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CAMPYLOBACTERIOSIS IN THE SPOTLIGHT: INSIGHTS FROM SOUTHEAST ASIA

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A B S T R A C T

Campylobacter has recently emerged as a significant contributor to bacterial foodborne and waterborne diarrheal infections, posing significant public health threats globally, including in both low-income countries and developed nations such as Europe and the USA. This pathogen is a primary cause of gastrointestinal infections, significantly elevating the burden of *Campylobacter*-related illnesses worldwide. As a commensal microorganism in the gastrointestinal tracts of numerous wild and livestock animals, as well as avian species, *Campylobacter* typically spreads via the fecal-oral route through the consumption of contaminated food and water, leading to zoonotic infections. The prevalence of *Campylobacter* infections, primarily attributed to *C. jejuni* and *C. coli*, has seen a notable increase, alongside the emergence of new *Campylobacter* species documented globally. Beyond gastrointestinal inflammation, it is associated with extra-intestinal disorders such as septicemia, meningitis, reactive arthritis, and Guillain-Barré Syndrome. In Southeast Asian countries, *Campylobacter* infections are commonly linked with traveler's diarrhea. Moreover, the rising antimicrobial resistance among *Campylobacter* species poses a significant public health challenge, compromising the efficacy of treatment measures. Our study aims to provide a comprehensive overview of *Campylobacter* infections, with a specific focus on Asian countries in the Southeast region, which necessitates effective remedial strategies and ensuring food safety. This review addresses *Campylobacter* pathogenic species, isolation and diagnosis, reservoirs, transmission pathways, epidemiology of outbreaks, prevention and treatment options, antibiotic resistance, and the control of antibiotic usage. This study will facilitate further research into *Campylobacter* infections globally and support

preventive initiatives, including health surveillance, rapid diagnostic services, identification of causative agents, vaccination of reservoir animals, and maintenance of proper food hygiene practices.

1. INTRODUCTION

Campylobacter is a member of the rRNA superfamily VI of Class Proteobacteria, specifically a subclass of specialized bacteria (Igwaran & Okoh, 2019). It displays a slender, rod-shaped, or spiral-shaped morphology and are equipped with either a solitary or a double flagellum. There are different species of *Campylobacter*, that have multiple flagella such as *C. showae*, while others, like *C. gracilis*, do not have any (Acke, 2018). The *Campylobacter* species are gram negative, nitrate positive, Hippurate positive, catalase positive, oxidase positive, indole negative, and glucose utilization negative (Pal, 2017). The family Campylobacteria consists of 39 species and 16 subspecies, collectively forming the genus *Campylobacter*. Food and water-borne diarrheal diseases are the leading cause of illnesses and deaths in developing countries(Schlundt et al., 2004). *Campylobacter* plays a significant role in causing gastrointestinal illness in humans (Bassal et al., 2016). Many of the *Campylobacter* species are zoonotic pathogens, causing gastrointestinal disorders and, in some cases, campylobacteriosis, a potentially fatal infection that extends beyond the intestines (Man, 2011). According to recent global data, *Campylobacter* is the leading cause behind foodborne gastroenteritis in humans (Ma et al., 2022). People who are infected may experience a variety of symptoms, ranging from mild, watery diarrhea to more severe cases with inflammation, blood, and leukocytes. With the low infectious dosage of *Campylobacter* , 500 to 800 cfu, infections in humans are quite prevalent (Janssen et al., 2008) and causes 5%–14% of all cases of diarrhea worldwide in the human population (Kaakoush et al., 2015a). Besides the gastrointestinal infections, it causes many other infections in humans, including, systemic infections like endocarditis, septic thrombophlebitis, pneumonia, neonatal sepsis, acute peritonitis, acute colitis of inflammatory bowel disease, and bloodstream infections (Morishita et al., 2013). The majority of these infections are caused by *C. jejuni* and *C. coli*, with *Campylobacter* jejuni accounting for 90% of cases and *C. coli* accounting for the remaining 10% (Janssen et al., 2008). Individuals infected with *C. jejuni* and, to a lesser extent, C. *coli* may experience either watery or bloody diarrhea, as well as symptoms like fever, stomach pains, and vomiting. Post-infection, there can be additional severe consequences such as demyelinating neuropathy, Guillain-Barre syndrome (GBS), and Miller-Fisher syndrome (MFS) which significantly increases the *Campylobacter* disease burden (Scallan et al., 2015). In studies, researchers have discovered that patients with the syndrome exhibit a wide range of *Campylobacter* species, including *C. showae, C. hominis, C. fetus, C. hyointestinalis, C. insulaenigrae, C. lari, C. ureolyticus, C. sputorum, C. curvus, C. gracilis, C. concisus, C. rectus, and C. upsaliensis* (F. Liu et al., 2018). Enteritis induced by these bacteria is usually sporadic and tends to resolve without treatment. However, along with gastrointestinal infections like Barrett's esophagus and colorectal cancer, *Campylobacter* species are responsible for developing some extra gastrointestinal complications such as bacteremia, hepatic disease, pancreatitis, pulmonary infection, cerebral abscesses, meningitis, and reactive arthritis (Hlashwayo et al., 2021). Human infection with *Campylobacter* can occur through a variety of sources including poultry, meat, milk, water, and direct contact with farm animals, which are the primary reservoirs of *Campylobacter* species (Sheppard et al., 2011). Most food-borne *Campylobacter* infections resolve without intervention and only require supportive care, however, patients with severe and persistent symptoms may find relief through appropriate antibiotic treatment (Pacanowski et al., 2008). This infection can have serious consequences and can lead to Guillain-Barre syndrome for children, elderly, and those with weakened immune systems

(Del Collo et al., 2017). Antimicrobial resistance poses an additional threat as infections caused by antibiotic-resistant *Campylobacter* species lead to extended hospital stays, reduced treatment efficacy, and increased rates of illness and mortality (Llor & Bjerrum, 2014). In addition, it is worth noting that farm animals are the major source of *Campylobacter* foodborne gastrointestinal diseases and bacterial food poisoning worldwide (Del Collo et al., 2017; Seguino et al., 2018). Foodborne infections caused by *Campylobacter* are a major public health concern with significant financial impact. The majority of cases of campylobacteriosis are classified as individual occurrences that affecting a single household, rather than being classified as widespread outbreaks. The Southeast Asia (SEA) region is renowned as a premier tourist place globally, offering substantial economic and social advantages to the area. With rising worries about food-borne infections associated with travels, ensuring food safety emerges as a significant concern (Hall & Page, 2012). As a result, elucidating and understanding the situation of human *Campylobacter* infection in the SEA region is critical for reducing the infection burden and implementing mitigation strategies.

