

Mapping trends and hotspots regarding clinical research on monkeypox: A bibliometric analysis of global research

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ABSTRACT

A large number of papers have been published since the discovery of the monkeypox virus (MPXV). In 2022, human MPXV broke out in the USA and many European countries, and on July 23 of that year, the World Health Organization declared the MPXV outbreak a "Public Health Emergency of International Concern." In this study, we performed bibliometric analysis of MPXV literature published in core journals of the Web of Science core Collection database, which was conducted on 956 articles from 2000 to 2022. We analyzed the publication country, subject category, main authors and institutions, research hotspots of important publications and research frontiers. Through the analysis of keywords co-occurrence, multi-cited literature and co-cited literature, the research hotspots and trends were summarized. This report revealed that MPXV research has focused on hot areas such as infection and vaccination. Since the 2022 human MPXV outbreak, researchers have increasingly focused on infection control, vaccines, and treatment of monkeypox. This article summarizes the research directions and hotspots of MPXV related literature since the 2000, and we hope to provide support and clear research ideas for the future research and prevention of MPXV in humans.

Key words: monkeypox virus, bibliometric analysis, research hotspots

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INTRODUCTION

Monkeypox is a newly-developing zoonotic infection caused by monkeypox virus (MPXV) which has an incubation period of up

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to 21 days.^[1,2] The MPXV is a large double-stranded DNA virus belonging to the orthopoxvirus genus, it is similar to Vaccinia virus and Variola virus. Monkeypox viruses are genetically of two distinct phylogenetic clades, one is the Central African clade, the other is West African clade.^[3] In endemic areas, various of mammalian species can carry MPXV, and periodically the transmission of the virus to human will take place.^[4] There are three potential routes of exposure to the virus, interaction with wild animals, close proximity to sick individuals, and contact with infectious fomites.^[5,6]

Monkeypox was first reported by Preben von Magnus in 1958 in laboratory cynomolgus monkeys. The first human monkeypox virus infection was reported in Democratic Republic of Congo (DRC) in 1970.^[7] After that, MPXV infection was discovered in 11 African countries. The first MPXV infection out of Africa was in the USA, in 2003.^[8] We could speculate that the source of the 2003 MPXV infection in the USA was a shipment of rodents from West Africa. Before the 2017 outbreak of Nigeria, the MPXV has been reported to spread around the south and southeast of the country.^[9] During 2017 to 2018, 118 confirmed cases were reported in Nigeria. From 2018 to 2022, a number of cases of MPXV carriers from Nigeria spread to other countries, including Israel, the UK, Singapore, and the USA.^[10-13] In 2022, the outbreak of MPXV in many European and American countries aroused the concern of the World Health Organization (WHO). On July 23, the WHO declared the MPXV outbreak a "Public Health Emergency of International Concern".^[14]

In this study, we performed bibliometric analysis of MPXV literature published in core journals of the Web of Science core Collection database, including number of national contributions, number of annual publications, number of institutions, number of authors, subject category, and keyword collinear. We intended to clarify the research trends and hotspots of MPXV through

bibliometric analysis through this study, and also we hope to provide a new perspective and reference for future research and prevention of monkeypox in humans.

MATERIALS AND METHODS

Data Sources and Search Strategies

The data in this study were all from the Web of Science Core Collection database (WOS), with the topic of "Monkeypox" as the search strategy. The document type was limited to "Article", "Review Article" and "Meeting Abstract", and the language was "English". The publications were published in 2020 and 2021 (February) with articles and abstracts. The analyzed literature was published from January 2000 to October 2022, and the retrieval time is October 16, 2022.

Visual Analysis Method

This study adopted bibliometric method and scientific knowledge graph analysis. Bibliometric method is a comprehensive scientific method that uses statistical methods to quantitatively analyze the literature information resources retrieved.^[15, 16] Online Analysis Platform of Literature Metrology (<http://bibliometric.com>) were applied for the presentation, analysis, and description of the data. Microsoft Excel 2020 software (Microsoft, Redmond, USA)) was used to visualize the annual publication by line graph. Scientific knowledge graph analysis was used to analyze countries/regions, research institutions, research hotspots and frontier hotspots, and to visualize the structure and development rules of discipline knowledge. CiteSpace 6.1.R3 software (Drexel University, Philadelphia, USA) was used to analyze the "keyword" node of the literature, and to explore the development context, research hotspots

