Campylobacter *and antimicrobial resistance in dogs and humans: "One Health" in practice*

Filomena Iannino*, Stefania Salucci, Guido Di Donato, Pietro Badagliacca, Giacomo Vincifori and Elisabetta Di Giannatale

Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise 'G. Caporale', Campo Boario, 64100 Teramo, Italy

**Corresponding author at: Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise 'G. Caporale', Campo Boario, 64100 Teramo, Italy. Tel.: +39 0861 332249, e-mail: f.iannino@izs.it.*

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Summary
Increasing antimicrobial resistance in both medicine and agriculture is recognised as a major emerging public health concern. Since 2005, campylobacteriosis has been the most zoonotic disease reported in humans in the European Union. Human infections due to *Campylobacter* spp. primarily comes from food. However, the human-animal interface is a potential space for the bidirectional movement of zoonotic agents, including antimicrobial resistant strains. Dogs have been identified as carriers of the *Campylobacter* species and their role as a source of infection for humans has been demonstrated. Furthermore, dogs may play an important role as a reservoir of resistant bacteria or resistance genes. Human beings may also be a reservoir of *Campylobacter* spp. for their pets. This review analyses the current literature related to the risk of *Campylobacter* antimicrobial resistance at the dog-human interface.

Campylobacter *e resistenza antibiotica nel cane e nell'uomo: uno studio "One Health"*

Parole chiave
Campylobacter,
Resistenza antimicrobica,
Cani,
Geni di resistenza.

Riassunto
La resistenza antimicrobica in medicina e in agricoltura è uno dei problemi emergenti più importanti di Sanità Pubblica. Dal 2005 la campilobacteriosi è tra le zonosi alimentari più diffuse in Europa. L'infezione può essere contratta consumando cibo o bevande contaminate o entrando in contatto con individui o animali infetti. I cani sono portatori di *Campylobacter*. Possono quindi essere fonte di infezione per l'uomo o svolgere un ruolo importante come reservoir di batteri resistenti o di geni di resistenza. L'uomo, a sua volta, può essere serbatoio di *Campylobacter* spp. per gli animali domestici. Questa review analizza la letteratura corrente relativa al rischio di resistenza antimicrobica di *Campylobacter* nell'interfaccia cane-uomo.

Introduction

Notes on *Campylobacter* infections and therapy in humans and dogs

Campylobacteriosis is a collective description for infectious diseases caused by members of the genus *Campylobacter* which are ubiquitous bacteria. They are frequently found in the digestive tracts of mammals and wild and domestic birds. They commonly contaminate their surrounding environment, including water.

Diseases are mainly characterized by acute enteritis, extraintestinal infections, and post-infectious complications.

Campylobacteriosis has been the most frequently reported zoonotic disease in humans in Europe since 2005, and the annual number of notified campylobacteriosis cases has increased in many European countries in recent years (EFSA 2015, Tam *et al.* 2003).

Campylobacteriosis in humans is mainly caused by thermotolerant *Campylobacter* spp., however other species including the non-thermophilic *C. fetus*, are also known to cause human infection.

The species most commonly associated with human infection are *C. jejuni*, followed by *C. coli*, *C. lari*, and *C. upsaliensis* (Wieland *et al.* 2005, Leonard *et al.* 2011, EFSA 2012). In most symptomatic cases, campylobacteriosis occurs as mild and self-limiting gastroenteritis characterised by 1-3 days of low fever, vomiting, myalgia, and headaches, followed by 3-7 days of abdominal pain with watery or bloody diarrhoea. Acute infection sometimes begins with a high fever, peaking during the first days of illness. Excretion ends within 10-14 days and severe complications are uncommon (Altekruse and Tollefson 2003, Blaser and Engberg 2008, Bolton 2015).

Chronic infections or extra-intestinal infections can occur with fatal bacteraemia, hepatitis, pancreatitis, meningitis, recurrent colitis, acute cholecystitis and cystitis, cardiovascular complication, abscesses, and complications of the reproductive system (Goossens *et al.* 1987, Manfredi *et al.* 1999, Acke *et al.* 2009, Keithlin *et al.* 2014).

Antimicrobial therapy may be required in severe cases, in immune-compromised patients, or in prolonged disease.

In humans, macrolides (primarily erythromycin, or alternatively one of the newer macrolides, such as clarithromycin or azithromycin) remain the frontline agents for treating culture-confirmed *Campylobacter* cases (Ge *et al.* 2013). Quinolones (e.g., ciprofloxacin) are also commonly used because of their common use in the empirical treatment of undiagnosed diarrheal illness such as travellers' diarrhoea (Guerrant *et al.* 2001). Tetracycline, doxycycline, and chloramphenicol are alternative treatments (Ge *et al.* 2013). Serious systemic infections should be treated with aminoglycosides such as gentamicin or beta-lactamases including carbapenem and imipenem (Okada *et al.* 2008). Third-generation cephalosporins have not been proven effective for treating bacteremia due to the *Campylobacter* species other than *C. fetus* (Pacanowski *et al.* 2008).

Dogs have been identified as asymptomatic carriers of some species of *Campylobacter* and their role as a source of infection for humans has been demonstrated (Skirrow 1991, Siemer *et al.* 2004, Karenlampi *et al.* 2007, Koene *et al.* 2004). The high prevalence of *Campylobacter* infection in dogs is an important topic of public health, as shown in Table I.

Approximately 6% of human cases of campylobacteriosis are due to contact with pets (Tenkate and Stafford 2001, Rossi *et al.* 2008).

The role of *Campylobacter* as an enteric pathogen in dogs is unclear. Some studies did not find any significant relationship between diarrhoea and *Campylobacter* spp. infection (Sandberg *et al.* 2002, Workman *et al.* 2005, Acke *et al.* 2006), suggesting that the organism is a commensal, while others reported an association between infection and clinical signs (Guest *et al.* 2007, Chaban *et al.* 2010), particularly in younger dogs (Parson *et al.* 2010, Burnens *et al.* 1992).

In immune-compromised or febrile dogs, or in dogs with evidence of hemorrhagic diarrhoea, antimicrobial treatment may be indicated. In these cases, macrolides or quinolones are the antibiotics most commonly used (Marks *et al.* 2011).

Risk factors at the dog-human interface

Environment

Poor hygiene conditions may be an important source of *Campylobacter* spp. These bacteria can survive on dry surfaces for at least 7 days (Ullman and Kischkel 1981), however in slurries and dirty water, *Campylobacter* can survive for up to 3 months (Nicholson *et al.* 2005). Most surface water sources are contaminated by animal manure, which contains *Campylobacter.*

Age

Many studies demonstrated that younger dogs were more likely to act as carriers of *Campylobacter* spp. and to shed the organism (Sandberg *et al.* 2002). This may suggest an age predisposition and immunity development (Sandberg *et al.* 2002, Workman *et al.* 2005, Acke *et al.* 2006, Parsons *et al.* 2010). In a study conducted in Barbados, over 70% of *Campylobacter* positive dogs were under 1-year-old, and of these, 32.8% were younger than 9 weeks old (Workman *et al.* 2005).

Diarrhoea and enteric disease

This topic is controversial. However, as a precautionary measure, diarrhoea should be included among the risk factors.

High density housing

The prevalence of *Campylobacter* spp. is higher in dogs living in groups (for example in kennels or shelter) than in households (Workman *et al.* 2005, Acke *et al.* 2006). This is probably due to stress, increased prevalence of gastrointestinal disease, close contact with other animals, and dietary variation (Table I).

