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REVIEW ARTICLE

Worldwide Prevalence of Colistin Resistance among Enterobacteriaceae: a Systematic Review and Meta-Analysis

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SUMMARY

Background: **The aim of the present meta-analysis is to estimate the prevalence of colistin resistance among the Enterobacteriaceae family.**
Methods: **Articles from various databases (Medline, Scopus, Web of Science, and Embase) examining colistin resistance among Enterobacteriaceae in human, animal, and environmental specimens were searched from 2016 to 2021 using related keywords. The Cochran's Q-test and I^2 were applied to evaluate heterogeneity and a random-effects model was used to assess the pooled prevalence. The meta-regression method was applied to determine heterogeneity among the studies.**
Results: **Of 5,145 articles, 60 articles with a sample size of 404,856 was included. The pooled estimate for prevalence of bacterial resistance were 9.13% (95% CI: 6.96 to 11.56; I-squared = 99.4%) in total, 8.34% (95% CI: 5.87 to 11.16; I-squared = 99.3%) for *Klebsiella spp.* subgroup and 3.44% (95% CI: 2.46 to 4.57; I-squared = 98.4%) for *E. coli* subgroup. The pooled prevalence for human and animal settings were 9.07% (95% CI: 6.77 to 11.67; I-squared = 99.3%) and 9.73% (95% CI: 484 to 16.02; I-squared = 99.4%), respectively. The continent (coefficient: 3.51; 95% CI: 0.08 to 6.94, p: 0.045) and bacterial type (coefficient: 0.03; 95% CI: 0.01 to 0.05 p: 0.042) had significant effects on heterogeneity among studies.**
Conclusion: **The results of this study showed that the prevalence of colistin resistance in Enterobacteriaceae was similar between animals and humans, with the highest colistin resistance found in *Klebsiella* strains.**
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KEYWORDS

antimicrobial resistance, colistin, Enterobacteriaceae, systematic review, meta-analysis

INTRODUCTION

Enterobacteriaceae are a heterogeneous family of Gram-negative bacteria, many members of which are the normal gut flora of humans and animals, while others are found in water, soil or live on plant tissues. Some Enterobacteriaceae are important pathogens causing diseases such as meningitis, sepsis and urinary tract infections and are associated with significant mortality rates. Enterobacteriaceae infections are usually difficult to treat due to their ability to modify the levels of outer

membrane proteins such as porins and efflux pumps which makes their membrane impermeable to antibiotics. In addition, the overuse of antibiotics has led to increased multidrug resistance (MDR) among these bacteria, posing further obstacles to the treatment of these infections [1,2].

MDR in Enterobacteriaceae is often defined as resistance to at least one agent in the antibiotic categories fluoroquinolones, cephalosporins, and aminoglycosides [3]. Extensively drug resistant (XDR) and Pandrug resistant (PDR) bacteria have also been reported in this family. XDR includes resistance to at least one agent in all but 2 antibiotic categories and PDR includes resistance to all agents in all the available antibiotic categories [4]. According to a report from Saudi Arabia, the prevalence of Enterobacteriaceae MDR and XDR infections were 57.3% and 3.5%, respectively [5]. A study in 2019 in Portugal also reported an increased prevalence of MDR infections (above 60%) caused by Enterobacteriaceae in animal and environmental settings [6]. A Din et al. from Pakistan have reported the prevalence of XDR and PDR Enterobacteriaceae infections as 4.5% 1.8%, respectively. PDR Enterobacteriaceae were resistant to all the antibiotics tested in the aforementioned study including polymyxin B, colistin, tigecycline and etc. [7]. Colistin is used as the last resort antibiotic for the treatment of multidrug-resistant and carbapenem-resistant Enterobacteriaceae [8]. It is a polypeptide antibiotic that, by targeting lipid A in the LPS molecule, is only effective against Gram-negative bacteria. Lipid A has a negative charge due to the presence of free phosphate groups which bind to cations such as Ca^{2+} and Mg^{2+} stabilizing LPS. Colistin can bind to LPS phosphate groups with high affinity, causing instability in LPS and reducing the integrity of the outer membrane, followed by leakage of intracellular material and cell death occurs [9]. Despite the efficacy of colistin in eliminating Gram negative bacteria, the increased use of this antibiotic has led to increased resistance of many microorganisms against this antibiotic. Resistance mechanisms include intrinsic and acquired resistance due to efflux pumps, capsule formation, LPS structural change, porin permeability reduction, and other factors [10,11]. In this review article, data regarding the prevalence of colistin resistance among the Enterobacteriaceae strains isolated from humans, animals and the environment worldwide was gathered from 2016 to 2021, and analyzed by meta-analysis to give an overall view of how this resistance has been disseminated among different settings throughout the world during this time period.

