Antibiotic Resistance in *Campylobacter jejuni*: Mechanism, Status, and Public Health Significance

Javed Ahamad Khan, Hussein Hasan Abulreesh, Ramesh Kumar, Samreen, and Iqbal Ahmad

Abstract

Emergence of antibiotic resistance is a never-ending process in the bacteria due its vast capacity to resist and acquire various resistance mechanisms against antibacterial drugs. *Campylobacter* is a well-known pathogenic bacteria to human and animals and survive in different environment including foods. Species of campylobacters is responsible of gastritis and diarrheal and other diseases. Common resistance mechanisms present in Gram-negative bacteria include modification in the target site of antibiotic, inability of the antibiotic to reach its target by expressing major outer membrane proteins (MOMPs), efflux action of the antibiotic through CmeABC pumps, and inactivation or modification of the antibiotic. The plasmid along with chromosomal encoded genes are responsible for resistance. Mutation and acquisition of resistance genes are the common genetic mechanism found in *Campylobacter* spp.; considering the widespread occurrence of drug-resistant campylobacters in the environment, specific strategies to control the emergence and spread are needed. In this chapter, we have reviewed the recent literature on the mechanism of resistance and current status of prevalence of *Campylobacter jejuni* in the environment and its significance in human health.

J. A. Khan
School of Graduate Studies, Quantum University, Roorkee, Uttrakhand, India

H. H. Abulreesh (✉)
Department of Biology, Faculty of Applied Science, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia
e-mail: hhabulreesh@uqu.edu.sa

R. Kumar
Division of Biochemistry, Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, India

Samreen · I. Ahmad
Department of Agricultural Microbiology, Faculty of Agricultural Sciences, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

I. Ahmad et al. (eds.), *Antibacterial Drug Discovery to Combat MDR*,
https://doi.org/10.1007/978-981-13-9871-1_4

Keywords
Campylobacter · *C. jejuni* · Antibiotic · Antibiotic resistance · Public health

1 Introduction

Campylobacters are spiral-shaped Gram-negative foodborne pathogenic bacteria which come in the family of *Campylobacteriaceae*. On the basis of morphological characteristics such as curved, spiral, or rod-shaped, the genus *Campylobacter* consists of 25 different species; two are provisional species and while eight are subspecies (Kaakouch et al. 2015). The natural habitat of *Campylobacter* species is believed to be the intestinal tracts of wild birds, poultry, pets (cats and dogs), cattle, and pigs (Abulreesh et al. 2017). The major primary cause of human campylobacteriosis is the intake of poultry-contaminated products. However, contaminated water, raw milk, and the handling of wild birds are also important sources of human infections (Abulreesh et al. 2006). Campylobacters are major cause of foodborne infections; it accounts for around 550 million foodborne illnesses annually, with 33 million cases of mortality worldwide, where children under the age of 5 years old are frequently susceptible, with estimated 220 million cases per year (Azrad et al. 2018). *C. jejuni* is the most common cause of human's gastroenteritis all over the world, whereas *C. coli* leads to total 1–25% of diarrheal infections associated with *Campylobacter* (Havelaar et al. 2015; Kaakouch et al. 2015; Natsos et al. 2016). Besides the clinical symptoms of gastroenteritis, *C. jejuni* can be responsible for further health complications, such as extraintestinal infections ranging from bacteremia to meningitis; furthermore, *C. jejuni* is a major risk factor for postinfectious complications like reactive arthritis, bowel syndrome, and Guillain-Barre syndrome (GBS), a neurological disorder causing immobilized muscles (Fitzgerald 2015; Kaakouch et al. 2015; Otigbu et al. 2018). Dissemination of *Campylobacter jejuni* to human populations occurs most commonly via the consuming foods of animal origin like incompletely cooked poultry meat or contaminated poultry products and unpasteurized milk. The ingestion of contaminated drinking water is also considered as an important route in transmission of the organism, while the handling of domestic pets, poultry, and wild birds is an established source of the infection (Abulreesh et al. 2006, 2017; Pitkanen 2013; Natsos et al. 2016). Although many of the infections of *Campylobacter* are mild, self-limiting, and generally resolved within a few days to weeks without follow-up of antibiotics, prolonged or complicated infections sometimes may occur, especially in young, elderly, and immune-compromised persons (Fitzgerald 2015; Kaakouch et al. 2015; Otigbu et al. 2018).

According to the World Health Organization (WHO), "antibiotic resistance" is the mechanism adopted by bacteria that makes them unresponsive toward antibacterial drugs (WHO 2018). A simple use of antibiotics creates the antimicrobial

resistance in microbes; however, the irrational consumption of antibiotics in humans including animals has developed the alarming situations and provided the opportunity for rising of superbugs also (WHO 2018). The antibiotic resistance is always developed by the bacterial cells using either natural (intrinsic) mechanisms such as modification of bacterial cell enzymes, restriction for the penetration of antibiotic in bacterial cell, and changes in the drug target site or acquired mechanisms such as antibiotic target modifications, reduction or barring cell permeability for penetration of drug, decreased influx of antibiotics by expressing efflux pumps, drug-inactivating enzyme production, and metabolism of an alternate pathway that bypass the mode of action of drug and biofilm development (Munita and Arias 2016).

One of the controlling measures of campylobacteriosis is fluid therapy which is most effective, whereas treatment with antibacterial agents is required in immunocompromised patients with severe symptoms. The most commonly used antimicrobial agents which is effective against *Campylobacter* infections are the class of macrolides (e.g., erythromycin) and fluoroquinolones antibiotics (e.g., ciprofloxacin). Tetracyclines have been regarded as an alternative drug of choice in treating the complications of campylobacteriosis; however, their use is limited (Wieczorek and Osek 2013). In recent years, the apocalypse of antimicrobial resistance and its spread has become a serious dilemma to public health in both developing and developed countries. *Campylobacter jejuni* with resistance to agents belonging to a wide number of antimicrobial classes like fluoroquinolones, macrolides, beta-lactams, tetracyclines, and aminoglycosides have been detected in clinical and environmental samples worldwide (Zhu et al. 2006; Luangtongkum et al. 2009; Mozina et al. 2011; Kaakouch et al. 2015; Geissler et al. 2017; Silva et al. 2018; Sierra-Arguello et al. 2018).

There are a number of contributing factors that have been recognized that are responsible for emergence and spread of antibiotic resistance in bacteria. These factors include indiscriminate use of antibiotics in routine clinical practice, particularly the unnecessary consumption of antibiotics during the course of viral infections, prescription of broad-spectrum antibiotics, and the overuse of antimicrobial agents in agricultural practices (Zhu et al. 2006; Luangtongkum et al. 2009; Reddy and Zishiri 2017). Antimicrobial resistance can spread easily through countries via travelling from one continent to another; migration of a large number of population to other countries due to increase in globalization, either for work or tourism, is believed to be common cause of the spread of antibiotic-resistant bacteria globally (Memish et al. 2003; von Wintersdorff et al. 2014; Anjum et al. 2016). Campylobacters have an intense alarming restriction modification system allowing bacteria to prevent the entry of foreign genetic material inside the cell. There is a built-in transformable system in *C. jejuni*, and the acquisition of various resistance genes from other related or unrelated bacteria has been described (Iovine 2013; Wieczorek and Osek 2013). Because of all these reasons, the study of the resistance mechanisms in *Campylobacter jejuni* is important for both human and veterinary medicine.

