Global research on *Clostridium difficile*-associated diarrhea: a visualized study

*Clostridium difficile*-associated diarrhea

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Abstract

BACKGROUND

*Clostridoides* (*Clostridium*) *difficile* is still the most common cause of healthcare-associated diarrhea and is becoming more prevalent as a community infection. In addition, the emergence of antibiotic resistance in *Clostridium difficile* (*C. difficile*) can increase the likelihood of the disease developing and/or spreading.

AIM

This study aimed to provide an up-to-date picture of the trends in publications related to *C. difficile* infection, together with specific insights into hot issues in this field.

METHODS

Publications on *C. difficile* infections in the field of microbiology between 2001 and 2020 were identified from the Scopus database. Bibliometric indicators were determined, including the number and type of publications, countries, affiliations, funding agencies, journals, and citation patterns. VOSviewer was used to determine research areas and hot issues by identifying recurring terms with high relative occurrence in the title and abstract.

RESULTS

A total of 8,127 documents on “*C. difficile*-associated diarrhea” published between 2001 and 2020 were retrieved from the Scopus database. During the previous decade, there has been a significant increase in the number of published papers, almost fourfold. The USA was among the countries (44.11%) with the most publications, and the most involved institution was the *University of Leeds* in the UK (2.50%). Three clusters of research were identified and included “illness spectrum and severity, as well as the signs, symptoms, and clinical pathogenesis of *C. difficile*”; “laboratory diagnosis and characterization of *C. difficile*”; and “risk factors for *C. difficile* infection”.

CONCLUSION
This study contains the most up-to-date and comprehensive data ever compiled in this field. More international research and cross-institutional collaboration are needed to address more global *C. difficile* concerns and benefit from a greater sharing of expertise, resulting in higher quality or more effective studies in the future. Promising research avenues in the near future may draw the attention of relevant scientists and funding organizations and open up novel *C. difficile* infections-based diagnosis and treatment approaches.

**Key Words:** *Clostridioides; Clostridium difficile;* Bibliometric; Scopus; VOSviewer; Diarrhea

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**Core Tip:** The significance of this study lies in the fact that, as far we are aware, there are no previous bibliometric studies on *C. difficile* infection research. This study presents the publication evolution of *C. difficile* infection-related publications over time. This bibliometric study will give clinicians and researchers in gastroenterology and microbiology with a quantitative and timely summary of *C. difficile* infection-related publications. Promising research avenues in the near future may draw the attention of relevant scientists and funding organizations and open up novel *C. difficile* infections-based diagnosis and treatment approaches.

INTRODUCTION
*Clostridium difficile* (*C. difficile*) has been reclassified as *Clostridioides difficile*, although the preferred term remains *Clostridium difficile*. *C. difficile* infections are becoming more prevalent and are among the most common healthcare-associated illnesses globally [1–3]. *C. difficile* infections, also known as *C. difficile*-associated diarrhea (CDAD), are the most
common signs of clinical infection and can range from mild diarrhea to fulminant colitis. C. difficile is frequently linked to the use of antibiotics. C. difficile was once thought to be predominantly a nosocomial illness; however, community-acquired C. difficile has already been identified.

Metronidazole and vancomycin have been the primary treatments for C. difficile infections for more than three decades. However, the low number of sustained cures and the rising incidence of C. difficile infections, as well as the accompanying morbidity and death, have necessitated the development and investigation of novel treatment medicines. Despite ongoing attempts to enhance C. difficile prevention and treatment, C. difficile continues to be a major public health concern. In both hospitals and the community, C. difficile infection is still a prevalent and dangerous problem. In recent years, fecal microbial transplantation has developed as a safe and successful method for treating recurrent infections. Therefore, fecal microbial transplantation will most likely become the standard therapy for recurrent infection as a novel technique.

Bibliometrics and research performance assessments were performed on a broad range of health areas, particularly in environmental and toxicology issues. Yet, to my knowledge, a broad number of bibliometric studies noticeably focused on microbiology have been conducted by using different databases for data analysis. Because of these studies found that microbiology research is recently being given increased scientific attention worldwide. Still, more research efforts are needed to thoroughly review and identify the existing literature related to C. difficile infection from different aspects, including authorships, country, affiliation, journals, citation patterns, and content analysis to determine research area hot issues in this field.

