Antimicrobial Use and Resistance in Animals

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Food animals in the United States are often exposed to antimicrobials to treat and prevent infectious disease or to promote growth. Many of these antimicrobials are identical to or closely resemble drugs used in humans. Precise figures for the quantity of antimicrobials used in animals are not publicly available in the United States, and estimates vary widely. Antimicrobial resistance has emerged in zoonotic enteropathogens (e.g., *Salmonella* spp., *Campylobacter* spp.), commensal bacteria (e.g., *Escherichia coli*, enterococci), and bacterial pathogens of animals (e.g., *Pasteurella, Actinobacillus* spp.), but the prevalence of resistance varies. Antimicrobial resistance emerges from the use of antimicrobials in animals and the subsequent transfer of resistance genes and bacteria among animals and animal products and the environment. To slow the development of resistance, some countries have restricted antimicrobial use in feed, and some groups advocate similar measures in the United States. Alternatives to growth-promoting and prophylactic uses of antimicrobials in agriculture include improved management practices, wider use of vaccines, and introduction of probiotics. Monitoring programs, prudent use guidelines, and educational campaigns provide approaches to minimize the further development of antimicrobial resistance.

INDICATIONS FOR ANTIMICROBIAL USE IN FOOD ANIMALS

Antimicrobials are used in food animals to treat or prevent disease and also to promote growth (table 1). Various sources provide data on such uses of antimicrobials in animals, including dosing schedules, contraindications, and withdrawal times [1–3].

Therapeutic treatments are intended for animals that are diseased. In food animal production, individual animals may be treated, but it is often more efficient to treat entire groups by medicating feed or water. For some animals, such as poultry and fish, mass medication is the only feasible means of treatment. Certain mass-medication procedures, called metaphylaxis, aim to treat sick animals while medicating others in the group to prevent disease. Other prophylactic antimicrobial treatments are typically used during high-risk periods for infectious disease (e.g., after weaning or transport). Terminology is not uniform. For example, the American Veterinary Medical Association defines "therapeutic" as including treatment, control, and prevention of bacterial disease [4]. Typically, metaphylaxis involves administering drugs at therapeutic levels for short periods of time.

Some antimicrobials, described as coccidiostats (e.g., ionophores, sulfonamides), prevent coccidiosis, a common parasitic disease of poultry. Some coccidiostats, which are administered in feed at strategic intervals, also have antibacterial properties. Withdrawal times for antimicrobials are intended to prevent harmful drug residues in meat, milk, and eggs. These waiting periods, which are indicated on labels, must be observed between treatment and slaughter [2, 3]. Meat and meat products that contain antimicrobial residues exceeding a certain level at the end of the withdrawal period may be banned from human consumption [1].

Producers may also administer antimicrobials to food animals (except farmed fish) to promote growth and to enhance feed efficiency. The distinction between

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disease prophylaxis and growth promotion is less clear than between prophylaxis and therapy. In North America, certain antimicrobial drugs may be approved for both purposes, and some growth promoters may help to prevent disease, even at subtherapeutic doses [5]. This is an important point because administration of antimicrobials, at least for limited time periods, can almost always be justified on the grounds of disease prevention. Growth promoters are usually administered in relatively low concentrations, ranging from 2.5 to 125 mg/kg (ppm), depending on the drug and species treated [5–9]. In the United States, "subtherapeutic" means uses of antimicrobials in feeds at concentrations <200 g per ton for >2 weeks [10]. However, the term "nontherapeutic," which seems more precise [11], could include both growth-promotion and disease-prophylactic uses. In practice, nontherapeutic treatment often occurs early in production and is typically discontinued as the animals mature.

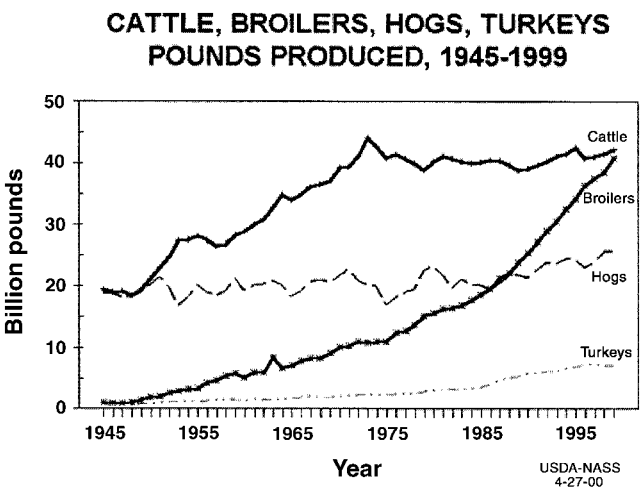

Figure 1. US meat production, 1945–1999. From US Department of Agriculture (http://www.usda.gov/nass/aggraphs/lbspr.htm).

FOOD ANIMAL PRODUCTION AND ANTIMICROBIAL USE PRACTICES

Since World War II, food animal production in the United States has been characterized by greater intensity (i.e., fewer but larger farms) and scale of production (figure 1), improved infectious disease management, and better nutrition [5]. Many antimicrobials are approved for treatment or growth promotion in the United States (table 2).

Beef. After weaning at ~7 months, beef calves typically are shipped to stock or backgrounder farms and then to feedlots, where they are maintained in large groups and fed high-energy rations. Beef cattle feedlot sizes (animals per feedlot) have been increasing: in 2000, ~35% of cattle were fed on farms of 32,000 head or more [12]. Pneumonia and diarrhea are major causes of calf mortality, and calves are often treated with individual or group medication [13]. A variety of important viral infections contribute to pneumonia and diarrhea, but bacterial agents (e.g., *Escherichia coli,* pasteurellae, *Haemophilus* spp., and *Salmonella* spp.) may also be involved. Shipping fever complex (pneumonia) is a major feedlot health problem and an important determinant of antimicrobial use [1, 14]. Comparatively little antimicrobial use occurs in cow-calf production [15].

