MAJOR ARTICLE

Prolonged Diarrhea Due to Ciprofloxacin-Resistant *Campylobacter* Infection

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Background. *Campylobacter* causes >1 million infections annually in the United States. Fluoroquinolones (e.g., ciprofloxacin) are used to treat *Campylobacter* infections in adults. Although human infections with ciprofloxacin-resistant *Campylobacter* have become increasingly common, the human health consequences of such infections are not well described.

Methods. A case-control study of persons with sporadic *Campylobacter* infection was conducted within 7 FoodNet sites during 1998–1999. The E-test system (AB Biodisk) was used to test for antimicrobial susceptibility to ciprofloxacin; ciprofloxacin resistance was defined as a ciprofloxacin minimum inhibitory concentration of ≥ 4 μg/mL. We conducted a case-comparison study of interviewed persons who had an isolate tested.

Results. Of 858 isolates tested, 94 (11%) were ciprofloxacin resistant. Among 290 persons with *Campylobacter* infection who did not take antidiarrheal medications, persons with ciprofloxacin-resistant infection had a longer mean duration of diarrhea than did persons with ciprofloxacin-susceptible infection (9 vs. 7 days [$P = .04$]). This difference was even more pronounced among the 63 persons who did not take antidiarrheal medications or antimicrobial agents (12 vs. 6 days [$P = .04$]). In a multivariable analysis-of-variance model, the persons with ciprofloxacin-resistant infection had a longer mean duration of diarrhea than did the persons with ciprofloxacin-susceptible infection ($P = .01$); this effect was independent of foreign travel. The association between ciprofloxacin resistance and prolonged diarrhea is consistent across a variety of analytical approaches.

Conclusions. Persons with ciprofloxacin-resistant *Campylobacter* infection have a longer duration of diarrhea than do persons with ciprofloxacin-susceptible *Campylobacter* infection. Additional efforts are needed to preserve the efficacy of fluoroquinolones.

It is estimated that >1 million persons are infected with *Campylobacter* in the United States annually [1]. Of these infections, an estimated 10,000 result in hospitalization, and an estimated 90 result in death [1, 2]. Antimicrobial agents are commonly prescribed for patients with *Campylobacter* infection and may be lifesaving for persons with severe infection. In the United States, the first fluoroquinolone (ciprofloxacin) was approved for use in human medicine in 1986. Since then, ciprofloxacin has been a commonly prescribed antimicrobial agent for the treatment of campylobacteriosis in adults and has been shown to reduce the duration of diarrhea associated with *Campylobacter* infection [3].

An increasing proportion of human infections with *Campylobacter* are caused by ciprofloxacin-resistant strains [4, 5]. In a national survey conducted by the Centers for Disease Control and Prevention (CDC) in 1990, none of the 297 *C. jejuni/coli* isolates tested were ciprofloxacin resistant [5]. In 1997, the National An-

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timicrobial Resistance Monitoring System (NARMS) began monitoring the prevalence of ciprofloxacin-resistant *Campylobacter* in the United States and found that 13% of *C. jejuni/coli* isolates were ciprofloxacin resistant, which increased to 20% in 2001 [4, 5].

Although studies have described differences in clinical outcomes (e.g., higher mortality, prolonged symptoms, and more-frequent hospitalizations) for other pathogens in persons with antimicrobial-resistant infection, compared with clinical outcomes in persons with antimicrobial-susceptible infection [6, 7], the human health consequences of ciprofloxacin resistance in persons with *Campylobacter* infection are not well described [8]. We therefore conducted a study to determine whether persons with ciprofloxacin-resistant *Campylobacter* infection have a more severe or prolonged illness than do persons with ciprofloxacin-susceptible *Campylobacter* infection.

PARTICIPANTS, MATERIALS, AND METHODS

The Foodborne Diseases Active Surveillance Network (FoodNet), part of the CDC's Emerging Infections Program, monitors the burden of foodborne diseases, such as campylobacteriosis. FoodNet is a collaboration of the CDC, the US Food and Drug Administration (FDA), the US Department of Agriculture (USDA), and selected state health departments. The design and collection of data for this study were conducted at participating state health departments and the CDC; all collaborators, including the CDC, the FDA, and the USDA, approved the finished manuscript. When the study was being designed, the appropriate human-subjects approvals were obtained by participating state health departments and the CDC. We obtained informed consent from participants and conducted the present study in accordance with the guidelines for human research specified by the US Department of Health and Human Services.

