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# Gram Negative bacteria and their Antibiotic Resistance: A Bibliometric Analysis

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Antibiotic resistance; Gram-negative bacterial; OmpC; OmpF; PCR

## Abstract

**Background:** Antibiotics are compounds made from microorganisms that destroy or prevent the growth of other microbes. The constant failure to engineer new antibiotics and imprudent usage of antibiotics resulted in the rise of antibiotics. In 2017, the World Health Organization released a list of the most pathogenic bacteria having the highest resistance against antibiotics which also included many Gram-Negative bacteria. In this study, we reviewed the data on publications on antibiotic resistant (ABR) Gram-negative bacteria by bibliometrics.

**Methods:** The data from 2003 to 2022 were retrieved from the Web of Science and used further for statistical analysis. Both qualitative and quantitative analysis of the characteristics of publications, authors, top countries, leading journals, funding agencies and collaboration aspects.

**Result:** The results showed a total of 10,350 publications with 7.94% annual growth rate in a linear pattern and 23.71 average citations per document on the subject. Lists of the most cited papers and papers with ranking by highest total citations per year were also retrieved. 98% of articles were published in English. Greater research output is from developed countries i.e., USA, China, India, England, Spain, Iran, Italy, Germany, and Japan. USA has the highest number of publications, citations, and Single Country Publications. USA is also the top country to have the highest collaborations with other countries.

**Conclusion:** The study is suggestive for most developing and least developed countries to develop collaborations with researchers from developed countries, especially the USA and UK having domination in research productivity and sources of funding. The results of this study may provide potential prospects for the study of ABR Gram-negative bacteria in the future.

## Introduction

Antibiotic resistance has emerged as one of the leading public health threats of the 21st century. Bacteria are developing resistance towards antibiotics at an alarming rate [1,2]. Constant failure to engineer new antibiotics and imprudent usage of antibiotics are the major reasons behind the rise of antibiotic resistance [3]. Resistant Gram-negative bacteria are the real threat and contributing factors in sinking health and economy status around the globe. ABR Gram-negative pathogens have acquired resistance to almost all antibacterial medications available, resulting in pre-antibiotic era circumstances. [4,5]. The development of Multidrug Resistant (MDR) Gram-negative bacteria has significantly affected the antibiotic potential. Agents of highest concern are the Gram-negative contagions found in medical settings. *Acinetobacter* species, *P. aeruginosa*, and Enterobacteriaceae (mostly *K. pneumoniae*) are primarily responsible for these. MDR Gram-negative bacteria, such as beta-lactamase-producing *E. coli* and *N. gonorrhoeae*, are also spreading rapidly among people [5].

In 2017, the World Health Organization (WHO) released a list of bacteria requiring novel antibiotics on an emergency basis to stop their emergence. WHO has grouped these bacteria according to their resistance severity and named them as critical, high, and medium. Critical gram-negative bacteria include *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae. High priority list consists of ABR *Helicobacter pylori*, *Campylobacter spp.*, *Salmonellae* and *Neisseria gonorrhoeae* while *Haemophilus influenzae* and *Shigella spp.* are listed in the medium priority list [6].

Bibliometric analysis is the most common methodology commonly used in research to assess a certain topic and the research conducted on it [7, 8]. It gives us information about most prominent countries, the top funding organizations, and top contributing authors [9, 10]. It also presents year-wise growth of publications and international collaboration. In some bibliometric studies, co-occurrence maps are developed to present bibliometric indicators such as most used keywords or countries collaboration. This type of analysis also identifies the most dominating areas of the past research in a research field, by analyzing the most-cited work currently, which can be helpful to predict the type of future research in the same field. Web of Science is the most common source for such studies but other platforms like PubMed, Google Scholar and Scopus are also used by some researchers. Basic data is retrieved from these sources and then analyzed further through different software.

Numerous bibliometric studies on different kinds of pathogens [11-12] and other microbiology fields have

been published [13-15]. However, no bibliometric investigations have been carried out on ABR Gram Negative bacteria. Therefore, this analysis was conducted to analyze and show bibliometric indicators related to literature on ABR Gram Negative bacteria.

In this study, we reviewed the publication data on ABR Gram-negative bacteria by bibliometrics. This study is designed to investigate the trend of ABR Gram-negative bacteria research in last twenty (20) years. For the study the list of most pathogenic gram-negative bacteria, as released by WHO in 2017 (Table 1), was used to search for the publications. The results of this study may provide potential prospects for the study of antibiotic resistance of Gram-negative bacteria in the future.

