



## Research article

# Hotspots and frontiers in *Helicobacter pylori* biofilm research: A bibliometric and visualization analysis from 1998 to 2023

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## ABSTRACT

**Background:** *Helicobacter pylori* (*H. pylori*) biofilm formation is a key factor in refractory *H. pylori* infection. The aim of this study was to understand research trends in *H. pylori* biofilms.

**Methods:** The Web of Science Core Collection database was used to retrieve publications published from 1998 to 2023. Different kinds of software, EXCEL, an online bibliometric analysis platform, and the VOS viewer were used to evaluate and visualize the bibliometric data.

**Results:** In total, 184 publications were identified, and the number of publications increased annually. The USA made the greatest contributions to this research field, while *Helicobacter* was the most productive journal. Grande rossella published the most papers, and the most productive institution was Gabriele D'Annunzio university. Co-occurrence network maps revealed that the keyword "*Helicobacter pylori*" ranked first in research field, and the keyword of "biofilm formation" and "in vitro" began to appear in the past three to five years. The majority of the five most-cited articles (60%) were published in USA and focused on the mechanism of *H. pylori* biofilm formation.

**Conclusion:** The annual number of publications on *H. pylori* biofilms has increased steadily over the past two decades and will continue to increase. Future studies should focus on evaluate the pharmacological effects, efficacy and safety of these anti-biofilm treatments in animal models and clinical trials.

## 1. Introduction

*Helicobacter pylori* (*H. pylori*) is a gram-negative curved *pylori* that adheres to the gastric mucosa and intercellular space, and over 50% of the population is infected in worldwide [1]. *H. pylori* infection causes gastric diseases such as peptic ulcer and gastritis; approximately 1 % of the *H. pylori*-positive people will develop gastric cancer, which has a strong infectivity and can be transmitted between people through mouth-to-mouth, feces-to-mouth, and vertical transmission [2]. *H. pylori* infection has a collective aggregation phenomenon and causes great social harm. In 1994, the World Health Organization classified *H. pylori* as a class I carcinogen [3]. For the eradication of *H. pylori*, although various treatments, such as bismuth quadruple therapy, they have been used in clinical practice, factors such as improper use of antibiotics and biofilm formation make eradication increasingly challenging [4,5].

According to the data from National Institutes of Health and Centers for Disease Control and Prevention, biofilms has caused more than 80 % of human infection and 60 % of chronic infection [6]. Biofilm plays a vital role in resisting external threats. The formation of

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biofilm made *H. pylori* colonized for a long time or lead to reinfection, which was the main contributing factor for recurrent and refractory *H. pylori* infection [7]. Biofilm as a barrier to bacteria can resist drugs and the host immune system. The secretion of extracellular polymers and upregulation of efflux pump gene expression enhanced the tolerance of biofilm cells to harsh environments [8]. *H. pylori* has the ability to form biofilm in vivo and in vitro [9,10]. In some cases, antibiotic concentrations required to eradicate bacterial biofilm cells may be 100–1000 times higher than those required to eradicate planktonic cells [5]. Therefore, the presence of biofilms may increase the drug dose required for *H. pylori* eradication, thereby increasing the prevalence of drug-resistant strains.

In recent years, bibliometric analysis has been successfully applied to a series of research fields to help researchers efficiently familiarize themselves with a certain field of interest [11–14]. However, bibliometric analysis has not been applied to the research field of *H. pylori* biofilms. Therefore, in this study, we conducted a bibliometric analysis of publications in the field of *H. pylori* biofilm research, revealing the global situation in the past two decades and the research trends in the next decade.

## 2. Methods

### 2.1. Data sources and search strategy

In this study, we used the Web of Science Core Collection (WoSCC) to search for relevant literature on Oct 20, 2023 (<http://cwres.ncu.edu.cn/s/cn/clarivate/webofscience/G.https/wos/alldb/summary/a3b52f28-e0e7-4a5e-9092-096332c58c17-af973cb8/relevance/5>). The search strategy was TS= *Helicobacter* biofilm OR *H. pylori* biofilm OR *Helicobacter pylori* biofilm AND Language = (English) AND Document types = (REVIEW OR ARTICLE). Furthermore, each final included paper was carefully read and strictly screened by two authors independently; 184 publications were finally included in our study, including 144 original articles and 40 reviews. Fig. 1 shows the study screening process.

