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ORIGINAL ARTICLE

Human *Campylobacter* spp. infections in Italy

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Abstract
Purpose *Campylobacter* is a frequent cause of enteric infections with common antimicrobial resistance issues. The most recent reports of campylobacteriosis in Italy include data from 2013 to 2016. We aimed to provide national epidemiological and microbiological data on human *Campylobacter* infections in Italy during the period 2017–2021.
Methods Data was collected from 19 Hospitals in 13 Italian Regions. Bacterial identification was performed by mass spectrometry. Antibiograms were determined with Etest or Kirby-Bauer (EUCAST criteria).
Results In total, 5419 isolations of *Campylobacter* spp. were performed. The most common species were *C. jejuni* (n = 4535, 83.7%), followed by *C. coli* (n = 732, 13.5%) and *C. fetus* (n = 34, 0.6%). The mean age of patients was 34.61 years and 57.1% were males. Outpatients accounted for 54% of the cases detected. *Campylobacter* were isolated from faeces in 97.3% of cases and in 2.7% from blood. *C. fetus* was mostly isolated from blood (88.2% of cases). We tested for antimicrobial susceptibility 4627 isolates (85.4%). Resistance to ciprofloxacin and tetracyclines was 75.5% and 54.8%, respectively; resistance to erythromycin was 4.8%; clarithromycin 2% and azithromycin 2%. 50% of *C. jejuni* and *C. coli* were resistant to ≥ 2 antibiotics. Over the study period, resistance to ciprofloxacin and tetracyclines significantly decreased ($p < 0.005$), while resistance to macrolides remained stable.
Conclusion *Campylobacter* resistance to fluoroquinolones and tetracyclines in Italy is decreasing but is still high, while macrolides retain good activity.

Keywords (6): *Campylobacter* spp · Antimicrobial resistance · Multidrug-resistant · Italy · Surveillance · *Campylobacter jejuni*

Introduction

Campylobacter spp. are a common cause of acute enteric infections in humans. In immunocompromised or elderly patients, *Campylobacter* spp. rarely causes extraintestinal infections (e.g. bacteraemia, abscess, meningitis). Patients with campylobacteriosis can develop post-infectious complications (e.g. Guillain–Barré syndrome, reactive arthritis, irritable bowel syndrome) [1].

Campylobacteriosis is a zoonotic diseases. The primary route of transmission to humans is the consumption of contaminated food and water. Poultry is the most important reservoir of *Campylobacter* spp., but cattle, domestic animals and swine can also be involved [2]. *Campylobacter* spp. can also cause a range of infections in animals [3].

C. jejuni is the most relevant species and the first cause of gastroenteritis worldwide in humans [3, 4]. *C. jejuni* is

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followed by *C. coli*, which causes 1 to 25% of all *Campylobacter*-related diarrhoeal diseases. *C. fetus* is another relevant species that includes three subspecies: *C. fetus* subsp. *fetus*, *C. fetus* subsp. *venerealis*, *C. fetus* subsp. *testudinum.* The first one is typically involved in human disease, the other two are predominantly isolated in cattle and reptiles, respectively, and only sporadically in humans [3].

Other *Campylobacter* species are emerging as causes of human infections. Among these we include: *C. hyointestinalis*, *C. upsaliensis, and C. ureolyticus*. *C. hepaticus* is an emerging species of campylobacteriosis in poultry [3].

According to the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC), campylobacteriosis has been the most commonly reported zoonosis in Europe, since 2005. In 2021, 127.840 cases of campylobacteriosis were notified to the ECDC, accounting for more than 62% of all zoonoses reported in Europe [5].

Campylobacter spp. acute gastroenteritis cases are largely self-limited and patients tend to recover without antimicrobial treatment [1]. According to Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and management of infectious diarrhea, empiric antibacterial treatment is not generally recommended in case of diarrhea, except for a few conditions (infants < 3 months of age, suspicion of enteric fever, immunocompromised people, severe illness) [6]. No specific international guidelines are present for campylobacteriosis management and treatment. However, the most used antimicrobials are: fluoroquinolones, macrolides and tetracycline. *C. fetus* infections are generally treated with parenteral antibiotics, particularly aminoglycosides and/or carbapenems [7]**.**

Antimicrobial resistance in *Campylobacter* spp. is increasing worldwide [8]. Fluoroquinolone-resistant *Campylobacter* spp. is listed by the World Health Organization (WHO) among high priority pathogens for research and development of new antibiotics [9]. In 2021 ECDC reported high resistance to fluoroquinolones (65% for *C. jejuni* and 70% for *C. coli*) and tetracycline (70% for both *C. jejuni* and *C. coli*). Macrolides still retain good activity against *Campylobacter* spp. (1% resistance for *C. jejuni* and 9% for *C. coli*) [10].