2.0 PATHOGENIC SPECIES OF *CAMPYLOBACTER*

Two subgroups of *Campylobacter* species include the Lior and Penner serotypes, with 100 Lior and 600 Penner serotypes identified. Thermotolerant *Campylobacter* species are the only ones among the Lior and Penner serotypes that have been acknowledged for their clinical significance (Lee et al., 2013). Each year, the pathogenic *Campylobacter* species including *C. jejuni*, *C. rectus*, *C. concisus*, *C. hyointestinalis*, *C. sputorum*, *C. helveticus*, *C. lari*, *C. fetus*, *C. mucosalis*, *C. coli*, *C. ureolyticusm*, and *C. insulaenigrae*, affect approximately 400-500 million humans (Heredia & García, 2018). Notable human intestinal pathogens include *C. jejuni*, *C. coli*, *C. fetus* while minor pathogens like *C. concisus*, *C. lari*, *C. hyointestinalis* also exists. Furthermore, *C. fetus* subsp. venerealis (Cfv) is a notable veterinary pathogen (Taheri et al., 2019).

2.1 *Campylobacter jejuni*

C. jejuni belongs to the bacterial family Campylobacteriaceae, alongside *Arcobacter* and *Sulfurospirillium* (Science et al., 2021). The bacterium possesses several key characteristics, including being catalase and oxidase positive, gram-negative, fastidious, non-spore forming, non-saccharolytic, and exhibiting positive hippurate hydrolysis (Science et al., 2021; Snelling et al., 2005). These bacteria exhibit a helical movement that resembles a corkscrew, which is caused by a polar flagellum located at the ends of their spirally curved or s-shaped cells. These cells have a width of 0.2 to 0.8 µm and a length of 0.5 to 5 µm, and are accompanied by particles with a diameter of 0.2 to 0.8 µm (Gilbreath et al., 2011). It is widely recognized as the most common enteric pathogen, exhibiting varying degrees of pathogenicity among different strains (Hofreuter et al., 2006). This species is particularly notable for causing illnesses compared to other *Campylobacter* species, with a higher proportion of cases (K. C. Liu et al., 2017). It is the most frequent cause of diarrhea, especially in young individuals (Haddock et al., 2010). *C. jejuni* is the most common species that infects young individuals (Haddock et al., 2010). Acquiring infections can result from direct contact with domestic and farm animals or consuming contaminated food and water (Domingues et al., 2012). Symptoms such as acute enteritis, severe stomach discomfort, fever, and bloody diarrhea with mucus can indicate an infection(Biswas et al., 2011a). In addition, studies have established a connection between *C. jejuni* and immunoreactive conditions such as Miller-Fisher syndromes (Dingle et al., 2001).

2.2 *Campylobacter coli*

C. coli is a helical bacterium with a curved shape, measuring between 0.2 and 0.5 micrometers in length (Igwaran & Okoh, 2019). This organism possesses a single flagellum and bears a strong resemblance to *C.*

jejuni (Igwaran & Okoh, 2019). This particular *Campylobacter* species ranks as the second most commonly identified source of human illnesses (Tack et al., 2019). Both bacterial strains cause inflammation and diarrhea in the intestines of individuals. Infections are characterized by symptoms including watery diarrhea, abdominal pain, bloating, fever, inflammatory enterocolitis, malaise, and nausea. Studies have shown that *C. coli* is the second most common cause of campylobacteriosis in developed countries (Beier et al., 2018). Within affluent communities, *C. coli* infections tend to occur sporadically, displaying seasonal fluctuations, with most cases occurring in early fall or late summer (Beier et al., 2018). The *C. coli* bacterium can be categorized into three distinct groupings, commonly referred to as clades. In *C. coli* clade 1, the most common strains found in both humans and cattle are prevalent. Human infections are primarily caused by *C. coli* clade 1, with occurrences of infections from *C. coli* clade 2 and 3 being rare.

2.3 Other *Campylobacter* pathogens

Various *Campylobacter* species have been identified, including *C. fetus*, *C. upsaliensis*, *C. lari*, *C. curvus*, *C. mucosalis*, *C. insulaenigrae*, *C. concisus*, *C. doylei*, *C. helveticus*, and *C. rectus*. *C. fetus* is a curved, mobile, and highly specialized bacteria known for causing septic abortion in animals due to its specific growth requirements. One can get infected through direct contact with animals, eating undercooked meat, or consuming contaminated food or water. The symptoms in human linked to *C. fetus* infections encompass endocarditis, meningitis, septicemia, septic arthritis, peritonitis, and cellulitis (Hur et al., 2018). Occasionally, it can result in systemic infections, such as bloodstream infections in people with weakened immune systems (Wagenaar et al., 2014). However, the frequency of such infections is quite low. Five species belong to the *C. lari* group: *C. lari*, *C. subantarcticus*, *C. insulaenigrae*, *C. volucris*, and *C. peloridis*. Moreover, there is a category of strains referred to as UPTC and strains similar to *C. lari* (Miller et al., 2014). *C. lari* has been linked to a variety of health issues in human, such as enteritis, purulent pleurisy, bacteremia, urinary tract infection, reactive arthritis, and prosthetic joint infection. *Campylobacter upsaliensis* falls under the category of thermotolerant species in the *Campylobacter* genus. Both sick and healthy dogs and cats have been found to carry the pathogen (Labarca et al., 2002). It is also widely recognized *Campylobacter* species that can lead to diarrhea in both dogs and cats too (Steinhauserova et al., 2000). *C. upsaliensis*, like *C. jejuni*, is a species of *Campylobacter* that has been associated with human illnesses (K. Premarathne & Amila, n.d.). In addition to the extensively studied pathogenic species, recent discoveries of pathogenic species, including *C. sputorum* biovar sputorum, *C. ureolyticus*, *C. peloridis*, *C. gracilis*, and *C. showae*, have been linked to human illnesses. Infections can have serious consequences for hospitalized patients (K. Premarathne & Amila, n.d.). Identifying these new species poses a major risk to human health as the mode of transmission to humans is unknown, raising concerns.

