



The use of antibiotics critical to human medicine in food-producing animals in Taiwan

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There are increasing public health concerns about antibiotics used in food-producing animals that may contribute to the development of resistance in human pathogens. Such resistance may be critical to human medicine when resistance develops to drugs that treat certain pathogens of which there is no good alternative therapy. We surveyed 10 farms, eight feed mills, and one animal drug distributor in Taiwan to determine the major antibiotics used in food-producing animals, and the extent of use of five drugs that may select for resistance to antibiotics that are critical for human medicine. The five animal drugs, and the resistance of human drug/class they may select for, included avoparcin (vancomycin/glycopeptides), avilomycin (zircin/envirinomycins), enrofloxacin (ciprofloxacin/fluoroquinolones), virginiamycin (quinupristin and dalfopristin combination/streptogramins), and kanamycin (gentamicin/aminoglycosides). Tetracyclines were the class of antibiotic that was most widely used in the greatest amounts. Over the past 12 months, the number of farms, chicken feed mills, and pig feed mills, that have respectively reported the use of avoparcin was 1 (10%), 5 (63%), 0; avilomycin 0, 0, 3 (50%); enrofloxacin 4 (40%), 1 (13%), 3 (50%); virginiamycin 2 (20%), 5 (63%), 0; and kanamycin 3 (30%), 1 (13%), 1 (17%). We conclude that although the most commonly used antibiotics (ie tetracyclines) have little effect on human medicine, there is a widespread use of antibiotics that may select for critical forms of resistance in human pathogens in food-producing animals.

Key words: Antibiotics in food-producing animals, antibiotic resistance

There are increasing public health concerns over the possibility that antibiotics fed to food-producing animals may contribute to the resistance of human pathogens [1-5]. The use of antibiotics in animals can be divided into two broad categories [3]. The first category is therapeutic use that involves the prophylaxis or treatment of diseased animals. The second one involves the administration of sub-therapeutic doses of antibiotics that, for reasons not wholly understood, is thought to accelerate increases in body weight of the animal (ie growth promotion). Both antibiotics used for routine prophylaxis as well as those for growth promotion are often added to animal feed. Moreover, both of these antibiotics are usually administered to entire flocks or groups of animals, rather than to individual animals. Thus, these two broad categories of antibiotic may be indistinguishable from the perspective of selecting resistant phenotypes of bacteria.

The majority of antibiotics used in animals include

drugs that have never been used in clinical trials and drugs that, although currently used, are no longer heavily relied on in treating humans [3,6]. Certain antibiotics, however, are critical to human medicine because there is no other drug available to treat human infections caused by multi-drug resistant pathogens, or because alternative therapies are less effective or are associated with increased side effects. When resistance develops to these critical drugs, it may be termed as a "critical" form of resistance. There are now an increasing number of reports suggesting critical forms of resistance arise in human pathogens as a result of using certain antibiotics in food-producing animals, and that such resistance can be transmitted to humans via the food chain [1,2,7,8].

Although the Council of Agriculture in Taiwan regulates all antibiotics that are used in food-producing animals, the relative frequency of antibiotic use in animals that may promote resistance to critical human drugs is unknown. We thereby surveyed a sample of farms, feed mills, and distributors of animal drug to determine the most commonly used antibiotics by amount. We also determined how widespread, over the

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past 12 months, was the use of the five antibiotics that have either been demonstrated to, or may reasonably be expected to, select for resistance to drugs that are critically important to human medicine.

Methods

A survey instrument was developed to ask farmers, feed mill operators, and drug distributors about the size and the type of their facility, its number of years in operation, and the leading antibiotics (in descending order) administered, admixed, or distributed for animal use over the past 12 months. The questionnaires were distributed during the winter of 1999. Farmers were queried about the drugs they used most commonly (by total amount) for therapy, and what drugs, if any, they had administered to their animals for an expressed purpose of growth promotion. Feed mill operators were queried about the drugs they added most commonly (by total amount) to chicken broiler or pig feed. Animal drug distributors were asked about the drugs most commonly distributed (by total amount) for use in chickens or in pigs. Each party was also questioned whether they had administered, admixed, or distributed any amount of the following drugs over the past 12 months: avoparcin, avilomycin, enrofloxacin, virginiamycin, and kanamycin.

