A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential

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ABSTRACT

Antibiotic use plays a major role in the emerging public health crisis of antibiotic resistance. Although the majority of antibiotic use occurs in agricultural settings, relatively little attention has been paid to how antibiotic use in farm animals contributes to the overall problem of antibiotic resistance. The aim of this review is to summarize literature on the role of antibiotics in the development of resistance and its risk to human health. We searched multiple databases to identify major lines of argument supporting the role of agricultural antibiotic use in the development of resistance and to summarize existing regulatory and policy documents. Several lines of reasoning support the conclusion that agricultural antibiotics are associated with resistance, yet most public policy is based on expert opinion and consensus. Finally, we propose strategies to address current gaps in knowledge.

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Antibiotic resistance is a looming public health crisis. While once believed to be the province of hospitals and other health-care facilities, a host of community factors are now known to promote antibiotic resistance, and community-associated resistant strains have now been implicated as the cause of many hospital-acquired infections.[1,2] An inherent consequence of exposure to antibiotic compounds, antibiotic resistance arises as a result of natural selection.[3] Due to normal genetic variation in bacterial populations, individual organisms may carry mutations that render antibiotics ineffective, conveying a survival advantage to the mutated strain. In the presence of antibiotics, advantageous mutations can also be transferred via plasmid exchange within the bacterial colony, resulting in proliferation of the resistance trait.[4] The emergence of drug resistance has been observed following the introduction of each new class of antibiotics, and the threat is compounded by a slow drug development pipeline and limited investment in the discovery and development of new antibiotic agents.[5–7]

International, national, and local antibiotic stewardship campaigns have been developed to encourage prudent use of and limit unnecessary exposure to antibiotics, with the ultimate goal of preserving their effectiveness for serious and life-threatening infections.[8,9] In practice, however, clinicians must balance the utilitarian goal of preserving the effectiveness of antibiotics with ethical obligations to patients who present with conditions that are unlikely to be harmed and may benefit from antibiotic use. There is also considerable debate in veterinary medicine regarding use of antibiotics in animals raised for human consumption (food animals). The potential threat to human health resulting from inappropriate antibiotic use in food animals is significant, as pathogenic-resistant organisms propagated in these livestock are poised to enter the food supply and could be widely disseminated in food products.[10–15] Commensal bacteria found in livestock are frequently present in fresh meat products and may serve as reservoirs for resistant genes that could potentially be transferred to pathogenic organisms in humans.[16,17]

While antibiotic use in food animals may represent a risk to human health, the degree and relative impact have not been well characterized. Given divergent stakeholder interests and inadequate research to date, public policy discussions of this issue are often contentious and highly polarized. The aim of this review is to examine the scope and nature of antibiotic use in food animals and summarize its potential impact on human health. We also review key national and international policies on use of antibiotics in food animals. Finally, we propose future directions for research and monitoring of the agricultural use of antibiotics.

METHODS

We searched three online databases of medical and scientific literature citations—the National Library of Medicine's MEDLINE®, the U.S. Department of Agriculture's National Agricultural Library Catalog (known as AGRICOLA), and Thomson Reuter's Web of Science—for English-language documents from 1994–2009 containing the keywords "antibiotic," "antibiotic resistance," "antimicrobial," "antimicrobial resistance," "agriculture," "livestock," "food animal," "farm animal," "pig," "swine," "cattle," "cow," "poultry," and "chicken." Two authors reviewed the references and selected exemplary original research articles examining the association between antibiotic use in food animals and antibiotic-resistant bacteria in humans. We also performed searches of the ROAR Commensal Literature Database (part of the Reservoirs of Antibiotic Resistance [ROAR] project, coordinated by the Alliance for Prudent Use of Antibiotics and funded by a grant from the National Institute of Allergy and Infectious Diseases) and the World Health Organization (WHO) website to identify research articles and policy documents pertaining to antibiotic use in food animals. An online search engine was used to locate policy statements published by governmental agencies.

RESULTS

In our review, we found that the use of antibiotics in food animals is widespread, yet poorly characterized. Furthermore, in existing studies, neither the risks to human health nor the benefits to animal production have been well studied. We also found a lack of consistency in national and international policies.

In the following sections, we review the current literature on the nature and scope of antibiotic use in food animals, and on the epidemiologic links between use of antibiotics in food animals and resistance in humans. We then provide an overview of the complex risk analysis framework required to understand this problem. Finally, we review key national and international policy and regulatory recommendations.

Literature on the nature and scope of antibiotic use in food animals

The high population density of modern intensively managed livestock operations results in sharing of both commensal flora and pathogens, which can be conducive to rapid dissemination of infectious agents.

As a result, livestock in these environments commonly require aggressive infection management strategies, which often include the use of antibiotic therapy.

Antibiotics are used in food animals to treat clinical disease, to prevent and control common disease events, and to enhance animal growth.[18] The different applications of antibiotics in food animals have been described as therapeutic use, prophylactic use, and subtherapeutic use. Antibiotics can be used to treat a single animal with clinical disease or a large group of animals. However, these various uses are frequently indistinct; definitions of each type of use vary, and the approaches are often applied concurrently in livestock populations.[19] For example, 16% of all lactating dairy cows in the U.S. receive antibiotic therapy for clinical mastitis each year, but nearly all dairy cows receive intramammary infusions of prophylactic doses of antibiotics following each lactation to prevent and control future mastitis—primarily with penicillins, cephalosporins, or other beta-lactam drugs.[20] Similarly, 15% of beef calves that enter feedlots receive antibiotics for the treatment of clinical respiratory disease, but therapeutic antibiotic doses are also administered to 10% of apparently healthy calves to mitigate anticipated outbreaks of respiratory disease.[21] Forty-two percent of beef calves in feedlots are fed tylosin—a veterinary macrolide drug—to prevent liver abscesses that negatively impact growth, and approximately 88% of growing swine in the U.S. receive antibiotics in their feed for disease prevention and growth promotion purposes, commonly tetracyclines or tylosin.[22] Most antibiotic use in livestock requires a veterinary prescription, although individual treatment decisions are often made and administered by lay farm workers in accordance with guidelines provided by a veterinarian.[23,24]

Despite the widespread adoption of antibiotic use in food animals, reliable data about the quantity and patterns of use (e.g., dose and frequency) are not available.[25] Quantifying antibiotic use in food animals is challenging due to variations in study objectives—investigators may measure only therapeutic uses, only nontherapeutic uses, or a combination thereof, depending on their outcome of interest—and lack of clarity surrounding the definitions of therapeutic vs. nontherapeutic uses.[26] Although limited, the available data suggest that food animal production is responsible for a significant proportion of antibiotic use. In 1989, the Institute of Medicine estimated that approximately half of the 31.9 million pounds of antimicrobials consumed in the U.S. were for nontherapeutic use in animals.[27] More recent estimates by the Union of Concerned Scientists, an advocacy group that supports reduced agricultural antimicrobial use, suggest that 24.6 million pounds of antimicrobials are used for nontherapeutic purposes in chickens, cattle, and swine, compared with just 3.0 million pounds used for human medicine. Calculations by the pharmaceutical industry-sponsored Animal Health Institute are more conservative, suggesting that of 17.8 million pounds of antimicrobials used for animals, only 3.1 million pounds are used nontherapeutically.[26] Twelve classes of antimicrobials—arsenicals, polypeptides, glycolipids, tetracyclines, elfamycins, macrolides, lincosamides, polyethers, beta-lactams, quinoxalines, streptogramins, and sulfonamides—may be used at different times in the life cycle of poultry, cattle, and swine.[25] While some of the antimicrobials used in animals are not currently used to treat human disease, many, such as tetracyclines, penicillins, and sulfonamides, are also used in the treatment of infections in humans.[26] The WHO has developed criteria for the classification of antibiotics as "critically important," "highly important," and "important" based on their importance in the treatment of human disease.[28,29]

