Antibiotic Stewardship in Food-producing Animals: Challenges, Progress, and Opportunities

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ABSTRACT

Purpose: Approximately two thirds of the tonnage of antibiotics sold in the United States are intended for use in food production, and global use is projected to increase. This review summarizes the rationale for antibiotic use in animal agriculture, therapeutic classes used, risks from antibiotic-resistant organisms, and limits of existing regulation. In addition, opportunities for improved surveillance, stewardship, and advocacy will be highlighted.

Methods: A transdisciplinary narrative review of drivers of antibiotics in food production was conducted, including concepts from population health, infectious diseases, veterinary medicine, and consumer advocacy.

Findings: Globally, antibiotics of many important classes in human medicine are given to animals for the treatment of a diagnosed illness, disease control and prevention, and growth promotion. Extensive antibiotic use on farms drives the emergence of antibiotic-resistant organisms in food-producing animals, which can be transmitted to people and the environment. Antibiotic stewardship in food production has been associated with decreased rates of resistance in both animals and humans, without reducing farm productivity. Multiple European nations have successfully implemented stewardship strategies, including banning uses for disease prevention, benchmarking antibiotic utilization, and setting national reduction targets. In the United States, medically important antibiotics are no longer permitted for growth promotion; however, antibiotics may be prescribed for other indications with limited veterinary oversight and requirements for reporting. Marked reductions in use have been achieved in the poultry industry, although use in the pork and beef industries remain high.

Implications: Despite some progress, significant challenges in surveillance and regulatory oversight remain to prevent the overuse of antibiotics in food production. Consumers remain a potent force via market pressure on grocery stores, restaurants, suppliers, and farmers. Improved, verified labelling is important for informing consumer choices. Numerous public health agencies, consumer groups, and professional societies have called for judicious antibiotic use, but increased direct advocacy from health care professionals is needed. (*Clin Ther*. 2020;42:1649–1658) © 2020 Elsevier Inc.

Key words: Food production, Resistance, Stewardship.

INTRODUCTION

Antibiotic-resistant bacterial infections are a threat to public health and have been associated with increased mortality, prolonged hospitalization, and increased health care costs.[1] Per the Centers for Disease Control and Prevention, >2.8 million antibiotic-resistant infections occur in the United States each year, causing at least 35,000 deaths.[2] Globally, 700,000 people each year die from infection with antibiotic-resistant organisms (AROs), one third in children aged under 5 years.[3] Antimicrobial resistance is projected to cause 10 million deaths per year globally by the year 2050.[4] Recognizing that the primary driver of antibiotic

Accepted for publication July 13, 2020
https://doi.org/10.1016/j.clinthera.2020.07.004
0149-2918/$ - see front matter

resistance is the overuse of antibiotics, antibiotic stewardship—the commitment to the judicious use of antibiotics—is mandated across health care settings by the Centers for Medicare and Medicaid Services.[5]

Antibiotic use is common in the raising of animals for food in the United States. Approximately two thirds of the tonnage of antibiotics considered medically important to humans is sold for use in food-animal production.[6] Meat producers in the United States use antibiotics far more intensely than do their counterparts in other countries.[7] Both in the United States and globally, widespread antibiotic use on farms contributes to an increasing burden of antibiotic-resistant infections, with grave consequences for human health. In this review, we describe drivers of antibiotic use in meat production and therapeutic classes given to animals. Second, we summarize the epidemiology of AROs from food-producing animals and its impact on human health. Last, we describe current regulations, opportunities for improvement, and advocacy efforts to promote judicious use.