Surveillance personnel within the FoodNet sites ascertain all culture-confirmed cases of *Campylobacter* infection within the surveillance area. In 1998, the FoodNet surveillance area consisted of the entire states of Connecticut, Minnesota, and Oregon and of selected counties in California (Alameda and San Francisco), Georgia (Barrow, Bartow, Carroll, Cherokee, Clayton, Cobb, Coweta, DeKalb, Douglas, Fayette, Forsyth, Fulton, Gwinnett, Henry, Newton, Paulding, Pickens, Rockdale, Spalding, and Walton), Maryland (Anne Arundel, Baltimore, Baltimore City, Carroll, Harford, and Howard), and New York (Genesse, Livingston, Monroe, Ontario, Orleans, Wayne, and Yates). This surveillance area included 341 clinical laboratories and covered an estimated population of 20,723,982 (7.7% of the US population).

FoodNet conducted a case-control study within these sites during 1998–1999, primarily to determine risk factors for becoming infected with *Campylobacter*. With the exception of Connecticut, all persons with culture-confirmed *Campylobacter* infection ascertained by FoodNet personnel between February 1998 and January 1999 were eligible for the case-control study; in Connecticut, only residents of 3 (Hartford, New Haven, and Fairfield) of the 8 counties in the state were eligible for the case-control study. Interviews were not conducted with persons who did not speak English or who refused or were unable to answer questions (e.g., due to incapacitation). Interviewed persons were not included in the analysis if they did not report diarrhea ($\geqslant$3 loose stools in a 24-h period), if they still had diarrhea at the time of the interview, or if they were unable to give an estimated duration of diarrhea.

In the FoodNet case-control study, a standardized questionnaire was administered via telephone. Participants were asked questions concerning the clinical course of the *Campylobacter* infection, the presence of preexisting medical conditions, and foreign travel during the 7 days before the onset of illness. Some persons with culture-confirmed *Campylobacter* infection were excluded (e.g., patients who were unable to recall an estimated illness-onset date) but were still interviewed about their illness; clinical data were collected from these persons, but questions about foreign travel were not asked. If a participant was <12 years of age, the questionnaire was administered to an adult member of the household, who answered questions about the child. Before speaking with a participant between 12 and 18 years of age, permission from a parent or guardian was obtained.

Connecticut and Minnesota required, and New York requested, that clinical laboratories in their states submit all *Campylobacter* isolates to the state public-health laboratory during the study period. Although California, Georgia, Maryland, and Oregon did not request the routine submission of Campylobacter isolates, these states arranged for 1 isolate/week/state from $\geqslant$1 clinical laboratories in each state to be submitted to NARMS at the CDC. *Campylobacter* isolates were tested for susceptibility to ciprofloxacin by the E-test system (AB Biodisk) at Connecticut, Minnesota, and New York state public-health laboratories and at the CDC. Ciprofloxacin resistance was defined as a ciprofloxacin MIC of $\geqslant$4 μg/mL.

As a supplemental study of the FoodNet case-control study, we conducted a case-comparison study, to analyze differences in illness outcome between persons infected with ciprofloxacin-resistant *Campylobacter* and persons infected with ciprofloxacin-susceptible *Campylobacter*. For this case-comparison study, we included persons with culture-confirmed *Campylobacter* infection who (1) had been interviewed for the FoodNet case-control study and (2) had had an isolate tested for susceptibility.

Potential differences between the characteristics of the persons with ciprofloxacin-resistant *Campylobacter* infection and the persons with ciprofloxacin-susceptible *Campylobacter* infection were examined by use of Fisher's exact test. The potential association between (1) ciprofloxacin resistance and illness outcomes and (2) the characteristics of the persons infected with

