Extraordinary health benefits have accrued from the discovery of antimicrobials since the mid-twentieth century. However, as T.S. Eliot wrote, “In my beginning is my end.” The use of antibiotics has driven the evolution and spread of antimicrobial resistance from the beginning. Fleming himself noticed this in his laboratory studies and, soon after, Starr and Reynolds warned of the public health risks of the novel application of these drugs to feeds for farm animals. Antimicrobial-resistant bacteria now constitute a significant proportion of the emerging infectious disease pathogens that have been reported since 1940. This has led to the dystopian declaration that we have entered the “postantibiotic era.”

From an evolutionary perspective, selection for antimicrobial resistance is an inevitable biological response to continued exposure to antimicrobial agents. Bacteria have evolved in the presence of naturally occurring antimicrobial agents. Many of the antimicrobials used in clinical medicine are analogs of compounds produced by organisms such as Streptomyces, Bacillus, Penicillium and Cephalosporum. However, human exploitation of these agents has accelerated the global development of resistance. This is often ascribed to clinical health care settings involving practitioners and consumers, supporting the assumption that the increasing prevalence of drug-resistant infections is nosocomial, or health care-associated, in origin; and the result of overly broad treatment regimens, incomplete treatment, or patient non-
compliance. Health care settings are clearly important in the evolution and spread of resistant bacteria, but the fact that most resistant infections are identified in a hospital does not necessarily imply that resistance originates there. There is growing recognition of the importance of community origins as “feeders” of pathogens into the clinical setting. Methicillin-resistant Staphylococcus aureus (MRSA) serves as a model for re-focusing the lens of research on the origins of emerging infections. The rapidly evolving epidemic of community-acquired MRSA has directed new attention to the importance of investigating nonhospital antecedents of antimicrobial resistance. An exclusive focus on the hospital setting restricts the scope of action to late stages of control. Moreover, interventions that target the development of antibiotic resistance in the community offer greater potential for success in preventing disease before it can enter and be transmitted in the hospital.

In this review, the authors focus on a major component of the drivers for antimicrobial resistance in the community: the use of antimicrobial drugs as feed additives for animals grown for human consumption. Antimicrobial feed additives are now the major use of antimicrobials in the United States and many countries. This fact is not generally recognized in clinical medicine; for example, a recent analysis of the problem of antimicrobial resistance devotes less than one page to the issue of antimicrobial use in agriculture. The purposes of agricultural antimicrobial use lie in the transformation of agricultural practices over the past 50 years, away from many small-scale family farms across the United States to fewer intensive, large-scale operations (known as CAFOs, or confined animal feeding operations) that are concentrated regionally. The transformation of food animal agriculture – involving changes in methods of production, ownership, and stewardship – promotes the development of antimicrobial resistance. These changes also contribute to economic marginalization of workers and socioeconomic decline in rural communities, factors that may increase the difficulty in monitoring and early detection of resistant infections.

THE HOSPITAL IN THE COMMUNITY AND THE COMMUNITY IN THE HOSPITAL

Hospitals are a focal point for recognizing the health problems of the community. As a result, antimicrobial-resistant infections are more likely to be accurately diagnosed in patients in the hospital setting as compared with clinics or by individual practitioners. But patients in hospital bring their community with them, carrying their individual microcommunities of pathogens and commensal bacteria. In the face of widespread antimicrobial use in the hospital setting, these microcommunities can shift toward a higher prevalence of resistant organisms, and resistance determinants may be transferred from commensals to pathogens. The hospital setting also enhances transmission from new entrants to nonexposed patients, some of whom may be especially susceptible to infection. As a result, hospitals are both a surveillance point and a multiplier for resistant infections.

There are standard methods for classifying strains as hospital-acquired or community-acquired (Box 1). This categorization may obscure rather than illuminate the inter-relationships that exist between health care environments and the community because identification of a health care-associated risk factor is often a disincentive for further exploration of additional risk factors. The Centers for Disease Control (CDC) classification for infections is neither definitive nor exclusive. Identifying health care-associated risk factors does not address the potential for entrance of a pathogen from the community into the health care system. There is evidence for the increasing prevalence of community sources of other antimicrobial-resistant infections isolated from patients in the hospital setting. For
example, in a study of incoming patients at a tertiary care hospital in Boston, from 1998 to 2003, the likelihood of multidrug resistance in *Escherichia coli* increased from 2% to almost 20% (Fig. 1).14

