

Antibiotic Resistance of the *Campylobacter* Isolates According to Their Species in Different Samples of Broiler Chicken in Many Regions

(Resistensi Antibiotik dari Isolat *Campylobacter* Menurut Spesiesnya Pada Berbagai Sampel Ayam Pedaging di Berbagai Daerah)

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ABSTRACT

Campylobacter jejuni and *C. coli* are contaminants of broiler skin, and in unauthorized numbers cause campylobacteriosis in consumers where symptoms range from gastrointestinal to life-threatening. The number of chicken bacteria and their genetic diversity depend on the growing conditions, and the presence of antibiotic resistance genes is the result of irrational use of antibiotics. The purpose of this paper is to point out the importance of reducing the contamination of *Campylobacter* spp. in broiler production as well as the importance of the rational use of antibiotics in the production of broilers with a contribution to the prevention of the spread of campylobacteriosis and antibiotic resistance. The incidence of campylobacteriosis can be prevented by the concept of *Hazard Analysis Critical Control Point* (HACCP) in broiler production and the use of probiotics as biological preservatives in broiler meat. The spread of antibiotic resistance genes can be reduced by prohibition of antibiotic use for prophylaxis and only permitted for medication.

Key words: Antibiotic resistance, chicken meat, *Campylobacter* spp., prevention

ABSTRAK

Campylobacter jejuni dan *C. coli* adalah kontaminan pada kulit ayam pedaging, dan dalam jumlah banyak yang tidak semestinya menyebabkan campylobacteriosis pada konsumen di mana gejala berkisar dari gangguan pencernaan hingga mengancam jiwa. Jumlah bakteri ayam dan keragaman genetiknya tergantung pada kondisi pertumbuhan, dan adanya gen resistensi antibiotik merupakan akibat dari penggunaan antibiotik yang tidak rasional. Tujuan dari makalah ini adalah untuk menunjukkan pentingnya mengurangi kontaminasi *Campylobacter* spp dalam produksi ayam pedaging serta pentingnya penggunaan antibiotik yang rasional dalam produksi ayam pedaging dengan kontribusi terhadap pencegahan penyebaran campylobacteriosis dan resistensi antibiotik. Kejadian campylobacteriosis dapat dicegah dengan konsep *Hazard Analysis Critical Control Point* (HACCP) dalam produksi ayam pedaging dan penggunaan probiotik sebagai pengawet biologis pada daging ayam pedaging. Penyebaran gen resistensi antibiotik dapat dikurangi dengan pelarangan antibiotik dalam ransum ayam untuk pencegahan dan hanya diijinkan untuk pengobatan.

Kata kunci: Resistensi antibiotik, daging ayam, *Campylobacter* spp., pencegahan

INTRODUCTION

Thermophilic *Campylobacter* spp. (*C. jejuni*, *C. coli*) are microaerophilic, gram-negative bacteria, and zoonotic potential that cause campylobacteriosis. The most common causes of the disease are: *C. jejuni* (95%) and *C. coli* (2-5%) (Wieczorek & Osek 2013). Campylobacteriosis is a seasonal zoonosis, and bacteria most often exert their harmful effects on the epithelium of the intestinal and reproductive tract (Chukwu et al. 2019). Campylobacteriosis is a leading public health problem in Europe, the United States, Australia, New Zealand, but it is also present in Africa and Asia, but

research is scarce (Hanson et al. 2018). The first measure to control the spread of *C. jejuni* and *C. coli* in the skin of broiler carcasses is laboratory detection and compliance with biosecurity measures in production to maintain microbiological/health safety of food, provide safe and quality food for consumers (Furmeg et al. 2020). Prevention includes *Good Hygienic Practice* (GHP) and *Good Manufacturing Practice* (GMP) in broiler production (Hrustemović et al. 2021b).

There is no relevant scientific evidence that humans can be carriers, while warm-blooded animals are considered reservoirs of infection, especially poultry (Sheppard & Maiden 2015). *Campylobacter*

jejuni and *Campylobacter coli* are found in the digestive tract of seemingly healthy poultry, often in a percentage of 100%, and are also found on feathers and are a source of infection for humans (Laconi et al. 2021).

Cross-contamination, mixing roasted meat with raw chicken meat is a high risk factor for getting campylobacteriosis in consumers. Food should be handled with care to prevent possible food poisoning. Contamination of raw chicken meat largely depends on the processing of the slaughter (Silva et al. 2018; Alarjani et al. 2021). The dangers are different phases of primary production (fattening, slaughter and primary processing of chicken meat), so it is important to respect sanitary standards in different phases of primary production, "from farm to table" (Crim et al. 2014).

Each country should have a strategic plan and strict biosecurity measures to prevent contamination of production facilities with thermophilic *Campylobacter* spp. which is the obligation of EU member states (Bilska & Kowalski 2014; Facciola et al. 2017; Ben Romdhane & Merle 2021).

A review of the literature indicates that *C. jejuni* and *C. coli* are significant contaminants of broiler carcass skin, and that antibiotic resistance is a global public health problem (Hrustemović et al. 2021b). When we talk about *C. jejuni* and *C. coli* as contaminants of chicken meat, it is most often a bacterium of poultry origin (Vizzini et al. 2021). Food contaminants, in addition to the danger of causing alimentary intoxications in humans, can also mediate the spread of antibiotic resistance (ABR) genes to bacteria of human origin. Antibiotic resistance in isolates of *C. jejuni* and *C. coli* is present in the highest percentages in fluoroquinolones, macrolides and tetracyclines used in human and veterinary medicine, which indicates the importance of monitoring and rational use of antibiotics (Collignon & McEwen 2019; Premaratne et al. 2017).

In order to reduce the growth of ABR, international protocols have been developed with recommendations for the choice of AB in the treatment of bacterial infections in human and veterinary medicine, and EU member states have banned the use of AB in poultry (Wernicki et al. 2017). The problem of the validity of international protocols is reflected in the possibility of changing the genetic material of bacteria that carry with them and the change of resistance. Bacteria are short-lived, grow, multiply and transmit genetic material to their offspring (Sheppard & Maiden 2015). The genetic material of bacteria is variable and can be changed depending on external influences, including the use of antibiotics. In this regard, the effectiveness of certain AB in the treatment

of bacterial infections is changing (Hrustemović et al. 2021b; Hrustemović et al. 2022).