However, other classes of antimicrobials used in agriculture have not led to concerns about dissemination of resistance in humans. For example, some of the most frequently used antibiotics in ruminants are ionophores, a distinctive class of antibiotics that alter intestinal flora to achieve increased energy and amino acid availability and improved nutrient utilization. Most beef calves in feedlots and some dairy heifers receive this drug routinely in their feed. Because of their specific mode of action, ionophores have never been used in humans or therapeutically in animals. While some bacteria are intrinsically resistant to these drugs, there is currently no evidence to suggest that ionophore resistance is transferable or that co-selection for resistance to other classes of antimicrobials occurs.[30]

Literature suggesting epidemiologic evidence of an association between antibiotic use in food animals and antibiotic resistance in humans

Evidence that antibiotic use in food animals can result in antibiotic-resistant infections in humans has existed for several decades. Associations between antibiotic use in food animals and the prevalence of antibiotic-resistant bacteria isolated from those animals have been detected in observational studies as well as in randomized trials. Antibiotic-resistant bacteria of animal origin have been observed in the environment surrounding livestock farming operations, on meat products available for purchase in retail food stores, and as the cause of clinical infections and subclinical colonization in humans. Figure 1 outlines a sampling of prevalence studies, outbreak investigations, ecological

Figure 1. Literature providing evidence in support of an association between antibiotic use in food animals and antibiotic-resistant bacteria in humans

Study author, year (country)	*Study description*	*Findings*
Associations between antibiotic use in food animals and antibiotic resistance in bacteria isolated from food animals		
van den Bogaard et al., 1997[a] (Netherlands)	Prevalence study of VRE in turkeys, turkey farmers, turkey slaughterers, and neighboring community residents	VRE was isolated from 50% of the turkey samples, 39% of farmers, 20% of turkey slaughterers, and 14% of community residents. VRE was significantly more prevalent among turkeys that were fed avoparcin (60% vs. 8%).
van den Bogaard et al., 2002[b] (Netherlands)	Prevalence study of resistant enterococci in fecal isolates from broiler chicken farmers and broiler chickens, for which antibiotics are used heavily, and laying hen farmers and laying hens, for which antibiotics are used rarely	Resistance was more prevalent among broiler chicken farmers and broiler chickens than among laying hen farmers and laying hens. Molecular characteristics of the isolated bacteria suggested that resistance traits were transferred from enterococci in chickens to enterococci in humans.
Funk et al., 2006[c] (United States)	Randomized study of the effects of feeding chlortetracycline subtherapeutically to pigs on antibiotic resistance observed in gram-negative fecal isolates from pigs	Resistance to tetracycline, ampicillin, gentamicin, and ceftriaxone was more prevalent among bacteria isolated from pigs that were fed chlortetracycline. Chlortetracycline in feed was significantly associated with increased resistance to tetracycline, ceftriaxone, and ampicillin.
Harada, 2008[d] (Japan)	Retrospective cohort study of the association between therapeutic antibiotic use on pig farms and antibiotic resistance observed in *E. coli* strains isolated from pigs	Compared with no exposure to antibiotics, tetracycline exposure was associated with resistance to ampicillin, dihydrostreptomycin, oxytetracycline, kanamycin, and trimethoprim; combination penicillin-streptomycin exposure was associated with resistance to ampicillin, dihydrostreptomycin, oxytetracycline, and kanamycin; penicillin exposure was associated with resistance to ampicillin and trimethoprim; and combination methoprim-sulfonamide exposure was associated with resistance to trimethoprim.
Antibiotic-resistant bacteria released from livestock farming operations		
Chapin et al., 2005[e] (United States)	Antibiotic susceptibility analysis of Enterococcus, coagulase-negative staphylococci, and viridians group streptococci isolated from air samples in an indoor swine feeding operation	Nearly all isolates (98%) were resistant to at least two antibiotics commonly used in swine production. None of the isolates was resistant to vancomycin, which has never been approved in the U.S. for use in livestock.
Sapkota et al., 2007[f] (United States)	Comparative analysis of enterococci, fecal coliforms, and *E. coli* in surface water and groundwater, upstream and downstream from swine production facilities	Concentrations of enterococci, fecal coliforms, and *E. coli* were between four and 33 times higher downstream than upstream.
Graham et al., 2008[g] (United States)	Antibiotic susceptibility analysis of enterococci and staphylococci isolated from poultry litter and flies near poultry farms	Enterococci and staphylococci were often recovered from flies captured near poultry farms. Isolates from flies carried resistance traits similar to those observed in isolates from poultry litter.
Rule et al., 2008[h] (United States)	Enumeration and antibiotic susceptibility analysis of bacteria isolated from air and surface samples taken from vehicles driving behind trucks transporting live poultry	Air and surface samples collected behind vehicles transporting poultry contained significantly more bacteria than air and surface samples collected behind control vehicles. Bacteria collected during poultry transport were more likely to carry resistance traits than bacteria collected during control samples (25% vs. 0%).

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Figure 1 (continued). Literature providing evidence in support of an association between antibiotic use in food animals and antibiotic-resistant bacteria in humans

Study author, year (country)	*Study description*	*Findings*
Prevalence of antibiotic-resistant bacteria on food products available to consumers		
Cui et al., 2005[i] (United States)	Prevalence study and antibiotic susceptibility analysis of campylobacter and salmonella isolated from organic and conventional retail chicken carcasses	Campylobacter was recovered from 76% of organic and 74% of conventional chicken; isolates from organic chicken were resistant to tetracycline and erythromycin more often than isolates from conventional chicken (81% and 49%, respectively vs. 69% and 36%, respectively). Salmonella was recovered from 61% of organic and 44% of conventional chicken; resistance varied according to serotype, but was generally more prevalent among isolates from conventional chicken.
Gundogan et al., 2005[j] (Turkey)	Prevalence study and antibiotic susceptibility analysis of *Staphylococcus aureus* isolated from retail calf, lamb, and chicken products	*Staphylococcus aureus* was recovered from 53% of meat samples; 7% of isolates were resistant to erythromycin, 53% were resistant to penicillin, 68% were resistant to methicillin (MRSA), and 88% were resistant to bacitracin.
Kim et al., 2005[k] (United States)	Antibiotic susceptibility analysis of *Klebsiella pneumonia* isolated from turkey, cattle, and chicken farms, as well as retail meat and poultry products	All *Klebsiella pneumonia* isolates were resistant to ampicillin, tetracycline, streptomycin, gentamycin, and kanamycin.
Parveen et al., 2007[l] (United States)	Prevalence study and antibiotic susceptibility analysis of Salmonella isolated from processed poultry	Salmonella was recovered from 88.4% of processed chicken carcasses before chilling and 84.1% after chilling. Antibiotic resistance was detected in 79.8% of isolates.
Antibiotic-resistant bacteria of animal origin isolated in humans		
Fein et al., 1974[m] (United States)	Comparison of antibiotic susceptibility patterns of *E. coli* strains isolated from farming families and their livestock	Resistance patterns observed in *E. coli* strains isolated from farming families were highly associated with those observed in *E. coli* strains isolated from their livestock.
Bezanson et al., 1983[n] (Canada)	Investigation of a *Salmonella typhimurium* outbreak in a neonatal intensive care unit	Maternal consumption of unpasteurized milk from cows infected with resistant *Salmonella typhimurium* resulted in asymptomatic shedding and subsequent transmission of the bacteria to a newborn infant and other patients in a neonatal intensive care unit.
Ramchandani et al., 2005[o] (United States)	Investigation of a multistate outbreak of urinary tract infections with trimethoprim-sulfamethoxazole-resistant *E. coli*	Resistant isolates from human infections were found to be nearly identical to strains isolated from food animals and environmental water sources, suggesting the bacteria were of animal origin and potentially acquired through food.
Smith et al., 2009[p] (United States)	Prevalence study of colonization with MRSA in swine and swine workers on two large swine production farms	Forty-five percent of swine workers and 49% of swine were colonized with MRSA. MRSA isolates from swine workers were closely related to MRSA isolates from swine and were different from strains commonly found in humans.

