Iran J Public Health, Vol. 53, No.3, Mar 2024, pp.508-523

Review Article

Antibiotic Resistance of Uropathogenic *Escherichia coli* (UPEC) among Iranian Pediatrics: A Systematic Review and Meta-Analysis

Aliasghar Fakhri-Demeshghieh, Abolghasem Shokri, *Saied Bokaie

Division of Epidemiology & Zoonoses, Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran

***Corresponding Author:** Email: sbokaie@ut.ac.ir

(Received 09 Apr 2023; accepted 11 Jul 2023)

Abstract

Background: Uropathogenic *Escherichia coli* is a major cause of urinary tract infections (UTIs). This systematic review and meta-analysis was conducted to determine the prevalence of antibiotic-resistant uropathogenic *E. coli* among Iranian children with confirmed bacterial UTIs from 2012 to 2022.

Methods: A systematic review was performed by searching PubMed, Scopus, Google Scholar, Web of Science, MagIran, Iranian Scientific Information Database, IranMedex, and Iranian Research Institute for Information Science and Technology. The antibiotic-specific pooled prevalence estimates were calculated by applying a random-effects model. Freeman-Tukey Double Arcsine transformation was applied. I-squared statistic, and Cochran's Q test were computed and meta-regression was conducted on latitude of sampling location.

Results: The literature search retrieved 2159 articles, among which 19 articles were included. The highest antibiotic resistance was related to doxycycline, ticarcillin-clavulanic acid, cefazolin, cefuroxime, and amoxycillin-clavulanic acid, 59%, 57%, 54%, 53%, and 52%, respectively. Meta-regression on the latitude was statistically significant for nitrofurantoin (P=0.05).

Conclusion: Resistant uropathogenic Escherichia coli strains were observed in the majority of confirmed bacterial UTIs among Iranian children. The most effective antibiotics for uropathogens were colistin, meropenem, and imipenem.

Keywords: Uropathogenic *Escherichia coli*; Antibiotic resistance; Pediatrics; Urinary tract infection

Introduction

Almost 138 years have passed since Theodore Escherich introduced the *Escherichia coli* germ to the world (1, 2). Infectious diseases such as bacterial infections are the main reasons for pediatric mortality (3). In several studies, uropathogenic *E. coli* (UPEC) has been identified as a significant cause of urinary tract infections (UTIs) (4). Moreover, urinary tract infections are one of the main causes of referrals to medical centers and are responsible for 40%-50% of nosocomial infections (5, 6).

Antibiotic resistance (AR) is one of the intensive threats to world public health (7). Resistance to antibiotics is increasing among uropathogenic agents particularly uropathogenic *E. coli* (8). The US Center for Disease Control and Prevention (CDC)

conservatively envisioned that, more than one million cases are affected by antibiotic-resistant infections every year resulting in 23,000 death per annum (9). Early diagnosis and treatment are critical in reducing kidney damage and complications in patients (10). Using predictive statistical models, 4.95 million deaths were related to bacterial resistance in 2019. The highest and lowest death rates of antibiotic resistance are 27.3 and 6.5 per 100,000 and occur in West Sub-Saharan Africa and Australia, respectively (9). Patients suffering from resistant uropathogens had 29% higher overall hospitalization costs ($3429 *vs* $2651; *P*= 0.004) (11).

Antibiotic-resistant *E. coli* is considered a paramount public health issue in Iran and the prevalence of antimicrobial resistance has increased in recent years with limited treatment options that lead to increased healthcare expenses and UTIs-related mortality (12, 13). Therefore, it is necessary to investigate the antimicrobial resistance of uropathogenic *E. coli* in order to increase our current knowledge in this issue.

This systematic review and meta-analysis aimed to determine the prevalence of antibiotic-resistant uropathogenic *E. coli* among Iranian children with bacterial UTIs from 2012 to 2022 and to investigate the statistical relationship between the prevalence of antibiotic resistance with the sampling location of the studies.

Materials and Methods

Search strategy

This systematic review and meta-analysis was conducted in compliance with Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, 2020) (14). The comprehensive search for studies was done by two (A. S and A. FD) of the authors from Nov to Jan 2021-2022.

The databases of PubMed, Scopus, Google Scholar, Web of Science, MagIran, Iranian Scientific Information Database, IranMedex, and Iranian Research Institute for Information Science and Technology (IranDoc) databases were searched by using the following keywords: "Uropathogenic *Escherichia coli*" OR "UPEC" OR "*Escherichia coli* infections" OR "*Escherichia coli*" AND "Antimicrobial resistance" OR "Antibiotic resistance" OR "Drug resistance" OR "multiple Drug Resistance" OR "MDR" AND "Pediatrics" OR "Infant" OR "Child*" AND "Iran". Only English keywords were used. The planned systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO), and the protocol was amended. The usage of RevMan 5.4.1 to create the risk of bias assessment table was added.

The overall antibiotic Escherichia coli resistance was omitted from the outcomes since the reported data in the articles reporting the resistance against different antibiotics were not independent and they were overlapping. Instead, the pooled estimations of resistance prevalence against each antibiotic among confirmed bacterial UTIs were calculated. The PROSPERO registration number of this systematic review and meta-analysis is CRD42022300370 (15).

Title and abstract screening

Only one copy of duplicate results was kept. The abstracts were searched by two independent reviewers based on the relevancy of the articles according to the eligibility criteria. When conflict rose on whether or not to include an article, the final decision was made by a third reviewer (S. B). The inclusion criteria included cross-sectional studies investigating the prevalence of urinary tract antibiotic-resistant *E. coli* among Iranian children during Jan 2012-Jan 2022. The exclusion criteria included articles that did not contain original data, published in languages other than English or Persian or did not have an available full text. The full text of the articles, which were deemed relevant, retrieved.

Full-text screening and data extraction

The relevancy of full-text articles was re-investigated. The reference lists of relevant articles were screened in order to find whether they contained relevant studies that were missed during the search by 2 independent reviewers. The corresponding

authors of the studies, which provided inadequate information in their articles, were contacted via e-mail. The articles, which their corresponding author did not respond or was unable to provide the necessary data for meta-analysis purposes were omitted.

