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Antibiotic Resistance: What Is the Impact of Agricultural Uses of Antibiotics on Children's Health?

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Abstract

Antimicrobial resistance has reached crisis stage in human medicine. The rapid acceleration of multidrug-resistant bacteria in the past 2 decades has overtaken new drug development, and patients and clinicians are faced with the prospect of untreatable infections. Although much of the problem stems from overuse and misuse of antimicrobial agents in human medicine, large-scale use of antimicrobials in agriculture also contributes to the crisis. Agricultural uses of antibiotics produce environmental exposures in a variety of reservoirs, which select for resistant microbes and microbial genes. This article presents the major lines of evidence documenting the risks to human health of some of the agricultural uses of antimicrobials. A brief review of the microbiologic antecedents of resistance is followed by a discussion of agricultural uses of antimicrobials and a targeted review of the literature, which provides the background knowledge and evidence necessary for pediatricians and other clinicians to be informed and to advocate for judicious use of antimicrobials in all sectors.

- **antibiotic**
- **antimicrobial**
- **resistance**
- **agriculture**
- **children**

After each new antimicrobial is introduced into clinical practice, development of resistance in human pathogens consistently follows.[1] During the initial decades of the antibiotic era, the rate of new drug development and patterns of use were such that when resistance to an agent developed, a new agent could be substituted to treat resistant pathogens. In the past 10 to 15 years, however, there has been a rapid acceleration in the emergence of multidrug-resistant pathogens, including some that are resistant to most or virtually all agents. The overuse and misuse of antimicrobials and the deceleration in the development of novel antimicrobial agents[2] have caused the crisis of antimicrobial resistance in

human medicine.[3] Pediatricians are at the forefront of efforts to change practice, promote judicious use, and eliminate unnecessary use of antimicrobials in medicine.[4] Despite success in reducing use of antimicrobials and decreasing resistance rates in some pathogens,[5] increasing numbers of highly resistant pathogens continue to emerge.[6]

Antimicrobials are now ubiquitous in the environment.[7] They are used in human medicine by prescription, in over-the-counter preparations, by veterinarians to treat disease in animals,[8] in cleaning products and other consumer products, as pesticides, in aquaculture (fish farming), and in animal agriculture. The largest use of antimicrobial agents outside human medicine is in food animals.[9] Because there are no uniform reporting requirements, the total amount of antimicrobials produced annually in the United States and the distribution of use among the sectors listed above are not precisely known and are matters of controversy.[10] All estimates indicate that millions of pounds of antimicrobials are used each year in animal agriculture (Table 1). During the past 30 years, studies have shown that use of antimicrobials in food animal production promotes the development and subsequent dissemination to humans of resistant organisms.[11] Experts continue to call for reevaluation of and changes in these practices, but in the United States, little action has been taken.[12]

TABLE 1.

Annual Antibiotic Use in the United States, According to the Institute of Medicine[9] and the Union of Concerned Scientists[10]

Children, particularly very young children, are at high risk of developing infections with drug-resistant organisms linked directly to the agricultural use of antimicrobials. Surveys of foodborne infections show that almost 20% of *Campylobacter* species infections and more than one third of nontyphoidal *Salmonella* species infections occur in children younger than 10 years.[13] Furthermore, the rate of infection with *Campylobacter* species in the first year of life is twice that in the general population, and the rate of infection with nontyphoidal *Salmonella* species in infants is 10-fold higher than that in the general population.[14] Young children and infants are at increased risk of developing extraintestinal focal disease and disseminated disease from enteric pathogens.[15] When pathogens are resistant to many drugs, there is increased risk of adverse outcomes, including fatality.

MICROBIOLOGIC ANTECEDENTS OF RESISTANCE

Bacterial resistance to antimicrobials is the evolutionary response of organisms in the presence of the selective pressure of antimicrobial agents. The following 4 basic mechanisms of resistance have been documented: 1) development of mechanisms that prevent antimicrobial access to the site of action by increasing efflux or decreasing influx through the cell membrane; 2) development of enzymes that degrade or alter the antimicrobial agent; 3) alteration of the site of antimicrobial action, rendering the drug ineffective; and 4) development of site-of-action bypass mechanisms.[16] These traits are encoded on bacterial genes located on chromosomal DNA or, more common, on plasmid DNA. Traits can be acquired by mutation and clonal spread or by horizontal gene transfer.

