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Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics

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abstract

Antimicrobial resistance is one of the most serious threats to public health globally and threatens our ability to treat infectious diseases. Antimicrobial-resistant infections are associated with increased morbidity, mortality, and health care costs. Infants and children are affected by transmission of susceptible and resistant food zoonotic pathogens through the food supply, direct contact with animals, and environmental pathways. The overuse and misuse of antimicrobial agents in veterinary and human medicine is, in large part, responsible for the emergence of antibiotic resistance. Approximately 80% of the overall tonnage of antimicrobial agents sold in the United States in 2012 was for animal use, and approximately 60% of those agents are considered important for human medicine. Most of the use involves the addition of low doses of antimicrobial agents to the feed of healthy animals over prolonged periods to promote growth and increase feed efficiency or at a range of doses to prevent disease. These nontherapeutic uses contribute to resistance and create new health dangers for humans. This report describes how antimicrobial agents are used in animal agriculture, reviews the mechanisms of how such use contributes to development of resistance, and discusses US and global initiatives to curb the use of antimicrobial agents in agriculture.

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INTRODUCTION

Antimicrobial resistance is a growing public health crisis. Antimicrobial-resistant infections are often more costly to treat, prolong health care use, and can increase morbidity and mortality.[1–3] The Centers for Disease Control and Prevention (CDC) reported that more than 2 million Americans become ill with antimicrobial-resistant infections each year, with more than 23 000 resulting deaths.[4] National costs to the US health care system attributable to antimicrobial-resistant infections have been estimated to be $21 billion to $34 billion annually, resulting in 8 million additional hospital days.[3,5–7] Although overuse and misuse of antibiotic drugs in human medicine play a significant role in the problem, the focus of this analysis is on a less commonly recognized contributor: the use of antimicrobial agents in food animals.

ANTIMICROBIAL USE IN FOOD ANIMALS

Scope of Use

Antimicrobial agents are widely used in food animals in the United States. In 2012, animal antimicrobial sales represented a substantial proportion of overall antimicrobial sales in the United States: more than 32.2 million pounds of antimicrobial drug active ingredients (including drug classes not used in humans, such as ionophores),[8] compared with an estimated 7.25 million pounds[9] of antimicrobial products for human use. Approximately 60% of the antimicrobial agents sold for use in food animals are considered to be important in human medicine. Many antimicrobial agents used in food animals are the same as or similar to those used in human medicine (Table 1).[10] Unlike in human medicine, antibiotic agents in food animals may often be used without a prescription or any veterinary oversight. The Food and Drug Administration (FDA) reported that at least 97% of medically important antimicrobial agents that were sold in 2012 for use in food-producing animals had an over-the-counter dispensing status.[11]

Indications for Use

In food animals, antimicrobial agents are approved for a variety of indications, commonly categorized into treatment, disease control, prevention, and production uses.[12] The FDA and the World Health Organization define antimicrobial use for treatment, prevention, and control of specific diseases as "therapeutic use." Treatment uses involve episodic use of therapeutic doses of antimicrobial agents for management of specified infectious diseases in clinically ill animals. When used to control spread of infection, antimicrobial agents are administered not only to ill animals but also to those that are likely to come into contact with ill animals.

Antimicrobial agents are also approved for use in animals without an identifiable infectious illness. Preventive uses of antimicrobial agents involve giving antimicrobial drugs to healthy animals at high risk of infection in situations in which there is a history of a specific disease, such as during transportation or when confined to crowded areas such as those common to animals raised under industrial conditions. Duration of preventive use can vary. Production uses (nontherapeutic use) include "feed efficiency" and "growth promotion" uses, which are unrelated to disease management. These uses typically involve administration of subtherapeutic antimicrobial agents in the feed or water of an entire herd or flock to promote faster growth with less feed. The mechanism of action is not fully understood; hypotheses include that production uses may have an overlapping effect of preventing disease, which facilitates more rapid growth or alterations in the microbiome. Animal studies link antibiotic-induced alterations in the microbiome to changes in metabolism, adiposity, and higher fat mass.[13]

Many antimicrobial agents used for growth promotion are also used for disease prevention, including antibiotic classes ranked by the FDA as critically or highly important to human medicine, such as macrolides, streptogramins, and tetracyclines.[11] National data describing antimicrobial use in food animals by indication are sparse. In 2012, most antimicrobial agents sold for food animal use in the United States (94%) were intended to be delivered through animal feed or water; only 4% of antibiotic drugs sold that year were intended to be administered by injection.[11]