Antibiotic resistance can be innate (natural, intrinsic) and acquired. Bacterial genetic material can mutate as a result of bacterial defense, adaptation, survival in the case of certain AB, and genes can move through the genomes of the bacterial cell and transmit resistance genes. In addition to genetically determined bacterial resistance, there are biochemical mechanisms of bacterial resistance to certain AB, namely: enzymatic inactivation and modification, changes in DNA gyrase and topoisomerase IV, target modification (change in target enzyme), changes in ribosome structure, active efflux, changes in metabolic pathway, altering the permeability of the bacterial cell membrane (Hrustemović et al. 2022).

With the uncontrolled use of AB, bacteria can change their hereditary material in order to survive and pass it on to their offspring, who become resistant to the once effective AB. A special danger is posed by microorganisms that are constantly present in the body, such as *C. jejuni* and *C. coli* in chickens, and the uncontrolled use of AB in chickens changes their hereditary material and becomes resistant to the AB used. The high risk of spreading ABR should be reduced by rational consumption of AB, with special emphasis on the limited use of AB in poultry (Premaratne et al. 2017).

This article describes the presence of antibiotic resistance in isolates of *Campylobacter* spp. from broiler chicken meat in different regions in order to indicate the importance of reducing the contamination of broilers with *Campylobacter* spp. in production as well as the importance of rational use of antibiotics in broiler production with contribution to the prevention of the spread of campylobacteriosis and antibiotic resistance.

GENERAL CHARACTERISTICS OF *CAMPYLOBACTER* SPP.

Campylobacter spp. belong to the genus *Campylobacter*. Thermophilic species are important for public health: *Campylobacter jejuni* (*C. jejuni*), *Campylobacter coli* (*C. coli*), *Campylobacter fetus* (*C. fetus*), *Campylobacter lari* (*C. lari*), *Campylobacter hyointestinalis* (*C. hyointestinalis*) and *Campylobacter sputorum* (*C. sputorum*) (Costa & Iraola 2019). Thermophilic species are found in the intestines of various animals. The most important reservoirs of infection are: poultry, domestic and wild animals, pets, birds, mollusks (Hansson et al. 2018; Hrustemović et al. 2021; Laconi et al. 2021). They show high sensitivity to disinfectants, acids and salts. Inactivation is achieved at -12°C, some species survive at -70°C. In general, storing chicken meat at a refrigerator

temperature of 4°C and a temperature of -20°C reduces the amount of *C. jejuni* and *C. coli* in chicken meat (Awadallah et al. 2014). They show sensitivity to high temperatures and gradual drying. The optimum temperature is 30-45.5°C (Chukwu et al. 2019). These are microaerophilic, gram-negative bacilli, seagull wing shapes or the letter S (Bronowski et al. 2014; Markey et al. 2013). They are asporogenic and motile. Most oxidases and catalases are positive, reduce nitrate to nitrite and do not break down glucose. In the differentiation of thermophilic species *C. jejuni* and *C. coli*, hydrolysis of hippurate, which is negative in *C. coli*, is performed and tested. To differentiate *C. lari*, a test is performed on nalidixic acid to which isolated *C. lari* is naturally resistant (Markey et al. 2013).

Colonies are not subject to hemolysis. They have a variable appearance depending on the *Campylobacter* species and the nutrient media used for cultivation. On Karmala agar they are flat, gray in color, moist and spill, while on Skirrow agar they are gray and brown. On modified agar with carbon-cefoperazone-deoxycholate (mCCDA) they are small and flat, gray-white in color, with a tendency to spill and are watery. *Campylobacter jejuni* form flat, gray, and water colonies, and *C. coli*, round, glossy, and white (Quinn et al. 2011; Hrustemović et al. 2021).

Bacteria possess the ability to adhere to the substrate. *Campylobacter* species characterized by mobility that has a directed movement (chemotaxis) towards various organs through the epithelium (translocation) (Lacini et al. 2021). They can invade the epithelium (invasion), form a biofilm, release endotoxins and resist immunity (Quinn et al. 2011; Bolton 2015; Kaakoush et al. 2015; Costa & Iraola 2019). Virulence is related to the strength of the released endotoxin (Markey et al. 2013).

CAMPYLOBACTERIOSIS IN ANIMALS AND HUMANS

Campylobacteriosis is a very rare animal disease. Animals are considered reservoirs of infection (Markey et al. 2013). Human-to-human transmission is also possible in immunocompromised humans (Bronowski et al. 2014). The sources of infection for humans are quite wide, because they are ubiquitous bacteria. Transmission is direct through animals and indirect through water and food (Wieczorek & Osek 2013).

Campylobacteriosis is caused pathogenic bacterial species of the genus *Campylobacter*, which in humans most often cause symptoms of acute food poisoning (Ruddell et al. 2020). Campylobacteriosis of humans belongs to the seasonal zoonoses, food poisoning diseases that most often occur in the warm season when the most favorable climatic conditions for the growth

and development of these pathogens in food (Kaakoush et al. 2015; Hrustemović et al. 2022b).

In humans, they most often cause diseases of the digestive tract, but various complications are possible in the form of hemorrhagic diarrhea, bacteremia, septicemia, reactive arthritis, Guillan-Barré syndrome with neurological consequences, autoimmune disorder of the peripheral nervous system where antibodies attack the myeloid envelope of other peripheral nerves. Septicemia is a rare complication with a possible fatal outcome (Chukwu et al. 2019). Campylobacteriosis in humans: a form of gastroenterocolitis, a septic form, subclinical, prolonged or chronic (Markey et al. 2013). The form of gastroenterocolitis most often occurs in children, as well as a septic form that can have a lethal outcome.