COMMUNITY RESERVOIRS OF ANTIMICROBIAL RESISTANCE: THE AGRICULTURAL INCUBATOR

Antimicrobial resistance reflects dynamic interactions among pathogens, drugs, and hosts (both animal and human) in shared environments.15,16 Human exposure to resistant pathogens occurs in the context of microbial ecosystems in which three mechanisms drive the development and, most importantly, the dissemination of resistance: natural selection, the sharing of resistance genes, and the reservoir of resistance. Industrial food animal production is in many ways the ideal setting for all of these events. The use of antimicrobials as feed additives results in uncontrolled and subtherapeutic doses over the lifetime of animals raised in grossly unhygienic surroundings. This presents the worst possible scenario for resistance selection and infection control. Coupled with incomplete biosecurity and biocontainment, and mostly nonexistent waste treatment,17 these conditions lead to dissemination into human hosts and the environment, with amplification of reservoirs of resistance.

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**Box 1**

Criteria for definition of hospital-acquired (HA) versus community-acquired (CA) risk factors for infection: the example of MRSA

**HA-MRSA**

- Recent or current exposure to hospital or outpatient clinic or long term care (eg, residence in a facility)
- Infection detected more than 48 hrs after admission to hospital or other health care facility

**CA-MRSA**

- No documented health care risk factors
- Infection detected before or within 48 hrs after admission to hospital or other health care facility

* Patients with prior MRSA colonization are often classified HA-MRSA.


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Fig. 1. Increasing prevalence of multidrug-resistant *E coli* isolated from incoming patients in Boston. Temporal increases were highly significant (*P*<.001). (Data from Pop-Vicas AE, D’Agata EM. The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. Clin Infect Dis 2005;40(12):1792–98.)
The reservoir of resistance or “resistome” represents the genetic resources available within a community of organisms. The availability and persistence of resistance determinants within the microbial ecosystem fuels the development and proliferation of resistance. The resistance reservoir must be taken to include both pathogenic and nonpathogenic organisms because of the wide-ranging ability of bacteria to share resistance genes through molecular mechanisms of horizontal gene transfer. The reservoir concept more broadly underscores the contribution of all sources of antimicrobial pressure to drug resistance, and it provides the theoretic construct for emphasizing the contribution of the nontherapeutic use of antimicrobials in food animal production to the resistance reservoir. This has been documented specifically for poultry and swine production.

The intensive use of antimicrobials as feed additives in food animal production began in the United States in the 1950s and paralleled other changes in the organization and structure of the industry. Current food animal production—including poultry, cattle, swine, and aquaculture—employs a wide variety of antimicrobial agents from all the major classes of antimicrobials approved for human clinical use. Antimicrobials are administered to food animals for three main purposes: therapeutic use for the treatment of sick animals, prophylaxis to prevent the spread of disease among susceptible animals, and, nontherapeutically, for growth promotion. The assumed benefit of antimicrobial feed additive use is to decrease the time and total feed consumption needed to grow an animal to market weight. Production-based estimates suggest that drug use in animal feeds accounts for between 60% and 80% of total antimicrobial production in the United States and, until recently, in the European Union as well. It is unfortunate, however, that direct information about antimicrobial uses is not available. In the United States, estimated antimicrobial use in animal feeds in North Carolina alone exceeds total human clinical use for the entire United States population. With relatively few exceptions, no data are available from the rest of the world, but the expansion of the modern industrial model of food animal production, including antimicrobial use in feeds, is particularly rapid in Asia and South America.

The sheer mass of antimicrobial use in agriculture suggests that the quantitative global impact of this use is likely to be significant. Practices common to modern food animal production enhance selection for resistance and sharing of pathogenic and commensal bacteria among animals. The overwhelming majority of animals grown for human consumption are raised in CAFOs in the United States and increasingly throughout the world, where thousands to tens of thousands of animals are crowded together close to or on top of their wastes. Crowding, stress, inappropriate feeds, ventilation practices, and waste management techniques inherent to this system enhance release of microbes to the external environment.

