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Campylobacter: A foodborne pathogen with emerging antimicrobial resistance

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Abstract

Campylobacter is one of the major foodborne pathogens of concern in its growing trend of antimicrobial resistance. *C. jejuni* and *C. coli* are the major causative agents, with *C. jejuni* contributing to most of the cases in approximately 90% of the world. Infection is transmitted to humans due to the consumption of contaminated food and water. Campylobacteriosis caused by *C. jejuni* is commonly presented with severe diarrhea, abdominal pain, fever, headache, nausea, and vomiting with some extreme cases resulting in Guillain–Barré syndrome (GBS) and acute flaccid paralysis. Symptoms are severe in cases of children below 5 years, the elderly, and individuals who are immunocompromised. The infection is usually sporadic, and self-limiting and thus does not require antibiotics for treatment. Still, the antimicrobial resistance

Campylobacter is a major concern because of the transmission of resistance from animal sources to humans. This review highlights the recent epidemiology, geographical impact, resistance mechanisms, spread of *Campylobacter* spp., and the strategies to control the transmission of *Campylobacter* from veterinary sources and its antimicrobial resistance.

Keywords: *Campylobacter*, antimicrobial resistance, foodborne pathogen, animal source.

Epidemiology of *Campylobacter*

Annually, approximately 0.8 million cases occur in the United States of America alone, with the incidence of high-income countries being 4.4-9.3 per 1000 population(Havelaar et al., 2015). In 2014, Europe reported a total of 240,379 confirmed cases from a total of 28 countries – an increase of 13% from the previous year.(*Campylobacteriosis - Annual Epidemiological Report 2016 [2014 Data]*, n.d.) In the Oceania regions, Campylobacteriosis was the most notified foodborne infection in Australia during 2010, with 16,968 cases.(Kaakoush et al., 2015)

Although surveillance data from developing countries are limited, Campylobacteriosis is notedto be endemic in certain parts of Africa, Asia, and the Middle East, especially in children under 2 years of age, who often have repeated and chronic infections.(Kaakoush et al., 2015)(Pascoeet al., 2020) *Campylobacter* infections rarely cause mortality, with occasional deaths occurring in the elderly, immunocompromised, or pediatric population.(Kaakoush et al., 2015)(Havelaar et al., 2015)

The geographical impact of *Campylobacter*

Campylobacter infection is transmitted from the zoonotic origin and studies reported its presencein domestic as well as wild birds and animals in different parts of the world.(Hald et al., 2016)(Truccollo et al., 2021)Spiking of infection rate around summer has been reported in Nordic countries like Sweden and Norway(Kuhn et al., 2020). However, the infection reports of Australia did not indicate the influence of the summer season on the number of reported infections(Bi et al., 2008). Weather and temperature influence on Campylobacteriosis is also not defined and is considered to be indirect as countries with a high-temperature range of 18.45 °C (65.21 °F) to 36.9 °C (98.4 °F) like Nigeria as well as countries with a low average temperature between 10° to 15°C (50-59°F) like Iceland have reported cases of Campylobacteriosis indicating no correlation of temperature does on the growth and spread of the *Campylobacter* species in different regions(Callicott et al., 2008). There are not many studies reporting the geographical, climate, and temperature impact of *Campylobacter* infections, and the available studies do not prove any significant correlation of geographical impact on the *Campylobacter* infection(Gwimi et al., 2015).

