Infection and Drug Resistance

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REVIEW

Prevalence of antibiotic resistance in *Escherichia coli* strains simultaneously isolated from humans, animals, food, and the environment: a systematic review and meta-analysis

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Background: Antimicrobial resistance is a serious public health problem worldwide. We aimed to investigate the prevalence of antibiotic resistance in *Escherichia coli* strains simultaneously isolated from humans, animals, food, and the environment.

Methods: Studies on PubMed, Embase, and the Cochrane Library published from January 1, 2000 to January 1, 2018 were searched. The quality of the included studies was assessed by the modified critical appraisal checklist recommended by the Joanna Briggs Institute. All analyses were conducted using Biostat's Comprehensive Meta-Analysis version 2.0. Depending on the heterogeneity test for each antibiotic, we used a random- or fixed-effect model for pooled prevalence of drug resistance. Studies were eligible if they had investigated and reported resistance in two or more isolation sources (human, animal, food, or environment). To decrease heterogeneity and bias, we excluded studies that had reported *E. coli* drug resistance isolated from one source only. We included publications that reported drug resistance with minimum inhibitory concentration or disk diffusion method (DDM) as antibiotic-susceptibility tests.

Results: Of the 39 included studies, 20 used the DDM and 19 minimum inhibitory concentration for their antibiotic-susceptibility testing. Colistin had the lowest prevalence, with 0.8% (95% CI 0.2%–3.8%) and amoxicillin the highest, with 70.5% (95% CI 57.5%–81%) in isolated human *E. coli* strains tested with the DDM. To assess historical changes in antimicrobial drug resistance, subgroup analysis from 2000 to 2018 showed a significant increase in ciprofloxacin resistance.

Conclusion: Monitoring and evaluating antibiotic-sensitivity patterns and preparation of reliable antibiotic strategies may lead to better outcomes for inhibition and control of *E. coli* infections in different regions of the world.

Keywords: antibiotic, drug resistance, *Escherichia coli*

Introduction

Antimicrobial resistance is a serious public health problem worldwide.[1–3] Inappropriate use of antibiotics by humans, factories, and farms, poor hygiene and sanitation, and inefficient prevention and control of infections in health-care settings are considered important reasons in the emergence and distribution of antibiotic-resistant bacteria.[4,5] Extended-spectrum β-lactamases (ESBLs) are enzymes that confer resistance to most β-lactam antibiotics, including penicillins, cephalosporins, and

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the monobactam aztreonam. Infections with ESBL-producing organisms have been associated with poor outcomes.[6] An important example of antibiotic resistance is multidrug-resistant (MDR) and ESBL-producing *Escherichia coli*, which can cause life-threatening infections.[7] *E. coli* is the predominant facultative flora in the gastrointestinal tract of humans and animals.[8] Some *E. coli* strains, however, have developed the ability to cause disease in the gastrointestinal, urinary, and central nervous systems.[9,10] Prolonged exposure of *E. coli* to antibiotics contributes to the development of antibiotic resistance.[11,12] Thus, antibiotic-resistant bacteria, including *E. coli*, in animals could serve as important reservoirs for colonization and infection in human beings.[8] Research has indicated that drug-resistant *E. coli* can be transmitted to human beings from the environment through direct or indirect contact (eg, consumption of contaminated food and water).[11] Therefore, assessing the prevalence of drug-resistant *E. coli* in different sources is critical for establishing guidelines in veterinary and human health care. To this end, we conducted a systematic review and meta-analysis to investigate the prevalence of antibiotic resistance in *E. coli* strains simultaneously isolated from humans, animals, food, and the environment.

Methods

Sources of information and search strategies

For papers from January 1, 2000 to January 1, 2018, PubMed, Embase, and the Cochrane Library were searched with the MeSH terms "*Escherichia coli*", "drug resistance", "antimicrobial resistance", "animal", "environment", and "food". These terms were combined with text searches that included "*E. coli*", "antibiotic(s)", "Gram-negative bacteria", "Enterobacteriaceae", "*Escherichia*", "antibiotic resistance", "antibacterial drug", and "meat". Contact was made with expert authors by mail to request any details not included in the original publications and unpublished work regarding our previous experiences.[13–15] In addition, we searched related reviews and references for relevant studies. We conducted our study according to PRISMA guidelines.[16]

Eligibility

Inclusion criteria

Two reviewers (TA and AP) independently carried out a review on titles and abstracts and chose those fitting the selection criteria for full-text evaluation. Discrepancies were discussed with a third reviewer (MJM). All original articles in the English language that simultaneously reported the prevalence of antibiotic resistance in *E. coli* strains isolated from humans, animals, the environment, and food with standard laboratory tests were included. Studies were eligible if they reported the prevalence of drug resistance in *E. coli* base on laboratory-standard guidelines. We considered all standard guidelines for inclusion in the study: Clinical and Laboratory Standards Institute (CLSI), National Committee for Clinical Laboratory Standards (NCCLS), Committee of the French Society of Microbiology, European Committee on Antimicrobial Susceptibility (EUCAST), British Standard for Antimicrobial Chemotherapy. However, only CLSI/NCCLS and EUCAST guidelines were used in all included studies.

Standard laboratory tests included disk diffusion method (DDM), minimum inhibitory concentration (MIC), andE. test. The aim of this study was to investigate the prevalence of drug-resistant *E. coli* strains from different sources and compare them with one another. As such, we included publications pursuing a common goal that reported the prevalence of drug resistance in *E. coli* from different sources. To decrease heterogeneity and bias, we excluded studies that reported *E. coli* drug resistance isolated from one source only. In this study, MDR strains were defined as resistant to three or more antimicrobial classes.

Data extraction and data collection

Data extracted were name of first author, publication date, sample size, time and location of study, total number of analyzed *E. coli* strains, and number of drug-resistant *E. coli* strains. Data were independently collected by two authors (AP and TA).

Exclusion criteria

Articles excluded were those that had not used standard methods (according to guidelines) for detection of drug resistance, had not reported the sample size, or had inappropriate data. Due to limted papers, we excluded studies that reported with Vitek (n=2), plate/replicator (n=1), Isosensitest (n=1), and Trek Diagnostic Systems products (n=1) for prevention of methodological bias (Figure 1). Furthermore, to reduce any potential heterogeneity that might be caused by different laboratory producers and quality of antibiotics, studies that reported the prevalence of antibiotic resistance from different sources (human, animal and environment) separately were excluded.