MATERIALS AND METHODS

Method of literature search

All steps in this systematic review and meta-analysis study were based on the preferred reporting items for systematic review and meta-analysis [PRISMA] guidelines. A complete and comprehensive search was performed using the combination of the keywords "Microbial drug resistance", "Bacterial drug resistance", "Colistin", "Polymyxin", "Enterobacteriaceae" and "Coliform bacilli", in the international databases Medline, Scopus, Web of Science, and Embase, to identify and retrieve articles on the prevalence of colistin resistance in Enterobacteriaceae from January 2016 to June 2021 without language restriction. Other scholarly databanks, including Social Science Research Network (SSRN), were also searched to identify the un-officially published studies. The PICOT used in this study was:

Population: Enterobacteriaceae family

Intervention/exposure: Colistin antibiotic

Comparison: None

Outcome: Prevalence of colistin resistance

Time: 1st of January 2016 until 10th of June 2021

The following text words and Medical Subject Headings (MeSH) terms, based on PICOT for MEDLINE (MeSH), used for searching were:

1. Enterobacteriaceae [text word] OR Enterobacteriaceae [Mesh term]
2. Coliform Bacilli [text word] OR Coliform Bacilli [Mesh term]
3. *Escherichia coli* [text word] OR *Escherichia coli* [Mesh term]
4. *Klebsiella* [text word] OR *Klebsiella* [Mesh term]
5. 1 OR 2 OR 3 OR 4
6. Bacterial Drug Resistance [text word] OR Bacterial Drug Resistance [Mesh term]
7. Microbial Drug Resistance [text word] OR Microbial Drug Resistance [Mesh term]
8. Antibiotic Resistance [text word] OR Antibiotic Resistance [Mesh term]
9. 6 OR 7 OR 8
10. Colistin antibiotic [text word] OR Colistin antibiotic [Mesh term]
11. Polymyxin [text word] OR Polymyxin [Mesh term]
12. Colimycin [text word] OR Colimycin [Mesh term]
13. 10 OR 11 OR 12
14. 5 AND 9 AND 13

Google Scholar was used to access gray literature. In addition, the bibliographic list of all the retrieved articles was investigated to identify any ignored articles. All the extracted data were imported into Endnote X6, and after removing the duplicated articles, the remaining studies were screened in three steps of titles, abstracts, and full text. The three steps were followed independently by two raters, "RP, FL" and inter-rater discrepancies were resolved based on the third person's opinion, "IP". Blinding and task separation were applied in the study procedure selection. The inter-rater agreement was 94%.

Inclusion and exclusion criteria

All studies, including prospective, retrospective, and cross-sectional studies that examined colistin resistance among Enterobacteriaceae, were collected. The articles that had assessed resistance to other antibiotics as well as *in vivo* articles were excluded.

Data extraction
In addition to the general information, including the name of authors, year of publication, country, study design, sample origin (whether environmental, from humans or animals) and sample size, other data including prevalence and type of bacterial resistance as well as colistin minimum inhibitory concentrations (MICs) were extracted from all the studies.

Variable definition
Bacterial types were classified into the different species of *Escherichia coli*, *Klebsiella pneumonia*, *Klebsiella oxytoca*, *Klebsiella varicola*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Enterobacter spp.*, *Salmonella typhimurium*, *Salmonella enterica*, *Salmonella wandsworth*, *Salmonella infantis*, *Raoultella terrigena*, *Hafnia alvei*, *Citrobacter spp*. Countries were categorized based on their relevant continent (Africa; Asia; Europe; North America; South America). Study designs were classified into prospective cross sectional, retrospective cross sectional, and mixed design.

Statistical analysis
All data were analyzed using Stata software 14.0 (College Station, TX, USA). As in previous studies [12-15], the number of samples, as well as the prevalence of bacterial resistance in total and based on different bacterial types were extracted from all studies included in this meta-analysis. Heterogeneity was determined using Cochran's Q test of heterogeneity, and the I^2 index was used to quantify heterogeneity. Following the Higgins classification approach, I^2 values above 0.7 were considered as high heterogeneity. The pooled prevalence with 95% confidence interval [CI] was calculated using the "metaprop" command, and to estimate the pooled prevalence, the random-effects model was used. It should be noted the “Freeman-Tukey double-arcsine transformation” method was used for estimating 95% CI to keeps the values between 0 and 100%. The meta-regression analysis was used to examine the continent, sample size, study design, publication year, setting and bacterial type, as factors affecting the heterogeneity among studies. The "metabias" command was used to check the publication bias. If there was any publication bias, the prevalence rate was adjusted with the "metatrim" command using the trim-and-fill method. In all analyses, a p-value of ≥ 0.05 was considered as significant.

RESULTS

Overall, 5,145 studies were found through databases and 94 studies were identified through other sources. After excluding redundant papers, 2,824 studies remained. Screening was done in three steps. In the first step, 1,647 studies were excluded after reviewing the titles, leaving 1,177 articles for further analysis. A total of 898 studies were excluded from the list following abstract review. Scrutinizing the full texts of the remaining 279 studies led to the exclusion of 219 studies. Finally, 60 studies [16-75] with a total sample size of 404,856 were included in the analysis. The flow chart of this selection process is illustrated in Figure 1 and the characteristics of the included studies are shown in Supplemental Table 1. Europe had the highest number of studies (19 studies) and South-America had the lowest number (1 study). All the included studies were published between 2016 to 2021. A total of 34 studies were designed as prospective cross-sectional, 22 as retrospective cross-sectional and 4 studies had mixed design. Forty-six studies were carried out in human settings, 12 in animals, and 2 in environmental settings.

