

Antimicrobial Use in Agriculture: Controlling the Transfer of Antimicrobial Resistance to Humans

Frederick J. Angulo, DVM, PhD, Nicole L. Baker, MPH, Sonja J. Olsen, PhD, Alicia Anderson, DVM, MPH, and Timothy J. Barrett, PhD

Salmonella and Campylobacter infections occur commonly in children. Some of these infections are severe, requiring treatment with antimicrobial agents. Many classes of antimicrobial agents that are used in humans also are used in food animals for growth promotion, disease prevention, and therapy. The use of such antimicrobial agents in food animals increases the likelihood that human bacterial pathogens that have food animal reservoirs, such as *Salmonella* or *Campylobacter*, will develop cross-resistance to drugs approved for use in human medicine. Resistance determinants also may be transmitted from food animals to humans through the food supply with bacteria that usually are commensal, such as *Escherichia coli* and enterococci. Clinicians should be aware that antimicrobial resistance is increasing in food-borne pathogens and that patients who are taking antimicrobial agents for any reason are at increased risk for acquiring antimicrobial-resistant food-borne infections. Several European countries have demonstrated that restricting the use of antimicrobial agents in food animals can be followed by a decrease in antimicrobial resistance in humans without compromising animal health or significantly increasing the cost of production. Appropriate use of antimicrobial agents in humans and food animals is an important factor in maintaining their effectiveness.

© 2004 Elsevier Inc. All rights reserved.

Salmonella and Campylobacter infections occur commonly in children. The Centers for Disease Control and Prevention (CDC) recently estimated that 1.4 million *Salmonella* and 2.4 million *Campylobacter* infections occur each year in the United States,¹ although the number of *Campylobacter* infections has declined recently.² Approximately 40 percent of culture-confirmed *Salmonella* infections and 18 percent of

Campylobacter infections occur in children 10 years of age and younger²; therefore, these estimates translate into 560,000 *Salmonella* and 432,000 *Campylobacter* infections in children of these ages each year in the United States. Compared with other enteric infections, *Salmonella* and *Campylobacter* infections are particularly common findings in infants, and such infections frequently may be severe, resulting in bacteremia, meningitis, or death.³ Increasing antimicrobial resistance among *Salmonella* and *Campylobacter* threatens the clinical utility of some antimicrobial agents. The agricultural use of antimicrobial agents that are used in humans or have a human analog increases the likelihood that human bacterial pathogens that have food animal reservoirs (ie, *Campylobacter*, *Salmonella*) will develop resistance or cross-resistance to drugs approved for use in human medicine.⁴

Antimicrobial agents have been used in agriculture, including livestock and poultry, since the early 1950s to treat infections and improve growth and feed efficiency. The precise amount of antimicrobial agents used in agriculture is not known; however, a substantial portion is given to food animals in subtherapeutic doses for promotion of growth in the absence of diseases, a practice that increasingly is coming under scrutiny.⁵ The World Health Organization, following consultations in 1997 and 1999, has recommended discontinuing use of antimicrobial growth promoters that belong to an antimicrobial class used in humans.^{6,7} In the

From the Foodborne, and Diarrheal Diseases Branch, Centers for Disease Control and Prevention, Atlanta, GA and International Emerging Infections Program, Centers for Disease Control and Prevention, 88/21 Department of Diseases Control, Muang, Nonthaburi Thailand.

This article is based in part on an appendix written for an Institute of Medicine workshop summary by Anderson AD, McClellan J, Rossiter S, Angulo FJ entitled Public Health Consequences of Use of Antimicrobial Agents in Agriculture in "The Resistance Phenomenon in Microbes and Infectious Disease Vectors: Implications for Human Health and Strategies for Containment—Workshop Summary," Stacey L. Knobler, Stanley M. Lemon, Marian Najafi, and Tom Burroughs (Eds.), Institute of Medicine of the National Academies, Washington, DC, The National Academies Press, 231-243, 2003.

Address reprint requests to Frederick J. Angulo, DVM, PhD, Foodborne, and Diarrheal Diseases Branch, Centers for Disease Control and Prevention, 1600 Clifton Road, NE MS-D63, Atlanta, GA 30333.

© 2004 Elsevier Inc. All rights reserved.

1045-1870/04/1502-0005\$30.00/0

doi:10.1053/j.spid.2004.01.010

United States, the Institute of Medicine made this same recommendation in 2003.⁸

Several European countries also have taken steps toward this goal. Because of consumer's concerns about antimicrobial resistance, farmers in Denmark voluntarily stopped using all antimicrobial agents as growth promoters in 1999.⁹ In Denmark, the amount of antimicrobial agents used for various purposes is reported annually, and this voluntary action has reduced by 60 percent (from 206 to 81 tons) the total volume of antimicrobial agents used annually in food animals.^{10,11} In 2001, the European Union banned the use of growth promotion drugs related to antimicrobial agents used in human medicine (avoparcin, tylosin, spiramycin, bacitracin, and virginiamycin).¹² Furthermore, the Health Ministries in the European Union recently agreed to discontinue the use of all antimicrobial growth promoters by 2006.¹³

Studies to investigate the influence of the ban have shown no negative consequence for farmers' profits or animal health in broiler chickens.¹⁴ Similar conclusions were reported in fattening pigs, although an increase in the incidence of diarrhea in weaned piglets required other interventions, such as a change in feeding and weaning procedures.¹⁴ In Sweden, all use of antimicrobial agents as growth promoters was banned in 1986, decreasing their total usage by 55 percent, without long-term adverse effects on productivity, demonstrating the ability to achieve competitive production results in the absence of antimicrobial growth promoters.^{15,16} The discontinuation of antimicrobial growth promoters in these countries has been followed by a decrease in antimicrobial-resistant bacteria in animals, food products, and humans.^{9,11,17-20}

Agricultural use of antimicrobial agents can impact the treatment of human disease. Antimicrobial resistance is increasing in the food-borne pathogens *Salmonella* and *Campylobacter* in the United States,²¹ limiting the choice of therapeutic agents and increasing the potential for treatment failures and adverse clinical outcomes.²² In addition, patients who are taking antimicrobial agents for any reason are at increased risk for acquiring antimicrobial-resistant food-borne infections.^{23,24} Appropriate use of antimicrobial agents in humans and food animals is necessary to maintain their effectiveness. Although therapeutic use of antimicrobial agents in food animals is important for animal health, the long-term effectiveness of antimicrobial agents used in human medicine must be preserved. This report presents information on the frequency of resistant food-borne infections in the United States, reviews scientific evidence linking usage of antimicrobial agent in agriculture with resistant food-borne infections in humans, and makes recommendations for measures to protect public health.

