QUINOLONE-RESISTANT *CAMPYLOBACTER JEJUNI* INFECTIONS IN MINNESOTA, 1992–1998

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ABSTRACT

Background Increasing resistance to quinolones among campylobacter isolates from humans has been reported in Europe and Asia, but not in the United States. We evaluated resistance to quinolones among campylobacter isolates from Minnesota residents during the period from 1992 through 1998.

Methods All 4953 campylobacter isolates from humans received by the Minnesota Department of Health were tested for resistance to nalidixic acid. Resistant isolates and selected sensitive isolates were tested for resistance to ciprofloxacin. We conducted a case-comparison study of patients with ciprofloxacin-resistant *Campylobacter jejuni* isolated during 1996 and 1997. Domestic chicken was evaluated as a potential source of quinolone-resistant campylobacter.

Results The proportion of quinolone-resistant *C. jejuni* isolates from humans increased from 1.3 percent in 1992 to 10.2 percent in 1998 (P<0.001). During 1996 and 1997, infection with quinolone-resistant *C. jejuni* was associated with foreign travel and with the use of a quinolone before the collection of stool specimens. However, quinolone use could account for no more than 15 percent of the cases from 1996 through 1998. The number of quinolone-resistant infections that were acquired domestically also increased during the period from 1996 through 1998. Ciprofloxacin-resistant *C. jejuni* was isolated from 14 percent of 91 domestic chicken products obtained from retail markets in 1997. Molecular subtyping showed an association between resistant *C. jejuni* strains from chicken products and domestically acquired infections in Minnesota residents.

Conclusions The increase in quinolone-resistant *C. jejuni* infections in Minnesota is largely due to infections acquired during foreign travel. However, the number of quinolone-resistant infections acquired domestically has also increased, largely because of the acquisition of resistant strains from poultry. The use of fluoroquinolones in poultry, which began in the United States in 1995, has created a reservoir of resistant *C. jejuni*. (N Engl J Med 1999;340:1525-32.)

CAMPYLOBACTER *jejuni* is the most commonly recognized cause of bacterial gastroenteritis in the United States.[1,2] When antibiotics are indicated for the treatment of campylobacter gastroenteritis, erythromycin or a fluoroquinolone such as ciprofloxacin is the drug of choice.[3-5] Fluoroquinolones are frequently prescribed empirically for diarrheal illness, including traveler's diarrhea, because of their effectiveness against a range of enteric bacteria.[3-7] Since the late 1980s, the resistance of campylobacter isolates to fluoroquinolones has been increasing, especially in Europe.[8] Poultry is a major source of campylobacter infections in humans, and some European investigators have proposed a causal relation between the use of fluoroquinolones in animals and the increase in fluoroquinolone-resistant campylobacter infections in humans.[8]

Current trends in antibiotic-resistant campylobacter infections in the United States have not been well documented. In the United States, fluoroquinolones were first licensed for use in poultry in 1995. Therefore, we conducted a study of campylobacter isolates obtained from humans during the period from 1992 through 1998 as part of statewide surveillance activities to analyze recent trends in quinolone-resistant campylobacter infections, risk factors for infection with resistant organisms, and poultry as a potential source of resistant organisms.

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METHODS

Surveillance and Characterization of Isolates

Cases of illness caused by campylobacter have been reportable in Minnesota since 1979. The Minnesota Department of Health Public Health Laboratory serves as a statewide reference laboratory for the confirmation and identification of campylobacter infections.[9] In 1995, the rules for reporting disease were changed to require the submission of isolates as part of the reporting process.

We screened all isolates received since 1992 for resistance to the quinolone antibiotic nalidixic acid with a preliminary disk-diffusion test.[10] We also tested every fifth isolate, all resistant isolates, and all sensitive isolates from the 1996 portion of our case-comparison study for resistance to nalidixic acid by a standardized disk-diffusion test[11] and for resistance to ciprofloxacin by the E test with use of a modification of the methods of Huang et al.[12] We tested 20 randomly selected ciprofloxacin-resistant isolates from 1997 for resistance to grepafloxacin, levofloxacin, and trovafloxacin (by the E test) and to the veterinary fluoroquinolones enrofloxacin (by the E test) and sarafloxacin (by the disk-diffusion test). We tested 28 isolates from 1992 and 1993 and every fifth isolate from 1994 through 1997 for resistance to erythromycin and tetracycline by the E test.

