to identify research trends in various fields (14). There are a few published studies about COVID-19 using bibliometric analysis to explore the activity and trends (18-20). However, no bibliometric study on recent scientific output and future research trends of COVID-19 vaccine was reported. In order to access the current status and provide a reference for later research of COVID-19 vaccines a bibliometric analysis was performed.

2. Methods

2.1. Data source and collection

We searched *Embase.com* and MEDLINE comprehensively and included articles, articles in press, reviews, short surveys, conference abstracts and conference papers about COVID-19 vaccines. To avoid bias caused by frequent database renewal, all the literature retrieval and data download were completed in a single day, February 18, 2021. There was no restriction on language and data category. The search terms were "coronavirus disease 2019", "severe acute respiratory syndrome coronavirus 2", "COVID-19", "2019-nCov", "SARS-CoV-2", "vaccine", "autovaccine". A detailed search strategy of *Embase.com* is presented in Supplementary Data 1 (<http://www.biosciencetrends.com/action/getSupplementalData.php?ID=71>).

2.2. Study selection

Two reviewers (YMC and LYC) independently extracted data including titles, countries, institutions, journals, authors and so on. Differences of opinion were settled by consensus or referral to a third review author (JHT).

2.3. Data analysis and visualization

We conducted a bibliometric analysis using VOSviewer 1.6.11 (Leiden University, Leiden, Netherlands), and constructed a map based on a co-occurrence matrix and identified clusters from the keywords network (21,22).

We standardized the data before performing analysis. To be specific, different expressions of the same keywords were standardized into Medical Subject Heading (MeSH) terms in order to avoid bias. The standardizations were carried out manually by the authors (23,24). The interpretation of a visualization map produced was based on three characteristics: size, distance, and colors (25). A node means a specific element, such as author, country, or keyword, and the size of the node shows the number of publications or frequency (24). The larger threshold means the more times it occurs, and the smaller threshold indicates the fewer occurrences. The link between the nodes means that they are connected, and the distance between two terms indicates the affinity and sparseness of the relationship. In other words, the smaller the line, the closer the relationship is, and vice versa. In terms of the cluster analysis of keywords, each color represents a cluster (25). In this study, the parameters of VOSviewer were as follows: counting method (fractional counting) and ignore documents with a large number of authors (maximum number of authors per document is 25). We regarded the Emtree Medical Index Terms (Major Focus) as keywords.

3. Results

3.1. Search results, journals, and date of publication

A total of 6,018 records were derived from *Embase.com* and MEDLINE. After two reviewers' independent screening, 1,312 papers were finally included, which were published in 576 journals. The number of journals that published more than five papers and only one study was 7.64% (44/576) and 70.14% (404/576). We have listed the top 20 journals, among them, the top five published journals were BMJ (64/1,312), Vaccines (Basel) (44/1,312), Vaccine (36/1,312), Human Vaccines and Immunotherapeutics (33/1,312), and New England Journal of Medicine (30/1,312) (Table 1). Publication dates of included articles are 2020 and 2021. Since 331 papers have no specific publication information, we only drew a histogram for the remaining 981 papers, as shown in Figure 1. Research on vaccines is increasing month by month, with the most in January 2021 (210/981). Limited by our search until February 18, so it does not mean that there are fewer studies in February and following months.

3.2. Institutions

More than two thousand institutions have paid attention to the research field of COVID-19 vaccine, most of them participated in only one study respectively. We listed the top 20 institutions in the ranking of publications (Table 2). The institutions with more than 20 publications were Harvard University (37 studies), University of Washington (36 studies), University of

