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RESEARCH PAPER

TITLE

CAMPYLOBACTER: A BRIEF REVIEW OF ITS CAUSES, DIAGNOSTIC APPROACHES AND PREVENTION

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Abstract

The most frequent bacterial which is cause of gastroenteritis in humans is *Campylobacter*. According to Centers for Disease Control and Prevention (CDC) reports around 1.3 million cases of *Campylobacter* infection in the US occurs per year. This review was designed with the aim to discuss in detail the root causing agents of Campylobacter infection, its diagnostic and prevention methods. Campylobacteriosis starts with the attachment of the pathogenic bacteria to intestinal cells, followed by colonization and, lastly, penetration of the cells following ingestion by the host. Consumption of raw milk, undercooked poultry, and contaminated water have all been associated with *Campylobacter* infection. Intestinal mucosal *Campylobacter* toxins proliferate, necrotizing the intestinal villi. A toxin known as cytolethal distending toxins (CDT) damages DNA by acting as a deoxyribonuclease (DNase). Old aged patients and immunocompromised patients are more at risk of morbidity, mortality, and long-term sickness. In addition to additional virulence and survival factors, this review gathers information on motility, chemotaxis, adhesion, invasion, multidrug resistance, and stress response variables. It has been found that mishandling of raw poultry and consumption of undercooked poultry are the major risk factors for human campylobectriosis. Various preventive measures can be adopted to decrease the transmission of the pathogens and the subsequent disease such as the vaccination of the poultry, the health surveillance and the precise food hygiene all over the entire production chain.

1 Introduction

Campylobacter has been derived from Greek word "campy" means "curved" and "bacter" means "rod". Campylobacteria is a member of the Campylobacter genus and Campylobacteraceae family, and belongs to class Epsilonproteobacteria, and phylum Proteobacteria, that are mostly found in curved or comma-shaped structure (Hagoa *et al.,* 2019). This family of bacteria is closely related to the Camylobacteraceae family, which also contains Arcobacter, Sulfospirillum, and Campylobacter. The digestive tracts of all warm-blooded organisms contain a member of the Campylobacter genus. Since its discovery in 1963, the Campylobacter genus has grown to include more species (Binney, 2015). C. jejuni and C. coli cause illnesses in almost every industrialized country, but C. lari and C. upsaliensis are involved in the aetiology of sickness in many other countries (Kaakoush *et al.*, 2015). *C. coli*, C. foetus sub sp., and C. jejuni sub sp. *foetal*, *C. upsaliensis*, *C. lari*, and *C. hyointestinalis* sub sp. *hyointestinalis* are a few of the significant species that cause intestinal illness in people. *C. jejuni* is the most common strain to be isolated and reported (80–90%), followed by *C. coli* (5–10%), with another member of the genus accounting for the remainder (Han *et al.*, 2016).

Campylobacter is the most frequent bacterial cause of gastroenteritis in people. Functional

bowel diseases such irritable bowel syndrome (IBS), Miller-Fisher syndrome (MFS), and Guillain-Barre syndrome (GBS) may be significantly impacted long-term by acute infections (Backert *et al.,* 2017). In certain nations, the organism is isolated 3–4 times more frequently from people with gastrointestinal problems than other bacterial entomopathogens (such Escherichia coli (E. coli) or Salmonella) (Porte *et al.,* 2016). Salmonellosis is more common than campylobacteriosis in high-income countries. Although there are little data from low- and middle-income countries, it appears that Campylobacter infection is a major source of illness in these areas (Dslahoy et al., 2018). Due to the illness's sporadic nature and the critical role that cross-contamination plays in the infection's propagation; it may occasionally be challenging to identify the origins of exposure to Campylobacter. Over the past ten years, a lot of success has been achieved in the fight against foodborne Campylobacteriosis, a disease that affects many different nations (Ferri *et.,* 2017). New techniques have been developed as a result of recent scientific developments; for instance, whole-genome sequencing has increased our understanding of the disease. Improvements in infection attribution to source and understanding of the role of immunity in preventing Campylobacter infection, in addition to risk assessments, have all enhanced the farm-to-table chain's risk management (Gonzalez *et al.,* 2016). Certain governments have made significant financial investments in an effort to halt the spread of campylobacteriosis through particular food chains, with varying degrees of success. Human Campylobacteriosis prevention, however, is still challenging on a global scale (Hansson *et al.,* 2018).

Campylobacter jejuni and Campylobacter coli are the main causes of campylobacteriosis, one of the world's most common forms of bacterial gastroenteritis. In developing countries, campylobacteriosis primarily affects newborns due to significant early exposure and acquired immunity (Oberhelman *et al.,* 2000), but in industrialized countries, the epidemiology is characterized by sporadic disease across all age groups (Olson *et al.,* 2008). Over 340,000 cases of Campylobacter infection are recorded in the United Kingdom each year, compared to an estimated 2.5 million cases in the United States each year (Acheson *et al.,* 2001; Kessel *et al.,* 2001), which is more than three times as many cases as Salmonella, Escherichia coli O157:H7, and Listeria monocytogenes combined.

It is still unknown how much each source of infection contributes to the overall burden of human disease, despite the fact that campylobacter infection is a significant public health issue and is estimated to have an annual economic burden of £500 million in the United Kingdom (Humphrey *et al.,* 1997) and $8 billion in the United States (Buzby *et al.,* 1997).

Contamination of human food can occur at any point along the food supply chain, from the farm to the consumer. The consumption of tainted meat and poultry, as well as water, milk, or contact with animals, are all possibilities among the causes of human illness (Neimman *et al.,* 2003). The majority of Campylobacter infections in humans are sporadic, and there have been very few outbreaks that have been linked to a single source of infection therefore analytical epidemiology techniques, such as risk assessment and case-control studies, do not fully address the question of where the illness originated (Pebody *et al.,* 1997; Frost *et al.,* 2002).