### 2.2. Data collection

The full records of each publication retrieved in the search were downloaded as an a.txt file from WoSCC and subsequently imported into Excel 2019.

### 2.3. Statistical analysis

We used “Prediction plate” of EXCEL to analyze the trend of the publications in next decade. In the present study, we used EXCEL, VOS viewer, and bibliometric analysis platform (<https://bibliometric.com>) for the analysis. EXCEL was used to count the number of annual and cumulative annual publications. VOS viewer (version 1.6.18, Leiden University, Leiden, The Netherlands) was used to visualize bibliometric networks, such as co-authorship and keyword analysis. In addition, an online bibliometric analysis software (<https://bibliometric.com/>) was used to analyze the dynamic changes in publications in each country and international collaboration between countries.

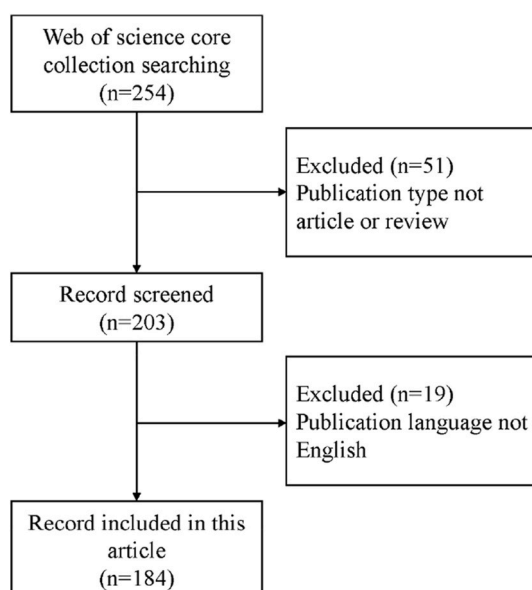


Fig. 1. Flowchart of study enrollment.

### 3. Results

#### 3.1. Trends in global publications

A total of 184 publications were published and their attributes are shown in Fig. 2. A growth trend in the number was observed (from 1 in 1998 to 18 in 2023), and with 150 articles published in recent 10 years (accounting for 82% of the total publications). The highest number of articles in the field was published in 2022 (in total 22), a rapid growth occurred in China in the last five years, and China has exceeded other countries by 2021 in publication number. The growth trend of the annual cumulative number of publications showed continued global growth globally (Fig. 3), thus the logistic regression model of EXCEL was used to create the predicted curve of the number of publications in the next decade (Fig. 4). This curve indicates that the field of *H. pylori* biofilm is currently in a decreasing trend in 2023 on global publication outputs; however, steady growth is expected in the next decade, and the cumulative number of publications will continue to grow.

#### 3.2. Contributions of top 5 productive countries, institutions, authors, and journals

The USA published the highest number of articles in the field (65; 35%), followed by China (45; 25%), Japan (29; 16%), Italy (22; 12), and UK (13; 7%). Meanwhile, the top 1 country with the highest number of total citations and average citations was the USA (12904times, 19.85times) (Table 1). The USA participated most frequently in international cooperation, followed by Italy and China. China cooperated more closely with the USA (Fig. 5).

Additionally, we evaluated the most productive institutions and authors in our study. Gabriele D'Annunzio university, published 12 publications, was the most reproductive institution, followed by Kyorin University (8), Wroclaw Medical University (7), and other institutions (Table 2). Kyorin University had the highest total number of citations (376) and the highest average number of citations (47). A total of 723 authors participated in these publications, with an average of 4.69 numbers of authors per publication. Grande rossella was the most productive researcher, with five publications, followed by Kamiya et al. (8), Osaki et al. (8), and other researchers (Table 3). Hanawa tomoko had the highest average number of citations (52).

