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GLOBAL TRENDS AND PERFORMANCES OF STUDIES ON ANTIBIOTIC RESISTANCE GENES

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Abstract

There are substantial publications about the research of antibiotic resistance genes (ARGs). The purpose of this paper is to identify the global trends and performances of ARGs research. Literatures of ARGs that published between 1974 and 2016 from Web of Science Core Collection were used to create the bibliometric database for the present study in which we coupled cluster analysis and network analysis to visualize research trends of ARGs with international collaborations and trans-disciplinary advances. Stage II (1998-2016) showed that international cooperation is much more prevalent than Stage I (1974-1997), especially among the United States, the United Kingdom and China. There were more researches about "Engineering", "Chemistry" and "Water resources" and more multidisciplinary cross in Stage β (1998-2016) compared to Stage α (1974-1997). There were also two stages about keywords analysis: Stage i (1991-2005) and Stage ii (2006-2016). Stage i focused on basic theoretical studies for antibiotic resistance. However, Stage ii mainly explored the relationship among antibiotics, ARGs and antibiotic resistant bacteria (ARB) in different environmental compartments. Specially, wastewater was the most studied environmental compartment, and was followed by soil. The most studied organism was bacteria especially ARB, and included Escherichia coli, Staphylococcus aureus and Methicillin-resistant staphylococcus aureus. Furthermore, swine was the hot research animal. Metagenomics, sulfonamides and some pathogens were the research hotspots. International cooperations and multidisciplinary cross can improve the quality of publications and increase the numbers of papers. The mechanisms research among antibiotics, ARGs and ARB and remove ways of ARGs are research hotspots in future.

Key words: antibiotic resistance genes, interdisciplinary advances, international collaboration, research hotspots

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1. Introduction

Antibiotic resistance genes (ARGs) as emerging environmental contaminants posed growing threat to human health (Ducey et al., 2017; Lv et al., 2018; Rizzo et al., 2013). Owing to the overuse and spread of antibiotics, a large number of antibiotic residues have been released into the environment, which led to emergence and evolution of antibiotic resistance (Baquero et al, 2008; Li et al., 2018a; Wang et al., 2018). Antibiotic resistance can produce selective pressure on antibiotic resistance bacteria (ARB) (Sommer et al., 2009; Zhang et al., 2009). Strikingly, these ARB can transfer the resistance genes to human pathogens by horizontal genes transfer (HGT), or vice versa (Su et al., 2015).

HGT is a major mechanism to exchange ARGs between microbes via mobile genetic elements

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(MGEs) including plasmids, transposons and integrons (Chopra and Roberts, 2001; Pruden et al., 2006; Salyers et al., 2004). Some researches focused on the distribution and widespread dissemination of ARGs in different environmental compartments such as aquatic systems, soils and sediments (Heuer et al., 2011; Li et al., 2015; Qiao et al., 2018; Schwartz et al., 2003; Ying et al., 2018). For example, Auerbach et al. (2007) conducted a study of tetracycline resistance on various wastewater treatment plants and two freshwater lakes, which indicated the highest concentration of *tet*Q and *tet*G was distint in different environmental media. Various ARGs have also been identified in river sediments such as sulfonamide resistance genes (*sul*I and *sul*II) and tetracycline resistance genes (*tet*W and *tet*O) (Pei et al., 2006). Noticeably, ARGs have been discovered to show multiple antibiotic resistance (MAR) resulting in multiple drug resistant bacteria even some superbugs (Allen et al., 2010; Forsberg et al., 2012; Munir et al., 2011; Su et al., 2019).

The objective of this paper is to synthesize what we know about ARGs using bibliometric and network analysis. Bibliometric analysis has been broadly applied to predict trends and hotspots based on historical publications information (Jiang et al., 2016; Khan and Ho, 2015). Some previous studies have used bibliometric analysis in different research areas, including medical research, biological resources, environmental issues etc. (Chen et al., 2014; Hulme et al., 2018; Ritz et al., 2010; Xu and Boeing, 2013).

In the present study, we used the Science Citation Index (SCI) database of Web of Science (WoS), which is the most frequently used data source of bibliometric information (Qian et al., 2015). Furthermore, network analysis is a useful tool to study sets of nodes and links among different themes including countries, subject categories and keywords (Li et al., 2018b). Meanwhile, network analysis can identify close relationships between different nodes (de Paulo and Porto, 2017).

Keywords analysis is beneficial to provide important information about research hotspots, and reveal future research direction (Li et al., 2018c). So far, there have been a few studies analyzing publications related to ARGs using bibliometric analysis. For example, Garrido-Cardenas et al. (2017) revealed metagenomics trend in the field of wastewater quality monitoring using bibliometric analysis. However, there was not a paper to conduct ARGs research by bibliometric analysis and network analysis.

Therefore, we analyzed the research status of ARGs using network analysis between 1974 and 2016. The present study mainly included the following three aspects of ARGs: (1) an analysis of temporal progression of international collaborations among the 20 most productive countries in different stages; (2) a ranking of the most commonly used journals and a quantification of various subject categories among the 20 most influential journals and disciplines; (3) an extraction of the 50 most frequently used keywords to confirm research trends.

2. Material and methods

We built a dataset of ARGs on 2 June, 2017 and data was downloaded from SCI database of the WoS (Clarivate Analytics) maintained by the Institute of Scientific Information (USA). “Antibiotic resistance genes” and “ARGs” were chosen as the topic during the collection time of WoS from 1900 to 2016. We downloaded full records such as author’s addresses (C1), published year (PY), subject categories (SC), author keywords (DE), journal name (JN) and cited documents (CD).

A total of 2776 published articles were compiled for the analysis. The available number of articles were less than 2776 because some published years of publications didn’t have the information of C1, SC and DE. Author’s addresses were used to get the information about countries that contributed to research of ARGs. Author keywords (not keyword plus) with identical meaning were merged into the highest frequency keywords. Noticeably, the published years of publications with keywords information started from 1990 in SCI database of the WoS.

Furthermore, articles from England, North Ireland, Scotland and Wales were reclassified as the publications of United Kingdom (UK). Articles from Hong Kong and Taiwan were included in the publications of China.

We analyzed the data of downloaded publications related to ARGs using hierarchical cluster analysis (HCA) to identify publication periods by the software of PC-ORD 4.0 (Wild Blueberry Media LLC). The distance measure of HCA was Jaccard or Sorensen (Bray-Curtis) and the group linkage method was Ward’s Method. HCA was performed using counts of publication times per country, science category and keyword. To show the changes in countries, science categories and keywords over time, the historical research efforts were grouped into different periods.