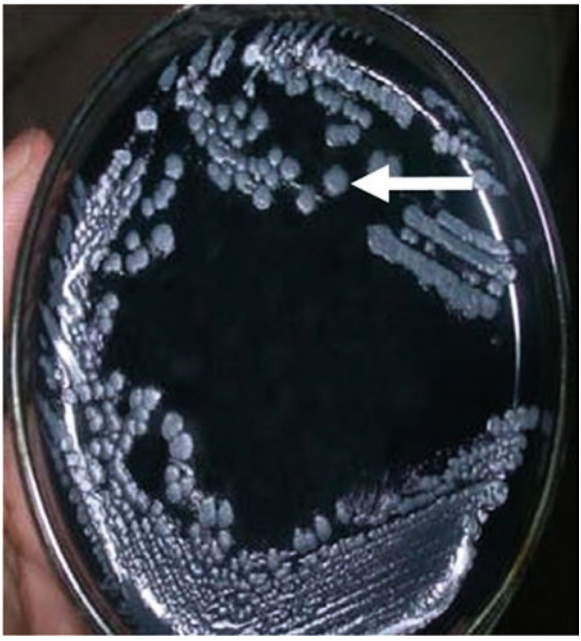

Fig. 1 *Campylobacter jeuni* colonies on modified charcoal cefoperazone deoxycholate agar (mCCDA), blood-free agar

The genetic elements that are involved in the resistance mechanisms may be either plasmid borne or chromosomal, representing a combination of indigenous and/or acquired genes. In *Campylobacter jejuni*, the mechanisms of antibiotic resistance involve (i) antibiotic target modification or alteration of its expression (i.e., mutations in DNA gyrase), (ii) accessibility of antibiotic to reach its target site (i.e., major outer membrane protein or MOMP expression, (iii) antibiotic extrusion through efflux pumps (i.e., such as CmeABC efflux pumps), and (iv) inactivation or modification of the antibiotic (i.e., β-lactamase production) (Iovine 2013; Wieczorek and Osek 2013; Allos et al. 2015). The purpose of the present review is to highlight the resistance mechanism acquired by *Campylobacter jejuni* against different antibiotics generally used for the treatment of Campylobacteriosis (Figs. 1 and 2).

2 Antibiotic Resistance Mechanism in *Campylobacter jejuni*

2.1 Resistance to Quinolones

The fluorinated 4-quinolones are a group of wide variety of antibiotics that are found effective against various infectious diseases. Few examples of the group include ciprofloxacin, moxifloxacin, and gatifloxacin. These groups of compounds possess carboxylic acid group at 3rd position of primary ring structure, whereas some newly

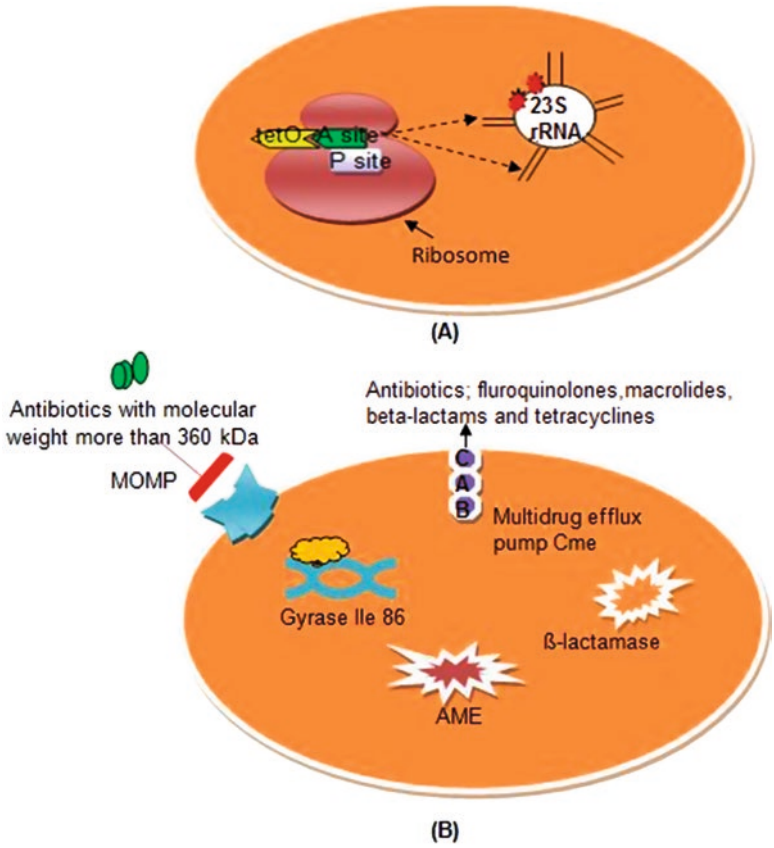

Fig. 2 Mode of antibiotic resistance in *Campylobacter jejuni*. (**a**) The ribosome is the site for the two main mechanisms of antibiotic resistance. Tetracycline is restricted at the A site through the binding of the tetO protein but for continued protein synthesis it still allows the access of tamino-acyl trNA. Point mutation in the domain v region of 23S rRNA (as shown in black) at position 2075 mainly and less frequently at position 2074 (indicated by red stars) decreases macrolides binding affinity and causing resistance toward these antibiotics. (**b**) The entry of most antibiotics having molecular weight larger than 360 kDa or negatively charged is restricted by the two major outer membrane proteins (MOMP). The most common mode of fluoroquinolone resistance is substitution of Thr-86-ile in DNA gyrase that confers high level of resistance toward such antibiotic. The resistance against fluoroquinolones, β-lactams, macrolides, and tetracyclines is contributed by CmeABC; multidrug efflux pump to aminoglycoside-modifying enzymes (AME) such as amino-glycoside phosphotransferase are the major mechanism of resistance of aminoglycoside, while β-lactam resistance is contributed by β-lactamases of the penicillinase type including Ambler class D OXA-61

identified fluoroquinolones antibiotics also have fluorine substituent at 6 position and a piperazine group at position 7 (Pomeri 2011).

The first documentation on quinolone-resistant *Campylobacter* was described during the late 1980s and suggested that such resistance was derived from the

acquisition of fluoroquinolone-resistant strains from animal sources (Iovine 2013). Furthermore, numerous research studies have highlighted that resistances emerged with injudicious usage of antimicrobial drugs particularly fluoroquinolones, in the form of growth supplements in food animals or as therapeutics in poultry flocks (Kovac et al. 2015; Collado et al. 2018; Khan et al. 2018; Wieczorek et al. 2018). It was also found that several clones of *Campylobacter* were selected by the fluoroquinolone drugs suggesting that the resistance did not arise from the spread of single resistant clone (Kovac et al. 2015; Collado et al. 2018).

Fluoroquinolones inhibits synthesis stages of *C. jejuni* DNA that causes cell death. These antibiotics target two important enzymes of bacterial replication machinery, topoisomerase IV, and DNA gyrase which participate mutually in transcription of bacterial DNA, replication repairing of DNA, and its recombination. The products of topoisomerase genes and gyrase are topoisomerase IV and DNA gyrase, respectively, whereas ParC and ParE and GyrA along with GyrB subunits pairs of gyrase and topoisomearse IV, respectively. It is found that the predominant resistance determinants of fluoroquinolone are chromosomally encoded and *Campylobacter jejuni* cells are devoid of plasmid-borne quinolone-resistant determinants like qepA and qnr, aac(6′)-Ib-cr have not distributed. Although the genes that encode topoisomerase IV (parC/parE) enzyme also participate in quinolone resistance in other Gram-negative bacteria, such genes are not present in *Campylobacter jejuni* (Ge et al. 2013; Iovine 2013; Wieczorek and Osek 2013; Gouvea et al. 2015; Tang et al. 2017a, b).