Various antimicrobials (table 2) are administered to cattle on feedlots for a variety of reasons, including control of liver abscesses, acceleration of weight gain, and prevention or treatment of respiratory disease outbreaks. According to a 1999 US Department of Agriculture survey of antimicrobial treatment practices [14], ~83% of feedlots administered at least one antimicrobial to cattle in feed or water for prophylaxis or growth promotion. Monensin and lasalocid were commonly used for growth promotion, whereas some producers used drugs such as neomycin and virginiamycin. Chlortetracycline was administered on 51.9% of feedlots, chlortetracycline-sulfamethazine combination on 16.8%, oxytetracycline on 19.3%, and tylosin (a macrolide antimicrobial) on 20.3%. On average, tetracyclines were administered for 4–12 days and tylosin for 138–145 days.

Table 1. Types of antimicrobials use in food animals.

Type of antimicrobial use	Purpose	Route or vehicle of administration	Administration to individuals or groups[a]	Diseased animals
Therapeutic	Therapy	Injection, feed, water	Individual or group	Diseased individuals; in groups, may include some animals that are not diseased or are subclinical
"Metaphylactic"	Disease prophylaxis, therapy	Injection (feedlot calves), feed, water	Group	Some
Prophylactic	Disease prevention	Feed	Group	None evident, although some animals may be subclinical
"Subtherapeutic"	Growth promotion	Feed	Group	None
	Feed efficiency	Feed	Group	None
	Disease prophylaxis	Feed	Group	None

[a] Food animals are usually grouped by pen, flock, pond, barn, or other aggregate.

Table 2. Examples of antimicrobials approved for use in the United States in food animals.

Purpose	Cattle	Swine	Poultry	Fish
Treatment of various infections	Amoxicillin	Amoxicillin	Erythromycin	Ormetoprim
	Cephapirin	Ampicillin	Fluoroquinolone	Sulfonamide
	Erythromycin	Chlortetracycline	Gentamicin	Oxytetracycline
	Fluoroquinolone	Gentamicin	Neomycin	
	Gentamicin	Lincomycin	Penicillin	
	Novobiocin	Sulfamethazine	Spectinomycin	
	Penicillin	Tiamulin	Tetracyclines	
	Sulfonamides	Tylosin	Tylosin	
	Tilmicosin		Virginiamycin	
	Tylosin			
Growth and feed efficiency	Bacitracin	Asanilic acid	Bambermycin	
	Chlortetracycline	Bacitracin	Bacitracin	
	Lasalocid	Bambermycin	Chlortetracycline	
	Monensin	Chlortetracycline	Penicillin	
	Oxytetracycline	Erythromycin	Tylosin	
		Penicillin	Virginiamycin	
		Tiamulin		
		Tylosin		
		Virginiamycin		

NOTE. Adapted from [5].

For individual animal therapy, ~50% of feedlots used tilmicosin, florfenicol, tetracyclines, or some combination of these drugs. Feedlots also used cephalosporins (38.1%), penicillins (31.1%), macrolides (17.4%), and fluoroquinolones (32.1%) for individual animal therapy. Approximately 41% of feedlots administered antimicrobials such as tilmicosin, florfenicol, and oxytetracylcines for metaphylaxis [14].

Veal. Typically, culled dairy bull calves in the veal industry are fed an iron-limited diet to produce pale muscle from shortly after birth until they reach 400–500 pounds [5]. Although many antimicrobials are available to treat respiratory and enteric diseases in such calves, little information is available describing which of these drugs are being used and at what frequency. Milk replacers for calves can contain antimicrobials for disease prophylaxis.

Dairy. On dairy farms, most calves are removed from dams within a day of birth, housed separately to control infection, fed milk or milk replacer (which may contain tetracycline) for 6–8 weeks, weaned, and then housed in groups. Antimicrobials (e.g., tetracyclines, penicillins, sulfonamides) may be administered orally or by injection (e.g., ceftiofur) to treat or prevent diarrhea and pneumonia, both of which are important diseases of dairy calves [16]. Although lactating dairy cows receive few antimicrobials in feed, antimicrobials (penicillins, cephalosporins, erythromycin, and oxtetracyclines) are administered through intramammary infusion to treat mastitis, an important disease caused by a variety of gram-positive and gram-negative bacteria [1, 5, 17, 18]. Such drugs are often routinely administered to entire herds to prevent mastitis during nonlactating periods [18].

Poultry. During 1945–1999, broiler chicken production increased from ~5 billion to nearly 40 billion pounds per year [19]; the industry grew to be highly integrated, with fewer companies controlling most sources of birds, feed mills, farms, and slaughter and processing facilities. Broilers are typically raised under confinement in pens containing 10,000–20,000 birds, and turkeys are raised in groups of 5000–10,000 [5]. Integration led to standardized management practices, including drug treatment policies and procedures, and to many successes in the prevention and control of infectious diseases. Many problematic infectious diseases are controlled with antimicrobials (table 2). For instance, broiler rations usually contain a coccidiostat, several of which are broader antimicrobials (e.g., ionophores, sulfonamides). Other antimicrobials (e.g., bacitracin, bambermycin, chlortetracycline, penicillin, virginiamycin, arsenical compounds) are approved for growth promotion and feed efficiency in broilers, turkeys, and egg layers (table 2). Bacitracin is used mainly for growth promotion and to control necrotic enteritis, an intestinal infection caused by *Clostridium perfringens,* with virginiamycin used to a lesser extent for these same purposes. Because older drugs such as the tetracyclines are considered ineffective (presumably because of the emergence of resistance), newer drugs such as the fluoroquinolones are used to treat *E. coli* infections, a major disease problem in poultry [20].

Fluoroquinolones are currently approved only for treatment

of certain infections in poultry (e.g., *E. coli*) to control mortality (table 2), although the US Food and Drug Administration (FDA) proposed to withdraw this approval as a result of concerns about fluoroquinolone resistance in *Campylobacter*. Treatment entails administration of the antimicrobial in water to an entire flock (usually thousands of birds contained within a single barn) because single-bird treatment is not practical.

Hatching eggs may be dipped in gentamicin to reduce mycoplasma or bacterial contamination (sarafloxacin, a fluoroquinolone, was formerly approved for in ovo injection but was withdrawn recently by its sponsor). Because of the risk of yolk sac infections (omphalitis) and vaccine-injection-site abscesses, day-old chicks may be injected with gentamicin, ceftiofur, or other drugs [20].