We developed the basis to accurately determine the grouped stages of all countries, subject categories, and the 200 most frequently used keywords by HCA under the same similarity level. Then, the software of Bibexcel and Pajek (Leydesdorff et al., 2017; Persson and Dastidar, 2013) were applied to perform the ranking of the most commonly used journals and different stages of visualization relationship among: a) the 20 most publication-productive countries, b) the 20 most popular subject categories and c) the 50 most frequently appeared keywords. We demonstrated the differences of individual stages with the visualization network and compared the network of countries, subject categories and keywords.

We performed statistical analysis of the data (e.g. publications and publication times in different stages, the number of publications of some typical countries) using Microsoft Excel 2010 and SigmaPlot 12.5. The publication times for countries, subject categories and keywords were computed by Eq. (1).

$$\textit{Publication times} = \sum_{N=1}^{N} \textit{Number of different "countries" per paper)} \tag{1}$$

where N is the number of papers, and “subject” refers to the category of interest, namely countries, subject categories and keywords (Zheng et al., 2018).

3. Results and discussion

3.1. Publication outputs and international collaborations

During the period from 1974 to 2016, the author’s addresses are available from 2,726 articles, which accounted for 98.2% of total 2,776 articles recorded in the SCI database WoS obtained. The dataset of author’s addresses for these 2,726 articles contained 100 countrieswith a total of 3,664 publication times. Of 100 countries, 21 countries published only once per each, and 55 countries published less than 10 times per each. There are 20 most productive countries each of which published more than 36 times. These 20 most productive countries contributed to 3,035 publication times, which account for 82.8% of total 3,664 publication times.

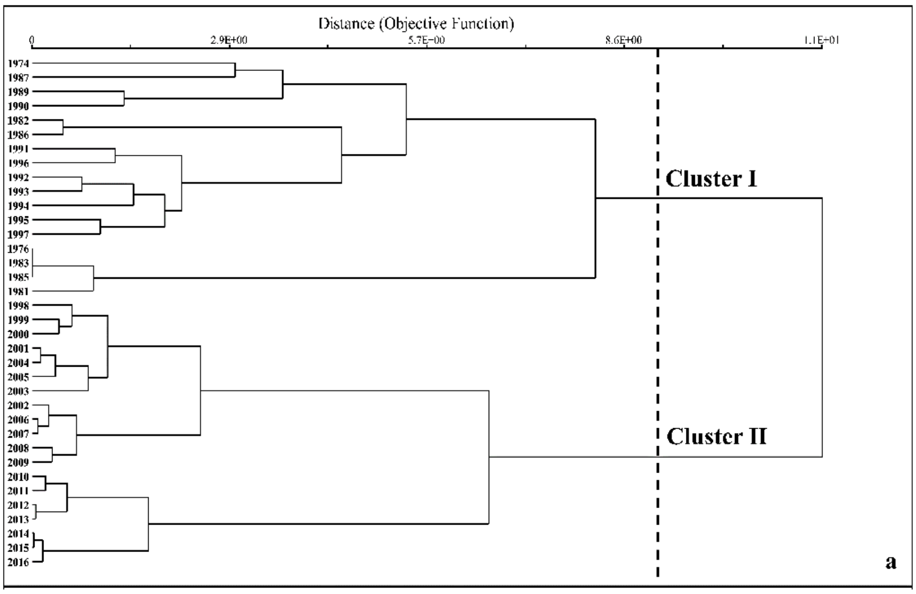
The cluster analysis on the matrix of publication times for year and country divided clearly the research effort of countries on ARGs into two stages (Stage I and II, Fig. 1a**)**. Research literature appeared earliest in WoS Core Collection in 1974. These two stages featured the increasing output of scientific knowledge and the changing contribution of countries (Fig. 2). Fig. 2 shows that the number of publications on ARGs was low at first and then increased gradually. During the period of Stage II, the United States published more articles than China until 2015.

The application of network analysis on collaboration times for publications within each of these two effort stages further found a dramatic shift in pattern of international collaborations on ARGs research (Fig. 3).

Stage I (1974-1997) lasted for 24 years (Fig. 3a), during which the earliest research efforts on ARGs were made. This stage can be characterized as the primary stage of research efforts, the longest period and the lowest publication output regarding ARGs. In this stage, the number of publications was 5 articles per year on average, and totaled 104 articles over the entire period, which accounted for only 3.8% of the total publications. The authors represented from 26 different countries with 119 publication times, corresponding to only 3.2% of total 3,664 publication times.

In Stage I, the 20 most productive countries spread to 4 different continents. Of these 20 countries, 12 countries were in Europe, including the United Kingdom, Spain, France, Norway, Czech Republic, Italy, Sweden, Germany, Netherlands, Swizerland, Ireland and Russia. There was only one country in Asia (China) and Australia (Australia). North and south America had 6 countries, including the United States, Canada, Argentina, Peru, Mexico and Chile. The network analysis showed that the international collaborations was strongest among the United States, the United Kingdom and Australia, which produced a triangle closed-loop. Furthermore, France, Norway, Italy and Peru were main international partners with the United States.

Stage II (1998-2016) lasted for 19 years, and can be characterized by the increased rates of publication for the research on ARGs (Fig. 3b). The publication output increased dramatically with more than 138 articles per year. In this stage, a total of 2,622 articles were published, corresponding to 96.2% of all 2,726 articles.