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Figure 1 (continued). Literature providing evidence in support of an association between antibiotic use in food animals and antibiotic-resistant bacteria in humans

Study author, year (country)	*Study description*	*Findings*
Ecological associations between antibiotic use in food animals and resistant bacteria in humans		
Endtz et al., 1991[q] (Netherlands)	Ecological study correlating use of fluoroquinolones to quinolone resistance in *Campylobacter* subspecies	Quinolone resistance increased from 0% to 11% in human stool and from 0% to 14% in poultry products between 1982 and 1989, during which time veterinary and human use of fluoroquinolones increased substantially.
Engberg et al., 2001[r] (multiple countries)	Ecological review of the emergence of resistance in *Campylobacter jejuni* and *Campylobacter coli* following the introduction of quinolone use in food animals	Antibiotic-resistant infections in humans emerged rapidly following the inception of quinolone use in food animals.
Unicomb et al., 2006[s] (Australia)	Prevalence study of fluoroquinolone resistance in *Campylobacter jejuni* isolates	In Australia, where use of fluoroquinolones in food animals is prohibited, only 2% of *Campylobacter jejuni* isolates from humans are resistant to ciprofloxacin.
Associations between human contact with food animals and human colonization and infection with antibiotic-resistant bacteria		
Gupta et al., 2003[t] (United States)	Case-control study and molecular characterization of *Salmonella* Newport-MDRAmpC	Exposure to dairy farms was a significant risk factor for *Salmonella* Newport-MDRAmpC infection in humans. Isolates recovered from humans had nearly identical antibiograms and pulsed-field gel electrophoresis patterns as those recovered from cows.
Aubry-Damon et al., 2004[u] (France)	Prevalence study of *Staphylococcus aureus* colonization and resistance to methicillin, macrolides, gentamicin, and pefloxacin among healthy pig farmers and non-farmers	*Staphylococcus aureus* colonization was significantly higher among pig farmers than non-farmers (44.6% vs. 24.1%). Resistance was more prevalent among pig farmers than non-farmers.
Lewis et al., 2008[v] (Denmark)	Case-control study of infection with MRSA CC398	Living or working with farms with animals was strongly and independently associated with MRSA CC398 infection.
Johnson et al., 2007[w] (United States)	Study of phylogenic and virulence markers of 931 isolates of human and poultry *E. coli* in hospitalized adults, outpatient vegetarians, and retail poultry samples	While human-resistant and sensitive *E. coli* were different, human-resistant and poultry-resistant strains were similar. Poultry-recovered resistant and sensitive strains were similar.

[a]van den Bogaard AE, Jensen LB, Stobberingh EE. Vancomycin-resistant enterococci in turkeys and farmers. N Engl J Med 1997;337:1558-9.

[b]van den Bogaard AE, Willems R, London N, Top J, Stobberingh EE. Antibiotic resistance of faecal enterococci in poultry, poultry farmers, and poultry slaughterers. J Antimicrob Chemother 2002;49:497-505.

[c]Funk JA, Lejeune JT, Wittum TE, Rajala-Shultz PJ. The effect of subtherapeutic chlortetracycline on antimicrobial resistance in the fecal flora of swine. Microb Drug Resist 2006;12:210-8.

[d]Harada K, Asai T, Ozawa M, Kojima A, Takahashi T. Farm-level impact of therapeutic antimicrobial use on antimicrobial-resistant populations of *Escherichia coli* isolates from pigs. Microb Drug Resist 2008;14:239-44.

[e]Chapin A, Rule A, Gibson K, Buckley T, Schwab K. Airborne multidrug-resistant bacteria isolated from a concentrated swine feeding operation. Environ Health Perspect 2005;113:137-42.

[f]Sapkota AR, Curriero FC, Gibson KE, Schwab KJ. Antibiotic-resistant enterococci and fecal indicators in surface water and groundwater impacted by a concentrated swine feeding operation. Environ Health Perspect 2007;115:1040-5.

[g]Graham JP, Price LB, Evans SL, Graczyk TK, Silbergeld EK. Antibiotic resistant enterococci and staphylococci isolated from flies collected near confined poultry feeding operations. Sci Total Environ 2009;407:2701-10.

[h]Rule AM, Evans SL, Silbergeld EK. Food animal transport: a potential source of community exposure to health hazards from industrial farming (CAFOs). J Infect Public Health 2008;1:33-9.

[i]Cui S, Ge B, Zheng J, Meng J. Prevalence and antimicrobial resistance of *Campylobacter spp.* and *Salmonella serovars* in organic chickens from Maryland retail stores. Appl Environ Microbiol 2005;71:4108-11.

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Figure 1 (continued). Literature providing evidence in support of an association between antibiotic use in food animals and antibiotic-resistant bacteria in humans

[j]Gundogan N, Citak S, Yucel N, Devren A. A note on the incidence and antibiotic resistance of *Staphylococcus aureus* isolated from meat and chicken samples. Meat Sci 2005;69:807-10.

[k]Kim SH, Wei CI, Tzou YM, An H. Multidrug-resistant *Klebsiella pneumoniae* isolated from farm environments and retail products in Oklahoma. J Food Prot 2005;68:2022-9.

[l]Parveen S, Taabodi M, Schwarz JG, Oscar TP, Harter-Dennis J, White DG. Prevalence and antimicrobial resistance of *Salmonella* recovered from processed poultry. J Food Prot 2007;70:2466-72.

[m]Fein D, Burton G, Tsutakawa R, Blenden D. Matching of antibiotic resistance patterns of *Escherichia coli* of farm families and their animals. J Infect Dis 1974;130:274-9.

[n]Bezanson GS, Khakhria R, Bollegraaf E. Nosocomial outbreak caused by antibiotic-resistant strain of *Salmonella typhimurium* acquired from dairy cattle. Can Med Assoc J 1983;128:426-7.

[o]Ramchandani M, Manges AR, DebRoy C, Smith SP, Johnson JR, Riley LW. Possible animal origin of human-associated multidrug-resistant, uropathogenic *Escherichia coli*. Clin Infect Dis 2005;40:251-7.

[p]Smith TC, Male MJ, Harper AL, Kroeger JS, Tinkler GP, Moritz ED, et al. Methicillin-resistant *Staphylococcus aureus* (MRSA) strain ST398 is present in midwestern U.S. swine and swine workers. PLoS One 2009;4:e4258.

[q]Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van der Reyden T, Mouton RP. Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. J Antimicrob Chemother 1991;27:199-208.

[r]Engberg J, Aarestrup FM, Taylor DE, Gerner-Smidt P, Nachamkin I. Quinolone and macrolide resistance in *Campylobacter jejuni* and *C. coli*: resistance mechanisms and trends in human isolates [published erratum appears in Emerg Infect Dis 2001;7:491]. Emerg Infect Dis 2001;7:24-34.

[s]Unicomb LE, Ferguson J, Stafford RJ, Ashbolt R, Kirk MD, Becker NG, et al. Low-level fluoroquinolone resistance among *Campylobacter jejuni* isolates in Australia. Clin Infect Dis 2006;42:1368-74.

[t]Gupta A, Fontana J, Crowe C, Bolstorff B, Stout A, Van Duyne S, et al. Emergence of multidrug-resistant *Salmonella* enteric serotype Newport infections resistant to expanded-spectrum cephalosporins in the United States. J Infect Dis 2003;188:1707-16.

