Original Article

Global trends and hotspots in research of carbapenem-resistant *Enterobacteriaceae* (CRE): a bibliometric analysis from 2010 to 2020

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Background: Infectious disease caused by carbapenem-resistant *Enterobacteriaceae* (CRE) has become one of the most serious challenges due to its high morbidity and mortality and research on it has aroused great concern worldwide in the last decade. Thus, a bibliometric analysis of relevant publications is needed to identify the situation of current investigations and prioritize the future research areas.

Methods: The current study retrieved articles related to CRE published between 2010 and 2020 from the Web of Science core collection database. The search strategy syntax included "carbapenem-resistant *Enterobacteriaceae*", "carbapenem-resistant *Klebsiella pneumoniae*", "carbapenemase producing *Enterobacteriaceae*" and "carbapenemase producing *Klebsiella pneumoniae*" which were searched in both Medical Subject Headings (MeSH) and titles. A bibliometric analysis was conducted using VOSviewer, Bibliographic Item Co-Occurrence Matrix Builder, gCLUTO and other machine learning tools. Key words, subject terms, contributions as well as collaborations were assessed. Moreover, hot off the press and future research trends were demonstrated.

Results: A total of 1,671 publications on CRE were finally included in the bibliometric analysis and 5 related theme clusters were identified which mainly focused on epidemiology, resistance mechanisms, antibiotics treatment and infection control. A total of 142 keywords occurred more than 5 times and the most frequent keyword was "carbapenem-resistant Enterobacteriaceae" with 247 occurrences and a total link strength of 559. The output on CRE has gradually increased during the last decade, and the USA has made the greatest contribution due to the 533 research papers. Agents that act against CRE, especially ceftazidime-avibactam (occurrences, 85; average publication year, 2018.26), and the early detection of CRE by genome sequencing techniques (occurrences, 97; average publication year, 2017.94) were emerging hot topics which would probably attract future research interest.

Conclusions: The bibliometric analysis revealed that development of antibacterial agents, early etiological detection and genome sequencing techniques were the hotspots and would probably direct the future research directions which would also facilitate a better understanding of the epidemiology of drug-resistant bacteria and implementing the antibiotic stewardship program.

Keywords: Bibliometric analysis; carbapenem-resistant *Enterobacteriaceae* (CRE); carbapenemase; hotspot; trends

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Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) is one of the fastest spreading multi-drug resistant (MDR) bacteria worldwide and is also a major cause of hospital-acquired infections (HAIs) (1). When first isolated from the stool sample of a 57-year-old woman with leukaemia (2), it has become a grave challenge and the all-cause mortality can reach as high as 32–65% (3,4). Therefore, much attention has been given to CRE infections in the fields of epidemiology, drug-resistant gene detection, infection control and antimicrobial therapy (5). However, most of them are still unresolved issues (6).

Research publications play vital roles in the scientific processes of bridging knowledge gaps, improving knowledge uptake, and knowledge application (7). For professionals who share similar interests in specific areas, academic collaborations will be facilitated by trust (8). Bibliometric analysis is an effective tool for quantitatively analysing academic research at the global, national, organizational and individual levels (9). Recently, it has been widely applied in various disciplines to comprehensively identify scientific advances, investigation hotspots, and research trends (10). The Web of Science (WoS) database is frequently chosen for retrieving publications, as it has a wide coverage of literature and provides comprehensive data for bibliometric analyses (11). VOSviewer is extensively used for tabulation, mapping, networking, and visualization to highlight the most influential countries, organizations, authors, sources, and documents (12). In addition, co-word biclustering analysis, a recently emerging bibliometric methodology, can generate a co-occurrence matrix and reveal research hotspots based on published evidence (13).

Therefore, a bibliometric analysis was conducted to overview of relevant publications and to assess the current status of contributors' linkage and research trends in the field of CRE. Our findings will be valuable for academic and clinical investigators, as well will map the CRE research landscape and forecast the future work.

Methods

Literature search

We conducted a comprehensive search using the Web of Science (WoS) core collection Science Citation Index Expanded (SCI-EXPANDED) database (Thomson Reuters, New York, NY, USA) and EmBase database from 2010 to June 19, 2020. The search strategy syntax included "carbapenem-resistant *Enterobacteriaceae*", "carbapenem-resistant *Klebsiella pneumoniae*", "carbapenemase producing *Enterobacteriaceae*" and "carbapenemase producing *Klebsiella pneumoniae*" searched in both Medical Subject Headings (MeSH) and titles. While different languages cannot be analysed together by the bibliometric analysis, some Chinese database like China national knowledge infrastructure (CNKI) was not included. Thus, the language was restricted to English, and the document type was restricted to original article.

Data collection

Two authors screened the retrieved literature independently and determined eligibility. The full data of included publications, including author, title, abstract, keywords, source, language, citation, etc., were downloaded in a text format from the WoS core collection SCI-EXPANDED and EmBase database.

Bibliometric analysis

WoS core database output analysis

The basic characteristics of the retrieved publications, including the total number of documents, annual, national, institutional, and individual article counts, research field distributions, and top cited literature, were described using the intrinsic functions of the WoS core database and Microsoft Excel (version Microsoft 365). The count of annual national publication and the relevant growth trend were analysed using the online analysis platform of literature metrology (http://bibliometric.com/).

Network analysis

To illustrate the CRE research collaboration network and identify research hotspots and future trends, we conducted a bibliometric analysis using VOSviewer (version 1.6.10, Leiden University, Leiden, the Netherlands) to import the collected data. Subsequently, networks connecting authors, organizations, countries, citations and other factors were generated using co-authorship, co-occurrence, citations, bibliographic coupling and co-citation analysis. Overlay mapping was conducted to show the time scale of themes in the CRE field. In the visual maps, different colours indicate different clusters, and connecting lines indicate collaboration or co-citation. The numbers of documents, citations and keyword occurrences are represented by circle size, while the strength of the links is represented by the

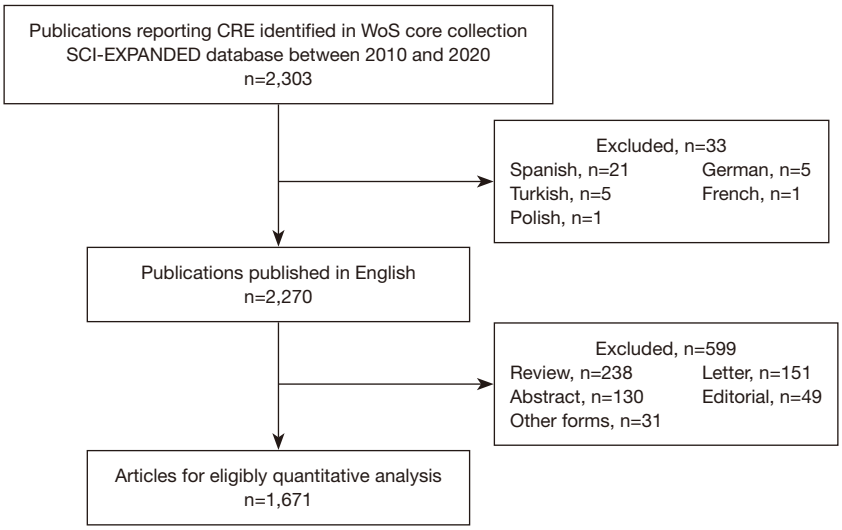


Figure 1 Flow diagram of included publications. CRE, carbapenem-resistant *Enterobacteriaceae*; WoS, Web of Science; SCI-EXPANDED, Science Citation Index Expanded.

thickness of connecting lines.

Keywords biclustering analysis

The connections between high-frequency keywords and source literature and the connections among high-frequency keywords were displayed by co-words biclustering. First, we constructed a co-occurrence matrix of high-frequency keywords with Bibliographic Item Co-Occurrence Matrix Builder (BICOMB) (version 2.0, designed by Professor Lei Cui from China Medical University). Second, the matrix was further clustered by gCLUTO (version 1.0, Graphical Clustering Toolkit, University of Minnesota, Minneapolis, MN, USA). The source literature was displayed in columns, and the high-frequency keywords were displayed in rows, and a binary matrix was generated. Finally, the semantic relationships between typical keywords and source literature in clusters of CRE research were mapped by matrix and mountain visualization.

Results

Bibliometric analysis of publication output

In total, 2,303 publications on the topic of CRE were identified in the WoS core database between 2010 and 2020. Thirty-three publications were excluded because they were published in non-English languages. Another 599 publications, included 238 reviews, 151 letters, 130 meeting abstracts, 49 editorials and 60 other types of publications, were also excluded due to non-target article types. Finally, 1,671 original articles were included for eligible quantitative analysis (*Figure 1*). Most of the publications (1,020, 61.0%) were open access.

The literature counts by country between 2010 and 2020 were ranked to explore the global geographic distribution of publications in the field of CRE (*Figure 2*). The United States of America (USA) [533], China [234], Italy [133], France [122], and England [88] ranked as the top five prolific contributors in terms of CRE research. The United States Department of Health and Human Services, with 209 studies indexed in the WoS core database, United States National Institutes of Health [180], National Natural Science Foundation of China [122], National Institute of Allergy and Infectious Diseases [86], and United States Centers for Disease Control and Prevention [35] were the top five funding agencies (Figure S1A). Infectious diseases; microbiology; pharmacology and pharmacy; public, environmental, and occupational health; and immunology were the most frequent study areas (Figure S1B). A total of 292 journals have published articles on the topic of CRE, among which 59 journals have published more than 5 manuscripts. Antimicrobial Agents and Chemotherapy (AAC), Infection Control and Hospital Epidemiology, Journal of Antimicrobial Chemotherapy, Diagnostic Microbiology and Infectious Disease, and American Journal of Infection Control were the top five most productive journals in the field of CRE (Figure S1C). Bonomo RA,

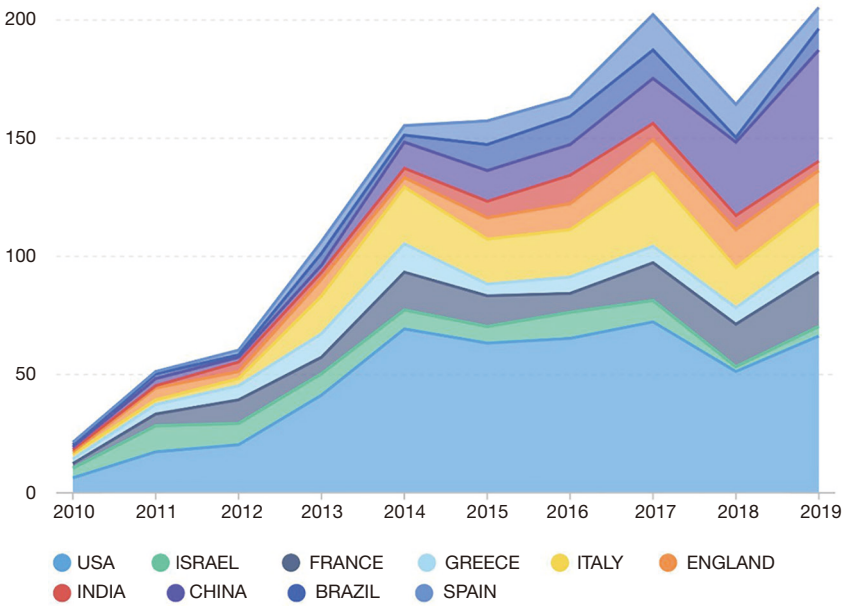


Figure 2 Bibliometric analysis of WoS core database output. The growth trends of the top 10 productive countries in CRE research from 2010 to 2020. WoS, Web of Science; CRE, carbapenem-resistant *Enterobacteriaceae*.

