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RESEARCH ARTICLE

Rise in *Campylobacter* species antimicrobial resistance in Split-Dalmatia County in a ten-year period

Dino Viduka[1, 2], Dina Mrčela[2], Merica Carev[2, 3, 4]

[1] University of Split, Faculty of Chemistry and Technology, Split, Croatia

[2] University of Split, School of Medicine, Split, Croatia

[3] University Department of Health Studies of the University of Split, Split, Croatia

[4] Teaching Institute for Public Health, Split-Dalmatia County, Split, Croatia

Correspondence to:
Merica Carev
Teaching Public Health Institute of Split and Dalmatia County, Vukovarska 46, 21000 Split, Croatia
mcarev3@gmail.com

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Aim: The aim of this study was to determine whether there are changes in *Campylobacter* species antimicrobial resistance, and epidemiological characteristics of campylobacteriosis in Split-Dalmatia County (SDC), Croatia, in 2021 compared to the period 2010-2012.

Methods: The data for this study were obtained from the database of the Teaching Public Health Institute of Split and Dalmatia County (TPHI SDC) Split, and they included all outpatients who have been diagnosed with *Campylobacter* spp. in their stool samples from January to December 2021. The study analyzed the frequency of infections caused by *Campylobacter* spp., their distribution according to age, gender, place of residence, and month of the year, as well as the antimicrobial resistance of *Campylobacter* spp. isolates.

Results: The total number of *Campylobacter* spp. stool isolates was 395, with the most common isolate being *Campylobacter jejuni* (365, 92.4%). *Campylobacter jejuni* isolates had high resistance to ciprofloxacin (74.8%), moderate resistance to tetracycline (21.2%) and co-resistance to tetracycline-ciprofloxacin (19.3%). The resistance rate to azithromycin was low (1.1%). Although *Campylobacter jejuni* isolates also showed low resistance to amoxicillin-clavulanate (5.3%), all *Campylobacter jejuni* strains resistant to amoxicillin-clavulanate were also multidrug-resistant to two or more tested antibiotics: ciprofloxacin and ceftriaxone (100%), tetracycline (15.8%), and azithromycin (5.3%). Epidemiological characteristics of campylobacteriosis in SDC in 2021 were similar to those from previous research in the same area.

Conclusions: The study revealed an increase in ciprofloxacin-resistant *Campylobacter jejuni* isolates in 2021, compared with findings from 2010 and 2012. However, the percentage of tetracycline-resistant and tetracycline-ciprofloxacin co-resistant isolates remained stable. Based on these results, azithromycin remains the drug of choice, but it is also possible to treat this infection with amoxicillin-clavulanate because of its low resistance rate.

Keywords: amoxicillin-clavulanate; antimicrobial resistance; azithromycin; campylobacteriosis; ciprofloxacin; epidemiology

Introduction

Campylobacteriosis is the most common foodborne infection worldwide. Its importance is enhanced by the chronic sequelae that can result from acute infection (*1*) and by its severe clinical outcomes. For example, *C. jejuni* can cause miscarriage or premature birth, perinatal sepsis, and neonatal meningitis in pregnant women. In addition, the disease is more severe and prolonged in immunocompromised patients, and bacteremia, extraintestinal rheumatologic, and neurologic complications are more common (*2*). The long-term consequences of campylobacteriosis can be very severe, including irritable bowel syndrome, reactive arthritis, bacteremia, and Guillain-Barré syndrome (*1*, *3*).

In a particularly severe case of campylobacteriosis, antimicrobial drugs should be included in therapy. The drug of choice is azithromycin, a macrolide antibiotic, or ciprofloxacin, a quinolone antibiotic (*2*). However, antibiotic-resistant *Campylobacter* spp. strains have rapidly emerged worldwide during the last decades and may be associated with treatment failure and prolonged disease duration (*4*, *5*).

