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Prevalence and Antimicrobial Resistance of *Campylobacter coli* and *Campylobacter jejuni* in the Animals, Food Products, and Human Clinical Specimens in Iran During 2004 - 2017: A Review Study

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Abstract

Context: Several studies reported that the prevalence and antibiotic-resistant of *Campylobacter coli* (*C. coli*) and *Campylobacter jejuni* (*C. jejuni*) are on the rise in Iran. To explain the prevalence and antibiotic-resistant of *Campylobacter coli* and *Campylobacter jejuni*, we reviewed related studies published from 2004 to 2017 in Iran.
Methods: We systematically searched biomedical databases (PubMed, Scopus, Google Scholar, and Web of sciences) to identify relevant studies from 2004 to 2017, either in English or in Persian. Out of 65 identified articles, 47 were published during 2004 - 2017.
Results: We found an increase in the prevalence of *C. coli* and *C. jejuni* in the animals (34.71%, 68.73%), food products (42.18%, 72%), and different clinical human samples (7.77%, 25.84%), respectively. This comprehensive review showed that *C. jejuni* is the foremost species in Iran. Accordingly, antimicrobial resistance studies performed during 2004 - 2017 reported a high rate of resistance to several antibiotics like ciprofloxacin, nalidixic acid, and tetracycline, with the exception of gentamicin, neomycin, and chloramphenicol that had a low resistance rate.
Conclusions: According to the results, novel prevention and treatment strategies against *C. coli* and *C. jejuni* infections are recommended, and these data may help in revising treatment guidelines in aviculture, stockyard and decreasing the antimicrobial resistance in human society.

Keywords: *C. coli*, *C. jejuni*, Prevalence, Antibiotic-resistant, Iran

1. Context

Campylobacter species are microaerophilic and gram-negative rods, non-fermenting, Oxidase-positive, and motile and spiral-shaped with a single polar flagellum. They can grow quite slowly (72 h - 96h) at 37°C or 42°C in primary isolation (1-3). However, *Campylobacter* is a common bacterium in animals, which is the main cause of *Campylobacter*iosis in humans. It is well documented that meat consumption may be the main source of infection in the most sporadic cases of *Campylobacter* enteritis. Consequently, *Campylobacter coli* (*C. coli*) and *Campylobacter jejuni* (*C. jejuni*) are the most common specimens isolated from human clinical specimens (3-6). Globally, 20% - 35% of human diarrheas can be attributed to *C. jejuni* (7). Illnesses caused by *Campylobacter* are usually self-limiting, hence, no treatment is required in most cases, except for immunocompromised patients that antibiotic therapy may be necessary. This therapeutic option can be a major reason for antimicrobial resistance in *Campylobacter* (8). Nowadays, several methods are available to identify *Campylobacter* spp. such as biochemical, molecular, and serological reaction methods (9-12). Indiscriminate application of antimicrobials in animal products and occurrence of antimicrobial-resistant foodborne *Campylobacter* is a serious issue in both veterinary and human medicines, which is mentioned as a public health problem by several studies (13-15).

The current review study intended to investigate the prevalence and antibiotic resistance of *C. coli* and *C. jejuni* in animal, food products, and human clinical specimens during 2004 - 2017 in Iran.

2. Evidence Acquisition

2.1. Search Strategy

We systematically searched biomedical databases (PubMed, Scopus, Google Scholar, and Web of sciences) to identify relevant studies from 2004 to 2017, either in English or in Persian. The search was performed using various combinations of the following keywords: "*Campylobacter* spp. AND Iran", "*Campylobacter* spp. AND human clinical samples AND Iran", "antimicrobial resistance AND *Campylobacter* spp. AND Iran", "*C. jejuni* OR *C. coli* AND animals AND Iran", "*C. jejuni* OR *C. coli* AND food products AND Iran". In addition, to increase the comprehensiveness of the search, additional studies were sought from the reference lists of included studies. To explain the spread and development of antibiotic resistance, we reviewed the literature published based on prevalence and antibiotic-resistant of *Campylobacter coli* and *Campylobacter jejuni*. Out of 65 identified articles, 47 were published from 2004 to 2017. The quality assessment was performed according to the Joanna Briggs Institute (JBI) checklist. It worth noting that we tried to find studies performed in various regions of the country to increase the comprehensiveness of the findings.