Antimicrobial Use in Food Animals

At least 17 classes of antimicrobial agents, including tetracyclines, penicillins, macrolides, lincomycin (an analog of clindamycin), and virginiamycin (an analog of quinupristin/dalfopristin), are approved for growth promotion (also called improved feed efficiency) in the United States. To

understand the human health consequences of the agricultural use of antimicrobial agents, evaluating the quantity of antimicrobial agents used in food animals in the United States is important. Unfortunately, no public health reporting system exists for the quantity of antimicrobial agents used in food animals in the United States. The Animal Health Institute, which represents 80 percent of the companies that produce antimicrobial agents for animals in the United States, estimated that their member companies produced 18 million pounds of antimicrobial agents for use in food animals in the United States in 1998.²⁵ An alternative estimate was provided by the Union of Concerned Scientists in 2001, which calculated that 31 million pounds of antimicrobial agents are used annually in food animals in the United States. According to the Union of Concerned Scientists estimates, 93 percent (28 million pounds) of the amount used in agriculture is used in the absence of disease.⁵ Although more precise data on the quantity and purpose (eg, therapeutic versus growth promotion) of antimicrobial agents used in food animals are needed, these initial estimates provide some perspective on the large quantity of antimicrobial agents used in food animals in the United States.

As in human medicine, the use of antimicrobial agents in agriculture creates a selective pressure for the emergence and dissemination of antimicrobial-resistant bacteria, including animal pathogens, human pathogens that have food animal reservoirs, and commensal bacteria that are present in food animals.²⁶⁻²⁸ These resistant bacteria may be transferred to humans either through the food supply or by direct contact with animals.²⁹⁻³¹ The transfer of resistant bacteria from food-producing animals to humans is most evident in human bacterial pathogens that have food animal sources, such as *Campylobacter*, which has reservoirs in chickens and turkeys,³²⁻³⁴ and *Salmonella*, which has important reservoirs in cattle, chickens, pigs, and turkeys.^{35,36} To monitor antimicrobial resistance in food-borne enteric pathogens, the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria was launched in 1996.

NARMS is a collaboration among the Centers for Disease Control and Prevention (CDC), the United States Food and Drug Administration (FDA) Center for Veterinary Medicine, and state and local health departments. In addition to NARMS, the Foodborne Diseases Active Surveillance Network (FoodNet) conducts population-based studies to estimate the burden and sources of specific food-borne diseases in 10 states.

Campylobacter

NARMS has monitored the prevalence of antimicrobial resistance among *Campylobacter jejuni*, the most common *Campylobacter* in the United States, and *Campylobacter coli* since 1997. In 1997, surveillance included isolates from 5 sites, and 28 (13%) of 217 *C. jejuni* and *C. coli* isolates were resistant to ciprofloxacin, a fluoroquinolone.²¹ In 2001, surveillance expanded to 9 sites, and 75 (19%) of 384 *C. jejuni* and *C. coli* isolates were resistant.²¹ This increase is statistically significant [odds ratio 2.4, 95% confidence interval

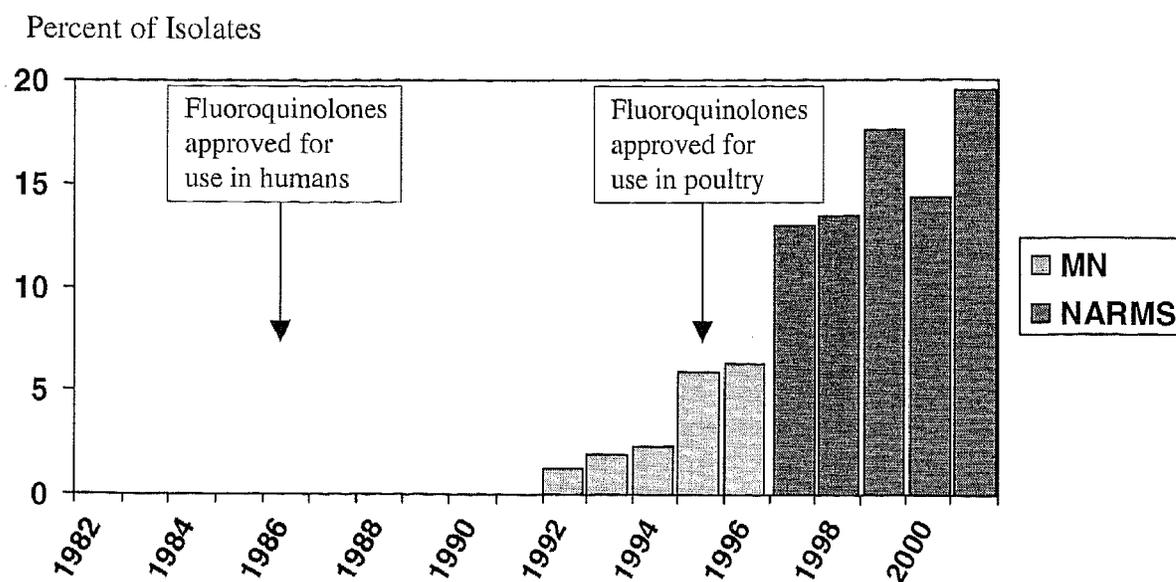


Figure 1. 1992 to 1996 quinolone-resistant *Campylobacter* in Minnesota³¹ and 1997 to 2001 fluoroquinolone-resistant *Campylobacter* in NARMS (unpublished data).²⁹