## Methods

The data from 2003 to 2022 were retrieved from Web of Science (Clarivate Analytics) on November 23, 2022. The methodology used was like that described in previously published bibliometric studies [16–18]. Keywords used for data extraction were obtained from published review articles on ABR Gram Negative Bacteria. The search was done using the keywords in title as "multidrug resistant" or "multi-drug resistant" or antibiotic\* or antibacterial or antimicrobial or anti-bacterial or anti-biotic or anti-microbial and title "gram negative" or "gram-\*" or "gram-negative" or "Acinetobacter baumannii" or "Pseudomonas aeruginosa" or "Enterobacteriaceae" or "Helicobacter pylori" or "Campylobacter spp." or "Salmonellae" or "Neisseria gonorrhoeae" or "Haemophilus influenzae" or "Shigella spp". The search was limited to the years; 2003-2022, and document types; article, review, meeting abstract, letter, proceedings paper.

Data was downloaded in clusters and all the duplicate entries were removed. Before statistical analysis and evaluation, two authors independently applied some basic analysis criteria to find out the discrepancies in the data and to apply all bibliometric tools later.

The downloaded data of publications was evaluated for different parameters which included authorship, total times cited, citations per document, year of research publication, countries, journals, keywords, co-authorship, and document type of the article. Data was downloaded in the BibTeX file format. Data were imported into RStudio v.4.1.2 software [19], converted to a bibliographic data frame, normalized for duplicate filing, and analyzed for bibliometric indicators.

## Results

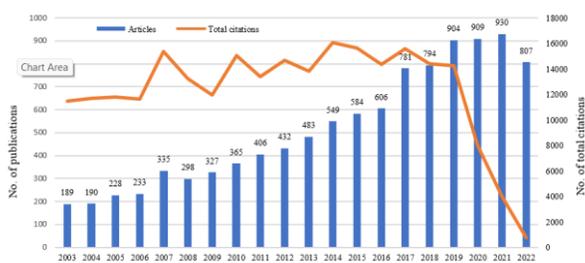
### Publication Characteristics

The Web of Science Core Collection database revealed 10,350 publications for the period 2003-2022, with 7956 research articles, 362 letters, 1359 meeting

abstracts and 673 reviews after application of methodology as described above. The annual growth rate of these articles is 7.94% with 23.71 average citations per document. A total of 41,484 authors contributed to these articles with 6.32 authors per document and 259 authors published their articles as solo author. 21.12% papers were having international co-authorships.

### Publications per year

The pattern for increase in number of publications and citations is given in Figure 1 when twenty-years span is considered. Publications on the subject from 2003 to 2022 show a progressive trend. As 2022 publications are still coming up when this article was being written, a slight decrease is acceptable. There is a huge increase in publication rate after 2017 with a total of 781 publications i.e. 175 papers more than 2016. The same trend can be seen in 2018-2022.



**Figure 1:** Growth of number of publications and total number of citations on ABR Gram Negative Bacteria research. ABR The publication growth is exponential showing researchers interest in the field.

### Most cited papers

The most cited papers are listed in Table 1. Research article titled “Silver nanoparticles as antimicrobial agent: a case study on E. coli as a model for Gram-negative bacteria” by Sondi I and Branka, 2004, published in Journal of Colloid and Interface Science, is ranked at top for having highest citations (4102) overall. The researchers are affiliated with Center for Marine and Environmental Research, Ruder Bosković Institute, Zagreb, Croatia. This article is also having the highest Total Citations per year i.e., 215.89. Other articles ranked by total citation per year are shown in Table 1.

An analysis of Total Citations Per Year (TC/Year) showed that four of top 10 papers (listed at Rank No’s 3, 4, 6 and 10) were published in last five years (2018-2022) and are still able to find place in top 10 list of publications having highest citations per year.

### Articles published in different languages

English was found to be the most used language for these articles with more than 98% (n = 10151) share. Spanish (n = 68, 0.665%), Turkish (n = 42, 0.403),

French (n = 27, 0.259), German (n = 19, 0.182) and Polish (n = 12, 0.115%) were the other prominent languages but none could achieve more than 1% share.

Paper	Total Citations (TC)	TC per Year
Sondi I, 2004, J Colloid Interf Sci	4102	215.89
Pal S, 2007, Appl Environ Microb	2803	175.19
Dijkshoorn L, 2007, Nat Rev Microbiol	1238	77.38
Falagas ME, 2005, Clin Infect Dis	1148	63.78
Lister Pd, 2009, Clin Microbiol Rev	1066	76.14
Li J, 2006, Lancet Infect Dis	989	58.18
Perez F, 2007, Antimicrob Agents Ch	883	55.19
Fayaz AM, 2010, Nanomed-Nanotechnol	847	65.15
Mah TF, 2005, Nature	794	39.7
Azam A, 2012, Int J Nanomed-A	791	71.91

**Table 1:** Top papers with total citations and citations per year. The list is ranked by total citations. Papers having the highest Total Citations also having Higher Total Citations per Year.