Risk of bias (quality) assessment

The risk of bias in all of the articles considered relevant was assessed by two independent reviewers engaged in the screening by using the Appraisal tool for Cross-Sectional Studies (AXIS) (16). Conflicts on the quality status of an article were resolved by the decision of a third reviewer.

Statistical analysis

The antibiotic-specific pooled prevalence estimates were calculated by applying a random-effects model. Freeman-Tukey Double Arcsine transformation was applied. The forest plot and funnel plot were drawn for each antibiotic. For antibiotics that were assessed in ten or more studies, Meta-regression was carried out to investigate the statistical relationship between the prevalence and the latitude of the sampling location.

All of the statistical analysis was performed by STATA 12.0. The summary of the findings table and the results of the risk of bias assessment table were created by RevMan 5.4.1 software.

Results

Literature search

The literature search retrieved 2159 articles and 140 records were deleted due to duplication. Overall, 1928 abstracts were excluded since they were considered not to meet the eligibility criteria. After retrieving the full texts of the remaining 91 articles, the eligibility of the mentioned articles was re-evaluated. The corresponding authors of 22 articles that provided insufficient data for our meta-analysis objectives were contacted via e-mail to investigate whether they were able to provide adequate data. The data from one of the articles was successfully retrieved by this method. Finally, 19 articles were used for meta-analysis. One of the final articles lacked information about its exact sampling location and the corresponding author was not able to clarify the issue. The data of this article was only used in meta-analysis and was excluded from meta-regression. The summary of the literature search and the flow chart of the study are presented in Fig. 1. The summary of population characteristics is summarised in Table 1.

Table 1: Characteristics of selected papers

Authors (Reference number)	*Year of publication*	*Tested antibiotics*	*Location*	*Age Range*	*Sex*
Afsharpaiman et al (17)	2012	Amikacin, Cefalotin, Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone, Cephalexin, Chloramphenicol,Gentamicin, Imipenem, Nalidixic acid, Nitrofurantoin, Trimethoprim-sulfamethoxazole	Tehran	-	-
Armin et al (18)	2018	Amikacin, Amoxicillin-clavulanic acid, Ampicillin, Ampicillin-sulbactam, Cefazolin, Cefepime, Cefotaxime, Cefuroxime, Ceftazidime, Chloramphenicol, Ciprofloxacin, Doxycycline, Gentamicin, Imipenem, Levofloxacin, Meropenem, Piperacillin, Piperacillin-tazobactam, Tetracycline, Ticarcillin-clavulanic acid, Tobramycin, Trimethoprim-sulfamethoxazole	Tehran	-	-

Table 1: Continued…

Behzadnia et al (19)	2014	Ampicillin, Ceftazidime, Ceftriaxone, Ciprofloxacin, Gentamicin, Imipenem, Nalidixic acid, Norfloxacin, Tetracycline, Trimethoprim-sulfamethoxazole	Mazandaran	1 day to 12 years	31 girls 30 boys
Ghadiri et al (20)	2019	Ampicillin, Aztreonam, Cefotaxime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Gentamicin, Imipenem, Tobramycin, Trimethoprim-sulfamethoxazole	Kermanshah	1 to 18 years	23 girls 55 boys
Goudarzi et al (21)	2013	Amikacin, Cefalotin, Cefepime, Cefixime, Cefotaxime, Ceftazidime, Gentamicin, Imipenem, Nitrofurantoin, Piperacillin-tazobactam, Trimethoprim-sulfamethoxazole	Tehran	Below 1 to 14 years	88 girls 12 boys
Habibian et al (22)	2014	Imipenem	Tehran	-	-
Hedayat Yaghoobi et al (23)	2019	Ampicillin-sulbactam, Cefepime, Ceftazidime, Ceftriaxone, Ciprofloxacin, Colistin, Gentamicin, Imipenem, Meropenem, Piperacillin-tazobactam, Trimethoprim-sulfamethoxazole	Hamadan	-	-
Mamishi et al (24)	2019	Amikacin, Cefepime, Cefotaxime, Gentamicin, Imipenem, Meropenem, Piperacillin-tazobactam, Trimethoprim-sulfamethoxazole	Tehran	-	58 girls 84 boys
Mamishi et al (25)	2020	Amikacin, Cefepime, Cefotaxime, Gentamicin, Nitrofurantoin, Piperacillin-tazobactam, Trimethoprim-sulfamethoxazole	Tehran	1 day to 16 years	130 girls 73 boys
Mansouri et al (26)	2015	Amikacin, Ampicillin, Cefixime, Cefotaxime, Ceftriaxone, Ciprofloxacin, Gentamicin, Imipenem, Nalidixic acid, Nitrofurantoin, Ofloxacin, Trimethoprim-sulfamethoxazole	Kermanshah	1 week to 8 years	-
Mashayekhi et al (27)	2014	Amikacin, Ampicillin, Cefalotin, Cefotaxime, Ceftazidime, Ciprofloxacin, Gentamicin, Imipenem, Mezlocillin, Norfloxacin, Nitrofurantoin, Ofloxacin Piperacillin, Tetracycline, Trimethoprim-sulfamethoxazole	Tehran	1 to 3 years	70 girls 51 boys
Pilevarzadeh et al (28)	2013	Amikacin, Ampicillin, Ciprofloxacin, Gentamicin, Imipenem, Ofloxacin, Sulfamethoxazole, Tetracycline	Tehran	1 to 12 years	70 girls 51 boys
Pouladfar et al (29)	2017	Amikacin, Amoxicillin, Ampicillin, Ampicillin-sulbactam, Aztreonam, Cefepime, Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefuroxime, Cephalexin, Chloramphenicol,Ciprofloxacin, Colistin, Gentamicin, Imipenem, Meropenem, Nalidixic acid, Nitrofurantoin, Piperacillin, Piperacillin-tazobactam, Tetracycline,	Shiraz	5.34±5.87 years	142 girls 60 boys