1.4, 4.1].²¹ Interviews of patients with ciprofloxacin-resistant *Campylobacter* infections in 1998 and 1999 found that most patients with ciprofloxacin-resistant infections had not traveled outside the United States before the onset of their illness.³⁷ Between 1997 and 2001, resistance to tetracycline decreased from 47 to 41 percent and resistance to erythromycin remained at 2 percent among *Campylobacter jejuni* and *Campylobacter coli*.²¹

The emergence of resistance to fluoroquinolone among domestically acquired *C. jejuni* and *C. coli* infections is an example of antimicrobial resistance resulting from the use of antimicrobial agents in food animals in the United States and the subsequent transfer via the food supply of resistant bacteria to humans. The timeline of emergence of quinolone resistance in human *Campylobacter* infections in the United States is depicted in Fig 1. Fluoroquinolones (eg, ciprofloxacin) were approved for human medicine in 1986. A national prospective study of reported cases of *C. jejuni* and *C. coli* cases conducted in sentinel counties between 1989 and 1990 found no *C. jejuni* or *C. coli* isolates to be resistant to fluoroquinolones.²¹ The first fluoroquinolones approved for use in food animals in the United States were sarafloxacin in 1995 and enrofloxacin in 1996. These fluoroquinolones were approved for the treatment of respiratory disease in chickens and turkeys. Experiments have demonstrated that resistance in *C. jejuni* to ciprofloxacin evolves rapidly in chickens treated with these drugs.³⁸

Cross-resistance among ciprofloxacin, enrofloxacin, and other fluoroquinolones also occurs; resistance to nalidixic acid, an elemental quinolone, correlates closely with resistance to fluoroquinolones. A study conducted in Minnesota reported that resistance in human *C. jejuni* infections to nalidixic acid increased from 1 percent in 1992 to 10 percent in 1998. Many of the early resistant cases were asso-

ciated with foreign travel.³⁹ Other countries began using fluoroquinolones before the United States did.⁴⁰ Nalidixic acid-resistant *Campylobacter* infections that were acquired domestically increased significantly from 1996 through 1998 in Minnesota, a finding temporally associated with the licensure of fluoroquinolones for use in poultry in 1995.³⁹ A comparison of molecular subtypes of isolates from humans and domestic chicken products from retail stores in Minnesota showed a significant association between resistant *C. jejuni* strains from chickens and domestically acquired infections in Minnesota residents.³⁹ This finding suggests that resistant infections in humans may be acquired through the domestic food supply as well as from abroad. Testing of 1997 NARMS *C. jejuni* isolates found resistance to fluoroquinolone among 12 percent of the isolates, increasing to 18 percent in 2001.²¹

In a case-control study of ciprofloxacin-resistant *Campylobacter* infections conducted in the FoodNet sites in 1998 and 1999, domestically acquired ciprofloxacin-resistant *Campylobacter* cases were compared with well controls; persons with ciprofloxacin-resistant *Campylobacter* infections were more likely to have eaten poultry cooked at a commercial establishment than were controls.⁴¹ Because chicken is not imported into the United States, this finding supports the hypothesis that poultry is an important source of domestically acquired ciprofloxacin-resistant *Campylobacter* infections in the United States. In a recent risk assessment, the FDA concluded that the use of fluoroquinolones in chickens in the United States has compromised the treatment with fluoroquinolones of almost 10,000 people a year, meaning that each year, thousands of people with *Campylobacter* infections seek medical care and are treated with fluoroquinolones, but their infection already is fluoroquinolone-resistant.⁴²

Salmonella

NARMS also has been used to monitor the prevalence of antimicrobial resistance among non-Typhi *Salmonella* since 1996. In 1996, surveillance included isolates from 14 sites, and 164 (11%) of 1527 *Salmonella* isolates were resistant to 5 or more of the 14 antimicrobial agents tested.²¹ As of 2001, surveillance had expanded to 17 sites, and 336 (15%) of 2,237 *Salmonella* isolates were resistant to 5 or more antimicrobial agents.²¹ In that same time period, resistance to ampicillin changed from 18 to 25 percent, and trimethoprim-sulfamethoxazole resistance increased from 3 to 10 percent.²¹

Third-generation cephalosporins, such as ceftriaxone, are used commonly for the treatment of invasive *Salmonella* infections in children because of their pharmacodynamic properties and the low prevalence of resistance to these agents. The potential emergence of ceftriaxone-resistant *Salmonella* is of concern. The first reported case of domestically-acquired ceftriaxone-resistant *Salmonella* in the United States was in a 12-year-old child in Nebraska.⁴³ An investigation by public health officials revealed that the child's father was a veterinarian. Before the child's illness, the father was treating several cattle herds for illnesses caused by culture-confirmed *Salmonella* infection. Although no information was available regarding the use of antimicrobials among the infected herds, a third-generation cephalosporin, ceftiofur, is used widely in cattle. Ceftriaxone-susceptible and ceftriaxone-resistant *Salmonella* were isolated from ill cattle treated by the veterinarian. Ceftriaxone-resistant and ceftriaxone-susceptible isolates from cattle and the ceftriaxone-resistant isolate from the child were serotype Typhimurium, and all had identical "molecular fingerprints" as determined by pulsed-field gel electrophoresis, which suggested that the infections in the cattle herd and in the child may have been related. The use of ceftiofur (or other antimicrobials to which the isolates were resistant) may have selected for ceftriaxone-resistant *Salmonella* serotype Typhimurium in the intestinal flora of the involved herds.

