

Research Trend of Antimicrobial Resistance in Livestock Farm of China in 21 Century: A Bibliometric Analysis

Abstract: Aiming to reveal the trends in AMR research in poultry and farm of China in 21 century, this bibliometric study carry out through the articles found in the Web of Science database. Search terms includes the keywords about AMR in livestock farm of China and excluded that about marine, vegetable, manure compost and humankind medical treatment. A summary quantity of 276 articles were included, publish between 2008 and 2020. It's evident that a growing research interest focus on this domain in the last decades with annual percentage growth rate is 30.09%, and 93.12% of the research articles (257 papers) was published after 2011. Through this period, the research categories recently became more diverse and focused on "One Health". The most published and cited documents were from the China Agriculture University, and research institutions in five provinces of east-costal China provided about 60% of publications. A frequency analysis of keywords showed a comprehensive ascendant of keywords about "prevalence", "poultry", "AMR", "genes", and "identification". The most common five research topic couples were *Enterobacteriaceae* and *identification*, *diversity* and *China*, *strains* and *genes*, *AMR* and *prevalence*. This pioneering study supplied a nationwide overview of spatial and temporal trends of research related to AMR in livestock farm of China. In view of the enhance tendency during the last years, it's estimated that scientific research will increase in the future. Unearthing scientific areas that should be explored in the future is key to design new strategic agendas for AMR research in livestock farm animals and to inform funding programs.

Keywords: China, livestock farm, AMR, One Health, bibliometric analysis

1. Introduction

Antimicrobial resistance (AMR) has spread all over the world, destroying the defence line of antimicrobial treatment from humankind to animals. Especially, it transported between food animal and human constituting a threat to public health significantly(Lu et al., 2010). The phenotypes of resistance are divided into the acquired and the natural, which is the result of natural selection in the process of gene mutations and horizontal gene transfer. The natural selection of drug resistance phenotypes comes from long and low levels of exposure to antibiotic environments, such as overuse of antibiotics in medical treatment, accumulation in environmental sewage waste and improperly use in farms(Bar-Yoseph, Hussein, Braun, & Paul, 2016; Li et al., 2017; McDanel et al., 2017). Among them, mainly to prevent and treat bacterial diseases and improve growth rate, antibiotic usage in farms is considered to be an important source of resistance pressure on One Health(Torres et al., 2021).

Propagation of AMR is a complex biogeographic problem. AMR in food animals are directly derived from the treatment and intake of antibiotics, which is regarded as the establishment promotion of bacterial adapting mechanisms and the horizontal gene co-transfer (HGcoT) between animals, humans and environment. For example, ducks farm is an important reservoir for NDM-positive *E.coli* in China(M. G. Wang et al., 2021). As a large country of animal production and consumption, China will under an incalculable influence imperceptibly from the increasing AMR of food animal, furthermore it will exceed the national boundary and bring burden to global health(Wu et al., 2018).

Research on AMR require a large number of disciplines, and solve the problem from a One Health point of view as a whole(J. J. Zhu, Dressel, Pacion, & Ren, 2021). At present, although the quantity and quality of research have been improved day by day, the research content of the literature is messy and not systematic. A bibliometric analysis that describe the AMR development of livestock farms in China in the 21st century will be meaningful and pioneering, which can provide diverse comprehensive information on the progress of scientific research in specific fields and assess the impact of specific events on the subject of research. This study filled the biogeographic gap in the AMR spread of livestock farms in China. The aim is (1) to take an overview of the development of China livestock farm AMR research temporally and (2) to provide and describe the trends in future AMR research.

Materials and Methods

Data preparation and collection

The raw data of the full publication records were retrieved from the Web of Science database in March, 2021. The search strategy combined the strings below linking by the Boolean operator: #1 “antimicrobial” OR “antibiotic” AND “resistant” OR “resistance” NOT “zoo” OR “wildlife” OR “wild animal”, #2 “poultry” OR “farm” OR “livestock” OR “ranch” NOT “marine” OR “mariculture” OR “fish” OR “fishery” OR “sea” OR “ocean” OR “seawater” OR “freshwater” OR “hospital” OR “shrimp” OR “manure compost” OR “aquatic” OR “vegetable”, #3 “China”. Research from different departments of the same research institution are assigned to the identical one.

Data preprocessing

This study focused on subjects with frequencies above the minimum threshold, which facilitate more effective retention of valuable information. Secondly, we applied Keywords and Keywords Plus in different research situations. Widely used in various research, Keywords Plus, which exclude article title information, is beneficial to reduce redundant information.