Oxford (31 studies), Johns Hopkins University (26 studies), National Institutes of Health (26 studies), Stanford University (18 studies), University of North Carolina (18 studies), University of Toronto (17 studies), Emory University (16 studies), and University of Maryland (16 studies), which demonstrated that most of the contributions came from universities. Network map of institutions with frequency more than seven are shown in Figure 2, which contains 34 nodes and seven clusters. The largest cluster (#1) consisted of Harvard University, Stanford University, University of Florida, University of Kwazulu-Natal, University of Toronto, University of Washington, and University of Yalu,

while the second largest cluster (#2) mainly consisted of Baylor College of Medicine, Emory University, New York University, Massachusetts Institute of Technology, University of Maryland, University of North Carolina, and University of Texas. Most of these institutions are in the United States and work closely together. The third cluster (#3) was Chinese Academy of Sciences, Peking University, Fudan University, National Institute for Food and Drug Control, and National Institutes of Health, which are in China and the United States. The fourth cluster (#4) was Duke University, Icahn School of Medicine at Mount Sinai, University of California, University of Michigan and University of Pennsylvania. Among the remaining clusters (#5, #6, #7), each cluster contained three institutions, most of which are universities.

Table 1. Top 20 productive journals of papers on COVID-19 vaccine

Rank	Journal	Frequency
1	BMJ	64
2	Vaccines (Basel)	44
3	Vaccine	36
4	Human Vaccines & Immunotherapeutics	33
5	New England Journal of Medicine	30
6	Frontiers in Immunology	26
7	Nature	22
8	Science	21
9	JAMA	17
10	Annals of Internal Medicine	16
11	Cell	16
12	International Journal of Environmental Research and Public Health	13
13	Clinical Infectious Diseases	12
14	Journal of Biomolecular Structure and Dynamics	12
15	Journal of Medical Virology	12
16	Nature Communications	12
17	Expert Review of Vaccines	10
18	Scientific Reports	10
19	The Lancet	10
20	PLoS One	9

3.3. Countries

In total, 95 countries have engaged in relevant research on COVID-19 vaccine, of them, 28 countries published one study, and 67 countries participated in two studies at least. We presented the top 20 countries in the ranking in Table 3. The United States ranked first, with 424 publications, followed by China (149 publications), India (145 publications), United Kingdom (145 publications), and Canada (57 publications). Figure 3 contains 44 countries with a frequency more than five, which had a connection with others, and seven clusters. It can be said that the United States and China have close ties with other countries. The largest cluster (#1) contained Australia, Germany, Greece, Israel, Italy, Netherlands, Romania, Russian Federation, Spain, and Switzerland. The second largest cluster (#2) contained Bangladesh, China, India, Indonesia, Iran, Japan, Nepal, South Korea, Sudan, and Turkey. The third largest cluster (#3)