Table 1: Continued…

		Ticarcillin, Tobramycin, Trimethoprim-sulfamethoxazole			
Rajabi et al (30)	2015	Cephalexin, Ciprofloxacin, Moxifloxacin, Nitrofurantoin, Tetracycline, Trimethoprim-sulfamethoxazole	Tehran	-	-
Rezaee et al (31)	2015	Amikacin, Cefotaxime, Ceftriaxone, Ceftizoxime, Ciprofloxacin, Gentamicin, Nalidixic acid, Nitrofurantoin, Trimethoprim-sulfamethoxazole	Tabriz	-	-
Salehi et al (32)	2016	Amikacin, Ampicillin, Cefotaxime, Ciprofloxacin, Gentamicin, Penicillin, Tetracycline, Trimethoprim-sulfamethoxazole	-	-	-
Shakibaie et al (33)	2014	Amikacin, Amoxicillin-clavulanic acid, Ampicillin, Cefepime, Cefixime, Cefotaxime, Ceftazidime, Gentamicin, Imipenem, Meropenem, Nalidixic acid, Trimethoprim-sulfamethoxazole	Kerman	Undue 5 years	-
Taheri et al (34)	2013	Amikacin, Ampicillin, Cefixime, Cefotaxime, Ceftazidime, Ceftizoxime, Ceftriaxone, Cephalexin, Ciprofloxacin, Gentamicin, Nalidixic acid, Nitrofurantoin, Norfloxacin, Trimethoprim-sulfamethoxazole	Tehran	14.14±7.68 d	22 girls 51 boys
Vakilzadeh et al (35)	2020	Amikacin, Amoxicillin, Ampicillin, Azithromycin, Cefazolin, Cefepime, Cefixime, Cefotaxime, Cefoxitin, Ceftazidime, Ceftizoxime, Ceftriaxone, Cephalexin, Ciprofloxacin, Doxycycline, Erythromycin, Gentamicin, Imipenem, Levofloxacin, Meropenem, Nalidixic acid, Nitrofurantoin, Penicillin, Tetracycline, Trimethoprim-sulfamethoxazole	Mashhad	1 to 13 years	-

Risk of bias (quality) assessment: The results of quality assessment by AXIS tool are presented in Fig. 2.

Pooled estimate: The highest pooled prevalence of antibiotic resistance of *E. coli* among confirmed bacterial UTIs was related to doxycycline (59%), ticarcillin-clavulanic acid (57%), cefazolin (54%), cefuroxime (53%), and amoxycillin-clavulanic acid (52%) while the lowest antibiotic-resistance prevalence of the pooled estimates was related to colistin (0%), meropenem (1%), and imipenem (2%). The pooled estimates are presented in Table 2.

For azithromycin, cefoxitin, clindamycin, erythromycin, mezlocillin, moxifloxacin, and sulfamethoxazole, the number of articles reporting the aforementioned antibiotics was 1. It was not feasible to perform a meta-analysis of these antibiotics. The descriptive data of the aforementioned antibiotics is presented in Table 3.