Swine. Swine are usually raised in confinement, either from birth through slaughter (farrow-finish) or in age-segregated management systems (e.g., nursery, grower, finishing) [21], with many farms of both types practicing all-in, all-out management to control infectious diseases. Average herd size is increasing; in 1995, ~60% of pigs were raised on farms of >1000 head [22]. Antimicrobial use is predominantly in feed, at relatively low concentrations, for growth promotion or disease prophylaxis [23], with antimicrobials typically removed at the finishing stages of production to avoid residues. Therapeutic treatments are also administered in feed, although producers also treat individual swine. Most pigs receive antimicrobials in feed after weaning ("starter rations") [24, 25], when they are most vulnerable to infectious disease.

Several antimicrobials (e.g., ceftiofur, sulfonamides, tetracyclines, tiamulin) are used to treat and prevent pneumonia, an important problem among swine [1]. Gentamicin, apramicin, and neomycin are used to treat bacterial diarrhea, another important problem, caused by organisms such as *E. coli* and *Clostridium perfringens.* Swine dysentery *(Serpulina hyodysenteriae)* and ileitis *(Lawsonia intracellularis)* are other important diseases that may be treated with antimicrobials such as lincomycin, tiamulin, or macrolides [26]. Overall, the antimicrobials used most frequently in swine are tetracyclines, tylosin, and sulfamethazine or other sulfas.

Aquaculture. Catfish, rainbow trout, salmon, tilapia, striped bass, shrimp, crawfish, and a variety of shellfish are the main species cultivated in the United States. No antimicrobials are approved for growth promotion in the United States, and only ormetoprim-sulfadiazine and oxytetracyline are approved for treatment of bacterial infections (e.g., bacterial hemorrhagic septicemia, furunculosis, enteric septicemia) in salmonids and catfish. Drugs are usually administered in feed to the entire group, although broodstock may be treated individually [27].

Organic food animal production. Organic foods account for ~1%–2% of total US food sales but are expected to increase 20%–30% annually [27]. US Department of Agriculture rules require that animals raised organically not receive antimicrobials. If sick, these animals must be removed from the organic operation.

ANTIMICROBIAL APPROVAL AND AVAILABILITY

National regulatory authorities, including the FDA [28], evaluate antimicrobials for use in animals on the basis of safety for humans consuming the foods, animal safety, efficacy, and effect on production. The FDA emphasized possible effects on humans of residues in edible products, although the agency also evaluates microbial effects of drugs intended for subtherapeutic administration [1, 29].

In 1998, the FDA proposed a "framework" for evaluating antimicrobials used in food animals and minimizing their adverse human health effects, including development of resistance [30]. That framework, which categorizes drugs according to their importance to human health, would establish "human health thresholds" for antimicrobial resistance [31]. This framework would help the agency comply with the Food, Drug, and Cosmetic Act, which specifies a "reasonable certainty of no harm" standard to regulations concerning human safety [31, p. 3].

Primary decision making about antimicrobial use ideally rests with veterinarians, who can diagnose diseases on the bases of symptoms and appropriate laboratory tests, including culture and susceptibility testing as they pertain to individual animals or groups. Other criteria, including herd production goals and animal welfare, should also be considered. Veterinarians can then recommend the most appropriate therapeutic regimen by use of the optimal drug, dosage, and duration of treatment.

In reality, however, antimicrobials are often used in food animal production with little or no veterinary consultation. In a 1995 US survey, for example, ~42% of pig farms used the services of a veterinarian [21], although a survey indicates this figure is up to 78% [22]. Producers have access to over-the-counter antimicrobials from retail outlets as well as in feeds containing nonprescription drugs. Various over-the-counter antimicrobials are made available to producers for purely practical reasons—for instance, they lack convenient access to veterinary services—and because the FDA deemed certain drugs safe for over-the-counter use [28]. In 1988, the FDA mandated that all new antimicrobials be prescription only.

Pharmaceutical companies, importers, pharmacies, and other retailers have financial incentives to market antimicrobials to animal producers. Some veterinarians also derive income from such sales. No published data demonstrate conclusively that profit motives routinely affect the antimicrobial-prescribing practices of veterinarians. Denmark placed restrictions on the

degree to which veterinarians can profit from antimicrobial prescriptions [32].

In the United States, the Animal Medicinal Drug Use Clarification Act enables veterinarians to prescribe approved drugs for extralabel use (additional uses not described in the product label). Veterinarians may prescribe extralabel antimicrobials when there is no suitable product approved for a specific species and indication, or when the approved product is ineffective, provided there is a valid veterinarian-client-patient relationship [28]. Extralabel use in food animals is not permitted in feed, by direction of a layperson, or at all for certain drugs such as fluoroquinolones or glycopeptides [28].

Several national veterinary organizations have developed judicious (or prudent) antimicrobial use principles and programs (e.g., American Veterinary Medical Association [4], American Association of Swine Veterinarians [33]). Moreover, the American Association of Avian Pathologists prepared guidelines for drug use in treating poultry diseases that are based in part on the importance of antimicrobials in human medicine [34]. It is too soon to evaluate the effect of these programs; however, if widely adopted, they could benefit both animal and human health.

Swine and cattle producer groups have also developed a variety of food animal quality assurance programs to enhance domestic and export markets. Until recently, these programs tended to focus on preventing antimicrobial residues as a result of consuming contaminated meat. Because concerns about resistance are receiving increased attention, some producers are changing antimicrobial use practices. For example, the Minnesota Certified Pork program requires member farms to use antimicrobials for therapeutic purposes only (University of Minnesota College of Veterinary Medicine, http://www.cvm.umn.edu/anhlth_foodsafety/MinnCERT.html).

QUANTITY OF ANTIMICROBIAL USE IN FOOD ANIMAL PRODUCTION

Reliable antimicrobial use data for animals are not publicly available, making it difficult to determine which drugs are used in what quantities and for what purposes. However, several organizations have published estimates. The most widely quoted of these is the 1989 report from the Institute of Medicine [10], which cited data from the National Research Council and the US International Trade Commission. The Institute of Medicine estimated that total US production of antimicrobials increased from ~1 million pounds in 1950 to ~44 million pounds in 1986.

