Public health consequences of use of antimicrobial agents in agriculture

Alicia D. Anderson, M. Nelson, Nicole L. Baker, Shannon Rossiter and Frederick J. Angulo
Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA, fja0@cdc.gov

Summary

The use of antimicrobial agents in food animals has caused concern regarding the impact these uses have on human health. Use of antimicrobial agents in animals and humans results in the emergence and dissemination of resistant bacteria. Resistant bacteria from food animals may be passed through the food chain to humans resulting in resistant infections. Increasing resistance to antimicrobial agents that are important in the treatment of human diseases, such as fluoroquinolones and third-generation cephalosporins for the treatment of *Salmonella* and *Campylobacter* infections, has significant public health implications. Efforts to mitigate the effects of increasing resistance require collaboration by several partners, including the farming, veterinary, medical, and public health communities.

Keywords: antimicrobial resistance, food animals, *Salmonella*, *Campylobacter*

1. Introduction

Antimicrobial agents have been used in agriculture, including livestock and poultry, since the early 1950's to treat infections and improve growth and feed efficiency. The actual amount of antimicrobial agents used in agriculture is unknown, however a substantial portion given to food animals is for subtherapeutic use (i.e., use in the absence of disease) for growth promotion, a practice that is becoming increasingly controversial. The agricultural use of antimicrobial agents that have a human analogue increases the likelihood that human bacterial pathogens that have food animal reservoirs will develop cross-resistance to drugs approved for use in human medicine. The World Health Organisation, following a series of consultations in 1997, 1999, and 2000, has recommended that the use of antimicrobial growth promoters that belong to an antimicrobial class used in humans be terminated in the absence of risk-based evaluations (WHO, 1997, 1999, 2000).

Several European countries have already taken steps toward this goal. In 1998, the European Union banned four growth promoters (tylosin, spiramycin, bacitracin, and virginiamycin) because of their structural relatedness to antimicrobial agents used in human medicine (European Commission, 1998). In that same year, chicken farmers and beef producers in Denmark voluntarily stopped using antimicrobial agents as growth promoters; swine farmers followed suit in 1999. This ban has reduced the total volume of antibiotics used in food animals in Denmark by 60% (from 206 to 81 tons) (Sundberg, 2002; Bager and Emborg,

2001). Studies to investigate the influence of the ban have shown no negative consequence for farmers' profits or animal health in broiler chickens (Emborg *et al.*, 2001). Similar conclusions were reported in fattening pigs, although diarrhoea in weaned piglets have required other interventions, such as improved feeding and weaning procedures (Sundberg, 2002). In Sweden, all antibiotics were banned as growth promoters in 1986, decreasing their total antibiotic usage by 55% and demonstrating their ability to achieve competitive production results in the absence of growth promotants (Wierup, 1998; Greko, 1999). The effects of discontinuation of growth promotants in these countries have been a decrease in antibiotic resistance in animals, food products, and humans (Bager and Emborg, 2001; Aarestrup *et al.*, 2001; van den Bogaard *et al.*, 2000; Klare *et al.*, 1999; Bager *et al.*, 1999; Pantosti *et al.*, 1999).

Clinicians should be aware that antimicrobial resistance is increasing in foodborne pathogens such as *Salmonella* and *Campylobacter* and that patients who are taking antimicrobial agents for any reason are at increased risk for acquiring antimicrobial-resistant foodborne infections. The increasing prevalence of antimicrobial resistance among these pathogens increases the potential for treatment failures and other adverse outcomes, including death. Appropriate use of antimicrobial agents in humans and food animals is necessary to maintain their effectiveness and reduce the potential for spread of resistant organisms. While therapeutic usage of antimicrobial agents in food animals is important to promote animal health and provide an affordable supply of meat, milk, and eggs, it is vital that the long-term effectiveness of antimicrobial agents used in human medicine be preserved. This report presents current surveillance information on the frequency of resistant foodborne infections in the United States, reviews scientific evidence linking antimicrobial agent usage in agriculture to resistant foodborne infections in humans, and makes recommendations for measures to protect public health.

