Agricultural Applications for Antimicrobials. A Danger to Human Health: An Official Position Statement of the Society of Infectious Diseases Pharmacists

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The use of antibiotics in agriculture, particularly in food-producing animals, is pervasive and represents the overwhelming majority of antibiotic use worldwide. The link between antibiotic use in animals and antibiotic resistance in humans is unequivocal. Transmission can occur by ingesting undercooked meats harboring resistant bacteria, by direct contact of animals by animal handlers, and by various other means. Antibiotics used in aquaculture and antifungals used in horticulture are also an evolving threat to human health. Regulations aimed at decreasing the amount of antibiotics used in food production to limit the development of antibiotic resistance have recently been implemented. However, further action is needed to minimize antibiotic use in agriculture. This article describes the extent of this current problem and serves as the official position of the Society of Infectious Diseases Pharmacists on this urgent threat to human health.

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The introduction of antibiotics revolutionized modern medicine. Antibiotics provide a treatment option for patients with an active infection and allow clinicians to perform modern medical techniques safely that are associated with frequent infectious complications. Without effective antibiotics, procedures such as myelosuppressive chemotherapy, organ transplantation, basic surgery, and invasive techniques (e.g., endotracheal intubation or implantation of cardiac devices) would not be feasible.[1] However, the growing rate of antibiotic resistance has been cited as a top threat to global health, with almost all facets of medical care potentially affected. The U.S. Centers for Disease Control and Prevention (CDC) states that ~2 million illnesses and 23,000 deaths annually are directly attributable to antibiotic resistance.[2] Efforts to bring novel antibiotics to the market, increased infection control efforts, and enhanced antimicrobial stewardship practices have so far not turned the tide.

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Unfortunately, most antibiotic use falls outside of the context of medical care and instead occurs overwhelmingly in agriculture and aquaculture and thus requires increased attention from society. In the early twentieth century, farmers struggled to meet dramatically increasing consumer demands for meat and meat products. In 1950 a study performed by American Cyanamid found that adding antibiotics to livestock feed accelerated animal growth rates and "[blew] the lid clear off the realm of animal nutrition" per the editors of *Successful Farming* magazine.[3] Shortly after this article was published, the use of antibiotics became more widespread for growth promotion and routine disease prevention. Notably absent was a corresponding editorial on the impact that this practice could have on antibiotics used in human medicine.

More than a decade after antibiotics began to be used in agriculture for nontherapeutic purposes, a 1966 editorial in the *New England Journal of Medicine* warned of the reality of antibiotic resistance.[4] The Swann Report of 1969 brought to light the possible dangers to the human population stemming from the use of antibiotics in food animal production.[5] Over the years, data linking routine nontherapeutic use of antibiotics in agriculture to antibiotic resistance have accumulated. A key turning point occurred in 2010, when the U.S. Food and Drug Administration (FDA), U.S. Department of Agriculture (USDA), and the CDC all testified before the U.S. Congress that there is a definite association between this nontherapeutic use of antibiotics in food animal production and the antibiotic-resistance crisis in humans.[6]

Despite significant warnings and evidence of harm, antibiotics continue to be used routinely in animal agriculture for the purposes of growth promotion, feed efficiency, and disease prevention. Moreover, current antibiotic use in agriculture dramatically exceeds antibiotic use in humans, with ~80% of antibiotics consumed annually in the United States being used for agricultural purposes (Figure 1).[7] The Animal Drug User Fee Amendments of 2008 (ADUFA 105) requires the FDA to issue an annual report of sales and distribution data for antimicrobials used in food-producing animals. Sales and distribution of medically important antimicrobials (Table 1) increased in the United States by 20% from 2009 to 2013, with over 9 million kg of medically important antimicrobial drugs sold in 2013. An estimated 95% of these antibiotics were used in food animals' feed and water. Furthermore, most of the sales of medically important antimicrobials were sold over the counter without any veterinary oversight.[8]

Our interconnected society and health system facilitates the global spread of antimicrobial resistance originating from agricultural practice. An understanding of these interactions can improve patient care by reducing infections caused by these organisms and guide consumers and policymakers to minimize nontherapeutic

