

## Quinolone and Macrolide Resistance in *Campylobacter jejuni* and *C. coli*: Resistance Mechanisms and Trends in Human Isolates

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The incidence of human *Campylobacter jejuni* and *C. coli* infections has increased markedly in many parts of the world in the last decade as has the number of quinolone-resistant and, to a lesser extent, macrolide-resistant *Campylobacter* strains causing infections. We review macrolide and quinolone resistance in *Campylobacter* and track resistance trends in human clinical isolates in relation to use of these agents in food animals. Susceptibility data suggest that erythromycin and other macrolides should remain the drugs of choice in most regions, with systematic surveillance and control measures maintained, but fluoroquinolones may now be of limited use in the empiric treatment of *Campylobacter* infections in many regions.

*Campylobacter jejuni* subsp. *jejuni* (*C. jejuni*) and *C. coli* have been recognized since the late 1970s as important agents of gastrointestinal infections throughout the world; in the United States, these infections affect approximately 1% of the population each year (1). Contaminated food is the usual source of human infections; therefore, the presence of fluoroquinolone- and macrolide-resistant strains in the food chain has raised concerns that the treatment of human infections will be compromised. Most cases of *Campylobacter* enteritis do not require antimicrobial treatment, being brief, clinically mild, and self-limiting (2-4). However, a substantial proportion of these infections require treatment. These include severe and prolonged cases of enteritis, septicemia, and other extraintestinal infections. Erythromycin has been the most commonly used agent for treating *Campylobacter* enteritis (2,5).

In the 1980s, the introduction of fluoroquinolones, which are effective against most major

pathogens causing bacterial enteritis, offered a new approach to antibiotic intervention (6). Fluoroquinolones initially had good in vitro activity for thermophilic *Campylobacter* species, as well as for members of the family of Enterobacteriaceae.

Early clinical trials of both community-acquired acute diarrhea and traveler's diarrhea caused by *Campylobacter* demonstrated that patients treated with a fluoroquinolone had good clinical response (6,7). It soon became apparent, however, that resistance in *Campylobacter* spp. could arise in vivo, sometimes after only one or two administrations of fluoroquinolones (8). Moreover, Endtz and colleagues (9) reported as early as 1991 that the emergence of quinolone-resistant *C. jejuni* and *C. coli* isolated from humans in the Netherlands coincided with the introduction of fluoroquinolones in veterinary medicine.

Fluoroquinolone resistance in *Campylobacter* from food animals is now recognized as an emerging public health problem. Smith et al. from Minnesota (10) found that patients infected with resistant *C. jejuni* had longer duration of

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diarrhea than patients with fluoroquinolone-sensitive isolates. As *Campylobacter* infections can be serious in immunocompromised patients, the identified treatment failure raises the concern that fluoroquinolone-resistant strains may increase *Campylobacter*-associated deaths in this group of patients.

## Mechanism of Macrolide Resistance in *Campylobacter*

Erythromycin binds to the ribosome but, unlike larger macrolides, appears to cause dissociation of the peptidyl-tRNA, rather than blocking the peptidyltransferase activity (11).

In *C. jejuni* and *C. coli*, erythromycin resistance is chromosomally mediated and is due to alteration of the ribosome (12); the resistance mechanism is not consistent with presence of an rRNA methylase, modification of the antibiotic, or efflux (13). Whole ribosomes or 50S subunits were purified from erythromycin-resistant strains and shown to bind much less erythromycin than ribosomes from sensitive strains. In a closely related bacterium, *Helicobacter pylori*, resistance to clarithromycin is due to an alteration of one of two adenine residues in the 23S rRNA at the erythromycin-binding site (14). Sequencing of the 23S rRNA genes from erythromycin-resistant *Campylobacter* spp. identified mutations at these same sites, which are most probably responsible for resistance (Figure 1) (15).

