

Adverse Health Events Associated with Antimicrobial Drug Resistance in *Campylobacter* Species: A Registry-Based Cohort Study

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(See the editorial commentary by Jones and Schaffner, on pages 1029–31.)

Background. Resistance to clinically important antimicrobial agents, particularly fluoroquinolones and macrolides, is increasing among *Campylobacter* isolates, but few studies have explored the human health consequences of such resistance.

Methods. In a registry-based cohort study, we determined the risk of invasive illness and death associated with infection with quinolone- and erythromycin-resistant *Campylobacter* strains, while adjusting for comorbidity. We linked data from the Danish Surveillance Registry for Enteric Pathogens with data from the Civil Registration System and National Health Registries.

Results. Of 3471 patients with *Campylobacter* infection, 22 (0.63%) had an adverse event, defined as invasive illness or death, within 90 days of the date of receipt of samples. Patients infected with quinolone-resistant *Campylobacter* strains had a 6-fold increased risk of an adverse event within 30 days of the date of receipt of samples, compared with patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains (adjusted odds ratio [AOR], 6.17 [95% confidence interval {CI}, 1.62–23.47]). However, infection with erythromycin-resistant strains was associated with a >5-fold risk of an adverse event within 90 days of the date of receipt of samples (AOR, 5.51 [95% CI, 1.19–25.50]).

Conclusions. The present study provides evidence of the human health consequences of resistance to clinically important agents among *Campylobacter* infections and the need for increased efforts to mitigate such resistance.

Campylobacter species are the most frequent cause of bacterial gastroenteritis in many countries [1, 2]. Most often, they cause a self-limiting diarrheal illness, and patients do not usually require antimicrobial treatment. Treatment may be prescribed for patients with severe and prolonged gastroenteritis, suspected septicemia, or

other invasive manifestations, as well as for patients who have a severe underlying illness. Drugs of choice typically include a fluoroquinolone for early empirical treatment in adults [3] and a macrolide for treatment after the microbiological diagnosis has been established [1, 4].

In recent years, fluoroquinolone and macrolide resistance has emerged, and fluoroquinolone-resistant *Campylobacter* strains, in particular, are now common in many countries [1, 5, 6]. Although there is increasing evidence of adverse events associated with antimicrobial drug resistance in *Salmonella* infection [7–9], limited information exists on the clinical consequences of resistance in *Campylobacter* infection. A major methodological problem is that the number of well-defined, severe, and relevant outcomes is bound to be limited in most studies. These outcomes include duration of illness, complications (e.g., gastrointestinal perforation or invasive illness), long-term (chronic) sequelae (e.g., Guillian-Barré syndrome or other severe reactive ill-

Received 10 August 2004; accepted 2 December 2004; electronically published 1 March 2005.

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Presented in part: Towards a Risk-Analysis of Antibiotic Resistance international symposium, Berlin, 10 November 2003 (J Vet Med B Infect Dis Vet Public Health 2004;51:364–9); Joint World Health Organization/Food and Agriculture Organization of the United Nations/World Organisation for Animal Health Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment, Geneva, 1–5 December 2003.

Financial support: Directorate for Food, Fisheries, and Agro Business (Danish Ministry of Food, Agriculture, and Fisheries, Denmark); Center for Veterinary Medicine, US Food and Drug Administration.

The Journal of Infectious Diseases 2005;191:1050–5

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nesses), and death. Recent observational studies from the United States and Denmark have suggested that infection with fluoroquinolone-resistant *Campylobacter* strains may be associated with a longer duration of illness [2, 10, 11]. In Thailand [12], it was observed that erythromycin resistance was common in *Campylobacter* isolates, which may have accounted for a reduced efficacy of antimicrobial treatment.

The objective of the present study was to determine the risk of invasive illness or death associated with quinolone or erythromycin resistance in *Campylobacter* strains. Using data from the unique Danish population-based registries, we compared the risk of an adverse event (i.e., invasive illness or death) within 30 and 90 days of the date of receipt of samples at the microbiological laboratory for persons infected with drug-resistant and -susceptible *Campylobacter* strains, adjusting for underlying illness.