2. Antimicrobial use in food animals

At least seventeen classes of antimicrobial agents are approved for growth promotion and feed efficiency in the United States, including: tetracyclines, penicillins, macrolides, lincomycin (analog of clindamycin), and virginiamycin (analog of quinupristin/dalfopristin). To understand the human health consequences of the agricultural use of antimicrobial agents, it is important to evaluate the quantity of antimicrobials used in U.S. agriculture. Unfortunately, no reporting system exists for the quantity of antimicrobials used in food animals in the U.S.. The Animal Health Institute, which represents 80% of the companies that produce antimicrobials for animals in the U.S., has estimated that their member companies produced 18 million pounds of antimicrobials for use in food animals in the U.S. in 1999 (AHI, Press release, 2000). An alternative estimate was provided by the Union of Concerned Scientists (UCS) in 2001 which calculated that 89% of the 35 million pounds of antimicrobial agents used annually in the United States is given to animals. Of the amount used in agriculture, 28 million pounds (93%) are used in the absence of disease (Mellon *et al.*, 2001). Though more precise data on the quantity of antimicrobial agents used in food animals is needed, these initial estimates provide some perspective on the quantity of antimicrobial agents used in U.S. agriculture.

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 which have food animal reservoirs, and other bacteria which are present in food animals (Cohen and Tauxe, 1986; van den Bogaard and Stobberingh, 1999; Levy, 1997). These resistant bacteria may be transferred to humans either through the food supply or by direct contact with animals (Levy, 1997; Oosterom, 1991; Khachatourians, 1998; Witte, 1998; 19-22). The transfer of resistant bacteria from food-producing animals to humans is most evident in human bacterial pathogens which have food animal sources, such as *Campylobacter*, which has a reservoir in chickens and turkeys (Altekruse *et al.*, 1999; Tauxe, 1992; USDA, 1996) and *Salmonella*, which has reservoirs in cattle, chickens, pigs, and turkeys (Meng and Doyle, 1998; Angulo *et al.*, 2000). To monitor antimicrobial resistance in foodborne 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 Food and Drug Administration (FDA) - Center for Veterinary Medicine, the United States Department of Agriculture (USDA), 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 foodborne diseases in nine states.

2.1 *Campylobacter*

NARMS has been used to monitor the prevalence of fluoroquinolone-resistant *Campylobacter* in the United States since 1997. The emergence of fluoroquinolone-resistance among *Campylobacter* is an example of antimicrobial resistance resulting from the use of antimicrobial agents in food animals and the subsequent transfer via the food supply of resistant bacteria to humans. The timeline of emergence of fluoroquinolone resistance in human *Campylobacter* infections in the United States is depicted in Figure 1. Fluoroquinolones were approved for human medicine in 1986. A national prospective study

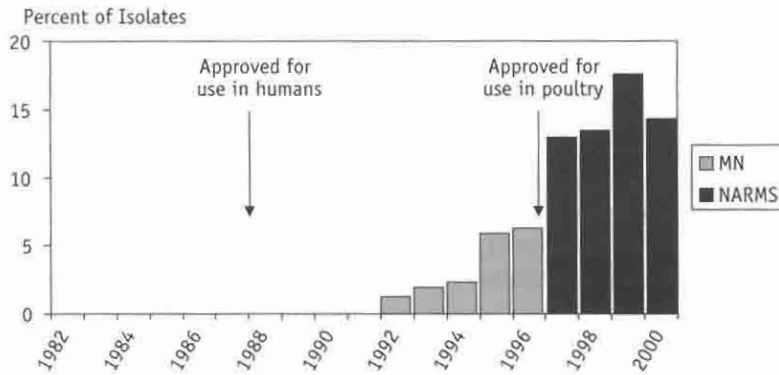

Figure 1. Fluoroquinolone-resistant Campylobacter *in the United States, 1982 - 2000.*

