International Journal of
Enteric Pathogens

Int J Enteric Pathog. 2019 December;7(4):113-120 **Review Article**

http://enterpathog.abzums.ac.ir

doi 10.15171/ijep.2019.24

A Systematic Review and Meta-analysis on the Epidemiology of Antibiotic-resistant *Yersinia* Species in Food and Clinical Specimens in Iran

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Published Online December 21, 2019

Keywords: Antibiotic resistance, *Yersinia*, Iran

Abstract

Objective: The aim of the present study was to investigate the antimicrobial susceptibility profiles of *Yersinia* species, especially *Y. enterocolitica* from non-clinical and clinical isolates in Iran.

Materials and Methods: We systematically searched PubMed, Scopus, Google Scholar, and the Scientific Information Database (SID) using "antibiotic resistance", "*Yersinia*", and "Iran" as major keywords until June 10, 2019. According to the predefined article selection criteria, published studies addressing the epidemiology of antibiotic-resistant *Yersinia* species in Iran were included in the meta-analysis. Data were extracted and exported to the Comprehensive Meta-Analysis Software to evaluate antibiotic resistance rates, heterogeneity of studies and publication bias.

Results: Twelve studies reported antimicrobial susceptibility testing using disk diffusion method. The pooled prevalence of antibiotic-resistant *Yersinia* species in food and clinical specimens in Iran was as follows: 22.4% to amoxicillin, 41.9% to ampicillin, 6% to gentamicin, 17% to trimethoprim/sulfamethoxazole, 19% to tetracycline, 10.3% to ciprofloxacin, 10.5% to streptomycin, 3.8% to chloramphenicol, 79.3% to cephalothin, 18.4% to nalidixic acid, 6.6% to cefotaxime, and 12.2% to trimethoprim.

Conclusion: This study revealed a high prevalence of resistant *Y. enterocolitica* strains isolated from food and clinical specimens in Iran to β-lactams, while the resistance rates to aminoglycosides, fluoroquinolone and chloramphenicol were low. Our findings recommended the necessity of a continuous surveillance of the resistance patterns and prudent use of trimethoprim/sulfamethoxazole, tetracycline, and nalidixic acid to prevent the development of antibiotic-resistant *Y. enterocolitica* strains in Iran.

Received July 17, 2019; **Revised** August 25, 2019; **Accepted** October 5, 2019

Background

The genus *Yersinia* belongs to the family Enterobacteriaceae and contains gram-negative, pleomorphic, facultative anaerobic and oxidase-negative rods with bipolar staining.[1,2] Among 15 identified *Yersinia* species, three are pathogenic to humans including *Yersinia pestis* and two food-borne pathogens that are the cause of enteric diseases, i.e., *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*.[1,2] Human is an accidental host for these zoonotic bacterial pathogens. [2] *Y. pestis* causes plague which is a rare infection in human, and rats are the natural reservoirs for human infection.[2] Streptomycin, tetracyclines, chloramphenicol, trimethoprim/sulfamethoxazole and gentamicin are the preferred choices for treating this zoonotic infection. Moreover, sulfonamide, trimethoprim/sulfamethoxazole and tetracycline are recommended for plague prophylaxis.[2,3] However, the emergence of high-level resistance to antimicrobial agents was observed in a clinical isolate of *Y. pestis* in 1995.[3] *Y. pseudotuberculosis* is a relatively uncommon causative agent of yersiniosis in human, which can be transferred from the natural reservoirs such as wild and domestic animals and birds.[4] Acute or chronic *Y. pseudotuberculosis* infections in human are transmitted through contaminated food or water, and the severity of infections vary from self-limiting infection to sepsis with a mortality rate as high as >75%.[4,5] *Y. enterocolitica* is the most common human pathogen of *Yersinia* species and is ubiquitously present in water, milk, soil, and domestic and wild animals including pigs, rodents, livestock, and rabbits.[6,7] Yersiniosis is a gastrointestinal infection caused by this psychrotrophic bacterium (*Y. enterocolitica*) and is most common among infants and young children under the age of five, especially in developing countries.[8] This food-borne disease is transmitted via the fecal-oral route after digestion of contaminated food products and water and is considered as a public health challenge especially in terms of food safety due to its ability to grow at 4°C.[9] In immunocompetent hosts, the bacterium causes local infection in the gastrointestinal tract, which is characterized as a mild and self-limiting diarrhea. However, antimicrobial therapy is required in immunocompromised patients due to the risk of systemic infection with a high mortality rate (50%).[4,6,7,9] Because of the high bacterial susceptibility to broad-spectrum cephalosporins, aminoglycosides, chloramphenicol, tetracyclines, trimethoprim/sulfamethoxazole and ciprofloxacin, these drugs are recommended by the World Health Organization (WHO) for treatment of human invasive infections caused by *Y. enterocolitica*.[2,9] However, some of these antibiotics have also been used for growth promotion, prophylaxis, and treatment in food-producing animals, which has led to the emergence of antimicrobial-resistant strains followed by transferring these antimicrobial-resistant food-borne pathogens to humans.[10] Hitherto, there has been no comprehensive information about the epidemiology of antibiotic-resistant *Yersinia* species in Iran. Therefore, the aim of this systematic review and meta-analysis was to investigate the antimicrobial susceptibility profiles of *Yersinia* species, especially *Y. enterocolitica* among non-clinical and clinical isolates in Iran.