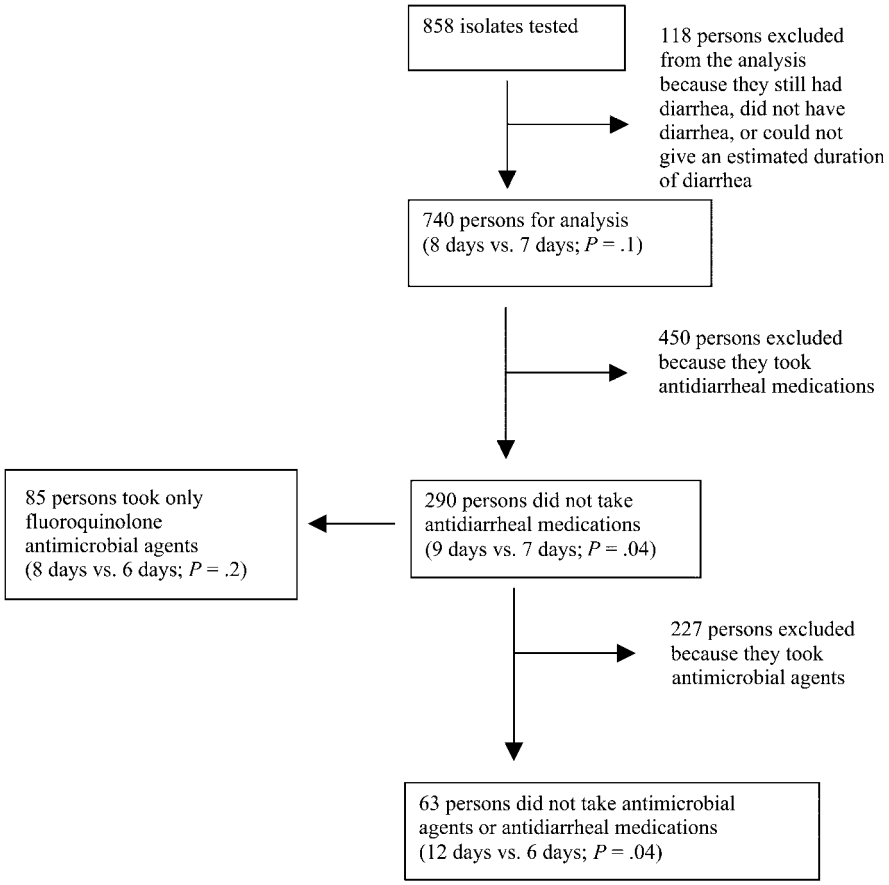

Figure 1. Diagram of persons included and excluded in the present analysis. Data in parentheses indicate the mean duration of diarrhea in persons with ciprofloxacin-resistant *Campylobacter* infection vs. that in persons with ciprofloxacin-susceptible *Campylobacter* infection.

ciprofloxacin-resistant *Campylobacter* and illness outcomes were analyzed by use of several methods. For dichotomous illness-outcome variables, Fisher's exact test was used. For continuous illness-outcome variables, analysis of variance (ANOVA) was used to analyze differences in means, and the Wilcoxon rank sum test was used to analyze differences in medians. Further analysis was conducted by use of a multivariable ANOVA model, to determine whether the persons with ciprofloxacin-resistant infection had a longer mean duration of diarrhea than did the persons with ciprofloxacin-susceptible infection when important covariates were controlled for (i.e., characteristics of infected persons). All covariates found in univariable ANOVA to be associated with mean duration of diarrhea were included in the multivariable ANOVA model.

To assess the effect that foreign travel has on the association between ciprofloxacin-resistant *Campylobacter* infection and mean duration of diarrhea, we repeated the multivariable ANOVA with an added variable for foreign travel. Because foreign travel information was missing for some persons, we imputed the missing data on foreign travel using a multiple-imputation technique described by Schafer [9] and then again repeated the multivariable ANOVA. We also repeated the ANOVA (1) using Box-Cox transformations of duration of diarrhea; (2) excluding and reducing duration of diarrhea for cases with various outlying durations (range, 22–35 days); and (3) using various censored-data models, to include cases with ongoing diarrhea. Statistical analyses were performed by use of SAS software (version 8; SAS Institute).