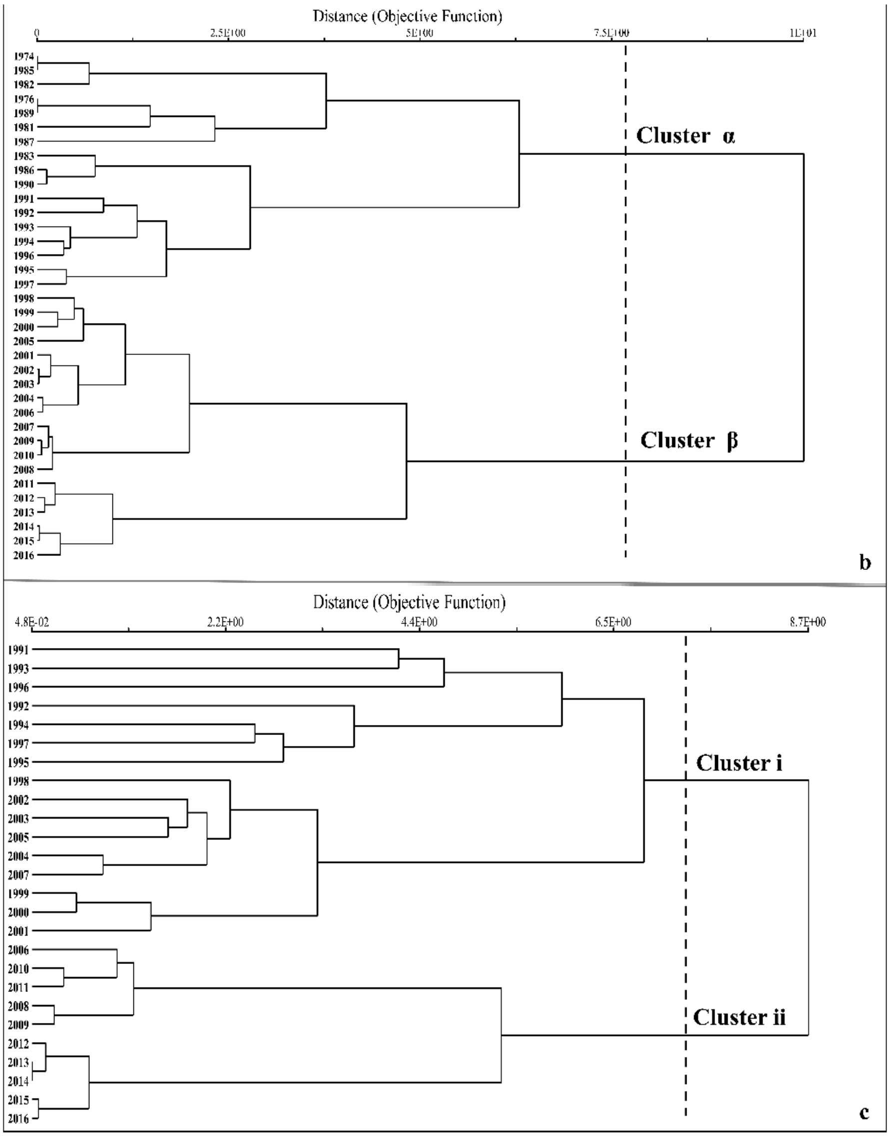


Fig. 1. Dendrograms of several stages of research efforts related to temporal development of international collaborations (a) variation of subject categories (b) and research trends (c) based on all the countries, subject categories and the 200 most frequent keywords of ARGs

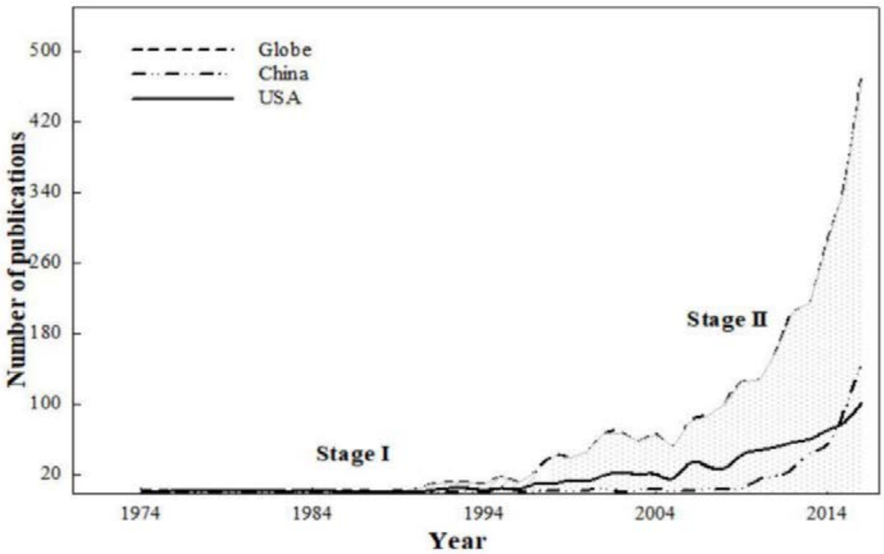


Fig. 2. Annual articles published globally, and by China and the United States, during 1974-2016 with different stages

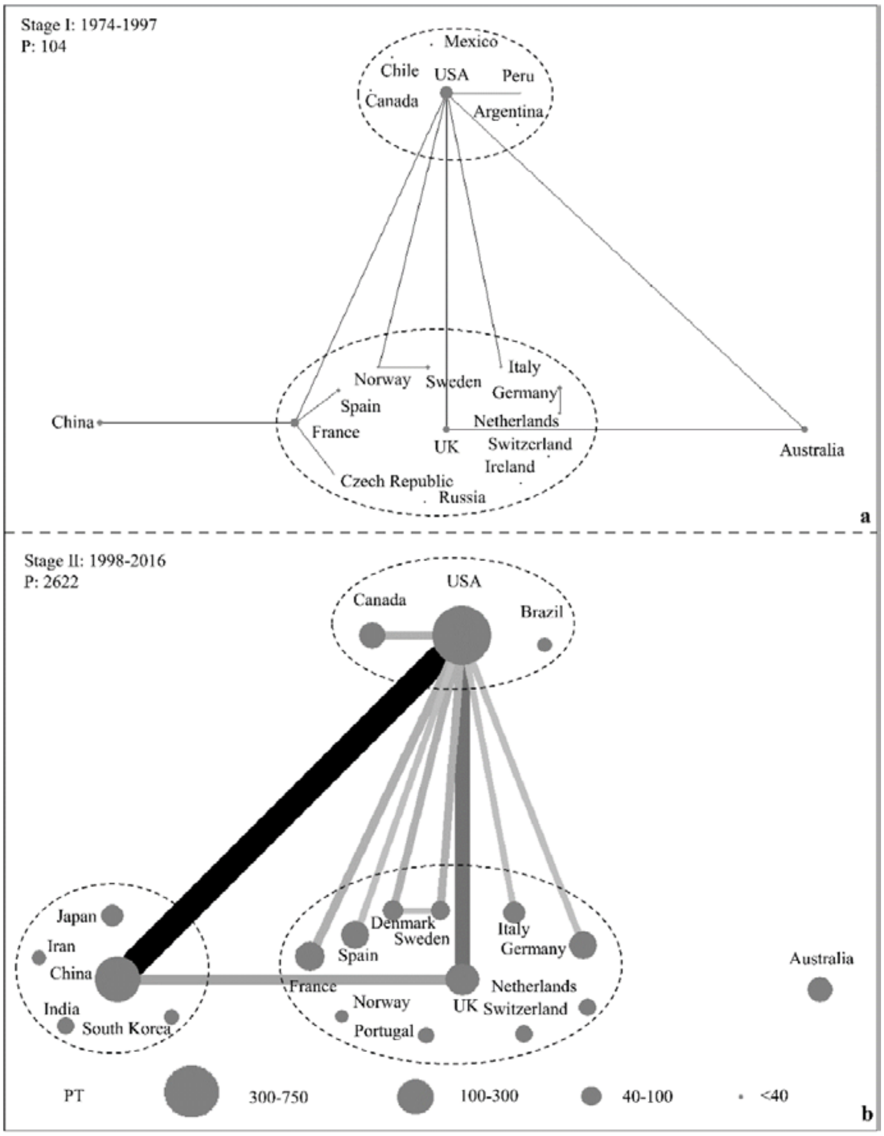


Fig. 3. The collaboration networks for the 20 most productive countries visualized at each of two stages based on publication times of each country of ARGs research. P is the number of publications and PT refers to t the publication times