Conventional statistical analysis

Conventional statistical analysis includes describing temporal and geospatial changes in publications, especially expatiate the citation and production changes in output of documents, institutions and authors.

Keywords Analysis

Keywords Analysis including trend analysis and co-occurrence analysis. Trend analysis can help us to understand the temporal evolution of research topics better, and the increased frequency indicates that keywords is more likely to show an upward trend. Co-occurrence analysis of keywords helps to reveal knowledge structure of a research field. The situation that two keywords found in the same document is called co-occurrence. High co-occurrence showed that the two keywords were used more frequently by together in research. In this study, we evaluated the connections among the keywords of the first 50 frequencies to assess the popularity of the research topic.

Analysis tools

The bibliometric analysis was implemented with full search results by using the “bibliometrix” package in R. The visualization analysis were created by using the “ggplot2”, “ggpubr”, “ggalt”, “circus”, “pheatmaps” and “wordcloud2” packages in R.

Discussion and Results

This study provides an overview of bibliometric analysis of scientific research related to AMR in livestock farm of Chinese during the time from 2000 to 2020. Of the 289 publications initially collected, 13 were removed because they were not research article, and finally 276 publications were included in the analysis. All publications have been vetted manually.

Analysis of publication and source

Temporal evolvement of research

Dated between 2000 to 2020, the temporal trend in research articles of antimicrobial resistance in livestock farm of China reveals an increase in the number of documents published per year, whose annual percentage growth rate is 30.09%. Obviously, the evolvement in scientific research can be divided into two different stages of growth: from 2000 to 2011, publications growth was slow, however, from 2012 to 2020, publication growth reached its peak, and 93.12% of the research article (257 papers) was published after 2011. This trend indicates that the research topic with one health as the core consideration has attracted the interest of researchers, which may be attributed to the generation and dissemination of AMR in livestock farm in China, and wider research funding in the last decade, especially from the public welfare industry project funds of the 13th Five-Year Plan of China.

Documents with significant impact

The top 10 cited papers related to AMR in livestock farm of China are listed in Table 1. The most cited paper was published in 2013 in *PNAS* by Yongguan Zhu from China Academy of Science, which indicated a result that swine farms in China have rich ARGs exactly(Y. G. Zhu et al., 2013). The second one and the third one describe how AMR occur and transit in Chinese rivers and the source of dynamics for AMR in China's eight provinces respectively.

The first research paper was published in *FEMS Microbiology Letter* by Dai Lei in 2008, which depicted the epidemiological investigation of AMR in 44 farms in China(Dai et al., 2008). Took by Cui Shenghui in 2009, the pioneering study determined MRSA colonization in livestock and related workers in four Chinese provinces, is the beginning research of the AMR transmission between human and animal(Cui et al., 2009). Farm animals with specific antibiotic resistant bacteria flow through circulation of commodities into areas without AMR or low AMR, such as Qinghai(Cao et al., 2020). The finding above suggests that AMR of food animals can be spread through food chains

and commodity chains, whose ecological niche plays an important role in antibiotic resistance ecology(Douglas & Langille, 2019; McInnes, McCallum, Lamberte, & van Schaik, 2020; J. Sun et al., 2020). After that, one of the hot spots of the study was to elucidate the transmission pathways and epidemic mechanisms of AMR between humans and food animals, and to conclude that the evolutionary patterns of AMR are similar or identical in humans and farm animals.

Evolution of Subject categories in publications

From 2000 to 2020, research articles are distributed in a wide range of scientific fields, including 20 categories. Among them, MICROBIOLOGY and FOOD SCIENCE TECHNOLOGY are the two fields with the most extensive research. No articles were produced between 2000 and 2007, therefore, they are not included in this study. MICROBIOLOGY always occupied an important part of the research field from 2008 to 2020, what's more, quantity of paper in ENVIRONMENT has increased rapidly, which indicated this subject is more significant than ever before. Over the past 20 years, the emphasis on "One Health" research has become more and more abundant, especially the emergence of ENVIRONMENT and INFECTIOUS DISEASE disciplines. This emphasis has prompted researchers to propose macroscopical solutions to AMR problems from a multidisciplinary and comprehensive research field, which are able to deal with the increasing AMR threat.

