

A global bibliometric and visualized analysis in the state of *Pseudomonas aeruginosa* efflux pump research

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Abstract

OBJECTIVE. This study was designed with the goal of surveying the current status of the *Pseudomonas aeruginosa* efflux pump research field in an effort to explore current and future trends in this clinically relevant research area.

METHODS. Bibliometric and visual analyses were used to conduct a global survey of the current status of *Pseudomonas aeruginosa* efflux pump research. All studies regarding *Pseudomonas aeruginosa* efflux that were published from 1994 to 2019 were retrieved from the Web of Science database, after which we conducted bibliographic coupling, co-authorship, co-citation, and co-occurrence analyses, and analyzed trends in *Pseudomonas aeruginosa* efflux pump research publications using the VOS Viewer software.

RESULTS. We identified 2583 total publications that were included in this study. The number of relevant studies from around the world was found to be rising over time. The USA was identified as a central player in this research field at a global level, as studies from the USA had the most citations, the highest H-index values, and the greatest total link strength. Three primary research directions were identified through this analysis, including studies of efflux pump resistance mechanisms, transfer mechanisms, and inhibitors.

CONCLUSIONS. Our visual analysis provides a quantitative overview for researchers who wish to quickly understand the past and current dynamics of the field of *Pseudomonas aeruginosa* efflux pump research. Overall, these findings suggest that future studies of efflux pump resistance mechanisms and efflux pump inhibitors may aid in overcoming clinical *Pseudomonas aeruginosa* resistance.

1. Introduction

Pseudomonas aeruginosa is an opportunistic pathogen responsible for high rates of nosocomial infections and mortality. *P. aeruginosa* strains commonly exhibit high rates of antibiotic resistance that are primarily attributable to the activity of the bacterial efflux pump system. Indeed, *P. aeruginosa* efflux pump research has become an area of active research interest in recent years¹⁻³. Efflux pump systems are commonly expressed by Gram-negative bacteria, and enable these microbes to expel drugs⁴. High levels of efflux pump expression can lead to robust drug resistance. Efflux pump systems are separated into five families based upon sequence homology and structural characteristics including the resistance nodulation cell division (RND), major facilitator super (MFS), multidrug and toxic compound extrusion (MATE), small multidrug resistance (SMR), and ATB-binding cassette (ABC) families. RND family efflux pump overexpression is the most common cause of multi-drug resistance in clinical *P. aeruginosa* isolates^{1,5}. Studies of *P. aeruginosa* efflux mechanisms offer valuable insights into the antibiotic resistance properties of these bacteria, highlighting novel approaches to developing new drugs to treat these dangerous bacterial infections.

Herein, we studied trends in the field of *P. aeruginosa* efflux pump research, using online databases to conduct bibliometric analyses in an effort to quantitatively evaluate the relative contributions of different

researchers, countries, and institutions⁶. Such analyses have previously been utilized to guide the design of clinical policies and guidelines⁷, and provide the added benefit of making research areas more transparent and approachable^{8,9}. To the best of our knowledge, no such bibliometric analyses of the *P. aeruginosa* efflux pump research field have been performed to date. As such, this study was designed to specifically evaluate trends in this field of research.

2. Materials And Methods

2.1. Data sources

These bibliometric analyses were conducted using the Science Citation Index-Expanded (SCI-E) database from the Web of Science (WoS)¹⁰.

2.2. Search strategy

Relevant studies published in the Web of Science as of December 31, 2019 were identified using the following search strategy: theme = *Pseudomonas aeruginosa* efflux pump * AND publishing year = (1994–2019) AND Language = (English) AND Document type = (ARTICLE OR REVIEW). Data regarding particular countries and regions was established through WoS indexing. In total, 2583 records were retrieved for analysis.

2.3. Data collection

For each publication, records pertaining to the year of publication, title, authors, nationality, affiliation, keywords, abstract, and journal were downloaded from the Web of Science in the form of a .txt document which was imported into Microsoft Excel 2016. These data were independently extracted by the authors of this study, and any inconsistencies were resolved through discussion or consultation of experts. GraphPad Prism 5 was used to analyze all data.

2.4. Bibliometric analysis

Basic characteristics of included studies were described using the functions of Web of Science. H-index values were used to measure the impact of these studies, and were calculated based upon h having published h studies that have been cited at least h times¹¹, providing a combined summary of publications and citations per publication. This index is thus a better indicator of scientific achievement relative to total numbers of papers or citations.

2.5. Visualized analysis

VOSviewer is a free bibliometric analytical program designed by Nees Jan van Eck and Ludo Waltman of the University of Leiden (The Netherlands) that allows for bibliometric map construction based upon co-citation principles in a range of research fields. These analyses facilitate overviews of research progress in different countries, institutions, and research teams while highlighting key journals and publications in

a given research context. These analyses also allowed us to identify key trends and future directions in this field, displaying these results in a readily-interpretable visual format ¹².

3. Results

3.1. *P. aeruginosa* efflux pump systems

Gram-negative bacteria possess efflux pump systems composed of an inner membrane transporter, an outer membrane channel, and membrane fusion proteins. Efflux activity does not require a given substrate to accumulate within the periplasmic space, indicating that these compounds are efficiently expelled through the inner and outer membranes (Fig. 1) ¹³. RND efflux pumps are able to effectively remove antimicrobial compounds from the cytoplasm through this mechanism (Poole 2004¹⁴; Piddock 2006¹⁵; Lister et al. 2009¹⁶). To date, 12 RND-type efflux pump systems have been described for *P. aeruginosa*, including the MexAB-OprM ¹⁷, MexCDOprJ ¹⁸, MexEF-OprN ¹⁹, MexXY²⁰, MexJK ²¹, MexGHI-OpmD ²², MexVW-OprM ²³, CzcCBA ^{24,25}, TriABC-OpmH ²⁶, MuxABC-OpmB ²⁷, MexPQOpmE, and MexMN-OprM ²⁸ systems. Given the low permeability of the outer bacterial membrane and the high efficiency of active efflux, these systems are key to the expulsion of antibiotics from these bacteria.