Due to the high cost of preventing Campylobacter transmission and the requirement that implementation take into consideration cost-effectiveness, effective public health intervention by governmental organizations and enterprises has been

hindered by the uncertainty surrounding the origins of human illness. Molecular typing has aided a number of epidemiological investigations, such as those that have discovered outbreaks of food-borne infections caused by L. monocytogenes (Olsen *et al.,* 2005), Salmonella enterica (Bender *et al.,* 2001), Campylobacter (Sails *et al.,* 2003), and E. coli O157:H7 (Bender *et al.,* 1997). The timely determination of the etiology of a disease epidemic is essential to the successful containment of the disease (Olsen *et al.,* 2005).

Reservoirs and transmission of Campylobacter

The commensal bacteria known as Campylobacter spp. can be found in the digestive tracts of a variety of wild species, such as birds like ducks and gulls, as well as agricultural animals and domestic pets (such as dogs and cats). In general, it is safe for humans to consume any and all kinds of birds (Damborg *et al.,* 2004; Bae *et al.,* 2005). Ingestion of infected food and water is a component of the fecal-oral mode of transmission, which is responsible for the zoonoses (Ternhag *et al.,* 2005; Newell *et al.,* 2001). All bird species, but poultry in particular (including broilers, laying hens, turkeys, ducks, and ostriches), which is thought to be the primary route of transmission (Newell et al., 2003; Stafford *et al.,* 2008; Mullner *et al.,* 2009), make up the primary environmental niche. In point of fact, the consumption of this meat is responsible for between 50 and 70 percent of all human instances of campylobacteriosis (Sheppard *et al.,* 2009). Fruits and vegetables have been identified as a possible source of transmission, despite the fact that raw milk, raw red meat, and raw beef are all known to be potential sources of the infection (Bakkenes *et al.,* 2011; Rapp *et al.,* 2012). According to Moore et al., the rate of Campylobacter spp. colonization in cattle varies widely and can be anywhere from 0 to 80%, but the rate of colonization in sheep is approximately 20%. Following are the main causes of spreading Campylobacteria infection.

1. Poultry

The primary risk factor for getting campylobacteriosis is either consuming raw or undercooked chicken meat or handling meat that has not been properly cooked (Mullner *et al.,* 2009; Mughini *et al.,* 2012; Meldrum *et al.,* 2005). It was found that infected hens might potentially excrete between 105 and 108 CFU per gramme. Because of these elevated levels, viruses are able to rapidly disperse throughout the environment, which contributes to pollution (Keener *et al.,* 2004). Between 60% and 80% of cases in Europe and up to 98% of cases in the US were estimated by Bull et al. to have chicken meat retail contamination with C. jejuni (Bull *et al.,* 2006). The same farm animals may contract the same disease from one another; this transmission may occur horizontally within the environment where the animals are raised (Stern *et al.,* 2000; Petersen *et al.,* 2001) or vertically (i.e., from hen to chick through egg), which is a highly infrequent event. Although the infection may start in the first few days of birth, the organism is not found in stool samples until the infant is two or three weeks old (Njstern *et al.,* 2001). The animal's microbial ecology or the protective effects of maternal antibodies may be to blame for this lag period, despite the fact that its exact etiology is unknown (Osahin *et al.,* 2003). In the second scenario, Campylobacter could be deterred from colonizing by the microbial flora present in the chicken digestive system (Pwvander *et al.,* 2000). On the other hand, it was demonstrated that the primary entry points for contaminating the carcass after slaughter occurred during the processes of plucking, evisceration, and final washing. In

spite of the fact that the bacterial burden is reduced after being treated with water that has been heated to a temperature of at least 60 degrees Celsius, it actually increases during the process of plucking, which leads to cross-contamination (M.guerin *et al.,* 2010; Y.hayma *et al.,* 2011). The evisceration procedure has the potential to result in an increase in the bacterial load as a consequence of the leaking of intestinal contents that are contaminated with Campylobacter (M.guerin *et al.,* 2010; H.rosenquist *et al.,* 2006).

2. Milk

Since 1978, when four cases of infection by Campylobacter fetus were detected at a hospital in Los Angeles County (Taylor *et al.,* 1979), unpasteurized cow's milk and dairy products have been recognized as common carriers of Campylobacter spp. as a result of this discovery. An outbreak of campylobacteriosis that occurred in the United Kingdom in 1996 has been linked to the consumption of raw milk, as stated by (Evans *et al.,* 1996). [Citation needed]. Later, Javid monitored studies on dairy cows and noted that 12% of the raw milk samples had *C. jejuni* contamination. Direct mastitis in cattle, dirty water, and probable contact with cow manure are the most frequent causes of milk contamination (Amgulo *et al.,* 2009).

3. Fruits and vegetables

According to various examinations, C. jejuni and C. coli have been discovered in peas, radishes, spinach, and lettuce (Brandal *et al.,* 2004; Abadias *et al.,* 2008; Gardner *et al.,* 2011) When vegetables are irrigated with contaminated water, when natural fertilizers are used, or when the same soil is contaminated with bird droppings, the likelihood of contamination increases (Butzler *et al.,* 1991; Kumar *et al.,* 2001). When handling and transporting food, as well as when chopping other foods, such chicken, with kitchenware, cross-contamination is also possible. Eating packaged fruit and vegetables, in particular, has been shown by Verhoeff-Bakkenes et al. to be a substantial risk factor for campylobacteriosis. 13 (0.23%) of the 5.640 samples of fruits and vegetables they tested were positive for Campylobacter, with packaged goods showing a higher rate (0.36%) than fresh goods (0.07%) (Bakkenes *et al.,* 2011). In the past, a report presented by Kirk et al and one by Blaser et al. described a Campylobacter pandemic that was sparked by, respectively, consuming cucumbers from a buffet (Kirk *et al.,* 1997) and consuming a salad cooked by a soup kitchen worker whose hands contained Campylobacter that had been recognized (Blaser *et al.,* 1982).