C. difficile infection is considered one of the most arguing topics in this era. Using the bibliometric approach in C. difficile infection would affect how scientists design and conduct studies and the selection of models that estimate risk. Using a bibliometric analysis of publications in Scopus, this study provides an up-to-date picture of the trends in publications related to C. difficile infection, together with specific insights into
hot issues in this field. The significance of this study lies in the fact that as far we are aware, there are no previous bibliometric studies on *C. difficile* infection research. Therefore, this study presents the evolution of *C. difficile* infection-related publications over time. This bibliometric study will give clinicians and researchers in gastroenterology and microbiology with a quantitative and timely summary of *C. difficile* infection-related publications. Furthermore, it aims to provide clinicians and researchers with a resource on principles, and current evidence. Understanding the historical trends of research in this field and its obstacles may establish the framework for future gastroenterology scholarship.

**MATERIALS AND METHODS**

*Data Acquisition*

The research data was taken from the Scopus bibliographic database. Scopus was chosen since it has a larger number of indexed journals than other databases (e.g., PubMed or Web of Science) and is completely inclusive of all journals in Medline [29,31]. Scopus is the most popular set of scientific publications used in bibliometric and scientometric studies together with PubMed or Web of Science [32]. In addition, Scopus also has indexed journals in the health, social, physical, and life sciences. This enhances the likelihood of retrieving as many relevant publications as feasible.

*Search strategy*

To identify research related to *C. difficile*-associated diarrhea, we have taken the following steps to carry out this study:

**Step one:** The data extraction was performed on July 25, 2021, and obtained within one day to avoid potential bias due to the regular updating of the database. The terms used in the search engines were applied in Title ((TITLE(Clostrid* difficile) OR TITLE("C. diff*")) OR TITLE("C. diff*"))) AND Title/ Abstract (TITLE-ABS(diarrh*) OR TITLE-ABS(antibiotic) OR TITLE-ABS(infection) OR TITLE-ABS(AAD)). To be more precise, in the results, the search strategy for research related to *Clostridium difficile* terms was limited to the title only to eliminate false negatives. Search terms with different suffixes
were truncated using an asterisk (*). The keywords used were chosen because they are commonly used in the literature related to *C. difficile*-associated diarrhea [13, 33-35].

**Step 2:** The year 2021 was omitted because the database records for this year would not have been completed at the time of the search.

**Step 3:** All retrieved documents were reviewed and analysed with respect to the following different bibliometric indicators as in previous bibliometric studies [16, 36-38]:

The annual number of publications on *C. difficile*-associated diarrhea indexed in Scopus and published from 2001 to 2020.

Prolific countries, journals, and authors in this field in relation to the number of publications.

Research collaboration among the most productive countries.

The most frequently cited publications. It is likely that certain articles were cited more frequently than others due to the considerable period passed since their publication. Therefore, a citation index was generated for each article to overcome the bias caused by the period passed after publication. The citation index is derived by dividing the average number of citations by years after the article was first published.

Hot issues in this field

**Step 4:** A network visualization map based on the publications retrieved from the Scopus database was created using VOSviewer (version 1.6.16) software (www.vosviewer.com). The output results from VOSviewer are displayed in clusters. The existing connections between the bibliometric data can be clearly visualized to analyze collaboration between countries. Furthermore, it illustrated the terms widely used in the titles and abstracts of the publications collected, showing the hot research topics.

**RESULTS**

**General Description of the Retrieved Publications**

A total of 8,127 documents on “*C. difficile*-associated diarrhea” published between 2001 and 2020 were retrieved from the Scopus database. From these publications, articles (n =
6,062) were the most often published documents with 74.59%, followed by reviews \((n = 1,016; 12.50\%)\) and letters \((n = 384; 4.72\%)\).

The trend of Global Publications

As shown in Figure 1, there was a growing trend in the number of publications on \(C.\) \textit{difficile}-associated diarrhea in the Scopus database between 2001 and 2020. It is obvious that there was an increasing number of publications mostly during two periods: from 2006 to 2013 and from 2014 to 2020. Since 2006, the number of relevant articles has grown significantly, which is notable. During the last seven years (2014 to 2020), published papers accounted for 60.16% of the total publications. As a result of these findings, the number of yearly publications grew progressively from 2014 to 2020, showing that the amount of research output increased steadily over that period.

Contributions of Countries

Table 1 shows that the USA is the most prolific country whose authors have published both more documents \((n = 3585)\), followed by the UK \((n = 1013)\), Canada \((n = 556)\), and Germany \((n = 434)\). The ten first countries in Table 1 produced 89.84% of the documents published related to \(C.\) \textit{difficile}-associated diarrhea. Analysis for international collaboration was carried out on the downloaded data based on co-authorship relationships between countries (Figure 2).

Contributions of Institutions

The top 10 most productive institutes for total papers were listed in Table 2. The major academic contributions mainly originated from University of Leeds \((2.50\%)\), Leiden University Medical Center \((2.35\%)\), and Harvard Medical School \((2.25\%)\).

