Industrial Food Animal Production, Antimicrobial Resistance, and Human Health

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Abstract

Antimicrobial resistance is a major public health crisis, eroding the discovery of antimicrobials and their application to clinical medicine. There is a general lack of knowledge of the importance of agricultural antimicrobial use as a factor in antimicrobial resistance even among experts in medicine and public health. This review focuses on agricultural antimicrobial drug use as a major driver of antimicrobial resistance worldwide for four reasons: It is the largest use of antimicrobials worldwide; much of the use of antimicrobials in agriculture results in subtherapeutic exposures of bacteria; drugs of every important clinical class are utilized in agriculture; and human populations are exposed to antimicrobial-resistant pathogens via consumption of animal products as well as through widespread release into the environment.

Antimicrobial resistance: the property of microbes to thwart the toxicity of agents designed to control them

Reservoirs of resistance: the collection of genetic information, encoding resistance, available to microbial communities through mechanisms of horizontal gene transfer

INTRODUCTION: ANTIMICROBIAL RESISTANCE AND AGRICULTURE

Antimicrobial resistance is an increasing crisis in clinical and veterinary medicine worldwide. Although antimicrobial resistance is an inevitable consequence of the evolutionary adaptation of microbes, human use and misuse of antimicrobial drugs have driven the increasingly rapid and prevalent emergence of resistance in a range of pathogenic and commensal organisms. This review focuses on agricultural antimicrobial drug use as a major driver of antimicrobial resistance worldwide for the following reasons: First, the largest use of antimicrobials worldwide occurs in the production of animals for human consumption of meat, milk, and eggs; second, antimicrobials are used as additives in animal feeds; third, drugs from almost every mechanistic class of clinically valuable agents are utilized in agriculture; and fourth, this use results in human exposure to antimicrobial-resistant pathogens via food and through widespread release into the environment.

Antimicrobial resistance is a major public health crisis (40), threatening the return of untreatable infections on a massive scale. Antimicrobial-resistant bacterial infections now account for many emerging infectious diseases worldwide (17, 54). In some pathogens, selection for resistance also results in increased virulence (73). There is a general lack of knowledge of the importance of agricultural antimicrobial use as a factor in antimicrobial resistance even among experts in medicine and public health. A recent analysis of the problem of antimicrobial resistance (36) devotes less than one page to the issue of agricultural antimicrobial use. Although clinical issues are not unimportant, the scale of clinical use and misuse is dwarfed by the magnitude of the largely unregulated use of antimicrobials in agriculture. Moreover, the increasing problems of food-borne drug-resistant infections are seldom linked to their origin in food animal production, which inhibits the effectiveness of public health policies to prevent food borne illness. Most importantly, the problem is often conceptualized in terms of resistance to specific antimicrobials in pathogens of clinical importance, rather than ecologically in terms of reservoirs of resistance genes that may flow across the microbial ecosystem.

The goal of this review is to elucidate these issues through a critical assessment of underlying biological mechanisms involved in the evolution and interecosystem spread of antimicrobial resistance from agriculture, and of the evidence associating agricultural use with the increasing prevalence of antimicrobial-resistant pathogens in food and the environment, as well as of resistant infections in human populations. As discussed below, evidence indicates that agricultural use of antimicrobials in feeds has compromised the efficacy of most antimicrobials used in the United States and throughout the world. For this reason, since 1997 the World Health Organization, together with the Food and Agriculture Organization and the International Organization for Epizootics, has consistently recommended restrictions on nontherapeutic uses of antimicrobials in agriculture, reporting on all antimicrobial uses, and veterinary oversight on the use of antimicrobials in food animals (85).

USE OF ANTIMICROBIALS IN AGRICULTURE

Antimicrobials are utilized in agriculture for veterinary medicine, as feed additives, and as biocides (in crop and fruit production). The major agricultural use of antimicrobials is in the production of poultry, swine, and cattle, but antimicrobials are also used in aquaculture (7) and there are limited uses for it in plants (44). These practices, which are relatively recent in agronomy, have been accompanied by an organizational transformation of agriculture over the past 60 years. It is important to understand how these changes have substantially altered the relationship between

humans and animals in terms of transmission of infectious disease through food and other pathways.

Intensive or industrial food animal production (IFAP) originated in the United States in the late 1930s (22). This has resulted in an integrated model of production, where large corporations control most aspects of animal husbandry, processing of animals into food products, and sales to the consumer market (43). Two aspects of IFAP have introduced new pathogen risks to both animal and human health: the dense confinement of large numbers of animals, and new formulations of animal feeds. Confinement of large populations of animals in buildings or feedlots is a characteristic of IFAP; these facilities are often referred to as concentrated animal feeding operations (CAFOs), depending upon their size. Confinement has several impacts on pathogen risks for animals as well as humans in that contact of large numbers of susceptible hosts facilitates the exchange and evolution of pathogens (61). In general, risks of zoonotic disease are greatly intensified by an increased scale of animal husbandry (18). Most importantly, confined animal populations are unavoidably exposed to their waste. Poultry are housed with their waste, while hogs are housed on top of waste pits. These conditions are illustrated in **Figure 1**, (**http://photogallery.nrcs.usda.gov**). CAFOs are comparable to poorly run hospitals, where everyone gets antibiotics, patients lie in unchanged beds, hygiene is nonexistent, infections and re-infections are rife, waste is thrown out the window, and visitors enter and leave at will. Finally, because these large numbers of animals produce large amounts of waste, which are largely untreated prior to land disposal, there are substantial environmental pathways of release and exposure.