Questionnaires were distributed to a convenient

sample of pig and broiler chicken farmers, feed mill operators, and animal drug distributors. The sample consisted of individuals who had been previously contacted through an outreach program of the Department of Animal Science of Chung Hsing University. Results of completed questionnaires were entered into a relational database (Microsoft Access, Redmond, WA, USA), converted to file format, and analyzed by using Epi Info 6.04b (Centers for Disease Control and Prevention, Atlanta, GA, USA). Each of the leading antibiotics administered, admixed, or distributed was assigned a rank order of 1 to 5, with 5 being the most commonly used agent. A summed frequency of the rank order of each antibiotic was used to determine the five agents most commonly used by each group of respondents.

Results

A total of 10 questionnaires were distributed, completed, and returned by farmers. Farm characteristics and the major antibiotics used by farmers for growth promotion and therapy (in descending rank order) are listed in Table 1. Tetracyclines were the most commonly used antibiotics for both therapeutic and growth promotion purposes in farms. Farmers designated fewer drugs as being expressly used for growth promotion than those for therapeutic purposes. For example, only four of the

Table 1. Farm characteristics and major antibiotics used in Taiwan, 1999

Characteristic	No. of farms, n = 10 (%)
Geographic location of farm	
Central region	6 (60)
Southern region	4 (40)
Respondent	
Owner or family member of owner	10 (100)
Median (range) years in operation	25 (15-40)
Type of farm and production	
Broiler farms	6 (60)
Median (range) annual broiler production	100 000 (30 000-550 000)
Pig farms	4 (40)
Median (range) annual pig production	1750 (1300-2400)
Major antibiotics given for growth promotion by decreasing rank, n = 10	
Tetracycline derivatives	4 (40)
Quinolones (non-fluorinated)	1 (10)
Tiamulin (animal drug with no human corollary)	1 (10)
Penicillins (amoxicillin)	1 (10)
Trimethoprim-sulfa drug combinations	1 (10)
Major antibiotics given therapeutically by decreasing rank, n = 10	
Tetracycline derivatives	10 (100)
Penicillins (amoxicillin)	8 (80)
Nitrofurantoin-like drug (furazolidone)	5 (50)
Trimethoprim-sulfa like drugs	5 (50)
Quinolones (fluorinated and non-fluorinated)	3 (30)

10 farmers directed the administration of tetracyclines to their flocks or herds for growth promotion, whereas all 10 reported that they used these drugs therapeutically. It is worth noting that quinolone antibiotics were the fifth highest-ranking antibiotics used by farmers for therapeutic purposes.

In contrast to those of the farm operators, only eight of the 10 questionnaires distributed to feed mill operators were completed and returned. They had been in operation for a median of 23 years (range, 12-35 years). Feed mill characteristics and the major antibiotics mixed into chicken broiler and pig feed (in descending rank order) are listed in Table 2. Again, tetracyclines were the most commonly added antibiotics, by amount and frequency, to both feed types. Glycopeptide avoparcin ranked fourth as the antibiotic most frequently added to chicken broiler feed, whereas macrolide tylosin ranked fourth as the antibiotic most frequently added to pig feed.

