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Campylobacter: understanding its role as the primary bacterial cause of food-borne illnesses – current state of knowledge

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ABSTRACT

Introduction

Campylobacteriosis, caused primarily by *Campylobacter jejuni* and *Campylobacter coli*, is a significant public health concern worldwide. Since 2007 it has been the most frequently reported zoonotic disease in humans across the European Union. Campylobacteriosis is also the leading cause of bacterial diarrhea.

Aim of the study

This review aims to provide a comprehensive overview of the epidemiology, clinical manifestations, transmission dynamics, diagnostic approaches, and prevention strategies associated with Campylobacter infections.

Brief description of the state of knowledge

The transmission of *Campylobacter spp*. typically occurs via the fecal-oral route, with contaminated food, especially poultry, and water serving as common sources of infection. Notably, *Campylobacter* infections exhibit distinct seasonal patterns and demographic trends, with children and young adults being particularly susceptible. Clinical manifestations range from mild gastrointestinal symptoms to more severe complications, such as reactive arthritis, and Guillain-Barré syndrome. Diagnosis usually relies on microbiological testing. Some of these methods require specialized cultivation techniques, with challenges posed by the phenotypic diversity of *Campylobacter* species.

Summary

Effective surveillance and prevention strategies are essential for mitigating the burden of campylobacteriosis and its associated sequelae on both individual and population health. Current research focuses on improving preventive measures, underscoring the importance of advancing public health strategies, and further studies into the epidemiology, pathogenesis, and treatment options. These efforts are crucial for effectively addressing Campylobacteriosis and reducing its effects on human health and agriculture.

Key words: Campylobacter spp., Campylobacter jejuni, campylobacteriosis, gastroenteritis, infection

INTRODUCTION

In 1963, the bacterium known as *Vibrio fetus* was officially named *Campylobacter fetus* and became one of the first bacteria of its kind. [1] Currently, the genus *Campylobacter* is an extensive group of microorganisms that cause a disease called campylobacteriosis which is a serious public health problem at the moment. [2]

Campylobacter spp. belong to the *Campylobacteriaceae* family, which also includes such genera as *Campylobacter*, *Arcobacter* and *Helicobacter*. The genus *Campylobacter*, on the other hand, contains approximately 26 species, the best known of which are: *C. jejuni*, *C. coli*, *C. concisus, C. upsaliensis, C. ureolyticus, C. hyointestinalis* and *C. sputorum*. It is a gram-negative bacilli, which do not have the ability to produce spores. [9, 12] They belong to the microaerophiles which means that in order to live, they require oxygen in a lower concentration than in the earth's atmosphere i.e. 5%. *Campylobacter* obtains energy from amino acids and tricarboxylic acids instead of carbohydrates. [9]

Campylobacter spp. are characterized by a specific optimum of external conditions that allow them to multiply and grow. Their optimum pH varies between 6.5-7.5, and the optimum temperature range is between 37-42. However, they do not grow above 55 or below 33 degrees because they do not have heat shock proteins which are adaptations to low temperatures. [9] Survival in suboptimal conditions of the external environment is possible for *Campylobacter* thanks to its ability to form a biofilm on abiotic surfaces (such as those used in the manufacture of household items), by using their ability to adhere and synthesize polymeric substances. [13] Moreover, many *Campylobacter* species, particularly *C. jejuni*, are characterized by intense phase variation, a phenomenon that involves changing bacterial phenotypes as a result of errors in DNA replication. The existence of multiple phenotypes and subpopulations, differing mainly in surface substances, is another way for them to adapt to changing environmental conditions. [14]

It is considered that the *Campylobacter spp*. are one of the most common causes of food poisoning and acute bacterial gastroenteritis among both adults and pediatric patients in

developed countries. Most commonly, the disease is caused by *Campylobacter jejuni* or *Campylobacter coli*, but there are also cases caused by *Campylobacter* lari, *C. fetus* and *Campylobacter upsaliensis*. [3] *Campylobacter* infections can cause a range of clinical conditions and complications beyond gastrointestinal issues, including reactive arthritis, endocarditis, brain abscesses, and Guillain-Barré syndrome (GBS).

The main symptoms that can be observed after infection are abdominal pain, diarrhea, fever and general malaise. Although *Campylobacter* can survive in the external environment, it only multiplies inside its hosts. It colonizes the digestive tract of food-producing animals (mainly birds) and humans. [2] Therefore, the most common infection is zoonotic infection via the fecal-oral route.

This paper reviews the current literature on *Campylobacter* taking into account the effects of bacteria on the human body, how the infection may manifest clinically, the model of its transmission and current methods of diagnosis of the *Campylobacter*. This review includes and focuses on methods of treatment, prevention strategies and how the disease itself affects the population in terms of clinical consequences, but also in terms of the economy.