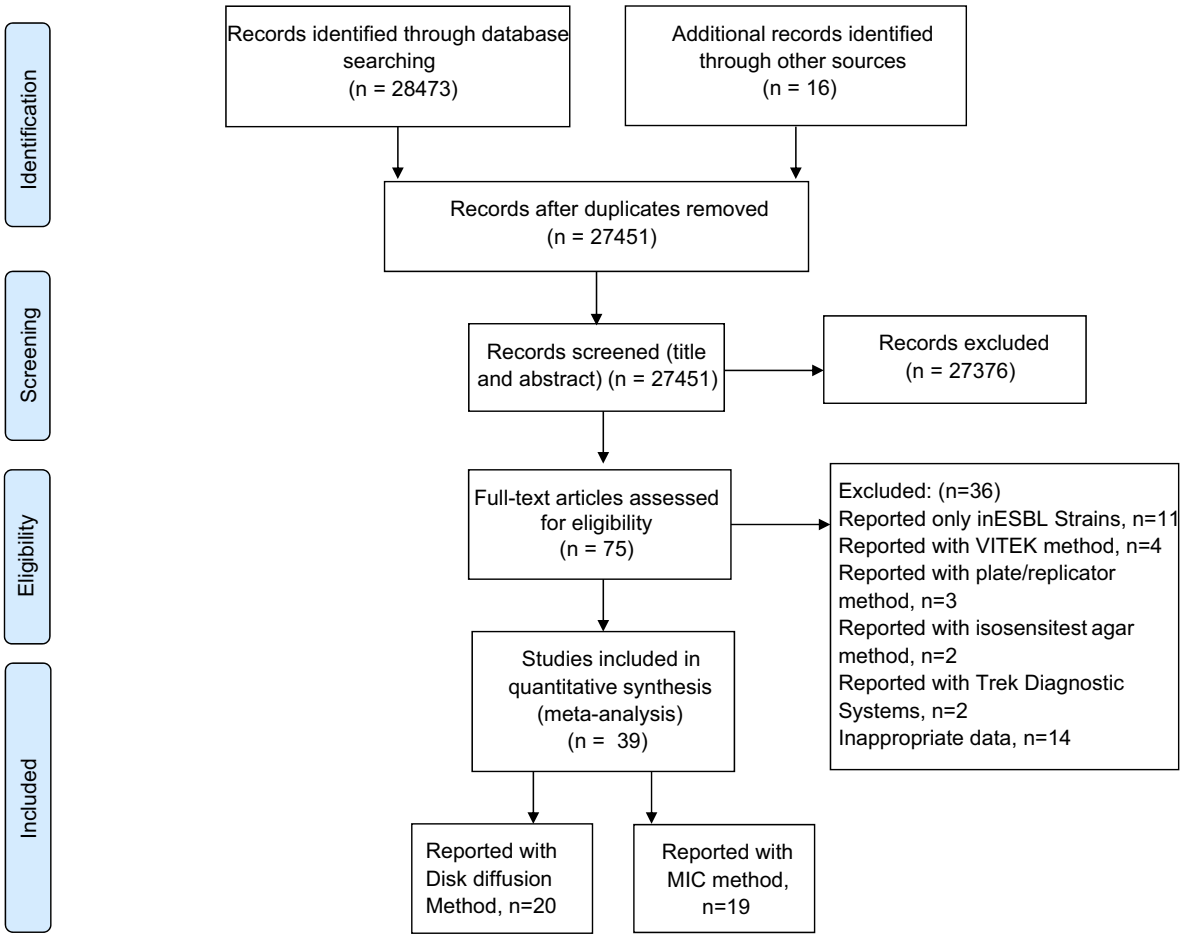


Figure 1 Flow diagram of literature search and study selection.

Quality assessment

Quality assessment of the studies were performed by two reviewers independently, according to the modified criticalappraisal checklist recommended by the Joanna Briggs Institute.[17] Disagreements were resolved by a consensus-based discussion. The checklist is composed of seven questions (question 4 has two scores) that reviewers answerfor each study. The "Yes" answer for each question receives 1 point. Final scores for each study can range from 0 to 8 (Table S1).

Meta-analysis approach

All statistical analyses were carried out with Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ, USA). Determination of the heterogeneity of studies was carried out using both chi-squared (Cochran's Q) and I^2 tests to assess the appropriateness of pooling data. Depending on the heterogeneity test, we used a random- or fixed-effect model for the pooled prevalence of drug resistance. In cases of high heterogeneity (I^2>50%), the random-effect model (Mantel–Haenszel

heterogeneity) was used, and for low heterogeneity (I^2<50%), the fixed-effect model was used.[18] Begg's and Egger's tests were used to assess publication bias. Point estimation of effect size, prevalence, and 95% CIs were measured for each study.

Ethics statement

The was a systematic review, so ethical approval was not required.

Results

Selection of studies

A total of 39 studies, selected from a total of 28,489 articles (0.137%, 39 of 28,489) found in the initial search, were included in the final analysis. The location of studies