Evolution of research objects in publications

The research objects of this study means the categories of microorganisms and livestock farm animals. The first three research objects of microorganisms are *Escherichia coli*, *Salmonella typhimurium* and *Klebsiella pneumoniae*. This indication may be related to their obvious pathogenicity to animals and their significant effect on public health(Bottery, Pitchford, & Friman, 2021). Among the research objects of livestock farm animals, swine, poultry and cattle is the top three. Such results are not surprising because the dominance of pig and chicken in food animals has attracted a large number of researchers to focus on them.

The selection of host animals in the research objects was closely related to their correlation as human foodborne microbial carriers(Bush & Bradford, 2020). Current studies of such animals tend to focus on the situation of AMR carrying in the animals themselves, or on exchanges and connections with other animals and the environment. The research that explain how AMR direct transmission and colonization between food animals and humans are relatively lacking, and it takes an important

relationship with food safety and livestock farm occupational safety exactly.

Evolution of research journals in publications

The top 10 journals were ranked by the number of papers and the number of total citations separately. Among the journals that included AMR research in livestock farm in China, *Frontier in Microbiology*, *Food Control* and *Foodborne Pathogen* lead the productivity of journals, which took the occupation of 80%. The top 10 journals per citations related to the role of China livestock farm in AMR are listed in Table 2. The most cited journal is *Antimicrobial Agents and Chemotherapy* (n = 517), followed by *Journal of Antimicrobial Chemotherapy* (n = 444) and *Frontier in Microbiology* (n = 351). Interestingly, *Frontier in Microbiology* is both one of the top productive journals and the most cited journals. This shows that publishing press of *Frontier in Microbiology* maintained the quality of published research papers while pursuing high circulation, which made itself widely praised by researchers and increased its reputation.

Outputs analysis of of regions, institutions and authors

The top three provinces of cumulative research article outputs are Beijing City (n = 52), Guangdong Province (n = 32), and Shandong Province (n = 24). It is clear from the map of China that the output of research papers in the eastern provinces is much higher than that in the western provinces(Fig.2). The top 10 institutions were ranked by the number of papers. Among the 340 institutions that participated in AMR research of China livestock farm, China Agriculture University (CAU) led the institutional productivity with 27 papers (9.78%), followed by South China Agriculture University (SCAU) with 26 papers (9.42%), and Yangzhou University (YZU) with 24 papers (8.64%). Coincidentally, Wang Y, from China Agriculture University, is regarded as one of the most cited researchers.

The institutions with high productivity are not all the same at different times, dominated by South China Agriculture University (SCAU) between 2008 and 2012, but by China Agriculture University (CAU) after 2012. The possible reason for this change is that CAU have received more funding in the last decade to take research in the AMR of livestock farms in northern China, especially swine farms, cattle farms and sheep farms(Gao et al., 2020; He et al., 2019; Lei et al., 2010; Liu et al., 2013; Wu et al., 2018).

In terms of research output, economically developed provinces are clearly the most productive areas. During the past two decades, research institutions in almost all provinces have published research

papers on livestock farm AMR of China. Among them, research institutions in five provinces provided about 60% of publications, which were located in Beijing and east costal of China. Such results are not surprising. The level of economic development and adequate financial support for researchers in this field are the reasons why they play a leading role in the field of research. For some provinces with rapid development of livestock farm, the research on AMR is still lacking, however, studies have shown that antibiotics are often used more in provinces of large food animal production than in other provinces(Paudyal et al., 2018; Y. Sun et al., 2021; Zhang et al., 2019).

The increase in production and demand for food animals has prompted researchers to focus on "One Health" and take action to prevent the spread and deterioration of AMR. For one hand, research funding of AMR research needs to deal out more to underdeveloped provinces in economy. On the other hand, based on the AMR spreading strategy, the developed provinces can establish a long-term and mutually beneficial scientific research cooperation relationship with the underdeveloped provinces, so as to found response mode at the macroscopical ecological perspective.

Analysis and assessment of keywords

Temporal evolution of research themes

Analysis of the keywords in the publications with time-series is helpful to reflect the research hot spots in different years, helping researchers to lead and explore the research themes. A clear trend is that keywords related to "research methods "(e.g .,"prevalence", "identification") have grown substantially since 2014 and are occupying the top position of the heatmap. This suggests that in the past five years, innovative progress and significant advance have been made in exploring research methods, which is beneficial to propose multidisciplinary, multidimensional and multi-perspective solutions to AMR problems.

