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Trends in Antimicrobial Resistance of Campylobacter Infections--United States, 2005-2017

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TRENDS IN ANTIMICROBIAL RESISTANCE OF *CAMPYLOBACTER* INFECTIONS – UNITED STATES, 2005-2017

By

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TRENDS IN ANTIMICROBIAL RESISTANCE OF *CAMPYLOBACTER* INFECTIONS – UNITED STATES, 2005-2017

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Abstract

Introduction

Campylobacteriosis, the most common bacterial foodborne illness, infects approximately 1.3 million people in the United States each year. Some *Campylobacter* infections have antimicrobial resistance to ciprofloxacin and erythromycin, which is a threat to public health given that physicians typically treat severe illnesses with these antimicrobial agents.

Aims

The objective of this study is to evaluate the change in incidence of *Campylobacter* over time and describe the trends in resistance to clinically significant antibiotics, including ciprofloxacin and erythromycin. This study will also compare hospitalizations and deaths among patients by resistance to clinically significant antibiotics.

Methods

A secondary analysis was performed using data from two Centers for Disease Control and Prevention (CDC) surveillance systems: Foodborne Diseases Active Surveillance (FoodNet) and National Antimicrobial Resistance Monitoring System (NARMS). We calculated the incidence of *Campylobacter* overall and by demographic characteristics for each year and compared resistance to ciprofloxacin and erythromycin in 2005 – 2012 and 2013 – 2017. Chi-Square and Fisher's Exact tests were used to test differences in resistance over time by demographic characteristics and travel history. Lastly, we assessed health outcomes (hospitalizations and deaths) by antimicrobial susceptibility during 2005 – 2012 and 2013 – 2017.

Results

During 2005 – 2017, incidence among culture-confirmed *Campylobacter* infections did not change substantially (12.71/100,000 persons in 2005 and 12.25/100,000 persons in 2017). The highest incidence was found in children younger than 5 years old: 25.24/100,000 persons in 2005 – 2008, 25.47/100,000 persons in 2009 – 2012, 21.92/100,000 persons in 2013 – 2016, and 19.75/100,000 persons in 2017. Notably, males had a higher incidence compared to females across all years. Resistance to ciprofloxacin increased from 24% in 2005 – 2012 to 27% in 2013 – 2017, and resistance to erythromycin increased from 2% in 2005 – 2012 and 3% in 2013 – 2017. Hospitalization was less likely in ciprofloxacin- and erythromycin-resistant cases than in ciprofloxacin- and erythromycin-susceptible cases, and results showed that only 1% of cases died due to infection, irrespective of antimicrobial susceptibility.

Discussion

The overall incidence and increase in resistance to first-line treatment antibiotics for *Campylobacter* infections remains a public health concern. The recent data used in our study highlight the importance of conducting *Campylobacter* surveillance and monitoring antimicrobial resistance.

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Author's Statement Page

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Lauren Ahart

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INTRODUCTION

Campylobacteriosis, one of the most common foodborne diseases, infects approximately 14 per 100,000 persons or 1.3 million people in the United States each year (Scallan et al., 2011). An estimated 13,000 hospitalizations and 120 deaths result from this bacterial diarrheal illness annually, among cases that were diagnosed and reported (Scallan et al., 2011). The majority of *Campylobacter* species are *Campylobacter jejuni* or *coli*, with *C. jejuni* causing approximately 90% of human infections and *C. coli* causing most of the remaining 10% (Bolinger & Kathariou, 2017). Causes of this illness most commonly include consumption of undercooked poultry, unpasteurized milk, contaminated water, or contact with infected animals (Taylor et al., 2013). Mild cases of illness can lead to hospitalization, while severe cases can lead to chronic conditions such as arthritis, irritable bowel syndrome (IBS), or Guillain-Barre syndrome (GBS) (Yuki & Hartung, 2012).

Campylobacter is a self-limiting illness, therefore treatment is only recommended for children, elderly, immunocompromised patients, or patients with a prolonged infection (Allos, 2001). Physicians treat severe cases of illness with antibiotics erythromycin and ciprofloxacin due to their satisfactory clinical response (Engberg, Aarestrup, Taylor, Gerner-Smidt, & Nachamkin, 2001). However, the overuse of antibiotics in humans is increasing antimicrobial resistance to these antibiotics and may lead to rising trends in *Campylobacter* infections over time (Payot et al., 2006).

