Research & Technology


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Livestock Drugs: More Questions Than Answers?

Use of antimicrobial (antibiotics and other) drugs in livestock production has been surrounded by controversy since the practice began in the 1940s. Antimicrobial drugs are designed to weaken or kill pathogens, which are disease-causing microorganisms such as bacteria and fungi. At high levels, these drugs are used to cure or contain livestock diseases. At low levels, antimicrobial drugs are used in livestock production to enhance feed efficiency and promote growth, fight infections not usually detectable without clinical examination, and prevent diseases. The selection of effective and reliable antimicrobial drugs is limited, and the same or related drugs are often used for both animals and humans. It is this dual human-livestock use that has generated concern.

It is primarily the low-level use of these drugs for livestock that comes under fire, particularly those used to promote growth. Administering low levels of antimicrobial drugs to food-producing animals has been postulated to threaten human health in two ways.

First, some fear that livestock drug residues may remain in final food products and cause human illness. According to the joint Committee on Drug Use in Food Animals, with members from the National Research Council and from the Institute of Medicine, the generally rapid breakdown of active ingredients in drugs, combined with Food and Drug Administration (FDA)-specified periods between last administration of the drug and slaughter, have limited this threat in the U.S.

Second, scientists have found that some microorganisms (particularly bacteria) are becoming resistant to antimicrobial drugs. This raises concerns about the role of livestock drug use in the emergence of drug-resistant bacteria and the ability of health-care practitioners to cope with them. Some microorganisms are naturally resistant to some antimicrobial drugs. Others become resistant by mutation or by incorporating genetic material for resistance from other microorganisms, by ingestion or by cellular contact.

Scientific Understanding of Resistance Falls Short

There is considerable uncertainty about many aspects of antimicrobial resistance. The U.S. General Accounting Office (GAO) has confirmed that the data on the public health threat of antimicrobial resistant bacteria are limited. Furthermore, they have confirmed that within the government there are differences of opinion among various branches about the risk to public health posed by antimicrobial use in animals and the best course of action. The GAO has encouraged various branches of the government to work together to address these critical information gaps and develop science-based decisions.

Any use of antimicrobial drugs in humans or animals can result in the appearance of drug resistance in some bacteria. The Committee on Drug Use in Food Animals estimated that as few as 10 percent of the incidences of antimicrobial resistance originate with livestock health practices, and concluded that not all instances of such resistance are clinically significant, involve resistance in disease-causing microorganisms, or cause an actual illness. Other instances of resistance stem from human use.

Farm animals carry many species of microorganisms, including some foodborne pathogens, like *Salmonella* and *Campylobacter*. Some microorganisms may contaminate carcasses and food products during processing, and, if this food is inadequately cooked or improperly handled, the pathogens can make people ill. If drug-resistant strains of these microorganisms cause human illnesses that require medical care, doctors may be limited in the antibiotics available for an effective cure.

In 1969, the first formal statement of the hypothesis that drug-resistant bacteria may be transmitted to humans through food and cause human illness was issued in London in the "Report of Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine." In a later report, scientists at the U.S. Centers for Disease Control and Prevention (CDC) state that the actual transmission of antimicrobial-resistant diseases between animals and humans is difficult to establish and involves documenting each of the following steps:

- the selection for and persistence of resistant bacteria in animals from low-level doses of antimicrobial drugs,
- the presence of resistant pathogens in animal products,

Major Classes of FDA-Approved Antimicrobial Drugs

Antibiotic class (selected)	Administered to food animals: Species	Disease treatment	Disease prevention	Growth promotion	Administered to humans
Aminoglycosides[1] (gentamicin, neomycin, streptomycin)	Beef cattle,goats, poultry,[2] sheep, swine	X	X		X
Ionophores (monensin, salinomycin, semduramicin, lasalocid)	Beef cattle, fowl,[3] goats, poultry, rabbits, sheep		X	X	
Quinolones (fluoroquinolones, sarafloxacin, enrofloxacin)	Beef cattle, poultry	X	X		X
Sulfonamides (sulfadimethoxine, sulfamethazine, sulfisoxazole)	Beef cattle, dairy cows, fowl, poultry, swine, catfish, trout, salmon	X		X	X
Bambermycin	Beef cattle, poultry, swine		X	X	
Carbadox	Swine		X	X	X
Novobiocin	Fowl, poultry	X	X		X
Spectinomycin	Poultry, swine		X		X
Beta-Lactams (penicillins: amoxicillin, Ampicillin)	Beef cattle, dairy cattle, fowl, poultry, sheep, swine	X	X	X	X
Cephalosporins:					
(Cefadroxil)					X
(Cefuroxime)					X
(Ceftiofur)	Beef cattle, dairy cows, poultry, sheep, swine	X	X		X
Lincosamides (lincomycin)	Poultry, swine	X	X		X
Macrolides (erythromycin, tilmicosin, tylosin)	Beef cattle, poultry, swine	X	X	X	X
Polypeptides (bacitracin)	Fowl, poultry, swine	X	X	X	X
Streptogramins (virginiamycin, synercid)	Beef cattle, poultry, swine	X	X	X	X
Tetracyclines (chlortetracycline, oxytetracycline,[4] tetracycline)	Beef cattle, dairy cows, fowl, honey bees, poultry, sheep, swine, catfish, trout, salmon, lobster	X	X	X	X