The result indicates that, in Stage II: (a) the research interests on ARGs started to grow rapidly involving 100 countries; (b) the research yielded a total of 3,545 publication times, corresponding to 96.8% of the total of 3,664 publication times; and (c) the 20 most productive countries published 2,930 publication times (82.7% of 3,545 publication times). The network analysis showed that the international collaborations involved more countries in Stage II than Stage I; i.e., Europe (Denmark and Portugal), America (Brazil) and Asia (Japan, Iran, India and South Korea).

The research efforts of ARGs became much more extensive in this stage. Furthermore, the line was the darkest and widest between the United States and China, which showed the most close international cooperation of the two countries. There was an obvious triangle closed-loop among the United States, the United Kingdom and China, which indicated they are main international partners.

3.2 Journals and interdisciplinary advances

In this study, we obtained 701 journals that published articles on ARGs. Of 701 journals, 404 (57.6% of all 701 journals) published only one paper and 648 journals (92.4%) published less than 10 papers on ARGs. The first paper on ARGs published in 1974 in the journal Molecular & General Genetics (Callen, 1974). The 20 frequently used journals published 1,005 articles, corresponding to 36.2% of all 2,776 articles (Table 1.). “Antimicrobial Agents and Chemotherapy” with highest h-index (48) published the largest number of articles (125), accounting for 4.5% of all publications. The journal “PloS ONE” ranked the second with the total of 92 articles. The journal “Applied and Environmental Microbiology”, “Frontiers in Microbiology” and “Journal of Antimicrobial Chemotherapy” ranked the third, fourth and fifth of the most frequently used journal, respectively. “mBio” (with the highest impact factor of 6.98) published 28 articles and ranked the thirteenth in the category list of "microbiology" (A).

We obtained 85 different subject categories of ARGs during the period from 1974 to 2016 from a total of 2,774 articles (99.93% of all 2,776 articles), which is equivalent to 4,654 publication times. The stages of research development for science categories could be grouped into two main clusters: Clusters α and β (Fig. 1b). These clusters show the change of combination of different disciplines over time. We also performed a network analysis on the 20 major subject categories for each of the cluster-defined two stages (Fig. 4). Given that the number of papers published annually on the subject has been increasing, the stage corresponding to the latter period has consequently more records.

In Stage α (1974-1997), 139 articles on ARGs were published, corresponding to 5.0% of all 2,774 articles, equivalent to 225 publication times (Fig. 4a). The 20 most common subject categories were grouped into seven main sections that represent the relationships between of different subject categories. Firstly, "Microbiology" was the most influential subject and occupied a central position in the network. "Biotechnology and applied microbiology" was also important to explore the mechanisms of ARGs from "Microbiology" and "Chemistry" was also important to explore the mechanisms of antibiotics in the aquatic environment. "Biochemistry and molecular biology", "Cell biology" and "Biophysics" provided some basic researches from biology.

The study of ARGs had some close links with medicine including including "Pharmacology and pharmacy", "Public, environmental and occupational health", "Infectious diseases", "Immunology", "Life science and biomedicine-other topics", "Research and experimental medicine", "General and internal medicine", "Genetic and heredity" and "Veterinary sciences". Secondly, "Plant sciences", "Food science and technology" and "Agriculture" may focus on the source and influence of ARGs. "Environmental sciences and ecology" is a comprehensive subject containing many areas related to the interrelationships of organisms and their environments. Finally, the sixth and seventh part were "Material sciences" and "Science and technology-other topics", respectively. The two sections showed that some chemical and engineered methods were used to reduce the abundance and diversity of ARGs.

In Stage β (1998-2016), 2,635 articles (95% of all 2,774 articles) are relevant to ARGs, which correspond to 4,429 publication times (Fig. 4b). The interactions among the subject categories increased compared to Stage α. Obviously, there were more interdisciplinary researches in this stage. "Marine and freshwater biology" appeared in the biological category, indicating that researchers started to focus on ARGs in aquatic systems.

Table 1. The most popularly used journals with ranks, the number of publications, citations, impact factors, h-index and category of journal in WSC position

JR	*AJN*	*TP*	*TP(%)*	*TC*	*TC/TP*	*IF*	*h-index*	*WSC(position)*
1	Antimicrob Agents Chemother	125	4.50	8634	69.07	4.42	48	A(22/123); B(34/255)
2	PloS ONE	92	3.31	1227	13.34	3.06	20	C(11/63)
3	Appl Environ MicrobI	87	3.13	3486	40.07	3.82	31	D(33/161); A(31/123)
4	Front MicrobI	83	2.99	699	8.42	4.17	16	A(23/123)
5	J Antimicrob Chemother	80	2.88	2425	30.1	4.92	31	E(9/83); A(19/123); B(20/255)
6	Environ Sci Technol	64	2.31	2111	32.98	5.39	29	F(3/50); G(14/225)
7	J Bacteriol	62	2.23	2351	37.92	3.20	29	A(44/123)
8	Sci Total Environ	49	1.77	765	15.61	3.98	16	G(32/225)
9	Water Res	43	1.55	1195	27.79	5.99	17	F(2/50); G(7/225); H(1/85)
10	FEMS Microbiol Lett	37	1.33	1457	39.38	1.86	17	A(86/123)
11	J Clin Microblol	32	1.15	1819	56.84	3.63	24	A(36/123)
12	Int J Food Microbiol	31	1.12	1003	32.35	3.45	13	I(14/125); A(39/123)
13	Environ Sci Pollut R	30	1.08	119	3.97	2.76	7	G(65/225)
14	Mol Microbiol	29	1.04	1469	50.66	3.76	20	J(86/289); A(32/123)
15	FEMS Microbiol Ecol	28	1.01	574	20.50	3.53	8	A(37/123)
16	mBio	28	1.01	336	12.00	6.98	12	A(13/123)
17	J Appl Microbiol	27	0.97	428	15.85	2.16	14	D(79/161); A(76/123)
18	Plasmid	27	0.97	430	15.93	1.73	12	K(126/166); A(89/123)
19	Int J Antimicrob Agents	26	0.94	357	13.73	4.10	10	E(16/83); A(25/123); B(432/255)
20	J Med Microbiol	25	0.90	519	20.76	2.27	14	A(72/123)