3.2. Global publication trends

3.2.1. Numbers of publications

We identified 2583 total studies published from 1994–2019 that met our search criteria. While 1994 was the first year in which a relevant study was published, the majority of identified studies were published from 2009–2019 (1915, 74.14%), indicating an upward publication trend in this field (Fig. 2b)

3.2.2. Contributions of individual nations

The countries that made the largest contributions to the field of *P. aeruginosa* research are shown in Fig. 2a. The USA published the largest number of articles in this field (759, 29.38%), followed by the UK (266, 10.30%), China (254, 8.94%), Japan (231, 8.94%), France (221, 8.56%), Canada (173, 6.70%), Spain (151, 5.85%), Germany (111, 4.30%), India(90, 3.48%), and Switzerland (64, 2.48%)(Fig. 2c).

3.3. Publication quality

3.3.1. Total citation frequencies

The overall frequency of research pertaining to *P. aeruginosa* efflux pumps was 112,062, the total number of citations removed from the citation is 87,308—the index of the cited article is 52,656, and the citation index for the self-introduction is 50,484, the average citation is The number of times is 46.81 and the h-index is 159. This underscores the rapid developments in the field of *P. aeruginosa* efflux pump research, and suggests that this is an active and collaborative research field. Publications from the USA exhibited

the greatest number of total citations (39,290), followed by Japan (9,569), the UK (9,342), Canada (9,163), France (8,951), Spain (6,504), Germany (4,970), Switzerland (3,462), Denmark (3,383), and Belgium (2,381) (Fig. 3a).

3.3.2. Average citation frequency

Publications from Denmark exhibited the highest average number of citations (89.03), followed by those from the UK (67.21), Canada (64.99), the USA (64.83), Switzerland (62.95), Germany (55.22), Belgium (54.11), Spain (50.42), Japan (49.07), and France (48.12) (Fig. 3b).

3.3.3. H-index values

Average H-index values were highest for relevant studies from the USA (104), followed by those for studies from Japan (52), Canada (51), England (50), France (49), Spain (45), Germany (37), Switzerland (32), Denmark (24), and Belgium (24) (Fig. 3c).

3.4. Bibliographic coupling analysis

We next performed bibliographic coupling analyses to evaluate the similarity relationships between different articles. Bibliographic coupling occurs when a given pair of articles cite a common third article, and serves as an indicator that these studies are focused on related topics.

3.4.1. Journal

A total of 134 journals were identified in this study and were analyzed using VOSviewer (Fig. 4a). The journals with the highest link strength values were, in order, Antimicrobial Agents and Chemotherapy (IF = 4.904, 2019, total link strength = 183,120 times), Journal of Bacteriology (IF = 3.004, 2019, total link strength = 88,379 times), Frontiers in Microbiology (IF = 4.235, 2019, total link strength = 78,825 times), The Journal of Antimicrobial Chemotherapy (IF = 5.439, 2019, total link strength = 53,582), PLOS ONE (IF = 2.24, 2018, total link strength = 50,901 times), and Clinical Microbiology Reviews (IF = 20.642 total link strength = 36,328 times).

3.4.2. Institutions

We assessed studies from 173 different research institutions in the present analysis, focusing on institutions with more than five publications (Fig. 4b). The institutions with the highest total link strength values were, in order, Univ Calif Berkeley, Csic, Queens Univ, Univ Oklahoma, and Unic Cambridge (with total link strength values of 107,430, 102,171, 95,375, 75,888, and 62,932 times, respectively).

3.4.3. Countries

We analyzed articles from 74 different countries in this analysis using VOSviewer, focusing specifically on countries with more than five publications (Fig. 4c). The countries with the greatest total link strength

values in this analysis were, in order, the USA, France, Japan, Canada, and the UK (with total link strength values of 694,743, 306,153, 299,809, 272,971, and 228,589 times, respectively).

3.5. Co-authorship analysis

3.5.1 Authors

A co-authorship analysis was used to evaluate the linkage strength based upon numbers of co-authored papers. In total, we identified 206 authors with over 5 documents (Fig. 5a). The authors with the greatest total linkage strength values were, as follows, Lee VJ, Lomovskaya O, Nakae T, Nishino Kunihiro, and Nakayama K (with total linkage strength values of 77, 64, 64, 64, and 50, respectively).

3.5.2. Institutions

We identified institutions with over 5 publications (Fig. 5b), and found that the institutions with the greatest total linkage strength values were, as follows, Osaka University, the University of Copenhagen, Colorado State University, Rigshosp, and Csic (with total linkage strength values of 32, 27, 22, 22, and 21, respectively).

3.5.3. Countries

We identified 51 total countries with over 5 publications in this study (Fig. 5c). The countries with the greatest total link strength were the USA, France, the UK, Germany, and Japan (link strength scores of 200, 97, 81, 70, and 64, respectively).

3.6. Co-citation analysis

3.6.1. Authors

A co-citation analysis was conducted based upon the number of times articles were cited together. We identified 867 references with over 20 citations (Fig. 6a). The authors with the greatest total linkage strength values in this analysis were, in order, Poole K, Nikaido H, Li XZ, Lomovskaya O, and Piddock LVJ (with total link strength scores of 66,431, 53,932, 53,887, 36,379, and 30,502 times, respectively).

3.6.2. Journal

Next, a co-citation analysis of 475 identified journals with over 20 citations was conducted (Fig. 6b). The journals with the highest total link strength values were, in order, Antimicrob Agents Chemother, J Bacteriol, J Antimicrob, Mol Microbiol, and P Nat Acad Sci USA (with total link strength scores of 1,489,446, 873,877, 593,826, 379,217, and 329,069 times, respectively).

3.7. Co-occurrence analysis

A co-occurrence analysis was additionally performed with the goal of identifying research directions within this field based upon specific keywords that were used at high frequencies in published studies ²⁹.

We specifically focused on keywords that were used five or more times in titles and abstracts, leading to the identification of 651 keywords that we were able to classify into three primary clusters: “Efflux pump resistance mechanism research”, “Multidrug efflux transporter mechanism research”, and “Efflux pump inhibitor research” (Fig. 7a). This suggests that these are primary areas of research interest in the *P. aeruginosa* efflux pump research field.