Complications occur if bacteria enter the bloodstream through the intestinal wall (Bintsis 2017; Chukwu et al. 2019). Young children and people with HIV, autoimmune and neoplastic diseases are very susceptible to campylobacteriosis (Kalenic et al. 2013; Bronowski et al. 2014). Subclinical is asymptomatic and can be proven only by laboratory examination. In the case of a prolonged form, complications may occur including Guillain Barre syndrome or Miller Fisher syndrome, with symptoms of partial or complete paralysis (Chukwu et al. 2019).

EPIDEMIOLOGY OF CAMPYLOBACTERIOSIS IN DIFFERENT REGIONS

Campylobacteriosis is a seasonal zoonosis that occurs in the spring-summer season (Chukwu et al. 2019). Epidemiological data indicate high prevalences of campylobacteriosis in many regions, and it is considered that the prevalences are even higher, because many countries do not have a legal obligation to monitor (Kaakoush et al. 2015; Ben Romdhane & Merle 2021).

Monitoring data suggest that the prevalence of campylobacteriosis is highest in Sweden, Denmark and the United States. Monitoring data are scarcer in Africa, Asia, and the Middle East and are not considered leading enteritis. In countries in Africa and Asia, one billion people get various intestinal infections each year (Sahin et al. 2012; Kaakoush et al. 2015; Silva et al. 2018).

In Southeast Asia, Thailand, campylobacteriosis is the leading cause of diarrhea as in European countries and the United States (Mason et al. 2017). The European Food Safety Authority (EFSA) and the European Center for Disease Prevention and Control (ECDC) report that a trend of campylobacteriosis growth has been recorded in Europe since 2005, which has not been recorded in any other alimentary epidemic

and that campylobacteriosis is the leading alimentary intoxication (Table 1) (EFSA & ECDC 2009-2021).

Many authors believe that data on the annual rate of campylobacteriosis are much higher than currently available and that control monitoring of preventive measures should be done in all regions /countries (Kaakoush et al. 2015; Ben Romdhane & Merle 2021).

Some authors believe that lower rates of campylobacteriosis in third-world countries are due to less infection reservoirs, and less exposure while others believe it is humoral immunity resulting from childhood exposure to *Campylobacter* bacteria (Ben Romdhane & Merle 2021; Hrustemović et al. 2021b). As bacteria in the genus *Campylobacter* are microaerophilic and extremely sensitive to the presence of oxygen, the methodology used for sampling, isolation, and identification may yield incorrect results (Bronowski et al. 2014; Kaakoush et al. 2015).

HUMAN IMMUNITY TO CAMPYLOBACTERIOSIS

Host immunity is based on cellular and humoral immunity, as well as non-immune defense mechanisms. Cellular immunity in the form of T lymphocyte production is important in immunocompromised patients, patients with autoimmune diseases, HIV infection, and neoplastic diseases (Costa & Iraola 2019). In campylobacteriosis, the humoral immune response is significant where IgA immunoglobulins (acute phase), IgG, IgM play an important role. Overcoming the infection leaves an insecure immunity (Markey et al. 2013; Costa & Iraola 2019; Ben Romdhane & Merle 2021). Immunity resistance is related to the lack of cytokine release. The clinical picture of the disease is related to cellular and humoral immunity. Cellular immunity refers to the release of T-lymphocytes, the so-called "Killer cell",

and humoral immunity to the production of antibodies, immunoglobulin IgA, IgG and IgM. The non-immune response depends on the composition of the intestinal flora. Bacteria of the genus *Lactobacillus* and *Bifidobacterium* play a significant role in alleviating the clinical picture, because they release bactericidal, fungicidal and viricidal substances (Zhang et al. 2017). Probiotics reduce the complications of campylobacteriosis in the form of celiac disease, Crohn's disease, ulcerative colitis, etc. (Lebwohl et al. 2015).

BENEFITS OF PROBIOTICS AND THEIR INHIBITORY EFFECT ON PATHOGENS

Food enriched with probiotic cultures of the genera *Lactobacillus* and *Bifidobacterium* contribute to health: As an example, *Lactobacillus acidophilus* (*L. acidophilus*) is a well-known species for the fermentation of dairy products (Fijan 2014). *Lactobacillus* convert sugars into lactic acid and serve in the preparation of fermented products (Hrustemović et al. 2021b). *Lactobacillus* has the ability to synthesize bacteriocins that damage pathogens (da Silva Sabo et al. 2014). The effect is still being investigated, and nisin is used (Cotter et al. 2013). *Lactobacillus salivarius* and *Lactobacillus plantarum* (*L. plantarum*) can inhibit the growth of *Campylobacter* spp. from food (Messaoudi et al. 2012; Wang et al. 2014). *Lactobacillus plantarum* is considered one of the most important species of the genus *Lactobacillus* (da Silva Sabo et al. 2014).

Bacteriocin enzymes, which are produced by probiotic bacteria, can also be used in food preservation as biological preservatives in the so-called "New food", which excludes the use of harmful, chemical compounds nitrite and nitrate, which are required for food to be pathogens free (da Silva Sabo et al. 2014).

Table 1. Campylobacteriosis in Europe

Europe / year	Frequency of campylobacteriosis from 2005 to 2019 in Europe		
	Growth (%)	No of cases	Source
Europe / 2005	6-7	195 426	EFSA & ECDC (2009)
Europe / 2007	2-3	200 507	EFSA & ECDC (2009)
Europe / 2010	5-6	212 064	EFSA & ECDC (2012)
Europe / 2011	3-4	220 209	EFSA & ECDC (2013)
Europe / 2014	7-8	236 851	EFSA & ECDC (2015)
Europe / 2016	3-4	246 307	EFSA & ECDC (2017)
Europe / 2018	0-1	246 571	EFSA & ECDC (2019)
The number of reported campylobacteriosis decreases, probably due to the COVID-19 pandemic, Europe / 2021	recorded a decline since 2019	120 946	EFSA & ECDC (2021)

Bacteriocins are used today as biological food preservatives, and canning of dairy products is also recommended (Perez et al. 2014). Probiotics are increasingly being used in addition to antibiotics as part of therapy to reduce the side effects in the form of diarrhea and stomach cramps. Recently, they are also used as biological preservatives. Such food preservatives are not harmful, are good for the microflora of the consumer and help strengthen the immune system (da Silva Sabo et al. 2014).