Kaye KS, Chen L, Kreiswirth BN, and Castanheira M were the most productive authors (Figure S1D). Case Western Reserve University, University of Pittsburgh, Zhejiang University, Tel Aviv University, and the Centers for Disease Control and Prevention were the most productive organizations (Figure S1E).

Bibliometric analysis of co-authorship

A total of 9,313 authors have published papers on CRE. VOS viewer was used to analyses a total of 239 authors with more than 5 publications in this field (*Figure 3A*). Among them, Bonomo RA from Case Western Reserve University, whose research mostly focused on ß-lactamase, was the author of 43 documents cited 1,186 times, with a total link strength of 276. The main collaborators were Kaye KS (link strength with Bonomo RA, 21; total link strength, 239) from the University of Michigan and Perez F (link strength with Bonomo RA, 21; total link strength, 184) from Louis Stokes Cleveland VA Medical Center.

A total of 2,690 organizations have published relevant papers, with 241 of them publishing more than 5 publications (*Figure 3B*). Case Western Reserve University has published 45 related papers with 1,140 citations, with a total link strength of 180. The main partners of the organization were the University of North Carolina (link strength with Case Western Reserve University, 17; total link strength, 127) and the Cleveland Clinic (link strength with Case Western Reserve University, 15; total link strength, 114).

The bibliometric analysis also showed that 91 countries have published relevant articles, with 52 publishing more than 5 publications (*Figure 3C*). The USA contributed most to the CRE field, publishing 533 documents that were cited 13,071 times, with a total link strength of 224. The main partners of the USA were China (link strength 21), Italy (link strength 18) and England (link strength 16) (*Figure 3D*).

The top ten countries, organizations and authors of CRE publications with the strongest co-authorship links are presented in Table S1.

Bibliometric analysis of keywords Co-Occurrence

Of the articles retrieved from the WoS core database, 1,988 author keywords were identified. A total of 142 keywords that occurred more than 5 times were defined as high-frequency keywords and enrolled in the analysis. The most frequent keyword was "carbapenem-resistant *Enterobacteriaceae*" (occurrences, 247; total link strength, 559), which had strong links to "*Klebsiella pneumoniae* carbapenemase" (link strength, 39; occurrences, 117), "*Klebsiella pneumoniae*" (link strength, 30; occurrences, 214),

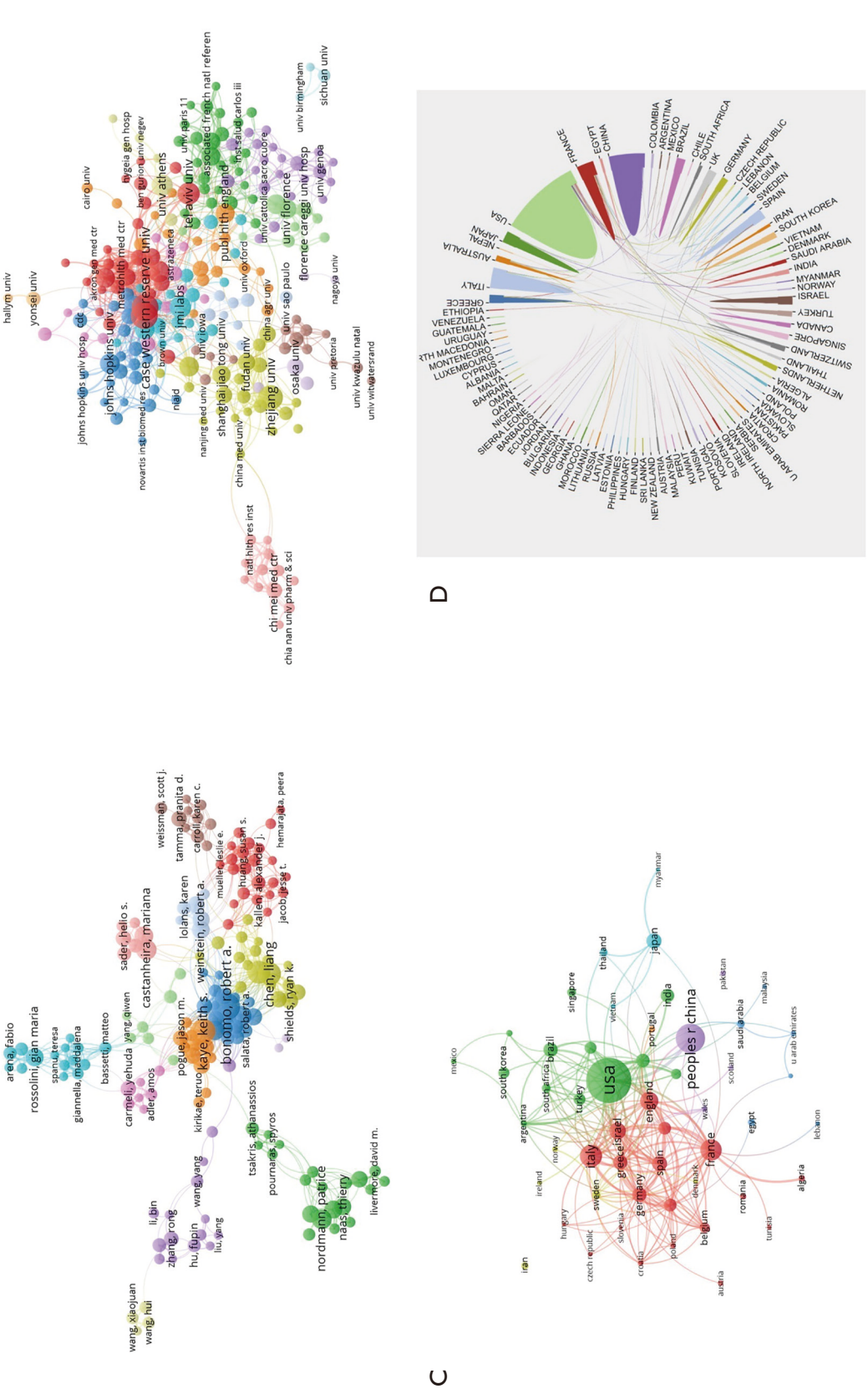


Figure 3 Bibliometric analysis of the co-authorship. The cooperation of authors (A), institutions (B), and countries (C,D) in field of CRE research. The color indicated clusters, circle size indicated number of publications, the thickness of lines indicated strength of linkage (A,B,C).

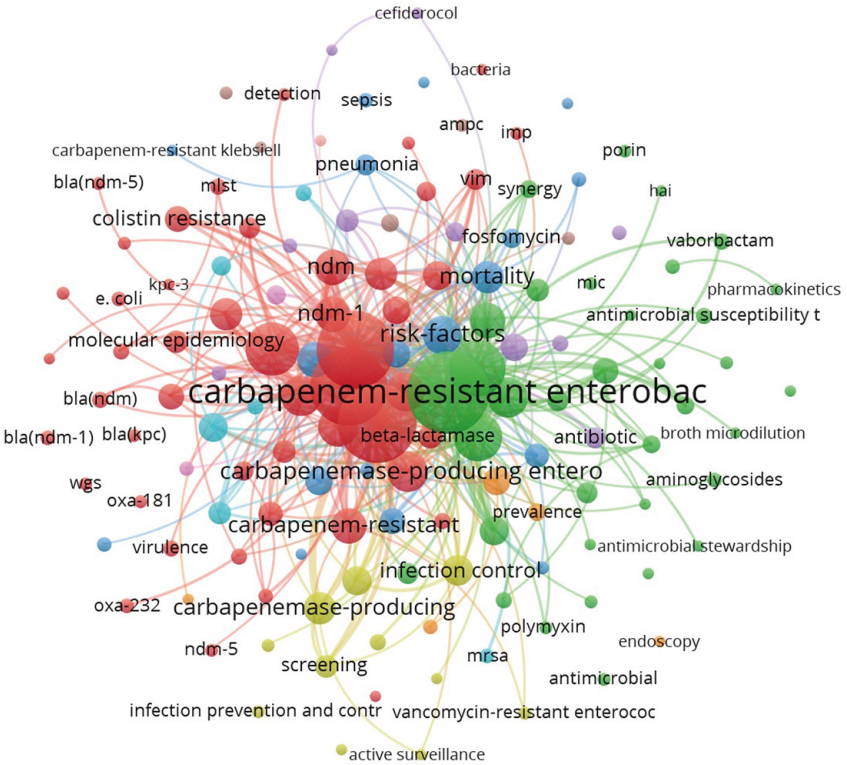


Figure 4 Bibliometric analysis of keywords. The co-occurrence of highly frequent author keywords. The color indicated clusters, circle size indicated number of occurrences, the thickness of lines indicated strength of linkage.