4. Water

In accordance with European legislation, naturally occurring mineral water that is drawn from springs or infrequently from drilling sources is free of viruses and parasites. Contrary to water that is given through taps, it cannot be subjected to any type of treatment that would alter its chemical composition (Barrel *et al.,* 2000). Numerous microorganisms, including coliforms, have been identified in mineral waters, particularly non-carbonated water that is served in plastic bottles and manually bottled (Hunter *et al.,* 1993); Gillespie et al. reported a case in which the bottled water was thought to be a potential source of Campylobacter infection (Gillespie *et al.,* 2002).

5. **Pets**

There have been a lot of different domestic animals found to be hosts for Campylobacter species (Lenz *et al.,* 2009; Chaban *et al.,* 2012). Canine faeces samples have been used by a number of researchers in Europe and Asia, and their findings have resulted in the isolation of the bacteria *C. jejuni, C. coli,* C. *upsaliensis,* and *C. helveticus* and *C. lari* (Tsai et al., 2007; Rossi *et al.,* 2008; Hald *et al.,* 2004). Contact with animals is a factor in 15% of Campylobacteriosis cases and 3% of

all salmonellosis cases in the US, according to Stehr-Green et al. (Stehr *et al.,* 1987). Chaban et al. reported extracting *C. jejuni* from the feces of 5 dogs in a proportion of 70 (7%), at concentrations as high as 106 CFU/g. Given approximately 500 germs are thought to be the infective dose of *C. jejuni* (Kothary *et al.,* 2001), the high numbers seen in feces offer a potential danger for environmental pollution and human infection through unintentional exposure. Veterinarians believe that animals may get contaminated with other species after eating raw meat (Weese *et al.,* 2005; Strohmeyer *et al.,* 2006). However, touching or handling objects that have come into contact with animals may contaminate human hands with germs from the fur or contaminated object (Hald & Madsen., 1997). It is still unknown how Campylobacter is transmitted from animals to humans.

6. Flies

Even flies have been shown to be a key Campylobacter carrier, making them capable of infecting both humans and animals (Pebody *et al.,* 1997; Rodrigues *et al.*, 2001). According to studies by Gordon et al. (Nichols., 2005) certain cases of diarrhea have increased, especially during the summer when more adult insects are present as the larvae grow and mature. There is scholarly support for this notion (Neal *et al.,* 1997) observed a decrease in the incidence of diarrheal symptoms following the application of fly control techniques. They presume that insects' paws, probosci, and body hair that have been exposed to excrement or other regurgitated material can transmit the disease by coming into touch with food directly (Nichols *et al.,* 2005). At any time throughout the food chain, contamination may happen.

Risk factors

The cause and propagation of any illness must satisfy the epidemiological triangle. The environment and the host agent are both components of the transmission chain. Numerous factors, which also help the sickness spread, damage the host's immune system (Van *et al.,* 2017). The main risk factors for developing Campylobacter illness in humans are eating contaminated foods including raw meat, raw milk, sausages, and semi-cooked hamburgers as well as handling poultry, other animals, and slaughtering and processing of animals and birds (MacDonald *et al.,* 2015; Barron *et al.,* 2021). The major risk factor for human sickness, according to analyses of water sample data, is hazardous drinking water (Khan & Bakar., 2020). Swimming and travelling to other countries raise the risk of campylobacteriosis (Ravel et al., 2016). In the majority of developed countries, the danger of Campylobacteriosis in people increases during the warmer months (Huang *et al.,* 2016). Using the toilet, handling meat without washing your hands, handling meat after it has been in contact with dirt during preparation are four situations when campylobacter is more likely to be present. Meat handlers who did not wash their hands before handling the meat had 11.6 times higher risk of contracting Campylobacter spp (Berhanu *et al.,* 2021). Lack of hygienic practices (Sibanda et al., 2018), depopulation of a flock in several batches, the presence of other farm animals and pets (Sanches *et al.,* 2018), the presence of multiple poultry houses, the presence of rodents on a farm, the use of nipples drinkers, the enormous size of the flock (Sibanda *et al.,* 2018), receiving chicks from the individual hatchery, and increasing ventilation are all factors that contribute to poultry colonization during summer (Hog *et al.,* 2016), and lack of fly screen (Zhang & Sahin., 2020).

EPIDEMIOLOGY of Campylobacter

Campylobacter is the most widespread bacterial zoonotic illness that can be found in many parts of the world. The majority of campylobacter comes from animals and