Resistance mechanism in the context of food poisoning of *Campylobacter*

The dynamic adaptation of *Campylobacter* is attributed to its genetic flexibility, which benefits the organism with rapid evolution. The innate error reading mechanisms, vulnerable genome for mutation, and cells exposed for receiving horizontal genes, collectively promote *Campylobacter* with positive selection for adaptability to colonize hosts and to develop antimicrobial resistance. (Costa & Iraola, 2019) As the bacteria passes through various host communities, the cost of bacterial fitness increases, and the *Campylobacter* infections in humans are commonly associated with antibiotic resistance(Costa & Iraola, 2019). Study of diarrheal cases caused by *C. jejuni* to determine the antibiogram associated with molecular resistance mechanism shows that resistance to fluoroquinolones (55.8%) and tetracyclines (49.7%) was high(Elhadidy et al., 2020). Concerning the past studies, resistance to ciprofloxacin and tetracycline had exponentially increased(Wieczorek et al., 2018) with a growing trend of treatment complications in infants as they are commonly used antibiotics for treating non-self-limiting diarrhea and systemic Campylobacteriosis.(Schiaffino et al., 2019)(Dai et al., 2020) DNA gyrase mutation C257T in *gyrA* gene and tetracycline resistance gene *tetO,* was detected in the majority of the clinical isolates, but few of them also seem to have developed resistance physiologically. The *tetO* gene contributing resistance to tetracycline was found to be horizontally transferred from poultry sources. (Avrain et al., 2004)Macrolideresistance in the diarrhoeal isolates resulted in 2% acquired by *ermB* coding for efflux pump,*rplD*, and *rplV* genes in 23s rRNA mutation of 50S ribosomal subunit resistance genes.(Elhadidyet al., 2020) This brings a future insight to explore physiologically resistant populations of *Campylobacter spp* in human infections. Thermotolerant communities of *Campylobacter* were encountered in the poultry and bovine meat with higher resistance to antibiotics.(Di Giannatale et al., 2019) As a gastrointestinal pathogen, thermotolerance and other physiological resistance to acids or salts is required for the survival instincts of the organism to the flow between hosts through the food chain. Such tolerance mechanism may be attributed to theresistance to antibiotics phenotypically. Antibiotic tolerance mechanism is common in *Pseudomonas aeruginosa* and it leads to treatment failure in chronic infections(Abishek et al., 2021). Further studies are required in the antibiotic tolerance of *Campylobacter*.

Morphophysiological Characteristics of *Campylobacter*

Campylobacter bacteria are small, Gram-negative, non-spore-forming that exist as either curved or spiral-shaped rods which are oxygen-sensitive, highly mobile, and prefer to grow under micro-aerobic conditions. They attain a polar flagellum at one or both ends of the cell, are catalase and oxidase-positive, and urease negative. They are fastidious organisms that belong to a distinct group designated rRNA superfamily VI and have been reported to change into coccoid forms on exposure to adverse conditions, especially oxidation. In general, these bacteria are fragile and easily destroyed by heat, acidity, desiccation, and disinfectants.

Virulence factors of *Campylobacter*

Enteric *Campylobacters* are predicted to express several putative virulence factors when colonizing the intestines, allowing for their survival against food processing and resistance to physiological stress.(Bolton, 2015) The different virulence-related mechanisms include invasive properties (facilitating binding and entry into host cells), bacterial adherence to the intestinal mucosa, oxidative stress defense, heat shock, toxin production (e.g., cytotoxins and cytolethal distending toxin, causing cell death), iron acquisition (for nutrition), and its ability to remain in a viable, but non-culturable (VBNC) state.(Backert et al., 2013) Other *Campylobacter* virulence factors entail secretion of some sets of proteins, translocation capabilities, chemotaxis (to traverse chemical gradients), and flagella-mediated motility (enabling movement into the mucous layer). (Biswas et al., 2011)

Impact of antimicrobial Resistance in *Campylobacter*

There is a sharp increase in the resistance of *Campylobacter* to fluoroquinolones, putting into consideration that there is an alarming increase in the fluoroquinolone's resistance on a global level. This has led to limiting the use of fluoroquinolone as a treatment option for human infection, yet there is relatively low resistance to macrolides.(Ruiz-Palacios, 2007) Campylobacteriosis is a foodborne zoonotic disease; hence the presence of resistant strains in the food chain will have an impact on human infection. (Wieczorek et al., 2018) Different

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studies have stated that being infected with quinolone or erythromycin-resistant strains of *Campylobacter* species are associated with increase adverse drug reactions when compared with susceptible species as well as long duration of illness, which will also lead to narrowing the options for treating the cases that need antibiotics and increasing in treatment failure for diarrheal disease.(Ruiz-Palacios, 2007)