A recent paper by Geissler et al. used national case data from FoodNet sites to estimate incidence rates of culture-confirmed *Campylobacter* cases in the United States during 2004-2012. Their research findings indicated that the average incidence was 11.4 cases/100,000 persons, although there was some variation in incidence geographically and demographically (Geissler et al., 2017). Researchers also found that incidence was highest among children 4 years old and younger (26.3 cases/100,000 persons), which is concerning for public health (Geissler et al., 2017). Nearly a quarter of isolates (23.4%) were resistant to ciprofloxacin and 2.1% of isolates were resistant to erythromycin. The number of *Campylobacter* infections with antimicrobial resistance to first-line treatment antibiotics highlighted the importance of continuing to monitor resistance trends and incidence rates.

We assessed *Campylobacter* data to evaluate the trends in infections in the U.S. reported between 2005 and 2017. We build on the work by Geissler et al. by updating incidence estimates and describing recent trends in resistance to clinically-significant antibiotics, including ciprofloxacin and erythromycin. Additionally, we compare health outcomes (i.e. the number of hospitalizations and deaths) of recent years to earlier years in order to describe the public health impact that this foodborne illness is having on the population.

METHODS

Data Sources

Data were retrieved from two Centers for Disease Control and Prevention (CDC) data systems: the Foodborne Diseases Active Surveillance Network (FoodNet) and National Antimicrobial Resistance Monitoring System (NARMS). FoodNet is a population-based, active surveillance system that collaborates with the U.S. Department of Agriculture's Food Safety Inspection Service (USDA-FSIS), the U.S. Food and Drug Administration (FDA) to collect epidemiological data on foodborne infections related to *Campylobacter*, *Listeria*, *Salmonella*, *Shiga* toxin-producing *Escherichia coli* (STEC) O157,

Shigella, *Vibrio*, and *Yersinia*. The FoodNet catchment area includes Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee and select counties in California, Colorado, and New York. These 10 sites are a representative sample of 15% of the U.S. population. Data collected through these programs are significant as they provide patient demographic, travel history, and clinical data for laboratory-confirmed cases, which is used to analyze disease burden.

NARMS is an isolate-based, passive surveillance system that collaborates with USDA-FSIS, FDA, and 54 sites in the U.S. to test *Campylobacter*, *Shigella*, *E. coli* O157, and *Vibrio*. For *Campylobacter*, NARMS only has programs in the respective 10 FoodNet sites. Isolates sent to NARMS include basic patient demographic and bacterial data for antimicrobial agents. As mentioned previously, this research will only investigate antimicrobial susceptibility to the two first-line antibiotics used to treat *Campylobacter*, ciprofloxacin and erythromycin.

Data Analysis

Data from the NARMS and FoodNet surveillance systems were merged using state laboratory IDs to assess the epidemiology and antimicrobial resistance of *Campylobacter* infections. A total of 80,495 culture-confirmed cases were found in the FoodNet database during 2005-2017. The NARMS database had 16,276 laboratory-approved isolates, in which approximately 85% successfully linked to a single case in the FoodNet database. After applying inclusion criteria to only include *Campylobacter* species *coli* and *jejuni*, NARMS lab-approval, and years 2005-2017, the total analytic sample included 13,454 cases.

First, we estimated incidence of *Campylobacter* by demographic characteristics of all culture-confirmed cases included in FoodNet during four time periods: 2005-2008, 2009-2012, 2013-2016 and 2017. We imputed missing values for race by distributing missing values to observed proportions of *Campylobacter* infections by race. All rates were calculated per 100,000 persons in the United States and were divided using population data retrieved from the most recent U.S. Census (U.S. Census Bureau, 2018).

Next, using isolates in the linked dataset, we compared resistance to ciprofloxacin and erythromycin during 2005-2012 and 2013-2017. Characteristics assessed in this analysis included demographic factors (i.e. age, sex, and race) as well as patient's travel history. Chi-Square tests were used to statistically test differences in resistance by year groupings ($p < .05$). A Fisher's Exact test supplemented the Chi-Square test when cells were less than 5. Last, we described health outcomes (hospitalizations and deaths) by antimicrobial susceptibility for antimicrobial agents ciprofloxacin and erythromycin during 2005-2012 and 2013-2017.