In Campylobacters including *C. jejuni*, the fluoroquinolone resistance is due to point mutations, which occurs through amino acids substitution in the resistance-determining region (QRDR) of quinolone in DNA gyrase A (GyrA) (Iovine 2013; Wieczorek and Osek 2013; Tang et al. 2017a, b). The quinolone-resistance-determining regions (QRDR) are localized inside DNA-binding domain that are making surface core of DNA gyrases (Ge et al. 2013). In *Campylobacter* species, several different single GyrA mutations such as Thr86Ile, Thr86Lys, Thr86Val, Asp90Asn, Asp90Tyr, and Thr86Ala have been recognized which are associated with fluoroquinolone resistance (Iovine 2013; Wieczorek and Osek 2013; Tang et al. 2017a, b). The most commonly observed mutation that leads to Thr86Ile substitution in the DNA gyrase causing high-level resistance to this group of antibiotics is the C257T. The mutations A70T, T86K, and D90N are some other but less commonly reported and do not show significant importance in quinolone resistance as high as found in Thr86Ile mutations (Iovine 2013; Wieczorek and Osek 2013; Tang et al. 2017a, b). A high resistance to ciprofloxacin has been observed due to point mutation Thr86Ile whereas Thr86Ala linked with resistance to nalidixic acid and lower ciprofloxacin resistance (Wieczorek and Osek 2013; Iovine 2013). Furthermore, double point mutations in the gene gyrA together with Asp90Asn or Asp85Tyr or Pro104Ser have also been previously reported (Iovine 2013; Wieczorek and Osek 2013). *C. coli* and *C. jejuni* are devoid of secondary target for the fluoroquinolones antibiotics facilitating the rise of

Table 1 Mode of antibiotic resistance in *Campylobacter jejuni*

Class of drug	Antibiotic	Resistance mechanism
β-lactam	Penicillin, oxacillin, ampicillin	1. Inactivation of the antibiotic by β-*lactamase* enzyme (*penicillinase*, OXA-61)
		2. Decreased membrane permeability of most anionic and Molecular weight higher than 360 kDa antibiotics due to MOMP
		3. Efflux action through CmeABC and possibly others
Fluoroquinolone	Ciprofloxacin, nalidixic acid	1. Modification of the target of enzyme DNA *gyrase* (Thr-86-ile; also Asp-90-Asn, Ala-70-Thr)
		2. Efflux action of CmeAB
Macrolides	Azithromycin, erythromycin	1. Mutations in 23S ribosomal RNA (rRNA)
		2. Contribution of mutations in ribosomal proteins L4/L22 is probably minor
		3. Efflux action through CmeABC and possibly others
		4. Decrease in membrane permeability due to MOMP
Aminoglycosides	Gentamycin	1. Modification of the antibiotic by aminoglycoside-modifying enzymes (AphA, Aade, Sat)
		2. Contribution of efflux action is not clear
Tetracyclines	Tetracycline	1. Modification of the target ribosomal A site by TetO binding
		2. Efflux action through CmeABC and possibly others
		3. Contribution of decreased membrane permeability due to MOMP is not clear

fluoroquinolone-resistant phenotype (Luangtongkum et al. 2009; Iovine 2013; Frasao et al. 2015; Tang et al. 2017a, b) (Table 1).

The decrease in permeability of outer membrane and an extrusion of drugs are two other mechanisms that have been found responsible for quinolone resistance in *Campylobacter jejuni*. The CmeABC multidrug efflux pump has been recognized as the major efflux mechanism that works in coordination with GyrA mutations and leads to antibiotic resistance toward the several antibiotics including fluoroquinolones and macrolides. CmeABC efflux pump is encoded by an operon of cmeC, cmeB, and cmeA genes (Ge et al. 2013; Tang et al. 2017a, b). These three genes encode an outer membrane protein channel, an inner membrane drug transporter, and periplasmic fusion protein, respectively (Iovine 2013; Wieczorek and Osek 2013). In addition, emergence of quinolone resistance during therapeutic treatment has also been well identified. It is predicted that 10% of *Campylobacter* enteritis patients treated with a fluoroquinolone harbor quinolone-resistant strains. This resistance development to fluoroquinolone has reported within 24 h of treatment with this group of antibiotics. However, prolonged treatment with these drugs, particularly in the immunocompromised patients, is also one of the risk factors observed associated with resistance. On the other hand, a naturally existing resistance toward the fluoroquinolone (ciprofloxacin) was also observed in the populations of bacteria found in environmental and food samples. The variation in DNA gyrase (target site of fluoroquinolones) was observed

to greater extent after DNA sequence analysis. It was also reported that there is same type of alterations in the target site sequence as found in isolated strains from clinical sources without applying any selective pressure (Alfredson and Korolik 2007; Weiczorek and Osek 2013; Reddy and Zishiri 2017).

2.2 Resistance to Macrolides

A majority of macrolide antibiotics are produced from Streptomyces and related genera. Erythromycin was the first macrolide antimicrobial isolated from natural product of Saccharopolyspora erythraea (Gaisser et al. 2000). Now the macrolides have become a drug of choice that has been regarded as safe and effective antimicrobial agents against most of Gram-positive as well as Gram-negative microorganisms involving *Campylobacter jejuni* and other members of this genus (Arsic et al. 2017). Macrolide antibiotics are large molecules with molecular weight larger than 700 kilobase (kb). The mechanism of action of these antibiotics is to bind reversibly to the 50S subunit of bacterial ribosomes on the P site and thus inhibiting protein synthesis. The associated members of the macrolides group include erythromycin, clarithromycin, azithromycin, telithromycin (a type of ketolide), tilmicosin, and tylosin. Erythromycin is considered as treatment of choice for campylobacteriosis. The latter two members (Tylosin and tilmicosin) are approved for the use as veterinary medicine (Hao et al. 2016).

The principal mechanisms of resistance to macrolides in *Campylobacter jejuni* include modification of target site and alteration in membrane permeability and efflux pump (Iovine 2013). The high-level macrolide resistance is facilitated by synergistical act of target modification and efflux pump mechanism by the organism. The high-level macrolide resistance has conferred due to point mutations within domain V of the 23S rRNA gene, in the peptidyl-encoding region at the position of 2074 and 2075 (corresponds to the position of 2058 and 2059 in *E. coli* numbering). The substitution at 2075 position has been observed more commonly (Bollinger and Kathariou 2017). Usually, *C. jejuni* comprises of mutated three copies of 23 s rRNA genes present in macrolide-resistant organisms. However, few strains of *C. jejuni* with decreased MICs to macrolides have been reported to carry only two copies of mutated genes and suggested macrolide dosage effect on genes responsible. *C. jejuni* strains having single point mutations in 23S rRNA genes have not been observed. On the other side, mutations (usually insertions) in the L22 ribosomal proteins (insertional mutation at position of 86 or 98) and L4 (G74D) have found responsible to macrolide resistance. However, these mutations are not recognized as major mode in case of tetracycline (Arsic 2012; Weiczorek and Osek 2013).

It is also observed that the greatest hurdle for the generation of macrolide resistance in strains of *Campylobacter jejuni* have been found with increased frequency compared to that of fluoroquinolone resistance. It is observed that tylosin resistance was developed after the administration of this antibiotic as growth promotion dose for several weeks in poultry. It is also found in a competition experiments that macrolide resistance imparts a fitness cost over fluoroquinolone-resistant *Campylobacter*.

These two important factors along with decreased spontaneous mutation frequency foremost to macrolide resistance (approximate 10^{-10}/cell/generation) making them drug of choice for treating complications of Campylobacteriosis. In multidrug efflux pump, a mechanism was adopted by *C. jejuni* against the action of macrolides antibiotics where CmeABC contributes an important role. It performs in a synergistic way with 23S rRNA mutations and exhibits elevated level of resistance toward this group of antibiotics. In macrolide-resistant mutant strains that lack mutations in 23S rRNA gene, antisense-mediated gene silencing of cmeA or disruption of cmeB gene causing deactivation of the CmeABC efflux pumps that leads to reversion into a macrolide-sensitive phenotype. It is also found that CmeG is assumed to act as efflux transporter, also contributing resistance to macrolide that has been examined in insertional mutagenesis experiments in erythromycin resistance vs. the wild-type parent of CmeG. It was revealed from the experiment that CmeG can cause an eight-fold reduction in erythromycin resistance. In *C. jejuni*, another mechanism for macrolide resistance that includes alterations in permeability of outer membrane mediated through expression of major outer membrane porin (MOMP) which is the product of chromosomal porA gene. These porins makes transmembrane pores in outer membrane facilitating the passive diffusion of many antibiotics including hydrophilic molecules in Gram-negative bacteria. The various properties of these pores such as size and ionic charge determine the selectivity for various molecules passing through these pores. In *C. jejuni*, these MOMP forms cation-selective pores which are smaller in size as found in the *E. coli*. Thus, it checks the influx of many antibiotics having molecular weight more than 360 kDa like the case of antibiotics macrolides having molecular weight more than 700 kDa, since macrolides have been found to show significant therapeutic efficacy against the *C. jejuni* strains. Therefore, such drugs must have the potential to cross the barriers of outer as well as cytoplasmic membranes. For this facilitation, these porins make an aqueous environment for the movement of hydrophilic molecules whereas hydrophobic macrolides are relatively considered to gain entry inside the cytoplasm through a "hydrophobic pathway in Gram-negative bacteria" (Iovine 2013).

