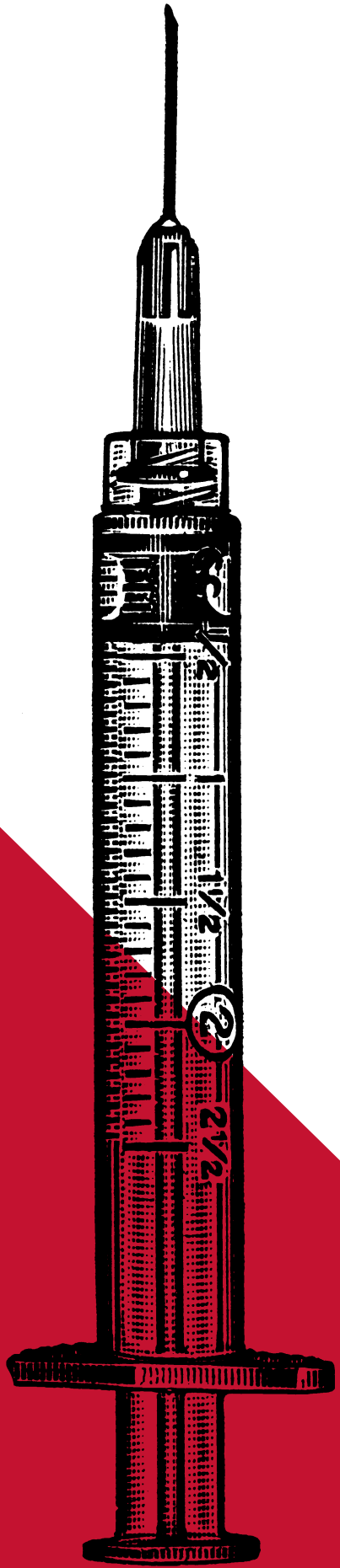
Antimicrobial Resistance and Human Health



A Report of the Pew Commission on Industrial Farm Animal Production

TOPIC:

Industrial Farm Animal Production, Antimicrobial Resistance and Human Health

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PCIFAP Staff Summary of Antimicrobial Resistance, and Human Health

The Pew Commission on Industrial Farm Animal Production was established by a grant from The Pew Charitable Trusts to the Johns Hopkins Bloomberg School of Public Health. The two-year charge to the Commission was to study the public health, environmental, animal welfare, and rural community problems created by concentrated animal feeding operations and to recommend solutions.

The problem of antimicrobial resistance (AMR) is growing in the United States and worldwide. The questions posed by the Commission were several: What is the scope of the AMR problem? What is the contribution of industrial animal agriculture to the problem? What is the history of and reasons for the use of antimicrobials in animal agriculture? What can or should be done about AMR, from the standpoint of animal agriculture?

It is difficult to calculate the scope of the AMR problem as it relates to animal agriculture because of the types of surveillance that are in place and the way that AMR is transmitted between bacteria. Only certain infectious bacteria are tracked by the Centers for Disease Control and Prevention (CDC) and state and local health agencies. Other types of bacteria, some infectious and some not, are not tracked, so only a certain cross section of the possible resistant microbes are seen by the tracking agencies. This is a problem because of the way resistance is spread between capable bacteria. These bacteria have a small "cassette" of genes that they transmit to each other in one piece. These cassettes can contain resistance to more than one antimicrobial, rendering formerly unexposed or nonresistant bacteria suddenly resistant to multiple kinds of antimicrobials. In addition, bacteria that are not tracked can still

transmit resistance elements. For example, many bacteria live in the human digestive tract or on human skin. These are not normally harmful (and are often helpful) and are not monitored. However, these harmless bacteria may still be capable of passing resistance to other bacteria that *are* harmful, or could then *become* harmful.

Exposure of bacteria to antimicrobials exerts a selective pressure, killing susceptible bacteria and allowing resistant ones to survive and reproduce. Sir Alexander Fleming, the father of antibiotics, described the phenomena of antibiotic resistance and suggested in the 1940s that extensive use of antibiotics would cause bacteria to develop resistance, and further pointed out that new antibiotics would be necessary to combat this on a regular basis. While it is difficult to measure what percent of resistance is caused by antimicrobial use in agriculture, as opposed to other settings, it can be assumed that the wider the use of antibiotics, the greater the chance for the development of antibiotic resistance.

Antibiotics were first used in the early 1950s as a growth promoter in food animals. As "resistance" developed and the antibiotics lost their ability to promote growth in the animal, new generations of antibiotics and antimicrobials were used. Today, estimates vary on the amounts of antimicrobials that are used in food animal production, as well as the amounts that are used nontherapeutically versus therapeutically.

Antimicrobials can save lives of humans and animals, but must be used judiciously given their biological properties. The greater the amount of antimicrobials present in the general environmental pool, the greater the

pressure for the development of resistance within many different bacterial populations. Animal agriculture industry representatives have recognized this in statements to the Commission. This report was commissioned to expand on these concepts.

By releasing this technical report, the Commission acknowledges that the author/authors fulfilled the request of the Commission on the topics reviewed. This report does not reflect the position of the Commission on these, or any other, issues. The final report of the Commission, and the recommendations included in it, represents the consensus position of the Commission.

Introduction

As a complex and important part of the US economy and landscape, the industrial production of animals for human food presents many issues of relevance to human health, including infectious pathogens. This background report will review one topic in depth: the role of industrial food animal production (IFAP) in the increasingly serious public health problem of antimicrobial resistance (AMR) in human pathogens. Industrial food animal production is defined in terms of both organization and methods: economically and structurally, IFAP is an integrated enterprise in which many aspects of food animal production are controlled by one entity; methodologically, it is a high throughput production system of animals for human food consumption, including poultry, swine, and cattle, in which animals of one species are raised in large groups in confinement in houses or enclosures under highly defined conditions of lighting, feed supply, and other aspects of animal husbandry (Martinez 2002).

Close contact between humans and the animals we grow for food has always been a source of transmissible pathogens between humans and animals among rural communities. Likewise, food-borne diseases have always been associated (if not recognized) with food products derived from animals (including meats, eggs, and milk) as a consequence of contamination throughout the processes of slaughter, butchering, storage, and preparation of consumable foods. In addition, domesticated animals have always (like humans) contaminated their environments —including fields and watersheds—through their wastes.

These traditional risks have been recognized for centuries. What is under consideration by the Pew Commission is how the *new* intensive methods of food animal production may both reduce and intensify these traditional risks as well as introduce new risks to both animal and human health. From this perspective, two aspects of IFAP are relevant to consider: the confinement of large numbers of animals for most and, in some cases, for all of their lifetimes, and new formulations of animal feeds.

Confinement of large populations of animals has several impacts on pathogen risks: first, close contact of large numbers of host animals facilitates the evolution and exchange of viruses, bacteria, and microparasites; second, stresses induced by confinement may increase the likelihood of infection and illness in animal populations; and third, these large populations produce large amounts of waste, which can exceed traditional methods of management. These impacts are not limited to the conditions of confinement and animal husbandry practices; however, they are in many cases exacerbated by practices common to the IFAP in the US.

Feed formulation influences pathogen risks because the feeds supplied to confined animal populations are significantly different from the unsupplemented foraged feeds of grains and grasses traditionally available to poultry, swine, or cattle (with relatively minimal supplementation by minerals or other substances). These feeds have been modified to meet the conditions of confined environments and also in response to research on animal growth and nutrition. The major goals in feed development have been twofold: to ensure healthy and uniform animals, and to reduce the costs of food animal production by reducing both the time needed to reach market weight for each species and the efficiency of feed conversion or the amount of food intake required to achieve this weight. In modern animal feeds, there is extensive recycling of animal fats and proteins through rendering, additions of industrial and animal wastes, and the addition of antimicrobials (AMs), including arsenicals, as feed additives (reviewed by Sapkota et al. 2007). *This latter innovation, which began more than 50 years ago in the US, has introduced a new public health risk into the context of food animal production,—the selection of antimicrobial -resistant bacteria.* Because of the importance of this issue for public health, its high profile, and its specificity for IFAP, this topic will be discussed in greatest depth in this background paper.

Problem Definition

Antimicrobial resistance is one of the major public health crises of our time. The discovery of AMs and their application to clinical medicine are among the triumphs of twentieth century pharmacology and medicine. This triumph has been eroded with the rise and spread of antimicrobial resistance, and it has been suggested that we are entering the "post antibiotic age" of medicine (Falagas and Bliziotis 2007). Antimicrobial-resistant bacterial infections now account for much of the problem of emerging infectious disease worldwide (Okeke, Laxminarayan et al. 2005; Velge, Cloeckaert et al. 2005; Seybold, Kourbatova et al. 2006; Erb, Sturmer et al. 2007; Laxminarayan 2007). In some cases, selection for resistance also results in more virulent strains, as in the case of *E. coli* and *S. aureus* (Ohlsen, Ziebuhr et al. 1998; Johnson, Kuskowski et al. 2005; Mora, Blanco et al. 2005; Stevens, Ma et al. 2007).

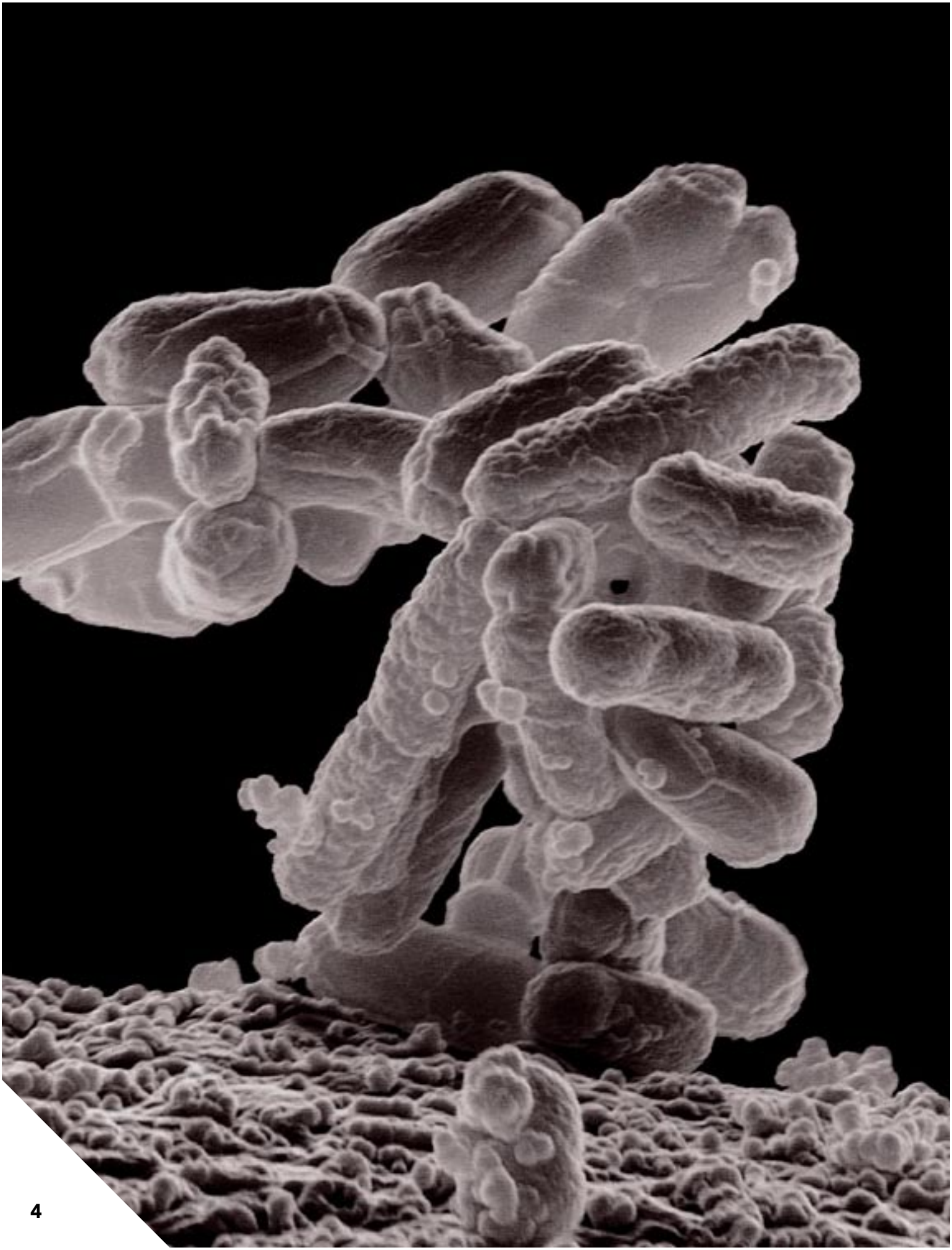
AMR infections are often more difficult to treat and are associated with increased morbidity and risks of death (Travers and Barza 2002). The burden of these poorly controllable infections on health care systems has been evaluated by the Organization for Economic Co-operation and Development (OECD) (OECD 2003), among others. A comprehensive review of the topic, including a discussion of method for computing loss of economic productivity, was recently published by Smith et al. (Smith, Yago et al. 2005). In addition to the direct costs of increased hospital stays and increased costs of treatment (which may increase costs of individual patient care by sixfold (Capitano, Leshem et al. 2003)), there are major cost impacts on the health care system to monitor and prevent spread of resistant infections, which have not been fully calculated (Laxminarayan 2007).

The scope and scale of AMR have been well characterized by Levy (Levy 1998; Levy and Marshall 2004). Information from the US government National Antimicrobial Resistance Monitoring System (NARMS) covers analyses of isolates from food, animals, and humans; this is available online (www.cdc.gov/narms). However, it is difficult to obtain data on trends in AMR from this source, given variability in sampling, or to test associations with antimicrobial use, or to draw associations between food, animals, and humans. Moreover, there are few studies in which the origin of food contamination is fully traced; in some cases for fruits and vegetables (as discussed below), this may be related to waste contamination and a secondary impact of antimicrobial use in food animals.

Longitudinal studies confirm the increasing severity of AMR (Erb, Sturmer et al. 2007). Specific analyses, using longitudinal data from clinical isolates collected by the same research group in the same setting, demonstrate increasing temporal trends in AMR in several pathogens, as shown on the following page in a study from Philadelphia (Lautenbach, Strom et al. 2004). Similar trends were observed for *P. mirabilis* and *K. pneumoniae*. These data underscore the increasing severity of the drug resistance crisis such that attention to all preventable sources of resistance pressure requires consideration.

