Correspondence

Extended-Spectrum β-Lactamases, Food, and Cephalosporin Use in Food Animals

To the Editor—Infections caused by *Escherichia coli* and other gram-negative bacteria are very common. A large proportion of these strains are resistant to oral antibiotics. When resistance to injectable antibiotics, such as third- and fourth-generation cephalosporins, is also present, the patient can experience grave consequences, because injectable antibiotics are often the last line of defense and are critically important in treating many life-threatening infections, including bacteremia and meningitis. Thus, the unexpected and increasing appearance of extended-spectrum β-lactamases (ESBLs) among community isolates of *E. coli* and other bacteria, as outlined in 2 articles recently published in *Clinical Infectious Diseases* [1, 2], is of major concern.

However, these articles do not mention that food might be a very important vehicle in the spread of these drug-resistant bacteria, as was again highlighted by a recent study from Spain [3]. The use of third- and fourth-generation cephalosporins in food animals results in the development of bacteria carrying ESBLs. This involves not only food-associated pathogens, such as *Salmonella* species [4], but also *E. coli.* These drug-resistant bacteria then spread to people via food and other routes (e.g., ground water). This is occurring around the world [4–7]. These drug-resistant bacteria and their genes (including CTX-M and CMY β-lactamases) are now widespread.

Antibiotic-resistant strains of *E. coli* probably spread via food much more commonly than we currently appreciate [8]. If drug-resistant bacteria are widespread in the intestinal tracts of people in the community, the treatment of these people with antibiotics will frequently result in the amplification of drug-resistant bacteria (and in the transfer of the genes encoding drug resistance into other bacteria). If such individuals are hospitalized for an incidental reason (e.g., biliary disease or trauma), then these bacteria can spread to other patients, especially if infection-control practices are not universally followed.

Worldwide, third-generation cephalosporins, such as ceftiofur, are widely used in many different food animals, because there are often only minimal restrictions in place on its use. Indeed, in the United States in 2001, ceftiofur was injected into the eggs of meat chickens just before hatching in 21 (78%) of 27 hatcheries (the hatcheries studied produced >500 million chickens per year; this US Food and Drug Administration data was obtained under a Freedom of Information search). In Australia, attempts to limit the widespread use of ceftiofur by placing "label restraints" on its use have been ignored by the agriculture regulatory agency. The use of third- and fourth-generation cephalosporins in most developing countries is even more widespread, because there are usually even fewer controls in place.

Recently, a fourth-generation cephalosporin (cefquinome) was approved for use by the European Union, and it is likely to also be approved soon by the US Food and Drug Administration, without any label restrictions. This will mean that it can be used in any food animal for almost any indication. Restrictions, such as requiring a prescription to dispense the drug, seem to make little difference in effective control, as is evidenced by the widespread use of fluoroquinolones and the resultant drug resistance that recently lead the US Food and Drug Administration to finally withdraw approval for their use in poultry (but only after a long and drawn-out legal battle with the manufacturer) [9]. Better "late than never," but why did we have to wait for drug resistance to be so widespread before taking action? How could we possibly have expected that the use of "critical" antibiotics, such as fluoroquinolones or third-generation cephalosporins, would not have resulted in the development of drug resistance?

Unlabeled but high levels of broad-spectrum cephalosporins (e.g., ceftiofur) [10] are allowed in some foods (maximum residual level, 6 mg per kg). These high levels mean that ceftiofur is used instead of narrower-spectrum antibiotics, because the much higher maximum residual levels of ceftiofur result in a much shorter period of withholding the treated animal from slaughter than would be the case with many other antibiotics. These high levels will also be an allergic risk to some people.

This all seems to be a recipe for disaster. We have already seen early warning signs that the use of ESBLs is starting to get out of control [1–7]. Surely, now is the time to act. The World Health Organization has defined third- and fourth-generation cephalosporins as being "critically important" for use in people [11]. Clearly, these antibiotics should not be used in food animals at all (or their use should be much more severely curtailed than is currently the case in most of the world). We also need to dramatically lower the residual levels of these drugs that we allow in some foods. The current widespread and increasing use of these antibiotics in food animals is inappropriate and poses a needless additional risk to both people in hospitals and the general community.

Acknowledgments

Potential conflicts of interest. P.C. and F.M.A.: no conflicts.

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Clinical Infectious Diseases 2007; 44:1391-2

1058-4838/2007/4410-0025$15.00
DOI: 10.1086/516612