Antimicrobial use in animal feeds has played a major role in the development and spread of fluoroquinolone-resistant Campylobacter jejuni, streptogramin- or vancomycin-resistant Enterococci (VRE), and multidrug-resistant Salmonella. The large community reservoir of VRE in Europe has been ascribed to the widespread use of avoparcin (a vancomycin-like glycopeptide) in food animal production, in contrast to the situation in the United States where avoparcin never was approved as an animal feed additive. At its peak, use of avoparcin in animals in Denmark was 1000 times the total clinical use of vancomycin. After the European Union ban on avoparcin in 1997, surveillance programs demonstrated a rapid decrease in the prevalence of vancomycin resistance in Enterococci in human isolates as well as in animal isolates, animal waste, and consumer food products.
reflecting the contribution of agricultural antibiotic use to resistance in the clinical setting.

**PATHWAYS OF HUMAN EXPOSURE TO ANTIMICROBIAL RESISTANCE FROM AGRICULTURE**

Food is clearly a significant pathway through which agricultural antimicrobial use affects human health. There are many reports worldwide on the presence of resistant bacteria and resistance genes in consumer meat products, including poultry, beef, and pork. The national market dissemination of commercial meat products promotes the rapid spread of resistant pathogens from the farm environment to the human community.

**OCCUPATIONAL AND COMMUNITY EXPOSURES**

Farmers and farm workers bridge the food animal production environment and nearby communities. Workers employed in CAFOs (particularly those who collect and transport live animals) are exposed to pathogens carried by live animals and their wastes. Typically, workers in CAFOs are provided little to no protective equipment and, as a result, have elevated odds of carrying drug-resistant bacteria when compared with community referents. They may also transmit these infections to their households. Because they lack adequate insurance and access to health care, hospital-based surveillance systems may not detect resistant infections in farm workers or their community contacts.

MRSA exemplifies these issues. In recent years, information on occupational risks for MRSA infection has emerged in the European Union and Canada. In central Europe, a community-acquired, nontypable-MRSA strain (NT-MRSA) was traced to hog farms, which were determined to be the origin of these new clones. Screening of a sample of pig farms showed that this strain of NT-MRSA colonized 40% of pigs overall, impacting 80% of farms. In the Netherlands, a high prevalence of MRSA was also identified in pigs. Also in the Netherlands, MRSA infections were identified in seven individuals who worked or lived on a farm and the infection was typed to a strain found among swine at the farm. In Canada, in a survey of pig farmers, 20% were colonized with the same strain of MRSA found in pigs, consistent with other cross-sectional studies. Weese and colleagues found increased prevalence of MRSA carriage among horse personnel and, notably, they identified animal density as a distinct risk factor for MRSA in both humans and horses.

Agricultural workers may transmit MRSA from the farm environment to the community at large. Using hospital surveillance data, van Loo and colleagues found that occupational exposure to farm animals or proximity to farms was a risk factor for MRSA infection. In a study with extraordinary implications, van Rijen and colleagues sampled patients arriving at a Dutch hospital for MRSA carriage. Risk of MRSA was strongly associated with exposure to pigs and veal calves; 32% of patients with these exposures were positive for MRSA. Taken together, these studies provide strong evidence that cattle, horse, and swine farms are significant sources for community-acquired MRSA and for the movement of this pathogen into the hospital setting.

**ENVIRONMENTAL RELEASES FROM CAFOs**

CAFOs, by design and operation, do not restrict the release of pathogens. High-throughput ventilation systems—essential for animal health when thousands of chickens or hogs are raised in close confinement—permit the release of bacteria
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<thead>
<tr>
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into the surrounding environment. For example, resistant *S. aureus* has been recovered downwind of a large swine operation.\(^5\) Resistant strains and resistance genes as well as antimicrobial parent compounds have been detected through air sampling in the confinement house itself.\(^5\)–\(^6\) Resistant bacteria and resistance genes have been detected in groundwater and surface water surrounding large swine facilities,\(^5\)–\(^7\) and resistance genes isolated from ground water were identical to isolates from nearby swine lagoons.\(^6\)