Campylobacteriosis notification in Italy was voluntary till 2022, so a comprehensive surveillance is not provided on the last EFSA-ECDC report [5]. The last large national data of campylobacteriosis in Italy was published through the Enter-Net Italia data of the period 2013–2016 [11]. However, additional Italian data relating solely to *C. jejuni,* have been recently published, showing high levels of resistance to ciprofloxacin and tetracycline, not only in humans but also in domestic and wild animals [12].

Therefore, the main aim of this study was to provide national epidemiological and microbiological data on *Campylobacter* spp. infections in humans during the period 2017–2021. In addition, antibiotic resistance trends during the same period were analysed as secondary aim.

Materials and methods

Study design and data collection

The study was a five-year multicentric retrospective observational study (January 2017—December 2021) including all consecutive isolates of *Campylobacter* spp. isolated from blood and/or stool cultures from 19 participating Italian hospitals (located in 13 Regions). Two centers provided data on consecutive strains of *Campylobacter* spp. isolated only from blood cultures.

For 17 centers the total amount of stool cultures performed for testing *Campylobacter* spp. over the five-year period of study were collected. For 15 centers we additionally collected the amount of stool cultures performed for testing *Salmonella* spp. In both cases we calculated the percentage of positive stool cultures.

For each isolate collected: age and gender of the patient, date of isolation, site of isolation (blood or stool samples), setting of isolation (outpatient, medical wards, emergency departments, surgical wards, intensive care units), species of *Campylobacter*, susceptibility tests performed, and rate of resistance were recorded. Subsequent isolation of a same organism from the same patient was considered a novel episode only if isolated at least 30 days after the previous isolation.

Campylobacter isolation was performed on selective agar plates at 42 °C under microaerophilic conditions for 48 h of incubation in all centers. Either Campylobacter Agar with 10% Sheep Blood or Campylobacter Agar Bloodfree Selective Medium has been used. In addition, three centers performed the stool filtration method for bacterial separation on blood agar plates.

Bacterial identification was performed by mass spectrometry in all centers.

Antimicrobial susceptibility testing was performed with Etest in 11 hospitals and with Kirby-Bauer method in 7 hospitals (1 center used both methods), following the indications of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

EUCAST criteria [13] have been used in all centers for the interpretation of antimicrobial susceptibility testing. As suggested by EUCAST, tetracycline was used to determine susceptibility to doxycycline and erythromycin was used to determine susceptibility both to azithromycin and clarithromycin.

Susceptibility data were available for macrolides (erythromycin, clarithromycin, azithromycin) ciprofloxacin, tetracycline, meropenem, and gentamicin. For gentamicin and meropenem, EUCAST PK/PD (non-species related) breakpoints were used.

We defined multidrug-resistant (MDR) those strains with acquired non-susceptibility to at least one agent in three or more antimicrobial categories.

Data analysis

The continuous variables were described as means and standard deviation (SD). The nominal variables were described as a number and percentage, and analysed with contingency tables and the chi-square test. Statistical analysis was performed to evaluate the trends in prevalence of antimicrobial resistance over the study period, overall and for the most prevalent species. The prevalence of antimicrobial resistance was calculated as the number of resistant isolates divided by the total number of tested isolates. Only antibiotics tested against at least ten isolates per year were considered for the analysis. The difference in resistance rate to different antimicrobial agents over the study years was analysed through the Mantel–Haenszel test for trend in proportions (linear-by-linear association). For all tests, the statistical significance was set at an alpha level of $p < 0.05$. Statistical analyses were performed using the software SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY).

Ethics

The study was approved by the Ethics Committee of Trieste University (n°V132_2806_23), in agreement with the Declaration of Helsinki (1964) and its later amendments.