[u]Aubry-Damon H, Grenet K, Sall-Ndiaye P, Che D, Cordeiro E, Bougnoux ME, et al. Antimicrobial resistance in commensal flora of pig farmers. Emerg Infect Dis 2004;10:873-9.

[v]Lewis HC, Mølbak K, Reese C, Aarestrup FM, Selchau M, Sørum M, et al. Pigs as source of methicillin-resistant *Staphylococcus aureus* CC398 infections in humans, Denmark. Emerg Infect Dis 2008;14:1383-9.

[w]Johnson JR, Sannes MR, Croy C, Johnston B, Clabots C, Kuskowski MA, et al. Antimicrobial drug-resistant *Escherichia coli* from humans and poultry products, Minnesota and Wisconsin, 2002–2004. Emerg Infect Dis 2007;13:838-46.

VRE = vancomycin-resistant enterococci

E. coli = *Escherichia coli*

MRSA = methicillin-resistant *Staphylococcus aureus*

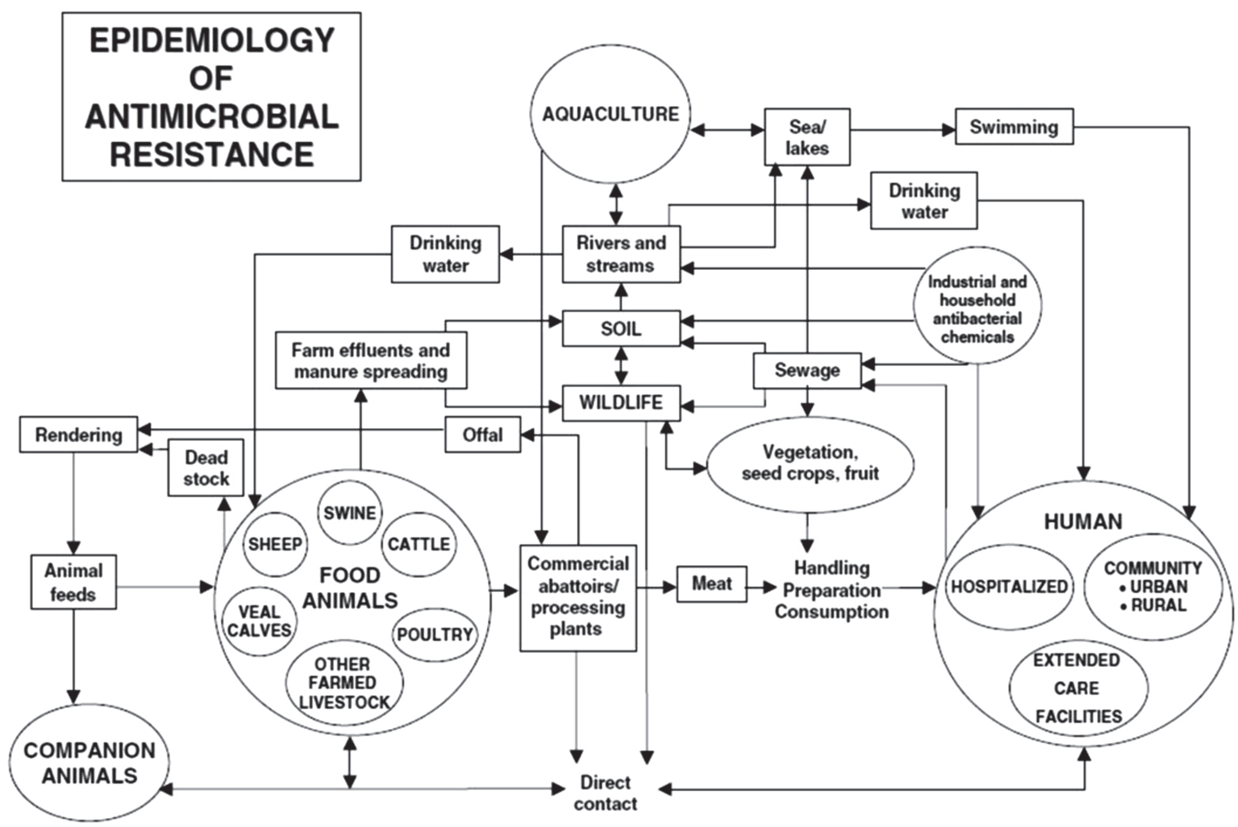
MRSA CC398 = methicillin-resistant *Staphylococcus aureus* clonal complex 398 studies, case-control studies, and randomized trials whose results suggest a potential relationship between antibiotic use in food animals and antibiotic resistance in humans.

Literature on the risks and benefits of antibiotic use in food animals

To understand how antibiotic use in agriculture might impact the emergence of antibiotic resistance, it is essential to consider the complex interaction of elements in the physical environment (e.g., air, soil, and water) with social exchanges (e.g., between animals within a herd, farmers and animals, and domestic poultry and migratory birds), in processing steps (e.g., farming activities, transportation, and storage), and in human use patterns (e.g., food preparation, meat consumption, and susceptibility to infection) (Figure 2). Antibiotic use in animals can have direct and indirect effects on human health: direct effects are those that can be causally linked to contact with antibiotic-resistant bacteria from food animals, and indirect effects are those that result from contact with resistant organisms that have been spread to various components of the ecosystem (e.g., water and soil) as a result of antibiotic use in food animals (Figure 3).

Given the multitude of factors that contribute to the pathways by which antibiotic use in food animals could pose risks to human health, it is not surprising that a wide variety of methods has been used by researchers in various disciplines to approach the problem. In general, risk assessment models in veterinary medicine emphasize animal health and treatment of diseases in animals, food scientists' studies focus on the safety of human food supplies and the presence of antibiotic-resistant bacteria on food products, clinicians and epidemiologists investigate human outbreaks caused by resistant infections for which animals are identified as primary sources, and molecular biologists examine relationships between resistant strains and the prevalence of specific resistance genes in human and animal bacteria. It is

Figure 2. Proposed mechanisms of transmission of antibiotic resistance[a]



[a]Health Canada, Veterinary Drugs Directorate. Uses of antimicrobials in food animals in Canada: impact on resistance and human health. June 2002 [cited 2010 Nov 11]. Available from: URL: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/pubs/amr-ram_final_report-rapport_06-27-eng.pdf. Reproduced with the permission of the Minister of Public Works and Government Services, Canada. ©2010 Health Canada.

Figure 3. Examples of direct and indirect effects of antibiotic use in food animals on human health

Direct effects	*Indirect effects*
Exposure to farm animals treated with antibiotics causes increased risk of resistant colonization or infection in humans.	Transport of animals causes dispersion of resistant bacteria along route.
Consumption of food contaminated with antibiotic-resistant bacteria causes an outbreak of resistant diarrheal disease.	Mobile genetic elements from antibiotic-resistant bacteria in animals are incorporated into pathogens that cause cases of human infection.
Consumption of antibiotic-containing meat products induces resistance in normal flora of the human gastrointestinal tract.	Resistant bacteria from animal waste used as fertilizer cause contamination of water supply and alterations in human flora.
	Companion animal contact with antibiotic-resistant-containing pet food results in animal or human colonization and infection.

unlikely that any single study will be able to fully and accurately quantify the relationship between antibiotic use in food animals and infections in humans. At best, only crude estimates of the etiologic fraction or "impact fraction" can be made for specific links in the ecologic chain.[31]

Several mathematical models have been proposed to quantify the overall risk associated with antibiotic use in animals, typically by estimating the prevalence of infection with a specific organism and its associated morbidity, and then multiplying by the proportion of these infections believed to be attributable to antibiotic use in food animals. While models of this nature have been rightfully criticized for failing to include indirect risk and, consequently, underestimating total potential risk, felicitous risk assessment strategies must also consider the potential benefits of antibiotic use in food animals. Even though agricultural antibiotic use carries a demonstrated risk, there are likely benefits to the agricultural use of antibiotics as well. For example, reducing animal microbial load and shedding could lead to safer, more affordable food. However, many of the claims of benefit have not been fully demonstrated in large-scale trials, and other trials have shown that the overall impact of the short-term benefit is poorly described.