Table 1 Characterization of included studies

Study	Time enrolled	Published	Country	Isolate source	Method	Interpret Guidelines	Sample
Adhiratha et al[5]	2012–2013	2014	Thailand	Humans, animals, food/environment	ADM	NOT	Stool samples, water samples collected from canals, fish and shrimp ponds- Rectal swabs, cooked food
Alali et al[19]	2004–2006	2008	USA	Food/environment, animals	ADM	CLSI	Human wastewater, swine fecal
Alexandra et al[21]	2011	2014	Portugal	Food/environment, humans	ADM	CLSI	Fecal, beach and waste waters
Kazemnia et al[22]	2012	2014	Iran	Humans,animals	DDM	CLSI	Urine samples, poultry carcasses
Azucena et al[23]	1992–1999	2005	Spain	Humans, animals, food/environment	DDM	NOT	Feces sample, food, beef meat
Baoguang et al[3,24]	2012–2014	2018	China	Humans,animals	BMD	CLSI	Blood, rectal swab
Bhoomika et al[3]	2014–2015	2016	India	Humans, animals, food/environment	DDM	CLSI	Urine and stool- Chicken meat, Chevon meat, Raw milk
Bogaard et al[25]	NS	2001	Netherlands	Humans, animals, food/environment	ADM	NOT	Feces sample, sample from slaughterers
Hanna et al[26]	2000–2001	2006	Australia	Humans, animals, food/environment	DDM	CLSI	Rectal swabs- environmental swabs
Iuliana et al[27]	2011–2012	2015	United Kingdom	Humans,animals	DDM	CLSI	Fecal samples
James[28]	2002–2004	2007	USA	Humans,animals	ADM	CLSI	Fecal sample-meat of chicken
James et al[29,*]	1998–2001	2003	USA	Humans,animals	ADM	CLSI	Intestinal and Extra intestinal sample
Wang et al[30]	2011–2013	2017	China	Humans, animals, food/environment	DDM	CLSI	Urine and fecal- food sample
Joanne et al[31]	2007–2009	2010	Australia	Humans,animals	DDM	CLSI	Urine- animal specimen
Jorge et al[32]	2009–2010	2013	Sweden	Humans,animals	DDM	CLSI	Fecal samples
Karen et al[33]	NS	2011	USA	Animals, food/ environment	DDM	CLSI	Feces sample, Wastewater
Katherine et al[34]	2007–2008	2009	USA	Humans,animals	DDM	CLSI	Fecal swab specimen
Krushna et al[8]	2010–2011	2012	Sweden	Humans, animals, food/environment	DDM	CLSI	Stool samples, cow-dung, drinking water
Wang et al[35]	1997–2009	2017	China	Humans, animals, food/environment	DDM	NOT	Fecal/diarrhea -cattle and swine feces-food sample
Purohit et al[36]	2015	2017	India	Humans, animals, food/environment	DDM	NOT	Stool- waste, drinking water
Sannes et al[37]	1998–1999	2004	USA	Humans,animals	DDM	CLSI	Urine-feces
Miles et al[38]	2000–2001	2006	Jamaica	Humans,animals	DDM	CLSI	Urine and wound specimens of hospitalized patients- fecal samples of broiler chickens
Sabate et al[39]	2005	2008	Spain	Humans, animals, food/environment	DDM	CLSI	Human and animal wastewater

(*Continued*)

Table 1 (Continued).

Study	Time enrolled	Published	Country	Isolate source	Method	Interpret Guidelines	Sample
Dhaka et al[40]	2014–2016	2016	India	Humans, animals, food/environment	DDM	NOT	Stool- diarrhea - food and environmental samples
Pasquali et al[41]	NS	2015	Italy	Humans,animals	ADM	CLSI	
Ross et al[42]	2014–2016	2016	USA	Humans,animals	ADM	CLSI	NOT
Koczura et al[43]	2008–2009	2012	Poland	Humans, food/ environment	DDM	CLSI	Urine, semen and wound swabs-raw sewage, aeration tank with activated sludge, and final effluent without disinfection
Sayah et al[44]	2002–2003	2005	USA	Humans, animals, food/environment	DDM	CLSI	Human septage - Animal fecal- Surface water, Farm environment
Scott et al[45]	2003–2004	2005	USA	Humans,animals	BMD	CLSI	Human fecal sample-swine fecal sample
Seputiene et al[46]	2005–2008	2010	Lithuania	Humans,animals	DDM	CLSI	Urine, cervix, vagina and prostate, and blood, pus and wounds-feces sample
Tao et al[47]	2007–2008	2010	China	Food/environment, animals	ADM	CLSI	Meat- feces or liver samples
Tatsuya et al[48]	2006–2008	2010	South Korea	Humans,animals	ADM	CLSI	Stool samples
Tatsuya et al[49]	2008	2011	South Korea	Humans,animals	ADM	CLSI	Stool- Feces
Thomas et al[50]	2002	2005	Canada	Food/environment, animals	ADM	NOT	Birds fecal sample-surface and waste waters
Thorstein et al[51]	2006–2007	2008	Iceland	Humans,animals	BMD	CLSI	Fecal samples-Caeca and food sample
Viktoria et al[52]	2008	2009	Denmark	Humans,animals	ADM	CLSI	Urine specimens-kidneys with chronic and / or acute lesions
Winokur et al[53]	1998–1999	2001	USA	Humans,animals	BMD	CLSI	Urine, blood- intestinal biopsy samples, feces
Yolanda et al[54]	1997–1999	2001	Spain	Humans, animals, food/environment	ADM	CLSI	Fecal, urine, blood, wound- fecal samples-food such as Hamburger, sausage and minced, chicken, Skin of chicken, Caecum of chicken, Breast of chicken, Pre-cooked chicken foods, Turkey products
Young et al[55]	2001–2003	2005	Korea	Humans, animals	ADM	CLSI	Clinical and Stool samples-large intestine

Abbreviations: ADM, agar dilution method; DDM, disk diffusion method; BMD, broth microdilution; NS, not specified.

Table 2. Prevalence of antibiotic resistance in human, animal, food/environment *E. coli* isolates with Disk Diffusion method

	HUMAN ISOLATES				ANIMAL ISOLATES				FOOD/ENVIRONMENT ISOLATES			
Antibiotic	**% PP (CI 95%)**	**n /N**	**N of study**	**I^2 (%)P**	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%)P**	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%)P**
CL	0.8 (0.2-3.8)	1/217	2	0.54	10 (1-45)	31/193	2	0.12	3.2 (0.1-63.3)	10/204	2	0.005
CIP	28.3 (17.2-42.7)	161/607	11	< 0.001	18.3 (5.7-50)	169/1039	8	< 0.001	14.4 (5.4-33.4)	152/555	7	< 0.001
TMP	16 (10-25)	123/697	3	0.001	9.2 (2.3-30)	92/784	3	< 0.001	24 (15-36.7)	14/58	1	1
SMZ	28.5 (25.5-33)	133/469	3	0.35	22.2 (9.8-43)	338/1596	3	< 0.001	21.3 (4.6-6)	49/314	2	< 0.001
CF	33.5 (16-57)	552/1078	7	< 0.001	17.5 (5.8-42.2)	401/1937	5	< 0.001	33.6 (13-63)	256/543	4	< 0.001
AK	2 (0.2-16.5)	10/355	3	< 0.004	1.8 (0.3-10)	8/707	3	0.03	4 (1.2-13.4)	10/262	3	0.05
AUG	2 (1.1-3.7)	10/597	6	0	1.5 (0.8-3)	8/637	3	0.2	4.8 (1.7-13)	3	2	0.73
AMX	70.5 (57.5-81)	41/58	2	0	96 (76-99)	24/25	1	1	58.4 (51.7-65)	125/214	1	1
CFX	5.5 (1.6-16.7)	98/1141	6	< 0.001	6.2 (5-47.2)	97/852	5	< 0.001	3.4 (1-11)	2/73	2	0.94
CTX	58 (52.3-63.6)	171/294	4	0.2	58 (16.5-90.5)	140/308	4	< 0.001	31.15 (16.3-52)	97/433	4	< 0.001
CHL	12.5 (6-25)	38/305	7	0.002	3 (1-8.5)	40/1629	3	< 0.001	10 (3-27.8)	93/592	5	< 0.001
CRO	3.3 (1-10)	2/187	3	0.2	0.2 (0-1.7)	0/592	2	0.34	1.6 (0.2-10.7)	0/73	2	0.54
IMP	2.7 (1.4-5)	7/634	6	0.15	0.9 (0.3-2.8)	1/833	5	0.17	2.7 (1.5-4.7)	10/431	4	0.57
SXT	27.6 (11-54.3)	580/1336	9	< 0.001	30 (7.7-69)	410/2170	9	< 0.001	25.8 (8-57.7)	109/597	7	< 0.001
TET	54.6 (37.3-71)	711/1192	13	< 0.001	53 (36-69.5)	861/2201	10	< 0.001	47 (25-70)	338/811	8	< 0.001
GM	21.5 (12.5-34.5)	329/1173	12	< 0.001	13.6 (5.6-29.4)	149/947	6	< 0.001	9 (3.223)	105/796	7	< 0.001