### Journals

Analysis of top journals in the field of our subject having highest number of publications showed that Journal “Antimicrobial Agents and Chemotherapy” is having highest number of publications i.e. 484 and having 4.64% share overall. Other top journals are “International Journal of Antimicrobial Agents” (n=404, 3.87%), “Journal of Antimicrobial Chemotherapy” (n=331, 3.17%) and Helicobacter (n=228, 2.18%).

### Geographical distribution

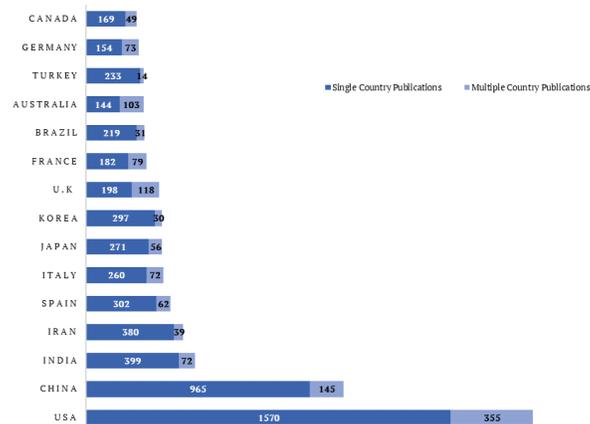
Most of the published research on subject is from U.S.A researchers with 2438 articles that make 23.59% share. U.S.A publications have also got highest number of citations for its total publications i.e., 86799. Other notable countries are China (n=1032), India (n=597), England (n=543), and Spain (n=504) that are subsequently holding the positions 2-5.

Figure 2 shows the ratio of Single Country Publications (SCP) to Multiple Country Publications (MCP) among top 15 most publishing countries, based on the share of the corresponding author. U.S.A also has maximum Single Country Publications (n=1570). Turkey has the highest ratio of SCP as compared to MCP i.e., 94.33%, with 233 publications. Australia is leading the chart with highest share of MCP with a percentage of 41.7%. It is important to mention that 964 papers do not have any specified corresponding authors status.

### Collaboration network

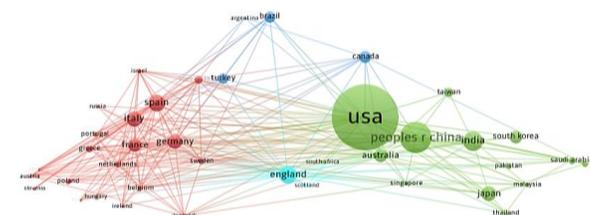
To construct a collaboration network/ map of co-authorship and countries on ABR gram-negative bacteria research, the following attributes were set in

VOS. Maximum number of countries per document was set at 25. Minimum number of documents per country was set at 5. Out of the 152 countries, 99 met the thresholds. Number of countries selected for visualization was 40 having the greatest total link strength.



**Figure 2:** Comparison of Single Country Publications to Multiple Country Publications based on corresponding author's country. USA is leading the chart with highest number of SCP but Turkey is having highest share of SCP i.e. 94.33% while Australia is leading the chart with highest share of MCP with a percentage of 41.7%.

Figure 3 shows that USA is the top county (documents=2438, citations=86799, total link strength=1125), followed by England (documents=543, citations=15216, total link strength=562), and Germany (documents=431, citations=13835, total link strength=473). Although China has second highest number of publications (n=1032), but it has link strength of 379 making it stand at position 5 in Collaboration Network /Map.



**Figure 3:** Collaboration Network/ Map of co-authorship and countries on ABR Gram-Negative Bacteria Research. The size of node signifies the number of publications, and the thickness of line represents the degree of cooperation between countries.

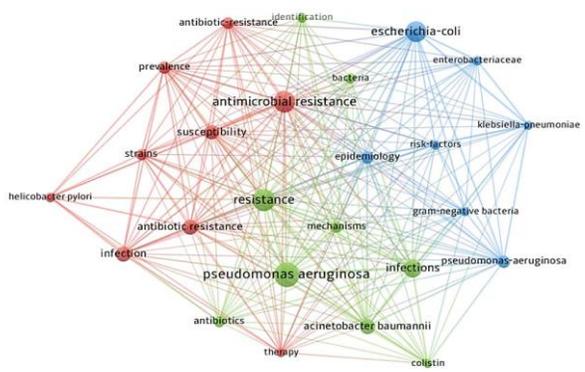
**Funding organizations**

Analysis of funding organizations revealed that highest number of studies in the subject field were funded by the United States Department of Health & Human Services, USA (n=704), National Institutes of Health (NIH), USA (n=677) and National Natural Science Foundation of China (NSFC) (n=433). European

Commission has also provided funding for ABR Gram-Negative Bacteria Research through different sources resulting in a considerable share (no=268, 2.57%) in global publications. Spain, Japan, Brazil and Australian funding agencies are also funding research in this subject.