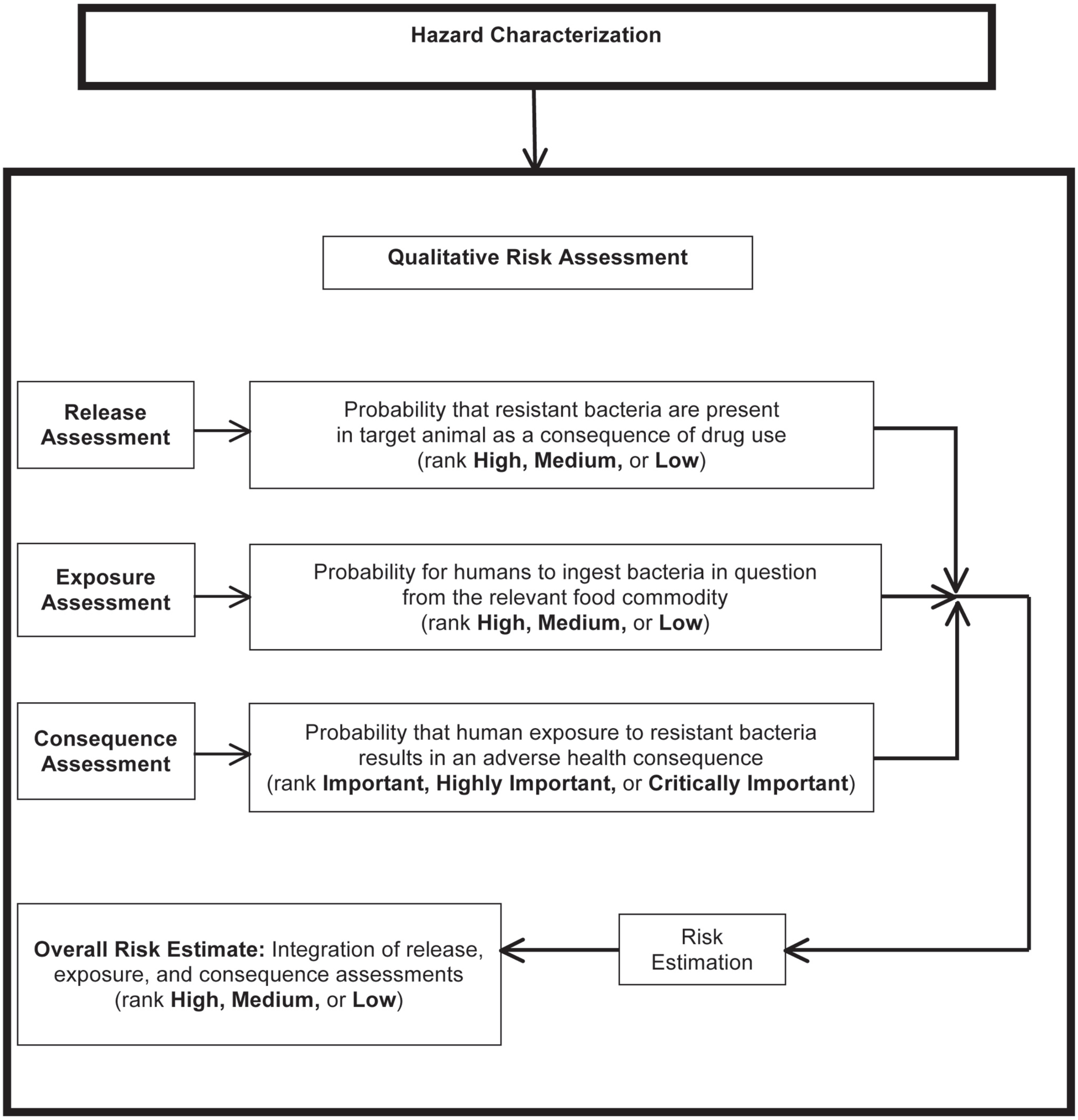
The U.S. Food and Drug Administration (FDA) requires manufacturers of new antibiotics to perform risk assessments to demonstrate that new drugs are safe and effective for use in animals and that "there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals."[32] To evaluate potential human health consequences, the FDA employs a qualitative framework to classify as "low," "medium," or "high" the probabilities that bacteria in the animal population will acquire resistance, that humans will ingest the resistant bacteria in food products, and that ingesting the bacteria will result in adverse health outcomes (Figure 4). Drug approval decisions are based on these risk estimations, along with information about proposed marketing status (e.g., prescription, over-the-counter, or veterinary feed additives), extent of limitations on extra-label use, and intended use patterns (e.g., duration of use and administration to individual animals vs. select groups of animals vs. flocks or herds of animals). "High-risk" drugs may be approved if the FDA determines that human health risk can be mitigated. "Medium-risk" drugs could be approved if appropriate label restrictions are required.

In addition to the direct risk assessment model, the FDA has developed guidance to determine the risk of antibiotic residues remaining on food products.[32] This guidance recommends determining the impact of antibiotic residues on normal human intestinal flora and the presence of resistance in these strains, and it provides guidelines for the calculation of Acceptable Daily Intake (ADI) for antibiotic residues that pose an appreciable risk to human health.

Guidelines and recommendations on the use of antibiotics in food animals

Given the importance of antibiotic resistance as a public health problem, many governments and professional societies have reviewed existing scientific evidence and developed recommendations to limit all types of antibiotic use, including use in food animals. Depending on the nature and jurisdiction of each group, the findings may provide best practice guidelines for antibiotic use, prioritized agendas for research on the emergence of antibiotic resistance, recommendations for legislative action to regulate drug approval and surveillance processes, or enforceable laws on the manufacture, distribution, and prescription of antibiotics. Figure 5 summarizes recommendations directly related to use of antibiotics in food animal production for a sample of national and international guidance and policy documents.

Figure 4. U.S. Food and Drug Administration risk assessment model for the impact of antibiotics on human health[a]



[a]Department of Health and Human Services (US), Food and Drug Administration, Center for Veterinary Medicine. Guidance for industry #152: evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. 2003 Oct 23 [cited 2010 Nov 11]. Available from: URL: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf

Figure 5. Guidance and policy on the use of antibiotics in food animal production[a]