Pooled prevalence of bacterial resistance
The prevalence of colistin resistance among Enterobacteriaceae from all the included studies is listed in Supplemental Table 1. In addition, Figure 2 shows the forest plot for the prevalence of Enterobacteriaceae resistance to colistin. The minimum and maximum reported prevalence of bacterial resistance were reported by Jiang et al. (prevalence: 0.22%; 95% CI: 0.12 to 0.27) from China [27] and by Garcia et al. (prevalence: 76.88%; 95% CI: 70.15 to 82.74) from Spain. Based on Figure 2 regarding the random effects model approach, the pooled estimate for prevalence of bacterial resistance was 9.13% (95% CI: 6.96 to 11.56). This means that in overall, of every 100 samples, 7 to 12 samples have bacterial resistance.

Pooled prevalence of bacterial coinfections based on different subgroups
Figure 3 and Table 1 show the pooled prevalence of bacterial resistance based on the bacterial type and origin, different continents, and the study design. The pooled prevalence of bacterial resistance was 8.34% (95% CI: 5.87 to 11.16; I-squared = 99.3%) for *Klebsiella spp.* and 3.44% (95% CI: 2.46 to 4.57; I-squared = 98.4%) for *E. coli*. The most and least pooled prevalence of bacterial resistance based on the study design was estimated as 10.34% (95% CI: 7.64 to 13.39; I-squared = 99.1%) in prospective cross-sectional studies and 5.04% (95% CI: 2.04 to 9.12; I-squared = 81.8%) in mixed studies, respectively. The pooled prevalence for Africa and Asia continents were 8.10% (95% CI: 3.09 to 13.11; I-squared = 89.7%) and 7.20% (95% CI: 3.71 to 10.69; I-squared = 99.38%), respectively. Finally, the pooled prevalence for human and animal settings were 9.07% (95% CI: 6.77 to 11.67; I-squared = 99.3%) and 9.73% (95% CI: 484 to 16.02; I-squared = 99.4%), respectively. More detail was shown in Figure 3 and Table 1. Figure 4 showed the pooled prevalence of colistin resistance based on different continent.

Table 1. Pooled prevalence estimates and 95% confidence interval of colistin resistance among Enterobacteriaceae and results of publication bias method.

Subgroup		Pooled Percent (95% CI)	I^2 %	p-value	Number of studies
Continent	Africa	8.10 (3.09 to 13.11)	89.7	< 0.001	7
	Asia	7.20 (4.71 to 10.69)	99.38	< 0.001	31
	Europe	15.27 (9.78 to 20.77)	99.58	< 0.001	19
	North America	1.53 (0.36 to 2.69)	0	---	3
	South America	13.89 (4.67 to 29.50)	0	---	1
Design	Prospective CS	10.34 (7.64 to 13.39)	99.1	< 0.001	34
	Retrospective CS	8.00 (4.38 to 12.55)	99.6	< 0.001	22
	Mixed	5.04 (2.04 to 9.12)	81.8	< 0.001	5
Setting	Human	9.07 (6.77 to 11.67)	99.3	< 0.001	46
	Animal	9.73 (4.84 to 16.02)	99.4	< 0.001	12
	Environmental	4.12 (2.94 to 5.48)	0	---	2
Bactria type	*E. coli*	3.44 (2.46 to 4.57)	98.4	< 0.001	34
	Klebsiella	8.34 (5.87 to 11.16)	99.3	< 0.001	35
	Enterobacter	3.87 (1.38 to 7.51)	99.7	< 0.001	11
	Salmonella	0.52 (0.11 to 1.15)	97.6	< 0.001	8
	Other	0.57 (0.01 to 2.69)	0	---	3

CI - Confidence Interval, CS - Cross-sectional.

Table 2. Results of the univariate meta-regression analysis on the heterogeneity of the determinants.

Variables	Coefficient	95% CI	p-value
Continent	3.51	0.08 to 6.94	0.045 *
Study design	3.25	-4.69 to 11.18	0.416
Publication year (yrs.)	-2.01	-6.92 to 2.91	0.418
Sample size (number)	0.02	0.01 to 0.03	0.063
Setting	0.20	-5.90 to 6.30	0.947
Bactria type	0.03	0.01 to 0.05	0.042 *

CI - Confidence Interval.
Continent coding - North America = 1, Asia = 2, Africa = 3, South America = 4, Europe = 5.
Study design coding - Mixed = 1, Retrospective = 2, Prospective = 3.
Setting coding - Animal = 1, Environmental = 2, Human = 3.
Bactria type coding - *Salmonella* = 1, other = 2, *E. coli* = 3, *Enterobacter* = 4, *Klebsiella* = 5.