Materials and Methods

Data Sources and Search Strategies

The study protocol was in accordance with PRISMA (the Preferred Reporting Items for Systematic Review and Meta-Analysis) checklist.[11] The main sources of data to investigate the prevalence of antimicrobial susceptibility profiles of *Yersinia* species in Iran in international and national databases were PubMed (https://www.ncbi.nlm.nih.gov), Scopus (https://www.scopus.com), Google Scholar (http://scholar.google.com), and the Scientific Information Database (SID) (www.sid.ir). Using some major keywords, i.e., "antibiotic resistance", "*Yersinia*", "Iran" and with the help of boolean operators (AND and OR) and the truncation mark (*), a complete search was performed in databases until June 10, 2019 followed by a supplementary literature search in the reference lists of included articles to identify eligible studies for the meta-analysis.

Screening of Studies and Selection Criteria

Collected records during literature search process were further evaluated for eligibility based on the inclusion and exclusion criteria. To start, duplicate records were removed through screening of titles. Then, the abstracts and full texts were screened by two investigators independently according to the inclusion criteria. Persian- and English-language articles containing sufficient and extractable data and studies focusing on antibiotic resistance rate of *Yersinia* species only in Iran were included in the study. Records other than cross-sectional studies, food and clinical specimens and *Yersinia* species, incomplete data and duplicate publications were excluded from the meta-analysis.

Data Extraction and Quality Assessment of Studies

A full-text review of articles meeting eligibility criteria was done in order to extract data and perform quality assessment of studies. Data were extracted for each study and sorted by first author details, area of the study, year of the study, type and number of *Yersinia* species isolated from different specimens, origin of samples, antibiotic susceptibility test methods and number of resistant *Yersinia* isolates for each species. Then, the quality of included studies was assessed using the Joanna Briggs Institute (JBI) checklist presented by Munn et al for studies reporting prevalence data.[12] The JBI checklist contained some items about the target population, sample size, statistical analysis, and methods used for the identification, and eligible studies receiving more than 5 scores were considered as high-quality, 4–5 scores as medium-quality and lower than 4 scores as low-quality studies (Table 1).

Data Processing and Analysis

All statistical analyses were performed using the CMA (Comprehensive Meta-Analysis) software, version 2.2 (Biostat, Englewood, NJ). The resistance rates of *Yersinia* species among included studies were determined using forest plots of pooled event rates and expressed as percentage and 95% confidence intervals (CIs). Subgroup analysis was done based on type of *Yersinia* species. Data analysis and synthesis were done by combining at least four studies. Depending on the existence of heterogeneity among included studies, data on the antibiotic resistance were pooled using random- or fixed-effects models. Heterogeneity degree of the studies was determined with the help of the I^2 statistic (25% (low), 50% (moderate), and 75% (high)) and the Chi-square test with Cochran's Q statistic (significant at $P < 0.1$). A potential publication bias in articles reporting resistance rate for each antibiotic was investigated through visually observation of symmetry in funnel plots.