It is important to tackle the rising *Campylobacter* antimicrobial resistance, especially when dealing with high-risk populations such as the elderly or immunocompromised. This is because ofthe high risk of bacteremia and other complications leading to the use of antibiotics for treatment. In some cases, they can even disseminate in the periphery and cause profound disease.(Yang et al., 2019)
Campylobacter bacteremia has a very low detection rate, which in Europe accounts for less than 1% of total patients with gastroenteritis. This can be attributed to many factors such as lack of diagnosis and avoiding blood cultures routines for gastroenteritis patients. (Mearelli et al., 2017). It is very serious in patients with immunodeficiency (mainly AIDS), gammaglobulinemia, diabetes mellitus, cirrhosis, and complement system disease, as well as in those who are receiving corticosteroid therapy. *Campylobacter jejuni* is the most isolated species among other *Campylobacter* spp. causing sepsis, a fatal septic shock with Multiple Organ Failure. *Campylobacter jejuni* case report was identified, where the culture did show resistance to cephalothin, amoxicillin, amoxicillin/clavulanate, aminoglycosides, erythromycin, and pefloxacin.(Meyrieux et al., 1996) Another case was presented with a septic shock with multi-organ failure due to fluoroquinolone-resistant *Campylobacter jejuni* where two blood cultures yielded *Campylobacter jejuni* resistant to fluoroquinolones and sensitive to macrolides. (Mearelli et al., 2017)Prevention and controlling measures to antimicrobial resistance are essentially needed to help to curb antimicrobial resistance which will have a positive impact on managing Campylobacter cases.

Sources of *Campylobacter*

The colonization of different animal reservoirs by *Campylobacter* poses an important risk for humans through the shedding of the pathogen in livestock waste and contamination of water sources, the environment, and food.(Igwaran and Okoh, 2019) Human infections may therefore be acquired via infected animals and their food products through various means including consumption of unpasteurized milk, untreated water, or undercooked poultry or red meat. Fecal contamination of meats, particularly of poultry origin, often occurs during slaughtering, resulting in cross-contaminated food products. *Campylobacter* infections can also be acquired through direct contact with infected pets within the family environment.(*Campylobacter Infections: Background, Pathophysiology, Epidemiology*, n.d.)(Asuming-Bediako et al., 2019)(Igwaran and Okoh, 2019) According to literature (2007-2013), a majority of *Campylobacter* outbreak cases were associated with poultry products (50-70%) and contaminated water, with colonized animals developing a lifelong carrier state.

Transmission of *Campylobacter*

Campylobacteriosis is a zoonotic disease, transmitted from animals or animal products to humans. The organism *Campylobacter* colonizes the gastrointestinal tract and reproductive tract of a wide variety of wild and domestic food animals including poultry, cattle, pigs, sheep, dogs and cats, ostriches, deer, and shellfish.(Liu et al., 2018)(Buchanan et al., 2017) The main route of transmission is through ingestion of contaminated food, water, or milk and consumption of eggs, raw or undercooked meat that become contaminated during slaughtering. Food, especially salads, can be cross-contaminated from raw meat when using the same cutting board, knives, and utensils. (*Information for Health Professionals | Campylobacter | CDC*, n.d.)(Newell and Fearnley, 2003). Consumption of contaminated raw milk, unpasteurized milk, or failure of milk pasteurization also is a source of transmission of Campylobacter infection. (Kenyon et al., 2020)(Kaakoush et al., 2015)

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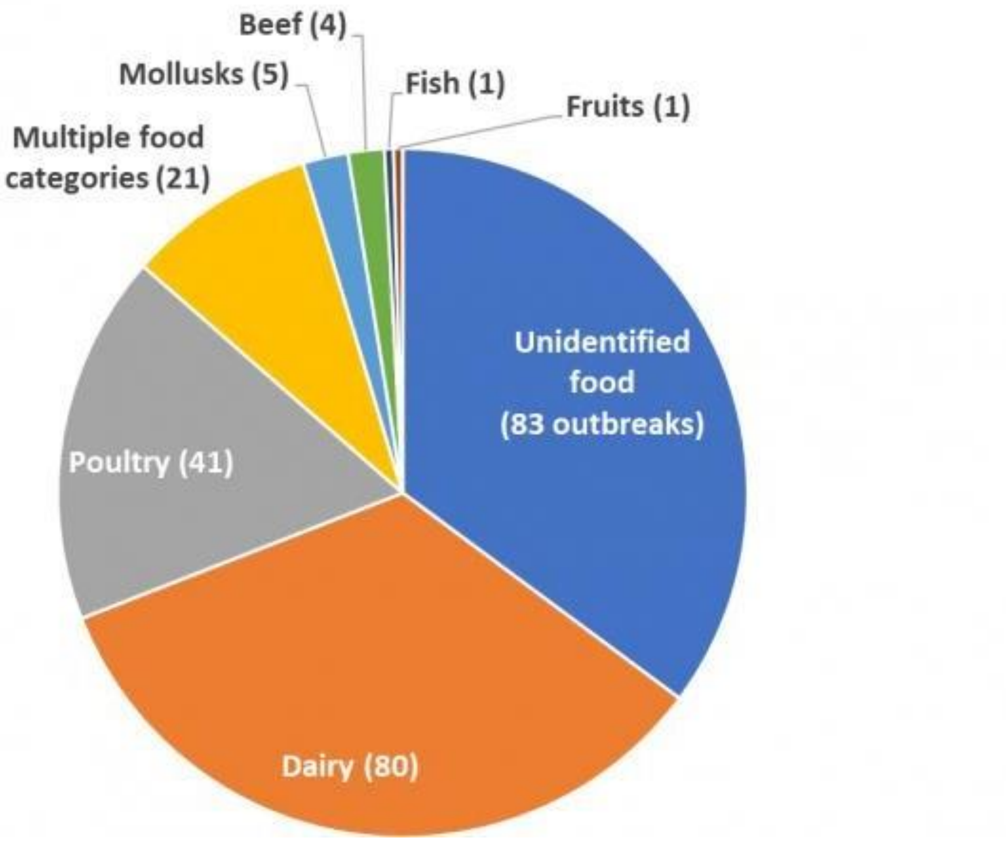