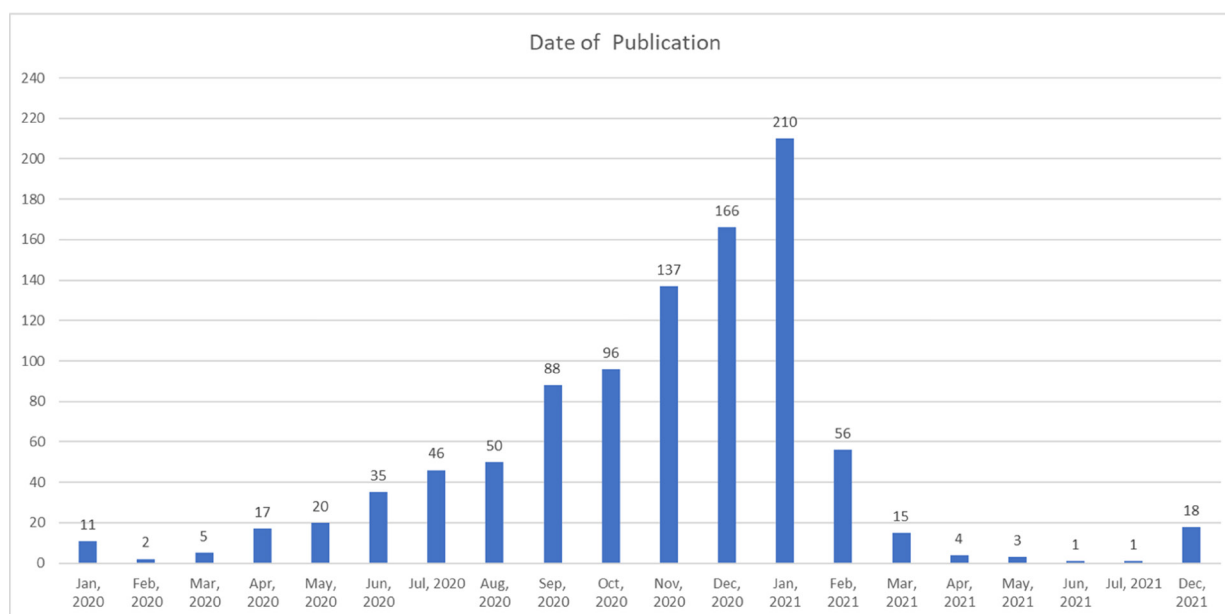


Figure 1. Date of publication of COVID-19 vaccine research.

Table 2. TOP 20 productive institutions of papers on COVID-19 vaccine

Rank	Institution	Frequency
1	Harvard University	37
2	University of Washington	36
3	University of Oxford	31
4	Johns Hopkins University	26
5	National Institutes of Health	26
6	Stanford University	18
7	University of North Carolina	18
8	University of Toronto	17
9	Emory University	16
10	University of Maryland	16
11	Yale University	16
12	Baylor College of Medicine	15
13	Imperial College London	15
14	University of California	15
15	University of Pennsylvania	14
16	Chinese Academy of Sciences	13
17	Icahn School of Medicine at Mount Sinai	13
18	Peking University	12
19	University of Florida	12
20	University of Texas	12

Table 3. Top 20 countries of papers on COVID-19 vaccine

Rank	Country	Frequency
1	United States	424
2	China	149
3	India	145
4	United Kingdom	145
5	Canada	57
6	Germany	56
7	Australia	52
8	Italy	52
9	Spain	38
10	France	36
11	Switzerland	32
12	Iran	31
13	Saudi Arabia	28
14	South Korea	25
15	Netherlands	24
16	Russian Federation	19
17	Brazil	18
18	Israel	18
19	South Africa	18
20	Pakistan	17

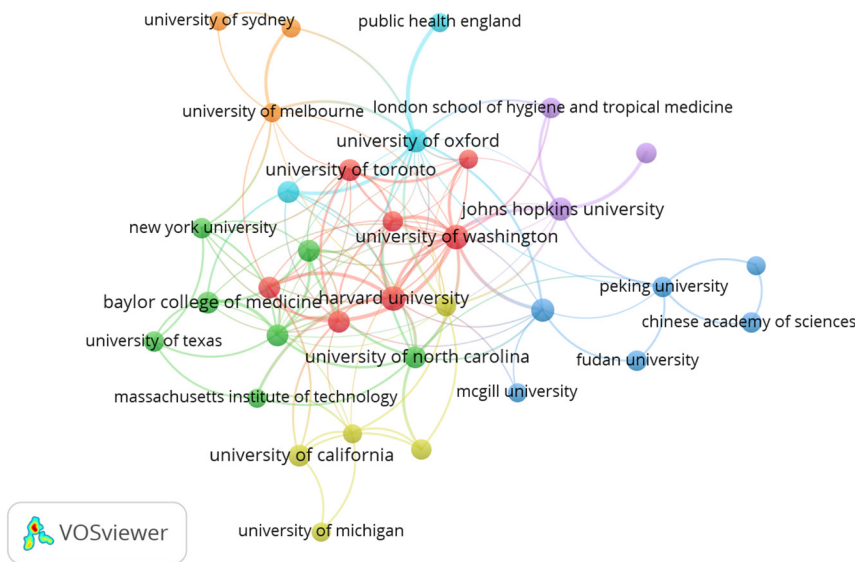


Figure 2. Network map of 19 institutions with frequency more than four.