Under optimal conditions, bacteria have a generation time of minutes to hours, allowing for ample opportunity for de novo mutations and selection.[17] It is estimated that resistance genes arise in this fashion once in every 1 million to 1 billion cells and usually result in resistance to a single antibiotic.[18] In addition, several highly efficient methods of horizontal gene transfer are increasingly documented to play important roles in the dissemination of resistance genes. These include transfer of DNA via bacteriophages and plasmids and direct uptake of bacterial DNA from lysed bacteria in the environment through transduction, conjugation, and transformation.[19] Some mechanisms of horizontal gene transfer, such as bacteriophage-mediated transduction, are limited to closely related bacterial species. Others, such as transformation, can be accomplished between different species or even genera of bacteria. Resistance genes can also reside in groups of 10 or more on plasmids or on self-transmissible transposons, permitting the selection of multidrug resistance as a response to the presence of a single antimicrobial agent.[20]

Resistance genes are bred and transferred within environmental reservoirs in which bacteria and antimicrobial agents coexist. Obvious reservoirs include the guts of humans and animals, in which horizontal resistance gene transfer has been documented among pathogenic[21] and commensal species.[22] Transfer of resistance between disparate bacterial species is also postulated to occur in the human oropharynx.[23] Nonanimal reservoirs are also of concern. Active antibiotics have been identified in water near wastewater treatment plants, animal waste lagoons,[24] surface waters, and river sediments.[25] This has resulted in speculation that environmental contamination with antibiotics can augment the selection and dissemination of resistance genes through a wide variety of routes involving animal and nonanimal reservoirs. Resistance genes identical to those found in swine waste lagoons have been found in groundwater and soil microbes hundreds of meters downstream.[26]Multiple animal and nonanimal resistance gene reservoirs likely exist.

THE IMPACT OF AGRICULTURAL USE OF ANTIMICROBIAL AGENTS ON HUMAN HEALTH

In livestock and poultry, antimicrobials are used to promote growth, prevent disease, and treat infection.[12] For the purposes of this article, growth promotion and disease prevention will be combined under the rubric "nontherapeutic uses." Therapeutic agents may be delivered to individual animals or to entire herds or flocks, depending on the disease, type of food animal, and type of production facility.

"Feed efficiency," or the ability to grow animals faster on less feed, is improved by adding small amounts of antibiotics to animal feed. First approved by US Food and Drug Administration (FDA) in the early 1950s, this practice results in shorter time to slaughter at less expense to the producer, improves profits, and decreases consumer costs.[27] Some of the antimicrobials used as growth promoters are chemically similar or identical to pharmaceutical agents that are important in the treatment of human disease; others are not currently used in human therapeutics (Table 2). One explanation of the growth promotion effect of antimicrobials is that subclinical infections are treated before animals become overtly ill, thus preserving animal health and enhancing growth rates. Therefore, it can be difficult to separate the growth promotion function from the disease prevention function of subtherapeutic antibiotics added to animal feed. Furthermore, because animals are grown in groups and increasingly on large industrial farms, infection in an individual animal can rapidly spread to hundreds or thousands of animals. Some proponents view antimicrobial use as an integral component of certain types of intensive livestock operations. For the purposes of analyzing the effect of these nontherapeutic uses of antimicrobials, however, growth promotion and disease prevention can be combined, because the environmental selection pressure presented to the bacterial flora of the animals is identical for both—very low-dose exposure to 1 or more antimicrobial agents over long portions of the life cycle in large numbers of healthy animals.

TABLE 2.