E-test strips (AB Biodisk, Piscataway, N.J.) were applied to agar plates prepared from a Mueller–Hinton base (Difco, Detroit), supplemented with 5 percent lysed sheep's blood, and incubated at 37°C for 48 hours in a microaerophilic atmosphere (Campy-Pak, BBL Microbiology Systems, Cockeysville, Md.). We used interpretive criteria for Enterobacteriaceae and quality-control guidelines established by the National Committee for Clinical Laboratory Standards.[13] Our definition of resistance to trovafloxacin, enrofloxacin, and sarafloxacin was the same as that of resistance to ciprofloxacin (a minimal inhibitory concentration of ≥ 4 μg per milliliter). Resistance to erythromycin was defined as a minimal inhibitory concentration greater than 8 μg per milliliter. Campylobacter isolates from 1996 and 1997 were subtyped by restriction-fragment–length polymorphism of the flagellin gene amplified by the polymerase chain reaction (PCR-RFLP).[14]

Comparison of Cases of Quinolone-Resistant and Quinolone-Sensitive *C. jejuni* Infection

Isolates obtained from Minnesota residents with *C. jejuni* infection during the period from 1996 through 1997 were classified as quinolone-sensitive or quinolone-resistant. A quinolone-resistant isolate was defined as having resistance to nalidixic acid on the standardized test; all resistant isolates were also resistant to ciprofloxacin. We matched each patient with a resistant isolate to two patients with sensitive isolates; patients were matched for age (within 10 years), residence (in the seven-county Minneapolis–St. Paul metropolitan area vs. elsewhere in Minnesota), and date of specimen collection.

Each patient answered a standardized questionnaire that included questions about clinical history, use of antibiotics after and during the month before the onset of illness, recent diarrheal illness and the use of antibiotics in household contacts, history of food consumption, contact with animals, and travel history. The period of interest for potential exposure, unless noted otherwise, was the seven days before the onset of illness. When patients could not answer questions about their use of antibiotics, we contacted their health care providers.

Evaluation of Retail Chicken Products

During the period from September 8 to November 3, 1997, we purchased 91 domestic chicken products in the Minneapolis–St. Paul metropolitan area from 16 retail markets representing 11 franchises. These products came from 15 poultry-processing plants in nine states. The products were various fresh or thawed items with and without the skin.

We cultured all chicken products for campylobacter,[15] and we tested isolates for resistance to nalidixic acid and ciprofloxacin as

described previously. For 76 products, we tested for resistance isolates from each product that was positive, using 3 to 10 campylobacter colonies from each product. The other 15 product samples were concentrated quantitatively, and serial dilutions were made in Mueller–Hinton broth (BBL Microbiology Systems). The samples were plated on Campy-BAP medium (BBL Microbiology Systems) in the presence of 8 μg of nalidixic acid per milliliter and in its absence. The concentration of agar was increased to 1.7 percent. We evaluated 1 nalidixic acid–resistant colony and 1 susceptible colony from each broth culture and 5 colonies of each from a dilution plate with 15 to 150 colonies. Isolates were subtyped by PCR-RFLP, and a random sample of ciprofloxacin-resistant isolates was tested for resistance to additional fluoroquinolones as described previously.

Statistical Analysis

Population estimates were obtained from *Minnesota Health Statistics, 1994*.[16] We determined univariate matched odds ratios, P values for tests for trend, and exact 95 percent confidence intervals with Epi Info software (version 6.04a, Centers for Disease Control and Prevention, Atlanta).[17] Mantel–Haenszel chi-square tests were used in univariate matched analyses.[17] We determined multivariate odds ratios and exact 95 percent confidence intervals with PC-SAS software (version 6.12, SAS Institute, Cary, N.C.) using exact conditional logistic regression with a forward, stepwise approach.[18] Variables with a P value of 0.1 or less in univariate analysis were included in the multivariate model. Variables independently associated with the outcome variable were included in the final multivariate model. The Kruskal–Wallis test was used to compare groups of patients with respect to the duration of diarrhea.[17] All reported P values are two-sided.