Contact with other animals

Contact between dogs and other animal species could be an important risk factor. Natural reservoirs

Table I. *Reported prevalence of dogs carrying* Campylobacter *spp. in relation to isolated species, type of sample, population sampled, geography, and detection methods.*

Bibliography	Population	Samples	Total dogs	*Campylobacter* spp.	Detection	Species	Identification Method	Geography
López *et al.* 2002	Household dogs	Faecal samples	380	17%	Culture	*C. jejuni* 12%	Phenotypic test	Argentina
Workman *et al.* 2005	Household dogs	Rectal swabs	130	46.9%	Culture	*C. jejuni* 26% *C. coli* 4% *C. upsaliensis* 2%	PCR	Barbados
Chaban *et al.* 2010	Healthy household dogs	Faecal samples	70	56%	PCR	*C. upsaliensis* 43% *C. hyointestinalis* 13% *C. jejuni* 7% *C. showae* 6% *C. coli* 0%	PCR	Canada
	Diarrhoeic Household dogs	Faecal samples	65	97%	PCR	*C. upsaliensis* 85% *C. jejuni* 46% *C. showae* 28% *C. coli* 25% *C. hyointestinalis* 18%	PCR	
Leonard *et al.* 2011	Dogs from veterinary clinics	Faecal swabs	240	22%	Culture	*C. upsaliensis* 19% *C. jejuni* 3%	PCR	Canada
Hald & Madsen 1997	Healthy puppies aged between 11 and 17 weeks	Rectal swabs	72	29%	Culture	*C. jejuni* 22.% *C. upsaliensis* 5% *C. coli* 1%	Phenotypic test	Denmark
Acke *et al.* 2009	Household dogs	Rectal swabs	147	41%	Culture	*C. upsaliensis* 10% *C. jejuni* 30% *C. coli* 1%	PCR	Ireland
Giacomelli *et al.* 2015	Household dogs	Rectal swabs	100	11%	Culture	*C. jejuni* 5% *C. upsaliensis* 5% *C. coli* 1%	PCR	Italy
	Shelter-housed dogs	Rectal swabs	50	26%	Culture	*C. jejuni* 16% *C. upsaliensis* 2% *C. hyointestinalis* 6% *C. lari* 2%	PCR	Italy
Mohan 2015	Faecal samples from walk way area	Faecal samples	498	13%	Culture	*C. jejuni* 5%	PCR	New Zealand
Salihu *et al.* 2010	Household dogs	Rectal swabs	141	28%	Culture	*C. upsaliensis* 21% *C. jejuni* 6%	Phenotypic test	Nigeria
Sandberg *et al.* 2002	Household dogs	Rectal swabs	529	23%	Culture	*C. upsaliensis* 20% *C. jejuni* 3%	Phenotypic test	Norway
	Diarrhoeic household dogs	Rectal swabs	66	27%	Culture	*C. upsaliensis* 23% *C. jejuni* 3%	Phenotypic test	
Engvall *et al.* 2003	Household dogs	Faecal samples	91	56%	Culture	*C. upsaliensis* 43% *C. jejuni* 11% *C. coli* 2% *C. helveticus* 2% *C. lari* 1%	PCR	Sweden
Holmberg *et al.* 2015	Healthy dogs under the age of 2	Rectal swabs	180	37%	Culture	*C. upsaliensis* 29% *C. jejuni* 4%	PCR	Sweden
Parson *et al.* 2010	Dogs from veterinary clinics	Faecal samples	249	38%	Culture	*C. upsaliensis* 37%	PCR	UK
Westgarth *et al.* 2009	Household dogs	Faecal samples	183	26%	Culture and direct PCR	*C. upsaliensis* 25%	PCR	UK

for *Campylobacter* spp. include chicken and other poultry, wild birds, pigs, cats, sheep, cows (Workman *et al.* 2005), and exotic pets such as turtles (Harvey and Greenwood 1985) and hamsters (Fox *et al.* 1983). The high prevalence (39.3%) reported by Workman and colleagues (Workman *et al.* 2005) in wild birds is of particular interest, as dogs can easily encounter bird faeces in parks.

Food

Any form of homemade cooked food in a dog's diet (or added to a dog's diet) may increase the risk of dogs carrying *Campylobacter* spp. (Leonard *et al.* 2011). Raw food, especially meat, is generally considered to be a source of *Campylobacter* spp. (Westgarth *et al.* 2009). A rapid change of diet can create a predisposition to enteric dismicrobism, which could in turn favour the onset of acute diarrhoea. In this condition, pathogens like silent *Campylobacter* spp., can take over, multiply, and exacerbate any gastroenteric symptoms.

Season

The season can affect both the patterns of infection in dogs and the way dogs shed *Campylobacter* spp. Some authors report a higher number of isolations during the summer and autumn months (López 2002, Mohan 2015). For example, in a study performed in Cordoba (Spain), Carbonero and colleagues (Carbonero *et al.* 2012) reported that *C. upsaliensis* peaked during the spring months, while *C. jejuni* peaked during the summer months. This is consistent with other studies performed on other species, such as cattle and sheep, where the highest prevalence was also found during the spring and summer months (Grove White *et al.* 2010).

Walking outdoors

Housed dogs have less opportunity to become infected. Dogs that escape from their homes, or are free to access the external environment, have a higher risk of being positive for *Campylobacter* spp. (Westgarth *et al.* 2009).

Note on the 'One Health' concept

The 'One Medicine' concept as described by Schwabe (Schwabe 1964) has seen unprecedented revival in the last decade. The concept has evolved into a way of thinking about epidemiology and public health that is now known as 'One Health' (Zinsstag *et al.* 2009). Rabinowitz suggested that, as humans, we should change the 'us versus them' paradigm, which implies thinking of animals as determinants of 'risk to human health', towards a perspective of 'shared risk' between humans and animals (Rabinowitz *et al.* 2008).

The 'One Health' approach recognises that the health of people is connected to the health of animals and the environment, and encourages physicians and veterinarians to work together.

According to American Veterinary Medical Association (AVMA 2008) 'One Health is the collaborative effort of multiple health science professions, together with their related disciplines and institutions (working locally, nationally, and globally) to attain optimal health for people, domestic animals, wildlife, plants, and our environment.'

Initially, 'One Health' research focused on zoonoses deriving from farm animals and wild animals. The enormous potential role of companion animals has been often disregarded. The growing number of household pets has given rise to new health issues. Among these, antimicrobial resistance is an important topic to consider within the 'One Health' approach.

Notes on antimicrobial resistance

Increasing antimicrobial resistance in both medicine and agriculture is recognised as a major emerging public health concern by various scholars and authorities, including the World Health Organization (Moore *et al.* 2002, Di Giannatale *et al.* 2014, Ozbey and Tasdemi 2014, Pezzotti *et al.* 2003, Aarestrup and Engberg 2001, WHO 2004). This has made the clinical management of campylobacteriosis cases more complex. Antimicrobial resistant enteric infections are highest in the developing world, where the use of anti-microbial drugs in animals is largely unrestricted (Lengerh *et al.* 2013). Companion animals may play an important role as a reservoir of resistant bacteria or resistance genes. Furthermore, human beings may be a reservoir of pathogens for their pets (Rutland *et al.* 2009).

Growing healthcare standards for an increasingly large population of household pets has led to a proliferation of geriatric animals that have extensive medical histories, which has included the administration of antimicrobial drugs. Large antimicrobial use exerts selective pressure on human and animal pathogens and is considered to be a major contributor to the development of antimicrobial resistance.