The formulation of feeds also influences pathogen risks. The feeds supplied to confined animal populations are significantly different from the foraged feeds traditionally available to poultry, swine, or cattle (with relatively minimal supplementation by minerals or other substances). Modern animal feeds are formulated with proteins and fats from crops (largely corn and soybean derived), animal fats and proteins (recycled through rendering), additions of industrial waste streams, animal waste, and antimicrobials (reviewed in Reference 64). This latter innovation, which began more than 50 years ago in the United States (51), has introduced a major driver for the selection and dissemination of antimicrobial resistance in bacteria

Industrial food animal production (IFAP): a mode of animal husbandry characterized by high density and confinement of animals (including poultry, pigs, cattle, and aquatic species) raised for human food

Until recently, there was no examination of the actual effect of antimicrobial feed additives on food animal production at the commercial scale. By using data published by the Perdue Company (16), Graham et al. (22) found a very small positive impact of antimicrobial feed additives such that the marginal benefit did not offset the cost of purchasing antimicrobials for addition to feeds. Moreover, the assumed benefits of antimicrobials as growth promoters can be achieved by improved cleanliness of animal houses (16, 46).

A wide range of antimicrobial drugs are permitted for use in food animal production in the United States and many other countries (65). As shown in **Table 1**, these drugs represent all the major classes of clinically important antimicrobials, from penicillin to third-generation cephalosporin compounds. In some cases, new drugs were licensed for agricultural use in advance of approvals for clinical use. In the case of quinupristin-dalfopristin (virginiamycin), this decision by the Food and Drug Administration resulted in the emergence of resistance in human isolates prior to eventual clinical registration (33), thus demonstrating how feed additive use can compromise the potential utility of a new tool in fighting infectious disease in humans. For existing drugs, Smith et al. (70) calculated that agricultural use can significantly shorten the useful life of antimicrobials for combating human or animal disease.

Table 1 Antimicrobials registered for use as feed additives in Australia, European Union, Canada, and the United States*

Countries	Group/Class	Antimicrobial	Usage
Australia	Arsenicals	3-nitro-arsonic acid	Pigs, poultry
	Glycopeptides	Avoparcin	Pigs, meat poultry, cattle
	Macrolides	Kitasamycin	Pigs
		Oleandomycin	Cattle
		Tylosin	Pigs
	Polyethers (ionophores)	Lasalocid	Cattle
		Monensisn (data available)	
		Narasin	Cattle
		Salinomycin	Pigs, cattle
	Polypeptides	Bacitracin	Meat poultry
	Quinoxalines	Olaquindox (data available)	Pigs
	Streptogramins	Virginiamycin	Pigs, meat, poultry
	Others	Flavophospholiphol or bambermycin	Pigs, poultry, cattle
European Union	Glycopeptides	Avoparcin	Banned, 1997
	Macrolides	Tylosin	Pigs
		Spiramycin	Turkeys, chickens, calves, lambs, pigs
	Oligosaccharides	Avilamycin	Pigs, chickens, turkeys
	Polyethers (ionophores)	Monensin	Cattle (growth promotion)
		Salinomycin	Pigs
	Polypeptides	Bacitracin	Turkeys, laying hens, chickens (growth promotion), calves, lambs, pigs
	Streptogramins	Virginiamycin	Turkeys, laying hens, cattle (growth promotion), calves, sows, pigs
	Others	Flavophospholiphol or bambermycin	Turkeys, laying hens, other poultry, calves, pigs, rabbits, cattle (growth promotion)
Canada	Aminoglycosides	Neomycin	Cattle
	Lincomsamides	Lincomycin hydrochloride	Breeder chickens
	Macrolides	Erythromycin	Chicken (broiler, breeder)
		Tylosin	Sheep
	Penicillins	Penicillin G	Chicken (broiler, breeder)
		Potassium	Turkey
		Penicillin G procaine	Chicken, turkey, sheep
	Tetracyclines	Chlortetracycline	Chicken (layer, breeder)
		Oxytetracycline	Turkey, swine, cattle, sheep
	Sulfonamides	Sulfamethazine	Pigs, cattle
	Ionophores	Lasolocid sodium	Cattle
		Monensin	Cattle
		Narasin	Pigs
		Salinomycin sodium	Pigs, cattle
	Polypeptides	Bacitracin	Chicken, pigs, turkey
	Glycolipids	Bambermycin	Turkey, breeder chickens

(*Continued*)

Table 1 (*Continued*)