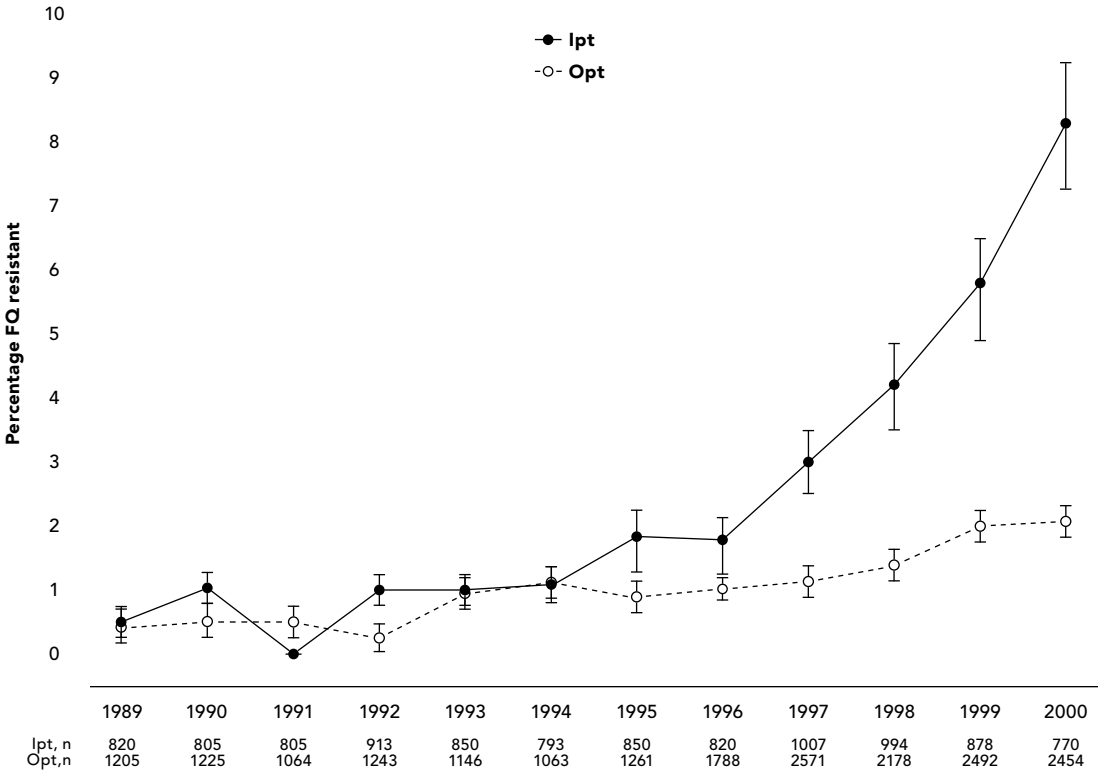
Estimates of AMR based upon analyses of persons with disease may significantly undercount the true prevalence of AMR exposure in the general population. In a study of *incoming* patients at a tertiary care hospital in Boston from 1998/9 to 2002/3, the likelihood of multidrug resistance in *E. coli* increased from 2% to almost 20% (Pop-Vicas and D'Agata 2005). A major study of *E. coli* isolated from newly hospitalized subjects not diagnosed with infectious disease reported that 20% of the isolates were resistant to fluoroquinolones, approximately twice the rates found by the same group in studies of hospital patients with diagnosed bacterial disease (Lautenbach, Tolomeo et al. 2006). Moreover, analyses based solely upon testing of pathogenic bacteria may miss the significance of increasing "reservoirs of resistance" in commensal (or nonpathogenic) organisms (Alekshun and Levy 2006). This broader view of microbial ecology and gene flow is an important issue for both science and policy (Summers 2002).

The issue for consideration by the Pew Commission is to consider the appropriate policy response to an evaluation of the contribution of antimicrobial use in food animal production to the national and global crisis of antimicrobial resistance. Because of its importance to public health, antimicrobial resistance (AMR) is one of the most important public health issues related to IFAP, recognizing the difficulty in assessing the associations between food animal production and AMR or to determine the fraction of AMR infections



that are attributable to food animal production. To assist the Commission in this task, this White Paper provides an overview of AMR in the context of microbiological issues in IFAP and then presents a brief review of the evidence base relevant to the issue of AMR and IFAP. The discussion includes information from the US and other countries; a global perspective is appropriate since AMR bacteria and resistance genes can be transferred globally through the movement of people, food, animals, and via wind and water.

Figure 1: Prevalence of fluoroquinolone resistance in *E. coli* isolates from inpatients (Ipt) and outpatients (Opt) in Philadelphia, from 1989 to 2000. Approximately 60% of the samples were from inpatients and 40% from outpatients over this period.



Problem Definition:

Antimicrobial[1] resistance (AMR) is defined as changes in microbial biology that occur in response to antimicrobials and that reduce or block the effectiveness of drugs, chemicals, or other agents to cure or prevent infections. AMR is determined by *in vitro* tests of strain-specific cultures in which survival of the bacterial isolates is tested under conditions of increasing AM concentrations. The *in vitro* concentration at which bacterial survival is significantly affected is then compared to benchmarks that signify impacts on clinical efficacy; thus the MIC (minimum inhibitory concentrations) values are set by the NCCLS (National Committee for Clinical Laboratory Standards) to reflect a level of resistance that is likely to compromise the efficacy of AM treatment in an infected patient (Ginocchio 2002; NCCLS 2006).

[1]antimicrobial refers to a category of agents, including both natural compounds (sometimes referred to as antibiotics) as well as synthetic chemicals

Microbiological Issues in Industrial Food Animal Production

At the outset, it should be recognized that the production of animals for human food has always involved public health risks related to microbial exposure. In addition to the traditional risks of disease from microbial contamination of food, IFAP has introduced a new risk related to practices in animal feeding.

From time immemorial, animals have been the source of some of the pathogens that can cause diseases in human populations (Orriss 1997; Bengis, Leighton et al. 2004; Fevre, Bronsvoort et al. 2006). In the process of domesticating animals into herds as livestock, we have over time created denser populations, in closer proximity to humans, with accompanying problems of waste management and increased likelihood of animal-human-animal microbial exchange and for pathogen mutation. These traditional risks have been recognized for centuries. We continue to be challenged by newly emerging zoonoses such as transmissible encephalopathies (mad cow disease), SARS, Nipah virus infection, and avian influenza—all diseases caused by pathogens that are predominantly carried by animals we raise or hunt for consumption.

Risks of zoonotic disease are greatly intensified by the changes in the scale of animal husbandry (Fevre, Bronsvoort et al. 2006). Large numbers of animal hosts in close contact facilitate the exchange and speed up the evolutionary transformation of pathogens (Saenz, Hethcote et al. 2006). Because of the confined conditions of IFAP, animal health and the health of humans involved in animal husbandry are at risk due to intensified exposures to a range of zoonotic pathogens, including macro- and microparasites, viruses, and bacteria. In addition, domesticated animals held in confinement are unavoidably exposed to their wastes. Farmers and farm workers in the confined spaces of animal houses containing thousands of animals are at increased risks of exposure to microbes and biotoxins. Air emissions from animal houses can release pathogens from the house into the ambient environment. Finally, and probably of greatest importance to public health, these large populations of animals produce large volumes of waste, which, because of the regional intensification of production, greatly exceed the capacity of traditional methods of management through their use as fertilizers of nearby soils. There are no requirements in the US for predisposal treatment of animal wastes (such as composting under controlled conditions). Pathogens, including bacteria and viruses, survive in animal wastes for extensive periods of time and can be recovered in soils that have been "amended" by these wastes (Gerba and Smith 2005).

Likewise, human food products derived from animals (including meat, eggs, and milk) have always presented microbial risks to human health. Slaughterhouses, until recently, were grossly unhygienic as described in 1906 by Upton Sinclair—rivaled probably only by hospitals prior to the 20th century as breeding grounds for virulent pathogens. From farm to market, there was little control over microbial contamination (and replication) at any stage. Meat products were sold in markets with no refrigeration, preservation, or containment; in addition, live animals were often sold at markets where slaughtering occurred at the place and time of sale—as it still does in many countries of the world.

With the recognition of the food-borne origin of many infectious diseases, and the realization that improvements in hygiene at the farm were essential to the control of animal diseases as well, great advances have been made in hygienic practices since the early 20th century, particularly with the advent in 1995 of a new philosophy of "farm to fork" and a systems approach to hygiene called Hazard Analysis and Critical Control Point (HACCP) in the US (Billy and Wachsmuth 1997). The endorsement of these principles by national and international agencies around the world and the adoption of food and phytosanitary standards by the World Trade Organization have in many cases extended these practices internationally. In an age of the global market basket, where consumers in the US purchase foods from international sources, this is a critical element in food safety (Naimi, Wicklund et al. 2003).

The application of HACCP in animal slaughtering and processing has reduced many risks of food contamination; however, new risks may not be effectively managed by older approaches (Morris 2003). While modern food processing plants have been greatly enhanced by the effective application of HACCP principles, the cost of failure is magnified by their high throughput and the highly efficient national distribution system of food, both of which facilitate the widespread propagation of food-borne risks.

The Science of AMR

Understanding the scientific events in antimicrobial resistance is important to an evaluation of the contribution of IFAP to this public health issue. *The first scientific principle is that from the perspective of fundamental biology and evolution, selection of AM resistance in response to exposure to AMs is inevitable; moreover, the prevalence and rates of resistance in bacteria are proportional to the degree of exposure to antimicrobials.* Microbes have evolved highly effective mechanisms to respond to environmental pressures, such as temperature change, oxygen concentrations, nutrient availability, and toxin exposure, including antimicrobial agents (AMs). Thus, exposure of bacteria to sublethal concentrations of AMs inevitably results in the selection of resistant strains, and under conditions of continued AM pressure, resistant strains will propagate and spread. Because most AMs are derived from natural products, bacteria have acquired, through evolution, biochemical responses to resist AM attack; and AMR can be observed in the absence of any deliberate human use of AMs. Because of the speed of bacterial reproduction, these changes can be expressed with great efficiency. Thus, through an evolutionary process of microbial response to the pressure of antimicrobial agents, resistance is an inevitable consequence of antimicrobial use, and it is not surprising that observations of resistance came soon after the identification and isolation of the first natural antimicrobial substance.

The second important scientific principle is that bacterial resistance to antimicrobials involves both genetic and nongenetic changes, of which the former have more serious implications for public health. Nongenetic changes typically involve enhanced activity or upregulation of physiological processes such as membrane transport pumps that extrude harmful agents, including antimicrobials. However, the capacity of these response mechanisms is limited, and usually bacteria express only low-level resistance as a consequence. Genetically encoded changes are more serious because these can usually confer higher-level resistance to specific agents and because they can be transferred among bacteria. Since most AMs are derived from fungal and other natural sources, bacteria have evolved in the presence of these toxins (Wright 2007), and it is therefore not surprising that, even in the absence of antimicrobial pressure, there are sources of resistance encoded by specific genes within the community repertoire of bacterial genomes. In the presence of selection pressure by an AM, bacterial populations quickly evolve to a resistant phenotype (Smith, Harris et al. 2002; Tenover 2006). The speed of this evasion process is hastened by two factors: the rapid rate of bacterial reproduction and the ability of bacteria to transfer genetic information among organisms even across broad phylogenetic categories.

Resistance spread. *The third important scientific principle is that bacteria can share resistance through the transfer of genes that encode resistance.* Resistance is a trait expressed by specific bacteria and can result from new mutations that occur spontaneously in bacteria due to their rapid rate of cell division or from the selection of resistance genes already present within a bacterial colony. In the presence of antimicrobial pressure, strains that express resistance traits through spontaneous mutation are favored in terms of survival, and they will rapidly supplant susceptible strains in microbial populations. But in addition, and potentially of greatest significance for

public health, bacteria have a third mechanism of rapid evolution towards a resistant phenotype through the sharing of genes that encode resistance. By this process, resistance can be propagated within and among bacterial strains, species, and genera, including commensals (nonpathogenic) and pathogens, by mobile genetic elements including plasmids, transposons, integrons, gene cassettes, and bacteriophages. In contrast to chromosomal-based resistance determinants, these transfers account for more than 95% of antibiotic resistance (Nwosu 2001). These events have been detected in resistant *E. coli* isolated from consumer meat products (Sunde and Norstrom 2006). This finding is of particular concern because integrons can transfer multiple resistance genes at a time (Zhang, Lin et al. 2003; Zhang, Sahin et al. 2006).

Bacteria operate at the community level in terms of responding to stress, and therefore they have developed mechanisms to share genetic information, often across broad species divisions. Because it is the community response that is crucial (Summers 2002; Heuer, Hammerum et al. 2006), genetic change in response to AM pressure is not dependent upon reproduction or cell division, as is the case for most higher organisms. Bacteria can exchange genetic information across broad classes by several mechanisms, as shown on the following pages. These mechanisms are in many cases enhanced by stressors such as AM pressures that can enhance the rates and efficiency of genetic recombination.

Microbiologists now refer to "reservoirs of resistance" in recognition of the fact that it is the *community* of genetic resources that determines the rate and propagation of resistance (Salyers and Shoemaker 2006). *The existence of these "reservoirs of resistance" has a considerable impact on how we conceptualize and deal with the challenge of AMR associated with food animal production.* Until recently, the focus of public health concern was on specific patterns of resistance in specific pathogens of concern, such as quinpristin/dalfopristin (Q/D) resistance in *Enterococcus faecium*. However, since genes for these and other resistance traits can be exchanged from a commensal or nonpathogenic species, such as *E. coli* in the gut of a patient being treated for campylobacteriosis, the "one bug one drug" definition of the scope of concern is increasingly recognized as inadequate (Summers 2002; Summers 2006). The contribution of agricultural AM use to environmental reservoirs of resistance has been documented for both poultry and swine (Nandi, Maurer et al. 2004; Jensen, Jakobsen et al. 2006).

The incorporation of these new perspectives into policy and risk assessment is of great importance. Aspects of this issue (such as the importance of commensals) have been considered by the FDA in its rulings on fluoroquinolones (Bartholomew, Vose et al. 2005). It is not clear how this will be utilized in evaluating other related issues.

Persistence of resistance. *The fourth important scientific principle is that resistance may continue even after AMs are no longer present.* As noted above, the microbial community can serve as a resource, or reservoir, of resistance genes. Earlier theories of microbial genetics assumed that this was unlikely to be a long-term phenomenon since the expression of resistance was thought to cost the organism (in terms of increased energy requirements, susceptibility to other stressors, or decreased reproductive rates) such that in the absence of AM pressure, its occurrence was rare. Current research has cast doubt on the concept of a "cost of resistance" (Salyers and Amabile-Cuevas 1997). While the prevalence of resistant strains markedly decreases when antimicrobials are no longer present, this is not always the case for several reasons. First, in some cases, resistant organisms may outcompete susceptible strains: for example, *Campylobacter jejuni* that are resistant to fluoroquinolones have greater ability to colonize the guts of animals, resulting in a selective advantage over wild strains in competing for the ecological niche of the host.