Title (organization, year)	*Recommendations*
Antimicrobial Resistance from Food Animals[b] (WHO, 2008)	• Promote/assist national implementation of WHO and OIE guidelines, and identify barriers to implementation • Encourage national participation in development of international antimicrobial use guidelines • Promote national surveillance of antimicrobial use and AMR, and creation of national AMR containment task forces • Establish international information sharing/monitoring networks for antimicrobial use and emerging AMR using existing training platforms • Conduct national surveillance of AMR in animals, humans, and food; use integrated data to identify AMR emergence arising from non-human use; implement timely measures to contain AMR • Consider potential development of AMR and cross-resistance during national prelicensing safety evaluation of veterinary drugs; conduct post-licensing surveillance of emerging AMR • Provide incentives for development of new antimicrobials; fund education and research • Control national sale and distribution of antimicrobials; prevent illicit manufacture, importation, and sale of veterinary antimicrobial drugs • Encourage good hygienic practices and farm management to ensure animal health without the use of antimicrobials • Require prescriptions for animal antimicrobial use; develop national veterinary guidelines for appropriate antimicrobial prescribing
Foodborne Antimicrobial Resistance as a Biological Hazard: Scientific Opinion of the Panel on Biological Hazards[c] (European Food Safety Authority, 2008)	• Target known routes of transmission for specific resistance traits • Prioritize interventions to reduce emerging resistance to fluoroquinolones and to third- and fourth-generation cephalosporins • Implement uniform adoption of risk assessment methodologies at the national and international level; encourage global adoption of EU standards for measuring the development of AMR • Investigate role of food, water, and the environment in the spread of epidemic plasmids that encode resistance • Consider the role of commensals and bacteria intentionally added to aid food processing in transmission of resistance • Develop new approaches for recognizing and controlling transmission of resistance genes based on epidemiologic and source attribution research
Putting Meat on the Table: Industrial Farm Animal Production in America[d] (Pew Commission on Industrial Farm Animal Production, 2008)	• Phase out nontherapeutic antimicrobial use in food animals; immediately ban nontherapeutic use of newly approved antimicrobials; clarify antimicrobial definitions to provide clear estimates of use and facilitate clear policy-making • Consolidate food safety roles of the USDA, FDA, and EPA into a single Food Safety Administration • Develop risk-based food safety system; strengthen FDA Guidance 152 and retroactively investigate previously approved antimicrobials with new criteria • Expand USDA's extension service to include educational programs on best practices for disease mitigation in animal husbandry; expand interdisciplinary education to strengthen partnerships among physicians, veterinarians, and public health professionals • Restrict public access to agricultural sources of antimicrobials; enforce restricted access to prescription drugs and veterinary oversight and authorization of all antimicrobial use in food animals • Implement national disease-monitoring database to allow 48-hour trace-back to individual animals • Require reporting of gross annual antimicrobial sales; incorporate into NAIS; link to NARMS • Increase monitoring of effects of antimicrobial exposure among farm workers and people living close to farms
Antimicrobial Resistance: Implications for the Food System[e] (Institute of Food Technologists, 2006)	• Conduct risk assessment to determine effects of specific antimicrobial-organism exposures on the development of resistance under various conditions and environments; determine relationship between use of specific antibiotics in food animal husbandry and resistance selection rates among major foodborne bacteria at slaughter; compare resistance rates between antibiotic-use farms and antibiotic-free farms • Advance understanding of the mechanisms of resistance; improve ability to predict the potential for cross-resistance • Increase research and development of antibiotic alternatives; examine whether microbial interventions are equally effective for antimicrobial-susceptible and -resistant microorganisms • Expand development of prudent use guidelines to include all antibiotic uses and modify as new evidence becomes available; use surveillance and food attribution models to measure the effectiveness of interventions

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Figure 5 (continued). Guidance and policy on the use of antibiotics in food animal production[a]

Title (organization, year)	*Recommendations*
Current Thinking on Risk Management Measures to Address Antimicrobial Resistance Associated with the Use of Antimicrobial Agents in Food-Producing Animals[f] (Veterinary Drugs Directorate, Health Canada, 2005)	• Invest in scientific risk-based analysis of new and existing antimicrobial agents used in veterinary medicine and food animals • Create expert advisory committee on AMR risk assessment • Require veterinary prescriptions for all antimicrobial agents used for disease treatment and control in animals • Convene a stakeholder committee on the prudent use of antimicrobial agents led by the Canadian Veterinary Medical Association
Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals[g] (U.S. General Accounting Office, 2004)	• Expedite FDA risk assessments of veterinary antibiotics identified as "critically important" to human health; determine if action is necessary to restrict or prohibit animal uses to safeguard human health • Develop and implement a plan headed by the Secretaries of Agriculture and Health and Human Services to collect data on the relationship between antimicrobial use in food animals and emerging AMR, the human health risks of antibiotic use in food animals, and strategies to mitigate AMR
Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options[h] (WHO, 2004)	• Establish national surveillance programs on non-human uses of antimicrobials and AMR bacteria from food and animals • Implement strategies to prevent transmission of AMR bacteria from animals to humans through food production; include specific management techniques to prevent emergence and dissemination of bacteria resistant to antimicrobials that are "critically important" for human therapy • Follow WHO/OIE guidelines on responsible and prudent antimicrobial use • Develop risk assessment/management protocols to control emergence and national/international dissemination of AMR • Enhance the capacity of countries (particularly developing countries) to conduct surveillance of antimicrobial use and AMR, implement strategies to contain AMR, and conduct risk assessments to select proper management approaches
Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment[i] (WHO, 2003)	• Establish national surveillance programs using internationally agreed upon antimicrobial classifications to capture standardized information on the quantity of antimicrobials used in specific food animals • Link antimicrobial usage data to human surveillance systems and susceptibility testing of isolates from food animals, food products of animal origin, and environments surrounding livestock operations • Avoid group medication by feed or water; require prescriptions for antimicrobial use; restrict off-label and growth-promoting use of antimicrobials; study impacts of various animal production systems with different antimicrobial usage patterns on AMR • Reduce profit from sales of antimicrobials by veterinarians; adopt Codex *Recommended International Code of Practice—General Principles of Food Hygiene* (Source: Joint FAO/WHO Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme. Available from: URL: http://www.fao.org/docrep/005/Y1579E/y1579e02.htm) • Develop and implement strategies to prevent and control Salmonella and Campylobacter in primary production • Identify antimicrobials critically important to human medicine and review/revise regularly; determine appropriate use of these agents (e.g., do not use, use only in individual animals, use only when deemed necessary by culture susceptibility, or use for herds only after risk assessment demonstrates acceptable safety) • Develop plan to control zoonotic pathogenic bacteria resistant to at least two critically important antimicrobials in the food supply by recalling affected foods, restricting movement of infected or colonized animals, implementing processing methods that remove all resistant bacteria, destroying all affected food, and/or destroying colonized or infected animals • Conduct pre- and post-marketing risk assessments for new antimicrobials, reevaluate existing antimicrobials with new criteria, require peer review of risk assessment strategies, and develop risk management strategies and implement when appropriate • Assist countries (particularly developing countries) with conducting surveillance, expanding food hygiene education programs, and containing the spread of AMR; quantify spread of resistance from international trading of food animals and food products of animal origin • Approach AMR with interdisciplinary research and policy development teams • Study co-selection of resistance determinants by antimicrobials, selection by other substances with antimicrobial activity, the flow of resistance determinants between humans and animals, the role of commensals as reservoirs of resistance, the appearance and disappearance of multiresistant clones, and human health consequences such as the association between resistance and virulence in humans and the cost of resistant infections

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Figure 5 (continued). Guidance and policy on the use of antibiotics in food animal production[a]