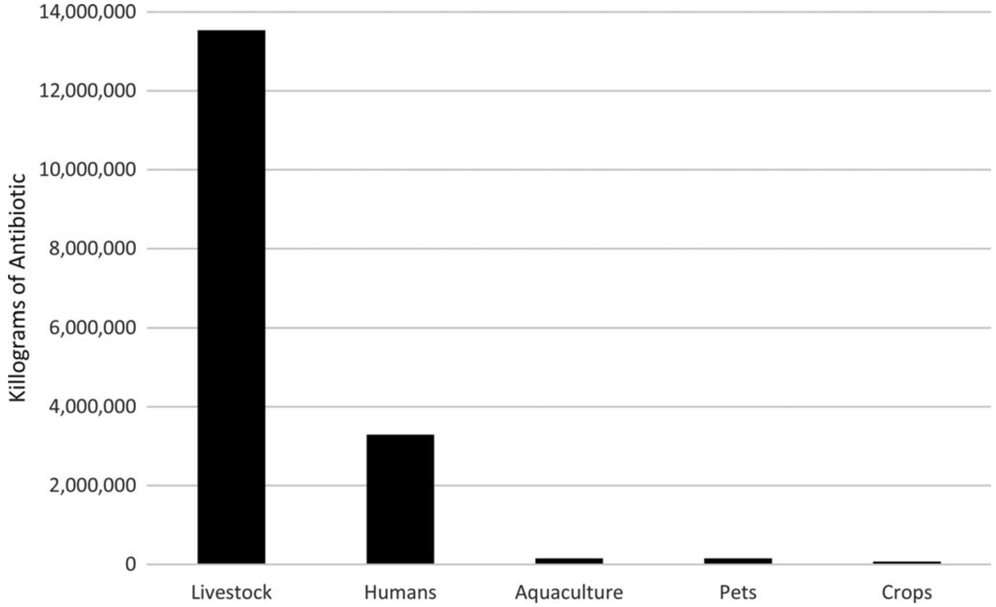


Figure 1. Estimated antibiotic consumption in the United States. (Adopted from reference 7 with permission).

Table 1. Antibiotic Importance Categories According to FDA Guidance for Industry #152

Risk category	Antibiotic classes
Critically important	Third-generation cephalosporins, fluoroquinolones, macrolides, trimethoprim/sulfamethoxazole
Highly important	Natural penicillins and semisynthetic penicillins, fourth-generation cephalosporins, carbapenems, clindamycin, aminoglycosides, tetracyclines, streptogramins, glycopeptides, oxazolidinones, rifamycins, chloramphenicol, metronidazole, polymyxin B
Important	First-generation cephalosporins, second-generation cephalosporins, monobactams

Table 2. Position Statements from the Society of Infectious Diseases Pharmacists on Antibiotics in Agriculture

1. The agricultural industry should minimize agricultural consumption of all antibiotics that the Food and Drug Administration (FDA) has deemed important to human health.
2. The agricultural industry should be required to report what antibiotics are being utilized, in which settings they are being used, and for what purposes.
3. The FDA should require mandatory, rather than voluntary, changes in the labeling of antibiotics used in agriculture to prevent their use as growth promoters.
4. Funding should be established to further investigate the magnitude of the interaction between antibiotics used in agriculture and human health.
5. Funding should be established to investigate alternative agriculture practices that optimize food production without utilizing antibiotics that have important public health risks.
6. Antifungal and antibacterial agents used in horticulture may also be impacting human health and should receive similar attention as antibacterial usage in animals.

uses of these important agents. This review highlights evidence supporting the harm of nontherapeutic use of antimicrobials in agriculture to human health and serves as an official position statement of the Society of Infectious Diseases Pharmacists (SIDP), as approved by the board of directors, on antimicrobial use in agriculture (Table 2). The society urges the agricultural industry, the U.S. government, and other governments around the world to act on these five items as a step in combating antibiotic-resistance development as a result of antimicrobial use in agriculture. This review describes the nature of common mechanisms of antibiotic resistance, how resistance mechanisms can move from animals to humans, links between animal antibiotic resistance and human health, and the potential effects of antibiotics used in animals on human health outside of antibiotic resistance. Lastly, the review discusses how antimicrobials currently being used in nonanimal agriculture may also be affecting human health. Public policies and legislative action concerning the use of antimicrobials in agriculture are rapidly evolving. Table 3 lists up-to-date resources on these important U.S. and global issues.

Therapeutically Important Antibiotics to Humans: Reasons for Use and Classification

Antibiotics used in animal feed can be generally classified into two categories: ionophore and nonionophore. The ionophore antibiotics have no current use in human medicine and are used primarily to increase feed efficiency, a measure of how well animals convert feed into body mass or milk. Mechanistically the ionophore antibiotics can transport cations and amines across biological membranes. This disrupts cellular cation gradients, arresting bacterial and fungal cell growth and inducing cell death.[9] The nonionophore antibiotics, which are often the same antibiotics used in human medicine, improve feed efficiency through a number of mechanisms including changes in volatile fatty acid ratios, changes in ammonia digestion, and inhibition of inhibiting lactic acid–producing bacteria with a subsequent decrease in the energy-intensive production of methane.[9]

Although the exact mode of action for antibiotics in growth promotion is unknown, antibiotics given in subtherapeutic doses can increase the feed efficiency and promote growth via alterations of the animal's microflora. Suppressing commensal bacteria that would otherwise divert nutrition from the animal maintains a more effective and absorptive gut lining, allowing for greater returns in weight gain without providing any additional feed for the animals.[3] In addition, nonionophore antibiotics have been used to increase feed efficiency by preventing infection in the intensive farm systems commonly seen in poultry and swine production.