3.0 EPIDEMIOLOGY

Southeast Asia is a fascinating region with eleven diverse nations. These countries, including Brazil, Burma (Myanmar), Cambodia, Timor-Leste, Indonesia, Laos, Malaysia, the Philippines, Singapore, Thailand, and Vietnam, offer a rich tapestry of religion, culture, and history (*Campylobacter Jejuni from Farm to Fork: Campylobacteriosis and Chicken Meat | Journal of Current Science and Technology*, n.d.). There is a significant disparity in the data regarding the occurrence of *Campylobacter* outbreaks in different countries, making it difficult to determine the true global incidence rate (WHO, 2013). There are several factors that contribute to the lack of a specific rate of incidence for *Campylobacter* outbreaks. These include the underreporting of *Campylobacter* infection cases, variations in reporting systems,

challenges in diagnosis, and discrepancies in outbreak monitoring (Hansson et al., 2018). Food or waterborne illnesses are responsible for the majority of *Campylobacter* outbreaks, impacting a significant number of individuals (Frost et al., 2002) with a high incidence rate. In addition, a considerable number of *Campylobacter* outbreaks are caused by animal illnesses (Wilson et al., 2008). However, in economically underdeveloped nations, the main reason behind *Campylobacter* outbreaks is the presence of environmental reservoirs like rivers and streams. These water sources are relied upon by a large portion of the population for safe drinking water (Clark et al., 2003). According to reports, it was on October 8th, 1980, when countries in Southeast Asia, including Singapore, witnessed the emergence of the first recorded case of *Campylobacter* illness. An infection was observed in a male tourist who was visiting as an adult. During the next month, two additional cases were documented in children, and it was later confirmed that both were caused by *C. jejuni* and *C. coli* (*Campylobacter Enteritis in Singapore - PubMed*, n.d.). Throughout the years 2001 to 2014, the predominant pathogen identified in the reported cases was *Campylobacter* jejuni, consistently found in a prevalence ranging from 84% to 100%. According to the data, *C. coli* had a prevalence of 0-4%, followed by *C. lari* with 0-0.2%, and various other species of *Campylobacter* with a prevalence of 0-12% (Kaakoush et al., 2015b). From January 1st, 2016 to March 28th, 2016, Thailand experienced an annual incidence rate of reported cases of diarrheal diseases of 424.16 per 100,000 inhabitants. Out of the 27,623 cases, unfortunately, two lives were lost. In that particular time frame, there were a total of 30,203 reported cases of food poisoning. Interestingly, the gender distribution ratio was 1 male for every 1.47 females. However, the vast majority of these occurrences, specifically 99.3%, remained unexplained (Rakprasit et al., 2017). Between 2000 and 2014, there was an average of 1,762 cases of acute diarrhea and 201 cases of food poisoning reported annually in Thailand. From 2000 to 2014, acute diarrhea was consistently widespread and closely monitored in Thailand, making it one of the leading causes of illness. In addition, it was found that food poisoning ranked among the top 10 causes of morbidity, with a total of 76 cases reported. During the period from 2000 to 2010, Vietnam faced a significant number of foodborne outbreaks, leading to a large number of people falling ill and unfortunately, a considerable loss of lives. There has been a significant decrease in the incidence of acute watery diarrhea in the Philippines, with the number of cases dropping from 866,411 in 2000 to 235,110 in 2012. Furthermore, it was found that acute diarrhea was a major contributor to infant mortality, resulting in 78 deaths. On February 24th, 2016, the Ministry of Health in Brunei Darussalam documented a total of 727 cases of gastrointestinal illnesses. Most of these cases occurred in children who were younger than five years old. There has been an increase in the number of reported cases compared to the previous year. In 2010, Brunei Darussalam experienced the highest number of recorded cases of food poisoning, totaling 177 instances (J. M. K. J. K. Premarathne et al., 2017). Between 2005 and 2012, Brunei Darussalam documented a total of 25 cases of *Campylobacter* infection. In 2011, there were a total of 9 cases, making it the year with the highest number of cases. From 2000 to 2012, the health reports for Cambodia documented a significant number of hospital admissions and outpatient visits specifically related to diarrhea. This disease ranks among the most extensively studied illnesses across the country (Merali et al., 2018). An investigation was conducted to explore the factors contributing to acute diarrhea in children aged 0-35 months who underwent treatment at a hospital in Myanmar between 1982 and 1985. The study incorporated controls that were carefully selected to match the cases in terms of age and sex. The study revealed that the prevalence of *C. jejuni* in both the case and control groups of Burmese children was 2% (Vu Nguyen et al., 2006). Figure 1 represents the Southeast Asian countries with specific timeframes within which outbreaks of diarrheal infections associated with *Campylobacter* occurred.

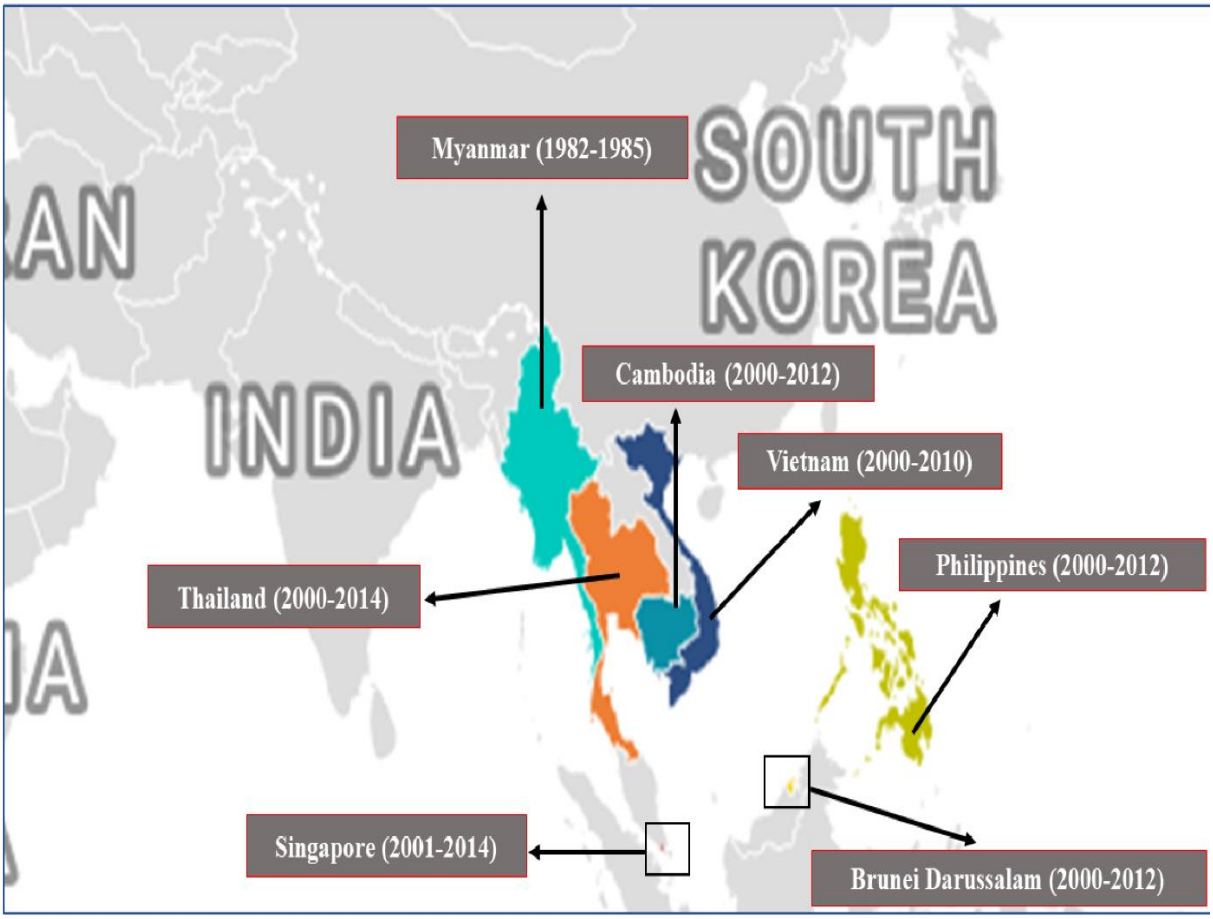

Figure 1: Countries of Southeast Asia that experienced diarrheal outbreaks caused by *Campylobacter*.