Results

A total of 5419 isolates of *Campylobacter* spp. were collected. *Campylobacter* spp. were isolated from faeces (n = 5271, 97.3%) and blood (n = 144, 2.7%). We excluded from the analysis 4 isolations from other sites: 3 from abdominal abscesses (2 *C. jejuni* and one *C. fetus*), and one *C. fetus* from synovial fluid. The final analysis was performed on 5415 isolates.

The most frequently isolated species was *C. jejuni* (n = 4535, 83.7%), followed by *C. coli* (n = 732, 13.5%) and *C. fetus* (n = 34, 0.6%). In 22 cases another species was identified (21 *C. upsaliensis* and one *C. hyointestinalis*), while for 92 cases no typing was made.

The mean age of patients was 34.61 years (± 27.9), 57.1% (n = 2807) of patients were males. 35.1% of cases were found in the age group 0–16 years (n = 1900), 44.1% between 17 and 64 years (n = 2387), 20.8% over 65 years (n = 1128).

For 11 patients, a concomitant isolation from blood and stool samples was recorded. Isolations from blood cultures have been reported in 53.5% of cases in patients ≥ 65 years. *C. fetus* was isolated from blood cultures in 88.2% of cases. Characteristics of patients in addition to the setting type are shown in Table 1.

Table 1 Characteristic of patients

	All species n = 5415	*C. jejuni* n = 4535	*C. coli* n = 732	*C. fetus* n = 34	Other species n = 114	p-value
Patient's age (years)						< 0.001
0–16	1900 (35.1%)	1661 (36.6%)	199 (27.2%)	0 (0%)	40 (35.1%)	
17–64	2387 (44.1%)	1975 (43.6%)	352 (48.1%)	12 (35.3%)	48 (42.1%)	
≥ 65	1128 (20.8%)	899 (19.8%)	181 (24.7%)	22 (64.7%)	26 (22.8%)	
Patient's gender						0.054
Female	2323 (42.9%)	1913 (42.2%)	348 (47.6%)	12 (35.3%)	49 (42.7%)	
Male	3092 (57.1%)	2622(57.8%)	384 (52.4%)	22 (64.7%)	65 (57.3%)	
Samples						< 0.001
Blood cultures	144 (2.7%)	101 (2.2%)	9 (1.2%)	30 (88.2%)	4 (3.5%)	
Stool cultures	5271 (97.3%)	4434 (97.8%)	723 (98.8%)	4 (11.8%)	110 (96.5%)	
Setting of diagnosis						< 0.001
Outpatients	2931 (54.1%)	2447 (54%)	398 (54.4%)	4 (11.8%)	82 (71.9%)	
Accident & Emergency	593 (11%)	531 (11.7%)	53 (7.2%)	6 (17.6%)	3 (2.6%)	
Inpatients (Medicine)	1732 (32%)	1431 (31.6%)	259 (35.4%)	20 (58.8%)	22 (19.3%)	
Inpatients (Surgery)	138 (2.5%)	110 (2.4%)	18 (2.5%)	4 (11.8%)	6 (5.3%)	
Inpatients (Intensive Care Unit)	21 (0.4%)	16 (0.4%)	4 (0.5%)	0 (0%)	1 (0.9%)	

Campylobacter spp. isolation showed a summer peak, with an average of 35% of all the annual cases reported in the June–August trimester (Fig. 1).

A total of 4627 strains (85.4%) were tested for antimicrobial susceptibility. The most common tested antibiotics were: erythromycin (n = 4566, 98.7%), ciprofloxacin (n = 4409, 95.3%), tetracycline (n = 4396, 95.0%), clarithromycin (n = 698, 15.1%), and azithromycin (n = 666, 14.39%). Meropenem and gentamicin were tested in less isolates (in 248 and 31 cases, respectively), most of the time in case of multiple resistances to common drugs (Fig. 2).

Considering all *Campylobacter* species, resistance to ciprofloxacin and tetracycline was reported in 75.5% and 54.8% of cases, respectively, while a low rate of resistance was documented for erythromycin (4.8%), gentamicin (3.6%), clarithromycin and azithromycin (both 2%), and meropenem (0%). Figure 2 shows antibiotic resistance profiles according to *Campylobacter* species. For *C. jejuni* a higher resistance to ciprofloxacin was observed when compared to *C. coli*, whereas, *C. coli* showed higher resistance to tetracycline and macrolides, when compared to *C. jejuni.*

We observed, for both *C. jejuni* and *C. coli*, at least a double antimicrobial resistance in approximately 50% of cases. We observed MDR strains for 17.1% of *C. coli* and only for a minimal percentage of *C. jejuni* (0.9%) (Fig. 3).