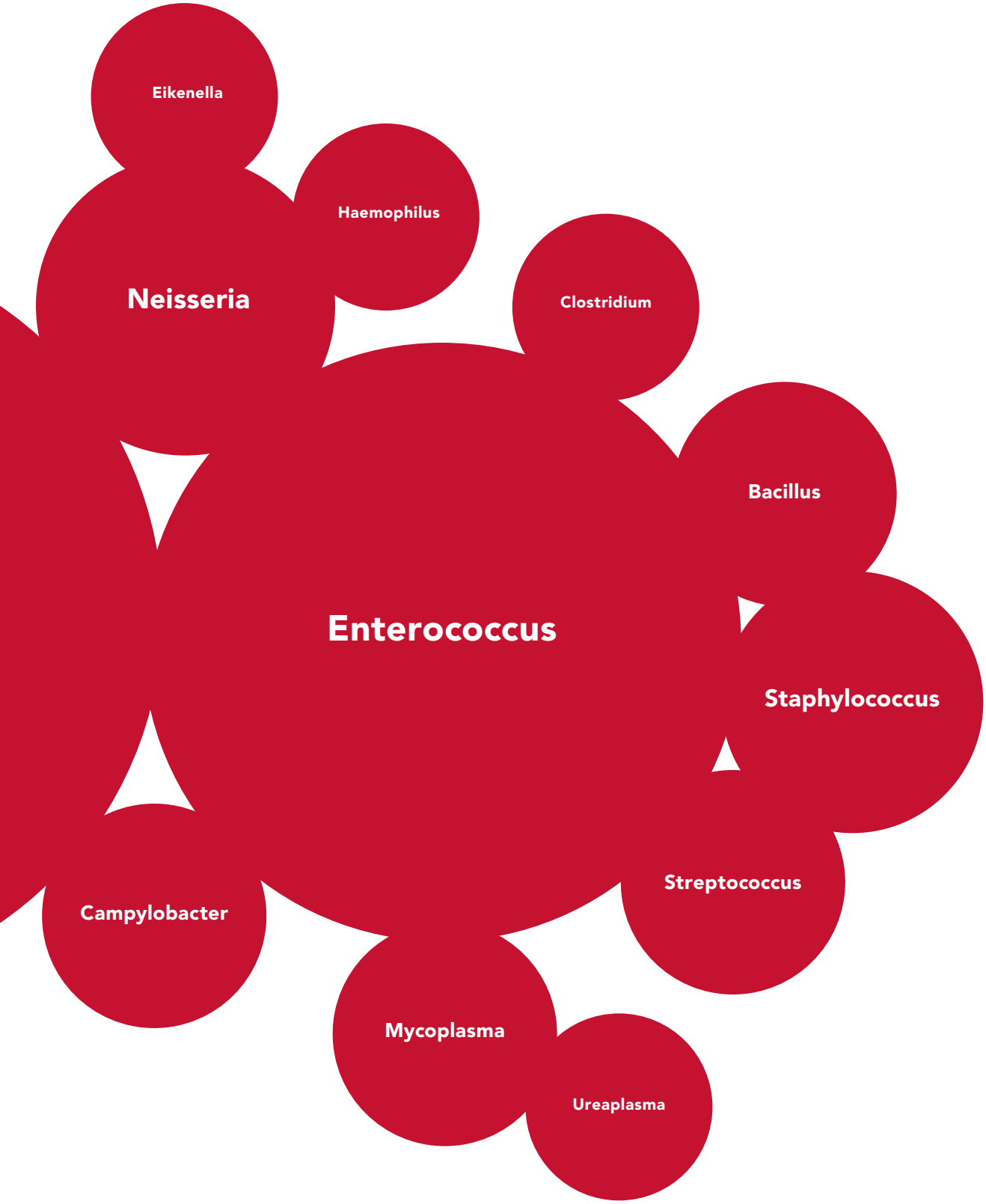
Second, resistance may also persist due to the clustering of resistance genes on the same transposable elements such that eliminating only one antimicrobial may not reduce the prevalence of the cluster (Aarestrup, Agerso et al. 2000). Such events have been observed in the setting of swine farms (Gebreyes and Thakur 2005). Third, 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 (Levin, Perrot et al. 2000; Wright 2007). Finally, it may be the case that AM pressure is now so widespread, due to multiple uses of AMs for many purposes, that there is a community benefit of maintaining the genetic reservoir of resistance such that the frequency of genetic mutations encoding resistance has increased.

Empirical evidence supports this: even after the removal of AMs from animal feeds, researchers in Europe have reported on the persistence of resistant pathogens in animal houses, wastes, and food products from several types of food animals (Sorum, Johnsen et al. 2006). Similar findings are reported by Price et al. (Price, Johnson et al. 2005; Price, Graham et al. 2007; Price, Lackey et al. 2007) on the continuing prevalence of fluoroquinolone-resistant *Campylobacter* in chicken products sold in US supermarkets, after voluntary actions by producers and the FDA ban on fluoroquinolone use in poultry production.

The History of Antimicrobial Resistance

Bacteria acquired the genetic and physiological tools to resist antimicrobials long before scientists isolated and identified these natural agents in the early 20th century (Wright 2007). Because many antimicrobials are natural products of fungi and other organisms, bacteria have evolved these mechanisms over millions of years, and thus it is possible to detect AMR in bacteria that have not been exposed to our uses of AMs in medicine or agriculture. Antimicrobial resistance was evident from the early history of penicillin. The isolation of the first naturally occurring antimicrobial (penicillin) in the 1930s ushered in a major change in clinical and veterinary medicine, and food animal production as well. With the discovery of natural antimicrobial compounds, the balance seemed at last to be tipped against the pathogens, but victory was short-lived. Even in the laboratory, Fleming observed that his bacterial cultures quickly demonstrated resistance to penicillin, and in 1945, he warned that the misuse of penicillin could lead to selection of resistant forms of bacteria (Levy 1998). Fleming suggested that resistance to penicillin could be conferred in two ways—either through changes in the bacterial cell wall, which was the target of penicillin action, or through the selection of bacteria expressing mutant proteins capable of degrading penicillin. Unfortunately, in the early period of its use, penicillin was available orally to the public without prescription until the mid 1950s. By 1946, one hospital reported that 14% of the strains of staphylococci isolated from sick patients were penicillin resistant (Barber, Hayhoe et al. 1949). By the 1950s, this same hospital reported that 59% of the strains of staphylococci were penicillin resistant.

Figure 2: Genetic exchange among bacterial species (Adapted from Levy and Miller, 1989).


Eikenella
Haemophilus
Neisseria
Clostridium
Bacillus
Enterococcus
Staphylococcus
Streptococcus
Campylobacter
Mycoplasma
Ureaplasma

The Role of IFAP in AMR

All uses of AMs contribute to the likelihood that bacteria will be resistant to AM drugs. The focus on IFAP is justified by three factors:

- the nontherapeutic and prophylactic uses of antimicrobials as feed additives (as distinct from therapy; see below) set the stage for selection of resistant strains;
- the antimicrobial drugs currently used as feed additives represent many of the critically important classes of AMs, and resistance to one AM results in resistance to all drugs in the same class;
- the amounts of AMs utilized in modern food animal production dwarf the amounts used in clinical and veterinary medicine.

A wide range of AM drugs are permitted for use in food animal production in the US and many other countries (Sarmah, Meyer et al. 2006). As shown in Table 1, these drugs represent all the major classes of clinically important pharmacotherapies, from penicillin to third generation compounds. In addition, arsenicals are also permitted for use as growth promotants and for enhancing skin quality (Roxarsone and arsanilic acid). In some cases, new AMs have been licensed for agricultural use in advance of approvals for clinical use. In the case of quinpristin-dalfopristin (virginiamycin), this practice resulted in the emergence of resistance prior to eventual clinical registration, thus demonstrating how feed additive use can compromise the potential utility of a new tool in fighting infectious disease in humans (Kieke, Borchardt et al. 2006). For existing drugs, Smith et al. (Smith, Harris et al. 2002) 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, Denmark, European Union (EU), Canada, and the United States (Data from Sarmah et al. 2006).

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
		Monensin (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
		Spiramycina	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
	Lincosamides	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

Table 1. Antimicrobials registered for use as feed additives in Australia, Denmark, European Union (EU), Canada, and the United States (Data from Sarmah et al. 2006).

Countries	Group/Class	Antimicrobial	Usage
Canada	Polypeptides	Bacitracin	Chicken, pigs, turkey
	Glycolipids	Bambermycin	Turkey, breeder chickens
	Quinoxalines	Carbadox	Pigs
	Others	Arsanilic acid	Broiler, turkey, pigs
USA	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
	Polyethers (ionophores)	Monensin	Cattle
		Lasalocid	Cattle
	Penicillins	Penicillin	Poultry
	Quinoxalines	Carbadox	Pigs
	Streptogramins	Virginiamycin	Swine
	Sulfonamides	Sulfamethazine	Cattle, pigs
		Sulfathiazole	Pigs

Many of these antimicrobials are widely used in US livestock production, as shown in the figures below from the USDA (USDA/APHIS 2003). The most recent data reported to be available to the USDA are from 1994–5. Depending upon stage of growth, feeds with antimicrobials were supplied to between 38% and 70% of pigs in the US and between 30% and 58% of cattle raised in feedlots (with higher percentages in the larger operations). A broad range of antimicrobials was supplied to these cattle, with 45% of operations using chlortetracycline and 42% using tylosin. Similar data were published on antimicrobial use in poultry, based upon reporting by poultry production units (defined as a set of farms served by one feed mill) as shown in Figure 2D (Chapman and Johnson 2002).

Figure 2A. Use of antimicrobials in swine production, by route of administration and by type of pig (Data from USDA/APHIS 2003).

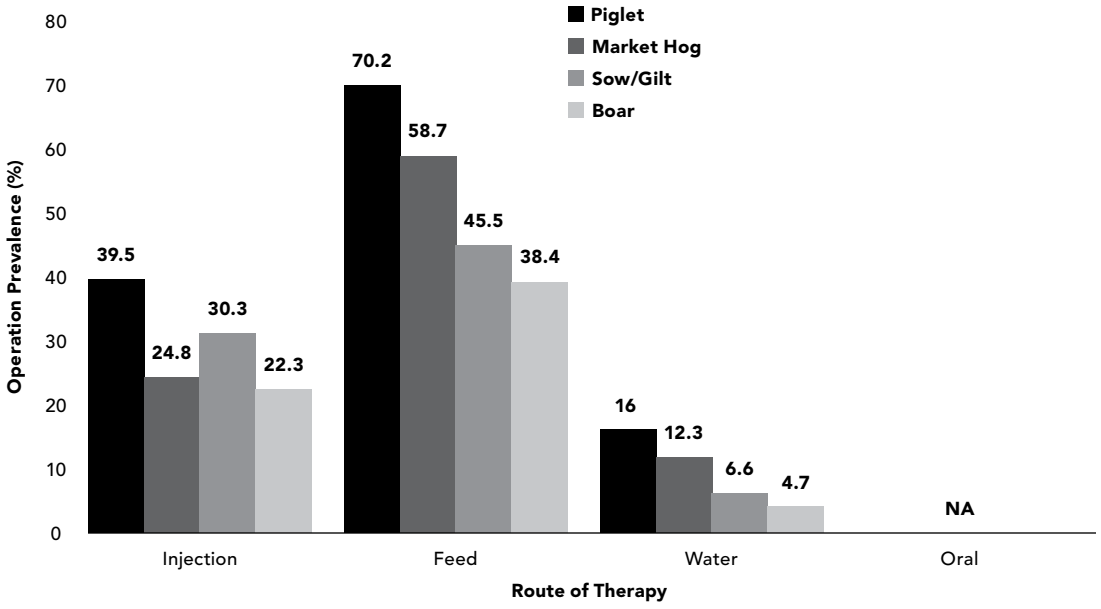


Figure 2B. Antimicrobials used in feed or water for cattle fed in feedlots (Data from USDA/APHIS 2003).

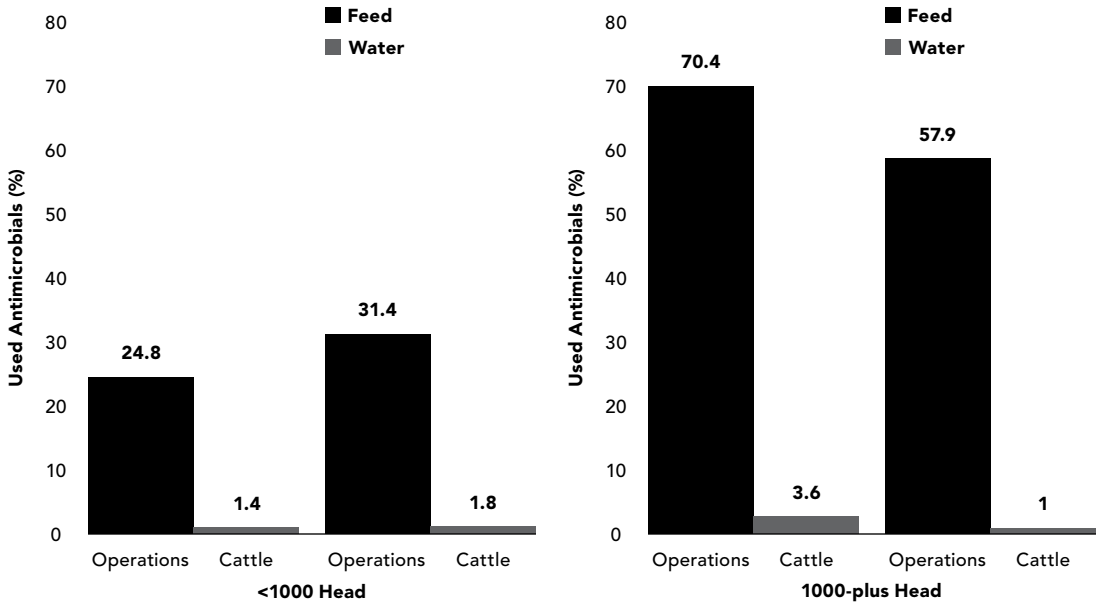


Figure 2C. Types of antimicrobials utilized in feed or water supplied to cattle in larger feedlots (1000-plus head) (Data from USDA/APHIS 2003).