EPIDEMIOLOGICAL ASPECTS

Campylobacter spp. are transmitted via the fecal-oral route and infection most commonly occurs through the consumption of contaminated food. The actual number of foodborne cases is not precisely known, but at this point it is estimated that approximately 75% of cases can be attributed to such a cause. [4] Besides foodborne pathway, infection can occur through direct contact with an animal that is a carrier of *Campylobacter*, however, in the case of pets such as dogs or cats, infections occurs relatively rarely and among people who work with farm and food-producing animals, natural immunity to this bacteria often develops. [5]

In most regions of the world, more than half of chicken flocks are colonized by *Campylobacter*. The bacterium can be transmitted between individuals through contact with feces, contaminated water or soil, and can also be carried by insects. Furthermore, it may be transmitted vertically from adult chickens to their offspring, but it does not happen very often. [2] Therefore, infection commonly arises from the consumption of raw or undercooked poultry meat. For this reason, people should prioritize proper thermal processing of meat, as *Campylobacter spp*. do not proliferate at elevated temperatures. Additionally, human infection with *Campylobacter* can occur through direct contact with raw meat or through cross-

contamination of raw products, such as vegetables consumed without cooking. [5] Moreover, not only poultry, but also beef, pork, sheep and offal, carry the risk of infection because *Campylobacter spp.* tend to colonize their digestive system. Although the risk of *Campylobacter* presence in this type of meat is much lower than in the case of poultry – it varies between 1%-4%. [5]

Campylobacteriosis may also be associated with infected water. A possible source of this kind of transmission could be environmental water contaminated with animal feces, wastewater from farms and slaughterhouses. [6] Private water supplies such as wells and rainwater harvesting may be also a source of *Campylobacter* infection, as they can be contaminated with animal feces, mainly birds, that carry this bacterium. Moreover, it has been discovered that *Campylobacter spp.* can survive in water reservoirs even if environmental conditions such as temperature are not optimal, owing to their ability to form a protective biofilm. [7] Many outbreaks of Campylobacteriosis have been caused by contaminated water, highlighting the critical need for ensuring the safety of drinking water and water used in the food industry.

A 2013 Gras et al. study revealed that dog or cat feces can also be a source of *Campylobacter*. Dogs often roll in feces, and then transfer the bacteria onto their fur, which can spread further when they are petted. Inadequate hygiene can result in infection. Consequently, pet ownership, especially owners of cats or dogs, presents another risk factor for campylobacteriosis. [8] These animals can probably get infected by the consumption of raw meat. Whereas the exact way of transmission of the bacteria from pets to humans is not precisely known, it is believed that this occurs through the transfer of the pathogen to the hands during contact with fur or feces. Infection subsequently occurs when contaminated hands are used to eat food. [9]

Due to *Campylobacter* being transmitted via the fecal-oral route, a connection between infections in children and playgrounds which can be contaminated with feces of birds, dogs or cats-animals carrying the bacteria, has been observed. This is because kids often put their dirty hands in their mouths, which may lead to *Campylobacter* infection in pediatric patients. [9]

Even flies can be a source of contamination, as it has been shown that they can carry contaminated material on their bodies and onto food, contaminating it. [9, 10]

In terms of morbidity trends, men are more often affected by campylobacteriosis than women, for unknown reasons. The peak incidence is in children at 1 year of age and in people aged 15-44. [11] During the year, most infections occur from May to August. The potential reason for this phenomenon can be the increased outdoor activity of people, such as swimming in the

pools, ponds, and lakes, where *Campylobacter* could be transmitted through water. However, this is not a confirmed cause because it has been proven that there are fewer bacteria in water at high temperatures than at low winter temperatures. [2,11]

Campylobacteriosis stands out as a leading contributor to foodborne illness on a global scale, with prevalence data exhibiting variability across different sources. This bacterial infection holds notable significance in both developed and developing nations, where it ranks prominently among the causes of food poisoning. In regions with advanced industrialization, such as highly developed countries, campylobacteriosis tends to manifest without a clear seasonal pattern and is less likely to present asymptomatically. Conversely, in less developed regions, the disease often progresses without overt symptoms and occurs during the specific months mentioned earlier. Understanding these epidemiological facts is crucial for effective surveillance and management strategies adjusted to diverse socio-economic contexts. [11]

PATHOGENESIS

All species, except *Campylobacter gracilis*, can move due to the presence of flagella at one or both poles of the cells. *Campylobacter showae* has multiple flagella. Both the tendrils and the spiral shape allow bacteria to have a corkscrew motion which makes it easier for them to move through the thick mucus in the digestive system. [9, 15] The strands of these bacteria have a length of approximately one helical coil, or 3.53 ± 0.52 μm, and are composed of a basal body, a hook and a filament. [14] Interestingly, *Campylobacter* flagella do not contain molecular patterns that would allow them to be detected by pattern recognition receptors (PRRs) such as TLR5 on host immune cells. [14, 16]