1. Streptomycin has been approved for use on food plants.
2. Includes at least one of the following: broiler chickens, laying hens, and turkeys.
3. Fowl includes at least one of the following: ducks, pheasants, and quail.
4.Oxytetracycline has been approved for use on food plants.

Source: "The Agricultural Use of Antibiotics and Its Implications for Human Health," Appendix II, GAO/RCED-99-74, U.S. General Accounting Office, April 1999.

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- transmission of these pathogens to humans, and
- diagnosis of human diseases caused by these pathogens.

Studies that positively trace drug-resistant, foodborne human illnesses back through the food chain to a resistant livestock source are not common. Much of the other evidence is circumstantial, but enough evidence has accumulated that CDC and FDA scientists are concerned that drug-resistant varieties of *Salmonella* and *Campylobacter* have passed from livestock to humans and caused human illnesses.

Advances in medical technology, such as DNA fingerprinting, are helping to make these connections, and data to address these issues are becoming available. In 1996, the FDA, the CDC, and the USDA established the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS). NARMS monitors changes in antimicrobial susceptibilities of intestinal pathogens that affect both humans and animals from human and animal clinical specimens, from healthy farm animals, from retail food, and from carcasses of food-producing animals at slaughter. Animal-isolate testing is conducted at the USDA Agricultural Research Service Russell Research Center. Human-isolate testing is conducted at the CDC National Center for Infectious Diseases Foodborne Disease Laboratory. Retail food testing is conducted at the FDA Center for Veterinary Medicine Office of Research Laboratories. All laboratories use comparable isolation, identification, and susceptibility testing procedures.

There is also uncertainty about drug levels needed to cause resistance. Studies by the CDC have found relatively high correlations between feeding of low levels of antimicrobial drugs to livestock and the presence of drug-resistant bacteria in animals. However, in a 1986 paper, a member of the University of Liverpool's veterinary faculty suggested that some critical threshold or level of antibiotics is needed to cause microorganisms to become resistant and that this threshold may not be reached by low levels of livestock drug use.

Another difficulty with establishing the extent of livestock-sourced, resistant foodborne illness is that only about ten percent of people who become ill from a foodborne pathogen seek medical care. This results in uncertainty about how many of the estimated 76 million annual foodborne illnesses in humans involve an organism that is resistant to antimicrobials and where that resistance has impacted the health care or the outcome for the patient. Furthermore, the contribution of antimicrobial drug use in livestock cases is unknown.

The Effect of Human Use Of Antimicrobial Drugs

The development of antimicrobial drug resistance in bacteria and fungi also occurs through the use of these drugs by people, particularly any long-term use of these drugs. Microbial resistance to antimicrobial drugs in humans is believed to stem largely from over-reliance on antimicrobial drugs in human medicine, failure to adhere to prescriptions for the full duration of treatment, and increased clustering of people in institutions such as hospitals and day care centers. The U.S. Congress, Office of Technology Assessment, and the Committee on Drug Use in Food Animals found that the two greatest sources of drug-resistant pathogens observed in humans are misuse of antibiotics by both doctors and patients, and the emergence of drug-resistant pathogens in hospitals.

Nearly 2 million people each year have hospital-acquired infections, many of which are difficult to treat because they are caused by pathogens which are resistant to the drugs commonly used to treat them. The Committee on Drug Use in Food Animals stated in a 1998 report that the risk of these hospital-acquired infections might more likely be considered life threatening than illnesses potentially caused by antimicrobial resistance originating in animals, because hospital-acquired infections occur in patients who are already medically stressed.

Bans against using antimicrobial drugs in livestock are often discussed as a precaution to protect the effectiveness of antimicrobial drugs in human health care. The question then becomes: "Would the development of bacterial resistance actually decline in livestock if low-level use of these drugs was stopped?"

Studies that compare use versus nonuse of livestock antimicrobial drugs as growth promotants are inconclusive—some find reduced resistance in pathogens in livestock when drugs are withdrawn, while others find no change or increased resistance. Studies from Europe since the ban on antimicrobial growth promoters have demonstrated lower percentages of resistant bacteria from livestock where use of antimicrobial drugs for growth promotion was stopped.