The observed resistance rates for *Campylobacter* spp. vary across different regions. According to the studies, the lowest resistance rates were observed in Scandinavian countries (*6*) and Australia (*7*) as opposed to the highest ones in Asian countries (*8*, *9*) and Spain (*5*). International travel has been suggested to contribute to antimicrobial resistance in human *Campylobacter* strains, and an increased risk of infection with *Campylobacter*-resistant strains has been observed in certain tourist destinations (*10*). It is important to monitor the resistance of *Campylobacter* strains to antibiotics in the local environment because knowledge of antibiotic resistance is critical for selecting the appropriate treatment required in severe cases of the disease. This helps in selecting the most effective antibiotics and avoiding treatment failure. Given the rapid emergence of antibiotic-resistant *Campylobacter* spp. strains worldwide, alternative therapies are being investigated to treat the disease. However, their efficacy and reliability are not yet sufficient (*11*).

In this study, we aimed to determine the susceptibility of each *Campylobacter* spp. to antibiotics such as ciprofloxacin, erythromycin, azithromycin, tetracycline, gentamicin, amoxicillin-clavulanate and ceftriaxone. The number of double- and multidrug-resistant isolates isolated from stool samples of outpatients in Split-Dalmatia County (SDC) was also analyzed and compared with results from the same area in 2012 (*4*). As part of our study, we analyzed the epidemiological characteristics of campylobacteriosis in the SDC region in 2021 and compared our results with a previous study conducted in the same region in 2007-2012 (*12*). This can help to improve existing reporting systems, surveillance, and prevention of this disease (*12*).

Methods

Samples

Campylobacter spp. isolates were systematically collected from stool samples of all the outpatients with diarrhea in Split-Dalmatia County (SDC). The County encompasses 14 045 km^2, with a population of approximately 420.000 individuals, representing around 11% of the Croatian population, and is a popular tourist destination (*13*, *14*). Samples were sent from diverse locations throughout the County from January 2021 to December 2021 and analyzed at the Teaching Public Health Institute (TPHI) of Split and Dalmatia County.

The anonymized computer database of TPHI was used to collect patient data such as age, gender, and place of residence. Patients who had a residence in SDC were of both genders and all age groups, while repeated *Campylobacter* spp. isolates from the same patient (copy strains) were excluded. In total, 395 single-patient stool samples, each representing a unique *Campylobacter* spp. infection, were analyzed.

Ethical approval: In our study, bacterial isolates were obtained from routine and voluntary diagnostic procedures from patients at the Teaching Public Health Institute of Split-Dalmatia County. We also used an anonymized computer database with sociodemographic data of patients from the same Institute and therefore did not require ethical approval from the institution. Nevertheless, we adhered to the principles of the Declaration of Helsinki in our work.

Diagnostic procedure

Gram-stain method was used to prepare smears from the stool samples. Isolation of *Campylobacter* spp. from diarrheal stool samples was performed by primary plating of stool samples on selective Karmali agar (Oxoid Ltd, Altrincham, England) and incubation at 42°C during 48–72 h in a micro-aerobic atmosphere (Genbox Microaer; Oxoid Ltd, Altrincham, England). *Campylobacter* isolates with typical colonial and Gram stain morphology were identified at the species level using standard biochemical tests (oxidase test and the hippuric acid test). A positive oxidase test indicated the presence of the *Campylobacter* genus, while a positive hippuric acid hydrolysis reaction showed the presence of *C. jejuni*. For complete identification of hippurate-negative *Campylobacter jejuni* and other *Campylobacter* spp., ApiCampy test (bioMerieux, Marcy l'Etoile, France) was used. Finally, the strain was identified using the computer program "Api Lab" (bioMerieux, Marcy-l'Etoile, France).

Antimicrobial susceptibility testing

Antibiotic susceptibility testing was performed using the disc-diffusion method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (*15*). The guidelines specify the correlation between the susceptibility of the strain to certain antibiotics and the diameter size of the zone of inhibition of bacterial growth expressed in millimeters. Based on the the diameter size of the zone of inhibition, the tested strain is classified into one of three categories:

1. S – Susceptible, standard dosing regimen: A microorganism is categorized as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
2. I – Intermediate susceptible, increased exposure: A microorganism is categorized as "Susceptible, increased exposure" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
3. R – Resistant: A microorganism is categorized as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure (*15*).

