AEM Journals.ASM.org

The Challenge of Regulating Agricultural Ceftiofur Use To Slow the Emergence of Resistance to Extended-Spectrum Cephalosporins

Thomas E. Wittum

Department of Veterinary Preventive Medicine, The Ohio State University College of Veterinary Medicine, Columbus, Ohio, USA

My collaborators and I report elsewhere (22) the detection of *Salmonella* expressing extended-spectrum cephalosporin resistance not previously recognized in U.S. livestock. This new milestone of resistance again raises questions of how to define and regulate the appropriate use of vital classes of antimicrobial drugs in animals that will enter the food supply. Opponents of agricultural antimicrobial use will naturally view our results as further validation of their existing beliefs, while proponents will undoubtedly find no evidence of significant risk attributable to current agricultural antimicrobial use practices. But how can our current scientific knowledge of antimicrobial resistance support, refute, or reconcile these strongly divergent viewpoints? Some reconsideration and discussion of these issues may be warranted in light of our results and the U.S. Food and Drug Administration (FDA)'s recent attempts to restrict extended-spectrum cephalosporin use in food animals.

Veterinary antimicrobial use in food animals is commonly perceived to be an important contributor to the problem of antimicrobial resistance by both medical professionals and the general public (17). In particular, the common use of antimicrobials for agricultural production purposes (19–21), including growth promotion, is frequently described as a needless contributor to the emergence of resistant bacteria (10). While that is a valid hypothesis, there is currently little direct evidence of harm to the public health resulting from the use of growth-promoting antimicrobials as they are currently applied in agriculture. This type of disconnect between the available science and public perception can itself have negative consequences on the public health. For example, the mistaken belief that childhood vaccination caused autism resulted in decreased vaccination rates and needlessly increased the risk of morbidity and mortality in children, and it redirected precious scientific resources away from other valid hypotheses (7). In order to avoid similar negative consequences, it is critical that discordance between science and public perception be resolved regarding the public health risks of agricultural antimicrobial use.

Critics of agricultural antimicrobial use commonly emphasize the frequency and amount of antimicrobial use in food animals as a risk to the public health. Given the nearly ubiquitous exposure of food animal populations to unknown quantities of a wide variety of antimicrobial drugs (19–21), this is not an unreasonable concern. In addition, outbreaks resulting from the zoonotic food-borne transmission of resistant pathogens originating on farms provide powerful evidence to support their position (5). However, the common arguments, including proposed legislation (http://www.gpo.gov/fdsys/pkg/BILLS-112hr965ih/pdf/BILLS-112hr965ih.pdf) to broadly restrict veterinary antimicrobial use in food animals, ignore the large differences in risk that result from the diverse applications of antimicrobial drugs in animal agriculture. For example, large quantities of ionophores are commonly fed to beef cattle exclusively to promote growth, but this class of antimicrobials is not used in humans and there is no evidence that they provide selection pressure for resistance to other classes of antimicrobial drugs (2). As a result, the true risk resulting from the production use of agricultural antimicrobials may be made to appear greater than it really is, and other antimicrobial use practices of genuine public health concern may not receive the attention needed to ensure that they are appropriately resolved.

Conversely, proponents of agricultural antimicrobial use commonly defend the need for veterinarians to have effective therapies available for sick animals in order to maintain animal welfare and food safety. They also frequently cite the extensive U.S. FDA approval process and required withholding times that prevent antimicrobial residues from entering the food supply. These assertions are true and supported by evidence that restricting antimicrobial exposure has little impact on the resistance of pathogens on U.S. farms (18). However, these arguments do not address the vast numbers of healthy food animals that are routinely exposed to antimicrobial drugs, and thus, they ignore the issues of greatest concern to both consumers and scientists, including antimicrobial use for growth promotion and for mass therapy of large, intensively managed livestock populations. In addition, they fail to address the marginal role of veterinarians today in individual- and population-level antimicrobial-use decisions made routinely on farms. Consequently, the practices of real public health concern are not addressed and may not receive the attention needed to ensure that they are appropriately resolved.