"ceftazidime-avibactam" (link strength, 26; occurrences, 45), "carbapenemase" (link strength, 17; occurrences, 220), and "colistin" (link strength, 16; occurrences, 58) (*Figure 4*). A word cloud was also generated to show the occurrence rates of high-frequency keywords. "Carbapenem-resistant *Enterobacteriaceae*", "*Enterobacteriaceae*", "carbapenemase", "*Klebsiella pneumoniae*", and "KPC" were ranked as the top five active keywords (Figure S2).

Bibliometric analysis of citations

The ranking of the top 10 cited articles in the field of CRE is shown in *Table 1* (the top 100 cited articles are presented in Table S2). Most of the articles were randomized clinical trials focused on antimicrobial therapies or observational studies on outcomes and risk factors for CRE infection. Additionally, numerous *in vitro* studies have concentrated on carbapenem-resistance mechanisms, such as the genome of the CRE plasmid and the genotype of carbapenemase. Epidemiological studies revealing the prevalence of and mortality due to CRE infections, as well as methodological studies investigating the rapid detection of CRE, have also been extensively reported. The average number of citations in the top 100 most widely cited articles was 118 (range, 63–503). The article "Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole-Genome Sequencing", written by Snitkin *et al.* and published in *Science Translational Medicine* in 2012, was the most cited document (cited 503 times).

The top ten most-cited journals, countries, organizations and authors of CRE publications were ranked. The most cited journal was the AAC (impact factor 4.904), publishing 171 articles on CRE with 5,387 citations. Bonomo RA. from Case Western Reserve University, who published 43 articles, was the most cited author (cited 1,186 times) (Figure S3A). An institution analysis revealed that the University of Pittsburgh was the most cited institution, publishing 44 articles that were cited 1,636 times (Figure S3B). The USA was ranked highest for citations (13,071 times), publishing a total of 533 papers, with a total link strength of 3,508

Table 1 The top ten most cited articles in the field of CRE

Rank	Title	Journal	Publication year	Citations
1	Tracking a Hospital Outbreak of Carbapenem-Resistant Klebsiella pneumoniae with Whole-Genome Sequencing	*Sci Transl Med*	2012	503
2	Rapid Detection of Carbapenemase-producing Enterobacteriaceae	*Emerg Infect Dis*	2012	410
3	Treatment Outcome of Bacteremia Due to KPC-Producing Klebsiella pneumoniae: Superiority of Combination Antimicrobial Regimens	*Antimicrob Agents Chemother*	2012	351
4	Vital Signs: Carbapenem-Resistant Enterobacteriaceae	*MMWR-Morb Mortal Wkly Rep*	2013	309
5	Carbapenemase-Producing Klebsiella pneumoniae Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems	*Antimicrob Agents Chemother*	2014	306
6	Containment of a Country-wide Outbreak of Carbapenem-Resistant Klebsiella pneumoniae in Israeli Hospitals via a Nationally Implemented Intervention	*Clin Infect Dis*	2011	266
7	Sequence-specific antimicrobials using efficiently delivered RNA-guided nucleases	*Nat Biotechnol*	2014	241
8	What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline	*Int J Antimicrob Agents*	2011	223
9	Early Dissemination of NDM-1-and OXA-181-Producing Enterobacteriaceae in Indian Hospitals: Report from the SENTRY Antimicrobial Surveillance Program, 2006-2007	*Antimicrob Agents Chemother*	2011	220
10	New Delhi Metallo-beta-Lactamase-Producing Carbapenem-Resistant Escherichia coli Associated With Exposure to Duodenoscopes	*JAMA-J Am Med Assoc*	2014	203

CRE, Carbapenem-resistant *Enterobacteriaceae*.

(Figure S3C).

Bibliometric analyses of bibliographic coupling and co-citation

Bibliographic coupling analysis assesses links between documents that cite the same literature. The bibliographic coupling networks for authors, documents, journals and countries are shown in Figure S4. For document analysis, 9 clusters were formed; the largest cluster (277 items) focused on CRE infection outbreaks and relevant intervention strategies (shown in red). The representative paper was published in *Science Translational Medicine* in 2012 by Evan S. Snitkin. Co-citation analysis evaluates the link between two documents that are both cited in the same manuscript. The co-citation networks for authors, references and journals are shown in Figure S5. For authors, 17 clusters were identified, and Patrice Nordmann was the most co-cited author. For journals, 37 clusters were generated, and the largest cluster included 115 items. Amongst them, AAC was the representative journal.

Bibliometric analyses of theme terms and topic trends

There were 1,019 terms that occurred more than 10 times in the retrieved articles. In total, 10 CRE-related theme clusters were identified. The red cluster represents clinical trials of antimicrobial therapies for CRE infection, and the green cluster represents underlying mechanistic investigations of CRE. The blue cluster represents *in vitro* studies on CRE susceptibility or the activity of agents against CRE (*Figure 5A*). *Figure 5B* shows the overlay of

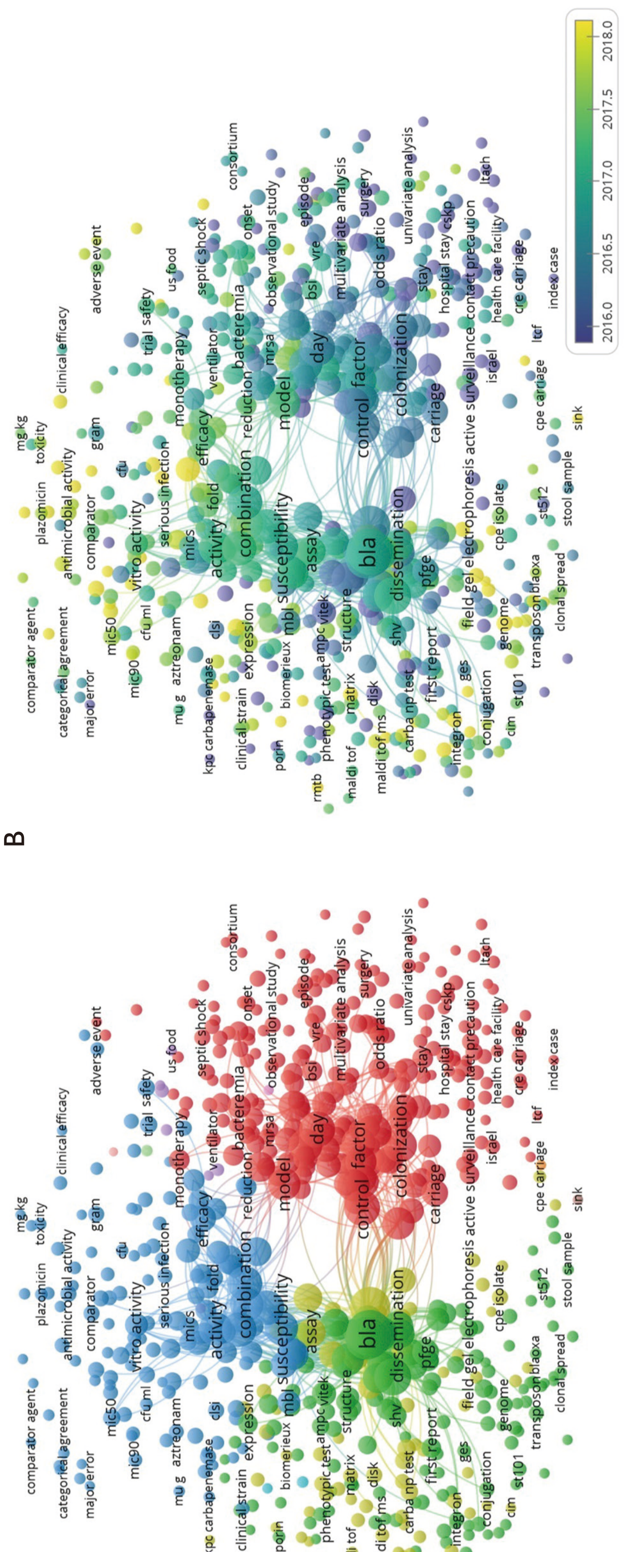
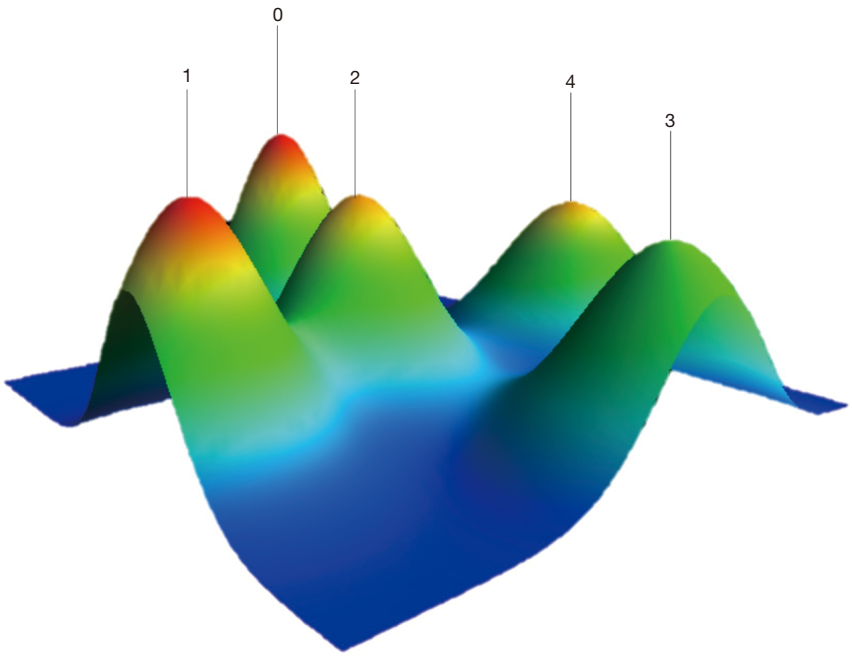


Figure 5 Bibliometric analysis of the theme terms. (A) Distribution of the theme terms. (B) Overlay visualization map of the topic trends. The size of the circles indicated the occurrences of theme terms. The distance between circles indicated their relationship, different colors indicated variety of clusters (A) and average publication year (B) respectively.