4.1 ROUTES OF *CAMPYLOBACTER* TRANSMISSION IN CAUSING HUMAN INFECTIONS

The gastrointestinal tracts of chickens, European blackbirds, cattle, sheep, ostriches, cats, dogs, and pigs are host to the majority of *Campylobacter* species (Adhav & Saikrishnan, 2023). The pathogens are expelled into the immediate surroundings in the feces of these animals (Goni et al., 2017). Close interaction with animals, especially domesticated animals, has the potential to transfer *Campylobacter* to people. Dog owners are particularly susceptible to *Campylobacter* infection. In addition to pets, cattle and other domestic animals are often colonized by *Campylobacter* species. People who handle these animals are likewise very vulnerable to *Campylobacter* infection (Hansson et al., 2018). Furthermore, those who work on farms and in slaughterhouses who sometimes neglect to follow appropriate hand hygiene and food safety measures are at an increased risk of *Campylobacter*iosis. However, it is crucial to find and understand the mechanisms by which *Campylobacter* infections are transmitted in order to effectively prevent and manage them (Newell et al., 2017). The primary and important modes of transmission for *Campylobacter*iosis are via the fecal-oral route(Maësaar et al., 2020), ingesting undercooked meats that are infected, or intake of contaminated food or water (Grzybowska-Chlebowczyk et al., 2013). Figure 2 illustrates the several paths via which *Campylobacter* infection may be spread.

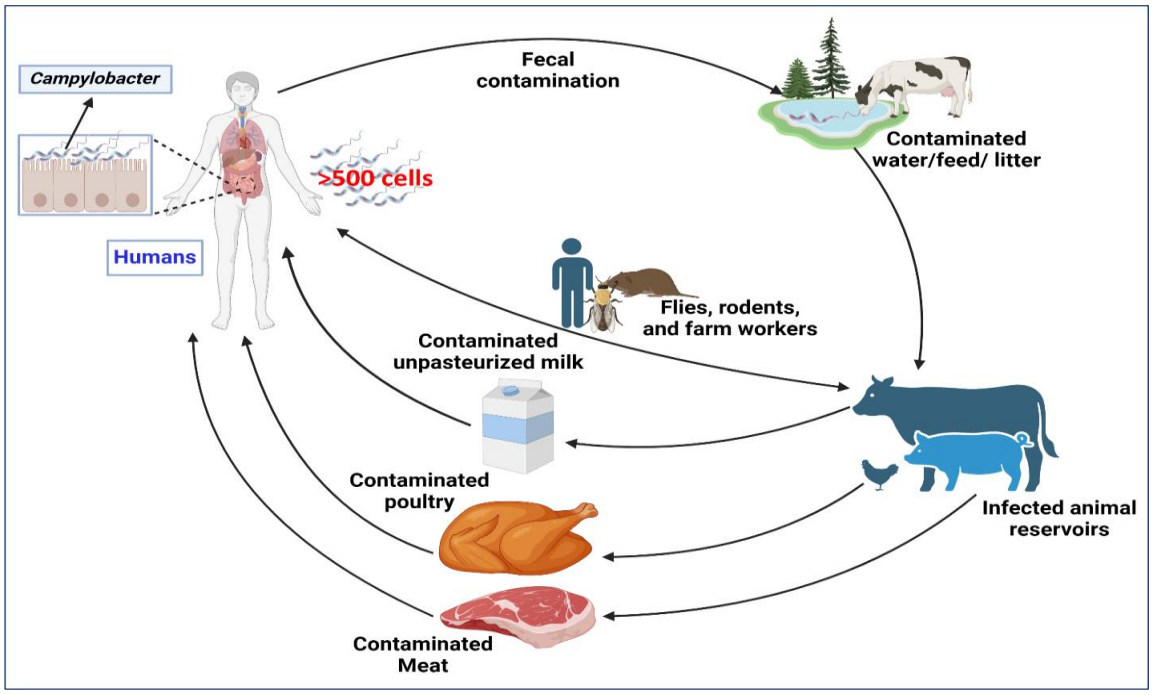

Figure 2: Transmission of *Campylobacter* infections via fecal-oral route; The feed or water of domestic and farm animals become contaminated with *Campylobacter* spp. that is released in the environment through the feces of infected humans. Animals after ingesting such water and feed get infected and carry the pathogen as reservoirs. Humans' intake the meat or dairy product from those animals that are not properly processed to minimize the contamination or due to lack of hygiene practice. Even if 500 cells of *Campylobacter* have the potential to cause significant gastrointestinal illnesses by colonizing the intestinal epithelial cells of humans.

4.1.1 Meat of *Campylobacter* infected animals

Animals that are usually defined as reservoirs or amplifying hosts, and food and direct contact with animals as primary transmission routes, with meat and meat related products serving as examples of exposures (Newell et al., 2017). Poultry serves as the primary reservoir for *Campylobacter* infection, which stands as the predominant factor behind bacterial food-borne disease(Wieczorek et al., 2015). Poultry include culinary products produced from chicken, turkey, duck, and goose (Szosland-Fałtyn et al., 2018). Contaminated meat is the main source of *Campylobacter* enteritis (Ono & Yamamoto, 1999). Chicken meat consumption, seems to explain (as transmission route) only about half of the human *Campylobacter*iosis cases attributable to a given food-producing animal reservoir(Mughini-Gras et al., 2021). That's why, FAO and WHO joint committee *Codex Alimentarius* urge the authorities around the world to establish preventive precautionary measures to control the *Campylobacter* in poultry meat due to its possibility of vertical transmission (Food and Agriculture Organization of the United Nations. et al., 2009). Besides *Campylobacter* species have been detected in other types of meat, such as pork, beef, and mutton, in addition to poultry (Igwaran & Okoh, 2019).