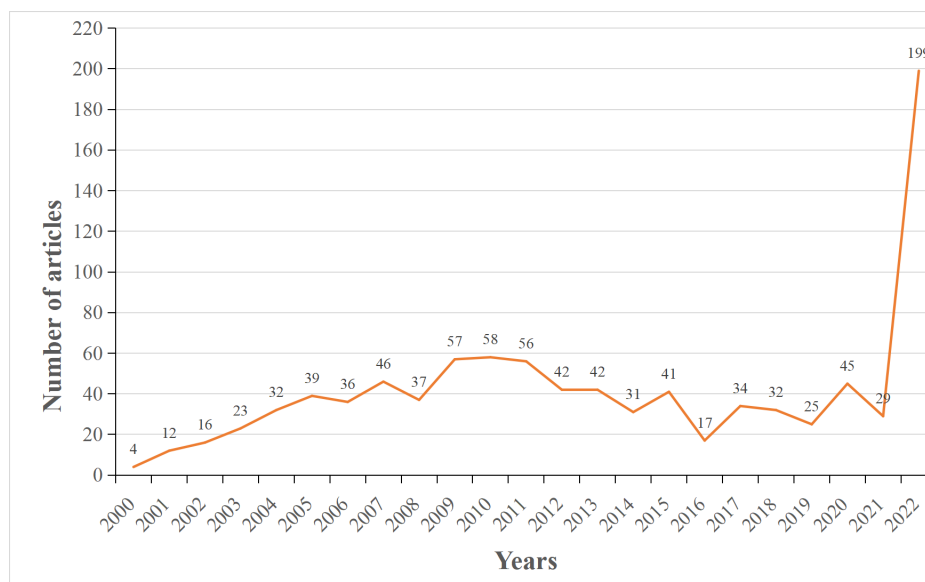


Figure 1. The publication year distribution of monkeypox related literatures included in the Web of Science Core Collection database from 2000 to 2022.

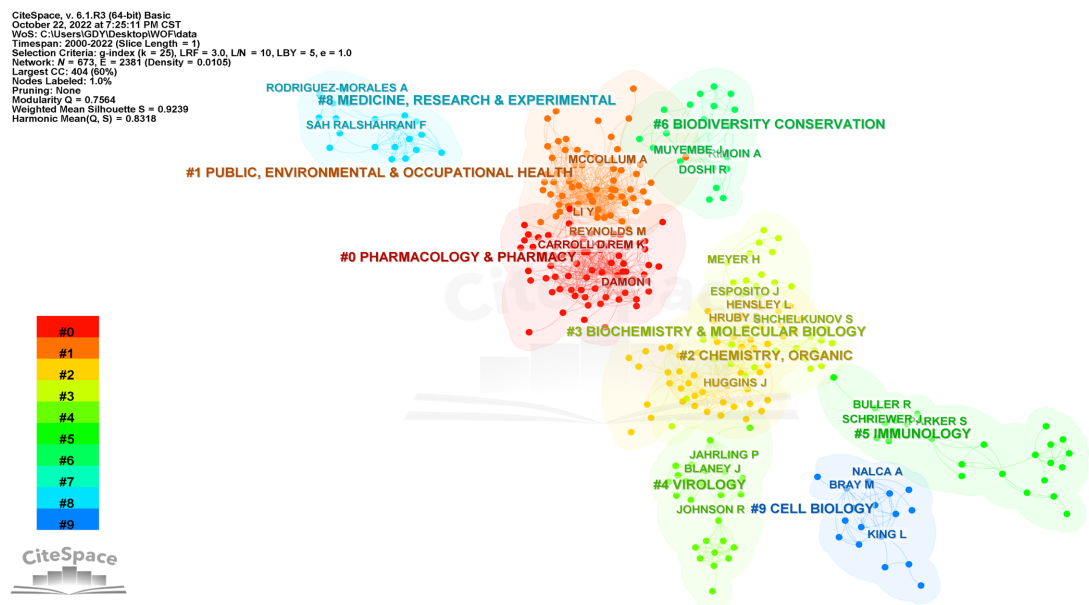


Figure 2. The top 10 subject categories related to monkeypox research.

