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Recent government regulations in the United States seek to ensure the effectiveness of antibiotics by limiting their agricultural use

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ABSTRACT

The development of bacteria resistant to antibiotics is viewed as a medical health threat. Because thousands of people die every year due to antibiotic-resistant bacteria, efforts are underway to reduce antibiotic usage which in turn will reduce the development of antibiotic-resistant bacteria. In the United States, the use of antibiotics in the production of food animals to enhance animal growth has been identified as contributing to resistance. In 2015, a veterinary feed directive was adopted by the U.S. federal government prohibiting nontherapeutic uses of antibiotics in food animals that should reduce usage. The continued usage of antibiotics by producers for preventing disease may mean the directive is insufficient to reduce nontherapeutic antibiotic administration. This may lead some consumers to seek meat products from animals raised without antibiotics. A governmentally-sponsored labeling program could encourage reduction in antibiotic usage.

1. Introduction

Legislators, governmental officials, health advocates, and consumers are concerned about the rapid development of antibiotic-resistant bacteria and the potential emergence of a post-antibiotic era (McKenna, 2013). The concerns are related to the overuse of veterinary drugs in food animals which research suggests contributes to a bacterium's mutation and acquired resistance (Gilchrist et al., 2007; Holmes et al., 2015). In the absence of regulatory action, the use of antimicrobials in animals raised for food might increase by 67% with a corresponding increase in the development of antimicrobial resistance (Van Boeckel et al., 2015).

The US Centers for Disease Control and Prevention (CDC) consider antimicrobial resistance to be one of the nation's most serious health threats. Two million illnesses in the United States result from drug-resistant bacteria each year (CDC, 2013), and an estimated 700,000 deaths around the world (O'Neill, 2014). In a 2013 report, the CDC noted that "[a]ntibiotic use in food animals can result in resistant *Campylobacter* that can spread to humans" (CDC, 2013, p. 62). The European Food Safety Authority has concluded that uses of antibiotics in animals results in the continuous positive selection of resistant bacterial clones (EFSA, 2014). Given the costs of these illnesses and deaths, President Obama issued an executive order in 2014 calling for the implementation of measures to reduce the emergence and spread of antibiotic-resistant bacteria (President of the United States, 2014). The President created an advisory council and task force for combating antibiotic-resistant bacteria. Other provisions of the executive order called for reviewing existing regulations, proposing new regulations, strengthening surveillance efforts, responding to antibiotic-resistance outbreaks, and promoting the discovery of new antibiotics.

In 2015, the White House issued a National Action Plan for Combating Antibiotic-Resistant Bacteria enumerating five goals: "to strengthen healthcare, public health, veterinary medicine, agriculture, food safety, and research and manufacturing" (White House, 2015). With respect to limiting the use of antibiotics in animal production, two categories of antibiotic usage were identified: therapeutic and nontherapeutic. Greater veterinary oversight was recommended to reduce therapeutic usages for treating, controlling, and preventing disease. Nontherapeutic antibiotics administered to animals to increase rates of weight gain or improve feed efficiency were labeled "production uses" which should be eliminated to slacken the development of resistant bacteria (FDA, 2012, 2013).

To address agriculture's contribution to the emergence of resistant bacteria, the Federal Food and Drug Administration (FDA) issued veterinary feed directive (VFD) regulations in 2015. These regulations alter the classification of selected over-the-counter antimicrobial drugs and prohibit animal production uses of VFD drugs (CFR, 2015; FDA, 2015). Under US federal law, drugs intended for use in or on animal feed meeting certain criteria are VFD drugs (United States Code, 2012, § 354). VFD drugs can only be fed to animals based on a VFD order "issued by a licensed veterinarian in the course of the veterinarian's professional practice" (FDA, 2015). The effect of the VFD regulations is that certain over-the-counter antimicrobial animal drug products currently

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approved for use in or on animal feed will be reclassified as VFD drugs so they can only be administered under a VFD order with veterinary oversight (FDA, 2015).

One of the objectives of the VFD regulations was to slow the potential for the development of drug-resistant bacteria by eliminating production uses of antibiotics in raising food animals. The elimination of production uses of antibiotics comes two decades after several northern European countries took actions to ban selected uses of antibiotics with relatively minor impacts on productivity (Wegener, 2003). Uses of agricultural antibiotics were reduced by approximately 65% in Sweden, 47% in Denmark, 40% in Norway, and 27% in Finland (Bengtsson and Wierup, 2006). Although the VFD regulations should help curtail the use of antibiotics in food animal production, a number of limitations suggest that the FDA may need to revise the regulations in the future to ensure the objectives of the VFD are being met. One possible revision to strengthen the VFD is a governmentally-sponsored antibiotic labeling program to help curb the overuse of antibiotics (Animal Legal Defense Fund, 2013). By adopting a recordkeeping and labeling program with information about whether antibiotics were administered, consumers may be more certain about actual antibiotic usage during animal production.