TABLE 1 Antimicrobial Drugs Approved for Use in Food-Producing Animals: 2012 Sales and Distribution Data Reported[67] by Drug Class, United States[8]

Antimicrobial Class	Annual Totals (Pounds of Active Ingredient)
Aminoglycosides	473 761
Cephalosporins[a]	58 667
Lincosamides[a]	419 100
Macrolides	1 284 931
Penicillins[a]	1 940 424
Sulfas[a]	817 958
Tetracyclines[a]	12 439 729
Not independently reported[b]	3 330 237

[a] Includes antimicrobial drug products that are approved and labeled for use in multiple species, including both food-producing and non–food-producing animals, such as dogs and horses.

[b] Antimicrobial classes for which there were less than 3 distinct sponsors actively marketing products in the United States were not independently reported. These classes included aminocoumarins, amphenicols, diaminopyrimidines, fluoroquinolones, glycolipids, pleuromutilins, polypeptides, quinoxalines, and streptogramins.

ANTIMICROBIAL USE IN FOOD ANIMALS AND ANTIMICROBIAL RESISTANCE

Antimicrobial Resistance

Antimicrobial resistance is an organism's ability to evade inhibition by an antimicrobial agent. Resistance traits can be acquired either through new mutations[14] or through transfer of genetic material between organisms (by bacteriophages or mobile genetic elements, such as plasmids, naked DNA, or transposons).[15] Any use of antimicrobial agents leads to elimination of susceptible organisms, allowing resistant organisms to survive. Overuse or misuse of antimicrobial agents places antimicrobial pressure on bacteria,[16] selecting for resistant organisms and facilitating overgrowth of resistant organisms as susceptible flora are eradicated. Long-term use of a single antimicrobial agent can lead to resistance not only to that agent but to multiple agents.[13,14]

Antimicrobial Use in Food Animals and Antimicrobial Resistance

Therapeutic and subtherapeutic use of antimicrobial agents in animals has been shown to lead to antimicrobial resistance.[17–26] In a classic experiment, Levy et al[27] demonstrated that in chickens receiving a prolonged course of low-dose tetracycline administered in feed, single-drug resistance developed and led rapidly to multidrug resistance; resistance then spread beyond individual animals exposed to the antimicrobial agent to other members of their species in the same environment, and resistant organisms were also identified in specimens from humans living on the farm. Once tetracycline feed supplementation was stopped, there was a decrease in resistant organisms detected in the farm-dwelling humans.

In recent years, evidence has emerged linking additional resistant pathogens to antibiotic use in food animals. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been found to acquire tetracycline and methicillin resistance in livestock.[28] MRSA has also been found to be prevalent in meat and poultry in the United States; samples from 5 US cities[29] demonstrated *S. aureus* contamination in 77% of turkey samples, 42% of pork samples, 41% of chicken samples, and 37% of beef samples. Ninety-six percent of *S. aureus* isolates were resistant to at least 1 antimicrobial agent, and many were additionally resistant to other antimicrobial classes, including tetracycline, ampicillin, penicillin, erythromycin, quinupristin/dalfopristin, fluoroquinolones, oxacillin, daptomycin, and vancomycin. More than half of samples were multidrug resistant, defined as intermediate or complete resistance to 3 or more antimicrobial classes. Patient exposure to swine or livestock industrial agriculture exposure has also been associated with increased risk of community-acquired and health care–associated MRSA infection.[30,31]

Extraintestinal *Escherichia coli* infections have also been linked to antibiotic use in food animals.[32] Extraintestinal pathogenic *E. coli* is a term used to describe *E. coli* lineages that cause disease at nonintestinal sites. Extraintestinal pathogenic *E. coli* organisms, including antimicrobial strains, have been associated with human urinary tract infections, sepsis, and other infections.[33,34]

Antimicrobial Agents Commonly Used in Food Animals

Since 2008, the FDA has been collecting limited data about antimicrobial drug sales for use in food animals in the United States and publicly reports sales data by drug class (Table 1).

TRANSMISSION OF PATHOGENS FROM ANIMALS TO HUMANS[16,35,36]

Susceptible and resistant animal pathogens can reach humans through the food supply, by direct contact with animals, or through environmental contamination.