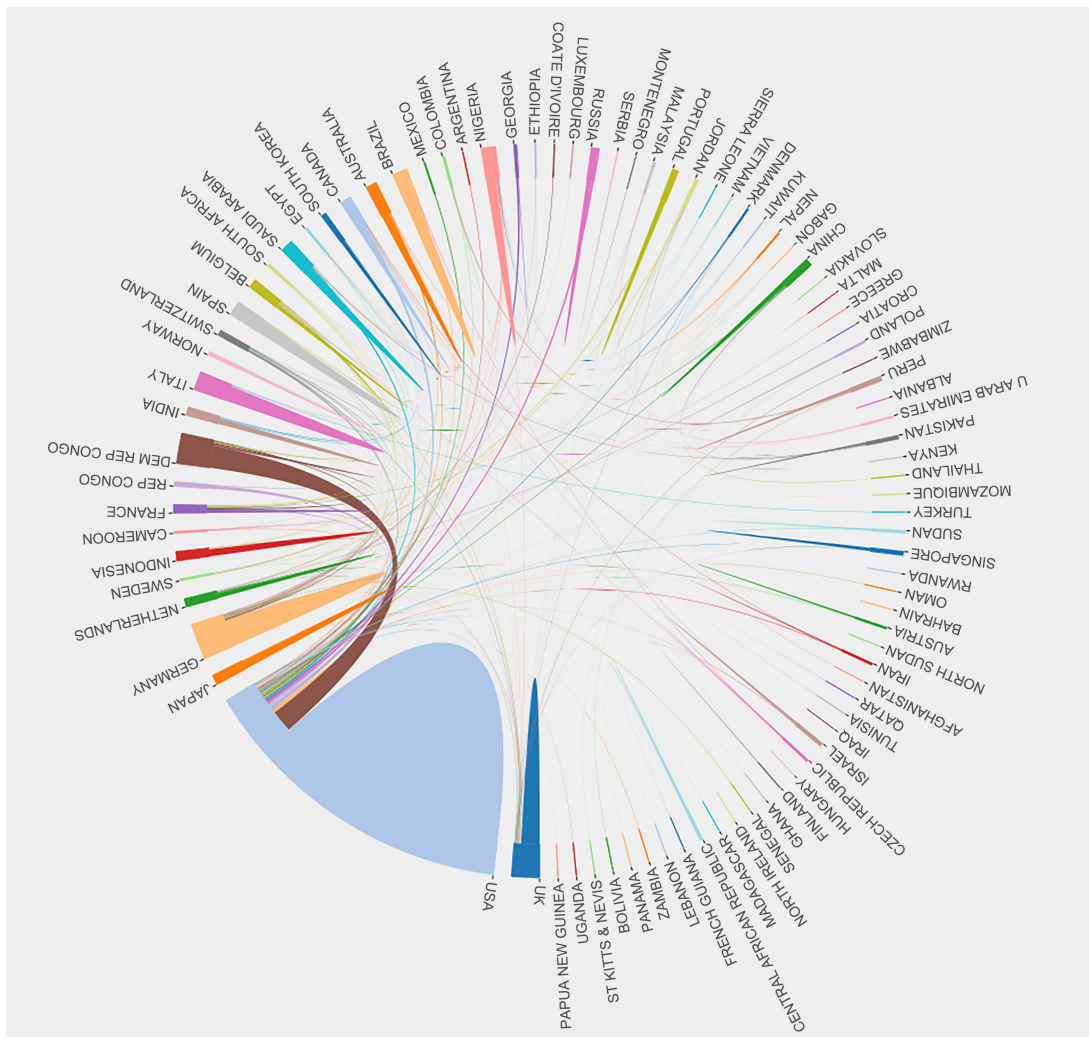


Figure 3. Country cooperation in monkeypox research.

and frontiers of this field.

RESULT

General Features of monkeypox Literature

From 2000 to 2022, 956 articles related to monkeypox were indexed by the WOS in accordance with the search strategy, and 953 effective articles were obtained after using the CiteSpace 6.1.R3 software to remove the data, including 792 articles (83.1%) and 161 reviews (16.9%), no Meeting Abstract was included. The number of literatures related to monkeypox showed an overall increasing trend during the ten years from 2000 to 2010, and the number of literatures decreased from 2011 to 2021 compared with that in 2010, which showed a certain fluctuation. It is noteworthy that the number of articles published in 2022 has increased dramatically, with a total of 199 articles published before the retrieval date (Figure 1).

Figure 2 revealed the top 10 subject categories related to monkeypox research. Pharmacology & pharmacy and public environmental & Occupational health were the most frequent topics (Figure 2). Most of the research disciplines related to monkeypox were independent, but there were different degrees of overlap between public environmental & Occupational health with Pharmacology & Pharmacy and Biodiversity Conservation.

Contributions of Countries to monkeypox research

The "country" nodes in CiteSpace 6.1.R3 software were used to analyze the country distribution of literature in the field of monkeypox from 2000 to 2022. There were 89 countries in total. The USA ranked first with 591 articles (62.0%), accounting for about two-thirds of the total number of articles published, and followed by Germany (82 articles [8.6%]), the UK (62 articles [6.5%]) and Republic of the Congo (53 articles [5.6%]). The top 10 countries/regions with the number of literatures were listed in Table 1. The USA cooperated

with many countries around the world on monkeypox research, with Republic of the Congo being the leading partner (Figure 3).

Institutions and Author with Research Publications on Monkeypox

The "Institution" node analysis showed that the top 10 research institutions with the number of published literatures on monkeypox were mainly located in the USA, Republic of the Congo and Germany (Table 2).

The analysis of "Institution" node showed that Centers for Disease Control and Prevention (the USA) (161 articles [16.9%]), United States Army Medical Research Institute of Infectious Diseases (the USA) (73 articles [7.7%]) and National Institute of Allergy and Infectious Diseases (the USA) (62 articles [6.5%]) were the institutions that published the most literature related to monkeypox research. Institutions with more than 10 publications were included in Figure 4, there was more

Table 1. The top 10 countries in number of published literatures concerning monkeypox

Ranking	Country	Number of publications, <i>n</i> (%)
1 st	The USA	591 (62.0)
2 nd	Germany	82 (8.6)
3 rd	The UK	62 (6.5)
4 th	Rep Congo	53 (5.6)
5 th	Canada	41 (4.3)
6 th	Russia	38 (4.0)
7 th	France	31 (3.3)
8 th	India	29 (3.0)
9 th	Italy	28 (2.9)
10 th	Belgium	27 (2.8)

Table 2. The top 10 institutions in number of published literatures about monkeypox.