Title (organization, year)	*Recommendations*
Uses of Antimicrobials in Food Animals in Canada: Impact on Resistance and Human Health[j] (Health Canada, Veterinary Drugs Directorate, 2002)	• Consider human health impacts when regulating antimicrobial licensing, sale, distribution, and compliance; define resistance thresholds for post-approval surveillance; provide remedial action if thresholds are surpassed, up to and including modification of approval or suspension of marketing • Ban importation, sale, and use of antimicrobials not evaluated and registered by Health Canada • Require prescriptions for all antimicrobials; prohibit extra-label use of antimicrobials important to human health • Ban use of antimicrobials important to human health (or likely to promote resistance to such agents) for growth promotion • Conduct risk-based evaluations of the potential human health effects of antimicrobial drugs in food animals; prioritize antimicrobials important to human medicine; improve transparency of risk assessment and management • Develop NARMS-compatible national AMR surveillance system to monitor isolates from domestic and imported food animals and food of animal origin; link to human infection surveillance system; analyze and publish surveillance data with input from pharmaceutical and food-producing industries; provide annual report of antimicrobial use • Develop farm food safety programs that address AMR; implement Canadian Veterinary Medical Association prudent-use principles on farms; conduct farm audits to ensure proper management techniques are in place • Promote preventive medicine and prudent use of antimicrobials in veterinary undergraduate, postgraduate, and continuing education programs; evaluate effectiveness of educational programs • Charge government with leadership role in encouraging AMR research and policy; encourage producer associations, research foundations, and national funding agencies to prioritize support for AMR research; seek independent, expert advice on AMR issues on a regular basis • Eliminate financial incentives to prescribe antimicrobials; ensure that advertisements do not promote antimicrobial uses that encourage resistance • Harmonize veterinary drug regulations with those used in other countries, especially the United States • Educate consumer groups about the human health aspects of antimicrobial use in food animals and efforts underway to reduce adverse effects
WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food[k] (WHO, 2000)	• Adopt national efforts to reduce the need for antimicrobials in animals • Inform the public about potential human health risks of antimicrobial use in food animals • Consider human health risks, resistance in related bacterial strains, optimal therapeutic dosages, pharmacokinetics, clinical efficacy, and residues when licensing antimicrobials; review existing labeling to ensure compliance with updated guidelines; conduct post-approval surveillance to detect and manage emerging AMR • Ban use of antimicrobials important to human medicine for growth promotion and other extra-label uses; only allow therapeutic use of these agents if deemed necessary based on culture susceptibility • Control distribution and sale of counterfeit, subpotent, and misbranded veterinary antimicrobials; restrict antimicrobial advertising that encourages non-prudent use; permit direct advertising of prescription antimicrobials only to veterinary professionals • Establish surveillance programs to track susceptibility trends of zoonotic bacteria and antimicrobial use in food animals; make data available to health professionals and the general public • Develop and regularly review prudent use guidelines that include locally derived, species-specific treatments; educate veterinary students and professionals to follow guidelines and self-evaluate prescribing practices • Require veterinarians to record antimicrobial use, bacterial susceptibility, and treatment outcomes for food animals; allow veterinarians to prescribe antimicrobials only to animals under their direct care; encourage veterinarians and farmers to collaboratively develop integrated animal health programs focused on disease prevention
Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health[l] (U.S. General Accounting Office, 1999)	• Develop and implement plan headed by the Secretaries of Agriculture and Health and Human Services that contains specific goals, time frames, and resources needed to evaluate the risks and benefits of existing and future uses of antibiotics in food animals

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Figure 5 (continued). Guidance and policy on the use of antibiotics in food animal production[a]

Title (organization, year)	*Recommendations*
Opinion of the Scientific Steering Committee on Antimicrobial Resistance[m] (European Commission, 1999)	• Educate veterinarians, farmers, food producers, and consumers about the rationale for the prudent use of antimicrobials, disease prevention methods in animals, and prevention of zoonotic infections in humans and animals • Collect data on individual prescribing practices, and provide feedback as needed • Phase out and ban use of antimicrobials used in humans (or that select for cross-resistance to such agents) as growth promoters; discourage all antimicrobial use for growth promotion purposes • Reduce need for herd treatments by improved husbandry, vaccination, and infectious disease control and eradication; only allow herd treatment with antimicrobials if no other alternative is available; investigate failures of preventive measures; maintain records of all antimicrobial use on farms • Evaluate means and likelihood of pathogenic organisms acquiring resistance from normal host flora in vivo • Adopt EU-wide coordination of organism collection and of susceptibility testing methods to monitor resistance patterns over time; monitor antimicrobial consumption over time • Quantify impact of AMR on human mortality and morbidity
The Medical Impact of Antimicrobial Use in Food Animals[n] (WHO, 1997)	• Cease use of antimicrobials used therapeutically in humans (or that select for cross-resistance to such agents) for animal growth promotion; develop alternative non-antimicrobial growth promoters • Monitor national prevalence of AMR in food animals and animal food products • Maintain national records of bulk chemicals with potential antimicrobial use • Assess public health risks as part of approval process for antimicrobials used in food animals; implement post-marketing plan to detect AMR emergence; set national AMR thresholds to determine when to withdraw drug approval • Quantify transfer rate of resistance genes and bacteria from animals to humans; determine rate of AMR emergence for medically relevant bacteria in food animals; measure effects of duration/concentration of antimicrobial exposure on the rate of resistance selection; examine effects of antimicrobial cessation on the prevalence and persistence of AMR • Include AMR in the Codex Committee on Residues of Veterinary Drugs in Foods; internationally standardize residue guidelines and nationally monitor compliance; study selection potential of antimicrobials at permitted residue levels • Evaluate impacts of antimicrobial use in domestic pets on development of resistance on farms; study risks posed by resistance genes in bacteria used in probiotic therapy; determine means to reestablish susceptible flora following antimicrobial usage • Establish and enforce national regulations to control the distribution and sale of antimicrobials; convene WHO/FAO expert consultation to develop practice guidelines for prudent use of antimicrobials in food animals • Expand WHONET software (available from: URL: http://www.who.int/drugresistance/whonetsoftware/en) to include specific ways of collecting and analyzing bacteria from food animals; coordinate with emerging networks, such as Enter-net and the European zoonoses laboratories

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Figure 5 (continued). Guidance and policy on the use of antibiotics in food animal production[a]

Title (organization, year)	*Recommendations*
The Use of Antibiotics in Food-Producing Animals: Antibiotic-Resistant Bacteria in Animals and Humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR)[c] (Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry—Australia, 1999)	• Provide regulatory controls on the use of antibiotics, particularly as growth promoters, and improved tracking of antibiotic use in food animals • Provide monitoring and active and passive surveillance of antibiotic resistance • Develop infection prevention strategies and measures targeting critical control points for the spread of antibiotic resistance infection and the use of the most effective treatment strategies in intensive animal production facilities • Provide education on appropriate use of antibiotics from professional organizations, industry, and governmental agencies • Continue research on alternatives to the use of antibiotics in animal production, molecular and gene transfer studies, the effect of intervention programs, and improved diagnostic methods

[a]The table summarizes only those recommendations directly related to the use of antibiotics in food animal production.

[b]World Health Organization, International Food Safety Authorities Network (INFOSAN). INFOSAN information note no. 2/2008—antimicrobial resistance, 2008 Mar 7. Antimicrobial resistance from food animals [cited 2010 Nov 11]. Available from: URL: http://www.who.int/foodsafety/fs_management/No_02_Antimicrobial_Mar08_EN.pdf

[c]European Food Safety Authority. Foodborne antimicrobial resistance as a biological hazard: scientific opinion of the Panel on Biological Hazards. EFSA J 2008;6(8). Also available from: URL: http://www.efsa.europa.eu/en/efsajournal/pub/765.htm [cited 2011 Sep 12].