Cluster	Keywords
Cluster 0	KPC
	NDM
	Carbapenemase
	OXA-48
	NDM-1
	MBL
	Antibiotic resistance
Cluster 1	resistance
	carbapenem
	plasmid
	Escherichia coli
	Colistin resistance
	Klebsiella pneumoniae
	Carbapenem resistance
Cluster 2	Colistin
	Meropenem
	Carbapenem-resistant Enterobacteriaceae
	Ceftazidime-avibactam
	Multidrug resistance
	Multidrug-resistant
	ESBL
Cluster 3	Epidemiology
	Drug resistance
	Bloodstream infection
	Colonization
	Risk factors
	Mortality
	Intensive care unit
	Carbapenem-resistant Klebsiella pneumoniae
Cluster 4	Surveillance
	Carbapenemase-producing Enterobacteriaceae
	Whole-genome sequencing
	Antimicrobial resistance
	Infection control
	Outbreak
	Carbapenemase-producing
	Enterobacteriaceae
	Carbapenem-resistant

Figure 6 Mountain visualization of biclustering of highly frequent keywords and literatures on CRE. Each peak represented a cluster. The distance between the peaks indicated the similarity between clusters. The height of the peak indicated the internal similarity of keywords in the cluster. The volume of the peak represented the number of high-frequency keywords in a cluster. The color of the peak top revealed internal standard deviation of a cluster, the red indicated low internal standard deviation, while blue means high. CRE, carbapenem-resistant *Enterobacteriaceae*.

the theme terms representing the topic trends of CRE research. The colour of the circle indicates the average year of publication. Recent frequent theme terms are marked in yellow. It was demonstrated that "ceftazidime-avibactam" (occurrences, 85; average publication year, 2018.26) and "whole-genome sequencing" (occurrences, 97; average publication year, 2017.94) are emerging hot topics.

Keywords biclustering analysis and CRE research hotspots

A total of 2,066 keywords were obtained from the 1,671 retrieved studies. The total number of keywords including repeats was 5,782. Keywords that appeared more than 20 times were defined as high-frequency keywords. There were 38 high-frequency terms, which are listed in Table S3. The cumulative proportion of these terms was 43.9% (2,538/5,782). The high-frequency keyword/source article matrix and high-frequency keyword co-word matrix were generated by BICOMB (Table S4 and Table S5). According to subsequent biclustering, 38 terms were divided into 5 clusters, and the results are shown in the mountain diagram (*Figure 6*) and matrix diagram (*Figure 7*). Clustered keywords were analysed to determine the theme of each cluster.

Cluster 0: carbapenemases associated with CRE antibiotic resistance.

Cluster 1: the role of plasmids in carbapenem or colistin resistance in *Enterobacteriaceae*.

Cluster 2: first-line antimicrobial agents against CRE and their efficacy and safety.

Cluster 3: epidemiology, clinical features and outcomes of CRE infections.

Cluster 4: genome sequencing of CRE and infection control.

Discussion

In our bibliometric analysis of CRE, a total of 1,671 publications

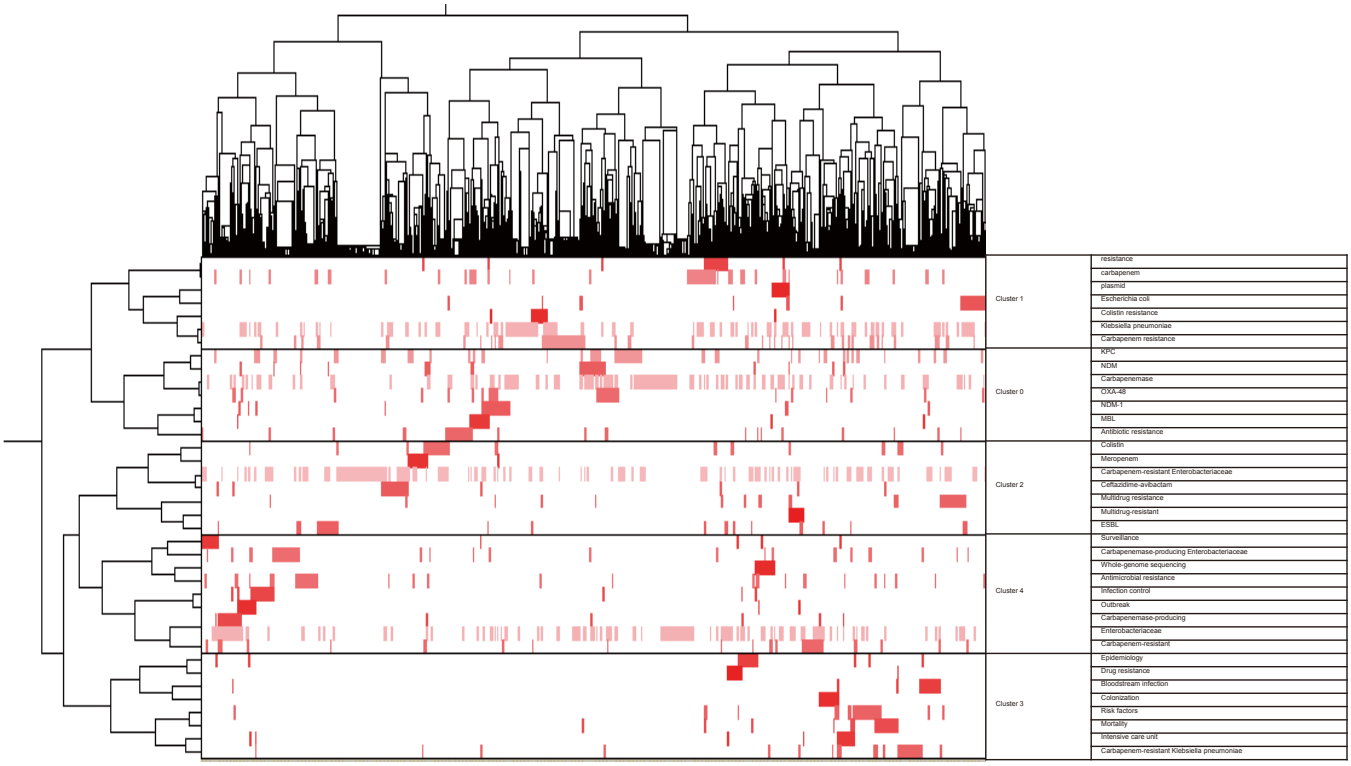


Figure 7 Visualized matrix of biclustering of highly frequent keywords and identify numbers of literatures on CRE. The highly frequent keywords were shown as row labels, the sequence number of source articles were shown as column labels. The connection between highly frequent keywords were represented in the left cluster tree. The connection between source articles were exhibited in the above cluster tree. The color of the blocks indicated the frequency of keywords occurred in articles. Darker color revealed higher frequency. CRE, Carbapenem-resistant *Enterobacteriaceae*.

on CRE were finally included in the bibliometric analysis and 5 related theme clusters were identified which mainly focused on epidemiology, resistance mechanisms, antibiotics treatment and infection control. A total of 142 keywords that occurred more than 5 times and the most frequent keyword was "carbapenem-resistant Enterobacteriaceae" with 247 occurrences and the total link strength was 559. The output on CRE has gradually increased during the last decade, and the USA has made the greatest contribution due to the 533 research papers. Agents that act against CRE, especially ceftazidime-avibactam (occurrences, 85; average publication year, 2018.26), and the early detection of CRE by genome sequencing techniques (occurrences, 97; average publication year, 2017.94) were emerging hot topics would probably attract future research interest.

Top-cited contributors in the CRE field

Citation analysis is extensively used to evaluate the quality of research work, as citation counts generally represent scientific acknowledgement by professionals (14). This study showed that the USA produced the highest number of publications and had the highest citation rate. A majority of the top 10 most-cited academic institutions and authors were located in the USA. This superior contribution by the USA can be attributed to the large number of prolific researchers and funding sources. Robert A. Bonomo was the top-cited author. His focus areas included antibacterial resistance, genetic epidemiology, CRE outbreaks, CRE treatment, surveillance and antimicrobial stewardship; therefore, he was the author most widely cited by scholars (15).

International collaborations

Co-authorship analysis showed that the USA played a leading role in the field of CRE research and was involved in the most collaborations worldwide. European countries such as France, Italy and England produced a large number

of publications and gradually increased their collaboration with other countries. The number of research about CRE from China has increased rapidly since 2018 and therefore it has become the second most productive country. However, the total link strength of China ranked only 15th, reflecting moderate collaboration between China and other countries. A variety of practices have facilitated collaboration between China and other developed countries, such as increasing international collaboration funding, importing outstanding expatriate scientists, and promoting academic visits or exchanges with outstanding institutions.

Research hotspots and trends

Epidemiology of CRE

CRE is a serious pandemic with the isolation rate of 10.32 per 100,000 in hospital days and most of them were isolated from airway secretion and urinary samples (16). *Klebsiella pneumoniae (K. pneumoniae)* was the most prevalent organism, followed by *E. coli* and *E. cloacae* which were also with high all-cause mortality. Therefore, the epidemiology and prevention of CRE is highlighted.

Carbapenemases

The alarmingly rapid worldwide spread of carbapenemase-producing *Enterobacteriaceae* (CPE) is another research hotspot (16). According to amino acid sequences, carbapenemases are divided into different Ambler classifications (A, B and D) on the basis of a variety of carbapenem-hydrolysing activities (4). *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo (NDM), and oxacillinases (OXA)-type beta-lactamases are the dominant carbapenemases detected in CRE (17). Among them, KPC is frequently identified in mobile genetic elements and is potentially being widely disseminating (17).

Emerging CRE detection technology

The early detection of carbapenemase-producing *Enterobacteriaceae* (CPE) is a critical issue in preventing CPE dissemination (18) and genetic methods for detection have been extensively investigated. WGS is a superior discriminatory typing technology used in pathogen transmission research (19). Nucleotide-level variations within and the horizontal spread of carbapenemases can be determined by short/long-read genetic sequencers (20). The Xpert Carba-R kit, a well-adapted genetic measurement tool, is able to detect five major carbapenemases with high accuracy (21). The BD MAX instrument with Check-Direct CPE screen was also used for the detection of carbapenemase genes, reducing the turn-around time to only 3 h (22). In addition, rapid and affordable phenotypic assays are available for CPE detection, including matrix-assisted laser-desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), carbapenem hydrolysis assays that can detect the disappearance of the original carbapenem and/or the hydrolysis of the carbapenem after incubation with *Enterobacteriaceae* isolates (23). Future tests should be quick and simple (i.e., with a point-of-care device), providing physicians enough information for immediate action. They can then prescribe antibiotics more appropriately and avoid unnecessary antibiotic use.