2.3 Resistance to Tetracyclines

The tetracyclines resistance in *Campylobacter jejuni* is contributed by the (*O*) gene, which is widely distributed in the bacterium (Dasti et al. 2007). These tetracyclines bind to magnesium cations (Mg^{2+}) and pass through the outer membrane porin channels followed by periplasmic space where they dissociate from magnesium and passively travel into the cytoplasm to bind with 30S ribosomal subunit. The primary antimicrobial action of tetracycline is carried out through directed steric hindrance via binding to 30S ribosomal subunit on the A site. Thus, it hinders the easy movement of charged amino acyl transfer RNA (tRNA) and consequently inhibits elongation of peptide. The (*O*) gene encodes ribosomal protection proteins (RPPs), and it is localized on 45–58 kb self-transmissible plasmid. The (*O*) gene has been shown

to provide increased expression of tetracycline resistance (512 mg/L). The studies demonstrate that these RPPs have been found to recognize an open bacterial ribosomal A site and then bind to it. This induces a conformational change and release bounded tetracycline molecule. Tetracycline antibiotics are the subject of ribosomal protection protein (RPP)-mediated resistance that includes Tet(M) and Tet(O). The typical tetracycline binds to ribosome and inhibits elongation phase of protein synthesis by preventing lodgings of the aminoacyl-tRNA (aa-tRNA) on A site of ribosomal. The introduction of new amino acids is, therefore, prevented in the growing polypeptide chain. The presence of an insertion element IS607 showing similarity to IS607 present on the genome of *Helicobacter pylori* has been reported to found on (*O*)-carrying plasmids. Moreover, it is possible that dissemination and acquisition of (*O*) is mediated through mobile genetic elements other than transmissible plasmids. The G-C ratio, hybridization analysis, sequence homology, and codon usage demonstrate that the *Campylobacter* (*O*) gene was probably inherited through horizontal gene transfer from either *Enterococcus* spp., *Streptococcus*, or *Streptomyces*. The (*O*) genes that are showing 75–76% sequence homology with *Streptococcus pneumoniae* tet (M) genes with 40% G-C content (Alfredson and Korolik 2007; Iovine 2013).

2.4 Aminoglycoside Resistance

Aminoglycosides are also inhibitors of protein synthesis in various Gram-positive and Gram-negative bacteria. They are amino-modified sugars with a molecular weight that ranges from 445 to 600 kDa positively charged and hydrophilic in nature. The most commonly used members of aminoglycosides group include neomycin, amikacin, tobramycin, gentamicin, streptomycin, and kanamycin. Firstly, the aminoglycosides bind to the negatively charged membranes of bacteria followed by reversible attachment to the 30S subunit of the ribosome. This second phase of interaction is rapid but reversible compared with initial slow and weak electrostatic interaction. The aminoglycosides are transferred across the bacterial cytoplasmic membranes is with the involvement of electron transport system, ATP and oxygen. The antimicrobial activity of aminoglycosides is contributed by two major modes: (i) interfering with the nascent polypeptide peptide chain translocation from the A to the P site ribosome that leads premature termination of protein synthesis, and (ii) interfering with proofreading activity, leads to incorporation of mismatched amino acids, thus making the protein dysfunctional. In *C. jejuni*, one of the major mechanisms of resistance to aminoglycoside is through the expression of aminoglycoside modifying enzymes that are usually plasmid mediated (Iovine 2013; Garneau-Tsodikova and Labby 2016).

The first incidence of aminoglycoside resistance was detected in *C. coli* which was mediated by aphA-3 gene product, i.e., a 3′-aminoglycoside phosphotransferase enzyme that had been previously known to confer resistance of kanamycin in *Staphylococcus* and *Streptococcus*. This aphA-3 gene is frequent cause of

aminoglycoside resistance in *Campylobacters* including strains of *C. jejuni*. In some of the strains, aphA-3 is found to be localized downstream of IS607, an insertion sequence that shows similarity with IS607 present in *H. pylori*. On the other hand, in some of the strains, aphA-3 is found to be present with genes that encode streptothricin, encoded by sat gene, an acetyl transferase and streptomycin resistance (encoded by aadE, a 6′-adenylyl transferase). The existence of a similar type of resistance cluster present in strain of *Enterococcus* spp., strongly suggests that there is significant contribution of horizontal transfer mechanisms in *Campylobacter* spp. Other strains of *Campylobacter* harbor mosaic plasmids that carry various aminoglycoside resistance determinants along with transposon or insertion sequences of Gram-negative (i.e., *Salmonella*, *E. coli*, and *H. pylori*) and Gram-positive bacteria (i.e., *Enterococcus*) including tetO. The acquired inheritance of resistance plasmids by sensitive *C. jejuni* strains makes a huge repertoire of multidrug-resistant phenotype in the environment that leads a clinical challenge in human as well as veterinary system. Other common genes that provide resistance to kanamycin include aphA-1 and aphA-7. Both types of genes were found on the plasmids of *C. jejuni*. The aphA-7 composed of same G-C content as the chromosomal DNA of *C. jejuni* advocating that such genes intrinsic in *Campylobacter* while aphA-1 and aphA-3 are thought to be acquired by means of horizontal gene transfer. There are few reports available on ribosomal protein S12 mutations (encoded by gene rpsL) in *C. coli* that imparts resistance to streptomycin. However, such type of similar mutations has not been identified in *C. jejuni* strains. Additionally, the significance of efflux pump transporters in resistance of aminoglycoside has not been clear. In a study, it was revealed that putative efflux pump inhibitors phenylarginine-β-naphthylamide and 1-(1-naphthylmethyl)-piperazine did not cause any reduction in the kanamycin minimum inhibitory concentration (MIC) of five *C. jejuni* strains indicating that they are less important compared to plasmid-borne modifying enzyme for aminoglycoside resistance (Alfredson and Korolik 2007; Iovine 2013).

2.5 β-Lactam Resistance

The antibiotics belonging to β-lactam group have variety of chemical compounds which comprises of a β-lactam ring required for their antimicrobial action. The most frequently used members of this group include penicillins, cephalosporins, monobactams, and carbapenems. Each member of this family can be characterized on the basis of presence of various side chains that provides specialized properties such as increased tolerance to stomach acid, pharmacokinetics, and hydrolysis by β-lactamase enzyme. These antibiotics act by binding to bacterial cell wall, inactivating the expression of bacterial peptidoglycan transpeptidase (also referred to as penicillin-binding proteins) that acts as a catalyst in a final cross-linking step of cell wall synthesis. Therefore, resulting effect weakens the cell wall with alteration in its structural integrity that leads to osmotic lysis and consequently cell death. In *Campylobacter jejuni*, the three most common means of β-lactam resistance mechanisms that have been