Economic Effects Difficult to Measure

The economic consequences of resistance to antimicrobial and other drugs are difficult to measure precisely. Issues include changes in costs of production, effects of drug bans on trade, losses associated with resistant foodborne illness including medical expenses, productivity losses, and deaths.

There are very little data on the economic costs associated with human illness caused by antimicrobial-resistant microorganisms, much less illness involving resistant pathogens directly related to livestock drug use. According to CDC, one study estimated that drug-resistance to *Staphylococcus aureus* (a pathogen associated with hospitals rather than livestock) had an annual cost of $122 million.

Effects on livestock from resistant microbes and their associated costs can range from virtually none (no impact on animal health) to costs that exceed the value of an animal. Economic analyses based on limited data generally demonstrate short-run increases in production costs and prices for livestock and livestock products in the U.S. in the aggregate.

For producers who currently use low levels of antimicrobial drugs in livestock feed, it is possible that costs of treating livestock diseases could increase if pathogens were resistant and if producers had to resort to more expensive or less effective drugs to cure or contain the disease. There are currently no data to suggest this is occurring. On the other hand, producers not currently feeding antimicrobial drugs may be able to use less expensive antimicrobial drugs to treat disease outbreaks caused by susceptible pathogens.

One effect from using antimicrobial drugs in livestock is a change in the balance of the intestinal microbes in livestock. Currently there are no data to suggest that such shifts result in increased carriage or shedding of potential foodborne pathogens.

In the 1970s and 1980s, studies were conducted on bans or limits on using low levels of antimicrobial drugs in livestock feeds. Estimated annual net losses to producers and/or consumers ranged from just under $1 billion to about $12 billion. More recent studies are needed. Further, the perceived benefits from a livestock drug ban might not offset the higher food costs to consumers.

Research Needs & Implications

There are voids in basic data about many aspects of antimicrobial drug use in U.S. livestock production. The probabilities of humans becoming ill due to drug-resistant bacteria are thought to be quite low, although they remain unknown. Precise estimates of these probabilities are needed to evaluate risks of resistant foodborne illnesses in humans associated with livestock drug use.

In addition, production practices in the U.S. differ from those in Europe, so data and research specific to the U.S. are needed to estimate the biological and economic effects of bans against antimicrobial drugs used in U.S. livestock production. Long-term effects of livestock drug bans have not been adequately demonstrated or studied. Some European studies suggest that long-term benefits might outweigh short-term costs to producers and consumers. Much of the livestock research in the U.S. is geared toward demonstrating the benefits of antimicrobial drugs in terms of improved productive performance in livestock, with little focus on pathogen characteristics, such as resistance, or economic considerations such as associated drug and feed costs.

The possibility of resistant livestock pathogens affecting humans has heightened concerns about livestock drug use and motivated regulatory actions in the U.S. and abroad. In early 1999, the Center for Science in the Public Interest, representing 37 health and consumer groups, petitioned the FDA to ban the use of seven antimicrobial drugs in livestock production (bacitracin, erythromycin, lincomycin, penicillin, tetracycline, tylosin, and virginiamycin). A bill banning low-level feeding of these seven antimicrobials (unless the sponsors could demonstrate no adverse effects within two years) was introduced into the House of Representatives in November 1999 (H.R. 3266). FDA has also proposed a framework for evaluating and assuring the human safety of new antimicrobial drugs intended for use in food animals. The proposed guidelines classify antimicrobial drugs according to the extent to which they are useful in human health care, the propensity for resistance to develop, and effects on pathogen load in animal products. The new guidelines also propose setting predetermined thresholds for when actions should be taken to stem the emergence of resistant pathogens.

Many European countries have already banned low-level feeding of specific antimicrobial drugs used to enhance livestock growth or feed efficiency. In May 1999, the Scientific Steering Committee of the European Commission concluded that action should be taken promptly to reduce overall use of antimicrobial drugs used in livestock production.

On the basis of ongoing work of this committee and other available information, the Agriculture Ministers in the European Union (EU) in 1999 banned four antimicrobial drugs widely used at low levels to promote animal growth (bacitracin zinc, spiramycin, tylosin, and virginiamycin). In June 2001, the Agriculture Ministers banned the remaining growth-promoting livestock drugs that are also used for humans. A ban against low-level use of antimicrobial drugs in U.S. livestock production would likely raise costs to producers and consumers in the short run; long-term impacts are still unknown. AO

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Antimicrobial Drug Use and Veterinary Costs in U.S. Livestock Production

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