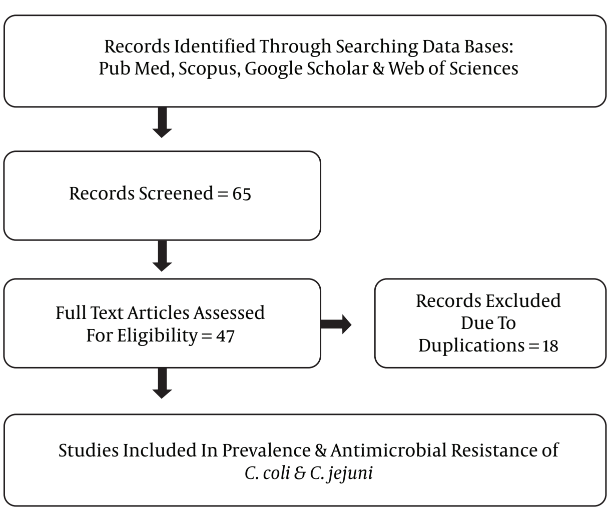

Figure 1. Flowchart of study

2.2. The Inclusion Criteria

1) Data on prevalence studies were selected and categorized based on their sample, the frequency of animal and food products separated by the region, sample size, and sample collection according to the publication year (from 2004 to 2017).

2) Clinical specimens, including blood, stool, and acute diarrhea, were collected from hospitalized patients in five studies on animal sources and food products, which typically were collected from a slaughterhouse, stockyard, and stores.

3) Research studies that were employed different methods such as bacteriological culture, biochemical tests, PCR Methods (RT-PCR, Multiplex PCR, Nested PCR, and PCR-RFLP), PFGE genotyping, and blood culture were included.

4) Studies on antimicrobial susceptibility tests (AST). In all of the studies, AST was performed by the disk diffusion (Kirby-Bauer) method using the Mueller Hinton agar. These data are provided in Tables 1-3.

2.3. Exclusion Criteria

1) Studies that did not investigate the prevalence and antimicrobial resistance on *C. coli* and *C. jejuni*.

2) Studies about other *Campylobacter* spp. and case reports.

3) Duplicate documents.

2.4. Data analysis

Statistical analyses were performed using EXCEL 2019, including numerical and averaging calculations.

3. Results

3.1. Prevalence Rates for Different Samples

Data of the spread of the investigated agent were available for the period of 2004 to 2017 (13 years). In total 9933 specimens from human tissues, as well as animal and food products, were investigated (Tables 1 and 2). The prevalent rate of *C. coli* and *C. jejuni* in several regions are provided in these with with a mean of 34.71% and 68.73% in the animals, 42.18% and 72% in the food products, and 7.77% and 25.84% in the human samples, respectively. These data demonstrated an excessive rate of *C. coli* and *C. jejuni* prevalence in Iran, especially in broilers and poultry meat. During this period, most of the studies mentioned the *C. jejuni* as the predominant bacteria, which is detected in several animal products or human specimens in different regions of the country, especially in industrial cities such as Tehran, Isfahan, and Shiraz.

Table 1. Prevalence Studies of *Campylobacter* Infections Based on Clinical Human Specimens

Authors, Publication Year	Performed Year	Region	Human Sample	Sample Size, No	Positive sample, No. (%)	Age Group	*C. coli*, %	*C. jejuni*, %	Detection Method	References
Feizabadi et al., 2007	2004 - 2005	Tehran	Diarrheic	500	40 (8)	≤ 1-12	14.2	85.8	Biochemical, PCR	(16)
Hassanzadeha et al., 2007	2007	Shiraz	Acute diarrhea	114	40 (35)	2-58	-	9.6	Culture, biochemical	(17)
Ghorbanalizadgan et al., 2014	2012 - 2013	Tehran	Stool specimens	200	12 (6)	≤ 5	1.5	4.5	Biochemical, PCR	(18)
Mobaien et al., 2016	2013 - 2014	Zanjan	Stool specimens	864	40 (4.6)	adult	-	4.6	RT-PCR	(19)
Ranjbar et al., 2017	2016	East Azerbaijan	Stool samples	1020	79 (7.7)	18 - 70	7.6	24.7	Culture, PCR	(20)