In total, 184 inclusive publications were published in 109 journals. The top 5 productive journals have totally published 34 publications, accounting for 21% of the total articles. The most productive journal was *Helicobacter* (12), followed by *Frontiers in Microbiology* (9), the *Journal of Applied Microbiology* (5), *Antibiotics-Basel* (4), and *Scientific Reports* (4). The *Journal of Applied microbiology* (65times), *Frontiers in microbiology* (39times), and *Helicobacter* (24times) and were the first three journals with the highest total number of citations; the first three journals with average citations per paper were the *Journal of Applied microbiology* (13times), *Frontiers in microbiology* (4.33 times), and *Antibiotics-Basel* (3.5times). *Frontiers in microbiology* had the highest IF (2023,5.2) (Table 4).

#### 3.3. Keywords visualization

In this study, VOS viewer software was used to visualize the occurrence frequency and time trend of keywords. Keywords were identified as words that were used more than 10 times in titles and abstracts among all included publications. 21 keywords totally introduced into the analysis. We found that “*Helicobacter pylori*,” “biofilm” and “biofilm formation” were the most prominent keywords. The identified keywords were classified broadly into three clusters: (1) diagnosis and therapy, (2) antibiotic resistance and biofilm, and (3) biofilm formation, virulence, and expression (Fig. 6A). These clusters reflect the most prominent research topics on

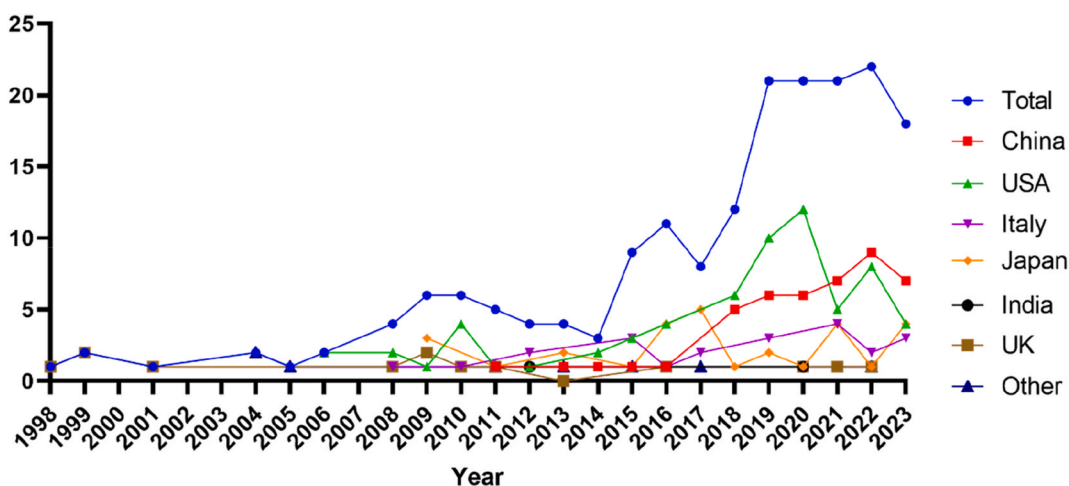


Fig. 2. Global number of the published publications by countries in the field of helicobacter biofilm from 1998 to 2023.

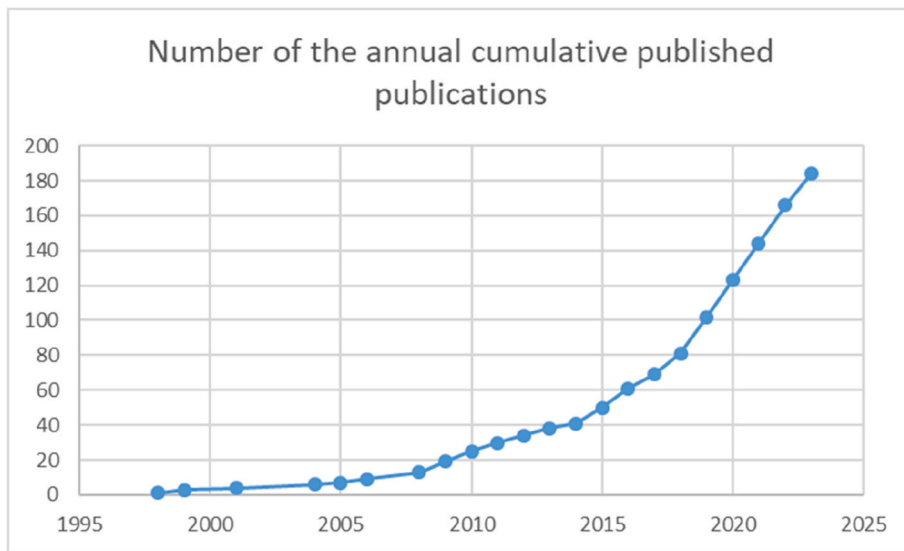


Fig. 3. Global annual cumulative number of the published publications in the field of helicobacter biofilm from 1998 to 2023.