4.1.2 Milk contaminated with *Campylobacter*

Since *Campylobacter* cannot grow naturally outside the gut of a warm-blooded animal, the general environment can only serve as a vehicle for transmission, and not as an amplification niche (Newell et al., 2017). Raw milk is a well-known vehicle for multiple pathogens, including *Campylobacter*(Heuvelink et al., 2009). Internationally, outbreaks and sporadic cases of *Campylobacter*iosis have been associated with

the consumption of unpasteurized or raw milk (Christidis et al., 2016). Milk is a nutrient-dense liquid generated within mammals' mammary organs. It serves as a nourishing source of protein, dietary fats, and essential minerals such as calcium and magnesium, which are crucial for development, especially in youngsters (O'Callaghan et al., 2018). Animal milk has a natural antibacterial system that has short-term germicidal or bacteriostatic capabilities. Nevertheless, bacterial proliferation is sometimes unavoidable unless it is subjected to thermal processing or freezing (S, 2016). Milk serves as a conducive medium for bacterial proliferation (*(PDF) Campylobacter in Raw (Unpasteurised) Milk Risk Profile*, n.d.), and it is recognized as one of the primary pathways via which *Campylobacter* is transmitted to people (El-Zamkan & Hameed, 2016). Milk contamination often stems from environmental factors such as water, grass, milking equipment, feed, air, teat apex, dirt, and other causes (Coorevits et al., 2008). The occurrence of *Campylobacter* species in raw milk samples is believed to be a result of fecal contamination (Oliver et al., 2005).

4.1.3 *Campylobacter* transmission via contaminated water

Though Poultry is the best-known source of *Campylobacter* infection (Skarp et al., 2016), but *Campylobacter* can also be transmitted to humans via contaminated water. This can happen directly via drinking water or recreational use of water or indirectly by colonizing livestock(Sales-Ortells & Medema, 2015; Schönberg-Norio et al., 2004). Waterborne outbreaks have shown that *Campylobacter* can be effectively transmitted via water but the role of water as a source for sporadic infections might still be underappreciated (Nilsson et al., 2018b). Compared to other foodborne pathogens, *Campylobacter* is very susceptible to various environmental stressors, but can survive for a certain period of time in water or other environmental habitats (Whiley et al., 2013). Some C. jejuni strains have been shown to persist for weeks in water at low temperatures, but inter-strain differences have been reported (Nilsson et al., 2018a). Survival of *Campylobacter* in water is enhanced in the presence of protozoa, such as amoebae(Vieira et al., 2015). *Campylobacter* in VBNC(viable but non cultureable) state are more resistant to disinfectants, can survive for up to 7 month in water, are able to initiate biofilm formation, and are still infective (Magajna & Schraft, 2015). Waterborne diseases caused by *Campylobacter* (Mossong et al., 2016) have the potential to impact a considerable number of persons(Pitkänen, 2013). The water samples collected from beaches and rivers have been shown to include pathogenic species of *Campylobacter*, including *C. coli*, *C. jejuni*, and *C. lari* (Igwaran & Okoh, 2019). These bacteria have also been detected in other water sources including ponds, streams, lakes (Sails et al., 2002), children's paddling pools (Gölz et al., 2018), groundwater, and saltwater(Kemp et al., 2005).

5.0 *CAMPYLOBACTER* INFECTIONS

The majority of bacterial infections in the gastrointestinal system are caused by the species *Campylobacter* (Shane, 2000). *Campylobacter*iosis is a bacterial illness that primarily causes gastroenteritis in humans, but it can also affect other areas of the body. There are two main types of *Campylobacter* infections: one that affects the gastrointestinal tract (GI tract) and another that occurs outside of the GI tract (extra gastrointestinal infection). The occurrence of gastrointestinal infection, also referred to as GI infection, involves the inflammation of the gastrointestinal system, encompassing the small intestine and stomach. Diarrhea is a common symptom that frequently accompanies gastrointestinal (GI) disorders (J. Liu et al., 2023). In addition, it is the main and consistent cause of traveler's diarrhea (Bullman et al., 2011). Extra gastrointestinal infections (EI) are infections that occur outside the intestines, although the symptoms are caused by an issue originating from inside the gut (Hernandez & Green, 2006). *Campylobacter* infections have been associated with a range of non-gastrointestinal disorders, including bacteremia, septicemia, endocarditis, meningitis, reactive arthritis, Guillain-Barre syndrome (GBS), inflammatory bowel disease

(IBD) and neonatal sepsis. Table 1 represents some of the illnesses caused by different *Campylobacter* spp. inside and outside of the GI tract.

Table 1: *Campylobacter* species associated with human gastroenteritis and extra-gastrointestinal infections.

***Campylobacter* species**	**Gastrointestinal infections**	**Extra-gastrointestinal infections**
C. coli	Gastroenteritis and acute cholecystitis	Bacteremia, sepsis, meningitis and spontaneous abortion
C. jejuni	Acute cholecystitis and celiac disease	Sequelae such as bacteremia, urinary tract infection, GBS, reactive arthritis, MFS, sepsis, meningitis and hemolytic uremic syndrome
C. lari	Gastroenteritis and septicemia	Bacteremia
C. fetus	Gastroenteritis	Meningitis, vertebral osteomyelitis, brain abscess, cellulitis, septic abortion and bacteremia
C. curvus	Liver abscess, Barrett esophagitis and gastroenteritis	Bronchial abscess and bacteremia
C. ureolyticus	Gastroenteritis, Crohn's disease and ulcerative colitis	Reactive arthritis and rheumatoid arthritis
C. concisus	Gastroenteritis and Barrett esophagitis	Brain abscess, reactive arthritis and rheumatoid arthritis
C. helivectus	Diarrhea	--
C. hominis	Ulcerative colitis and Crohn’s disease	Bacteremia
C. hyointestinalis	Diarrhea and gastroenteritis	Fatal septicemia
C. insulaenigrae	Abdominal pain, diarrhea and gastroenteritis	Septicemia
C. mucosalis	Gastroenteritis	--
C. rectus	Ulcerative colitis, gastroenteritis and Crohn’s disease	Necrotizing soft tissue infection and empyema thoracis
C. showae	Ulcerative colitis and Crohn’s disease	Intraorbital abscess
C. sputorum	Gastroenteritis	Axillary abscess and bacteremia
C. upsaliensis	Gastroenteritis	Breast abscess, bacteremia and spontaneous abortion

There is a striking similarity between the clinical presentations of *Campylobacter* infections and the symptoms of illnesses caused by *Shigella* and *Salmonella* (Hansson et al., 2018). Our understanding of the mechanisms behind the persistence and induction of infection by *Campylobacter* is limited. Nevertheless, if it affects the ileum, jejunum, and colon, it can occasionally result in infection, whether or not there are

noticeable symptoms. Figure 3 schematically depicts the pathway of pathogen transmission and occurrence of diseases associated with *Campylobacter* infections.