An outbreak was defined as two or more cases of campylobacter infection in separate households with a common epidemiologic exposure. A case cluster was defined as two or more cases occurring within two weeks of one another among members of the same household. Only the isolate from the first case in each outbreak was included in analyses of resistance to antibiotics. All outbreak-associated cases were excluded from the case-comparison study, and only the index case from identified clusters was included in the case-comparison study.

RESULTS

Surveillance of Campylobacter and Resistance to Quinolones

During the period from 1992 through 1998, 6674 cases of campylobacter infection among Minnesota residents were reported to the Minnesota Department of Health. The median number of cases reported annually was 946 (range, 785 to 1181), with a median annual incidence of 20.7 cases per 100,000 population (range, 17.2 to 25.8). During the period from 1992 through 1998, 4953 viable campylobacter isolates from various patients (74 percent of all reported cases) were submitted to the Minnesota Department of Health; from 1996 through 1998, 91 percent of all isolates were submitted. *C. jejuni* constituted 95 percent of all campylobacter isolates. Seven outbreaks of *C. jejuni* infection were identified; six occurred during 1992, 1993, 1994, 1995, or 1998 and involved 71 *C. jejuni* isolates, all of which were sensitive to nalidixic acid. An outbreak in October 1997 among personnel of the Minnesota Army National Guard who were returning from training in Greece accounted for 29 *C. jejuni* isolates; all were resistant to nalidixic acid and ciprofloxacin.
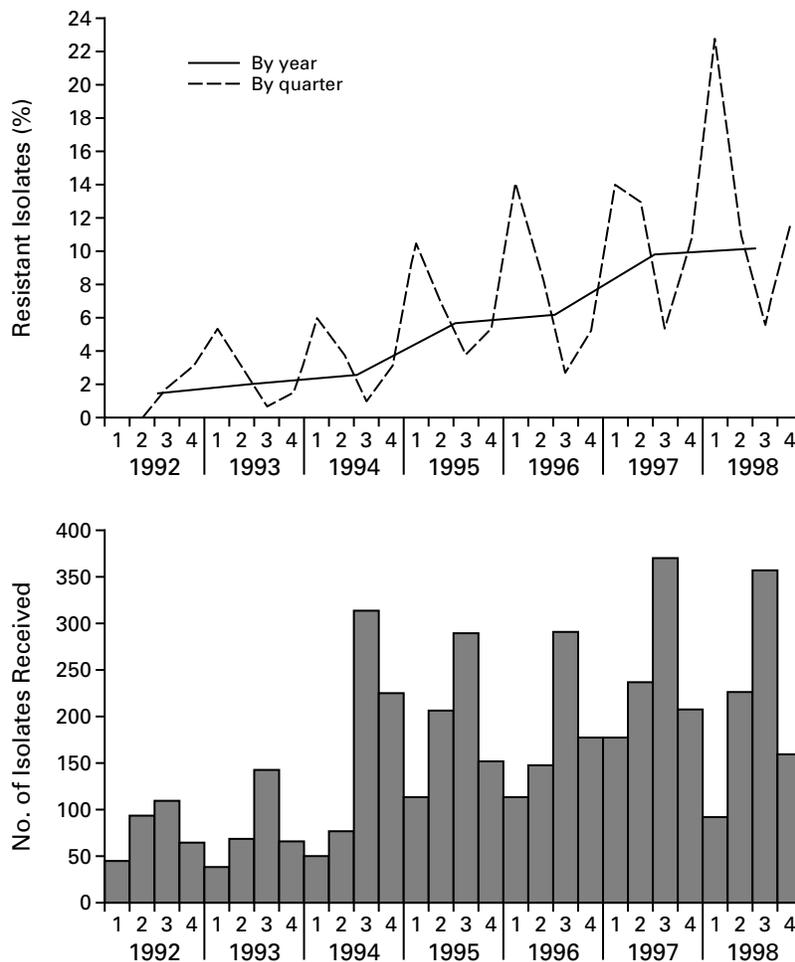
Figure 1. Percentage of *Campylobacter jejuni* Isolates Obtained from Minnesota Residents and Submitted to the Minnesota Department of Health That Were Resistant to Nalidixic Acid (Top Panel) and Total Number of *C. jejuni* Isolates from Minnesota Residents Submitted (Bottom Panel), According to the Year and the Quarter, 1992–1998.

For the outbreaks, only the index case is included.

