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TECHNICAL REPORT

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

ABSTRACT. Antimicrobial resistance is widespread. Overuse or misuse of antimicrobial agents in veterinary and human medicine is responsible for increasing the crisis of resistance to antimicrobial agents. The American Academy of Pediatrics, in conjunction with the US Public Health Service, has begun to address this problem by disseminating policies on the judicious use of antimicrobial agents in humans. Between 40% and 80% of the antimicrobial agents used in the United States each year are used in food animals; many are identical or very similar to drugs used in humans. Most of this 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 health dangers for humans. This report will describe how antimicrobial agents are used in animal agriculture and review the mechanisms by which such uses contribute to resistance in human pathogens. Although therapeutic use of antimicrobial agents in agriculture clearly contributes to the development of resistance, this report will concentrate on nontherapeutic uses in healthy animals. *Pediatrics* 2004; 114:862–868; *antibiotic, antimicrobial, resistance, child, infant, agriculture, foodborne, epidemiology.*

ABBREVIATIONS. NARMS, National Antimicrobial Resistance Monitoring System; VRE, vancomycin-resistant enterococci; Q-D, quinupristin-dalfopristin.

ANTIMICROBIAL USE IN ANIMAL FEEDS

Rationale for Use

In livestock and poultry production, antimicrobial agents are used therapeutically, prophylactically, and to promote growth and improve feed efficiency.[1] Therapeutic use in clinically ill animals involves using curative doses of antimicrobial agents for a relatively short period of time. However, antimicrobial agents used for acute illness may be delivered not just to sick individuals but to the entire group of animals to which the sick individuals belong. Many therapeutic antimicrobial agents are administered in water to animals raised in large numbers under industrial conditions, which may result in individual animals or birds receiving inadequate doses. The nature of swine and poultry production makes it difficult to treat individual animals; if a few birds show signs of clinical illness, the entire house (10 000–30 000 birds) is treated. Of the wide variety of agents approved for therapeutic use in animals, many are identical or similar to drugs used in human medicine[2] (Table 1). Only some require a veterinarian's prescription. Although the therapeutic uses of antimicrobial agents in agriculture have significant impact on the development of resistant organisms, they are not the focus of this report.

Antimicrobial agents are also used in animal production to promote growth, primarily by enhancing feed efficiency; the mechanism of action is not known. When used for this purpose, low doses of antimicrobial agents are added to the feed of healthy animals for much of their life span. In addition, prophylactic antimicrobial agents are used to control the dissemination of clinically diagnosed infectious diseases identified within a group of animals or to prevent an infectious disease that has not yet been clinically diagnosed.[1] Prophylactic antimicrobial agents may be used at either low doses or therapeutic doses. These uses generate selection pressure on microbial populations that is similar to growth-promotion use and will be discussed under the common term "nontherapeutic use" to denote their use in healthy animals. Prophylactic antimicrobial agents are used to prevent diseases common to animals grown under industrial conditions.[1] Feed efficiency refers to the ability to grow animals faster with less food. This results in shorter time to slaughter at less expense to the producer, improving profits and decreasing consumer costs.[3] Addition of subtherapeutic doses of antimicrobial agents to feed also results in bigger animals, an effect known as growth promotion.

Scope of Use

Manufacturers and users of antimicrobial agents are not required to report data on production or use for human or food-animal applications. Annual production estimates range from 35 million[4] to 50 million[5] pounds per year. The major nonhuman use of antimicrobial agents is in food-animal production. The Institute of Medicine estimates that 40% of an-

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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TABLE 1. Major Antimicrobial Agent Classes Approved for Nontherapeutic Use in Animals

