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Implications of on-farm antibiotic use for public health

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Background

Antimicrobial agents are commonly used in agriculture for the treatment of infectious diseases, prevention of diseases, and for growth promotion of food animals including poultry, cattle, and pigs. The human health relevance of antimicrobial-resistant bacteria from food production animals has long been, and continues to be, a point of contention between the public health and animal health communities. Most public health officials recognize the primary role of antimicrobial use in food animals in the increasing resistance in food-borne bacterial pathogens, but many representatives of the animal health community deny this relationship, citing a perceived lack of scientific evidence. It has been established that administration of antimicrobials to food animals can select for resistance among bacteria which are subsequently transmitted to humans through food or animal contact. However, the exact magnitude of the resulting human health problems has been difficult to quantify. That there is a risk to human health from antimicrobial-resistant food-borne bacteria as a result of the selective pressure applied by antimicrobial use in food animals is logical. However, because the chain of events from antimicrobial use in food animals to clinically significant resistant bacterial infections in humans is complex, documenting comprehensive evidence of cause and effect is very difficult. Nonetheless, recent years have witnessed a rapidly growing body of information on the human health consequences of agricultural use of antimicrobials. These human health consequences are most evident for, but not limited to, *Campylobacter*, *Salmonella*, and enterococci.

Quinolone-resistant *Campylobacter*

Campylobacter is the most commonly recognized cause of bacterial gastroenteritis in the United States and many other developed countries and is a frequently diagnosed cause of traveler's diarrhea. When antibiotics are indicated for treatment of campylobacter gastroenteritis, erythromycin or a fluoroquinolone is cited as the drug of choice. Fluoroquinolones also are cited as the drugs of choice for the prevention and treatment of traveler's diarrhea and are used empirically for the treatment of bacterial gastroenteritis owing to their effectiveness against a range of bacterial enteric pathogens.

Increasing resistance to fluoroquinolones among human *Campylobacter* isolates was first documented in the late 1980s[9] and continues to be a public health problem (see Smith et al.[18] for a review). Emerging resistance to fluoroquinolones has been documented in numerous countries; in some countries the rise in resistance has been remarkably rapid. The cumulative evidence from numerous countries strongly suggests that fluoroquinolone use in veterinary medicine, especially in poultry, is a major contributor to the increase in human infections with fluoroquinolone-resistant *Campylobacter*[18]. This evidence can be summarized as follows:

- Poultry repeatedly has been documented as a major food reservoir of *Campylobacter* for human infections[20]. Person-to-person transmission occurs relatively uncommonly and is not epidemiologically important.
- It has been shown experimentally that enrofloxacin treatment of chickens infected with quinolone-sensitive *C. jejuni* does not eradicate the organism; rather, fluoroquinolone resistance in *C. jejuni* can consistently be selected[12].
- Fluoroquinolone use in poultry and livestock for treatment of disease is widespread in many regions of the world, including Europe, the United States, Asia, Latin America, and South Africa[27]. In some regions, fluoroquinolones also are used for disease prevention. Generic or counterfeit quinolone products are known to be used substantially in many countries; the use of these nonproprietary products is believed to exceed that of proprietary products in many countries[27].
- A temporal relationship between the licensure of fluoroquinolones for use in food animals, particularly poultry, and a subsequent increase in quinolone resistance among *Campylobacter* isolates from humans has been documented in the Netherlands, Spain, the United Kingdom, and the United States[18]. This effect has been most dramatic in Spain, where fluoroquinolones are reportedly used widely in all facets of poultry production.

- Fluoroquinolone-resistant *Campylobacter* has been isolated from retail chicken products in the Netherlands, Spain, Taiwan, the United Kingdom, and the United States[17,18]. The percentage of *Campylobacter* isolates from chicken products in any given country that are quinolone resistant generally corresponds well to the percentage of human isolates that are resistant in that country; i.e., countries with a high percentage of resistance among chicken isolates have a high percentage of resistance among human isolates[18].
- In the United States, molecular subtyping by PCR-FLA identified indistinguishable strains of quinolone-resistant *C. jejuni* among isolates from domestically acquired human cases and locally available retail chicken products[19]. In fact, a statistically significant association was made between molecular subtypes of quinolone-resistant *C. jejuni* isolated from patients with domestically acquired cases and from retail poultry products. This association is not surprising, since many studies using a variety of laboratory characterization techniques have demonstrated similarities among *Campylobacter* isolates from humans and retail poultry products[20].
- A recent case-control study in the United States indicated that domestically acquired cases of fluoroquinolone-resistant *Campylobacter* infection were associated with consumption of poultry in commercial food establishments[13].
- Several studies have shown that, while human quinolone use has undoubtedly contributed to the increase in resistance among *Campylobacter* isolates, the relative contribution compared to quinolone use in veterinary medicine appears to be small[18].