Results

As shown in Figure 1, a total of 12 studies were selected for meta-analysis among 1019 identified citations through database searching. *Y. enterocolitica* (61.3%), *Y. frederiksenii* (12.2%) and *Y. intermedia* (6.1%) were the most common species of the genus *Yersinia* and their antibiotic resistance rates was investigated in the included articles through disk diffusion method in Iran. Additionally, *Y. enterocolitica* strains were isolated from both non-clinical and clinical samples, while *Y.*

Table 1. Information Extracted from Eligible Studies Included in the Meta-analysis

Author (Ref)	Quality score	Study area	Year	*Yersinia* species	Sample origin	Strain (n)	AST	Antibiotic resistance (n)															
								AMX	AMP	GEN	TMP-SMX	TET	CIP	STR	CHL	CEF	KAN	NAL	AMK	ERY	CTX	NIT	TMP
Fazlara[13]	5	Ahvaz	NA	*Y. enterocolitica*	Milk	36	Disk diffusion	30	ND	1	8	3	0	ND	ND	29	4	6	ND	35	ND	ND	ND
Soltan Dallal[14]	8	Behshahr	NA	*Y. enterocolitica*	Milk	7	Disk diffusion	7	7	ND	0	0	ND	0	0	ND	ND	ND	ND	ND	ND	ND	ND
Ghanbari[15]	8	Fuladshahr	2015-2016	NA	Clinical	3	Disk diffusion	ND	ND	0	0	ND	1	ND	ND	2	ND	2	ND	ND	ND	0	ND
Kazemi[16]	8	Hamadan	2013-2014	*Y. enterocolitica*	Clinical	3	Disk diffusion	ND	ND	2	0	ND	ND	ND	0	ND	ND	ND	2	3	ND	ND	ND
Noorbakhsh Sabet[17]	5	Qom	2004-2007	NA	Clinical	2	Disk diffusion	ND	ND	2	2	ND	0	ND	ND	ND	ND	ND	0	ND	2	ND	ND
Soleymani-Rahbar[18]	6	Qom	NA	*Y. enterocolitica*	Clinical	14	NA	ND	14	0	2	1	0	ND	0	14	0	ND	ND	14	0	ND	ND
Aghamohammad[19]	9	Tehran	2013-2014	*Y. enterocolitica*	Chicken Beef	48	Disk diffusion	ND	27	0	ND	6	0	5	0	47	ND	11	ND	ND	0	ND	3
			2013-2014	*Y. frederiksenii*	Chicken Beef	7	Disk diffusion	ND	4	0	ND	0	0	0	0	7	ND	2	ND	ND	0	ND	0
			2013-2014	*Y. intermedia*	Chicken Beef	4	Disk diffusion	ND	0	0	ND	1	0	0	0	4	ND	0	ND	ND	0	ND	0
Jamali[20]	9	Tehran	2008-2010	*Y. enterocolitica*	Milk	19	Disk diffusion	1	3	0	2	10	5	2	0	3	ND	1	ND	ND	ND	ND	ND
			2008-2010	*Y. frederiksenii*	Milk	9	Disk diffusion	0	1	0	0	4	0	0	0	1	ND	0	ND	ND	ND	ND	ND
Jamali[21]	9	Tehran	2008-2010	*Y. enterocolitica*	Ducks Geese	45	Disk diffusion	7	9	0	ND	17	6	4	0	27	ND	6	ND	ND	ND	ND	8
			2008-2010	*Y. frederiksenii*	Ducks Geese	21	Disk diffusion	1	5	0	ND	6	2	0	0	13	ND	0	ND	ND	ND	ND	3
			2008-2010	*Y. intermedia*	Ducks Geese	14	Disk diffusion	1	3	0	ND	0	0	1	0	1	ND	0	ND	ND	ND	ND	3
Yazdi[22]	9	Tehran	2007-2008	*Y. enterocolitica*	Chicken Beef	48	Disk diffusion	ND	27	0	ND	6	0	5	0	47	ND	11	ND	ND	0	ND	3
			2007-2008	*Y. frederiksenii*	Chicken Beef	7	Disk diffusion	ND	4	0	ND	0	0	3	0	7	ND	2	ND	ND	0	ND	0
			2007-2008	*Y. intermedia*	Chicken Beef	4	Disk diffusion	ND	0	0	ND	1	0	0	0	4	ND	0	ND	ND	0	ND	0
Soltan Dallal[23]	7	Tehran	2006-2007	NA	Chicken Beef	60	Disk diffusion	ND	31	ND	ND	ND	57	ND	ND	59	ND	ND	ND	ND	ND	ND	ND
Soltan Dallal[24]	6	Tehran	2002	NA	Clinical	8	Disk diffusion	ND	8	0	0	0	ND	0	0	8	0	0	0	ND	ND	0	ND