Quinolone-resistant *Campylobacter* isolates usually have a chromosomal point mutation that results in alterations of the A subunit of DNA gyrase. For *Campylobacter* species, single chromosomal point mutations have been demonstrated to be sufficient to cause an amino acid change and to result in resistance to the first-generation quinolone nalidixic acid [1, 13, 14] and to fluoroquinolones, which may indicate a poor outcome of treatment for all quinolones, including fluoroquinolones.

MATERIALS AND METHODS

Surveillance. In Denmark, the diagnosis of human *Campylobacter* infection is done at our laboratory, Statens Serum Institut (SSI), and at 10 clinical microbiology laboratories. The SSI receives notifications of laboratory-positive findings and isolates from the microbiology laboratories, and information is entered in the national surveillance registry of enteric pathogens at the SSI. Routinely, the physician who requested the fecal sample or blood culture is asked to forward information concerning whether the patient who provided the sample traveled abroad within the 2 weeks before the onset of illness.

If a *Campylobacter* isolate was found on >1 occasion from the same person during a period of 6 months, only the first positive sample was registered. As part of this laboratory-based surveillance system, monitoring for macrolide and quinolone resistance in *Campylobacter* species was initiated in 1996. From 1996 through 1998, a random sample of 10 strains/month was tested, but, from 1999 onward, all *Campylobacter* strains were tested for susceptibility. The present study includes all *Campylobacter* isolates examined at the SSI during the period 1 January 1996–31 December 2000.

Antimicrobial susceptibility testing was performed by tablet diffusion on Danish blood agar (SSI Diagnostica) by use of Neosensitabs (Rosco) [15]. Isolates were considered to be re-

sistant if they had an inhibition zone of <27 mm for nalidixic acid or erythromycin.

Registry linkage study. All live-born children and citizens of Denmark are assigned a personal identification number within the Danish Civil Registration System (CRS) [16] that uniquely identifies each person. Demographic data—including vital status, emigration or immigration status, and address of residence—are kept in the CRS. For every patient, we randomly selected 10 persons from the CRS who were matched for age, sex, and county of residence and who were alive on the date when the sample was received. We obtained information on date of death or emigration for patients and for the persons selected from the general population. Finally, data were obtained from the national registry of patients on all hospital admissions, outpatient clinic attendances, and discharge diagnoses within 5 years of entry in the study until 90 days after entry [17]. This allowed us to control for preexisting illness (comorbidity) and to ascertain a diagnosis of invasive illness during the episode of campylobacteriosis. The national registry of patients contains data on all patients discharged from non-psychiatric departments since 1 January 1977 and on outpatient attendances since 1 January 1995. Diagnoses are coded according to the *International Classification of Diseases* (ICD) 8 or ICD 10 (from 1993 onward).

The outcome variable in the present study was a diagnosis of either invasive illness or death (an adverse event). A person with a diagnosis of septicemia, endocarditis, aneurysm, meningitis, pneumonia, abscesses, pancreatitis, or hepatitis in the national registry of patients within 90 days of the date of receipt of samples (the study period) was classified as having invasive illness [18].

Because of the logistics of the surveillance program, the date of receipt at the SSI is 1–7 days after the sample-collection date, and this date was not available in all cases. Therefore, we included patients who had an adverse event between 7 days before and 90 days after the date of receipt of samples.

Statistical methods. The sample of 10 control subjects/patient selected from the general population was used to calculate the comorbidity index [18–20]. Using data from the national registry of patients and the cancer registry, we first calculated the relative mortality associated with the different diagnostic groups included in the comorbidity index (e.g., metastatic cancer, hematologic malignancies, HIV, and liver disease). The index was defined as the logarithm to this relative mortality. For each patient, the comorbidity weight was then calculated as the sum of indices corresponding to the number and severity of coexisting illnesses within 5 years of entry in the study. Because data from outpatient clinics were only available from 1995, and to avoid possible bias when adjusting for comorbidity, data

Table 1. *Campylobacter* infections, Denmark 1996–2000—details on age, sex, and comorbidity, according to antimicrobial susceptibility pattern, in 22 patients with invasive illness or fatal outcome.