Studies in the United States have demonstrated that ciprofloxacin-resistant *Campylobacter* infections result in a longer duration of illness than do ciprofloxacin-susceptible *Campylobacter* infections[15,19].

Multidrug-resistant *Salmonella* Typhimurium

Nontyphoidal *Salmonella enterica* (over 2,000 serotypes) is another common cause of bacterial gastroenteritis in the United States and other developed countries. The principal reservoirs of nontyphoidal *Salmonella* serotypes are animals, particularly food production animals. As with *Campylobacter*, the most common illness is comprised of fever and diarrhea, but *Salmonella* causes invasive illness (e.g., bacteremia) more commonly than *Campylobacter*, making the availability of effective antimicrobial therapy even more important than with *Campylobacter*.

Multidrug resistance in *Salmonella enterica* serotype Typhimurium has emerged as an important public health problem in the last decade. One particular strain of *S.* Typhimurium definitive type 104 (DT104), which is resistant to at least five antimicrobials (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline [R-type ACSSuT]), has been the largest specific problem documented to date (see Akkina et al.[1] for a review). DT104 was detected in the United Kingdom in humans and cattle in the 1980s. The prevalence of DT104 infections increased rapidly in many food animal species and in humans during the 1990s in the United Kingdom, and DT104 is now the second most common strain of *Salmonella* isolated from human cases there. The primary food animal reservoir of DT104 in the United Kingdom is cattle, but the organism frequently has been isolated from poultry, sheep, and pigs. Human infections with DT104 in the United Kingdom have been associated with the consumption of chicken, beef, pork sausages, and meat paste, as well as contact with farm animals[1].

DT104 also has been reported from several other European countries, the United States, and Canada[1]. In the United States, DT104 emerged at approximately the same time as in the United Kingdom; 36% of *S.* Typhimurium isolates from humans in the United States were R-Type ACSSuT by 1996[4,11]. In the United States, DT104 has been isolated from cattle, pigs, sheep, horses, chickens, turkeys, cats, dogs, and a variety of wild mammals and birds[1,3,]. United States DT104 outbreaks in humans have involved contact with ill dairy cattle and consumption of unpasteurized milk; consumption of noncommercial, homemade cheese made from unpasteurized milk[6]; contact with cats from a humane society or in veterinary hospital settings; and person-to-person spread in child daycare settings.

Additional antimicrobial resistance in DT104 beyond resistance to ACSSuT has further compounded the public health problem posed by this strain of *S.* Typhimurium in Europe[16,21-2]. By 1996, 21% of DT104 R-type ACSSuT isolates in England and Wales were resistant to trimethoprim-sulfamethoxazole, possibly owing to attempts to combat DT104 infections in cattle with trimethoprim. In addition, the percentage of DT104 R-type ACSSuT isolates in England and Wales that also had reduced susceptibility to ciprofloxacin (MIC ≥0.5 mg/L) increased from 1% in 1994 to 13% in 1996. This increase coincided with the licensing of enrofloxacin for veterinary use in the United Kingdom late in 1993; this drug has been used for treatment and prophylaxis in both cattle and poultry in the United Kingdom. In 1998, a strain of DT104 resistant to nalidixic acid and with reduced susceptibility to ciprofloxacin caused an outbreak involving 25 culture-confirmed human cases in Denmark[1]. The source of the outbreak was a Danish swine herd. Two of the patients died. Investigation suggested reduced clinical effectiveness of treatment with fluoroquinolones, which are considered the drugs of choice for the treatment of invasive salmonellosis in adults. Quinolone-resistance in DT104 in the United States has not yet been detected, probably owing to more recent and more limited use in food animals there.

Salmonella Typhimurium with a second penta-resistant pattern (resistant to ampicillin, kanamycin, streptomycin, sulfamethoxazole, and tetracycline [R-type AKSSuT]) distinct from DT104 has emerged in the United States[3,5,7,8]. In 1999, 11% of human isolates in the United States tested through the National Antimicrobial Resistance Monitoring system had this resistance pattern[5]. Cattle appear to be a major reservoir of R-type AKSSuT *S.* Typhimurium[3,5,7,8].

Resistance to extended-spectrum cephalosporins, which are important drugs in the treatment of salmonellosis in children, is beginning to emerge among *S.* Typhimurium in the United States[5]. A case report in 2000 documented the first domestically acquired ceftriaxone-resistant salmonella infection in the United States[10]. The source of infection likely was cattle. Ceftiofur, another third-generation cephalosporin, is licensed for use as a therapeutic agent and is widely used to treat disease in cattle in the United States.