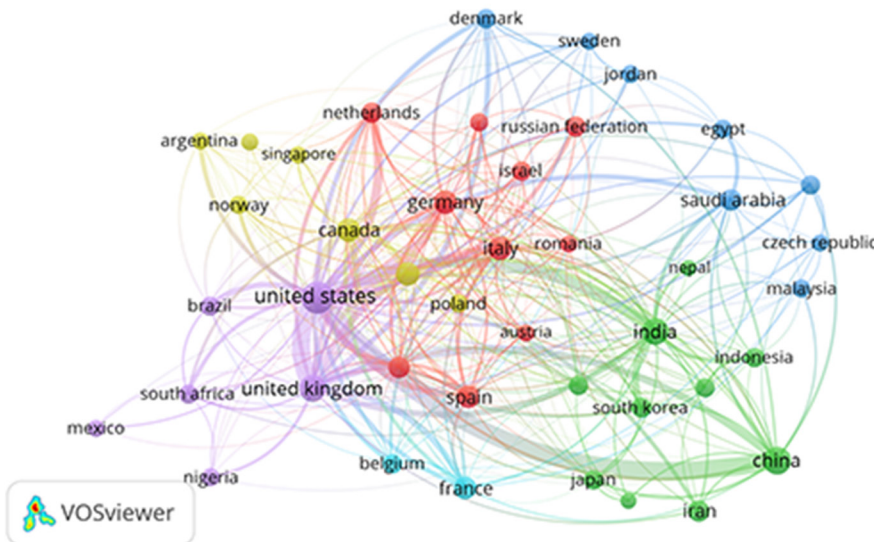


Figure 3. Network map of 40 countries with frequency more than two.

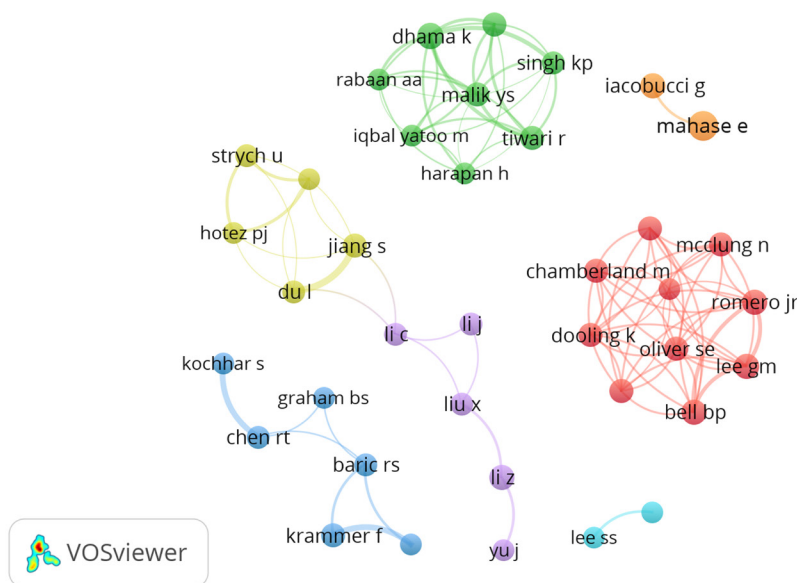


Figure 4. Network map of 29 authors with frequency more than three.

contained Czech Republic, Denmark, Egypt, Jordan, Malaysia, Pakistan, Saudi Arabia, and Sweden.

3.4. Authors

More than five thousand authors contributed to the publications of COVID-19 vaccine. 38 authors who had a connection with others, constituted seven clusters as shown in Figure 4, the threshold is four. The red cluster in the right corner of the picture was the largest cluster containing ten authors from United States, which cooperate closely. The yellow cluster, purple cluster and the blue cluster consisted mainly of American authors, Indian authors, Chinese authors and British authors. The detailed address and nationality of the authors in Figure 4 are shown in Supplementary Data 2 (<http://www.biosciencetrends.com/action/getSupplementalData.php?ID=71>).

3.5. Keywords

869 COVID-19 vaccine research hotspots keywords were extracted from 1,312 publications. Table 4 shows the top 20 keywords, among them, with a frequency of occurrence more than 30 is COVID-19 (1,075 publications), vaccination (212 publications), pandemic (153 publications), immunity (101 publications), vaccine hesitancy (39 publications), prevention and control (32 publications), and drug design (30 publications).