of reported *Campylobacter* cases between 1989-1990 found no *Campylobacter* isolates to be resistant to fluoroquinolones (CDC, 2001). The first fluoroquinolones approved for use in food animals in the United States were sarofloxacin in 1995 and enrofloxacin in 1996. These fluoroquinolones were approved for the treatment of respiratory disease in chickens and turkeys. A study conducted in Minnesota reported that resistance of human *Campylobacter jejuni* infections to quinolones increased from 1% in 1992 to 10% in 1998. Resistant infections that were domestically acquired increased significantly from 1996 through 1998, a finding that was temporally associated with the licensure of fluoroquinolones for use in poultry in 1995. Molecular subtyping of human isolates and domestic chicken products from retail stores showed a significant association between resistant *Campylobacter jejuni* strains from chickens and domestically acquired infections in residents (Smith *et al.*, 1999). Testing of 1997 NARMS *Campylobacter jejuni* isolates found fluoroquinolone resistance among 13% of the isolates; this figure has remained high at 14% of isolates in 2000 (CDC, 2001).

In a case-control study of fluoroquinolone-resistant *Campylobacter* infections conducted in the FoodNet sites, 58% of resistant infections were acquired domestically (Kassenborg, *et al.*; unpublished data). When domestically acquired fluoroquinolone-resistant *Campylobacter* cases were compared with well controls, cases were 10 times more likely to have eaten poultry cooked at a commercial establishment. Since chicken is not imported into the United States, this observation supports the conclusion that poultry is the dominant source of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in the United States. In a recent risk assessment, 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 is already fluoroquinolone-resistant (FDA, 2001).

2.2 *Salmonella*

In addition to fluoroquinolone-resistant *Campylobacter*, there is also the potential for an emergence of domestically acquired fluoroquinolone-resistant *Salmonella* in the United States. Fluoroquinolones are the most commonly used antimicrobial for the treatment of invasive *Salmonella* infections in adults (Angulo *et al.*, 2000). In 2000, 1.4% of *Salmonella* isolates collected by NARMS had a decreased susceptibility to fluoroquinolones (MIC > 0.25 μg/ml), an increase from 0.4% in 1996 (CDC, 2001). This decreasing susceptibility to fluoroquinolones among *Salmonella* infections is of immediate concern as isolates with a MIC > 0.25 μg/ml typically only require a single additional point mutation to become resistant (MIC > 4 μg/ml), and therefore represent a potential reservoir for the emergence of resistant *Salmonella* should such isolates be exposed to continued selective pressure (Nakamura *et al.*, 1993). 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 (Angulo *et al.*, 2000; Molbak *et al.*, 1999).

Third-generation cephalosporins, such as ceftriaxone, are commonly used for treatment of invasive *Salmonella* infections in children because of their pharmacodynamic properties and low prevalence of resistance to these agents. There is therefore concern about the potential

emergence of ceftriaxone-resistant *Salmonella*. The first reported case of domestically acquired ceftriaxone-resistant *Salmonella* was in a 12-year-old child in Nebraska (Fey *et al.*, 2000).

Investigation by public health officials revealed that the child lived on a farm and his father was a veterinarian. Before the child's illness, the father was treating several cattle herds for outbreaks due to culture-confirmed *Salmonella* infection. Although no information was available regarding the use of antimicrobial agents among the infected herds, a third-generation cephalosporin, ceftiofur, is widely used in cattle. Ceftriaxone-susceptible and ceftriaxone-resistant *Salmonella* were isolated from ill cattle treated by the veterinarian. Both ceftriaxone-resistant and ceftriaxone-susceptible cattle isolates and the ceftriaxone-resistant isolate from the child had similar genetic structures as determined by pulsed-field gel electrophoresis (PFGE). These similar molecular "fingerprints" and their temporal isolation suggest that ceftriaxone resistance emerged in the cattle herds, probably following use of ceftiofur or other antibiotics that would have selected for and maintained the ceftriaxone-resistant determinant within 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 13 fold from 0.1% in 1996 to 1.3% in 2000 (CDC, 2001). When patients from whom isolates were received in 1996-1998 were interviewed, few reported international travel, suggesting that most infections were domestically acquired (Fey *et al.*, 2000). Furthermore, ceftriaxone resistance in most domestically acquired infections is due to a unique *Amp*C-type resistance gene (*CMY-2*), which resides on a plasmid. The finding of a similar molecular mechanism of resistance among different *Salmonella* strains supports horizontal dissemination of a resistance determinant (Dunne *et al.*, 2000). A 1999 study at the University of Iowa found multidrug resistant, cephalosporin-resistant bovine, porcine and human *Salmonella* isolates from the same geographic region. All human and animal resistant isolates encoded a *CMY-2 Amp*C-like gene (Winokur *et al.*, 2000).