We additionally separated these keywords by color based on the frequencies with which they appeared in included publications in a time-dependent fashion, with blue and red keywords corresponding to terms that appeared less recently and more recently, respectively (Fig. 7b). This approach suggested that most research before 2019 was primarily focused on “resistance molecular mechanism research” and “transfer mechanism research”, whereas “inhibitor research” represents a growing area of future research interest.

4. Discussion

4.1. Trends in *Pseudomonas aeruginosa* efflux pump research

Bibliometrics and visual analyses provide a high-level overview of a given research field, offering key insights regarding the top researchers, institutions, and countries active in a given area of research. By analyzing these trends and assessing core research topics in a given field, it is possible to gauge and guide future research directions^{30,31}. The *P. aeruginosa* efflux pump system enables these clinically relevant pathogens to resist antibiotic treatment³², and it is thus a topic of significant research interest. We therefore surveyed the field of *P. aeruginosa* efflux pump research with respect to contributing countries, institutions, and research topics, revealing clear increases in the volume of research in this field in recent years. Overall, we found that 74 countries had published articles in this research field, including 759 articles (29.38%) from the USA, which was also home to 6 of the top 10 most productive journals in this research field. The prominence of the USA in this field may be associated with social and economic trends, or with the overall strength of research in this nation.

4.2. Global publication quality and status

The H-index was first proposed by J. E. Jirsch in 2005 as a superior metric for individual scientific research performance³³, yielding an effective balance between quality and quantity. Researchers that focus specifically on quantity are less likely to explore important research topics in detail, making it vital that quantity not be the sole focus of research output. Total numbers of citations and H-index values for a given country thus correspond to the quality and impact of its publications. We found that the USA had made the greatest contributions to the field of *P. aeruginosa* efflux pump research, followed by Japan, France, Canada, and the UK with respect to both H-index value and numbers of publications. Denmark had the highest average number of citations, whereas China exhibited the seventh-highest total number of publications but had H-index values and total numbers of citations which did not rank in the top 10 of analyzed nations. This discrepancy between the number of citations and the number of publications

from China may be attributable to the fact that the Chinese academic system primarily focuses on publication quantity rather than quality³⁴. This has led the Chinese government to call for the reorientation of academic evaluation processes, and as the quality of these publications improves, Chinese publication trends may become more consistent with those of global publications in this field.

Journals shown in Fig. 4a represent the primary sources of publications in the *P. aeruginosa* efflux pump research field, including Antimicrobial Agents and Chemotherapy (USA), the Journal of Bacteriology (USA), the Journal of Antimicrobial Chemotherapy (USA), PLOS One (The UK), and the International Journal of Antimicrobial Agents (The Netherlands). Research institutions from the top 5 countries have made significant contributions to this field, and thus represent important centers for future academic exchange and cooperation. These institutions include Consejo Superior De Investigaciones Cientificas Csic (Spain), Centre National De La Recherche Scientifique Cnrs (France), the University of California System (USA), Csic Centro Nacional De Biotecnologia Cnb (Spain), and Aix Marseille Universite (France). The top nations from which these studies originated were distinct from the nations wherein the top five journals were published, suggesting that American journals remain the most prominent in this field. Almost all of the top 20 research institutions were located in the top 6 nations (the USA, Japan, France, Canada, the UK, and Spain), suggesting that these countries are home to first-class research institutions that are improving their overall academic rankings.

We additionally performed a bibliographic coupling, co-authorship, and co-citation analyses to better understand the collaborative nature of research in the *P. aeruginosa* efflux pump field. These analyses revealed that Antimicrobial Agents and Chemotherapy is the most frequently cited journal in this field, that the USA is the leading nation in this field with respect to research output, and that articles published by Poole K are the most commonly cited with a total link strength of 66,431 times. In 1995, this author published in Antimicrobial Agents and Chemotherapy that “some proteins contribute to the intrinsic resistance of *P. Aeruginosa* through the multi-drug active efflux process.”³⁵. Many other prominent researchers likely to shape this research field are also listed in this study, and their research output should be closely monitored to clearly identify the latest developments in this field.

4.3. Trends in *Pseudomonas aeruginosa* efflux pump research

Co-occurrence analyses can be used to define popular areas of research in a given field and to predict future research trends associated with a given discipline. As such, we performed a co-occurrence analysis of keywords appearing more than 5 times in the titles and abstracts of articles included in this study, enabling us to classify these 651 keywords into three primary clusters: “Efflux pump resistance mechanism research”, “Efflux pump transfer mechanism research”, and “Efflux pump inhibitor research”. This suggests that these are the three main *P. aeruginosa* efflux pump research topics at present. When we assessed time-dependent trends in the frequencies with which these keywords were used, we found that most studies before 2019 had focused upon “resistance mechanism research”, and “transfer mechanism research”, whereas “inhibitor research” is likely to be a primary focus of future research.

4.4 Strengths and limitations

This study utilizes a bibliometric and visualized analysis approach to analyze the current status and trend of development of *Pseudomonas aeruginosa* efflux pump research. This gives a large amount of information that reveals important trends through many different dimensions. Nevertheless, the analyses are hardly without certain limitations. First, it surveyed just the publications in the WoS database. Although WoS is the most frequently used and trusted search engine, a few outlier publications might not have been included. Second, only English language studies from the WoS database were included in the analysis, leading to language bias. Third, the standardization of terms were completed based on findings on the VOSviewer®, and may not be accurate in certain cases, which causes another sort of bias. For example, some authors might have different spelling of names, This might generate inaccurate research output for these authors.

5. Conclusion

Rates of *P. aeruginosa* multidrug resistance are steadily rising, posing a significant threat to human health. Active efflux pump systems mediate *P. aeruginosa* resistance to antibiotics, thereby improving the pathogenicity and stress resistance of these bacteria. Our results indicate that the USA remains a global leader in *P. aeruginosa* efflux pump research, with most studies of this topic having been published in the Antimicrobial Agents and Chemotherapy journal. Poole K is the most cited researcher in this field, and future studies of new antibiotics that are not efflux pump substrates or of the use of EPIs to inhibit efflux pump activity hold great promise.