We presented the main keywords density in Figure 5, with frequency greater than eight. 55 nodes are shown in the map, and the brightest three were COVID-19 and vaccination in the center of the map. In Figure 6, 55 keywords that appeared more than eight times are included and classified into seven clusters in the map:

Table 4. Top 20 keywords of papers on COVID-19 vaccine

Rank	Keywords	Frequency
1	coronavirus disease 2019	1,075
2	vaccination	212
3	pandemic	153
4	immunity	101
5	vaccine hesitancy	39
6	prevention and control	32
7	drug design	30
8	drug efficacy	29
9	public health	28
10	antibody response	27
11	immunogenicity	24
12	middle east respiratory syndrome	22
13	drug safety	21
14	receptor binding	21
15	spike	20
16	t lymphocyte	20
17	drug development	18
18	virus pneumonia	18
19	ethics	17
20	vaccine production	17

cluster 1 (clinical research about vaccination, in red); cluster 2 (immunological research on vaccines, in green); cluster 3 (immunoinformatics on the vaccine, in blue); cluster 4 (infection prevention, in yellow), cluster 5 (herd immunity of public health, in purple), cluster 6 (vaccine delivery in bright blue) and cluster 7 (vaccine production, in orange). Circles with a large size represent the keywords that appeared at a high frequency. Within cluster 1, the following keywords frequently occurred: administration and dosage, age, attitude to health, clinical trial, controlled study, ethics, health care system, influenza vaccination, organization and management, practice guideline, pregnancy, prevention and control, procedures, psychology, trust, and virus pneumonia. In

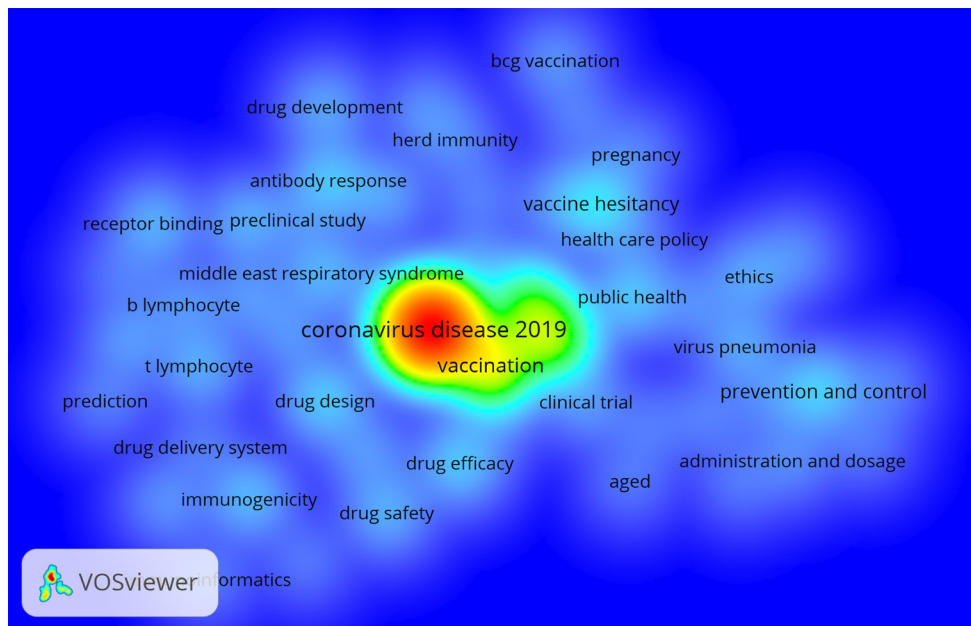


Figure 5. Density map of main keywords.