In the present study, the authors conducted further antibiotic susceptibility testing for amoxicillin-clavulanate, gentamicin, and ceftriaxone, following the method of Schiaffino et al. (*16*). The results based on the diameter size of the zone of inhibition were then classified into one of the three antibiotic susceptibility categories and the criteria for it is presented in **Table 1**.

Table 1. Interpretation criteria of the antibiotic susceptibility test of *Campylobacter* spp. according to EUCAST and Schiaffino (*15*, *16*)

Tested antibiotic	Category of susceptibility to the tested antibiotic* and diameter of the zone of inhibition of bacterial growth (mm)		
	S≥	I	R≥
Amoxicillin-clavulanate (AUG)	18	14-17	13
Erythromycin, *C. jejuni* (E)	20		20
Erythromycin, *C. coli* (E)	24		24
Gentamicin (GM)	15	13-14	12
Tetracycline (T)	30		30
Ciprofloxacin (CIP)	50		26
Ceftriaxone (CRO)	23	20-22	21

* S=susceptible, I=intermediate susceptible R=resistant.

Susceptibility to azithromycin was determined based on the result for erythromycin, as both antibiotics have similar mechanisms of action (*15*).

Geographic distribution

Based on the population density and accessibility of the Cunty's main urban center, the City of Split, and 55 towns and municipalities were categorized as follows:

1. urban (>500 inhabitants per km^2, <5 km from Split city center),

2. suburban (150-500 inhabitants per km^2, 5-30 km from Split city center) and

3. rural (<150 inhabitants per km^2, >30 km from Split city center) (*12*):

Data analysis

Descriptive and inferential analytical methods were used for data analysis. Social Science Statistics (*17*) and VassarStats (*18*) statistical software were utilized for statistical analysis. Data were presented as frequencies and percentages, or medians with interquartile range (IQR). Significant differences between frequencies of campylobacteriosis with a 95% confidence interval (CI) according to age and gender, as well as differences in the rates of resistance of *Campylobacter* isolates to the antibiotics, were analyzed using the chi-square test and pairwise binomial post hoc test with Bonferroni adjustment. The significance level was set to α=0.001 (P<0.001).

Results

Characteristics of patients and distribution of species of Campylobacter genus

During the study period, 395 strains of *Campylobacter* spp. were isolated from diarrheal stool samples of outpatients in Split-Dalmatia County. 179 (45.3%) samples were from female and 216 (54.7%) were from male patients. There was no significant difference in the frequency of infections between genders (χ^2=6.93; P>0.001). The median age of the patients was 23 years (IQR=5 years, 43 years). The highest number of *Campylobacter* infections in SDC was recorded in the age group 0 to 4 years (n=93, 23.5%) and 20 to 29 years (n=63, 15.9%), while the least affected age group was 80 to 89 years (n=8, 2%).

The majority of infections were diagnosed during the seasonal peak of the disease, from May to October (n=192, 65.1%), with the peak in May (n=51, 12.9%). The lowest number of infections was recorded during the winter months from November to February (n=103, 34.9%).

Campylobacteriosis was more frequent in urban areas (n=332, 81.5%) compared with suburban (n=31, 8%) and rural (n=27, 6.9%) areas. The majority of infections were caused by *Campylobacter jejuni* (n=365, 92.4%), the remainder by *Campylobacter* spp. (24, 6.1%), *Campylobacter coli* (n=5, 1.3%) and *Campylobacter lari* (n=1, 0.2%)

Antibiotic susceptibility of the isolates

Out of the total 395 Campylobacter spp. stool isolates obtained in 2021 from outpatients in Split-Dalmatia County (SDC), antibiotic susceptibility testing was performed on 366 (92.7%) isolates. 29 (7.3%) isolates could not be tested due to insufficient microbiological culture growth or subcultivation failure. The results showed high resistance of *Campylobacter jejuni* isolates to ceftriaxone and ciprofloxacin, and moderate resistance to tetracycline. However, the resistance of *Campylobacter jejuni* isolates to erythromycin, azithromycin, gentamicin, and amoxicillin-clavulanate was very low, ranging from 1.1% to 5.3% (**Table 2** and **Table 3**).