The Nebraska child's ceftriaxone-resistant infection was not an isolated event. The percentage of non-Typhi *Salmonella* isolates in NARMS resistant to ceftriaxone increased from 0.1 percent in 1996 to 1.5 percent in 2001.²¹ When patients from whom isolates were received in 1996 to 1998 were interviewed, few reported international travel, suggesting that most infections were acquired domestically.⁴³ Furthermore, resistance to ceftriaxone in most infections acquired domestically is caused by an AmpC-type resistance gene (*bla_{CMY-2}*), which resides on a plasmid. The finding of a similar molecular mechanism of resistance among different *Salmonella* strains suggests that horizontal dissemination of a resistance determinant from one bacterial strain to another may be occurring.⁴⁴ A 1999 study at the University of Iowa found multidrug-resistant, cephalosporin-resistant bovine, porcine, and human *Salmonella* species isolates from the same geographic region. All human and animal resistant isolates encoded a CMY-2 AmpC-like gene.⁴⁵

The emergence in the United States and other countries of multidrug-resistant *Salmonella* serotype Typhimurium Definitive Type 104 (DT104), which is resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (ACSSuT), is an example of how a highly resistant clone of *Salmonella* has the ability to spread effectively among animals and then to humans. Described in 1998 by Glynn and colleagues, the emergence of *S. Typhimurium* DT104 in the United States can be traced back to as early as 1985.⁴⁶ Although national surveillance data are lacking, available data indicate that *S. Typhimurium* DT104 ACSSuT became disseminated among animals and then humans in the early 1990s.⁴⁷ The prevalence of *S. Typhimurium* isolates with the ACSSuT pattern of resistance increased among human *S. Typhimurium* isolates collected in periodic surveys from 0.6 percent in 1979 to 1980 to 34 percent in 1996.⁴⁶ Among human *S. Typhimurium* isolates submitted to NARMS, the prevalence of the ACSSuT resistance pattern was 28 percent in both 1999 and 2000 and 30 percent in 2001.²¹

Another multidrug-resistant strain of *Salmonella* that is becoming increasingly common is *Salmonella* Newport; it is resistant to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline, amoxicillin/clavulanate, cephalothin, cefoxitin, and ceftiofur, and it possesses a decreased susceptibility to ceftriaxone (MIC ≥ 16 $\mu\text{g}/\text{mL}$), designated as MDR *S. Newport* Amp-C. This strain combines the broad resistance spectrum seen in DT104 with an Amp-C determinant similar to that identified in the Nebraska child in 1998. *S. Newport* now is the third most common serotype of *Salmonella*, and of all *Salmonella* Newport isolates submitted to NARMS in 2001, a remarkable 25 percent were multidrug-resistant Amp-C.²¹ Field investigations have demonstrated an association between human MDR *S. Newport* Amp-C infections and eating ground beef,⁴⁸ drinking and eating unpasteurized dairy products,⁴⁹ and living on a dairy farm,³⁰ suggesting that cattle are an important reservoir for MDR *S. Newport*.

In addition to fluoroquinolone-resistant *Campylobacter*, domestically acquired fluoroquinolone-resistant *Salmonella* also has the potential for emergence. Fluoroquinolones are the antimicrobial most commonly used for the treatment of invasive *Salmonella* infections in adults.³⁶ In 1996, fewer than 1 percent of non-Typhi *Salmonella* isolates collected by NARMS had a decreased susceptibility to ciprofloxacin (MIC ≥ 0.25 $\mu\text{g}/\text{mL}$). In 2001, 3 percent of isolates had decreased susceptibility to ciprofloxacin.²¹ The rising proportion of *Salmonella* isolates that have decreased susceptibility to ciprofloxacin is of immediate concern because isolates with a MIC of 0.25 $\mu\text{g}/\text{mL}$ or greater typically require only a single additional point mutation to become resistant (MIC ≥ 4 $\mu\text{g}/\text{mL}$) and, therefore, represent a potential reservoir for the emergence of resistant *Salmonella* should such isolates be exposed to continued selective pressure.⁵¹ Furthermore, patients infected with *Salmonella* strains with a decreased susceptibility to fluoroquinolones may respond poorly to treatment with fluoroquinolones and have been associated with apparent treatment failures.^{36,52} For these and other reasons, authors have suggested lowering the

clinical breakpoint for determining a resistant infection to this antimicrobial agent.⁵³

In addition to having decreased susceptibility to fluoroquinolones, some *Salmonella* isolates have been resistant to ciprofloxacin (MIC ≥ 16 $\mu\text{g/mL}$). The limited number of fluoroquinolone-resistant *Salmonella* appears to be related to foreign travel and particularly to persons hospitalized overseas. These patients have introduced fluoroquinolone-resistant *Salmonella* into hospital and nursing home settings on returning to the United States.⁵⁴ Thus, the limited number of fluoroquinolone-resistant *Salmonella* infections isolated through 2001 may have emerged in nosocomial settings rather than agricultural ones.

Commensal Bacteria

Pathogenic bacteria, such as *Campylobacter* and *Salmonella*, are not the only concern when considering antimicrobial resistance in bacteria with food animal reservoirs. Commensal bacteria, which are naturally occurring host flora, exposed to antimicrobial agents may become resistant and then constitute a reservoir of resistance genes that could be transferred to pathogenic bacteria. The prevalence of antimicrobial resistance in the commensal bacteria of humans and animals is an indicator of the selective pressure of antimicrobial agent use and reflects the potential for future resistance in future pathogens.⁵⁵⁻⁵⁸

Most resistant bacteria have mobile genetic elements such as R-plasmids and transposons that carry the resistance genes. As the reservoir of resistant commensal bacteria increases, the plasmid population becomes larger and enables more frequent transfer of resistance to pathogenic bacteria, including *Salmonella* and *Shigella*. *Escherichia coli*, which is the predominant species in the aerobic fecal flora in humans and many animals, has demonstrated its ability to transfer resistance genes to other species, including pathogenic bacteria.^{57,59-64} Recent studies have shown an emerging resistance in *E. coli* to third-generation cephalosporins. Winokur and coworkers found 59 (16%) of 377 clinical *E. coli* isolates from cattle and swine and 6 (1%) of more than 1,000 clinical human *E. coli* isolates collected in Iowa to be resistant to extended-spectrum cephalosporins. This study also identified identical CMY-2 genes in resistant isolates from both humans and animals, suggesting transfer of the resistance gene between food animals and humans had occurred.⁶²