RESULTS

During the 12-month study period, 4000 persons with culture-confirmed *Campylobacter* infection were identified within the FoodNet sites; 2093 (52%) were interviewed for the FoodNet case-control study. The results of this study have been reported elsewhere [10]. Isolates were available and susceptibility was tested for 858 (41%) persons. Of the 858 isolates tested, 94 (11%) were resistant to ciprofloxacin. For our case-comparison study, 15 persons who had reported not having diarrhea, 68 persons who still had diarrhea at the time of the interview, and 35 persons who had been unable to give an estimated duration of diarrhea were excluded from the main analysis, leaving 740 (86%) persons for analysis (figure 1). Of these persons, 653 (89%) were white and 395 (54%) were male; the median age was 34 years (range,

<1–96 years). A high proportion of the persons lived in an urban/suburban area (68%), had at least a bachelor's degree (43%), and had an annual income >$60,000 (42%). Clinical symptoms included abdominal cramps (85%), fever (83%), bloody stool (43%), and vomiting (28%); 354 (48%) reported a duration of diarrhea ⩾7 days (mean, 7 days [range, 1–60 days]) (median, 6 days). Of the 740 persons, 647 (87%) provided information about foreign travel, of which 77 (12%) reported foreign travel during the 7 days before the onset of illness.

Of the 740 persons with culture-confirmed *Campylobacter* infection, 83% took an antimicrobial agent for their illness. Of those who took an antimicrobial agent for their illness, 19% did not know which antimicrobial agent they took. Of the 497 who knew which antimicrobial agent they took, 56% took fluoroquinolones, of which 93% took no other antimicrobial agent. Sixty percent of the persons with culture-confirmed *Campylobacter* infection took antidiarrheal medication for their illness. Twenty-nine (4%) persons reported having preexisting medical conditions, of whom 17 had diabetes, 6 had cancer, and 6 had other medical conditions. Ninety-two (12%) persons with culture-confirmed *Campylobacter* infection were hospitalized for a mean of 3 days (range, 1–21 days) (median, 3 days). Eighty-five percent reported missing work, and 83% reported interruption of daily activities due to their illness.

Of the 740 persons in the case-comparison analysis, 82 (11%) had ciprofloxacin-resistant infection; the prevalence of ciprofloxacin resistance was 38% (29 of 77) in foreign travelers and was 7% (41 of 570) in non–foreign travelers. With regard to race, sex, age, and preexisting medical condition, there were few differences between the 82 persons with ciprofloxacin-resistant infection and the 658 persons with ciprofloxacin-susceptible infection (table 1). Persons with ciprofloxacin-resistant infection were more likely to live in an urban/suburban area ($P = .02$), have at least a bachelor's degree ($P < .01$), and have an annual income >$60,000 ($P = .02$) than were persons with ciprofloxacin-susceptible infection.

We looked for differences in several illness outcomes between persons infected with ciprofloxacin-resistant *Campylobacter* and persons infected with ciprofloxacin-susceptible *Campylobacter* (table 2). The persons with ciprofloxacin-resistant infection and the persons with ciprofloxacin-susceptible infection were equally likely to be hospitalized. The mean duration of hospitalization was longer for the susceptible group (3 days) than for the resistant group (2 days) ($P = .01$); days of missed work or usual activities did not significantly differ between the 2 groups. The mean duration of diarrhea was 8 days (range, 2–21 days) (median, 7 days) for the 82 persons with ciprofloxacin-resistant infection and was 7 days (range, 1–60 days) (median, 6 days) for the 658 persons with ciprofloxacin-susceptible infection ($P = .1$).

Further analysis was conducted on duration of diarrhea. We looked at differences in mean and median duration of diarrhea and potential covariates (table 3). There was a marked difference in mean and median durations of diarrhea between persons who did and did not take antidiarrheal medication. The mean duration of diarrhea was 8 days (range, 1–30 days) (median, 7 days) for the 444 persons who took antidiarrheal medication and was 7 days (range, 2–60 days) (median, 6 days) for the 290 persons who did not take antidiarrheal medication ($P = .01$). Similarly, the mean duration of diarrhea was 8 days (range, 2–28 days) (median, 7 days) for the 77 foreign travelers and was 7 days (range, 1–60 days) (median, 6 days) for the 570 non–foreign travelers ($P = .09$).

Because of the marked association between taking antidiarrheal medication and mean duration of diarrhea, we analyzed the difference in mean duration of diarrhea between the persons with ciprofloxacin-resistant infection and the persons with ciprofloxacin-susceptible infection among those persons who did not take antidiarrheal medication. Thirty-nine percent (290 of 734)

Table 1. Characteristics of persons with *Campylobacter* infection ($n = 740$) in the case-comparison study, by susceptibility status.