Current therapies for CRE

There are limited treatment options for CRE-induced infection (4). Novel high-affinity carbapenemase inhibitors, including AVI, relebactam and vaborbactam, have been recently developed to overcome this dilemma (24). Among them, CAZ-AVI has been marketed in many countries and can be used as a salvage therapy for CRE-related infections, including complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) (25). Plazomicin is a novel aminoglycoside maintaining activity against CPE, with good efficacy in patients with serious infection due to CRE (26). Eravacycline is a new fluorocycline antimicrobial agent in the tetracycline class that has shown *in vitro* activity against CRE and has demonstrated noninferior efficacy in patients with cIAI compared to ertapenem (27). Furthermore, polymyxins, which are considered "old antibiotics", have re-emerged in the clinic as an option for CRE infection, and combination therapy has been suggested to be superior to monotherapy in reducing mortality (28).

Strengths and limitations

Our study is the first bibliometric analysis evaluating publications on CRE extracted from the WoS core database. The data analysis is objective and comprehensive. The present study provides a large quantity of information illustrating the current status, hotspots and future outlook of CRE research. Additionally, the results were visualized by a variety of tools demonstrating the bibliometric results clearly. Nevertheless, some limitations are inevitable. First, while different languages cannot be analysed together by the bibliometric analysis, some Chinese database like CNKI was not included. Thus, the language was restricted to

English which led to the neglection of some high-quality work in non-English media. Second, we attempted to avoid bias due to updated publications by conducting all the database searches in one day. There might be some new data missing, although the impact on citation frequency is likely minimal. Third, there might be some inaccurate data or deficiencies in the databases that we cannot identify. Finally, some keywords were presented as singular and plural and as abbreviations and full names; such inconsistent information can reduce the accuracy of bibliometric analyses. To account for this, time-consuming data combing was necessary.

Conclusions

The bibliometric analysis revealed that development of antibacterial agents, early etiological detection and genome sequencing techniques were the hotspots and would probably direct the future research directions which would also facilitate a better understanding of the epidemiology of drug-resistant bacteria and implementing the antibiotic stewardship program.

Acknowledgments

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-87). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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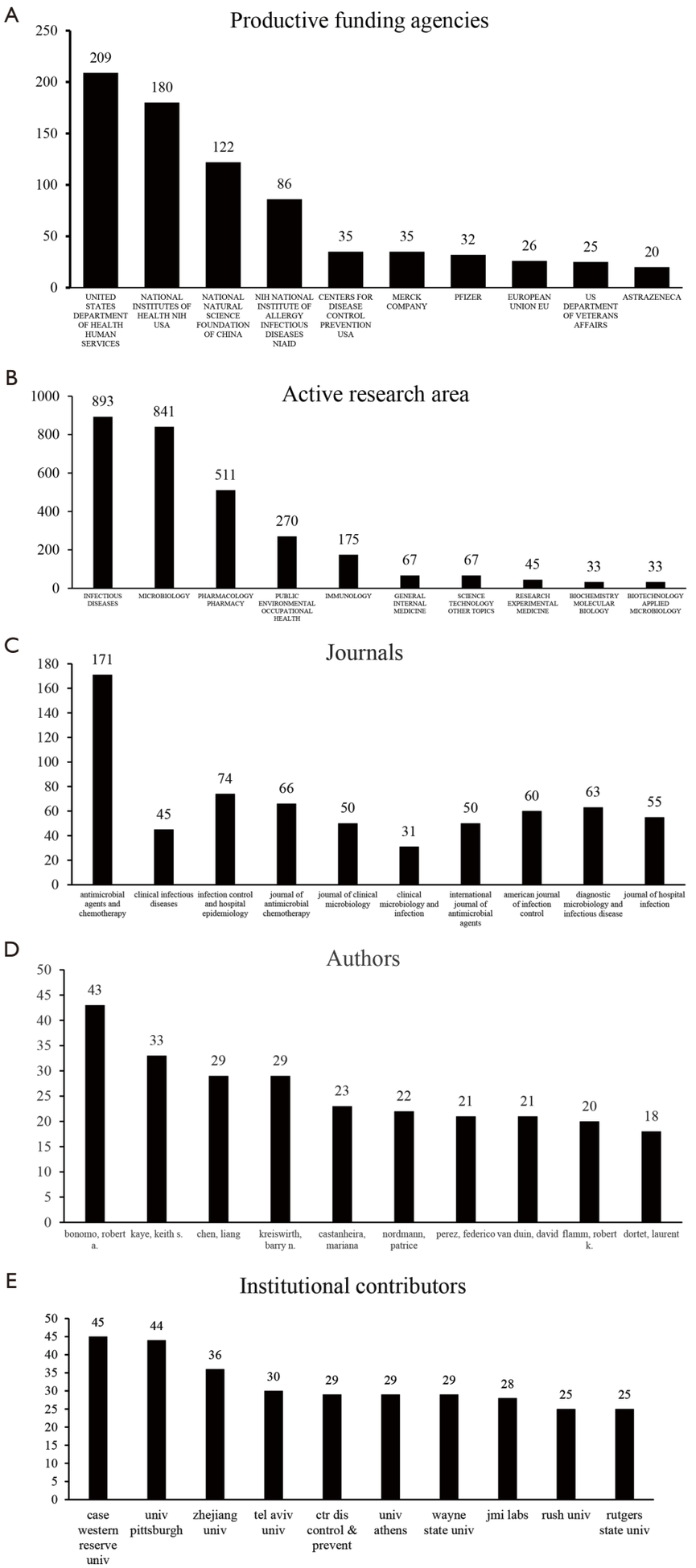

Figure S1 Bibliometric analysis of Web of Science core collection output in terms of Carbapenem-resistant Enterobacteriaceae (CRE) research. A: Top ten productive funding agencies; B: Top ten active research area; C: Top ten journals with highest number of publications; D: Top ten fruitful authors; E: Top ten institutional contributors.

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Table S1 Top ten co-authorship link strength countries, organizations and authors.

Country	Documents	Citations	Total link strength
USA	533	13071	224
France	122	2960	165
Italy	133	2561	150
England	88	2548	140
Spain	61	1531	124
Germany	53	1115	116
Greece	57	1901	116
Switzerland	47	1262	105
Israel	72	3048	102
Netherlands	43	1152	101
Organization	Documents	Citations	Total link strength
Case Western Reserve Univ	45	1140	180
Univ Pittsburgh	44	1636	146
Univ N Carolina	24	640	127
Duke Univ	16	555	118
Cleveland Clin	17	592	114
Metrohlth Med Ctr	13	458	108
Wayne State Univ	29	886	104
Univ Michigan	19	348	84
Louis Stokes Cleveland Dept Vet Affairs Med Ctr	12	528	80
Univ Florence	25	521	80
Author	Documents	Citations	Total link strength
Bonomo, Robert A.	43	1186	276
Kaye, Keith S.	33	1041	239
Perez, Federico	21	791	184
van Duin, David	21	639	169
Richter, Sandra S.	13	395	130
Cober, Eric	11	362	127
Hujer, Andrea M.	13	344	126
Kalayjian, Robert C.	11	371	125
Salata, Robert A.	11	371	125
Evans, Scott	10	359	118

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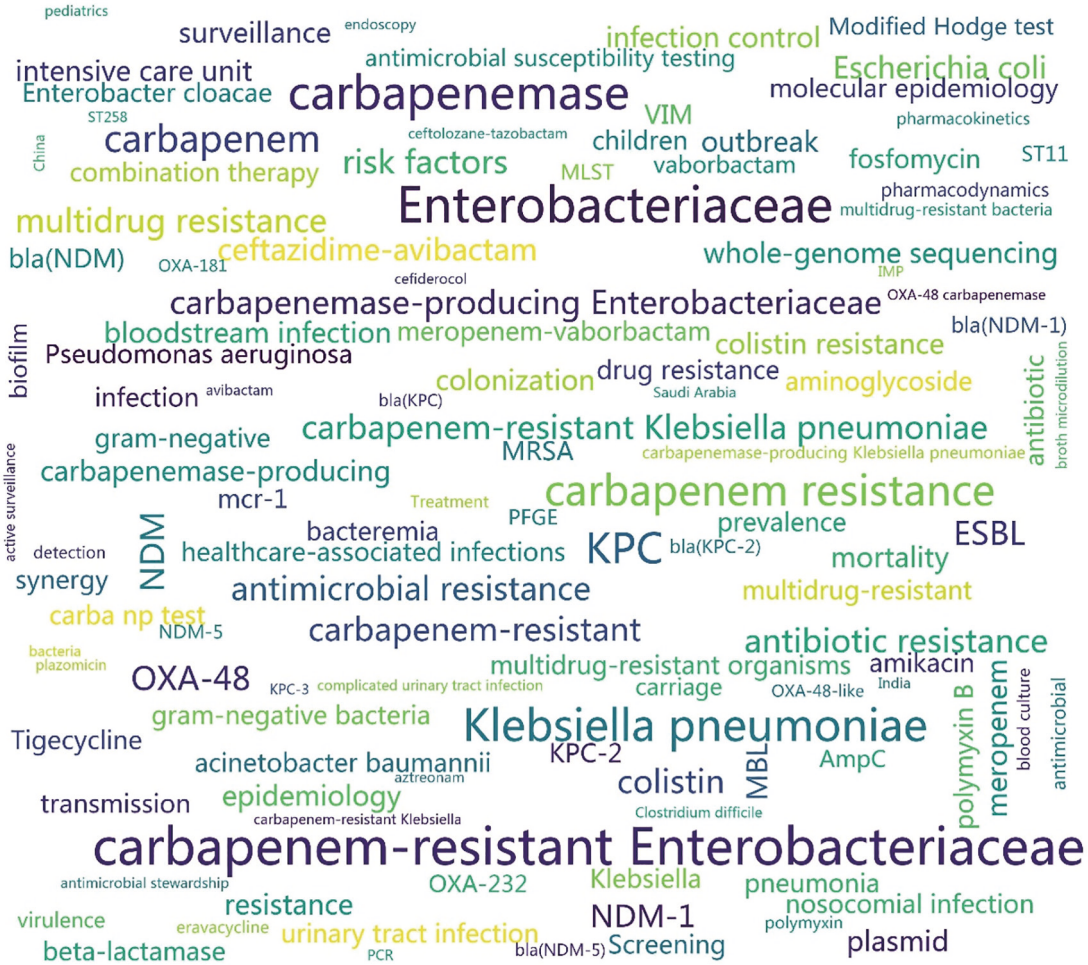

Figure S2 The word cloud of highly frequent keywords. The size of keywords indicated number of occurrences.