Antibiotic use in animals can be classified into 3 major categories per the World Health Organization (WHO): therapeutic use, disease prevention, and growth promotion.[8] *Therapeutic* refers to the use of antibiotics for treating animals with clinically diagnosed infectious diseases or illnesses. For example, according to the US Department of Agriculture (USDA), one fourth of all dairy cows in the United States in 2014 were diagnosed with clinical mastitis, of which 87% were treated with antibiotics, most commonly cephalosporins.[9] *Disease prevention* refers to the use of antibiotics in healthy animals considered to be at risk for infection or prior to the onset of clinical infectious disease. This includes the prevention of infectious diseases not yet diagnosed in individual animals or groups of animals (prophylaxis) or for controlling the dissemination of disease within an infected animal or from one animal to another within a group (metaphylaxis).[10] Disease prevention is a common category of use that includes administration to prevent infection during stressful conditions (eg, transportation of young animals) or the prevention of disease in crowded conditions. For example, per the USDA, 60%−80% of nursery hogs were administered antibiotics for disease prevention in 2009.[11] *Growth promotion* is the use of antibiotics, often at subtherapeutic concentrations, to increase the rate of weight gain and/or the efficiency of feed utilization in animals by other than purely nutritional means. The mechanism for which growth promotion occurs is unknown—proposed theories include alterations in the gut microbiota that may reduce competition for nutrients, improved nutrient absorption, or reduction in pathogenic bacteria, particularly in animals living in crowded conditions.[12]

As with many other human medicines, the discovery of antibiotics was soon followed by their incorporation into veterinary medicine. In the 1940s, penicillin was used for treating bovine mastitis to ensure supplies of milk during World War II, even when quantities for the civilian population were limited.[13] In 1948, sulfaquinoxaline became the first antibiotic to be routinely administered in poultry feed to prevent coccidiosis.[14] Soon afterward, supplementation of chick diets with vitamin B_{12} made by *Streptomyces auerofaciens* (with trace amounts of tetracyclines) was accidently discovered to cause better weight gain than supplementation with vitamin B_{12} made from other sources.[15] In 1951, the US Food and Drug Administration (FDA) first approved the use of antibiotics in livestock. Mass medication in feed and water soon followed at subtherapeutic concentrations to quickly achieve growth to market size with less feed. These uses of antibiotics were heralded as a major advance in food production in a rapidly expanding post-war US population. Rising American per-capita meat consumption over the ensuing decades was largely driven by the increase in large-scale farming operations reliant on antibiotic use.[13]

Globally, meat production has more than quadrupled in the past 50 years.[16] The demand for animal protein has increased concurrently with rising incomes, particularly in Asia.[17] Between 2010 and 2030, the global consumption of antibiotics is expected to increase by 67%, largely driven by a shift to large-scale, intensive livestock-production systems heavily reliant on antibiotic use. In Brazil, Russia, India, China, and South Africa, the projected increase is 99%, 7-fold the projected population growth during the same period.[18] Tracking of antibiotic use may be not be available in many countries, and regulatory oversight may be limited.[13]

Many antibiotic classes used in humans (medically important) are currently utilized in the beef, dairy, pork, and poultry industries. In 2018, tetracyclines accounted for 66%, penicillins for 12%, macrolides for 8%, sulfonamides for 5%, aminoglycosides for

5%, lincosamides for 2%, cephalosporins for 1%, and fluoroquinolones for <1% of antibiotic sales for livestock.[19] In the United States, the cattle and hog industries are involved in 42% and 39%, respectively, of antibiotic sales intended for use in food-producing animals.[19] Antibiotic use in chickens has decreased significantly. In 2018, 92% of broiler chickens sold in the United States were produced without the routine use of medically important antibiotics. Much of that change in chicken has happened recently, dropping roughly >70% between 2013 and 2017.[20] Globally, penicillins and tetracyclines are the antibiotics most commonly used in pigs.[21]