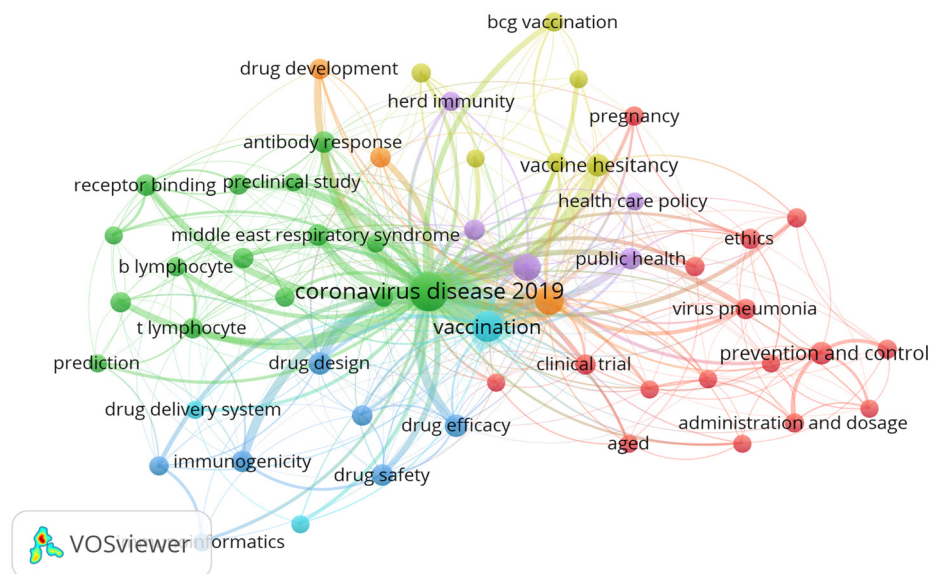


Figure 6. Network map of 44 keywords with frequency more than four.

cluster 2, relevant keywords included antibody response, b lymphocyte, cellular immunity, computer model, coronavirus disease 2019, humoral immunity, innate immunity, middle east respiratory syndrome (MERS), nonhuman, preclinical study, prediction, protein domain, receptor binding, spike, and t lymphocyte. Similarly, in cluster 3, the main keywords are bioinformatics, drug design, drug efficacy, drug safety, immunogenicity, immunoinformatics, and vaccine immunogenicity. In cluster 4, the primary keywords are BCG vaccination, epidemic, health care personnel, infection prevention, mortality, and vaccine hesitancy. In cluster 5, they are communicable disease, health care policy, herd immunity, immunity, and public health. In cluster 6,

the keywords are drug delivery system, nanomedicine, and vaccination. The keywords of the last cluster are drug development, pandemic, and vaccine production. To sum up, COVID-19 vaccine research hotspots can be classified as clinical trials on vaccine safety and efficacy, research on vaccine immunology and immunoinformatics, herd immunity of public health and vaccine production and delivery.

4. Discussion

As we all know, the pandemic of COVID-19 has caused high alarm worldwide because of its morbidity and mortality. The battle against COVID-19 is still going on,

and there are still new cases of COVID-19 in China (18). The most urgent task for medical doctors or scientists is to control COVID-19, including the development of a safe and effective vaccine. Many diverse studies addressing COVID-19 vaccine have sprung up owing to the urgent necessity of prevention and control. Global efforts should continue on vaccines for COVID-19.

In this study, we analyzed the journals, date of publication, institutions, countries, authors, and keywords of published studies on COVID-19 vaccine based on bibliometric and visualization methods, in order to reveal the current status of COVID-19 vaccine worldwide.

Based on the results of the analysis about journals, the BMJ was the top journal with publications on the COVID-19 vaccine up to February 18, 2021. Medical journals with high impact such as the BMJ, JAMA, Science, Cell, Nature, Lancet and the New England Journal of Medicine have also published papers for COVID-19 vaccine, which means that the vaccine received extensive attention from researchers around the world and had a crucial role in the prevention of COVID-19. Studies with high impact factors have involved COVID-19 vaccine development, safety and immunogenicity of the vaccine, vaccine hesitancy, and COVID-19 vaccine trials (26-29). Variations in the number of academic papers on a certain research field are important indicators for the developing trend. Plotting the number of publications over time and conducting multivariate statistical analysis help to comprehend the research level and future trends (19). As for 981 publications with specific dates, the quantity increased month by month from January 2020 to January 2021. Since our search was completed on February 18, 2021, the publications of February and the following months are incomplete. We predict that the publications will be more than that shown in Figure 1, according to the fact that some vaccines have been widely introduced. Thus, vaccines will be a research hotspot in the future until COVID-19 is controlled.