frequently observed include (i) enzymatic destruction of antibiotics through chromosomally encoded β-lactamase, (ii) alterations in outer membrane porins that leads reduced uptake of drug, and (iii) efflux-mediated resistance. In *Campylobacter jejuni,* the increased expression of β-lactamase (penicillinase-type) corresponds to ampicillin, amoxicillin, and ticarcillin resistance, and such high level of resistance can be overcome by using inhibitors of β-lactamase, i.e., sulbactam, clavulanic acid, and tazobactam. A few years back, OXA-61, a class D β-lactamase, has been found in *Campylobacter jejuni* and other related species that shows resemblance to other type of OXA genes present in *Fusobacterium*, *Pseudomonas*, and *Acinetobacter* and mediating resistance toward penicillin, ampicillin, oxacillin, piperacillin, carbenicillin, and amoxicillin-clavulanate. From the previous studies, it has been postulated that OXA-61 have increased prevalence in human populations including veterinary animals. Consequently, two genes that encodes metallo-β-lactamase type of enzyme have been identified. However, their increased expression leads to β-lactamase resistance is a matter of new findings yet. The data on the ubiquity of resistance to β-lactam is not generally accessible from various antibiotic resistance monitoring authorities such as NARMS, due to no or least use of β-lactams against *Campylobacter jejuni*. In *C. jejuni*, the cation-selective MOMP are responsible for extrusion of most β-lactams which are anionic in nature similar to the macrolides or having molecular weight more than 360. The small molecular size of ampicillin (MW 333 kDa), imipenem (MW 299 kDa), and cefpirome (MW 347 kDa) and presence of partial positive charge are consistent with easy passage through MOMP and susceptibility of such antibiotics in the absence of another mechanism of resistance such as production of β-lactamase. The amoxicillin antibiotic having MW 365 kDa appears to impede the well-organized passage via MOMP. However, its partial positive charge is responsible for the influx through MOMP. Thus, non-MOMP-dependent mechanism may bring out alternatively its entry. Therefore, the efflux pump CmeABC may also facilitate β-lactam resistance. In *C. jejuni* strain 81-176 and another strain cmeB insertional mutagenesis have resulted in approximately 32-fold increase in ampicillin susceptibility. The mutants of cmeB show four times more susceptibility toward ampicillin related to the parent strain found in a study by using NCTC strain 11,168. The overexpression of cmeB may result rise in ampicillin resistance by fourfolds approximately. Similarly, it is also observed in human outbreak of *C jejuni* strain 11,168 and 81-176 that putative efflux pump CmeDEF have been inactivated by means of insertion mutagenesis of cmeF that can only lead to an increase in cefotaxime and ampicillin resistance by twofolds. However, in *C. jejuni* strain 11,168, inactivation of the CmeG efflux pump did not alter resistance of cefotaxime. The conclusion is therefore that putative CmeABC is most powerful efflux pump transporter for β-lactam class of antibiotics (Alfredson and Korolik 2007; Iovine 2013; King et al. 2017; Palzkill 2018).

3 Status of Resistance in *Campylobacter jejuni* to Various Antibiotics

Fluoroquinolone resistance in *Campylobacter jejuni* was first reported in the late 1980s, four decades ago, and since then, it has been increasing regularly in most countries all over the world. The resistance to fluoroquinolone among *Campylobacter jejuni* isolates of animals or food of animal origin and human has been observed. In Asian countries such as India, 80% isolates have been reported to be fluoroquinolone resistant, whereas 77% have been found in Thailand. In China also higher resistance rates of 95.8–99.0% toward the ciprofloxacin antibiotic has been reported or *Campylobacter* isolates isolated from swine. The quite similar resistance incidences of 91% and 85.4% have been observed also in the South Africa and United Arab Emirates, respectively. The emergence of fluoroquinolone resistance in Spain was evaluated between 1993 and 2003 in Europe. The statistically significant increase of 46.7% for nalidixic acid and 52.2% for ciprofloxacin was observed. Similarly, in the United Kingdom, an increase in fluoroquinolone resistance from poultry-isolated strains of *Campylobacter* was also observed, whereas in Poland, 47.9% and 90.2% of these resistant isolates were found ciprofloxacin resistant from 1994–1996 to 2005–2008, respectively. The proportion of ciprofloxacin-resistant human *Campylobacter* isolates in Germany was observed in 41–46%, whereas 42% of *C. jejuni* strains isolated from chicken were ciprofloxacin resistant in 2001. In the mid-1990s, the sarafloxacin and enrofloxacin were permitted in poultry flocks as growth promoters, contributing resistance to fluoroquinolone in the United States, and resistance among *Campylobacter* isolates from humans was expanded from 1.3% to 10.2% between 1992 and 1998. Several studies, on the other hand, show a lack or even low number of *Campylobacter* isolates resistance to fluoroquinolones. In Grenada 9.4% of the strains of *campylobacters* were found resistant only, whereas in Norway, Finland, no strain was found resistant. In another study from Denmark, it was found that resistance rates to tetracycline, nalidixic acid, and ciprofloxacin in travel-associated infections were significantly much more pronounced as compared to acquired infections domestically. From 2006 to 2007, the occurrence of these types of resistance was raised. In Australia, quinolone resistance among *Campylobacter* strains was found low. Furthermore, this resistance is allocated to the rare consumption of antibiotics for the diarrhea treatment and also utilization of fluoroquinolones in food-producing animals (Weiczorek and Osek 2013). In a study conducted by Vaishnavi and her colleagues at Institute Ethical Committee between May 2009 and January 2013 in India, the study was aimed to evaluate the burden of campylobacter infections in northern region of India. The pediatric and adult patients complained with diarrhea were screened in this study. A total of 1145 patients were screened for the isolation of *Campylobacter* species, and in 2.6% samples, the *Campylobacter* species were identified (Mukherjee et al. 2013). After analyzing antimicrobial sensitivity test, it was found that 23.3% isolates of *Campylobacter* species were found ciprofloxacin resistant (Vaishnavi et al. 2015).

Generally, the macrolides are considered as optimal treatment of choice infections associated to *Campylobacter.* Macrolides resistance in human *Campylobacter* isolates, however, has become a serious public health concern in several countries. The resistance of macrolides among *Campylobacter* strains has been found for a longer time at a stable and low level. However, the resistance to the erythromycin and other macrolides in *Campylobacter jejuni* is increasing gradually. As mentioned above, resistance to fluoroquinolone is globally distributed; the macrolides have become therapeutic drug of choice in campylobacteriosis, which also leads to the development of resistance. *Campylobacter* isolates recovered from poultry in China showed 8.9% resistance to erythromycin, and 26.7% and 13.9%, azithromycin and clindamycin, respectively, among *C. jejuni* strains. In Poland, the percentage of *Campylobacter* strains is an intermediate resistance toward erythromycin which has been increased significantly. These poultry isolates of *Campylobacter* were obtained between 1994 and 1996, whereas an increased resistance of 49.3% and 88.9% was observed between 2005 and 2008. In addition to this, *Campylobacter* isolated from human clinical samples have reported to express a decreased level of erythromycin resistance still found in several countries. Recently in northern India a study was conducted by our group where strains of *Campylobacter jejuni* were isolated from poultry meat and its related products. These isolates were assessed for the antimicrobial resistance against eight classes of antibiotics including macrolides by disc diffusion method. The study revealed drug resistance (97.0%) among *Campylobacter jejuni* isolates. Higher resistance (81.1% and 59.4%) was observed toward the cephalosporin (cephalothin) and tetracycline, whereas fluoroquinolone (ciprofloxacin), quinolone (nalidixic acid), macrolide (azithromycin, erythromycin), and aminoglycoside (gentamycin) showed a lower resistance from 6.9% to 8.9% (Weiczorek and Osek 2013; Khan et al. 2018).

The tetracyclines antibiotics were discovered in the late 1940s that showed activity against Gram-positive and Gram-negative bacteria. In the past, because of their heavy usage for both veterinary medications and in humans, their use in present days is somewhat limited (Iovine 2013). Fallon et al. (2003) studied antimicrobial-resistant pattern of 78 *C. jejuni* strains to 8 different classes of antibiotics by disc diffusion assay. The higher rates of resistance were recorded to tetracycline (20.5%). Ge et al. (2002) determined antimicrobial susceptibilities of three seventy-eight *Campylobacter* isolates and found that resistance to tetracycline antibiotics was highest (82%) related to the resistance of doxycycline (77%). In a study, a large-scale survey was conducted in seven European countries during the period from 2004 to 2007 for evaluating the antimicrobial resistance pattern of *C. jejuni*. The average tetracycline resistance varied between 23% and 33% (EFSA 2010). In India, a study was conducted by Khan and his colleague in 2012 for examining the antimicrobial status of *C. jejuni*. They examined thirty isolates of *C. jejuni* against nine antibiotics where azithromycin and nalidixic acid found most effective antibiotics against majority of examined isolates (Khan 2012). The higher resistance was observed against tetracycline (60%). The close similar resistance level was also observed few years back in India (Nigatu 2007).