Antimicrobials Approved by the FDA for Growth Promotion in Food Animals[11]

The literature examining the impact of antimicrobial use in food animals on the development of resistance is not large but is consistent with what would be anticipated by extrapolating from resistance studies performed with human populations. Levy et al[28]examined the effect of chlortetracycline in feed on the intestinal flora of chickens and farm dwellers. Using a controlled experimental design, chickens were divided into 2 groups: the experimental group received feed that contained subtherapeutic doses of oxytetracycline, and the control group received feed without the drug. After 2 weeks, 90% of the experimental chickens excreted 100% resistant organisms. Multidrug resistance developed as well (resistance to sulfonamides, streptomycin, ampicillin, and carbenicillin); by 12 weeks, almost two thirds of the experimental chickens excreted organisms that were resistant to more than tetracycline, and greater than one quarter were resistant to all 4 antimicrobials. Chickens in the control group, despite isolation in different pens, also developed resistance but at lower levels. By 4 months, almost one third of the control animals excreted >50% resistant organisms. Resistance also

transferred to humans. Within 6 months, >30% of the fecal samples from farm dwellers contained >80% tetracycline-resistant bacteria, compared with 6.8% in neighborhood control subjects ($P <$ .001). The same 4-drug resistance pattern was found in farm families as was found in the experimental chickens but was not found in neighborhood control families. Six months after all tetracycline-containing feed was removed from the farm, no tetracycline-resistant organisms were isolated from stool samples in 8 of 10 farm dwellers tested. This classic study documents the selection of single and multidrug resistance in the intestinal flora of animals in response to the use of a single antimicrobial agent, the environmental or occupational transfer of resistance to humans, and the potential for reversal to wild-type flora when the antimicrobial selective pressure is removed.

Holmberg et al[29] studied a 6-state outbreak of illness caused by a plasmid-mediated, multidrug-resistant strain of *Salmonella newport*. Human illness was attributed to beef consumed by humans and then traced back to a feedlot that was using subtherapeutic doses of chlortetracycline as a growth promoter. Investigators were also able to document the presence of the outbreak organism in isolates from animals and humans on an adjacent dairy farm. In addition, the study identified an increased risk of illness with a resistant (versus sensitive) *S newport* strain in patients who were taking antibiotics for other infections (odds ratio: 51.3; $P = .001$). The rapid onset of gastrointestinal symptoms (24–48 hours after beginning therapy) and the presence of unrelated symptoms before onset of enteric illness suggest that symptomatic infection was converted from asymptomatic carriage of the epidemic strain by the use of antibiotics. This study enhances our understanding of the risk of transmission of resistant organisms through the food chain. The study has particular importance for children and other populations who frequently require treatment with antimicrobial agents.

Several studies have documented nosocomial spread of resistant enteric organisms from the food chain to infants in the newborn nursery. Bezanson et al[30] documented that a plasmid-mediated, 6-drug-resistant strain of *Salmonella typhimurium* was acquired by a pregnant woman after she drank raw milk. The mother was asymptomatic, but the organism was passed to her infant at birth. The infant became ill within 24 hours and subsequently developed meningitis and sepsis. Three and 4 days later, several other infants in the newborn nursery developed diarrhea caused by the same organism. Lyons et al[31]described an outbreak of diarrhea in a newborn nursery caused by multidrug-resistant*Salmonella heidelberg*. The index case was an infant who was born at term by cesarean section after the mother had been in labor for 18 hours. The mother was a farmer's daughter who had worked with new calves until the delivery. The herd contained several sick calves. Although the mother did not develop diarrhea until after delivery, the infant developed diarrhea on day 4 of life and had blood and stool cultures positive for *S heidelberg* resistant to chloramphenicol, sulfamethoxazole, and tetracycline. Two other infants in the nursery developed diarrhea and positive stool cultures with the same organism. These studies emphasize the unique vulnerability of infants to infection via perinatal exposures, the higher risk of disseminated and extraintestinal disease in infants, and the occurrence of infant-to-infant spread. The conditions that facilitate spread within the hospital setting are similar to conditions in child care centers where young children may attend in large numbers, are not yet toilet trained, and are cared for by shared staff.[32]When infections caused by multidrug-resistant bacteria become systemic or spread among individuals, adverse outcomes are more likely.