Heterogeneity and meta-regression

Figure 3 and Table 1 present the results of the heterogeneity. According to Cochran's Q test of heterogeneity, there was significant heterogeneity among studies ($p < 0.001$). The I^2 index for total bacterial resistance was 99%. According to meta-regression results (Table 2), continent (Coefficient: 3.51; p: 0.045) and bacterial type (Coefficient: 0.03; p: 0.042) had significant effects on heterogeneity among studies. In other words, the prevalence of bacterial resistance was 3.51% higher in Europe compared to South America, in South America compared to Africa, in Africa compared to Asia, and in Asia compared to North America. Also, the prevalence of bacterial resistance was 0.03% higher in *Klebsiella spp.* compared to *Enterobacter spp.*, in *Enterobacter spp.* compared to *Escherichia spp.*, in *Escherichia spp.* compared to other *Enterobacteriaceae spp.*, and in most *Enterobacteriaceae spp.* compared to *Salmonella spp.* Other variables including study design, setting, sample size (Figure 5A) and publication year (Figure 5B) had

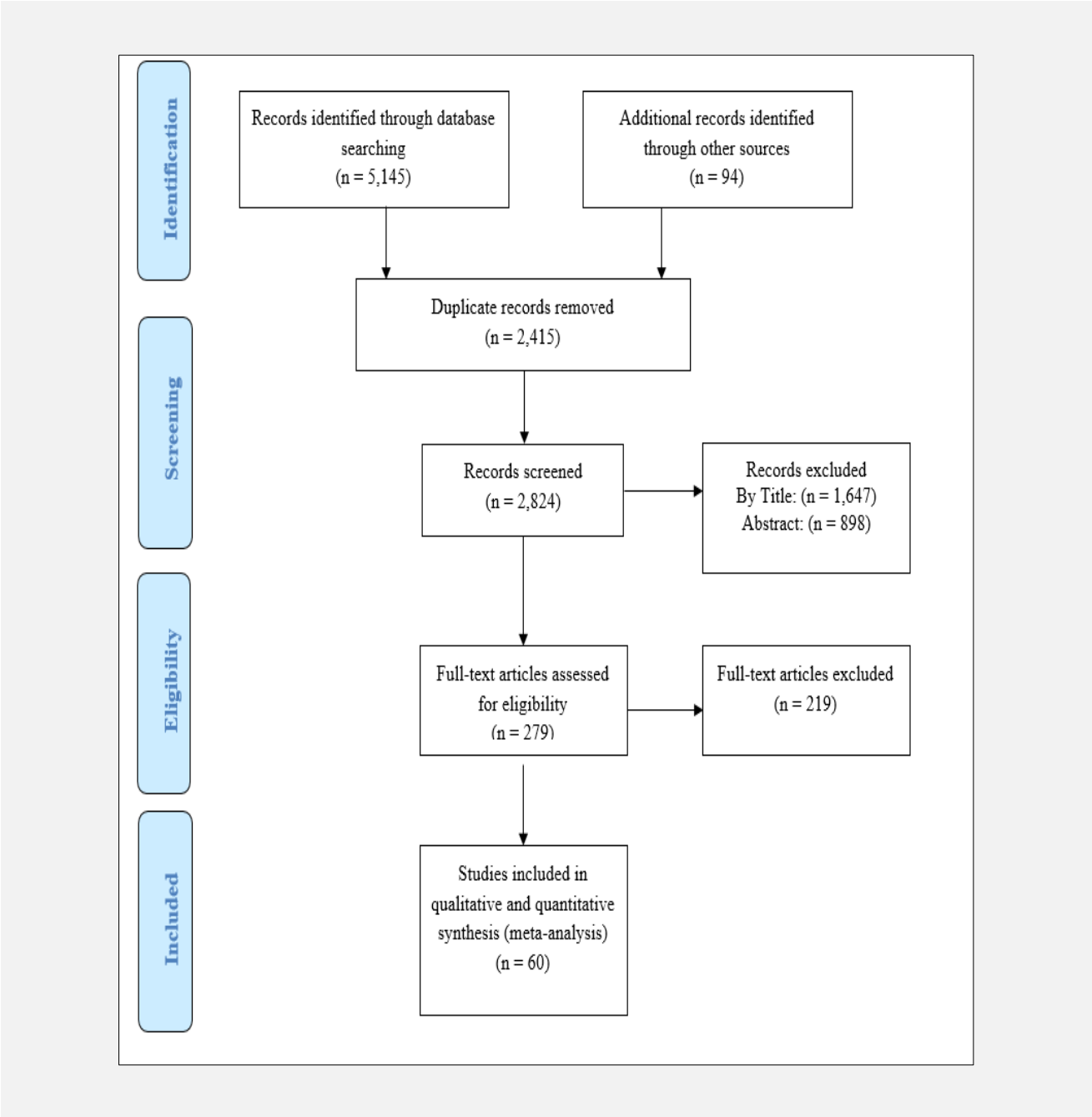

Figure 1. RISMA flow diagram of the study selection procedure.

no significant effect on heterogeneity among studies.

Publication bias

Based on the results of the Begg's test, a significant publication bias was observed for total bacterial coinfections (Z-score: 4.19; $p < 0.001$). Therefore, the fill and trim adjusted pooled prevalence of bacterial resistance (10.94%; 95% CI: 7.11 to 14.23) was generated, which was not significantly different from the original pooled prevalence (9.13%; 95% CI: 6.96 to 11.56). This means the results have robustness.