Only one of the two drug distributors surveyed returned an adequately completed questionnaire. Because the number of animal drug distributors in Taiwan is small, demographic information for these respondents is not reported to ensure confidentiality. According to the distributors, the 10 antibiotics most commonly used in chicken broilers, in descending order of the quantity sold, were nicarbazin (a coccidiostat), bacitracin, chlortetracycline, salinomycin and lasalocid

(coccidiostat ionophores), neomycin, oxytetracycline, tylosin, maduramicin (coccidiostat ionophore), and tiamulin (a semi-synthetic agent used only in animals with a quinolone-like structure). The 10 antibiotics used most commonly in pigs, in descending order, were chlortetracycline, oxytetracycline, tiamulin, lincomycin, carbadox (a quinoxaline used only in animals), neomycin, sulfamethazine, tylosin (a macrolide), bacitracin, and spectinomycin (an aminoglycoside). The drug distributors denied the distribution of any amounts of avoparcin, avilomycin, enrofloxacin, virginiamycin, and kanamycin over the past 12 months.

Discussion

In many countries, it has been proven that reliable data regarding the amount and types of antibiotic used in food-producing animals is difficult to obtain [9]. Although the relative amount of antibiotic use in animals compared to human use in the United States has been estimated, there are no reliable data regarding the actual amount of different types of antibiotic used in animals [10]. Other countries such as Denmark [6] and Australia [3] have fared better. In Australia, all antibiotics are imported, thereby making it less difficult to track the amount of drugs used in animals [3].

Some drugs in Taiwan are imported for direct sale, others are imported in bulk form and reformulated for sale, and still others are synthesized or produced *de*

Table 2. Feed mill characteristics and major antibiotics admixed in pig and broiler chicken feed in Taiwan, 1999

Characteristic	No. of feed mills, n = 8 (%)
Geographic location of feed mill	
Central region	4 (50)
Southern region	2 (25)
Northern region	2 (25)
Respondent	
Manager	4 (50)
Owner or family member of owner	1 (13)
Other	2 (25)
Feed types produced	
Broiler chicken only	2 (25)
Both broiler chicken and pig	6 (75)
Major antibiotics mixed in broiler feed by descending rank, n = 8	
Tetracycline derivatives	6 (75)
Peptides (bacitracin, enramycin)	8 (100)
Aminoglycoside (neomycin)	5 (63)
Glycopeptide (avoparcin)	4 (50)
Lincosamide (lincomycin)	3 (38)
Major antibiotics mixed in pig feed by descending rank, n = 6	
Tetracycline derivatives	6 (100)
Carbamate (carbadox)	5 (83)
Aminoglycoside (neomycin)	5 (83)
Macrolide (tylosin)	4 (67)
Assorted antibiotics (amoxicillin, colistin, tiamulin)	3 (50)

novo, which make it more difficult to determine the amounts of different antibiotics used in animals reliably. For these reasons, we undertook a survey among the end-users of animal-use antibiotics. To keep the survey simple, we focused on determining the rank order of major antibiotics used, and on whether farmers, feed mill operators, or drug distributors specifically used drugs that are likely to select for resistance to critical human drugs.

The specific antibiotics we asked about were included because they had been approved for animal use in Taiwan by the Council of Agriculture, and have either been demonstrated to, or may be reasonably expected to, select for resistance that is important for human medicine. Avilomycin is an enverninomycin related to an investigational new human drug, zirconin, which is currently undergoing clinical trials for treating multidrug resistant, gram-positive infections [9,11]. Avoparcin is a glycopeptide related to vancomycin. In Europe, where avoparcin had been used as a growth promoter, there is now ample evidence to suggest that vancomycin-resistant enterococci is transmitted via the food chain [7, 9].

Enrofloxacin is a fluoroquinolone that may reasonably be expected to select for resistance to a broad range of fluoroquinolones. An increase in fluoroquinolone-resistance in *Campylobacter* spp. contaminating retail chicken carcasses and infecting humans has already been reported [1]. Kanamycin and neomycin are well-known human antibiotics. Virginiamycin is a streptogramin related in structure and is known to select for cross-resistance to the recently approved human drug, quinupristin/dalfopristin [9], which is an alternative to vancomycin [12]. In Europe and the United States, where virginiamycin is also used in broiler chickens, quinupristin/dalfopristin-resistance is frequently found in *Enterococcus faecium* recovered from retail chicken carcasses at a time when human isolates are still infrequently resistant [13,14].