More recently, a report from the Union of Concerned Scientists [11] estimated that ~50 million courses of treatment, or ~3 million pounds, are administered to humans annually; it also estimated that an additional 1.5 million pounds of antimicrobials are used in topical creams, soaps, and disinfectants, contributing to a total of 4.5 million pounds being used annually in humans. The report further estimated that 27.5 million pounds of antimicrobials are used for "nontherapeutic" purposes (growth promotion and disease prophylaxis), and another 2 million pounds are used for therapeutic purposes in animals. All these figures were based on extrapolations and indirect methods [11].

In February 2000, according to a survey of the members of the Animal Health Institute, 17.8 million pounds of antimicrobials were used in animal production in 1998—14.7 million pounds (83%) for prevention and treatment of disease, and 3.1 million pounds (17%) for growth promotion [35].

Having access to accurate values will be essential for overcoming the marked discrepancies among estimates and would help to put these issues into perspective. Accurate estimates of use are needed for each drug by animal species, purpose (e.g., therapy, growth promotion), route of administration, and duration of treatment. Figures related to human use are also needed. To date, few countries possess information at this level of detail, although some European countries have established veterinary databases that come close. For example, the Danish VETSTAT program is designed to monitor the use of antimicrobials on all food animal herds in the country, the species and age class of animals treated, and reasons for treatment [36].

Volume estimates and other simple comparisons between antimicrobials used for animals and humans can give only a very rough idea of the potential effect of those uses on the development of antimicrobial resistance and human health. Total volume figures do not account for differences in drug potencies or resistance selection pressures. For example, ionophores, which are counted among the Union of Concerned Scientists' antimicrobial totals, are widely used in food animal production but not in human medicine and presumably do not contribute significantly to the development of resistance in clinically useful drugs. On the other hand, drugs such as the fluoroquinolones are used extensively to treat diseases in humans, and their agricultural uses may exert considerable selection pressure for pathogens to develop resistance.

EFFECTS OF WITHDRAWAL OF GROWTH PROMOTERS OR OTHER ANTIMICROBIALS

Members of the agricultural and allied industries are concerned over the possibility that restrictions may be placed on the use of therapeutic or nontherapeutic antimicrobials in food animal production [5]. If restrictions were to be imposed, they would most likely include limitations on new drug approvals or elimination of antimicrobial growth promoters. Possible consequences of such restrictions include the following: (1) decreased incentive for new drug development, (2) poorer production

efficiency, (3) compensatory increases in prophylaxis or therapy, (4) increases in the incidence of infectious disease in animals, and/or (5) limitations on the ability of veterinarians and farmers to treat and prevent disease. Alternatively, restrictions could also result in little or no change in animal health or production efficiency.

How antimicrobials improve growth or feed efficiencies in farm animals is not fully understood [1]. One possibility is that antimicrobials dampen the effects of subclinical disease on growth and also suppress certain sensitive bacteria that compete with host animals for nutrients [8, 9, 37, 38]. Another possibility is that growth promoters enhance the immune system of recipient animals by affecting hormones, cytokines, and other immune factors [39–42]. Antimicrobials at subtherapeutic levels may also modulate the metabolic activity of bacteria in the gut or shift the balance among microbial species, resulting in weight-gain benefits.

Although some reports indicate that such uses yield 1%–11% weight-gain improvements [8], these benefits may not be realized amid other modern production practices. Moreover, such benefits tend to be greater when hygiene is poor [7]. With improvements in hygiene and other measures in place to control disease (e.g., biosecurity, vaccination, improved management), questions are being raised as to whether intensive animal husbandry practices eliminate the benefits of growth promoters. For example, according to a Danish study [43], removal of antimicrobial growth promoters reduces broiler chicken feed efficiency by <1% without affecting other measures of production efficiency. Despite an increase in the rate of necrotic enteritis infections, death rates did not change, and there was no decrease in kilogram broilers produced per square meter [43].

Danish scientists also evaluated how a 1999 ban on the use of growth promoters in pigs and broilers affected antimicrobial use and resistance in fecal enterococci [44]. In 1994, farmers used 206,000 kg of antimicrobials for growth promotion and therapy in Denmark. After the elimination of growth promoters, overall antimicrobial use levels dropped to 80,900 kg in 2000 [44], although there has been some increase in use of therapeutic antimicrobials [32]. Decreases in use of virginiamycin and avilamycin were also accompanied by decreases in resistance to these drugs [44]. However, since the ban, *Lawsonia intracellularis,* an intestinal pathogen that infects pigs, has become a problem [32]. Meanwhile, the 1995 ban on avoparcin use in broilers in Denmark was followed by a substantial decrease (72.7% to 5.8%) in glycopeptide-resistant *Enterococcus faecium* in commercial flocks. A substantial resistance decrease was not observed in pig enterococci until after the decrease in use of tylosin in 1998–1999. Subsequently, it was shown that the genes encoding macrolide (tylosin) and glycopeptide resistance were genetically linked. Decreases in use of virginiamycin and avilamycin were also accompanied by decreases in resistance to these drugs [44]. These studies offer evidence that the prevalence of resistance can be reversed, even if not eliminated, suggesting that unidentified environmental factors may help in sustaining resistant microbial populations (see Summers, this supplement). Avoparcin has never been used in animal agriculture in the United States.

In 1986, Sweden banned the use of growth promoters in animal production [45] and began monitoring antimicrobials sold for use in animals. Shortly after the ban, there were some increases in morbidity and mortality among farm animals (e.g., postweaning diarrhea in piglets, necrotic enteritis in chickens); those increases were counteracted by administration of antimicrobials for prophylaxis during high-risk periods and by adoption of other management improvements. In the early 1990s, zinc oxide replaced antimicrobials as prophylactics for piglets, but by 1998, Swedish officials designated this product as prescription-only, leading to a 90% decline in its use. Total sales of all antimicrobials for animals also decreased by a substantial 60% [46]. Whether this ban affected resistance prevalence is not known.