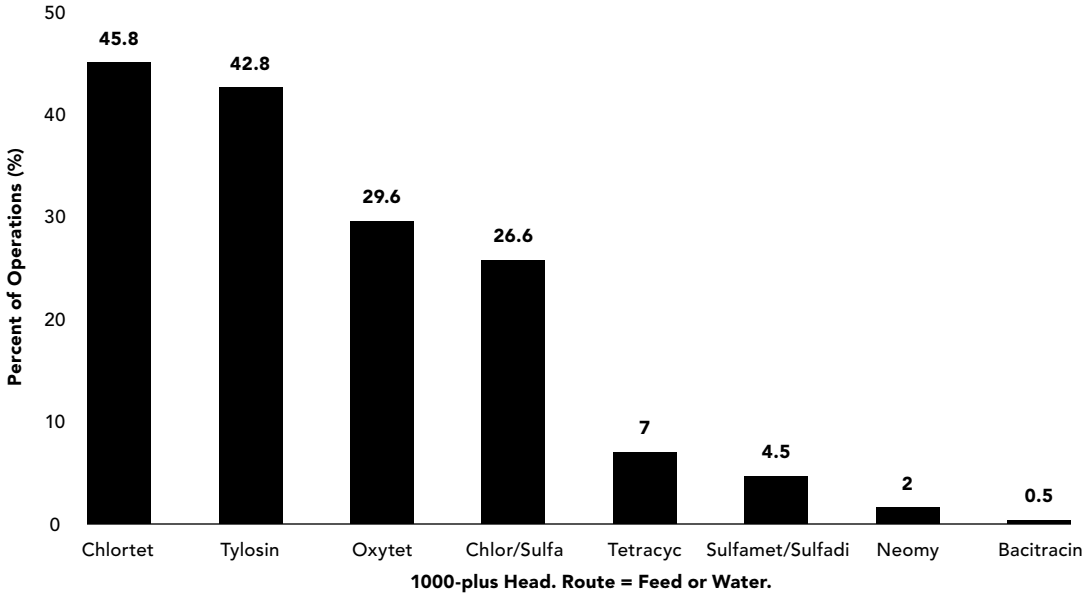
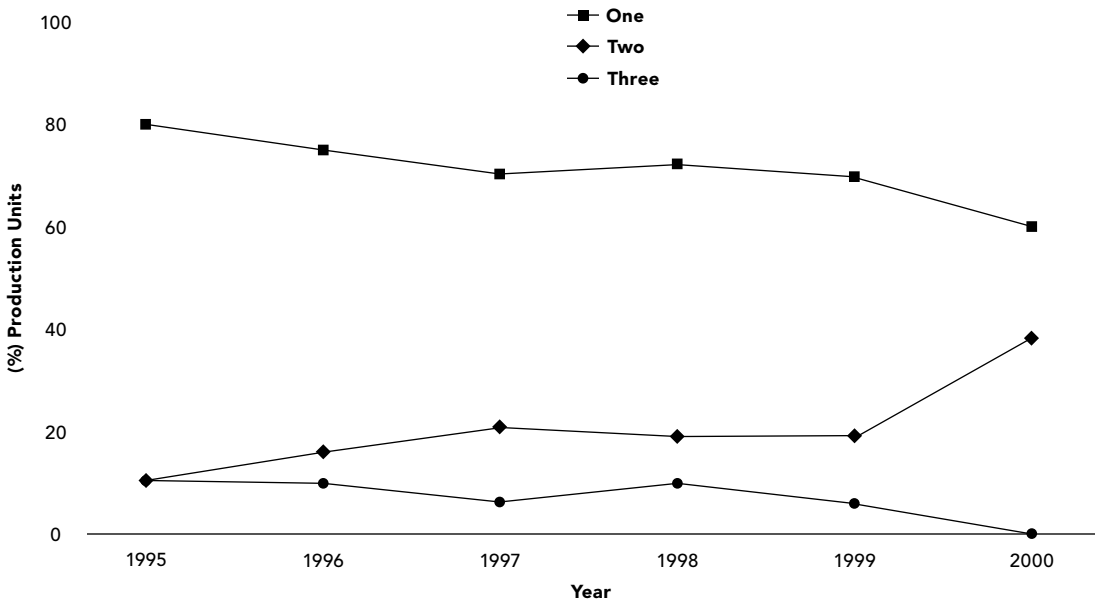


Figure 2D. Average reported use of antimicrobials as feed additives in broiler poultry production, from 1995–2000 (Data from Chapman and Johnson 2002).



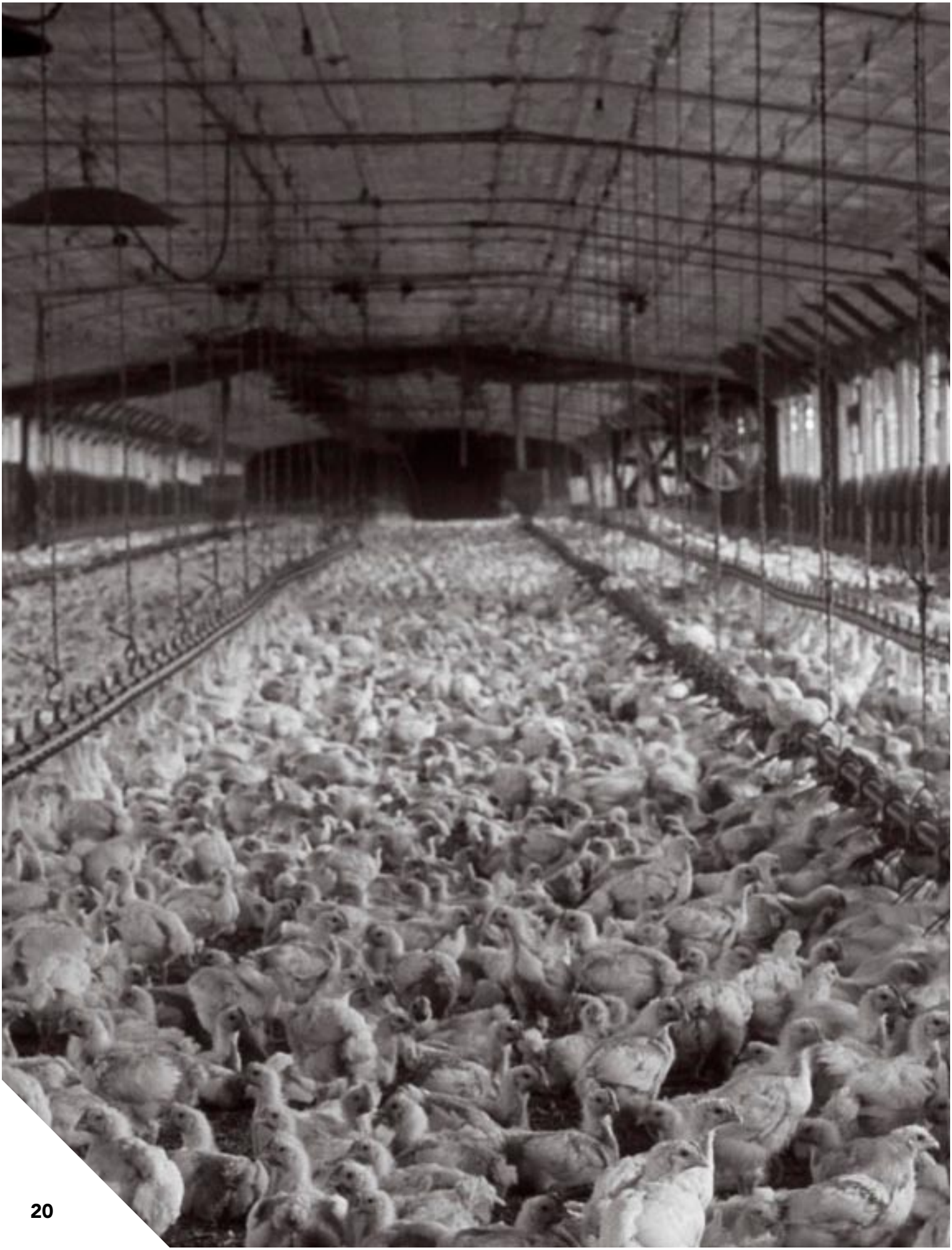


Table 2. Prevalence of multiple antimicrobial use in broiler feeds (Chapman and Johnson 2002). BAC = bacitracin; BAM = bambermycin; LIN = lincomycin; TYL = tylosin; VIR = virginiamycin.

One antibiotic		Two antibiotics		Three antibiotics	
Antibiotic	**%PU**	**Antibiotic**	**%PU**	**Antibiotics**	**%PU**
BAC	13.7	BAC, VIR	37.8	BAC, BAM, VIR	5.0
BAM	3.0	BAC, BAM	16.0	BAC, BAM, LIN	1.8
LIN	3.1	BAC, LIN	9.3	FLA, VIR, LIN	0.7
VIR	2.0	BAC, TYL	3.1	BAC, VIR, LIN	0.6
–	–	VIR, BAM	2.5	–	–

As with cattle, several antimicrobials were used in feeds for broilers, with 37% reporting use of bacitracin and virginiamycin, as shown in Table 2 above (Chapman and Johnson 2002).

There is a lack of publicly available validated information on the volume of AM use as feed additives in IFAP in the US and many other countries. In the EU, several countries collaborate in data collection and publication through the Veterinary Antibiotic Usage and Resistance Surveillance Working Group (VANTURES). However, there are still limitations on data availability in the EU; for example, in the Netherlands, information on antimicrobials in feeds for growth promotion is not under veterinary authorization and not disclosed by feed manufacturers (MARAN 2002). In contrast, Denmark has maintained a publicly available national database of AM use for more than 10 years (DANMAP 2000). In the US, there are unresolved debates over the proportion of AM use in agriculture for this purpose, as compared to human and veterinary medicine. Most estimates suggest that nontherapeutic, agricultural use accounts for between 60% and 80% of total AM production in the US (Mellon et al. 2001) and, until recently, in the EU as well (Teuber 2001). These estimates are contested by industry sources (e.g., Animal Health Institute in the US). Global use is increasing as the IFAP model of production is adopted in other countries (Sarmah, Meyer et al. 2006). Information on the amounts of AMS utilized as feed additives in the US is not available since feed formulations are considered confidential business information under US law. Because of the relatively greater transparency of the Union of Concerned Scientists (UCS) calculation methods, some authorities have utilized those estimates (e.g., US EPA, APUA, etc.), but validated use information from the industry would be of great value in evaluating the relative importance of different uses of AM in agriculture as well as in clinical and veterinary medicine. *Because of the importance of obtaining reliable and accurate information on AM use in agriculture, the PCIFAP may consider recommendations to improve access and transparency of data on this topic.*

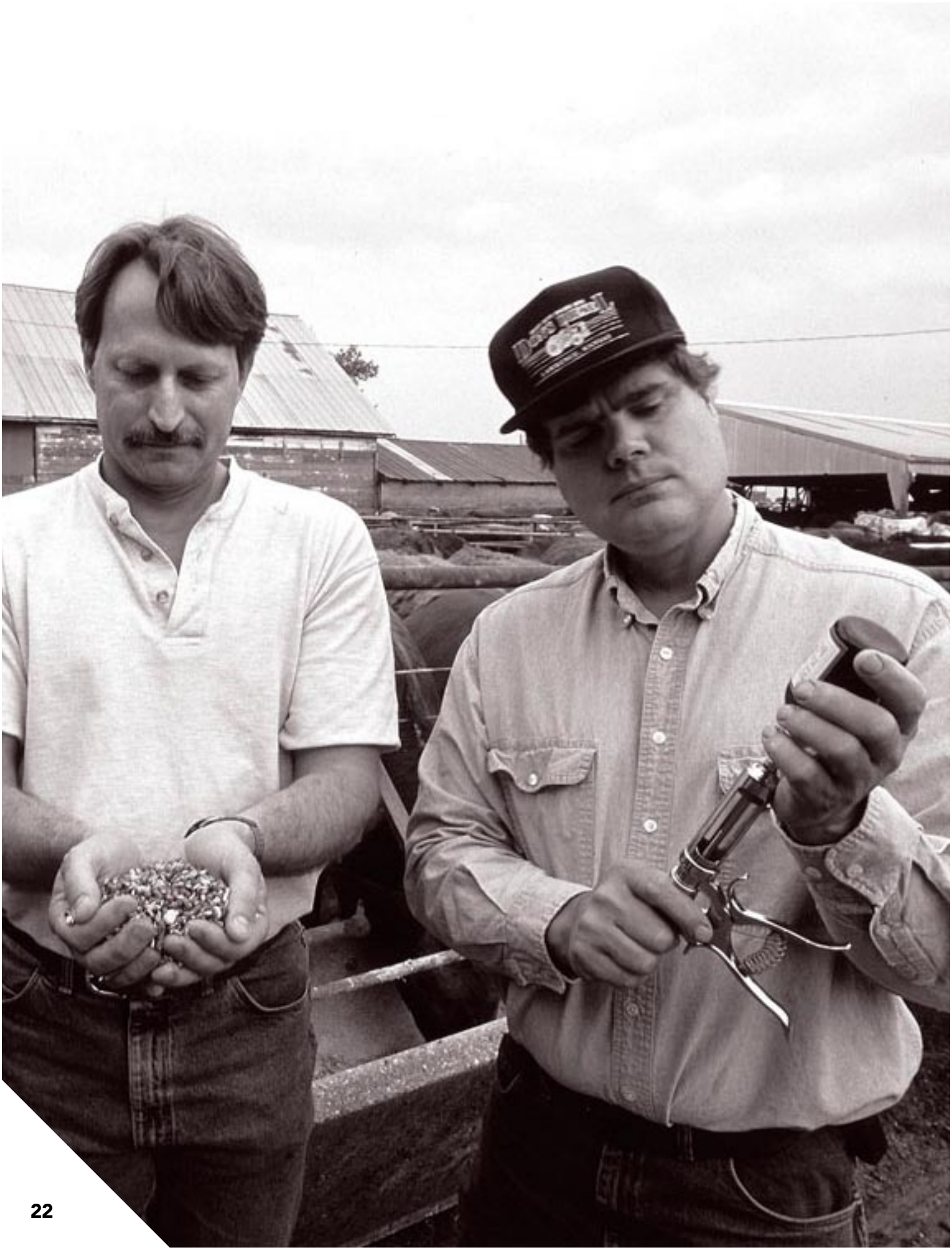
The Union of Concerned Scientists, a nongovernmental organization, utilized the registration data published by the FDA and animal census figures from USDA (Mellon et al. 2001). The Animal Health Institute, an industry trade organization, published data based upon information from its members. These two estimates are shown in Figure 3.

One source of controversy arises from the problems in distinguishing between therapeutic and nontherapeutic uses. The use of AMS for treatment and prevention of animal diseases is an important component for ensuring the health and well-being of domesticated animals. However, the addition of antimicrobials to feeds is claimed to be prophylactic as well as growth promoting. The World Organisation for Animal Health (OIE), NCCLS, and others divide medical use into different categories of use by purpose as shown in Table 3.

There is some controversy over the validity of distinctions made in practice between prophylaxis and metaphylaxis and concerns that growth promotion is sometimes claimed to be prophylactic (see, for instance, (Phillips, Casewell et al. 2004)). Interestingly, the World Health Organization (WHO) in its report on antimicrobial resistance and agricultural antimicrobial use does not include metaphylaxis in its list of definitions (surveillance standards for AMR downloadable from http://www.who.int.emc).