Campylobacter forms a polysaccharide capsule-CPS that determines its pathogenicity and allows it to protect itself from the host immune response. [14] The outer membrane is composed of lipopolysaccharides (LPS) and lipooligosaccharides (LOS) and contains sialic acids. Both the LPS and LOS may be subject to the phase variation mentioned earlier. [14] It was discovered that LOS play an important role not only in cell adhesion, but also in initiating the innate immune response because they act as a chemoattractant. [17]

Both gastric and bile juice are the first effective barrier to *Campylobacter*, which is why people with reduced gastric acidity can more easily get infected. [12] If bacteria manage to survive in the stomach, they enter the lumen of the small intestine where *Campylobacter* begins to adhere to the host intestinal epithelium. Adhesion is possible thanks to the

chemoreceptors A, B, R, W, Z, and Y located on the surface of the bacterial cell, which attach to mucins and glycoproteins of epithelial cells. Then, the bacteria bind to intestinal epithelial cells via flagella, the adhesins-heads of the CADF protein, the CapA protein and the *Campylobacter* adhesion protein. *Campylobacter* begins to secrete harmful cytokines, such as CDT which consists of three different subunits: CdtA, CdtB, and CdtC that together create an active holotoxin. It inhibits the cell cycle leading to chromosomal DNA dispersion and destruction, causing cell apoptosis. [9, 18] This is to cross the mucous layer of the intestinal tract, which is an excellent, nutrient-rich site used by *Campylobacter* for colonization. That process facilitates the passage through the mucous. In addition, this enables *Campylobacter* to penetrate cells and promotes their intracellular survival in vacuoles. [18, 19] Recent studies have shown that inflammasomes are involved in the removal of intracellular *Campylobacter*, however the mechanism is not yet fully understood. [19]

Additionally, *Campylobacter spp.* have the ability to secrete toxins that create pores in the membrane leading to disruption of the ionic balance across the membrane, which contributes to apoptosis. [19]

The immune response mainly involves the secretion of pro-inflammatory cytokines (IL-8 and TNF α) following the attachment of PAMPs (such as capsule components, LPS, bacterial DNA or toxins) with pattern recognition receptors, mainly TLRs, which activate the NF-κB signaling path. Once released, IL-8 recruits neutrophils, macrophages and dendritic cells at the site of infection leading to major inflammation. [19] This causes an excessive production of reactive oxygen and nitrogen species mainly by neutrophils, which likewise results in further cell apoptosis and ulcer formation in the gastrointestinal wall. [17]

Although the cellular response is important, the humoral response plays a far greater role in fighting infection. In the first 2 weeks after infection, the number of *Campylobacter*-specific serum IgA antibodies rises sharply. The levels of IgM and IgG antibodies gradually increase, reaching their peak 2 to 3 weeks after symptom onset, with IgE levels rising during the same period. [12] This secondary antibody wave fortifies the body's defense mechanisms, creating a multi-layered defense against *Campylobacter spp.* intrusion.

TYPICAL SYMPTOMS AND COURSE OF INFECTION

Campylobacter infection can lead to a serious clinical condition known as gastroenteritis. Furthermore, these bacteria have been associated with numerous other severe

gastrointestinal diseases, such as inflammatory bowel disease (IBD), esophageal disease, periodontitis, functional gastrointestinal disorders, celiac disease, cholecystitis, and colon cancer. [1]

After two to five days of incubation, *Campylobacter* usually causes an infection in humans. [20] Infections with low doses may take longer to manifest symptoms. [21] A prodromal phase, marked by fever, headache, and muscle soreness, first appears. Subsequently, diarrhea that is watery and occasionally bloody is observed, along with acute, uncomplicated enterocolitis. There is a chance of experiencing cramp-like stomach pain, and general symptoms, such as fever, headaches, and exhaustion are frequently mentioned. Most of the time, the illness resolves on its own in 5 to 7 days without any problems. [22]

The development of foodborne gastroenteritis-associated sequelae, such as post-infectious functional gastrointestinal disorders (PFGDs), is linked to *C. jejuni* and other *Campylobacter* species. The two PFGDs that have drawn the greatest attention are functional dyspepsia (FD) [23, 24] and irritable bowel syndrome (IBS). [23, 25]

Approximately 70% of cases of dyspepsia are classified as functional dyspepsia, which is characterized by epigastric discomfort lasting at least one month and no signs of organic disease on upper endoscopy. Functional dyspepsia is characterized by postprandial fullness, early satiety, and burning or pain in the epigastrium. [1, 26]