Campylobacter jejuni causes systematic infection in humans that can be treated with aminoglycosides. Gentamycin (an aminoglycoside) is considered as drug of choice for such treatments. Generally, gentamycin resistance is lower and stable. However, in the

last decade, an increase in gentamycin resistance has marked. A significant resistance (12.2%) was observed in human isolates in the United States in 2011, while a slightly higher resistance (18.1%) was observed in retail isolates (Yao et al. 2017). In Japan, the antibacterial profile was assessed for *Campylobacter jejuni* and *Campylobacter coli* isolates in beef cattle and pigs from 25 farms. A higher resistance (66.6%) was observed in *C. jejuni* isolates against oxytetracycline. None of the isolate was found resistant toward the gentamycin in the survey (Haruna et al. 2012). Similar observation against gentamycin was observed also in Jordan where no resistance was noticed among *Campylobacter jejuni* isolated from layer farms. Highest resistance (100%) toward both ciprofloxacin and tetracycline was observed (Al Natour et al. 2016).

β-lactam class of antibiotics are generally not recommended for treating *Campylobacter* infections; however, due to regular increase in resistance toward the common antibacterial treatment choices, these β-lactams are considered as alternative chemotherapeutic agents. In Australia, the resistance mechanisms of *Campylobacter jejuni* poultry and pig isolates toward the different antimicrobials including ampicillin were assessed. The study showed extensive resistance (33.3–60.2%). The antibiotic resistance gene bla were found among 82.6–92.7% of these ampicillin-resistant isolates (Obeng et al. 2012). Sierra-Arguello and his colleagues observed a high resistance (65%) toward the ampicillin among *Campylobacter* species including *Campylobacter jejuni* isolated from Brazilian broiler slaughterhouses (Sierra-Arguello et al. 2015). A total of 98 *Campylobacter* isolates from vegetable farms and retail farms were assessed for antimicrobial susceptibility in Malaysia. The study suggested that approximate half of the isolates (51.0%) had multiple antibiotic resistance including toward ampicillin. However, study also suggested that the contamination in vegetables was due to cross-contamination and *Campylobacter jejuni* in small-scale vegetable production was less exposed toward the random use of antibiotics (Huat Tang et al. 2016).

4 Conclusion: Problems and Future Concerns

Antibiotic-resistant *Campylobacter jejuni* has been considered as a serious public health problem worldwide due to increased prevalence regularly. This is leading to the significant compromise in chemotherapeutic effectiveness of current antimicrobials used against the human campylobacteriosis treatment. The antimicrobial resistance trends are showing an accessible association between the usage of antibiotics in veterinary industry and human *Campylobacter*-resistant isolates. The dissemination and spread of antibiotic resistance among pathogenic bacteria is mediated through the acquisition of resistance genes by means horizontal gene transfer mechanisms. It is also marked that resistance determinants in *Campylobacter jejuni* can also be from other Gram-positive bacteria in addition to its own *Compylobacter* genus. These genes may incorporate into plasmids or chromosome through integrons or insertion sequences on transposons. It is possible that the spread of these resistance determinants both within and outside of *Campylobacter* genus. In the past few years, it is also observed that *Campylobacter jejuni* may also develop biofilms on various abiotic surfaces that may help in survival in the environment of the bacterium. Therefore, it is possessing

resistance towards the various key antibiotics used against the *Campylobacter jejuni* (Bae et al. 2014; Szcepanska et al. 2017). The resistance incidences to the several key antibiotics playing crucial role in the treatment of *Campylobacter* infections has raising regularly and several resistance patterns to the diverse array of antibiotics are markedly emerging in all over the world. Resistance to fluoroquinolones resistance in *Campylobacter* in many countries has limited their effectiveness as a treatment of choice for *campylobacter* infections. Although the fluoroquinolones are still prevailing drug in several countries such as Australia, for treating campylobacteriosis, resistance toward antibiotic in *Campylobacter* remains a public health challenge. An upgraded research initiatives are therefore essential to understand the underlying factors responsible for persistence and the transmission of *Campylobacter* resistance to fluoroquinolones in various hosts and environmental settings. It is also going to be a matter of interest to identify that how the strength of *Campylobacter* influences resistance to fluoroquinolones. In addition, new fluoroquinolones that show efficacy against *Campylobacter* strains resistant to ciprofloxacin and employing the new schemes of treatment avoiding resistant mutant selection of fluoroquinolones should also be evaluated (Tang et al. 2017a, b).

Similarly, *Campylobacters* erythromycin resistance is raising at the top regularly in some countries. However, erythromycin (macrolide) incidence of resistant *Campylobacter* in human is still somewhat low and stable. The drug is also considered as the choice of medication for the treating the *Campylobacter jejuni* infection currently. More studies are required to get deep insights that how under the selective pressure of macrolide *Campylobacter jejuni* resistance emerges. Gentamycin also found effective antibiotic against *Campylobacters*. The resistance of *Campylobacter jejuni* to specific antibiotics or multiple antibiotics could be due to dissemination of resistance patterns in the environment increasing by the misuse of antibiotics among the general population. Veterinary prescription of antimicrobials is also contributing the problem of resistance (ElHadidy et al. 2018). An estimated 50% in tonnage of total antimicrobial production in North America and Europe is used in poultry and food-producing animals. Such worldwide consumption of antimicrobials for the control of disease and growth promoters in animals has been identified as paramount cause of resistance emergence in bacteria that can disseminate from animals, often through food products that leads to infections in human. The prevalence of foodborne-resistant *Campylobacter jejuni* has increased due to increase in number of foodborne infections and the corresponding use of antimicrobials also. Global concern over the use and misuse of antimicrobials and subsequent emergence of antibiotic-resistant microbe has increased during the last decade. In developing countries, constant and irrational consumption of antibiotics in both human medicine and veterinary coupled with current understanding of transfer of antibiotic resistance between different bacteria making it important for monitoring the susceptibilities of pathogenic bacteria toward an array of antibiotics (Okeke and Edelman 2001; Bisht et al. 2009). The environmental eco-social status overcrowding, close association between human and animals, and poor hygienic conditions in the area of study might have significantly contributed role in dissemination of *Campylobacter jejuni* in developing countries like India. The transmission of the bacteria in food chain and indiscriminate use of antibiotics might

have resulted in increased emergence of resistance to common antibiotics used in veterinary and medical sciences (Vila and Pal 2010). Since multiple type of antimicrobials clinical treatment of campylobacteriosis are redundant, new generation of antibiotics and novel treatment schemes must be evaluated to prevent the fluoroquinolone-resistant mutant selection. It is expected the advanced molecular approaches, like proteomics and genomics, could provide deeper insights into the mechanistic view of molecular machinery involved in antimicrobial resistance development in *Campylobacter*. Some important steps can be followed to limit the dissemination of antibiotic resistance such as:

(i) Use antibiotics only when prescribed by a certified health practitioner and follow the complete prescription.
(ii) Never use leftover antibiotics and do not share them with the others.
(iii) Prevent infections by regular washing of hands and keep important vaccination up to date.
(iv) The antibiotics used for treating infectious diseases in animals should be given under supervision of veterinary practitioner.
(v) Vaccinate the animals to reduce the need for antibiotics and develop the other alternatives also.
(vi) Introduce good practices at all stages of food production and processing from both plant and animal sources.
(vii) Implement the international standards or guidelines proposed by WHO, FAO, or any national organization for using antibiotics.