Fig 1. Outbreaks caused in the United States by *Campylobacter*, by food category, 2010–2017(https://www.cdc.gov/Campylobacter/technical.html

Clinical Manifestations of *Campylobacter* Infection in Humans

Ingestion of 500–800 bacteria can result in human disease. However, there are reports of 100 Campylobacter cells or less causing infections in humans.(Frirdich et al., 2017) Acute diarrhea (including traveler's diarrhea and children's diarrhea) is the major infection caused by *Campylobacter*. Watery or bloody diarrhea, accompanied by fever, stomach cramps, abdominal pain, nausea, and vomiting is most common. Bloating, headache, and muscle pain may also occur in some patients. Symptoms of Campylobacteriosis usually begintwo to five days after exposure, but it can also be as little as one day or in ten days. These symptoms generally last three to six days, although occasionally they may last longer.(Gharstet al., 2013)(Scallan et al., 2015) *Campylobacter* has been reported as one of the pathogens responsible for benign convulsions with mild gastroenteritis (BCWG), especially in summer and autumn.(Chen et al., 2019) Childhood *Campylobacter* has been reported to manifests as a single gastroenteritis complication in a previously healthy young child or as recurrent episodes in an older, immune-compromised child, usually without gastrointestinal symptoms.(Bi et al., 2008)

Current guidelines to tackle *Campylobacter* and its drawbacks.

The epidemiology of Campylobacteriosis revealed an increasingly important role for *Campylobacter* infection in public health, not only for the prevalence but also for the high level of resistance in humans. In humans, *Campylobacter* spp. was the 50% of all reports alone (220,682 confirmed cases) on the last annual report of the European Food Safety Authority (EFSA) and the European Centre for Disease prevention and control (ECDC) on zoonoses, zoonotic agents and on epidemic outbreaks of transmitted diseases food, relating to data collected in 2019, from 36 European countries (28 EU Member States and 8 non-members)(Food Safety Authority et al., 2021). The most effective strategies are based on the interactive epidemiological information from surveillance systems. One example of them is The Foodborne Diseases Active Surveillance Network (FoodNet) for the identification of food infections caused by *Campylobacter* and other pathogens FoodNet monitors over 300 laboratories in various US states and approximately 25 million people. Briefly, the lines of control are established following the last Regulation (EU) 2017/1495 of August 23, 2017, that amends the Regulation (No. 273/2005) and the EFSA studies. The 2011 EFSA opinion on *Campylobacter* was updated using more recent scientific data and reviewed the control options for *Campylobacter* in broilers at primary production. The guidelines of control of *Campylobacter* are divided into three main pillars, farms, food industry, and distribution. In the food industry the important steps are the sanitization considering the sensitivity to biocides (for a reduction> 5 log CFU/mL of *Campylobacter jejuni*); the capacity of forming mono biofilms and multispecies, both in aerobic conditions as anaerobic; the greater resistance to environmental conditions and the increased cell transfer capacity (*Seliwiorstow, T 2016).* Thesolution is neither simple nor easy. We should dedicate effort to harmonize methodologies of control all along with the chain food and to push the research and exchange of information (fig.2). The most important challenges are the standardization of validation measures, biocontrol methodologies in the poultry sector (principal source mediating Campylobacter transmissionto humans), including a harder promotion of innovation and efficacy skills among all ecosystem actors. All actions need to go in parallel with policies for control and notification of contamination, and at the same time to increase the consumer's protection.(Kaakoush et al., 2015)