Journals rank (JR): 1=Antimicrobial Agents and Chemotherapy; 2=PloS ONE; 3=Applied and Environmental Microbiology; 4=Frontiers in Microbiology; 5=Journal of Antimicrobial Chemotherapy; 6= Environmental Science and Technology; 7=Journal of Bacteriology; 8=Science of the Total Environment; 9=Water Research; 10=FEMS Microbiology Letters; 11=Journal of Clinical Microbiology; 12=International Journal of Food Microbiology; 13=Environmental Science and Pollution Research; 14=Molecular Microbiology; 15=FEMS Microbiology Ecology; 16=mBio; 17= Journal of Applied Microbiology; 18=Plasmid; 19=International Journal of Antimicrobial Agents; 20=Journal of Medical Microbiology. Web of science categories (WSC): A=Microbiology; B=Pharmacology and pharmacy; C=Multidisciplinary Sciences; D=Biotechnology and applied microbiology; E= Infectious diseases; F= Engineering, environmental; G=Environmental sciences; H=Water resources; I=Food science and technology; J=Biochemistry and molecular biology; K=Genetics and heredity. AJN=Abbreviations of journals name, TP=Total publications, TC=Total citations, TC/TP=average of citations per articles, IF=Impact factor (2016)

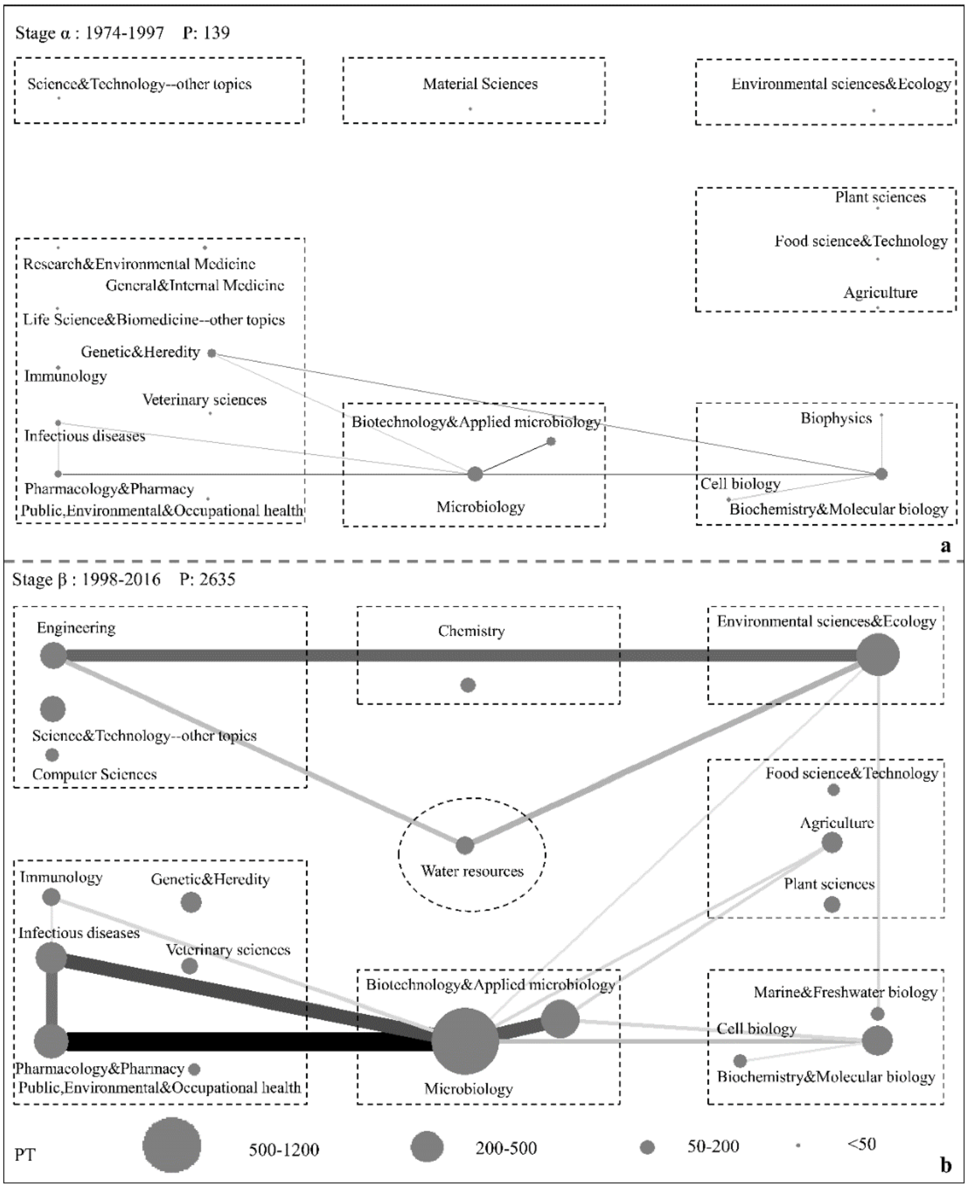


Fig. 4. The variation for the 20 most productive subject categories visualized at each of two stages based on publication times of each subject category of ARGs research. P means the number of publications and PT is the publication times

The new part “Water resources” also can prove the result. The subject category “Chemistry” replaced “Material sciences” in Stage α, showing that more chemical theories and methods were applied to explore the produced mechanism of resistance. Furthermore, “Engineering” and “Computer sciences” joined in the list of the 20 most frequently used subjects, which means some advanced technologies used to research ARGs. Noticeably, there were two obvious triangle closed-loops including “Microbiology”-“Pharmacology and pharmacy”-“Infectious diseases” and “Water resources”-“Environmental sciences and ecology”-“Engineering”. Interdisciplinary collaborations not only improved the quality of publications, but also increased the number of papers on ARGs research (Tanase et al., 2018). Meanwhile, more interdisciplinary collaborations are beneficial for researchers to understand the sources, diffusion and risks of ARGs.

3.3 Key words and research hotspots

In the analysis of keywords, we found 1,640 articles on ARGs for the period from 1990 to 2016, which accounted for 67.1% of all 2,776 articles, equivalent to 8,281 publication times. These 1,640 articles had 4,184 unique keywords; of which 3,315 keywords appeared in only one article and 4,096 keywords appeared in less than 10 articles, making up 79.3% and 97.9% of total 4,184 keywords, respectively. The literature pertaining to keywords of ARGs could be divided into two main stages (Stages i and ii, Fig. 1c)). The relationships of the 50 most frequently used keywords are shown in different stages using the co-words network (Fig. 5).

