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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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Supplementary Data

Table S1. Characteristics of the studies investigating the prevalence of colistin resistance among Enterobacteriaceae during 2016-2021.

ID	Author	Year of publication	Place	Design	Sample origin	Sample size	Bacterial species	Prevalence of colistin resistance n (%)	Other data
1	Bi et al. (18)	2017	China	PCS	Human	706	*E. coli*	25 (3.54)	Type of sample = faecal Colistin, MIC = 3 to 6 µg/mL ESBL
2	Bilal et al. (19)	2020	Pakistan	PCS	Human	35	*K. pneumonia*	4 (11.43)	Type of sample = urine Colistin MIC = 4 to 8 µg/mL ESBL
3	Cao et al. (20)	2018	China	RCS	Human	1112	*E. coli*	6 (0.54)	Type of sample = 3 urine, 2 pus, 1 sputum Colistin MIC = 4 to 16 µg/mL
4	El-mokhtar et al. (21)	2021	Egypt	PCS	Human	140	*E. coli*	21 (15.00)	Type of sample = Sputum and aspirate Colistin MIC = 4 to 16 µg/mL Note = samples were collected from the Intensive Care Unit (ICU) with pneumonia
5	Chan et al. (22)	2018	China	PCS	Human	672	*E. coli*	11 (1.64)	Type of sample = faecal Colistin MIC > 2 µg/mL
6	Jubair et al. (23)	2020	Iraq	RCS	Human	22	*K. pneumoniae*	3 (13.64)	Type of sample = 2 Wound, 1 burn Colistin MIC = NR CRE (carbapenem resistant Enterobacteriaceae)
7	Huang et al. (24)	2020	China	PCS	Human	376	*E. coli*	10 (2.66)	Type of sample = 5 sputum, 2 blood, 1 Throat, 1 Drainage, 1 pus Colistin MIC = 2 µg/mL CRE
8	Han et al. (16)	2020	Korea	PCS	Human	249	*E. coli*	3 (1.20)	Type of sample = NR Colistin MIC > 2 CRE
9	Hazirolan et al. (25)	2020	Turkey	RCS	Human	2259	*K. pneumoniae*	93 (4.12)	Type of sample = 34 blood, 26 urine, 13 abscess, 11 tracheal aspirate, 4 peritoneal fluid, 2 cerebrospinal fluid, 1 synovial fluid, 1 pleural fluid, 1 pericardial fluid Colistin MIC = 4 to 128 µg/mL CRE
10	Mathur et al. (26)	2019	India	RCS	Human	846	*K. pneumoniae*	34 (4.02)	Type of sample = Bronchoalveolar lavage, Blood, urine, Cerebrospinal fluid Colistin MIC = 4 to > 1024 µg/mL

Table S1. Characteristics of the studies investigating the prevalence of colistin resistance among Enterobacteriaceae during 2016-2021 (continued).

ID	Author	Year of publication	Place	Design	Sample origin	Sample size	Bacterial species	Prevalence of colistin resistance n (%)	Other data
11	Jiang et al. (27)	2020	China	PCS	Human	6401	*E. coli*	14 (0.22)	Type of sample = IAI, UTI Colistin MIC = 4 to 8 µg/mL Note = UTI = urinary tract infection, IAI = intra abdominal infection
12	Lu et al. (28)	2019	China	RCS	Human	62	*S. typhi-murium*	3 (4.84)	Type of sample = feces Colistin MIC = 8 µg/mL
13	Lu et al. (17)	2019	China	RCS	Human	12053	*S. typhi-murium*	35 (0.29)	Type of sample = Faecal Colistin MIC = 4 to 8 µg/mL
							S. wands-worth	1 (0.01)	
							S. enterica	1 (0.01)	
							Total	37 (0.31)	
14	Luxmi et al. (29)	2018	Pakistan	PCS	Human	177	*K. pneu-moniae*	5 (2.82)	Type of sample = blood, tracheal secretions Colistin MIC > 4 µg/mL ESBL
15	Mariani et al. (30)	2020	Italy	RCS	Human	1557	*E. coli*	14 (0.90)	Type of sample = blood Colistin MIC = 4 to 8 µg/mL
16	Moubareck et al. (31)	2018	Dubai	PCS	Human	89	*K. pneu-moniae*	24 (26.97)	Type of sample = NR Colistin MIC = 32 CRE
17	Ghasemian et al. (32)	2018	Iran	PCS	Human	60	*K. oxytoca*	5 (8.33)	Type of sample = stool Colistin MIC = 8 µg/mL Note = Stool samples from patients with pseudomembranous colitis associated with antibiotic use were used to assess colistin resistance
18	Qamar et al. (33)	2017	Pakistan	PCS	Human	251	*K. pneu-moniae*	20 (7.97)	Type of sample: NR Colistin MIC ≥ 4 µg/mL CRE
							Entero-bacter spp.	4 (1.59)	
							K. oxytoca	3 (1.20)	
							E. coli	3 (1.20)	
							R. terrigena	10 (3.98)	
							Total	40 (15.94)	

Table S1. Characteristics of the studies investigating the prevalence of colistin resistance among Enterobacteriaceae during 2016-2021 (continued).