## Mechanism of Fluoroquinolone Resistance in *Campylobacter*

Fluoroquinolone resistance in *C. jejuni* appears to be due most often to mutations in the genes encoding subunits of DNA gyrase (*gyrA*) and only occasionally to topoisomerase IV (*parC*) (Figure 1). DNA gyrase purified from quinolone-resistant mutants of *C. jejuni* was 100-fold less sensitive to inhibition by quinolones than the wildtype gyrase (19). Cloning and sequencing of the *C. jejuni gyrA* gene demonstrate that mutations in *gyrA* at positions Thr-86, Asp-90, and Ala-70 were responsible for resistance (16,17). Mutations at Thr-86 are associated with higher level resistance to nalidixic acid (MIC 64-128 µg/mL) and ciprofloxacin (MIC 16-64 µg/mL) than mutations at Asp-90 or Ala-70. *C. jejuni* isolates resistant to even higher levels of quinolones (ciprofloxacin MIC of 125 µg/mL) carry two mutations, one in *gyrA* Thr-86 and the other in the topoisomerase IV subunit *parC* at Arg-139 (18).

<u>Resistance</u>	<u>Mutation</u>
Macrolide	<p>—————&gt; Domain V of 23S rRNA A2058 → G A2059 → G</p>
Fluoroquinolone	<p>—————&gt; <i>gyrA</i> → Thr - 86 (higher MIC) Thr - 90 Ala - 70 (lower MIC)</p> <p>—————&gt; <i>gyrA</i> → Thr - 86 + <i>parC</i> → Arg - 139 (highest MIC)</p>

Figure 1. Macrolide and fluoroquinolone resistance mechanisms reported in *Campylobacter* species. For macrolide resistance, mutations are at either position shown (*Escherichia coli* coordinates) in up to all three copies of ribosomal RNA (14,15, and CA Trieber & DE Taylor, unpub. data). Fluoroquinolone resistance depends on a mutation in the quinolone resistance determining region of DNA gyrase A (*GyrA*). For typical MICs see text and references 16-18. The strains with highest resistance levels had mutations in both *GyrA* and topoisomerase IV *ParC*.

Evidence of efflux of fluoroquinolones in *C. jejuni* (20) also exists. Passage of the bacteria on pefloxacin-containing agar has led to the isolation of a fluoroquinolone-resistant strain. This strain was also resistant to tetracycline, erythromycin, chloramphenicol, and several β-lactams. The pefloxacin-resistant strain carried a mutation at Thr-86 of *gyrA*, likely responsible, in part, for fluoroquinolone resistance. Broad-specificity efflux pumps in *C. jejuni*, which cause fluoroquinolone resistance, have not yet been shown to be clinically relevant.

## Use of Macrolides and Quinolones in Food Animals

Antibiotics of the macrolide-lincosamide group have been used in treating food animals worldwide for several decades. The most commonly used agents have been lincomycin and tylosin for controlling dysentery and *Mycoplasma* infections in swine and spiramycin for treating mastitis in cattle. For the past 20 years, tylosin has also been the most commonly used agent for growth promotion in swine production worldwide, whereas spiramycin has been

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commonly used in poultry. The use of macrolides for growth promotion has been banned in all European Union countries since July 1999.

Several fluoroquinolones are available for treating food animals, such as poultry, cattle, pigs, and fish, in many countries. While information on global use is limited, worldwide use in food animals was estimated at 120 tons in 1997; use in humans has been estimated at more than 800 tons (21). Data are available only for the year of veterinary licensing of fluoroquinolones by country (Table 1). Licensing for use does not

necessarily mean that the drug is actually used, so even these data have to be considered with caution. However, quinolone treatment of *Campylobacter*-colonized broiler chickens has induced quinolone resistance under experimental conditions (23).