Patient	Sex	Age, years	Comorbidity	Resistance to		Outcome	Time to adverse event, days ^a
				Erythromycin	Quinolone		
1	M	80	Peripheral vascular illness	No	No	Pancreatitis	–5
2	F	81		No	Yes	Septicemia	–2
3	F	0		No	Yes	Focal infection	–1
4	F	79	Hematologic malignancy	Yes	Yes	Meningitis	–1
5	M	27	Renal disease	No	Yes	Septicemia	0
6	F	37	Congestive heart failure	No	No	Septicemia	0
7	F	35		No	No	Septicemia	4
8	M	85	Non-COPD pulmonary illness	Yes	No	Death	5
9	M	73		No	Yes	Death	6
10	M	88		No	Yes	Death	6
11	M	29	Cerebral tumor	No	No	Death	18
12	F	69	Biliary tract disease	No	Yes	Aneurysm	24
13	M	88	COPD	Yes	No	Death	26
14	F	82	Movement disorders	Yes	Yes	Death	36
15	M	54	Metastatic colon tumor	No	No	Death	37
16	F	91	Non-COPD pulmonary illness	Yes	No	Death	49
17	F	88	Urothelial tumor	No	No	Death	51
18	F	89		No	No	Death	64
19	M	79	Dementia	No	No	Death	77
20	F	85		Yes	No	Death	80
21	M	73		No	No	Death	83
22	M	67	Dementia	Yes	Yes	Death	84

NOTE. COPD, chronic obstructive pulmonary disease.

^a Time from receipt of sample at the laboratory.

form outpatient clinics were restricted to within 1 year of entry in the study.

To investigate the relative risk of invasive illness or death associated with antimicrobial resistance, we used a logistic regression model that adjusted for age, sex, and comorbidity. The analyses were conducted by use of the PROC GENMOD procedure in SAS (version 8.2; SAS Institute). Odds ratios are expressed as the odds of an adverse event in persons infected with antimicrobial-resistant *Campylobacter* strains, compared with those for patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains.

RESULTS

Of the isolates responsible for the 14,443 culture-confirmed *Campylobacter* infections reported during January 1996–December 2000, 3541 (24.5%) were tested for antimicrobial drug susceptibility, and a positive match to the CRS was obtained for 3471 (98.0%). A total of 2506 *Campylobacter* isolates (72.2%) were quinolones and erythromycin susceptible, 760 (21.9%) were quinolone resistant, 109 (3.1%) were erythromycin resistant, and 96 (2.8%) were quinolone and erythromycin resistant.

Information on travel history was available for 3380 (97.4%) patients; 554 (16.4%) of these had a history of travel within 2 weeks of the onset of illness. Spain, Thailand, and Turkey were

the most common destinations. A total of 2826 (83.6%) patients had acquired the infection domestically.

Among the isolates responsible for travel-associated infections, 268 (48.4%) were quinolone resistant, compared with 550 (19.5%) responsible for domestically acquired infections ($P < .001$). The prevalence of quinolone resistance was particularly high among patients returning from Thailand (81.3%), India (71.1%), and Spain (62.5%).

Thirty-five (6.3%) of the travel-associated *Campylobacter* isolates and 163 (5.8%) of the domestically acquired isolates were erythromycin resistant ($P = .61$). The prevalence of erythromycin resistance was high among patients returning from India (15.8%) and Spain (10.0%).

Overall, we identified 5 persons (0.14%) who died within 30 days of the date of receipt of samples. Within 90 days of the date of receipt of samples, 22 patients (0.63%) had an adverse event—15 died (0.43%), and 7 (0.20%) were diagnosed with invasive illness (table 1). The median age of patients with an adverse event was 78.8 years (range, 0.5–90.6 years), whereas patients with no record of an adverse event had a median age of 27.4 years (range, 0.2–92.3 years). Comorbidity was more common among patients with an adverse event—14 (63.6%) of 22 patients—than among the 614 patients (17.8%) without such an event ($P < .001$).

Patients infected with a quinolone-resistant *Campylobacter* strain had a 3-fold (95% confidence interval [CI], 0.99–9.39) increased risk of adverse events within 90 days of infection, after adjustment for sex, age, and comorbidity, compared with patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains (table 2). However, there were no additional cases of invasive illness or deaths among patients infected with quinolone-resistant *Campylobacter* strains during the 30–90 days of the date of receipt of samples. Therefore, we also examined the effect of infection with quinolone-resistant *Campylobacter* strains within 30 days of the date of receipt of samples. During this period, patients quinolone-resistant *Campylobacter* infection had a 6.17-fold (95% CI, 1.62–23.47-fold) increased risk of adverse events, after adjustment for sex, age, and comorbidity, compared with patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains.