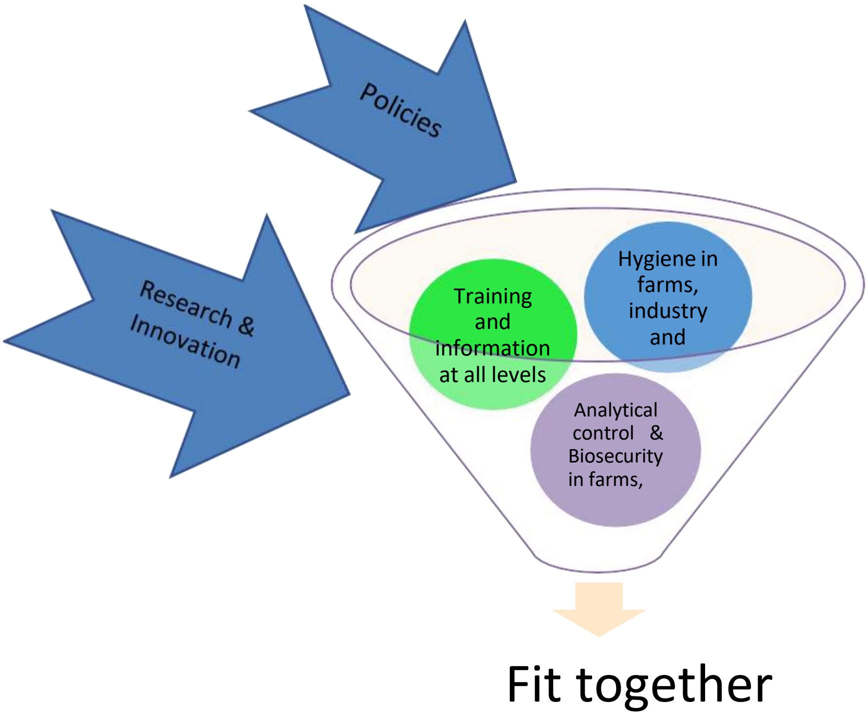

Fig 2: Conjugate all the strategies to fight against *Campylobacter* Global Health Issue.

Recent interventions and their conclusion

Multiple strategies have been implemented to reduce *Campylobacter* colonization in the food chain. Recently, scientists have started looking at alternatives to antibiotics to mitigate multidrug-resistant *Campylobacter*. Scientists have explored prebiotics as a supplement to prevent colonization in the gut of animals.(Dai et al., 2020) However, the findings were inconsistent. The researchers also moved their focus towards chemical-based antimicrobials such as trisodium phosphate (TSP), peracetic acid (PAA), acidified sodium chlorite (ASC), and cetylpyridinium chloride (CPC). These chemicals are usually applied as spray or surface sanitizers in the poultry farms and the places where broilers are processed.(Johnson et al., 2017) Currently, major investigations are being conducted to improve intervention methods in poultry processing. Processing plants cannot rely on the integrity of cold transportation of food products to retailers and therefore, must prioritize advancements on antimicrobial interventions. Many factors are driving industrial changes but one of the most prominent factors is pressure by public demand for safer mechanisms.(MacRitchie et al., 2014) People are not only exploring alternative methods but also looking at novel methods to kill these microbes such as electrostatic spraying, cold plasma treatment, and bacteriophages-based methods.(Soro et al., 2020)

Campylobacter is the most notorious bacterium accounting for its rapid spread and colonization in animals and humans through food and excreta. There is a debate regarding the administration of antimicrobial regimen in the management of uncomplicated *Campylobacter* infections since it is usually self-limited and most patient recovers without administration of antibiotics. Antibiotics should be reserved for cases of *C. jejuni* with indicated risk for severe illness with systemic manifestation (Ruiz-Palacios, 2007). According to the CDC guidelines, antibiotics should be reserved for elderly people (65 years or older), pregnant women, and immunocompromised. The government bodies need to pay more attention to the interventions of *Campylobacter* spread. Better guidelines and novel intervention might give a new perspective and a better chance to mitigate *Campylobacter*.

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