### Macrolide and Quinolone Resistance in Isolates from Food Animals and Foods of Animal Origin

*Campylobacter* is carried in the intestinal tract of wild and domestic animals and, as result

Table 1. Veterinary licensing of fluoroquinolones in selected countries

Country	Substance	Licensing year	Animal species	
Austria (22)	Enrofloxacin	1992	Cattle, pigs, poultry	
	Danofloxacin	1996	Poultry	
	Difloxacin	1998	Poultry	
Canada <sup>a</sup>	Enrofloxacin	1987 (withdrawn in 1997)	Turkey (egg dip)	
Denmark (22)	Enrofloxacin	1991	Cattle, pigs, poultry	
	Danofloxacin	1993	Poultry	
	Difloxacin	1998	Poultry, turkey	
	Marbofloxacin	1998	Cattle, pigs, dogs, cats	
Finland (22)	Enrofloxacin	1992 (oral use withdrawn in 1999)	Pigs	
	Difloxacin	1998	Poultry	
France (22)	Enrofloxacin	1991	Cattle, poultry	
	Danofloxacin	1996	Cattle	
	Marbofloxacin	1993	Cattle	
	Difloxacin	1998	Poultry	
	Enrofloxacin	1989	Cattle, pigs, poultry	
Italy (22)	Difloxacin	1998	Poultry	
	Enrofloxacin	1991	Cattle, poultry	
Japan <sup>b</sup>		1992	Pigs	
	Danofloxacin	1992	Poultry	
		1993	Cattle, pigs	
	Ofloxacin	1992	Poultry	
	Orbifloxacin	1993	Cattle, pigs	
	Difloxacin	1996	Pigs	
	Norfloxacin	1998	Poultry	
	Netherlands (22)	Enrofloxacin	1987	Cattle, pigs, poultry
		Difloxacin	1998	Poultry
	Spain (22)	Enrofloxacin	1986	Cattle, pigs, poultry
Difloxacin		1998	Poultry	
United Kingdom (22)	Enrofloxacin	1993	Cattle, pigs, poultry	
	Danofloxacin	1993	Poultry	
	Marbofloxacin	1995	Cattle	
	Difloxacin	1998	Poultry	
USA <sup>c</sup>	Enrofloxacin	Approx. 1987-88	Dogs, cats	
		1996	Poultry	
	Sarafloxacin	1999	Cattle	
	1995	Poultry		

<sup>a</sup>RJ Irwin, Health Canada, 1999. pers. comm.

<sup>b</sup>Y Tamura, National Veterinary Assay Laboratory, Japan, 1999. pers. comm.

<sup>c</sup>JL Watts. Pharmacia/Upjohn, Kalamazoo, Michigan, 1999. pers. comm.

of fecal contact during processing, frequently contaminates foods derived from animals. *C. jejuni* is predominant in broilers and cattle but is infrequent in pigs (where *C. coli* predominates) (24). In food animals, the prevalence of resistance to erythromycin is generally higher in *C. coli*, in particular in *C. coli* isolates from pigs, than in *C. jejuni* (24-26). In a recent study from Spain (27), rates of erythromycin and quinolone resistance in *C. coli* from pigs were 81% and 100%, respectively. High erythromycin resistance in pigs may be related to extensive veterinary use of macrolides (5,28).

In food products of animal origin, the occurrence of *Campylobacter* is much higher in poultry than in other categories, e.g., pork or beef (29). Therefore, *Campylobacter* resistance data are primarily based on poultry products, especially broiler meat. For a number of countries, fluoroquinolone-resistance rates are similar in isolates from poultry products and humans (10,25,27,30-32). In the United Kingdom, enrofloxacin (a derivative of ciprofloxacin) was first licensed in late 1993; before then, domestically bred chickens were less frequently infected with quinolone-resistant campylobacters than imported chicken products. Using a simple model, researchers were able to correlate the previously observed resistance percentage in domestically acquired cases with estimates of the amount of imported chicken consumed in the United Kingdom (32). In recent data from Spain and Taiwan, rates of erythromycin resistance were 17% and 17%, respectively, in *C. jejuni* isolated from foods, whereas for *C. coli* the figures were 50% and 83%, respectively (27,31).