Abbreviations, AMX, amoxicillin; AMP, ampicillin; GEN, gentamicin; TMP/SMX, trimethoprim/sulfamethoxazole; TET, tetracycline; CIP, ciprofloxacin; STR, streptomycin; CHL, chloramphenicol; CEF, cephalothin; KAN, kanamycin; NAL, nalidixic acid; AMK, amikacin; ERY, erythromycin; CTX, cefotaxime; NIT, nitrofurantoin; TMP, trimethoprim; AST, antimicrobial susceptibility testing; ND, not determined

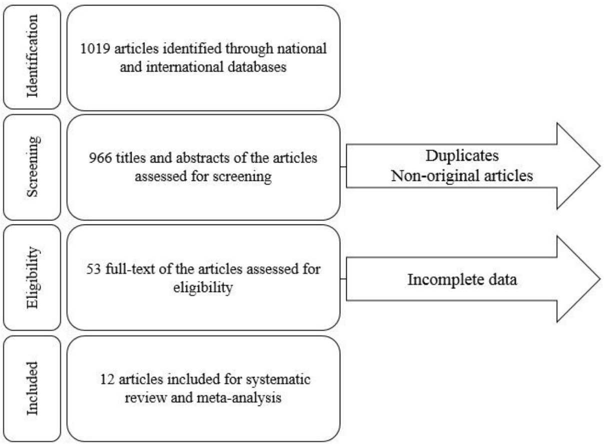

Figure 1. PRISMA Flow Diagram Describing the Study Selection Process

frederiksenii and *Y. intermedia* strains were isolated only from non-clinical samples. In this study, 91.6% of *Yersinia* species were isolated from the food products including milk, chicken and beef meats as well as duck and goose intestinal contents and 8.4% from the clinical samples. Clinical samples were diarrheal stool, blood, cerebrospinal fluid (CSF), urine and wound. As shown in Table 1, eligible studies were from Ahvaz, Behshahr, Fuladshahr, Hamadan, Qom and Tehran with quality scores of ≥5. We assessed the resistance prevalence of *Yersinia* species and the potential publication bias for each antibiotic using forest plots (Figures 2A, B and C) and funnel plots (Figures 3A, B and C), respectively. Overall resistance prevalence of *Yersinia* species against selected antimicrobial agents that were isolated from food products and clinical specimens in Iran was as follows: 22.4% (95% CI: 4.8-62.3; I^2 = 88.7%; Q = 53.1; P = 0.00) to amoxicillin, 41.9% (95% CI: 29-56.1; I^2 = 71.9%; Q = 49.8; P = 0.00) to ampicillin, 6% (95% CI: 2.8-12.4; I^2 = 30.8%; Q = 23.1; P = 0.11) to gentamicin, 17% (95% CI: 10.5-26.3; I^2 = 0.0%; Q = 7.8; P = 0.44) to trimethoprim/sulfamethoxazole, 19% (95% CI: 11.8-29.2; I^2 = 58.8%; Q = 33.9; P = 0.00) to tetracycline, 10.3% (95% CI: 3.6-26.2; I^2 = 80.8%; Q = 78.2; P = 0.00) to ciprofloxacin, 10.5% (95% CI: 7-15.3; I^2 = 0.0%; Q = 8.3; P = 0.76) to streptomycin, 3.8% (95% CI: 1.9-7.6; I^2 = 0.0%; Q = 5; P = 0.98) to chloramphenicol, 79.3% (95% CI: 60.6-90.5; I^2 = 80.4%; Q = 76.7; P = 0.00) to cephalothin, 18.4% (95% CI: 13.9-23.9; I^2 = 11.1%; Q = 14.6; P = 0.33) to nalidixic acid, 6.6% (95% CI: 1.9-20.8; I^2 = 39.9%; Q = 11.6; P = 0.11) to cefotaxime and 12.2% (95% CI: 8.1-17.9; I^2 = 0.0%; Q = 6; P = 0.64) to trimethoprim. Finally, we performed a subgroup analysis of antibiotic resistance profile of *Yersinia* species against selected antibiotics (Table 2).