Another example of potential animal-to-human transfer of resistant commensal bacteria is quinupristin/dalfopristin-resistant *Enterococcus faecium*. Quinupristin/dalfopristin (Synercid®) was approved for use in humans in 1999 for treatment of vancomycin-resistant *E. faecium* infections. However, virginiamycin, an analog of quinupristin/dalfopristin, has been used as a growth promoter in food animals in the United States since 1974.^{65,66} A study conducted by the CDC in 1998 to 1999, before the approval of use of Synercid® in humans, found quinupristin/dalfopristin-resistant *E. faecium* in 58 percent of chickens purchased in grocery stores from four different states.⁶⁷ Additionally,

quinupristin/dalfopristin-resistant *E. faecium* was found in 1 percent of the stools from nonhospitalized people who submitted a stool specimen to clinical laboratories. These findings suggest that use of virginiamycin in chickens has created a large reservoir of quinupristin/dalfopristin-resistant *E. faecium* to which humans commonly are exposed. The use of quinupristin/dalfopristin in humans for the treatment of vancomycin-resistant *E. faecium* and other serious infections may contribute additional selective pressure, leading to an increased prevalence of quinupristin/dalfopristin resistance in humans. Similar data in Europe led the European Union in 1998 to ban the subtherapeutic use of virginiamycin in food animals.⁶⁸

Clinical Implications

One human health consequence of the increasing antimicrobial resistance in food-borne bacteria is an increase in food-borne illnesses. Increased incidence of human infections of antimicrobial-resistant food-borne pathogens occurs because of an interaction among antimicrobial-resistant *Salmonella* that are ingested, the native host flora, and antimicrobial treatment. Treatment may suppress normal protective flora, giving a temporary advantage to resistant bacteria. Taking an antimicrobial agent may lower the infectious dose for *Salmonella* if the pathogen already is resistant to that antimicrobial agent.^{23-24,69} Analyses of outbreaks of antimicrobial-resistant *Salmonella* have demonstrated that concurrent exposure to antimicrobial agents can result in a larger number of cases than would have occurred had the outbreak been caused by a sensitive strain.²⁶ Bohnhoff and colleagues showed in the early 1960s that mice with an "undisturbed" normal intestinal flora have a *Salmonella* infectious dose of approximately 10^6 organisms.⁷⁰ When they "disturbed" the normal flora by administering streptomycin, the infectious dose for streptomycin-resistant *Salmonella* decreased to only 10 organisms. In *Salmonella* outbreaks, studies have shown that antimicrobial treatment that precedes and is unrelated to the *Salmonella* infection can predispose humans to infection with either resistant⁷¹⁻⁷³ or susceptible *Salmonella*.⁷⁴ Similarly, in studies of sporadic salmonellosis, previous treatment with an antimicrobial agent was a risk factor for acquisition of an antimicrobial-resistant infection, compared with susceptible infections.⁷⁵⁻⁷⁷

Physicians should be aware that as food-borne pathogens become increasingly resistant, treating patients with antimicrobial agents, regardless of the reason, increases the risk for that patient to develop an infection caused by resistant food-borne bacteria soon thereafter. The public health impact of this potentiation effect is more cases of illness and larger outbreaks, depending on the frequency of resistance and the frequency of administration of an antibiotic treatment.²² Therefore, reducing inappropriate use of antimicrobial agents in humans, such as effort of the American Academy of Pediatrics to reduce inappropriate use of antimicrobial agents in the treatment of upper respiratory infections in children,⁷⁸ also will yield a concur-

rent reduction in the number of children infected with antimicrobial-resistant *Salmonella* and *Campylobacter* agents.

In addition to causing more human illnesses, increasing antimicrobial resistance in food-borne pathogens may result in treatment failures if the food-borne pathogen is resistant to an antimicrobial agent used for treatment. As previously described, resistance is emerging to antimicrobial agents commonly used for treatment of serious *Salmonella* infections, that is, fluoroquinolones in adults and extended-spectrum cephalosporins in patients of all ages. An example of probable treatment failures was described recently by researchers in Denmark, where an outbreak of multidrug-resistant *S. Typhimurium* DT104 attributed to contaminated pork was traced back to a swine herd.⁵² The *Salmonella* isolates from humans and pork samples had decreased susceptibility to fluoroquinolones, and two patients who were treated with fluoroquinolones died. An official review of these deaths concluded that decreased susceptibility to fluoroquinolones was a contributing factor.

Conclusion

Antimicrobial resistance is posing an important public health challenge. The prevalence of resistance is increasing and has clinical implications. For food-borne pathogens, intervention strategies can focus on a variety of different steps in the chain of transmission from humans to animals. Efforts to improve appropriate use of antimicrobial agents in humans and animals will require collaborative efforts by several partners, including the farming, veterinary, medical, and public health communities. Enhanced surveillance of resistance and antimicrobial use is essential for evaluating and directing prevention efforts.