humans since they have a warm body temperature (mammals and birds). Infection with Campylobacter can also be acquired from animals such as dogs and cats that are kept as pets, as well as from wild animals and domesticated animals such as chickens, pigs, cattle, and sheep that are raised for their meat. In these animals, the infection with Campylobacter almost always does not produce any symptoms. Campylobacter can be transmitted from animals to humans by direct animal contact, the environment, the handling of animal food products, and consumption of those products (Wagenar *et al.,* 2013; (Domingues *et al.,* 2012). Numerous statistics point to the fact that chicken reservoirs are the source of between 50 and 70 percent of the Campylobacter strains that are linked to human infections (Wagenaer *et al.,* 2013). The prevalence of Campylobacter infections in people in Iceland, New Zealand, Belgium, and the Netherlands has dropped from 40% to 72% as a result of targeted and organic treatments (Stem *et al.,* 2003; Sears *et al.,* 2011; Friesema *et al.,* 2012). In addition, surface water, including drinking water and swimming pools, can be a dependable vector for the transmission of Campylobacter to humans. Food and water have both been identified as important transmission vectors in Campylobacter outbreaks. However, outbreaks are not unheard of and sporadic Campylobacter infections are common (Little *et al.,* 2010; Batz et al., 2012). The peak seasons for Campylobacter infections in the United States and Europe are the summer and early fall; in low-resource countries, seasonal changes are less pronounced. The increasing use of diagnostic techniques that are not based on culture has made it more difficult to compare and interpret surveillance data (CIDTs). In the United States, the rate of Campylobacter infections that were confirmed by culture fell from 1996 to 2016, reaching an average of 17.4 instances (confirmed cases plus CIDT-positive cases alone) per 100,000 people in 2016 (Marder *et al.,* 2017). This number represents a drop over the previous decade. 18 In New Zealand, the incidence saw a similar dramatic fall, going from 400 cases per 100,000 people in 2006 to 135 cases per 100,000 people in 2015 (Lopez *et al.,* 2016). This is a drop from 400 cases per 100,000 people in 2006. In the European Union, each year there are between 30 and 80 cases of persons becoming infected with Campylobacter for every 100,000 people (Bouwknegt *et al.,* 2013; Steens *et al.,* 2014). Monitoring enteric diseases, such as campylobacteriosis, is performed often in nations with high incomes, while it is performed seldom in other regions of the world (Platts et al., 2014; Jount et al., 1995). 1,23 Campylobacter isolation rates were found to range from 5% to 20% in research conducted on children suffering with diarrhea in low-income nations located in Asia, Africa, and Latin America. The investigations were conducted on children. Adults rarely become infected with the virus and typically do not display any symptoms. This is likely because adults have established an acquired immunity to the illness over the course of their lifetime (Mason *et al.,* 2013). A recent study that was conducted in Africa found that campylobacter infections are rather common among young newborns (Manson *et al.,* 2013) Campylobacter has been linked to diarrhea and a large burden of illness in three Asian nations, but not in the four African countries that were part of the same study (Kotloff *et al.,* 2013). This finding stands in contrast to the findings of the same study in Africa.

In particular, travelers are more prone to diarrheal infections, which are typically caused by germs like Campylobacter (Tribble *et al.,* 2017). The destination of the vacation will probably have a big impact on the risk of travelers' diarrhea. Asia, Africa, and Central

and South America are the areas with the greatest risk (Connor *et al.,* 2013). Other considerations include length, objective, trip style (luxury vs. trekking), and season (Steffen *et al.,* 2017). The spread of the several illnesses that are frequently linked to these people is influenced by the trip's destination. In contrast to individuals who have just returned from Africa, patients who have recently visited Southeast Asia appear to isolate Campylobacter spp. more frequently (Tribble *et al.,* 2017; Shah *et al.,* 2009). Chronic Campylobacter-related side effects travelers' diarrhea is post-infectious IBS. Post-infectious IBS was shown to occur in 5.4% of patients with traveler's diarrhea in a recent meta-analysis. 30 Other long-term issues that are closely linked to *Campylobacter*-related travel diarrhea include ReA and GBS (Steffen *et al.,* 2017).

Pathogenicity and virulence factors

Chemotactically controlled cellular motility, bacterial adherence, host cell penetration, and toxin production are just a few Campylobacter virulence mechanisms that cause disease. Recent study has shown that genes, antigens, iron utilization systems, and responses to oxidative and environmental stress, as well as virulence factors, are involved in host colonization. Detecting whether bacterial and cellular components are involved in pathogenicity is complicated by genetic inter- and intrastrain variability, laboratory strains, host cell lines, and methods (Poli *et al.,* 2012). Despite the unknown mechanism, three basic stages of infection in humans can be identified (Konkel *et al.,* 2001). The gut mucosa crypts are colonized first. After invading intestinal cells and translocating trans- or paracellularly, the bacteria attach to host epithelial proteins. Campylobacter on gut mucosa emits toxins that necrotize intestinal villi. Damage to the intestinal epithelium causes severe and bloody diarrhea, inflammation, the breakdown of the protective barrier and tight junctions, and loss of function. Bacteria adhesion to epithelial cells causes a robust pro-inflammatory immune response (Aguilar *et al.,* 2014).

1. **Adherence**

Campylobacter must first attach itself to the intestinal epithelium of the host in order to colonize. The many adhesins that are produced by *C. jejuni* have the potential to influence or act as a mediator of bacterial adherence to a range of cell types and hosts (Rubinchik et al., 2012). This influence or mediation could occur on an individual or collective level. The flagellum (Grant *et al.,* 1993), outer membrane proteins (OMPs), and lipopolysaccharide (LPS) (Schroder *et al.,* 1997) are all examples of potential adhesins. The following section includes a list of adhesins that are known as well as those that are suspected. CadF, also known as Campylobacter adhesion protein to fibronectin, is a 37 kDa protein that is found in the outer membrane (Konkel *et al.,* 1997). It is the adhesin that has received the most attention from researchers. It interacts to the epithelial cells' fibronectin, which is its ligand. fibronectin, a glycoprotein with a molecular weight of 220 kDa, can be found in both the lamina propria and the basement membrane of the intestinal epithelium (Monteville et al., 2003). A sequence of four amino acids called Phe-Arg-Leu-Ser was discovered in 2005 to be the one that represents the fibronectin-binding domain of CadF (Konkel *et al.,* 2005).

Another protein that binds fibronectin is called fibronectin-like protein A (FlpA). It is a polymer with a molecular weight of 46 kilodaltons and interacts with a 9-amino acid-binding motif in its ligand (Flanagri *et al.,* 2009; Larson *et al.,* 2013). *CadF* and *FlpA* are both required in order for *C. jejuni* to both bind to fibronectin that is present on host cells and for *C. jejuni* Cia effector proteins to enter the cytosol of the target cells that are hosted

by the host. According to (Talukdar *et al.*, 2020), this causes the MAPK/ERK signaling pathway to become activated, which is a prerequisite for bacterial invasion of the host cell. The roles of the two fibronectin-binding adhesins are completely separate from one another (Talukdar et al., 2020). An autotransporter-active, outer membrane, surface-exposed lipoprotein that regulates Campylobacter's ability to attach to and penetrate human epithelial cells as well as the colonization of poultry, CapA (Campylobacter adhesion protein A) is encoded by capA (Flanagri *et al.,* 2009; Ashgar *et al.,* 2007). Due to their function as chaperones, which transfer CadF to the outer membrane, the periplasmic-binding proteins Peb1, Peb3, and Peb4 are also believed to have a role in adhesion to host cells, although indirectly (Asakura *et al.,* 2007; Pei *et al.,* 1998).