All statistical analyses and data merging were performed in SAS software version 9.4. Chi-Square and Fisher's Exact test were used to analyze if changes in antimicrobial resistance for more recent years were statistically significantly different compared to earlier years.

RESULTS

Demographics

Among the population of *Campylobacter* cases, 41% were between 30-59 years old and 19% were 60 years or older (Note: percentages not shown in table). There were more males (55%) than females (45%), and 66% of cases self-reported as White race. The state of residence varied; however, this is

expected as population sizes vary across years. An estimated 8% reported international travel within seven days of illness onset.

Incidence

The incidence among culture-confirmed cases has remained fairly stable over the 13-year period, with an incidence of 12.71/100,000 persons in 2005 and 12.25/100,000 persons in 2017. The overall incidence in 2005 – 2008 was 12.72/100,000 persons, 13.75/100,000 persons in 2009 – 2012, 12.91/100,000 persons in 2013 – 2016, and 12.25/100,000 persons in 2017. The highest incidence occurred in years 2009 – 2012.

By age, children between ages 0 and 4 years old had the highest incidence: 25.24/100,000 persons in 2005 – 2008, 25.47/100,000 persons in 2009 – 2012, 21.92/100,000 persons in 2013 – 2016, and 19.75/100,000 persons in 2017. Across all year groups, males had a higher incidence than females. Based on imputed values for race, American Indian or Alaskan Natives had the highest incidence in 2005 – 2008 (25.23/100,000 persons), 2009 – 2012 (17.88/100,000 persons), and 2017 (16.62/100,000 persons). In 2013 – 2016, Whites had a higher incidence (14.56/100,000 persons) than the American Indian and Alaskan Natives (Table 1).

Table 1. Incidence rates of Culture-Confirmed *Campylobacter* Infections, 2005-2017

Characteristic	2005-2008		2009-2012		2013-2016		2017	
	N = 23, 192	Incidence per 100,000	N = 26,036	Incidence per 100,000	N = 25,175	Incidence per 100,000	N = 6,092	Incidence per 100,000
AGE, in years								
0-4	3039	25.24	3071	25.47	2591	21.92	584	19.75
5-9	1222	10.30	1323	10.76	1095	8.86	253	8.28
10-19	2186	8.52	2366	9.27	2133	8.45	513	8.08
20-29	3226	13.02	3752	14.45	3671	13.61	857	12.50
30-59	10039	12.98	10616	13.52	10226	12.93	2448	12.34
60+	3467	11.34	4895	14.00	5457	13.75	1437	13.44
Unknown	13		13		2			
SEX								
Male	12,733	14.24	14,280	15.38	13,756	14.36	3279	13.43
Female	10,441	11.24	11,737	12.17	11,393	11.46	2808	11.09
Unknown	18		19		26		5	
RACE*								
Asian (includes Pacific Islander or Native Hawaiian)	808	12.89	968	13.09	1023	10.76	309	11.28
Black	898	4.34	1041	4.57	1174	4.36	336	4.55
American Indian or Alaskan Native	378	25.23	307	17.88	284	13.89	93	16.62
Multiracial	93	3.61	162	4.95	159	3.80	60	5.02
White	14394	14.09	16502	15.34	17832	14.56	4388	13.41
Other	381		647		825		276	
STATE OF RESIDENCE								
California	3699	28.56	4406	32.42	3160	21.96	800	21.65
Colorado	1783	16.95	1587	14.06	1410	11.61	301	9.55
Connecticut	2098	14.88	2323	16.21	2727	18.96	508	14.16
Georgia	2537	6.87	2775	7.11	2568	6.33	616	5.91
Maryland	1627	7.21	2183	9.39	2730	11.41	661	10.92
Minnesota	3533	17.04	3852	18.07	3712	16.97	1049	18.81
New Mexico	1442	18.26	1316	15.93	1398	16.77	478	22.89
New York	2030	11.75	2416	13.95	2610	15.12	599	13.92
Oregon	2670	18.07	3418	22.19	3204	20.05	629	15.18
Tennessee	1773	7.24	1760	6.90	1656	6.30	451	6.72
Average overall incidence		12.72		13.75		12.91		12.25

*Data shown are based on true counts before imputation of unknown data.