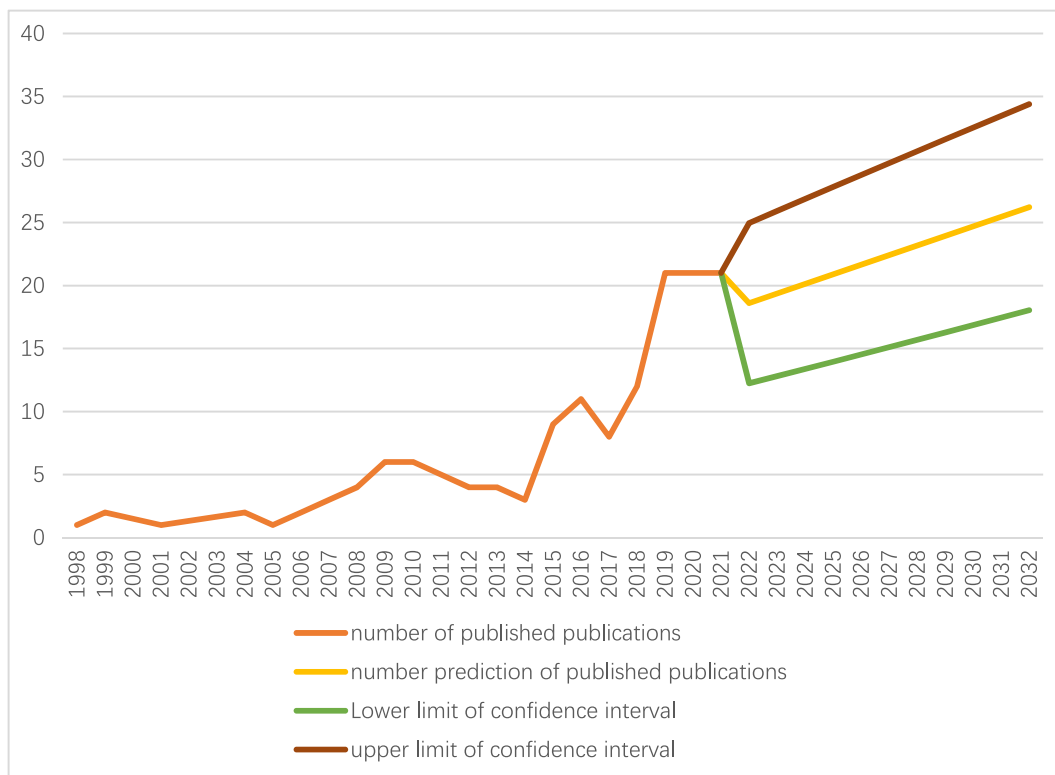
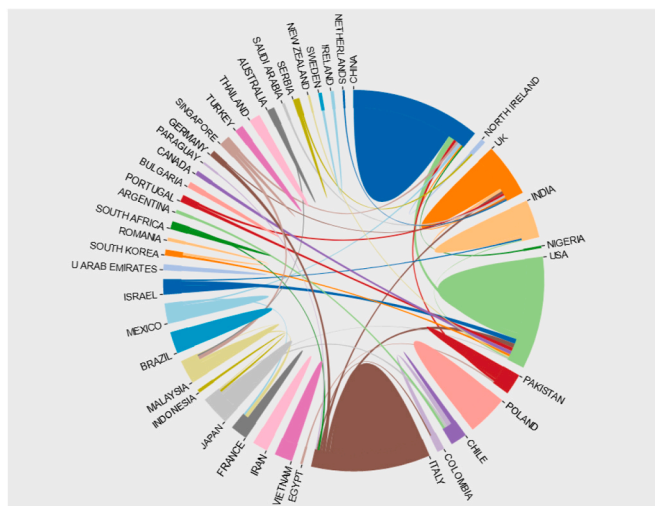