Antimicrobial resistance can be classified into 3 groups: intrinsic, mutational, and acquired resistance. Intrinsic resistance refers to the inherent resistance to an antibiotic that is a naturally occurring feature of the micro-organism.

Mutational resistance occurs due to a spontaneous chromosomal mutation that produces a genetically altered bacterial population that is resistant to a drug. Resistant bacteria transfer their resistance genes to a bacteria's progeny during DNA replication. Acquired resistance refers to the horizontal acquisition of a genetic element that encodes antibiotic resistance from another micro-organism. This implies that genetic elements transfer from some outside source, such as other bacteria of the same species or even between different species (Soares *et al.* 2012).

Horizontal transfer resistance genes can function through 3 main routes: conjugation, transformation, and transduction. Conjugation is the transfer of DNA fragments through a conjugative pilus or pore that forms a channel that facilitates the passage of plasmids (bacteria to bacteria). Transformation is the process whereby bacterial cells take-up free DNA from the environment and incorporate it into their genomes ('free DNA transfer'). Transduction occurs when a bacteriophage that has previously replicated in another bacterial cell, packages a portion of the host genome (donor) into the phage head and transfers the genes to another (recipient) bacterial cell ('bacteriophage-mediated transfer') (Huddleston *et al.* 2014).

Mobile genetic elements fall into 2 general types: elements that can move from one bacterial cell to another, which includes resistance plasmids and conjugative resistance transposons, and elements that can move from one genetic location to another in the same cell, which includes transposons and gene cassettes (Bennett 2005).

Plasmids are the elements that move bacterial genes from one bacterial cell to another. Conjugative plasmids are able to promote their own transfer and the transfer of other plasmids from one bacterial cell to another. In general, they exist separately from the main bacterial chromosome, although the majority of replication functions are provided by the host cell and carry a considerable variety of genes, including those that confer antibiotic resistance (Bennett 2008).

The spread of antimicrobial-resistant bacteria can occur through direct contact (petting, licking, etc.) or indirectly via the household environment, contamination of food, furnishings, etc. (Guardabassi *et al.* 2004). When they reach the new host, resistant bacteria can either colonise and infect, or remain for only a very short period of time. During this period, the resistant bacteria can not only spread their resistance genes to other bacteria residing in the new host (commensals or pathogens), but also accept resistance genes from other bacteria (da Costa *et al.* 2013).

Antimicrobial drugs exert a selection pressure on pathogenic bacteria and on commensal micro-organisms of the intestinal tract of humans and animals. Resistant commensal bacteria can constitute a reservoir of resistant genes for potentially pathogenic bacteria (Guardabassi *et al.* 2004).

Antimicrobial resistance in *Campylobacter* spp. at the dog-human interface

Several studies have shown that antimicrobial use in food animals contributes to the selection of antimicrobial resistance. It furthermore poses risks to humans because of the transmission of resistant zoonotic bacteria via the food chain and the indirect transfer of resistance genes from animals to man. Antimicrobial resistance amongst companion animals, particularly dogs, is a complex area representing an increasing public health concern. At the crux of this critical issue is the fact that dogs often live in a close proximity to humans. Close physical contact through touching, petting, and licking occurs often as a result of the perception of household pets as family members. This creates opportunities for the interspecies transmission of *Campylobacter* spp., including multidrug-resistant *Campylobacter.* However, it is difficult to ascertain how antimicrobial resistance in dogs is increasing because there is little useful data on antimicrobial drug use and resistance in companion animals. Furthermore, the heterogeneity of studies, different analytical methods employed for the isolation, identification, typing, and resistance assessment make the result comparison difficult. This indicates a need to harmonise and standardise diagnostic methods. In order to determine the real extent of antimicrobial resistance and to be able to compare data between laboratories monitoring resistance trends, standardised protocols for the determination of susceptibility to antibiotics should be used.

Table II and Figure 1 summarises the relevant literature on antimicrobial resistance in human *Campylobacter* isolates.

Among fluoroquinolones, the range of ciprofloxacin varies from 16% to 86%. A rapid increase in the proportion of *Campylobacter* strains resistant to fluoroquinolones has been reported in many countries worldwide (Luangtongkum *et al.* 2009). These antibiotics are usually employed for the treatment of undiagnosed diarrheal illnesses.

Among macrolides, the prevalence of erythromycin resistance varies from 1.5% to 28.5%. High erythromycin resistance levels were observed among strains isolated from Africa (Lengerh *et al.* 2013). Macrolides are usually employed as frontline agents for treating culture-confirmed *Campylobacter* infection.

Among aminoglycosides, gentamicin resistance varies from 0% to 18%. Aminoglycosides are used for serious systemic *Campylobacter* infections in humans.

The *Campylobacter* resistance to cephalosporins is very high (27%-100%). However, these antibiotics are limited to the treatment of *C. fetus* (Pacanowski *et al.* 2008).

Table III and Figure 2 summarises the relevant literature on antimicrobial resistance in dog *Campylobacter* spp. isolates. The highest frequency of *Campylobacter* resistance has been recorded for ampi-cloxacillin (88.2%), clindamycin (73%), and azithromycin (64.7%).

Resistance mechanisms

A combination of endogenous and acquired genes underlies resistance mechanisms. In general, mechanisms of antibiotic resistance include:

Table II. *Humans.* Relevant literature detailing *Campylobacter* antimicrobial resistance according to detection method, antimicrobial, species isolated, breakpoints, cut-off values, and geography. — *cont'd*

Author	Method	Antimicrobial	Species	Resistant	Breakpoints and cut-off values and notes	Country
Liao *et al.* 2012	Agar dilution	Ampicillin-sulbactam	*Campylobacter* spp.	5/24 (20.8%)	Breakpoints in: CLSI guidelines (CLSI 2012)	Taiwan
		Cefotaxime	*Campylobacter* spp.	21/24 (87.5%)		
		Ceftriaxone	*Campylobacter* spp.	24/24 (100%)		
		Ertapenem	*Campylobacter* spp.	3/24 (12.5%)		
		Imipenem	*Campylobacter* spp.	0/24 (0%)		
		Meropenem	*Campylobacter* spp.	0/24 (0%)		
		Doripenem	*Campylobacter* spp.	0/24 (0%)		
		Gemifloxacin	*Campylobacter* spp.	15/24 (62.5%)		
		Ciprofloxacin	*Campylobacter* spp.	15/24 (62.5%)		
		Levofloxacin	*Campylobacter* spp.	14/24 (58.3%)		
Lengerh *et al.* 2013	Agar disc diffusion	Erythromycin	*Campylobacter* spp.	10/37 (27.7%)	Concentration: Ampicillin 30 µg Amoxicillin-Clavulanic acid 30 µg Gentamicin 10 µg Tetracycline 30 µg Doxycycline 30 µg Chloramphenicol 30 µg Ciprofloxacin 5 µg Norfloxacin 5 µg Ceftriaxone 5 µg Erythromycin 15 µg Clindamycin 15 µg Trimethoprim-Sulphamethoxazole 25 µg	Ethiopia
		Clindamycin	*Campylobacter* spp.	18/44 (40,9%)		
		Trimethoprim-Sulfamethoxazole	*Campylobacter* spp.	24/44 (54.5%)		
		Ciprofloxacin	*Campylobacter* spp.	7/44 (16%)		
		Ceftriaxone	*Campylobacter* spp.	10/37 (27.7%)		
		Chloramphenicol	*Campylobacter* spp.	5/44 (11.4%)		
		Nalidixic acid	*Campylobacter* spp.	4/44 (9.1%)		
		Cephalotin	*Campylobacter* spp.	39/44 (88.6%)		
		Gentamicin	*Campylobacter* spp.	8/44 (18.2%)		
		Amoxicillin-Clavulanic acid	*Campylobacter* spp.	16/44 (36.4%)		
		Ampicillin	*Campylobacter* spp.	16/44 (36%)		
		Tetracycline	*Campylobacter* spp.	25/44 (56,8%)		
		Doxycycline	*Campylobacter* spp.	7/44 (15,9%)		
		Norfloxacin	*Campylobacter* spp.	6/44 (11.6 %)		
Abay *et al.* 2014	Disk diffusion and Etest	Amoxicillin-Clavulanic acid	*C. jejuni*	12/100 (12%)	Disk diffusion test breakpoints: Amoxicillin Clavulanic acid 30 µg Ampicillin 10 µg Gentamicin 10 µg Nalidixic Acid 30 µg Streptomycin 10 µg Tetracycline 30 µg Etest breakpoints: Ciprofloxacin ≥ 4 Enrofloxacin ≥ 2 Erythromycin ≥ 32	Turkey
		Ampicillin	*C. jejuni*	44/100 (44%)		
		Gentamicin	*C. jejuni*	0/100 (0%)		
		Nalidixic acid	*C. jejuni*	84/100 (84%)		
		Streptomycin	*C. jejuni*	3/100 (3%)		
		Tetracycline	*C. jejuni*	38/100 (38%)		
		Ciprofloxacin	*C. jejuni*	81/100 (81%)		
		Enrofloxacin	*C. jejuni*	85/100 (85%)		
		Erythromycin	*C. jejuni*	6/100 (6%)		