The steady research hot point on AMR of livestock farm in China are microbial infectivity and microbial susceptibility to antibiotics. The ability of microorganism to determines the transmission ability of the disease, and the sensitivity of bacteria to antibiotics determines the control of the disease. These two factors influence the importance that researchers attach to specific microbial populations together.

Obviously, both of whom are regarded as important sources of food animals, poultry, often acquired much more research than it on pig. As a matter of fact, poultry is more facile than domestic animal as an AMR reservoirs for storage, variation and exchange, of which the reason is that poultry is

more likely to exchange bacteria with migratory birds or surrounding birds during transportation, and getting antibiotic resistance under unaware(Dai et al., 2008; J. Wang et al., 2017; M. G. Wang et al., 2021). Due to the food consumption habits of people in southern China, it is of great and far-reaching significance to strengthen the AMR monitoring and management of poultry farms in the south of the Yangtze River.

Among all kinds of microorganisms, *Enterobacteriaceae* represented by *Escherichia coli* significantly occupied the dominant position in the study, which is closely related to their important role as human foodborne pathogenic factors(McDanel et al., 2017). Over a period of time, most studies have focused on finding bacteria that carry special antimicrobial resistance, such as ESBL-producing *Escherichia coli*(Doi, Iovleva, & Bonomo, 2017). But as the technology of metagenome matures, the focus has tended to explore in the whole bacterial community at an ecological niche, that is, the evolution of AMR between bacteria and the environment, or it between bacteria and bacteria(Douglas & Langille, 2019; McInnes et al., 2020; Zbrun et al., 2020).

Keyword analysis of publications shows that the most used keywords are AMR (Antimicrobial resistance & Antibiotic resistance), prevalence, poultry, identification and gene, which revealed that the key point of research on AMR in livestock farm of China is the prevalence investigation and gene identification of antimicrobial resistance in poultry. During the continuous antimicrobial resistance monitoring, the *Tet(X4)* of degradation enzymes found in animals and breeding environments that can lead to the inactivation of Tetracycline, which is the last line of defense(Chen et al., 2020). As for gene identification, the brightest finding in it is the discovery of MCR-1 genes, which leads to the resistance to polymyxin, threatening the safety of antibiotics usage in livestock farm(Y. Wang et al., 2020). However, in the long run, such a research model has always been limited, mainly reflected in the size of the monitoring range, the span of monitoring time and the timeliness of monitoring. It is self-evident that the future research should pay more attention to the genome function regulation of ARGs, as well as the choice and use of sentinel animals, so as to curb and prevent the malignant development of AMR fundamentally, and quickly confirm the real-time AMR prevalence situation in the target areas.

Co-Occurrence Demonstration Analysis of Keywords

The co-occurrence of key words proves the correlation among the research topics, what's more, the deeper color and the larger width mean that there is obvious co-occurring, between the two research

topics and are usually under research in pairs.

The most common five research topic couples were *Enterobacteriaceae* and identification, diversity and China, strains and genes, AMR and prevalence. Co-occurring trend up topics were identified based on the co-occurrence analysis: 43 couple keywords had a co-occurrence of 10 and greater, and 24 of them were strongly connected with co-occurrences appeared more than 15 times. Of all co-occurrence of keywords, it can be clearly classified into four categories: microorganism (like *Typhimurium* and *Klebsiella Pneumoniae*), host animal (like human and swine), antibiotic or hydrolytic enzyme (like tetracycline and CTX-M), mediating or methods (like dissemination and plasmid). The results above reveals that identification of AMR in *Enterobacteriaceae* will still maintain a high research heat, but other pathogens such as *Klebsiella pneumoniae* will not significantly reduce the research heat. Additionally, bacteria carrying special ARGs and the expression pathway of newly discovered ARGs will become an indispensable research content in this field.

Conclusions

This bibliometric study of AMR on livestock farm in china reports a number of valuable information related to annual publication volume, categories, researchers and keywords. From the 21 century, the bibliometric variables of AMR on livestock farm in china have increased significantly, both in terms of scientific output and interdisciplinary cooperation. By using data-driven analysis methods, we decipher the co-occurrence and interrelation between keywords, identify and discuss temporal trends of keywords, and list and analyze rising trends and promising topics. Although the research scope of AMR on livestock farm in china has been expanded to include more research categories and topics, there are still shortcomings, mainly reflected in inefficient regional cooperation, uneven distribution of funds and innovative-lack research methods. Most of the studies initially focused on microbiology category and food science category, but after a period of development, this research field became more multidisciplinary based on the framework of One Health. Admittedly, research of AMR on livestock farm in china needs to be discussed from a macro-ecological perspective in order to be meaningful(Earle et al., 2016). Future research in this field must be combined with environmental science, bioinformatics and public health science to summarize the drivers and directions of dissemination.