Declarations

Funding Information

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Ruiqin Zhang: Conceptualization-Equal, Data curation-Equal, Formal analysis-Equal, Writing-original draft-Supporting, Writing review & editing-Supporting;

Siyang Wang: Conceptualization-Equal, Formal analysis-Equal, Investigation-Equal, Writing-original, draft-Lead, Writing-review & editing-Lead;

Jian Ren: Data curation-Equal, Investigation-Equal, Methodology-Equal, Writing review & editing-Supporting;

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Hongxia Wang: Data curation-Equal, Investigation-Equal, Methodology-Equal, Writing review & editing-Supporting;

Tingting Zhi: Data curation-Equal, Investigation-Equal, Methodology-Equal, Writing review & editing-Supporting;

Yuanyuan Zhu: Conceptualization-Equal, Formal analysis-Equal, Supervision-Equal, Writing-review & editing-Equal;

Yanhui Wang: Data curation-Equal, Investigation-Equal;

Zhiqing Yao: Data curation-Equal, Investigation-Equal;

Huizi Zhang : Data curation-Equal, Investigation-Equal;

Jinju Duan: Conceptualization-Equal, Formal analysis-Equal, Funding acquisition-Lead, Supervision-Equal, Writing-original draft-Supporting, Writing-review & editing-Equal.

ETHICS STATEMENT

None required.