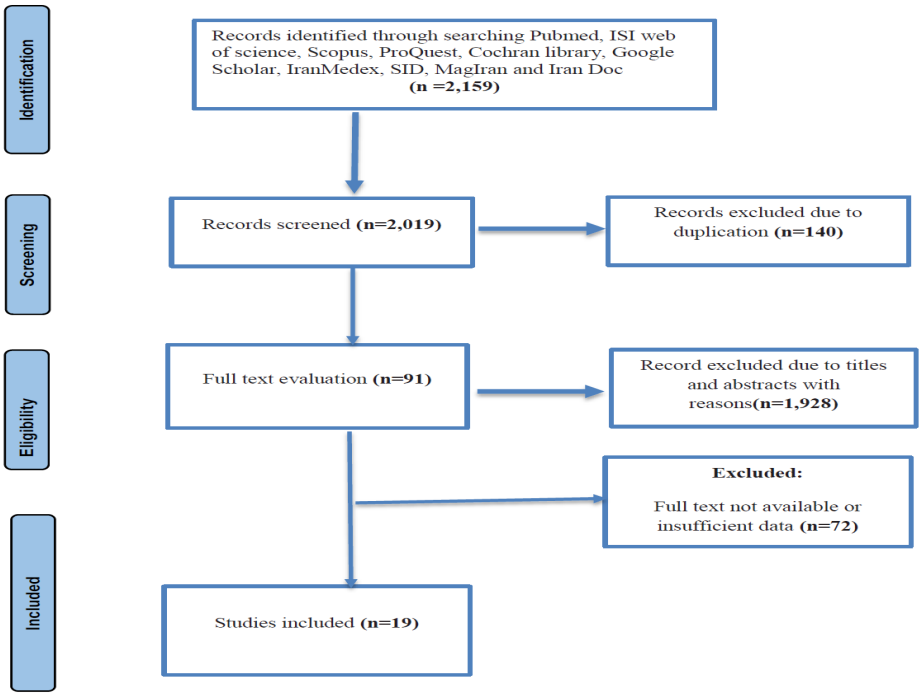

Fig. 1: Flow chart of the article selection process of the systematic review

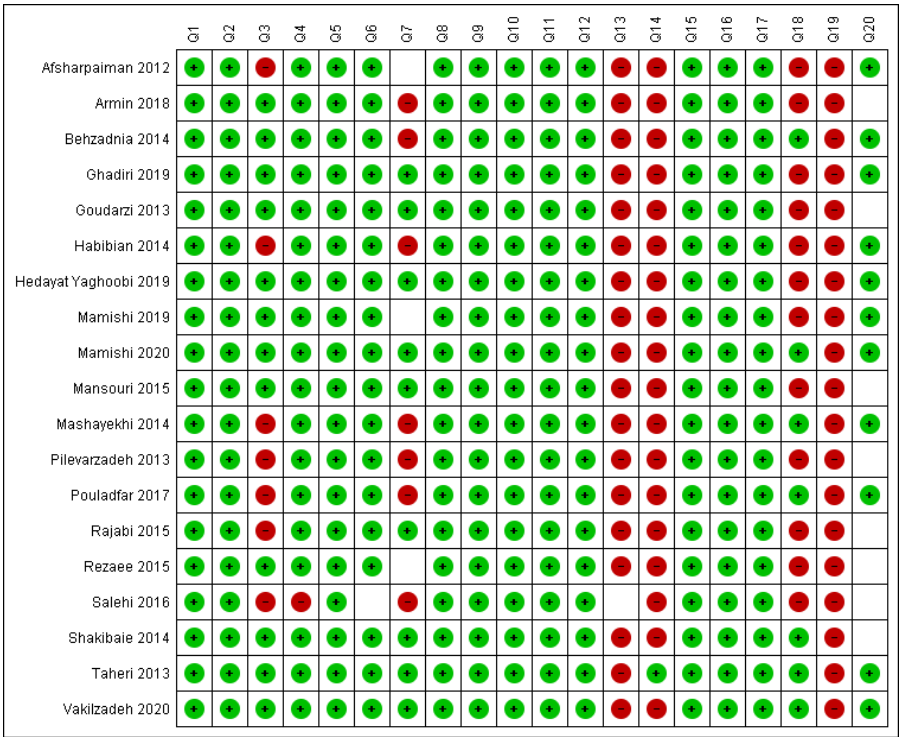

Fig. 2: Results of risk of bias assessment of the articles with AXIS tool. Green=Yes, Red=No, White=Unclear

Table 2: Pooled estimates of the prevalence of antibiotic-specific resistance of *E. coli* among Iranian children.

Antibiotic	*Pooled prevalence*	*95% Confidence interval*	*I-squared*
Amikacin	0.07	(0.03-0.13)	96.2
Amoxycillin	0.39	(0.32-0.45)	0
Amoxycillin-clavulanic acid	0.52	(0.48-0.56)	0
Ampicillin	0.42	(0.32-0.52)	93.17
Ampicillin-sulbactam	0.24	(0.02-0.60)	98.95
Aztreonam	0.23	(0.18-0.28)	0
Cefalotin	0.36	(0.13-0.62)	95.82
Cefepime	0.15	(0.03-0.33)	98.29
Cefixime	0.24	(0.15-0.34)	90.9
Cefotaxime	0.26	(0.18-0.35)	95.76
Ceftazidime	0.14	(0.08-0.21)	90.57
Ceftizoxime	0.18	(0.08-0.30)	89.34
Ceftriaxone	0.19	(0.13-0.25)	88.32
Cefuroxime	0.53	(0.49-0.57)	0
Cephalexin	0.23	(0.09-0.42)	94.78
Cefazolin	0.54	(0.50-0.59)	0
Chloramphenicol	0.31	(0.04-0.69)	99.02
Ciprofloxacin	0.13	(0.08-0.19)	92.87
Colistin	0	(0.00-0.01)	0
Doxycycline	0.59	(0.55-0.63)	0
Gentamicin	0.17	(0.12-0.22)	92.21
Imipenem	0.02	(0.01-0.05)	86.66
Levofloxacin	0.59	(0.55-0.63)	0
Meropenem	0.01	(0.00-0.02)	64.5
Nalidixic acid	0.23	(0.14-0.33)	94.34
Nitrofurantoin	0.13	(0.06-0.23)	96.01
Norfloxacin	0.1	(0.00-0.39)	96.87
Ofloxacin	0.11	(0.05-0.2)	84.35
Penicillin	0.4	(0.31-0.49)	0
Piperacillin	0.34	(0.09-0.65)	98.54
Piperacillin-tazobactam	0.12	(0.00-0.37)	99.05
Tetracycline	0.3	(0.16-0.47)	96.87
Ticarcillin-clavulanic acid	0.57	(0.54-0.61)	0
Tobramycin	0.27	(0.05-0.57)	98.3
Trimethoprim-sulfamethoxazole	0.34	(0.25-0.44)	96.68

Table 3: Antibiotics only reported by one paper and excluded from the meta-analysis

	Antibiotic	*Paper ID*	*prevalence*
1	Azithromycin	Vakilzadeh[40]	0.1
2	Cefoxitin	Vakilzadeh[40]	0
3	Clindamycin	Vakilzadeh[40]	0
4	Erythromycin	Vakilzadeh[40]	0.03
5	Mezlocillin	Mashayekhi[32]	0.05
6	Moxifloxacin	Rajabi[35]	0.03
7	Sulfamethoxa-zole	Pilevarza-deh[33]	0.39

Funnel plots

Symmetry was observed in the funnel plot of colistin. Partial symmetry was observed in the funnel plots of cefixime and meropenem. The rest of the funnel plots displayed significant asymmetry. The funnel plots are shown in Fig. 3 A-E.