The symptoms of IBS include recurrent abdominal pain or discomfort that has occurred at least three days per month for the previous three months, along with a change in bowel habits (constipation, diarrhea, or both). [27] There is a lack of understanding regarding the mechanisms underlying post-infectious irritable bowel syndrome, but they may involve mucosal immunocytes, mast cells, enterochromaffin cells, and persistent changes in the gut microbiota. The development of post-infectious irritable bowel syndrome is also associated with host factors, such as female gender, depression, hypochondria, smoking, unfavorable life events within the previous three months, and antibiotic use. [28] Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic conditions that affect the gastrointestinal tract. [1]

Over the past thirty years, research has been conducted on the role of *Campylobacter* species in IBD. [29] In 2009 Gradel and colleagues provided evidence that indicated an association between *C. jejuni* infection and an increased risk of IBD. [30]

Barrett's esophagus (BE), esophageal adenocarcinoma, and gastroesophageal reflux disease (GERD) are examples of esophageal disorders associated with *Campylobacter* infection. The

chronic illness known as GERD is caused by stomach acid causing damage to the esophageal mucous membrane. BE is a preneoplastic condition characterized by the replacement of normal squamous mucosa by distal esophageal metaplastic columnar mucosa. This incident heightens the susceptibility to esophageal adenocarcinoma development. [1]

New research indicates that *Campylobacter* species, specifically *C. concisus*, are prevalent in individuals with GERD and BE. A study conducted by Macfarlane and his team revealed that after analyzing esophageal aspirates and mucosal samples for aerobic, microaerobic, and anaerobic microorganisms, 57% of patients with BE were colonized with *Campylobacter* species, with a majority being *C. concisus*. [31]

There is growing evidence that colorectal cancer is influenced by dysbiosis of the gut microbiota. The connection between *Campylobacter* species and colorectal cancer cannot be proven as if there is unsubstantial evidence resulting from the lack of epidemiological studies. Nevertheless, a recent investigation by Warren and associates, using metatranscriptome data from control and colorectal cancer tissues, revealed that *Campylobacter* species, primarily *C. showae*, form coaggregates with *Leptotrichia* and *Fusobacterium* species. [32] However, further studies are needed to determine whether there is a connection between *Campylobacter* and the development of colorectal cancer.

Campylobacter species not only cause gastrointestinal infections but also a variety of clinical manifestations affecting other parts of the body. These may include isolated local infections, systemic infections subsequent to an episode of enteritis, or immune disorders following an infection. A number of conditions can present, such as reactive arthritis, endocarditis, myocarditis, brain abscesses, meningitis, bacteremia, sepsis, and Guillain-Barré syndrome. [1] In these instances, a mortality rate of 2% to 3% is noted largely as a result of respiratory failure. [33]

Guillain-Barré syndrome (GBS) is a rare but potentially fatal immune-mediated disorder of the peripheral nerves and nerve roots, typically caused by infection. [34] Guillain-Barré syndrome is primarily caused by *C. jejuni* infection, and there is an evidence of a direct link between the yearly incidence of campylobacteriosis and GBS. For instance, lower rates of GBS were noted in New Zealand after tighter hygienic regulations were put in place for poultry meat. This was correlated with a decline in the number of cases of campylobacteriosis. [35] According to studies on the clinical course of GBS, cases of the disease that are preceded by an infection with Campylobacter spp. are more severe, result in worse therapeutic outcomes, and may cause long-term disability. [36, 37] In compliance with more current

study conducted in Bangladesh, *Campylobacter spp.* were responsible for 57% of GBS cases. [38]

Bacteremia is one of the most frequent extragastrointestinal signs of *Campylobacter* species, and it is primarily linked to *C. jejuni*, *C. coli* and *C. fetus* contagions. [39] There have been reports of bacteremia involving at least ten distinct species of *Campylobacter*. [40] The majority of cases involve elderly or immunocompromised patients who have one or more concurrent illnesses, such as liver cirrhosis or neoplasia. Approximately 10% to 15% of these patients pass away within 30 days after being diagnosed with the disease. [41, 42]

A variety of cardiovascular problems, including endocarditis, myocarditis, pericarditis, myopericarditis (pericarditis with concomitant myocardial involvement), atrial fibrillation, and aortitis with aortic dissection, have been linked to *Campylobacter* species, primarily *C. jejuni* and *C. fetal.* In immunocompetent people, myopericarditis associated with bacterial enteritis is an uncommon but dangerous illness. Complications, such as arrhythmia, dilated cardiomyopathy, congestive heart failure, and sudden cardiac death can result from these illnesses. [1] It has been suggested that bacterial exotoxins, cytotoxic T cells, circulating immune complexes, and tissue invasion by the heart are all involved. However, the precise mechanisms by which definite *Campylobacter* species induce myo(peri)carditis remain unknown. [43]