Consent for publication

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Figures

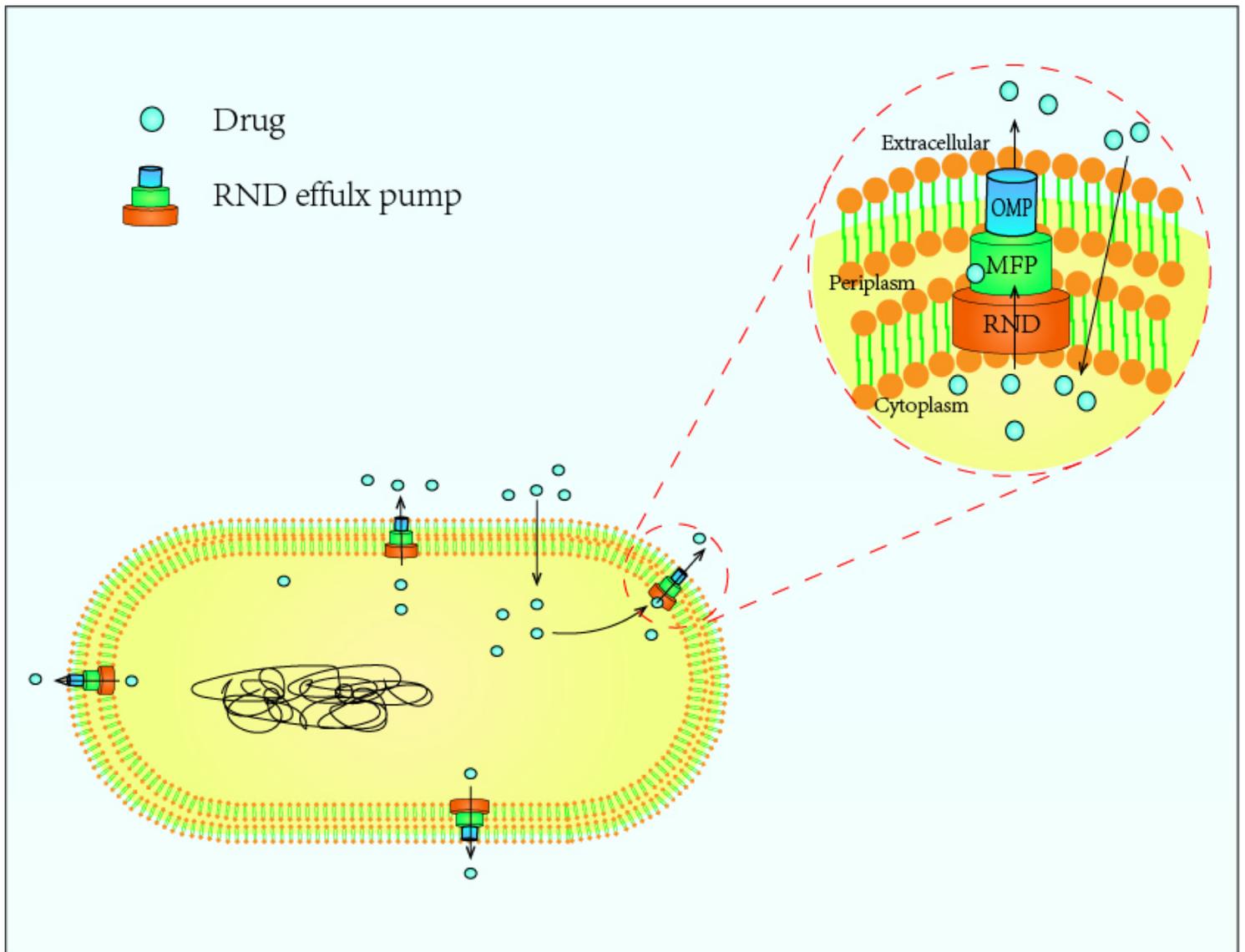


Figure 1

An overview of *Pseudomonas aeruginosa* RND efflux pump structure

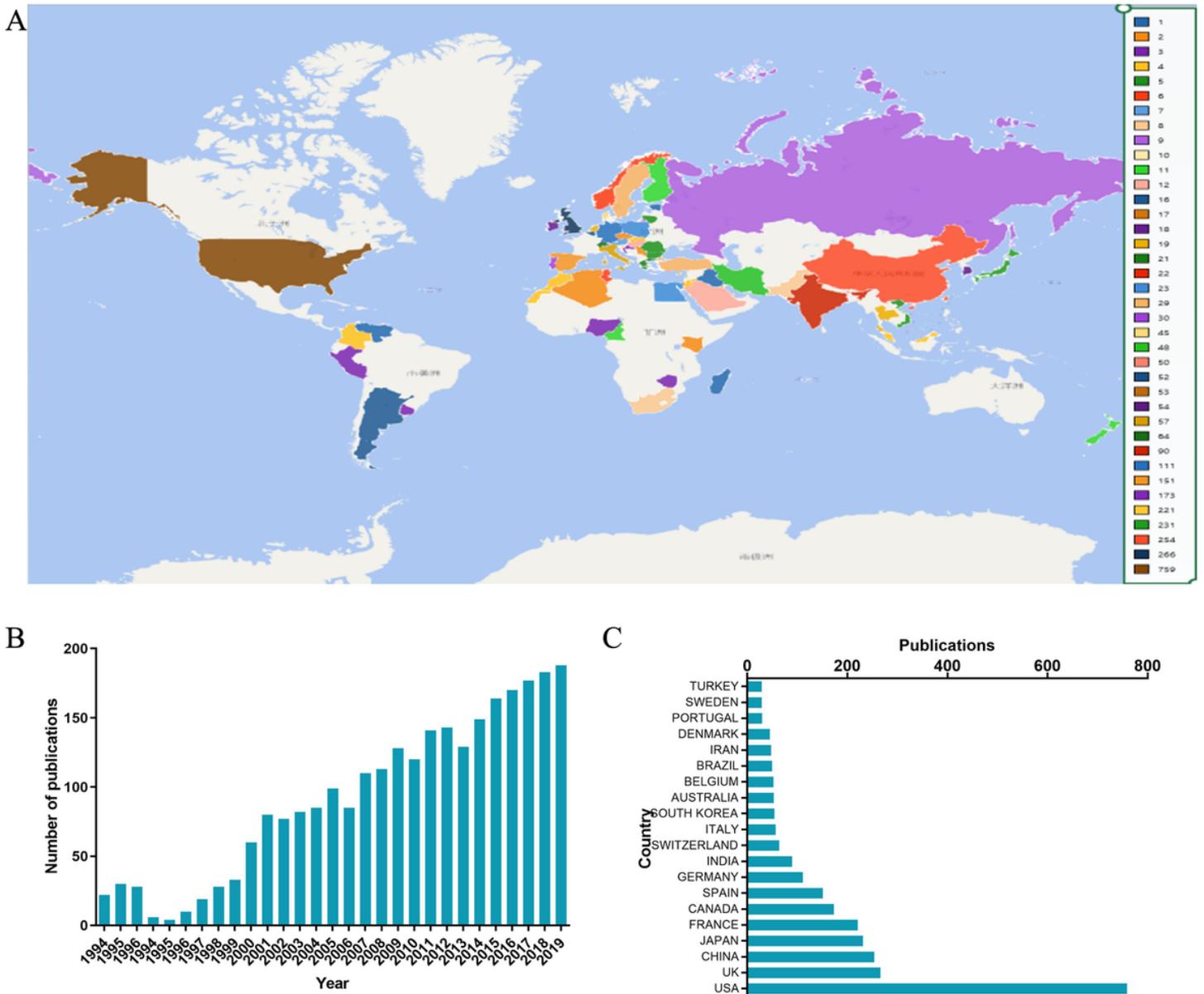


Figure 2

Global trends in *P. aeruginosa* efflux pump research. (a) A world map highlighting *P. aeruginosa* efflux pump research distribution patterns. (b) Numbers of publications per year over the past 25 years in the field of *P. aeruginosa* efflux pump research. (c) The total number of relevant articles from the top 20 countries.

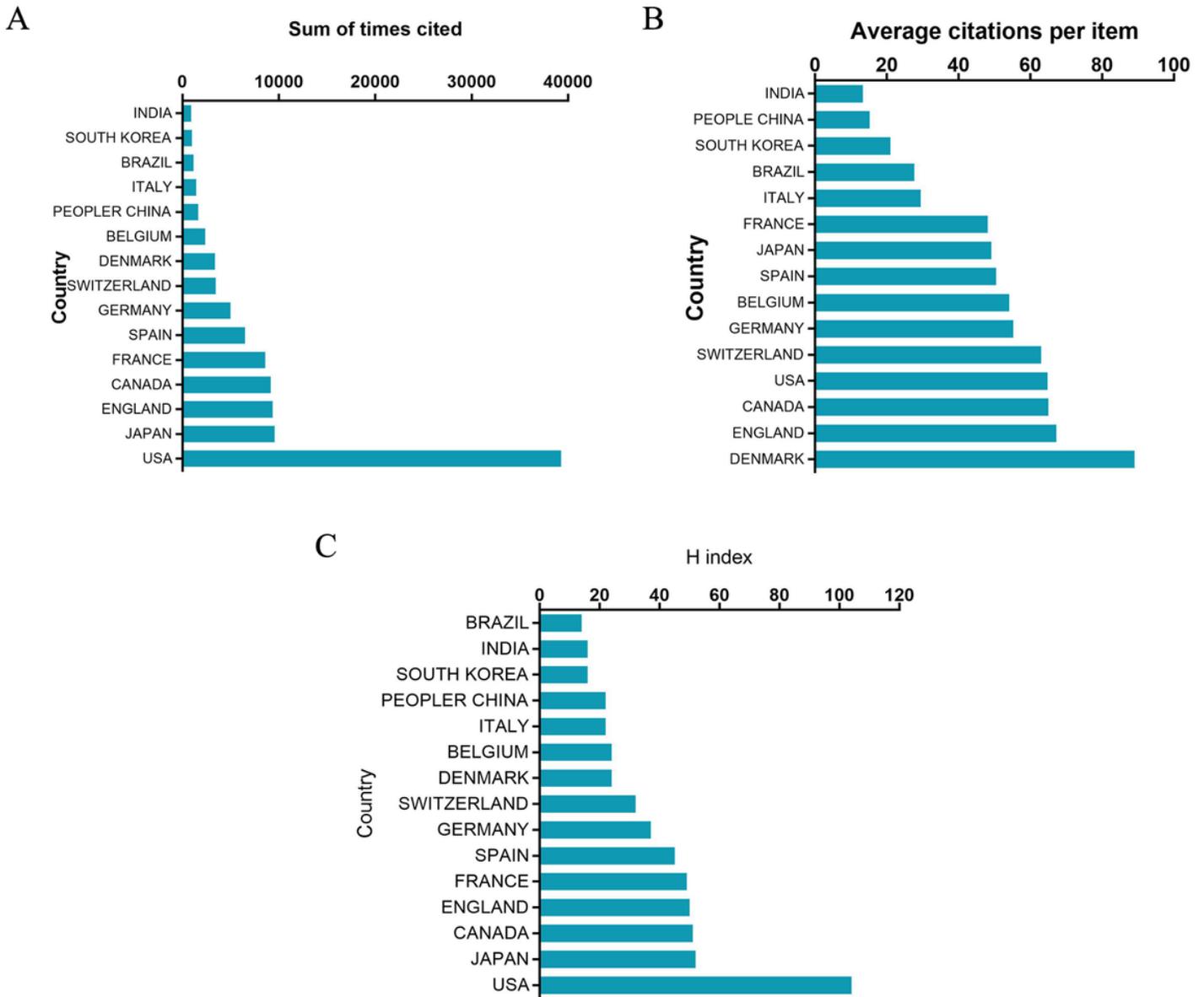


Figure 3

Citation frequencies and H-index values in different nations. (a) Total *P. aeruginosa* efflux pump research-related citations from the indicated nations. (b) Average citations per paper for articles from the indicated nations. (c) H-index values for publications from the indicated nations.