(*Continued*)

Table 2. (Continued).

	HUMAN ISOLATES				ANIMAL ISOLATES				FOOD/ENVIRONMENT ISOLATES			
Antibiotic	**% PP (CI 95%)**	**n /N**	**N of study**	**I^2 (%)P**	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%)P**	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%)P**
KAN	51 (15.2-85.7)	85/253	4	< 0.001	6.2 (4.4-8.7)	32/514	1	1	30.4 (1.4-93)	155/272	2	< 0.001
NA	32 (12.3-61)	161/468	9	< 0.001	21.4 (2-80)	132/1765	6	< 0.001	8.5 (2.8-22.7)	31/473	2	0.004
AMP	49.7 (35.3-64)	556/1211	14	< 0.001	44.4 (19-73)	443/2190	10	< 0.001	40.2 (16.5-69.5)	322/811	8	< 0.001
CAZ	49.2 (32-66.7)	106/204	3	0.007	57.4 (23-97)	85/111	2	< 0.001	10 (3.8-24.4)	36/358	2	0.003
STR	39.7 (30.3-50)	172/458	4	0.03	30.5 (15-52.4)	44/1938	5	< 0.001	28.4 (10.7-56.8)	74/363	3	< 0.001
MDR	22 (5.2-58.6)	475/1310	4	< 0.001	5.7 (3.3-9.6)	13/249	3	0.18	31.3 (24-33.3)	45/144	1	1
ESBL	13 (2-52.7)	77/211	4	< 0.001	26.3 (6-66.5)	73/287	3	< 0.001	25 (18.6-32.7)	36/144	1	1

Abbreviations: MDR, Multidrug Resistant; ESBL, Extended Spectrum β-lactamase; PP, Pooled prevalence; n or N, Number; PP, Pooled prevalence; CL, Colistin; CIP, Ciprofloxacin; TMP, trimethoprim; SMZ, Sulfisoxazole; CF, Cephalothin; AK, Amikacin; AUG, Amoxicillin-clavulanic acid; AMX, amoxicillin; CFX, Cefoxitin; CTX, Cefotaxime; CHL, Chloramphenicol; CRO, Ceftriaxone; IMP, Imipenem; SXT, Trimethoprim-sulfamethoxazole; TET, Tetracycline; GM, Gentamicin; KAN, kanamycin; NA, Nalidixic acid; AMP, Ampicillin; CAZ, Ceftazidime; STR, Streptomycin.

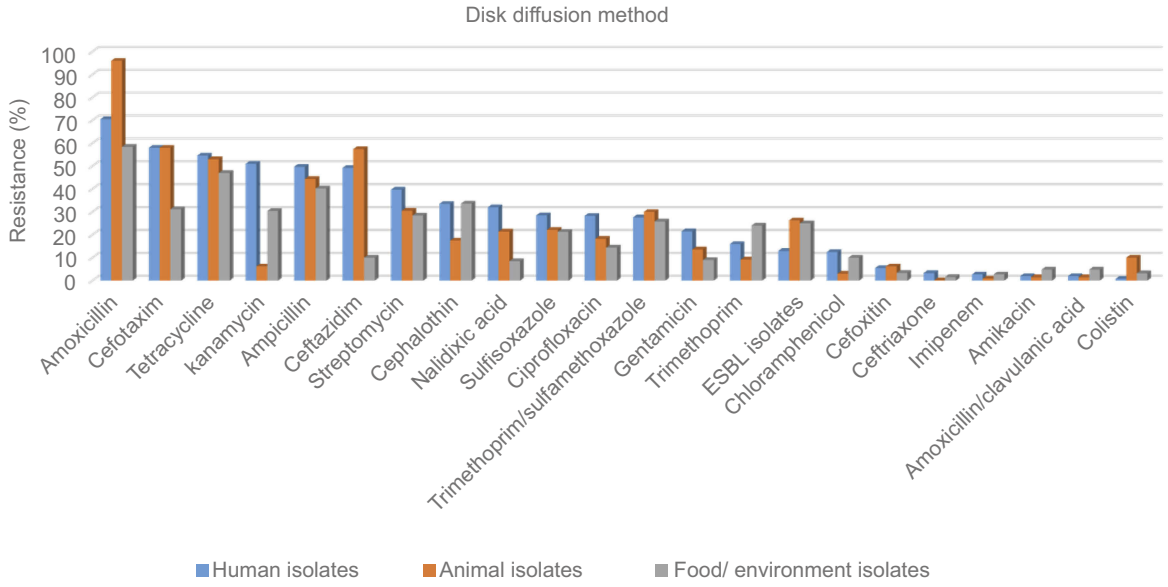


Figure 2 Prevalence of antibiotic resistance in human, animal, food/environment *E. coli* isolates with disk diffusion method.

covered east to west and north to south of the world, with the majority of patients from the US, China, and India. Each assessment with more than one isolation source was treated as a separate study. Figure 1 shows the selection process. Characteristics of the selected articles are summarized in Table 1. Of the 39 included studies, 20 used the DDM, 15 agar dilution, and four broth microdilution as the antibiotic-susceptibility test. Some studies used agar dilution and broth dilution combined, referred to as MIC testing for the analysis. In the included studies, 20 studies simultaneously reported prevalence data in humans and animals, 13 in humans, animals, food, and theenvironment, five in animals, food, and the environment and one in human, food, and the environment.