Characteristic	Persons with ciprofloxacin-resistant infection ($n = 82$)	Persons with ciprofloxacin-susceptible infection ($n = 658$)	P[a]
Race, white	73/82 (89)	580/654 (89)	1.00
Sex, male	41/81 (51)	354/651 (54)	.55
Residence, urban/suburban	65/82 (79)	435/655 (66)	.02
Education, bachelor's degree or higher	51/81 (63)	261/647 (40)	<.01
Household income, >$60,000	37/66 (56)	223/547 (41)	.02
Preexisting medical condition	4/82 (5)	25/653 (4)	.55
Foreign travel	29/70 (41)	48/577 (8)	<.01

NOTE. Data are proportion (%) of persons, unless otherwise noted. Excluded from the study were persons who reported not having diarrhea, who still had diarrhea at the time of the interview, and who were unable to give an estimated duration of diarrhea.

[a] Determined by Fisher's exact test.

Table 2. Illness characteristics of persons with *Campylobacter* infection ($n = 740$) in the case-comparison study, by susceptibility status.

Characteristic, category	Persons with ciprofloxacin-resistant infection ($n = 82$)	Persons with ciprofloxacin-susceptible infection ($n = 658$)	P[a]
Duration of diarrhea, ⩾7 days	47/82 (57)	307/658 (47)	.08
Symptoms			
Fever	63/76 (83)	526/630 (83)	.87
Vomit	24/79 (30)	182/648 (28)	.69
Abdominal cramps	68/78 (87)	544/640 (85)	.74
Bloody stool	35/77 (45)	264/612 (43)	.72
Age, years			
Mean (25th–75th percentile)	36 (24–47)	34 (18–49)	.30
Median	31	34	.40
Duration of diarrhea,[b] days			
Mean (25th–75th percentile)	8 (5–10)	7 (4–8)	.10
Median	7	6	.08
Hospitalization			
Admission	10/82 (12)	82/654 (12)	1.00
Length,[b] days			
Mean (25th–75th percentile)	2 (1–3)	3 (2–4)	.01
Median	2	3	.03
Missed work,[b] days			
Mean (25th–75th percentile)	3 (2–4)	4 (2–5)	.40
Median	3	3	.20
Missed usual activities,[b] days			
Mean (25th–75th percentile)	6 (3–6)	6 (3–7)	.80
Median	4	5	.30
Antidiarrheal medication	56/82 (68)	388/652 (59)	.15

NOTE. Data are proportion (%) of persons, unless otherwise noted. Excluded from the study were persons who reported not having diarrhea, who still had diarrhea at the time of the interview, and who were unable to give an estimated duration of diarrhea.

[a] Fisher's exact test was used for dichotomous variables; differences in mean duration of diarrhea were determined by analysis of variance (ANOVA); differences in median duration of diarrhea were determined by nonparametric 1-way ANOVA (Wilcoxon rank sum test).

[b] Statistics were computed for individuals with positive values.

did not take antidiarrheal medication for their illness. The mean duration of diarrhea among persons who did not take antidiarrheal medication was 9 days (range, 2–21 days) (median, 7 days) for the 26 persons with ciprofloxacin-resistant infection and was 7 days (range, 2–60 days) (median, 6 days) for the 264 persons with ciprofloxacin-susceptible infection ($P = .04$). The mean duration of diarrhea among persons who did not take antidiarrheal medications was 7 days (range, 2–21 days) (median, 6 days) for the 19 foreign travelers and was 7 days (range, 2–60 days) (median, 6 days) for the 235 non–foreign travelers ($P = .9$).

We also explored the effect that taking antimicrobial agents, particularly fluoroquinolones, has on the difference in mean duration of diarrhea between persons with ciprofloxacin-resistant infection and persons with ciprofloxacin-susceptible infection. Of the 740 persons, 85 (11%) took fluoroquinolones and no other antimicrobial agent or antidiarrheal medication for their illness. The mean duration of diarrhea among persons who took fluoroquinolones and no other antimicrobial agent or antidiarrheal medication was 8 days (range, 3–14 days) (median, 7 days) for the 9 persons with ciprofloxacin-resistant infection and was 6 days (range, 2–31 days) (median, 5 days) for the 76 persons with ciprofloxacin-susceptible infection ($P = .2$). Among persons who took fluoroquinolones and no other antimicrobial agent or antidiarrheal medications with known travel history, the mean duration of diarrhea was 6 days (range, 2–12 days) (median, 6 days) for the 11 foreign travelers and was 6 days (range, 2–31 days) (median, 5 days) for the 63 non–foreign travelers ($P = .6$).