Considering all species, a statistically significant decrease in ciprofloxacin and tetracycline resistance rate over the study period was documented. Resistance to macrolides

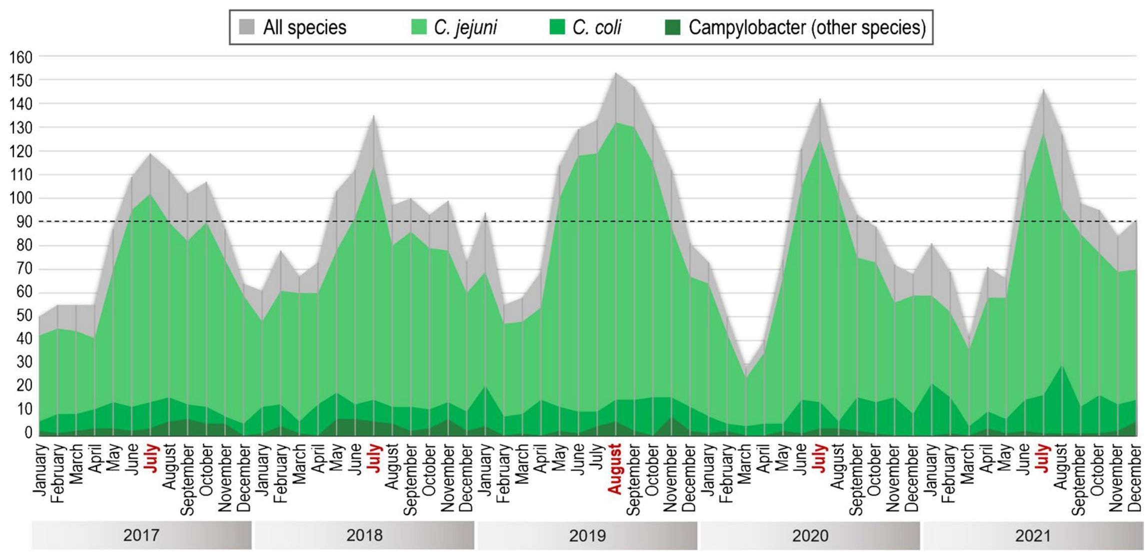

Fig. 1 Month-by-month prevalence of *Campylobacter* infections during the study period. Dashed black line: overall median prevalence (all species). Bold red text: months with the higher annual prevalence