3.2. Antibiotic Resistance Patterns of Campylobacter

Antimicrobial susceptibility data for *C. coli* and *C. jejuni* isolates are shown in Table 3. These data reflect the 13-year period from 2004 to 2017 of sampling time in all identified studies. In this review, common antibiotics used for antibiotic susceptibility test with minimum and maximum resistance for *C. coli* and *C. jejuni* were selected from various studies and then listed in Table 3. In all of the studies, *C. coli* and *C. jejuni* isolates showed the lowest resistance to gentamicin, neomycin, and chloramphenicol (0% - 10%). According to the studies, *C. coli* showed the highest resistance to streptomycin (4.3% - 89.7%), ampicillin (4.3% - 82%), amoxicillin (3.7% - 79.5%), and erythromycin (0% - 40%) in comparison with the *C. jejuni*. Moreover, seven studies reported a similar resistance to the colistin (0% - 35%). The maximum resistance rate in *C. coli* and *C. jejuni* was due to ciprofloxacin (29% - 100%), nalidixic acid (13% - 100%), and tetracycline (18% - 94%). In summary, these data demonstrate a high resistance rate to these antimicrobial agents.

4. Discussion

Campylobacter is one of the most common bacterial causes of food-borne diseases. Unlike in humans, the intestinal tracts of all avian, including turkey, chicken, and quail, are suitable environments for *Campylobacter* colonization. Although it is often at a high level but brings little or no disease (11, 47). Since the numbers of cases of *Campylobacter*iosis have increased in North America, Europe, and Australia and epidemiological data from Africa, Asia, and the Middle East are still incomplete (48, 49), we performed this review to investigate the distribution of prevalence rates and antibiotic-resistant of *C. coli* and *C. jejuni* using approved, published studies in Iran for the period of 2004 to 2017. According to these results, *Campylobacter* spp. is one of the most important bacteria isolated in slaughterhouses with high resistance to different antimicrobial agents. Besides, the prevalence of *C. coli* and *C. jejuni* in animal sources (34.71%, 68.73%), food products (42.18%, 72%), and human clinical specimens' (7.77%, 25.84%) showed high rating, respectively. In Iran, the overall mean prevalence of *Campylobacter* in human clinical specimens ranged from 7.77 to 25.84%, which is within the ranges reported in low- and middle-income countries. For instance, between 2005 and 2009, 14.9% of patients in Beijing, China, were reported to be positive for *Campylobacter* species (50, 51). However, the prevalence of *Campylobacter* in animal sources and food products was higher or lower than that reported values in Korea and the USA (52, 53). This variation may be attributed to the fact that *Campylobacter*iosis is hyperendemic in these countries and due to the poor sanitation, proximity of humans and domestic animals, various sampling sizes, employing various laboratory techniques, and the effect of geographical characteristics in different studies (30, 32). Similar to other countries, human infections caused by *C. coli* and *C. jejuni*, which was detected in identified studies, typically results from consuming undercooked poultry or via cross-contamination from the inadequate handling of poultry or avian products. For example, between 1992 and 2009, 143 outbreaks were reported in England and Wales, United Kingdom. Of these, 114 were due to contaminated food or water (54). Therefore, studies recommended that the incidence of *Campylobacter* spp. in the animal product, especially in avian, can be reduced by following public biosafety principles in poultry farms and pre-slaughterhouse carcasses processing. Besides, properly cooking is necessary for killing infectious agents. Since there are no internationally agreed criteria of antibiotic susceptibility testing and breakpoint assessment for *Campylobacter* spp., it is difficult to understand the available information and draw a conclusion (55). In developing countries like Iran, most of the antimicrobial agents in the human pharmacopeia are also used in the poultry industry and there is a significant concern about the increasing antibiotic resistance in *Campylobacter* spp. isolated from both humans and animals. For instance, the tetracycline class is the most commonly used antibiotic in domestic animals farming for treatment aims, because of

Table 2. Prevalence Studies of *Campylobacter* spp. Based on Animal Sources and Food Products