Table 2. Antibiotic resistance of *Campylobacter jejuni* isolates in Split-Dalmatia county in 2021

Tested antibiotic	*Campylobacter jejuni* isolates resistant to antibiotics (n=358)	
	Number	%
Amyxycillin-clavulanate	19	5.3
Erythromycin	4	1.1
Azithromycin	4	1.1
Ciprofloxacin	268	74.9
Tetracycline	76	21.2
Gentamicin	7	2.0
Ceftriaxone	346	96.6

A small number of other *Campylobacter* spp. were isolated and tested. Results were as followed: the resistance rate of *Campylobacter coli* isolates to ciprofloxacin was 3/5 to ceftriaxone was 5/5 and to tetracycline was 2/5. The susceptibility of *Campylobacter coli* isolates to amoxicillin-clavulanate, erythromycin, azithromycin, and gentamicin was 5/5. *Campylobacter lari* also showed resistance to ciprofloxacin (1/1) and ceftriaxone (1/1), while it was susceptible to all other tested antibiotics (1/1). Similarly, other isolates of *Campylobacter* spp. showed resistance to ciprofloxacin (1/2) and ceftriaxone (2/2) and susceptibility to other tested antibiotics (2/2).

Table 3. Comparison of frequencies of *Campylobacter jejuni* isolates resistant to antibiotics in Split-Dalmatia Coiunty in 2021

	*P-values**						
Antibiotic	Amyxycillin-clavulanate	Erythromycin	Azithromycin	Ciprofloxacin	Tetracycline	Gentamicin	Ceftriaxone
Amyxycillin-clavulanate	/	0.055	0.055	<0.001	<0.001	0.608	<0.001
Erythromycin		/	1.000	<0.001	<0.001	0.549	<0.001
Azithromycin			/	<0.001	<0.001	0.549	<0.001
Ciprofloxacin				/	<0.001	<0.001	0.039
Tetracycline					/	<0.001	<0.001
Gentamicin						/	<0.001
Ceftriaxone							/

*Chi-squarepairwise binomial *post hoc* test with Bonferroni correction.

Double, triple, and multidrug-resistant isolates

The study found that among the *Campylobacter* isolates, there were 69 (19.3%) ciprofloxacin-tetracycline co-resistant strains (TcR/CipR) of *Campylobacter jejuni* and 2 (40%) of *Campylobacter coli*, as well as multidrug-resistant strains (resistant to three or more types of antibiotics) of *Campylobacter jejuni.*

Multidrug-resistant isolates were recorded only among *Campylobacter jejuni* isolates, with 19 (5.3%) isolates being multidrug-resistant with resistance to amoxicillin-clavulanate, while 7 isolates (2%) were multidrug-resistant with resistance to gentamicin. Out of a total of 358 *C. jejuni* isolates, the number of isolates resistant to amoxicillin-clavulanate, ciprofloxacin, and ceftriaxone was 15 (4.2%), while the number of isolates resistant to amoxicillin-clavulanate, ciprofloxacin, ceftriaxone and tetracycline was 3 (0.8%), and the number of isolates resistant to amoxicillin-clavulanate, ciprofloxacin, ceftriaxone, erythromycin, and azithromycin was 1 (0.3%). In total, all 19 amoxicillin–clavulanate-resistant *C. jejuni* isolates were resistant to ciprofloxacin and ceftriaxone (100%), 3 such isolates were resistant to tetracycline (15.8%), and 1 was resistant to erythromycin (5.3%) (*13*).

The number of *C. jejuni* isolates resistant to gentamicin, ciprofloxacin, and ceftriaxone was 4 (1.1%), one isolate was simultaneously resistant to gentamicin, ciprofloxacin, ceftriaxone, and tetracycline (0.3%), one to gentamicin, erythromycin, and azithromycin (0.3%) and one to gentamicin, ciprofloxacin, ceftriaxone, erythromycin, and azithromycin (0.3%) (*13*).