After we excluded all except the initial case in each identified outbreak, the annual percentage of *C. jejuni* isolates that were resistant to nalidixic acid on the preliminary disk-diffusion test increased from 1.3 percent in 1992 to 10.2 percent in 1998 (chi-square for linear trend, 75.3; P<0.001) (Fig. 1). The prevalence of nalidixic acid–resistant isolates exhibited a marked seasonality characterized by peaks during the first quarter and valleys during the third quarter of each calendar year (Fig. 1).

Ciprofloxacin resistance was confirmed in 285 *C. jejuni* isolates from the study period: 1 in 1993, 16 in 1994, 41 in 1995, 44 in 1996, 98 in 1997 (excluding all but the first isolate from the outbreak), and 85 in 1998. The minimal inhibitory concentration of ciprofloxacin was at least 32 μg per milliliter in the case of 274 of the ciprofloxacin-resistant iso-

lates (96 percent). With use of the E test for resistance to ciprofloxacin as the standard, testing of 1230 isolates by the preliminary test for resistance to nalidixic acid resulted in a sensitivity of 99.6 percent, a specificity of 98.4 percent, a positive predictive value of 94.9 percent, and a negative predictive value of 99.9 percent.

All 20 ciprofloxacin-resistant *C. jejuni* isolates from 1997 that we tested were also resistant to grepafloxacin, trovafloxacin, enrofloxacin, and sarafloxacin. Seventeen of 20 isolates were resistant to levofloxacin; the other 3 isolates had intermediate levels of resistance. Minimal inhibitory concentrations of at least 32 μg per milliliter were noted for grepafloxacin (20 isolates), enrofloxacin (17 isolates), trovafloxacin (12 isolates), and levofloxacin (12 isolates). Eighteen of 827 clinical isolates (2 percent) obtained during 1992

TABLE 1. POTENTIAL RISK FACTORS FOR INFECTION WITH QUINOLONE-RESISTANT *CAMPYLOBACTER JEJUNI* AS COMPARED WITH QUINOLONE-SENSITIVE *C. JEJUNI* AMONG MINNESOTA RESIDENTS, 1996–1997.*

POTENTIAL RISK FACTOR†	PATIENTS WITH RESISTANT ISOLATE (N=130)	PATIENTS WITH SENSITIVE ISOLATE (N=260)	UNIVARIATE ANALYSIS‡		MULTIVARIATE ANALYSIS‡	
			MATCHED ODDS RATIO (95% CI)	P VALUE	MATCHED ODDS RATIO (95% CI)	P VALUE
	no. (%)§					
Foreign travel	96 (75)	59 (23)	16.0 (7.8–38.8)	<0.001		
To Mexico	47 (36)	30 (12)	5.6 (3.1–12.6)	<0.001	26.0 (8.6–78.6)	<0.001
To Caribbean countries, South America, or Central America (not Mexico)	14 (11)¶	7 (3)	4.5 (1.6–14.2)	<0.001	45.5 (9.7–214)	<0.001
To Asia	23 (18)‖	8 (3)	7.3 (2.8–21.7)	<0.001	40.7 (10.2–163)	<0.001
To Spain	7 (5)	1 (<1)	14.0 (1.8–631)	0.001	48.6 (4.1–570)	0.002
Use of a quinolone before the collection of stool specimens	26 (20)	7 (3)	7.4 (3.1–20.3)	<0.001	7.5 (2.6–21.3)	<0.001
Drinking untreated water	37 (34)	48 (20)	2.0 (1.1–3.7)	0.02	—	
Swimming	51 (41)	67 (26)	2.2 (1.3–3.7)	0.002	—	
Contact with pets	43 (36)	157 (62)	0.3 (0.2–0.6)	<0.001	—	
Travel within the United States outside of Minnesota	6 (5)	44 (17)	0.3 (0.1–0.7)	0.002	—	

*In this matched case-comparison study, two patients with quinolone-sensitive isolates were matched for age, residence, and date of stool-specimen collection to each patient with a quinolone-resistant isolate. CI denotes confidence interval.

†All potential risk factors except the use of quinolones pertain to the seven-day period before the onset of illness that yielded the *C. jejuni* isolate. The use of a quinolone before collection of stool specimens indicates treatment after the onset of illness but one or more days before culture or use of a quinolone for any reason during the month before the onset of illness.