Of the 740 persons in the case-comparison analysis, 63 (8%) reported not taking an antimicrobial agent or an antidiarrheal medication for their illness. The mean duration of diarrhea among persons who did not take an antimicrobial agent or an antidiarrheal medication was 12 days (range, 4–20 days) (median, 9 days) for the 7 persons with ciprofloxacin-resistant infection and was 6 days (range, 2–14 days) (median, 5 days) for the 56 persons with ciprofloxacin-susceptible infection ($P = .04$). Among those with known travel history, 1 of the 51 persons who did not take an antimicrobial agent or an antidiarrheal medication for their illness reported foreign travel.

Factors that were associated in the univariable analysis with mean duration of diarrhea for the 740 persons with *Campylobacter* infection were analyzed in a multivariable ANOVA model (table 4). Factors included in the final multivariable model were antimicrobial medication, antidiarrheal medication, and antacid use (table 4). When these factors were controlled for, the mean duration of diarrhea for persons with ciprofloxacin-resistant infection was 9 days, whereas the mean duration of diarrhea for persons with ciprofloxacin-susceptible infection was 8 days ($P = .01$).

Similar differences in duration of diarrhea between the persons with ciprofloxacin-resistant infection and the persons with ciprofloxacin-susceptible infection were determined when we repeated the analysis using (1) Box-Cox transformations of duration of diarrhea and (2) excluding and reducing duration of diarrhea for cases with various outlying durations (range, 22–35 days). Furthermore, the use of various censored-data models to include cases with ongoing diarrhea also determined a longer duration of diarrhea for persons with ciprofloxacin-resistant infection.

The longer mean duration of diarrhea observed for persons with ciprofloxacin-resistant infection was independent of foreign travel; a variable representing foreign travel did not contribute to the final multivariable ANOVA model. Similar differences in the duration of diarrhea between the persons with ciprofloxacin-resistant infection and the persons with ciprofloxacin-susceptible infection were evident when only foreign travelers or only non–foreign travelers were included in the multivariable model. Finally, after including foreign travel in

Table 3. Univariable analysis of the associations between potential covariates and mean duration of diarrhea.

Characteristic, category	Duration of diarrhea		P^a
	With characteristic	Without characteristic	
Antimicrobial use			
Fluoroquinolone	7.1 (1–31)	7.6 (1–60)	.18
Other	8.0 (2–60)	7.0 (1–31)	.01
Antidiarrheal medication use	7.7 (1–30)	6.8 (2–60)	.01
Antacid use	7.7 (1–31)	7.2 (1–60)	.28
Ciprofloxacin resistance[b]	8.0 (2–21)	7.2 (1–60)	.13
Plus no antidiarrheal medication use	8.8 (2–21)	6.6 (2–60)	.04
Plus antidiarrheal medication use	7.7 (2–21)	7.7 (1–30)	.99

NOTE. Data are mean (range) days of duration of diarrhea.

[a] Differences in mean duration of diarrhea were determined by analysis of variance.

[b] Determined on the basis of comparison within the antidiarrheal-use and nonuse subgroups.

the multivariable ANOVA model and imputing missing foreign travel data, the mean duration of diarrhea remained longer in persons with ciprofloxacin-resistant infection, compared with persons with ciprofloxacin-susceptible infection ($P < .05$).

DISCUSSION

The present multistate case-comparison study, which was part of a larger FoodNet case-control study conducted during 1998–1999, has demonstrated that ciprofloxacin resistance is common in human *Campylobacter* infection and provides evidence that persons with ciprofloxacin-resistant *Campylobacter* infection have a longer duration of diarrhea than do persons with ciprofloxacin-susceptible *Campylobacter* infection. This effect appears to be independent of foreign travel. Our finding of an association between ciprofloxacin-resistant *Campylobacter* infection and a longer duration of diarrhea is consistent with the results of at least 2 other studies that have examined similar associations [8, 11]. In Minnesota, Smith et al. reported that persons with quinolone-resistant infection had a median duration of diarrhea that was 3 days longer than that of persons with quinolone-susceptible infection [11]. In Denmark, Neimann et al. reported that persons with ciprofloxacin-resistant infection who were treated with fluoroquinolones had a median duration of illness that was 5 days longer than that of persons with ciprofloxacin-susceptible infection [8].

