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...
the monobactam aztreonam. Infections with ESBL-producing organisms have been associated with poor outcomes.\textsuperscript{6} An important example of antibiotic resistance is multidrug-resistant (MDR) and ESBL-producing Escherichia coli, which can cause life-threatening infections.\textsuperscript{7} E. coli is the predominant facultative flora in the gastrointestinal tract of humans and animals.\textsuperscript{8} Some E. coli strains, however, have developed the ability to cause disease in the gastrointestinal, urinary, and central nervous systems.\textsuperscript{9,10} Prolonged exposure of E. coli to antibiotics contributes to the development of antibiotic resistance.\textsuperscript{11,12} Thus, antibiotic-resistant bacteria, including E. coli, in animals could serve as important reservoirs for colonization and infection in human beings.\textsuperscript{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).\textsuperscript{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.

\section*{Methods}

\subsection*{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.\textsuperscript{13–15} In addition, we searched related reviews and references for relevant studies. We conducted our study according to PRISMA guidelines.\textsuperscript{16}

\subsection*{Eligibility}

\subsection*{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), and E. 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.

\subsection*{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).

\subsection*{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 limited 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.
Quality assessment
Quality assessment of the studies were performed by two reviewers independently, according to the modified critical appraisal checklist recommended by the Joanna Briggs Institute. Disagreements were resolved by a consensus-based discussion. The checklist is composed of seven questions (question 4 has two scores) that reviewers answer for 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. 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      | 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          | 2004–2006     | 2008      | USA              | Food/environment, animals              | ADM    | CLSI                 | Human wastewater, swine fecal                                          |
| Alexandra et al      | 2011          | 2014      | Portugal         | Food/environment, humans               | ADM    | CLSI                 | Fecal, beach and waste waters                                         |
| Kazemnia et al       | 2012          | 2014      | Iran             | Humans, animals                        | DDM    | CLSI                 | Urine samples, poultry carcasses                                      |
| Azucena et al        | 1992–1999     | 2005      | Spain            | Humans, animals, food/environment      | DDM    | NOT                  | Feces sample, food, beef meat                                         |
| Baoguang et al       | 2012–2014     | 2018      | China            | Humans, animals                        | BMD    | CLSI                 | Blood, rectal swab                                                    |
| Bhoomika et al       | 2014–2015     | 2016      | India            | Humans, animals, food/environment      | DDM    | CLSI                 | Urine and stool-Chicken meat, Chevon meat, Raw milk                   |
| Bogaard et al        | NS            | 2001      | Netherlands      | Humans, animals, food/environment      | ADM    | NOT                  | Feces sample, sample from slaughterers                                 |
| Hanna et al          | 2000–2001     | 2006      | Australia        | Humans, animals, food/environment      | DDM    | CLSI                 | Rectal swabs-environmental swabs                                      |
| Iuliana et al        | 2011–2012     | 2015      | United Kingdom   | Humans, animals                        | DDM    | CLSI                 | Fecal samples                                                         |
| James et al          | 2002–2004     | 2007      | USA              | Humans, animals                        | ADM    | CLSI                 | Fecal sample-meat of chicken                                          |
| James et al          | 1998–2001     | 2003      | USA              | Humans, animals                        | ADM    | CLSI                 | Intestinal and Extra intestinal sample                                |
| Wang et al           | 2011–2013     | 2017      | China            | Humans, animals, food/environment      | DDM    | CLSI                 | Urine and fecal-food sample                                           |
| Joanne et al         | 2007–2009     | 2010      | Australia        | Humans, animals                        | DDM    | CLSI                 | Urine- animal specimen                                                |
| Jorge et al          | 2009–2010     | 2013      | Sweden           | Humans, animals                        | DDM    | CLSI                 | Fecal samples                                                         |
| Karen et al          | NS            | 2011      | USA              | Animals, food/ environment              | DDM    | CLSI                 | Feces sample, wastewater                                               |
| Katherine et al      | 2007–2008     | 2009      | USA              | Humans, animals                        | DDM    | CLSI                 | Fecal swab specimen                                                   |
| Krushna et al        | 2010–2011     | 2012      | Sweden           | Humans, animals, food/environment      | DDM    | CLSI                 | Stool samples, cow-dung, drinking water                               |
| Wang et al           | 1997–2009     | 2017      | China            | Humans, animals, food/environment      | DDM    | NOT                  | Fecal/diarrhea -castle and swine feces-food sample                     |
| Purohit et al        | 2015          | 2017      | India            | Humans, animals, food/environment      | DDM    | NOT                  | Stool- waste, drinking water                                          |
| Sannes et al         | 1998–1999     | 2004      | USA              | Humans, animals                        | DDM    | CLSI                 | Urine-feces                                                           |
| Miles et al          | 2000–2001     | 2006      | Jamaica          | Humans, animals                        | DDM    | CLSI                 | Urine and wound specimens of hospitalized patients-fecal samples of broiler chickens |
| Sabate et al         | 2005          | 2008      | Spain            | Humans, animals, food/environment      | DDM    | CLSI                 | Human and animal wastewater                                           |