‡The univariate analysis was by Mantel–Haenszel chi-square test. The multivariate analysis was exact conditional logistic regression with use of a forward, stepwise approach. Variables with a P value of 0.1 or less in univariate analysis were used in the multivariate model; subgroups of foreign travel rather than the composite variable of foreign travel were used in the multivariate model. Multivariate matched odds ratios are listed only for variables that were independently associated with having a resistant strain.

§The percentages are based on the number of patients for whom information was available; some patients could not recall exposure to specific potential risk factors.

¶The 14 patients traveled to Jamaica (6 patients), Peru (3 patients), Venezuela (2 patients), or another country (3 patients).

‖The 23 patients traveled to India (5 patients), Thailand (4 patients), Japan (3 patients), Nepal (2 patients), or another country or multiple countries (9 patients).

through 1997 were resistant to erythromycin, and 501 (61 percent) were resistant to tetracycline. There were no significant changes in the proportion of isolates that were resistant to either of these antibiotics during the study period.

Comparison of Cases of Quinolone-Resistant and Quinolone-Sensitive *C. jejuni* Infection

Of the patients who had had a *C. jejuni* isolate submitted to the Minnesota Department of Health during the period from 1996 through 1997, 142 had quinolone-resistant isolates (including only the first patient in the 1997 outbreak), 1576 had quinolone-sensitive isolates, and 2 had isolates that were resistant to nalidixic acid on the preliminary test but that were not available for confirmation. Of the patients with quinolone-resistant *C. jejuni* infection, 130 (92 percent) were enrolled in the case-comparison study, along with 260 matched patients with quinolone-sensitive *C. jejuni* infection. Of the 12 patients with

quinolone-resistant infection who were not enrolled, 6 patients were not the index patient in five household clusters, 1 patient was the first patient associated with the 1997 outbreak, and 5 patients could not be contacted.

The risk factors that were identified by univariate analysis are shown in Table 1. According to the multivariate analysis, the only variables independently associated with resistant *C. jejuni* infection were foreign travel, foreign travel to specific regions, and the use of a quinolone beginning one or more days before the collection of stool specimens (Table 1). Among patients who did not use quinolones before the collection of stool specimens, 78 of 133 patients (59 percent) who traveled abroad had a resistant isolate, whereas 24 of 222 patients (11 percent) who did not travel abroad had a resistant isolate.

The use of a quinolone beginning one or more days before the collection of stool specimens occurred in 26 of the 130 patients with resistant *C. jejuni* in-

TABLE 2. NUMBER OF PATIENTS IN MINNESOTA WITH QUINOLONE-RESISTANT *CAMPYLOBACTER JEJUNI* INFECTION WHO USED A QUINOLONE BEFORE CULTURE, ACCORDING TO FOREIGN-TRAVEL STATUS AND YEAR, 1996–1997.*

HISTORY OF FOREIGN TRAVEL†	NO. WHO USED A QUINOLONE BEFORE CULTURE/TOTAL NO. (%)		
	1996	1997	1996–1997
No foreign travel	1/7 (14)	7/25 (28)	8/32 (25)
Travel to Mexico	3/18 (17)	4/29 (14)	7/47 (15)
Travel to Caribbean countries, South America, or Central America (not Mexico)	1/3 (33)	3/11 (27)	4/14 (29)
Travel to Asia	1/7 (14)	2/16 (12)	3/23 (13)
Travel to Spain	0/2	1/5 (20)	1/7 (14)
Travel to other foreign country	0/1	3/4 (75)	3/5 (60)
Unknown travel history	0/2	—	0/2
Total	6/40 (15)	20/90 (22)	26/130 (20)

*The use of a quinolone includes treatment beginning one or more days before stool-specimen collection and use for any reason during the month before the onset of illness.

†The foreign travel took place during the seven days before the onset of illness.

fection (20 percent) and did not differ significantly according to the year or travel status (Table 2). Twenty-four patients began treatment with a quinolone after the onset of illness but before the collection of stool specimens, and two patients took prophylactic ciprofloxacin while traveling. When patients were grouped according to their history of foreign travel, the use of a quinolone before the collection of stool specimens remained a significant risk factor for patients with resistant *C. jejuni* infection who had a history of foreign travel (matched odds ratio, 6.0; 95 percent confidence interval, 2.3 to 18.5) and those who did not (matched odds ratio, 16.0; 95 percent confidence interval, 2.2 to 710). Among patients who used a quinolone before the collection of stool specimens, the use began a median of 5 days (range, 1 to 30) before culture.