Because the treatment of diarrheal illness with antidiarrheal medications is associated with the duration of diarrhea—and because such treatment is common—it is important to control for the effects of such treatment. In our analysis that controlled for the effect of taking antidiarrheal medication, there was a consistent association between ciprofloxacin resistance and a longer duration of diarrhea across a variety of mathematical models, including (1) Box-Cox transformations of duration of diarrhea and (2) excluding and reducing duration of diarrhea for cases with various outlying durations (range, 22–35 days).

It has been suggested that the observed longer duration of diarrhea in the present analysis could be explained by foreign travel rather than by ciprofloxacin resistance [12]. Researchers for the animal-drug industry analyzed our data, which they had obtained under the Freedom of Information Act, and concluded that foreign travel confounded the association between fluoroquinolone resistance and duration of diarrhea [13]. Their analysis, which did not consider the effect of taking antidiarrheal medication, concluded that fluoroquinolone resistance was not associated with an increased duration of diarrhea. We therefore included foreign travel as a variable in the present analysis and found that, when antidiarrheal medication is included in the model, the inclusion of foreign travel does not change the consistent association observed between ciprofloxacin resistance and duration of diarrhea. Foreign travel is not consistently or strongly associated with a longer duration of diarrhea, nor does it confound the observation that ciprofloxacin resistance is associated with a longer duration of illness. Failure to include the effect of antidiarrheal treatment leaves a major associated factor uncontrolled, resulting in spurious results.

More studies are needed to determine why there is an association between ciprofloxacin-resistant *Campylobacter* infection and a longer duration of diarrhea. It has been observed that treatment with antimicrobial agents (including fluoroquinolones), if given early in the clinical course, can shorten the duration of illness [14]. Therefore, one explanation for a longer duration of diarrhea in persons with ciprofloxacin-resistant *Campylobacter* infection who are treated with fluoroquinolones is that fluoroquinolones are less efficacious against ciprofloxacin-resistant *Campylobacter,* thus prolonging the diarrheal illness.

Our data are consistent with such an effect, although our sample of persons treated with a fluoroquinolone in the absence of an antidiarrheal agent was small. Importantly, we also found that, even in the absence of ciprofloxacin treatment, the duration of diarrhea was longer for ciprofloxacin-resistant infection than for ciprofloxacin-susceptible infection. This result suggests that the virulence of resistant organisms may differ

Table 4. Multivariable analysis of mean duration of diarrhea, including risk factors found to be associated with mean duration of diarrhea in the univariable analysis.

Variable, category	F	*P*	Estimate of effect (95% CLs)[a]
Antimicrobial use			
Fluoroquinolone	0.25	0.62	0.21 (−1.06, 0.63)
Other	7.45	0.01	1.27 (−0.36, 2.18)
Antidiarrheal medication use	7.72	0.01	1.14 (0.34, 1.96)
Antacid use	4.33	0.04	0.98 (0.06, 1.90)
Ciprofloxacin resistance	7.83	0.01	2.98 (0.89, 5.07)
Ciprofloxacin resistance plus antidiarrheal medication use	4.29	0.04	−2.68 (−5.21, −0.14)

NOTE. Differences in mean duration of diarrhea were determined by analysis of variance. CLs, confidence limits.

[a] Estimates are mean no. of days. Negative nos. reflect decreased duration of diarrhea. The last 2 lines reflect that, among non–antidiarrheal medication users, ciprofloxacin resistance is associated with 3 additional days of diarrhea, but among antidiarrheal medication users, resistance is associated with 0.3 additional days of diarrhea.

from that of susceptible strains; mutations in gyrase genes could be associated with a difference in virulence or other resistance effectors, such as the recently described CmeABC efflux pump [15] or compensatory mutations in other genes [16], such as those described in *Escherichia coli* [16].