It is known that meat is susceptible to spoilage and meat quality is related to microbiological and biochemical quality. There is a trend of "New food" on the market and consumers want the meat to be with as few chemical additives as possible (Ibrahim et al. 2021). Reduced salt content, reduction of chemical preservatives, use of vacuum, is known as a "Mild technology" whose disadvantages are the increase of bacteria in various meat products (Verma et al. 2022). For this reason, the use of probiotics and metabolites in meat as competitive antagonists of pathogenic bacteria and natural preservatives is being studied. Probiotics are in use, which has been tested for many years, as well as their products such as nisin (Juturu & Wu 2018; Verma et al. 2022).

The use of probiotics should not change the taste of meat (da Silva Sabo et al. 2014). Probiotics reduce the growth of food pathogens with their metabolites, but this inhibition must last for some time for the probiotic to be a good biological preservative, to have good metabolic activity, and to survive at low temperatures (Ghanbari et al. 2013). Bacteria of the genus *Lactobacillus* spp. have those abilities. Their metabolic products with which they competitively inhibit the growth of pathogenic bacteria are bacteriocins, organic acids (lactic acid), diacetyl, hydrogen peroxide, and carbon dioxide (Hwanhlem & Aran 2015). Bacteriocins are synthesized peptides and act by signaling cells (Chikindas et al. 2018). They have an inhibitory effect on bacteria in the immediate vicinity. Organic acids lower the pH value and thus reduce the population of pathogens. Fat-soluble, have the ability to enter the cell of pathogenic bacteria and reduce pH, and also affect bacterial metabolism. Hydrogen peroxide causes permeability of the pathogen membrane. Carbon dioxide creates an anaerobic environment and causes the permeability of lipid membranes. Diacetyl acts on the protein responsible for binding arginine and bacteria (Neal-McKinney et al. 2012).

SANITATION AS A HYGIENIC MEASURE IN CHICKEN MEAT PRODUCTION

One of the measures to reduce *C. jejuni* and *C. coli* in the primary production of broiler chicken meat

is the application of hygienic and sanitary standards in primary production (Hrustemović et al. 2021). The effect of probiotics in chicken meat as a natural preservative on reducing contamination with *C. jejuni* and *C. coli* is also being investigated (Wang et al. 2014).

In order to reduce the occurrence of campylobacteriosis, the following are important: hygienic food handling, avoidance of contamination, storage of food in refrigerators, chlorination of water, *Hazard Analysis Critical Control Point* system (HACCP), *Good Hygienic Practice* (GHP), *Good Manufacturing Practice* (GMP) (Bilska & Kowalski 2014; Facciola et al. 2017; Hrustemović et al. 2021b).

Subsequent contamination of meat most often occurs in primary production, so it is important to respect hygienic and sanitary standards at different stages of primary production (fattening, slaughter, primary processing) (Crim et al. 2014). The application of *Hazard Analysis Critical Control Point* (HACCP), *Longitudinal Integrated Safety Assurance* (LISA), *Quality, Safety, Acceptability* (QSA) and *Specific Pathogen Free* (SPF) systems for the purpose of "Safe food" production is very important. The most commonly used disinfectants in primary production are halogens, phenols, cationic surfactants, cresols, and aldehydes (Hrustemović et al. 2021b).

Chlorine is the best bactericide, and it is also a fungicide and viricide. It is used for sanitation in the form of chlorinated lime, calcium hypochlorite, and as a gas for water disinfection. Stabilized liquid chloride has no negative characteristics, toxicity, and corrosivity (Hadžiabdić et al. 2013).

Phenols are bactericides, fungicides, and viricides, but they are not sporocides. They are toxic, corrosive, strong-smelling, and environmentally unacceptable. Cationic surfactants work best on gram-positive bacteria. They also act on fungi and viruses. They are non-toxic, corrosive, and odorless (Hrustemović et al. 2021b).

Cresols are bactericides, fungicides and viricides. The disadvantage is corrosivity and reduced action in organic matter. Formaldehyde is a bactericides, fungicides and kills viruses, but it is toxic, corrosive, and strongly odorous (Quinn et al. 2011; Hrustemović et al. 2021b).

PROBLEMS OF ANTIBIOTIC RESISTANCE CAMPYLOBACTER JEJUNI AND CAMPYLOBACTER COLI

In Bosnia and Herzegovina, various types of antibiotics (AB) are still used in the production of broiler chicken meat in prophylaxis, therapy, and for the purpose of increasing production. Prophylactically, it is usually sought to reduce the number of pathogenic

bacteria in chicken intestines in order to reduce meat contamination with intestinal bacteria, including *C. jejuni* and *C. coli*, which are potential causes of campylobacteriosis in humans, during slaughter, spreading, and processing of chicken carcasses (Hrustemović et al. 2021b; Vizzini et al. 2021). This method of reducing contaminants in chicken meat is not recommended because it increases the risk of antibiotic resistance (ABR), and there is another problem of residues in meat that can harm consumers (Hrustemović et al. 2022).

The use of large quantities of AB in the production of broiler chicken meat in European Union (EU) member states has long been recognized as bad therefore, this prophylactic method was rejected and the ban on the use of AB in chicken production is regulated by law. Given that Bosnia & Herzegovina (B&H) desires to join the EU, we should expect harmonization of legal preconditions in B&H with the laws of EU member states, which would greatly contribute to reducing the spread of antibiotic resistance. Monitoring the spread of ABR of food contaminating bacteria is very important in order to identify the problem and act in a timely manner to rationalize the use of antibiotics (Ben Romdhane & Merle 2021; Hrستمović et al. 2022).

The trend of spreading antibiotic resistance to bacteria requires all countries of the world to rationalize the consumption of AB in order to maintain their effectiveness. Continuous monitoring is recommended as a control measure of measures taken to spread ABR (Ma et al. 2021).