It has to be said that this study has general limitations of bibliometrics research: #1 we only searched

articles that have been published in Web of Science, excluding the amount of work that may have been published in other formats and databases, #2 this study was restricted because of the international journals in English, which is a bias in language, #3 bibliometric variables only include the topic-related object. Nevertheless, we still believe that the results of this study can provide an effective overview of the research in this field at the national level in China.

Funding

Competing interests:

None declared

Ethical Approval:

Not required

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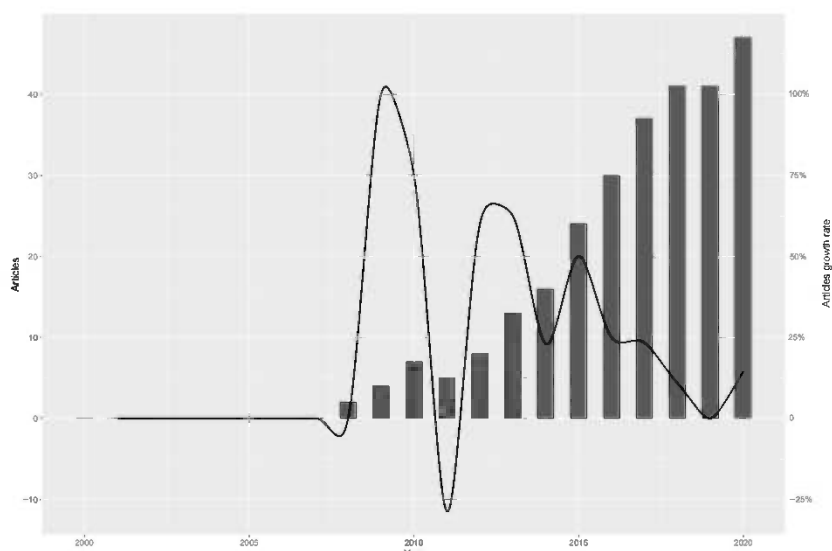


Figure 1. Annual evolution of research articles from 2000 to 2020.

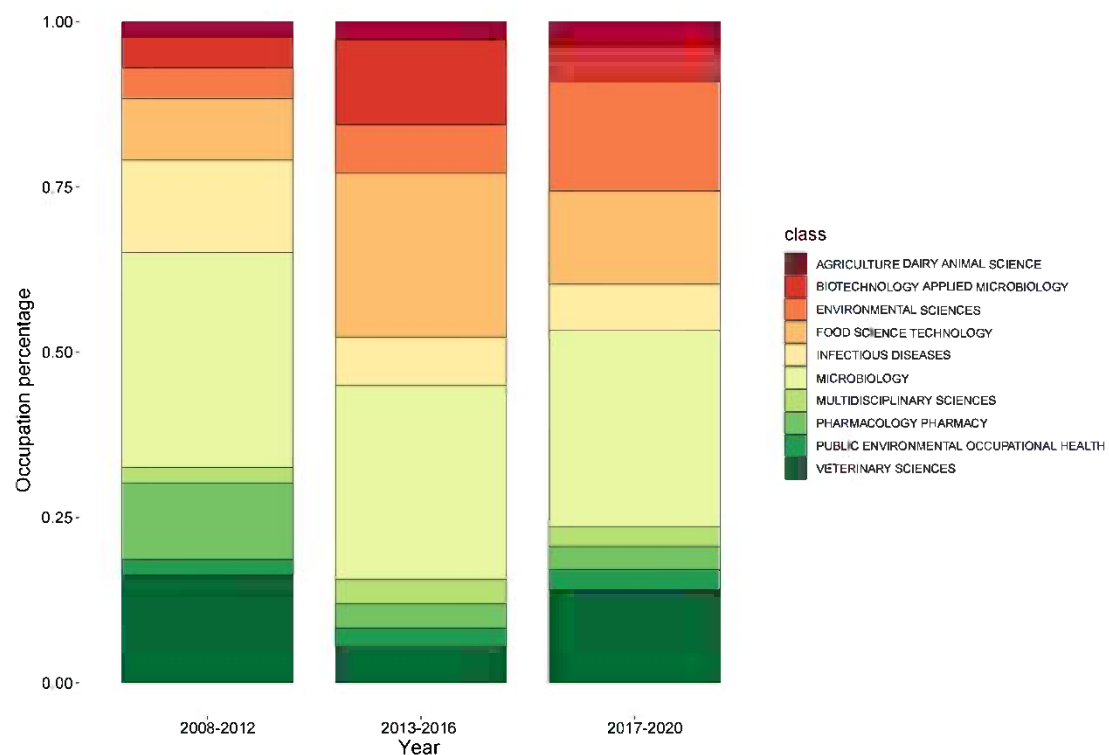


Figure 2. Evolution of research categories from 2008 to 2020.