Overall, 110 of the 130 patients with resistant *C. jejuni* infection (85 percent) were treated with an antibiotic, as compared with 212 of the 260 patients with sensitive *C. jejuni* infection (82 percent). Of the patients with resistant *C. jejuni* infection who were treated with an antibiotic, we identified the antibiotic used for 106 patients; 69 patients (65 percent) received a fluoroquinolone, and 26 patients (25 percent) received a macrolide. Of the 212 patients with sensitive *C. jejuni* infection who were treated, we identified the antibiotic used for 182; 115 patients (63 percent) received a fluoroquinolone, and 45 patients (25 percent) received a macrolide. Of the patients identified during 1997 who were treated with a fluoroquinolone after the collection of stool spec-

imens, the duration of diarrhea was longer for the patients with quinolone-resistant *C. jejuni* infections (median, 10 days) than for the patients with quinolone-sensitive *C. jejuni* infections (median, 7 days; P=0.03).

Quinolone-Resistant Infections Acquired Domestically, 1996 to 1998

Figure 2 shows the reported cases of quinolone-resistant *C. jejuni* infection during the period from 1996 through 1998 among Minnesota residents who did not use a quinolone before the collection of stool specimens, whose infection was not associated with an outbreak, and who were index patients in identified clusters of cases. When these criteria were used in the analysis, the percentage of confirmed *C. jejuni* infections that were resistant to quinolones and acquired domestically increased from 0.8 percent in 1996 to 3.0 percent in 1998 (chi-square for linear trend, 9.8; P=0.002). In 1998, 75 of 80 patients with quinolone-resistant infections (94 percent) did not use a quinolone before culture; when the data were combined with the data from 1996 and 1997, 179 of 210 patients with quinolone-resistant infections (85 percent) did not use a quinolone before culture.

Evaluation of Retail Chicken Products

Of the 91 retail chicken products obtained, campylobacter was isolated from 80 (88 percent), including *C. jejuni* from 67 (74 percent) and *C. coli* from 19 (21 percent). Ciprofloxacin-resistant campylobacter was isolated from 18 products (20 percent), including resistant *C. jejuni* from 13 (14 percent) and resistant *C. coli* from 5 (5 percent). The minimal inhibitory concentration of ciprofloxacin was at least 32 μg per milliliter for all resistant isolates. Products that yielded resistant isolates were purchased at 11 retail markets representing eight franchises. They originated in seven poultry-processing plants in five states (Florida, Georgia, Minnesota, Missouri, and Ohio).

Eight of 11 campylobacter-positive chicken products (73 percent) tested quantitatively yielded a combination of species and types of resistance to ciprofloxacin; for example, 1 product yielded sensitive *C. jejuni,* sensitive *C. coli,* and resistant *C. coli*. Of eight ciprofloxacin-resistant *C. jejuni* isolates from chicken products, all were also resistant to grepafloxacin, trovafloxacin, enrofloxacin, and sarafloxacin; six isolates were resistant to levofloxacin, and the other two had intermediate levels of resistance.

Molecular Subtyping of *C. jejuni* Isolates from Humans and Retail Chicken Products