Antimicrobial Class	Species	Prophylaxis	Growth Promotion
Aminoglycoside	Beef cattle, goats, poultry, sheep, swine	Yes	No
β-Lactam (penicillin)	Beef cattle, dairy cows, fowl, poultry, sheep, swine	Yes	Yes
β-Lactam (cephalosporin)	Beef cattle, dairy cows, poultry, sheep, swine	Yes	No
Ionophore	Beef cattle, fowl, goats, poultry, rabbits, sheep	Yes	Yes
Lincosamide	Poultry, swine	Yes	Yes
Macrolide	Beef cattle, poultry, swine	Yes	Yes
Polypeptide	Fowl, poultry, swine	Yes	Yes
Streptogramin	Beef cattle, poultry, swine	Yes	Yes
Sulfonamide	Beef cattle, poultry, swine	Yes	Yes
Tetracycline	Beef cattle, dairy cows, fowl, honey bees, poultry, sheep, swine	Yes	Yes
Other			
Bambermycins	Beef cattle, poultry, swine	Yes	Yes
Carbadox	Swine	Yes	Yes
Novobiocin	Fowl, poultry	Yes	No
Spectinomycin	Poultry, swine	Yes	No

Source: US General Accounting Office. *The Agricultural Use of Antibiotics and Its Implications for Human Health*. Washington, DC: General Accounting Office; 1999. Publication no. GAO-RCED 99–74

nual antimicrobial use in the United States is veterinary, and approximately three fourths of this use is categorized as nontherapeutic "supplements" in food animals.[5] Other estimates of nontherapeutic use in livestock are as high as 78%[4] of the total annual use of antimicrobial agents in the United States.

EVIDENCE OF SELECTION FOR ANTIMICROBIAL RESISTANCE ATTRIBUTABLE TO AGRICULTURAL USES OF ANTIMICROBIAL AGENTS

One of the most efficient ways to select for resistance genes in bacteria is to expose bacteria chronically to low doses of broad-spectrum antimicrobial agents. Levy et al[6] examined the effect of low-dose tetracycline in feed on the intestinal flora of chickens. Chickens were divided into experimental and control groups; the experimental group received feed containing oxytetracycline at concentrations similar to those used for therapy or prophylaxis; the control group received feed without oxytetracycline. The baseline resistance to tetracycline was generally less than 10%, with many samples exhibiting less than 0.1% resistance. Within 36 hours, resistance began to increase, and after 2 weeks, 90% of the chickens in the experimental group were excreting bacteria that were 100% resistant to tetracycline. Chickens in the control group did not exhibit an increase in resistant organisms during this same time period. Although the chickens were exposed only to tetracycline, multidrug resistance developed (to tetracycline, sulfonamides, streptomycin, ampicillin, and carbenicillin) through plasmid transfer. By 12 weeks, almost two thirds of the chickens in the experimental group excreted organisms resistant to tetracycline and at least 1 additional antimicrobial agent, and more than one quarter were resistant to 4 antimicrobial agents (tetracycline, ampicillin, streptomycin, and carbenicillin). Over time, chickens in the control group, despite isolation in different pens, also developed resistance, although at lower levels. One third of chickens in the control group were excreting more than 50% resistant organisms after 4 months. Transfer of resistance to humans also occurred, although more slowly and at lower levels than in the control-group chickens. Within 6 months, more than 30% of fecal samples from farm dwellers contained more than 80% tetracycline-resistant bacteria versus 6.8% from control neighbors ($P < .001$). A 4-drug resistance pattern was found in farm families corresponding to that of the experimental-group chickens but was not found in neighborhood controls. Six months after the removal of all tetracycline feed from the farm, no tetracycline-resistant organisms were isolated from stool samples in 8 of 10 farm dwellers tested. This experiment demonstrated that resistance can develop quickly in the presence of antimicrobial pressure, that single-drug resistance becomes multidrug resistance, that resistance spreads beyond individuals exposed to the antimicrobial agent to other members of their species within the environment and to humans living and working on the farm, and that stopping feed supplementation with oxytetracycline leads to decreased incidence of resistance.

MECHANISMS OF SPREAD OF RESISTANT BACTERIA TO HUMANS

When animals become colonized with resistant organisms, these organisms can eventually reach humans through the food chain, direct contact, or contamination of water or crops from animal excreta.[7] Increasingly, food animals are raised in large numbers under close confinement, transported in large groups to slaughter, and processed very rapidly.[8] These stressful conditions cause increased bacterial shedding and inevitable contamination of hide, carcass,[9] and meat[10] with fecal bacteria. Dissemination of resistant pathogens via the food chain is facilitated further by centralized food processing and packaging, particularly of ground meat products, and broad distribution through food wholesalers and retail chains.[11] Farmers, farm workers, and farm families[6] as well as casual visitors[12] are at risk of infection with resistant organisms.