The emergence of multidrug-resistant *Salmonella typhimurium* definitive type 104 (DT104) in the United States and the United Kingdom, 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 effectively spread among animals and then to humans. Described in 1998 by Glynn *et al.*, the emergence of *S. typhimurium* DT104 in the United States can be traced back to as early as 1985. The prevalence of *typhimurium* isolates with the five-drug pattern of resistance increased from 0.6 percent in 1979-1980 to 34 percent in 1996 (Glynn *et al.*, 1998). Among *typhimurium* isolates submitted to NARMS, the prevalence of the ACSSuT resistance pattern was 28% in both 1999 and 2000 (CDC, 2001). The highest frequency of ceftriaxone-resistant *Salmonella* among NARMS isolates is emerging in multidrug-resistant (MDR) *Salmonella newport*, which is defined as resistance to at least ampicillin, chloramphenicol, streptomycin, sulfamethoxazle, and tetracycline. Of all MDR *Salmonella* Newport isolates submitted to NARMS in 2000, a remarkable 50% are resistant to ceftriaxone (28).

2.3 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, constitute an enormous potential reservoir of resistance genes for pathogenic bacteria. The prevalence of antibiotic resistance in the commensal bacteria of humans and animals is considered to be a good indicator of the selective pressure of antibiotic usage and reflects the potential for resistance in future infections (Murray, 1992; Lester *et al.*, 1990; Hummel *et al.*, 1986; van Den Bogaard *et al.*, 2000).

Most resistant bacteria have mobile genetic elements such R-plasmids and transposons. As the reservoir of resistant commensal bacteria increases, the plasmid reservoir becomes larger and enables more frequent transfer of resistance to pathogenic bacteria including *Salmonella* and *Shigella*. *Escherichia coli*, which is the predominant isolate of aerobic faecal flora in humans and most animals, has demonstrated its ability to transfer resistance genes to other species, including pathogenic bacteria (Hummel *et al.*, 1986; Shoemaker *et al.*, 1994; Nikolich *et al.*, 1994; Chaslus-Dancla *et al.*, 1986; Winokur *et al.*, 2001; Berkowitz and Metchok, 1995; Tauxe *et al.*, 1989). Recent studies have shown an emerging resistance in *E. coli* to fluoroquinolones and third-generation cephalosporins. A study by Garau *et al.*, demonstrated an increase in quinolone-resistant *E. coli* infections in Spain from 9% to 17% over the course of five years. This study also showed a high prevalence of quinolone-resistant *E. coli* in healthy children and adults (26% and 24% respectively) which could not be explained by previous use of quinolones. Animal testing from slaughterhouses in the area found a high rate of quinolone-resistant *E. coli* in swine and chickens (45% and 90%, respectively) (Garau *et al.*, 1999). Winokur *et al.* (2001) found 16% of clinical *E. coli* isolates from cattle and swine and 1% of 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.

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 analogue of quinupristin/dalfopristin that is cross-resistant, has been used as a growth promoter in food animals in the United States since 1974 (Rende-Fournier *et al.*, 1993; NRC, 1999). A study conducted by CDC in 1998-1999, before the approval of Synercid® use in humans, found quinupristin/dalfopristin-resistant *E. faecium* on 58% of chickens purchased in grocery stores from four different states. Additionally, quinupristin/dalfopristin-resistant *E. faecium* was found in 1% of the stools from non-hospitalized people who submitted a stool specimen to clinical laboratories (McDonald *et al.*, 2001). Similar data in Europe led the European Union to ban the subtherapeutic use of virginiamycin in food animals in 1998 (Wegener *et al.*, 1999). These findings suggest virginiamycin use in chickens has created a large reservoir of quinupristin/dalfopristin-resistant *E. faecium* to which humans are commonly 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.