Among patients infected with erythromycin-resistant *Campylobacter* strains, we found a 5.51-fold (95% CI, 1.19–25.50-fold) increased risk, after adjustment, of invasive illness or death within 90 days, compared with patients infected with quinolone- and erythromycin-susceptible strains (table 2). None of these 22 patients had a history of travel abroad within the 2 weeks before infection. Therefore, we performed a subanalysis among the 2826 persons with domestically acquired infection. Patients infected with quinolone-resistant *Campylobacter* strains had a 9.68-fold (95% CI, 2.23–42.04-fold) increased risk of adverse events within 30 days of infection, adjusted for sex, age, and comorbidity.

Information on antimicrobial treatment was only available for a subset of 163 patients infected with erythromycin-resistant *Campylobacter* strains. Fifty-two (31.9%) patients had been prescribed an antimicrobial drug within 30 days of infection. Among these patients, we identified 3 who received a diagnosis

of invasive illness or who died—1 received ciprofloxacin and 2 received broad-spectrum penicillin.

DISCUSSION

The present study has shown that patients infected with a quinolone- or erythromycin-resistant *Campylobacter* strain have an increased risk of an adverse event, compared with patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains. Our results corroborate those of other studies from the United States, Thailand, and Denmark [10–12], which showed that infection with quinolone- or erythromycin-resistant *Campylobacter* strains causes a longer duration of illness.

Our data also show that invasive illness and death associated with *Campylobacter* infection are rare events, particularly in comparison with nontyphoidal *Salmonella* infection, the other major cause of foodborne bacterial gastroenteritis in industrialized countries. The overall case-fatality rate in the present study was 0.14% (5 deaths within 30 days of infection), which is lower than that of nontyphoidal *Salmonella* infection but is in line with data from previous studies [18]. Although severe adverse events caused by *Campylobacter* infection are, in general, rare, the relative effect associated with quinolone resistance is of a magnitude similar to the increased mortality associated with quinolone-resistant *Salmonella* infection [20–22].

In the present study, we examined the most severe adverse events—invasive illness and death—associated with quinolone- and macrolide-resistant *Campylobacter* infection. The present study used data from registries created for other purposes, and these data can be regarded as an unbiased sample of the culture-confirmed cases of *Campylobacter* infection. The present study was particularly unique because we were able to include data from the general population, which allowed us to adjust for imbalances in comorbidity.

Table 2. No. of cases of invasive illness and death among 3471 patients with *Campylobacter* infection, Denmark 1996–2000, according to resistance profile.

Resistance/susceptibility profile	0–30 days			0–90 days		
	Adverse event/alive ^a	Crude OR (95% CI)	Adjusted OR ^b (95% CI)	Adverse event/alive ^a	Crude OR (95% CI)	Adjusted OR ^b (95% CI)
Resistance to						
Quinolone only	6/754	4.97 (1.40–17.67)	6.17 (1.62–23.47)	6/754	2.20 (0.78–6.21)	3.06 (0.99–9.47)
Erythromycin only	2/107	11.68 (2.12–64.49)	4.70 (0.54–40.72)	4/105	10.55 (3.20–34.82)	5.51 (1.19–25.50)
Both	1/95	6.58 (0.73–59.42)	2.36 (0.18–31.46)	3/93	8.94 (2.38–33.55)	1.76 (0.29–10.69)
Susceptible to quinolone and erythromycin	4/2500	1.00	1.00	9/2493	1.00	1.00
Total	13/3456			22/3445		

NOTE. Two and 4 patients emigrated within 30 and 90 days of infection, respectively. Because we did not have complete follow-up data on these patients, they were excluded from the statistical analysis. Also shown are the crude and adjusted relative risk of invasive illness or death within 30 and 90 days of date of the receipt of samples. CI, confidence interval; OR, odds ratio.

^a No. of deaths or subjects with invasive illness/no. who survived.

^b Adjusted for age, sex, and comorbidity.