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Table S2 The top 100 most cited articles in the field of CRE.

Rank	Title	Journal	Publication year	Citations
1	Tracking a Hospital Outbreak of Carbapenem-Resistant Klebsiella pneumoniae with Whole-Genome Sequencing	Sci. Transl. Med.	2012	503
2	Rapid Detection of Carbapenemase-producing Enterobacteriaceae	Emerg. Infect. Dis	2012	410
3	Treatment Outcome of Bacteremia Due to KPC-Producing Klebsiella pneumoniae: Superiority of Combination Antimicrobial Regimens	Antimicrob. Agents Chemother.	2012	351
4	Vital Signs: Carbapenem-Resistant Enterobacteriaceae	MMWR-Morb. Mortal. Wkly. Rep.	2013	309
5	Carbapenemase-Producing Klebsiella pneumoniae Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems	Antimicrob. Agents Chemother.	2014	306
6	Containment of a Country-wide Outbreak of Carbapenem-Resistant Klebsiella pneumoniae in Israeli Hospitals via a Nationally Implemented Intervention	Clin. Infect. Dis.	2011	266
7	Sequence-specific antimicrobials using efficiently delivered RNA-guided nucleases	Nat. Biotechnol.	2014	241
8	What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline	Int. J. Antimicrob. Agents	2011	223
9	Early Dissemination of NDM-1- and OXA-181-Producing Enterobacteriaceae in Indian Hospitals: Report from the SENTRY Antimicrobial Surveillance Program, 2006-2007	Antimicrob. Agents Chemother.	2011	220
10	New Delhi Metallo-beta-Lactamase-Producing Carbapenem-Resistant Escherichia coli Associated With Exposure to Duodenoscopes	JAMA-J. Am. Med. Assoc.	2014	203
11	Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study	Lancet Infect. Dis.	2017	193
12	Activities of NXL104 Combinations with Ceftazidime and Aztreonam against Carbapenemase-Producing Enterobacteriaceae	Antimicrob. Agents Chemother.	2011	188
13	Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015	Eurosurveillance	2015	179
14	Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant Enterobacteriaceae isolates	J. Antimicrob. Chemother.	2011	177
15	Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections	Clin. Infect. Dis.	2016	171
16	Single-molecule sequencing to track plasmid diversity of hospital-associated carbapenemase-producing Enterobacteriaceae	Sci. Transl. Med.	2014	168
17	High rate of colistin resistance among patients with carbapenem-resistant Klebsiella pneumoniae infection accounts for an excess of mortality	Clin. Microbiol. Infect.	2013	163
18	Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections	Clin. Microbiol. Infect.	2012	163
19	Emergence and Rapid Regional Spread of Klebsiella pneumoniae Carbapenemase-Producing Enterobacteriaceae	Clin. Infect. Dis.	2011	154
20	Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study	Lancet Infect. Dis.	2017	146
21	Characteristics of Extended-Spectrum beta-Lactamase- and Carbapenemase-Producing Enterobacteriaceae Isolates from Rivers and Lakes in Switzerland	Appl. Environ. Microbiol.	2013	145
22	Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae	Clin. Infect. Dis.	2018	140
23	A sensitive and specific phenotypic assay for detection of metallo-beta-lactamases and KPC in Klebsiella pneumoniae with the use of meropenem disks supplemented with aminophenylboronic acid, dipicolinic acid and cloxacillin	Clin. Microbiol. Infect.	2011	140
24	Outbreak of Colistin-Resistant, Carbapenem-Resistant Klebsiella pneumoniae in Metropolitan Detroit, Michigan	Antimicrob. Agents Chemother.	2011	138
25	Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program	Clin. Infect. Dis.	2016	137
26	Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013	JAMA-J. Am. Med. Assoc.	2015	137
27	Outbreak of OXA-48-Positive Carbapenem-Resistant Klebsiella pneumoniae Isolates in France	Antimicrob. Agents Chemother.	2011	132
28	An Ongoing National Intervention to Contain the Spread of Carbapenem-Resistant Enterobacteriaceae	Clin. Infect. Dis.	2014	126
29	Double-Carbapenem Therapy for Carbapenemase-Producing Klebsiella pneumoniae	Antimicrob. Agents Chemother.	2011	125
30	Antibacterial Activity of Eravacycline (TP-434), a Novel Fluorocycline, against Hospital and Community Pathogens	Antimicrob. Agents Chemother.	2013	124
31	Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program	Clin. Infect. Dis.	2016	121
32	The Importance of Long-term Acute Care Hospitals in the Regional Epidemiology of Klebsiella pneumoniae Carbapenemase-Producing Enterobacteriaceae	Clin. Infect. Dis.	2013	121
33	Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant Klebsiella pneumoniae in critically ill patients: a prospective evaluation	Clin. Microbiol. Infect.	2010	121
34	Potential Role of Active Surveillance in the Control of a Hospital-Wide Outbreak of Carbapenem-Resistant Klebsiella pneumoniae Infection	Infect. Control Hosp. Epidemiol.	2010	119
35	A Randomized, Double-Blind, Placebo-Controlled Trial of Selective Digestive Decontamination Using Oral Gentamicin and Oral Polymyxin E for Eradication of Carbapenem-Resistant Klebsiella pneumoniae Carriage	Infect. Control Hosp. Epidemiol.	2012	116
36	Molecular Dissection of an Outbreak of Carbapenem-Resistant Enterobacteriaceae Reveals Intergenus KPC Carbapenemase Transmission through a Promiscuous Plasmid	mBio	2011	111
37	Epidemic Klebsiella pneumoniae ST258 Is a Hybrid Strain	mBio	2014	108
38	Risk factors for developing clinical infection with carbapenem-resistant Klebsiella pneumoniae in hospital patients initially only colonized with carbapenem-resistant K pneumoniae	Am. J. Infect. Control	2012	107
39	Nationwide Surveillance of Clinical Carbapenem-resistant Enterobacteriaceae (CRE) Strains in China	EBioMedicine	2017	104
40	Infections caused by carbapenem-resistant Klebsiella pneumoniae among patients in intensive care units in Greece: a multi-centre study on clinical outcome and therapeutic options	Clin. Microbiol. Infect.	2014	102
41	Treatment and outcomes in carbapenem-resistant Klebsiella pneumoniae bloodstream infections	Diagn. Microbiol. Infect. Dis.	2011	100
42	Comparing the Outcomes of Patients With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Bacteremia	Clin. Infect. Dis.	2017	99
43	Endoscopic Retrograde Cholangiopancreatography-Associated AmpC Escherichia coli Outbreak	Infect. Control Hosp. Epidemiol.	2015	99
44	Prevalence and Risk Factors for Acquisition of Carbapenem-Resistant Enterobacteriaceae in the Setting of Endemicity	Infect. Control Hosp. Epidemiol.	2013	98
45	The global distribution and spread of the mobilized colistin resistance gene mcr-1	Nat. Commun.	2018	95
46	Vaborbactam: Spectrum of Beta-Lactamase Inhibition and Impact of Resistance Mechanisms on Activity in Enterobacteriaceae	Antimicrob. Agents Chemother.	2017	94
47	Prevention of Colonization and Infection by Klebsiella pneumoniae Carbapenemase-Producing Enterobacteriaceae in Long-term Acute-Care Hospitals	Clin. Infect. Dis.	2015	91
48	Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacteriaceae in international travelers returning to Germany	Int. J. Med. Microbiol.	2015	90
49	Colistin resistance is superimposed to endemic carbapenem-resistant Klebsiella pneumoniae: a rapidly evolving problem in Italy, November 2013 to April 2014	Eurosurveillance	2014	89
50	Rapid emergence and spread of OXA-48-producing carbapenem-resistant Enterobacteriaceae isolates in Belgian hospitals	Int. J. Antimicrob. Agents	2012	89
51	Duration of carriage of carbapenem-resistant Enterobacteriaceae following hospital discharge	Am. J. Infect. Control	2013	86
52	Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia	Antimicrob. Agents Chemother.	2017	85
53	Carriage rate of carbapenem-resistant Klebsiella pneumoniae in hospitalised patients during a national outbreak	J. Hosp. Infect.	2010	83
54	Complete Sequences of mcr-1-Harboring Plasmids from Extended-Spectrum-beta-Lactamase- and Carbapenemase-Producing Enterobacteriaceae	Antimicrob. Agents Chemother.	2016	82
55	Activity of Meropenem Combined with RPX7009, a Novel beta-Lactamase Inhibitor, against Class A-Negative Clinical Isolates in New York City	Antimicrob. Agents Chemother.	2015	82
56	A quarantine process for the resolution of duodenoscope-associated transmission of multidrug-resistant Escherichia coli	Gastrointest. Endosc.	2015	80
57	Vital Signs: Estimated Effects of a Coordinated Approach for Action to Reduce Antibiotic-Resistant Infections in Health Care Facilities - United States	MMWR-Morb. Mortal. Wkly. Rep.	2015	80
58	Surveillance of Carbapenem-Resistant Klebsiella pneumoniae: Tracking Molecular Epidemiology and Outcomes through a Regional Network	Antimicrob. Agents Chemother.	2014	80
59	Mortality associated with carbapenem-resistant Klebsiella pneumoniae infections in liver transplant recipients	Liver Transplant.	2012	80
60	Modified Carbapenem Inactivation Method for Phenotypic Detection of Carbapenemase Production among Enterobacteriaceae	J. Clin. Microbiol.	2017	79
61	Molecular Characterization of Carbapenemase-Producing Escherichia coli and Klebsiella pneumoniae in the Countries of the Gulf Cooperation Council: Dominance of OXA-48 and NDM Producers	Antimicrob. Agents Chemother.	2014	79
62	Laboratory and Clinical Evaluation of Screening Agar Plates for Detection of Carbapenem-Resistant Enterobacteriaceae from Surveillance Rectal Swabs	J. Clin. Microbiol.	2011	79
63	In Vitro Evaluation of Antibiotic Synergy for Polymyxin B-Resistant Carbapenemase-Producing Klebsiella pneumoniae	J. Clin. Microbiol.	2010	79
64	Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial	Infect. Dis. Ther.	2018	77
65	Risk factors for carbapenem-resistant Klebsiella pneumoniae bloodstream infection among rectal carriers: a prospective observational multicentre study	Clin. Microbiol. Infect.	2014	77
66	Asymptomatic rectal carriage of blaKPC producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected?	Clin. Microbiol. Infect.	2013	76
67	Carbapenemase-producing Enterobacteriaceae in Finland: the first years (200811)	J. Antimicrob. Chemother.	2012	76
68	Prospective Multicenter Study of Carbapenem-Resistant Klebsiella pneumoniae Bacteremia: 30-Day Outcome and Impact of Ineffective Empirical Therapy	Antimicrob. Agents Chemother.	2015	75
69	Carbapenemase-Producing Enterobacteriaceae in Spain in 2012	Antimicrob. Agents Chemother.	2013	75
70	Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial A Randomized Clinical Trial	JAMA Surg.	2017	74
71	Carbapenem-resistant Klebsiella pneumoniae bacteremia: factors correlated with clinical and microbiologic outcomes	Diagn. Microbiol. Infect. Dis.	2010	74
72	Outbreak of Carbapenem-Resistant Klebsiella pneumoniae in Puerto Rico Associated with a Novel Carbapenemase Variant	Infect. Control Hosp. Epidemiol.	2010	73
73	Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms	Antimicrob. Agents Chemother.	2017	72
74	Evaluation of the RAPIDEC (R) CARBA NP, the Rapid CARB Screen (R) and the Carba NP Test for biochemical detection of carbapenemase-producing Enterobacteriaceae	J. Antimicrob. Chemother.	2015	72
75	Large Nosocomial Outbreak of Colistin-Resistant, Carbapenemase-Producing Klebsiella pneumoniae Traced to Clonal Expansion of an mgrB Deletion Mutant	J. Clin. Microbiol.	2015	72
76	Secular Trends in Gram-Negative Resistance among Urinary Tract Infection Hospitalizations in the United States, 2000-2009	Infect. Control Hosp. Epidemiol.	2013	71
77	Recent Exposure to Antimicrobials and Carbapenem-Resistant Enterobacteriaceae: The Role of Antimicrobial Stewardship	Infect. Control Hosp. Epidemiol.	2012	71
78	Comparison of methods to detect the in vitro activity of silver nanoparticles (AgNP) against multidrug resistant bacteria	J. Nanobiotechnol.	2015	69
79	Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy	Bone Marrow Transplant.	2015	69
80	High colonization rates of extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli in Swiss Travellers to South Asia - a prospective observational multicentre cohort study looking at epidemiology, microbiology and risk factors	BMC Infect. Dis.	2014	69
81	Phase 2, Randomized, Double-Blind Study of the Efficacy and Safety of Two Dose Regimens of Eravacycline versus Ertapenem for Adult Community-Acquired Complicated Intra-Abdominal Infections	Antimicrob. Agents Chemother.	2014	69
82	A hospital-based matched case-control study to identify clinical outcome and risk factors associated with carbapenem-resistant Klebsiella pneumoniae infection	BMC Infect. Dis.	2013	69
83	NDM-1, OXA-48 and OXA-181 carbapenemase-producing Enterobacteriaceae in Sultanate of Oman	Clin. Microbiol. Infect.	2012	69
84	Comparative Effectiveness of Aminoglycosides, Polymyxin B, and Tigecycline for Clearance of Carbapenem-Resistant Klebsiella pneumoniae from Urine	Antimicrob. Agents Chemother.	2011	69
85	Emergence of a hypervirulent carbapenem-resistant Klebsiella pneumoniae isolate from clinical infections in China	J. Infect.	2015	68
86	Down the drain: carbapenem-resistant bacteria in intensive care unit patients and handwashing sinks	Med. J. Aust.	2013	68
87	Bacteremia due to OXA-48-carbapenemase-producing Enterobacteriaceae: a major clinical challenge	Clin. Microbiol. Infect.	2013	68
88	Carbapenem-Resistant Klebsiella pneumoniae in Post-Acute-Care Facilities in Israel	Infect. Control Hosp. Epidemiol.	2011	68
89	Multicenter Clinical and Molecular Epidemiological Analysis of Bacteremia Due to Carbapenem-Resistant Enterobacteriaceae (CRE) in the CRE Epicenter of the United States	Antimicrob. Agents Chemother.	2017	67
90	Impact of carbapenem resistance on the outcome of patients' hospital-acquired bacteraemia caused by Klebsiella pneumoniae	J. Hosp. Infect.	2013	67
91	Comparison of BD Phoenix, Vitek 2, and MicroScan Automated Systems for Detection and Inference of Mechanisms Responsible for Carbapenem Resistance in Enterobacteriaceae	J. Clin. Microbiol.	2010	67
92	Emergence of carbapenem-resistant Enterobacteriaceae as causes of bloodstream infections in patients with hematologic malignancies	Leuk. Lymphoma	2013	66
93	Effect of the beta-Lactamase Inhibitor Vaborbactam Combined with Meropenem against Serine Carbapenemase-Producing Enterobacteriaceae	Antimicrob. Agents Chemother.	2016	65
94	Carbapenem-Resistant Klebsiella pneumoniae Strains Exhibit Diversity in Aminoglycoside-Modifying Enzymes, Which Exert Differing Effects on Plazomicin and Other Agents	Antimicrob. Agents Chemother.	2014	65
95	Outbreak of OXA-48 carbapenemase-producing Klebsiella pneumoniae in Greece involving an ST11 clone	J. Antimicrob. Chemother.	2013	65
96	Phenotypic Screening of Carbapenemases and Associated beta-Lactamases in Carbapenem-Resistant Enterobacteriaceae	J. Clin. Microbiol.	2012	65
97	Colistin Resistance in Carbapenem-Resistant Klebsiella pneumoniae: Laboratory Detection and Impact on Mortality	Clin. Infect. Dis.	2017	64
98	Rising Rates of Carbapenem-Resistant Enterobacteriaceae in Community Hospitals: A Mixed-Methods Review of Epidemiology and Microbiology Practices in a Network of Community Hospitals in the Southeastern United States	Infect. Control Hosp. Epidemiol.	2014	64
99	Carbapenem-Resistant Klebsiella pneumoniae Exhibit Variability in Capsular Polysaccharide and Capsule Associated Virulence Traits	J. Infect. Dis.	2014	63
100	Activity of biapenem (RPX2003) combined with the boronate -lactamase inhibitor RPX7009 against carbapenem-resistant Enterobacteriaceae	J. Antimicrob. Chemother.	2013	63