3. Clinical implications

Two human health consequences of increasing antimicrobial resistance in foodborne bacteria are an increase in foodborne illnesses and an increase in number of treatment failures. Increased human infections of resistant foodborne pathogens occur as the prevalence of resistance increases and as humans are exposed to antimicrobial agents. Taking an antimicrobial may lower the infectious dose for *Salmonella* and potentially other foodborne bacteria, if the pathogen is resistant to that antimicrobial (Ryan, C. *et al.*, 1985). Analyses of antimicrobial resistant *Salmonella* outbreaks have demonstrated that previous exposure to antimicrobials can result in a larger number of cases than would have occurred if the outbreak had been caused by a sensitive strain (Cohen *et al.*, 1986). Bohnhoff and Miller showed in the early 1960's that mice with an "undisturbed" normal intestinal flora have a *Salmonella* infectious dose of about 10^6 organisms (Bohnhoff and Miller, 1962). When they "disturbed" the normal flora by administering streptomycin, the infectious dose for streptomycin-resistant *Salmonella* decreased to only 10 organisms. In *Salmonella* outbreaks, it has been observed that preceding, unrelated treatment with an antimicrobial can predispose humans to infection with resistant (Holmberg *et al.*, 1984; Ryan *et al.*, 1987; Spika *et al.*, 1987) or susceptible *Salmonella* (Pavia *et al.*, 1990). Similarly, in studies of sporadic salmonellosis, preceding treatment with an antimicrobial was a risk factor for a resistant infection, compared to susceptible infections (Riley *et al.*, 1984; MacDonald *et al.*, 1987; Lee *et al.*, 1994). Physicians should be aware that as foodborne pathogens become increasingly resistant, treating patients with antimicrobials, regardless of the reason, increases the risk for that patient to develop a subsequent infection caused by resistant foodborne bacteria. The public health impact of this potentiation effect is more cases of illness and larger outbreaks.

In addition to causing more human illnesses, increasing antimicrobial resistance in foodborne pathogens may result in treatment failures if the foodborne pathogen is resistant to an antimicrobial used for treatment. As previously described, resistance is emerging to antimicrobials commonly used for treatment of serious *Salmonella* infections; that is fluoroquinolones in adults and extended-spectrum cephalosporins in children. An example of probable treatment failures was recently described by researchers in Denmark, where a multidrug-resistant *S. typhimurium* DT104 outbreak attributed to contaminated pork was traced back to a swine herd (Molbak *et al.*, 1999). 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.

4. Conclusion

Given that there is an increasing prevalence of antimicrobial resistance and that this resistance has clinical implications, there is a need for mitigation efforts. Such actions will require collaborative efforts by several partners, including the farming, veterinary, medical, and public health communities. Enhanced surveillance is essential for evaluating and directing these efforts. There is a particular need to establish surveillance of antimicrobial usage in animals.

In the United States, collaborative federal actions 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 (ITFAR, 2000). Action items in this plan include improved 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 antimicrobials used in animals (FDA, 1999). It intends to ensure the human safety of antimicrobials used in animals by prioritizing these drugs according to their importance in human medicine. Additionally, it proposes to establish required mitigation actions with increasing resistance and to account for resistance developing from specific animal uses. Education of veterinarians regarding appropriate use of antibiotics has been promoted by the American Veterinary Medical Association (AVMA) with published guidelines for the therapeutic use of antibiotics (AVMA, 2004).

The widespread use of antimicrobial agents in food animals is associated with increasing antimicrobial resistance in foodborne 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 by increasing the number of foodborne illnesses and increasing the potential for treatment failures. To address this public health problem, overuse and misuse of antimicrobial agents in food animals and humans must be reduced. This will be accomplished by adherence to guidelines for therapeutic use of antimicrobial agents in food animals, and the discontinuation of use of antimicrobial agents with a human analogue as growth promotants unless risk assessments have indicated their safety for public health. Several European countries have already demonstrated the feasibility of such measures and the effectiveness of these interventions to combat antimicrobial resistance and reduce public health risks.

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