Contributions of Funding Agencies

Table 3 Lists the global’s top 10 funding agencies that sponsored the research output in \(C.\) \textit{difficile}-associated diarrhea. Among them, eight agencies were from the United States, and two agencies were from the UK. The National Institutes of Health ranked first, supporting the highest number of 884 studies. The U.S. Department of Health and Human Services ranked second \((n = 841)\), and the National Institute of Allergy and Infectious Diseases ranked third \((n = 539)\).
**Top Active Journals**

The ten most prolific journals are presented in Table 4. The most productive journal was *Infection Control and Hospital Epidemiology* (n = 304), *Anaerobe* (n = 276), *Clinical Infectious Diseases* (n = 251), and *Journal of Hospital Infection* (n = 212). Thus, the ten first journals in Table 4 produced 23.97% of the documents published related to *C. difficile*-associated diarrhea.

**Top cited documents**

In terms of the most cited papers published in *C. difficile*-associated diarrhea [39-48], Table 5 presents the top 10 highly cited articles.

**Top frequent topics**

We studied the distribution of co-occurrence terms through VOSviewer software (The minimum number of occurrences of a term in all publications is 100 times in titles and abstracts) to detect directions and topics in *C. difficile*-associated diarrhea research and understand the growth of this discipline. The size of the circle or node of a term equals that particular term's number of occurrences. For example, in Figure 3, Of the 84,961 terms, 385 terms occurred at least 100 times, distributed in three clusters: Cluster #1, shown by green dots, includes those terms commonly found in studies related to clinical features of *C. difficile*, including the illness spectrum and severity, as well as the signs, symptoms, and clinical pathogenesis of *C. difficile*. Cluster #2, shown by blue dots, includes those terms commonly found in laboratory diagnosis and characterization studies of *C. difficile*. Cluster #3, indicated by red dots, includes terms commonly found in studies related to risk factors for *C. difficile* infections. To investigate the changes in hotspots over time, a network visualization map of the most frequent terms in the titles/abstracts of the retrieved documents was generated using VOSviewer software, and the results revealed that the topic "risk factors for *C. difficile* infection" began to appear more frequently in the last five years (Figure 4).

**DISCUSSION**
The current study was a descriptive study on global research output in publications related to *C. difficile* infection. It is important to examine the quantity and quality of research in this field, given the changing epidemiology of *C. difficile* morbidity and mortality, worldwide escalation in antibiotic resistance, and limited alternative preventive strategies for *C. difficile* infection. This bibliometric analysis will aid in revealing key milestones and progressions in this field, detecting current shortages and developing trends, and directing the field's future research path. The current study showed a 4-fold increase in publications in the last decade. These results reflect those of Balsells *et al.* [49] and Ofosu [50], who also stated that over the recent years, there had been a growing understanding of the principle of *C. difficile* infection, the risk factors associated with *C. difficile* infection, the pathogenesis and clinical manifestation, prevention, diagnosis, *C. difficile* infection treatment including new emerging therapies, and fecal microbiota transplantation.

The United States was the leading country in *C. difficile* infection-related publications, contributing about half of all Scopus publications in this field. This is presumably due to economic prosperity and population growth, and many microbiology researchers [51, 52]. The economic basis plays an essential part in supporting scientific research in the current study. The majority of the top ten funding agencies were based in the United States. High-income countries have published most publications in *C. difficile* infection-related publications, with limited input from low- and middle-income countries. An analysis of the countries that generated the most *C. difficile* infection-related publications indicates that countries with economic power indicators have a say in this field. This finding broadly supports the work of other studies in different areas linking that scientific research output is associated with geographical location and financial growth [14, 15, 53, 54]. Various bibliometric analysis studies have also shown that the United States is the most prolific country in microbiology research output [22, 23, 25, 27, 55, 56].

The current study showed that the most frequently cited article on *C. difficile*-associated diarrhea written by Cohen *et al.* [39] and published in 2010, with 2370 citations, is a guideline that updates recommendations for epidemiology, diagnostics, therapeutics,
infection control, and environmental management. The second most frequently cited paper has 2140 citations and addresses the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile* infection; this article published in 2013, was written by Van Nood *et al* [46]. These two papers receive approximately 237 and 305.7 citations per year on average, respectively. However, the article with the second-highest number of citations per year placed fourth in the ranking and was published in 2015 and was written by Lessa *et al* [48]. This paper aimed to produce more accurate national estimates of illness burden, incidence, recurrence, and death by collecting data from a variety of health care delivery and community contexts. Note that five papers published after 2010 appear in the top 10 most cited publications between 2001 and 2020 in *C. difficile*-associated diarrhea.