Ranking	Institution	Country	Number of publications, <i>n</i> (%)
1 st	Centers for Disease Control and Prevention	The USA	161 (16.9)
2 nd	United States Army Medical Research Institute of Infectious Diseases	The USA	73 (7.7)
3 rd	National Institute of Allergy and Infectious Diseases	The USA	62 (6.5)
4 th	Saint Louis University	The USA	30 (3.1)
5 th	Ministry of Health and Populations	Rep Congo	28 (2.9)
6 th	SIGA Technologies Inc	The USA	23 (2.4)
7 th	University of Kinshasa	Rep Congo	22 (2.3)
8 th	University of Pennsylvania	The USA	22 (2.3)
9 th	Robert Koch Institute	Germany	21 (2.2)
10 th	United States Food and Drug Administration	The USA	21 (2.2)

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Timespan: 2000-2022 (Slice Length = 1)
Selection Criteria: Top 10 per slice, LRF = 3.0, L/N = 10, LBY = 5, e = 1.0
Network: N = 424, E = 1080 (Density = 0.012)
Largest CC: 292 (68%)
Nodes Labeled: 1.0%
Pruning: Pathfinder
Modularity Q = 0.8598
Weighted Mean Silhouette S = 0.5979
Harmonic Mean(Q, S) = 0.7053

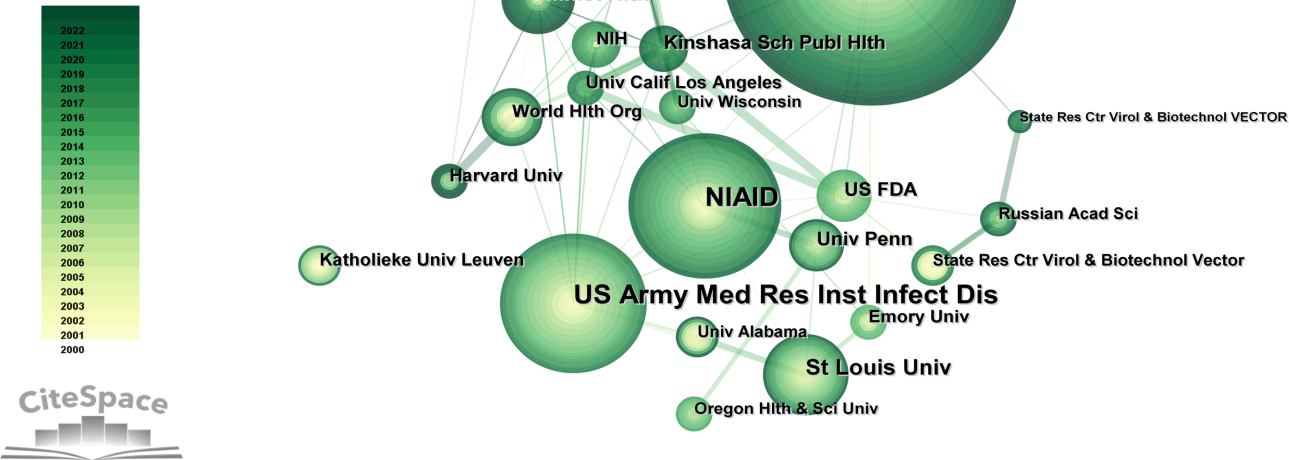


Figure 4. Cooperative network of major research institutions for literatures.

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Timespan: 2000-2022 (Slice Length = 1)
Selection Criteria: g-index (k = 25), LRF = 3.0, L/N = 10, LBY = 5, e = 1.0
Network: N = 673, E = 1893 (Density = 0.0084)
Largest CC: 404 (60%)
Nodes Labeled: 1.0%
Pruning: Pathfinder