Prevalence of antibiotic resistance in *E. coli* isolates using DDM

Prevalence of different antibiotic resistance in *E. coli* strains isolated from humans is shown in Figure 2, Table 2, and Figures S1–S25.

As shown in Table 2 and Figures S26–S65, high rates of resistance to amoxicillin were observed in samples from all sources (humans 70.5%, 95% CI 57.5%–81%; animals 96%, 95% CI 76%–99%; and food/environment 58.4%, 95% CI 51.7%–65%). Human isolates had very low rates of resistance to colistin (0.8%, 95% CI 0.2%–3.8%), which were the lowest resistance rates across all antimicrobials and isolation sources.

Prevalence of antibiotic resistance in *E. coli* isolates using MIC

As shown in Figure 3, Table 3, and Figures S66–S87 and S89–S90, in *E. coli* strains isolated from humans, the lowest resistance rate was for imipenem (0.1%, 95% CI 0–0.3%) and the highest for amoxicillin (53.4%, 95% CI 22%–82.3%; Table 3 and Figure S91). In *E. coli* strains isolated from animals, the lowest and highest resistance rates were for colistin (0.1%, 95% CI 0–2%) and tetracycline (60%, 95% CI 50%–72.5%), respectively. In *E. coli* strains isolated from food and environmental sources, resistance to imipenem, cefotaxime, and ceftazidime was 1% (95% CI 0.1%–14.5%) and for nalidixic acid 53% (95% CI 39%–67%).

Prevalence of ciprofloxacin resistance in *E. coli* strains isolated from human

Ciprofloxacin was the most reported antibiotic used for *E. coli* in the included studies, so we analyzed ciprofloxacin resistance in more detail. In studies that had used DDM or MIC, the prevalence of ciprofloxacin-resistant *E. coli* strains isolated from humans was higher than the isolated resistant strains from animals, food, and environmental sources. The prevalence of ciprofloxacin-resistant clinical human isolates among different countries included in these studies is shown in Figure 4. In the studied countries, Spain had the lowest prevalence of ciprofloxacin resistance (0.4%) and Iran the highest (52%) with the DDM. The US had the lowest

Table 3. Prevalence of antibiotic resistance in human, animal, food/environment *E. coli* isolates with MIC method

	HUMAN ISOLATES				ANIMAL ISOLATES				FOOD/ENVIRONMENT ISOLATES			
Antibiotic	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%) p**	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%) p**	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%) p**
CL	7.8 (6-10.4)	44/616	3	0.16	0.1 (0-2)	0/400	1	1	-	-	-	-
CIP	7.7 (3.7-15.4)	1288/9899	18	0	7.5 (3.7-14.4)	956/7400	15	0	5.7 (1-26.8)	64/550	4	0
TMP	22.2 (10-42)	216/749	8	0	31 (18-48)	437/1481	6	0	23.7 (16-33)	22/93	1	1
SMZ	22.5 (10.5-42.5)	496/3962	3	0.001	38.3 (16-67)	980/3560	3	0	-	-	-	-
CF	13.3 (1.3-63)	144/501	2	0.01	12.5 (4-33)	120/628	3	0	6.5 (4-10.4)	15/232	1	1
AK	0.8 (0-13.6)	95/7660	5	0	7.8 (4-14.5)	513/5977	5	0	2.6 (1-6)	5/225	2	0.5
AUG	4.5 (2-10)	4497/7967	6	0	2.5 (2.1-3)	99 / 4074	5	0.8	12.8 (6-25.6)	6 / 47	1	1
AMX	53.4 (22-82.3)	74 / 164	2	0	30 (6-73)	326 / 676	3	0	11.5 (1-61)	37 / 325	2	0
CFX	3 (1.6-6)	230/8365	8	0	2.5 (0.5-10)	449 / 6011	7	0	6.5 (2-8)	3 / 47	1	1
CTX	0.5 (0.3-0.8)	16/3585	3	0.8	0.5 (0.1-1.7)	2 / 521	2	0.64	1 (0.1-14.6)	0 / 47	1	1
CHL	6.6 (3-13.5)	745/8564	12	0	8 (2.523)	1042 / 6497	11	0	13.5 (1.6-60)	98 / 457	3	0
CRO	9 (3-24)	633 / 5593	6	0	12.5 (6-24.5)	1238 / 6790	7	0	1.7 (0.5-5)	3 / 178	1	1
IMP	0.1 (0-0.3)	3/3510	2	0.6	0.3 (0-4.3)	0 / 177	1	1	1 (0.1-14.5)	0 / 47	1	1
SXT	11.5 (4.5-26.2)	1594/8468	6	0	8 (1.6-30)	262 / 4455	5	0	34 (22-48.5)	16 / 47	1	1
TET	37.3 (27-48)	1401/5610	15	0	60 (50-72.5)	6289 / 8596	16	0	41 (0.4-92)	189 / 457	3	0
GM	5 (2-12.2)	401 / 8594	12	0	9.5 (3.6-23)	1400 / 7597	11	0	10.5 (20-40.5	69 / 457	3	0

(*Continued*)

Table 3. (Continued).