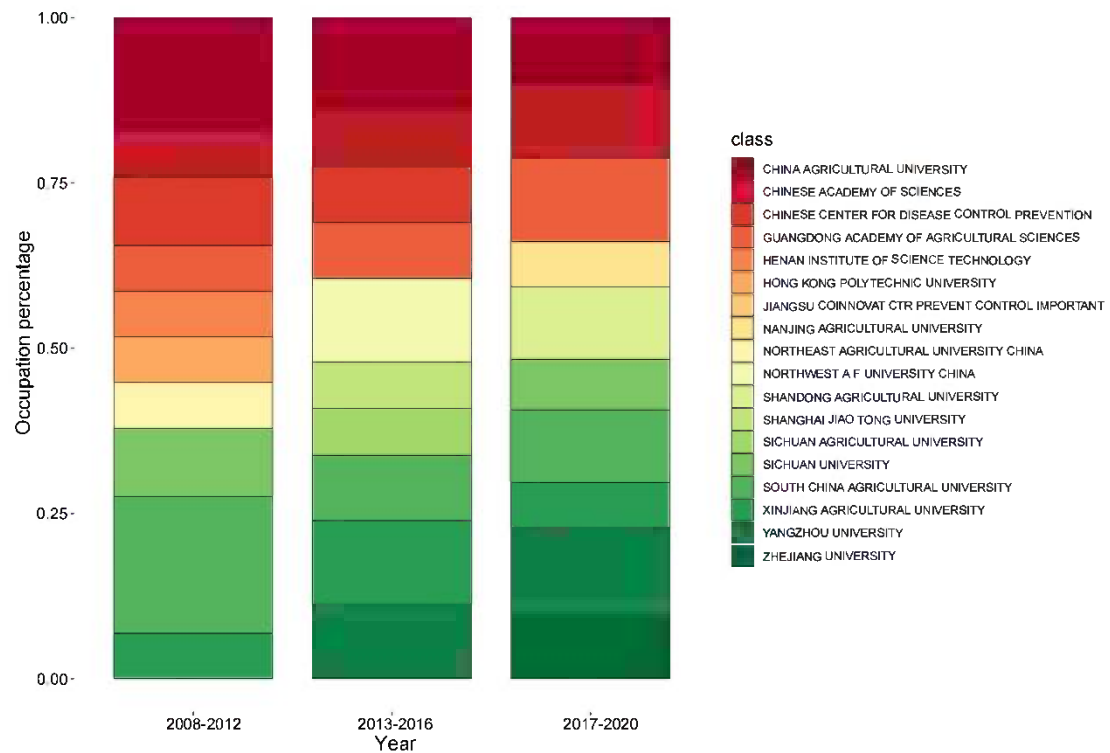


Figure 3. Evolution of research institutions from 2008 to 2020.