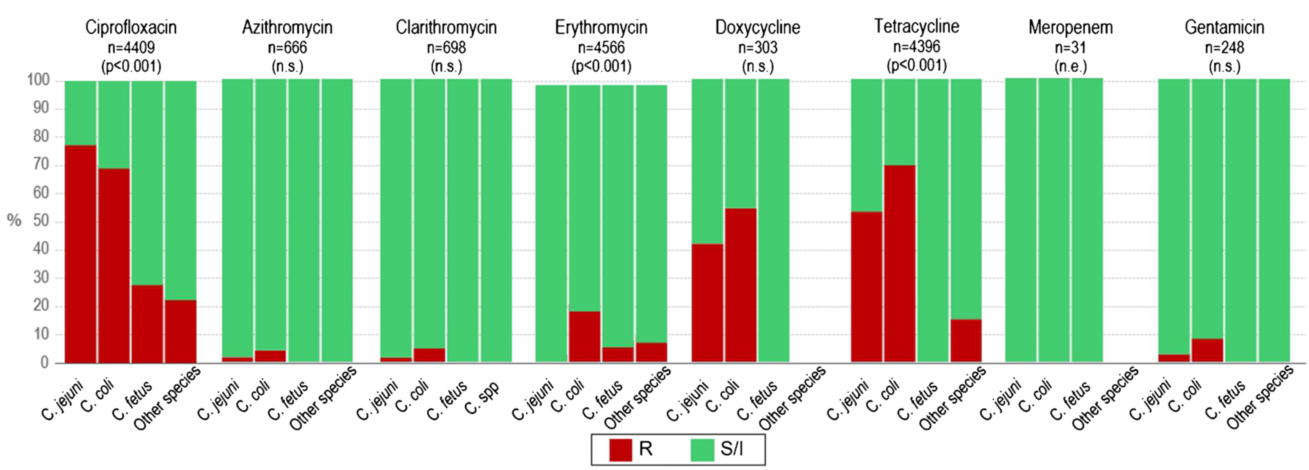

Fig. 2 Antibiotic resistance profiles according to *Campylobacter* species. n.s.: not statistically significant. n.e.: not evaluable. S: susceptible. I: susceptible at increased exposure. R: resistant

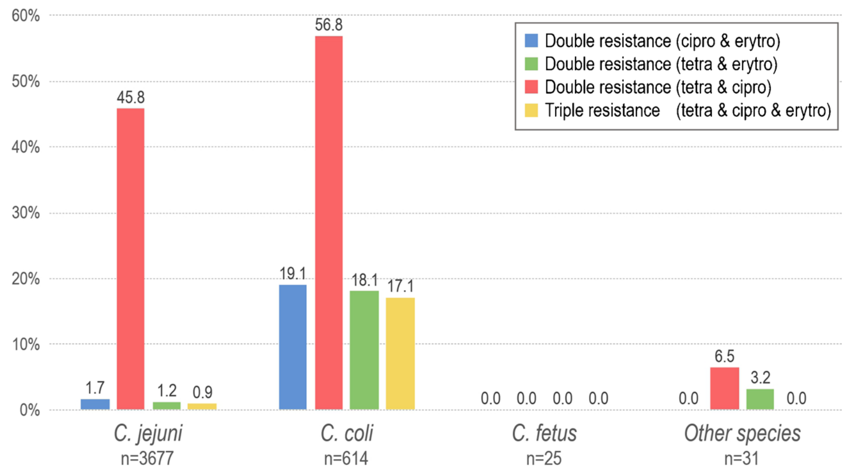

Fig. 3 Rate of multiple antimicrobial resistance — ciprofloxacin, tetracycline and erythromycin alongside (n = 4347)

generally remained stable over the years, except for erythromycin, which showed a slight significant decrease in resistance trend (Fig. 4A). This has been reported specifically also for *C. coli*. Moreover, we observed a statistically significant decrease in double and multidrug resistances both for *C. jejuni* and *C. coli* (Fig. 4B).

We studied the distribution of available minimum inhibitory concentration (MIC) values for ciprofloxacin, tetracycline, and erythromycin. The distribution of MIC values was similar between *C. jejuni* and *C. coli* for all three considered antibiotics (Fig. 5).

Considering all stool cultures performed for testing *Campylobacter* spp. (253.454), 2.1% were positive. For 15 centers we additionally collected the amount of *Salmonella* spp. isolations on stool culture. Of the total amount of stool cultures performed for testing *Salmonella* spp. (241.467), 2.5% were positive.

Discussion

In the present study, *C. jejuni* was the most prevalent species, followed by *C. coli* and *C. fetus*. The relative between-species prevalence was uniform over the study period. This finding is unsurprising, as previously documented by the latest European [10] and Italian reports [11].

The mean age of patients was 34.61 years (± 27.9). Most patients were adults, one third were pediatrics patients, and 20% were over 65 years. *C. jejuni* prevailed in pediatric age, and *C. coli* in adults, in line with previous findings [14]. Elderly age is a well known risk factor for *C. fetus* infections [15]. Considering all *C. fetus* infections, more than half of cases were reported in the elderly population.

Higher rates of infection in male have been observed in Europe, with a male-to-female ratio of 1.2:1, reported in the last ECDC report [10]. Similarly, in our study, 57% of patients were males. This is also consistent with previous Italian surveillance of 2013–2016 [11]. In our study, males account for the majority of patients in all three age groups considered. Other studies reported higher prevalence in females in their twenties because of childcare activities' involvement [16]. Also considering the age group 20–30 years, males were more represented in our work. Over the years, various hypotheses have been formulated to justify the excess of cases in males. Occupational [17] or sexual habits [18] prevail among them all. A recent meta-analysis has revealed that male predominance in campylobacteriosis begins in childhood [19]. Genetic and immunological differences, not yet fully understood, are likely to be involved.