The economic effects from banning subtherapeutic antimicrobial uses in US agriculture were estimated in a 1999 report from the National Academy of Sciences [5]. According to that report, nearly 100% of chickens and turkeys, 90% of swine and veal calves, and 60% of beef cattle were fed rations medicated with antimicrobials. Even so, according to the report, meat producers following good management practices would not be greatly affected by such a ban, in part because antimicrobial growth promotants are not particularly effective unless animals are living under stress and suboptimal sanitation conditions. In economic terms, such a ban of subtherapeutic drug use would cost, on a per capita basis, $4.84 to $9.72 per year ($1.2–$2.5 billion overall). Estimated increases in cost per pound were lowest for chicken ($0.013–$0.016) and highest for beef and pork ($0.03–$0.06) [5].

Hayes et al. [47] estimated the economic effect in the United States of a ban on the use of over-the-counter antimicrobials in pork production, basing their analysis on figures from the Swedish pork industry. A comparable US ban would increase production costs by $6.05 initially per animal, dropping to $5.24 per animal after 10 years. Higher pork prices would be anticipated because of reduced supply (as a result of anticipated increased feed costs, changes in sow productivity, and piglet loss), and net profits would decline by $0.79 per head, increasing the retail price of pork by $0.05 per pound. Some projected costs include addition of space and troughs to allow restricted feeding. Another estimate of the effects of discontinuing antimicrobial use in hog production suggests that feed efficiency would decrease, feed costs would rise, and production would decrease, leading to higher prices for consumers [48].

ANTIMICROBIAL USE IN ANIMALS AND EMERGENCE AND SPREAD OF RESISTANT BACTERIA

Several recent reviews survey antimicrobial resistance across many animal species [49–52]. In animals, antimicrobial resistance in zoonotic enteropathogens (e.g., *Salmonella, Campylobacter, Yersinia,* and some strains of *E. coli,* such as serotype O157:H7) and commensals (e.g., enterococci, most generic *E. coli*) is of special concern to human health because these bacteria are most likely to be transferred through the food chain to humans, or resistance genes in commensal bacteria may be transferred to the zoonotic enteropathogens [53]. There is considerable evidence that antimicrobial use in animals selects for resistance in commensals [54–58] and in zoonotic enteropathogens [59–61].

However, other studies (on-farm and experimental) failed to show an association between antimicrobial use and resistance [62, 63], suggesting that the development of resistance is a complex process, and perhaps easier to acquire and maintain for some species of bacteria than others. Nonetheless, antimicrobial use in animals apparently contributes to the selection and spread of resistance among populations of bacteria in animals; other forces also contribute to its spread in animal populations. Examples include the movement of carrier animals between herds or between countries, the assembly of susceptible animals in close confinement, and the movement of resistance determinants throughout the ecosystem (figure 2) by means of vectors such as rodents, insects, and birds. Moreover, some bacteria cause disease regardless of resistance status, meaning we need to maintain surveillance programs while trying to reduce both resistant and susceptible zoonotic pathogens.

Some antimicrobial animal-treatment practices may exert greater selective pressures for resistance than others. For example, feeding animals growth promoters, which entails exposing bacteria to sublethal concentrations of drugs over long periods, would appear conducive to selecting and maintaining resistant organisms [1]. This practice in effect corresponds to the general principle in which fit microorganisms able to withstand the effects of antimicrobial agents survive and flourish, whereas those that are not resistant do not survive. Many infeed medications are administered at comparatively low concentrations to animals for weeks and often for years in successive generations of animals.

Although not everyone agrees that such uses of subtherapeutic drugs lead to the development of resistance, considerable selection pressure may be applied when animals are treated in this way. Moreover, not all mass medication is administered at subtherapeutic doses. For instance, many antimicrobials are administered at therapeutic doses in feed or water, or by injection to all or a substantial proportion of individuals in herds or flocks for prophylactic or metaphylactic purposes. Fluoroquinolone resistance in *Campylobacter* and gentamicin resistance in some serotypes of salmonellae of poultry appears to have been amplified, at least in part, by this practice [64]. However, there are differences among drugs in the rate at which resistance occurs. Thus, when assessing resistance risks from uses of antimicrobials in animals and attempting to reduce those risks, it is important to consider other factors that may contribute to selection and spread of resistance among animals. These factors may include species of animal, dose, duration of treatment, numbers of animals treated, animal husbandry practices, animal movement, and potential for environmental spread.

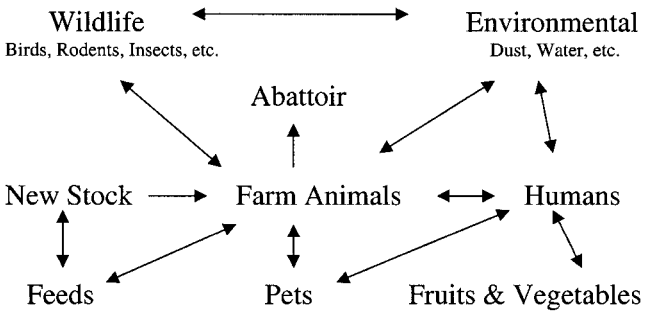

Figure 2. Complexity of the problem and interaction between groups

The fecal waste from thousands of animals reared under intensive conditions often is spread as fertilizer or spread on pasturelands, sometimes after composting. Alternatively, swine operations typically construct lagoons to hold such wastes, and they are implicated in the contamination of the environment with resistant bacteria [65]. Groundwater, streams, and other waterways contaminated with these wastes also may facilitate the spread of bacteria carrying antimicrobial resistance traits.

Food animal production is by no means the sole contributor to this problem. Human wastes from homes, offices, and especially hospitals frequently spill into rivers and waterways from defective septic or municipal systems [66]. Pharmaceutical compounds have been detected in low levels throughout waterways in Europe [67]. How these environmentally borne antimicrobials might affect resistance patterns among microorganisms is not well understood [68] (see also Summers, this supplement). Resistant organisms may also spread between farms by means of infected carrier animals [69], contaminated feedstuffs, wildlife vectors, or on humans wearing pathogen-contaminated clothing. A few studies document the role of antimicrobial treatment in spread of resistance [56], although other studies indicate that such use may select for resistance in individuals (e.g., nosocomial *Salmonella* infections in horses) [70], groups (*E. coli* in pigs or poultry) [57], or in regional populations (e.g., temporal relations between quinolone use in the United Kingdom and the emergence of reduced susceptibility in salmonellae) [71].