	HUMAN ISOLATES				ANIMAL ISOLATES				FOOD/ENVIRONMENT ISOLATES			
Antibiotic	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%) p**	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%) p**	**% PP (CI 95%)**	**n/N**	**N of study**	**I^2 (%) p**
KAN	6.2 (2-17.5)	193/5275	10	0	15 (7.3-29)	1323 / 6477	10	0	17 (4-50)	88 / 457	3	0
NA	6.6 (4-10.6)	252 / 4841	7	0	7 (12.5-18)	657 / 5736	8	0	53 (39-67)	25 / 47	1	1
AMP	33.4 (18.5-52.5)	3128/8564	12	0	31 (17-49.5)	2167 / 6497	11	0	29.5 (5-76.3)	145 / 457	3	0
CAZ	1.3 (0.2-7.5)	33/4032	7	0	0.8 (0.4-1.6)	6 / 1172	4	0	1 (0.1-14.6)	0 / 47	1	1
STR	27.7 (14-47.3)	718/5060	11		36 (24-51.5)	1727 / 5527	10		4 (2-75)	9 / 232	1	
MDR	12.6 (4.6-30)	253/4170	3	0	22.2 (21-23.4)	1128/5351	5	0	-	-	-	-
ESBL	42.4 (30.5-55.4)	25/59	1	1	63.2 (60.8-65.6)	1073/1748	2	0	28.6 (15-47.7)	8/28	2	0.77

Abbreviations: MDR, Multidrug Resistant; ESBL, Extended Spectrum β-lactamase; PP, Pooled prevalence; n or N, Number; CL, Colistin; CIP, Ciprofloxacin; TMP, trimethoprim; SMZ, Sulfisoxazole; CF, Cephalothin; AK, Amikacin; AUG, Amoxicillin-clavulanic acid; AMX, amoxicillin; CFX, Cefoxitin; CTX, Cefotaxime; CHL, Chloramphenicol; CRO, Ceftriaxone; IMP, Imipenem; SXT, Trimethoprim-sulfamethoxazole; TET, Tetracycline, GM, Gentamicin; KAN, kanamycin; NA, Nalidixic acid; AMP, Ampicillin; CAZ, Ceftazidime; STR, Streptomycin.

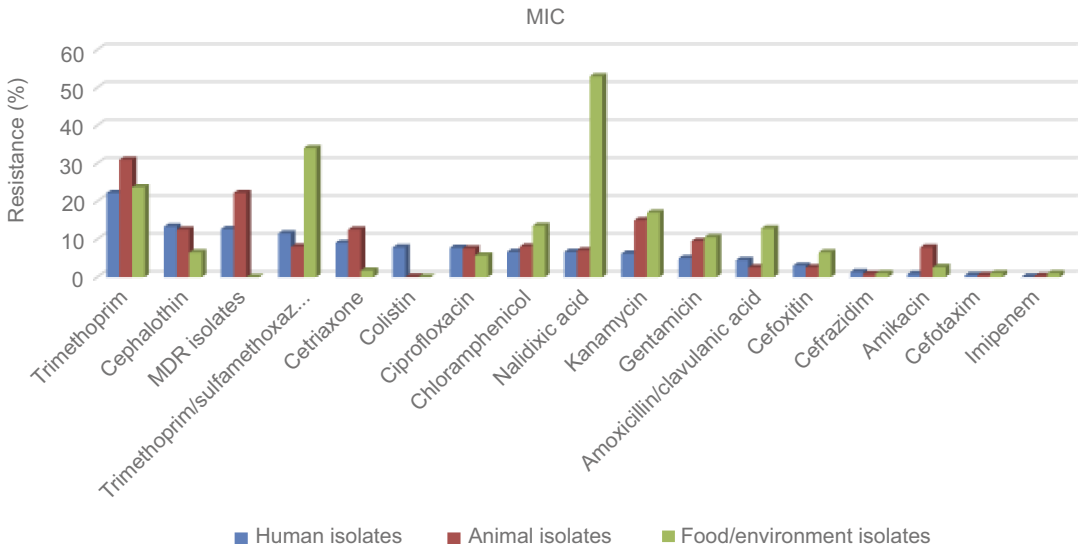


Figure 3 Prevalence of antibiotic resistance in human, animal, food/environment *E. coli* isolates with MIC method.
Abbreviation: MIC, minimum inhibitory concentration.

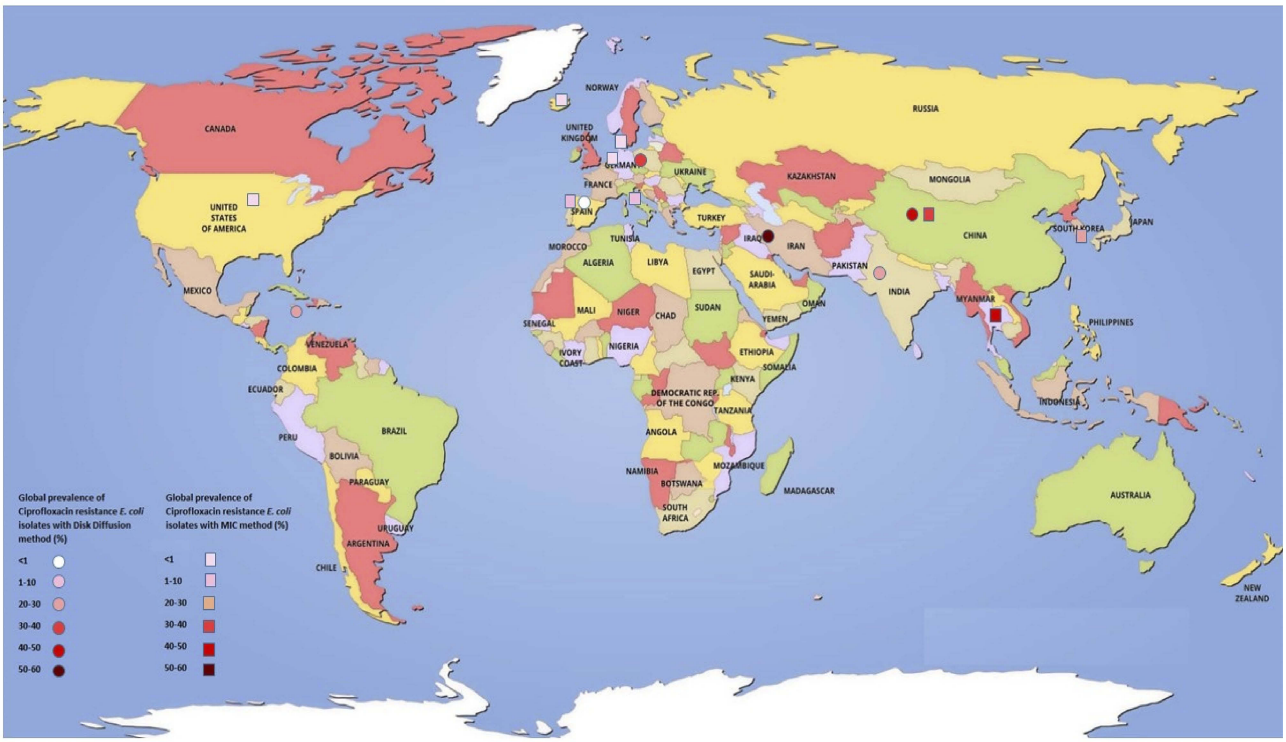


Figure 4 The global prevalence of ciprofloxacin-resistant clinical (human) isolates with DDM and MIC method.
Abbreviations: MIC, minimum inhibitory concentration; DDM, disc diffusion method.