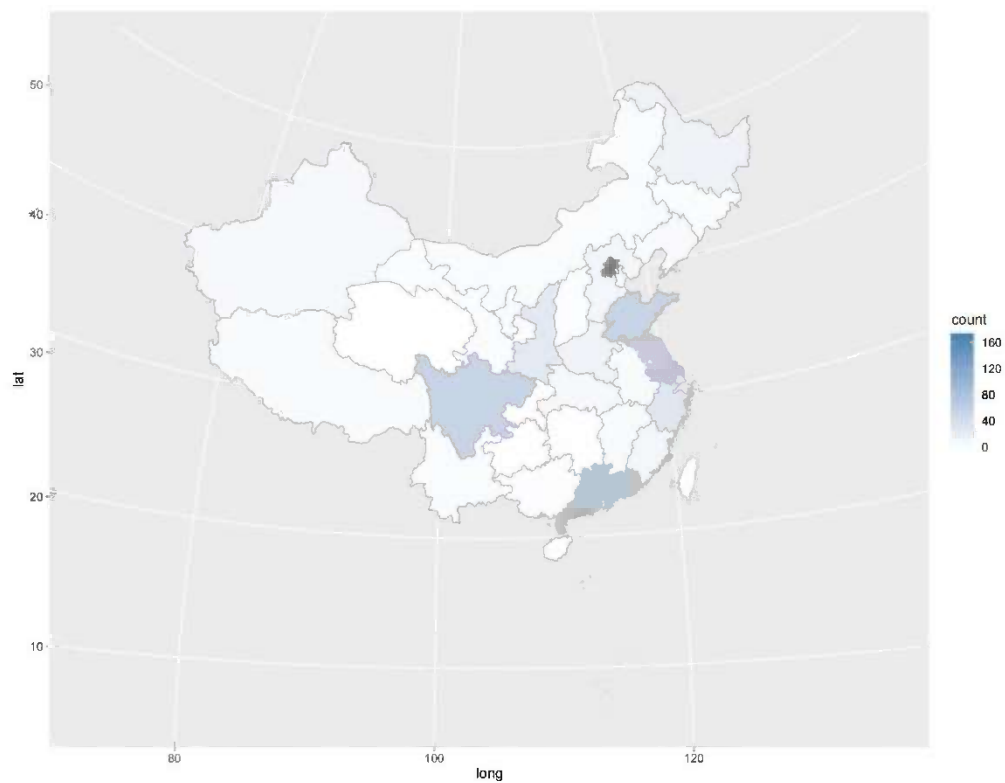


Figure 4. Nationwide scientific production on AMR in livestock farm animal of China.