Like appropriate clinical use of AMS, the appropriate use of antibiotics in veterinary medicine, to treat or prevent disease, can also contribute to AMR. There has been some discussion as to whether the veterinary need for AMS is increased by the conditions of confined animal husbandry. As discussed in detail in other Commission reports, broiler poultry and other birds raised for meat are customarily housed on bedding or litter that is not cleaned after each flock; swine raised in confinement are often housed on slatted floors above cesspits that hold their wastes; dairy and beef cattle are also sometimes exposed to their wastes in feedlots and milking barns.

It is the use of AMS in feeds for food animal production that has raised the greatest concerns in terms of driving selection for resistance as discussed above. *The key differences characterizing use of AMS as feed additives are: addition of AMS in the absence of specific medical purpose; administration in feeds provided ad libitum and thus without control over dose; and application at rates that result in exposures that are insufficient to kill bacteria.* The focus of public health concerns on AMS in animal feeds is based on the following: first, in many cases, AMS are administered throughout the lifetime or for most of the lifetime of the animals; second, AMS are delivered to the entire flock



through additions to feed; third, the concentrations of AMs are sufficiently low and uncontrolled such that doses to individual animals are likely to be subtherapeutic; and fourth, the use of AMs as feed additives involves many of the major classes of AMs useful in clinical and veterinary medicine. There is evidence to indicate that this use compromises the efficacy of AMs used in the US and throughout the world, and for this reason, the WHO, together with the Food and Agriculture Organization (FAO) and OIE, convened several international expert work groups and conferences since 1997 on the issue of agricultural antimicrobial use and AMR. At that time, an expert work group made the following recommendations:

- the use of any antimicrobial growth promoters should be terminated if they are used as human therapeutics, or known to select for cross-resistance to antimicrobials used in human medicine;
- no antimicrobial should be administered to a food animal unless it has been evaluated and authorized by competent national authorities;
- a systematic approach aiming at replacing growth-promoting antimicrobials with safer nonantimicrobial alternatives should be established;
- national authorities should maintain records of export/import figures of bulk chemicals with potential antimicrobial use as such information is vital for quantitative assessments of the medical risks related to the use of antimicrobials in livestock production;
- national authorities should continue to monitor and review levels of antimicrobial agent residues in food from animal sources and ensure compliance with national standards.

(surveillance standards for AMR downloadable from http://www.who.int.emc).

These principles have been repeatedly referenced, for example, in the WHO Global Strategy for the Containment of Antimicrobial Resistance (2001; WHO/CDS/CSR/RDS 2001.2a).

Figure 3: Estimated antimicrobial use in food animal production (in millions of pounds).

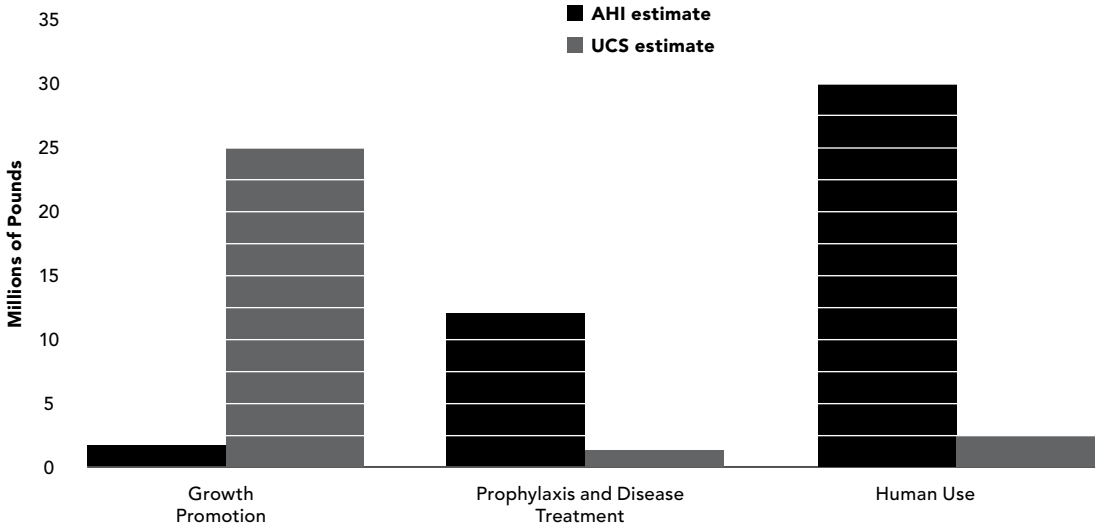


Table 3: Definitions of antimicrobial use in veterinary medicine.

Therapy:	administration to an animal or animals showing clinical disease
Control:	administration to a group of animals in which rates of disease or death have exceeded a baseline
Prophylaxis:	administration to healthy animals at risk of disease but without signs of disease or infection
Metaphylaxis:	the timely mass medication of large groups of animals in the presence of disease in some animals
Growth Promotion:	administration, usually in feed, to improve growth or other physiological performance

How did AMs enter industrial food animal production?

The history of the use of AMs in IFAP has been examined by several, including a recent paper by Graham et al. (Graham, Boland et al. 2007). Most accounts indicate that wastes from pharmaceutical fermentation processes were utilized as protein sources in feeds late in the 1940s (NRC 1999). Empirical observation, followed by relatively limited experiments (Stokstad and Jukes 1958-1959; Jukes 1979), indicated that these unpurified additions appeared to enhance growth rates without increasing food consumption. Further experimentation demonstrated that the observed effect was due to AMs, and from the period from 1947 to 1955, there was active investigation of different AMs for this valued property. It is noteworthy that even in the early literature two phenomena were observed: increased hygiene produced the same results in terms of productivity, and the efficacy of each AM appeared to attenuate over time. For that reason, the food-producing industry has sought, and obtained until recently, permission from regulatory authorities in the US register many AMs for use as growth promoters.

Associations between IFAP AM use in feeds and AMR in human pathogens

Extensive literature exists on the prevalence of antimicrobial resistance in both commensal and pathogenic bacteria in association with AM use in food animal production. The major papers on this topic have been reviewed in the annotated bibliography provided to the Commission. There is substantial evidence that the use of AMs in animal feeds is associated with the presence of AMR bacteria in the animal environment, that is, in the guts of animals (including cows, pigs, and poultry), in their feces, and in containers and confinements in which they are held (Mathew, Upchurch et al. 1998; Aarestrup, Agerso et al. 2000; Joseph, Hayes et al. 2001; Wegener 2003; Hayes, English et al. 2004; Boerlin, Travis et al. 2005; Berge, Moore et al. 2006; Donaldson, Straley et al. 2006). The causal role of AMs has been clearly demonstrated in studies where dairy cattle, pigs, and poultry have been raised with and without AM additives to feed (Aarestrup, Seyfarth et al. 2001; Halbert, Kaneene et al. 2006; Ray, Warnick et al. 2006). AMR bacteria have been isolated from environmental samples in and near production facilities, including air, water, and soils (Chee-Sanford, Aminov et al. 2001; Nwosu 2001; Jensen, Agerso et al. 2002; Chapin, Rule et al. 2005; Anderson and Sobsey 2006; Gibbs, Green et al. 2006; Schmitt, Stoob et al. 2006).

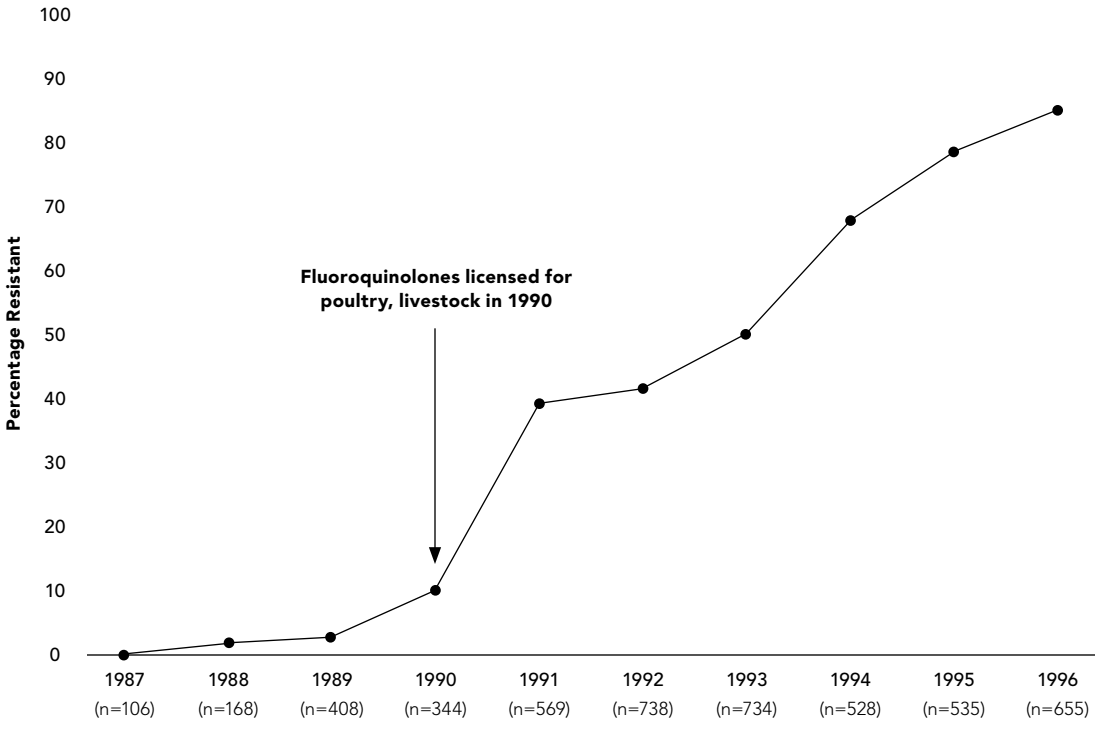
In order to review the large body of literature on the presence of AMR bacteria resulting in both food-borne and environmental exposures, this review focuses on four types of studies. The first type is ecological, that is, studies that have followed the prevalence of AMR after changes in agricultural antibiotic use (either introduction or removal of specific drugs). The second type is cross-sectional, that is, studies of specific groups in close contact with food animal production settings where antibiotics are used (such as farmers and farm families) as well as the presence of AMR bacteria in animals, animal houses, animal wastes, and the environment. A third type of study has examined the prevalence of AMR in bacteria isolated from consumer products produced by conventional producers (i.e., using antibiotics) and those produced by organic and other producers not using antibiotics. A fourth type of study has attempted to develop models, based upon molecular microbiology and evolutionary theory, to discern the contribution of agricultural antimicrobial use on risks of human infection by AMR pathogens.

Evidence for food-borne exposures to AMR

Repeated studies by FDA and others have reported on the high prevalence of AMR in pathogenic bacteria isolated from consumer food products in the US, and there is an extensive literature on the topic from the EU and many other countries (e.g., Emborg, Andersen et al. 2003; Johnson, Kuskowski et al. 2005). Simjee et al. (Simjee, White et al. 2002), from the FDA, conducted one of the more comprehensive surveys of antibiotic resistance in consumer poultry products (turkey and chicken) in the US. Enterococcus isolates were tested for antibiotic resistance, with an emphasis on resistance to virginiamycin and quinpristin-dalfopristin. The streptogramins are commonly used to treat infections that are resistant to older antibiotics. The presence of specific streptogramin-resistant genes was assessed using Pulsed Field Gel Electrophoresis (PFGE) and Polymerase Chain Reaction (PCR). Over 80% of non *faecalis* enterococci were resistant to streptogramins. In addition, a high prevalence of resistance to penicillin, tetracycline, and erythromycin in enterococci was also found. Between 75% and 100% of *E. faecium* isolates were resistant to these antibiotics. The FDA has reported similar findings for meat products as well (White, Zhao et al. 2001; Hayes, English et al. 2003). Correlations among Q/D resistance in *E. faecium* isolates have been drawn between humans, farm animals, and grocery store meats in the US (Donabedian, Perri et al. 2006).

There have also been studies demonstrating associations between AM use in animal feeds and AMR bacteria isolated from US consumer food products (Price, Johnson et al. 2005; Luangtongkum, Morishita et al. 2006). It is noteworthy that in both studies the conventionally produced meats and poultry were not less likely to carry pathogens; producers and the drug industry have sometimes claimed that the nontherapeutic use of AMs in food animal production in some way reduces pathogen carriage.

Figure 4. Trends in prevalence of fluoroquinolone (FQ) resistance in clinical isolates of Campylobacter jejuni in Spain, examined for resistance from 1987 to 1996. As indicated, before the approval of FQ use in poultry and livestock production, resistance was relatively rare (<10%); after approval, the prevalence of resistance rose quickly (Data from Smith, in Nachamkin 2000).