2. Governmental actions

Several important antibiotics are used in animal production that are also used to treat humans (Table 1). These agricultural uses may contribute to the emergence of antibiotic-resistant bacteria that pose a human health threat. The environmental advocacy group Center for Food Safety (2015) estimates that 60–80% of antibiotics used in the United States are administered to food animals for production uses. Given this estimate, considerable attention is focused on adopting regulations that would reduce the amounts used for the production of animal products. Similar efforts are being advanced by Health Canada's Veterinary Drugs Directorate (Health Canada, 2014). The adoption of the VFD regulations instituted five features that will reduce antibiotic usage (CFR, 2015; FDA, 2015), while other ideas for curtailing usage of antibiotics can be identified to encourage producers to reduce antibiotic usage (Table 2).

Table 1
Critically and highly important antibiotics.*.[a]*

Antibiotic	Animal use	Concerns about the continued use for humans
Tetracyclines	Cattle, swine, poultry	*Brucella*, *Chlamydia* ssp. and *Rickettsia* spp. infections
Macrolides	Cattle, swine, poultry	Limited therapy for *Legionella*, *Campylobacter* and MDR *Salmonella* and *Shigella* infections; may result from transmission of *Campylobacter* spp. and *Salmonella* from non-human sources
Aminoglycosides	Swine, poultry	Transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*) and *Mycobacterium* spp. from non-human sources
Sulfonamides	Cattle, swine, poultry	One of the limited therapies for acute bacterial meningitis, systemic non-typhoidal salmonella infections and other infections; may result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Lincosamides	Swine, poultry	Human infection may result from transmission of *Enterococcus* spp. and *Staphylococcus aureus* including MRSA from non-human sources

[a] WHO, 2011.

Table 2
Features to encourage the reduction in uses of antibiotics in animal production.

Feature	VDF Rule	Possible New Rule
Regulate additional over-the-counter drugs	x	
Prohibited use for weight gain or feed efficiency	x	
Veterinary-client relationship	x	
Distributor records	x	
Veterinarian misconduct and misbranding	x	
Site visit prior to prescribing a VFD		California Code of Regulations § 2032.1
Proscribe disease prevention		California Senate Bill No. 27, 2015
Producer records		California Senate Bill No. 27, 2015
Stewardship guidelines		California Senate Bill No. 27, 2015
Best management practices		California Senate Bill No. 27, 2015
Penalties for violations		California Senate Bill No. 27, 2015
Educational rehabilitation for violators		California Senate Bill No. 27, 2015
Ban specific antibiotics		EU Council Regulation (EC) No. 2821/98
Minimal selective concentrations		Bengtsson-Palme and Larsson, 2016
Require labeling on antibiotic usage		Animal Legal Defense Fund, 2013

2.1. The need for the VFD: human acquired antibiotic resistance from animals raised for food

The use of antibiotics in agriculture has raised concerns about antibiotic resistance for decades (Aarestrup, 2015; Centner, 2008). In 1969, the Swann Report recommended that antibiotics used in human patients should not be used as growth promoters in livestock (Swann Committee Report, 1969). In the United States, the FDA established a task force of scientists to undertake a comprehensive review of the use of antibiotics in animal feed in 1970, which recommended steps to limit the use of nontherapeutic antibiotics in farm animals for growth promotion (FDA, 2012). Antimicrobial use in animals amplifies the presence of resistant microorganism strains in animals' intestinal tracts (Sun et al., 2014). Resistance genes can be transferred between bacterial species and resistant zoonotic bacteria may be acquired by humans via the food chain or through contact with infected animals, their feces, or contaminated environments (Chenney et al., 2015).

In 1998, the American Institute of Medicine noted relationships between the use of tetracycline-supplemented feed fed to chickens, the development of tetracycline-resistant coliforms in the chickens, and the prevalence of tetracycline-resistant coliform organisms in the intestinal tracts of persons caring for the chickens (American Institute of Medicine, 1988). The problem is that the use of antibiotics in animals increases the size of the gene pool to further the emergence of multi-resistant enterococci causing human infections (Bates, 1997). Evidence of potential relationships between the use of animal drugs with resistant bacteria affecting humans have been established by a number of researchers (Alba et al., 2015; Argudín et al., 2015; Feßler et al., 2012; Graveland et al., 2010; Nóbrega and Brocchi, 2014; Schmithausen et al., 2015).

Researchers have concluded that livestock serve as a reservoir for transferable resistance genes directly or through food products (Alba et al., 2015; Monaco et al., 2013; Nóbrega and Brocchi, 2014; Schmithausen et al., 2015). Argudín et al. (2015) observed that methicillin-resistant *Staphylococcus epidermidis* populations in healthy pigs may be transmitted between humans and pigs. Colonized farm personnel and dogs may also contribute to the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) within different compartments of the farm (Feßler et al., 2012). Cuny et al. (2015) estimated that livestock-associated MSRA was associated with at least 10% of these infections in humans. MRSA may enter the human food