SERIOUS CLINICAL COMPLICATIONS

The term "cholecystitis" describes gallbladder inflammation, which typically develops when gallstones obstruct the cystic duct, causing bile to build up inside the gallbladder. Cholecystitis has been connected to *C. jejuni*, although this is considered uncommon because only 15 cases have been reported in the literature over the last 30 years. Some cases of *Campylobacter*-associated cholecystitis may have gone unnoticed because conventional culture conditions for bacteria from bile samples often do not encourage the growth of *Campylobacter* species. [44]

One type of arthritis, that most frequently affects people in their 30s or 40s, is reactive arthritis, a complication after gastrointestinal or genitourinary infections. This illness can impact the eyes, genital, urinary, and digestive systems, as well as joints including knees and ankles. After infection, symptoms can appear about one month later and subside within one year, however in some cases, they can last up to five years. [45] Pope and colleagues

conducted a systematic study in 2007 and reported that 1% to 5% of cases of reactive arthritis were linked to *Campylobacter* infection. [38]

Campylobacter infections have been connected to immunoproliferative small intestinal illness, a type of lymphoma. Antimicrobial therapy directed against *C. jejuni*, which was identified in biopsy specimens from multiple individuals, resulted in a fast remission of the immunoproliferative small intestine illness. [46]

The development of meningitis in humans has been linked to both *C. jejuni* and *C. fetus* subsp. *fetus*. [47] Only eight cases of meningitis caused by *C. fetus* subsp. *fetus* were documented between 1983 and 1998, and most of those cases have been observed in immunocompromised individuals. [48]

CLINICAL VARIANTS DEPENDING ON AGE AND HEALTH CONDITION

Compared to patients infected with *C. jejuni* and *C. coli*, those infected with *C. concisus* and some other *Campylobacter* species typically have milder symptoms, with fewer people experiencing fever, chills, weight loss, with mucus and blood in their stools. [39, 49] The disease frequently progresses slowly and severely in older people aged over 65 as well as in youngsters. Sepsis cases have been documented in immunocompromised people, particularly HIV-positive patients; however, under effective, highly active anti-retroviral medication, this risk is minimal. [22] Although patients of all ages can become infected with *C. jejuni* or *C. coli*, a recent Danish study revealed that toddlers (1 to 4 years old) and young people (15 to 24 years old) are more likely to become infected than patients in other age groups. [50]

Despite being uncommon, perinatal *C. jejuni* infection has been reported. Abortion, early labor, newborn septicemia, meningitis, and/or other complications are possible outcomes. Neonates may also experience symptomatic gastroenteritis, which may manifest as fever or bloody stools. The majority of infections occur in perinatals from moms who either symptomatically or asymptomatically shed *Campylobacter*. There have been documented outbreaks caused by nosocomial transmission in neonatal wards. [51]

DIAGNOSIS

The absence of specialized cultivation techniques, such as the use of microaerobic or anaerobic conditions enriched with hydrogen, causes many diagnostic laboratories to miss out

Campylobacter species. [39] *C. jejuni* can be grown from fresh samples for clinical diagnosis. Therefore, ensuring selectivity for *Campylobacter* from extremely complicated and polluted fecal cultures is the primary challenge. [14] Blood and polymorphonuclear leukocytes are seen in the stool, and colonic biopsy samples from patients with infection show widespread inflammatory colitis. [21] Usually, test plates are incubated at 37°C with 6% oxygen, 10% carbon dioxide, and 84% nitrogen content in a microaerophilic environment. Media that include the five antibiotics, to which *Campylobacter* is innately resistant, cefoperazone, vancomycin, trimethoprim, polymyxin B, and rifampicin, are used. [14]

Several *Campylobacter* species that are isolated from human samples are sometimes difficult to identify. The morphological appearance of colonies, biochemical responses, and ideal growth temperature are examples of phenotypic markers that can be used to identify only *C. jejuni*. Other species require a polyphasic approach that combines phenotypic and molecular markers. [9] The Butzler selective medium, the Blaser media, and the Skirrow media are the three most often used cultural media among those that include blood. The Preston medium, which contains cefoperazone, is perhaps the most popular coal-containing medium. [9, 52]

One popular technique for analyzing the species of *Campylobacter* is stool culture. The oxidase and catalase production, together with the distinctive appearance of a comma, or spiral shaped gram-negative bacillus, are characteristics that distinguish *Campylobacter*. Generally, species-level identification is not carried out, and management usually does not require differentiating *C. jejuni* from *C. coli.* For epidemiological reasons or in cases where species other than *C. jejuni* or *C. coli* are suspected, strain typing might be useful. [12] A few examples of clinical diagnostic techniques are immunochromatography, ELISA, and PCR. These antigen- or DNA-specific assays, known as culture-independent diagnostic tests (CIDTs), are being used more often to identify bacterial enteric illnesses like *Campylobacter*. Immunochromatography uses tagged anti-*Campylobacter* antibodies to produce immune complexes that are used to identify the presence of a particular antigen or DNA. If the immunoreaction is positive, the complex binds to either colloidal gold or streptavidin through the antibody-coupled biotin, causing color to develop. [14] If a patient has negative stool tests and has reactive arthritis or GBS, serologic testing can be performed to identify a recent *Campylobacter* infection.