continued

1. The modification of the antibiotic's target and/or its expression (i.e., DNA gyrase mutations);
2. The inability of the antibiotic to reach its target (i.e., expression of the major outer membrane protein, or MOMP);
3. The efflux of the antibiotic (i.e., multidrug efflux pumps such as CmeABC);
4. The modification or inactivation of the antibiotic (i.e., β-lactamase production) (Iovine 2013).

Active efflux pump systems extrude antimicrobial agents out of bacterial cells. The best-described multi-drug efflux pump in *Campylobacter* is CmeABC, which consists of 3 components: an inner membrane transporter (encoded by *cmeB*), a periplasmic fusion protein (encoded by *cmeA*), and an outer membrane protein (encoded by *cmeC*).

CmeABC extrudes a broad range of antibiotics, dyes, heavy metals, bile salts, and detergents. Other putative efflux pumps, including CmeDEF and CmeG, may also contribute to antibiotic resistance (Akiba *et al.* 2006, Iovine 2013, Lin *et al.* 2002).

Table II. *Humans.* Relevant literature detailing *Campylobacter* antimicrobial resistance according to detection method, antimicrobial, species isolated, breakpoints, cut-off values, and geography. — *cont'd*

Author	Method	Antimicrobial	Species	Resistant	Breakpoints and cut-off values and notes	Country
Gaudreau *et al.* 2014	Disk diffusion and Etest	Erythromycin	*C. jejuni*	16/440 (3.6%)	Breakpoints in: CLSI guidelines (CLSI, 2010) susceptibilities were assessed initially by disk diffusion and later confirmed by Etest	Canada
			C. coli	7/38 (18%)		
		Ciprofloxacin	*C .jejuni*	180/440 (41%)		
			C. coli	19/38 (50%)		
		Tetracycline	*C. jejuni*	274/440 (62.3%)		
			C. coli	20/38 (52.6%)		
Riley *et al.* 2015	Broth microdilution	Ciprofloxacin	*C. jejuni*	55/180 (30.5%)	Breakpoints in: CLSI guidelines 2010 (Clinical and Laboratory Standards Institute, 2010)	Canada
			C. coli	16/39 (41%)		
		Erythromycin	*C. jejuni*	7/180 (3.9%)		
			C. coli	5/39 (12.8%)		
		Tetracycline	*C. jejuni*	116/180 (64.4%)		
			C. coli	21/39 (53.8%)		
Stockdale *et al.* 2015	Disk diffusion	Fluoroquinolone	*Campylobacter* spp.	1,710/5,890 (29.0%)	/	UK
		Macrolides	*Campylobacter* spp.	129/5,881 (2.2%)		
Thompson *et al.* 2015	Agar disk diffusion	Amoxicillin-Clavulanic acid	*C. coli*	0/20 (0%)	Breakpoints in: CLSI guidelines Clinical and Laboratory Standards Institute, 2012	Vietnam
			C. jejuni	2/44 (4.5%)		
		Ampicillin	*C. coli*	5/20 (28%)		
			C. jejuni	12/44 (26.5%)		
		Ceftazidime	*C. coli*	5/20 (25%)		
			C. jejuni	5/44 (11.3%)		
		Chloramphenicol	*C. coli*	0/20 (0%)		
			C. jejuni	1/44 (2,3%)		
		Ciprofloxacin	*C. coli*	20/20 (100%)		
			C. jejuni	30/43 (69.7%)		
		Erythromycin	*C. coli*	5/20 (25%)		
			C. jejuni	0/42 (0%)		
		Gatifloxacin	*C. coli*	2/20 (10%)		
			C. jejuni	6/44 (13.6)		
		Nalidixic acid	*C. coli*	20/20 (100%)		
			C. jejuni	34/44 (77.2)		
		Ofloxacin	*C. coli*	20/20 (100%)		
			C. jejuni	32/44 (72.7)		
		Trimethoprim	*C. coli*	17/20 (85%)		
			C. jejuni	32/43 (74.4%)		

continued

Table II. *Humans.* Relevant literature detailing *Campylobacter* antimicrobial resistance according to detection method, antimicrobial, species isolated, breakpoints, cut-off values, and geography. — *cont'd*

Author	Method	Antimicrobial	Species	Resistant	Breakpoints and cut-off values and notes	Country
Lapierre *et al.* 2016	Agar dilution	Ciprofloxacin	*C. jejuni*	20/66 (30.3%)	Breakpoints: Ciprofloxacin ≥ 4 µg/ml Erythromycin ≥ 32 µg/ml Gentamicin ≥ 16 µg/ml Tetracycline ≥ 16 µg/ml	Chile
			C. coli	4/7 (57.2%)		
		Erythromycin	*C. jejuni*	1/66 (1.5%)		
			C. coli	2/7 (28.5%)		
		Gentamicin	*C. jejuni*	0/66 (0.0%)		
			C. coli	0/7 (0.0%)		
		Tetracycline	*C. jejuni*	16/66 (24.3%)		
			C. coli	2/7(28.5%)		
Olkkola *et al.* 2016	Broth microdilution	Ciprofloxacin	*C. jejuni*	8/95 (8.4%)	Cut-off values: Ciprofloxacin 0.5 µg /l Erythromycin 4 µg /l Tetracycline 1 µg /l Streptomycin 4 µg /l Gentamicin 2 µg /l Nalidixic acid 16 µg /l	Finland
		Erythromycin	*C. jejuni*	0/95 (0%)		
		Tetracycline	*C. jejuni*	2/95 (2.1%)		
		Streptomycin	*C. jejuni*	1/95 (2.1%)		
		Gentamicin	*C. jejuni*	0/95 (0.0%)		
		Nalidixic acid	*C. jejuni*	8/95 (8.4%)		
Zhou *et al*. 2016	Agar dilution	Ciprofloxacin	*C. jejuni*	176/203 (86.7%)	Breakpoints µg/ml: Ciprofloxacin ≥ 4 µg/ml Nalidixic acid ≥ 64 µg/ml Doxycycline ≥ 8 µg/ml Tetracycline ≥ 16 µg/ml Gentamicin ≥ 8 µg/ml Chloramphenicol ≥ 32 µg/ml Florfenicol ≥ 8 µg/ml Erythromycin ≥ 32 µg/ml.	China
		Nalidixic acid (Nal)	*C. jejuni*	176/203 (86.7%)		
		Doxycycline (Dox)	*C. jejuni*	162/203 (80.8%)		
		Tetracycline (Tet)	*C. jejuni*	186/203 (91.6%)		
		Gentamicin (Gen)	*C. jejuni*	15/203 (7.4%)		
		Chloramphenicol (Chl)	*C. jejuni*	25/203 (12.3%)		
		Florfenicol (Ffc)	*C. jejuni*	64/203 (31.5 %)		
		Erythromycin	*C. jejuni*	4/203 (2.0%)		
		Cip-Nal-Dox-Tet	*C. jejuni*	151/203 (74.4%)		
		Ffc-Cip-Nal-Dox-Tet	*C. jejuni*	61/203 (29.9%)		
		Chl-Ffc-Cip-Nal-Dox-Tet	*C. jejuni*	21/203 (9.9%)		
		Gen-Ffc-Cip-Nal-Dox-Tet	*C. jejuni*	12/203 (5.9%)		