### Transmission of Resistant *Campylobacter* from Animals to Humans

Campylobacteriosis is primarily a zoonosis. Evidence to indicate that fresh raw meat, especially poultry, is a major source of infection is ample, even though other sources such as raw milk, water, and pets may contribute to human infection (1,5,33-38).

Studying the transmission of antimicrobial resistance from animals (especially poultry to humans) has been difficult because the chain of transmission is often complex. The number of macrolide- and fluoroquinolone-resistant isolates from humans is influenced by several factors including veterinary use of macrolides

(approved for use as antimicrobial growth promoters or as therapeutic drugs) and fluoroquinolones (only approved as therapeutic drugs) at a given location (24,39); association with recent or current antimicrobial treatment of patients; the origin of isolates (children vs. adults; inpatients vs. outpatients); travel (10,40-45); and sampling strategy and susceptibility testing procedures (no consensus as to method, media, culture conditions, or breakpoints [43,46]). These factors stress the need for cautious interpretation and comparison of data from different centers. However, several studies have shown that food animals can be a substantial source of infection in humans and that the same serotypes and genotypes can be isolated from humans and food animals (29,36,37,47-49). DNA profiling of Danish *C. jejuni* serotype O:2 strains using pulsed-field gel electrophoresis with four restriction enzymes identified common genotypes in humans, poultry, cattle and swine (SLW On, EM Nielsen, and J Engberg, unpub. data). Typing data on resistant isolates is sparse, but Smith and colleagues (10) found DNA fingerprints of quinolone-resistant *C. jejuni* from U.S.-produced poultry identical to those of resistant *C. jejuni* from domestically acquired infections in humans. Therefore, the susceptibility of humans strains originating in animals to antibiotics can be related to the exposure of animal strains to antibiotic agents used in farming.

### Is There a Link Between Macrolide and Fluoroquinolone Use in Humans and Resistant *Campylobacter* Infections?

Some investigators suggest that resistance in *C. jejuni* and *C. coli* is driven by use of antibiotics for treating human infections rather than by veterinary use. Induction of macrolide resistance during treatment has been reported infrequently (50). However, induction of macrolide resistance may play a role in areas with a large reservoir of asymptomatic *Campylobacter* carriers and frequent use of macrolides in humans.

Induction of fluoroquinolone resistance during treatment is well recognized and often reported (8,51-53). A predicted 10% of patients treated with a fluoroquinolone for *Campylobacter* enteritis harbor quinolone-resistant *Campylobacter* strains (6). Recently, Ellis-Pegler (53) found that fluoroquinolone resistance developed in 18% to 28% of patients in their prospective trial. Development of resistance has been

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reported within 24 hrs of treatment, but prolonged therapy, e.g., in immunosuppressed patients, is also a risk factor (52,54).

Smith et al. (10) showed that use of a quinolone before culture accounted for a maximum of 15% of resistant isolates during 1996 to 1998. In addition, an increasing number of reports claim that fluoroquinolone-resistant strains have been isolated from patients who had not received medical treatment, suggesting that strains were already fluoroquinolone resistant before causing the infection (7,31,32,55-57). Since human-to-human transmission of *C. jejuni* and *C. coli* is rare (9), patients infected with resistant *Campylobacter* are not an important source of resistant *Campylobacter* for other humans.

Before fluoroquinolones were introduced in veterinary medicine, they were widely used in human medicine in a number of countries,

including the Netherlands and the United States (since 1985 and 1987, respectively), without emergence of quinolone resistance in *Campylobacter* in humans. In contrast, emerging quinolone resistance in humans often coincides with or follows the approval of fluoroquinolones in animal husbandry (Table 1, Figure 2). Thus, while human macrolide and fluoroquinolone use contributes to the increase in resistance in humans, their relative contribution to increase in resistance compared to the use of these agents in husbandry appears to be small.