DISCUSSION

Today, treatment of infections caused by multidrug-resistant and carbapenem-resistant bacteria is a major global health problem. This has made the increased use

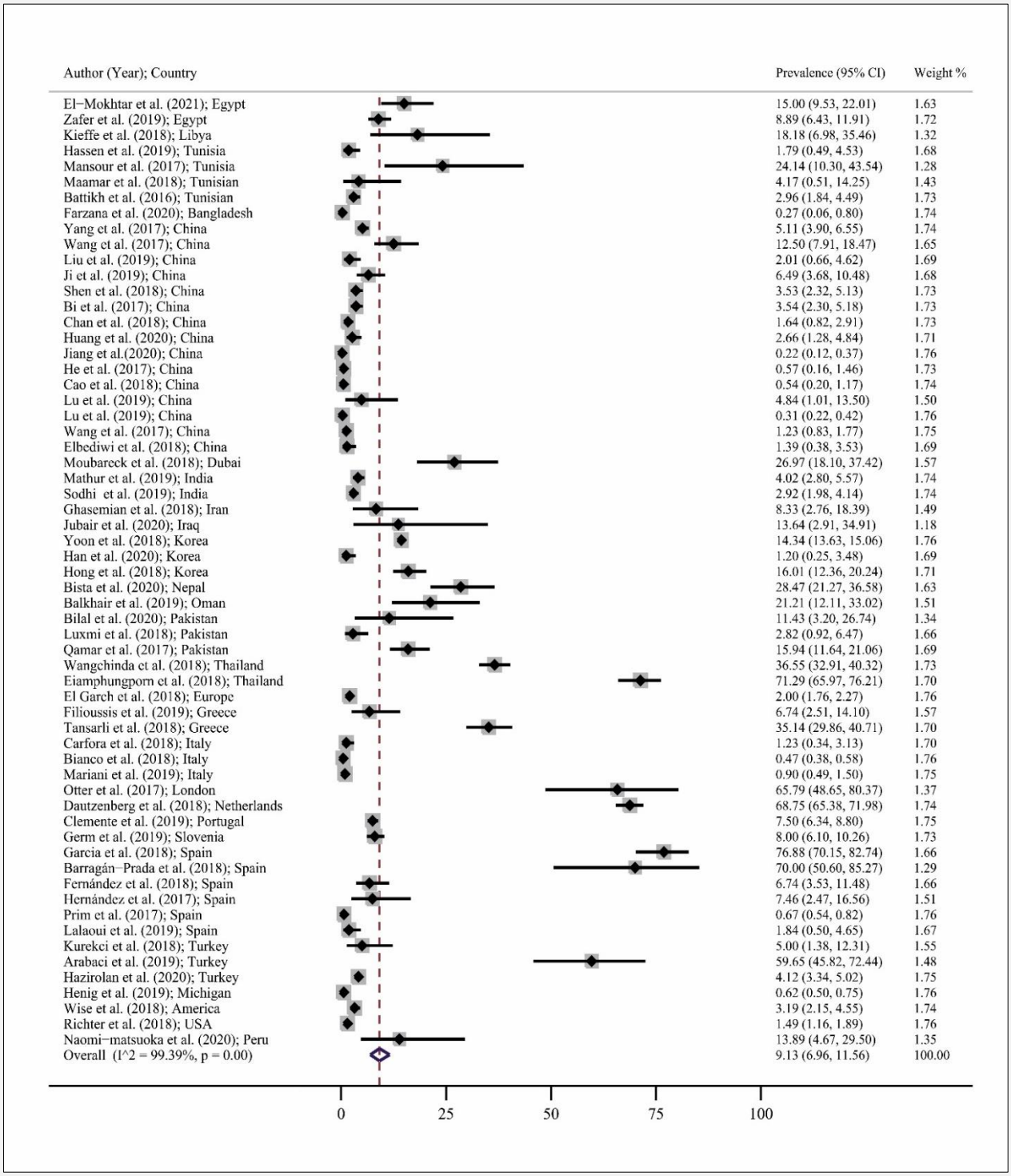

Figure 2. Forest plot for prevalence of bacterial resistance based on a random-effects model.

Each study identifies by the first author (year) and country. Each line segment's midpoint shows the prevalence estimate, length of line segment indicates 95% confidence interval (CI) in each study, and diamond mark illustrates the pooled estimate.