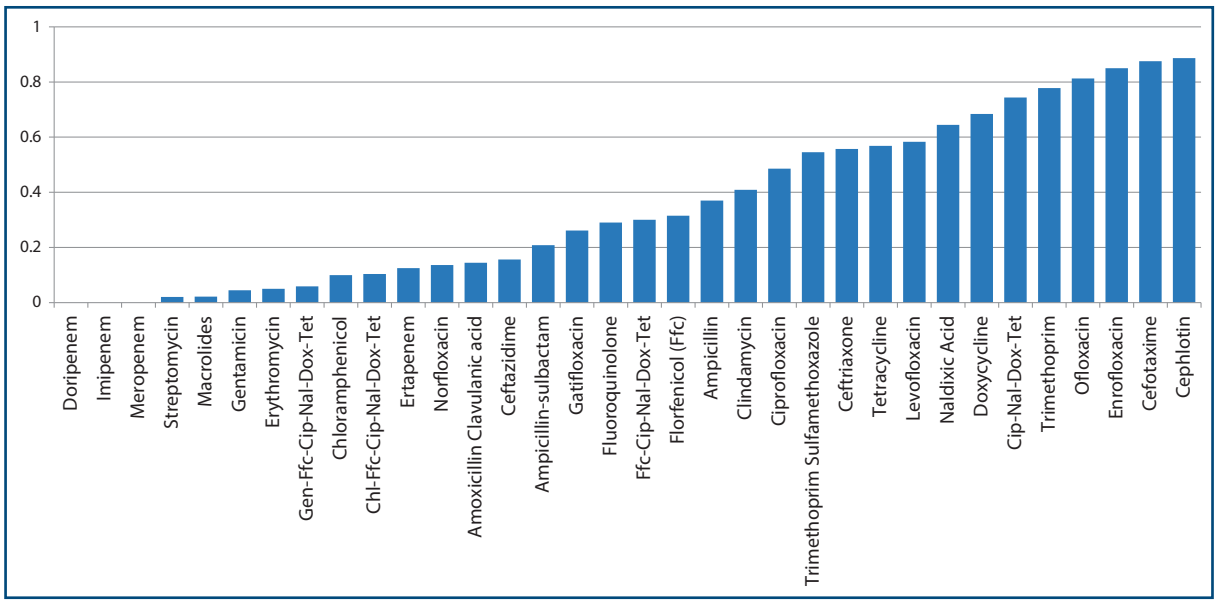

Figure 1. *Humans.* Literature detailing *Campylobacter* antimicrobial resistance.

Table III. *Dogs.* Relevant literature detailing *Campylobacter* antimicrobial resistance according to detection method, antimicrobial, species isolated, breakpoints, cut-off values, and geography. — *cont'd*

Author	Method	Antimicrobial	Species	Resistant	Breakpoints and cut-off values and notes	Country
Sandberg *et al.* 2002	E-test	Ampicillin	*C. jejuni*	0/22 (0,0%)	Isolates from dogs and cats Breakpoints: Nalidixic acid ≥ 32 µg/mL Streptomycin ≥ 8 µg/mL The other breakpoints are not available	Norway
			C. upsaliensis	0/20 (0,0%)		
		Ciprofloxacin	*C. jejuni*	0/22 (0,0%)		
			C. upsaliensis	0/20 (0,0%)		
		Chloramphenicol	*C. jejuni*	0/22 (0,0%)		
			C. upsaliensis	0/20 (0,0%)		
		Erythromycin	*C. jejuni*	0/22 (0,0%)		
			C. upsaliensis	0/20 (0,0%)		
		Gentamicin	*C. jejuni*	0/22(0,0%)		
			C. upsaliensis	0/20 (0.0%)		
		Nalidixic acid	*C. jejuni*	0/22(0,0%)		
			C. upsaliensis	1/20 (5,0%)		
		Streptomycin	*C. jejuni*	1/22 (4,5%)		
			C. upsaliensis	18/20 (90.0%)		
		Tetracycline	*C. jejuni*	0/22 (0.0%)		
			C. upsaliensis	0/20(0.0%)		
Lee *et al.* 2004	E-test	Gentamicin	*C. jejuni*	0/11 (0.0%)	Breakpoints Gentamicin 16 µg/mL Erythromycin 8 µg/mL Ciprofloxacin 4 µg/mL Tetracycline 16 µg/mL	United States
		Erythromycin	*C. jejuni*	0/11 (0.0%)		
		Ciprofloxacin	*C. jejuni*	1/11 (9.1%)		
		Tetracycline	*C. jejuni*	2/11 (18.2%)		
Tsai *et al.* 2007	E-test	Azithromycin	*C. jejuni*	32/33 (93.9%)	Break point Azithromycin ≥ 2 µg/ml Chloramphenicol ≥ 32 µg/ml Ciprofloxacin ≥ 4 µg/ml Clindamycin ≥ 4 µg/ml Erythromycin ≥ 8 µg/ml Gentamicin ≥ 16 µg/ml Nalidixic acid ≥ 32 µg/ml Tetracycline ≥ 16 µg/ml	Taiwan
		Chloramphenicol	*C. jejuni*	23/33 (69.7%)		
		Ciprofloxacin	*C. jejuni*	6/33 (18.2%)		
		Clindamycin	*C. jejuni*	29/33 (87.9%)		
		Erythromycin	*C. jejuni*	27/33 (81.8%)		
		Gentamicin	*C. jejuni*	10/33 (33.3%)		
		Nalidixic acid	*C. jejuni*	17/33 (51.5%)		
		Tetracycline	*C. jejuni*	26/33 (78.8%)		
Rossi *et al.* 2008	Agar dilution	Erythromycin	*C. jejuni*	0/24 (0,0%)	Isolates from dogs and cats Breakpoints: Erythromycin ≥ 8 µg/ml^{-1} Chloramphenicol ≥ 32 µg/ml^{-1} Gentamicin ≥ 16 µg/ml^{-1} Ampicillin ≥ 32 µg/ml^{-1} Tetracycline ≥ 16 µg/ml^{-1} Nalidixic acid ≥ 32 µg/ml^{-1} Ciprofloxacin ≥ 4 µg/ml^{-1} Enrofloxacin ≥ 4 µg/ml^{-1} One *C. jejuni* strain was multi-drug resistant to nalidixic acid, ciprofloxacin, tetracycline, and ampicillin, 5 were resistant to nalidixic acid, ciprofloxacin, and tetracycline.	Italy
			C. upsaliensis	0/38(0,0%)		
			C. helveticus	3/16 (18.7%).		
		Chloramphenicol	*C. jejuni*	1/24 (4.2%)		
			C. upsaliensis	0/38 (0,0%)		
			C. helveticus	0/16 (0,0%)		
		Gentamicin	*C. jejuni*	0/24 (0,0%)		
			C. upsaliensis	0/38 (0,0%)		
			C. helveticus	3/16 (18.7%)		
		Ampicillin	*C. jejuni*	3/24 (12.5%)		
			C. upsaliensis	3/38 (7.8%)		
			C. helveticus	0/16 (0,0%)		
		Tetracycline	*C. jejuni*	3/24 (12.5%)		
			C. upsaliensis	0/38 (0,0%)		
			C. helveticus	0/16 (0,0%)		
		Nalidixic acid	*C. jejuni*	15/24 (62.5%)		
			C. upsaliensis	3/38 (7.9%)		
			C. helveticus	1/16 (6.2%)		
		Ciprofloxacin	*C. jejuni*	15/24 (62.5%)		
			C. upsaliensis	3/38 (7.9%)		
			C. helveticus	1/16 (6.2%)		
		Enrofloxacin	*C. jejuni*	14/24 (58.3%)		
			C. upsaliensis	3/38 (7.9%)		
			C. helveticus	1/16 (6.2%)		