Ecological evidence: studies of temporal trends

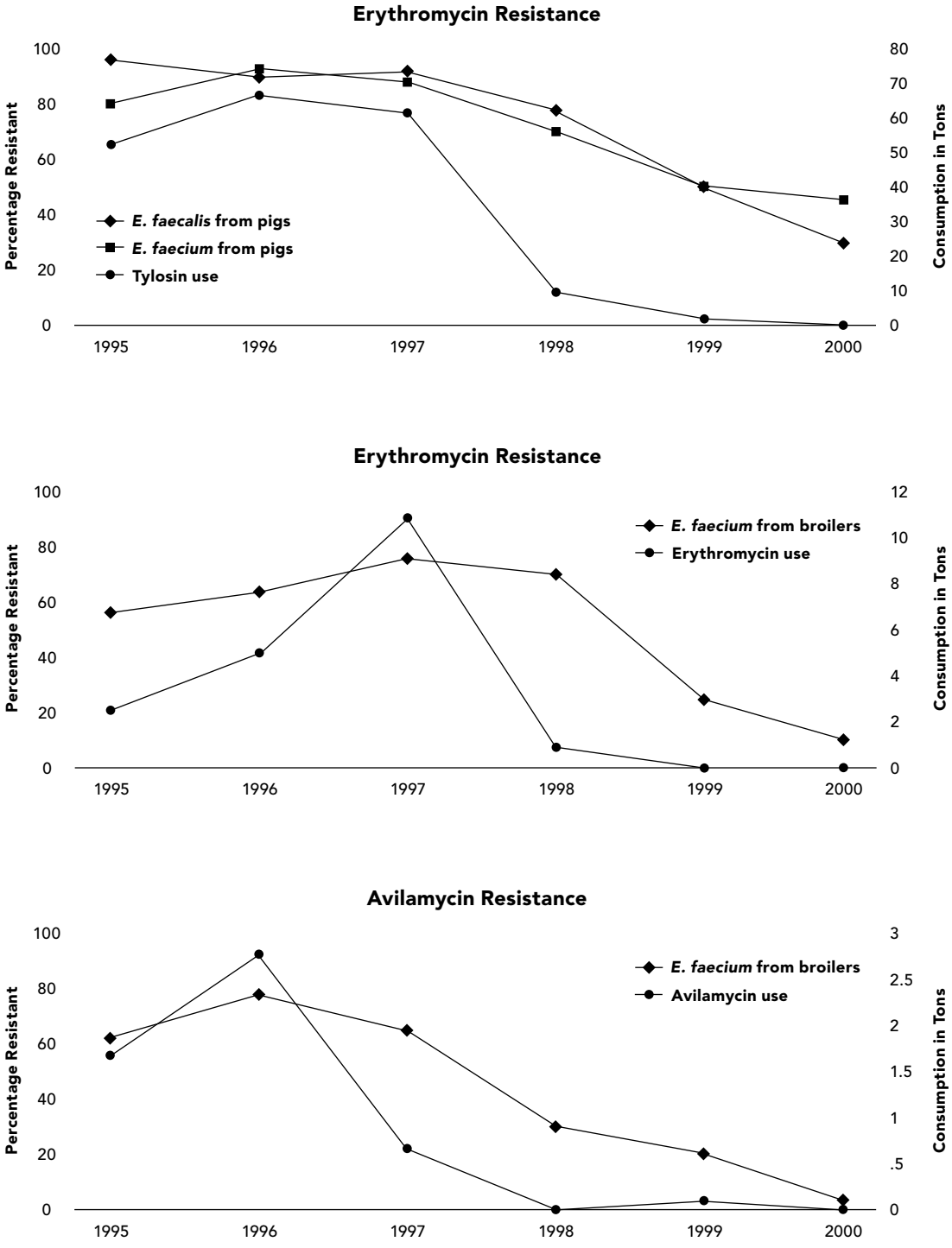
These studies utilize data collected at different time points and often from different sources. With these limitations, it can be concluded that, taken together, the data provide additional evidence for the role of agricultural AM use in changes in the prevalence of AMR on the farm, in consumer food products, and in the general population. Although causal inferences may be contested (Radostits 2004), the studies are consistent with an association between registration of AMs for agricultural use and increasing risks of AMR in bacterial isolates from human populations. The use of vancomycin and pristinamycin in swine production was associated with increased prevalence of AMR enterococci in humans in the Netherlands (van den Bogaard et al. 1997). A sharp increase in drug-resistant Campylobacter infection in the US was associated with AM use in IFAP in an analysis by the CDC (Gupta, Nelson et al. 2004; Collignon 2005). In Spain, where fluoroquinolones were introduced into poultry production in 1993, the rates of resistance in human isolates quickly rose to over 80% (Nachamkin 2000), (Figure 4); separate studies reported that by 2000 approximately 99% of poultry- associated Campylobacter isolates were fluoroquinolone resistant (Garau, Xercavins et al. 1999; Saenz, Zarazaga et al. 2001).

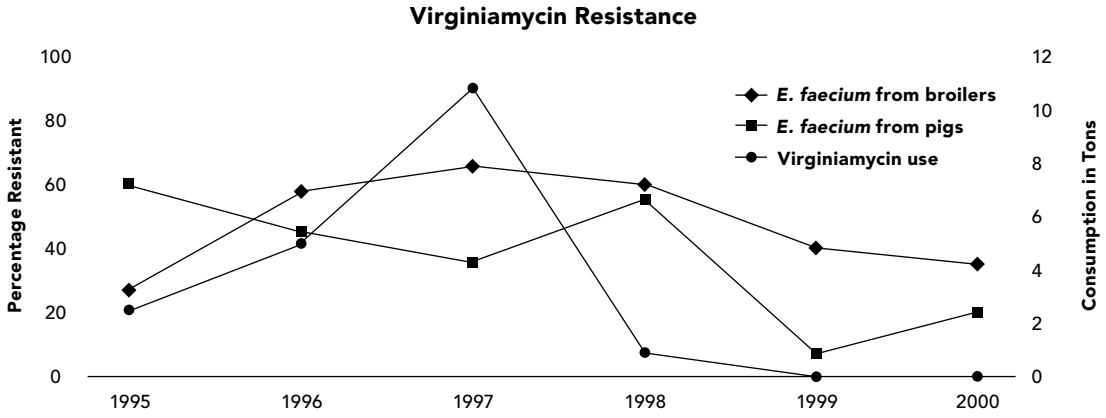
In a study by the CDC on trends in resistant Campylobacter, no isolates from US hospital patients were found to be resistant to fluoroquinolones prior to 1991, before this family of compounds was permitted in poultry production by the FDA; after this time, there has been a steady increase in the prevalence of resistance ((Gupta, Nelson et al. 2004) comment by (Collignon 2005)). In contrast, the relatively low rate of fluoroquinolone resistance in clinical isolates in Australia has been attributed to the ban on use of this drug in agriculture (Unicomb, Ferguson et al. 2006). Similar data were found in studies of isolates from poultry and humans in Norway (Norstrom, Hofshagen et al. 2006) and the Netherlands (Endtz, Ruijs et al. 1991).

Some of 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 have demonstrated a rapid and parallel decrease in antimicrobial use and the prevalence of antibiotic-resistant *E. faecium* recovered from pigs or broilers, as shown in Figure 5 (Aarestrup, Seyfarth et al. 2001). A similar pattern of decreases in vancomycin resistance in poultry isolates was observed in Taiwan after a ban on avoparcin in 2000 (Lauderdale, Shiau et al. 2007).

Until recently, there has been no examination of large-scale data on the actual effect of AMs in any food animal production system (NRC 1999). Graham et al. (Graham, Boland et al. 2007) recently addressed this using data from a large-scale real-world experiment carried out by researchers at Perdue Corporation, who conducted the largest study of AMs as growth promoters in broiler poultry (Engster, Marvil et al. 2002). They found that the positive impacts of AMs as feed additives were very small and the marginal benefit (in terms of growth rates, feed conversion efficiency, uniformity of the flock, and reduced illness or other losses) did not offset the cost of purchasing AMs for addition to feeds. These findings suggest that since the early 1950s innovations and improvements in poultry production—such as selective breeding, managed environments, and developments in feed formulation—may have replaced the production benefits reported earlier as associated with AMs as feed additives. Studies of poultry and swine production in the US and Europe indicate that the assumed benefits of AMs as growth promoters can be achieved by improved cleanliness of animal houses (Emborg, Ersboll et al. 2001; Engster, Marvil et al. 2002; Miller, Algozin et al. 2003).

Figure 5. The impact of banning antimicrobials from animal feeds on the prevalence of erythromycin, vancomycin, avilamycin and virginiamycin resistance in *E. faecium* and *E. faecalis* isolates from pigs and broilers in Denmark (Aarestrup, Seyfarth et al. 2001).




Virginiamycin Resistance
Percentage Resistant
Consumption in Tons
100
80
60
40
20
0
12
10
8
6
4
2
0
1995
1996
1997
1998
1999
2000
E. faecium from broilers
E. faecium from pigs
Virginiamycin use

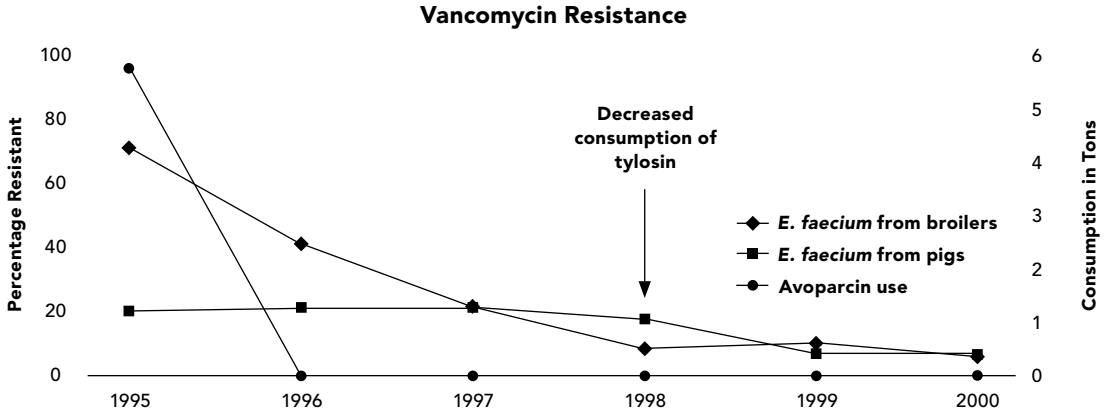
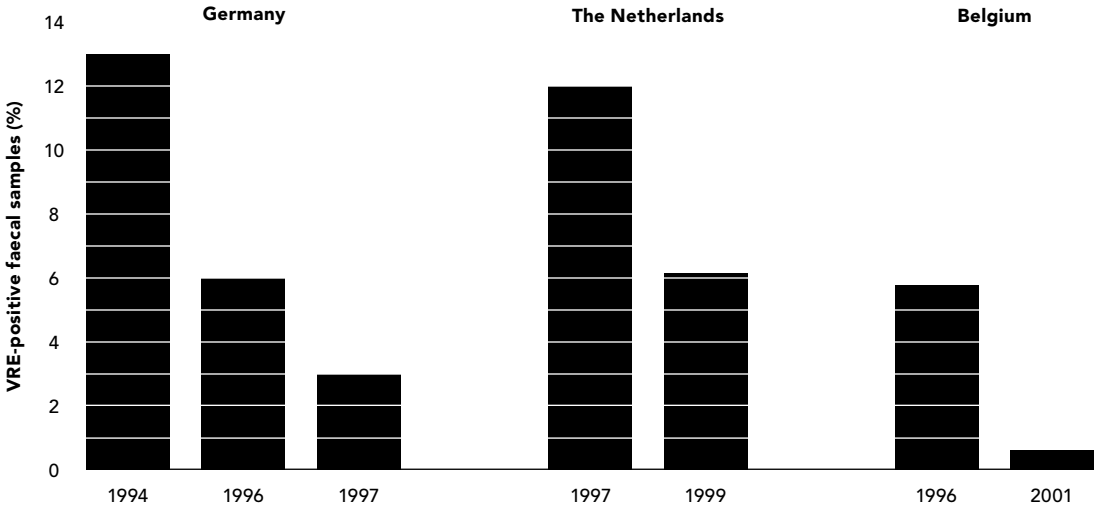

Vancomycin Resistance
Percentage Resistant
Consumption in Tons
100
80
60
40
20
0
6
5
4
3
2
1
0
1995
1996
1997
1998
1999
2000
Decreased consumption of tylosin
E. faecium from broilers
E. faecium from pigs
Avoparcin use

Figure 6. The impact of banning avoparcin from animal feeds on the prevalence of VRE in stool culture samples collected from healthy human subjects in the Netherlands and Germany and in hospitalized patients in Belgium (Klare, Badstubner et al. 1999).



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The prevalence of resistant-enterococci isolates from human subjects also declined in the EU over the same period (Klare, Badstubner et al. 1999; Wegener 2003). As shown in Figure 6, the carriage of vancomycin-resistant enterococci (VRE) in human isolates from Germany, the Netherlands, and Belgium declined over the period after banning avoparcin use as a feed additive.

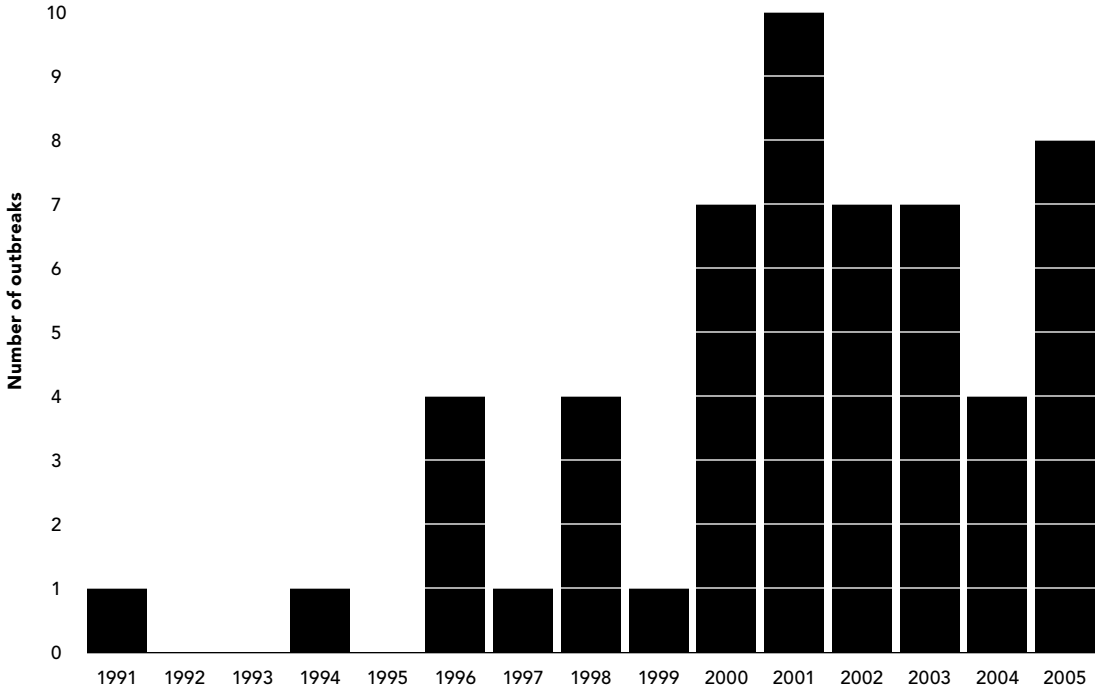
Evidence for nonfood exposures to AMR: farming communities, farmers, and farm workers

The issue of nonfood pathways of exposure has only recently received substantial attention. *This is a central matter in evaluating the effectiveness of current policies, such as HACCP, which are designed to reduce risks "from farm to fork," not including releases along the process to environmental pathways.* For this reason, this topic is discussed at length in this technical paper.

Most of the earlier studies have consisted of case reports, exemplified by the report by Fey et al. (Fey, Safranek et al. 2000), who carried out a case investigation of a child infected by ceftriaxone-resistant Salmonella acquired from living on a farm. Molecular methods (including DNA sequencing) were utilized to compare the salmonella isolate from the affected child with salmonella from the farm environment. Studies of farmers and farm workers have also reported that these groups are at high risk of exposure to AMR pathogens in and around animal houses, and they may transfer resistant infections to the general community. Two studies have examined exposures of farmers and farm workers to AMR pathogens in poultry houses. Van den Bogaard and Stobberingh et al. (van den Bogaard and Stobberingh 1999) reported that poultry farmers were at greatly increased risks of carrying drug-resistant Enterococci as compared to community referents, while Price et al. (Price, Graham et al. 2007) found that poultry house workers were 30 times more likely to carry gentamicin-resistant *E. coli* as compared to community referents. More recently, Huijsdens et al. (Huijsdens, van Dijke et al. 2006) reported on a case of methicillin-resistant *Staphylococcus aureus* infection in seven persons living or working at a large hog farm in the Netherlands; molecular methods were also used to confirm the clonality of the human and hog isolates. In a follow-up study, this group found a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in pigs sampled at slaughterhouses in the Netherlands (39% of 540 pigs) (de Neeling, van den Broek et al. 2007).