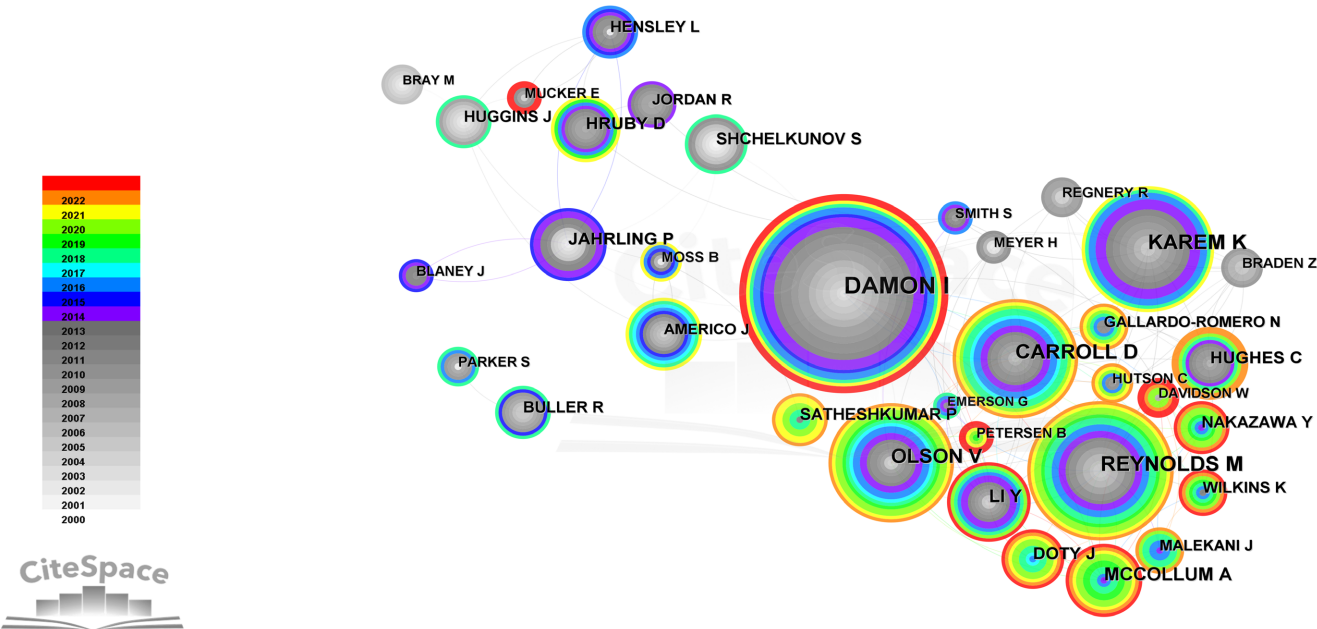


Figure 5. Cooperative network of leading researchers for literatures concerning monkeypox.

Table 4. The Top 10 Cited Papers in monkeypox research

Title	Corresponding authors	Journal abbreviation	IF*	Publication year	Total citations
The detection of monkeypox in humans in the Western Hemisphere	Reed, KD	New Engl J Med	176.082	2004	404
The role of evolution in the emergence of infectious diseases	Antia, R	Nature	69.504	2003	344
Pathways to zoonotic spillover	Plowright, Raina K	Nat Rev Microbiol	78.297	2017	341
Poxvirus tropism	McFadden, G	Nat Rev Microbiol	78.297	2005	303
Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox	Moss, B	Nature	69.504	2004	272
A preliminary assessment of silver nanoparticle inhibition of monkeypox virus plaque formation	Rogers, James V	Nanoscale Res Lett	5.418	2008	271
Poxvirus genomes: a phylogenetic analysis	Smith, GL	J Gen Virol	5.141	2004	258
Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo	Rimoin, Anne W	P Natl Acad Sci Usa	12.779	2010	243
Current concepts - Diagnosis and management of smallpox	Breman, JG	New Engl J Med	176.082	2002	241
Panmicrobial oligonucleotide array for diagnosis of infectious diseases	Lipkin, W. Ian	Emerg Infect Dis	16.126	2007	235

*Impact factors (IF) based on Clarivate Analytics Journal Citation Reports (JCR) 2021.

factors (IF), IF (2021) = 6.549, had the most published ($n = 50$), followed by Vaccine ($n = 46$; IF [2021] = 4.169), Plos One ($n = 42$; IF [2021] = 3.752), and Viruses-basel ($n = 40$; IF [2021] = 5.818).

The citation counts for the top 10 articles ranged from 235 to 404 (Table 4). These documents were published in 7 different journals. The most cited article about the use of publications on monkeypox worldwide was the detection of monkeypox in humans in the Western Hemisphere, which was published by Reed, Kurt D in the USA, and this article was cited 404 times.

Analysis of Keywords About Research Literatures on Monkeypox

The keywords chosen by article authors when they submitted their manuscripts for publication were extracted with CiteSpace 6.1.R3. We analyzed the keywords extracted from 953 publications, defined as terms that occurred more than 10 times within titles and abstracts in all articles during the analysis. In total 108 keywords were included in the keyword co-occurrence network (Figure 6). The circle nodes represent the keywords, the size represents the frequency of occurrence, and the color changes of the node circle indicate the year, and the light to dark reflected the year of publication from far to near.

Log-likelihood (LLR) clustering was used to analyze the keywords of monkeypox related literatures monkeypox research, and the research hotspots of monkeypox research was visualized and presented in the way of network visualization. The results show that, $Q = 0.7276 > 0.3000$, $S = 0.9221 > 0.500$, indicating that the effect of clustering map was better. Figure 7 shows the top 10 most used topic clusters, with purple to red indicating the intensity of the clusters and arrows indicating the trends of hotspots. As shown in timeline view of keyword research hotspots, skin lesion, monkeypox virus, sexual health, viral shedding were new keywords in 2022 (Figure 8).