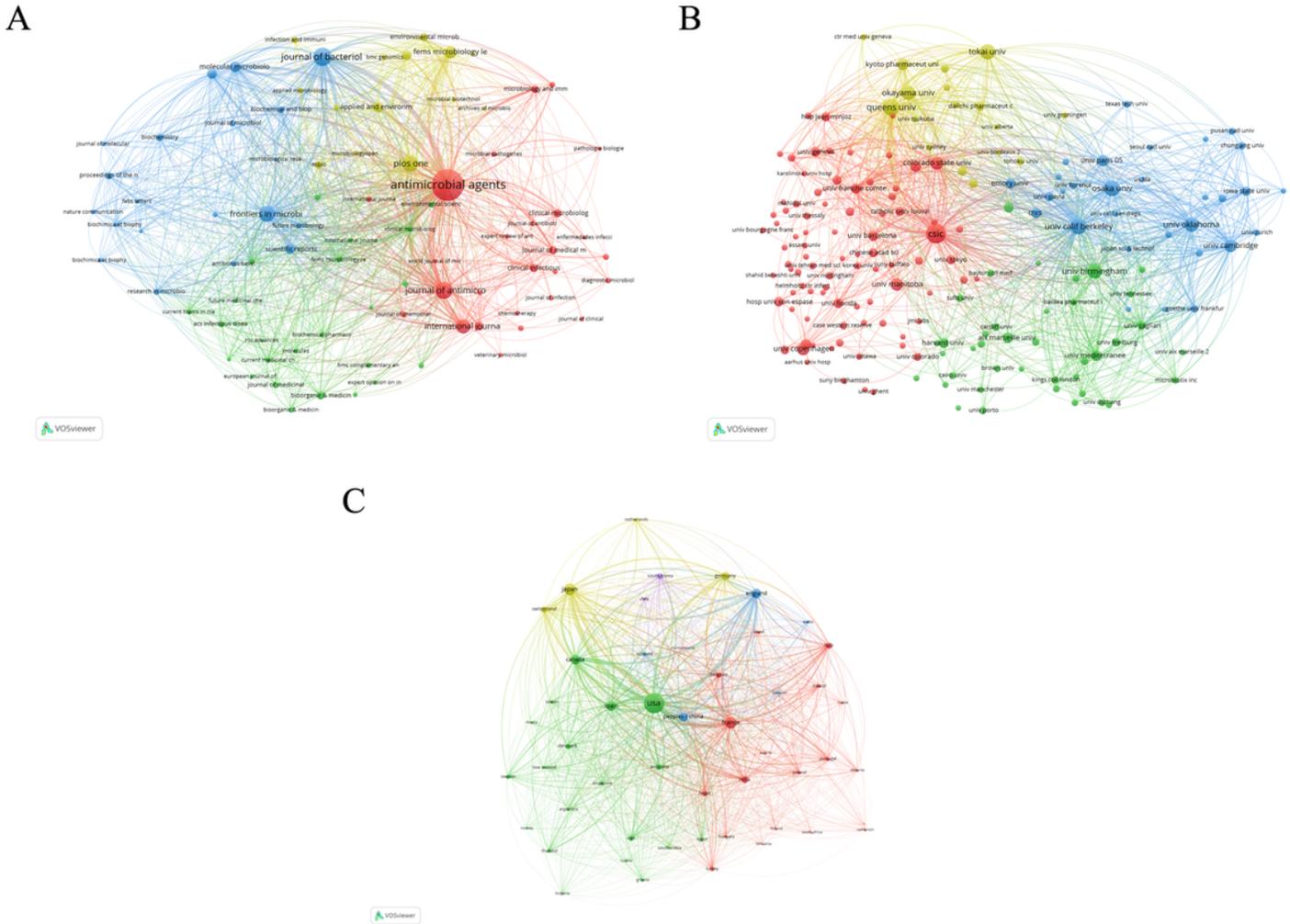


Figure 4

A Bibliographic analysis of global *P. aeruginosa* efflux pump research trends. (a) An overview of the 134 different journals in which *P. aeruginosa* efflux pump-related research has been published. (b) An overview of the 173 research institutions associated with publishing *P. aeruginosa* research to date. (c) An overview of the 74 countries that have published research in this field. Lines between two pounds correspond to journals, countries, and institutions with an established similarity relationship. Thicker lines correspond to closer associations between these journals/institutions/countries.