Unfortunately, such multidrug-resistant enteric organisms are being increasingly documented. The prevalence of multidrug-resistant, nontyphoidal *Salmonella* species among human isolates has been increasing since the early 1980s and reached 19% in 1995 in the United States.[33] Although most cases of salmonellosis are self-limited, 3% to 10% progress to bacteremia and may require treatment. Because of the increasing prevalence of multidrug resistance in several enteric pathogens, particularly *S typhimurium* serotype DT104,[34,35] fluoroquinolones have become the drugs of choice for empiric treatment in adult patients, and third-generation cephalosporins are the drugs of choice in pediatric patients. The efficacy of these drugs may now be threatened. In 1998, Molbak et al[36]described an outbreak of *S typhimurium* serotype DT104 resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, tetracycline, and quinolones, which was linked by sophisticated molecular epidemiology to 2 swine herds in Denmark. Two patients died in this outbreak, and therapeutic failure was considered causal. A case report from Nebraska described a child who was infected with *S typhimurium* that was resistant to ampicillin, chloramphenicol, tetracycline,

sulfisoxazole, kanamycin, streptomycin, broad-spectrum cephalosporins, extended-spectrum cephalosporins, aztreonam, cefoxitin, gentamicin, and tobramycin.[37] This boy recovered without therapy, but it is estimated that 600 deaths occur annually from *Salmonella* species infections, primarily in the elderly and the very young.[38] The main reservoir for these highly resistant organisms is believed to be food animals. Recent reports document the presence of multidrug-resistant *Salmonella*species in retail meats.[39] Logically, some of the increase in resistance must be a result of nontherapeutic uses of antimicrobials in these animals.

Multidrug resistance is found not only in human pathogens. Commensal organisms exhibit high rates of resistance, causing illness in debilitated individuals. Enterococci are commensal organisms in food animals, companion animals, wild animals, and humans. A nosocomial epidemic of vancomycin-resistant enterococci (VRE) emerged in the United States in the 1990s, and VRE is now the second most common cause of bacterial nosocomial infection in the country.[40] It is interesting that VRE prevalence patterns are different in the United States, compared with Europe. An examination of these differences can help to elucidate the links between antimicrobial use in animals and resistance in humans.

The VRE epidemic in the United States seems to be the result of a large increase in vancomycin use in human medicine,[41] but the situation in Europe seems to have an agricultural cause. Vancomycin is not used widely in Europe to treat human disease, but a related glycopeptide, avoparcin, has been used as a growth promoter in animal husbandry for decades.[42] Avoparcin selects for cross-resistance to vancomycin when used in farm animals.[43,44] Although in the United States VRE is rarely cultured from healthy individuals in the community,[45] it is not unusual to find VRE in healthy community members in Europe.[46] Furthermore, in Europe, VRE can be cultured from healthy poultry, pigs,[47]ponies, and dogs[48]; from uncooked chicken meat[49] and minced pork; and from raw sewage from urban and rural locations.[50] Molecular fingerprinting shows much higher heterogeneity in the European isolates, compared with isolates from the United States, strongly suggesting that VRE in Europe is a response of multiple bacterial populations in a variety of host species and locations to the presence of avoparcin.

Therapeutic Use—Fluoroquinolones: A Case Study

Many antimicrobials that are used therapeutically in humans are also used therapeutically in food animals (Table 3). Although issues of resistance may be similar in some applications (eg, when disease is diagnosed and treated in individual animals by a veterinarian), there are major differences in the administration of therapeutic drugs in other settings. Animals, such as broiler chickens, are often raised in enclosed barns that contain tens of thousands of birds.[51] Individual therapy in these intensive livestock operations is not the standard. Instead, when disease is diagnosed in individuals in the flock, the entire flock is treated, usually by adding therapeutic doses of antimicrobial agents to the drinking water. Precise control of the dose received by individual animals is not ensured, and environmental discharge of antibiotic is probable.