Authors, Publication Year	Performed Year	Region	Animal and Food Sample	Type of Sample	Sample Size, No	Positive Sample, No. (%)	From Positive Sample		Method	Reference
							C. coli%	*C. jejuni*%		
Bakhshi et al., 2016	2004 - 2005	Tehran	Food product	Food product, Patients with Diarrhea	45	30 (66)	66.6	33.3	PCR, biochemical tests	(21)
Dallal et al., 2011	2006 - 2007	Tehran	Animal product	Chicken, beef	379	109 (28)	24	76	Culture, biochemical tests	(22)
Rahimi et al., 2010	2007	Isfahan	Animal product	Commercial poultry	348	216 (62)	19	81	PCR method	(23)
Rahimi et al., 2008	2006 - 2008	Isfahan	Animal product	Poultry meat, quail, ostrich	800	377 (47)	23.6	76.4	Culture	(24)
Kazemeini et al., 2011	2008 - 2009	Isfahan	Food product	Bovine milk	120	3 (2.5)	No detect	100	Culture, biochemical tests	(25)
Ansari-Lari et al., 2011	2009	Shiraz	Animal product	Broiler flocks	100	76 (76)	56.5	43.5	Multiplex PCR	(26)
Abdi-Hachesoo et al., 2014	2009	Shiraz	Animal product	Broiler flocks	100	83 (83)	48.2	51.8	Multiplex PCR	(27)
Jamali et al., 2015	2008 - 2010	Tehran	Animal product	Duck, goose intestinal content	471	161 (34)	14.3	85.7	Culture	(28)
Rahimi et al., 2013	2009 - 2010	Chaharmahalva Bakhtiari, Khuzestan	Animal product	Raw meat, Camel, Buffalo	379	31 (8)	22.6	77.4	Culture, Nested PCR	(29)
Rahimi et al., 2011	2009 - 2010	Shahrekord	Animal product	Chicken, turkey, quail, ostrich	494	187 (37)	8	92	Cultural, PCR	(30)
Shahrokhabad et al., 2011	2010	Rafsanjan	Animal product	Broilers slaughter	100	31 (31)	38.71	61.29	Culture	(31)
Mirzaie et al., 2011	2010	Tehran	Animal product	Turkeys, quails	125	52 (41)	80.5	19.5	Culture, biochemical tests	(32)
Rahimi et al., 2011	2011	Shahrekord	Animal product	Raw duck, goose meat	169	169 (100)	88.5	11.5	Cultural& PCR	(33)
Rahimi et al., 2013	2011	Sharekord	Animal product	Chicken, quail, sheep turkey, goat, Ostrich	214	213 (99.5)	9.3	90.7	Culture, biochemical, PCR	(34)
Hosseinzadeh et al., 2015	2011	Uremia	Animal product	Chicken wings	96	40 (41.6)	No detect	No detect	Cultural, PCR	(35)
Dabiri et al., 2014	2011 - 2012	Tehran	Animal product	Chicken, beef meat	450	121 (26.8)	23.2	76.8	Culture	(36)
Zendehbad et al., 2013	2012	Khorasan	Animal product	poultry meat, partridge, turkey	300	149 (49.6)	19.2	80.8	Cultural, PCR assay	(37)
Raissy et al., 2014	2012	Azerbaijan	Animal product	Crayfish	97	2 (2)	No detect	No detect	Cultural, PCR	(38)
Khoshbakht et al., 2015	2012	Shiraz	Animal product	Broiler feces	90	90 (100)	53.4	46.6	Multiplex PCR, PCR RFLP	(39)
Zendehbad et al., 2015	2013	Mashhad	Animal product	Broiler meat	360	227 (63)	11.9	88.1	Cultural, PCR	(40)
Khoshbakht et al., 2016	2011-2013	Shiraz	Animal product	Fecal samples of slaughtered cattle, sheep	302	270 (89)	No detect	No detect	Culture, multiplex PCR	(41)
Ehsannejad et al., 2015	2014	Tehran	Animal product	Pet birds	660	20 (3)	20	80	Cultural, multiplex-PCR	(42)
Haghi et al., 2015	2014	Zanjan	Food product	Bovine and ovine raw milk	60	0 (0)	No detect	No detect	PCR	(43)
Jonaidi-Jafari et al., 2016	2014-2015	Isfahan	Food product	Avian eggs	440	34 (7.7)	17.7	82.3	Culture, PCR	(44)
Rahimi et al., 2017	2017	Isfahan	Animal product	livestock feces from sheep, goat, cattle	400	28 (7)	21.5	78.5	Culture, PCR	(45)

its low cost and efficacy; however, it has led to a high tetracycline resistance in *Campylobacter* spp. isolated from different animal samples in Iran (30, 56-58). This resistance is comparable with the findings reported by studies performed in Poland and the USA, as well as the collective estimate prevalence worldwide (94.3%) (55, 59, 60). In this review, we observed a high rate of tetracycline, nalidixic acid, and ciprofloxacin resistance in *Campylobacter* spp., as reported by studies performed in various regions of the country from 2004 to 2017. Similar to our evaluation in 2013, the study by Wieczorek (61) found that *C. coli* had higher levels of resistance to ciprofloxacin, nalidixic acid,