In the United States, collaborative federal actions designed to address antimicrobial resistance in agriculture are outlined in the Public Health Action Plan to Combat Antimicrobial Resistance, released in 2001 by an interagency task force.⁷⁹ Action items in this plan include improving surveillance of antimicrobial drug use and resistance, research and education, and, as a top priority item, refining and implementing the FDA's Framework Document. This Framework Document proposes a modified approval process for use of antimicrobials in animals.⁸⁰ It intends to ensure the human safety of antimicrobials used in animals by prioritizing these drugs according to their importance in human medicine. The American Veterinary Medical Association has promoted education of veterinarians regarding appropriate use of antimicrobial agents, with published guidelines for the therapeutic use of antimicrobial agents.⁸¹

The widespread use of antimicrobial agents in food animals is associated with increasing antimicrobial resistance in food-borne pathogens, which subsequently may be transferred to humans. The transfer of these resistant bacteria or the genetic determinants for resistance causes adverse health consequences in humans, including increasing the potential for treatment failures. To address this public health problem, inappropriate use of antimicrobial agents

in food animals and humans must be reduced. This reduction will be facilitated by adherence to guidelines for appropriate use of antimicrobial agents in food animals. In Denmark and Sweden, the feasibility of implementing measures has been demonstrated to reduce dramatically the use of antimicrobial agents with human analogues as growth promoters and were associated with reduced incidence of antimicrobial resistance and public health risks.^{10,14-16}

References

1. Mead PS, Slutsker L, Dietz V, et al: Food-related illness and death in the United States. *Emerg Infect Dis* 5:607-625, 1999
2. Centers for Disease Control and Prevention: FoodNet: 2001 Annual Report. Atlanta, GA, US, Department of Health and Human Services, CDC2003
3. Pickering LK, ed: American Academy of Pediatrics, Committee on Infectious Diseases. 2000 Red Book: Report of the Committee on Infectious Diseases (25th ed). Elk Grove Village, IL, American Academy of Pediatric, 2000
4. Shea KM: Antibiotic resistance: What is the impact of agricultural uses of antibiotics on children's health? *Pediatrics* 112: 253-258, 2003
5. Mellon M, Benbrook G, Benbrook K: *Hogging It: Estimates of Antimicrobial Abuse in Livestock*. Cambridge, Union of Concerned Scientists Publications, 2001
6. World Health Organization: The medical impact of the use of antimicrobials in food animals: report and proceedings of a WHO meeting. Berlin, Germany, October 13-17, 1997
7. World Health Organization: Containing Antimicrobial Resistance: Review of the literature and report of a WHO workshop on the development of a global strategy for the containment of antimicrobial resistance. Geneva, Switzerland, February 4-5, 1999
8. Microbial Threats To Health: Emergence, Detection, and Response. Report of the Institute of Medicine <http://www.nap.edu/books/030908864X/html>
9. Aarestrup FM, Seyfarth AM, Emborg HD, et al: Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob Agents Chemother* 45:2054-2059, 2001
10. Sorensen TL, Wegener HC, Frimodt-Moller N: Resistant bacteria in retail meats and antimicrobial use in animals. *N Engl J Med* 346:777-79, 2002 (letter)
11. DANMAP 2000: consumption of antimicrobial agents and resistance to antimicrobial agents in bacteria from food animals, food and humans in Denmark: report from Statens Serum Institut, Danish Veterinary and Food Administration, Danish Medicines Agency and Danish Veterinary Laboratory, 2001. Available at: http://www.keepantibioticsworking.com/library/uploadedfiles/Danmap_2000.pdf
12. Commission regulation of amending council directive 70/524/EEC concerning additives in feedingstuffs as regards withdrawal of the authorization of certain antibiotics. Document No. VI/7767/98. European Commission, Brussels, Belgium
13. Report on the proposal for a European Parliament and Council Regulation on additives for use in animal nutrition. Document No.: A5-0373/2002. Available at <http://www.health.fgov.be/WHI3/krant/krantarch2002/kranttekstnov2/02114m13eu.htm>
14. Impacts of antimicrobial growth promoter termination in Denmark. The WHO International Review panel's evaluation of the termination of the use of antimicrobial growth promoters