References

Abulreesh, H. H., Paget, T. A., & Goulder, R. (2006). Campylobacter in waterfowl and aquatic environments: Incidence and methods of detection. *Environmental Science and Technology, 40*, 7122–7131.

Abulreesh, H. H., Organji, S. R., Elbanna, K., Osman, G. E. H., Almalki, M. H. K., & Ahmad, I. (2017). Campylobacter in the environment: A major threat to public health. *Asian Pacific Journal of Tropical Diseases, 7*, 374–384.

Alfredson, D. A., & Korolik, V. (2007). Antibiotic resistance and resistance mechanisms in Campylobacter jejuni and Campylobacter coli. *FEMS Microbiology Letters, 277*(2007), 123–132.

Allos, B. M., Iovine, N. M., & Blaser, M. J. (2015). Campulobacter jejuni and related species. In *Principles and practices of infectious diseases, Douglas and Benetteds* (8th ed.). Philadelphia: Elsevier.

Al-Natour MQ., Alaboudi AR, Osaili, TM. And Obaidat MM (2016).Resistance of Campylobacter jejuni isolated from layer farms in northern Jordan using microbroth dilution and disc diffusion techniques. Journal of Food Science 81(7):M1749-M1753.

Anjum, A., Brathwaite, K. J., Aidley, J., Connerton, P. L., Cummings, N. J., Parkhill, J., Connerton, I., & bayliss, C. D. (2016). Phase variation of type IIG restriction modification enzyme alert site specific methylation patterns and gene expression in Campylobacter jejuni strain NCTC11168. *Nucleic Acids Research, 44*(10), 4581–4594.

Arsic, B. (2012). *Macrolide antibiotics as anti-bacterial and potential anti-malarial medicines*. PhD thesis submitted to University of Manchester, UK.

Arsic, B., Barber, J., Cikos, A., Mladenovic, M., Stankovic, N., & And Novak, P. (2017). 16-membered macrolides antibiotics: A review. *International Journal of Antimicrobial Agents, 51*(3), 283–298.

Azrad, M., Tkhawkho, L., Isakovich, N., Nitzan, O., & Peretz, A. (2018). Antimicrobial susceptibility of Campylobacter jejuni and Campylobacter coli: Comparison between Etest and broth dilution method. *Annals of Clinical Microbiology and Antimicrobials, 17*, 23.

Bae, J., Oh, E., & Jeon, B. (2014). Enhanced transmission of antibiotic resistance in Campylobacter jejuni biofilms by natural transformation. *Antimicrobial Agents and Chemotherapy, 58*(12), 7573–7575.

Bisht, R., Katiyar, A., Singh, R., & Mittal, P. (2009). Antibiotic resistance-A global issue of concern. *Asian Journal of Pharmaceutical and Clinical Research, 2*(2), 34–39.

Bollinger, H., & Kathariou, S. (2017). The current state of macrolides resistance in Campylobacter spp.: Trends and impacts of resistance mechanism. *Applied and Environmental Microbiology, 83*(12), e00416–e00417.

Collado, L., Munoz, N., Porte, L., Ochoa, S., Varela, C., & Munoz, I. (2018). Genetic diversity and clonal characteristics of ciprofloxacin-resistant Campylobacter jejuni isolated from Chilean patients with gateroenteritis. *Infection, Genetics and Evolution, 58*, 290–293.

Dasti, J. I., Groß, U., Pohl, S., Lugert, R., Weig, M., & Schmidt-Ott, R. (2007). Role of the plasmid-encoded tet(O) in tetracycline-resistant clinical isolates of Campylobacter jejuni and Campylobacter coli. *Journal of Medical Microbiology, 56*, 833–837.

EFSA. (2010). Antimicrobial resistance in zoonotic and indicator bacteria from animals and food in the European Union in 2004-2007. *The EFSA Journal, 8*, 1309.

ElHadidy, M., Miller, M. G., Arguello, H., Alvarez-Ordonez, A., Durate, A., Dierick, K., & Bottledoorn, N. (2018). Genetic basis and clonal population structure of antibiotic resistance in Campylobacter jejuni isolated from broiler carcasses in Belgium. *Frontiers in Microbiology, 9*, 1–9.

Fallon, R., O'Sullivan, N., Maher, M., & Carrol, C. (2003). Antimicrobial resistance of Campylobacter jejuni and Campylobacter coli isolates from broiler chickens isolated at an Irish poultry processing plant. *Letters in Applied Microbiology, 36*, 277–281.

Fitzgerald, C. (2015). Campylobacter. *Clinical Laboratory Medicine, 35*, 289–298.

Frasao, B. D., Medeiros, V., Barbosa, A. V., de Aguiar, W. S., dos Santos, F. F., Abreu, D. L., Clementino, M. M., & de Aquino, M. H. (2015). Detection of fluoroquinolone resistance by mutation in gyrA gene of Campylobacter spp. isolates from broiler and laying (Gallus gallus-domesticus) hens, from Rio de Janeiro State, Brazil. *Ciencia Rural, 45*(11), 2013–2018.

Gaisser, S., Reather, J., Wirtz, G., Kellenberger, L., Staunton, J., & Leadlay, P. F. (2000). A defined system for hybrid macrolide biosynthesis in Saccharopolysporaerythraea. *Molecular Microbiology, 36*(2), 391–401.

Garneau-Tsodikova, S., & Labby, K. J. (2016). Mechanism of resistance to aminoglycoside antibiotics: Overview and perspective. *MedChemComm, 7*(1), 11–27.

Ge, B. L., Zhao, S. H., Hall, R., & Meng, J. H. (2002). A PCR-ELISA for detecting Shiga toxin-producing Escherichia coli. *Microbes and Infection, 4*, 285–290.

Ge, B., Wang, F., Sjolund-Karlsson, M., & McDermott, P. F. (2013). Antimicrobial resistance in Campylobacter: Susceptibility testing methods and resistance trends. *Journal of Microbiological Methods, 95*, 57–67.

Geissler, A. L., Bustos Carrillo, F., Swanson, K., Patrick, M. E., Fullerton, K. E., Bennett, C., Barrett, K., & Mahon, B. E. (2017). Increasing Campylobacter infections, outbreaks, and antimicrobial resistance in the United States, 2004-2012. *Clinical Infectious Diseases, 65*, 1624–1631.

Gouvea, R., Dos Santos, F. F., De Aquino, M. H. C., & Pereia VL De, A. (2015). Fluoroquinolones in industrial poultry production, bacterial resistance and food residues: A review. *Brazilian Journal of Poultry Science, 17*(1), 1–10.

Hao, H., Sander, P., Iqbal, Z., Wang, Y., Cheng, G., & And Yuan, Z. (2016). The risk of some veterinary antimicrobial agents on public health associated with antimicrobial resistance and their molecular basis. *Frontiers in Microbiology, 7*, 1626.

Haruna, M., Sasaki, Y., Murakami, M., Mori, T., Asai, T., Ito, K., & Yamada, Y. (2012). Prevalence and antimicrobial resistance of campylobacter isolates from beef cattle and pigs in Japan. *Journal of Veterinary Medical Science, 75*(5), 625–628.

Havelaar, A. H., Kirk, M. D., Torgerson, P. R., Gibb, H. J., Hald, T., Lake, R. J., et al. (2015). World Health Organization Global estimates and regional comparisons of the burden of foodborne disease in 2010. *PLoS Medicine, 12*, e10011923.

Huat Tang, J. Y., Khalid, M. I., Aimi, S., Abu Bakar, C. A., & Radu, S. (2016). Antibiotic resistance profile and RAPD analysis of campylobacter jejuni isolated from vegetables farms and retail markets. *Asian Pacific Journal of Tropical Biomedicine, 6*(1), 71–75.

Iovine, N. M. (2013). Resistance mechanisms in Campylobacter jejuni. *Virulence, 4*, 230–240.

Kaakouch, N. O., Castano-Rodriguez, N., Mitchell, H. M., & Man, S. M. (2015). Global epidemiology of Campylobacter infection. *Clinical Microbiology Reviews, 28*, 687–720.