Fig. 4. The predicted curve of annual number of the published publications in the field of helicobacter biofilm in next decade.

helicobacter biofilms to date. Meanwhile, Keywords that appeared on average during earlier time periods were denoted by colors toward the blue end of the spectrum, while keywords that appeared later on average were denoted by colors toward the yellow end. As shown in Fig. 6B, most publications prior to 2016 appeared to focus on “biofilm” and “resistance” while “biofilm formation” and “in vitro” appeared to be a topic of focus in recent years and may become an important topic in the future. In 2016, the publications mainly focused on the formation of *Helicobacter pylori* biofilm in vitro, After 2 years of in-depth research, it began to turn to *Helicobacter pylori* biofilm therapy and in vivo research in 2018. The same identified keywords were mapped based on their density (Fig. 6C).

**Table 1**  
Top 5 leading counties related to *H. pylori* biofilm research from 1998 to 2023.

Counties	records	Total citations	Average citations
USA	65	1290	19.85
China	45	395	8.78
Japan	29	585	20.17
Italy	22	411	18.68
UK	13	65	5



**Fig. 5.** International collaboration between countries in the field of helicobacter biofilm. The countries were labelled using different colors and the links represented international collaborations.

**Table 2**  
Top 5 leading institutions related to *H. pylori* biofilm research from 1998 to 2023.

Institutions	Countries	records	Total citations	Average citations
Gabriele D'Annunzio university	Italy	12	290	24.17
Kyorin university	Japan	8	376	47
Wroclaw medical university	Poland	7	56	8
University of Concepcion	Chile	6	84	14
Sun yat sen university	China	6	98	16.33

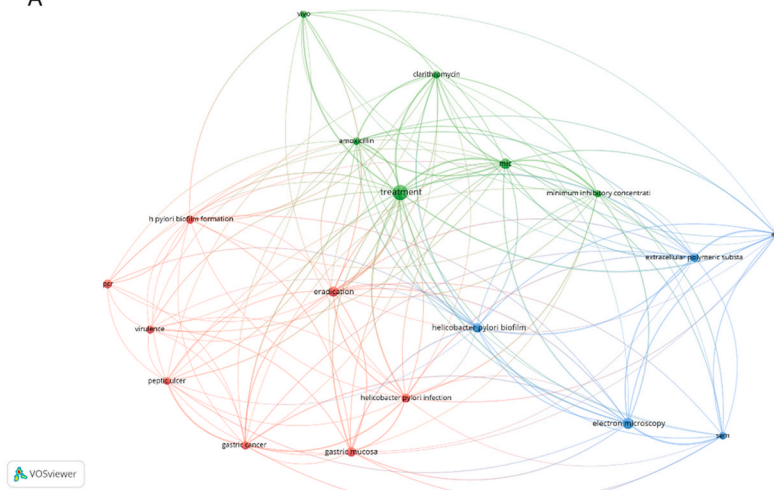
**Table 3**  
Top 5 leading authors related to *H. pylori* biofilm research from 1998 to 2023.

Authors	Countries	Institutions	Records	Citations	Average citations
Grande rossella	Italy	Department of Pharmacy, "G. d'Annunzio" University of Chieti-Pescara	10	218	21.8
Kamiya shigeru	Japan	Department of Infectious Diseases, Kyorin University School of Medicine	8	376	47
Osaki takako	Japan	Department of Infectious Diseases, Kyorin University School of Medicine	8	376	47
Yonezawa hideo	Japan	Department of Infectious Diseases, Kyorin University School of Medicine	8	376	47
Hanawa tomoko	Japan	Department of Infectious Diseases, Kyorin University School of Medicine	6	312	52