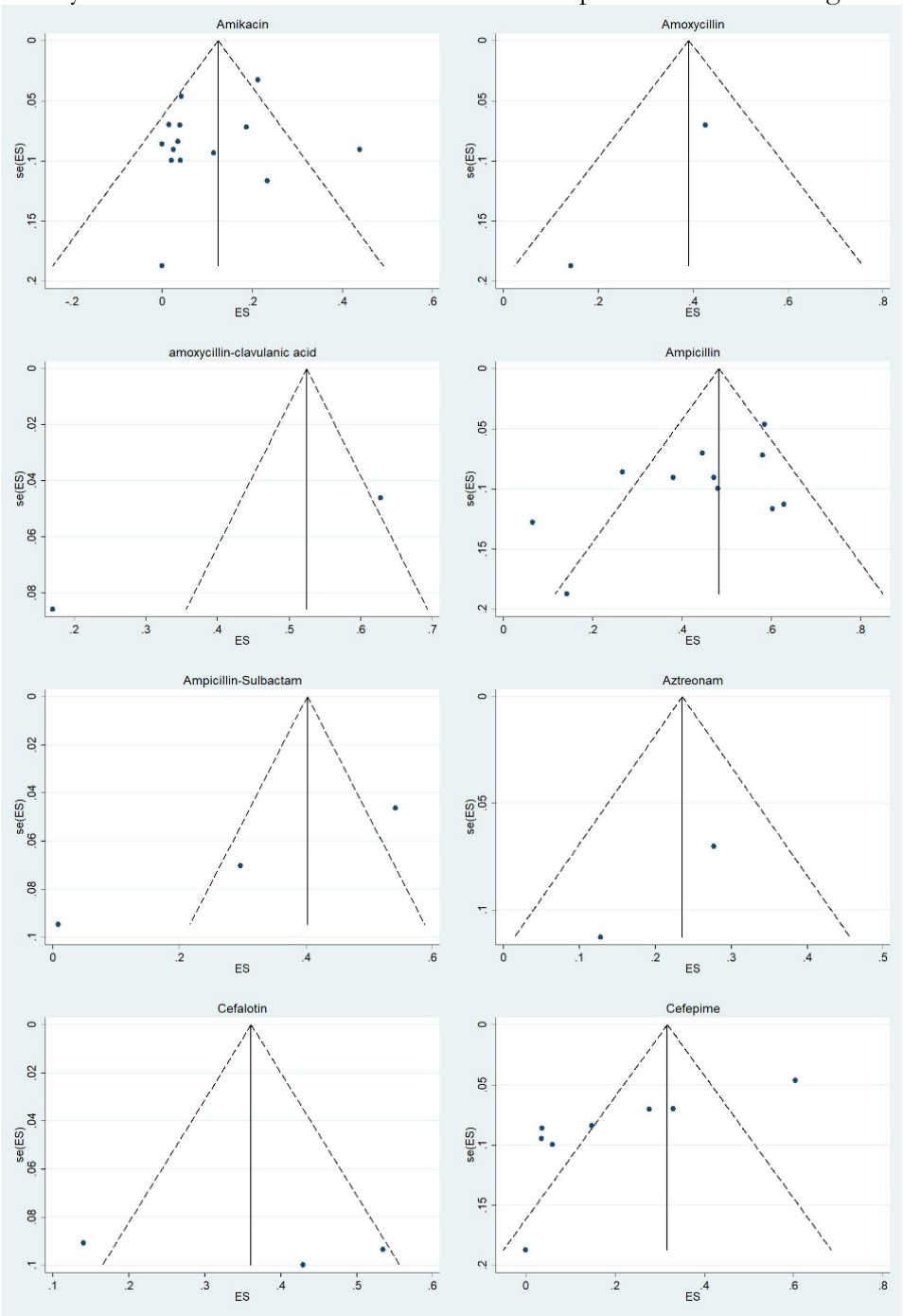

Fig. 3: A Funnels plots of the pooled estimates of prevalence of antibiotic resistance drawn against their standard errors with pseudo 95% confidence limits

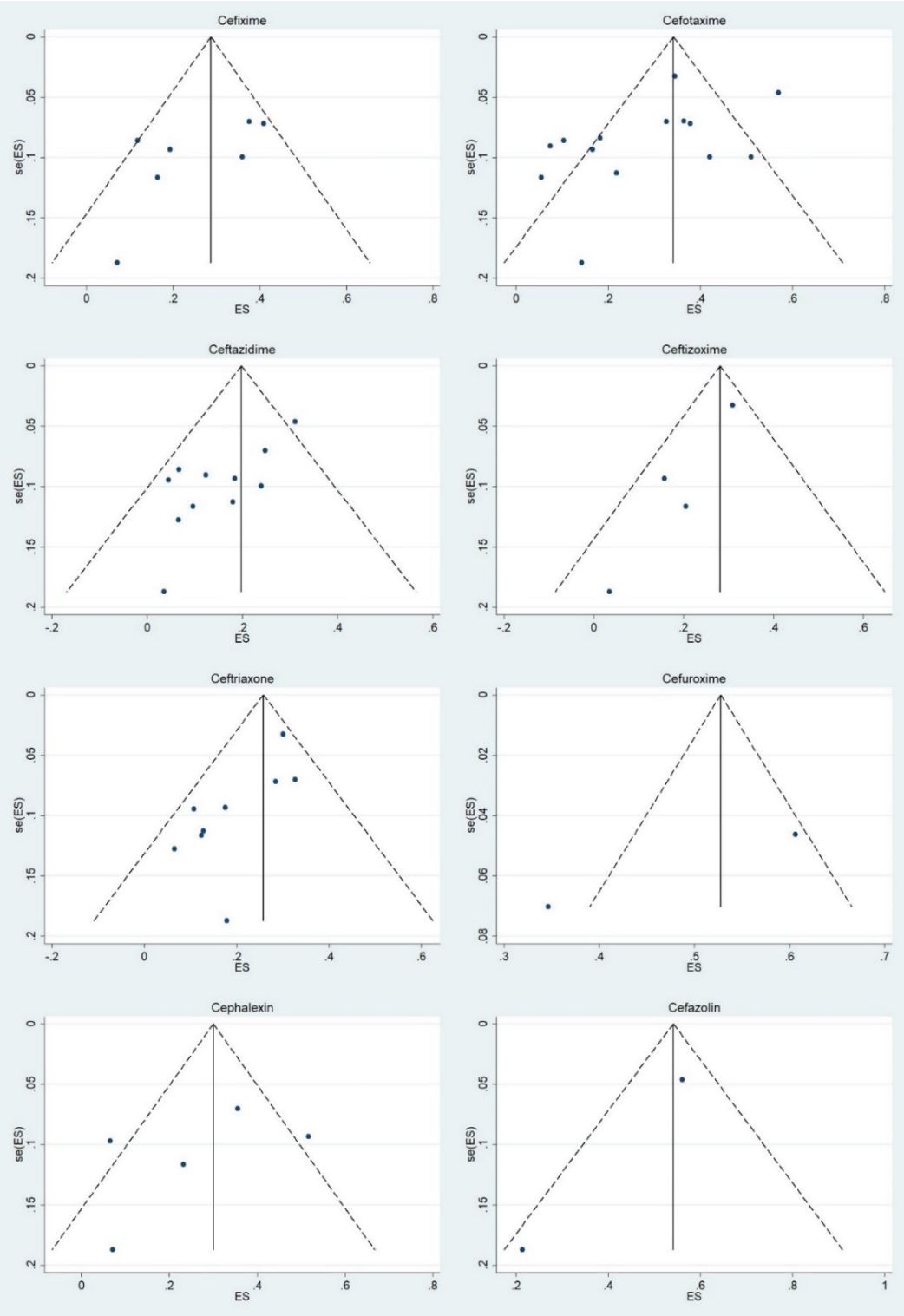

Fig. 3: **B** Funnels plots of the pooled estimates of prevalence of antibiotic resistance drawn against their standard errors with pseudo 95% confidence limits