The clinical significance of a longer duration of diarrheal illness may extend beyond a need for medications and its effects on work, study, and other daily activities. For example, Neal et al. recently reported that persons with prolonged *Campylobacter* infection (i.e., diarrheal illness lasting >15 days) were more likely to develop symptoms of reactive arthritis [17], perhaps due to longer or more-intense antigenic stimulation. We did not observe a difference in hospitalization rate associated with ciprofloxacin resistance, such as was recently reported for non-Typhi *Salmonella* infection with some resistant strains [18]. Longer term effects of infection with ciprofloxacin-resistant *Campylobacter* remain unevaluated. In a registry-based analysis in Denmark, persons with quinolone-resistant *Salmonella* infection were significantly more likely to die within 2 years of becoming infected than were persons with quinolone-susceptible *Salmonella* infection [7]. A similar approach to analyzing *Campylobacter* infection would be of interest.

Several recent investigations have explored factors associated with acquiring ciprofloxacin-resistant *Campylobacter* species. A related FoodNet *Campylobacter* case-control study, which compared exposure between persons with ciprofloxacin-resistant *Campylobacter* infection and healthy control subjects, demonstrated that, in the United States, eating poultry outside the home was associated with domestically acquired ciprofloxacin-resistant *Campylobacter* infection; foreign travel was another important source of ciprofloxacin-resistant *Campylobacter* infection [19]. In Minnesota, Smith et al. reported that ciprofloxacin-resistant *Campylobacter* was isolated from 14% of raw poultry products obtained from retail markets in 1997 [11]. In a similar multistate survey, ciprofloxacin-resistant *Campylobacter* was isolated from 11% of raw chickens obtained from retail markets in 1999 [5].

Among *Campylobacter* species, there is cross-resistance among fluoroquinolones; strains resistant to ciprofloxacin are also resistant to sarafloxacin and enrofloxacin, fluoroquinolones that were approved in the United States in 1995 and 1996, respectively, for the treatment of respiratory diseases in poultry [20]. Enrofloxacin is given to chickens and turkeys by adding it to drinking water, thereby administering it to tens of thousands of birds at once (i.e., on a housewide basis). Several investigations have demonstrated that the use of enrofloxacin in poultry results in the rapid emergence of ciprofloxacin resistance among *Campylobacter* species in poultry [21–25]. The FDA conducted a quantitative risk assessment that concluded that the use of fluoroquinolone agents in poultry resulted in the emergence and dissemination of ciprofloxacin-resistant *Campylobacter* species, which are transmitted to humans through the food supply. It has been estimated that this transmission annually results in the infection of thousands of persons with ciprofloxacin-resistant *Campylobacter* species, who seek medical attention for campylobacteriosis and are prescribed fluoroquinolones [26, 27]. In 2000, the FDA proposed the withdrawal of approval for use of fluoroquinolones in chickens and turkeys [28].

The present study has provided a case-comparison analysis of persons with culture-confirmed *Campylobacter* infection, conducted within the parameters of a larger FoodNet case-control study. Being an observational study, potential confounding variables were accounted for by statistical modeling, not by experimental randomization. The selection of cases for inclusion in the present study likely was not influenced by antimicrobial-susceptibility results, because isolates were selected for testing without knowledge of resistance results. Not surprisingly, the prevalence (11%) of ciprofloxacin resistance observed in the present study is similar to that (13%) observed by NARMS in 1998 [4]. Furthermore, participants were interviewed without knowledge of resistance results as well. Therefore, although the outcomes of interest depended on the memories of the participants, such recall would unlikely be influenced by resistance results. Information on travel history was missing for a fraction of persons. Imputation is a statistical tool now used regularly to estimate the likely values of missing data on the basis of

cases with complete information. Imputation did not change our results, indicating that our findings are robust. Although the 2 groups being compared were, in general, quite similar demographically, the persons with ciprofloxacin-resistant infection tended to have more education and higher incomes than did the persons with ciprofloxacin-susceptible infection—characteristics that may be associated with foreign travel.

Fluoroquinolones are important antimicrobial agents in human medicine for the treatment of enteric illnesses, including campylobacteriosis. We found that, in the absence of antidiarrheal treatment, the persons in our study who acquired ciprofloxacin-resistant *Campylobacter* infection experienced a longer diarrheal illness than did the persons with ciprofloxacin-susceptible *Campylobacter* infection. This result indicates that there is a human health consequence of fluoroquinolone-resistant *Campylobacter* infection, emphasizing the need for additional efforts to preserve the efficacy of fluoroquinolones.

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