Countries	Group/Class	Antimicrobial	Usage
	Quinoxalines	Carbadox	Pigs
	Others	Arsanilic acid	Broiler, turkey, pigs
United States	Arsenicals	Arsenilic acid	Poultry
		Roxarsone, cabarsone	Poultry
	Polypeptides	Bacitracin	Cattle, pigs, poultry
	Glycolipids	Bambermycin	Pigs, poultry
	Tetracyclines	Tetracycline	Pigs
		Chlortetracycline	Cattle, pigs, poultry
		Oxytetracycline	Cattle, pigs
	Elfamycine	Efrotomycin	Pigs
	Macrolides	Erythromycin	Cattle
		Oleandomycin	Chicken, turkey
		Tylosin	Cattle, pigs, chicken
		Tiamulin	Pigs
	Lincosamides	Lincomycin	Pigs
	Ionophores	Monensin	Cattle
		Lasalocid	Cattle
	Penicillins	Penicillin	Poultry
	Quinoxalines	Carbadox	Pigs
	Streptogramins	Virginiamycin	Swine
	Sulfonamides	Sulfamethazine	Cattle, pigs
		Sulfathiazole	Pigs

*Table adapted from Reference 65.

THE SCIENCE OF ANTIMICROBIAL RESISTANCE

Understanding the events in the evolution and spread of antimicrobial resistance is important to evaluating IFAP's contribution to this public health issue. The first scientific principle is that, from the perspective of fundamental biology and evolution, the rise of antimicrobial resistance in response to exposure to antimicrobial agents is inevitable. Over millennia, microbes evolved highly effective mechanisms to respond to environmental pressures, including naturally occurring antimicrobial agents (86). Exposure of bacteria to sublethal concentrations of antimicrobial agents is particularly effective in driving the selection of resistant strains, and under conditions of continued antimicrobial pressure, resistant strains are advantaged in terms of reproduction and spread. Because of the rapidity of bacterial reproduction, these changes can be expressed with great efficiency.

The second important scientific principle is that bacterial resistance to antimicrobials involves both genetic and regulatory changes, of which the former have more serious implications for public health. Regulatory changes typically involve enhanced activity of physiological processes such as membrane transport pumps that extrude harmful agents, including antimicrobials. However, this mechanism is relatively rare, and because the capacity of these mechanisms is limited, bacteria usually express relatively low-level resistance as a consequence. Genetically encoded changes are more serious because these can confer high-level resistance to specific or multiple

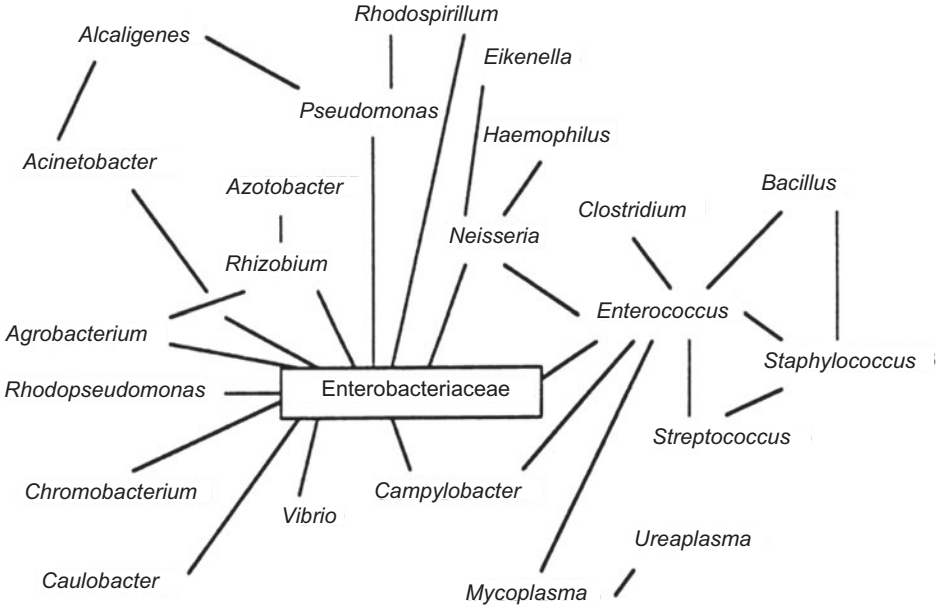

Figure 2

Genetic exchange among bacterial species. This process demonstrates the importance of bacterial reservoirs of resistance, including both pathogenic and nonpathogenic organisms (39).

agents and because they can persist and transfer among bacteria. In the presence of selective pressure, bacterial populations quickly evolve to a resistant phenotype through the mutation of target genes and sharing of resistance determinants (79).

The third important scientific principle is that bacteria can share resistance genes. In addition to spontaneous mutations that favor survival in the presence of antimicrobial pressure, bacteria have an additional mechanism of rapid evolution toward a resistant phenotype through the sharing of genes that encode resistance. Movement of resistance determinants can occur by the uptake of naked DNA by competent species and by plasmid transfers, by which resistance can be propagated within and among bacteria, including commensals (nonpathogenic) and pathogens (60), often across broad species divisions, as shown in **Figure 2** (39). It is this latter facility that is most dangerous in terms of propagation of resistance in the public health context (75). It is estimated that mobile genetic elements including plasmids, transposons, integrons, gene cassettes, and bacteriophages account for more than 95% of antibiotic resistance (52). These events have been detected frequently in resistant *Escherichia coli* isolated from consumer meat products (77). This finding is of particular concern because integrons can transfer multiple resistance genes at a time. Some of these mechanisms can be enhanced by stressors, including antimicrobial pressure (4).