(Continued)
| Study            | Time enrolled | Published | Country     | Isolate source                          | Method | Interpret Guidelines | Sample                                                                 |
|------------------|---------------|-----------|-------------|-----------------------------------------|--------|----------------------|-------------------------------------------------------------------------|
| Dhaka et al      | 2014–2016     | 2016      | India       | Humans, animals, food/environment       | DDM    | NOT                  | Stool - diarrhea - food and environmental samples                       |
| Pasquali et al   | NS            | 2015      | Italy       | Humans, animals                         | ADM    | CLSI                 | Urine, semen and wound swabs-raw sewage, aeration tank with activated sludge, and final effluent without disinfection |
| Ross et al       | 2014–2016     | 2016      | USA         | Humans, animals                         | ADM    | CLSI                 | Urine, cervix, vagina and prostate, and blood, pus and wounds-feces sample |
| Koczura et al    | 2008–2009     | 2012      | Poland      | Humans, food/environment                | DDM    | CLSI                 | Urine, cervix, vagina and prostate, and blood, pus and wounds-feces sample |
| Sayah et al      | 2002–2003     | 2005      | USA         | Humans, animals, food/environment       | DDM    | CLSI                 | Human septage - Animal fecal- Surface water, Farm environment           |
| Scott et al      | 2003–2004     | 2005      | USA         | Humans, animals                         | BMD    | CLSI                 | Human fecal sample-swine fecal sample                                   |
| Seputiene et al  | 2005–2008     | 2010      | Lithuania   | Humans, animals                         | DDM    | CLSI                 | Urine, cervix, vagina and prostate, and blood, pus and wounds-feces sample |
| Tao et al        | 2007–2008     | 2010      | China       | Food/environment, animals               | ADM    | CLSI                 | Meat- feces or liver samples                                            |
| Tatsuya et al    | 2006–2008     | 2010      | South Korea | Humans, animals                         | ADM    | CLSI                 | Stool samples                                                           |
| Tatsuya et al    | 2008          | 2011      | South Korea | Humans, animals                         | ADM    | CLSI                 | Stool- Feces                                                            |
| Thomas et al     | 2002          | 2005      | Canada      | Food/environment, animals               | ADM    | NOT                  | Birds fecal sample-surface and waste waters                              |
| Thorstein et al  | 2006–2007     | 2008      | Iceland     | Humans, animals                         | BMD    | CLSI                 | Fecal samples-Caeca and food sample                                     |
| Viktoria et al   | 2008          | 2009      | Denmark     | Humans, animals                         | ADM    | CLSI                 | Urine specimens-kidneys with chronic and / or acute lesions             |
| Winokur et al    | 1998–1999     | 2001      | USA         | Humans, animals                         | BMD    | CLSI                 | Urine, blood- intestinal biopsy samples, feces                           |
| Yolanda et al    | 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      | 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