Food animal production in North America is becoming progressively more intensive, especially in poultry, swine, and beef feedlot production: the number of farms is steadily decreasing while total production is increasing. Grouping large numbers of susceptible animals in close confinement no doubt facilitates the spread of resistant bacteria, much as occurs in human hospital settings. Improvements in animal disease control and disease-exclusion programs ("biosecurity") help to limit the spread of some animal diseases. However, these programs are not usually designed to control commensal bacteria or even multiple zoonotic enteropathogens (e.g., *Salmonella* and *Campylobacter*); rather, they are designed to control a single or particular pathogen, such as *Salmonella* serotype Enteritidis. However, improved management and biosecurity likely will also reduce levels of other pathogens and improve overall herd or flock health.

ANTIMICROBIAL USE AFFECTS SHEDDING OF ENTEROPATHOGENS AND SUSCEPTIBILITY TO PATHOGENS

Treatment of animals with antimicrobials that are active against enteropathogens such as *Salmonella* (e.g., apramycin and oxytetracycline in pigs [72], oxytetracycline in calves [73], and oxytetracycline in poultry [73]) can reduce fecal shedding, providing a potential public health benefit by reducing pathogenic loads. In general, however, food animals are not treated with antimicrobials specifically to reduce fecal carriage and shedding of enteropathogens. Any public health benefits of this type would accrue indirectly.

Conversely, treatment may increase pathogen loads in the food chain by selecting for resistant nontarget pathogens with increased fitness, increasing the likelihood that animals will be infected with resistant pathogens and increasing the duration of infection. These effects may be specific to particular combinations of drug and bacterial species; for instance, when swine infected with *Salmonella* serotype Heidelberg were treated with ceftiofur or enrofloxacin, shedding was reduced compared with untreated controls infected with *Salmonella* [74].

Antimicrobials may increase the susceptibility of animals to infection by suppressing normal flora and increasing the probability that pathogens will colonize a site (the "competitive effect") or, if administered at the time of exposure to a resistant pathogen, by facilitating the infection because of a selective effect (the "selective effect") (see Barza and Travers, this supplement). Resistant nosocomial salmonellosis attributable to antimicrobial therapy occurs in horses [70], cats [75], and probably other species, although little is published on this subject. Between 3% and 26% of resistant *Salmonella* infections of humans are acquired through a selective mechanism associated with antimicrobial treatments, according to Barza and Travers (this supplement). Comparable estimates for animals remain to be determined.

Antimicrobials may prolong shedding or elevate levels of antimicrobial resistant pathogens in feces. In its Framework document, the FDA states a concern about antimicrobial use in food animals increasing the pathogen load in an animal's intestinal tract, which could increase infection risks for consumers. When challenged with *Salmonella* and exposed to antimicrobials in feed, poultry shedding increases and is prolonged compared with untreated controls, according to some studies [76, 77]. Other studies in swine do not indicate that the pathogen load increases; rather, it appears to decrease [74]. Further, a review of the published literature found that antimicrobial use in food animals is not always associated with increased pathogen loads [78]. Most of these studies, however, were conducted in the 1970s and 1980s, focused on *Salmonella,* and involved exposure challenges, which may not accurately reflect production environments.

POSTHARVEST FOOD SAFETY

Various government and industry programs are designed to reduce the flow of foodborne pathogens from animals to humans, including programs for meat and poultry inspection, standard operating procedures for sanitation, and the Hazard Analysis Critical Control Point (HACCP) system [79]. HACCP programs specifically focus on product safety and have been widely adopted, especially at slaughter and meat-processing plants. Some slaughter or processing HACCP programs include generic *E. coli* and pathogen testing as verification measures. These programs could also help to reduce the flow of antimicrobial-resistant pathogens associated with foods into humans.

ANTIMICROBIAL RESISTANCE AND ANIMAL HEALTH

Antimicrobial resistance is also a concern for animal health, but little is known about the magnitude of this problem. Surveillance of resistance in exclusive animal pathogens (e.g., *Moraxella bovis, Actinobacillus pleuropneumoniae,* and *Pasteurella multocida*) is poor compared with surveillance of zoonotic enteropathogens. Veterinary diagnostic laboratories typically test clinical outbreak specimens in limited fashion, often without identifying species. Because of costs, susceptibility testing of animal pathogens is performed only at the request of practicing veterinarians. Rarely do producers screen herds or flocks for bacteria that may be endemic, so few data are available on the prevalence of resistance in those bacteria. Lack of resources; cost of culture or sensitivity testing; perceived low priority; lack of coordination for collection; culture, and antimicrobial

testing methods; and concerns about sampling bias (because most bacterial infections of animals are not officially reportable except *Salmonella* in some countries) are some of the barriers to better surveillance.

Resistance among animal pathogens reduces the effectiveness of some drugs. This effect could potentially affect public health if drug use in food animals increases to compensate for this drop in effectiveness or if alternative drugs that are crucial to human health are used to treat animals. There is a belief among some veterinarians that new antimicrobials are needed to combat disease in animals [5]. Some of this perceived need appears to reflect experiences with reduced efficacy related to resistance. Antimicrobial resistance has been reported in a wide variety of animal pathogens—for example, *E. coli* of calves, pigs, and poultry; *Pasteurella multocida* and *Mannheimia (Pasteurella) haemolytica* from cattle; and *Actinobacillus pleuropneumonia* and *Streptococcus suis* from pigs [80–83]. However, other factors also play a role in perceived need (e.g., spectrum of activity, withdrawal time, nonresistance efficacy issues, pharmacodynamics).

Some animal pathogen surveillance has been organized in France [84], and in Denmark within the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) program, in which clinical isolates from diagnostic submissions are collected and tested for susceptibility to panels of drugs [36]. Other reports arise from diagnostic laboratories or researchers [85, 86]. In general, resistance is highly variable among animal pathogens in different geographic areas [62, 63]. Additionally, although some isolates of pathogens (e.g., *E. coli*) are resistant to multiple antimicrobials, others remain susceptible.