Widespread antibiotic use drives the emergence of AROs in food-producing animals, including organisms that can cause disease in humans, such as enterococci, *Escherichia coli*, campylobacters, and salmonellae.[21] The use of antibiotic growth promotants at low doses and extended durations is particularly favorable for the selection of AROs, and use in concentrated animal-feed operations permits rapid propagation.[22] Exposure to a single agent can select for antibiotics in other classes via linkage of genes on plasmids and transposons. In a meta-analysis of data from 901 point-prevalence studies from low- and middle-income countries from 2000 to 2018, the proportion of antibiotics with resistance higher than 50% increased from 0.15 to 0.41 in chickens, 0.13 to 0.34 in pigs, and 0.12 and 0.23 in cattle. The highest resistance rates were observed among antibiotics used most commonly (tetracyclines, sulfonamides, and penicillins).[23] Fluoroquinolone use in poultry in the 1990s led to an increasing rate of resistance among campylobacters in the United States, not seen in countries where this use was more restricted.[24] More recently, *E coli* containing *mcr-1*, coding for plasmid-mediated colistin resistance, has emerged in pigs in China, where agricultural use of colistin is common, and has since spread across the world.[25]

Both pathogenic bacteria (eg, salmonellae) and commensals (*E coli)* may be transmitted from farm animals to humans. AROs such as campylobacters can be spread via direct consumption of meat or milk, from surfaces on which the food is prepared, or via water and soil containing animal feces.[26] In addition, produce may contain AROs from contaminated water or soil. Ribotyping of isolates of vancomycin-resistant enterococci from farm animals, raw sewage, and nearby hospitalized patients, demonstrated that farm animals may serve as a reservoir for these organisms.[27] The US National Antimicrobial Resistance Monitoring System reported in 2017 that 14.1% of all tested *Salmonella* isolates from retail chickens were resistant to ≥4 antibiotic classes.[28] Enterobacteriaceae containing *mcr-1* have been found in river water, soil, symptomatic patients, and asymptomatic carriers. Drivers of spread include the global meat trade as well as infected and colonized humans.[29] AROs in food is a global concern, as food-borne diseases cause 600 million illnesses and 420,000 deaths per year, disproportionately in children.[30]

Many countries, particularly those in Europe, have made substantial efforts to curb antibiotic use in food-producing animals, employing a range of stewardship interventions.[31] Since 1996, the Danish government has produced an annual report of antibiotic usage and resistance in humans and farm animals, with documentation of use on individual farms tied electronically to billing.[32] In the Netherlands, antibiotic usage is benchmarked between farms, identifying moderate, high, and very high users as well as veterinarian prescribers, with potential for disciplinary sanctions.[33] Some countries have employed national targets; for example, Belgium has committed to reducing total antibiotic usage by 50% in 2020 compared to 2011.[31] The European Union banned the use of antibiotic growth promotants in 2006, and new regulations set to begin in 2022 include a ban on the preventive use of antibiotics in groups of animals and medicated feeds, restrictions on metaphylactic antibiotics, a reinforced ban on growth promotion, obligations of member states to collect data on the sale and use of antibiotics, potential to reserve certain antibiotics for human use only, and a ban on imported meat raised using growth promotants.[34] With all efforts, transparent, objective assessment of trends in antibiotic usage is crucial to understanding the impact of policy initiatives.

In 2017, the WHO, in collaboration with the Food and Agriculture Organization and the World Organization for Animal Health, released a global action plan for combating antibiotic resistance by reducing unnecessary antibiotic use in animals and humans.[8] The WHO Action plan is grounded in a

"One Health" model, a "collaborative, multisectoral, and transdisciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment."[35] The plan recommends an overall reduction in antibiotics in food-producing animals. Importantly, it recommends a complete restriction of use of all classes of medically important antibiotics in food-producing animals for growth promotion and prevention of infectious diseases that have not yet been clinically diagnosed. In addition, there are recommendations that antibiotics classified as *critically important for human medicine* should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals, and that those that are *highest-priority critically important for human medicine* should not be used in food production for any reason, including the treatment of food-producing animals with a clinically diagnosed infectious disease. There were additional recommendations that any new class of antibiotics or new antibiotic combination developed for use in humans will be considered as critically important for human medicine unless categorized otherwise by the WHO, and that medically important antibiotics that are not currently used in food production should not be used for that purpose in the future. Originally created in 2007, revised definitions of *importance* and *priority* were released in 2019 and are provided in Table I.[36] The highest-priority critically important antibiotics are quinolones, cephalosporins (third-generation and higher), macrolides and ketolides, glycopeptides, and polymyxins.