### Frequency of Macrolide Resistance in Human Isolates

Data on erythromycin and azithromycin resistance in *C. jejuni*, *C. coli*, and the two organisms combined, isolated from humans around the world since 1989, differ by country

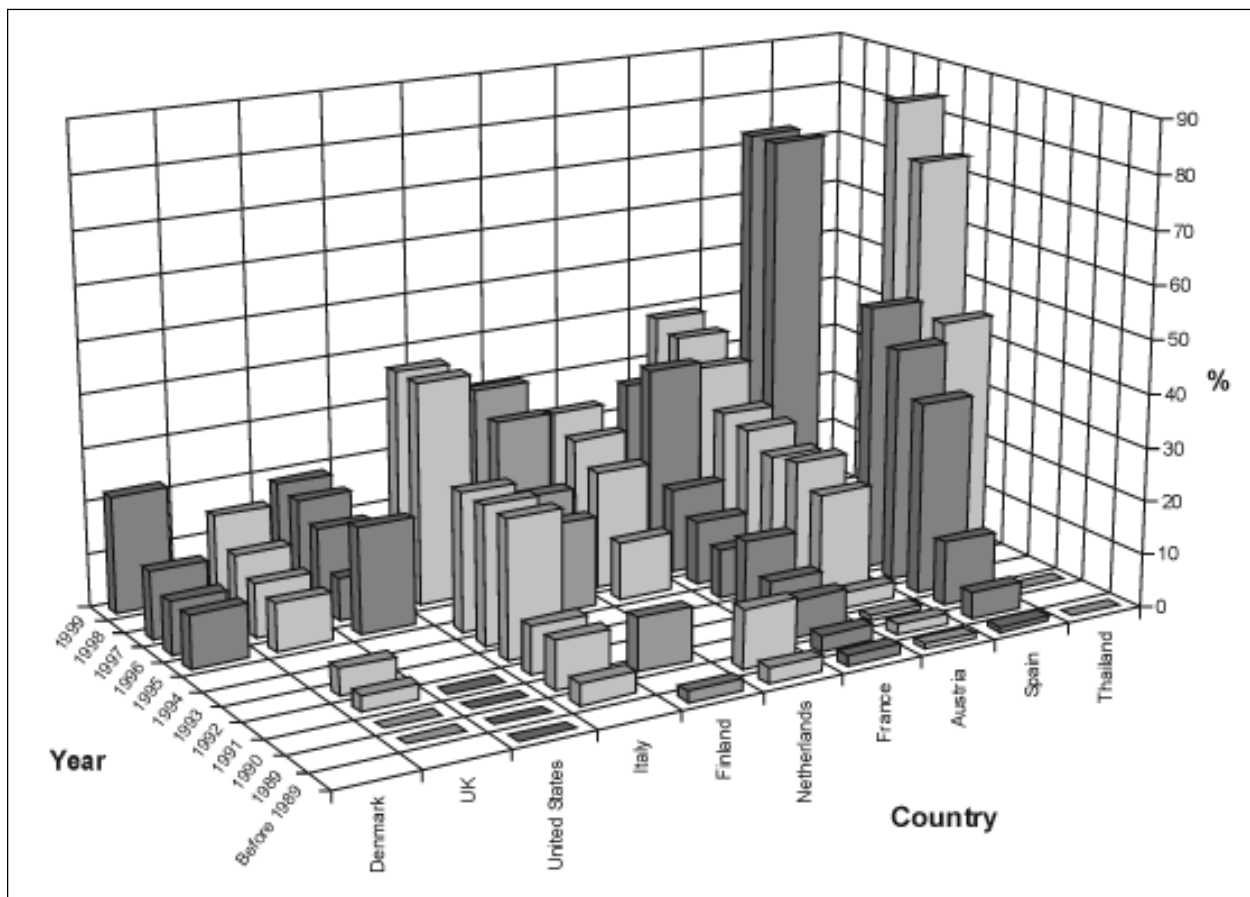


Figure 2. Trends for quinolone resistance rates (in percentages) among *Campylobacter coli* and *C. jejuni* combined from human sources around the world. The bars represent both nalidixic acid and fluoroquinolone resistance and are based on mean values of resistance from numerous reports (9,17,24,27,39,43,56-58,61-64,72-75,78,88, plus pers. comm. from Feirel G and Rautelin H, and unpub. data from Nachamkin I).