ANTIMICROBIAL RESISTANCE MONITORING–PROGRAMS IN BACTERIA OF ANIMAL ORIGIN

History of antimicrobial susceptibility monitoring in the United States. Susceptibility testing of bacterial isolates not only allows for discrimination between isolates, but for assessment of developing resistance. Susceptibility testing methods include disk diffusion [87], agar dilution [88], E-test (AB Biodisk), and broth microdilution [89, 90] assays. Determination of MICs by means of the broth microdilution assay is particularly useful in evaluating incremental changes in the development of resistance.

Because of public health concerns, the Food and Drug Administration Center for Veterinary Medicine proposed a postmarketing antimicrobial resistance–monitoring program for veterinary antimicrobials, especially fluoroquinolones. In 1996, the FDA, US Department of Agriculture, and the Centers for Disease Control and Prevention established the National Antimicrobial Resistance Monitoring System (NARMS; formerly the National Antimicrobial Susceptibility Monitoring Program but changed to NARMS–Enteric Bacteria) to monitor changes in antimicrobial susceptibilities of zoonotic pathogens from human and animal diagnostic specimens, from healthy farm animals, and from raw product of food-producing animals at slaughter and processing [91]. Nontyphoid *Salmonella* was selected as the sentinel organism, *Campylobacter* was added to the animal arm in 1998, and generic *E. coli* and *Enterococcus* species were added in 2000.

The goals and objectives of the monitoring program are as follows: (1) to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in *Salmonella* and other enteric organisms from the human and animal populations, (2) to facilitate the identification of resistance in humans and animals as it arises, (3) to provide timely information to veterinarians and physicians, (4) to prolong the life span of approved drugs by promoting the prudent use of antimicrobials, and (5) to identify areas for more detailed investigation. Data are published annually and may be accessed online (http://www.fda.gov/cvm/index/narms/narms_pg.htm). Additional data, including percent resistance by animal species for each year tested can be found at (http://www.ars-grin.gov/ars/SoAtlantic/Athens/arru).

This information may enhance prudent drug use to diminish the development and spread of resistance. For example, when analyses reveal major shifts or changes in resistance patterns in either animal or human isolates, outbreak investigations and field studies will follow. In the long term, these analyses can be incorporated into strategies to alter veterinary prescribing practices in collaboration with professional practitioner groups.

Other monitoring programs. Monitoring programs and methodologies differ from country to country; they are based on agricultural practices, monitoring needs, and antimicrobial uses and guidelines. In Europe, 13 countries (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom) have established their own monitoring programs [92].

The Danish government established DANMAP to monitor trends in antimicrobial resistance among bacteria from animals, food, and humans and to monitor consumption of antimicrobial agents with the intent to model transmission of resistance from animals to humans [36]. Results from the DANMAP program are reported annually and may be accessed at the Zoonosis Centre home page (http://www.svs.dk).

The French Agency for Food Safety (Agence Francaise de Securite Sanitaire des Aliments, AFSSA) organized 2 types of surveillance programs [84]. One monitors resistance from nonhuman zoonotic *Salmonella* (AFSSA, Paris), and the other deals with bovine pathogenic strains by collecting resistance data from local public veterinary diagnostic laboratories (AFSSA, Lyon).

The Spanish government established a network, "Red de

Vigilancia de Resistencias Antimicrobialas en Bacterias de Origen Veterinario," which covers bacteria from sick animals, healthy animals, and food animals [93]. This network reports both qualitative (SIR [sensitive/intermediate/resistant]) and quantitative (MIC) data and provides information methods, analysis and reporting of data.

The Department for Environment, Food and Rural Affairs (DEFRA, formerly the Ministry of Agriculture, Fisheries and Food) from Great Britain compiles antimicrobial resistance and prevalence data in salmonellae. These data are reported by animal species and feed/feedstuffs. DEFRA can be accessed at http://www.maff.gov.uk. Prevalence data on *Salmonella* are also collected in Australia and published annually (http://www.imvs.sa.gov.au).

MONITORING SYSTEMS REQUIRE APPROPRIATE PLANNING

Operating properly designed monitoring programs increases the likelihood of obtaining relevant, high-quality data with which to assess antimicrobial resistance trends. Considerations include selection of sentinel and other relevant organisms, sampling and culture of the isolates, and test methodologies. Failure to standardize surveillance systems could lead to data that are subject to misinterpretation. Moreover, underreporting resistance could result in failure to implement mitigation strategies, with animal and public health consequences, such as lost drug efficacy and higher morbidity and mortality rates. Overreporting of data could lead to unnecessary actions being taken.

Some surveillance programs track *Salmonella* and *Campylobacter* in poultry operations. *Salmonella* in chickens appears to have a commensal relationship without affecting health and birds do little to exclude the organism once *Salmonella* is established [94]. Less is known about *Campylobacter,* which is difficult to recover early in production, often not appearing until 2–4 weeks after hatch [95]. Although environmental reservoirs of *Campylobacter* in poultry houses remain unknown [95–100], prevalence can approach 100% [95]. Nelson Cox (personal communication) implicated breeder stock as one source for its transmission.

Surveillance of resistance in commensals is important because they can be reservoirs of resistance determinants and because they are more ubiquitous than pathogens. Exchange of resistance genes occurs between pathogens and nonpathogens, even between gram-positive and gram-negative organisms [53]. Pathogenic bacteria such as *Salmonella* and *Campylobacter* are not typically present in the gut environment, although once acquired, particularly by animals, they can be carried in the host without sign of clinical disease [101]. The intestinal flora of animals that have been treated with antimicrobial agents can also serve as a reservoir of resistance factors [53]. Of particular interest are enterococci and *E. coli* that can play a role in transmission of mobile resistance genes [53].

Serotype. One of the most critical differences in analysis of resistance data between studies, especially in the case of *Salmonella,* includes accurate description of the serotype or serotypes involved. Generalizations of resistance in "*Salmonella*" will often be inaccurate because resistance between serotype can be significant. For *Campylobacter, C. coli* appears to acquire resistance more readily than *C. jejuni* [86]. Moreover, within serotypes, acquisition of resistance may act as a virulence attribute, altering colonization factors or pathogenesis, as occurs for *Salmonella* DT104. Exposing chicks to a resistant strain of DT104 increases colonization and shedding, whereas a similar exposure to a pan-sensitive strain of DT104 did not [102] (also see Swartz, this supplement).