Environmental reservoirs may also contribute to the movement of resistance genes. Active antimicrobial agents have been detected in water near animal

waste lagoons,[13] surface waters, and river sediments,[14] giving rise to 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. Supporting this concern, investigators recently found resistance genes identical to those found in swine waste lagoons in groundwater and soil microbes hundreds of meters downstream.[15]

Finally, there may also be direct human exposure to antimicrobial agents. Because many antimicrobial agents used in food-animal production can be obtained without a veterinarian's prescription, they are available for direct purchase and are often manually added to feed or water at farm level. This may be another pathway leading to development of resistance in occupationally exposed individuals, their families, and neighbors.[6]

EFFECT ON TREATMENT OF INFECTIONS IN CHILDREN

This section of the report reviews evidence that links agricultural use of antimicrobial agents to disease in infants and children for 2 major foodborne pathogens, *Campylobacter* species and *Salmonella* species, and for the opportunistic pathogen *Enterococcus* species.

Campylobacter Species

Campylobacter organisms cause approximately 2.5 million cases of foodborne illness annually in the United States and are the leading cause of bacterial foodborne illness.[16] The incidence of *Campylobacter* infections in infants younger than 1 year is twice that in the general population (54.1 vs 21.7 per 100 000 population).[17] Almost 20% of all reported cases of *Campylobacte*r infections occur in children younger than 10 years.[18]

Erythromycin or another macrolide is the drug of choice for *Campylobacter* infections in infants and children; fluoroquinolones and tetracyclines are used frequently in adults. Antimicrobial resistance in *Campylobacter* species is an increasing problem.[19] Currently, macrolide resistance in human isolates of *Campylobacter jejuni*, the species causing 90% of human infections, is stable and usually less than 5%.[19] *Campylobacter coli*, which causes approximately 10% of human infections, has a much higher resistance rate, reaching 70%.[20] The major reservoirs are poultry for *C jejuni* and turkeys and swine for *C coli*.[21] Differences in resistance rates may reflect differences in the use of antimicrobial agents.[20] Erythromycin and tetracyclines are approved for use in food-producing animals for therapeutic and growth-promotion purposes.

Fluoroquinolone resistance in *Campylobacter* species demonstrates the links among agricultural use of antimicrobial agents, selection of resistance, and dissemination of resistant infections through the food chain. Fluoroquinolones were approved for use by prescription in diseased poultry flocks in the United States in 1995.[22] In Minnesota between 1996 and 1998, infections in humans caused by fluoroquinolone-resistant organisms increased, parallel with the prevalence of retail domestic chicken products contaminated with fluoroquinolone-resistant organisms. Data from the National Antimicrobial Resistance Monitoring System (NARMS) demonstrate that fluoroquinolone resistance among *Campylobacter* isolates from humans began to increase nationwide in the late 1990s, from 13% in 1997 to 20.5% in 1999.[23] A 1999 survey of grocery store chicken found that 44% of samples were contaminated with *Campylobacter* species; 24% of the isolates were resistant to ciprofloxacin, and 32% were resistant to nalidixic acid.[24] Increasing resistance is even more worrisome, because data suggest that strains of resistant *Campylobacter* species may be more virulent than sensitive strains. In a case-control telephone study, investigators found that untreated patients with fluoroquinolone-resistant *Campylobacter* infection had an average of 12 days of diarrhea versus 6 days in patients with sensitive strains ($P = .02$).[25] For patients who were treated with fluoroquinolones, the duration of diarrhea was significantly longer in those infected with resistant versus sensitive strains (8 vs 6 days [$P = .02$]).