Both age and the presence of coexisting illness are important predictors of outcome. The comorbidity index used in the present study was based on diagnoses at discharge and on data from outpatient clinics but did not include data from general practitioners. It could be argued that this weakens the index. However, we assumed that any patient with a preexisting disease that was severe enough to alter the outcome of a foodborne infection was likely to have come into contact with a hospital or an outpatient clinic within the 5 years before infection.

Foreign travel is a major risk factor for the acquisition of quinolone-resistant *Campylobacter* infection [2, 5, 23, 24]. It is furthermore likely that the average traveler is in better general health than the average patient with domestically acquired infection; therefore, travel may confound the association measurements toward 1. This point was corroborated by the sub-analysis that excluded travel-associated cases; the relative risk of an adverse event after infection with quinolone-resistant *Campylobacter* strains was higher in patients who acquired the infection domestically than in patients who acquired the infection while traveling.

Antimicrobial drug resistance in *Campylobacter* species may be associated with adverse events in several ways, including reduced efficacy of treatment. This may especially be the case for fluoroquinolones, which commonly are used early during the empirical treatment of severe gastroenteritis in patients with underlying illness or at the extremes of age. This notion is corroborated by the fact that most adverse events occurring after the acquisition of quinolone-resistant *Campylobacter* infection were observed within 30 days of diagnosis. Unfortunately, we had no data on treatment with quinolones. Therefore, it was impossible to explore the extent to which the increased risk of an adverse event in patients infected with quinolone-resistant strains was caused by reduced efficacy of drugs.

The excess morbidity and mortality associated with erythromycin resistance may, however, have a different explanation. The risk of an adverse event was most convincingly observed within 90 days of the date of receipt of samples.

Information on antimicrobial treatment was available for a subset of patients infected with erythromycin-resistant strains; none of the patients with adverse event had been treated with erythromycin. On this basis, it is unlikely that the adverse effect of erythromycin resistance is caused by therapeutic failure. Erythromycin resistance is more common in *Campylobacter coli* than in *Campylobacter jejuni* infection [1], and it has also been suggested that *C. coli* is more invasive than is *C. jejuni* [25]. Hence, it is possible that the marked increased risk of invasive illness or death associated with erythromycin-resistant strains is confounded by *Campylobacter* species. Only 2 strains from patients with an adverse event had been speciated, and they were *C. jejuni* strains, which suggests that the results are unlikely to be confounded by a possible increased virulence of *C. coli*. Ad-

ditionally, strains were available from 17 other patients who died within 1 year of *Campylobacter* infection, and these strains were all *C. jejuni* (data not shown). This does not preclude that markers of virulence may be associated with erythromycin resistance. If macrolide resistance is associated with some unknown virulence markers, the use of macrolides in any ecosystem may select such strains. In other words, antimicrobial drug resistance may be of public-health importance even in the absence of evidence of therapeutic failure.

Fluoroquinolones have been part of human medicine since the 1980s, with no or very limited resistance in *Campylobacter* species. It was not until the license of fluoroquinolones in food-animal production in the early 1990s that resistant *Campylobacter* strains emerged [1, 2, 26]. Also, in Australia, the use of quinolones has never been approved in food animals; as a result, very few domestically acquired quinolone-resistant *Campylobacter* infections have been seen [27]. Macrolide resistance is less common, and most studies have not shown a clear trend over time [1, 4]. Nevertheless, a modest increase was observed in studies from Japan, Spain, Sweden, and Thailand [5, 6, 28, 29]. In Denmark, there have been signs of a decreased prevalence of macrolide resistance in *Campylobacter* species since the ban of antimicrobial growth promoters, including macrolides [10].

In conclusion, the present study has shown that infection with either quinolone- or macrolide-resistant *Campylobacter* strains is associated with an increased risk of invasive illness or death, compared with infection with drug-susceptible *Campylobacter* strains. Macrolide and quinolone resistance in *Campylobacter* species is mainly a consequence of the use of antimicrobials in food-animal production, and our findings emphasize the need for limitation of the use of antimicrobial drugs in agriculture, which is critical to human medicine.

Acknowledgments

We thank Jørgen Engberg, Peter Gerner-Smidt, Ingrid B. Jensen, Joan Nevermann Jensen, and Eva Møller Nielsen (National Reference Centre for Enteric Pathogens at the Department of Bacteriology, Mycology and Parasitology, Statens Serum Institut).

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