| Antibiotic | HUMAN ISOLATES | | | ANIMAL ISOLATES | | | FOOD/ENVIRONMENT ISOLATES | |
|------------|----------------|---|---|----------------|---|---|----------------|---|
|            | % PP (CI 95%)  | n/N | I² (%P) | % PP (CI 95%)  | n/N | I² (%P) | % PP (CI 95%)  | n/N | I² (%P) |
|            |                |     |         |               |     |         |                |     |         |
| CL         | 0.8            | 1/217 | 2 | 0.54 | 10 | 31/193 | 2 | 0.12 | 3.2 | 10/204 | 2 | 0.005 |
|            | (0.2-3.8)      |     |     |     | (1-45) |     |     | (0.1-63.3) |     |     |
| CIP        | 28.3           | 161/607 | 11 | < 0.001 | 183 | 169/1039 | 8 | < 0.001 | 14.4 | 152/555 | 7 | < 0.001 |
|            | (17.2-42.7)    |     |     |     | (5.7-50) |     |     | (5.4-33.4) |     |     |
| TMP        | 16             | 123/697 | 3 | 0.001 | 9.2 | 92/784 | 3 | < 0.001 | 24 | 14/58 | 1 | 1 |
|            | (10-25)        |     |     |     | (2.3-30) |     |     | (15-36.7) |     |     |
| SMZ        | 28.5           | 133/469 | 3 | 0.35 | 22.2 | 338/1596 | 3 | < 0.001 | 21.3 | 49/314 | 2 | < 0.001 |
|            | (25.5-33)      |     |     |     | (9.8-43) |     |     | (4.6-6) |     |     |
| CF         | 33.5           | 552/1078 | 7 | < 0.001 | 17.5 | 401/1937 | 5 | < 0.001 | 33.6 | 256/543 | 4 | < 0.001 |
|            | (16-57)        |     |     |     | (5.8-42.2) |     |     | (13-63) |     |     |
| AK         | 2              | 10/355 | 3 | < 0.004 | 1.8 | 8/707 | 3 | 0.03 | 4 | 10/262 | 3 | 0.05 |
|            | (0.2-16.5)     |     |     |     | (0.3-10) |     |     | (1.2-13.4) |     |     |
| AUG        | 2              | 10/597 | 6 | 0 | 1.5 | 8/637 | 3 | 0.2 | 4.8 | 3 | 2 | 0.73 |
|            | (1-1.3-7)      |     |     |     | (0.8-3) |     |     | (1-1.7) |     |     |
| AMX        | 70.5           | 41/58 | 2 | 0 | 96 | 24/25 | 1 | 1 | 58.4 | 125/214 | 1 | 1 |
|            | (57.5-81)      |     |     |     | (76-99) |     |     | (51.7-65) |     |     |
| CFX        | 5.5            | 98/1141 | 6 | < 0.001 | 6.2 | 97/852 | 5 | < 0.001 | 3.4 | 2/73 | 2 | 0.94 |
|            | (1.6-16.7)     |     |     |     | (5-47.2) |     |     | (1-11) |     |     |
| CTX        | 28             | 171/294 | 4 | 0.2 | 58 | 140/308 | 4 | < 0.001 | 31.15 | 97/433 | 4 | < 0.001 |
|            | (52.3-63.6)    |     |     |     | (16.5-90.5) |     |     | (16-3-52) |     |     |
| CHL        | 12.5           | 38/305 | 7 | 0.002 | 3 | 40/1629 | 3 | < 0.001 | 10 | 93/592 | 5 | < 0.001 |
|            | (6-25)         |     |     |     | (1-8.5) |     |     | (3-27.8) |     |     |
| CRO        | 3.3            | 2/187 | 3 | 0.2 | 0.2 | 0/592 | 2 | 0.34 | 1.6 | 0/73 | 2 | 0.54 |
|            | (1-10)         |     |     |     | (0-1.7) |     |     | (0-10.7) |     |     |
| IMP        | 2.7            | 7/634 | 6 | 0.15 | 0.9 | 1/833 | 5 | 0.17 | 2.7 | 10/431 | 4 | 0.57 |
|            | (1-4.5)        |     |     |     | (0.3-2.8) |     |     | (1.5-4.7) |     |     |
| SXT        | 27.6           | 580/1336 | 9 | < 0.001 | 30 | 410/2170 | 9 | < 0.001 | 25.8 | 109/597 | 7 | < 0.001 |
|            | (11-54.3)      |     |     |     | (7.7-69) |     |     | (8-57.7) |     |     |
| TET        | 54.6           | 71/1192 | 13 | < 0.001 | 53 | 861/2201 | 10 | < 0.001 | 47 | 338/811 | 8 | < 0.001 |
|            | (37.3-71)      |     |     |     | (36-69.5) |     |     | (25-70) |     |     |
| GM         | 21.5           | 329/1173 | 12 | < 0.001 | 13.6 | 149/947 | 6 | < 0.001 | 9 | 105/796 | 7 | < 0.001 |
|            | (12.5-34.5)    |     |     |     | (5.6-29.4) |     |     | (3.2-23.3) |     |     |
Table 2. (Continued).