Increasingly, food animals are raised in large numbers under close confinement, transported in large groups to slaughter, and processed very rapidly. These conditions can cause increased bacterial shedding and contamination of hide, carcass, and meat with fecal bacteria. Dissemination of pathogens through the food chain is amplified by centralized food processing and packaging processes and broad distribution through food wholesalers and retail chains. By these mechanisms, organisms found in contaminated meats and other food products have been shown to be transmitted to humans through the food supply.[32,37,38]

Resistant bacteria can spread to humans through direct exposure[39–41] from infected or contaminated animals, such as on farms or in processing facilities. Farmers, farm workers, and farm families[16] as well as casual visitors[42] are at greater risk of infection compared with the general population.[27]

Resistant bacteria from animals can be spread through fecal material, wastewater, or environmental contact, leading to environmental reservoirs of pathogens and resistance genes.[43,44] Animal feces can contaminate foods when manure containing resistant organisms is applied to agricultural soils and the organisms are then present in farm runoff.[45] Cross-contamination of fruits and vegetables can occur when wastewater is used to irrigate crops, and fish raised in contaminated water can also be exposed. Active antimicrobial agents have been detected in surface waters and river sediments,[46] and resistance genes identical to those found in swine waste lagoons have been found in groundwater and soil microbes hundreds of meters downstream.[47] These findings raise concerns that environmental contamination with antimicrobial agents from agricultural and human use could present microbial populations with selective pressure, stimulate horizontal gene transfer, and amplify the number and variety of organisms that are resistant to antimicrobial agents.

CHILD HEALTH EFFECTS

Infants and children are affected by transmission of susceptible and resistant food zoonotic pathogens through the food supply, direct contact with animals, and environmental pathways. In 2013, a total of 19 056 infections, 4200 hospitalizations, and 80 deaths were reported to the Foodborne Diseases

Active Surveillance Network, a CDC surveillance system covering 15% of the US population.[48] For most infections, incidence was highest among children younger than 5 years.[49] Data on food-related transmission of *Campylobacter* species, *Salmonella* species, and *E. coli* are summarized here.

Salmonella Species

Nontyphoidal *Salmonella* species are a leading cause of foodborne illness in children. In 2013,[50] the incidence of laboratory-confirmed *Salmonella* infections per 100 000 children was 63.49 in children younger than 5 years, 19.33 in children 5 through 9 years of age, and 11.26 in children 10 to 19 years of age.[51] Scallan et al[52] estimated that *Salmonella* results in 123 452 illnesses, 44 369 physician visits, 4670 hospitalizations, and 38 deaths annually among children younger than 5 years. Neonatal infections caused by *Salmonella* species have been attributed to indirect exposure to foodborne sources.[39,53] Pediatric *Salmonella* infections caused by exposure to contaminated pet food have also been documented.[54] Food contaminated with *Salmonella* is not the only route of transmission; children have also acquired *Salmonella* infections from direct contact with livestock[55] and live poultry and other animals or their environments.[56,57]

The CDC estimated in 2013[4] that there are 1.2 million *Salmonella* infections in the United States per year, of which 100 000 are drug-resistant. Five percent of nontyphoidal *Salmonella* are resistant to 5 or more classes of antibiotic drugs. Of particular note, 3% are resistant to ceftriaxone, the first-line therapy for salmonellosis in pediatrics.

Campylobacter Species

Campylobacter species are also a leading cause of foodborne illness in children. In 2013,[50] the incidence of laboratory-confirmed *Campylobacter* infections per 100 000 children was 24.08 in children younger than 5 years, 10.54 in children 5 through 9 years of age, and 9.42 in children 10 to 19 years of age.[45] *Campylobacter* species have been estimated to cause 81 796 illnesses, 28 040 physician visits, 1042 hospitalizations, and 6 deaths annually in children younger than 5 years.[46] *Campylobacter* infection has been associated with eating poultry and nonpoultry meat products and unpasteurized dairy products as well as exposure to untreated water and contact with farm animals.[58]

Antimicrobial resistance, specifically resistance to ciprofloxacin, in *Campylobacter* species is increasing[59]; resistance increased from 13% in 1997 to almost 25% in 2011.[4] The CDC estimated in 2013[4] that there are 1.3 million *Campylobacter* infections per year, of which 310 000 are drug resistant. Of all *Campylobacter* samples tested, 23% were resistant to ciprofloxacin, and 2% were resistant to erythromycin. In children, azithromycin and erythromycin are the preferred treatment of *Campylobacter* gastrointestinal tract infection. Fluoroquinolones may be effective against *Campylobacter* species, but resistance is common, and fluoroquinolones are not approved for this indication by the FDA for use in children.