Resistance determinant: gene(s) that encode changes in proteins, which result in antimicrobial resistance in bacteria

The concept of reservoirs of resistance reflects the fact the community of genetic resources determines the rate and propagation of resistance (62). The contribution of agricultural antimicrobial use to environmental reservoirs of resistance has been documented for both poultry and swine (31, 48). The existence of these reservoirs of resistance challenges the current focus of public health concern on specific patterns of resistance in specific pathogens (36). Because genes for resistance traits can be exchanged from commensal to pathogenic bacteria, the "one bug, one drug" definition of the problem is inadequate (76).

The fourth important scientific principle is that resistance may continue even after antimicrobials are no longer present. Earlier theories of microbial genetics assumed that

resistance was unlikely to persist because the expression of resistance was thought to cost the organism (in terms of increased energy requirements, susceptibility to other stressors, or decreased reproductive rates) (38). This is clearly not always the case: For example, strains of *Campylobacter jejuni* that are resistant to fluoroquinolones have a selective advantage over wild strains in competing for the ecological niche of the host (87). More fundamentally, it may in some cases be cheaper for a resistant bacterial strain to acquire an additional genetic change that reduces the biological cost of resistance rather than to revert genetically and phenotypically to the wild or susceptible state (86). Resistance may also persist owing to the clustering of resistance genes on the same transposable elements such that eliminating only one antimicrobial may not reduce the prevalence of the cluster (1). Empirical evidence indicates that even after the removal of antimicrobials from animal feeds, the prevalence of resistance decreased significantly but could still be detected in animal houses, waste, and food products in Europe (72).

THE ROLE OF INDUSTRIAL FOOD AND ANIMAL PRODUCTION IN ANTIMICROBIAL RESISTANCE

Understanding the contribution of agricultural antimicrobial use to antimicrobial resistance requires information on agriculture uses. As shown in **Table 1**, drugs from almost every clinically essential class are permitted for use in some country as feed additives. Unfortunately, we lack definitive information on the volume of antimicrobial use as feed additives in most countries, including the United States, where feed formulations are considered confidential business information under U.S. law. Global use is unknown but likely to increase as the IFAP model of production is adopted in other countries (65). Because of the general lack of data, there are unresolved debates over the proportion of antimicrobial use in agriculture for this purpose, as compared with human and veterinary medicine. Most estimates suggest that nontherapeutic agricultural use accounts for between 60% and 80% of total antimicrobial production in the United States (45) and until recently in the European Union as well (80).

Associations Between Antimicrobial Use in Animal Feeds and Resistant Pathogens

The extensive literature on the prevalence of antimicrobial resistance in both commensal and pathogenic bacteria in association with antimicrobial use in food animal production has examined associations in the contexts of producing cows, pigs, and poultry. The first type of study is ecological, that is, studies that have followed the prevalence of antimicrobial resistance after changes in agricultural antibiotic use. The second type is cross-sectional, that is, studies of specific groups in close contact with food animal production settings where antimicrobials are used (such as farmers and farm families) as well as of the presence of antimicrobial-resistant bacteria in animals, animal houses, animal waste, and the environment. A third type of study has examined the prevalence of resistance in bacteria isolated from consumer products from conventional producers using antibiotics and those from producers not using antibiotics.

Ecological Evidence: Studies of Temporal Trends

These studies utilize data collected at different time points and often from different sources. Despite these limitations, they provide evidence consistent with an association between registration of antimicrobials for agricultural use and increasing risks of resistance in bacterial isolates from human populations. For example, the introduction of vancomycin and pristinamycin in swine production was associated with increased prevalence of resistant enterococci from human fecal samples in the Netherlands (84). A sharp increase in the