Although it is challenging to reveal the quality or impact of publications through bibliometric analysis, to some degree, citations are considered an indirect measure of an article's contribution to the knowledge generated in the field, i.e., the connection between the research finding and its significance for science [57, 58]. However, these analyses of the top 10 most cited publications will aid guide microbiologists interested in further studies by updating knowledge of current developments in *C. difficile* infection-related publications and potential future directions for study.

Analyzing the occurrence frequencies of the terms in publications can offer insights into certain fields' main and hot topics [59]. The current study found that highly cited literature focused on the signs, symptoms, and clinical pathogenesis of *C. difficile* concepts and risk factors for *C. difficile* infections. A clear theme to emerge from the results is that the most frequently cited publications on *C. difficile* infections highlighted a range of subtopics similar to hot research topics. A recent bibliometric study [60] was defined to assess global research activity on antimicrobial stewardship as one measure for efforts dedicated to containing antimicrobial resistance. This study found that *C. difficile* was frequently encountered as author keywords in the retrieved literature on antimicrobial stewardship. The United States Centers for Disease Control and Prevention (CDC) has considered *C. difficile* infection an urgent danger in its 2019
Antibiotic Resistance Threats Report \cite{61}. In a European point prevalence study, C. difficile was rated sixth among bacteria responsible for healthcare-associated illnesses \cite{62}. The majority of C. difficile infections in the United States are considered hospital-acquired \cite{63}.

**Strengths and limitations**

This study offered the first bibliometric study of C. difficile infections from the unique perspective of its research hotspots to determine the influencing scientific areas and global trends. Published articles on C. difficile infection-based publications in microbiology were collected in the online Scopus database and analyzed comprehensively, thoroughly, and objectively. As with all previous bibliometric studies \cite{16 28 36 37}, the current study has some limitations. First, we selected preferred English articles from the database but lost some articles that were not English. Second, we chose Scopus alone as the data source for C. difficile infection research because it presented the most reliable and credible information. Inevitably, any useful information from other medical sources like PubMed and Web of Science would be skipped. On the other hand, Scopus remains the greatest database available for analyzing research activity and identifying research hotspots on a certain topic. Given these limitations, we believe that this study offers a qualified global view of C. difficile infection-based publications in the field of microbiology from 2001 to 2020.

**CONCLUSION**

The current study used a bibliometric analysis of C. difficile infection-based publications in the fields of microbiology and gastroenterology during the period 2001-2020 to determine research hotspots for possible future research directions. The results showed that C. difficile-based publications grew rapidly since 2006. Research activity on C. difficile infections has been an emerging research topic during the last two decades, which has been developed predominantly by scientists from the United States of America, the United Kingdom, Canada, Germany, France, and China. Risk factors for C. difficile infection, laboratory diagnosis and characterization of C. difficile, signs,
symptoms, and clinical pathogenesis of *C. difficile* concepts were the main research hotspots in *C. difficile* infection, and related studies should pioneer these fields in the future. Promising research avenues in the near future may draw the attention of relevant scientists and funding organizations and open up novel *C. difficile* infection-based diagnosis and treatment approaches.

**ARTICLE HIGHLIGHTS**

**Research background**

*C. difficile* infections are growing more prevalent and are now one of the most often encountered healthcare-associated infections worldwide.

**Research motivation**

To my knowledge, however, a large number of bibliometric studies notably focused on microbiology have been undertaken by using various databases for data analysis. More research efforts are still required to thoroughly analyze and identify the existing literature related to *C. difficile* infection from many perspectives in order to identify study area hot issues in this field.

**Research objectives**

This study gives an up-to-date picture of the trends in publications linked to *C. difficile* infection, as well as unique insights into hot topics in this field.

**Research methods**

This study was based on a bibliometric analysis of Scopus publications

**Research results**

Three clusters of research were highlighted as hot topics: "Illness spectrum and severity, as well as signs, symptoms, and clinical pathogenesis of *C. difficile*"; "laboratory diagnosis and characterization of *C. difficile*"; and "risk factors for *C. difficile* infection."
Research conclusions
The current study conducted a bibliometric analysis of *C. difficile*-related publications in the disciplines of microbiology and gastroenterology from 2001 to 2020 to identify research hotspots for potential future research directions. Results revealed that the topic "risk factors for *C. difficile* infection" began to appear more frequently in the last five years.

Research perspectives
This bibliometric study will provide clinicians and researchers in gastroenterology and microbiology with a quantitative and timely summary of publications linked to *C. difficile* infection. It also intends to be a resource for clinicians and researchers on principles and current evidence.

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