Antimicrobial Resistance

Of isolates that could be linked to a FoodNet case, there were 3,344 ciprofloxacin-resistant and 357 erythromycin-resistant isolates in NARMS during 2005 – 2017. Resistance to ciprofloxacin steadily increased over the years, with 29% of isolates conferring resistance to ciprofloxacin in 2017. During 2013-2017, 1451 (27%) of isolates were ciprofloxacin-resistant and 187 (3%) were erythromycin-resistant (Table 2). Compared to the earlier years (2005-2012), the increase in resistance to both antibiotics were statistically significant.

Resistance to ciprofloxacin increased over time among people under 30 years old, males, females, Whites, travel-associated and non-travel associated cases (Table 2). Resistance to erythromycin increased over time among people 30 years and older, males, females, Multiracial, Whites, and non-travel associated acquired cases for erythromycin-resistant cases (Table 2).

Table 2. Characteristics by antibiotic drug resistance, 2005-2017

	Ciprofloxacin-Resistant		P-value	Erythromycin-Resistant		P-value
	2005-2012	2013-2017		2005-2012	2013-2017	
AGE, (YEARS)	n (%)	n (%)		n (%)	n (%)	
0-4	143 (14%)	118 (21%)	0.0009*	7 (1%)	9 (2%)	0.093
5-9	64 (15%)	51 (21%)	0.0472*	5 (1%)	3 (1%)	0.9407
10-19	160 (21%)	139 (30%)	0.0006*	11 (1%)	14 (3%)	0.0631
20-29	321 (28%)	259 (33%)	0.0216*	34 (3%)	36 (5%)	0.0638
30-59	904 (27%)	624 (29%)	0.1795	90 (3%)	82 (4%)	0.0242*
60+	301 (22%)	260 (22%)	0.7778	23 (2%)	43 (4%)	0.0026*
SEX						
Male	1034 (23%)	773 (26%)	0.0031*	87 (2%)	92 (3%)	.0014*
Female	857 (24%)	674 (27%)	0.0043*	82 (2%)	95 (4%)	.0005*
RACE*						
Asian (includes Pacific Islander or Native Hawaiian)	78 (37%)	60 (34%)	0.5221	5 (2%)	7 (4%)	0.3708
Black	101 (26%)	56 (22%)	0.2943	8 (2%)	10 (4%)	0.1499
American Indian or Alaskan Native	14 (11%)	13 (13%)	0.6711	1 (1%)	1 (1%)	0.8715
Multiracial	10 (23%)	13 (39%)	0.129	0 (0%)	3 (9%)	0.0437*
White	1221 (22%)	1078 (26%)	<.0001*	124 (2%)	127 (3%)	0.0121*
Other	26 (28%)	42 (29%)	0.8547	2 (2%)	4 (3%)	0.7675
Unknown	443 (27%)	189 (34%)	0.0039*	30 (2%)	35 (6%)	<.0001*
TRAVEL-ASSOCIATED						
Yes	658 (63%)	561 (75%)	<.0001*	48 (5%)	43 (6%)	0.2645
No	688 (15%)	701 (18%)	<.0001*	71 (2%)	123 (3%)	<.0001*
TOTAL	1893 (24%)	1451 (27%)		170 (2%)	187 (3%)	

*Statistical significance is defined as $p < .05$

Health Outcomes

During 2013-2017, 179 (13%) patients with a ciprofloxacin-resistant *Campylobacter* infection were hospitalized, compared to 746 (19%) of patients with ciprofloxacin-susceptible *Campylobacter* infections (Table 3). These findings are comparable to those in the earlier years, with 214 (12%) of resistant cases and 979 (17%) of susceptible cases being hospitalized (Table 3). As shown in Table 3, mortality associated with a *Campylobacter* infection is less than 1% among persons with both resistant and susceptible *Campylobacter* infections.

Table 3. Health outcomes by ciprofloxacin susceptibility, 2005-2017

	Ciprofloxacin			
	2005-2012		2013-2017	
	Resistant	Susceptible	Resistant	Susceptible
Total	1893 (24%)	6134 (76%)	1451 (27%)	3976 (73%)
HOSPITALIZATION				
Yes	214 (12%)	979 (17%)	179 (13%)	746 (19%)
No	1592 (88%)	4924 (83%)	1230 (87%)	3133 (81%)
OUTCOME				
Alive	1706 (99.8%)	5631 (99.9%)	1422 (100%)	3903 (99.9%)
Dead	3 (0.2%)	3 (0.1%)	0 (0%)	6 (0.1%)

Patients with either an erythromycin-resistant or erythromycin-susceptible *Campylobacter* infection were slightly more likely to be hospitalized in the more recent years (17% and 18% hospitalized during 2013 – 2017 among patients with resistant and susceptible infections, respectively) (Table 4). There was a higher proportion of hospitalization among the erythromycin-resistant cases compared to the ciprofloxacin-resistant cases. Regardless of the susceptibility to erythromycin status, mortality due to *Campylobacter* infection is less than 1% (Table 4).