Table I. Classification of medically important antimicrobials.

Medically important antimicrobials (35 classes). *Apply criteria:*		
Criterion 1: Sole, or one of limited available therapies, to treat serious bacterial infections in people.		Criterion 2: Used to treat infections caused by bacteria (1) possibly transmitted from nonhumansources, or (2) with resistance gene s from nonhuman sources.
Neither criteria met: important antimicrobials One criterion met: highly important antimicrobials Both criteria met: critically important antimicrobials. *Apply prioritization factors:*		
P1: Used to treat a large number of people with infections for which limited antimicrobials are available	P2: Used with high frequency in human medicine or in certain high-risk groups	P3: Used to treat human infections in which extensive evidence exists on the transmission of resistant bacteria or genes from nonhuman sources
Not all prioritization factors met: high priority All prioritization factors met: highest priority		

Reproduced from the World Health Organization.[36]

Antibiotic stewardship on farms has been associated with reductions in antibiotic resistance in food-producing animals. When Denmark banned the use of avoparcin, an antibiotic similar to vancomycin, levels of vancomycin-resistant enterococci found in livestock and humans dropped within 2 years.[37] Australia has not permitted the use of quinolones in food-producing animals. As a result, resistance to this drug class among pathogens such as *E coli* and campylobacters has been low compared to that in other nations.[24] Commissioned by the WHO, a systematic review of data from 81 studies found that interventions to reduce antibiotic use decreased the prevalence of antibiotic-resistant bacteria in animals by about 15% and multidrug-resistant bacteria by 24%−32%.[38] In 13 studies in humans, the pooled prevalence of antibiotic-resistant bacteria in humans was 24% lower in the intervention groups (decreased antibiotic) compared with control groups. Antibiotic usage can be reduced without reducing farm productivity and profitability.[37] The administration of products such as organic acids, probiotics, and vaccines can reduce the need for antibiotics.[39]

Progress in antibiotic stewardship has been modest in the United States compared to that in European nations. Starting in the 1980s, veterinary oversight has been required for medically important antibiotics used in animals. Since 1990, the USDA has intermittently collected nationally representative survey data on animal health, productivity, and management practices—including limited information related to antibiotic stewardship.[40] In 2012, the FDA released guidance 209, a framework for the voluntary adoption of practices to promote the judicious use of medically important antimicrobials in food-producing animals and encouraging veterinary oversight.[41] A significant milestone was reached in 2017, when the FDA announced full implementation of guidance 213, which called for oversight of a licensed veterinarian for antibiotics administered via animal feed and water, and the removal of growth promotion as an indication for use. In a major point of contention with the WHO recommendations, the USDA has rejected the cessation of using medically important antibiotics for disease prevention.[42] Therefore, producers may be able to relabel the indication of use as preventive rather than for growth promotion, since many classes of antibiotics used for growth promotion are also used for disease prevention. Many of the drugs have indications that are not for a specific pathogen or disease, such as the maintenance of weight gain during times of stress, the prevention of early mortality, or disease prevention during times of stress. In addition, approximately one third of medically important antibiotics approved for use in food animals have no defined limits of duration.[43] While most antibiotic use in livestock requires a prescription or a veterinary feed directive from a veterinarian, individual decisions on administration are often made by farmers via guidelines provided by a veterinarian. Currently, surveillance data do not indicate dosages, or whether antibiotics were administered to prevent, control, or treat a disease. In 2018, the FDA's Center for Veterinary Medicine released a 5-year blueprint for antibiotic stewardship, calling for additional veterinary oversight, limits on duration, and enhanced data reporting.[44] However, more detailed roadmaps on how these objectives will be achieved have yet to be released. While antibiotic use decreased by 30% after the enactment of guidance 213, it increased by 8% the following year, raising concerns about the effectiveness of policy changes without stronger mandates and enforcement.[45] Overall, the US livestock industry uses medically important antibiotics at a rate 61% higher than that in livestock industries in 31 European countries, collectively, according to the National Resources Defense Council's (NRDC) analysis of the most recent data.[46] Current antibiotic stewardship gaps include:

