Fluoroquinolone-Resistant *Escherichia coli*: Food for Thought

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(See the articles by Johnson et al. and by Lautenbach et al., on pages 71–8 and 79–85, respectively.)

Although antimicrobial resistance among *Escherichia coli* is likely to be predominately the consequence of use of antimicrobial agents in humans and inadequate infection control, hygiene, and sanitation, articles by Johnson et al. [1] and Lautenbach et al. [2] in this issue of the *Journal of Infectious Diseases* suggest that the use of antimicrobial agents in food animals may make a greater contribution to such resistance than has been previously suspected. Large volumes and a wide variety of antimicrobial agents, including fluoroquinolones, are used in food animals (chickens, cattle, fish, pigs, and turkeys) [3–6]. The use of antimicrobial agents in food animals inevitably results in the development and spread of resistant bacteria in animals and the environment. These resistant bacteria frequently spread to humans via food, water, direct animal contact, and other pathways [3, 4]. Although the intestinal tract of most people who ingest these resistant bacteria is typically only transiently colonized, persistent colonization can occur. Whether resistant bacteria colonize, resistant genes may be horizontally transferred to other bacteria in the intestinal tract [3, 4]. If present, resistant bacteria can proliferate when people carrying them receive any antimicrobial agent to which the bacteria are resistant.

Every day, a large turnover of *E. coli* strains in the human intestinal tract occurs, predominately as a consequence of the foods eaten. Almost 20 years ago, Corpet [7] demonstrated, using tetracycline-resistant *E. coli*, marked daily variations in the strains of *E. coli* in the bowel, depending on the foods eaten. When volunteers were fed sterile foods, tetracycline-resistant *E. coli* in their intestinal tracts quickly fell to very low numbers. Despite such experiments, the extent of the contribution of the food supply to antimicrobial resistance among human *E. coli* has not been well understood.

The studies by Johnson et al. [1] and Lautenbach et al. [2] suggest that the intestinal tract of humans in Spain (Barcelona), the United States (Philadelphia), and presumably elsewhere is commonly colonized with fluoroquinolone-resistant *E. coli*. Because the human intestinal tract is the immediate source of *E. coli* that cause most human *E. coli* infections, the carriage of fluoroquinolone-resistant *E. coli* has important clinical implications. Furthermore, other recent studies have suggested that resistance to important antimicrobial agents among *E. coli* is not limited to fluoroquinolones. *E. coli* carrying β-lactamases, particularly the *cmy* gene, have been found in the human intestinal tract and on meats in the United States and Spain—this is thought to be caused by expanded-spectrum cephalosporin use in food animals [8–10].

Fluoroquinolone use in food animals has been of particular concern, because fluoroquinolones are critically important for treating serious infections in humans [3, 11]. In many areas of the world, however, fluoroquinolones are commonly used in food animals and are often administered via the drinking water. The use of fluoroquinolones in food animals has resulted in substantial numbers of fluoroquinolone-resistant bacteria in these animals and in foods derived from them [3, 4, 12, 13]. The US Food and Drug Administration (FDA) recently banned fluoroquinolone use in poultry, after it was associated with the rapid rise in ciprofloxacin resistance in human *Campylobacter* infections [13]. Attempts to limit the use of antimicrobial agents in food animals have been controversial; some animal-pharmaceutical and food-industry representatives dispute that the use of antimicrobial agents in food animals has any adverse effect on human health [14, 15], despite the now overwhelming evidence to the contrary [3, 4, 13]. The US FDA ban on fluoroquinolone use in poultry, for example, was delayed for years by legal action by one manufacturer.

The public-health concern with fluo-
roquinolone use in food animals has focused on zoonotic pathogens, such as *Salmonella* and *Campylobacter* species, in which there is clear evidence that fluoroquinolone resistance is predominately a consequence of fluoroquinolone use in food animals. The US FDA ban on the use of fluoroquinolones in chickens and turkeys [13] means that there will be a marked reduction in the use of fluoroquinolones in food animals in the United States. However, fluoroquinolones continue to be used in cattle in the United States, and large quantities of fluoroquinolones are used in other countries, particularly in poultry and aquaculture.