- in Denmark. Available at <http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf>
15. Wierup M: Preventive methods replace antibiotic growth promoters: ten years experience from Sweden. *APUA Newsletter* 16:1-4, 1998
 16. Greko C: Antibiotics as growth promoters. *Acta Vet Scand* 92(suppl):87-100, 1999
 17. van Den Bogaard AE, Bruinsma N, Stobberingh EE: The effect of banning avoparcin on VRE carriage in the Netherlands. *J Antimicrob Chemother* 46:146-147, 2000
 18. Klare I, Badstubner D, Konstabel C, et al: Decreased incidence of VanA-type vancomycin-resistant enterococci isolated from poultry meat and fecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry. *Microb Drug Resist* 5:45-52, 1999
 19. Bager F, Aarestrup FM, Madsen M, et al: Glycopeptide resistance in *Enterococcus faecium* from broilers and pigs following discontinued use of avoparcin. *Micro Drug Res-Mech Epidemiol Dis* 5:53-56, 1999
 20. Pantosti A, Del Grosso M, Tagliabue S, et al: Decrease of vancomycin-resistant enterococci in poultry meat after avoparcin ban. *Lancet* 354:741-742, 1999 (letter)
 21. Centers for Disease Control and Prevention: National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): 2001 Annual Report. Atlanta, GA, US Department of Health and Human Services, CDC2003
 22. Travers K, Barza M: Morbidity of infections caused by antimicrobial-resistant bacteria. *Clin Infect Dis* 34(suppl):131-134, 2002
 23. Barza M, Travers K: Excess infections due to antimicrobial resistance: the "Attributable Fraction." *Clin Infect Dis* 34(suppl):126-130, 2002
 24. Barza M: Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. *Clin Infect Dis* 123-125, 2002 (suppl)
 25. Animal Health Institute: "Survey indicates most antibiotics used in animals are used for treating and preventing disease." Press release. February 14, 2000. Available: <http://www.ahi.org/news%20room/press%20release/2000/feb/antibiotic%20usage%20data.htm>
 26. Cohen ML, Tauxe RV: Drug-resistant *Salmonella* in the United States: an epidemiological perspective. *Science* 234:964-969, 1986
 27. van den Bogaard AE, Stobberingh EE: Antibiotic usage in animals: impact on bacterial resistance and public health. *Drugs* 58:589-607, 1999
 28. Levy SB: Antibiotic resistance: an ecological imbalance, in Levy SB, Good J, Chadwick DJ (ed): *Antibiotic Resistance: Origins, Evolution, Selection, and Spread*. New York, John Wiley & Sons, 1997, pp 1-9
 29. Oosterom J: Epidemiological studies and proposed preventive measures in the fight against human Salmonellosis. *Int J Food Microbiol* 12:41-51, 1991
 30. Khachatourians GG: Agricultural use of antibiotics and the evolution and transfer of antibiotic-resistant bacteria. *CMAJ* 159:1129-1136, 1998
 31. Witte W: Medical consequences of antibiotic use in agriculture. *Science* 279:996-997, 1998
 32. Altekruse S, Stern N, Fields P, et al: *Campylobacter jejuni*—an emerging foodborne pathogen. *Emerg Infect Dis* 5:28-35, 1999
 33. Tauxe R: Epidemiology of *Campylobacter jejuni* infections in the United States and other industrialized nations, in Nanchamkin I, Blaser MJ, Tompkins LS (eds): *Campylobacter jejuni: Current Status and Future Trends*. Washington, DC, American Society for Microbiology, 1992, pp 9-19
 34. United States Department of Agriculture, Food Safety and Inspection Service, Science and Technology Microbiology Division, April 1996 Nationwide Broiler Chicken Microbiological Baseline Data Collection Program, July 1994-June 1995. Available at <http://www.fsis.usda.gov/OPHS/baseline/contents.htm>
 35. Meng J, Doyle MP: Emerging and evolving microbial foodborne pathogens. *Bull Inst Pasteur* 96:151-164, 1998
 36. Angulo FJ, Johnson KR, Tauxe RV, et al: Origins and consequences of antimicrobial-resistant nontyphoidal *Salmonella*: Implications for the use of fluoroquinolones in food animals. *Microb Drug Resist* 6:77-83, 2000
 37. Kassenborg H, Smith K, Vugia D, et al: Eating chicken or turkey outside the home associated with domestically acquired fluoroquinolone-resistant *Campylobacter* infections: A FoodNet case-control study. Program and Abstract of the 2nd International Conference on Emerging Infectious Diseases. Atlanta, GA, 2000
 38. McDermott PF, Bodies SM, English LI, et al: Ciprofloxacin resistance in *Campylobacter jejuni* evolves rapidly in chickens treated with fluoroquinolones. *J Infect Dis* 185:837-840, 2002
 39. Smith KE, Besser JM, Hedberg CW, et al: Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998. *N Engl J Med* 340:1525-1532, 1999
 40. Division of Emerging and Other Communicable Disease Surveillance and Control: Use of quinolones in food animals and potential impact on human health: report of a WHO meeting: Geneva, Switzerland; 1998 Jun 2-5. Geneva, World Health Organization, 1998
 41. Kassenborg HD, Smith KE, Vugia DJ, et al: Fluoroquinolone-resistant *Campylobacter* infections: eating poultry outside the home and foreign travel are risk factors. *Clin Infect Dis* suppl 3:S279-284, 2004
 42. Food and Drug Administration, Center for Veterinary Medicine: Risk assessment of fluoroquinolone use in poultry. Available: <http://www.fda.gov/cvm/antimicrobial/Riskasses.htm>
 43. Fey PD, Safranek TJ, Rupp ME, et al: Ceftriaxone-resistant *Salmonella* infection acquired by a child from cattle. *N Engl J Med* 342:1242-1249, 2000
 44. Dunne EF, Fey PD, Kludt P, et al: Emergence of domestically acquired ceftriaxone-resistant *Salmonella* infections associated with *ampC* beta-lactamase. *JAMA* 284:3151-3156, 2000
 45. Winokur PL, Brueggemann A, DeSalvo DL, et al: Animal and human multidrug-resistant, cephalosporin-resistant *Salmonella* isolates expressing a plasmid-mediated CMY-2 AmpC beta-lactamase. *Antimicrob Agents Chemother* 44:2777-2783, 2000
 46. Glynn MK, Bopp C, Dewitt W, et al: Emergence of multidrug-resistant *Salmonella enterica* serotype Typhimurium DT104 infections in the United States. *N Engl J Med* 338:1333-1338, 1998
 47. Ribot EM, Wierzbicka RK, Angulo FA, et al: *Salmonella enterica* serotype Typhimurium DT104 Isolated from Humans, United States, 1985, 1990, and 1995. *Emerg Infect Dis* 8:387-391, 2002
 48. CDC: Outbreak of multidrug-resistant *Salmonella* Newport—United States, January-April 2002. *MMWR* 51:545-548, 2002
 49. McCarthy T, Phan Q, Mshar P, et al: Outbreak of multi-drug resistant *Salmonella* Newport associated with consumption of Italian-style soft cheese, Connecticut. Program and Abstract of the 2nd International Conference on Emerging Infectious Diseases. Atlanta, GA, 2000
 50. Gupta A, Fontana J, Crowe C, et al: Emergence of multidrug-resistant *Salmonella enterica* serotype Newport infections resis-