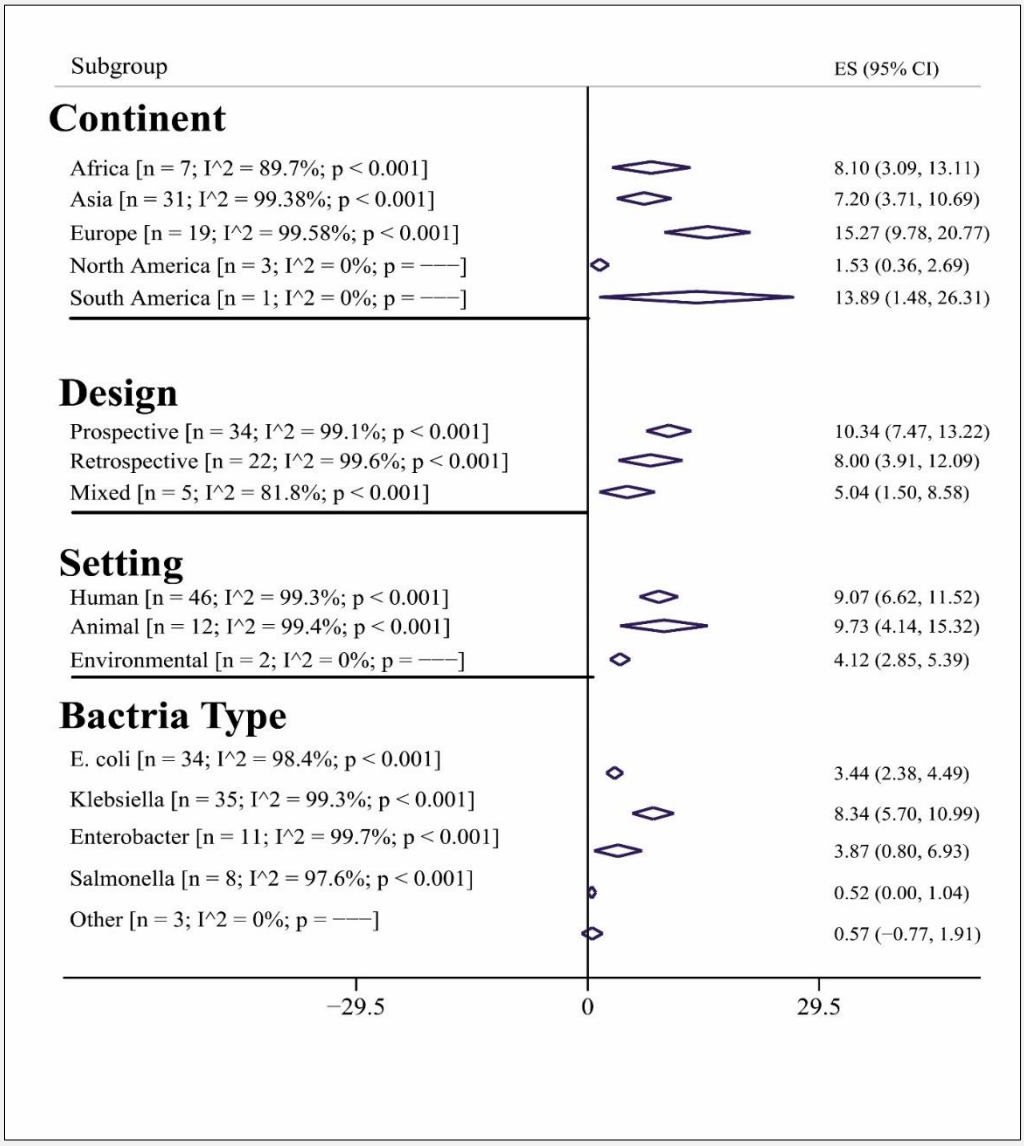

Figure 3. Pooled prevalence with 95% confidence interval [CI] and heterogeneity indexes of bacterial resistance based on type of the bacteria, different continent, setting and type of the study design.

The diamond mark illustrates the pooled prevalence and the length of the diamond indicates the 95% CI. N is the number of the study in the analysis.

of colistin inevitable as the last therapeutic resort for these infections, despite its many neurological and renal side effects. The overuse of colistin, on the other hand, has also increased resistance to this antibiotic among many bacterial genera including members of Enterobacteriaceae [10].

Resistance to colistin can be due to acquired and intrinsic resistance. Acquired resistance can be chromosomal or coded on plasmids. Acquired chromosomal resistance mechanisms include: 1) alteration of the LPS by adding a number of positively charged compounds leading to a decreased affinity of LPS to colistin (this is also the mechanism of intrinsic resistance in a number of bacteria including *Serratia spp.*), 2) capsule production, such as that in *Klebsiella pneumoniae*, which reduces the binding of colistin to the bacterial surface, 3) efflux pumps which pump the antibiotic out of the cell and 4) loss of LPS, which may occur in limited cases such as