Results of the survey suggest that all five antibiotics that we specifically asked about were used not infrequently in food-producing animals in the recent

past. Moreover, some of these drugs are among the top five antibiotics most frequently added to some animal feeds mixed in Taiwan (eg avoparcin in broiler feed). The limitation of this study was that we have sacrificed thoroughness for simplicity. We have determined only the rank order, but not the amounts, of different drugs used. Of the several drugs available in the same class (eg enrofloxacin and kanamycin), we have asked about only one drug; whereas in the case of enrofloxacin, at least one other fluoroquinolone (norfloxacin) and several non-fluorinated quinolones (eg naladixic acid and flumequine) are approved and used in animals in Taiwan.

Our findings suggest that tetracyclines are the most frequently used antibiotics in food-producing animals by farmers in Taiwan, for both therapeutic and growth promotion use (Table 1). It should be noted, however, that few farmers used any antibiotics for the expressed purpose of growth promotion, perhaps because commonly the feed mills have already do so in mixing the feed.

Some preliminary data suggest that antibiotic use in animals in Taiwan may have an adverse impact on the susceptibility of some human pathogens. Vancomycin-resistant enterococci (VRE) was first reported in Taiwan in 1996, and recent data from the Taiwan Surveillance of Antibiotic Resistance suggests that less than 3% of all enterococci isolates are VRE [15]. Although this rate is much lower than that of the United States [16], there is data to suggest that the rate of human vancomycin use in Taiwan is also lower than that of the United States. We have recently reported that a large proportion of retail chicken carcasses purchased from traditional markets and supermarkets around Taipei were contaminated with VRE [17,18]. A large proportion of chickens also carried *E. faecium* that were resistant to quinupristin/dalfopristin (unpublished data). Interestingly, a recent report from Taiwan highlights the unusual finding of quinupristin/dalfopristin-resistance in several human isolates of VRE [18]. We have also recently reported on the widespread emergence of reduced-susceptibility and full-resistance to fluoro-

Table 3. Use of critical antibiotics over the past 12 months in farms and feed mills in Taiwan, 1999

Antibiotic	Use by farmers, n = 10 (%)	Use by feed mill operators in chicken feed, n = 8 (%)	Use by feed mill operators in pig feed, n = 6 (%)
Avoparcin	1 (10)	5 (63)	0
Avilomycin	0	0	3 (50)
Enrofloxacin	4 (40)	1 (13)	3 (50)
Virginiamycin	2 (20)	5 (63)	0
Kanamycin	3 (30)	1 (13)	1 (17)

quinolones among human isolates of *Salmonella* spp. and *Escherichia coli* in Taiwan [15]. Possibly related to this emerging human resistance, we have found that *Salmonella* spp. and *E. coli* with similar forms of resistance have contaminated a large proportion of retail chicken carcasses sold in the Taipei area [19].

Although none of the above findings prove that antibiotics used in food-producing animals in Taiwan are related to critical forms of human resistance, the findings of our survey, coupled with data from Europe and the United States regarding food-borne antibiotic resistance, call for concerns. As far back as 1969, when the Swann report [20] prepared by a committee of the British Parliament was published, it has been recommended that no antibiotics that are either critical to human medicine or may select for critical forms of resistance in human pathogens should be used in animals. The Scientific Committee of the European Union prohibited the continued use of avoparcin in all member states in 1997 [4], and the use of virginiamycin, bacitracin, tylosin, and spectinomycin as growth promoters in 1998 [5]. In 2000, the Council of Agriculture in Taiwan prohibited the use of the following antibiotics as growth promoters: avoparcin, kanamycin, kitasamycin, lasalocid, salinomycin, spiramycin, and streptomycin. Nonetheless, additional research is necessary to determine what other measures should be taken by the Council to further reduce the risk of an increasing resistance in human pathogens caused by antibiotic use in food-producing animals.

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