These exposures can translate into community risks as well, through person-to-person contacts (Smith, Dushoff et al. 2005). Smith et al. (Smith, Besser et al. 1999) carried out investigations of AMR *C. jejuni* in Minnesota, confirming elevated risks among communities in close contact with IFAP operations. As shown in Figure 7, an increasing number of outbreaks of enteric disease have been reported in association with animal contact, including farms as well as petting zoos and other events, to indicate the importance of ascertaining nonfood pathways of exposure (Steinmuller, Demma et al. 2006). Salmonella and *E. coli* 0157 were the most frequently reported pathogens in these outbreaks.

Figure 7. Number of reported outbreaks of enteric disease associated with animals in public settings in the US, by year, 1991-2005 (Steinmuller, Demma et al. 2006).



Environmental routes of release of AMR bacteria

Increasing attention is now being paid to nonfood routes of exposure, through environmental pathways of air, water, and dusts or soils. Exposures via these routes may contribute to the community burden, and they are also of importance because increased vigilance in terms of food safety and consumer initiatives (such as improved handling and cooking of meat products) will not diminish these nonfood risks. *Because of the failure of current regulations and practice to cover nonfood routes of exposure to AMR from IFAP, this issue is examined in further detail in this section.* AMR pathogens can be released into the general environment from animal houses through ventilation and waste disposal. 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. Tunnel ventilation systems that are increasingly used in the US industry generally consist of eight 1-meter-diameter fans positioned at one end of the building. These fans generate large quantities of aerosolized dust. Emissions of small particles (<10 m in size) from broiler house fans over a period of 24 hours can range from 25 to 40 grams per cubic meter, representing a million-fold increase of aerosolized dust near poultry house fans as compared to air sampled in a semi-rural area (Power 2004). AMR bacteria, originating in swine houses, have been detected in the environs of these houses as far as 30 meters (m) upwind and 150 m downwind (Gibbs, Green et al. 2006). Campylobacter strains with identical DNA fingerprints to those colonizing broilers have been measured in air up to 30 m downwind of broiler facilities. In addition, the antimicrobial drugs themselves have been found in dust from swine CAFOs (Hamscher, Pawelzick et al. 2003). There is evidence for the spread of resistant bacteria from animal houses by insects, rodents, and wild avians that may be particularly attracted to poultry Concentrated Animal Feeding Operations (CAFOs) where sources of food exist (e.g., spilled feed, animal manure, and poultry carcasses). For example, flies are found in significantly increased numbers in areas close to animal houses (Winpisinger, Ferketich et al. 2005). Houseflies have been found to play a major role in the epidemiology of Campylobacter infections in communities near CAFOs (Nichols 2005). Rodents can also transfer pathogens in and out of animal houses (Henzler and Opitz 1992). 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 isolates from birds in proximity to swine waste lagoons as compared to a reference set of samples (Cole, Drum et al. 2005). Additionally, the resistance patterns observed matched those most commonly reported by the National Antimicrobial Resistance Monitoring System for *Enterobacteriaceae* isolated from swine (Cole, Drum et al. 2005).

The major route of transfer of AMR pathogens to the environment is via waste generation and disposal on land. The magnitude of this transfer is more fully described in another technical paper. According to the US Department of Agriculture, confined food animals produce roughly 335 million tons (dry wt.) of waste per year (USDA National Program Annual Report—www.ars.usda.gov/research/programs/programs.htm?np_code=206&docid=13337), which is more 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, although levels of pathogens, as well as antimicrobial-resistant bacteria, are often higher than levels found in human feces. For swine and cattle (i.e., beef feedlots and dairy cows), an estimated 95% to 99% of the waste produced is applied to land (USDA/APHIS 1995; Walton 2002), and for poultry litter (i.e., excreta, spilled feed, feathers, soil, and bedding material), over 90% is applied to land (Moore, Daniel et al. 1995).

Animal wastes carry a vast number of bacteria (Gerba and Smith 2005), and in cases where animals are exposed to AMs, these bacteria include resistant strains. A study of fecal samples from dairy cattle in Minnesota found significant increases in the prevalence of multidrug resistant *E. coli* from animals provided AMs in feed as compared to those from organic farms (Sato, Bartlett et al. 2005). Land disposal of animal wastes can have near and distant impacts. Tetracycline-resistant genes in pig waste are highly persistent in lagoons of hog waste and in soils amended with these wastes (Jensen, Agerso et al. 2002; Schmitt, Stoob et al. 2006). AMR *E. coli* from IFAP have been detected in surface waters and in groundwater sources for drinking water sampled near hog farms in Maryland (Sapkota, Curriero et al. 2007; Stine, Johnson et al. 2007), North Carolina (Anderson and Sobsey 2006), and Iowa (Chee-Sanford, Aminov et al. 2001), and in soils amended with hog wastes (Jensen, Agerso et al. 2002). In terms of public health significance, it should be noted that groundwater makes up roughly 40% of the water used for public water supplies and provides drinking water for more than 97% of rural US populations (Hutson et al. 2005). However, no studies have been done on population exposures via drinking water or water contact.

Contamination of surface waters from waste disposal can also impact food safety through irrigation (Stine 2005). Runoff from land amended with CAFO wastes has been implicated as a source of AMR pathogens recovered from food crops grown in soils amended by animal wastes or irrigated with contaminated water (Tauxe 2002; Islam, Doyle et al. 2004; Sivapalasingam, Friedman et al. 2004). These events can occur through water contamination from relatively distant sites of land disposal. This is the probable pathway for two recent outbreaks of *E. coli 0157:H7* in the US involving spinach and green onions used by fast food restaurants.

Health and Societal Impacts of AMR

The burden of food-borne disease in the US and other countries has been dealt with extensively (OECD 2003); this burden is increased in terms of direct and indirect health care costs when bacterial disease involves AMR organisms (see introduction; also review by (Barza and Travers 2002), among others). Thus, for example, in the case of Campylobacteriosis, one of the leading food-borne causes of gastroenteritis in the US, the additional costs of infections by AMR Campylobacteriosis in humans was considered by the FDA in evaluating regulatory interventions to remove fluoroquinolones from use in poultry production (Bartholomew, Vose et al. 2005).

Attributable risk of AM use in agriculture to AMR as a public health problem

An important element in policy making is estimating the proportion of the risk that can be attributed to a specific source or activity; this information permits estimation of the benefit (risk reduction) that may be attained by controlling this source or activity. *Attributable risk is the amount of proportion of the incidence of a disease or other adverse health impact in populations exposed to a specific risk factor that can be attributed to exposure to that factor* (Last 1995). It is an important concept in medicine and epidemiology, and it has real-world importance in evaluating options for controlling or reducing a risk. As noted in the introduction to this technical report, AMR is associated with all uses of AMs, including clinical, veterinary, and agricultural (nonveterinary). Both appropriate and inappropriate uses contribute to AMR as we have learned from studies of AMs in the laboratory as well as in practice. Moreover, from the microbial "point of view," all sources of selection pressure contribute to AMR, and its appearance (in a hospital or food-borne illness outbreak) may result from multiple sources. For this reason, it may not be possible or even appropriate to determine the attributable risk of AM use specific to agriculture or to the use of AMs as feed additives, in terms of the overall incidence of AMR in human infections given a community model of both risk and exposure.

Overall, there is a lack of critical data on human exposures to AMR from agricultural sources sufficient to support a rigorous analysis of the attributable risks of agricultural AM use. The existing monitoring and surveillance programs are passive systems, and the investigations following detection of AMR usually focus on nosocomial (hospital or healthcare or food sources of exposure and infection. For example, waterborne infections are not usually traced back to agricultural inputs (for example, Lee, Levy et al. 2002).

Moreover, the surveillance network (FoodNet) does not provide coverage of those regions in the US where most IFAP are located. Thus, our ability to evaluate these impacts is significantly limited by the data available for source attribution (Sivapalasingam, Friedman et al. 2004). It is both methodologically difficult and scientifically inappropriate to attempt an apportionment of the burden of these impacts to agricultural AM use and other uses given the flow of resistance among bacterial species and human populations. That is, in attempting to calculate attributable risks on the basis of data related to infections by specific pathogens with specific resistance traits, it is imperative to incorporate the concepts of resistance reservoirs, movement of resistance cassettes, and gene flow among commensals and pathogens, as discussed previously. Moreover, a simple concept of antimicrobial pressure in terms of mass action supports the conclusion that the preponderant use of antimicrobials—which is in food animal production—must be a significant source of antimicrobial resistance.

Some of the research discussed earlier, in terms of time trend studies, can be related to the question of attributable risk. As discussed above, there are data to indicate that substantial increases in AMR in bacterial isolates from human populations have followed on the registration of AMs for application in drinking water for animals or use in animal feeds. These data are reviewed here to emphasize their relevance to discussions of attributable risk. In Spain, a striking increase was observed starting in 1990 in the prevalence of fluoroquinolone resistance in *C. jejuni* isolates from hospitalized patients in Spain. In 1990, the Spanish government authorized the use of fluoroquinolones in poultry production; otherwise, no dramatic changes occurred in the volume of clinical use of this antimicrobial. In a study by the CDC on trends in resistant *Campylobacter*, no isolates from US hospital patients were found to be resistant to fluoroquinolones prior to 1991, at which point this family of compounds was permitted in poultry production by the FDA; after this time, there has been a steady increase in the prevalence of resistance, as shown below (Gupta, Nelson et al. 2004) comment by (Collignon 2005)). While these studies did not trace the origin of resistant isolates in the population

sampled, the trend is consistent with an impact associated with governmental registration.

The intervention studies conducted by European researchers following up on AMR in animals, food products, and clinical isolates subsequent to the ban on avoparcin in agriculture are also relevant. As discussed previously, monitoring of food animals in Denmark indicates a significant decline within five years in the prevalence of vancomycin-resistant isolates collected from pigs and poultry, as well as in the prevalence of vancomycin resistance in human isolates. These data are not conclusive, but they are also consistent with a role for animal agriculture use of antimicrobial resistance in that resistance prevalence appears to rise and fall with regulatory decisions and practice concerning agricultural use.

While these studies provide some measure of the likely contribution of agricultural AM use to the incidence and prevalence of vancomycin-resistant enterococci in human isolates, the incompleteness of these data must be recognized (Bywater 2004). More importantly, AMR may be "silent" in the reservoir of microbial communities or within asymptomatic persons. Its impact—expressed as incidence of an AMR infection—will appear only when a person enters medical treatment and treatment failure is recognized.

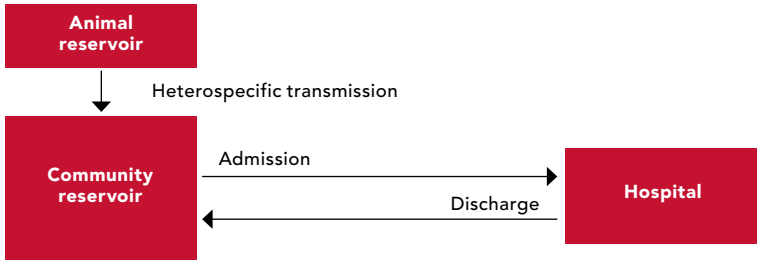
These data are also of special interest since they indicate that interventions to reduce agricultural AM use can have a significant public health benefit in the relatively short term.

There may be more fundamental challenges to estimating attributable risk in terms of any specific use, such as agricultural vs. clinical AM uses, given the flow of resistance among bacteria and human populations (Summers 2006; Wright 2007). 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, in contrast with assumptions that AMR infections in hospitals were largely associated with hospital use of AMs (Smith, Yago et al. 2005). While hospital use of AMs has generally been assumed to generate the highest risk of AMR and transmission of AMR infection, this conclusion may be biased by the fact that most resistant infections are identified in hospitals. From an ecological perspective, the greater selection pressure for resistance generated by agricultural uses may result in carriage of AMR bacteria, both pathogenic and commensal, by persons in the nonhospitalized population. When these people enter hospital, they may be a major source of transmitted infections in the hospital environment. The community basis of hospital infections is increasingly recognized (Pop-Vicas and D'Agata 2005; de Neeling, van den Broek et al. 2007). Although hospital use of AMs may generate the highest risk of transmission of resistant infection (due to opportunities for contact among large populations of susceptible populations, similar to poultry houses), agricultural uses may result in a larger reservoir of antimicrobial resistance outside the hospital, in the form of pathogenic and nonpathogenic bacteria, as well as transposable genetic elements. As these people enter hospital, they may be a major source of resistant infections to the hospital environment. Because conditions in the hospital enhance the likelihood of person-to-person transmission, the risks of becoming infected by a resistant pathogen are higher in hospitals, but the source of resistance from outside the hospital is largely determined by this larger community reservoir of resistance (which, for many reasons discussed in this paper, is driven in large part by the magnitude of agricultural uses and affects environmental and dietary pathways of exposure through drinking water and consumer meat and poultry products). As Smith et al. (Smith, Yago et al. 2005) 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. This is shown visually in Figure 8.

Valuation of impacts

The same limitations on attributing risk also impede our ability to value the impacts of AMR on human health, in monetized and other metrics. The economic burden of AMR on medical care systems has been evaluated in studies carried out in specific hospitals (Kim, Oh et al. 2001; Capitano, Leshem et al. 2003) and more generally (Okeke, Laxminarayan et al. 2005; Smith, Yago et al. 2005) as well as by governmental and international organizations (OECD, CDC) as well as Non-Governmental Organizations (NGOs) (APUA). The FDA also conducted an impact analysis in connection with its regulatory assessment for the ban on fluoroquinolones in poultry production. This analysis was challenged by industry.

Figure 8. How large is the impact of antibiotic use in agriculture? The community reservoir is driven by the animal reservoir, which then largely determines the entry of resistance into the hospital (From Smith et al. (2005).



Risk Assessments of AMR

Because of the importance of risk assessment as a formal method in policy making in the US, we review risk assessments and scientific issues relevant to IFAP.

The principles of risk assessment have been adopted by international organizations and national agencies, including the US FDA, in activities to evaluate agricultural antimicrobial use (Doyran 2004; Helmuth and Hensel 2004; Maudoux, Saegerman et al. 2006). While there is an extensive literature and research base on risk assessment methods with respect to chemicals and agents such as ionizing radiation, the methodologies and critical evaluations are more limited with respect to microbial risk assessment *(see AMR annotated bibliography)*. These methods are not as sophisticated as those that have been developed for chemical regulation, particularly with respect to the incorporation of biological and mechanistic principles such as growth rates, evolutionary rates, and gene flow.