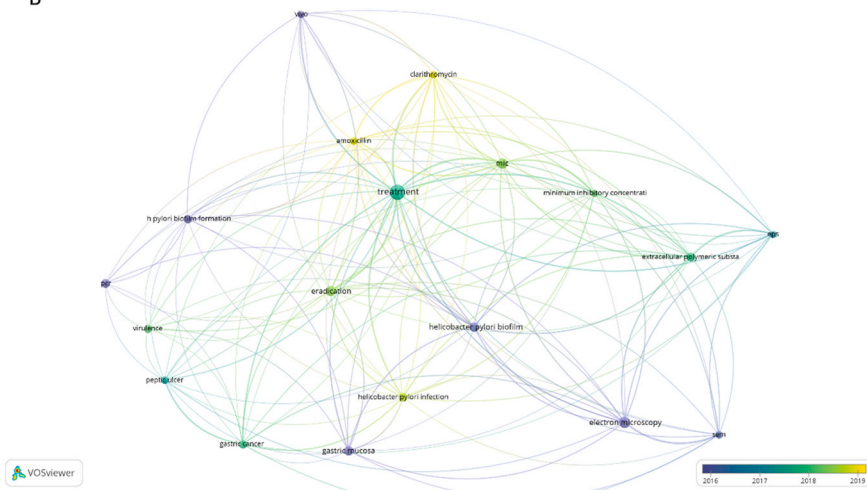
**Table 4**  
Top 5 leading journals related to *H. pylori* biofilm research from 1998 to 2022.

Journals	Records	Total citations	Average citations	H-index	JCR partition	IF(2023)
Helicobacter	12	24	2	71	Q1	4.4
Frontiers in microbiology	9	39	4.33	88	Q1	5.2
Journal of applied microbiology	5	65	13	140	Q2	4
Antibiotics-Basel	4	14	3.5	-	Q2	4.8
Scientific reports	4	9	2.25	149	Q1	4.6

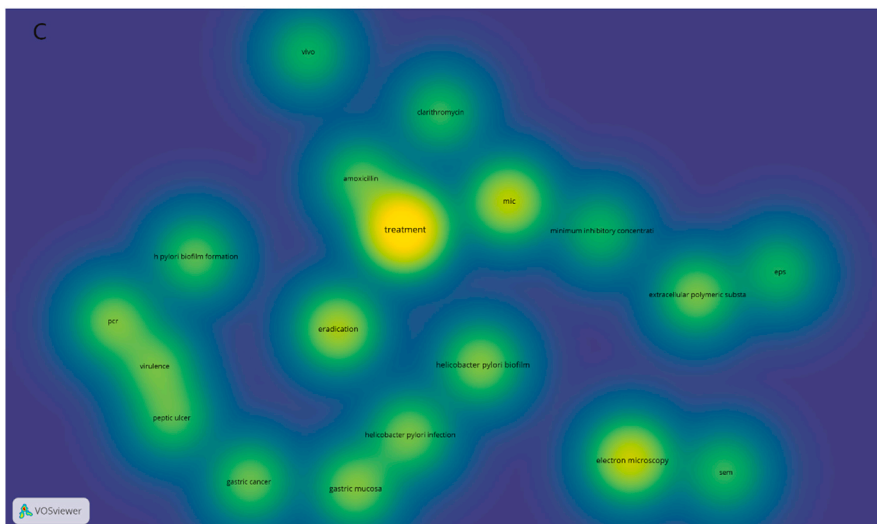
A



B



C



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**Fig. 6.** Keywords visualization related to *H. pylori* biofilm research from 1998 to 2022. (A) Network visualization of the keywords; (B) Time-based visualization of keywords variation; (C) Density visualization of the keywords. Dots represented keywords and larger dot indicated higher occurrence frequency of keywords, the clusters were labelled using different colors and the links represented the co-occurrence of keywords.

### 3.4. The most-cited articles

Among the five most-cited articles, 80 % were articles. The earliest was published in the JOURNAL of BACTERIOLOGY in early 2004 by Sheri P Cole, rank 2 with 76 citations. This study found that OMV produced from TK1402 play an important role in biofilm formation in strain TK1402 (*H. pylori*). The latest was published in MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS in 2018, rank 5 with 43 citations. The majority of the five most-cited articles (60%) were published in USA (Table 5). In addition, the important findings of these studies are also shown in Table 5, which focuses on the mechanism of *H. pylori* biofilm formation (Rank 1 and 2) and anti-biofilm strategies (Rank 4). A study first to photographically document the existence of *H. pylori* biofilms on human gastric mucosa in 2006 (Rank 3), therefore, it can be highly cited.