The main goal of locating the infection source in the event of a suspected or confirmed Campylobacter infection is to stop other people from contracting the illness. Inquiries

concerning exposures, such as undercooked food, tainted fruits or vegetables, interaction with animals, and ingestion of raw milk or polluted drinking water should be made of the families. Past traveling might be important as well. [12]

There are also a number of enzyme immunoassays available for identifying *C. jejuni* and *C. coli* in clinical specimens. In a recent research, Granato and colleagues compared three commercially available kits with culture-based methods and discovered that conventional culture had a sensitivity of 94.1%, whereas the three immunoassays had sensitivity ranges of 98.5 to 99.3% and specificities ranging from 98.0 to 98.2%. [1, 53] Additionally, there are a few real-time tests for the identification of *Campylobacter* species. Some of them have the ability to detect several species simultaneously. [12, 54]

STRATEGIES FOR PREVENTING CAMPYLOBACTERIOSIS

Campylobacter spp. have been reported not only in many middle- and low-income countries, but also in high-income countries. In most cases, *Campylobacter* is primarily transmitted to humans through contaminated undercooked meat (especially poultry), dairy products (for example unpasteurized milk), or via drinking contaminated water. Moreover, *Campylobacter* infections can be transmitted by direct contact with infected domestic pets. [55]

Studies show that itemized cleaning and disinfection programs may lead to a reduction in the number of infections from one flock of broiler chickens to the next one. The proposed program [56a] shows the capacity to eradicate *Campylobacter* from the floor and drinkers of facilities. It yielded favourable effects on the bird performance and contributed to diminishing environmental contamination among broiler chickens.

Contaminating broiler chickens with *C. jejuni* during slaughter is a high risk. There are several options that are tested. One of them is freezing contaminated poultry, which is very successful. It is a reliable process to achieve a 2-log reduction of *Campylobacter*. [57] Outside the European Union chemical treatments can be another effective method to decrease the number of *Campylobacter*-positive broilers. This approach may occur to be a useful treatment in chill water tanks for poultry processors. [58]

One of the most common sources of *Campylobacter* infection is undercooked poultry. Reducing the chances of infection involves cooking meat at a high temperature, up to 70°C, before consumption, and washing items that had contact with raw poultry. [59]

Recent developments show that food can be contaminated during food preparation by cutting boards made of wood, plastic and steel. The period of risk exposure after chicken preparation may last from 3 to 4,5 hours. [60] Therefore, it is crucial to educate chefs about proper hygiene in their workplace.

The presence of *Campylobacter spp*. in raw milk can be connected with the farm environment via feces, during milking process, or post-milk process, for instance inadequate hygienic conditions during milk storage. Workers also play a significant role in accelerating *Campylobacter* infection through cross contamination. [61] Therefore, farmers have to be aware of their impact of spreading *Campylobacter spp.* and follow the hygienic procedures. A lower temperature in a refrigerator helps reducing the number of bacteria in pasteurized and UHT milk. [62] Consequently, improving the hygiene and safety of dairy products is recommended. Producers, milk collection centers, processors and retailers should be educated more and more on account of increasing bacterial infections.

Water, including rivers, agricultural waters, and lakes, is a natural environment, where *Campylobacter spp.* live. Furthermore, the transmission of *C. jejuni* to water can occur through contamination by wild birds, ruminants, pigs, and poultry. [63] Water plays a huge role in the transmission cycle and as a source of *Campylobacter* contamination or infection may be underestimated. *C. jejuni* survival depends on many factors, such as the concentration of dissolved oxygen, the presence of ammonium, chloride ions, phosphate, and the presence of other microorganisms. *C. jejuni* can also increase aerotolerance and resistance to low temperatures due to different stress conditions. [64] This might contribute to the transmission of *C. jejuni* and an increase of human infections.

Summarizing, cross-contamination leads a significant role in spreading infections in the domestic environment, emphasizing the importance of learning the proper way to eradicate bacteria effectively. People should also be aware of proper methods of food storage. Additionally, it is crucial for individuals to acknowledge that environmental water sources can harbor infectious agents, underscoring the necessity of obtaining water from reliable and tested sources.