Table 3. Characteristic of Antimicrobial Resistance Pattern of *C. coli* and *C. jejuni* in Studies Performed in Iran

Antimicrobial Agent	Studies Year (2004 - 2017), Number of Study	Min-Max resistant reported articles for *C. coli*, %	Min-Max Resistant Reported Articles for *C. jejuni*, %	References
Gentamicin	(2004 - 2013, 2017), (14)	0 - 8.3	0 - 10	(16, 18, 22, 28, 29, 31-34, 36, 37, 41, 44, 45)
Neomycin	(2004 - 2013, 2015), (8)	0 - 9	0 - 8.5	(16, 22, 28, 32, 36, 37, 41, 44)
Chloramphenicol	(2004 - 2013, 2017), (15)	0 - 8.4	1.4 - 8.3	(16, 22, 28, 29, 31-34, 36, 37, 40, 41, 45, 46)
Erythromycin	(2004 - 2013, 2017), (14)	0 - 40	0.8 - 7.1	(16, 22, 28, 31-34, 36, 37, 44, 46)
Streptomycin	(2004 - 2013, 2017), (12)	4.3 - 89.7	1.7 - 8.6	(16, 22, 28, 29, 31, 33, 34, 36, 37, 44-46)
Amoxicillin	(2006 - 2012, 2015 - 2017), (12)	3.7-79.5	1.7 - 31.9	(22, 28, 29, 31, 33, 34, 36, 37, 40, 44-46)
Ampicillin	(2004 - 2013, 2015 - 2017), (15)	4.3 -8 2	6.5 - 50	(16, 22, 28, 29, 31-34, 36, 37, 41, 44-46)
Colistin	(2004 - 2012, 2015), (7)	0 - 35	0 - 34.2	(16, 22, 28, 36, 37, 41, 44)
Tetracycline	(2004 - 2013, 2017), (14)	18.2 - 94	22.2 - 80	(16, 22, 28, 29, 31-34, 36, 37, 41, 44-46)
Nalidixic acid	(2004 - 2013, 2017), (14)	14.3 - 100	13 - 75.8	(16, 22, 28, 29, 31-34, 36, 37, 41, 44-46)
Ciprofloxacin	(2004 - 2013, 2017), (15)	30.3 - 100	29 - 87.7	(16, 22, 28, 29, 31-34, 36, 37, 40, 41, 44-46)

tetracycline, and streptomycin. In France, a 5-year survey of fecal samples from cattle recovered *Campylobacter* species showed an increase in the rates of resistance to fluoroquinolones (29.7 to 70.4%) (62). To be specific, these differences in occurrences of antimicrobial resistance reflect the widespread usage of these antimicrobial agents for the prevention of poultry diseases. It worth noting that these antibiotics may be inappropriate for empirical therapy in many cases. In the current review, all *C. coli* and *C. jejuni* isolates were susceptible to gentamicin. In addition, low levels of gentamicin resistance are potentially owing to the lower administration of this antimicrobial agent in poultry, duck, and goose rearing.

5. Conclusions

The findings of this review indicate that consuming poultry meat, broiler, duck, goose, camel, beef, buffalo, cow, and turkey is a potential public health risk regarding food-borne *Campylobacter*iosis and *C. jejuni* remains a predominant species in Iran. So antimicrobial resistance studies performed during 2004 and 2017 showed a high rate of resistance to several antibiotics such as ciprofloxacin, nalidixic acid, and tetracycline, except for gentamicin, neomycin, and chloramphenicol that had a low resistance rate. The surveillance of *Campylobacter* spp. and monitoring of antimicrobial agent usage in aviculture and stockyard would be useful for reducing the risk of meat contamination. Moreover, these data may assist in revising treatment guidelines as well as decreasing the antimicrobial-resistant in human societies.

Footnotes

Authors' Contribution: FM developed the study concept and wrote the first draft of the article. MASG and RR collected and interpreted the data. HZ and RR performed Critical revision of the manuscript.

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