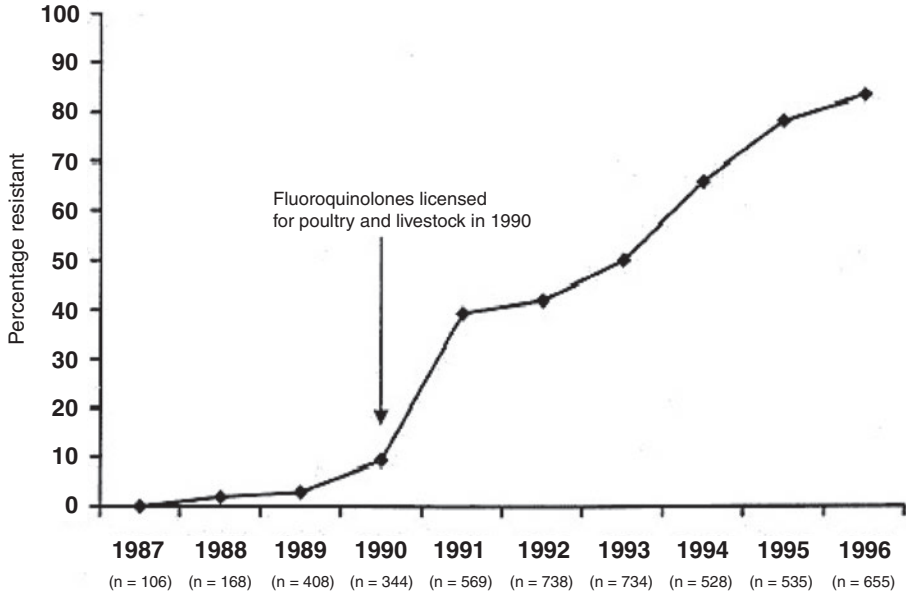

Figure 3

Trends in the prevalence of fluoroquinolone resistance in clinical isolates of *Campylobacter jejuni*, in Spain, examined for resistance from 1987 to 1996. Before approval of fluoroquinolones in poultry and livestock production, resistance was relatively rare (<10%); after approval, the prevalence of resistance rose quickly. Data used with permission from Reference 47.

prevalence of ciprofloxacin resistance among clinical *Campylobacter* isolates in the United States was associated with introduction of a fluoroquinolone analog (enrofloxacin) into IFAP in 1990 (23; comment by Reference 11). As shown in **Figure 3**, following the introduction of fluoroquinolones into poultry production in Spain in 1993, the rates of resistance in human isolates quickly rose to over 80% (47). Similar data were found in studies of isolates from poultry and humans in Norway (50) and in the Netherlands (15). In contrast, the relatively low rate of fluoroquinolone resistance in clinical isolates in Australia has been attributed to the fact that this drug was never used in agriculture (81).

The most powerful temporal data are drawn from surveillance of both antimicrobial use in agriculture and trends in resistance in bacterial isolates from several sources, carried out in Europe prior to and following the ban on feed additive use of antimicrobials. For example, studies carried out in Denmark over this period demonstrated a rapid and parallel decrease in antimicrobial use and the prevalence of antibiotic-resistant *Enterococcus faecium* recovered from pigs or broilers (from Reference 2). The prevalence of resistant enterococci isolates from human subjects also declined in the European Union over the same period (34).

Cross-Sectional Studies on Food Contamination with Antimicrobial-Resistant Bacteria

There is extensive literature on the topic of resistant pathogens in animal-derived food products. Repeated studies by the U.S. FDA have reported on the high prevalence of antimicrobial resistance in pathogenic bacteria isolated from consumer food products in the United States, and similar findings have been reported in the European Union (14,

32). Simjee et al. (67), from the FDA, conducted one of the more comprehensive surveys of antibiotic resistance in consumer poultry products in the United States. More than 80% of non-*faecalis* enterococci were resistant to streptogramins (quinupristin-dalfopristin), and a high prevalence of resistance to penicillin, tetracycline, and erythromycin was also observed in enterococci. Similar findings were reported by the FDA for nonpoultry meat products as well (25). Correlations among quinupristin-dalfopristin resistance in *E. faecium* isolates have been drawn between humans, farm animals, and grocery store meats in the United States (13).

Production methods have been associated with the likelihood of resistant pathogens on the farm and in the food supply. For example, significantly higher prevalence of multidrug-resistant *E. coli* was found in animals that were supplied antimicrobials in feed as compared with those from organic farms (66). Two studies have demonstrated associations between antimicrobial use and prevalence of resistant bacteria isolated from consumer food products (41, 58). In both studies, the conventionally produced meats were more likely to carry resistant bacteria.

Evidence for Nonfood Exposures to Antimicrobial-Resistant Bacteria: Farming Communities and Farm Workers

The issue of nonfood pathways of exposure has only recently begun to receive attention. Most of the earlier studies have consisted of case reports, exemplified by the report by Fey et al. (19), who carried out a case investigation of a farm child infected by ceftriaxone-resistant *Salmonella*. More recently, Huijsdens et al. (28) reported on methicillin-resistant *Staphylococcus aureus* infections in seven people (including an infant) living or working at a large hog farm in the Netherlands; molecular methods confirmed the clonality of the human and hog isolates. Two studies have examined exposures of farmers and rural communities to antimicrobial resistance associated with IFAP. Van den Bogaard & Stobberingh (83) reported poultry farmers were at greatly increased risks of carrying drug-resistant enterococci as compared with urban residents, while Price et al. (59) found that poultry house workers were 32 times more likely to carry gentamicin-resistant *E. coli* as compared with community referents. In an ingenious study, Ojeniyi (53) carried out an experiment in which chickens in a university-based operation were inoculated with an introduced strain of *E. coli*; the poultry house workers were rapidly infected by this indicator strain.

Exposures of farmers and farm workers to antimicrobial-resistant bacteria are of wider concern for public health, as these exposures can translate into community risks, especially via person-to-person contacts (61, 71). Smith et al. (69) carried out investigations of resistant *C. jejuni*, confirming elevated risks among communities in close contact with CAFOs.

Environmental Routes of Release of Antimicrobial-Resistant Bacteria

The location and methods used in IFAP, especially related to waste management, result in environmental releases of resistant bacteria from confined animal houses and feedlots into air, water, and soils. Resistant bacteria have been isolated from environmental samples in and near food animal production facilities (3, 9, 21, 30, 42, 63, 74). The public health significance of these releases is increased by the growing geographic concentration in the United States of IFAP over the past 50 years (43). Similar trends are emerging globally (20). As a consequence, the use of both antimicrobials and pathways for pathogen releases have been similarly intensified (65).