In contrast to *Salmonella* and *Campylobacter* infection, *E. coli* infection more commonly results in severe clinical consequences (bacteremia, abdominal sepsis, and death). Tens of thousands of bloodstream *E. coli* infections occur each year in the United States [16], most of which are acquired outside the hospital. Effective antibiotic therapy is life-saving in patients with bloodstream and other serious infections. Fluoroquinolones, which have good oral bioavailability, penetrate well into almost all tissues. Fluoroquinolones were previously effective against almost all of the important gram-negative pathogens and are commonly used to treat serious *E. coli* infections. Increasing fluoroquinolone resistance among *E. coli* threatens to increase mortality, morbidity, and treatment costs for associated infections.

Lautenbach et al. [2] report a high prevalence of fluoroquinolone resistance among *E. coli* isolated from the intestinal tract (i.e., normal flora) of hospitalized patients. In that study, the prevalence of resistance among *E. coli* isolates was similar at the tertiary referral hospital and the community hospital, which suggests that many of these resistant bacteria were brought into the hospital from the community rather than acquired at the hospitals. The study is also noteworthy because the fluoroquinolone-resistant isolates were genetically diverse, not clonal. These data indicate the widespread emergence of fluoroquinolone resistance, given that resistance is not simply a consequence of the dissemination of ≥1 resistant clone. Furthermore, many of the fluoroquinolone-resistant *E. coli* isolates were multidrug resistant, and some had efflux pump resistance mechanisms.

So where are the numerous diverse fluoroquinolone-resistant *E. coli* strains isolated from humans coming from? Horizontal gene transfer has recently been reported for fluoroquinolone resistance [17], but this remains uncommon. Thus, fluoroquinolone-resistant *E. coli* strains probably emerged as a consequence of fluoroquinolone use in either humans or animals. The study by Johnson et al. [1] provides important new evidence that the emergence and dissemination of fluoroquinolone-resistant *E. coli* is a consequence of fluoroquinolone use in animals. Using molecular analysis, they found that the most likely evolutionary source of human fluoroquinolone-resistant *E. coli* strains is from fluoroquinolone-susceptible chicken strains and not from fluoroquinolone-susceptible human strains. The study also illustrates that *E. coli* are not species-specific. The fluoroquinolone-resistant isolates in humans were similar to resistant isolates in chickens and were quite different from susceptible human isolates. Arguments that antimicrobial-resistant *E. coli* strains in humans are unrelated to antimicrobial-resistant *E. coli* in animals (and that, therefore, antimicrobial use in food animals has no consequence for humans) are based on the belief that *E. coli* and other enteric bacteria of animals and humans are species specific. The studies reported in this issue of the *Journal of Infectious Diseases* and other studies provide strong evidence against this point of view [12].

Taken together, the studies by Johnson et al. [1] and Lautenbach et al. [2] indicate that fluoroquinolone use in food animals is an important source of the emerging fluoroquinolone resistance among *E. coli* and that resistant *E. coli* should therefore be considered a foodborne pathogen. More studies are needed to confirm this conclusion. One such study could compare events in the United States and Australia. Fluoroquinolones are commonly used in adults in both countries. Fluoroquinolones are also used in food animals in the United States but have never been allowed for use in food animals in Australia. Fluoroquinolone resistance is becoming increasingly prevalent among human clinical *E. coli* isolates in the United States. By contrast, the prevalence of fluoroquinolone resistance among human clinical *E. coli* isolates in Australia is very low (only a few percent) and stable, even in intensive care units (P.C., unpublished data). In countries with more liberal use of fluoroquinolones in food animals [18], such as China and Spain, fluoroquinolone-resistant *E. coli* (and *Campylobacter* and *Salmonella*) is an even larger problem than in the United States [19, 20]. This situation could easily rapidly worsen if genes encoding for fluoroquinolone resistance become common on transferable genetic elements, such as plasmids. The finding, therefore, of plasmid-mediated low-level quinolone resistance *E. coli* and other enteric bacteria [21–23] is troubling.

Reducing fluoroquinolone use in food animals will improve human health. Widespread use of these critically important antimicrobial agents in food animals poses a needless additional risk to humans in both the community and the hospital.

References