| Antibiotic | HUMAN ISOLATES | ANIMAL ISOLATES | FOOD/ENVIRONMENT ISOLATES |
|------------|----------------|----------------|--------------------------|
|            | % PP (CI 95%)  | n/N            | N of study               | % PP (CI 95%)  | n/N            | N of study               | % PP (CI 95%)  | n/N            | N of study               | I² (%) P      | I² (%) P      | I² (%) P      |
| KAN        | 51 (15.2-85.7) | 85/253         | 4                        | 6.2 (4.4-8.7)  | 32/514         | 1                        | 30.4 (1.4-93)  | 155/272        | 2                        | < 0.001       |
| NA         | 32 (1.2-61)    | 161/468        | 9                        | 21.4 (2-80)    | 132/1765       | 6                        | 8.5 (2.8-22.7) | 31/473         | 2                        | 0.004         |
| AMP        | 49.7 (35.3-64) | 556/1211       | 14                       | 44.4 (19-73)   | 443/2190       | 10                       | 40.2 (16.5-69.5)| 322/811        | 8                        | < 0.001       |
| CAZ        | 49.2 (32-66.7) | 106/204        | 3                        | 57.4 (23-97)   | 85/111         | 2                        | 10 (3.8-24.4)  | 36/358         | 2                        | 0.003         |
| STR        | 39.7 (30.3-50) | 172/458        | 4                        | 30.5 (15-52.4) | 44/1938        | 5                        | 28.4 (10.7-56.8)| 74/363         | 3                        | < 0.001       |
| MDR        | 22 (5.2-58.6)  | 475/1310       | 4                        | 5.7 (3.3-9.6)  | 13/249         | 3                        | 31.3 (24-33.3) | 45/144         | 1                        | 1            |
| ESBL       | 13 (2-52.7)    | 77/211         | 4                        | 26.3 (6-66.5)  | 73/287         | 3                        | 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; CI, Confidence Interval; LI, Likelihood index; KAN, Kanamycin; NA, Nalidixic acid; AMP, Ampicillin; CAZ, Ceftazidime; STR, Streptomycin.
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 the environment, 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

| Antibiotic | HUMAN ISOLATES | | | ANIMAL ISOLATES | | | | FOOD/ENVIRONMENT ISOLATES | | |
|------------|----------------|--|--|--|--|--|--|--|--|--|--|--|
|            | % PP (CI 95%)  | n/N | N | I² (%) | p | % PP (CI 95%)  | n/N | N | I² (%) | p | % PP (CI 95%)  | n/N | N | I² (%) | 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 | 1.2 (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 (1-61) | 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 |
| SX T       | 1.15 (4.5-26.2) | 1594/8468 | 6 | 0 | 8 (1.6-30) | 262 / 4455 | 5 | 0 | 3.4 (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).

| Antibiotic | HUMAN ISOLATES | ANIMAL ISOLATES | FOOD/ENVIRONMENT ISOLATES |
|------------|----------------|-----------------|---------------------------|
|            | % PP (CI 95%) | n/N | N of study | I² (%) | % PP (CI 95%) | n/N | N of study | I² (%) | % PP (CI 95%) | n/N | N of study | I² (%) |
| KAN        | 6.2 (2.1-17.5) | 193/5275 | 10 | 0 | 15 (7.3-29) | 1323 / 6477 | 10 | 0 | 17 (4.5-50) | 88 / 457 | 3 | 0 |
| NA         | 6.6 (4.1-18.6) | 252 / 4841 | 7 | 0 | 7 (12.5-18) | 657 / 5736 | 8 | 0 | 53 (39.6-67) | 25 / 47 | 1 | 1 |
| AMP        | 33.4 (18.5-52.5) | 3128/8564 | 12 | 0 | 31 (17.4-49.5) | 2167 / 6497 | 11 | 0 | 29.5 (5.7-63.3) | 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 (14.4-47.3) | 718/5060 | 11 | 0 | 36 (24.5-51.5) | 1727 / 5527 | 10 | 0 | 4 (2.7-5) | 9 / 232 | 1 | 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 (15.4-47.7) | 8/28 | 2 | 0.77 |

Abbreviations: MDR, Multidrug Resistant; ESBL, Extended Spectrum β-lactamase; PP, Pooled prevalence; CL, Colistin; CIP, Ciprofloxacin; TMP, trimethoprim; SMZ, Sulfoxazole; CF, Cephalothin; AK, Amikacin; AUG, Amoxicillin-clavulanic acid; AMX, amoxicillin; CFX, Cefotaxin; 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.
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 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.
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 world. 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 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. 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. 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. 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.