### A RIVER OF PATHOGENS: DISPOSAL OF FOOD ANIMAL WASTES

Waste disposal is the major source of antimicrobial-resistant pathogens entering the environment.\(^1\) Unlike human biosolids, in the United States there are no requirements for the treatment of animal wastes, which are typically applied to land, generally on-site or within 10 miles of the farm, following storage in lagoons (for swine and cattle manure) or in dry heaps (poultry manure). These practices contaminate air, water, and soils in the vicinity of both storage and field application.\(^6\) Large-scale animal agriculture problems are compounded because of the large amount of animal wastes that are produced in small geographic areas by thousands of animals held in open...
or closed confinement. According to the US Department of Agriculture (USDA), confined food animals excrete approximately 335 million tons (dry weight) of waste per year, more than 40 times the total mass of human biosolids produced annually. These wastes are of concern for the emergence and spread of resistant bacteria for the following reasons: (1) resistant pathogens at infectious levels are present in animal wastes; (2) wastes contain active forms of antimicrobial agents; and (3) transfer of resistance genes occurs within the waste environment. Infectious levels of enteric bacteria are recoverable from CAFO wastes.\textsuperscript{61} \textit{Staphylococcus} and \textit{Enterococcus} spp with high levels of resistance to clarithromycin, erythromycin, clindamycin, and tetracycline (along with multidrug phenotypes) have been isolated from poultry litter collected from farms across Georgia.\textsuperscript{63} Antimicrobial-resistant \textit{Enterococci} and resistance genes in swine waste can persist in soil for more than five months.\textsuperscript{64} Wastes from CAFOs, which include spilled feeds, also contain antimicrobial compounds and metabolites. Also, food animals excrete significant amounts of biologically active forms of the antimicrobials administered in feeds.\textsuperscript{65} Many antimicrobials used in food animal production are poorly absorbed in the gut of the animal, and as much as 90% of the parent compound can be excreted in urine and up to 75\% in feces.\textsuperscript{66} Antimicrobials in wastes may select for resistance in soil environments after land disposal of animal wastes, inferring from macrocosm experiments conducted on chlortetracycline and selection for resistance in aerobic bacteria.\textsuperscript{67} The geographic concentration of large-scale agricultural operations in the United States results in the frequent application of high levels of animal wastes to geographically confined regions, which increases the risks of environmental contamination in these regions. This factor has been related to contamination of soils and irrigation water for food crops and with the presence of antimicrobial-resistant bacteria in vegetables.\textsuperscript{68–70}

INTERVENTION POINTS: LOOKING DOWNSTREAM, ACTING UPSTREAM

As shown in Fig. 3, there are several pathways by which animal antimicrobial use contributes to community exposures and reservoirs of resistance: contact with and consumption of food products, occupational exposures, and environmental contamination. The authors consider this schematic in the context of two philosophies relevant to preventing human exposures to pathogens originating in food animal production: Hazard Analysis and Critical Control Point (HACCP), a set of guidelines and regulations promulgated by the US Food and Drug Administration (FDA) and USDA,\textsuperscript{71} and the hierarchy of controls, a strategy used in occupational and environmental health to prevent chemical exposures and injury.\textsuperscript{72} HACCP focuses on preventing consumer exposure to foodborne pathogens by regulating points along the path of food “from farm to fork.” Preventing contamination of meat products and worker infection at slaughter and processing, as well as at the stages of food handling and consumption, is important independent of concerns over transmission of resistant pathogens. However, these strategies rely heavily on practices at the slaughter house, on proper storage and handling of food products, and on behavioral changes among consumers. Recent outbreaks in the United States suggest that these strategies do not completely prevent transmission of microbial pathogens on food and that assurance is ultimately based on a monitoring program that may be infeasible for a globalized food supply.

Mostly importantly, HACCP does not address the pathways of community exposure by way of occupational or environmental routes. For this purpose, the hierarchy of controls model, adapted from the industrial hygiene literature, is a useful way to
identify and evaluate interventions in terms of effective risk reduction (Fig. 4). In this model, the most effective type of intervention is elimination of the hazard; followed in decreasing order by engineering controls, administrative controls, and personal protective equipment or behavior. This analysis demonstrates that eliminating the use of antimicrobial agents in food animal production – particularly for functions unrelated to disease treatment – emerges as the most effective means of preventing further contributions to the resistance reservoir. Controls further down the hierarchy are valuable tools in mitigating human health hazards in industrial food animal production and as such are critically important. However, applying controls at these stages is complex and resource intensive. Reducing environmental contamination requires substantial investments at the CAFO level, including advanced waste treatment and changes in ventilation. Reducing worker exposure requires improved hygiene and protective equipment. Biosecurity between farm and community requires improved hygiene and pathogen control, as well as improvements in animal transport and waste management.