1 Clinical indications for which antibiotics were administered (clinical syndrome, disease prevention vs treatment)
2 Duration and dosage of antibiotics
3 Drivers of changes in trends in use
4 Animal-husbandry practices of farms that use no antibiotics
5 Farm-level antibiotic-utilization rates
6 Veterinarian-level prescribing rates
7 Correlation of ARO surveillance data with antimicrobial use
8 Environmental testing for AROs around concentrated feed operations for local communities
9 Benchmarking with other countries, corrected for animal population biomass

Numerous professional and advocacy organizations have argued for additional measures to promote antibiotic resistance on farms. Formed in 2001, the

Table II. Opportunities for antibiotic stewardship on farms.

Role	Opportunities
Federal and state government	Collect annual data surveillance data on antibiotic resistance in humans, animals, retail meat, and environment samples
	Require farms to report antibiotic use by indication, drug class, dose, and duration
	Mandate comprehensive veterinary oversight and accountability for all antibiotic use on farms
	Set clear, time-defined targets for reductions in antibiotic use
	Subsidize non-antibiotic interventions for disease prevention on farms
Farmers	Limit durations of antibiotic use for specific indications with clearly defined exceptions
	Eliminate routine use of antibiotics for disease prevention
	Utilize non-antibiotic prevention strategies
Restaurants/grocers	Commit to sourcing meat raised without antibiotics
	Support clear antibiotic labelling standards from suppliers
Medical and veterinary professions	Educate patients about antibiotic resistance
	Collect and benchmark antibiotic prescriptions by veterinarians and physicians
	Establish certification standards for antibiotic stewardship
	Lobby hospitals and health care institutions to source meat raised without antibiotics
	Collaborate with advocacy groups to promote One Health stewardship
Advocacy groups	Lobby decision makers for local, state, and federal legislation supporting stewardship
	Benchmark antibiotic use purchased by restaurants chains and suppliers
	Conduct public education campaigns
Consumers	Support local restaurants and restaurants who commit to stewardship
	Lobby representatives to pass legislation supporting stewardship
	Encourage government institutions (eg schools) to source meat raised without antibiotics

Keep Antibiotics Working Coalition is an alliance of 18 national advocacy groups, including the Food Animal Concerns Trust, the Pew Charitable Trusts, the NRDC, the US Public Interest Research Group (PIRG), and Health Care Without Harm, which support transparent reporting of data on the production, sales, and use of antibiotics in animal agriculture as well as reducing overall antibiotic use and eliminating the routine use of medically important antibiotics in food-animal production.[47] US PIRG, a federation of independent, state-based, citizen-funded public-interest groups, champions state-level legislation to reduce antibiotic use, educates the public and health care professionals, and leads national campaigns to encourage restaurant chains to commit to responsible meat purchasing.[48] Health Care Without Harm, in conjunction with the Pediatric Infectious Diseases Society, has developed a toolkit for antibiotic stewardship that includes guidance for health care institutions on purchasing meat from animals raised without antibiotics.[49]

When political hurdles hinder the implementation of new regulations, consumer choices can affect change through market pressure on grocery stores, restaurants, suppliers, and ultimately farmers. In a *Consumer Reports* survey, 43% of respondents answered that they often or always purchased meat from animals raised without antibiotics. Additionally, nearly 60% indicated that they would be more likely to eat at a restaurant serving meat from animals raised without antibiotics and would pay more for a burger sourced from animals raised without antibiotics.[50] The Chain Reaction Report is an influential yearly publication from *Consumer Reports*, the NRDC, the Antibiotic Resistance Action Center at George Washington University, the Center for Food Tolerability, Food Animal Concerns Trust, and the US PIRG Education Fund, that ranks America's top restaurant chains on their policies related to antibiotic use in their food-supply chains.[51] The Chain Reaction Report lays out clear criteria for restaurants to source meat from animals raised without the routine use of medically important antibiotics, and it has had an effect. Thirteen of the top 25 restaurant chains in the United States now serve only chicken raised without the routine use of medically important antibiotics, with an additional 4 chains finalizing commitments. The fifth report, released in October 2019, focused on beef, with 15 of 25 chains receiving a failing grade because of a lack of any policy on sourcing beef from cattle raised without the routine use of medically important antibiotics. Encouragingly, McDonald's, the largest single purchaser of beef in the United States, released a plan that calls for the end of the routine use of medically important antibiotic use in its supply chain. It is committed to public reporting and will set reduction targets for antibiotic use in beef by the end of 2020.[51]