[d]The Pew Charitable Trusts, Johns Hopkins Bloomberg School of Public Health. Putting meat on the table: industrial farm animal production in America. A report of the Pew Commission on Industrial Farm Animal Production. 2008 [cited 2010 Nov 11]. Available from: URL: http://www.ncifap.org/_images/PCIFAPFin.pdf

[e]Institute of Food Technologists. Antimicrobial resistance: implications for the food system. 2006 Aug 2 [cited 2010 Nov 11]. Available from: URL: http://www.ift.org/knowledge-center/read-ift-publications/science-reports/expert-reports/antimicrobial-resistance.aspx?page=viewall

[f]Health Canada, Veterinary Drugs Directorate, Health Products and Food Branch. Current thinking on risk management measures to address antimicrobial resistance associated with the use of antimicrobial agents in food-producing animals. 2005 Jun 4 [cited 2010 Nov 11]. Available from: URL: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/vet/amr-ram_rep-rap_06_05-eng.pdf

[g]General Accounting Office (US). Antibiotic resistance: federal agencies need to better focus efforts to address risk to humans from antibiotic use in animals. Report to congressional requesters. April 2004 [cited 2010 Nov 11]. Available from: URL: http://www.gao.gov/new.items/d04490.pdf

[h]Food and Agriculture Organization of the United Nations, World Health Organization, World Organisation for Animal Health (Organisation International des Epizooties). Second joint FAO/OIE/WHO expert workshop on non-human antimicrobial usage and antimicrobial resistance: management options, 2004 Mar 15–18, Oslo [cited 2010 Nov 11]. Available from: URL: http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_ZFK_2004.8.pdf

[i]Food and Agriculture Organization of the United Nations, World Health Organization, World Organisation for Animal Health (Organisation International des Epizooties). Joint FAO/OIE/WHO expert workshop on non-human antimicrobial usage and antimicrobial resistance: scientific assessment, 2003 Dec 1–5, Geneva [cited 2010 Nov 11]. Available from: URL: http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_ZFK_2004.7.pdf

[j]Health Canada, Veterinary Drugs Directorate. Uses of antimicrobials in food animals in Canada: impact on resistance and human health. June 2002 [cited 2010 Nov 11]. Available from: URL: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/pubs/amr-ram_final_report-rapport_06-27-eng.pdf

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Figure 5 (continued). Guidance and policy on the use of antibiotics in food animal production[a]

[k]World Health Organization. WHO global principles for the containment of antimicrobial resistance in animals intended for food: report of a WHO consultation with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties, 5–9 Jun 2000, Geneva [cited 2010 Nov 11]. Available from: URL: http://whqlibdoc.who.int/hq/2000/who_cds_csr_aph_2000.4.pdf

[l]General Accounting Office (US). Food safety: the agricultural use of antibiotics and its implications for human health. Report to the Honorable Tom Harkin, Ranking Minority Member, Committee on Agriculture, Nutrition, and Forestry, U.S. Senate. April 1999 [cited 2010 Nov 11]. Available from: URL: http://www.gao.gov/archive/1999/rc99074.pdf

[m]European Commission. Opinion of the Scientific Steering Committee on Antimicrobial Resistance, 28 May 1999 [cited 2010 Nov 11]. Available from: URL: http://ec.europa.eu/food/fs/sc/ssc/out50_en.pdf

[n]World Health Organization. The medical impact of antimicrobial use in food animals. Report of a WHO meeting, 16–17 Oct 1997, Berlin [cited 2010 Nov 11]. Available from: URL: http://whqlibdoc.who.int/hq/1997/WHO_EMC_ZOO_97.4.pdf

[o]Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries, and Forestry (Australia). The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR), 1999 [cited 2010 Nov 8]. Available from: URL: http://www.health.gov.au/internet/main/publishing.nsf/content/2A8435C711929352CA256F180057901E/$File/jetacar.pdf

WHO = World Health Organization

OIE = World Organisation for Animal Health (Organisation International des Epizooties)

AMR = antimicrobial resistance

EU = European Union

USDA = United States Department of Agriculture

FDA = Food and Drug Administration (US)

EPA = Environmental Protection Agency (US)

NAIS = National Animal Identification System

NARMS = National Antimicrobial Resistance Monitoring System

FAO = Food and Agriculture Organization of the United Nations

DISCUSSION

Despite increasingly widespread recognition that antibiotic use in food animals is an important contributor to human infections with antibiotic-resistant bacteria (Figure 1), there remains a significant need for scientific evidence of the antibiotic use practices that create the greatest human health risk. Our goal with this article was not to propose specific solutions to the problem—in part because we believe there are no easy, specific answers—but rather to reiterate and summarize the importance of this issue and to suggest some general policy directions that are indicated. As the importance of the problem and complexity of the issues are increasingly appreciated by the public, policy dialogue, focused research, and informed regulatory action can be undertaken. To facilitate further research and timely action in response to emerging knowledge on this issue, we propose the following measures, which are in concert with WHO's global strategy for the containment of antimicrobial resistance, the U.S. Interagency Task Force on Antibiotic Resistance's public health action plan to combat antimicrobial resistance, and the Infectious Diseases Society of America's call to action.[33–35]

Develop a scientific agenda to recommend appropriate study designs and specific aims related to antimicrobial use in food animals

A coordinated plan is needed to identify missing scientific data and to specify research designs and methods to address these needs. Although rigorous studies have been conducted in some disciplines, there has been a lack of serious and harmonized interdisciplinary effort to expand on the corpus of knowledge, which should be used to inform public policy. To result in a useful and complete list of research priorities, the agenda must include contributions by experts in basic sciences (e.g., genetics and microbiology), clinical sciences (e.g., veterinary medicine and human medicine), public health (e.g., epidemiology and nursing), social sciences (e.g., anthropology and sociology), economics (e.g., health and agriculture), and public policy (e.g., legislative and regulatory). Research goals put forth in the agenda should be reflective of methodological weaknesses identified in the existing literature. For example, definitions of antibiotic uses in food animals (e.g., therapeutic and subtherapeutic) should be standardized and designed to reflect specific goals (e.g., improving production or preventing economic loss from unrestrained disease); the terms should be recognized across disciplines and used to classify the potential effects of different types of antibiotic use on human health. Another potential focus could be whether to approach research on the development of resistance narrowly (i.e., the causes and effects of specific drug-organism combinations) or broadly (i.e., the causes and effects of all antibiotics used in animals on microbial flora) to develop public health recommendations.

Fund agricultural research that reflects the priorities identified by the research agenda

Inadequate funding for agricultural research has likely contributed to the lack of sufficient scientific evidence necessary for informing public health decisions. For example, in the United States, it was recently estimated that the $101 billion in combined governmental and biomedical industry research funding represents almost 5% of national health expenditures each year.[36] In 2007, the U.S. Department of Agriculture provided more than $32 million in external research funding, representing less than one one-thousandth of 1% of annual U.S. livestock and poultry sales.[37] In contrast, one single Institute within the National Institutes of Health—the National Institute of Allergy and Infectious Diseases—directed more than 20 times this amount to antimicrobial resistance research (more than $800 million) in the same year.[38] Given the scale of the antibiotic resistance problem and the demonstrated role of agricultural antibiotic uses in this impending public health crisis, adequate support for research specific to the role of agricultural uses of antibiotics in the development of resistance must be a national priority. Considering that the U.S. funds 70% to 80% of biomedical research worldwide, the need for appropriate levels of funding is especially acute.[36]

Urgently address barriers to the collection and analysis of antimicrobial use data

Complex political, economic, and social barriers limit the quality of data on the use of antibiotics in food animals. Currently, such data are provided on a voluntary basis, and the methods used to collect and compile reports are not standardized or fully transparent. While voluntary industry compliance with antibiotic reporting is commendable, the long-term effectiveness of nonbinding auditing programs is unproven. Effective surveillance of veterinary antimicrobial production and administration to food animals is a key first step toward ascertaining realistic estimates of the full scope of antibiotic use. These data will be useless, however, unless an agency with adequate analytic, regulatory, and enforcement capabilities exists. Because the commercial interests of antibiotic manufacturers must be appropriately balanced with the public health urgency for development of new antibiotics, any agency tasked with monitoring antibiotic resistance must operate independently of commercial influences when releasing data to the public and drafting evidence-based regulations to safeguard human health.

CONCLUSION

It is evident that at present, the resources devoted to studying the role of antibiotic use in food animals—both in terms of funding and scientific inquiry—are insufficient. It is now critical that agricultural use of antibiotics be recognized as one of the major contributors to the development of resistant organisms that result in life-threatening human infections and included as part of the strategy to control the mounting public health crisis of antibiotic resistance.

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