This analysis supports the conclusions of the World Health Organization (WHO), the World Organization for Animal Health, and the Food and Agriculture Organization of the United Nations. These organizations have specifically recommended ending the practice of adding antimicrobials to feed. The European Union recently legislated restrictions on antimicrobial feed additives. However, in the United States only the use of ciprofloxacin analogs has been banned, and in much of the rest of the world these uses have not been restricted. Thus, the majority of antimicrobial production continues to be used for this purpose.11

Prohibiting the first use of new antimicrobials in animal feeds is critically important. The practice of registering new antimicrobials for use in animal feeds before registration for human medicine is encouraged by the high barriers to approval for new agents for clinical use. This can be predicted to impair the clinical life span of the same drug.73 For example, quinupristin/dalfopristin was first approved for use in animal feeds and

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**Fig. 3.** Spread of antimicrobial-resistant pathogens (X) from agriculture to the community and hospital. Pathogens from CAFOs (pig-farm house) spread through food products, manure lagoons, air, wildlife (birds), animal transport trucks, and deposit of manure on crop-land. (Courtesy of Salvador Saenz, El Paso, TX. Copyright ©2008, Salvador Saenz.)
only years later for treatment of otherwise resistant infections in clinical medicine. Because of prior use in feeds, clinicians quickly found resistance in human isolates.

Further, the long-term implications of antimicrobial use in agriculture underscore the importance of prudent drug registration and usage policies. Evidence suggests that a ban on antimicrobial usage in feeds may not result in complete eradication of resistance in bacteria isolated from the agricultural setting or the food supply. In the European Union, the introduction and subsequent removal of avoparcin from use in pig farming demonstrates a trend of concern. While hospital prevalence rates of VRE fell after the ban, VRE continued to be found in broiler chicken flocks in Denmark. In the United States, fluoroquinolone-resistant *Campylobacter* were still isolated in 2006 from poultry products from two companies that voluntarily stopped using enrofloxacin in 2002.

**SUMMARY**

The growing appreciation of the role of the community as a source of the increasing prevalence of antimicrobial-resistant infections supports the importance of understanding nonnosocomial drivers of resistance. The emergence of community-acquired MRSA highlights the relevance of reservoirs of antimicrobial resistance in...
humans and animals in the community environment. Although hospital use of antimi-
crobials has been assumed to generate the highest risk of resistance and transmission
of resistant infections, the greater load of antimicrobial use in food animal production
makes a larger contribution to the reservoir of resistance. Multiple routes of expo-
sure connect human populations with this reservoir: food consumption, animal-to-hu-
man and human-to-human contacts, and environmental contamination. Agricultural
use of antimicrobial feed additives is a major driver for these reservoirs. Evidence
points to agriculture as a source of community MRSA and other drug-resistant infec-
tions—such as fluorquinolone-resistant campylobacteriosis in the United States and
VRE in Europe. Based on this evidence, it is imperative to implement policies that pre-
vent increases in community reservoirs of antibiotic resistance. Such policies have
been repeatedly urged for health care providers and consumers. These policies are
important. However, there has been little or no attention by medical practitioners or
the general population to current practices in agricultural use of antimicrobials.

Adopting a public health perspective of the hierarchy of controls provides a policy
framework for regulation of antimicrobials in food animal production. Just as agricul-
tural antimicrobial use dwarfs clinical use, agricultural drivers of resistance likely ex-
ceed the impact of hospital-based factors to promote and maintain reservoirs of
resistance. The authors conclude that three steps are critical to reducing transmis-
sion from agriculture to these reservoirs: eliminating antimicrobial use in animal
feeds, reducing animal-to-human spread of resistant organisms, and preventing
microbial contamination of both the environment and the food supply. Banning
antimicrobial use in animal feeds is the responsibility of the FDA, while reducing
contamination of the environment—by both antibiotics and resistant microorgan-
isms—involves the Environmental Protection Agency, as well as the USDA. More
accurate assessment of the complex interactions between hospital and community
will improve characterization of community risk factors and will enhance the under-
standing of the linkages between human populations in and out of health care set-
tings as well as improve surveillance for resistance of community origin, including
agriculture. It is time to acknowledge and act upon the warning words of Starr
and Reynolds in 1951, “It would be unfortunate if a large reservoir of drug-fast
[sic] enteric pathogens were to accumulate in the [food animal] population. The au-
thors hope that those charged with the protection of public health will objectively
evaluate this situation.” This evaluation is long overdue.

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