Staphylococcus aureus

MRSA infections cause a variety of human illnesses, including skin and wound infections, pneumonia, and sepsis. MRSA has been demonstrated to be transmitted from animals to humans through close contact with livestock.[60] In recent years, a MRSA clone, which originated in the community and is associated with exposure to livestock, has emerged in different countries worldwide, including the United States. Even more concerning, countries with a historically low prevalence of MRSA, including the Netherlands and Denmark, have seen an increase in livestock-associated MRSA.[61,62]

The CDC estimates that there are 80 461 severe MRSA infections in the United States per year and 11 285 deaths.

EVIDENCE FROM AROUND THE WORLD

Despite the evidence that nontherapeutic use of antibiotic agents selects for resistance, that bacterial resistance in humans is determined by the same mechanism as in animals, and that resistance genes can disseminate via the food chain, initiatives to reduce antibiotic have met with opposition from the agriculture and farming industry.

The first ban on farm use of antibiotic agents as growth promoters was enacted in 1986 in Sweden, followed by Denmark, the United Kingdom, and other countries of the European Union. In 1995, Denmark established DANMAP, a system for monitoring antibiotic resistance in farm animals to follow the effect of banning antibiotic drugs as growth promoters. Danish swine and poultry production continues to thrive without a loss in meat production, and Denmark has experienced major reductions in antimicrobial consumption and resistance. Likewise, using a similar monitoring program, Sweden has noted no loss of production after the ban and dramatic reductions in the sales of antibiotic agents for animals, from 45 tons to approximately 15 tons by 2009.[63]

In 2013, the FDA implemented a plan to phase out the use of medically important antimicrobial agents in food animals for food production purposes, such as to increase growth or improve feed efficiency. The plan is not a ban but a roadmap for animal pharmaceutical companies to voluntarily revise their approved labels for antibiotic use in animals. The CDC encourages and supports efforts to minimize inappropriate use of antibiotic agents in animals, including the FDA's strategy to promote the judicious use of antibiotic drugs that are important in humans. The CDC has also contributed to curriculum for veterinarians on the prudent use of antibiotics in animals.[4] Despite the FDA's policy, a recent report by the Pew Charitable Trusts identified many antibiotic agents approved for disease prevention purposes that were also approved for growth promotion. A quarter (66) of the 287 antibiotic agents reviewed can be used for disease prevention at levels that are fully within the range of growth promotion dosages and with no limit on the duration of treatment. Because the lines between disease prevention and growth promotion are not always clear, the current FDA policy may allow drug manufacturers to continue using ambiguous language on labels of antibiotic drugs. The Pew Charitable Trusts urged the FDA to take additional steps to ensure that food animals receive antibiotic agents only when medically necessary.[64]

Congress is also pursuing a path to curb antibiotic use in animals. The Preservation of Antibiotics for Medical Treatment Act (H.R. 1150) would protect 8 classes of antibiotic agents important for treating infections in humans. The act proposes withdrawal of antibiotic use from food animal production unless animals or herds are sick with disease or unless pharmaceutical companies can prove that their use does not harm human health. A bipartisan companion bill, the Preventing Antibiotic Resistance Act (S. 1256), was introduced in the 113th Congress. Bills have also been introduced to improve data collection and reporting on antibiotic use in food animals: the Antimicrobial Data Collection Act (S. 895) and the Delivering Antimicrobial Transparency in Animals Act (H.R. 820). In September 2014, the President's Council of Advisors on Science and Technology released its report, "Combating Antibiotic Resistance," and President Obama signed an executive order directing key federal departments and agencies to take action to combat the increase of antibiotic-resistant bacteria. Among these, the FDA was directed to continue taking steps to eliminate agricultural use of medically important antibiotics for growth promotion purposes.[65]

Finally, the World Health Organization, in its recent report on antimicrobial resistance, outlined a global plan that includes integrated surveillance of food-producing animals and the food chain.[66]

CONCLUSIONS

Antimicrobial resistance is considered one of the major threats to the world's health. The use of antimicrobial agents in agriculture can harm public health, including child health, through the promotion of resistance. Because of the link between antibiotic use in food-producing animals and the occurrence of antibiotic-resistant infections in humans, antibiotic agents should be used in food-producing animals only to treat and control infectious diseases and not to promote growth or to prevent disease routinely.

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ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
FDA: US Food and Drug Administration
MRSA: methicillin-resistant *Staphylococcus aureus*

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