Efficient production of food animals generally requires that they be housed in population-dense environments that are conducive to the sharing of enteric flora (16). In fact, these intensively managed production systems may produce an environment in which there is effectively a common flora. As a result, selection pressure applied to an individual may hasten the emergence of resistant pathogens or resistance genes that can be quickly and easily transmitted to others in the same population, often by means of horizontally transmissible genetic elements (4, 14). Fecal flora from these animals may then contaminate carcasses during processing, which can result in zoonotic food-borne transmission (1, 13). These population-dense environments that facilitate production efficiency are also conducive to the efficient transmission of production-limiting infectious pathogens, many of which may require mass prophylactic or metaphylactic antimicrobial therapy to prevent production losses (12, 15).

Published ahead of print 7 September 2012

Address correspondence to Thomas E. Wittum, Thomas.Wittum@cvm.osu.edu.

doi:10.1128/AEM.01967-12

The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.

The mass application of therapeutic doses of antimicrobial drugs to populations of livestock is common when health problems are anticipated and preemptive antimicrobials are known to reduce morbidity and mortality (12). This practice can effectively prevent and control disease but requires that many apparently healthy animals receive therapeutic doses of antimicrobial drugs. Ceftiofur, including its extended-activity formulation (ceftiofur crystalline free acid), is applied in this manner in U.S. livestock populations. Some examples include the injection of shipments of day-old turkey poults to control mortality, the treatment of barns of piglets at weaning to control respiratory disease in the nursery barn, the treatment of truckloads of beef calves upon arrival at feedlots to control respiratory disease, and the intrauterine infusion of mares in a breeding facility to improve conception rates. Similar situations may occur when eggs are injected prior to hatching to control chick mortality or when dairy cows are commonly treated in early lactation to control metritis. This practice may well have contributed to the emergence of *Salmonella* harboring $bla_{\text{CTX-M}}$ in turkey, swine, and horse populations that my collaborators and I reported previously (22).

The application of ceftiofur requires a veterinarian-client-patient relationship (VCPR) which represents the legal and ethical requirement that the veterinarian assume responsibility for determining the need for medical treatment of animals based on direct knowledge of their health and management (3; https://www.avma.org/KB/Policies/Pages/Principles-of-Veterinary-Medical-Ethics-of-the-AVMA.aspx). However, the specific labeled indication of ceftiofur for the somewhat ambiguous "control" of disease in populations may actually undermine the original intent of the VCPR because treatment decisions are made for healthy animals based on perceived risk rather than for sick animals based on a diagnosis. As a result, the decision to apply ceftiofur to control disease in livestock populations may frequently be made by farm personnel as a production decision following guidelines provided by a veterinarian familiar with but lacking direct knowledge of the animals being treated. In the absence of direct guidance from a veterinarian in the form of a strong VCPR, the intended distinction between prevention and control can easily become blurred. Thus, it may be hypothesized that the conditions that can lead to the emergence and dissemination of extended-spectrum cephalosporin-resistant *Salmonella* in U.S. livestock populations are the mass application of ceftiofur to animals housed in population-dense environments in the absence of a strong veterinarian-client-patient relationship.

This hypothesis is an extension of the "selection focus hypothesis" previously proposed to explain the emergence and dissemination of multiresistant strains of *Salmonella* (8). Hancock et al. suggested that calf ranches serve as ecological niches that favor the emergence of *Salmonella* resistance due to the frequency of infection with competing endemic strains together with the common application of antimicrobial drugs to a dynamic population of animals and their microflora while housed in a population-dense environment. These same conditions are also likely met in the examples of ceftiofur application to the various livestock production systems described above. Thus, selection foci for the emergence and dissemination of extended-spectrum cephalosporin-resistant *Salmonella* may well be points in multiple livestock production systems rather than specific types of agricultural operations.