ID	Author	Year of publication	Place	Design	Sample origin	Sample size	Bacterial species	Prevalence of colistin resistance n (%)	Other data
19	Del Bianco et al. (34)	2018	Italy	PCS	Human	19053	*E. coli*	63 (0.33)	Type of sample = NR Colistin MIC > 2 µg/mL
							K. pneumoniae	22 (0.12)	
							E. cloacae	4 (0.02)	
							H. alvei	1 (0.01)	
							Total	90 (0.47)	
20	Arabaci et al. (35)	2019	Turkey	PCS	Human	57	*K. pneumoniae*	34 (59.65)	Type of sample = NR Colistin MIC = 0.25 to 64 µg/mL CRE
21	Wangchinda et al. (36)	2018	Thailand	PCS	Human	673	Total	246 (36.55)	Type of sample = 166 stool or swab rectal, 70 sputum, 10 urine Colistin MIC = 4 to 128 µg/mL Note = Patients received colistin, which increased the prevalence of resistance
22	Balkhair et al. (37)	2019	Oman	RCS	Human	66	*K. pneumoniae*	14 (21.21)	Type of sample = blood Colistin MIC = NR CRE
23	Battikh et al. (38)	2016	Tunisia	RCS	Human	709	*K. pneumoniae*	21 (2.96)	Type of sample = 15 blood, 4catheters, 2 transtracheal aspiration Colistin MIC = 8 to 12 µg/mL
24	Barragán-Prada et al. (39)	2018	Spain	PCS	Human	30	*K. pneumoniae*	21 (70.00)	Type of sample = 10 urine, 9 rectal, 1 sputum, 1drain Colistin MIC = 4 to 32 µg/mL MDR
25	Zafer et al. (40)	2019	Egypt	PCS	Human	450	*K. pneumoniae*	22 (4.89)	Type of sample = 24 blood, 7 pus, 1 wound, 1 drain, 1 sputum, 1 Throat, 1 Nephrostomy, 2 cvp, 1 Chest tube, 1 oral Colistin MIC = 4 to 32 µg/mL Note = resistance has been studied in cancer patients
							E. coli	18 (4.00)	
							Total	40 (8.89)	

Table S1. Characteristics of the studies investigating the prevalence of colistin resistance among Enterobacteriaceae during 2016-2021 (continued).

ID	Author	Year of publication	Place	Design	Sample origin	Sample size	Bacterial species	Prevalence of colistin resistance n (%)	Other data
26	Yoon et al. (41)	2018	Korea	RCS	Animal	9396	*K. pneumoniae*	810 (8.62)	Type of sample = urine Colistin MIC ≥ 2 µg/mL
							E. coli	340 (3.62)	
							Enterobacter spp.	197 (2.10)	
							Total	1347 (14.34)	
27	Dautzenberg et al. (42)	2018	Netherlands	PCS	Human	784	*E. cloacae*	539 (68.75)	Type of sample = ICU Colistin MIC > 2 µg/mL MDR
28	Wise et al. (43)	2018	America	PCS	Human	908	*E. coli*	27 (2.97)	Type of sample = 6 blood, 10 wound, 2 urine, 3 abscess, 5 peritoneal fluid, 1 gangrene, 1 gl tract, 1 endotracheal aspirate Colistin MIC ≥ 4 µg/mL
							K. pneumoniae	1 (0.11)	
							E. cloacae	1 (0.11)	
							Total	29 (3.19)	
29	Wang et al. (44)	2017	China	RCS	Human	2353	*K. pneumoniae*	23 (0.98)	Type of sample = 21 blood, 5 abdominal fluid, 1 wound secretion, 1 sputum, 1 urine Colistin MIC > 2 µg/mL
							E. coli	6 (0.25)	
							Total	29 (1.23)	
					Animal	168	*K. pneumoniae*	11 (6.55)	Type of sample = 6 dead chicken anal swab, 12 healthy chicken anal swab, 2 dead chicken liver, 1 breeding chicken anal swab Colistin MIC > 2 µg/mL
							E. coli	10 (5.95)	
							Total	21 (12.50)	
30	Tansarli et al. (45)	2018	Greece	PCS	Human	313	*K. pneumoniae*	110 (35.14)	Type of sample = blood Colistin MIC > 2 µg/mL CRE
31	Eiamphungporn et al. (46)	2018	Thailand	PCS	Human	317	*E. coli*	13 (4.10)	Type of sample = NR Colistin MIC > 2 µg/mL Note = samples were isolated from the infectious diseases department
							K. pneumoniae	213 (67.19)	
							Total	226 (71.29)	
32	El Garch et al. (47)	2018	Europe	RCS	Animal	11980	*E. coli*	148 (1.24)	Type of sample = cattle, pigs and chickens Colistin MIC > 2 µg/mL
							Salmonella spp.	92 (0.77)	
							Total	240 (2.00)	
33	Elbediwi et al. (48)	2018	China	RCS	Human	287	*S. enterica*	4 (1.39)	Type of sample = faecal Colistin MIC = 4 to 16 µg/mL
34	Farzana et al. (49)	2020	Bangladesh	PCS	Human	1097	*K. pneumoniae*	3 (0.27)	Type of sample = 2 urine, 1 blood Colistin MIC > 2 µg/mL