## 4. Discussion

For a researcher, bibliometric analysis can help recognize important advances in research on *H. pylori* biofilms and provide useful perspectives on historical developments in our research field, which can provide information about authors, institutions, and journals. To the best of our knowledge, this is the first comprehensive bibliometric analysis to reveal research trends in *H. pylori* biofilms.

Many researchers have reported biofilms in almost all natural and industrial ecosystems, especially in infectious diseases [15–20]. Bacterial biofilms can lead to chronic infection. *H. pylori* biofilm is a microecosystem formed by *H. pylori* attached to biological or abiotic surfaces. It increases the refractory of *H. pylori*, eventually leading to chronic persistent infection of *H. pylori* [21]. Initially, *H. pylori* was observed to form a water-insoluble biofilm in vitro, which was defined as a static cell aggregate in extracellular polymer [22,23]. *H. pylori* with biofilm status was also observed in the gastric mucosa of patients with peptic ulcer [24,25].

In this study, we used a combination of bibliometric and visualized analyses to determine the current state of the field of *H. pylori* biofilm research. These articles reflected major advances and trends in annual publications on *H. pylori* biofilms during the last two decades. Since the field was first picked up in 1998, there has been a steady increase in publication output in the field, leading up to 2023, with particularly dramatic increases observed over the past three to five years. The decline in the number of publications in 2020 may be linked to the global impact of COVID-19 globally [26]. This trend is due to the pronounced ability of *H. pylori* biofilms to increase the rate of antibiotic resistance in *Helicobacter* [27].

In our study, bibliographic coupling was found for publications arising from 253 institutions in 42 countries worldwide in the field that have appeared since 1998. The USA occupies a leading position in *H. pylori* biofilm research. In the past five years, the number of publications on *H. pylori* biofilm research in China has increased rapidly, but the total citations and average citations of publications from the USA were the highest, indicating that publications from the USA had the highest quality and academic influence in this field. In addition, the USA contributed >50% of the most-cited articles, demonstrating its overwhelming influence on medical research. More than half of the top five institutions were in Japan, indicating the high quality of articles published by Japanese institutions. Grande rossella, Kamiya shigeru, Osaki takako, Yonezawa hideo, and Hanawa tomoko had published many articles, and the latter four had closer cooperation and higher quality published articles, which can be regarded as the leader in this research field. At the same time, the journals of publications are concentrated in *Helicobacter* and *Frontiers in Microbiology*. *Helicobacter* is one of the top journals in the field of *H. pylori*.

Based on the publication trends observed in this study, it is likely that *H. pylori* biofilms will continue to be a research focus in the future, possibly with more studies focusing on biofilm formation, as indicated by co-occurrence analysis. Keywords co-occurrence analysis results showed that “*Helicobacter pylori*,” “biofilm” and “biofilm formation” were the most prominent keywords and the keywords identified into three clusters: (1) diagnosis and therapy, (2) antibiotic-resistance and biofilm, (3) biofilm formation, virulence and expression. Most publications prior to 2016 appeared to focus on “biofilm” and “resistance” while “biofilm formation” and “in vitro” appeared to be a topic of focus in recent years. Furthermore, we found that the development trend of this research field is from the observation of bacterial biofilms to the establishment of *H. pylori* biofilms in an in vitro model and the mechanism of *H. pylori* biofilm formation. In addition, the top five cited articles observed in this study focused on the mechanism of *H. pylori* biofilm formation and anti-biofilm strategies. These articles were highly cited because they are innovative. For example, first to photographically document the existence of *H. pylori* biofilms on human gastric mucosa, visually reveal the threat of *H. pylori* biofilm.

In recent years, many scholars have attempted to establish a model of *H. pylori* biofilms and seek drugs that interfere with biofilm formation in vitro [9,28–30]. Over the past five years, Chinese Professor YD Sun [31,32] of Shandong University and Professor H Yang [33–35] of Shanghai Jiao Tong University have published many articles in this field. There are two construction methods for *H. pylori* biofilms in vitro: dynamic and static [36,37]. Serum starvation can induce the formation of *H. pylori* biofilms [31]. In addition, some studies have explored the relationship between the biofilm-forming ability of *H. pylori* strains and antibiotic resistance; it was found that there was no significant difference in biofilm formation between resistant and antibiotic-sensitive strains [38]. However, a recent study that used 24 *H. pylori* strains with different sensitivities (levofloxacin, clarithromycin, and metronidazole) by the microfluidic system for the first time confirmed that the biofilm ability of multidrug-resistant *H. pylori* strain was the strongest [39]. The relationship between *H. pylori* biofilm formation and antibiotic resistance requires further study. In addition, new drugs for *H. pylori* biofilm intervention have recently emerged, such as nanomaterials, Chinese herbal extracts, and probiotics [40–45], but the