2. Invasion

Once the bacteria have attached themselves to the intestinal host cells, it is necessary for Campylobacter jejuni to induce a change of the cytoskeleton through microfilaments and microtubules in order for C. jejuni to enter the cells, predominantly by the process of endocytosis (Biswas *et al.,* 2003). The invasion process begins with membrane protrusion, which is managed by the tiny Rho-GTPases Rac1 and Cdc42 (Krause et al., 2009). Membrane protrusion is the first stage. Another fact that is common knowledge is that the in vitro invasiveness of *C. jejuni* is linked to the de novo creation of proteins that aid entry and need host cell signal transduction (Amill *et al.,* 2001). This is a well-established fact. In addition to this, it is believed that the flagellum contributes to the invasion by way of the proteins that are produced by the T3SS machinery. Research conducted by Eucker and Konkel (2012) (McKineey *et al.,* 2012) discovered a connection between a reduced pathogen's invasive potential and mutations in the FLG and FLA genes.

The flagellar secretion system is responsible for transporting the released proteins into the cytoplasm, where they play a vital role in the processes of invasion and colonization (Konkell *et al.,* 2004). Certain of these proteins, such as the Cia proteins (Campylobacter invasion antigens, such as *CiaB, CiaC,* and *CiaI*), not only contribute to the successful invasion and colonization of host cells, but they are also essential for the survival of the pathogen inside the host cell (Eucker *et al.,* 2012). Research has shown that when *C. jejuni* is co-cultured with epithelial cells, the genes that code for Cia proteins are activated. *C. jejuni,* upon coming into touch with epithelial cells, is capable of secreting approximately 18 different Cia proteins. According to Neal-McKinney and Konkel, Cia C is necessary for C. jejuni to fully penetrate host cells and is also largely responsible for the changes in the cytoskeleton that lead to membrane ruffling. Furthermore, they state that Cia C is required for *C. jejuni* to completely invade host cells.

3. Toxins

A CDT is the most major and well-known toxin that Campylobacter has produced, despite the fact that it has produced numerous other types of toxins. The toxin CDT damages DNA by acting as a DNAse (Pons *et al.,* 2019). CDT is produced once *C. jejuni* has entered the human intestinal epithelium. CDT is a very stable AB2 protein. CdtA, CdtB, and CdtC are the three components of the CDT toxin (Kreling *et al.,* 2020). The CDT toxins inflict bloody diarrhea on the host by colonizing and constricting epithelial cells (Dasti et al., 2010). When the toxin attaches to the cell membrane, the *CdtA* and *CdtC* subunits help release CdtB, an enzyme-active component that stops the cell cycle and causes cell death (Asakura *et al.,* 2008; Scuran *et al.,* 2016). CdtB causes endocytosis in the host cell by tying to cytoskeleton

microfilament proteins like vinculin by modifying the skeleton's structure and altering the function of the proteins. Investigations into the human clinical strain *C. jejuni* 81-176 in a mouse model have shown that it hastens colon cancer and alters transcriptome responses, both of which depend on CDT synthesis (He *et al.,* 2019).

Campylobacteriosis symptoms and disease progression

Campylobacteriosis is brought on by 10% of *C. coli*, 75% of *C. jejuni*, and 14% of *C. coli/jejuni* (not differentiated). Less than 1% of the total are made up of other species, such as *C. lari*, *C. upsaliensis*, and *C. fetus* (Sasse *et al.,* 2021). In humans, Campylobacter takes two to five days to incubate before causing an infection (CDC 2019). This illness's prodromal stage starts out with a fever, headache, and painful muscles. The next symptom is acute uncomplicated enterocolitis with aqueous and occasionally bloody diarrhea. There may be cramp-like stomach pain, and there are frequently reports of nebulous symptoms including fever, headaches, and tiredness. The sickness frequently self-limits without issues after 5 to 7 days. However, among people under the age of 65 and children, the condition frequently advances slowly and badly. In immunocompromised individuals, particularly HIV-positive patients, sepsis instances are recorded; however, with effective, highly active antiretroviral treatment, this risk is negligible (Sasse *et al.*, 2021). Irritable bowel syndrome and inflammatory diseases such reactive arthritis, Guillain-Barré syndrome, and Miller Fischer syndrome have also been associated to Campylobacter infections. The autoimmune disease Guillain-Barré results in sensory precipitation and paralysis due to the demyelination of peripheral nerves. In these cases, there is a fatality rate of 2–3 percent, with respiratory failure being the main factor (Molnar *et al.,* 1982). The Campylobacter outer membrane's LOS, which resembles human gangliosides, is associated with an increased risk of developing Guillain-Barré syndrome (Koga *et al.,* 2005).

Antimicrobial resistance of *Campylobacter*

The development of antimicrobial resistance, often known as AMR, is a survival strategy that allows for more successful colonization of hosts. Campylobacter, the pathogen that causes AMR, is becoming more and more dangerous for both animals and people. There are a variety of circumstances in which the development of antibiotic resistance and the utilization of antibiotics in human and veterinary medicine are connected (Noll *et al.,* 2018). As was mentioned before, macrolides, quinolones, and tetracyclines are commonly used to treat severe Campylobacter infections. Despite this, there is growing evidence to show that Campylobacter is developing resistant to the medications that are currently being used to treat it (Table 2). Therefore, before beginning clinical therapy, testing for antibiotic resistance should be performed, and the use of antibiotics should be carefully monitored (Kreling *et al.,* 2020). Organ arsenicals such as roxarsone, which are now banned in the United States and the European Union, were previously utilized in livestock and poultry production in the United States at concentrations ranging from 22.7 to 45.4 g/ton in an effort to combat intestinal parasites, improve feed efficiency, and stimulate growth.