Table S1. Characteristics of the studies investigating the prevalence of colistin resistance among Enterobacteriaceae during 2016-2021 (continued).

ID	Author	Year of publication	Place	Design	Sample origin	Sample size	Bacterial species	Prevalence of colistin resistance n (%)	Other data
35	Filioussis et al. (50)	2019	Greece	Mixed	Animal	89	*E. coli*	6 (6.74)	Type of sample = milk from bovine mastitis cases MIC = 4 to 8 µg/mL
36	Garcia et al. (51)	2018	Spain	RCS	Animal	186	*E. coli*	143 (76.88)	Type of sample = faeces of pigs suffering mostly of PWD Colistin MIC > 2 µg/mL PWD = post weaning diarrhea
37	Garcia et al. (52)	2018	Spain	PCS	Human	178	*K. pneumoniae*	6 (3.37)	Type of sample = 10 rectal, 2 stool Colistin MIC = 8 to ≥ 64 µg/mL
							K. variicola	2 (1.12)	
							E. coli	3 (1.69)	
							E. cloacae	1 (0.56)	
							Total	12 (6.74)	
38	Sodhi et al. (53)	2019	India	RCS	Human	1027	*K. pneumoniae*	30 (2.92)	Type of sample = Blood, urine, sputum and BAL Colistin MIC ≥ 4 µg/mL Note = BAL = Broncho alveolar lavage
39	Germ et al. (54)	2019	Slovenia	PCS	Human	700	*K. pneumoniae*	20 (2.86)	Type of sample = 22 urine, 16 rectal, 6 blood, 1 abdominal fluid, 5 TA/BAL, 6 sputum Colistin MIC = 4 to 64 µg/mL
							E. coli	13 (1.86)	
							Enterobacter spp.	22 (3.14)	
							Citrobacter spp.	1 (0.14)	
							Total	56 (8.00)	
40	Shen et al. (55)	2018	China	PCS	Environmental	737	*E. coli*	23 (3.12)	Type of sample = 10 elevator handrail, 9 escalator handrail, 7 ticket machine Colistin MIC > 2 µg/mL
							K. pneumoniae	3 (0.41)	
							Total	26 (3.53)	
41	Richter et al. (56)	2018	USA	RCS	Human	4557	*K. pneumoniae*	68 (1.49)	Type of sample = 12 blood, 37 respiratory, 12 external, 7 other Colistin MIC > 2 µg/mL

Table S1. Characteristics of the studies investigating the prevalence of colistin resistance among Enterobacteriaceae during 2016-2021 (continued).