Seventeen keywords with the strongest citation bursts from 2000 to 2022 were highlighted (Table 5). Keywords with the End year of 2022 were disease outbreak, zoonotic disease, infectious disease, and host range (Table 3). Combined with Figure 6, the research frontiers of monkeypox were monkeypox outbreak, human infection with monkeypox virus, the spread range of monkeypox.

DISCUSSION

Monkeypox is a zoonotic orthopoxvirus which has predominantly affected humans living in western and central Africa since the

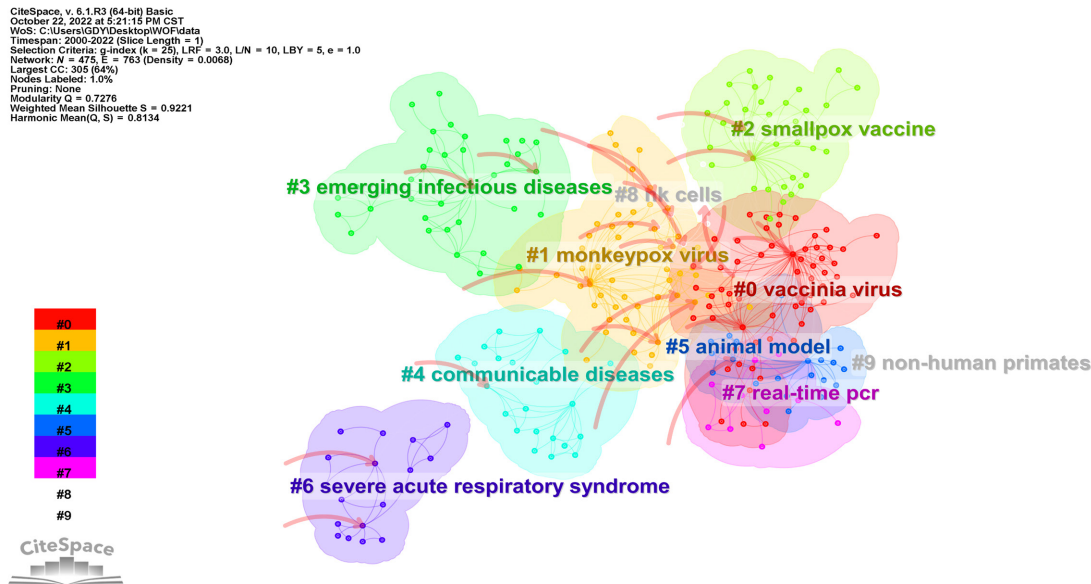


Figure 7. Clustering diagram of keywords in literatures concerning monkeypox.