We identified 45 subtypes on PCR-RFLP among 269 typable *C. jejuni* isolates from patients in the case-comparison study of 1996 and 1997. Among
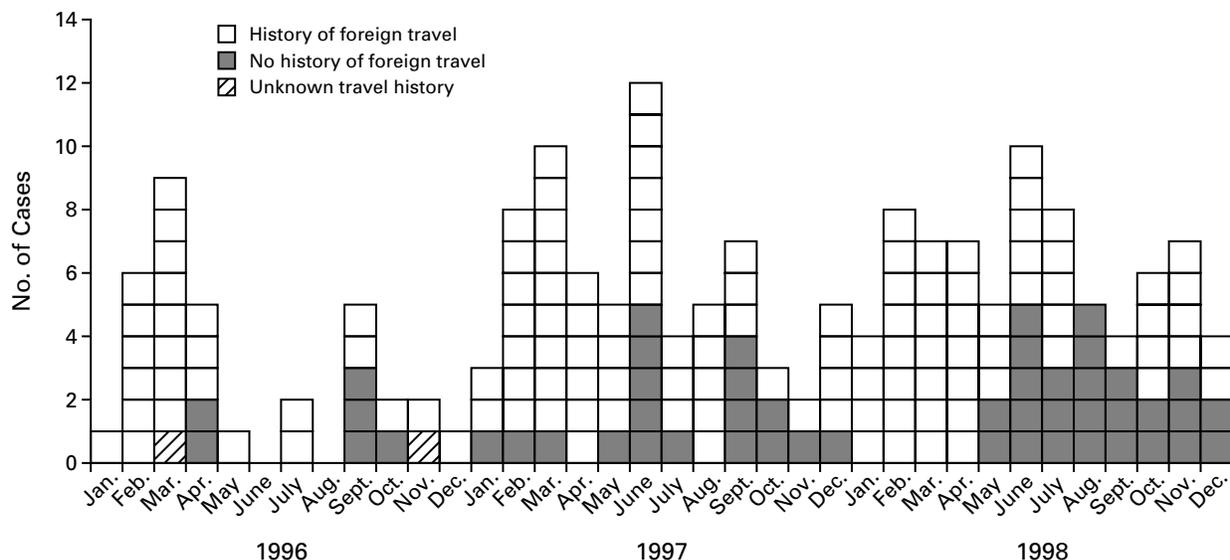
Figure 2. Reported Cases of Quinolone-Resistant *Campylobacter jejuni* Infection among Minnesota Residents Who Did Not Use a Quinolone before Stool-Specimen Collection, Whose Infection Was Not Associated with an Outbreak, and Who Were Index Patients in Identified Clusters of Cases, According to Month and History of Foreign Travel, 1996–1998.

the isolates from 1997, 5 subtypes were detected among quinolone-resistant isolates only, 24 among quinolone-sensitive isolates only, and 12 among both resistant and sensitive isolates.

Twelve subtypes were identified on PCR-RFLP among *C. jejuni* isolates from 13 positive chicken products. Three subtypes were detected among quinolone-resistant isolates only; five among quinolone-sensitive isolates only; and four among both resistant and sensitive isolates. Up to three subtypes were identified per product. Six of seven subtypes of quinolone-resistant *C. jejuni* identified among isolates from retail chicken products were also identified among quinolone-resistant *C. jejuni* isolates from humans. Among patients with infection in 1997 and excluding those who used a quinolone before culture, patients with quinolone-resistant *C. jejuni* infection that was acquired domestically were more likely to have a *C. jejuni* subtype that was also found among quinolone-resistant *C. jejuni* from chicken products than were patients with sensitive *C. jejuni* infection that was acquired domestically (12 of 13 vs. 40 of 90; odds ratio, 15.0; 95 percent confidence interval, 1.9 to 322) or patients with resistant *C. jejuni* infection that was associated with foreign travel (12 of 13 vs. 14 of 40; odds ratio, 22.3; 95 percent confidence interval, 2.5 to 508).

DISCUSSION

Our study had six major findings. First, we documented an increase in quinolone resistance among human *C. jejuni* isolates, from 1.3 percent in 1992 to 10.2 percent in 1998. Second, seasonal peaks in quinolone resistance occurred that were primarily related to foreign travel during winter. Third, the rate of resistant infections that were acquired domestically also increased significantly from 1996 through 1998. Fourth, domestic chicken products obtained from retail markets in 1997 had high rates of contamination with ciprofloxacin-resistant *C. jejuni*. Fifth, we identified an association between molecular subtypes of resistant *C. jejuni* strains that were acquired domestically in humans and those found in chicken products. Poultry has been documented repeatedly as a major food reservoir of campylobacter for infections in humans[2] and our data suggest that poultry is an important source of quinolone-resistant infections as well. Finally, the use of a quinolone before culture, shown previously to be capable of selecting for resistance in campylobacter,[8] contributed to the increase in resistant isolates; however, this mechanism could account for a maximum of only 15 percent of resistant cases identified here.