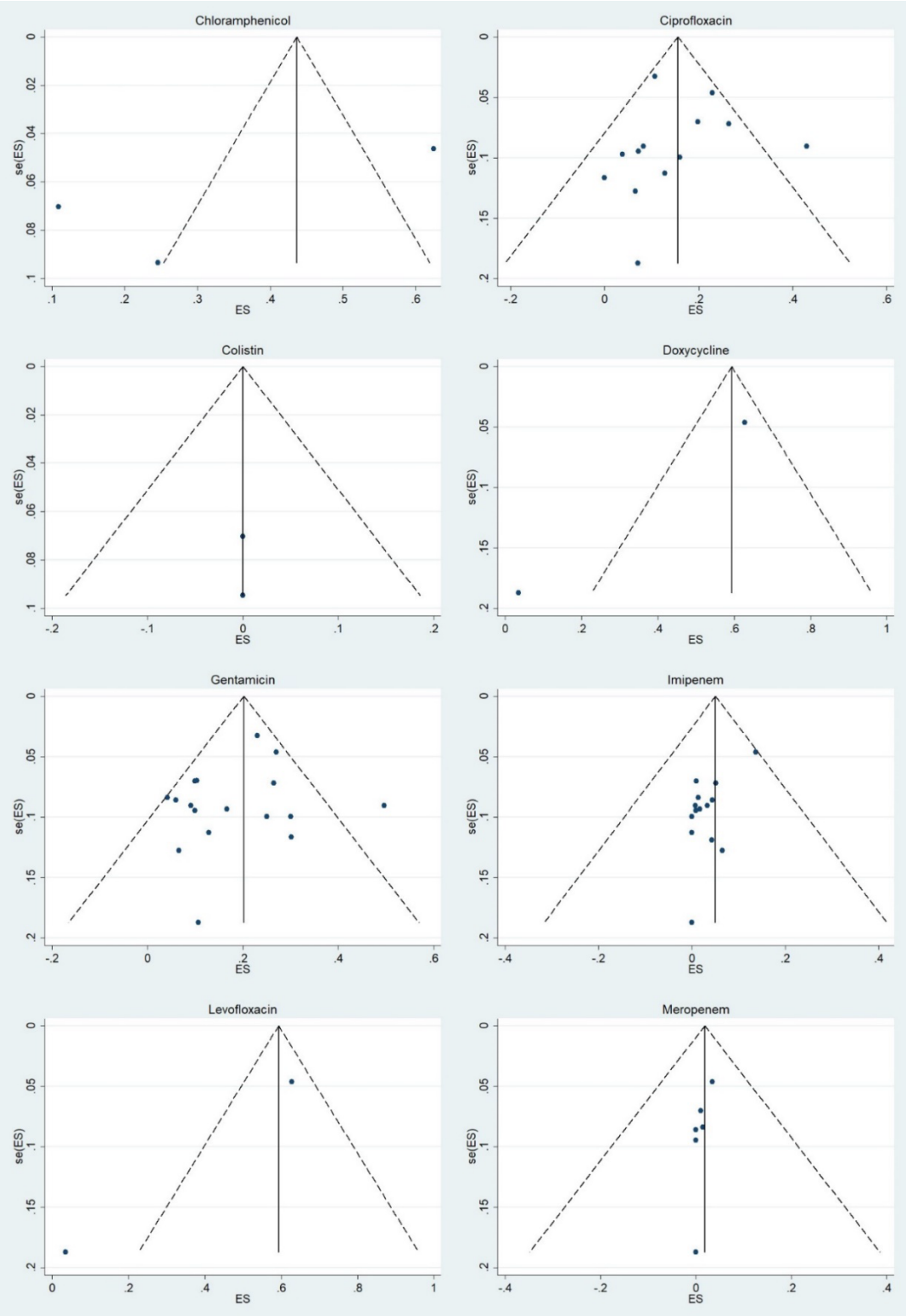

Fig. 3: **C** Funnels plots of the pooled estimates of prevalence of antibiotic resistance drawn against their standard errors with pseudo 95% confidence limits