Salmonella Species

Nontyphoidal *Salmonella* organisms cause 1.4 million illnesses annually, 95% of which are thought to be foodborne.[16] It is estimated that 600 deaths occur annually from *Salmonella* infections, primarily among the elderly and very young.[16] More than one third of all cases occur in children younger than 10 years,[18] and the incidence in children younger than 1 year is 10 times higher than in the general population (128.9 vs 12.4 per 100 000).[17] Ten percent of blood and central nervous system infections caused by *Salmonella* species as reported to the Centers for Disease Control and Prevention occur in children younger than 1 year.[26] Children of all ages with chronic conditions such as sickle cell anemia are at high risk of serious complications from infections with *Salmonella* species.[27]

The dissemination of resistant *Salmonella* infections through the food chain is well documented. A 6-state outbreak of plasmid-mediated, multidrug-resistant *Salmonella newport* infection attributed to consumption of contaminated beef was traced back to a feedlot that used nontherapeutic doses of chlortetracycline as a growth promoter in feed.[28] Investigators found the outbreak organism in isolates from both animals and humans on an adjacent dairy farm. An increased risk of illness caused by a resistant strain was observed in patients who were taking antimicrobial agents for other infections (odds ratio, 51.3; $P = .001$), suggesting that asymptomatic carriage was converted to symptomatic infection by the use of antimicrobial agents. Of 3 children younger than 10 years, 2 had received antimicrobial agents before onset of their illness.

Neonatal infections caused by *Salmonella* species also have been attributed to indirect exposure to foodborne sources. Bezanson et al[29] described a plasmid-mediated, 6-drug–resistant strain of *Salmonella*

serotype Typhimurium acquired asymptomatically by a pregnant woman from raw milk and passed to her infant at birth. The infant became ill within 24 hours with septicemia and meningitis. Three to 4 days later, several other infants in the newborn nursery developed diarrhea with the same resistant organism. In another newborn nursery outbreak, *Salmonella heidelberg* resistant to chloramphenicol, sulfamethoxazole, and tetracycline caused bloody diarrhea in 3 infants.[30] The index case was a term infant born by cesarean delivery after 18 hours of ruptured membranes. The mother was a farmer's daughter who, until shortly before delivery, had been working with new calves from a herd containing several sick calves.

The treatment of *Salmonella* infections, especially in young children, has become increasingly difficult because of antimicrobial resistance. In the early 1980s, the prevalence of multidrug-resistant *Salmonella* species began to increase and by 1995 had reached 19% in the United States.[31] Some strains, particularly *Salmonella* serotype Typhimurium DT104, cause invasive disease that frequently requires treatment but may be resistant to 5 or more classes of antimicrobial agents.[32,33] Currently, extended-spectrum cephalosporins have become the preferred drugs for empiric treatment in pediatrics, and fluoroquinolones are preferred in adults. The efficacy of these drugs may now be threatened. In 1999, Molbak et al[34] described an outbreak in Denmark of *Salmonella* serotype Typhimurium DT104 resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, tetracycline, and quinolones, linked by molecular fingerprinting (the process of identifying unique clones by DNA typing) to 2 swine herds. Two patients died in this outbreak, and therapeutic failure was considered related to antimicrobial resistance. Of 4 children, 1 was an infant who was hospitalized and treated with cefotaxime. Fey et al[35] reported on a child from Nebraska who became infected with *Salmonella* serotype Typhimurium DT104 resistant to ampicillin, chloramphenicol, tetracycline, sulfisoxazole, kanamycin, streptomycin, several classes of cephalosporins, aztreonam, cefoxitin, gentamicin, and tobramycin. An analysis of recent NARMS data revealed that 77% of patients with culture-proven ceftriaxone-resistant *Salmonella* infection between 1997 and 1998 were younger than 18 years and that the prevalence of ceftriaxone-resistant human isolates increased fivefold from 0.1% in 1996 to 0.5% in 1999.[36] Human isolates of *Salmonella* species resistant to 8 or more agents increased almost sevenfold from 0.3% in 1996% to 2% in 1999. Decreased susceptibility to fluoroquinolones may also be emerging. According to NARMS data, the prevalence of resistance to ciprofloxacin among *Salmonella* isolates increased from 0.4% in 1996 to 1% in 1999.

Major reservoirs for *Salmonella* infection are food animals, including poultry, cattle, and swine. Nontherapeutic antimicrobial agents are routinely used, particularly in swine. One survey of 825 retail samples of raw chicken, turkey, pork, and beef revealed an overall rate of 3% contamination with *Salmonella* species.[37] White et al[38] recently reported that 20% of retail ground meat samples were contaminated with *Salmonella* species; 80% of these samples were resistant to at least 1 antimicrobial agent, 53% were resistant to at least 3 antimicrobial agents, and 16% were resistant to ceftriaxone.