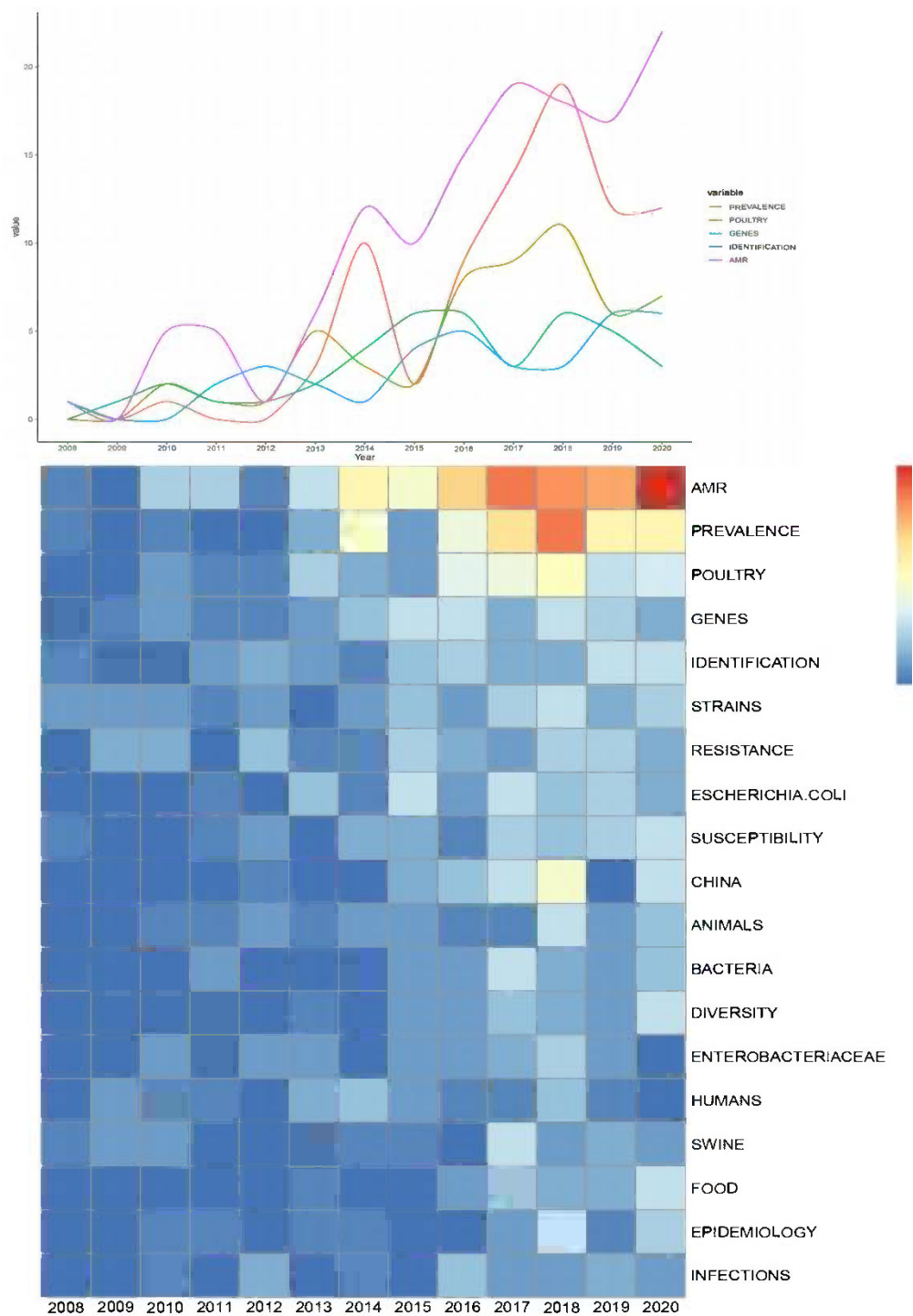


Figure 5. Keywords evolution related to research focused on AMR in livestock farm animal of China .

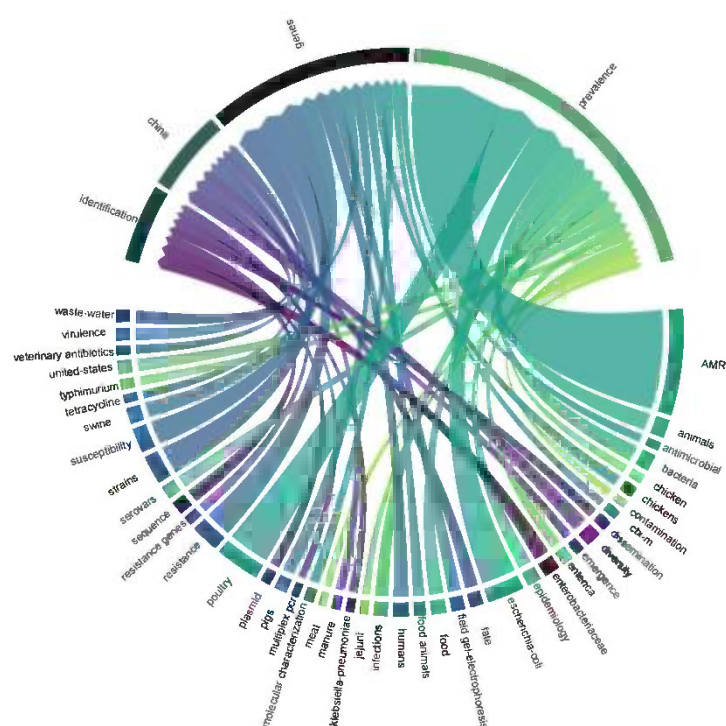


Figure 6. Co-occurrence of the top 50 frequent keywords (stemmed form) based on the circo plot. The keywords are ordered by their overall frequencies from green to purple color. Edge width and color are used to represent the co-occurrence between keywords; a thicker edge with green color means that the two keywords have a higher co-occurrence.

Paper	Total Citations (TC)	TC per Year
ZHU YG, 2013, PROC NATL ACAD SCI U S A	1035	115
LUO Y, 2011, ENVIRON SCI TECHNOL	536	48.727
ZHAO L, 2010, SCI TOTAL ENVIRON	419	34.917
YANG B, 2010, INT J FOOD MICROBIOL	180	15
CHENG W, 2013, ENVIRON INT	150	16.667
CUI S, 2009, J ANTIMICROB CHEMOTHER	138	10.615
TANG X, 2015, SOIL BIOL BIOCHEM	114	16.286
ZHENG H, 2012, INT J ANTIMICROB AGENTS	114	11.4
LI R, 2013, INT J FOOD MICROBIOL	98	10.889
CHEN X, 2010, VET MICROBIOL	98	8.167

385 **Table 1. The top 10 cited papers related to AMR in livestock farm of China.**

Sources	Citation
ANTIMICROB AGENTS CH	575
J ANTIMICROB CHEMOTH	490
APPL ENVIRON MICROB	385
J CLIN MICROBIOL	372
INT J FOOD MICROBIOL	348
VET MICROBIOL	300
FOODBORNE PATHOG DIS	252
ENVIRON SCI TECHNOL	251
PLOS ONE	225
FRONT MICROBIOL	200

386 **Table 2. The top 10 citation journals of AMR in livestock farm of China.**