Additionally, campylobacter can withstand exposure to arsenic (Sapkota *et al.,* 2007). During the course of the investigation, qPCR expression data for various arsenic resistance genes were utilized in order to test arsenic resistance in a total of 552 Campylobacter isolates (*arsP, arsR, arsC, acr3,* and *arsB*). The majority of the investigated isolates were able to maintain their viability despite being exposed to greater concentrations of organ arsenic chemicals such as arsanilic acid,

roxarsone, and arsenate (Sapkota *et al.*, 2016). The withdrawal of approval for arsenic-containing pharmaceuticals took place in the year 2015.

In a manner analogous to that of other bacteria, Campylobacter has acquired a number of resistance mechanisms, some of which include the production of efflux pumps, alterations to the molecular targets, and antibiotic-modifying enzymes (Table 2) (Iovine *et al.,* 2017). It is especially concerning since these pathways can give resistance to many antimicrobial medications.

For example, the *cfr* (C) gene variation that was discovered in 2017 encodes a methyltransferase that alters the 23S rRNA at position A2503 by adding a methyl group (Tang et al., 2017). This modification took place in 2017. Because many antibiotics target this region in the peptidyl transferase center, the bacteria have developed resistance to four distinct classes of antimicrobials. These antimicrobials are phenicol's, lincosamides, oxazolidinones, and pleuromutilin's. Because Campylobacter has an inherent resistance to streptogramin, which, in theory, is mediated in a similar manner by this gene, streptogramin resistance is useless against Campylobacter. Placing the gene on plasmids is very crucial due to the fact that horizontal gene transfer can quickly transmit the gene. Campylobacter multidrug resistance genomic islands, more commonly referred to as "MDRGIs" for short, present a one-of-a-kind set of challenges.

There are a number of open reading frames in these chromosomal regions that contribute to the induction of antibiotic resistance. These frames include readings for tetracyclines, macrolides, and aminoglycosides, among others. MDRGIs are capable of undergoing natural alteration and serve as a mediator of multi-resistance in Campylobacter species (Qin *et al.,* 2014). The activity of multidrug efflux pumps has a sizeable influence on a variety of factors, including innate and acquired resistance to a large number of antimicrobial medications. It also has an impact on the efficiency of the therapeutic treatment as well as its total duration.

Table 2 Antimicrobial resistance mechanisms in *Campylobacter (Lynch et al., 2020; Liu et al., 2019).*

Antibiotic classes in use against *Campylobacter*	Resistance mechanism of *Campylobacter*
Aminoglycosides	Aminoglycoside-modifying enzymes (AphA, AadE, Aad9, Sat, Hph, AacA4, Aac3, Aph(2″)-If (previously identified as AacA4/AphD), and Aph(2″)) are responsible for the modification. -Ib, -Ic, -Ig, -If, -If1, -If3, -Ih, Aac(6′)Ie/Aph(2″)-Ia, Aac(6')Ie/Aph(2″)-If2) -Ib, -Ic, -Ig, -If, -If1, -If3, -Ih, Aac(6′)I
β-Lactams	β-Lactams Inactivation of enzymes through the action of -lactamases (penicillinase, BlaOXA-61). A decrease in membrane permeability brought about by the primary outer membrane protein (MOMP). Efflux via CmeABC transporter.
Fluoroquinolones	GyrA was modified (T86I, T86K, T86A, T86V, D90N, D90Y, A70T; also in combination, for example, T86I/P104S, T86I/D90N). Efflux via CmeABC transporter.
Macrolides	mutations of a single base pair in the 23S rRNA genes. The L4 and L22 ribosomal proteins have undergone mutations. Erm(B)rRNA methyl transferase-mediated methylation of the target RNA. Efflux via CmeABC transporter. MOMP results in a decrease in the permeability of the membrane.

Tetracyclines	protection of ribosomes through the binding of TetO or TetO mosaic resistance determinants (for example, TetO/32/O). Efflux is accomplished through the CmeABC and CmeG transporters.
Organoarsenicals	Efflux via ArsP (methylarsenite efflux permease).
Fosfomycin	$fosX^{CC}$
Multiple drug resistance	CmeABC efflux system (significant role in acquired and intrinsic resistance). Re-CmeABC (a variation of CmeABC which imparts much higher levels of resistance) (a variant of CmeABC which confers significantly higher levels of resistance). CmeDEF efflux system (moderate role in intrinsic resistance). CfrC (rRNA methyl transferase) (rRNA methyl transferase). genetic islands with resistance to several drugs (MDRGIs).