Our observations indicate that multiple institutions published studies about COVID-19 vaccines, attributed to the fact that COVID-19 has affected more than 200 countries or regions around the world. After analyzing the top 20 institutions, we realized that most of the institutions are universities and located in the United States. The network map illustrated that research teams are formed between different institutions, which were connected but not close to each other. Regarding the contributions of countries, both the United States and China have played important roles in COVID-19 vaccine research, and their total numbers of studies ranked first and second, respectively. The United States seems to have superior conditions for basic medical research or clinical trials, which include adequate funding, advanced equipment, and professional researchers. All the characteristics also showed that the United States is

leading the field (30). The four institutions from China (Fudan University, Peking University, National Institute for Food and Drug Control and Chinese Academy of Sciences) also made some contributions. Part of the reason for this phenomenon was that China is one of the countries severely affected by the epidemic, which also demonstrated China's scientific research strength has increased in recent years. Notably, approximately two thousand authors contributed to the publication of COVID-19 vaccine, however, most were involved in one publication. The network map of more than four authors illustrated that independent research teams formed between different authors. The same result was attributed to the author's institution. More connections between different nodes indicate more cooperation between different countries. The biggest problem at present is insufficient cooperation between various countries, institutions, and authors, which greatly reduces research efficiency. If the exchanges and cooperation about research methods and results between institutions in various countries are improved, vaccine research on COVID-19 will make a huge breakthrough.

As for the keywords involved, 869 hotspots keywords were encountered, which covered common words used in COVID-19 vaccine research. The most frequent words were COVID-19, vaccination, pandemic, vaccine hesitancy, prevention and control, and drug design. Only 6.3% (55/869) of keywords had a frequency of ≥ 8 , indicating the importance of a few keywords. In bibliometrics, a network map of keyword co-occurrences reflects hot topics (31). Cluster analysis of co-occurrence keywords demonstrated that there were seven clusters in this field. Cluster 1 consisted of 16 keywords, mainly related to clinical research about vaccination, because clinical research on vaccination was carried out in many countries. WHO reported that at least seven different vaccines across three platforms have been rolled out. Vulnerable populations in all countries are the highest priority for vaccination. At the same time, there are currently more than 200 additional vaccine candidates in development, of which more than 60 are in clinical development, as of February 18, 2021 (32). Issues such as ethics and informed consent involved in vaccines are also hot topics in current research (33-37). Cluster 2 consisted of 15 keywords mainly about immunological research on vaccines, which was the key to vaccine development. The viral surface spike (S) protein of SARS-CoV-2 is a key target for prophylactic measures as it is critical for the viral replication cycle and the primary target of neutralizing antibodies, thus, researchers all over the world are targeting the S protein for the development of potential vaccines (38). A previous study showed that 4A8 binds to the N-terminal domain (NTD) of S protein with potent neutralizing activity, which means that the development of vaccines has made some progress (39). For cluster 3, seven keywords were mainly related to vaccine immunoinformatics. Some research

focused on designing a multi-epitope vaccine, using an immunoinformatics approach (40). Six keywords, BCG vaccination, epidemic, health care personnel, infection prevention, mortality, and vaccine hesitancy, formed cluster 4. Some studies have elaborated the vital role of vaccines in preventing infections and controlling epidemics (41,42). Study data supports the hypothesis that BCG vaccination is beneficial in reducing the morbidity and mortality of COVID-19. The data supporting this result may be inaccurate due to many confounders such as Polymerase Chain Reaction (PCR) testing rate, population characteristics, and protection strategies. The reliability of this result still needs to be verified by clinical trials (43). Vaccine hesitancy remains a challenge to full population inoculation against highly infectious diseases. Concern about the safety of COVID-19 vaccine could contribute to vaccine hesitancy (44). The effort of the scientific community in searching for a COVID-19 vaccine may be hampered by a diffused vaccine hesitancy. Some researchers have paid attention to factors that affect vaccine hesitancy, such as race, educational attainment, and whether to receive influenza vaccine (45). Cluster 5 that consisted of 5 keywords paid attention to research on vaccine research on herd immunity for public health. COVID-19 vaccines will be essential in the future for reducing morbidity and mortality and inducing herd immunity (46,47). In cluster 6, keywords were drug delivery system, nanomedicine, and vaccination. The recent success of mRNA vaccines in SARS-CoV-2 clinical trials is in part due to the development of lipid nanoparticle delivery systems, which not only efficiently express the mRNA-encoded immunogen after intramuscular injection, but also play roles as adjuvants and in vaccine reactogenicity (48). The last cluster that consisted of 3 keywords paid attention to research on vaccine production, which is one of the current challenges of COVID-19 vaccine. To sum up, COVID-19 vaccine research hotspots can be classified as clinical trials on vaccine safety and efficacy, research on vaccine immunology and immunoinformatics, the importance of vaccine to public health and vaccine production and delivery.