Khan, J. A. (2012). *Enumeration, detection and characterization of foodborne bacterial pathogens by conventional and molecular techniques*. PhD thesis submitted at Department of agricultural microbiology, Aligarh Muslim University, India.

Khan, J. A., Rathore, R. S., Abulreesh, H. H., Abul Qais, F., & Ahmad, I. (2018). Prevalence and antibiotic resistance profiles of Campylobacter jejuni isolated from poultry meat and related samples at retail shops in Northern India. *Foodborne Pathogens and Disease, 15*(4), 218–225.

King, D. T., Sobhanifar, S., & Strynadka, N. C. J. (2017). The mechanism of resistance to lactam antibiotics. In *Handbook of antimicrobial resistance* (pp. 177–201). Cham: Springer Nature.

Kovac, J., Cadez, N., Stessl, B., Stingl, K., Gruntar, I., Ocepek, M., Trkov, M., Wagner, M., & Mozina, S. S. (2015). High genetic similarity of ciprofloxacin-resistant Campylobacter jejuni in Central Europe. *Frontiers in Microbiology, 6*, 1169.

Luangtongkum, T., Jeon, B., Han, J., Plummer, P., Logue, C. M., & Zhang, Q. (2009). Antibiotic resistance in Campylobacter: Emergence, transmission and persistence. *Future Microbiology, 4*, 189–200.

Memish, Z. A., Venkatesh, S., & Shibl, A. M. (2003). Impact of travel on international spread of antimicrobial resistance. *International Journal of Antimicrobial Agents, 21*, 135–142.

Mozina, S. S., Kurincic, M., Klancnik, A., & Mavri, A. (2011). Campylobacter and its multiresistance in the food chain. *Trends in Food Science and Technology, 22*, 91–98.

Mukherjee, P., Ramamurthy, T., Bhattacharya, M. K., Rajendran, K., & Mukhopadhyay, A. K. (2013). Campylobacter jejuni in hospitalized patients with diarrhea, Kolkata, India. *Emerging Infectious Diseases, 19*(7), 1155.

Munita, J. M., & Arias, C. A. (2016). Mechanisms of antibiotic resistance. *Microbiology Spectrum, 4*, 1–37.

Natsos, G., Koutoulis, K., Sossidou, E., Chemaly, M., & Mouttotou, N. (2016). Campylobacter spp. infection in humans and poultry. *Journal of the Hellenic Veterinary Medical Society, 67*, 65–82.

Nigatu, S. (2007). *Detection of Campylobacter and Arcobacter species from various sources by conventional and molecular techniques*. MVSc thesis submitted in Department of Veterinary Public Health, India Veterinary Research Institute, India.

Obeng, A. S., Rickard, H., Sexton, M., pang, Y., peng, H., & Barton, M. (2012). Antimicrobial susceptibilities and resistance genes in Campylobacter strains isolated from poultry and pigs in Australia. *Jornal of Applied Microbiology, 113*(2), 294–307.

Okeke, I. N., & Edelman, R. (2001). Dissemination of antibiotic resistant bacteria across geographic borders. *Clinical Infectious Diseases, 33*, 364–369.

Otigbu, A. C., Clarke, A. M., Fri, J., Akanbi, E. O., & And Njom, H. A. (2018). Antibiotic sensitivity profiling and virulence potential of Campylobacter jejuni isolates from estuarine water in the Eastern Cape Province, South Africa. *International Journal of Environmental Research and Public Health, 15*(5), 925.

Palzkill, T. (2018). Structural and mechanistic basis for extended spectrum drug resistance mutation in altering the specificity of TEM, CTX-Mand KPC ß-lactamases. *Frontiers Molecular BioSciences, 5*, 16. https://doi.org/10.3389/fmolb.2018.00016.

Pitkanen, T. (2013). Review of Campylobacter spp. in drinking and environmental waters. *Journal of Microbiological Methods, 95*, 39–47.

Pomeri, A. P. (2011). *Quinolones antibiotics*. Uploaded on 25/04/2011.

Reddy, S., & And Zishiri, O. T. (2017). Detection and prevalence of antimicrobial resistance genes in Campylobacter spp. isolated from chickens and humans. *Onderstepoort Journal of Veterinary Research, 84*(1), a1411.

Sierra-Arguello, M. Y., Morgan, R. B., Perdoncin, G., Lima, L. M., MJP, G., & Pinheiro do Nascimento, V. (2015). Resistance to lactam and tetracycline in Campylobacter spp. isolated from broilers laughter houses in southern Brazil. *Pesquisa Veterinaria Brasileira, 35*(7), 637–642.

Sierra-Arguillo, Y. M., QuediFurian, T., Perdoncini, G., Moraes, H. L. S., Salle, C. T. P., Rodrigues, L. B., Dos Santos, L. R., & Pereira Gomes, M. J. (2018). Fluoroquinolone resistance in Campylobacter jejuni and Campylobacter coli from poultry and human samples assesses by PCR restriction fragment length polymorphism assay. *PLoS One, 13*(7), e0199974.

Silva, W. C., Tagino, B. N., Mendonca, R. S., San'Ana, A. S., & Hungaro, H. M. (2018). Campylobacter: An overview of cases, occurrence in food, contamination sources, and antimicrobial resistance in Brazil. *Food Reviews International, 34*, 364–389.

Szczepanska, B., Andrzejewska, M., Spica, D., & Klawe, J. J. (2017). Prevalence and antimicrobial resistance of Campylobacter jejuni and Campylobacter coli isolated from children and environmental sources in urban and suburban areas. *BMC Microbiology, 17*(80), 1–9.

Tang, Y., Fang, L., Xu, C., & Zhang, Q. (2017a). Antibiotic resistance and trends in the foodborne pathogen, Campylobacter. *Animal Health Research Reviews, 18*(2), 87–98.

Tang, Y., Sahin, O., Pavlovic, N., LeJeune, J., Carlson, J., Zuowei, W., Dai, L., & Zhang, O. (2017b). Rising fluoroquinolone resistance in Campylobacter isolated from feedlot cattle in the United States. *Scientific Reports, 7*, 494.

Vaishnavi, C., Singh, M., Thakur, J. S., & Thapa, B. R. (2015). Low prevalence of Campylobacteriosis in the northern region of India. *Advances in Microbiology, 5*, 155–165. https://doi.org/10.4236/aim.2015.53015.

Vila, J., & Pal, T. (2010). Update on antibacterial resistance in low-income countries: Factors favouring the emergence of resistance. *The Open Infectious Diseases Journal, 4*, 3854.

von Wintersdorff, C. J. H., Penders, J., Stobberingh, E. E., Lashof, A. M. L. O., Hoebe, C. J. P. A., Savelkoul, P. H. M., & Wolffs, P. F. G. (2014). High rates of antimicrobial drug resistance gene acquisition after international travel, the Netherlands. *Emerging Infectious Diseases, 20*, 649–657.

WHO. (2018). *Antibiotic resistance*. Fact sheet. http://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Accessed on 25 July 2018.

Wieczorek, K., & Osek, J. (2013). Antimicrobial resistance mechanisms among Campylobacter. *BioMed Research International, 2013*, 1–12. Article ID 340605.

Wieczorek, K., Wolkowicz, T., & Osek, J. (2018). Antimicrobial resistance and virulence-associated traits of Campylobacter jejuni isolated from poultry food chain and humans with diarrhea. *Frontiers in Microbiology, 9*, 1905.

Yao, H., Liu, D., Wang, Y., Zhang, Q., & Shen, Z. (2017). High prevalence and predominance of the aph(2″)-if gene conferreing aminoglycoside resistance in Campylobacter. *Antimicrobial Agents and Chemotherapy, 61*(5), e00112-17. https://doi.org/10.1128/AAC.00112-17.

Zhu, J., Zhang, Y., Hua, X., Hou, J., & Jiang, Y. (2006). Antibiotic resistant in Campylobacter. *Reviews in Medical Microbiology, 17*, 107–112.