prevalence of ciprofloxacin resistance (0.01%) and Thailand the highest (43%) on MIC. The prevalence of ciprofloxacin-resistant clinical (human) isolates in WHO regional offices with MIC is shown in Figure 5. Our analyses indicated that among WHO regional offices, America and Southeast Asia (0.008% and 43%, respectively) had the lowest and highest prevalence rates of ciprofloxacin resistance in human isolates using MIC . Overall, results showed that antibiotic resistance in American and European countries is lower than other regions of the world. Subgroup analysis from 2000 to 2018 also indicated a significant increase in ciprofloxacin resistance (Figures 6 and S88).

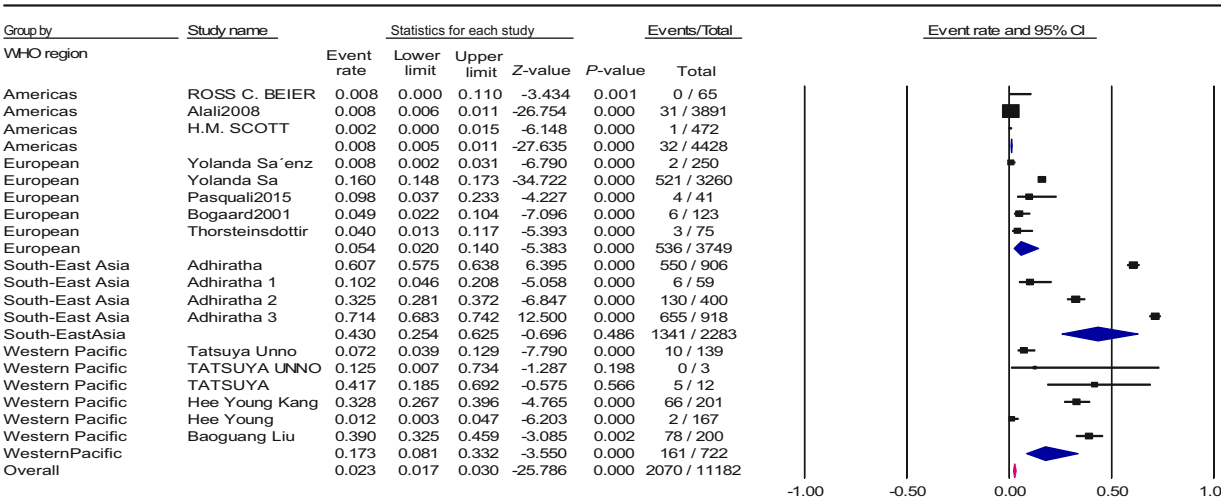
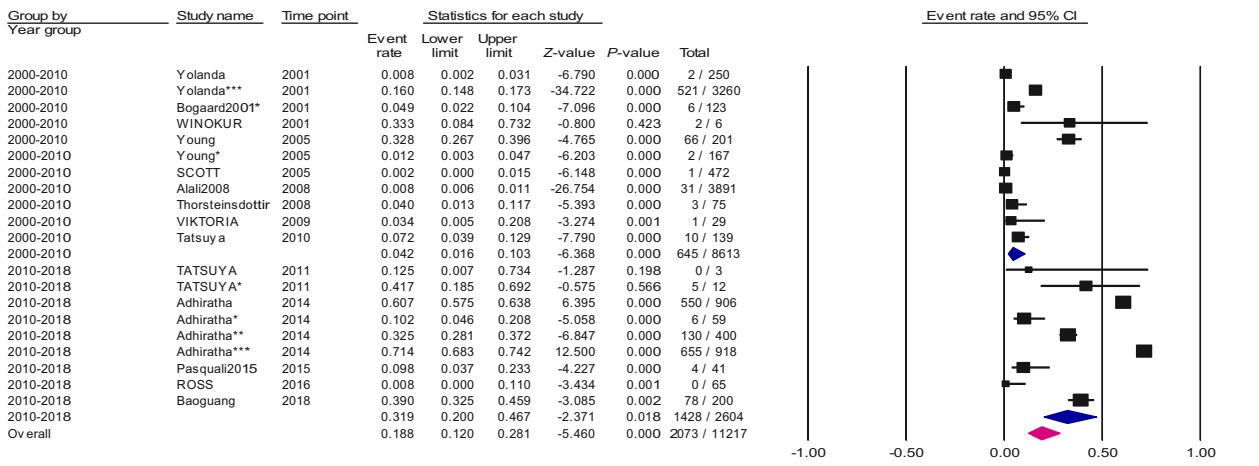


Figure 5 The prevalence of ciprofloxacin-resistant clinical (human) isolates in WHO regional offices with MIC method.

Discussion

The prevalence of antibiotic resistance in *E. coli* strains simultaneously isolated from human, animal, food, and environment samples from 2000 to 2018 were assessed in this meta-analysis . To our knowledge, the present study is the first comprehensive systematic review on the prevalence of antimicrobial resistance in *E. coli* from different sources. We hope presenting these data helps to prevent the spread of antimicrobial resistance by giving an appropriate vision of *E. coli* drug-resistance patterns in different regions of the word. Based on the meta-analysis results in this study, overall MDR prevalence in human, environmental, and animal *E. coli* isolates was 22%, 31.3%, and 5.7%, respectively, using the DDM. MIC resultsshowed that rates of MDR *E. coli* isolates in humans and animals were 12.6% and 22.2%, respectively. Comparison of MDR *E. coli* strains isolated from different sources showed higher prevalence in animal and environmental sources than humans. The prevalence of ESBL-producing *E. coli* based on MIC in human, animal, and environmental/food isolates was 42.4%, 63.2%, and 28.6%, respectively. The prevalence of ESBL-producing *E. coli* based on the DDM in human, animal, and environmental/food isolates was 13%, 26.3%, and 25%, respectively. The prevalence of ESBL antibiotic resistance in animal isolates was higher than in human isolates. Furthermore, there was high pooled prevalence of ESBL-producing *E. coli* using MIC, but this was low using the DDM. The uncontrolled use of antibiotics in domestic animals, as well as dietary supplements, could be one of the main reasons for high antimicrobial resistance in animal isolates in some countries.[19] In several countries, such as the Netherlands, nearly 300,000 kg of antibiotics are used every year in the treatment of animals, and this can be considered a possible reason for the emergence of extensive antimicrobial resistance.[20] In addition, colonization of healthy adult workers with ESBL-producing *E. coli* may be related to consumption of food and water contaminated with ESBL-producing bacteria.[5] However, Boonyasiri et al reported that ESBL-producing *E. coli* was found in the food from a market near a factory where stool samples were collected from workers.[5] Leading antibiotic-resistance