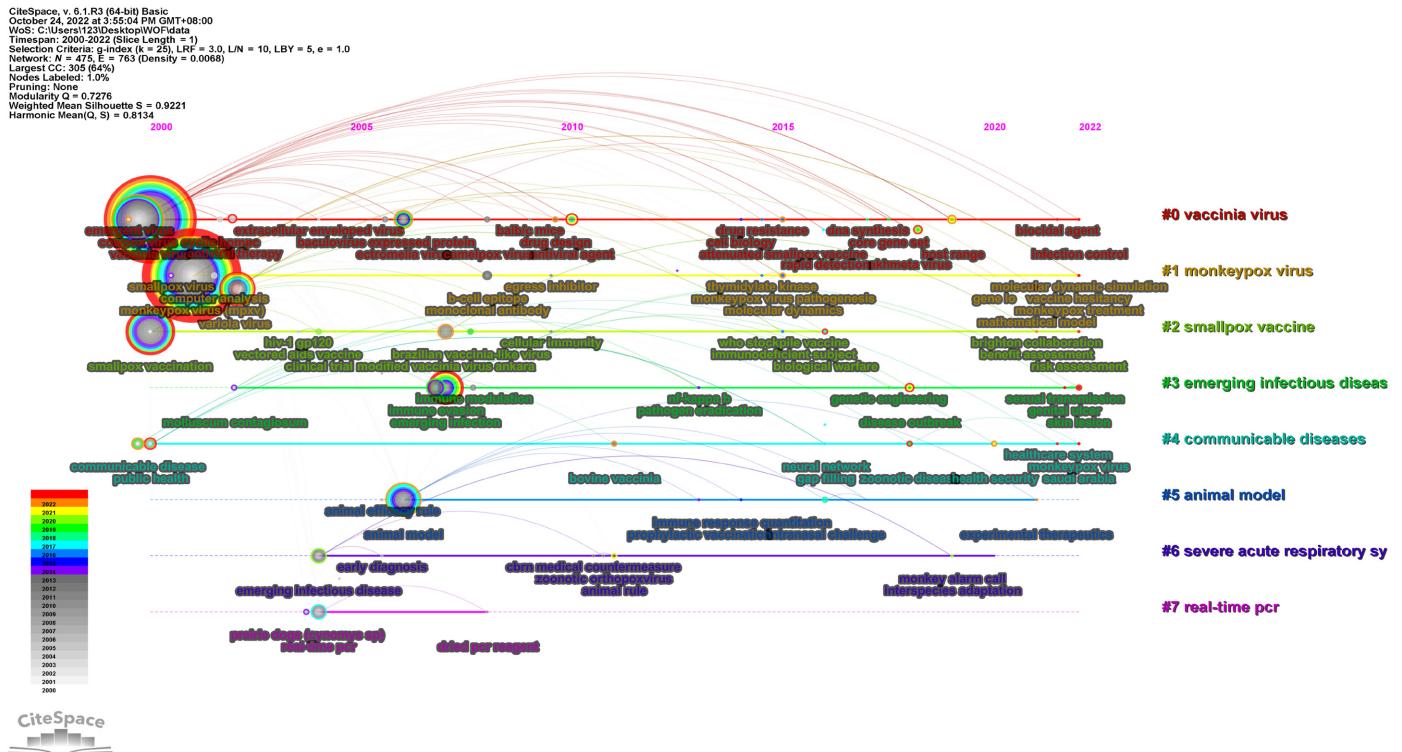


Figure 8. Timeline view of keyword research hotspots.

1970s.^[15] The first outbreak outside the continent was occurred in the USA in 2003.^[1] In September 2017, human monkeypox infection re-emerged in Nigeria. Isolated cases of monkeypox virus infections had been found in Israel, the UK and Singapore from 2018 to 2020.^[3,4] Since May 2022, human monkeypox had

erupted in multiple countries, with a total of 21,098 cases of human monkeypox reported worldwide, spanning across 41 non-endemic diseases with a high number of cases and no direct link to endemic countries.^[16,17]

In this study, from the annual number of papers published, the

Table 5. Keywords with the strongest citation bursts from 2000 to 2022

Order	Keywords	Strength	Begin year	End year
1	Cowpox virus	3.08	2000	2005
2	Real-time pcr	2.43	2004	2010
3	Severe acute respiratory syndrome	1.87	2005	2006
4	Invasive specy	1.83	2006	2010
5	Smallpox vaccination	3.75	2007	2010
6	Modified vaccinia virus ankara	2.76	2007	2010
7	Immune evasion	2.09	2007	2013
8	DNA vaccine	1.94	2007	2009
9	Neutralizing antibody	2.21	2008	2009
10	Cricetomys gambianus	1.61	2008	2010
11	Vaccinia virus	2.77	2009	2011
12	Animal model	3.01	2013	2017
13	Democratic republic of congo	2.20	2017	2019
14	Disease outbreak	1.85	2018	2022
15	Zoonotic disease	1.85	2018	2022
16	Infectious disease	2.84	2019	2022
17	Host range	1.68	2019	2022

number of literatures published before 2022 was small, with only a few years with more than 50 literatures published. There was a small peak in related literature reports from 2003 to 2005, possibly associated with the June 2003 outbreak of monkeypox in the Midwest of the USA. Seventy one cases of monkeypox had been reported from 6 states and human infections were associated with direct contact with ill pet prairie dogs.^[1,2] Of the top 10 cited literatures, 9 were published in 2010 or before, with the majority coming from the USA. Since 2000, most monkeypox research has been conducted in pharmacology and pharmacy, with A and D being the most prolific authors in this field, Damon Inger K, Carroll Darin and Reynolds Mary G, Mccollum Andrea were the most published scholars in these two fields respectively. In addition, researchers such as Shchelkunov Sergei, Jahrling Peter B, Buller R. Mark and Rimoin Anne W had conducted monkeypox related research in other disciplines, respectively, these researchers may be the leading in the field of monkeypox research.

The USA has a long history of research in monkeypox, with 62% of the literature published after 2000. The top 3 countries with the most publications were the USA, Germany and the UK, reflecting their influence in monkeypox research. Centers for Disease Control Prevention (the USA) was the most published institution and the most frequently cited institution, and cooperated with almost all influential scientific research institutions in the field of monkeypox research, including Ministry of Health and Populations (Rep

Congo) and Robert Koch Institute (Germany). It shows that international cooperation is necessary and will be the trend in the future in the treatment and prevention of monkeypox. Our results showed that the Journal of Virology, Vaccine, and Plos One were among the top 3 journals. The Journal of Virology has published the most literature related to monkeypox, and it was also the most frequently cited, indicating that monkeypox was of great value in virology research field.

Our study showed that since 2000, monkeypox research had mainly focused on the frequently occurring keywords such as vaccinia virus, monkeypox virus, smallpox vaccine, emerging infectious diseases, communicable diseases, etc. In 2022, new keywords such as infection control, vaccine hesitancy, molecular dynamic simulation, monkeypox treatment and healthcare system appeared in the field of monkeypox research, indicating that research on the treatment and control of monkeypox will be a research hotspot in the next few years. The reasons for change in keywords on monkeypox may be as follows. Firstly, the rapid increase of cases around the world has brought greater attention to disease control and treatment. Secondly, sexual transmission, especially same-sex transmission, has attracted much attention.