The significant increase from 1996 through 1998 in quinolone-resistant *C. jejuni* infections that were acquired domestically is temporally associated with the recent licensure of fluoroquinolones (sarafloxacin in 1995 and enrofloxacin in 1996) for use in poultry in the United States. Published epidemiologic and laboratory data from other countries also provide evidence that the use of fluoroquinolones in poultry has had a primary role in increasing resistance to quinolones among *C. jejuni* isolates from humans.[19-26] Treatment with enrofloxacin of broiler

chickens infected with quinolone-sensitive *C. jejuni* does not eradicate the organism; rather, it selects for quinolone resistance in *C. jejuni*.[19] Enrofloxacin was introduced in the Netherlands for veterinary use in 1987 and has been used extensively as a therapeutic agent in poultry since that time.[20] An increase in ciprofloxacin-resistant human campylobacter isolates in the Netherlands from 0 percent through 1985 to 11 percent in 1989 closely paralleled the increase in ciprofloxacin-resistant campylobacter isolates from retail poultry products.[20] In Spain, an increase in the percentage of ciprofloxacin-resistant human campylobacter isolates from 0 to 3 percent in 1989 to 30 to 50 percent in 1991 coincided with the licensure of enrofloxacin for veterinary use in 1990.[21-23] Ciprofloxacin-resistant campylobacter has also been isolated from retail poultry products in Spain,[24] Taiwan,[25] and the United Kingdom.[26] These ecologic data support the selective pressure created by veterinary use of fluoroquinolones in increasing the reservoir of resistant campylobacter. Because the use of fluoroquinolones in poultry in the United States began only recently, we are probably documenting the early emergence of quinolone-resistant campylobacter in this country. Curtailing such use may reverse or slow this trend. It may be suggested that the increasing use of quinolones among humans is responsible for the increase in resistance among campylobacter isolates from humans. However, the association with poultry found by us and researchers in other countries is a more biologically plausible mechanism for the increase, especially when one considers that person-to-person transmission of campylobacter is not important epidemiologically.

Other researchers have associated fluoroquinolone-resistant campylobacter infections with travel or military deployment to many countries in Africa, Asia, and the Mediterranean.[26-31] In our study, Mexico was the most frequent destination for patients with resistant *C. jejuni* infection. In Mexico, the amount of poultry meat produced increased from 0.77 billion kg (1.7 billion lb) in 1990 to 1.45 billion kg (3.2 billion lb) in 1997.[32] Sales of quinolones in Mexico for use in poultry, including the fluoroquinolones ciprofloxacin, enrofloxacin, and danofloxacin, increased by a factor of approximately four from 86 million liters in 1993 to 326 million liters in 1997.[33] Thus, the use of fluoroquinolones in poultry in Mexico may be an important contributor to infections with resistant *C. jejuni* among travelers to that country.

Fluoroquinolones shorten the duration and severity of symptoms caused by campylobacter gastroenteritis,[34,35] and our data indicate that ciprofloxacin is frequently prescribed to treat this condition in Minnesota. In our small sample of 20 human isolates, ciprofloxacin-resistant isolates were also generally resistant to the newer fluoroquinolones used in human medicine. Tetracyclines, cited as an alternative choice for treatment,[3,5] should not be used to treat campylobacter infections because of the high prevalence of resistance. In our study, the rates of resistance to erythromycin stayed low; therefore, this antibiotic may remain the most prudent choice for the treatment of campylobacter gastroenteritis.

Our findings highlight broader concern about the use of antibiotics in animals used for food and the development of resistant enteric pathogens. Partly because of the development of resistance to ciprofloxacin among multidrug-resistant *Salmonella typhimurium* definitive type 104 (DT104) in the United Kingdom[36] and the presence of DT104 in the United States,[37] in August 1997 the Food and Drug Administration banned the off-label use of fluoroquinolones in animals used for food. We believe that this ban is an appropriate and important measure for public health. In 1998, enrofloxacin was licensed for use in beef cattle in the United States. The use of fluoroquinolones in beef cattle should be monitored closely to detect any quinolone resistance in foodborne bacterial pathogens that may result from this practice. Despite these efforts, measures of control implemented in the United States alone will not be sufficient to curtail the development of quinolone resistance in foodborne bacterial pathogens. A well-coordinated international program is needed to assess worldwide use of antibiotics in animals used for food and to ensure appropriate limitations of such use if it is shown to be deleterious to human health.

APPENDIX

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