In Stage i (1991-2005), 242 articles were published, corresponding to 14.8% of all 1,640 articles, and was equivalent to 1,157 publication times (Fig. 5a). There were eight parts about the research of ARGs. The keyword "Antibiotic resistance" was the most cited keyword and "Resistance", "MAR" and "Beta-lactamase" were related to resistant theme. The source and "Evolution" of antibiotic resistance had some relationship with other themes. Owing to overuse of "Antibiotics" including "Beta-lactam", "Hygromycin" and "Tetracycline", some microorganisms especially "Bacteria" increased the resistance on antibiotics (Aminov et al., 2001; Martinez, 2008). "*Salmonella*", "*Streptomyces*", "*Escherichia coli*", "*Agrobacterium tumefaciens* (AT)" and "*Salmonella typhimurium* (ST)" were paid much attention on microorganism theme. "ARGs" and "Resistance genes" were spread by some mechanisms including "Conjugation", "Transformation", "Natural transformation", "Plasmid transformation", "Gene transfer", "HGT", "Lateral genes transfer", "Homologous recombination", "Site-specific recombination", "Oligonucleotides", "Poly-L-arginine", "Arginyl-tRNA synthetase", "Gene expression" and "Mutagenesis" (Liu and Pop, 2009). There were some MGEs such as "Transposon", "Gene cassette"," Integron", "Plasmid", "Conjugation transposon (CT)" that had close connections with antibiotic resistance (Mazel, 2006). Some researches showed that MGEs can enhance the abundance and diversity of ARGs (Chen et al., 2016; Recchia and Hall, 1995).

The keywords "Polymerase chain reaction (PCR)", "Pulse field gel electrophoresis (PFGE)", "Green fluorescent protein (GFP)" and "DNA" were related to the materials and methods to determine the ARGs. The last theme about "Food" and "Food safety" including "Transgenic plants", "Tobacco", "Attributed relational graph (ATRG)" and "Positive selection" may have less relations with the influences of ARGs in this study period.

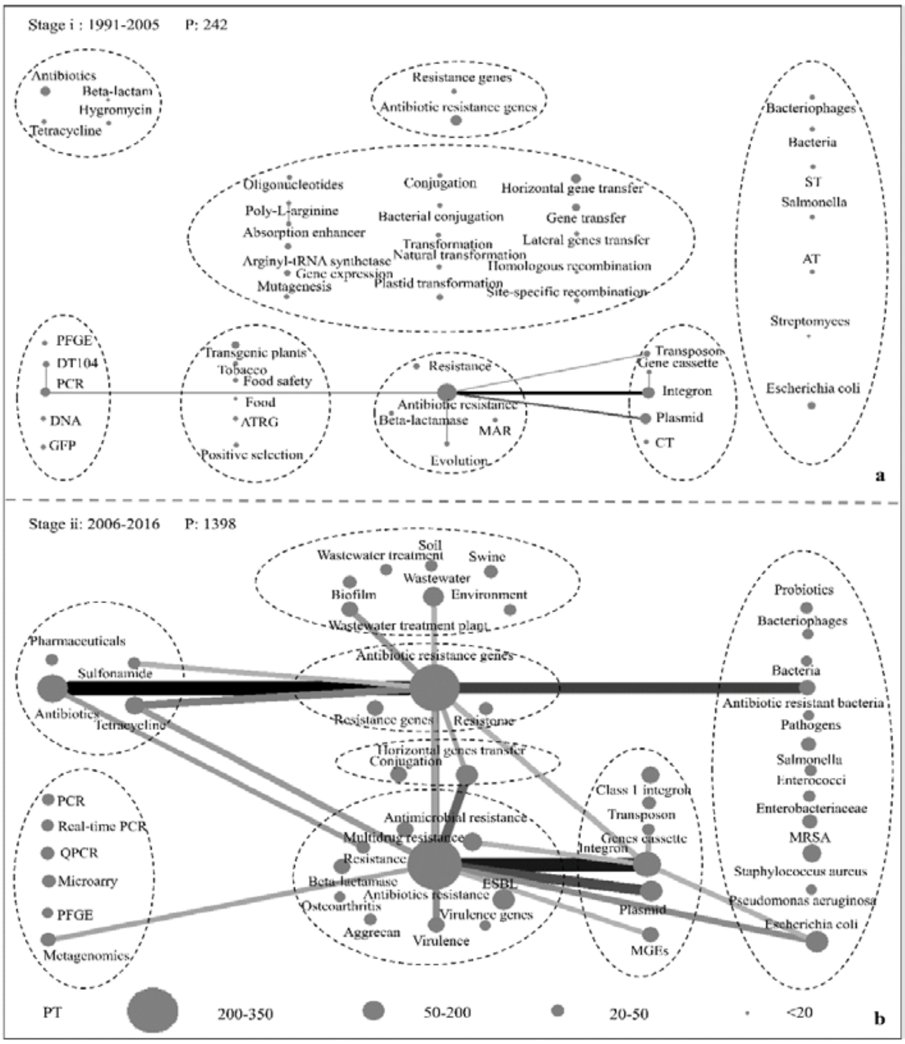


Fig. 5. The relationship among the top 50 keywords visualized at each of two stages based on publication frequencies of each keyword of ARGs research. P: refers to the number of publications for modeling network of each stage; PT: refers to the publication times of each keyword among the top 50 keywords; AT=*Agrobacterium tumefaciens*; ST=*Salmonella typhimurium*; CT=Conjugative transposon; MAR=Multiple antibiotics resistance; ATRG=Attributed relational graph; GFP=Green fluorescent protein; MGEs=Mobile genetic elements

Stage ii covers 11 years from 2006 to 2016. During this time, a total of 1,398 articles on ARGs were published, which accounted for 85.2% of all 1,640 articles, equivalent to 7,124 publication times (Fig. 5b). Although there were also eight parts in this stage, every theme had some difference compared to Stage i. A number of papers were related to resistant theme with terms of "Antimicrobial resistance", "Virulence genes", "Virulence" and "Extended-spectrum Beta-Lactamases (ESBL)". "HGT" was the main dissemination pathway of "ARGs" (Zhu et al., 2013). The keywords "Pharmaceuticals" and "Sulfonamide" were added to the antibiotic theme. Furthermore, "Probiotics", "ARB", "Pathogens", "*Enterococci*", "*Enterobacteriaceae*", "*Methicillin-resistant staphylococcus aureus* (MRSA)", "*Staphylococcus aureus*" and"*Pseudomonas aeruginosa*" appeared on microorganism theme. Meanwhile, papers about "Integron" mainly focused on "Class 1 integron" in the theme of "MGEs" (Collis and Holl, 1995; Uyaguari-Diaz et al., 2018). The result presented here is consistent with some researchers. It is worth noting that the researches about "Environment" theme including "Soil", "Wastewater", "Wastewater treatment plant", "Wastewater treatment", "Swine" and "Biofilm" appeared in this period, but not in Stage i (D'Costa et al., 2006).