continued

Table III. *Dogs.* Relevant literature detailing *Campylobacter* antimicrobial resistance according to detection method, antimicrobial, species isolated, breakpoints, cut-off values, and geography. — *cont'd*

Author	Method	Antimicrobial	Species	Resistant	Breakpoints and cut-off values and notes	Country
Acke *et al.* 2009	E-test	Nalidixic acid	*C. jejuni*	19/51 (37.3%)	Isolates from dogs and cats. Breakpoints not available	Ireland
		Ciprofloxacin	*C. jejuni*	10/51 (19.6%)		
		Tetracycline	*C. jejuni*	7/51 (13.7%)		
		Ampicillin	*C. jejuni*	7/51 (13.7%)		
		Erythromycin	*C. jejuni*	6/51 (11.8%)		
		Chloramphenicol	*C. jejuni*	3/51 (5.9%)		
Kurnar *et al.* 2012	Disk diffusion	Amikacin	*Campylobacter* spp.	0/51 (0.0%)	Breakpoints: Amikacin 30 µg Amoxycillin-Clavulanic acid 20 µg Ampi-Cloxacillin 10 µg Ciprofloxacin 30 µg Chloramphenicol 30 µg Enrofloxacin 10 µg Erythromycin 15 µg Levofloxacin 5 µg Streptomycin 10 µg Tetracycline 30 µg	India
		Amoxycillin-Clavulanic acid	*Campylobacter* spp.	10/51 (19.6%)		
		Apmpi-Cloxacillin	*Campylobacter* spp.	45/51 (88.2)		
		Ciprofloxacin	*Campylobacter* spp.	41/51 (80.4%)		
		Chloramphenicol	*Campylobacter* spp.	0/51 (80.0%)		
		Enrofloxacin	*Campylobacter* spp.	35/51 (68.6%)		
		Erythromycin	*Campylobacter* spp.	46/51 (90.2%)		
		Levofloxacin	*Campylobacter* spp.	0/51 (0.0%)		
		Streptomycin	*Campylobacter* spp.	0/51 (0.0%)		
		Tetracycline	*Campylobacter* spp.	45/51 (88.2%)		
Andrzejewska *et al.* 2013	E-test	Erythromycin	*C. jejuni*	0/2 (0.0%)	Erythromycin ≥ 32 µg/ml Azithromycin 32 µg/ml Ciprofloxacin 4 µg/ml ≥ Tetracycline 16 µg/ml	Poland
		Azithromycin	*C. jejuni*	0/2(0.0%		
		Ciprofloxacin	*C. jejuni*	2/2 (100%)		
		Tetracycline	*C. jejuni*	1/2(50.0%)		
		Erythromycin	*C. coli*	0/2(0.0%)		
		Azithromycin	*C. coli*	0/2(0.0%)		
		Ciprofloxacin	*C. coli*	1/2(50.0%)		
		Tetracycline	*C. coli*	1/2 (50.0%)		
Amar *et al.* 2014	Multi locus sequence typing (MLST) and *fla*-typing	Quinolones	*C. jejuni*	25/133 (20.9%)	/	Switzerland
			C. coli	3/6 (50%)		
Sahin *et al.* 2014	Broth microdilution	Azithromycin	*C. jejuni*	1/8 (12,2 %)	Breakpoints: Azithromycin ≥ 8 µg/ml Ciprofloxacin≥ 4 µg/ml Clindamycin ≥ 8 µg/ml Erythromycin ≥ 32 µg/ml Florfenicol ≥ 16 µg/ml Gentamicin ≥ 8 µg/ml Nalidixic Acid ≥ 32 µg/ml Telithromycin ≥ 16, µg/ml Tetracycline ≥ 16 µg/ml	United States
		Ciprofloxacin	*C. jejuni*	1/8 (12,2 %)		
		Clindamycin	*C. jejuni*	1/8 (12,2 %)		
		Erythromycin	*C. jejuni*	1/8 (12,2 %)		
		Florfenicol	*C. jejuni*	0/8 (0,0 %)		
		Gentamicin	*C. jejuni*	0/8 (0,0 %)		
		Nalidixic acid	*C. jejuni*	0/8 (0,0 %)		
		Telithromycin	*C. jejuni*	1/8 (12,2 %)		
		Tetracycline	*C. jejuni*	1/8 (12,2 %)		
Olkkola *et al.* 2015	Broth microdilution and agar dilution method for Streptomycin	Erythromycin	*C. jejuni*	0/2 (0.0%)	Erythromycin > 4 mg/l Tetracicline > 1 mg/l Streptomycin > 4 mg/l Gentamicin > 2 mg/l Ciprofloxacin > 0.5 mg/l Nalidixic acid > 16 mg/l	Finland
			C. upsaliensis	0/24 (0.0%)		
		Tetracycline	*C. jejuni*	0/2 (0.0%)		
			C. upsaliensis	0/24 (0.0%)		
		Streptomycin	*C. jejuni*	0/2 (0.0%)		
			C. upsaliensis	19/24 (79.1%)		
		Gentamicin	*C. jejuni*	0/2 (0.0%)		
			C. upsaliensis	0/24 (0.0%)		
		Ciprofloxacin	*C. jejuni*	0/2 (0.0%)		
			C. upsaliensis	1/24 (0.2%)		
		Nalidixic acid	*C. jejuni*	0/2 (0.0%)		
			C. upsaliensis	1/24 (0.2%)		