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and species (Table 2). Almost all studies report a higher frequency of erythromycin resistance in *C. coli* than in *C. jejuni* (0% to 11% in *C. jejuni* vs. 0% to 68.4% in *C. coli*). Trends over time for erythromycin resistance show stable and low rates in Japan, Canada, and Finland, but recent development of resistance in Thailand and Sweden (45,73).

### Trends over Time for Quinolone Resistance

Resistance to fluoroquinolones in *Campylobacter* has clearly increased over the past decade in many parts of the world (Figure 2). Before 1989, resistance was rare. With the introduction of enrofloxacin in veterinary medicine (Table 1) and (probably less important) fluoroquinolones in human medicine in mainland Europe (the Netherlands, Finland, France, and Spain), a rapid emergence of quinolone resistance in *Campylobacter* isolates from patients was noted (8,9,43,55,64,89,90).

Surveillance data on resistance rates in human isolates from Asia soon indicated an equal increase (84,91). Quinolones were approved for veterinary use in the United Kingdom and the United States in late 1993 and 1995, respectively; reports from these areas now show increasing quinolone-resistance profiles (10,39,88).

In the latest data from Taiwan, Thailand, and Spain, rates of fluoroquinolone resistance in

*C. jejuni*, or *C. jejuni* and *C. coli* combined were 56.9%, 84%, and 75% to 88%, respectively (27,31,40,73). In these regions, where quinolone resistance is highly endemic and *Campylobacter* spp. predominate, fluoroquinolones cannot be recommended for community-acquired bacterial diarrhea. Although lower frequencies are reported from other regions, recent trends show a clear tendency of emerging quinolone resistance in many countries. Quinolone resistance in human isolates often coincides with or follows the approval of fluoroquinolones for use in animal husbandry (Table 1, Figure 2), although some differences in resistance rates between countries may be explained by differences in association with foreign travel, commerce, methods of testing, and surveillance activity.

### Multidrug Resistance

Multidrug resistance to macrolides and fluoroquinolones must be considered highly undesirable in *Campylobacter* as these two classes are generally advocated as first- and second-line drugs for antimicrobial treatment of *Campylobacter* enteritis.

Additional resistance to other relevant therapeutic agents poses a risk when there is no effective antimicrobial regimen for *Campylobacter* infections. Recently, Hoge et al. (73) found 100% co-resistance between Thai isolates resistant to azithromycin and ciprofloxacin in the last 2 years

Table 2. Erythromycin and azithromycin resistance rates (%) in *Campylobacter* in humans, worldwide, since 1989

Country	<i>C. jejuni</i>	<i>C. coli</i>	<i>C. jejuni</i> and <i>C. coli</i>	Reference
Austria	0.7	5.5	<1-1.4	(58 & pers. comm. <sup>a</sup> )
Canada	0-3.3	-	-	(59,60)
Denmark	0	14.0	0-4	(24,61,62)
Finland	-	-	<1-3	(43,63, & pers. comm. <sup>b</sup> )
France	1.1	12.2	3.5	(64)
Hungary	-	-	0	(65)
Italy	1.2-6	16-68.4	7.8-11.6	(66-69)
Japan	0.8	-	-	(66)
New Zealand	-	-	1.5	(70)
Singapore	-	-	51	(71)
Spain	0-11.0	0-35.0	3.2-7.3	(17,27,56,57,72)
Sweden	6.4 <sup>c</sup>	11.1 <sup>c</sup>	7.3 <sup>c</sup>	(44)
Taiwan	10.0	50.0	18.3	(31)
Thailand	-	-	0-31.0	(73,74)
United Kingdom	1	13	1.8	(75)
United States	0-7.8	-	-	(10,76-78, & unpub. data <sup>d</sup> )

<sup>a</sup>G Feierl, 2000, pers. comm.