The U.S. FDA attempted to address this issue in 2008 with a proposed rule to limit cephalosporin use in food animals that was ultimately withdrawn (http://edocket.access.gpo.gov/2008/E8-15052.htm), but a revised rule has been enacted in 2012 (6). This new rule prohibits the off-label use of ceftiofur in food animals, including its use for disease prevention. However, given the currently approved label applications of this drug, the new rule may have little impact on many of the most common uses of ceftiofur in animal agriculture. This is because the mass application of ceftiofur in agricultural animal populations is defined as the therapeutic treatment of a population for disease control, and not as disease prevention (15). As a result of this broad interpretation of therapy, the above-described examples of mass ceftiofur application to livestock populations will not be specifically prohibited by this new rule, except for *in ovo* injection.

The current FDA Guidance for Industry number 209 (http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf) contains nonbinding recommendations that medically important drugs such as ceftiofur be used in food animals only when considered necessary to ensure animal health and only under veterinary oversight or consultation. Both of these very general conditions are already met for all of the above-described uses of ceftiofur in livestock, suggesting that the guidance may effect little change. Measures that will require a stronger veterinarian-client-patient relationship for the administration of ceftiofur may be needed to prevent the continued emergence and dissemination of extended-spectrum cephalosporin-resistant pathogens and of resistance genes such as $bla_{\text{CTX-M}}$.

The mass application of therapeutic enrofloxacin to control mortality in broiler chickens may have resulted in the emergence and zoonotic food-borne transmission of fluoroquinolone-resistant *Campylobacter jejuni* in the early 2000s (11). While that application is now prohibited, veterinary enrofloxacin use is currently allowed in both cattle and swine but with label restrictions that prevent its mass application for disease control and require a diagnosis by a veterinarian. Presently, there is no evidence of emerging fluoroquinolone resistance in these species (9). Thus, the manner in which enrofloxacin is applied in these animal populations may serve as one model for developing effective ceftiofur use guidelines that allow veterinarians and producers to take advantage of its benefits while preventing the emergence and dissemination of resistance, as has been observed with *Salmonella* strains that have acquired $bla_{\text{CTX-M}}$.

By focusing on subtherapeutic applications or therapy of individual sick animals, both opponents and proponents of agricultural antimicrobial use may be ignoring a common practice of real concern: the mass application of antimicrobial therapy for disease control in populations under an implied veterinarian-client-patient relationship that, while technically present, only marginally fulfills the spirit and intent of the requirement. Both the new FDA rule limiting cephalosporin use and Guidance for Industry number 209 attempt to directly address this issue but may be inadequate to effect change. As a result, the mass application of ceftiofur to food animals housed in intensively managed, population-dense environments in the absence of a strong veterinarian-client-patient relationship will almost certainly continue, leading to the further dissemination of extended-spectrum cephalosporin resistance among enteric pathogens.

ACKNOWLEDGMENTS

I gratefully acknowledge the contributions of Dixie F. Mollenkopf and Joshua B. Daniels in their thoughtful discussions of this issue and for their input and suggestions to help improve the manuscript.