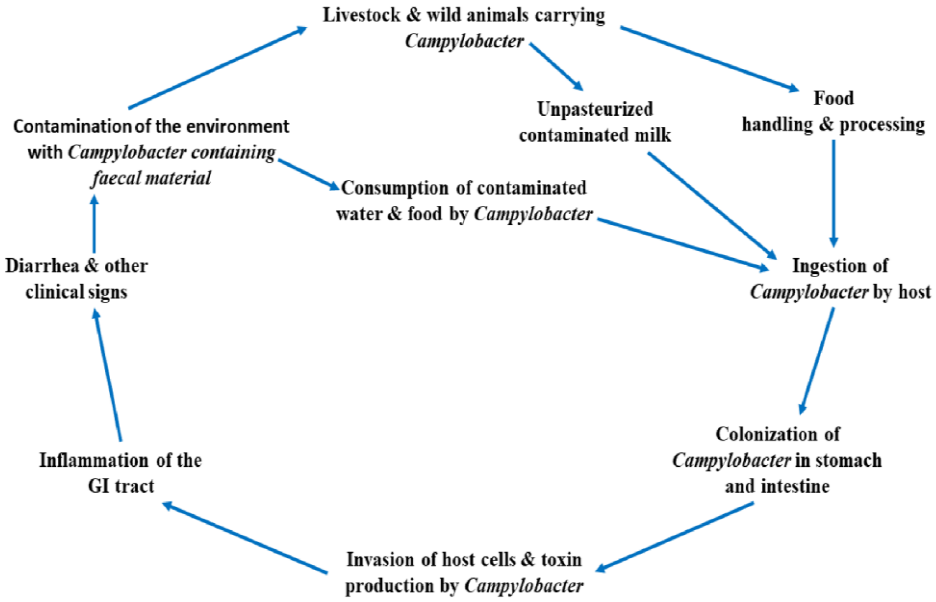

Figure 3: Schematic overview of transmission from contaminated sources, causation of illnesses in host body and spreading patterns of *Campylobacter* among susceptible hosts.

6.0 VIRULENCE FACTORS CONTRIBUTING TO THE PATHOGENICITY OF CAMPYLOBACTER SPECIES

The virulence of *Campylobacter* is determined by a complex combination of factors, involving numerous components (Larson et al., 2008). Virulence is influenced by various factors, including traits like invasiveness, resistance to oxidative stress, toxin production, iron acquisition, and the ability to survive in a non-culturable state (Bhavsar & Kapadnis, 2006). Furthermore, their capacity to withstand and overcome physiological stress also plays a role in their ability to induce illness (Casabonne et al., 2016). In addition, *Campylobacter* exhibits a range of virulence characteristics, such as the secretion of specific proteins, translocation, and the use of flagella for movement (Biswas et al., 2011b). It uses chemotaxis and flagellin as key virulence factors to find the colonization site and help in entering host cells (Van Vliet & Ketly, 2001). *Campylobacter* associated virulence factors with respective genes, proteins, and functions are summarized in table 2. The chemotaxis proteins Che A, B, R, V, W, and Z are linked to the virulence factors that can lead to infections in humans. These proteins are encoded by the genes *cheA*, *cheB*, *cheR*, *cheV*, *cheW*, and *cheZ* (Ortega et al., 2017). *Campylobacter* has the ability to stick to the cells lining the gastrointestinal tract of the host due to specific adhesions on the bacterial surface. The attachment plays a vital role in enabling the bacteria to successfully establish itself within the body (Jin et al., 2001). Adhesion proteins facilitating *Campylobacter* virulence include outer membrane protein, adhesion protein A, phospholipase A, lipoprotein, periplasmic binding protein, fibronectin like protein A, and Type IV secretion system which are encoded by the genes *cadF*, *capA*, *pldA*, *jlpA*, *peb1A*, *flpA*, and *virB11*, respectively (Igwaran & Okoh, 2019). One of the cytotoxins created by *Campylobacter* is the cytolethal distending toxin (CDT) (Igwaran & Okoh, 2019). The CDT toxin consists of three subunits which are encoded by the genes *cdtA*, *cdtB*, and *cdtC*. The regulation of cytolethal-distending toxin function involves three genes located within the *cdt* cluster (Martínez et al., 2006). All three of the *cdt* cluster genes must be

involved for the activation of these toxins to occur (Asakura et al., 2008). The flagella of *Campylobacter* contribute to its invasion capabilities, serving as an additional mechanism of pathogenicity (Poly & Guerry, 2008). The *Campylobacter* invasion process utilizes a range of virulence genes that are responsible for encoding the essential proteins, such as invasion antigens (*cia*) and flagellin C (*flaC*) genes. The flagella secretion system is essential for facilitating the transfer of these genes into the cytoplasm, which is crucial for invading and colonizing the host cell and inducing illness (Konkel et al., 2004). Among other virulence mechanisms inducing *Campylobacter* pathogenicity are the ability to obtain iron as a necessary growth nutrient from host body, the action by sialyltransferases (*cstII*) activity to produce lipopolysaccharide with a defensive barrier for the disruption of the host epithelial cells, stress response genes and cell surface modification genes. All these virulence-associated genes of *Campylobacter* discussed above have been found to contribute to human infections (Igwaran & Okoh, 2019).

Table 2: Virulence factors associated with *Campylobacter* pathogenicity

Virulence factors	**Encoded proteins**	**Encoding Genes**	**Biological Functions**	**References**
Chemotaxic proteins	CheA, CheB, CheR, CheV, CheW, and Che Z	*cheA*, *cheB*, *cheR*, *cheV*, *cheW*, and *cheZ*	Search for colonization site in the host cell	(Ortega et al., 2017)
Adhesion proteins	outer membrane protein, adhesion protein A, phospholipase A, lipoprotein, periplasmic binding protein, fibronectin like protein A, and Type IV secretion system.	*cadF*, *capA*, *pldA*, *jlpA*, *peb1A*, *flpA*, and *virB11*, respectively	Attachment to the cell lining of the host gastrointestinal tract	(Igwaran & Okoh, 2019)
Cytotoxin	Tripartite Cytolethal-distanding toxin (CDT)	*cdtA*, *cdtB*, and *cdtC*	Action in cellular cytotoxicity	(Martínez et al., 2006)(Asakura et al., 2008)
Flagella and invasion proteins	flagellin C, invasion antigens	*flaC*, *cia*	Entering into, invading, and colonizing the host cell	(Konkel et al., 2004)
Sialyltransferases activity	Sialyltransferases	*cstII*	Disrupting host epithelial cells	(Igwaran & Okoh, 2019)
Response to stress	Stress response proteins	*cosR*, *cj1556*, *spoT*, *ppk1*, *csrA*, *nuoK* and *cprS*	Resistance to cellular stress conditions	(Igwaran & Okoh, 2019)
Alteration of bacterial cell surface	Cell surface modification proteins	*waaF*, *pgp1* and *peb4*	Escape countering by host immunity	(Igwaran & Okoh, 2019)

7.0 DIAGNOSIS AND IDENTIFICATION OF *CAMPYLOBACTER*

Campylobacter associated diseases are markedly increasing and its similarity to other diarrheal illnesses like salmonellosis, shigellosis entails the identification of the pathogen by standard laboratory tests (Pal, 2017). Diagnosis and confirmation of *Campylobacter* can be performed by examining clinical specimens such as diarrheal stools, rectal swab, blood, body fluids, and tissues in several laboratory methods including direct microscopic examination, bacterial cultivation, biochemical tests, real time PCR, multiplex PCR, and immunological assays (passive hemagglutination, complement fixation, and ELISA) (Pal, 2017)(Igwaran & Okoh, 2019). Since this bacterial gastrointestinal disease is transmitted through the consumption of unpasteurized milk, raw or undercooked meat, and untreated water, examination of these food and environmental samples is also paramount to ensure the safety of food and reduce the spread of the disease. Several studies have been conducted by the researchers to isolate and identify *Campylobacter* spp. in associated clinical, food, and water samples which are summarized in table 2.