Enterococci

Enterococci are normal flora in food animals, domesticated animals, wild animals, and humans. In the 1990s, vancomycin-resistant enterococci (VRE) became common bacterial pathogens responsible for an increasing number of nosocomial infection in the United States, including in children.[39] Hospitalized and seriously ill children are increasingly affected.[40,41] Patterns in the prevalence of VRE infection have developed differently in the United States and Europe, helping to elucidate the links between use of antimicrobial agents in animals and resistance in humans. Whereas the epidemic of VRE infection in the United States seems related to the large increase in vancomycin use in human medicine,[42] the increased incidence of VRE infection in Europe seems to be attributable to the use of antimicrobial agents in animals. Vancomycin has not been used widely in Europe in human medicine, but avoparcin, a related glycopeptide, has been used as a growth promoter for decades.[43] Avoparcin selects for cross resistance to vancomycin when used in farm animals.[44,45] In the United States, VRE is rarely cultured from healthy individuals in the community,[46] but it is often isolated from healthy community members in Europe.[47] In Europe, VRE can also be cultured from healthy poultry, pigs,[48] ponies, and dogs[49]; uncooked chicken meat[50] and minced pork; and raw sewage from urban and rural locations.[51] Molecular fingerprinting of these isolates shows much higher heterogeneity in European isolates compared with US isolates, suggesting that the prevalence of VRE in Europe is a response of multiple enterococcal populations to the presence of avoparcin in a variety of host species and locations.

Recent reports from the United States, however, suggest a strong and emerging link between VRE and agricultural use of antimicrobial agents. In response to the epidemic of VRE infection, quinupristin-dalfopristin (Q-D) was licensed for use in 1999 by the US Food and Drug Administration as treatment for highly resistant strains. Q-D is a streptogramin, a class of antimicrobials not used previously in humans because of unacceptable toxicity.[52] Virginiamycin is a related streptogramin that has been used in the United States as a growth promoter for poultry, swine, and cattle since 1974.[53] In a recent study, 58% of 407 retail chicken samples and 1% of human stool samples were found to harbor Q-D-resistant enterococci 1 year before its release for human use, and humans were also found to carry resistant organisms without previous exposure to Q-D.[54] This suggests that ingestion of resistant enterococci in retail meats resulted in colonization of the human gut by these foodborne pathogens; such colonization of the gut of humans has been documented for up to 14 days after ingestion.[55] It also demonstrates the potential risks of using antimicrobial agents thought not to be impor-

tant to human medicine as growth promoters. As antimicrobial resistance increases, it is likely that more veterinary agents may be modified for human use. If resistance has already developed in animal populations, however, the period of their efficacy in human disease may be quite limited.

EUROPEAN EXPERIENCE

Sweden led Europe in banning antimicrobial growth promoters in 1986.[56] The ban in Sweden has resulted in decreased use of antimicrobial agents in food animals and, accompanied by improved animal husbandry practices, sustained productivity and profitability of the industry.[57] Denmark, which has a more industrialized animal production system similar to that in the United States, instituted a voluntary ban on antimicrobial growth promoters in 1998. Denmark has had a similar decrease in antimicrobial use and decreased prevalence of resistant organisms in food animals without loss of productivity or profitability.[58]

CONCLUSIONS

Resistance to antimicrobial agents is an increasing and serious problem. Judicious use of antimicrobial agents in humans will address only approximately 50% of use and will be insufficient to curb the accelerating upward trend in resistance. The largest nonhuman use of antimicrobial agents is in food-animal production, and most of this is in healthy animals to increase growth or prevent diseases. Evidence now exists that these uses of antimicrobial agents in food-producing animals have a direct negative impact on human health and multiple impacts on the selection and dissemination of resistance genes in animals and the environment. Children are at increased risk of acquiring many of these infections with resistant bacteria and are at great risk of severe complications if they become infected. Improved surveillance and continued documentation will elucidate the magnitude of the impact that these uses have on public health in general and children's health in particular.

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