Antimicrobial resistance in enterococci

Enterococci are a leading cause of serious infections in hospital patients and are resistant to most available antibiotics. Until recently, the glycopeptide antibiotic vancomycin was the only effective antibiotic available to treat many enterococcal infections. Vancomycin-resistant enterococci (VRE) were first reported in 1988 in Europe and are now a frequent cause of hospital infections worldwide. In Europe, use of the glycopeptide antibiotic avoparcin as a growth promoter for food animals created a substantial food animal reservoir of VRE and in turn an increased human reservoir of VRE colonization[25]. After the use of avoparcin as a growth promoter was banned by all European Union member states in 1997, the prevalence of VRE in food animals has declined markedly, while the change in incidence of food animal diseases which might be assumed to be prevented by the use of antimicrobial growth promoters has been very limited[24]. Chicken and pork production costs have remained stable, and consumer costs have not been affected. Avoparcin has never been approved for use in the United States and thus has not contributed to the human VRE problem here.

The streptogramin antibiotic quinupristin/dalfopristin (Synercid), has recently been licensed to treat bacteremia and life-threatening infection caused by vancomycin-resistant *Enterococcus faecium*. However, virginiamycin, another streptogramin antibiotic, has been used as a growth promoter for food animals (especially poultry) for decades in the United States and Europe. Recent evidence has indicated that virginiamycin use has created a large food animal reservoir of Synercid-resistant *E. faecium*[2,25]. This has created concern that resultant human colonization with these organisms through the food supply will shorten the useful life span of Synercid as a treatment for VRE infections. Once introduced into a medical facility, Synercid-resistant enterococci could rapidly become more prevalent under the selective pressures of antimicrobial use in humans. A similar situation may be developing with another promising new drug class for the treatment of enterococcal infections, the everninomicins.[25]

Gentamicin is another antibiotic that is important in the treatment of enterococcal infections. In the United States, where gentamicin is used extensively in the poultry industry, a large proportion of retail poultry products are contaminated with high level gentamicin-resistant enterococci (HLGRE), and recovery of HLGRE from human stools has raised concern of transmission through the food supply[14]. In Denmark, where gentamicin is not used in poultry production, HLGRE have not been detected in poultry or humans[14].

Efforts to mitigate antimicrobial resistance in foodborne pathogens

The World Health Organization (WHO) has a held a series of meetings since 1997 to identify and assess the risks associated with the use of antimicrobials in food animals. In 1998, the WHO recommended that quinolones should be registered for therapeutic use only and not for performance enhancement[27]. In addition, extra-label use of quinolones in food animals should be discouraged. On a broader scale, the WHO recommended that any antimicrobial agent should not be used for growth promotion in animals if it is used in human therapeutics or is known to select for cross-resistance to antimicrobials used in human medicine[26]. In August 2000 WHO recommended the following global principles for the containment of antimicrobial resistance resulting from antimicrobial use in animals intended for food[28]:

- obligatory prescriptions for all antimicrobials used for disease control in food animals;
- termination or rapid phasing-out of the use of antimicrobials for growth promotion if they are also used for treatment of humans in the absence of a public health safety evaluation;
- creation of national systems to monitor antimicrobial usage in food animals;
- prelicensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs;

- monitoring of resistance to identify emerging health problems and timely corrective actions to protect human health; and,
- guidelines for veterinarians to reduce overuse and misuse of antimicrobials in food animals.

The European Union banned the use of avoparcin in 1997. In December 1998, the European Union banned four additional growth promoters (tylosin, spiramycin, bacitracin, and virginiamycin) because of their structural relatedness to therapeutic antimicrobial drugs used for humans[25].

In 1998, the United States Food and Drug Administration (FDA) proposed a framework for evaluating and assuring the human safety of the microbial effects of antimicrobial new animal drugs intended for use in food-producing animals. This framework will establish a series of thresholds for antimicrobial resistance, with required mitigating actions when each threshold is met. This process will ultimately result in the withdrawal of the antimicrobial if the mitigating actions do not succeed in preventing increasing resistance. The public health effect of fluoroquinolone use in poultry has been a top priority for evaluation by the FDA. Since the widespread selection of fluoroquinolone-resistant *Campylobacter* may be impossible to avoid when fluoroquinolones are administered in the drinking water on a flock-wide basis, FDA announced in October 2000 its intent to ban fluoroquinolone use in poultry in the United States.

To detect or assess the potential of existing human health problems related to antimicrobial use in animals, a well-coordinated international surveillance and monitoring program is key. This pertains to bacterial isolates from cases of human illness as well as from food or animal sources. As a result of increasing foreign travel and the increasing international food trade, it is clear that control measures implemented only in individual countries will not be sufficient to curtail development of resistance in food-borne bacterial pathogens. For example, efforts to slow or stop the development of quinolone-resistant *Campylobacter* in poultry in the United States would largely interrupt the increasing problem of domestically acquired quinolone-resistant *C. jejuni* infections in Minnesota residents but would not address the problem of resistant infections acquired in foreign countries. Interventions must be applied both domestically and internationally to achieve a comprehensive solution.

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