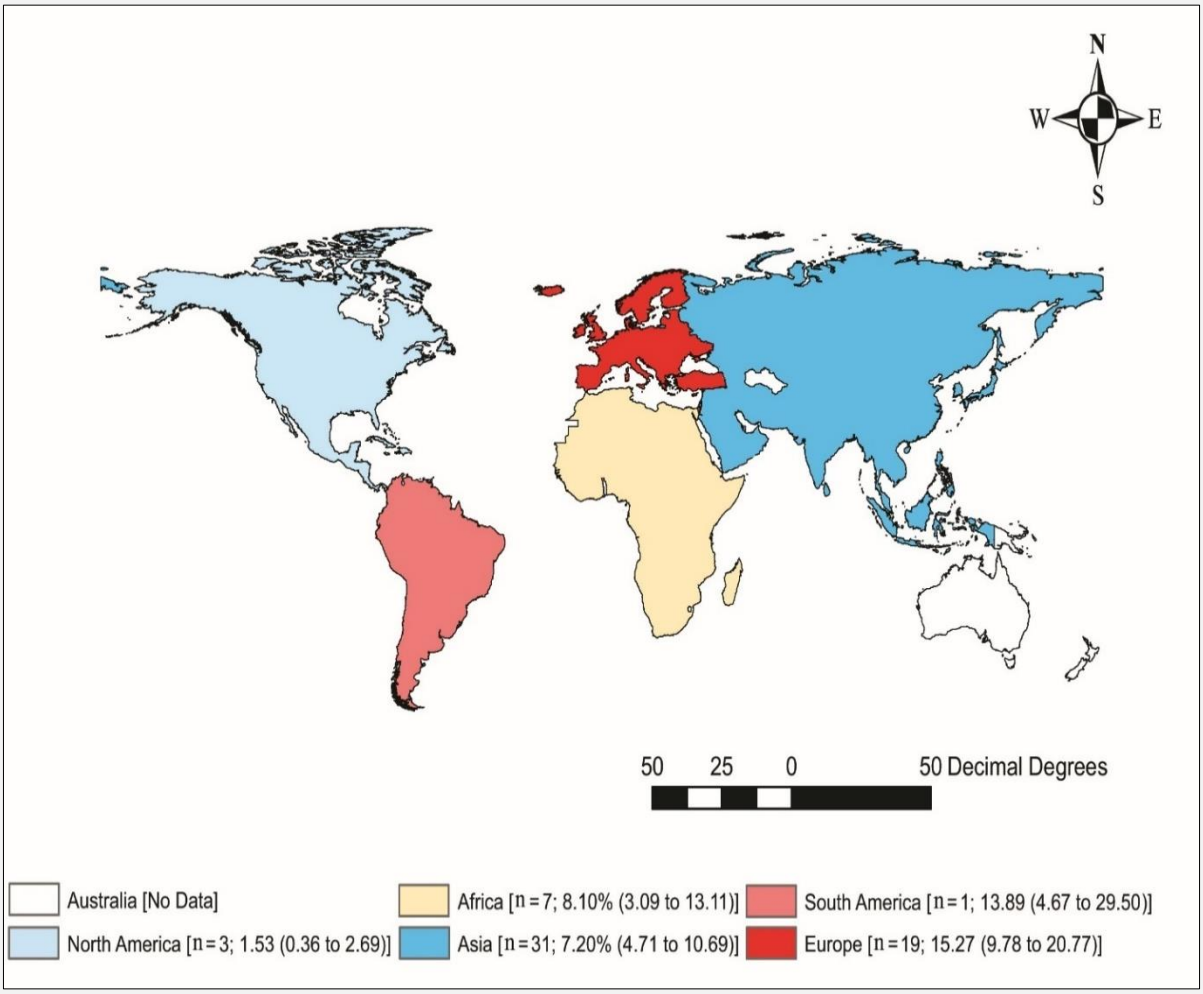

Figure 4. Pooled prevalence estimates and 95% confidence interval of bacterial resistance based on different continents.

that in *Acinetobacter baumannii*. Other modes of acquired resistance include the horizontal transfer of the colistin resistance genes into the susceptible strains by plasmids [9].

In this study, the prevalence of colistin resistance among Enterobacteriaceae strains from human, animal and environmental samples worldwide (Asia, Europe, Africa, North America, South America) has been analyzed from 2016 to 2021. Our results showed that 9.13% of all the Enterobacteriaceae species (including 9.73% of human, 9.07% of animal and 4.12% of environmental samples) are resistant to colistin with the highest and lowest resistance rates, respectively, reported in Europe (15.27%) and North America (1.53%). In a study in 2015 Bradford et al. collected 19,719 Enterobacteriaceae samples globally between 2012 and 2013 to test for colistin resistance and estimated a resistance rate of 1.6% (309 resistant samples) among Enterobacteriaceae isolates. The prevalence of colistin resistance among carbapenem resistant strains was reported as 12% which was different from that obtained by our study (9.13%). This discrepancy is mostly due to the fact that in our study, colistin resistance was assessed among strains that, for the most part, were already resistant against carbapenems. These results may confirm the association between the presence of carbapenemases and an increase in colistin resistance in Enterobacteriaceae specimens [76]. Increased colistin resistance, although it can occur due to previous excessive and inappropriate uses of this antibiotic, it can in some cases occur without the prior use of colistin by the patients. Due to the widespread use of colistin in veterinary medicine, it is possible that resistant bacteria are transmitted from animals to humans through food con-