ID	Author	Year of publication	Place	Design	Sample origin	Sample size	Bacterial species	Prevalence of colistin resistance n (%)	Other data
42	He et al. (57)	2017	China	PCS	Human	700	*E. coli*	4 (0.57)	Type of sample = 2 secretion, 2 drainage-fuid Colistin MIC = 4 to 16 µg/mL
43	Henig et al. (58)	2019	Michigan	PCS	Human	15894	*Entero-bacter spp.*	45 (0.28)	Type of sample = NR Colistin MIC ≥ 4 µg/mL
							K. pneu-moniae	20 (0.13)	
							E. coli	33 (0.21)	
							Total	98 (0.62)	
44	Hernández et al. (59)	2017	Spain	PCS	Human	67	*K. pneu-moniae*	5 (7.46)	Type of sample = 2 rectal, 2 tracheal aspirate, 1 surgical drain Colistin MIC ≥ 16 µg/mL CRE
45	Hong et al. (60)	2018	Korea	PCS	Human	356	*E. cloacae*	51 (14.33)	Type of sample = NR Colistin MIC = NR
							E. aerogenes	6 (1.69)	
							Total	57 (16.01)	
46	Prim et al. (61)	2017	Spain	PCS	Human	13579	*E. coli*	53 (0.39)	Type of sample = 56 urine, 10 blood, 5 sputum, 13 exudate, 7 others Colistin MIC = 24 to > 256 µg/mL
							E. cloacae	27 (0.20)	
							K. pneu-moniae	8 (0.06)	
							others	3 (0.02)	
							total	91 (0.67)	
47	Ji et al. (62)	2019	China	PCS	Environ-mental	231	*E. coli*	15 (6.49)	Type of sample = 3 waste water, 2 drinking water, 3 faeces, 2 river water, 1 vegetables, 1 outlet sediment, 3 river sediment Colistin MIC = 4 to 8 µg/mL ESBL
48	Otter et al. (63)	2017	London	PCS	Human	38	*K. pneu-moniae*	25 (65.79)	Type of sample = 1 soft tissue and bone (foot), 1 wound, 1 urine, 22 screening Colistin MIC = 4 to 32 µg/mL CRE
49	Kieffer et al. (64)	2018	Libya	Mixed	Human	33	*K. pneu-moniae*	6 (18.18)	Type of sample = 2 blood, 1 pus, 1 urine, 1 sputum, 1 swab Colistin MIC = 64 to 128 CRE

Table S1. Characteristics of the studies investigating the prevalence of colistin resistance among Enterobacteriaceae during 2016-2021 (continued).

ID	Author	Year of publication	Place	Design	Sample origin	Sample size	Bacterial species	Prevalence of colistin resistance n (%)	Other data
50	Kurekci et al. (65)	2018	Turkey	Mixed	Animal	80	*E. coli*	4 (5.00)	Type of sample = chicken meat Colistin MIC > 8 µg/mL
51	Naomi-matsuoka et al. (66)	2020	Peru	PCS	Human	36	*K. pneu-moniae*	5 (13.89)	Type of sample = 3 blood, 2 secretions Colistin MIC = 8 to 64 µg/mL MDR
52	Lalaou et al. (67)	2019	Spain	PCS	Human	217	*E. coli*	4 (1.84)	Type of sample = fecal Colistin MIC = 4 µg/mL
53	Maamar et al. (68)	2018	Tunisia	PCS	Animal	48	*E. coli*	2 (4.17)	Type of sample = gut microbiota from healthy chickens Colistin MIC = 8 µg/mL ESBL
54	Mansour et al. (69)	2017	Tunisia	RCS	Human	29	*K. pneu-moniae*	7 (24.14)	Type of sample = NR Colistin MIC > 2 µg/mL CRE
55	Clemente et al. (70)	2019	Portugal	RCS	Animal	1840	*E. coli*	103 (5.60)	Type of sample = 8 animal feed, 98 cecum sample, 19 meat, 13 faeces Colistin MIC = 8 to > 16 µg/mL
							Salmonella spp.	35 (1.90)	
							Total	138 (7.50)	
56	Hassen et al. (71)	2019	Tunisia	PCS	Animal	223	*E. coli*	4 (1.79)	Type of sample = 3 bovine faeces, 1 bovine raw milk Colistin MIC = 8 to 16 µg/mL ESBL
57	Liu et al. (72)	2019	China	RCS	Animal	249	*E. coli*	5 (2.01)	Type of sample = milk samples from cows with clinical mastitis Colistin MIC = 8 to 16 µg/mL
58	Yang et al. (73)	2017	China	Mixed	Animal	1136	*E. coli*	58 (5.11)	Type of sample = sick chickens MIC = 4 to 16 µg/mL
59	Carfora et al. (74)	2018	Italy	Mixed	Animal	324	*S. infantis*	4 (1.23)	Type of sample = 2 broilers, 2 broiler meat Colistin MIC = ≥ 4 µg/mL
60	Bista et al. (75)	2020	Nepal	PCS	Animal	144	*E. coli*	41 (28.47)	Type of sample = poultry liver Colistin MIC = 4 to 32 µg/mL