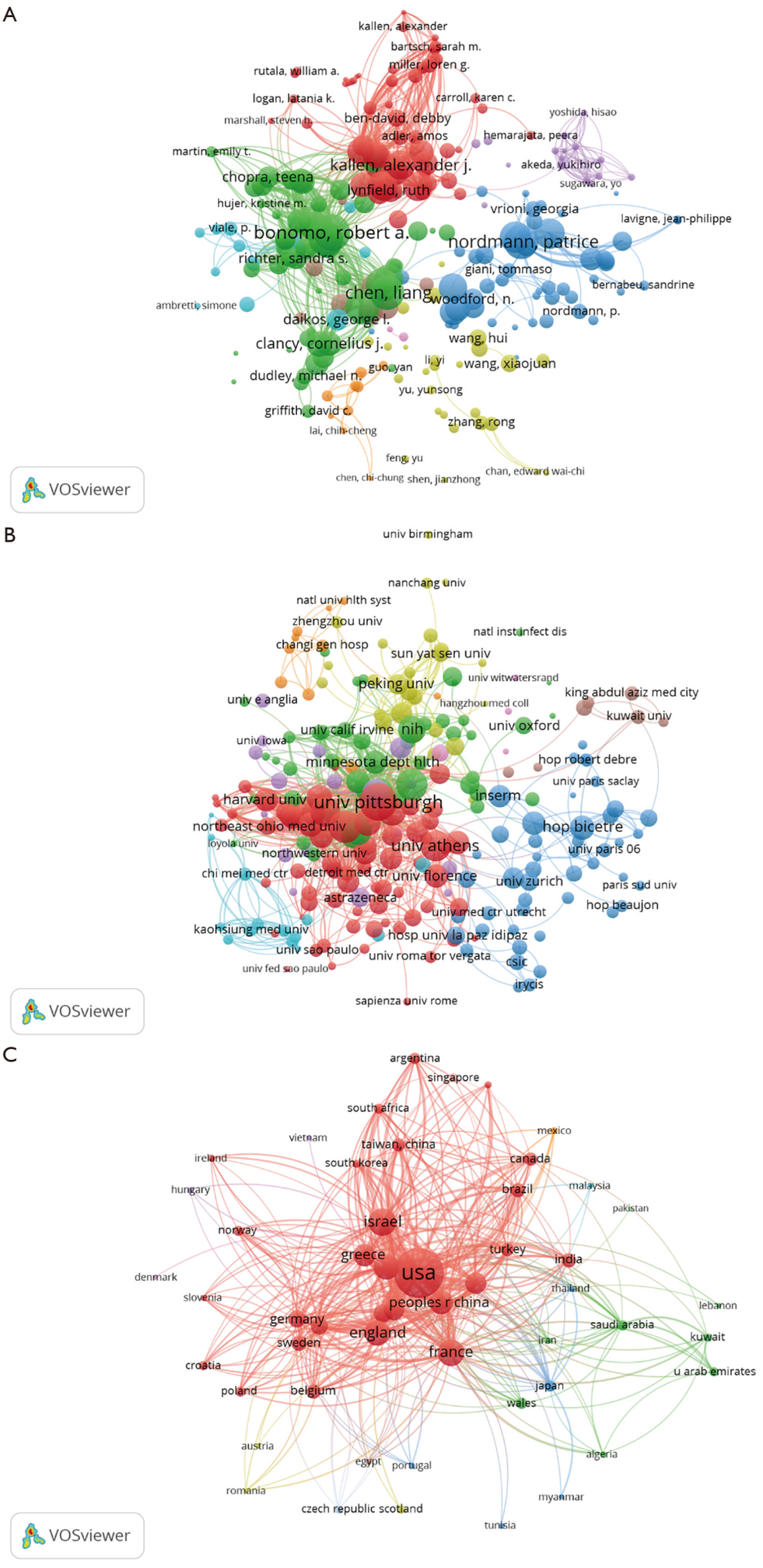

Figure S3 Bibliometric analysis of the citation. The citation of authors (A), institutions (B), and countries (C) in field of CRE research. The color indicated clusters, circle size indicated citations, the thickness of lines indicated strength of linkage.