With regards to the setting, more than half of cases were detected in outpatients, while among hospitalised patients almost 70% was documented in medical wards (Table 1). To the best of our knowledge, our study is the first that provides data about the setting of campylobacteriosis diagnosis.

In our study, the vast majority of *Campylobacter* isolates were obtained from faeces (97.3%). Among the positive blood cultures (2.7% of total isolates), *C. fetus* was identified in nearly 90% of cases. This finding is consistent with previous research [20], while more recent studies did not show this trend, with *C. jejuni* [21, 22] or *C. coli* [23] causing most of the bloodstream infections (BSI). Immunocompromised and elderly patients are at high risk of *Campylobacter* BSI [22]. We observed *Campylobacter* bacteraemia in more than half of cases (53.5%) in patients ≥ 65 years. Unfortunately, we did not collect data on the immune status of the patients.

Among the Italian centers participating in this epidemiological survey, a constant, reproducible seasonal trend in campylobacteriosis has been documented, with a clear peak of prevalence during the summer season and the lower rate of cases between winter and spring (Fig. 1). For the period 2013–2016, in Italy, 45% of the annual cases were reported in the trimester June–August [11]. This seasonality was also described in Europe during the last years of surveillance

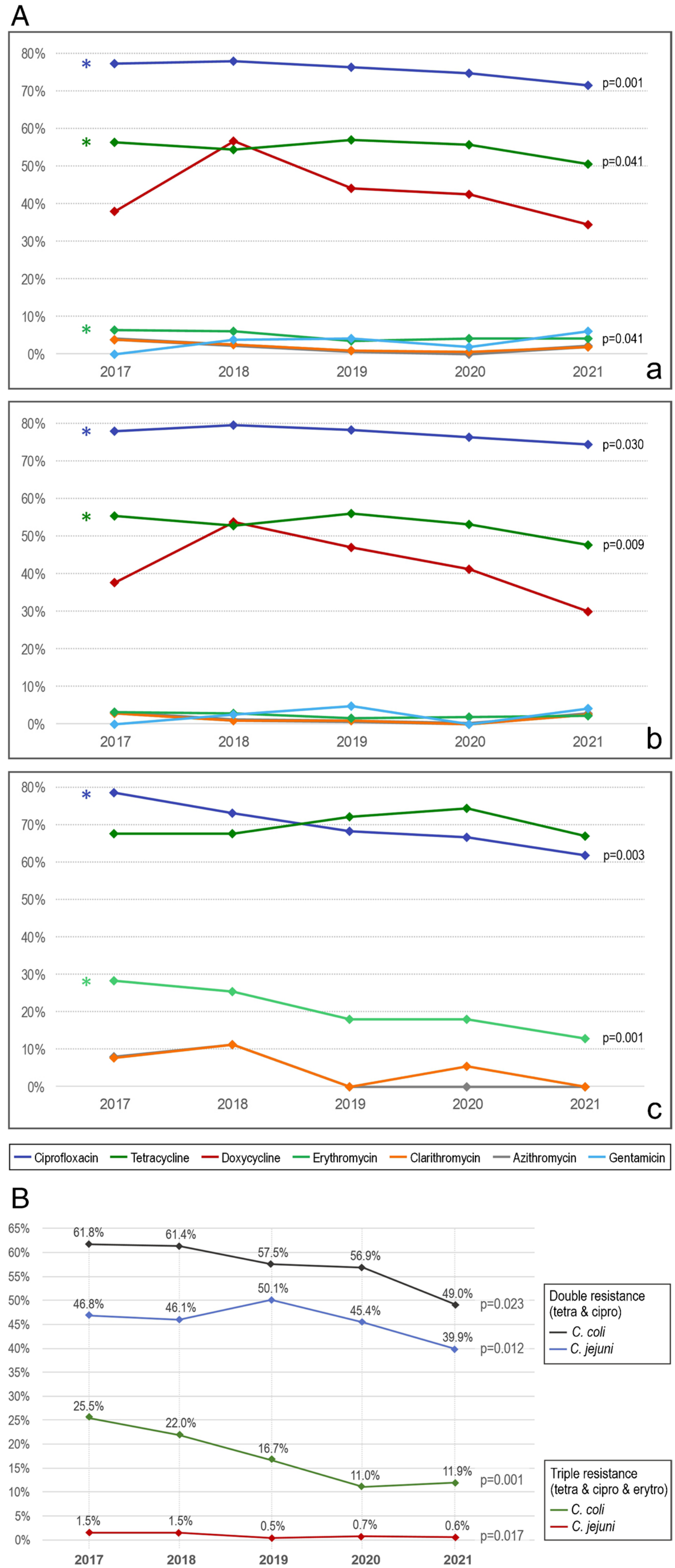

Fig. 4 **A** Trends in antimicrobial resistance over the study period (a: all species; b: *C. jejuni*; c: *C. coli*). Asterisks: statistically significant differences in trend. **B** Trends of double and multidrug resistances over the study period. Asterisks: statistically significant differences in trend

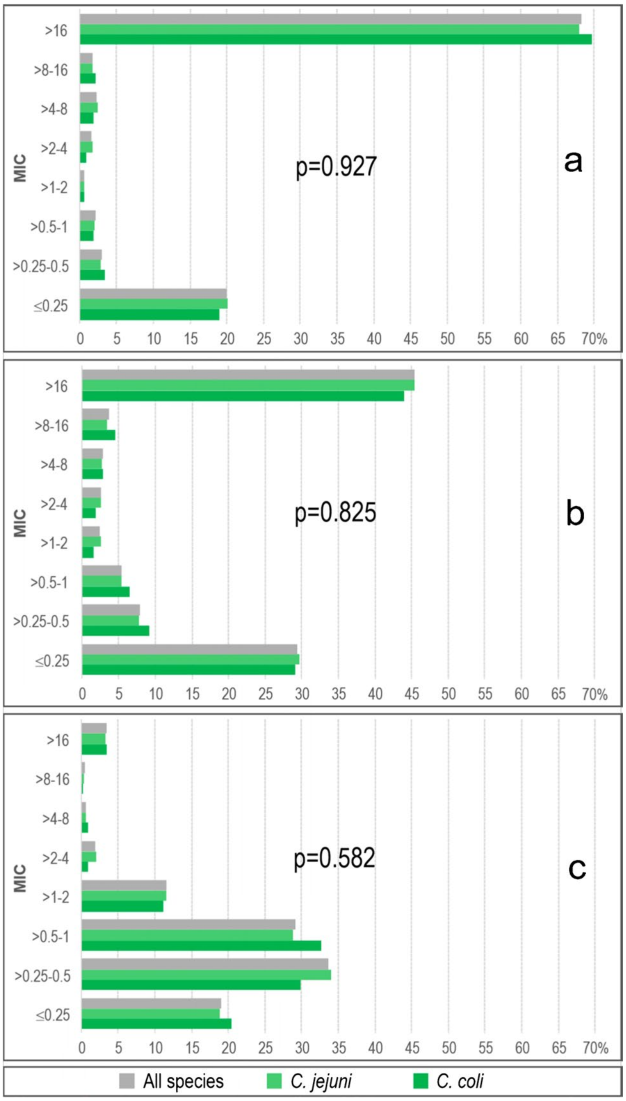

Fig. 5 MIC values for (**a**) ciprofloxacin (n = 2274), (**b**) tetracycline (n = 2222) and (**c**) erythromycin (n = 2242). p-values: comparisons between *C. jejuni* and *C. coli*

[10]. As expected, a drop of new cases was observed in the first months of 2020, probably due to the SARS-CoV-2 pandemic. In 2021 the number of cases started to increase again (Fig. 1).

The secondary aim of this study was to investigate the antimicrobial susceptibility of *Campylobacter* spp. and its trend over the period 2017–2021.