The major source of resistant pathogens entering the environment from IFAP is via waste disposal. According to the U.S. Department of Agriculture, confined food animals produce roughly 335 million tons (dry weight) of waste per year (82), which is more

Biosolids: nonliquid excreta from animals or humans

than 40 times the mass of human biosolids generated by publicly owned treatment works (7.6 million tons in 2005). In contrast to human biosolids, no treatment-process control requirements or prescribed criteria for pathogens have been established for animal waste prior to disposal, although levels of pathogens, as well as antimicrobial-resistant bacteria, are often higher than levels found in human feces. After land disposal, resistant bacteria can move into human exposure pathways and can occur through the contamination of crops fertilized with animal waste or irrigated with water contaminated by this waste; aerosolized particles of waste emitted from animal houses or waste storage facilities, fields fertilized with litter, or trucks transporting animals for processing; runoff of waste into groundwater and surface water; and contamination of other animals. There is evidence for the mechanical spread of resistant bacteria by insects, rodents, and wild avians that may be particularly attracted to poultry CAFOs where sources of food exist. Information on environmental pathways of exposure to resistant bacteria from CAFOs is provided here.

Waste. Hayes et al. (26) conducted a large study of antibiotic resistance and its development within the broiler poultry house, which demonstrated that multidrug resistance was observed in 53% of *E. faecium* and *Enterococcus faecalis* collected from poultry litter and from transport cages. Resistant pathogens persist in waste from poultry houses held under conventional conditions (without digestion or formal composting) for at least four months. Tetracycline resistance genes are highly persistent in lagoons of hog waste and in soils amended with this waste (30).

Air. Because confinement of thousands of animals requires controls to reduce heat and regulate humidity, poultry and swine houses are ventilated with high-volume fans that result in considerable movement of materials into the external environment. Emissions of particulate matter (<10 μm in size) from broiler house fans can range from 25 to 40 g m^{-3} in 24 hrs or a million-fold increase as compared with air sampled in a semirural area (57). At swine CAFOs that use ventilation systems, resistant bacteria have been detected in the air as far as 30 m upwind and 150 m downwind (21). Similarly, *Campylobacter* strains with identical DNA fingerprints to those colonizing broilers have been measured in air up to 30 m downwind of broiler facilities (5). In addition, the antimicrobial drugs themselves have been found in airborne dust from swine CAFOs (24).

Water. Resistant *E. coli* and resistance genes have been detected in groundwater sources for drinking water sampled near hog farms in North Carolina (3), Maryland (74), and Iowa (42). In terms of public health significance, groundwater provides drinking water for more than 97% of rural U.S. populations. In addition, antibiotics are regularly found in surface waters at low levels (micrograms per liter range) (65).

Soil. Only a few studies have looked at levels of resistant bacteria and resistance genes in soils associated with the application of animal waste to land. Because antibiotics occur naturally in soils, and resistance to antibiotics is commonly found in these dynamic microbial populations (12), it can be difficult to determine whether resistance in soil organisms is in response to land-applied animal waste. A study of dairy farm topsoil, from a farm using antimicrobials in feed, consistently identified multidrug resistant enteric bacteria that harbored resistance plasmids (6). In addition, because antimicrobials can also be transferred to soil via animal waste disposal, resistance may be generated de novo in soil bacteria (8). Additionally, laboratory tests have shown that resistance genes can be passed between enteric bacteria and soil bacteria (55).

Food crops. Contamination of surface waters from land disposal of animal waste can

impact food safety. Runoff from land amended with CAFO waste has been implicated as a source of resistant pathogens recovered from food crops grown in soils irrigated with contaminated water (29, 68, 78). These events can occur through water contamination from relatively distant sites of land disposal.

Environmental transfers via animal-to-animal contact. Antimicrobial resistance can also escape from CAFOs by means of contacts between animals in CAFOs and animals in the external environment. Insects are a potentially large contributor to these movements. Flies are found in significantly increased numbers in areas close to animal houses. Houseflies have been found to play a major role in the epidemiology of *Campylobacter* infections in communities near CAFOs (49). Rodents can also transfer pathogens in and out of animal houses (27). Wild avians are attracted to CAFOs and to the fields where poultry house waste is disposed because of the presence of spilled feed in this waste. In a study of antibiotic resistance in *E. coli* isolated from wild avians near CAFOs, the proportion of isolates resistant to antibiotics was significantly higher among those isolates from birds in proximity to swine waste lagoons as compared with a reference set of samples collected in settings with no animal production (10).