In all countries of the world, there is a growing trend of multidrug resistance (MDR), especially those bacteria that are pluripotent, ie. antibiotic resistance to one antibiotic entails antibiotic resistance to other antibiotics of the same class. The probable reason for this phenomenon is the same mechanism of action of antibiotics from the same class because the acquired mechanism of ABR is precisely related to the mechanism of action of antibiotics (Hrustemović et al. 2021a).

Problems with antibiotic resistance of thermophilic *C. jejuni* and *C. coli* is that these bacteria if they have an ABR biochemical mechanism (containing antibiotic resistance genes), are often active efflux. Active efflux is defense mechanism used by bacteria to protect themselves against various antibiotics and disinfectants (Tang et al. 2017). This is the only mechanism of bacterial resistance that is not related to the mechanism of action of antibiotics, and bacteria can expel the antibiotic with energy, regardless of the antibiotic class or type, or mechanism of action. Antibiotic resistance genes in the bacterial world can be transmitted from parents to offspring (vertically) and via plasmids between all nearby bacteria that are

competent (horizontally) (Sheppard & Maiden 2015; Ma et al. 2021; Hrستمović et al. 2021a).

A review of the literature in many countries revealed antibiotic resistance of isolates of *C. jejuni* and *C. coli*. *Campylobacter* species are constant contaminants of chicken skin, so it is important to wash your hands after manipulation, because in addition to possible campylobacteriosis, these bacterial species can transmit antibiotic resistance genes to bacteria from humans (Hansson et al. 2018; Hrستمović et al. 2022).

Based on monitoring data on antibiotic resistance of *C. jejuni* and *C. coli*, it is noticeable that ABR has been reported in many antibiotic classes, with a significant increase in ABR to fluoroquinolones (ciprofloxacin, marbofloxacin, enrofloxacin) and quinolones (nalidixic acid) (Mason et al. 2017; Silva et al. 2018). In veterinary medicine, fluoroquinolones are very often used in the treatment of various bacterial infections. They are important antibiotics for veterinary medicine *Veterinary Critically Important Antimicrobial Agents* - VCIA (Tang et al. 2017; OIE 2019). The increase in resistance to these antibiotics is not surprising, because they are empirically widely prescribed in human and veterinary medicine. They are most often prescribed empirically in the treatment of urinary tract infections due to their good effect on enterobacteria, which are common causes of infections in this region (Markey et al. 2013).

Cephalothin has also been linked to high rates of antibiotic resistance in *C. jejuni* and *C. coli* isolates (Giacomelli et al. 2014). It is a type of antibiotic that belongs to the class of β lactam antibiotics. It is an antibiotic of the first generation of cephalosporins (β lactams) that was discovered a long time ago and has been used for a long time in both human and veterinary medicine, so it is no wonder that many bacteria that were naturally sensitive to this type of antibiotic are now resistant. Resistance genes are spread to offspring and other bacteria, including those of different phylogenetic affiliations. Otherwise, irrational, frequent use of β -lactam antibiotics leads to acquired antibiotic resistance and bacteria defend themselves against antibiotics through a biochemical mechanism known as enzymatic modification and bacteria have the ability to secrete β -lactamase enzymes and less frequently amidase (Poirel et al. 2018; Hrستمović et al. 2021a).

Antibiotic resistance to cephalothin is not surprising, but the great danger to public health is the spread of antibiotic resistance to more recent β -lactam antibiotics such as cephalosporins III (cefotaxime) or the spread of antibiotic resistance to newer β -lactam antibiotics, reserve carbapenems. Generation III cephalosporins are more recent antibiotics with a broad spectrum of action and have been left to be used in the treatment of severe bacterial infections such as sepsis, various respiratory bacterial diseases, complicated

urinary tract infections, mastitis, etc. (Markey et al. 2013; OIE 2019). Otherwise, these antibiotics should be used only in emergencies, because in addition to spreading bacterial resistance to antibiotics, they also strengthen very dangerous anaerobic bacteria such as *Clostridium difficile* (Frieri et al. 2017).

The spread of antibiotic resistance of *C. jejuni* and *C. coli* isolates to tetracyclines is on the lesser rise, therefore, tetracyclines should never be the first drug of choice in the treatment of less dangerous bacterial infections due to their very broad spectrum of action (Pérez-Boto et al. 2014; Nemeth, Oesch & Kuster 2015; Shobo et al. 2016).

An increase in antibiotic resistance of *C. jejuni* and *C. coli* isolates to macrolides (erythromycin, azithromycin) has been reported worldwide (Shobo et al. 2016). There is also an increase in *C. jejuni* and *C. coli* multidrug resistance to fluoroquinolones, macrolides and tetracyclines used to treat campylobacteriosis (Mason et al. 2017; Premaratne et al. 2017).

Since 2013, antibiotic resistance has been presented as a global public health problem. Monitoring is an important control measure, but the spread can be reduced by rational use of antibiotics. When a bacterium acquires antibiotic resistance genes, it takes ten years for susceptibility to return (Schrijver et al. 2018).

RISKS AND PREVENTION OF CAMPYLOBACTERIOSIS AND ANTIBIOTIC RESISTANCE

Risk and prevention of campylobacteriosis

The food that is most often associated with reported epidemics of campylobacteriosis is chicken meat, unpasteurized eggs, unpasteurized dairy products, etc. (Silva et al. 2011; Tang et al. 2017; Silva et al. 2018). Poultry and domestic cattle are considered to be the most important reservoirs of infection (Sheppard & Maiden 2015; Ruddell et al. 2020).

It is primarily transmitted through contaminated water and food or by direct contact with animals that transmit the infection (Bronowski et al. 2014; Tang et al. 2017). Secondary transmission refers to subsequently contaminated food with animal feces (Markey et al. 2013). Subsequent contamination of meat most often occurs in primary production, so it is important to respect hygienic and sanitary standards at different stages of primary production (fattening, slaughter, primary processing) (Crim et al. 2014; Hansson et al. 2018).