Discussion

Our study on the prevalence of antibiotic-resistant *Yersinia* species in both food products and clinical samples in Iran

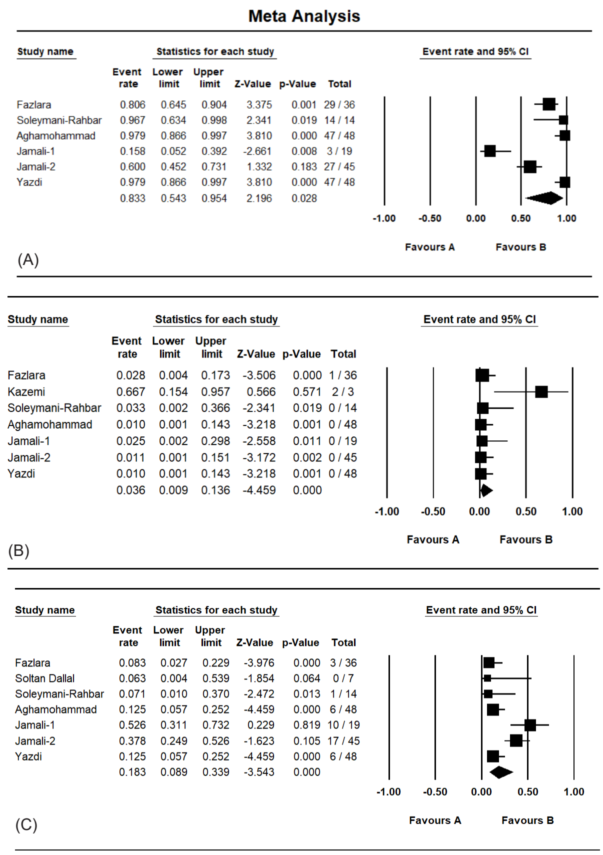

Figure 2. Forest Plots Showing the Prevalence of Antibiotic Resistance of *Y. enterocolitica* to Cephalothin (A), Gentamicin (B) and Tetracycline (C) in Food and Clinical Specimens.

showed high resistance rates against amoxicillin (22.4%), ampicillin (41.9%), trimethoprim/sulfamethoxazole (17%), tetracycline (19%), cephalothin (79.3%), nalidixic acid (18.4%), and trimethoprim (12.2%). In contrast, low resistance rates against gentamicin (6%), ciprofloxacin (10.3%), streptomycin (10.5%), chloramphenicol (3.8%), and cefotaxime (6.6%) were found. Among *Yersinia* species, *Y. enterocolitica* was the most common species in the present study. Pigs are considered as the most important source of human *Y. enterocolitica* infection in the world.[9] However, for religious reasons, pigs are not used in Iran and as shown in Table 1, milk, chicken and beef were the main sources of *Y. enterocolitica* in Iran.[20] Given that these kinds of food products are important sources of nutrients for Iranian people, there is a high risk of the outbreak of *Y. enterocolitica*-induced enteric infections associated with the consumption of contaminated food products in Iran. On the other hand, in this study, the prevalence of *Y. enterocolitica* strains isolated from the clinical samples was low. Studies have reported that clinical *Y. enterocolitica* infections were relatively infrequent in Iran, which can be explained by fact that *Yersinia* species are not routinely screened in most clinical laboratories.[14,20] Therefore, improving identification procedures for *Y. enterocolitica* from different samples is necessary to determine the