There were some new methods such as "qPCR", "Metagenomics" and "Microarray" applied to the field of ARGs study (Pei et al., 2006). It is observed that the relationships among antibiotics, ARGs, ARB and antibiotic resistance were very close, which indicated that much attention was paid on mechanism researches to improve the understanding about the source, spread and remove of ARGs.

4. Conclusions

In this paper, an overview of the research on ARGs was presented using bibliometric analysis and network analysis to gain better understanding of the developments and trends of the research on ARGs. The results showed that China developed rapidly in the field of ARGs and matched with the United States until 2015. Early work in this field was dominated by some developed countries (i.e., the United States and United Kingdom).

However, in recent years, Asia countries, especially China, excelled some countries from other continents in publication. The most close international collaboration took place between the United States and China. The top six journals that published articles on ARGs are "Antimicrobial Agents and Chemotherapy", "PloS ONE", "Applied and Environmental Microbiology", "Frontiers in Microbiology", "Journal of Antimicrobial Chemotherapy" and "Environmental Science and Technology" with an average impact factor (IF) of 4.30.

The analysis of subject categories indicated that there were more interdisciplinary researches about ARGs. "Microbiology" was the most studied subject category. In Stage β (1998-2016), there were two obvious triangle closed-loops including "Microbiology"-"Pharmacology and pharmacy"-"Infectious diseases" and "Water resources"-"Environmental sciences and ecology"-"Engineering". Eight themes were identified by keywords analysis. "Antibiotic resistance" had some close relationships with the use of "Antibiotics" such as "Sulfonamides" and "Tetracyclines". "ARGs" can be spread by "HGT" of "ARB" including "*Salmonella*", "*Escherichia coli*", "*Methicillin-resistant staphylococcus aureus*", "*Enterococci*", "*Staphylococcus aureus*" and "*Pseudomonas aeruginosa*". In the theme of "MGEs", researchers mainly focused on "Integron", especially "Class 1 integron". The studies of ARGs have been widely conducted in "Soil", "Wastewater", "Wastewater treatment plant" and "Biofilm". The main used methods to detect ARGs were "qPCR" and "Metagenomics".

Based on the conclusions, there are several suggestions for future research: 1) studies on ARGs need to be conducted among different environmental compartments and the relationships of them are worthy of further exploration. 2) The international collaborations are frequent between European and American countries. The cooperation in Asian countries should be strengthened. Furthermore, multidiscipline research also should be paid much attention. 3) It's important to develop some new technologies to explore the ways of removing ARGs. 4）It is highly recommended that the relationships among antibiotics, ARGs and ARB should be focused, especially the mechanism research among them to improve the understanding about the source and spread of ARGs.

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We agree with this final form of this paper.

References

Allen H.K., Donato J., Wang H.H., Cloud-Hansen K.A., Davies J., Handelsman J., (2010), Call of the wild: antibiotic resistance genes in natural environments, *Nature Reviews Microbiology*, **8**, 251-259.

Aminov R.I., Garrigues-Jeanjean N., Mackie R.I., (2001), Molecular ecology of tetracycline resistance: development and validation of primers for detection of tetracycline resistance genes encoding ribosomal protection proteins, *Applied and Environmental Microbiology*, **67**, 22-32.

Auerbach E.A., Seyfried E.E., McMahon K.D., (2007), Tetracycline resistance genes in activated sludge wastewater treatment plants, *Water Research*, **41**, 1143-1151.

Baquero F., Martinez J.L., Canton R., (2008), Antibiotics and antibiotic resistance in water environments, *Current Opinion in Biotechnology*, **19**, 260-265.

Callen D.F., (1974), Segregation of mitochondrially inherited antibiotic resistance genes in zygote cell lineages of *saccharomyces* cerevisiae, *Molecular and General Genetics*, **134**, 65-76.

Chen H., Yang Y., Zhou J., Yang Y., Jiang W., (2014), Global trends of compost research from 1997 to 2012: a bibliometric analysis based on SCI database, *Asian Journal of Chemistry*, **26**, 5242-5248.

Chen Q.L., An X.L., Li H., Su J.Q., Ma Y.B., Zhu Y.G., (2016), Long-term field application of sewage sludge increases the abundance of antibiotic resistance genes in soil, *Environment International*, **92**, 1-10.

Chopra I., Roberts M., (2001), Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance, *Microbiology and Molecular Biology Reviews*, **65**, 232-260.

Collis C.M., Holl R.M., (1995), Expression of antibiotic resistance genes in the integrated cassettes of integrons, *Antimicrobial Agents and Chemotherapy*, **39**, 155-162.

D'Costa V.M., McGrann K.M., Hughes D.W., Wright G.D., (2006), Sampling the antibiotic resistome, *Science*, **311**, 374-377.

de Paulo A.F., Porto G.S., (2017), Solar energy technologies and open innovation: a study based on bibliometric and social network analysis, *Energy Policy*, **108**, 228-238.

Ducey T.F., Collins J.C., Ro K.S., Woodbury B.L., Griffin D.D., (2017), Hydrothermal carbonization of livestock mortality for the reduction of pathogens and microbially-derived DNA, *Frontiers of Environmental Science & Engineering*, **11**, 1-8.

Forsberg K.J., Reyes A., Wang B., Selleck E.M., Sommer M.O., Dantas G., (2012), The shared antibiotic resistome of soil bacteria and human pathogens, *Science*, **337**, 1107-1111.

Garrido-Cardenas J.A., Polo-Lopez M.I., Oller-Alberola I., (2017), Advanced microbial analysis for wastewater quality monitoring: metagenomics trend, *Applied Microbioloy and Biotechnology*, **101**, 7445-7458.

Heuer H., Schmitt H., Smalla K., (2011), Antibiotic resistance gene spread due to manure application on agricultural fields, *Current Opinion in Microbiology*, **14**, 236-243.

Hulme M., Obermeister N., Randalls S., Borie M., (2018), Framing the challenge of climate change in nature and science editorials, *Nature Climate Change*, **8**, 515-521.

Jiang H., Qiang M., Lin P., (2016), A topic modeling based bibliometric exploration of hydropower research, *Renewable and Sustainable Energy Reviews*, **57**, 226-237.

Khan M.A., Ho Y.S., (2015), Impact of Brunauer Emmett Teller isotherm on research in Science Citation Index Expanded, *Environmental Engineering and Management Journal*, **14**, 2163-2168.