Culture, microscopic, and biochemical assays are used to identify *C. jejuni* and *C. coli* (Markey et al. 2013). The *Enzyme-linked immunosorbent assay*

(ELISA), *Randomly amplified polymorphic DNA* (RAPD) and repetitive sequence-based PCR (rep-PCR) are used for epidemiological purposes (Azizian et al. 2018).

In order to reduce the outbreak of campylobacteriosis epidemics, hand hygiene, hygienic food handling, heat treatment of food, pasteurization of milk, dairy products, and fruit juices, avoidance of cross-contamination, refrigeration, fruit and vegetable peeling, water chlorination, water chlorination, various sanitary standards are important. stages of primary production, HACCP system (GHP & GMP) (Bilska & Kowalski 2014; Facciola et al. 2017).

The sanitation procedure reduces the number of pathogenic microorganisms. Sanitation is a process that involves mechanical cleaning and disinfection of the space (Hrustemović et al. 2021b). Proper sanitation contributes to the evaluation of the veterinary health system, which represents protection against financial risk, health protection, and safety (Hrustemović et al. 2021a). A study in Germany, Bechstein et al. (2019) state that the use of disinfectant, without the application of hydrostatic pressure, has no significant effect on reducing contamination with *C. jejuni*, while a study in Mississippi, Nair et al. (2014) state that the use of lauric arginate reduces contamination without application of hydrostatic pressure. In a study in Arkansas (USA), Wagle et al. (2017), report a positive effect of the application of the disinfectant phytophenolic compound β -resorcil acid on the decrease in contamination of raw skins, chicken meat with *C. jejuni*, after cultivation.

A review of the current resistance study of *Campylobacter* spp. on antibiotics and disinfectants, in some cases variations were observed and in some not. It is evident that resistance to antibiotics and disinfectants is present in *Campylobacter* spp. (Hrustemović et al. 2021b). Microorganisms are the slowest to acquire resistance to disinfectants (Cantas et al. 2013; Pidot et al. 2018). If resistance occurs, it is usually acquired by biochemical mechanisms of resistance, such as: efflux pump or alteration of cell membrane permeability. If biochemical mechanisms of resistance to disinfectants are developed, cross-resistance to antibiotics is most common (Quinn et al. 2011). Since microorganisms are also able to acquire resistance to disinfectants, it is necessary to find a new means of providing an aseptic environment in the future (Högberg & Heddini & Cars). Recently, the effectiveness of natural, biocidal agents such as pine oil has been tested. Microorganisms have not yet shown resistance to natural, biocidal agents (Quinn et al. 2011).

Campylobacteriosis therapy can be suppurative, immunomodulatory, and antibiotic. The most commonly used antibiotics are macrolides and

fluoroquinolones, aminoglycosides, tetracyclines, and reserve carbapenems can also be used (Quinn et al. 2011; Premarathne et al. 2017).

Wrong choice of antibiotics, wrong dose, irrational use of antibiotics, prescribing for viral diseases, prophylaxis in delaying surgical work, etc., can contribute to the creation of antibiotic resistance. Good clinical practice, and correct use of antibiotics, achieve a therapeutic effect while reducing side effects (Hrustemović et al. 2021a).

Risk and prevention of antibiotic resistance

Antibiotic resistance is widespread in the world, and reducing the use of antibiotics is the only solution to this public health problem. Scientists are looking for solutions and finding adequate substitutes for antibiotics. Alternative therapies include the use of probiotic bacteria of the genus *Lactobacillus* (Saint-Cyr et al. 2016). Probiotics are increasingly being researched as a good solution in reducing pathogens in various types of food, ie their products bacteriocins that can be used as biological preservatives in food (Soltani et al. 2021). *Lactobacillus* probiotics that reduce *C. jejuni* and *C. coli* in chicken intestines can be used in the primary production of broiler chicken meat, which contributes to the prevention of campylobacteriosis in consumers (Neal-McKinney et al. 2012; Hrustemović et al. 2022b).

Antibiotic resistance of bacteria is a global public health problem that can arise spontaneously by mutation, be transmitted vertically from parents to offspring or by horizontal transfer to all bacteria in the immediate vicinity (Giedraitiene 2011). Bacteria can also acquire different biochemical mechanisms of resistance, which are related to the mechanisms of action of the used biocidal agent to which certain bacteria have acquired resistance (Markey et al. 2013).

In *Campylobacter jejuni* and *C. coli* the most common mechanism of antibiotic resistance is active efflux (Ma et al. 2021; Moradi & Baserisalehi 2022). In order to prove the antibiotic resistance of the tested bacteria, various detection methods are used, of which the disk diffusion method is routinely used the most, and molecular methods, and gene sequencing methods are also used (Markey et al. 2013).

ANTIBIOTIC RESISTANCE OF CAMPYLOBACTER ISOLATES ACCORDING TO THEIR SPECIES IN DIFFERENT SAMPLES IN MANY REGION

By monitoring the prevalence of antibiotic resistance of *C. jejuni* and *C. coli*, certain variations in the study results were observed. The high percentage of antibiotic resistance is evident in fluoroquinolones,

macrolides, and tetracyclines (Table 2) (Mason et al. 2017; Yamada et al. 2019). Monitoring has also confirmed that poultry is the most common carrier of campylobacteriosis in humans. Campylobacteriosis is the leading toxin infection in Europe, the United States, Australia, and New Zealand (Hanson et al. 2018).

In a study in Bosnia and Herzegovina related to the percentage of *C. jejuni* and *C. coli* in chicken meat, Alagić et al. (2016) state that most isolates were identified as *C. jejuni* (91.9%) and a smaller number as *C. coli* (8.1%). Samples were taken from the bodies of chickens on slaughter lines, with the assumption of intestinal contamination during slaughter, and the presence of contaminants in unauthorized numbers suggests poor production processes. Contamination with *C. jejuni* and *C. coli* was recorded on chicken carcasses in the percentage of 27.4% (23/84), on chicken breasts (19.0%), in the visceral cavity (15.5%) and in chicken liver (9.5%).