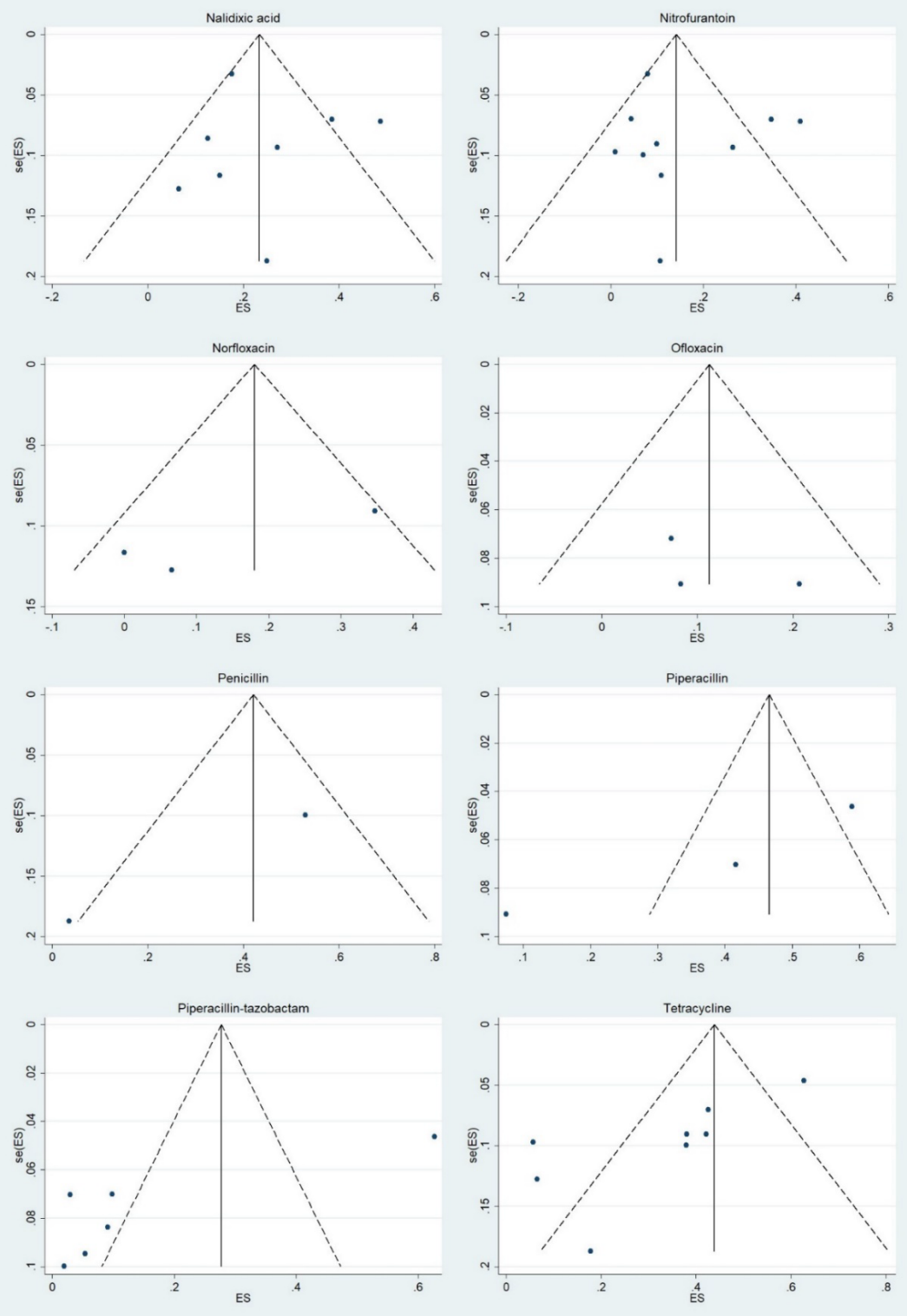

Fig. 3: **D** Funnels plots of the pooled estimates of prevalence of antibiotic resistance drawn against their standard errors with pseudo 95% confidence limits

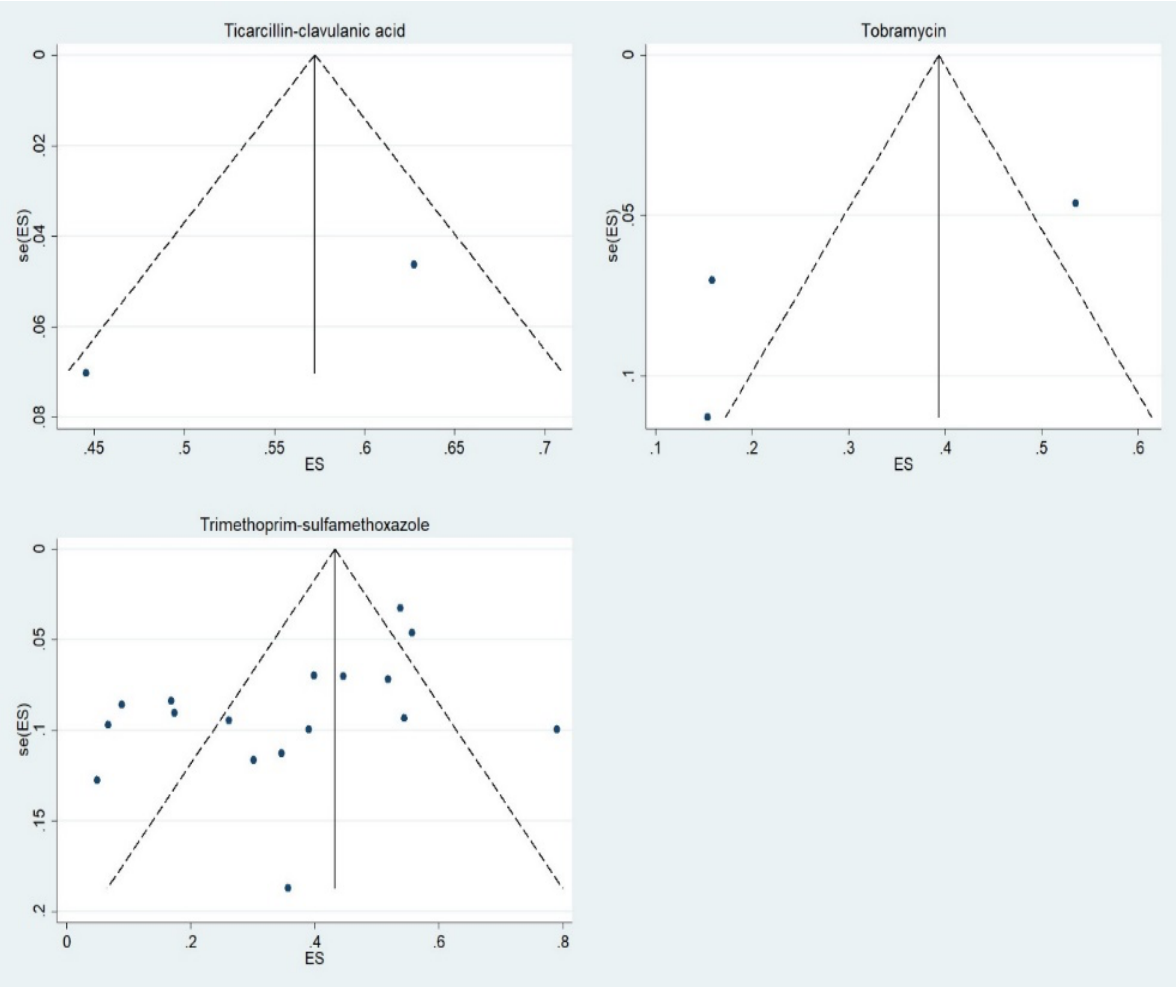

Fig. 3: E Funnels plots of the pooled estimates of prevalence of antibiotic resistance drawn against their standrard errors with pseudo 95% confidence limits