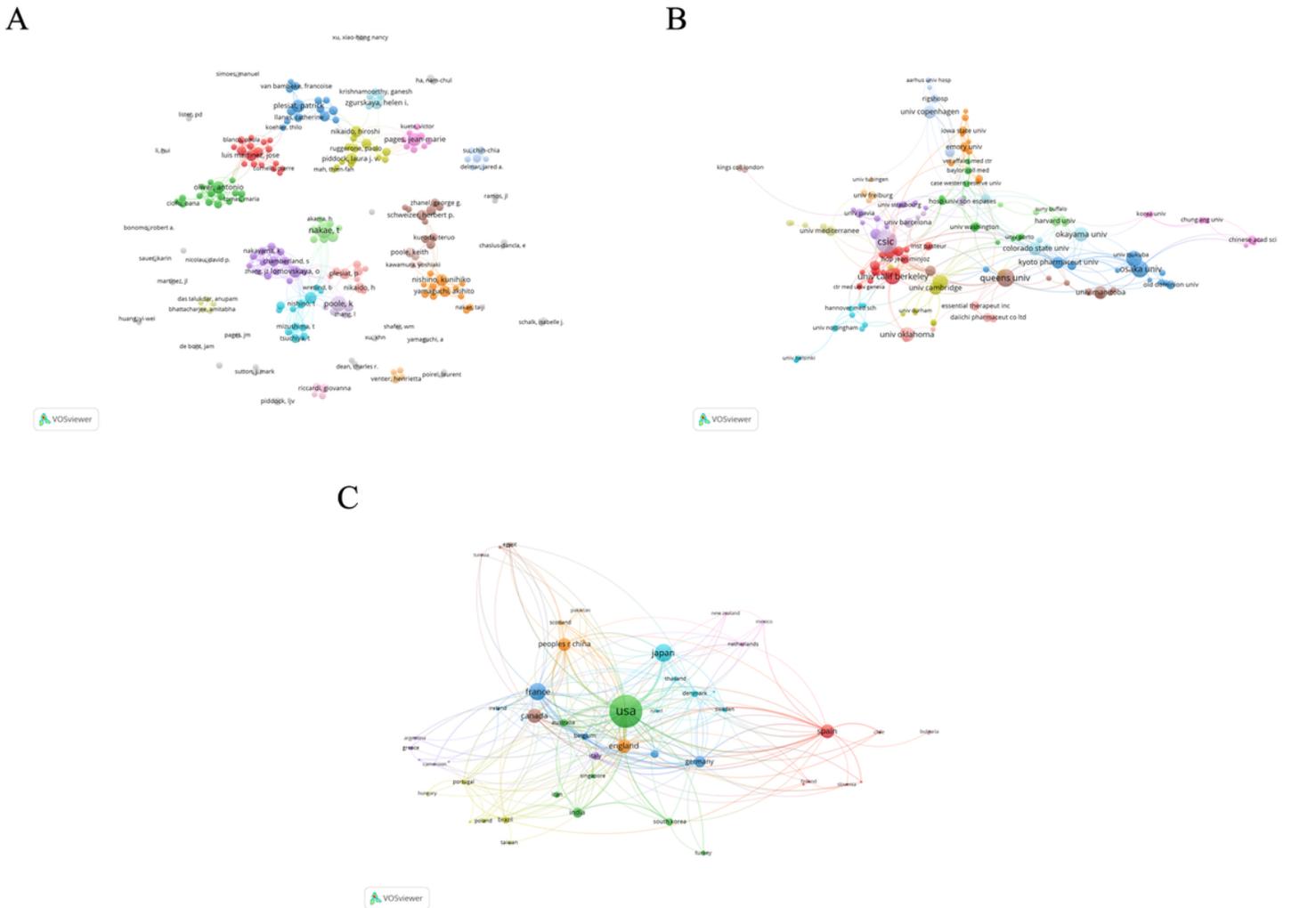
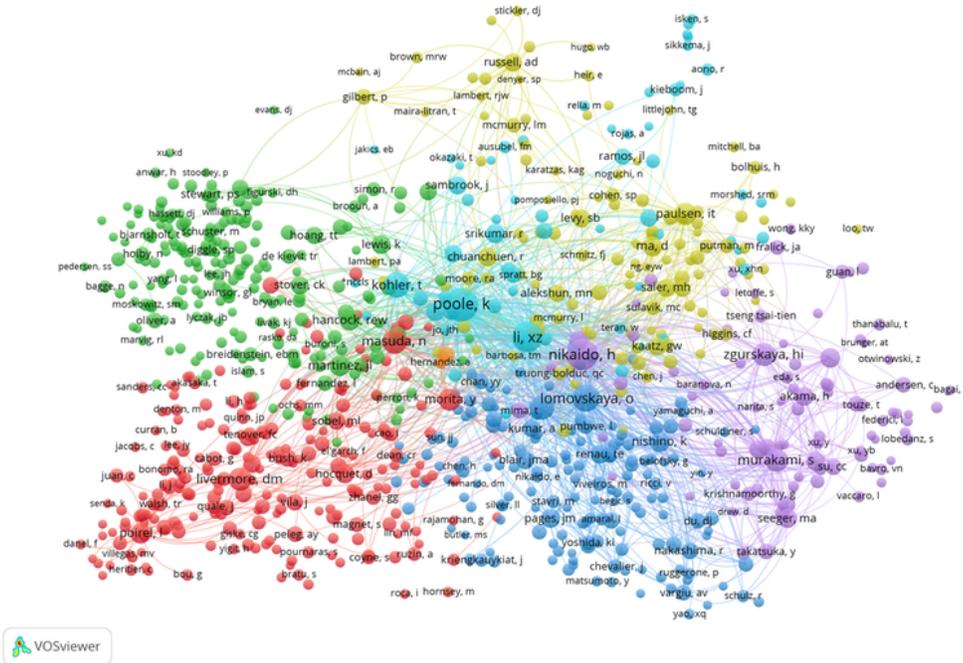


Figure 5

A co-authorship analysis of global research trends in the *P. aeruginosa* efflux pump research field. (a) A mapping overview of 206 authors in co-authorship analyses for this research field. (b) An overview of co-authorship analyses for the 173 research institutions associated with publishing *P. aeruginosa* research to date. (c) An overview of co-authorship analysis results for 50 countries in the *P. aeruginosa* efflux pump. Co-authorship frequencies are indicated by the size of individual points, while lines between points indicate an established collaboration between the indicated authors, institutions, or countries. Thicker lines correspond to closer collaborations.