Table 3: Isolation, identification, and diagnosis of *Campylobacter* species in different research

Country of study	**Type of sample**	***Campylobacter spp***	**Method of identification**	**References**
Korea	Continuous ambulatory peritoneal dialysis (CAPD) fluid	*C. fetus*	Bacterial cultivation, PCR, and 16s rRNA gene sequencing	(Hur et al., 2018)
Los Angeles, CA, USA	Human stool	*C.jejuni, C. coli, C. fetus and C. upsaliensis*	Laboratory culture method	(Labarca et al., 2002)
Lancashire, England	*Campylobacter* DNA from patients and livestock	*C. jejuni*	Multi-locus sequence typing (MLST)	(Wilson et al., 2008)
Walkerton, Canada	Rectal swabs and manures from livestock farms	*C.jejuni, C. coli*	Phenotypic and genotypic methods including serotyping, phage typing, biotyping, fla-RFLP typing and PFGE	(Clark et al., 2003)
Malaysia	Samples from dairy and beef cattle firms	*C.jejuni, C. fetus, C. lari, C. hyointestinalis, C. upsaliensis*	Multiplex PCR	(*Occurrence of Campylobacter in Dairy and Beef Cattle and Their Farm Environment in Malaysia | Request PDF*, n.d.)
Poland	Poultry caeca and carcasses	*C.jejuni, C. coli*	Bacterial cultivation and PCR	(Wieczorek et al., 2015)
Poland	Meat portions from chicken, turkey, duck and goose	*C.jejuni, C. coli*	Microbiological analysis and PCR	(Szosland-Fałtyn et al., 2018)
Netherlands	Children's stool	*C.jejuni*	PFGE and *flaA* PCR-	(Heuvelink et al., 2009)

	and feces and milk from dairy cattle		RFLP	
Qena, Egypt	Raw milk, cheese, and yoghurt	*C.jejuni, C. coli*	Bacterial cultivation, biochemical tests and PCR	(El-Zamkan & Hameed, 2016)
Sweden	Lake and well water	*C.jejuni, C. coli*	Whole genome sequencing and phenotypical analysis	(Nilsson et al., 2018b)
United Kingdom	Water samples from different environmental sources		Microbiological analysis, serotyping, PCR ELISA assay	(Sails et al., 2002)
Cork, Ireland	Faecal samples from diarrhoeal patients	*C. ureolyticus*	Multiplex PCR, a combination of 16S rRNA and highly specific HSP60 gene analysis	(Bullman et al., 2011)
Thailand	Chicken meat and offal samples	*C.jejuni, C. coli*	Microbiological analysis, multiplex PCR, MLST	(Wangroongsarb et al., 2021)

8.0 PREVENTION AND TREATMENT OF CAMPYLOBACTER INFECTION

Campylobacter is a widespread culprit of bacterial foodborne diseases, resulting in more than 400 million cases each year (Igwaran & Okoh, 2019). Those at highest risk of infection include the elderly, young people, individuals with weakened immune systems, cancer patients, people with immunodeficiency, smokers, and heavy alcohol consumers. Antibiotics like azithromycin and ciprofloxacin, as well as broad-spectrum macrolides, are commonly prescribed to individuals experiencing fever or bloody diarrhea lasting for seven days or longer (Hernandez & Green, 2006)(Hansson et al., 2018). In addition, other medications such as tetracycline, aminoglycosides, β-lactams, phenols, and the FOSFOMYCIN group may be utilized (Merrick et al., 2022) . However, some infections can improve on their own with sufficient rest and hydration (Cheng & Fischer, 2024). In case the condition deteriorates, it might be necessary to hospitalize the patient to restore fluids and electrolytes. Following proper hygiene practices and adhering to food safety protocols are essential for maintaining good health. In addition, it is important to consider getting enough sleep and receiving the right treatment. Prevention and treatment methods are crucial due to the high frequency and potential for antibiotic resistance. Following proper food safety protocols, including ensuring thorough cooking of poultry, pasteurizing milk, and cooking at temperatures of 165°F (74°C), greatly reduces the risk of contamination and ensures the safety of meat (FAO/WHO, 2009). Prompt identification and appropriate administration of antibiotics may successfully alleviate symptoms and reduce possible consequences. Ensuring proper personal hygiene, including practices like handwashing, limiting the transfer of contaminants, and periodically sanitizing kitchen surfaces and equipment, is crucial for reducing the risk of foodborne illnesses and infections. Tackling the obstacles in prevention and treatment include combating antibiotic resistance, pinpointing the origins

of illness, and providing public education on appropriate food handling practices. An all-encompassing strategy that includes healthcare experts, public health organizations, and people is necessary, along with public health campaigns, educational initiatives, and surveillance systems for identifying infections and implementing specific therapies.