Considering all species, resistance to ciprofloxacin and tetracycline was reported in 76% and 55% of cases, respectively, while macrolides showed, generally, better activity (resistance rates: erythromycin 4.8%; clarithromycin and azithromycin: 2%), as well as gentamicin and meropenem (resistance rates of 3.6% and 0%, respectively). *C. jejuni* was more resistant to ciprofloxacin than *C. coli* (Fig. 2), showing similar percentages of resistance when compared to the previous Italian surveillance (resistance to ciprofloxacin of 76% in *C. jejuni* and in 70% of *C. coli*) [11]. However, the last European data indicated *C. coli* as more resistant to fluoroquinolones than *C. jejuni* (70% vs 65%) [10]. Resistance to tetracycline was higher in *C. coli* than *C. jejuni* (Fig. 2) in our study, while the average percentage of resistance in Europe is 70% for both species [10]. *C. coli* was more resistant to macrolides than *C. jejuni*, especially as regarding erythromycin. This is consistent with the last European ECDC report (resistance to macrolides of 1% for *C. jejuni* and 9% for *C. coli*) [10].

Additionally, we observed at least a double antimicrobial resistance in approximately 50% of *C. jejuni* and *C. coli* cases. The most common resistance pattern was ciprofloxacin-tetracycline, both for *C. jejuni* and for *C. coli* (in 45.8% and 56.8% of cases, respectively). We also observed MDR strains. For *C. coli* the resistance pattern ciprofloxacin-tetracycline-erythromycin was present in 17.1% of isolates, showing a lower prevalence when compared to the previous Italian surveillance (36.6%) [11].

Over the study period, considering all *Campylobacter* species, we reported a statistically significant decrease of resistance percentages for ciprofloxacin, tetracycline, and erythromycin (Fig. 4A). Regarding double and multidrug resistances we recorded significantly decreasing trends both for *C. jejuni* and *C. coli* (Fig. 4B). As stated by ECDC, this downward trend is reported only in a few European Countries, while for the others the percentages of resistance are substantially stable during the last years [10]. Simultaneously, during the same years in Italy, a slow but gradual decline has been recorded in the use of antibiotics not only in humans, dropping from 21.4 defined daily dose (DDD)/1000 inhabitants per day in 2018 to 17.1 DDD/1000 inhabitants per day in 2021 [24], but also in food-producing animals [25]. The study had some limitations. Firstly, the study did not include data equally distributed between Italian regions. In fact, 12 hospitals of our surveillance were located in the northern region, four in the central regions and only 3 in the South. Moreover, two centers provided data only about *Campylobacter* bacteraemia. Secondly, in the case of gastroenteritis, often *Campylobacter* spp. is not investigated, so probably the data underestimates the prevalence of Italian campylobacteriosis. The introduction of multiplex nucleic acid amplification tests is helping to increase the number of *Campylobacter* diagnoses [26], leading in the near future to a change in the epidemiology of these infections. Moreover, the diagnosis of *Campylobacter* could potentially be more efficient in terms of both time and materials for laboratories. Thirdly, the incubation temperature (42 °C) for the isolates was not suitable for certain species, such as *C. fetus* and *C. upsaliensis* [7]; hence, these cases may have been underestimated. Fourthly, different methods were used for the *Campylobacter* antimicrobial susceptibility testing. Finally, no Whole Genome Sequencing was performed. In the future this could lead to a detailed analysis of the molecular mechanisms of resistance and the genetic phylogeny of our *Campylobacter* spp. collection.

Conclusions

Our study confirms that antimicrobial resistance in *Campylobacter* spp. is a major problem in Italy and a threat to public health. The percentages of resistance to fluoroquinolones and tetracyclines are high, while macrolides maintain good antimicrobial activity in vitro. This study represents a useful resource to guide clinicians in empiric therapy.

Authors' contributions SDB and LP conceived the idea of and designed the study with VZ; SA, SA, RA, MB, AB, GB, MB, GC, DC, AC, NC, EC, CC, GC, AC, VC, VC, MDS, SD, BF, EG, FG, NM, AEM, AM, DM, RM, CM, AM, GM, AM, GN, EP, EMP, SP, MS, AS, DT and CV contributed to investigation and data collection; GS, RP and VZ analysed the data; VZ wrote the first draft; SDB, LP, VZ, RP, AGF, LV, RMLR, CF and GS contributed to the interpretation of the data, writing and reviewing of the first draft of the manuscript. All authors reviewed and commented on subsequent versions of the manuscript. All authors approved the submitted version of the manuscript.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The planning, conduct and reporting of this study was in line with the Declaration of Helsinki. The study was approved by the Trieste University Ethical Committee (n°V132_2806_23). Consent to participate was assessed according to the Ethical Committee.

Consent to publish Not applicable.

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

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