- tant to expanded-spectrum *Cephalosporins* in the United States. *J Infect Dis* 188:1707-1716, 2003
51. Nakamura S, Yoshida H, Bogaski M, et al: Quinolone resistance mutations in DNA gyrase, in Andoh T, Ikeda H, Oguro M (eds): *Molecular Biology of DNA Topoisomerases and its Application to Chemotherapy*. London, England, C/D C Press, 1993, pp 135-143
 52. Molbak K, Baggesen DL, Aarestrup FM, et al: An outbreak of multi-drug resistant, quinolone-resistant *Salmonella* enterica serotype Typhimurium DT104. *N Engl J Med* 341:1420-1425, 1999
 53. Crump JA, Barrett TJ, Nelson JM, et al: Reevaluating fluoroquinolone minimum inhibitory concentration breakpoints for *Salmonella* Typhi and for non-Typhi *Salmonella*. *Clin Infect Dis* 37:75-81, 2003
 54. Olsen SJ, DeBess EE, McGivern TE, et al: A Nosocomial outbreak of fluoroquinolone-resistant *Salmonella* infection. *N Engl J Med* 344:1572-1579, 2001
 55. Murray BE: Problems and dilemmas of antimicrobial resistance. *Pharmacotherapy* 12(suppl):86-93, 1992
 56. Lester SC, del Pilar Pla M, Wang F, et al: The carriage of *Escherichia coli* resistant to antimicrobial agents by healthy children in Boston, in Caracas, Venezuela, and in Qin Pu, China. *N Engl J Med* 323:285-289, 1990
 57. Hummel R, Tschape H, Witte W: Spread of plasmid-mediated nourseothricin resistance due to antibiotic use in animal husbandry. *J Basic Microbiol* 26:461-466, 1986
 58. Antimicrobial resistance in pig faecal samples from The Netherlands (five abattoirs) and Sweden. *J Antimicrob Chemother* 45:663-671, 2000
 59. Shoemaker NB, Wang G, Salyers AA: Evidence for natural transfer of a tetracycline resistance gene between bacteria from the human colon and bacteria from the bovine rumen. *Appl Environ Microbiol* 58:1313-1320, 1992
 60. Nikolich MP, Hong G, Shoemaker NB, et al: Evidence for natural horizontal transfer of *tetQ* between bacteria that normally colonize humans and bacteria that normally colonize livestock. *Appl Environ Microbiol* 60:3255-3260, 1994
 61. Chaslus-Dancla E, Martel JL, Carlier C, et al: Emergence of aminoglycoside 3-*N*-acetyltransferase IV in *Escherichia coli* and *Salmonella typhimurium* isolated from animals. *Antimicrob Agents Chemother* 29:239-243, 1986
 62. Winokur PL, Vonstein DL, Hoffman LJ: Evidence for transfer of CMY-2 AmpC-Lactamase plasmids between *Escherichia coli* and *Salmonella* isolates from food animals and humans. *Antimicrob Agents Chemother* 45:2716-2722, 2001
 63. Berkowitz FE, Mechock B: Third-generation cephalosporin-resistant gram-negative bacilli in the feces of hospitalized children. *Pediatr Infect Dis J* 14:97-100, 1995
 64. Tauxe RV, Cavanaugh TR, Cohen ML: Interspecies gene transfer in vivo producing an outbreak of multiply resistant Shigellosis. *J Infect Dis* 160:1067-1070, 1989
 65. Rende-Fournier R, Leclercq R, Galimand M, et al: Identification of the *satA* gene encoding a streptogramin A acetyltransferase in *Enterococcus faecium* BM4145. *Antimicrob Agents Chemother* 37:2119-2125, 1993
 66. Committee on Drug Use in Food Animals, Panel on Animal Health, Food Safety, and Public Health, Board on Agriculture, National Research Council: The use of drugs in food animals—benefits and risk, Washington, DC, National Academy Press, 1999
 67. McDonald LC, Rossiter S, Mackinson C, et al: Quinupristin-dalfopristin-resistant *Enterococcus faecium* on chicken and in human stool specimens. *N Engl J Med* 345:1155-1160, 2001
 68. Wegener HC, Aarestrup FM, Jensen LB, et al: Use of antimicrobial growth promoters in food animals and *Enterococcus faecium* resistance to therapeutic antimicrobial drugs in Europe. *Emerg Infect Dis* 5:329-335, 1999
 69. Ryan C, et al: Interscience Conference on Antimicrobial Agents and Chemotherapy. Minneapolis, MN, American Society for Microbiology, 1985 (abstr)
 70. Bohnhoff M, Miller CP: Enhanced susceptibility to *Salmonella* infection in streptomycin-treated mice. *J Infect Dis* 111:117-127, 1962
 71. Holmberg SD, Osterholm MT, Senger KA, et al: Drug-resistant *Salmonella* from animals fed antimicrobials. *N Engl J Med* 311:617-622, 1984
 72. Ryan CA, Nickels MK, Hargrett-Bean NT, et al: Massive outbreak of antimicrobial-resistant salmonellosis traced to pasteurized milk. *JAMA* 258:3269-3274, 1987
 73. Spika JS, Waterman SH, Soo Hoo GW, et al: Chloramphenicol-resistant *Salmonella* Newport traced through hamburger to dairy farms. *N Engl J Med* 316:565-570, 1987
 74. Pavia AT, Shipman LD, Wells JG, et al: Epidemiologic evidence that prior antimicrobial exposure decreases resistance to infection by antimicrobial-sensitive *Salmonella*. *J Infect Dis* 161:255-260, 1990
 75. Riley LW, Cohen ML, Seals JE, et al: Importance of host factors in human salmonellosis caused by multiresistant strains of *Salmonella*. *J Infect Dis* 149:878-883, 1984
 76. MacDonald KL, Cohen ML, Hargrett-Bean NT, et al: Changes in antimicrobial resistance of *Salmonella* isolated from humans in the United States. *JAMA* 258:496-499, 1987
 77. Lee LA, Puhf ND, Maloney EK, et al: Increase in antimicrobial-resistant *Salmonella* infections in the United States, 1989-1990. *J Infect Dis* 170:128-134, 1994
 78. Marcy SM, Phillips WR, Dowell SF, et al: Principles of judicious use of antimicrobial agents for pediatric upper respiratory tract infections. *Pediatrics* 101(suppl):163-165, 1998
 79. Interagency Task Force on Antimicrobial Resistance. A Public Health Action Plan to Combat Antimicrobial Resistance. Available at: <http://www.cdc.gov/drugresistance/actionplan/html/index.htm>
 80. Food and Drug Administration—Center for Veterinary Medicine. A proposed framework for evaluating and assuring the human safety of the microbial effects of antimicrobial new animal drugs intended for use in food-producing animals. Available at: <http://www.fda.gov/cvm/index/vmac/antimi18.html#statement>
 81. American Veterinary Medical Association Judicious Therapeutic Use of Antimicrobials. Available at: <http://www.avma.org/scienact/jtua/jtua98.asp>