ATTRIBUTABLE RISK OF AGRICULTURAL ANTIMICROBIAL USE AND THE BURDEN OF ANTIMICROBIAL-RESISTANT INFECTIONS IN PUBLIC HEALTH

An important element in public health policy is estimating the proportion of a risk that can be attributed to a specific source or activity. Attributable risk is the amount or proportion by which the incidence rate of the outcome among the exposed would be reduced if the exposure were eliminated (35). As noted in the introduction, antimicrobial resistance is associated with all uses of antimicrobials including clinical, veterinary, and agricultural. Both appropriate and inappropriate uses contribute to the evolution and prevalence of resistance. Antimicrobial-resistant infections are often considered largely nosocomial in origin, because this is the usual setting in which they are most often diagnosed. As a result, programs for prevention have focused largely on hospitals and other clinical settings. Clearly, hospitals facilitate the spread of antimicrobial resistance for many reasons, including the presence of people with bacterial infections, the need to manage a large volume of contaminated materials (including bedding, clothing, and biological waste), intrusive medical procedures, immunocompromised persons, and so on. However, for purposes of truly understanding attributable risk, it is important to determine the origin of resistant infections that may be detected in hospitals. It is increasingly recognized that the community, that is, the extraclinical environment, is an important source of antimicrobial resistance.

Attributable risk: the amount by which the incidence rate of an outcome among an exposed group would be reduced if the exposure were eliminated

For all these reasons, it may not be possible to determine the attributable risk of antimicrobial use specific to agriculture or to the use of specific antimicrobials as feed additives—in terms of the overall incidence of resistant human infections, given a model that incorporates the notion of communities of humans and bacteria—as well as the importance of both gene flow and microbial transmission (76, 86). From the microbial point of view, all sources of selective pressure contribute to resistance, and its appearance may thus result from a variety of sources. In addition, there is increasing recognition of the importance of reservoirs of resistance, which may reside in both pathogenic and nonpathogenic bacteria.

In terms of human disease risk, there is a similar and increasing realization of the role of community infections as sources of nosocomial (hospital) infections (71). Although hospital use of antimicrobials can generate the highest risk of transmission of resistant infections (owing to opportunities in hospitals for contact among large populations of

susceptible populations, similar to CAFOs), the greater range of resistance generated by agricultural uses may result in a larger reservoir of nonhospitalized populations carrying antimicrobial resistance, in the form of pathogenic and nonpathogenic bacteria, as well as transposable genetic elements. As these people enter the hospital, they may be a major source of resistant infections to the hospital environment. Thus, the risks of becoming infected by a resistant pathogen are higher in hospitals, but the source of resistance is greater outside the hospital, largely related to the size of the animal reservoir of resistance (which includes consumer meats and poultry). Thus, as Smith et al. (71) conclude, a large number of people exposed to a low risk may generate more cases than a small number of people exposed to a high risk. Evidence for the increasing prevalence of community sources of multidrug resistance is found in a study of incoming patients at a tertiary care hospital in Boston: From 1998/9 to 2002/3, the likelihood of multidrug resistance in *E. coli* increased from 2% to almost 20% (56).

CONCLUSIONS

The use of antimicrobials for nontherapeutic purposes in agriculture is a major factor driving the emergence of antimicrobial resistance globally. Throughout the world, antimicrobial agents from every class of clinically important drugs have been introduced into agriculture as feed additives. In addition, the methods of modern food animal production, in which large numbers of animals are confined to houses or feedlots, creates opportunities for intensive host-to-host transfers. Crowding, inadequate housing, and unsanitary conditions facilitate the spread of infectious disease in human populations. Despite this knowledge, the industrial food animal model still concentrates animals in small, unsanitary spaces. In addition, IFAP results in an enormous burden of waste and in opportunities for uncontrolled emissions into the environment.

Evidence from many countries supports the role of agricultural antimicrobial use and increasing prevalence of resistance among commensal and pathogenic bacteria isolated from food animals, humans, the food supply, and the environment. Bradford Hill's criteria for considering a causal relationship between a risk factor and an outcome (35) are well met: A consistent temporal relationship between the introduction of antimicrobials into agricultural use and increases in the prevalence of resistant organisms has been found in animals, animal-derived food products, and humans; the associations between antimicrobial use and outcomes are highly significant and consistently reported; plausibility rests upon our understanding of microbial evolution; other sources of antimicrobial resistance have been examined; specificity has been confirmed by molecular methods demonstrating clonality among isolates from animals, the food supply, and exposed humans; the effects of intervention (banning specific drugs) on reducing the prevalence of resistance have been reported; and the data are coherent with our overall understanding of the drivers for selective evolution in bacteria.

Prudent public health policy thus indicates that nontherapeutic uses of antimicrobials in food animal production should stop. Economic analyses demonstrate that there is little economic benefit from using antimicrobials as feed additives, and that equivalent improvements in growth and feed consumption can be achieved by improved hygiene. Improved hygiene also has a moral imperative for the welfare of domesticated animals. Hogs raised in nonbedded confinement systems exhibit more aberrant behavior, have higher plasma cortisol levels, and suffer a greater incidence of injuries in contrast to hogs in less densely concentrated, bedded hoop housing (37).