A



B

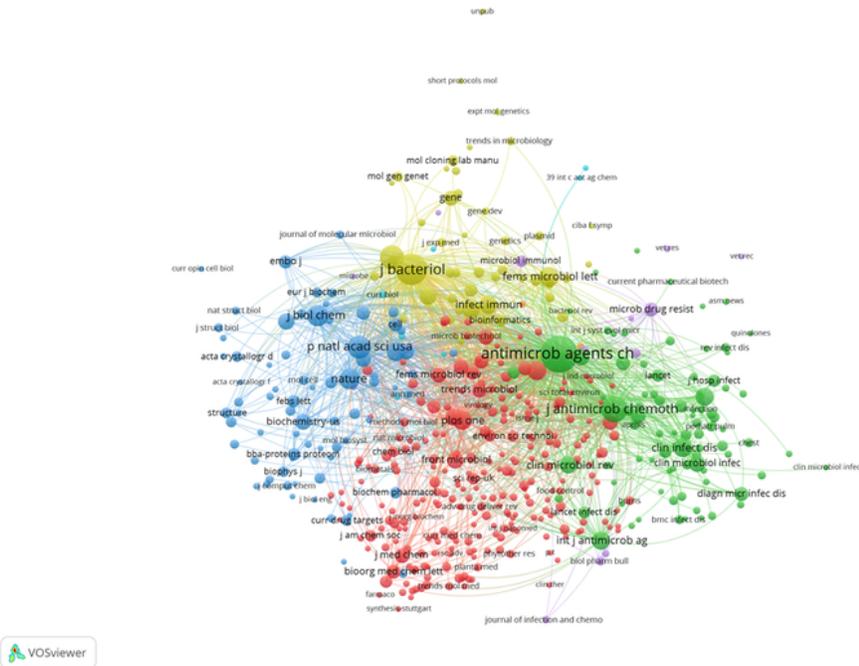


Figure 6

A co-citation analysis of research in the *P. aeruginosa* efflux pump research field. (a) An overview of co-cited authors in this research field, with 867 differently colored points corresponding to individual cited references, and with point size corresponding to the frequency of citation. Lines between points indicate that the linked articles were cited in a given paper, with shorter lines corresponding to closer links between papers. Points of a given color share a research direction. (b) An overview of co-cited journals in this

research field, with 475 points corresponding to 475 identified journals. Point sizes correspond to citation frequencies, while lines between points indicate that co-citation in a given journal. Shorter lines correspond to closer links between journals, while points of a given color share a research direction.

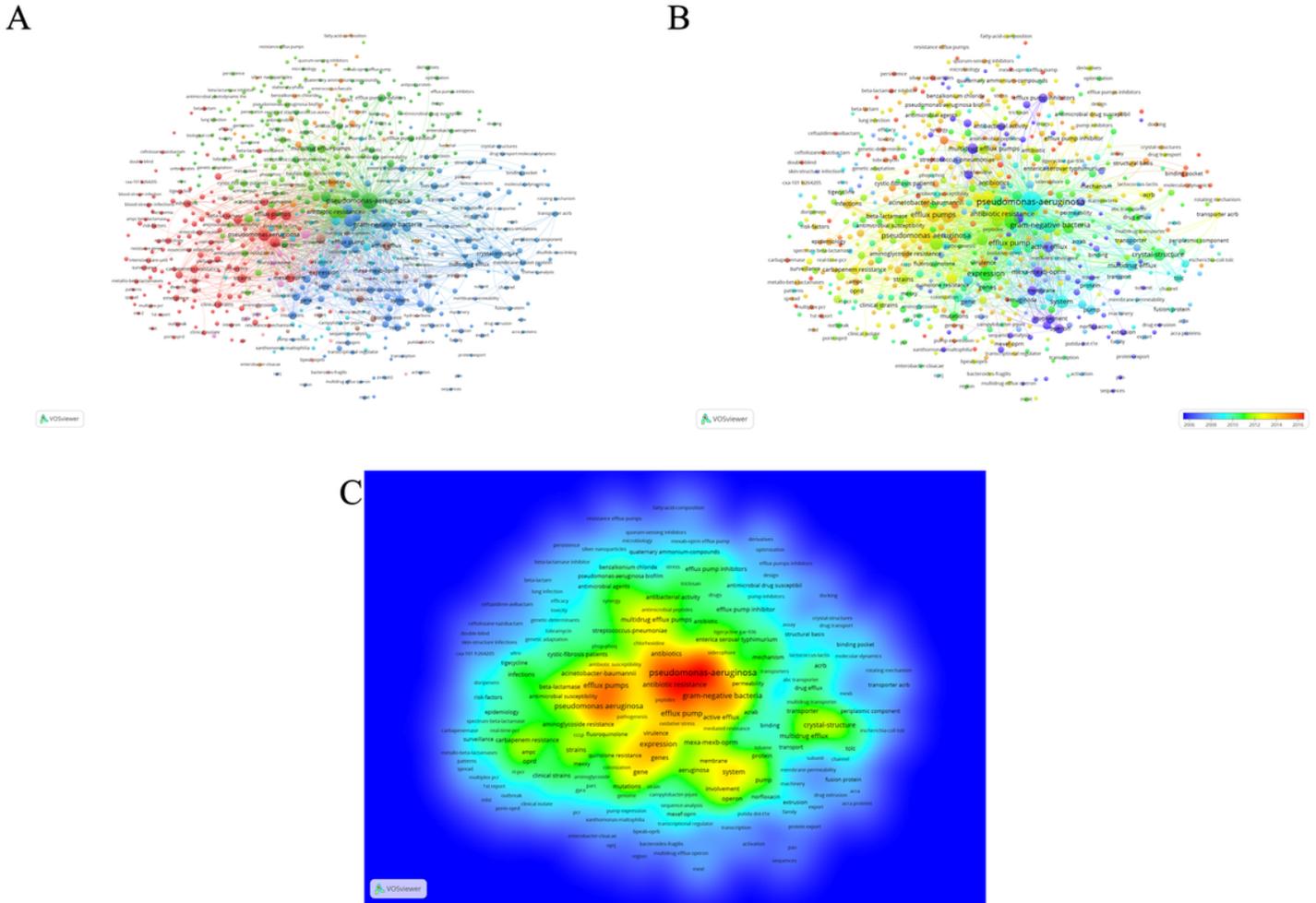


Figure 7

Co-occurrence analyses of global trends in the *P. aeruginosa* efflux pump research field. (a) An overview of keywords in this research area. Point sizes correspond to appearance frequencies, with keywords being separated into three primary clusters: blue (efflux pump resistance mechanisms), green (efflux pump transfer mechanisms), and red (efflux pump inhibitors). (b) Keyword distributions over time, with the most recent keywords being shown in red, followed by those in yellow and those in blue. (c) Keyword distributions based upon mean appearance frequency. Red keywords appeared most frequently, followed by those in yellow, green, and cyan