Groups		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity			
Group	Number Studies	Point estimate	Lower limit	Upper limit	*Z*-value	*P*-value	*Q*-value	*df* (Q)	*P*-value	*I*-squared
Mixed effects analysis										
2000-2010	11	0.042	0.016	0.103	-6.368	0.000	414.564	10	0.000	
2000-2018	9	0.319	0.200	0.467	-2.371	0.018	266.782	8	0.000	97.001
Total between							681.346	18	0.000	
Overall	20	0.188	0.120	0.281	-5.460	0.000	1216.600	1	0.000	
							1897.946	19	0.000	98.999

Figure 6 Subgroup analyses of ciprofloxacin-resistant clinical (human) isolates with the MIC method from 2000–2018.
Abbreviation: MIC, minimum inhibitory concentration.

issues may include indiscriminate use of antibiotics, poor hygiene and other preventive measures in veterinary medicine, insufficient staff training, deficiencies in health centers and infection-control programs in hospitals, and lack of proper management steps in animal farms, which may lead to a high prevalence of ESBL-producing *E. coli* isolates in animal (63%) and human samples (42%).

The prevalence of ciprofloxacin-resistant *E. co*li strains isolated from human with both the DDM and MIC was higher than counterparts isolated from animals, food, or the environment. There was very low pooled prevalence of cefotaxime and ceftazidime resistance in all sample types when tested using MIC (0.5%–1% and 0.8%–1.3%, respectively), but cefotaxime and ceftazidime resistance were much higher with the DDM (31.2%–58% and 10%–57.4%, respectively). Moreover, the prevalence of amoxicillin resistance in animal samples with the DDM was very high (96%), but amoxicillin resistance was lower with MIC (30%).

The main limitation for the current review is the lack of comprehensive studies in different regions of the world. The limited number of studies reporting drug resistance from different sources was another restriction. Split meta-regression, subgroup, and sensitivity analyses to detect the sources of heterogeneity, publication bias, and heterogeneity must be considered when interpreting the outcomes reported here.

For future direction and supporting the practice of evidence-based medicine, more notifications on *E. coli*-resistance status isolated from different sources (human, animal, and environment or food specimens) are needed. Such studies could enhance our knowledge of antibiotic-resistance status for *E. coli* and help us to provide prevention protocols to reduce the occurrence of resistant strains.

Conclusion

Analyses showed prevalence of drug resistance in different sources and documented increase in *E. coli* drug resistance. Our data demonstrated the evolution of antibiotic resistance and helped to describe drug-resistance prevalence in modern *E. coli* strains. Moreover, the results showed that the prevalence of ESBL antibiotic resistance and MDR *E. coli* strains in animal isolates was higher than in human isolates. According to our findings, systematic surveillance of hospital-associated infections, proper monitoring of disposal processes in hospitals, monitoring the use of antibiotics in animals, monitoring and evaluation of antibiotic-sensitivity patterns, and preparation of reliable antibiotic strategies may

ease more corrective actions for the inhibition and control of *E. coli* infections in different parts of the world.

Author contributions

TA conceived and designed the study, AP and TA performed the study, MJN analyzed the data, and AP, MJN and TA wrote the paper and participated in data analysis and manuscript editing..

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Characterization of included studies

First author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	End Point of 8
Adhiratha	1	1	0	1	1	0	1	5
Alali2008	1	1	1	2	1	1	1	8
AlexandraMoura	1	1	1	2	1	0	1	7
Ali Kazemnia	0	1	0	1	1	1	1	5
Azucena Mora	1	1	1	1	0	1	1	6
Baoguang	1	1	1	1	1	0	1	6
Bhoomika	0	1	1	0	1	0	1	4
Bogaard2001	1	1	1	1	1	0	1	6
Hanna E. Sidjabat	0	1	1	1	1	0	1	5
Iuliana E. Maciuca	0	1	1	1	1	1	1	6
James	1	1	1	2	1	1	1	8
Jing Wang	1	1	1	1	0	1	1	6
Joanne L. Platell	0	1	1	0	0	0	1	3
Jorge Hernandez	0	1	0	1	1	1	1	5
Karen Alroy	0	0	1	0	1	0	1	3
Katherine A. Stenske	1	1	1	2	1	1	1	8
Krushna Chandra	1	1	1	1	1	0	1	6
L. Wang	1	1	1	1	0	1	1	6
Manju Raj Purohit	1	1	1	1	1	1	1	7
Mark R. Sannes	1	1	1	2	1	1	1	8
Miles2006-1	1	1	1	1	0	1	1	6
Miles2006-2	1	1	1	1	0	1	1	6
Montserrat Sabate	1	1	1	1	1	0	1	6
Pankaj Dhaka	1	1	1	1	0	1	1	6
Adhiratha	1	1	0	1	1	0	1	5
Adhiratha Boonyasiri	1	1	0	1	1	0	1	5
TATSUYA	1	1	1	1	0	0	1	5
Pasquali2015	1	1	1	1	0	0	1	5
ROSS	0	1	1	1	0	1	1	5
Ryszard Koczura	1	1	1	2	1	1	1	8
Sayah2005	1	1	0	1	1	0	1	5
SCOTT	1	1	1	2	0	1	1	7
Thomas	1	0	0	1	0	0	1	3
Thorsteinsdottir	0	1	1	1	0	1	1	5
VIKTORIA	0	1	1	1	0	0	1	4
WINOKUR	0	1	1	1	1	0	1	5
Yolanda	0	1	1	0	1	0	1	4
Young	0	1	1	1	1	1	1	6

Abbreviations: ADM, agar dilution method; DDM, disk diffusion method; BMD, broth microdilution.