Culture. Use of selective media may result in the selection of a subpopulation of bacteria with specific phenotypic and genotypic characteristics that do not represent the entire population (P. J. F.-C., unpublished observations), raising questions as to whether reports are truly representative of the general population of bacteria whenever antimicrobials are used as a selection factor. Additionally, multiple serotypes sometimes aggregate, suggesting that special care is needed when analyzing environmental specimens [103]. Moreover, "subpopulations" of bacteria within samples are poorly understood; some isolates are more virulent and better able to establish niches within hosts. Conversely, other populations may be extremely sensitive to antimicrobials and easily eliminated. Thus, isolation and characterization of dominant or phenotypically different (e.g., resistant) subpopulations may mask other important subpopulations.

ALTERNATIVES TO ANTIMICROBIALS IN FOOD ANIMALS

Alternatives to antimicrobials in food animal production include management practices that reduce the likelihood and effect of infectious diseases and also increase the production efficiency. Established veterinary steps to prevent or control infectious diseases include improved husbandry practices, quarantines and other biosecurity measures, and vaccinations. Other treatments include genetic selection to enhance disease resistance, uses of antiseptics such as teat dipping to prevent mastitis, vector control, and use of probiotics or other competitive microorganisms to exclude pathogens [104–106]. Moreover, control of viral and other infections can reduce secondary bacterial infections, thus reducing the need for antimicrobial therapy [107].

Herd health and good management. Although some important infectious diseases (e.g., tuberculosis and brucellosis in cattle, Marek's disease in poultry, and Aujeszky's disease in swine) have been controlled or eradicated, others remain en-

demic or epidemic in herds in the United States. One way to improve control of horizontally transmitted diseases depends on veterinarians and farmers implementing biosecurity practices that reduce or eliminate opportunities for exposure between farms or between groups of animals within a farm, such as all-in, all-out management [106]. Strict disease-control programs such as screening of breeding studs, hatcheries, and artificial insemination centers can reduce or prevent vertical transmission of pathogens. Good sanitation on farms further reduces the spread of certain diseases (e.g., mastitis in dairy cows). It also is important to maintain suitable ambient temperature and air and water quality for healthy animals. Poor air quality in confinement housing can predispose animals to respiratory disease and may decrease production in pigs and poultry; low temperatures can predispose piglets to diarrhea.

Host resistance and vaccines. Vaccines are available to prevent many important bacterial and viral infections of animals, including cattle (e.g., *E. coli, Salmonella* and viral diarrhea, viral and bacterial respiratory disease), pigs (e.g., leptospirosis, *E. coli* and viral diarrhea, bacterial pneumonia), and poultry (e.g., *Pasteurella* infection, Marek's disease) [3, 108, 109]. Efforts are under way to develop a vaccine to prevent coccidiosis in poultry, for which large quantities of prophylactic antimicrobials are used [3, 109]. After vaccines were introduced to control *Vibrio salmonicida* and *Aeromonas salmonicida* in salmon, Norwegian fish farmers dramatically reduced antimicrobial use [110].

Several efforts are under way to develop live-attenuated or killed vaccines for protecting chickens against *Salmonella.* A live-attenuated, orally administered vaccine is expected to provide better protection because it appears to stimulate cell-mediated immune responses [111]. One promising candidate vaccine contains several specific nonreverting and multiple attenuating mutations [112]. Other approaches target their mutations to genes affecting smooth lipopolysaccharide [113], auxotrophic mutants that require metabolites not available in animal tissues [114–116], and mutations in global regulatory pathways [117–120]. Still other candidate vaccines were developed by repeated passage through porcine neutrophils [121].

In these development efforts, investigators typically insert antimicrobial resistance genes, particularly tetracycline and nalidixic acid markers, into the chromosome of candidate vaccine strains to use them as markers. We are unaware of any cases in which this practice leads to any increase in environmental saturation of these resistance genes, and the likelihood that these genes will be transferred to other bacteria after testing or use of these vaccines is not known.

Biosecurity. *Salmonella* is readily introduced onto farms and, once present, disseminates widely. Measures to block its introduction and spread include limiting access to farm sites, requiring visitors to change clothing and boots, controlling birds and rodents, using *Salmonella*-free feed, and treating animals with disinfectant foot baths [106]. Large farms and high stocking densities also apparently facilitate the dissemination of *Salmonella.*

Effective cleaning of sites and disinfection procedures offer additional means to control infectious diseases. Many farms now follow an all-in, all-out policy with animals, permitting adequate cleaning and disinfection after pens and barns are emptied. This practice tends to reduce the spread of pathogens. For instance, pigs can be kept relatively free of *Salmonella* when raised in clean and disinfected environments [122–125]. However, because antimicrobial and quaternary ammonium compound resistance genes may be linked, high-level uses of disinfectants might lead to the development of resistance to antimicrobial agents. All-in, all-out systems also keep successive herds (and their resident microbiota) physically separated, thus reducing the degree to which resistant bacteria can disseminate.

Feeding systems. Probiotics consist of live beneficial bacteria (e.g., lactobacilli, bifidobacteria, propionibacteria), the benefits of which are similar to antimicrobial growth promoters [135]. However, their use in feed is limited, and results have been variable.

Other competitive-exclusion strategies entail displacing pathogens with organisms that are better suited to establish and maintain themselves in a particular biologic environment, possibly by producing chemicals that are toxic to competing pathogens [94]. Salmonellae can colonize broiler chicks at least in part because modern mass-production methods delay establishment of intestinal microflora [126]. However, feeding such chicks anaerobic cultures of normal intestinal adult fowl flora may prevent such infections [126, 127]. The results of experiments [128, 129] and commercial field trials [130, 131] support the workability of the competitive-exclusion concept. PREEMPT [132] was the first competitive-exclusion product approved by the FDA for use in the United States. Currently, competitive-exclusion products are under study in swine [105, 133] and cattle [134], with preliminary results indicating that they can be effective.

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