Diagnosis of Campylobacter

1.Isolation

The development of thermotolerant Campylobacter in its native habitat is extremely difficult since it is microaerobic and sensitive to dehydration, freezing, and both low and high temperatures. Although there are no tried-and-true methods for isolating Campylobacter, several studies have been conducted to identify the ideal environments for the bacteria to grow in human, food, and other environmental samples. Numerous isolation strategies have been codified by the International Organization for Standardization (ISO) and are mentioned in ISO-10272, with further changes (ISO- 10272-2006 and ISO-10272-2010) produced in response to fresh research (Peters *et al.*, 2019). Samples must be taken from the field and transferred to the lab with the utmost caution due to the fragility of Campylobacter. Low temperature is combined with a transport medium during transportation, namely at 4 C, to prevent Campylobacter loss and protect the cell from drying and harmful consequences caused by oxygen (Cary & Blair., 1964). The quantity of microorganisms in dietary and environmental sources declines under unfavorable conditions. Pre-enriched broths with antibiotic additions are frequently used to avoid the problem and boost the population of microorganisms. Examples include Exeter, Bolton, Preston, Park and Sanders, Campylobacter enrichment, and Buffered Peptone Water (Skirrow *et al.*,1977; Bolton., 1982). Typically, 1 ml of an aliquot from homogenized materials was added to enrichment broth, which was subsequently incubated for 44 hours at 42 °C after the initial 44 hours at 37 °C (Bojanic *et al.*, 2019; Sidiqee *et al.*, 2019). The most popular selective media for Campylobacter isolation include Campy-cefex, Preston, Karmali, Charcol, Butzler, Abeyta Hunt Bark, and modified charcoal cefoperazone deoxycholate. To boost the recovery of Campylobacter bacteria and stop the growth of other organisms, several antibiotics are added to the medium. These medications, which include trimethoprim (which inhibits Proteus and gram-positive cocci), cefoperazone (which inhibits members of the Enterobacteriaceae family), vancomycin and rifampicin, polymyxin B, and amphotericin (which inhibits fungal growth), are used in a variety of combinations for isolation (Corry *et al.*, 1995; Marchant *et al.*, 2002; Zhang., 2020).

b. Identification

Depending on the type of medium used, Campylobacter grows colonies with a range of characteristics. Campylobacter colonies frequently form spherical, grey to slightly pink colonies with or without a metallic sheen on blood-containing media, in contrast to flat, glossy, grey-to-white colonies with or without a metallic sheen on charcoal medium (Adedapo *et al.*, 2018). They are mobile,

gram-negative, favorably oxidase and catalyze, and negatively reactive for the production of acetoin, indole, and methyl red (Wassenaar *et al.,* 2000). It is critical to recognize that conventional phenotypic approaches that depend on carbohydrate consumption are worthless for categorizing taxa since the majority of *Campylobacter* strains do not need them for energy (Oyarzabal., 2017).

Since *C. jejuni* and *C. coli* are often isolated, accurate identification of these bacteria is essential. Hippurate hydrolysis testing was used in conventional biochemical methods to differentiate between *C. coli* and *C. jejuni* (Pavlova *et al.,* 2016). *C. jejuni* normally yields a positive response in this test while C. coli typically yields a negative result. On the other hand, unfavorable effects are possible with some *C. jejuni* subsp. *jejuni* strains. Another difference between *C. jejuni* and *C. coli* is that the latter can use propionate as its primary carbon source, whilst the former cannot (Oyarzabal *et al.,* 2017).

1. Confirmation

The *Campylobacter* species can be confirmed by both phenotypic and genotypic methods.

i. Phenotypic

There are several methods for recognizing and classifying Campylobacter species. It's been practiced for a long time to distinguish isolates phenotypically based on the organism's representation of biological or metabolic activity (Eberle., 2012). The three phenotypic methods of bio typing, serotyping, and multilocus enzyme electrophoresis that are most often employed to distinguish Campylobacter isolates are (MEE). The bio typing process includes categorizing bacterial isolates based on the way that their metabolic activity manifests. Colony morphology, environmental tolerances, and biochemical processes are a few examples of metabolic activity (Natsos *et al.,* 2019). The first stages in identifying Campylobacter spp. involve cultivating the bacteria on a medium and inspecting their colonial structure. The quickest techniques for identifying Campylobacter cells include Gram staining, oxidase testing, and catalase tests. The latex agglutination test, the API Campy test, serotyping, and conventional biochemical identification and confirmation assays are a few of the tests (Jafari *et al.,* 2021).

API Campy is the name of one of the tests used to determine the presence of Campylobacter species (Biomerieux France). This exam consists of 9 assimilation and inhibition tests, 11 conventional tests, and 11 enzymatic tests. Studies have shown that API Campy is more sensitive and specific than traditional approaches, successfully detecting *C. jejuni* (94%), *C. coli* (74%), and *C. upsaliensis* (100%), while misidentifying 5% of other species. The traditional and API Campy approaches did not, however, vary in a statistically meaningful way. Additional commercial identification tools for Campylobacter species include the Campylobacter Latex Agglutination Kit (Microgen UK), Phoenix Automated Microbiology System (BD New Jersey USA), and Rap ID Remel (Remel USA). These tests can only identify Campylobacter at the genus level; specific Campylobacter species cannot be distinguished. In the latex agglutination test, polyclonal antibodies are used to identify the antigenic outer membrane protein of flagellar epitopes (Miller *et al.,* 2008; Nisar *et al.,* 2018).

2. Genotyping

The genotype of an organism is ascertained by looking at determinable areas of the genome, which enables the distinction of various subpopulations within a species as well as the genomic affiliation between isolates (Downes., 2001). Genotyping processes offer more precise strain separation as well as greater degrees of uniformity, type ability, and discriminating power when

compared to phenotypic typing techniques (Wassenar wet al., 2000; Wiedmamm., 1997). Multilocus sequence typing, polymerase chain reaction (PCR), pulsed-field gel electrophoresis (PFGE), ribotyping, and amplified fragment length polymorphism are common genotypic typing methods (AFLP). The amplifying of highly conserved genes in those species allows for the accurate identification of Campylobacter species.16S rRNA for the *Campylobacter* genus (Linton *et al.,* 1997; Cui *et al.,* 2016; Zbrun et al., 2021), *mapA* and *hipO* for C. *jejuni*, cueE for *C. coli* (Denis et al., 1999; Smith et al., 2021), and porA for *C. lari* and *C. upsaliensis* are some of the particular Numerous other genes, such as *CdtA*, *CdtB*, and *CdtC*, *CadF* (Cunningham et al., 2010), *sapB* and *glyA* (Wang *et al.,* 2002; Silva *et al.,* 2021), and *ipxA*, were also employed for genotyping (Klena *et al.,* 2004; Inglis *et al.,* 2019).