REFERENCES

1. **Baptista FM, Dahl J, Nielsen LR.** 2010. Factors influencing *Salmonella* carcass prevalence in Danish pig abattoirs. Prev. Vet. Med. **95**:231–238.
2. **Callaway TR, et al.** 2003. Ionophores: their use as ruminant growth promotants and impact on food safety. Curr. Issues Intest. Microbiol. **4**:43–51.
3. **Code of Federal Regulations.** 2012. Title 21. Food and Drugs. Chapter I. Food and Drug Administration. Subchapter E. Animal drugs, feeds, and related products. Part 530. Extralabel drug use in animals. 21 CFR 530. http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&rgn=div5&view=text&node=21:6.0.1.1.16&idno=21.
4. **Daniels JB, et al.** 2009. Role of ceftiofur in selection and dissemination of bla_{CMY-2}-mediated cephalosporin resistance in *Salmonella enterica* and commensal *Escherichia coli* isolates from cattle. Appl. Environ. Microbiol. **75**:3648–3655.
5. **Dutil L, et al.** 2010. Ceftiofur resistance in *Salmonella enterica* serovar Heidelberg from chicken meat and humans, Canada. Emerg. Infect. Dis. **16**:48–54.
6. **Federal Register.** 2012. New animal drugs; cephalosporin drugs; extralabel animal drug use; order of prohibition. Final rule. **77**:735–745. http://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf.
7. **Godlee F, Smith J, Marcovitch H.** 2011. Wakefield's article linking MMR vaccine and autism was fraudulent. Br. Med. J. **342**:64–66.
8. **Hancock D, et al.** 2000. The global epidemiology of multiresistant *Salmonella enterica* serovar Typhimurium DT104 C. Brown C, Bolin C (ed), Emerging diseases of animals, p 217–243. ASM Press, Washington, DC.
9. **Hurd HS, Vaughn MB, Holtkamp D, Dickson J, Warnick L.** 2010. Quantitative risk from fluoroquinolone-resistant *Salmonella* and *Campylobacter* due to treatment of dairy heifers with enrofloxacin for bovine respiratory disease. Foodborne Pathog. Dis. **7**:1305–1322.
10. **Marshall BM, Levy SB.** 2011. Food animals and antimicrobials: impacts on human health. Clin. Microbiol. Rev. **24**:718–733.
11. **McDermott PF, et al.** 2002. Ciprofloxacin resistance in *Campylobacter jejuni* evolves rapidly in chickens treated with fluoroquinolones. J. Infect. Dis. **185**:837–840.
12. **McEwen SA, Fedorka-Cray PJ.** 2002. Antimicrobial use and resistance in animals. Clin. Infect. Dis. **34**(Suppl 3):S93–S106.
13. **Mollenkopf DF, Kleinhenz KE, Funk JA, Gebreyes WA, Wittum TE.** 2011. *Salmonella enterica* and *Escherichia coli* harboring bla_{CMY} in retail beef and pork products. Foodborne Pathog. Dis. **8**:333–336.
14. **Mollenkopf DF, et al.** 2012. Variable within- and between-herd diversity of CTX-M cephalosporinase-bearing *Escherichia coli* isolates from dairy cattle. Appl. Environ. Microbiol. **78**:4552–4560.
15. **Phillips I, et al.** 2004. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. J. Antimicrob. Chemother. **53**:28–52.
16. **Sanderson MW, Sargeant JM, Renter DG, Griffin DD, Smith RA.** 2005. Factors associated with the presence of coliforms in the feed and water of feedlot cattle. Appl. Environ. Microbiol. **71**:6026–6032.
17. **Singer RS, et al.** 2003. Antibiotic resistance—the interplay between antibiotic use in animals and human beings. Lancet Infect. Dis. **3**:47–51.
18. **Thakur S, Gebreyes WA.** 2005. Prevalence and antimicrobial resistance of *Campylobacter* in antimicrobial-free and conventional pig production systems. J. Food Prot. **68**:2402–2410.
19. **US Department of Agriculture.** 2000. Feedlot 1999, part II: base line reference of feedlot health and health management, 1999. N335.1000. USDA-APHIS-VS-CEAH-NAHMS. United States Department of Agriculture, Fort Collins, CO.
20. **US Department of Agriculture.** 2007. Swine 2006, part II: reference of swine health and health management practices in the United States, 2006. N479.1207. USDA-APHIS-VS-CEAH. United States Department of Agriculture, Fort Collins, CO.
21. **US Department of Agriculture.** 2008. Dairy 2007, part III: reference of dairy cattle health and management practices in the United States, 2007. N482.0908. USDA-APHIS-VS-CEAH. United States Department of Agriculture, Fort Collins, CO.
22. **Wittum TE, Mollenkopf DF, Erdman MM.** 10 August 2012. First detection of Salmonella enterica producing CTX-M cephalosporinase in US livestock populations. Appl. Environ. Microbiol. doi:10.1128/AEM.01682-12.