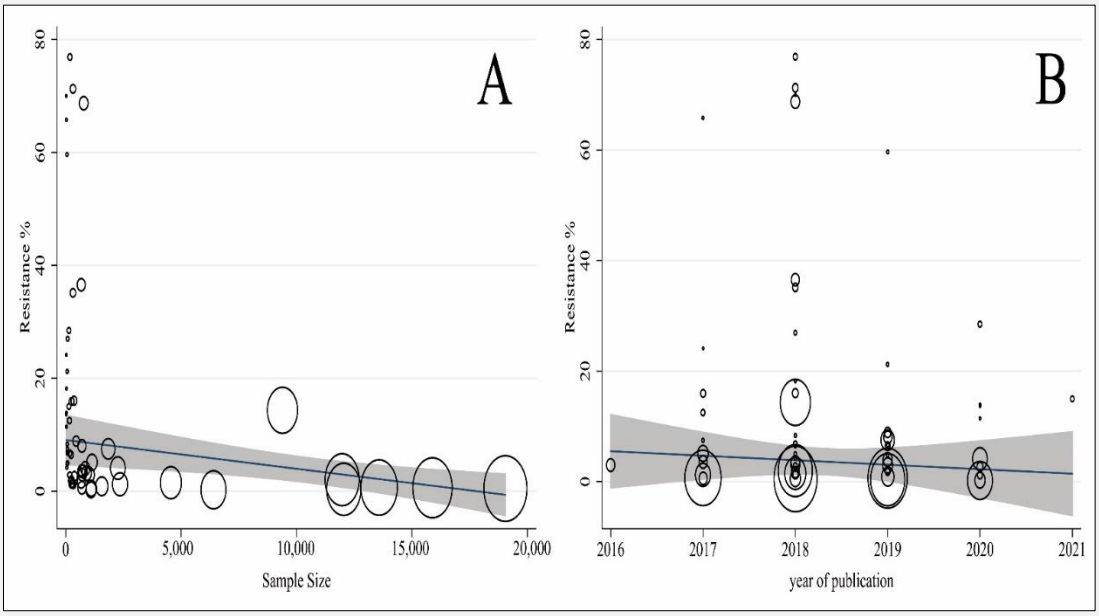

Figure 5. Association between the prevalence of bacterial resistance with sample size (A) and publication year (B) by means of meta-regression.

The size of circles indicates the precision of each study. There is no significant association between the prevalence of bacterial resistance, the sample size, and the publication year.

sumption or exposure to the animal's excretions.

In European countries, due to the excessive use of antibiotics (including colistin) in livestock, a higher colistin resistance rate has been reported among Enterobacteriaceae compared to other continents [77,78]. Although most studies included in this review are from China and despite the overuse of colistin in agriculture and animal husbandry in this country, the average colistin resistance in China is still lower than that in European countries, which might be due to the implementation of various measures to prevent infection transfer between different settings [79,18]. The lowest prevalence of Enterobacteriaceae colistin resistance in China was reported by Jiang et al. (0.22%), who collected samples from intra-abdominal and urinary tract infections. This low prevalence may have been due to the fact that Jiang et al. studied colistin resistance directly among *mcr-1* positive Enterobacteriaceae (MPE) strains to see the association between the *mcr-1* gene and colistin resistance. The results showed that most but not all of the strains possessing the *mcr-1* gene were resistant to colistin [27]. On the other hand, the highest prevalence of colistin resistance (76.88%) in Europe was observed by Garcia et al. from Spain, who isolated enteropathogenic *Escherichia coli* from fecal samples of pigs suffering from PWD (post weaning diarrhea). In European countries, colistin is used to treat pigs suffering from diarrhea after weaning and the excessive use of colistin in the treatment of such diseases has increased resistance to this antibiotic. Colistin resistance in enteropathogenic *Escherichia coli* occurs due to modifications in the LPS structure, which is the target of colistin [80,51]. Among Enterobacteriaceae, *Klebsiella* was shown to be the most resistant genus to colistin (8.34%), which again acquire resistance through LPS modifications and resistance genes. *Klebsiella spp.* are potential pathogens that can be the causative agents of diseases such as septicemia, pneumonia, and endocarditis, and an increase in the prevalence of colistin resistance among these microorganisms has recently become a major global health concern [78,79].

In this study, the heterogeneity of the available articles was very high (I^2 = 89.7% - 99.58%) except for those from North America and South America (I^2 = 0%). High heterogeneity can be due to different origins of samples used in studies (e.g. urine, feces, and blood culture samples). In some studies, colistin resistance was evaluated among carbapenem-resistant Enterobacteriaceae, while in others, it was examined among all Enterobacteriaceae strains. This discrepancy, as well as different methods of assessing colistin resistance, could be counted as limitations of the present study and it

should be noted that colistin resistance does not necessarily occur among carbapenem-resistant Enterobacteriaceae strains. Moreover, data regarding colistin resistance were not available from certain areas in the world (including countries of Australia), and our results, therefore, do not indicate the level of colistin resistance among Enterobacteriaceae strains in these areas.

CONCLUSION

This study shows a high prevalence of colistin resistance among Enterobacteriaceae strains worldwide from 2016 to 2021. Because colistin is the last drug option used to treat multidrug-resistant Enterobacteriaceae, this increase in colistin resistance is considered a major global health problem. The results of this study show the prevalence of colistin resistance in different continents, with the highest resistance rate in Europe due to the excessive use of colistin in veterinary medicine. The prevalence of colistin resistance was highest among *Klebsiella spp.* compared to other Enterobacteriaceae members, which raise extra concerns regarding the infections caused by these microorganisms. Studies that estimated colistin resistance among carbapenem-resistant Enterobacteriaceae strains mostly showed higher resistance rates compared to those that examined colistin resistance among all strains. These results may suggest the possibility of increased colistin resistance among carbapenem-resistant strains. Since colistin resistance is increasing among Enterobacteriaceae strains in all settings, preventive measures should be taken to minimize the use of colistin and the transfer of colistin resistant isolates from agriculture and veterinary medicine to clinical settings.

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