It is worth noting that two versions of the AstraZeneca/Oxford vaccine, produced by AstraZeneca-SK Bioscience (AZ-SKBio) and the Serum Institute of India (AZ-SII), were approved for emergency use, which were cheaper and easier to distribute than some rivals, including that of Pfizer-BioNTech (49). As of 24 February 2021, eight vaccines have been approved for emergency use. Among them, the vaccine named BNT162b2/COMIRNATY Tozinameran, which platform is nucleoside modified mRNA. The platforms of two vaccines that named AZD1222 and Covishield (ChAdOx1_nCoV-19) were Recombinant ChAdOx1 adenoviral vector encoding the spike protein antigen of SARS-CoV-2. The platform of SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV) and SARS-CoV-2

Vaccine (Vero Cell), inactivated, were produced in Vero cells. The platform of mRNA-1273 is mRNA-based vaccine encapsulated in a lipid nanoparticle. Meanwhile, the Ad26.COV2.S is Recombinant as well as replication-incompetent adenovirus type 26 vectored vaccine encoding the S protein. The last vaccine named Ad5-nCoV platform is Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)) (50). One widespread concern is adverse events after vaccination. It was reported that severe allergy-like reactions in at least 12 people who received BNT162b2 mRNA Covid-19 Vaccine may be due to a compound in the packaging of the mRNA that forms the vaccine's main ingredient (51). A similar mRNA vaccine developed by Moderna, which was authorized for emergency use in the United States, also contains the compound, polyethylene glycol (PEG). Therefore, attention should be paid to adverse reactions when performing large-scale clinical vaccinations. In summary, adverse reactions of vaccines will be other research hotspots.

To be the best of our knowledge, this is the first study to perform bibliometric analysis on COVID-19 vaccine research. To comprehensively capture the current status of research on COVID-19 vaccine, VOSviewer was used to identify the hotspots, cooperation among authors, countries, and institutions in this field. However, this study has some limitations. At first, the data was retrieved from *Embase.com* and MEDLINE. Nevertheless, the amount of data in our analysis is large enough to reflect the current status of COVID-19 vaccine. Second, since some authors have the same short name, some keywords have different expression, bias may still exist, although we have standardized them. At last, our study has been undertaken at the vortex of the epidemic, which may miss the most updated information. Therefore, all the results and conclusions of this study should be interpreted considering these limitations.

5. Conclusion

With the spread of the pandemic, more and more academic papers have been published. It is particularly important to evaluate the quality of such a great number of COVID-19 vaccine research papers and obtain valuable information. The results of bibliometrics show that the top one published journal was the BMJ. The United States and China have played important roles in COVID-19 vaccine research. Simultaneously, there is no doubt that universities have contributed the most publications. COVID-19 vaccine research hotspots are as follows: clinical research on vaccine safety and efficacy, research on vaccine immunology and immunoinformatics, infection prevention and herd immunity, and vaccine delivery and production. Furthermore, we can predict that there will be a lot of research focusing on vaccine adverse reactions. We also revealed that cooperation between countries, institutions,

and authors were insufficient. If the exchanges and cooperation between institutions in various countries are improved from now on, vaccine research of COVID-19 will make a huge breakthrough.

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