<sup>b</sup>H Rautelin, 1999, pers. comm.

<sup>c</sup>90% of isolates were acquired abroad.

<sup>d</sup>I Nachamkin, 2000, unpub. data.

of surveillance. In addition, the level of tetracycline and ampicillin resistance in Thailand is so high that these agents now have no role in the treatment of *Campylobacter* or noncholera diarrhea. Li et al. (31) reported that concomitant resistance rates among nalidixic acid-resistant *C. jejuni* isolates from their patients (exclusively children) were as follows: gentamicin 2%, erythromycin 12%, clindamycin 12%, tetracycline 97%, and ciprofloxacin 66%. All of these human erythromycin-resistant *C. jejuni* isolates and 90% of the *C. coli* isolates were concomitantly resistant to clindamycin.

### Consequences of Resistance for the Clinical Decision-making Process

Distinguishing infections caused by different enteric pathogens is seldom possible, so antimicrobial-drug use in the clinical setting is not confined to the treatment of *Campylobacter* spp. but rather to empiric treatment of community-acquired diarrhea in general. Increased rates of resistance have also been reported from nontyphoidal salmonellae (25,92), and documented failures in the treatment of human *Salmonella* infections have been described (93). Therefore, having continuous information on the resistance patterns of the most common bacteria causing gastrointestinal infections is critical.

### Control Measures

Surveillance of resistance in *Campylobacter* is of paramount importance when fluoroquinolones are used to treat human infections. Systematic surveillance and timely reporting of antibiotic resistance patterns in *C. jejuni* and *C. coli* and other enteric pathogens from different regions should become a high priority. The principal purpose of monitoring antimicrobial resistance trends in enteric pathogens is to provide clinicians with data that can be used to select appropriate treatment regimens. Surveillance should emphasize antibiotics that are being used routinely to treat diarrhea, as well as any alternatives, such as fluoroquinolones, macrolides, and gentamicin. Equally important is the accessibility of the data to those providing primary care. For quinolones, quantitative nalidixic acid susceptibility data are more sensitive than fluoroquinolone susceptibility data for detecting common first-step mutations causing reduced susceptibility.

To circumvent the development of resistance, we have two options: infection control (zoonoses control) and prudent use of antibiotics. Improved infection control strategies along the chain "stable to the table" and guidelines for prudent use of antimicrobial agents in food animal production should be developed (94,95). To prevent further development of resistance in *Campylobacter*, limiting the use of macrolides and fluoroquinolones for food animals as much as possible is recommended. In Denmark, fluoroquinolones are not essential for treatment of any type of infection in food animals, according to surveillance performed by the Danish Veterinary Laboratory, and their use is only recommended on the rare occasion when no other therapeutic option is available (22). Because of the selection for resistance, the use of macrolides for growth promotion has been banned in all European Union countries since July 1999. The effect on the occurrence of resistance in bacteria in food animals is still not known. However, preliminary results suggest that macrolide resistance in *C. coli* from pigs in Denmark has decreased along with the decreased use of tylosin (FM Aarestrup, unpub. data).

### Conclusions

Review of in vitro macrolide and quinolone resistance prevalence and trends in *Campylobacter* isolated from humans showed a temporal relationship between use of quinolones in food animals and resistant *Campylobacter* isolates in humans. The public health effects of antibiotic use in agricultural practice, including resistance of *C. jejuni* and *C. coli* to macrolides and quinolones, should be estimated. Adequate actions for control are strongly needed in both veterinary and human medicine. The public health issue of resistance in *Campylobacter* has global dimensions because of ever-increasing international trade and travel.

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