Vaccination is the most effective way to prevent infections and maintain healthy chickens. Both, Th1 and Th2 responses, are important in a long-term protection against spreading *Campylobacter* in chickens. Many different ways of vaccination were evaluating, including the use of a Crude cell lysate vaccine, a DNA vaccine, a subunit vaccine, a formalin-killed whole-cell vaccine, a *Lactobacillus* vectored vaccine, and a *Salmonella* based vaccine. [65]

Because *Salmonella* and *C. jejuni* are one of the most common causes of poultry infections and post-infection complications, a combined vaccine against both bacteria would be an ideal solution. The developed vaccine, which delivers *C. jejuni* antigens by using live attenuated *Salmonella* via a dual expression plasmid, activates MHC class I and II, which provides a balanced Th1 and Th2 response. Distinctive mechanisms of immune protection were validated against *Campylobacter* and *Salmonella*. [66]

The increasing prescription of antibiotics by physicians presents a significant challenge due to the presence of antibiotic resistance genes in *Campylobacter spp.* Detected genes include those conferring resistance to β-lactamase, tetracycline, aminoglycoside, and erythromycin, exacerbating the issue of antimicrobial resistance. [67] Because of the global spread of antibiotic resistance, it has become a public health concern. Numerous countries have established policies to regulate and control the use of antibiotics in animal production in order to protect public health, animal welfare and the environment. [68] It is important to raise awareness about the responsible use of antibiotics in agriculture.

TREATMENT

Campylobacter infections may resolve on their own, but typically, replenishing fluids and electrolytes is the primary supportive treatment. If symptoms persist, complications are suspected, or the patient has a compromised immune system or coexisting conditions, the use of antibiotics should be considered. [67]

Empirical antimicrobial therapy should rely on local sensitivity patterns. Recently, *Campylobacter* resistance to quinolones has reached 81%, due to antibiotic overuse. In Spain, for example, quinolones are no longer recommended for *Campylobacter* infections due to high resistance rates. Alternative antibiotics are advised to enhance effectiveness and prevent further resistance.

Macrolides are the first-line antibiotics for treating *Campylobacter spp.*, despite the fact that resistance rates range from 3% to 11%. Additionally, recent studies suggest that erythromycin treatment may be associated with clinical relapse in HIV-infected patients. While tetracyclines serve as an alternative option, resistance to these antibiotics has also been reported. Approximately 50% of *Campylobacter* strains exhibit resistance to ampicillin, whereas resistance to amoxicillin/clavulanate remains low, at about 2%. Although data on the efficacy of amoxicillin/clavulanate in treating *Campylobacter* bacteremia is limited, it is

considered a viable alternative. [41] In addition to the mentioned antibiotics, aminoglycosides, fluoroquinolones, and ciprofloxacin can also be used, following prior determination of the susceptibility of the specific strain. [67]

The ideal duration of antimicrobial treatment for patients with campylobacteriosis remains uncertain. In cases where bacteremia is detected in healthy individuals several days after blood cultures are drawn, typically following complete recovery, no targeted therapy is necessary. A 10- to 14-day antibiotic therapy is likely adequate for healthy patients with persistent bacteremia or those with compromised immune systems, including cases associated with acute gastroenteritis. However, immunocompromised patients presenting with bacteremia in the absence of prior acute gastroenteritis may require an extended course of therapy, lasting at least 3 weeks. [41]

HEALTH AND SOCIAL IMPLICATIONS

To estimate the cost of food-related illnesses we must consider medicine, transport, hospital visits, hospitalization, rehabilitation, and indirect costs due to particular illness. The costs of treatment of foodborne diseases, including campylobacteriosis, in selected countries are presented in the table [Tab. 1].

COUNTRY	FOODBORNE DISEASE	COST	REFERENCES
Sweden	-In general	-€142 million each year	[69]
	-Campylobacteriosis	-70% of the total cost	
The United Kingdom	-Campylobacteriosis	-£50 million in 2008	[70]
	-Campylobacter-related Guillain-Barré	-£1,26 million	
Switzerland	-Campylobacteriosis and acute gastroenteritis	-€29–45 million	[71]

The United States of America	-Campylobacteriosis	-$1.3–$6.8 billion annually	[59]

Tab. 1 – The costs of treatment of foodborne diseases in selected countries. [59, 69, 70, 71]

The cost of campylobacteriosis treatment should be considered in the expenditure to control this bacterium in agriculture, food production and retail. When addressing Campylobacteriosis, it is essential to include treatment expenses as part of the expenditure required to manage this bacterium within agriculture, food production, and retail sectors. [69, 70, 71]. The amount of money spent on the treatment raises with complications, such as Guillain–Barré syndrome, reactive arthritis or irritable bowel syndrome.