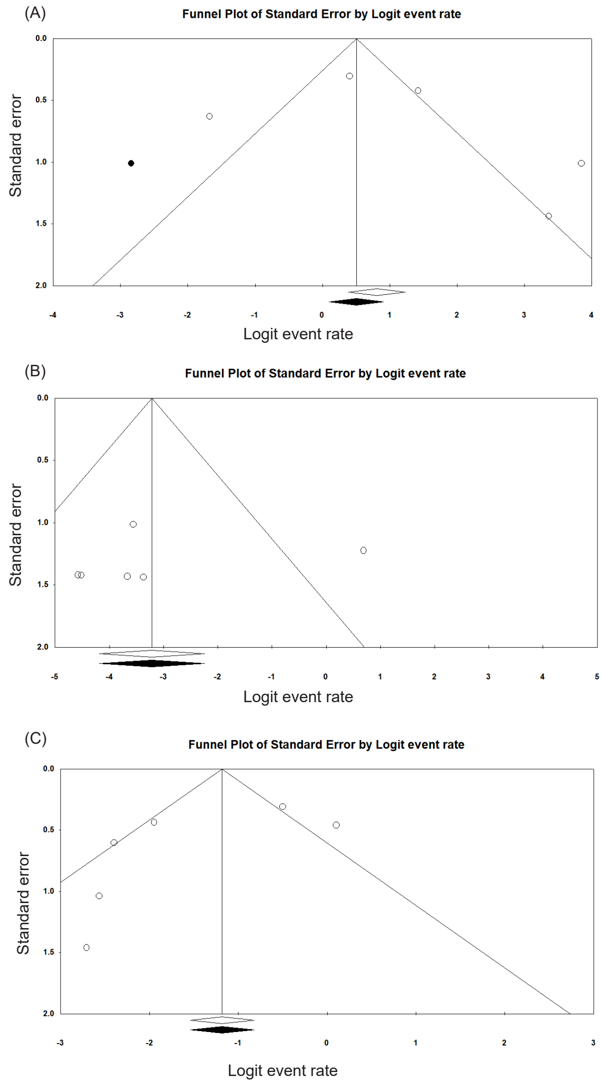

Figure 3. Funnel Plots Showing Publication Bias of Studies Addressing the Prevalence of Antibiotic Resistance of *Y. enterocolitica* to Cephalothin (A), Gentamicin (B) and Tetracycline (C) in Food and Clinical Specimens.

epidemiology of this microorganism. However, a more important issue is excessive administration of some antibiotics, i.e., tetracycline and ciprofloxacin for growth promotion, disease prevention and treatment of diseases in animals in Iran. This excessive use results in the emergence of antibiotic-resistant strains.[20,23] Our findings indicated that the prevalence of *Y. enterocolitica* strains resistant to tetracycline and ciprofloxacin antibiotics in both food products and clinical samples was 18.3% and 6%, respectively. Therefore, limiting the use of these antibiotics, especially tetracycline, in food-producing animals is recommended in order to prevent the emergence of antibiotic-resistant food-borne pathogens and their transmission to humans through food products. Reported resistance prevalence of *Y. enterocolitica* strains isolated from food products against quinolones, ciprofloxacin and nalidixic acid, and tetracycline in different countries is as follows: Italy (0%), China (1.4% to ciprofloxacin, 18.6% to nalidixic acid, and 8.6% to tetracycline), Austria (0%), Germany (0%), Turkey (0% to ciprofloxacin, 4.8% to nalidixic acid, and 4.8% to tetracycline), Korea (0%), and Malaysia (62.5% to nalidixic acid and tetracycline).[25-31] Reports have proven the resistance of *Y. enterocolitica* to first-generation cephalosporins and ampicillin.[1] Similarly, the resistance of *Y. enterocolitica* to β-lactams including amoxicillin (45.9%), ampicillin (50.3%), and cephalothin (83.3%) was high in Iran. This high percentage of resistance can be attributed to β-lactamases A and B produced by *Y. enterocolitica*.[25] Similar results in accordance with our meta-analysis were observed for *Y. enterocolitica* strains isolated from food products in Italy (100% to ampicillin and cephalothin), China (98.6% to ampicillin and 95.7% to cephalothin), Germany (83.3% to amoxicillin, 50% to ampicillin, and 83.3% to cephalothin), Turkey (57.1% to amoxicillin, 64.3% to ampicillin, and 86.9% to cephalothin), Korea (94% to ampicillin and 100% to cephalothin) and Malaysia (92.6% to amoxicillin and 96.3% to ampicillin).[25,26,28-31] Gentamicin