For these reasons, there are substantial limits on current methods of risk assessment (Barza and Travers 2002). Most risk assessments continue to focus on specific resistance traits in specific bacteria, with an emphasis on resistance to clinically important antimicrobials in clinically significant pathogens (e.g., NRC 1999). As discussed above, this approach does not reflect current understanding of the role of resistance reservoirs and the multiple opportunities for exposures to AMR pathogens. There is moreover a lack of attention to the importance of bacteria as *living organisms*—which are fundamentally different from chemicals—since living organisms are capable of expanding in number and potential risk. This complicates the notion of "threshold of resistance," which is utilized by the EPA in its microbial risk assessments.

US Government Risk Assessments

The risks of consumer exposure to AMR pathogens via food consumption have stimulated considerable regulatory and voluntary risk reduction activity. The nature of the hazard—AMR in food-borne pathogens—is recognized in the HACCP principles, which cover *from* farm to fork (emphasis added) and not *within* the farm. Thus, HACCP accepts the fact that, under current practices, animals will be contaminated with pathogens and AMR pathogens during their raising; controls are instituted to contain this problem *after* the animals leave the farms. *Whether this is an effective or reliable policy approach is an issue for the PCIFAP to consider.* The focus of HACCP is to reduce, insofar as possible, the presence of all pathogenic bacteria, whether or not they are resistant, through ensuring a high standard of operations at the processing plant, including slaughter, processing, packaging, storage, and shipment. Additional guidance is provided to wholesale and retail sales outlets, restaurants and food service organizations, as well as to consumers. From the perspective of a fully implemented HACCP system, there is no added burden on the management of all aspects of food animal production to contain risks of AMR bacteria as compared to susceptible bacteria. HACCP does not consider the potential for health risks associated with nonfood pathways of release and exposure, as discussed above.

In the process of reviewing and eventually revoking the registration for fluoroquinolones in poultry production, the FDA has recently developed approaches to the risk assessment of AMS as feed additives (Bartholomew, Vose et al. 2005). This approach utilizes a linear model for estimating risk that is consistent with a conservative approach utilized in chemical risk assessment (NRC 1983; NRC 1990). This approach has been criticized by industrial consultants (Phillips, Casewell et al. 2004; Cox 2005 but see many commentaries on this article), but constitute US policy at the present time. In the context of recent proposals to register a fourth-generation cephalosporin (cefquinome) for use in confined food animals, some limitations on the scope of the FDA risk assessment guidelines as proposed have emerged. These concern the barriers to assessing risks of a novel antimicrobial for which the first use will be in agriculture as well as the lack of a comprehensive risk assessment that incorporates both-food borne risks as well as contributions to the AMR reservoir.

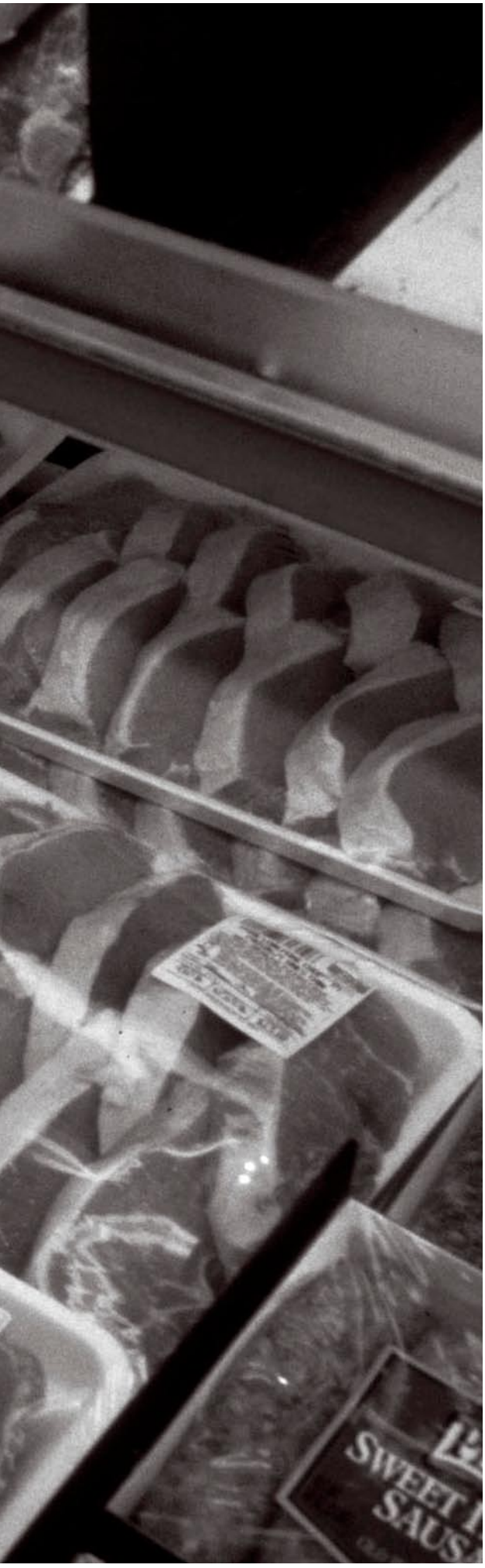
World Health Organization (WHO)/ Food and Agricultural Organization (FAO)/CODEX Alimentarius (CA) Risk Assessments

These three organizations coordinate many international activities related to food safety, and they have explicitly coordinated their consultations and policies on the subject of antimicrobial resistance (see above). In addition, these organizations are now reference organizations under the World Trade Organization (WTO) with respect to resolution of national differences on risk assessment and other policies related to international trade in animals, animal products, and other foods (Luetzow et al. 2003). Thus, if there were trade issues arising from different policies on agricultural antimicrobial use (for example, between the US and the EU), the risk assessment methods of the FAO and CA would be dispositive in any adjudicative process, as they were in the US/EU dispute over hormonal additives for cattle production (EEA 2001).

The FAO/WHO/CODEX adopted principles for risk assessment of microbiological risks (sometimes referred to as "risk analysis" in Europe) in 1999.

The elements of risk assessment are similar to those first explicated in the US (NRC 1983), that is, consisting

Definitions and methodologies (US):
Risk assessment is the process of assembling, evaluating, and integrating information related to hazard, dose-response, and exposure in order to inform appropriate management and protection of health.



of hazard identification (nature of the toxicity or health impact associated with the entity being assessed), dose/response evaluation, quantitation of the magnitude (severity or likelihood) associated with the amount or duration of exposure, and exposure assessment (evaluation of the range of likely exposures to be encountered by human populations). A report on recent assessments by FAO, WHO, and OIE on agricultural antimicrobial use and AMR is available in a set of papers published in the *Journal of Veterinary Medicine Series B*, Volume 51 (2004).

Conclusions

One of the most significant public health issues associated with IFAP is its contribution to the increasing crisis of antimicrobial resistant infections worldwide. All uses of antimicrobials contribute to the selection of resistance among commensal and pathogenic bacteria, and for that reason, controls over inappropriate use are of high priority internationally. There is considerable evidence associating antimicrobial use in agriculture with resistant pathogens in the food supply, on the farm, and in the environment. Temporal studies following both the introduction and the removal of antimicrobials from feeds and water have demonstrated strong associations between these uses and the prevalence of antimicrobial resistance in animal wastes, human food, and isolates from human populations. Because of opportunities for dispersal from farms into the environment, agricultural antimicrobial use is a significant contributor to the expanding reservoir of resistance within microbial communities. It is increasingly recognized that the reservoir of resistance is the source of resistance genes in pathogens that may be recognized in hospitals.

Finally, the use of antimicrobials for nontherapeutic purposes (growth promotion) in agriculture is not justified for economic reasons in the modern food animal production setting. Several large-scale studies conducted in poultry and swine operations have demonstrated that the cost of antimicrobials as feed additives outweighs any marginal increase in profits, and that improvements in growth and disease prevention can be accomplished by increasing the hygienic conditions in which animals are held. As the industrial model of food animal production is adopted worldwide for poultry, swine, beef, and aquatic organisms, there is an urgent need to institute guidelines for prudent use of drugs in food animal production and for excluding the use of the drug as growth promoters.

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Glossary

Antibiotic (classic definition): A substance produced by a microorganism that has the ability to kill or inhibit the growth of other microorganisms. Synthetic antibiotics, usually chemically related to natural antibiotics, can now be produced.

Antibiotic (popular usage): A drug used to treat infections caused by bacteria. Most antibiotics in use are specific to bacteria because they act on aspects of bacterial growth, development, and/or structure that are specific to bacteria and are not part of the growth, development, or structure of the host organism. Thus, the bacterium is harmed, but not its host.

Antibiotic Resistance: The ability of microorganisms to withstand the effects of one or multiple antibiotics (can be innate or acquired). Resistance to multiple drugs is known as multidrug resistance. Some bacteria are naturally resistant to multiple drugs; all can acquire resistance genes. Selective pressure from exposure to antibiotics is among the most potent forces that drive antibiotic resistance.

Antibiotic Resistance (modified from WHO): Resistance to antimicrobials is a natural biological phenomenon that can be amplified or accelerated by a variety of factors, including exposure to antibiotics. Use of antimicrobials (whether for treatment or prophylaxis) forces microbes to adapt or die. Those that survive carry genes for resistance that can be passed on.

Antimicrobials: Substances that kill or inhibit the growth of microorganisms. The terms "antibiotics" and "antimicrobials" are often used interchangeably, although "antimicrobial" actually covers a wider range of substances.

Category 1 Drugs: Drugs that do not require a withdrawal period prior to slaughter. A withdrawal period is a period of time before the animal is slaughtered (for human consumption) during which the drug may not be administered to the animal. If the category 1 drug is being administered at doses above the approved dose for the particular purpose, a withdrawal period may still be necessary.

Category 2 Drugs: Drugs that require a withdrawal period prior to slaughter, regardless of the dose. It must be shown that no drug residues are found in the slaughtered animal.

Commensal Bacteria: Bacteria that share a symbiotic relationship with their host are termed commensal. That is, both the bacteria and their host benefit from the bacteria living within the host. In humans, and all other animals, the largest example is the bacteria that populate the gut. Those bacteria perform a wide range of tasks, from metabolism to defense, which benefit the host. The bacteria benefit by being provided room and board. However, when commensal bacteria replicate to levels higher than their normal population, they can be harmful to the host.

Concentrated Animal Feeding Operations (CAFOs): For regulatory purposes, the EPA defines CAFOs as: "New and existing operations which stable or confine and feed or maintain for a total of 45 days or more in any 12-month period more than 1,000 animal units from a combination of slaughter steers and heifers, mature dairy cattle, swine over 55 pounds and sheep; OR new and existing operations which discharge pollutants into navigable waters either through a man-made ditch, flushing system, or other similar man-made device, or directly into waters of the United States, and which stable or confine and feed or maintain for a total of 45 days or more in any 12-month period more than 300 animal units (from a combination of slaughter steers and heifers, mature dairy cattle, swine over 55 pounds and sheep). Provided, however, that no animal feeding operation is a concentrated animal feeding operation as defined above if such animal feeding operation discharges only in the event of a 25-year, 24-hour storm event." The EPA is currently in the process of reviewing this definition. In general, the term CAFO is popularly used to refer to animal production in confined, high-density conditions.

Confinement Agriculture/Systems: This refers to types of agriculture in which the movement of animals is confined and they are raised in high density, usually with stimulated feeding, and weight gain optimized so as to decrease time to mature weight.

Control: In terms of antibiotic use, this refers to the administration of antibiotics when morbidity (instances of disease) or mortality (instances of death) is elevated above normal levels. These antibiotics are usually administered at the herd or flock level.

Dosage: The amount of antibiotic administered to the animal(s), often in weight of antibiotic per weight of feed (i.e., X grams of antibiotic per ton of feed).

Federal Food, Drug, and Cosmetic Act: A regulatory act in the United States that, since 1938, has regulated all use of antibiotics in the United States. The Food Additives Amendment of 1958 pertains to the use of antibiotics in feed for animals and products for direct human consumption. The Animal Drug Amendments of 1968 added new drugs and antimicrobials used in animals to this regulation.

Feed Efficiency: This term refers to the efficiency by which an individual converts food into weight. For example, chickens have very high feed efficiency, on average converting two pounds of food into one pound of weight at slaughter. Other larger and longer-lived animals, such as cattle, are less efficient, needing ten or more pounds of food to create one pound of animal weight at slaughter. Increasing feed efficiency decreases costs of production and generally decreases the amount of time needed to produce a mature (in terms of weight) individual.

Growth Promoter: Compounds used as additives to animal feed which are intended to increase the rate of growth or maximal size and/or weight of the individual.

Ionophore: A lipid-soluble molecule made by microorganisms such as bacteria to transport ions into and out of the cell is called an ionophore. They are carriers for ions which otherwise would not be able to move into or out of the cell.

Medically Important Antibiotics: This term is used to describe antibiotics used in treatment of human disease and designated by the FDA as highly or critically important for the treatment of disease in humans.

Medicated Feeds: Animal feeds sold with antibiotics or other drugs in the feed mixture may be called medicated feeds. The majority of these are sold over the counter, with the exception of a very few which require a Veterinary Feed Directive (akin to a prescription in human medicine) for sale.

Metaphylaxis: This term may refer to the use of high doses of antibiotics over short periods of time to control the spread of bacterial infection from animal to animal. It is meant to treat disease in one individual while preventing disease in other individuals.

Microbiological Safety: This is terminology used by the FDA in determining the safety of antibiotics, for example the probability that use in animal feed will result in the creation of resistance in bacterial populations.

Natural Growth Promoters: Agents added to animal feed intended to increase the rate of growth or the size of the individual that do not contain antibiotics, are often called "natural growth promoters." Common classes of natural growth promoters include: acidifiers, probiotics, prebiotics, synbiotics, phytogenics, feed enzymes, and immune stimulants.

New Animal Drug Application: This is the current regulatory procedure for approval of antibiotics and other drugs for use in animals, either intended for veterinary or agricultural use.

Nontherapeutic: The use of antimicrobials in food animals in the absence of microbial disease or known (documented) microbial disease exposure; i.e., any use of the drug as an additive for growth promotion, feed efficiency, weight gain, routine disease prevention in the absence of documented exposure, or other routine purpose is considered nontherapeutic.

Prophylactic: The use of antimicrobials in healthy animals in advance of an expected exposure to an infectious agent or following such an exposure but before onset of laboratory-confirmed clinical disease as determined by a licensed professional. Prophylactic use of antibiotics is usually employed in situations where there is a high risk of developing disease or illness. In human medicine, this usually involves situations of high-density cohabitation where a disease has been detected (i.e., meningitis diagnosis of one student may result in treatment of an entire dorm). In food animals, the term has also been used to describe situations where a drug is used due to the high probability of the development of a disease, without actual diagnosis.

Subtherapeutic: The use of antibiotics at doses or concentrations below those known to effectively harm or kill bacteria so as to prevent or cure disease is called subtherapeutic use.

Therapeutic: This term refers to the use of antimicrobials in food animals with diagnosed microbial disease.

Veterinary Feed Directive: A prescription for a medicated feed or antibiotic to be added to animal feed is called a Veterinary Feed Directive.

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