Discussion

According to our data, the number of *Campylobacter jejuni* isolates resistant to ciprofloxacin significantly increased in SDC in 2021 compared to previous study conducted in the same area in 2010 (*19*), and in 2012/2013 (*4*). This increase in resistance is consistent with the trend observed in nine EU countries, where a decrease in susceptibility to ciprofloxacin was reported (*5*).

However, we found no significant increase in *Campylobacter* resistance to tetracycline and ciprofloxacin-tetracycline co-resistance in 2021 compared with results from 2012/2013 (*4*).

The number of *Campylobacter jejuni* isolates that were triple-resistant to tetracycline, ciprofloxacin, and erythromycin was low, similar to findings from 2012/2013 (*4*). However, in this study, for the first time in Split-Dalmatia County, multidrug-resistant isolates of *Campylobacter jejuni* were detected, including resistance to ceftriaxone and gentamicin. It seems that this was not accompanied by increased antibiotic consumption in humans. According to the Croatian Committee for Antibiotic Resistance Surveillance Report, in 2020, antibiotic consumption among outpatients in Croatia, representing 92% of total antibiotic consumption, was the lowest in 2020 since antibiotic consumption monitoring began in 2001 (*20*). These observations do not support the hypothesis that antibiotic consumption in humans is the predominant factor contributing to the emergence of antibiotic resistance in human isolates. On the contrary, studies of the genetic attributes of campylobacteriosis in humans have indicated that food animals may contribute to global transmission networks for human *Campylobacter* spp. (*4*, *21*) and thus may affect local resistance rates. Patterns of antibiotic use and the resulting selection of resistance in one part of the world are now spreading globally through the international food trade chain and international travel (*22*), which has intensified in Split-Dalmatia County (SDC) over the past decade. Research on the resistance of *Campylobacter* isolates from poultry was conducted in the Republic of Croatia (*23*) and proved the high resistance of these isolates to antibiotics. In contrast, the lowest rates of antibiotic resistance were found in countries where a restric-

tive approach to antibiotic use in animal husbandry was introduced (*24*). To draw more reliable conclusions about a causal relationship between antibiotic use in food animals and the prevalence of drug-resistant foodborne campylobacteriosis in humans, it is necessary to monitor antibiotic use in veterinary medicine and to perform molecular analyses to determine the relationship between resistant isolates and their sources in reservoirs and the local environment.

We found that only 5.3% of *Campylobacter jejuni* strains were resistant to amoxicillin-clavulanate. This is somewhat different from the study by Schiaffino and colleagues (*16*), in which the resistance rate to amoxicillin-clavulanate was only 0.7%. However, the resistance rate of 5.3% should still be considered low. Interestingly, all *Campylobacter jejuni* strains that were resistant to amoxicillin-clavulanate were also resistant to two or more other antibiotics. However, the relatively low resistance rate of *Campylobacter* to this antibiotic (5.3%) makes it a potential therapeutic choice in the treatment of certain cases of campylobacteriosis. We have found that resistance of *Campylobacter jejuni* to antibiotics from the macrolide group, such as erythromycin or azithromycin, is very low, so azithromycin remains the drug of choice for severe cases of campylobacteriosis. In cases where patients cannot receive azithromycin because of resistance or other clinical indications, amoxicillin-clavulanate may be a possible alternative.

A limitation of this study is that the susceptibility of *non-jejuni Campylobacter* spp., *Campylobacter lari,* and *Campylobacter coli* to antibiotics was tested on only a small number of isolates, which does not allow a definitive conclusion about their susceptibility to antibiotics.

The distribution of patients with *Campylobacter* infections according to age and months of the year did not differ from the epidemiological characteristics of campylobacteriosis in the same area in 2007-2012 (*12*). Our results showed a significant difference between the number of patients in urban, suburban, and rural areas of the region, the prevalence of the disease in younger age groups and in the warmer season. These results confirm that the epidemiological characteristics of campylobacteriosis in SDC still correspond to those of developed countries with a temperate climate (*12*).

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ORCID

Dina Mrčela https://orcid.org/0000-0001-7610-4891

Merica Carev https://orcid.org/0000-0002-5260-6106

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