9.0 RESISTANCE TO ANTIBIOTICS

Antibiotic resistance is a pressing global health concern, leading to an alarming number of 1.2 million deaths in 2019 (FAO/WHO, 2009; Murray et al., 2022). If left unaddressed, it is projected to result in 10 million fatalities by 2050 (de Kraker et al., 2016). In 2017, the Centers for Disease Control and Prevention (CDC) reported that in 2017, 28% of *C. jejuni* and 38% of *C. coli* isolates in the United States exhibited resistance to ciprofloxacin (*Antibiotic Resistance | Campylobacter | CDC*, n.d.). In addition, the CDC has reported a notable increase in the resistance of 3% of *C. jejuni* and 7% of *C. coli* isolates to azithromycin. This is a significant change compared to the absence of resistance observed in 1997. For *C. coli* strains, the resistance rates were significantly higher, reaching 100% for erythromycin, 98.1% for azithromycin, and 100% for clindamycin. In a study carried out in China, it was discovered that chicken-derived *Campylobacter* isolates displayed resistance rates of 8.9%, 26.7%, and 13.9% to erythromycin, azithromycin, and clindamycin, respectively, in the case of *C. jejuni* isolates (*Antibiotic Resistance | Campylobacter | CDC*, n.d.). A study conducted in South Korea revealed that *Campylobacter* isolates exhibited high levels of resistance to ciprofloxacin (100%), nalidixic acid (100%), and tetracycline (93.9% for *C. jejuni* and 83.3% for *C. coli*) (Bunduruș et al., 2023). Another study conducted in Vietnam has provided further evidence of a resistance gene that is capable of resisting multiple antibiotics, including chloramphenicol, gentamicin, kanamycin, lincomycin, ciprofloxacin, fluoroquinolone, and streptomycin (Zarske et al., 2024). Thailand's study also reveals concerning levels of antibiotic resistance in *C. coli* and *C. jejuni* isolates found in chicken samples (Wangroongsarb et al., 2021). The isolates exhibit varying degrees of resistance to quinolones, cyclines, macrolides, clindamycin, and gentamicin (Wangroongsarb et al., 2021). It's important to highlight that 37.7% of *C. coli* isolates and 1.8% of *C. jejuni* isolates showed resistance to multiple drugs (Wangroongsarb et al., 2021). The finding highlights a significant global challenge to the effectiveness of antibiotics. This challenge is primarily due to the misuse and overuse of antibiotics in chicken populations and animal husbandry practices. Resistance in *Campylobacter* can be acquired through different mechanisms, including horizontal gene transfer, mutations, and plasmid-mediated resistance (Iovine, 2013). Macrolide resistance in *Campylobacter* can occur through enzymatic methylation that impacts the ribosomal target, as well as point mutations in ribosomal proteins L4 and L22 (Gibreel & Taylor, 2006). The predominant mechanism for macrolide resistance is Erm(B), which is closely linked to multidrug resistance genomic islands (Del Grosso et al., 2007). Resistance to tetracycline is attributed to the presence of the ribosomal protection protein Tet(O) and the efflux pumps CmeABC and CmeG. These proteins work together to remove tetracycline from the ribosome (Gibreel et al., 2007). Both CmeABC and CmeG play a role in both inherent and acquired resistance, as stated in reference (Gibreel et al., 2007). It is speculated that the *Campylobacter* tet(O) gene was acquired through horizontal gene transfer from a Gram-positive source (Ma et al., 2021). In the pCG8245 plasmid, the aadA gene was discovered, which is linked to multidrug resistance in *C. jejuni* (Qin et al., 2012). In contrast, the aadE gene was linked to the aadE-sat4-aphA-3 gene cluster in *C. jejuni* and *C. coli*, leading to resistance against aminoglycosides (Zhang et al., 2021). Over the course of many decades, there has been a significant increase in the

occurrence of β-lactam-resistant bacteria. This is due to *Campylobacter*'s heightened resistance to enzymatic inactivation, diminished uptake, and efflux pump mechanisms (Helmy et al., 2023; Iovine, 2013). The fosXCC gene, found in *Campylobacter*, is the primary determinant of fosfomycin resistance (Wang et al., 2015). Efflux transporters play a vital role in the development of resistance to various antimicrobial substances, whether acquired or naturally occurring. Researchers have analyzed the functional properties of three different *Campylobacter* multidrug efflux pumps (CmeABC, CmeDEF, and CmeG) to understand their importance in antibiotic resistance (Mavri & Možina, 2013)(Jeon et al., 2011)(Hwang et al., 2012).

10. REGULATING THE USE OF ANTIBIOTICS

The emergence of drug-resistant strains of *Campylobacter* poses a significant threat to public health. Due to the overuse and misuse of medications, drug-resistant strains have become a major concern when it comes to effectively managing *Campylobacter* infections. To address this issue effectively, it is crucial to establish antibiotic stewardship programs and encourage the adoption of alternative treatment options (Ha et al., 2019). Education, awareness campaigns, and enhanced diagnostics may provide help in reducing the misuse and abuse of antibiotics. Phage therapy and other alternative therapies may reduce reliance on antibiotics (Lin et al., 2017). Surveillance and monitoring systems efficiently monitor antibiotic prescription practices and detect resistance tendencies. Efficient cooperation across healthcare institutions, labs, and public health organizations is essential for recognizing patterns, detecting epidemics, and directing intervention methods. Allocating resources towards research and innovation in the field of antibiotics may expand the range of available treatment alternatives and reduce reliance on traditional antibiotics. Develop and enforce protocols and regulations for the prescription of antibiotics in cases of *Campylobacter* infections, while actively engaging stakeholders in talks to achieve a thorough and all-encompassing approach. Regularly evaluating and adjusting strategies may optimize endeavors to combat antimicrobial resistance and protect public health. Proposing improvements or supplementary regulations can bolster control measures, such as implementing stricter enforcement of antibiotic stewardship programs in healthcare facilities, promoting responsible utilization of antibiotics in veterinary medicine, and establishing surveillance systems to oversee antibiotic usage in agriculture (Da Silva et al., 2023). Strengthening international collaborations and sharing data on antibiotic resistance will help uncover global trends and facilitate coordinated efforts to address this growing public health issue.

11. CONCLUSION

Campylobacter is a significant contributor to foodborne bacterial gastrointestinal infections worldwide, often leading to post-infectious complications like Guillain-Barre syndrome. In most cases, Campylobacteriosis resolves by itself, but in some instances, antimicrobial treatment may be necessary, with macrolides and fluoroquinolones being the preferred medications. Concerns are rising due to the growing resistance to important antibiotics, which is associated with the use of antimicrobials in food animals. Dealing with antimicrobial resistance is a significant hurdle in managing Campylobacteriosis, especially for those with weakened immune systems who may face serious complications. The rise in Campylobacteriosis worldwide, mainly spread through contaminated foods, is worsened by the resistance to antibiotics in *Campylobacter*, especially in poultry, due to the use of antibiotics in livestock. To tackle *Campylobacter* resistance in the poultry

industry, it is crucial to decrease antimicrobial usage, advocate for correct practices, and ensure safe food handling. To combat resistance effectively, it is essential to focus on developing new antibiotics and ensuring proper domestic hygiene. Association of this infection with contaminated food and water necessitates the development of rapid detection methods to identify the pathogen and ensure the supply of safe food to the consumers. In addition to inventing quick detection kits, novel vaccines, and potential antibiotics, national and international health sectors should promote public awareness and participation in disease control and eradication programs.

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Competing Interests

The authors' have declared that there is no competing of interest.

Data availability

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Authors' contributions: NS, UPB, SD, MH carried out the studies (data collection, data validation, data curation, and data analysis) and participated in drafting the manuscript. NS, UPB, SD, MH, NHS, SR, LRR and SCS critically reviewed and drafted the manuscript. NS, MH, NHS visualized figures, interpreted data and results, critically reviewed and edited the manuscript. NS and UPB supervised the whole work. NS developed the hypothesis, supervised the whole work, and helped to prepare and critically revise the manuscript. All authors read and approved the final manuscript.

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