Consistent global action has been repeatedly recommended by the World Health Organization, International Organization for Epizootics, and Food and Agriculture Organization. Yet these issues are still considered

controversial in the United States, and there are even proposals to make new antimicrobials, such as fourth-generation cephalosporins, available for agricultural use. From the scientific perspective, it is difficult to define what additional research is needed to support a change in public policy on antimicrobial use in agriculture. Some responsibility for the gap between policy and science is due to the failure of the public health community to identify agricultural antimicrobial use as a major preventable driver of the clinical crisis in antimicrobial resistance. Moreover, in outbreaks of resistant infections, the ultimate source of drug-resistant pathogens in the food supply is rarely identified, as in the case of vegetables contaminated via irrigation water into which pathogens have entered from fields amended with animal waste. Calls for increased investment in surveillance of the food supply are justified, but, because surveillance programs can never be fully protective, opportunities for prevention should not be neglected.

Finally, the true scope of the impacts of agricultural antimicrobial use must be recognized. This is not simply a food safety problem, but a problem involving occupational health and environmental exposures through air, soils, and water. The current systems in the United States, combining surveillance (National Antimicrobial Resistance Monitoring System) and regulation (Hazard Analysis and Critical Control Point, HACCP), cover from farm to fork but not very effectively within or nearby the farm. HACCP accepts the fact that, under current practices, animals and the human food supply will be contaminated by pathogens and resistant organisms; controls are instituted to contain this problem after the animals leave the farms. HACCP places no additional burden on the management of food animal production to contain risks of antimicrobial resistance. HACCP does not deal with the potential for health risks associated with nonfood pathways of release and exposure. Also, the responsibility for these pathways has not been taken up by environmental agencies. In the United States, the recent regulations proposed by the Environmental Protection Agency for management of IFAP waste do not cover pathogens or antimicrobials, but only nutrient overloads and odors.

We therefore conclude with two fundamental observations: First, a mass flow concept of antimicrobial pressure and resistance evolution supports the importance of controlling the agricultural use of antimicrobials because this is the primary category of use worldwide; and second, the problem must be redefined as one of resistance and gene flow, thus challenging the basis of policies that respond to or prioritize specific drug/bug combinations. Recognition of these principles significantly impacts current methods of policy making by risk assessment methods, as employed by the U.S. government and by the Codex Alimentarius. This approach does not reflect the current understanding of the role of resistance reservoirs and the multiple opportunities for exposures to antimicrobial resistance. There is, moreover, a lack of attention to the importance of bacteria as living organisms, which are fundamentally different from chemicals because living organisms are capable of expanding in number and potential risk and bacteria can transfer their toxic properties. This confounds the notion of threshold of resistance, which is utilized by the FDA and Environmental Protection Agency in their microbial risk assessments.

The goal of this review has been to provide a scientifically informed overview of the nature and extent of antimicrobial use in agriculture and the complex pathways by which this use can affect food safety, environmental quality, and community health risks, with a view to identifying feasible opportunities for prevention and harm reduction. A central concept is that of reservoirs of resistance within microbial ecosystems in which resistance can flow among organisms. The contribution of agriculture to these reservoirs is significant, and the consequences for public health are far-reaching.

HACCP: Hazard Analysis and Critical Control Point, a set of integrated guidelines and recommendations by the USDA and FDA to reduce health hazards associated with production of meat and poultry

SUMMARY POINTS

1. The use of antimicrobials as feed additives in food animal production is a major cause of increasing antimicrobial resistance in human pathogens. This use accounts for much of total drug production and is increasing worldwide.
2. Agricultural antimicrobial use results in the exposure of farmers, farm workers, rural communities, and the general public to antimicrobial resistant pathogens, as well as contamination of air, water, and soils near food animal production sites.
3. For public health, the most significant impact of agricultural antimicrobial use is the expansion of reservoirs of resistance because these genes can be transferred widely among microbial communities.
4. Reducing or banning agricultural antimicrobial use can reduce risks of antimicrobial resistance in the food supply.
5. Disposal of animal waste is a major route of environmental contamination by antimicrobials and resistance determinants.
6. Farmers and farm workers are at significantly increased risks of infection by antimicrobial-resistant bacteria; they may serve as entry points for the general community and transfers into health care settings.

FUTURE ISSUES

1. The role of agricultural antimicrobial use will be recognized as one of the most important drivers of increasing multidrug-resistant pathogens.
2. Research using advanced molecular methods will increasingly demonstrate the importance of reservoirs of resistance and gene flow as driving mechanisms for the spread of antimicrobial resistance from agricultural use into the environment and human populations.
3. Research will challenge current assumptions of public health policy that are based only on preventing resistance to clinically important antimicrobials in pathogens associated with serious human diseases.

DISCLOSURE STATEMENT

L.B.P. is a member of the following organizations, all of which have expressed concerns over the use of antibiotics in food animal production: American Society for Microbiology, Alliance for the Prudent Use of Antibiotics, and the Center for Livable Future.

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(a)

Figure 1

(*a*) Broiler chickens in a conventional facility. From hatching the chickens are housed in confinement, where there is no removal of waste during the 6- to 7-week growing period. Usually there is only superficial removal of the top layer of litter (decrusting) between flocks. Note the fans at the end of the building, as well as the overall lack of biocontainments. (*b*) Swine held in a conventional facility. There is a slotted floor over a cess pit, into which waste is collected with intermittent washing of the flooring. Animals are held in these conditions for several months until transport to slaughterhouses. From **http://www.usda.gov.**

(b)

Figure 1 (*Continued*)

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