3. Molecular detection

i. Conventional PCR

Genetic material is amplified using the PCR technique, which offers good sensitivity and specificity. A precise genetic sequence must be used, and contamination must be maintained to a minimum, in order to obtain correct results (Datta *et al.,* 2003). By amplifying genetic material in a selected area using a specific primer, PCR may be used to identify the gene of interest (virulence gene or housekeeping gene) (Bang *et al.,* 2003; Devane *et al.,* 2005). Nested PCR, gradient PCR, multiplex PCR, real-time PCR (RT-PCR), and other variations of PCR exist. They all have distinctive qualities that let scientists quantify the number of organisms and identify between closely similar species (Reischal., 1995; Waage *et al.,* 1999; Josefon *et al.,* 2004).

ii. Digital PCR

Through digital PCR (dPCR), the precise copy number of a gene target is determined. Inhibitors of enzyme amplification have less of an effect on precise dPCR measurement (Ricke *et al.,* 2019). Campylobacter remnants were discovered using dPCR, which is frequently more sensitive than Qpcr (Peruzy et al., 2019).

iii. Real-Time PCR

Today, RT-PCR is employed for numerous diagnostic reasons as well as the identification and quantification of microorganisms in food items. In RT-PCR, the target sample is amplified concurrently with internal and external controls of known quantities. By comparing the findings of the unknown samples to those of the control, the result is computed. The RT-PCR technique is particularly sensitive and can identify just a few organisms in a sample, such as 10–100 Campylobacter cells (Waage *et al.,* 1999). For the purpose of identifying certain species, RT-PCR uses a variety of primer and probe types. The calculations and measurements of the outcomes are done in "real-time," while amplified products track changes in florescence signals. These are measured by the exponential phase of amplification because after each cycle, the copies of the DNA sequences double. In RT-PCR, the lag phase, exponential phase, linear phase, and plateau phase may all be separated from one another. Computer screens may be used to monitor all of these phases. The ratios of PCR templates to products might be biased (Suzuki., 1996).

4. Whole Genome Sequence

By resolving pathogens with just a single base pair of differences, whole-genome sequencing (WGS) gives epidemiological research a high level of discriminating ability. Although WGS only has a small number of species, including *C. jejuni,* it can describe diseases. One of the first bacterial strains for whole genome sequencing and next-generation sequencing (NGS) technology analysis was *C. jejuni*. Analysis of WGS in epidemics is now feasible because to advancements in NGS (Hofreuter *et al.,* 2006; Pearson *et al.,* 2007). The 1.6–1.7 Mb short

genome of Campylobacter species makes it simple to sequence them (Cooper et al., 2011). In addition, WGS requires knowledge of and access to bioinformatics tools and resources. Recently, WGS data were used to provide a framework for assessing the effectiveness of various molecular techniques for *C. jejuni* and *C. coli* (Golz *et al.*, 2020).

5. Prevention and Control

Since the majority of Campylobacter infections are contracted by eating or handling poultry, the greatest method to decrease the incidence of human illnesses would be to avoid contaminating chicken flocks. Due to the large bacterial load in these flocks and the practically universal Campylobacter infection of poultry, it is difficult, if not impossible, to completely eliminate Campylobacter in chickens (Hood *et al.*, 1988). It's possible that future research will lead to the creation of a method for producing chickens that are only minimally infected with Campylobacter. The current mass distribution and processing of chicken might increase the bacterial load. Some of the new strategies are anticipated to include reducing animal usage of antibiotics, cleaning their food and water, treating their waste, and isolating contagious sick people. Maybe one day the public will embrace the irradiation of meals made from animals in a way that makes it a workable way to reduce bacterial contamination in food.

By adopting careful food preparation methods in the kitchen, infections can be prevented. The chicken shouldn't be overcooked on the outside or undercooked close to the bone. You may confirm that the temperature is high enough to eradicate Campylobacter species organisms by using a meat thermometer. Cutting boards and other implements used to handle raw meat or poultry should be washed in hot, soapy water before being used to make salads or other meals that are intended to be eaten raw. The results of a study done in Belgium show that skinless, frozen chicken meat had a higher Campylobacter content than skin-on meat (Korsak *et al.,* 2015). Chlorinated water and nitrogen-containing salt significantly decrease Campylobacter, Salmonella, and E. coli in the intestines of sheep, cattle, and poultry. Utilizing acetic acid in meat and caprylic acid in animal feed can significantly reduce population (Marmion *et al.*, 2021). This bacterium is prevented from colonizing chickens by adopting a technique known as competitive exclusion. The practice of feeding competitive exclusions to freshly hatched chicks reduce Campylobacter on a commercial basis. Recent research has shown that bacteriophage therapy in broiler flocks is an efficient treatment for the control and transmission of Campylobacter at the farm level.

Summary and conclusion

Campylobacter is currently the most common cause of bacterial gastroenteritis and a substantial public health concern, in addition to its developing drug resistance. Despite the ongoing advancement of molecular biological tools, many aspects of the epidemiology of several Campylobacter infections are still unclear. This may be partially explained by Campylobacter's significant genetic variability. Although we are getting more knowledgeable about the virulence aspects of Campylobacter, there is still potential for improvement in efficient prevention measures. Pharmacological substances with ant virulence effect against bacterial adhesion and/or invasion to and into the host cells may help to open up a new field of antibacterial. The virulence and aggressiveness of a bacteria can be influenced by chemotaxis, quorum sensing, biofilm growth, secretion systems, or toxin production by certain inhibitors. In order to gain a deeper knowledge of this complex and well adapted organism, additional research and analysis are thus required. This will

eventually result in better and more effective management measures.

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Conflict of Interest

The authors declare no conflict of interest.

Authors Contribution

SR conceived the original idea and designed the outlines of the study. All the authors equally contributed and wrote the 1st draft of the manuscript. SR revised the whole manuscript and formatted it accordingly. All authors have read and approved the final manuscript.

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