Forest plots

By visually-examining the forest plots, it was detected that in the forest plots of colistin, imipenem, meropenem, and piperacillin-tazobactam the between-study variation was very low. I-squared statistics of each meta-analysis are presented in Table 3. The forest plots are presented as a supplementary file.

Meta-regression

The regression model based on the effect size and latitude of sampling locations for nitrofurantoin was statistically significant with a coefficient of -0.0383623 (95%CI: -0.0766199, -0.0001046), an adjusted R-squared of 47.78%, and tau-squared of 0.007638, suggesting that 47.78% of the variability of the mean effect size could be explained by location variability. The coefficient in regression models for amikacin, ampicillin, cefotaxime, ceftazidime, ciprofloxacin, gentamicin, imipenem, and trimethoprim-sulfamethoxazole were not statistically significant. The results of meta-regressions are presented in Table 4.

Table 4: Results of meta-regression of prevalence of antibiotic resistance with the latitude of sampling location

Antibiotic	*Latitude coefficient*	*Standard error*	*t*	*P>|t|*	*95% confidence interval*		*Tau-squared*	*I-squared residual (%)*	*Adjusted R-squared (%)*	*Number of observations*
					Lower bound	Upper bound				
Amikacin	0.0175035	0.0141967	1.22	0.243	-0.0137433	0.0487504	0.008039	57.12	11.49	13
Ampicillin	0.0012053	0.0260278	0.05	0.964	-0.058815	0.0612255	0.02592	72.59	-23.18	10
Cefotaxime	0.010273	0.0206247	0.50	0.628	-0.0351217	0.0556677	0.02267	80.72	-8.31	13
Ceftazidime	-0.0004119	0.0151283	-0.03	0.979	-0.0346345	0.0338108	0.005786	38.56	-22.66	11
Ciprofloxacin	-0.0115777	0.0158734	-0.73	0.483	-0.0469459	0.0237904	0.007019	48.35	-15.61	12
Gentamicin	0.0169267	0.0125871	1.34	0.200	-0.01007	0.0439234	0.005777	45.17	14.53	16
Imipenem	0.0069778	0.0103956	0.67	0.515	-0.156722	0.0296279	0	0.00	100.00	14
Nitrofurantoin	-0.0383623	0.0165905	-2.31	0.050	-0.0766199	-0.0001046	0.007638	49.30	47.78	10
Trimethoprim-sulfamethoxazole	0.0142434	0.025091	0.57	0.579	-0.0395714	0.0680581	0.03793	83.40	-5.54	16

Discussion

Uropathogenic *E. coli* bacteria are the most common cause of urinary tract infection among neonatal, children and adults in the world (36, 37). In this study, the pooled prevalence of antibiotic resistance of *E. coli* isolates were assessed for 35 antibiotics among Iranian children with confirmed bacterial UTIs between Jan 2012- Jan 2022. The highest observed pooled prevalence of antibiotic resistance was found for doxycycline (59%), followed by ticarcillin-clavulanic acid (57%), cefazolin (54%), cefuroxime (53%), and amoxycillin-clavulanic acid (52%). The lowest antibiotic-resistance prevalence of the pooled estimates was found for colistin (0%), meropenem (1%), and imipenem (2%), suggesting these antibiotics could be better treatment choices for *E. coli* UTIs in Iranian children. The resistant uropathogenic *E. coli* strains were observed in the majority of confirmed bacterial UTIs among Iranian children. Hadifar et al. have conducted a systematic review and meta-analysis to estimate the multidrug resistance of uropathogenic *E. coli* strains in Iran and have reported that the multidrug resistance of *E. coli* strains is 49.4% (95%CI: 48.0-50.7%) (38).

According to a survey in the United States, about 30% of important care antibiotic prescriptions had been labelled as insufficient (39), a number of other factors, including the spread of pathogens, antibiotic-resistant genes, as well as hygienic behaviors of people affect the level of antibiotic resistance (40).

Moreover, in this study, the meta-regression of the prevalence of nitrofurantoin-resistant *E. coli* in Iran was statistically significant; suggesting that with a one-degree increase in latitude, the prevalence of resistance against nitrofurantoin would decrease by 3%. Therefore, the location of sampling might have a role in the observed heterogeneity in resistance against nitrofurantoin in *E. coli* isolates.

Despite the acceptable progress in selective treatment and efforts to discover new drugs, the rise of antibiotic resistance in microorganisms has become a major problem in the treatment of infectious diseases. Today, due to the acquisition of resistant genes, the change in the pattern of antibiotic sensitivity, and the global increase in drug resistance among bacteria causing urinary tract infections, especially *E. coli*, the type of chosen antibiotic for treatment, is a challenge.

Limitations

The number of publications from some provinces were high, which could affect the whole estimation.

Conclusion

Antibiotic-resistant Uropathogenic *E. coli* is a common pathogen among Iranian paediatrics. The most effective antibiotics for uropathogens are colistin, meropenem, and imipenem among Iranian children. In general, the rational use of antibiotics by developing national guidelines for the correct use of antibiotics can reduce the antibiotics resistance rise.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

Authors kindly thank Dr. Laleh Sharifi who helped in the editing of the manuscript.

Availability of data and materials

The datasets used and/or analyzed in this study are available by the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable

Conflict of interest

The authors declare that they have no conflict of interest.

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