**Table 5**  
The top 5 cited papers in *H. pylori* biofilm.

Citations	Title	Important findings	Study type	Year	Country	Journal	Authors
86	Outer membrane vesicles of <i>Helicobacter pylori</i> TK1402 are involved in biofilm formation.	OMV produced from TK1402 play an important role in biofilm formation in strain TK1402	article	2009	Japan	BMC Microbiology	Hideo Yonezawa
76	Characterization of monospecies biofilm formation by <i>Helicobacter pylori</i> .	The quorum-sensing gene, luxS, and the cagE type IV secretion gene were associated with <i>H. pylori</i> biofilm formation.	article	2004	USA	JOURNAL OF BACTERIOLOGY	Sheri P Cole
53	Identification of <i>Helicobacter pylori</i> biofilms in human gastric mucosa.	First to photographically document the existence of <i>H. pylori</i> biofilms on human gastric mucosa.	article	2006	USA	JOURNAL OF GASTROINTESTINAL SURGERY	Michael A Carron
52	Multidimensional effects of biologically synthesized silver nanoparticles in <i>Helicobacter pylori</i> , <i>Helicobacter felis</i> , and human lung (L132) and lung carcinoma A549 cells.	AgNPs have multidimensional effects such as anti-bacterial and anti-biofilm activity against <i>H. pylori</i> .	article	2015	Korea	Nanoscale Research Letters	Sangiliyandi Gurunathan
43	<i>Helicobacter pylori</i> Biofilm Formation and Its Potential Role in Pathogenesis.	Discuss the potential roles of <i>H. pylori</i> biofilms in the failure of antibiotic treatment and in infection recurrence.	review	2018	USA	MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS	Skander Hathroubi, Stephanie L Servetas

mechanism by which they reduce *H. pylori* biofilm formation is not clear.

*H. pylori* biofilms remain a niche research field. More and more study occurred in recent 5 years, although its IF was not high, it is meaningful for long-term academic development in the future. These results may represent rapidly evolving topics in the field of *H. pylori* biofilm research, where substantial research activity has already begun, and will see significant developments in the near future, such as reducing biofilm formation of *H. pylori* thus increasing the eradication rate of *H. pylori*. There are some limitations to our study. First, we only included English language journals. Second, we only searched the Web of Science database, and the publication type only included original articles and review articles.

Although significant progress has been made in understanding *H. pylori* biofilm formation and developing potential eradication methods, further studies are needed to evaluate the pharmacological effects, efficacy and safety of these treatments in animal models and clinical trials. By addressing these research gaps, we can achieve more effective and personalized strategies to combat *H. pylori* infection and its related complications.

## 5. Conclusion

In conclusion, our study demonstrated the twenty-year span of global *H. pylori* biofilm trends based on bibliometric and visualized analyses of publication data. The USA made the greatest contributions to this research field, while the Journal of Helicobacter produced the greatest number of relevant articles. The annual number of publications on *H. pylori* biofilms has grown steadily over the past two decades and is expected to continue to grow. Future studies should focus on evaluate the pharmacological effects, efficacy and safety of these anti-biofilm treatments in animal models and clinical trials.

## Authors contributions

YX designed the experiment and supervised the study; JYW and YH contributed to the formal analysis and wrote the manuscript; YX reviewed and revised the manuscript. All authors have read and approved the final manuscript.

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## Ethics approval and consent to participate

Not applicable.



## Consent for publication

All authors consent for publication.  
The preprint was previously published [Wang JY et al., 2022] [46].

## Data availability statement

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

## CRedit authorship contribution statement

**Jinyun Wang:** Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Yang Hu:** Writing – original draft, Software, Formal analysis. **Yong Xie:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

## Declaration of competing interest

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

## Data availability

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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