According to the epidemic statistics of monkeypox released by the WHO on August 31, there were 50,496 confirmed monkeypox cases in the world, and the Americas has the highest number of

monkeypox infections in the world, with more than 60% of cases occurring in the Americas and about 30% in Europe.^[18] Several studies had shown that the 2022 outbreak of monkeypox virus belongs to the same lineage as the 2018 monkeypox virus strain, illustrating the genomic evolution of the ongoing MPXV outbreak. Compared with the monkeypox virus strain in 2018, in total 46 new consensus mutations were observed in the MPXV-2022 strains, including 24 nonsynonymous mutations.^[19] Another study showed 15 single nucleotide polymorphism sites, secondary variants and gene deletions appeared. These microevolutions showed signs of better adaptation to the human body.^[20] Most cases of monkeypox have occurred in men, mostly homosexual, bisexual, and other men who have sex with men (MSM). Among the MSM cases, many of them presented atypical clinical manifestations of monkeypox and with other sexually transmitted diseases co-infection. Therefore, in this outbreak, some cases were misdiagnosed as herpes simplex virus or varicella zoster virus infection. Regarding the high social interactivity in MSM, there is a relatively higher risk of monkeypox transmission in this population.^[21]

Case reporting, epidemiological investigation, laboratory testing, isolation and treatment of cases and close contacts are important components in controlling the spread of monkeypox. As the incubation period of monkeypox virus ranges from 5 to 21 days, 21-day quarantine of suspected infected individuals is a necessary measure to reduce contagion. National Health Commission of the People's Republic of China has recommended and adopted a 21-day quarantine for suspected or confirmed cases.^[22] Monkeypox is usually a self-limited disease with the symptoms lasting from 2 to 4 weeks. Most patients recover without medication.^[23] WHO recommends that clinical care focus on alleviate symptoms, manage complications and prevent long-term sequelae. Certain antiviral drugs have been shown to be effective against human monkeypox infection. An oral antiviral drug-tecovirimat, was approved as an investigational New drug (EA-IND) for the clinical treatment of human monkeypox in the USA in 2022, at the meantime the drug was officially approved by The European Medicines Agency and the UK for the treatment of human monkeypox virus using the same animal studies reviewed by the U.S. Food and Drug Administration (FDA).^[24,25] However, the access of the drug is still extremely limited, and more data on its efficacy and safety remains to be clinically tested and verified. For populations in high-risk areas, vaccination remains the primary measure for the prevention and control of human monkeypox. Some countries are adopting or exploring policies to provide vaccines to people who may be at risk, such as laboratory personnel and health workers. Vaccination against smallpox was demonstrated in preventing monkeypox, and unvaccinated people were more likely to become infected with human monkeypox virus.^[26] While the first-generation smallpox vaccine used in the smallpox eradication program had been discontinued, the development of second- and third- generation smallpox vaccines driven by concerns about smallpox as a biological weapon.^[27] The FDA has approved two vaccines in the USA, ACAM2000 (a live-attenuated replicating vaccine) and JYNNEOS

(a live-attenuated, nonreplicating vaccine) that can prevent human monkeypox. However, the development of an effective and safe new generation human monkeypox vaccine is extremely necessary due to the serious complications that may result from vaccination of ACAM2000 and JYNNEOS.^[28,29] Establishing rapid diagnostic testing and laboratory response networks for surveillance and rapid detection of new cases is an important part of controlling monkeypox outbreaks.^[30] It is essential to investigate the source of this outbreak, to study all possible modes of transmission and to limit further spread.^[31] Raising awareness of risk factors and educating people about what can be done to reduce exposure to the virus are the main prevention strategies for monkeypox. Surveillance and rapid detection of new cases are essential to contain the outbreak.

CONCLUSIONS

This study conducted bibliometric analysis of monkeypox related literatures published from 2000 to 2022 based on Web of Science Core Collection database. In the past 22 years, monkeypox research has mainly focused on such hotspots as infection and vaccination. Since the outbreak of human monkeypox in 2022, researchers on this tend to pay attention to infection control, vaccine and monkeypox treatment. Contact tracing, testing, surveillance, and vaccination are the main measures to contain human monkeypox outbreak. Controlling the spread of monkeypox is of top priority, but how to deal with the relationship between human and nature may be the deep thinking brought by the outbreak of human monkeypox virus as a zoonotic disease.

Author contribution

Wu X, Tang S and Zhang Z designed the study and revised the manuscript. Tan J, Zhang Z and Yuan Y collected the data. Zhao Y, Lin X, Ning J, Zhang Z and Yuan Y did the statistical analysis. Zhang Z and Yuan Y prepared the manuscript.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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