In a study of the presence of *Campylobacter* spp. on the skin of broiler carcasses in northern Croatia, Furmeg et al. (2021) report more dramatic results, stating that out of a total of 60 tested samples, as many as 28 (46.67%) had a result above the limit value (>1000 CFU/g) according to Regulation (EU) 2017/1495, emphasizing the importance of implementing biosecurity measures in slaughterhouses as and monitoring the prevalence of *C. jejuni* and *C. coli* to ensure food safety.

In a study of the percentage of *Campylobacter* spp. in chicken meat in Indonesia (Lampung, Jakarta and Central Java), Syarifah et al. (2020) report that out of a total of 105 examined samples, as many as 65 (61.9%) had positive results. Most of the positive results are from Lampung and Jakarta with a prevalence of 80%, and from Central Java 30%.

Based on alarming data on the incidence of campylobacteriosis in humans in Barbados, isolation of *Campylobacter* spp. from faecal samples in 596 animals and 311 food samples of animal origin. The highest percentages of isolated *Campylobacter* spp. were recorded in chickens (94.2%), pigs (90.5%), dogs (46.9%), cats (37.3%) and wild birds (39.3%). In chickens, the most common species is *C. jejuni* (79.8%), in pigs *C. coli* (98.4%), and in cats *C. upsaliensis* and *C. helveticus*. Researchers state that people are most often infected by consuming contaminated chicken meat, but also that pets are significant reservoirs of infection (Mughini et al. 2013).

Table 2. Antibiotic resistance of *Campylobacter* isolates from different samples in many regions

Regions/country/year	Prevalence of antibiotic resistance of <i>Campylobacter</i> spp. isolates from broiler chicken samples			
	Sample	Antibiotic classes	ABR (%)	Source
Southwest Asia/Iran/2018	Broiler	Tetracyclines	<i>Campylobacter</i> spp: 70.6 %	Azizian et al. (2018)
Southwest Asia/Iran/2018	Broiler	Fluoroquinolones	<i>Campylobacter</i> spp: 63.7 %	Azizian et al. (2018)
Southwest Asia/Iran/2018	Broiler	Penicillins	<i>Campylobacter</i> spp: 27.5 %	Azizian et al. (2018)
Europe/Central Italy/2017	Broiler cloaca	Fluoroquinolones	<i>C. jejuni</i> : 39 %; <i>C. coli</i> : 70 %	Pergola et al. (2017)
Europe/Central Italy/2017	Broiler cloaca	Tetracyclines	<i>C. jejuni</i> : 10 %; <i>C. coli</i> : 70 %	Pergola et al. (2017)
Europe/Central Italy/2017	Broiler cloaca	Macrolides	<i>C. jejuni</i> : 100 %; <i>C. coli</i> : 30 %	Pergola et al. (2017)
South Africa /2016	Health center	Fluoroquinolones	<i>C. jejuni</i> : 20.4 %; <i>C. coli</i> : 33.3 %	Shobo et al. (2016)
South Africa /2016	Health center	Macrolides: erythromycin	<i>C. jejuni</i> : 31.5 %; <i>C. coli</i> : 38.9 %	Shobo et al. (2016)
South Africa /2016	Health center	Macrolides: azithromycin	<i>C. jejuni</i> : 50 %; <i>C. coli</i> : 77.8 %	Shobo et al. (2016)
Southeast Asia/Thailand/2017	Production chains	Fluoroquinolones: enrofloxacin	<i>C. jejuni</i> : 100 %; <i>C. coli</i> : 98.9 %	Thomrongsuwannakij et al. (2017)
Southeast Asia/Thailand/2017	Production chains	Tetracyclines: tetracycline	<i>C. jejuni</i> : 55.6 %; <i>C. coli</i> : 97.9 %	Thomrongsuwannakij et al. (2017)
Southeast Asia/Thailand/2017	Production chains	Tetracyclines: doxycycline	<i>C. jejuni</i> : 50 %; <i>C. coli</i> : 79 %	Thomrongsuwannakij et al. (2017)
Southeast Asia/Thailand/2017	Production chains	Sulfonamides: trimethoprim-s.	<i>C. jejuni</i> : 36.1 %; <i>C. coli</i> : 81.9 %	Thomrongsuwannakij et al. (2017)
South Asia/India/2018	Skin of broiler	Cephalosporins: cephalothin	<i>C. jejuni</i> : 81.1 %	Khan et al. (2018)
South Asia/India/2018	carcasses,	Tetracyclines	<i>C. jejuni</i> : 59.4 %	Khan et al. (2018)
South Asia/India/2018	intestines,			
South Asia/India/2018	cutting boards.			
Europe/Turkey/2009	Slaughterhouses	Tetracyclines	<i>C. jejuni</i> : 76.3 %	Cokal et al. (2009)
Europe/Turkey/2009	Slaughterhouses	Fluoroquinolones: ciproflox.	<i>C. jejuni</i> : 74.2%; <i>C. coli</i> : 65.5%	Cokal et al. (2009)
Southeastern region of the	Chicken liver	Fluoroquinolones: ciproflox.	<i>C. jejuni</i> : 33%	Yeh et al. (2022)
United States of	Chicken liver	Tetracyclines	<i>C. jejuni</i> : 14%	Yeh et al. (2022)
America/Georgia/2022				

Bartkowiak-Higgo et al. (2006) in a pilot study in South Africa, reported the percentage of *C. jejuni* and *C. coli* in broilers, citing positive skin and liver results of broilers contaminated with *C. jejuni* and *C. coli* (24%) as well as intestinal contamination (28 %), which indicates an increased risk of consumer disease in Africa, where trials are rare and scarce epidemiological data do not classify campylobacteriosis as the leading enteritis.