TABLE 3.

Some Antibiotics Used for Treatment of Infections in Food Animals[11]

In August 1995, the FDA issued the first of several approvals for use of fluoroquinolones in poultry for the treatment of *Escherichia coli* and *Pasteurella* species infections,[52] allowing administration of the drug via drinking water by veterinary prescription. The 2 sponsoring manufacturers agreed to participate in a national bacterial resistance surveillance program, and the FDA Center for Veterinary Medicine instituted strategies intended to prevent development of resistance. Nonetheless, between 1997 and 1999, fluoroquinolone resistance increased from 12.9% in *Campylobacter* species to 17.6% in *Campylobacter jejuni*and 30% in *Campylobacter coli*.[53] Similar increases were documented in isolates from chicken in slaughter houses and retail stores. In October 2000, because of these alarming increases in resistance rates, the Center for Veterinary Medicine initiated the process of withdrawing approvals for therapeutic use of fluoroquinolones in poultry.[54] The reasons were as follows:

- The use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant *Campylobacter*, a pathogen to humans, in poultry
- This fluoroquinolone-resistant *Campylobacter* is transferred to humans and is a significant cause of the development of fluoroquinolone-resistant *Campylobacter* infections in humans
- Fluoroquinolone-resistant *Campylobacter* infections are a hazard to human health[55]

The US experience recapitulates the experience in a number of European and Asian countries in which fluoroquinolones were approved up to 10 years earlier for use in food animals and resistance in humans is now firmly established.[56] Adding to the urgency of the problem is the discovery that diarrhea caused by fluoroquinolone-resistant *Campylobacter* species has a median duration 3 days longer than does diarrhea from sensitive strains, hinting at possible increased virulence.[57] Finally, the minimum inhibitory concentrations for fluoroquinolones in *Salmonella* species are beginning to increase in US isolates, raising additional concern that the utility of fluoroquinolones in these potentially much more serious pathogens is threatened.[58] Currently, fluoroquinolones are not used extensively in pediatrics. This example, however, illustrates that under current animal husbandry practices in the United States, just as with nontherapeutic uses, therapeutic uses of antimicrobials in food animals lead to increased drug resistance in humans.

CONCLUSIONS

There is a long-standing debate over the exact role that agricultural use of antimicrobials plays in the current antibiotic resistance crisis.[59] Although data gaps complicate the debate somewhat,[60,61] existing evidence proves that part of the crisis is caused by antimicrobial use in livestock.[62] Experience in Europe shows that changing animal husbandry practices and removing growth-promoting antimicrobials from feed results in decreased resistance in animals without loss of productivity or value of food animals.[63] For example, when avoparcin, a glycopeptide similar to vancomycin, was banned as a growth promoter in Denmark in 1995, the rate of VRE in broiler chickens decreased from 72.7% in 1995 to 5.8% in 2000. It is in everyone's best interest to slow the development of antimicrobial resistance, but no single user group can do it alone.[64] To make progress, the debate must not become polarized.[65] Medical professionals must work with all stakeholders to find strategies to slow the resistance trajectory.[66] Although the precise combination of actions required to arrest the current global increase in resistance is unknown, essential elements must include 1) elimination of unnecessary use, overuse, and abuse of antimicrobial agents in all sectors; 2) universal adherence to principles of judicious use; 3) collection and analysis of data on antimicrobial use; 4) surveillance of antimicrobial resistance in all potential reservoirs; 5) mechanisms for identification of and rapid response to dangerous resistance trends; 6) application of infection control strategies, including hygiene and immunization, in human and animal settings; and 7) promoting aggressive research and development of new antimicrobial agents. Infants and young children are especially vulnerable to infections, including foodborne infections. Pediatricians, as important guardians of children's health, should be leaders in bringing the concepts and experiences of judicious use of antimicrobials in pediatrics to the larger discussion.[67]

FDA, Food and Drug Administration • VRE, vancomycin-resistant enterococci

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