Table 2. Characteristics of Antibiotic Resistance of *Yersinia* Species in Iran

Yersinia species		Antibiotic Resistance (n)															
		AMX	AMP	GEN	TMP-SMX	TET	CIP	STR	CHL	CEF	KAN	NAL	AMK	ERY	CTX	NIT	TMP
Y. enterocolitica	%	45.9	50.3	3.6	17.1	18.3	6	9.9	2.5	83.3	-	**18.8**	-	-	-	-	-
	95% CI	7.3-90	27.4-73	0.9-13.6	10.1-27.3	8.9-33.9	1.8-17.6	6.2-15.4	0.9-7	54.3-95.4	-	13.8-25.1	-	-	-	-	-
	I^2	92.5	83.5	54	0.0	76.7	63.2	0.0	0.0	87.7	-	0.0	-	-	-	-	-
	Q	40.2	30.4	13	1.9	25.8	13.6	0.2	2.9	40.7	-	3.9	-	-	-	-	-
	P	0.00	0.00	0.04	0.74	0.00	0.01	0.99	0.81	0.00	-	0.41	-	-	-	-	-
Y. frederiksenii	%	-	35.4	4.6	-	26.2	7.7	10.5	4.6	67.3	-	**23.1**	-	-	-	-	-
	95% CI	-	16.5-60.2	1.1-16.6	-	12.1-47.7	2.7-19.9	1.9-41.8	1.1-16.6	23.7-93.1	-	9.3-46.7	-	-	-	-	-
	I^2	-	48.5	0.0	-	26.3	0.0	55	0.0	71.3	-	0.0	-	-	-	-	-
	Q	-	5.8	0.3	-	4	0.2	6.6	0.3	10.4	-	1.6	-	-	-	-	-
	P	-	0.12	0.94	-	0.25	0.97	0.08	0.94	0.01	-	0.43	-	-	-	-	-
Y. intermedia	%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	95% CI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	I^2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Q	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations, AMX, amoxicillin; AMP, ampicillin; GEN, gentamicin; TMP/SMX, trimethoprim/sulfamethoxazole; TET, tetracycline; CIP, ciprofloxacin; STR, streptomycin; CHL, chloramphenicol; CEF, cephalothin; KAN, kanamycin; NAL, nalidixic acid; AMK, amikacin; ERY, erythromycin; CTX, cefotaxime; NIT, nitrofurantoin; TMP, trimethoprim.

in combination with either fluoroquinolones or third-generation cephalosporins was recommended in life-threatening *Y. enterocolitica* infections, such as sepsis and meningitis.[1, 9] Regarding aminoglycosides, gentamicin, and streptomycin, low levels of resistance have been reported among *Y. enterocolitica* strains isolated in Iran, which is in accordance with reports from Italy (0%), China (4.3% to gentamicin and 8.6% to streptomycin), Austria (0%), Germany (0%), Turkey (0% to gentamicin and 4.8% to streptomycin), and Korea (0%).[25-30] The prevalence of resistance to other antibiotics used for the treatment of human yersiniosis (i.e., trimethoprim/sulfamethoxazole) was higher (17.1%) than those reported from Italy (0%)[25] and Malaysia,[31] but lower than that of China (74.3%).[26]

Conclusion

Among *Yersinia* species, *Y. enterocolitica* was found as the most prevalent food-borne pathogen isolated from food products and clinical specimens in this research. Results revealed a high rate of contamination of food products and human specimens with β-lactams-resistant strains of *Y. enterocolitica* in Iran. Therefore, there is a risk of transmission of these antibiotic-resistant strains to humans through the consumption of food products. Furthermore, *Y. enterocolitica* strains in Iran were mostly susceptible to aminoglycosides, fluoroquinolone, and chloramphenicol, making these antibiotics relevant for human invasive infections. However, the present results suggested that resistance to trimethoprim/sulfamethoxazole, tetracycline, and nalidixic acid was increasing in Iran, with a caveat of becoming a public health concern in the future. Therefore, to prevent the spread of bacterial antibiotic resistance and subsequent treatment failure, cautionary measures should be applied. These measures include (1) limiting the use of antibiotics in both animal and human (2) continuous monitoring of resistance, and (3) taking sanitary precautions such as consumption of pasteurized milk and cooked food products.

Authors' Contributions

FK presented the idea and performed the systematic search, data collection and meta-analysis; AS contributed to the systematic search, the analysis of the results, and the writing of the manuscript.

Ethical Approval

Not applicable.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Financial Support

None.

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