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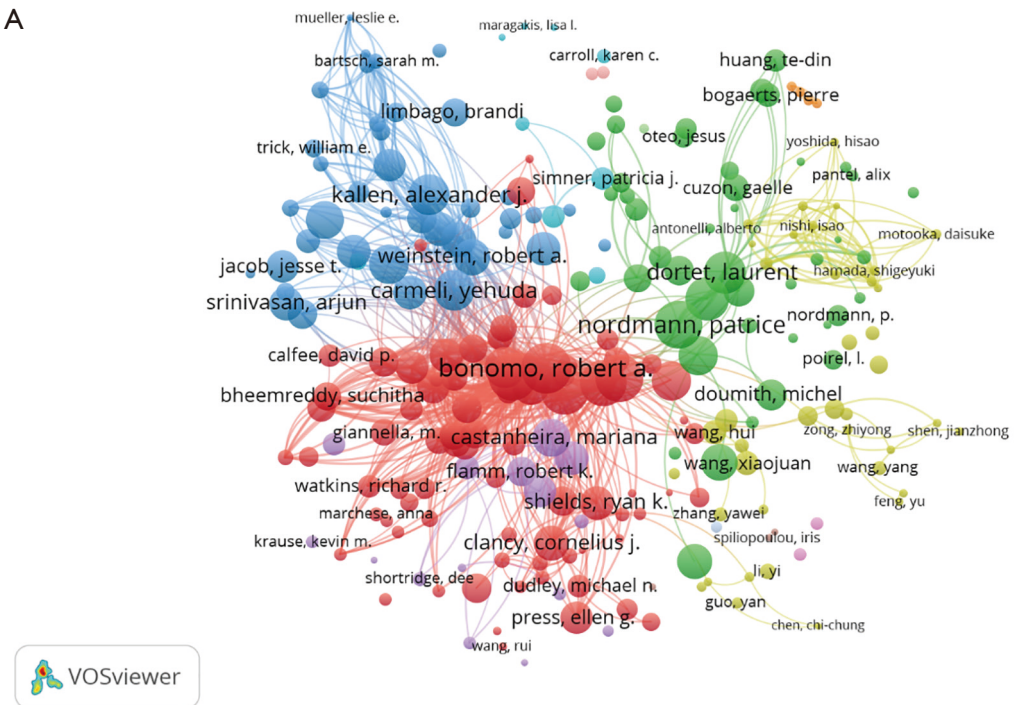

Figure S4 Bibliographic coupling analysis. The bibliographic coupling networks of authors (A), documents (B), journals (C) and countries (D) were shown. The color indicated clusters, circle size indicated number of citations, the thickness of lines indicated strength of linkage.

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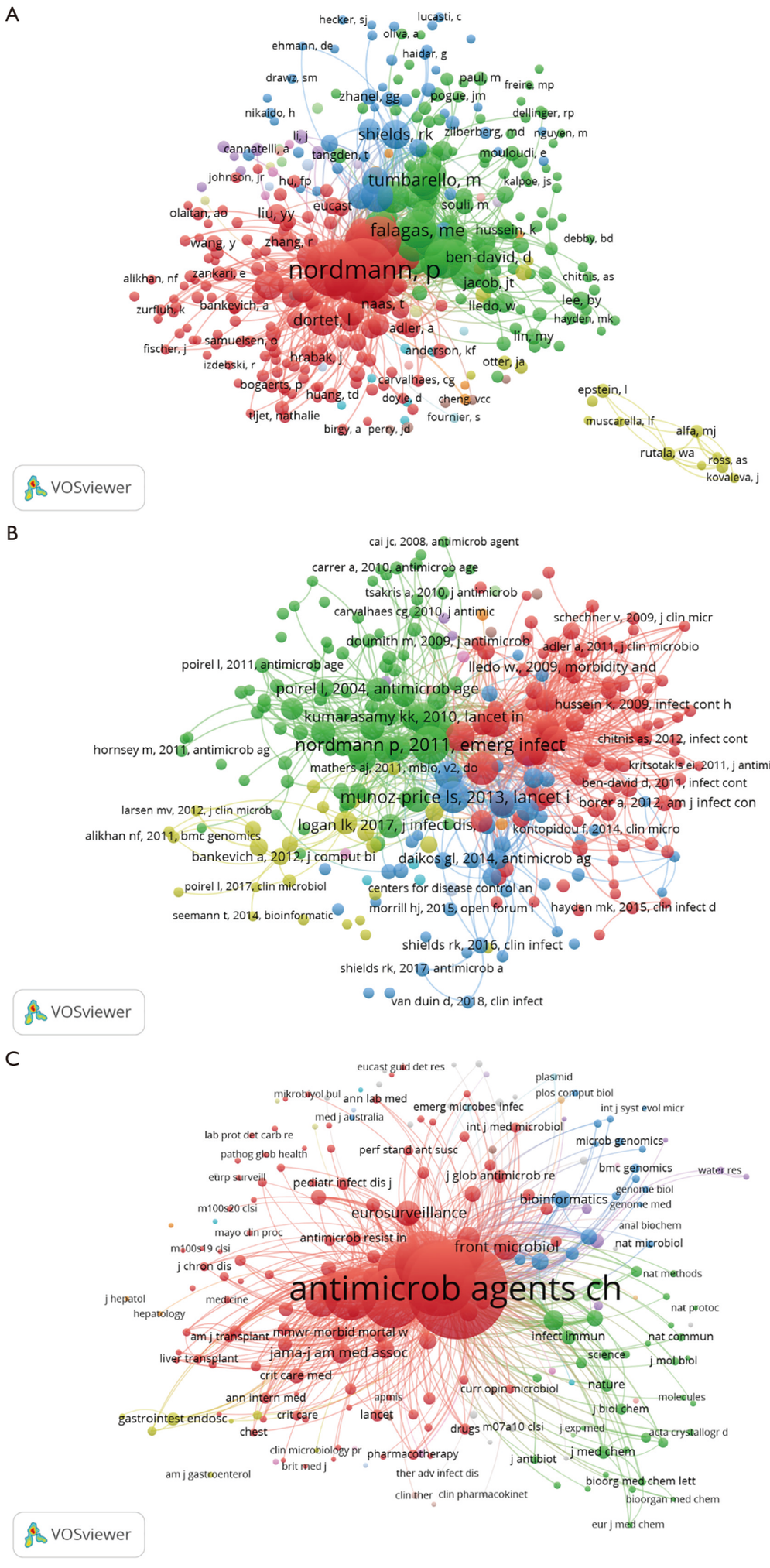

Figure S5 Co-citation analysis evaluate the link between two documents that are both cited by the same literature. The co-citation network of authors (A), references (B) and journals (C) were shown. The color indicated clusters, circle size indicated number of citations, the thickness of lines indicated strength of linkage.

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Table S3 Highly frequent major keywords from the included publications on CRE (n = 5,782).

Rank	Keywords	Occurrence	Percentage of occurrence (%)	Cumulative percentage (%)
1	carbapenem-resistant Enterobacteriaceae	284	4.9118	4.9118
2	Enterobacteriaceae	234	4.047	8.9588
3	carbapenemase	223	3.8568	12.8156
4	Klebsiella pneumoniae	218	3.7703	16.586
5	KPC	122	2.11	18.696
6	carbapenem resistance	111	1.9198	20.6157
7	carbapenem	88	1.522	22.1377
8	carbapenemase-producing Enterobacteriaceae	64	1.1069	23.2446
9	antimicrobial resistance	62	1.0723	24.3168
10	OXA-48	60	1.0377	25.3545
11	colistin	59	1.0204	26.375
12	carbapenem-resistant	57	0.9858	27.3608
13	antibiotic resistance	56	0.9685	28.3293
14	carbapenem-resistant Klebsiella pneumoniae	55	0.9512	29.2805
15	ESBL	54	0.9339	30.2145
16	multidrug resistance	54	0.9339	31.1484
17	risk factors	53	0.9166	32.065
18	NDM	51	0.882	32.9471
19	NDM-1	47	0.8129	33.7599
20	ceftazidime-avibactam	47	0.8129	34.5728
21	Escherichia coli	45	0.7783	35.3511
22	mortality	39	0.6745	36.0256
23	carbapenemase-producing	37	0.6399	36.6655
24	infection control	36	0.6226	37.2881
25	resistance	35	0.6053	37.8935
26	epidemiology	33	0.5707	38.4642
27	bloodstream infection	32	0.5534	39.0176
28	MBL	30	0.5189	39.5365
29	intensive care unit	29	0.5016	40.038
30	surveillance	29	0.5016	40.5396
31	meropenem	27	0.467	41.0066
32	outbreak	26	0.4497	41.4562
33	colonization	26	0.4497	41.9059
34	colistin resistance	25	0.4324	42.3383
35	whole-genome sequencing	25	0.4324	42.7707
36	plasmid	24	0.4151	43.1857
37	drug resistance	21	0.3632	43.5489
38	multidrug-resistant	20	0.3459	43.8948

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Table S4 High-frequency keyword/source article matrix.

No	Keywords	Sequence of publications				
		1	2	3	…	1671
1	carbapenem-resistant Enterobacteriaceae	0	0	0	…	0
2	Enterobacteriaceae	0	1	1	…	0
3	carbapenemase	0	0	0	…	0
4	Klebsiella pneumoniae	0	0	0	…	1
…	…	…	…	…	…	…
38	multidrug-resistant	0	0	0	…	0

Table S5 Co-word matrix of high frequent keyword.

No	Keywords	carbapenem-resistant Enterobacteriaceae	Enterobacteriaceae	carbapenemase	…	multidrug-resistant
1	carbapenem-resistant Enterobacteriaceae	284	15	22	…	9
2	Enterobacteriaceae	15	234	79	…	6
3	carbapenemase	22	79	223	…	3
…	…	…	…	…	…	…
38	multidrug-resistant	9	6	3	…	20

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