Informed purchasing requires unambiguous labeling at the point of purchase, verified by inspections to ensure authenticity. Currently, labels stating "no antibiotic administered/USDA verified" are meaningful, as the language is clear that antibiotics were not administered and are certified by government inspectors. Other labels are also clear but lack language indicating verification, such as "raised without antibiotics." Finally, some labels are vague, such as "natural," or may be misleading, such as "no antibiotic residues," or "antibiotic-free," since antibiotics, even when given during the animals' lives, are mandated to be withheld prior to slaughter so that no antibiotic residues remain in the meat when purchased. These misleading terms should not be used when communicating with the public. Furthermore, AROs that emerge during the raising of animals persist beyond the discontinuation of antibiotics and can be transmitted.[26] Meat producers can utilize certification programs to ensure responsible antibiotic use. The Certified Responsible Antibiotic Use (CRAU) program allows for the minimal use of medically important antibiotics in poultry production.[52] It is the first responsible-use standard certified by the USDA, and companies must undergo regular USDA audits to ensure compliance.

Reducing antibiotic use in agriculture and human medicine is paramount to public health. The Infectious Diseases Society of America has released a position paper stating that antibiotic use in agriculture contributes to the emergence of resistant bacteria that can spread to humans, and that antibiotic use in animals should be carried out under veterinary supervision.[53] The FDA has released a 5-year plan, Supporting Antimicrobial Stewardship in Veterinary Settings, building on guidance 213. However, meat producers continue to use medically important antibiotics routinely to prevent disease brought on by industrial farming conditions. To safeguard the efficacy of these life-saving medicines, medically important antibiotics should be used in food-animal production only to treat disease that has been diagnosed by a licensed veterinarian, or in limited circumstances to control a verified disease outbreak. Opporunities for stewardship are listed in Table II.

More direct advocacy is needed, as the general population may perceive antibiotic-resistant bacterial infections as an abstract threat, not realizing the public health danger. Health care professionals including physicians, pharmacists, nurses, and others can use their own professional experiences to relay compelling stories of the impact of AROs on their patients. Health care professionals can sway decision makers using their expertise and credibility as voices for health. Physicians can partner with advocacy organizations to develop media-communication strategies and network with professionals in other disciplines. The COVID-19 pandemic has acutely demonstrated the importance of a global, data-driven, and transdisciplinary approach to combat infectious-disease threats. Advocacy by health care professionals, combined with an educated citizenry, is crucial for combating antibiotic resistance.

DISCLOSURES

M. Wellington is the Public Health Campaigns Director of US PIRG and US PIRG Education Fund and the Director of the Comprehensive Champions in Antibiotic Stewardship (CCCAS) Collaborative. US PIRG advocates for the responsible use of antibiotics in animal agriculture. The CCCAS Collaborative is a joint committee of Health Care Without Harm, the Pediatric Infectious Diseases Society, the Sharing Antimicrobial Reports for Pediatric Stewardship group, and the US Public Interest Research Group, which advocates for responsible use of antibiotics in animal agriculture. S. Patel is a steering committee member of CCCAS and a volunteer with US PIRG and Illinois PIRG and has received education funding from the Ann & Robert H. Lurie Children's Hospital of Chicago for advocacy work related to promoting antibiotic stewardship in animal agriculture. M. Ferreira is an employee of the Directorate of Operational Medicine, Bureau of Medical Services with the US Department of State. The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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