**Co-occurrence of keywords**

The density visualization map of co-occurrence of all keywords is given in Figure 4. The density of a term reflects the number of related keywords in various documents in which both were found. The minimum number of occurrences of a keyword was set at 10. Out of the total 18207 keywords, only 1197 keywords met the threshold. Number of keywords selected for visualization was 25 having the greatest total link strength. The most frequent keyword was “pseudomonas aeruginosa” with 1333 occurrences and a total link strength of 2317, followed by “resistance” (occurrences=1180, total link strength=2153), and “antimicrobial resistance” (occurrences=1149, total link strength=2565).



**Figure 4:** Co-occurrence of keywords in the research publications on ABR Gram-Negative Bacteria Research. The size of node signifies the occurrence of keyword, and the thickness of line represents the co-occurrence between keywords. The density of a term reflects the number of related keywords in various documents in which both were found.

**Discussion**

This study gives a deeper review of research on ABR Gram-Negative Bacteria Research on international level with results showing greater research output from developed countries i.e., USA, China, India, England, Spain, Iran, Italy, Germany, and Japan. It proves that when better funding is provided, better research is conducted which is acknowledged by such data.

The publication trend shows upward growth in a linear pattern. It is also showing the potential growth of ABR Gram-Negative Bacteria Research in the future. The publications from 2003 to 2022 show an annual publication growth rate of 7.94% with a higher growth recorded since 2017 when WHO updated its list of most

pathogenic resistant bacteria which shows the matter is being taken seriously by researchers in recent years and more research is being carried out which shows interest of researchers and importance of the subject in recent years. More and more countries and research organizations are devoting themselves to this subject [14]

The country wise research output shows results with U.S.A. being ahead of all the other countries. This agrees with most of other bibliometric studies in different subject areas that confirm USA as the global leader in research not just quantity wise but quality wise as well [11, 20]. USA also has the maximum number of single country publications (1570) as compared to other countries. China (965) and India (399) are having second and third slots, respectively.

United States's *Department of Health & Human Services* is the top-most funding source having funded the greatest number of articles. If funded publications of all the sub organizations of USA's *National Institutes of Health (NIH)* are combined then it may take the top lead with 1131 publications altogether. Other notable organizations include *National Natural Science Foundation of China (NSFC)* and European Commission. This also clarifies the leading positions of USA, England, and China. The results clearly reveal that the more research funding is provided the better those countries perform [21].

We can see only a small tendency of collaboration with developing countries by technologically advanced and developed countries which also has resulted in a low productivity in developing countries in ABR Gram-Negative Bacteria research. Same result was also reported by Bai and Li [23]. Our study shows that USA's 77% articles have been published in collaboration with technologically advanced countries and only 33% articles are having authors from developing or under-developed countries. It is evident that international collaboration is need of the time for better research output in any field [22].

Many interesting keywords with high co-occurrence frequency through co-word analysis have been observed. According to our research pathogens such as *pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacteriaceae*, *helicobacter pylori*, and *klebsiella pneumoniae* were among the top 25 keywords showing the researchers' interest in these pathogens. Colistin was the only antibiotic as a term found in top 25 keywords which shows that antibiotic specific publications are not much in trend.

This study presents a visual and comprehensive overview of ABR Gram-Negative Bacteria Research. Over time, ABR Gram-Negative Bacteria have posed a global threat owing to being causation agents of many serious diseases in humans because of resistance to

most available antibiotics. This has attracted an increasing amount of related research in the field. We made both qualitative and quantitative analysis of the characteristics of publications, authors, top countries, leading journals, funding agencies and collaboration aspects. The rapid increase in number of publications showed that scientists are paying increasing attention to this area. Our study showed that both developed and developing countries have focused research on this field. USA is top representative of the developed countries while China made top contributions as a developing country. The present study has presented a point of concern that although least developing countries, especially from Africa are also affected seriously by ABR Gram-Negative Bacteria, not much research is being done in these countries in this area. The study is suggestive for most developing and least developed countries to develop collaborations with researchers from developed countries especially USA and UK having domination in research productivity and sources of funding. Our study will provide an insight for researchers from multidisciplinary areas focusing on BR Gram-Negative Bacteria Research as the research trend, research hotspots, and directions for future research. A major limitation in the study may be data extraction from Web of Science only as publications from database such as Scopus, PubMed were not included in this study and give future bibliometric researchers an area to explore.

## Author Contributions

Jamila Ahmed: Planned and designed study, conducted literature survey, collected, and analyzed data, drafted first draft of article.

Saima Nasir: Planned the research, analyzed data, reviewed, and amended first draft of article.

Dr. Ikram Ullah: Planned the research, reviewed the draft article.

Dr. Farhan Younas (Corresponding Author): Planned and supervised the study, reviewed the draft article.

## Conflicts of interest

The authors declare no conflict of interest.

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