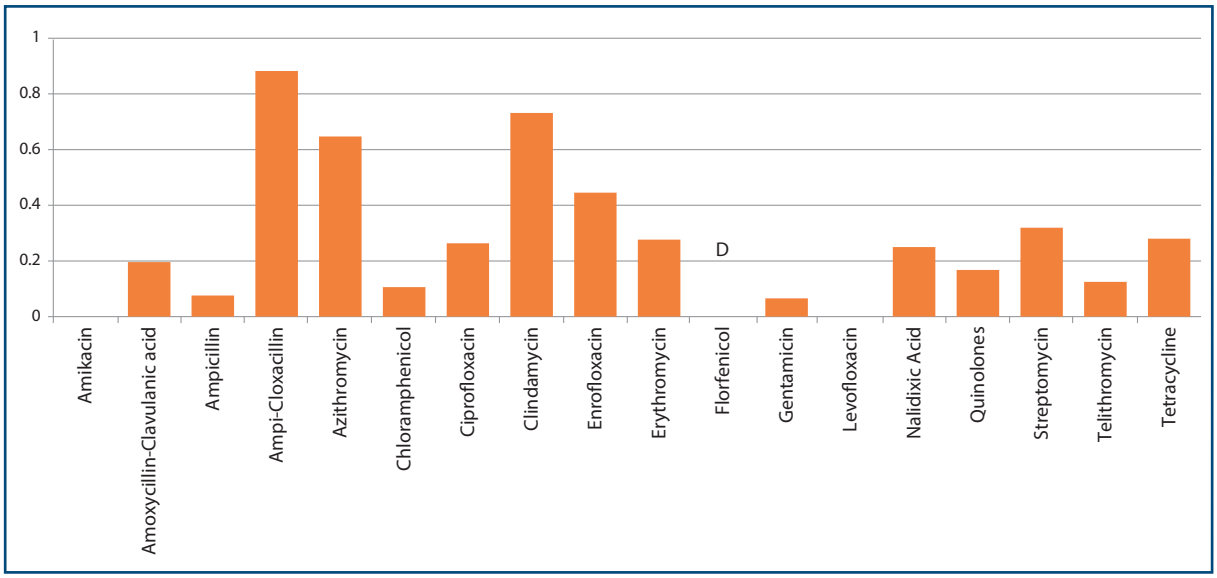

Figure 2. *Dogs.* Literature detailing *Campylobacter* antimicrobial resistance.

Multiple mechanisms of resistance can occur in a single isolate, leading to higher levels of resistance.

Resistance to quinolones

Quinolones and fluoroquinolones are broad-spectrum antibiotics used in both human and veterinary medicine and are generally considered the first choice to treat acute undiagnosed diarrhoeal illness. Campylobacteriosis in humans is clinically indistinguishable from other causes of bacterial diarrhoeal illness, and so, without evidence of *Campylobacter* infection, many cases are treated empirically with quinolones (Iovine 2013). These antibiotics inhibit the synthesis of bacterial DNA, causing cell death. Their targets are 2 bacterial enzymes, DNA gyrase and topoisomerase IV, that act in bacterial DNA replication, transcription, recombination, and repairing (Wieczorek and Osek 2013). DNA gyrase is a tetrameric enzyme that catalyses negative DNA supercoiling and consists of 2 different subunits, GyrA and GyrB (encoded by the *gyrA* and *gyrB* genes). *Campylobacter* species lack topoisomerase IV, and resistance to quinolones is mainly due to amino acid(s) substitution(s) in the *gyrA*-encoding subunit of the DNA gyrase in a region identified as the quinolone-resistance determining region (QRDR) (Dionisi *et al.* 2004, Griggs *et al.* 2009).

There are several different single GyrA modifications reported to be associated with quinolone resistance in *Campylobacter* species. The most frequently observed mutation resulting in the substitution of aminoacids is the C257T change in the *gyrA* gene, which leads to the Thr86Ile substitution, and confers high-level resistance. Other reported resistance-associated mutations include T86 K, A70T, Asp-203-Ser, Asp85Tyr, Asp90Asn, Pro104, and D90N, which are less common and do not play an important role in quinolone resistance as that which has been observed around the Thr86Ile mutation (Luo *et al.* 2003, Payot *et al.* 2006, Bachoual *et al.* 2001). Multiple mechanisms for antibiotic resistance have also been reported, including active efflux pump systems and decreased outer membrane permeability (Charvalos *et al.* 1995, Taylor and Tracz 2005). In addition to the mutations in GyrA, the multi-drug efflux pump, CmeABC, also contributes to quinolone resistance by reducing the accumulation of the agents in *Campylobacter* cells. This efflux pump acts synergetically with DNA gyrase mutation to effect high-level quinolone resistance (Iovine 2013, Wieczorek and Osek 2013).

Resistance to macrolides

Macrolides, and particularly erythromycin, are drugs that are used when campylobacteriosis is strongly suspected (Guerrant *et al.* 2001).

Macrolides interrupt protein synthesis in bacterial ribosome by targeting the 50S subunit and inhibit bacterial RNA-dependent protein synthesis. The main mechanisms of resistance to macrolides in *Campylobacter* are target modification, efflux, and altered membrane permeability. These mechanisms might act synergistically to confer high-level macrolide resistance (Iovine 2013, Cagliero *et al.* 2006). Macrolide resistance in *Campylobacter* is mainly associated with point mutation(s) occurring in the peptidyl-encoding region in domain V of the 23S rRNA gene at positions 2074 and 2075, with the 2075 substitution being the more common position (Gibreel and Taylor 2006, Vacher *et al.* 2005,

Luangtongkum *et al.* 2009). These mutations confer a high-level resistance to macrolide antibiotics (erythromycin MIC >128 µg/ml) in *C. jejuni* and *C. coli* (Gibreel *et al.* 2005). These species carry 3 copies of 23s rRNA gene, all of which are usually mutated in macrolide-resistant strains. However, some strains with lower MICs to macrolides have been found to have only 2 mutated gene copies, suggesting a gene dosage effect (Iovine 2013, Vacher *et al.* 2005). Other mutations (usually insertions) in the ribosomal proteins L4 and L22 that have lead to macrolide resistance have been described (Cagliero *et al.* 2006).

Efflux is another mechanism that causes macrolide resistance in *Campylobacter.* The CmeABC multi-drug efflux pump functions synergistically with 23S rRNA mutations to effect high-level macrolide resistance (Cagliero *et al.* 2006). In addition, the putative efflux pump CmeG may also contribute to macrolide resistance (Iovine *et al.* 2013).

Other mutations (usually insertions) in the ribosomal proteins L4 and L22 that have lead to macrolide resistance have been described. These have been associated with a low level of macrolide resistance (Lehtopolku *et al.* 2011). Macrolide resistance in *C. jejuni* and *C. coli* was conferred also from the synergy between the CmeABC efflux pump and mutations in the ribosomal proteins L4 (G74D) and L22 (insertions at position 86 or 98) (Caldwell 2008). Resistance to macrolides may also be caused by altered (decreased) membrane permeability that resulted from major outer membrane porin, which was chromosomally encoded by *porA*. (Pumbwe *et al.* 2004)

Resistance to β-lactam antibiotics

β-lactam antibiotics are the most commercially available antibiotics. In 2009, beta-lactam antibiotics accounted for more than half of the total antibiotic sales globally (Hamad 2010). Although β-lactams are still not a drug of choice for treating *Campylobacter* infections, it has recently been proposed that an oral combination of amoxicillin, a β-lactam antibiotic, and potassium clavulanate, a β-lactamase inhibitor, may provide an alternative therapy for *Campylobacter* infection (Elviss *et al.* 2009, Zeng *et al.* 2015).

These antibiotics inhibit biosynthesis of the bacterial cell wall. Several β-lactam resistance mechanisms have been described, and the most widespread and threatening mechanisms are the production of β-lactamases (the enzymes that hydrolyse the β-lactam ring) and the CmeABC multi-drug efflux pump (Lin *et al.* 2002, Alfredson and Korolik 2005). Another mechanism is the reduced uptake due to alteration in the outer membrane porine (Iovine 2013). Recently Zeng (Zeng *et al.* 2015) described a putative lytic transglycosylase (LT) Cj0843c that is required for intrinsic and acquired β-lactam resistance in *C. jejuni*.