RISKS AND COMPLICATIONS ASSOCIATED WITH CAMPYLOBACTER INFECTIONS IN PREGRANANCY AND LONG-TERM PATIENTS

Bacteraemia caused by *C. jejuni* during pregnancy may lead to intrauterine infection of the fetus, resulting in stillbirth, miscarriage, or early neonatal death. [72, 77] Infection of a newborn may be the reason of complications, such as meningitis, low birth-weight, and rectal bleeding. [73, 74, 75] Expectant mothers with infections or at high risk of infection are more likely to have newborns with an increased susceptibility to early-onset neonatal infections. [76] Pregnancy represents a critical period, as certain antibiotics can pose risks to the fetus, and Campylobacter jejuni exhibits resistance to many first-line antibiotics. Due to the risks posed by campylobacteriosis infections to both fetuses and pregnant women, it is imperative for expectant mothers to be extremely careful in food handling and preparation to prevent such infections.

Long-term patients colonized with *Campylobacter* can experience serious complications. For instance, the bacteria can undergo mutation and become resistant to antibiotic during periods of antibiotic therapy. [78] Furthermore, evidences suggest that bacteria can adapt to the environment, including the human body, through the accumulation of non-synonymous SNPs and frameshifts in genes involved in cell motility, signal transduction, and major outer membrane proteins. [79, 80]

SUMMARY

This paper provides a comprehensive review of campylobacteriosis, highlighting its clinical manifestations, associated complications, epidemiological aspects, pathogenesis, diagnostic approaches, and preventive strategies. The literature emphasizes the significance of *Campylobacter spp.* as a leading cause of bacterial gastroenteritis globally and its association with severe gastrointestinal and extra-gastrointestinal conditions.

Campylobacteriosis has been the most commonly reported zoonosis in humans across the European Union since 2007 and in 2021 was verified as the second most prevalent foodborne agent associated with the number of hospitalizations, after salmonellosis. This presents a serious public health problem in many countries that generates high healthcare costs and losses for the economy. Consequently, there is a pressing need for further investigation into the health and social costs associated with campylobacteriosis. Furthermore, the monitoring of zoonotic transmission and improving public health surveillance should be enhaced.

Campylobacteriosis can be primarily transmitted via the fecal-oral route, chiefly through contaminated poultry. Contaminated water sources and environmental factors, such as playgrounds, may also contribute. The disease presents as a gastroenteritis, implicated in some cases in serious complications such as inflammatory bowel disease, Barret's esophagus, colorectal cancer, and disorders of cardiovascular and neurological system. Increasing number of evidences suggesting association of *Campylobacter spp.* with a wider spectrum of diseases, shows that the bacteria have a greater impact on human health than previously recognized. Furthermore, by identifying specific environmental factors that contributes to the transmission of *Campylobacter spp*., this review emphasizes the importance of maintaining hygiene practices and safe food handling to reduce the risk of infection.

Seasonal trends of campylobacteriosis vary, with developed nations experiencing year-round symptomatic cases, whereas asymptomatic cases peak during specific months in developing countries.

Additionally, the review shows various mechanisms by which bacteria adapt to changing environmental conditions, and how *Campylobacter* affects the human body, highlighting optimal growth conditions, biofilm formation aiding survival, phase variation, and bacterial structures facilitating adhesion and immune evasion. Enhaced knowledge of the pathogenicity of *Campylobacter spp.* provides a deeper understanding and greater insights into its adaptability and persistence in various environments.

Advances in diagnostic methods, including stool culture, PCR, immunochromatographic tests, and enzyme-linked immunosorbent tests, have notably improved the detection and identification of *Campylobacter spp*. However, diagnosis is difficult due to difficult culture conditions and therefore a limited number of laboratories detecting Campylobacter. The coming years and the rapid development of technology will certainly soon enable the discovery of newer and better diagnostic and treatment methods.

Effective prevention measures are crucial to reduce Campylobacter colonization and transmission. These include purchasing poultry from reputable suppliers, proper meat cooking methods, safe water sources, proper ways of pasteurization and the storage of milk. Furthermore, there is promising evidence that vaccinating poultry flocks can significantly reduce both Campylobacter colonization and its subsequent transmission to humans.

Antibiotic overuse contributes to antibiotic resistance, with treatment costs being substantial globally due to post-infectious complications. Therefore, proper education of doctors about reducing antibiotic use should result in a decrease in the number of infections and healthcare costs, as well as improved population immunity.

In conclusion, campylobacteriosis presents a significant challenge to public health. Ongoing research aims to refine preventive strategies, emphasizing the need for improved public health strategies, continued research into epidemiology, pathogenesis, and treatment options to effectively combat Campylobacteriosis and mitigate its impact on human health and agriculture.

DISCLOSURE

Author`s contribution:

Conceptualization: KB; methodology: KR, WK, MN, KB; check: KB, EP; formal analysis: DGD; investigation: MN, WK, KR; resources: WK, KR, MN; data curation: MN, WK, KR; writing - rough preparation: WK, MN, KR; writing - review and editing: KB, EP, DGD; visualization: KR, MN, WK; supervision: DGD, EP; project administration: EP, DGD, KB

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Conflicts of Interest

The authors declare no conflict of interest.

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