Table 4. Health outcomes by erythromycin susceptibility, 2005-2017

	Erythromycin			
	2005-2017		2013-2017	
	Resistant	Susceptible	Resistant	Susceptible
Total	170 (2%)	7857 (98%)	187 (3%)	5280 (97%)
HOSPITALIZATION				
Yes	23 (14%)	1170 (16%)	31 (17%)	894 (18%)
No	144 (86%)	6372 (84%)	150 (83%)	4213 (82%)
OUTCOME				
Alive	157 (100%)	7180 (99.9%)	181 (99.5%)	5144 (99.9%)
Dead	0 (0%)	6 (0.1%)	1 (0.5%)	5 (0.1%)

DISCUSSION

The incidence for culture-confirmed cases of *Campylobacter* remained relatively stable between 2005 and 2017. Consistent with previous literature, findings showed that children under 5 years old and males had the highest incidence of *Campylobacter* infections (Geissler et al., 2017). American Indian and Alaskan Natives had a higher incidence compared to all other racial groups, which has also been found previously (Geissler et al., 2017).

Resistance to clinically-significant antibiotics ciprofloxacin and erythromycin increased during 2005 – 2017. In travel-associated cases, resistance to ciprofloxacin increased from 63% to 75% between 2005 – 2012 and 2013 – 2017, while resistance to erythromycin increased from 5% to 6% between 2005 – 2012 and 2013 – 2017. These findings were based on complete case data, and data on recent travel were missing for 54% of cases. Previous studies also show that more than half of international travel-associated cases involve ciprofloxacin-resistant *Campylobacter* infections (Geissler et al., 2017; Ricotta et al., 2014). Education about risks and preventative measures should be taken to reduce the number of antimicrobial resistant *Campylobacter* infections among international travelers.

We observed a higher percentage of hospitalizations among the susceptible cases, which may be partially confounded by young adult age (20-29 years) or “healthy traveler effects,” both of which are

negatively associated with hospitalization and positively associated with having a resistant infection. Previous research has shown that traveling can positively impact your health and decrease the likelihood of hospitalization or mortality due to a diarrheal infection (Ricotta et al., 2014). This is known as the “healthy traveler effect” (Ricotta et al., 2014).

There were a few limitations to this study, some of which were related to the surveillance systems used. As mentioned previously, the FoodNet data system includes 10 sites or state health departments in the United States. The FoodNet surveillance systems collect quality data that is representative of the entire country; however, the surveillance only covers 15% of the U.S. leaving the potential for some trends not being captured. Additionally, the FoodNet data analyzed only included *Campylobacter* with culture-confirmed cases. In other words, these data excluded any case without a culture or cases diagnosed using culture-independent diagnostic testing (CIDT). The technological advancement of CIDTs aids in faster detection and diagnosis of infection, however these tests do not provide enough information to capture incidence.

Another limitation was the variation in *Campylobacter* sampling. The different sampling schemes in FoodNet sites impacts the number of isolates shipped to CDC NARMS laboratory for testing. Due to the inconsistent number of isolates shipped to CDC, only a subset of antimicrobial susceptibility testing (AST) results were available. Isolates with finalized results were linked to FoodNet cases. Lastly, analyses were limited to *Campylobacter jejuni* and *coli* because there currently are no breakpoints interpretations established for other *Campylobacter* species.

One of the advantages of this study is that it adds to previous literature around this topic with use of more current data. Although incidence has remained steady over the years, an increase in antimicrobial resistance to first-line treatment antibiotics remain a public health concern. This study also reiterates the importance of ordering *Campylobacter* cultures. Surveillance data from studies such as this keeps treatment guidelines up-to-date and informs physicians on how to treat individual cases of *Campylobacter* infections using antimicrobial agents.

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