Resistance to tetracyclines

Tetracyclines are alternative agents for antimicrobial therapy in campylobacteriosis. These are lipophilic protein synthesis inhibitors. Their primary antimicrobial effect takes place by binding to the A site in the 30S subunit, thus hindering the movement of transfer RNA and inhibiting peptide elongation (Harms *et al.* 2003). Resistance to tetracycline in *Campylobacter* principally involves a ribosomal protection protein termed Tet(O), which is widely present in *Campylobacter* isolates recovered from various animal species. This protein is part of a larger group of proteins called ribosomal protection proteins (RPPs), which includes Tet(M), Tet(Q), Tet(S), Tet(T), Tet(W), and OtrA (Chopra and Roberts 2001). Tetracycline resistance conferred by Tet(O) has become highly prevalent in *Campylobacter* worldwide. This gene is usually carried in a plasmid, although it can be chromosomally encoded (Wieczorek and Osek 2015, Connell 2003, Gibreel *et al.* 2005). The gene, which encodes ribosomal protection proteins, is located on a self-transmissible plasmid, and is probably acquired through horizontal gene transfer from *Streptomyces*, *Streptococcus*, and *Enterococcus* spp. (Batchelore *et al.* 2004). Mutations in efflux pumps can also lead to resistance to tetracyclines.

Resistance to aminoglycosides

Aminoglycoside drugs are not a priority for treating *Campylobacter* infections but, in serious bacteremia, may be used by intravenous infusion. Their bactericidal activity is due to the inhibition of bacterial protein synthesis to binding 16S rRNA (Mingeot *et al.* 1999). Aminoglicosydes exert antimicrobial activities in 2 ways: through alterations at the ribosomal binding sites, or through the production of aminoglycoside-modifying enzymes.

Mutations at the site of aminoglycoside attachment may interfere with ribosomal binding. This can cause resistance to streptomycin, since this agent binds to a single site on the 30S subunit of the ribosome. Resistance to other aminoglycosides as a result of this mechanism are uncommon since they bind to multiple sites on both ribosomal subunits and high-level resistance cannot be selected through a single step. Enzymatic modification is the most common type of aminoglycoside resistance and mechanism is of clinical importance since the genes encoding aminoglycoside-modifying enzymes can be disseminated through plasmids or transposons. The enzymatic modification decreases affinity of

aminoglycosides for the rRNA A-site (Wieczorek *et al.* 2013, Llano-Sotelo *et al.* 2002). Multiple aminoglycoside-modifying enzymes, including 3'-aminoglycoside phosphotransferase types I, III, IV, and VII, 3',9-aminoglycoside adenyltransferase, and 6-aminoglycoside adenyltransferase, have been described in *Campylobacter* infection (Zhang *et al.* 2008).

Aminoglycoside resistance was first detected in *C. coli* and was mediated by a 3'-aminoglycoside phosphotransferase (encoded by *aphA-3*). This *aphA-3* gene remains the most common source of aminoglycoside resistance in *Campylobacter* and is located in an insertioning sequence, IS607, or is found with genes encoding streptomycin resistance (encoded by aadE, a 6'-adenylyl transferase). The existence of a similar resistance cluster in *Enterococcus* suggests that *Campylobacter* acquired these genes through horizontal transfer (Gibreel *et al.* 2005). Other genes that confer kanamicine resistence in *C. jejuni* are apha-1 and apha-7 (Iovine 2013). Moreover, 9 variants of gentamicin resistance genes have been identified: *aph(2")-Ib, Ic, Ig, If, If1, If3, Ih, aac(6')-Ie/aph(2")-Ia,* and *aac(6')-Ie/aph(2")-If2*. The *aph(2")-Ib, Ic, If1, If3, Ih,* and *aac(6')-Ie/aph(2")-If2* variants were identified for the first time in *Campylobacter* (Zhao *et al.* 2015). The contribution of efflux to aminoglycoside resistance is less clear, but is less important than the plasmid-borne drug-modifying enzymes described previously (Iovine 2013).

Antimicrobial susceptibility testing methods

Several antimicrobial susceptibility testing (AST) methods such as disk diffusion, e- test, broth dilution, and agar dilution are available to test *in vitro* bacterial susceptibility to antimicrobials and to provide a reliable predictor of how an organism is likely to respond to antimicrobial therapy in the infected host. This type of information helps clinicians to select the appropriate antimicrobial agent. The use of genotypic approaches for the detection of antimicrobial resistance genes has also been promoted as a way to increase the speed and accuracy of susceptibility testing.

When used in conjunction with phenotypic analysis, genetic tests increase sensitivity, specificity, and the speed of detection for specific resistance genes.

Conclusions

Antimicrobial resistance in *Campylobacter* is a public health challenge. Dogs live in close contact with humans and there is increasing evidence that pets and their stools may be a reservoir for antimicrobial-resistant bacteria. This poses a new threat to urban hygiene.

Campylobacter spp. continues to be a leading cause of bacterial diarrhoea illness throughout the world. Antimicrobial resistance to the drugs used to treat these illnesses can prolong the duration of illness and may compromise the treatment of patients with bacteraemia.

The same antimicrobials used in dogs are used in humans. The major concern to both humans and animals is the resistance to macrolides, quinolones, and aminoglycosides such as gentamicin, which are the drugs used to treat serious campylobacteriosis.

Drug-resistant *Campylobacter* can spread from humans to dogs and viceversa through direct contact or, indirectly, through the common environment. Thus, an integrated 'One Health' approach to surveillance and intervention is required. Antimicrobials are essential for the health of animals and humans, but it is extremely important to apply the principles of prudent use in order to contain the development of antimicrobial resistance.

It is advised that veterinarians strictly observe the following instructions from the EU-COMMISSION NOTICE - Guidelines for the prudent use of antimicrobials in veterinary medicine (EU-COMMISSION NOTICE 2015):

- The prescription and dispensation of antimicrobials must be justified by a veterinary diagnosis in accordance with the current status of scientific knowledge.
- Where it is necessary to prescribe an antimicrobial, the prescription should be based on a diagnosis made following the clinical examination of the dog by the prescribing veterinarian. Where possible, antimicrobial susceptibility testing should be carried out to determine the choice of antimicrobial.
- Routine prophylaxis must be avoided.
- All information relating to the animals, the cause and the nature of the infection, and the range of available antimicrobial products must be taken into account when making a decision regarding antimicrobial treatment.
- A narrow-spectrum antimicrobial should always be the first choice unless prior susceptibility testing – where appropriate supported by relevant epidemiological data – shows that this would be ineffective. The use of broad-spectrum antimicrobials and antimicrobial combinations should be avoided (with the exception of fixed combinations contained in authorized veterinary medicinal products).
- The off-label use of the compounds in dogs

should be avoided and strictly limited to very exceptional cases, and only when laboratory antimicrobial susceptibility tests have confirmed that no other antimicrobial would be effective.

- Antimicrobial treatment must be administered to dogs according to the instructions given in the veterinarian's prescription.
- The need for antimicrobial therapy should be reassessed on a regular basis in order to avoid unnecessary medication.
- The perioperative use of antimicrobials should be minimized by using aseptic techniques.
- The pharmacovigilance system should be used to obtain information and feedback on therapeutic failures, so as to identify potential resistance issues in the case of use of existing, new or alternative treatment options.

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