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 world. 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 the DDM in human, animal, and environmental/food isolates was 13%, 26.3%, and 25%, 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-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-producing *E. coli* based on the DDM in human, animal, and environmental/food isolates was 13%, 26.3%, and 25%, respectively.
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. coli* 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 ceftaxime and ceftazidime resistance in all sample types when tested using MIC (0.5%–1% and 0.8%–1.3%, respectively), but ceftaxime 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 in human samples with both the DDM and MIC was 0.5%.

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 help to describe drug-resistance prevalence in modern *E. coli* strains.
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              |
| Alaii2008    | 1  | 1  | 2  | 1  | 1  | 1  | 8  |                |
| Alexandre2012| 1  | 1  | 2  | 1  | 0  | 1  | 7  |                |
| Ali Kazennia | 0  | 1  | 0  | 1  | 1  | 1  | 5  |                |
| Azucena Mora | 1  | 1  | 1  | 1  | 0  | 1  | 6  |                |
| Baoguang     | 1  | 1  | 1  | 1  | 0  | 1  | 6  |                |
| Bhoomika     | 0  | 1  | 1  | 0  | 1  | 0  | 4  |                |
| Bogaard2001  | 1  | 1  | 1  | 1  | 0  | 1  | 6  |                |
| Hanna E. Sidjabat | 0  | 1  | 1  | 1  | 0  | 1  | 5  |                |
| Julianna E. Maciuca | 0  | 1  | 1  | 1  | 1  | 1  | 6  |                |
| James        | 1  | 1  | 1  | 2  | 1  | 1  | 8  |                |
| Jing Wang    | 1  | 1  | 1  | 0  | 1  | 1  | 6  |                |
| Joanne L. Platell | 0  | 1  | 1  | 0  | 0  | 0  | 3  |                |
| Jorge Hernandez | 0  | 1  | 0  | 1  | 1  | 1  | 5  |                |
| Karen Alroy  | 0  | 0  | 1  | 0  | 1  | 0  | 3  |                |
| Katherine A. Stenske | 1  | 1  | 1  | 2  | 1  | 1  | 8  |                |
| Krushna Chandra | 1  | 1  | 1  | 1  | 1  | 0  | 6  |                |
| L. Wang      | 1  | 1  | 1  | 1  | 0  | 1  | 6  |                |
| Manju Raj Purohit | 1  | 1  | 1  | 1  | 1  | 1  | 7  |                |
| Mark R. Sannes | 1  | 1  | 1  | 2  | 1  | 1  | 8  |                |
| Miles2006-1  | 1  | 1  | 1  | 1  | 0  | 1  | 6  |                |
| Miles2006-2  | 1  | 1  | 1  | 1  | 0  | 1  | 6  |                |
| Montserrat Sabate | 1  | 1  | 1  | 1  | 1  | 0  | 6  |                |
| Pankaj Dhaka | 1  | 1  | 1  | 0  | 1  | 1  | 6  |                |
| Adhiratha    | 1  | 1  | 0  | 1  | 1  | 0  | 5  |                |
| Adhiratha Boonyasiri | 1  | 1  | 1  | 0  | 1  | 0  | 5  |                |
| TATSUYA      | 1  | 1  | 1  | 1  | 0  | 0  | 5  |                |
| Pasquali2015 | 1  | 1  | 1  | 1  | 0  | 0  | 5  |                |
| ROSS         | 0  | 1  | 1  | 1  | 0  | 1  | 5  |                |
| Ryszard Koczura | 1  | 1  | 1  | 2  | 1  | 1  | 8  |                |
| Sayah2005    | 1  | 1  | 0  | 1  | 1  | 0  | 5  |                |
| SCOTT        | 1  | 1  | 2  | 0  | 1  | 1  | 7  |                |
| Thomas       | 1  | 0  | 0  | 1  | 0  | 0  | 3  |                |
| Thorsteinsdottir | 0  | 1  | 1  | 0  | 1  | 1  | 5  |                |
| VIKTORIA     | 0  | 1  | 1  | 1  | 0  | 0  | 4  |                |
| WINOKUR      | 0  | 1  | 1  | 1  | 0  | 1  | 5  |                |
| Yolanda      | 0  | 1  | 1  | 0  | 1  | 0  | 4  |                |
| Young        | 0  | 1  | 1  | 1  | 1  | 1  | 6  |                |

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