Leydesdorff L., Bornmann L., Wagner C.S., (2017), Generating clustered journal maps: an automated system for hierarchical classification, *Scientometrics*, **110**, 1601-1614.

Li B., Yang Y., Ma L., Ju F., Guo F., Tiedje J.M., Zhang T., (2015), Metagenomic and network analysis reveal wide distribution and co-occurrence of environmental antibiotic resistance genes, *ISME Journal*, **9**, 2490-2502.

Li J., Cao J., Zhu Y.G., Chen Q.L., Shen F., Wu Y., Xu S., Fan H., Da G., Huang R.J., Wang J., de Jesus A.L., Morawska L., Chan C.K., Peccia J., Yao M., (2018a), Global survey of antibiotic resistance genes in air, *Environmental Science & Technology*, **52**, 10975-10984.

Li J., Wang Y., Yan B., (2018b), The hotspots of life cycle assessment for bioenergy: a review by social network analysis, *Science of the Total Environment*, **625**, 1301-1308.

Li N., Han R., Lu X., (2018c), Bibliometric analysis of research trends on solid waste reuse and recycling during 1992–2016, *Resources, Conservation and Recycling*, **130**, 109-117.

Liu B., Pop M., (2009), ARDB--antibiotic resistance genes database, *Nucleic Acids Research*, **37**, 443-447.

Lv B., Cui Y., Tian W., Li J., Xie B., Yin F., (2018), Abundances and profiles of antibiotic resistance genes as well as co-occurrences with human bacterial pathogens in ship ballast tank sediments from a shipyard in Jiangsu province, China, *Ecotoxicology and Environmental Safety*, **157**, 169-175.

Martinez J.L., (2008), Antibiotics and antibiotic resistance genes in natural environments, *Science*, **321**, 365-367.

Mazel D., (2006), Integrons: agents of bacterial evolution, *Nature Reviews Microbiology*, **4**, 608-620.

Munir M., Wong K., Xagoraraki I., (2011), Release of antibiotic resistant bacteria and genes in the effluent and biosolids of five wastewater utilities in Michigan, *Water Research*, **45**, 681-693.

Pei R., Kim S.C., Carlson K.H., Pruden A., (2006), Effect of river landscape on the sediment concentrations of antibiotics and corresponding antibiotic resistance genes (ARG), *Water Research*, **40**, 2427-2435.

Persson O., Dastidar P.G., (2013), Citation analysis to reconstruct the dynamics of antarctic ozone hole research and formulation of the montreal protocol, *Current Science*, **104**, 835-840.

Pruden A., Pei R., Storteboom H., Carlson K.H., (2006), Antibiotic resistance genes as emerging contaminants: studies in northern Colorado, *Environmental Science & Technology*, **40**, 7445-7450.

Qian F., He M., Song Y., Tysklind M., Wu J., (2015), A bibliometric analysis of global research progress on pharmaceutical wastewater treatment during 1994-2013, *Environmental Earth Sciences*, **73**, 4995-5005.

Qiao M., Ying G.G., Singer A.C., Zhu Y.G., (2018), Review of antibiotic resistance in China and its environment, *Environment International*, **110**, 160-172.

Recchia G.D., Hall R.M., (1995), Gene cassettes: a new class of mobile element, *Microbiology*, **141**, 3015-3027.

Ritz L.S., Adam T., Laing R., (2010), A bibliometric study of publication patterns in access to medicines research in developing countries, *Southern Medical Review*, **3**, 2-6.

Rizzo L., Manaia C., Merlin C., Schwartz T., Dagot C., Ploy M.C., Michael I., Fatta-Kassinos D., (2013), Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review, *Science of the Total Environment*, **447**, 345-360.

Salyers A.A., Gupta A., Wang Y., (2004), Human intestinal bacteria as reservoirs for antibiotic resistance genes,

Trends in Microbiology, **12**, 412-416.
Schwartz T., Kohnen W., Jansen B., Obst U., (2003), Detection of antibiotic-resistant bacteria and their resistance genes in wastewater, surface water, and drinking water biofilms, *FEMS Microbiology Ecology*, **43**, 325-335.
Sommer M.O., Dantas G., Church G.M., (2009), Functional characterization of the antibiotic resistance reservoir in the human microflora, *Science*, **325**, 1128-1131.
Su J.Q., Wei B., Ou-Yang W.Y., Huang F.Y., Zhao Y., Xu H.J., Zhu Y.G., (2015), Antibiotic resistome and its association with bacterial communities during sewage sludge composting, *Environmental Science & Technology*, **49**, 7356-7363.
Su Y., Wang J., Xia H., Xie B., (2019), Comparative network analysis revealing the mechanisms of antibiotic resistance genes removal by leachate recirculation under different hydraulic loadings, *Science of the Total Environment*, **649**, 318-326.
Tanase C., Cosarca S., Toma F., Mare A., Man A., Miklos A., Imre S., Boz I., (2018), Antibacterial activities of beech bark (Fagus sylvatica L.) polyphenolic extract, *Environmental Engineering and Management Journal*, **17**, 887-884.
Uyaguari-Diaz M.I., Croxen M.A., Luo Z.Y., Cronin K.I., Chan M., Baticados W.N., Nesbitt M.J., Li S.R., Miller K.M., Dooley D., Hsiao W., Isaac-Renton J.L., Tang P., Prystajecky N., (2018), Human activity determines the presence of integron-associated and antibiotic resistance genes in Southwestern British Columbia, *Frontiers in Microbiology*, **9**, 1-20.
Wang R., Wei Y.S., Ge Z., Zhao X., Zhong W.K., Liu P., Li B., (2018), Effects of chlortetracycline and cooper on swine manure anaerobic digestion, *Environmental Engineering and Management Journal*, **17**, 3013-3024.
Xu Y.Y., Boeing W.J., (2013), Mapping biofuel field: a bibliometric evaluation of research output, *Renewable and Sustainable Energy Reviews*, **28**, 82-91.
Zhang X.X., Zhang T., Fang H.H., (2009), Antibiotic resistance genes in water environment, *Applied Microbiology and Biotechnology*, **82**, 397-414.
Zheng C.L., Cotner J.B., Sato C., Li G., Xu Y.Y., (2018), Global development of the studies focused on antibiotics in aquatic systems from 1945 to 2017, *Environmental Science and Pollution Research*, **25**, 22023-22034.
Zhu Y.G., Johnson T.A., Su J.Q., Qiao M., Guo G.X., Stedtfeld R.D., Hashsham S.A., Tiedje J.M., (2013), Diverse and abundant antibiotic resistance genes in Chinese swine farms, *Proceedings of the National Academy of Sciences of the United States of America*, **110**, 3435-3440.