In a study of the percentage and distribution of antibiotic resistance of *Campylobacter* spp. from chickens in Iran, Azizian et al. (2018) report that 55% of chickens were contaminated with *Campylobacter* spp., of which 67 isolates were typified by the molecular polymerase chain reaction (rep-PCR) method of which 57 (85.1%) were identified as *C. jejuni* and 10 (14.9%) as *C. coli*. Significant genetic differences were observed in *C. jejuni* isolates. Antibiotic resistance of *C. jejuni* and *C. coli* isolates was performed using the disk diffusion method and the highest percentages were recorded for tetracyclines (70.6%), fluoroquinolones (63.7%), penicillins (27.5%). By monitoring the prevalence of antibiotic resistance of *C. jejuni* and *C. coli* isolates, the highest percentages of fluoroquinolone resistance were observed (Mason et al. 2017; Yamada et al. 2019).

In a study of the percentage of antibiotic resistance in isolates of *C. jejuni* and *C. coli* obtained from broiler cloaca from a farm in central Italy, Pergola et al. (2017) report an increasing prevalence of antibiotic resistance to fluoroquinolones, macrolides, and tetracyclines. In the corresponding number of samples (n = 116) the highest percentage of isolates was identified as *C. jejuni* (n = 99) and a slightly smaller number as *C. coli* (n = 41) which are common statistical differences. *Campylobacter jejuni* isolates showed the highest percentages of resistance to fluoroquinolones (39%), slightly less to tetracyclines (10%), and all other isolates of *C. jejuni* were resistant to macrolides. *Campylobacter coli* isolates showed the highest percentages of resistance to fluoroquinolones (70%), tetracyclines (70%) and slightly less to macrolides (30%).

Shobo et al. (2016) in the study of the prevalence and distribution of antibiotic resistance of *Campylobacter* spp. from a private health center in South Africa, using a molecular PCR method, identified 72 isolates of *Campylobacter* spp. of which 54 (75%) were identified as *C. jejuni* and *C. coli* 18 (25%). Isolates of *C. jejuni* and *C. coli* in the highest percentages showed resistance to fluoroquinolones: ciprofloxacin, in *C. jejuni* 11 (20.4%) and *C. coli* 6 (33.3%). Isolates of *C. jejuni* also showed resistance to macrolides: erythromycin 17 (31.5%) and azithromycin 36 (50%), and isolates of *C. coli* to erythromycin 7 (38.9%) and azithromycin 14 (77.8%). High

percentages of resistance are also evident for tetracyclines in isolates of *C. jejuni* 14 (25.9%) and isolates of *C. coli* 10 (55.6%). Recent research on the presence of South African isolates of *C. jejuni* and *C. coli* resistant to fluoroquinolones, macrolides and tetracyclines, raises concerns among scientists who call for the importance of the rational use of antibiotics.

Thomrongsuwannakij et al. (2017) in a study in Thailand, report the percentage of antibiotic resistance in isolates of *C. jejuni* and *C. coli* from broiler production, following two production chains, where the presence of most multidrug-resistant isolates (*C. jejuni*: 100%; *C. coli*: 98.9%). The highest antibiotic resistance was again recorded on fluoroquinolones: enrofloxacin which is exclusively a veterinary antibiotic, then on tetracyclines: tetracycline, sulfo preparations: trimethoprim-sulfamethoxazole and tetracyclines: doxycycline (*C. jejuni*: 100%, 55.6%, 36.1%, 50%; *C. coli*: 98.9%, 97.9%, 81.9%, 79%).

Research in India, Khan et al. (2018) report that the highest percentages of *C. jejuni* contamination were recorded on broiler carcass skin (38.6%) and intestines (24%), and the lowest on cutting boards and knives (14.0%). Antibiotic resistance was found in (97%) isolates of *C. jejuni*, and the highest percentages were recorded for cephalosporins: cephalothin (81.1%) and tetracyclines (59.4%). Lower percentages of antibiotic resistance are evident in first generation quinolones: nalidixic acid, cephalosporins: ciprofloxacin, macrolides: erythromycin, azithromycin and aminoglycosides: gentamicin (6.9-8.9%), which differs to a lesser extent from previous studies.

A review of the literature concludes that *C. jejuni* and *C. coli* are significant contaminants of broiler carcass skin, and that antibiotic resistance is a global public health problem (Hrustemović et al. 2021b). Antibiotic resistance in isolates of *C. jejuni* and *C. coli* is present in the highest percentages in fluoroquinolones, macrolides and tetracyclines used in human and veterinary medicine, which indicates the importance of monitoring and rational use of antibiotics (Collignon & McEwen 2019; Premaratne et al. 2017). Campylobacteriosis is a leading public health problem in Europe, the United States, Australia, New Zealand, but it is also present in Africa and Asia, but research is scarce (Baker et al. 2020; Collignon & McEwen 2019; Hanson et al. 2018). The first measure to control the spread of campylobacteriosis from broiler chicken meat to humans is laboratory detection of *C. jejuni* and *C. coli* and compliance with biosecurity measures in production to maintain microbiological/health safety of food, provide safe and quality food for consumers (Furmeg et al. 2020). Prevention includes GHP and GMP in the production of broiler chicken meat (Hrustemović et al. 2021b). The spread of antibiotic resistance of *C. jejuni* and *C.*

coli isolates through chicken meat can be mitigated by cessation of antibiotic use in prophylaxis as prescribed by European Union legislation, which is not the case in Bosnia and Herzegovina (Hrustemović et al. 2021b). Other options should be considered in improving the health safety of broiler chicken meat, which exclude the prophylactic use of antibiotics in broiler chickens. As a new prophylactic measure in maintaining the microbiological/health safety of broiler chicken meat, the use of *Lactobacillus* probiotics as biological preservatives is offered (Soltani et al. 2021).

CONCLUSIONS

Campylobacteriosis is the leading alimentary intoxication in Europe and the United States, and antibiotic resistance is a global public health problem. Prevention of campylobacteriosis includes sanitation in primary production, avoidance of cross-contamination, and use of probiotic bacteria as biological preservatives in food. The spread of antibiotic resistance to *C. jejuni* and *C. coli* from chicken meat is possible with the cessation of antibiotic use in prophylaxis in broilers.

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