The extent to which antibiotics increase food production efficiency depends on a number of variables including the diet fed to the animal and the conditions in which the animal is raised.[8] Changes in animal feed during the last few decades calls into question the extrapolation of early studies demonstrating a benefit of antibiotics on food efficiency. Although commercial interests continue to claim that the withdrawal of growth-promoting antimicrobials will

Table 3. Websites Describing Public Policy and Actions Steps Enacted Regarding Antibiotics in Agriculture

Pew Research Center: http://www.pewtrusts.org/en/projects/antibiotic-resistance-project/about/antibiotic-use-in-food-animals
Center for Global Development: http://www.cgdev.org/
United States President's Council of Advisors on Science and Technology: http://www.whitehouse.gov/ostp/pcast
One Health: http://www.cdc.gov/onehealth/
European Medicines Agency: http://www.ema.europa.eu/ema/

lead to an adverse impact on the cost of production, the only controlled study conducted to date found that the minimal increase in production efficiency was not enough to offset the additional cost of the antimicrobials used during production.[10] Despite this, additional data on the economic impact of antimicrobial use in agriculture are sorely needed.[11]

To assess the potential impact of veterinary antimicrobial use on human health, an understanding of the medical importance of any antimicrobial that might be used in animals is of critical importance. In its 2003 Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern," the FDA established classifications of the medical importance of different antibiotics, classifying each agent as "important," "highly important," and "critically important."[12] These categorizations take into account their therapeutic uses in humans, whether alternatives exist, cross-resistance (both within drug classes and with other drug classes), and the relative difficulty of the transmission of resistance elements (Table 1). In addition, this document provides a framework for assessing the overall risk to humans for each antimicrobial using qualitative assessments of the risk of resistant bacteria developing in treated animals, the likelihood that humans would ingest the resistant bacteria, and, finally, the clinical consequences of human exposure to resistant bacteria. Despite this framework, antibiotics deemed "critically important" for humans continue to be used as feed additives, accounting for greater than 80% of all veterinary use of medically important antibiotics in the United States.[8] Furthermore, a 2014 study released by the National Resources Defense Council found of the 30 antibiotic feed additives currently marketed, none would be approved under current FDA guidance. Of these 30, 18 were classified as "high risk" for the transmission of antibiotic resistance to humans.[13] In addition, resistance to certain antibiotics in one category may lead to cross-resistance with antibiotics in other categories as described here.

Antibiotics, Antibiotic Resistance, and the Antibiotic Resistome

Recognizing the structural similarity that exists between many antibiotics used in both agriculture and human health is fundamental to understanding how resistance can spread from animals to humans. Antibiotics in human medicine have traditionally been grouped into classes based on chemical similarity and mechanism of action. Many of these classes have at least one drug registered in the United States for use in animal feed; still other antibiotics and classes are used in other countries.[14] Antibiotic-resistance mechanisms can also be grouped together. An initial classification first separates resistance into either intrinsic or acquired. As it relates to antibiotic-resistance development in the animal food industry, acquired antibiotic resistance is a more concerning problem. Acquired resistance can be further divided into four fundamental categories: preventing antibiotic access to the target, modifying the antibiotic target, protecting the target site from interaction with the antibiotic, and modification of the antibiotic.[15]

The first mechanism of resistance, preventing antibiotic access to the target, is achieved through two methods. The first is reduced permeability of the drug into the cell and generally results from a reduction in the number of outer-membrane porins that act as channels for antibiotics to pass into the cell. This mechanism can produce nonsusceptibility by itself or it can combine with other resistance mechanism(s) to produce significant resistance.[16] An example of this is the combination of decreased porin expression with β-lactamases leading to carbapenem resistance in *Enterobacteriaceae*. Because porins may facilitate the entry of multiple classes of antibiotics into the cell, decreased porin expression can result in cross-class resistance, such as combined fluoroquinolone and carbapenem resistance. The second mechanism that results in decreased antibacterial access to the target are changes in efflux pump selectivity and activity.[16] Although many bacterial species express efflux pumps as intrinsic resistance mechanisms, plasmids may also carry genes encoding for the efflux of numerous antibiotics leading to multidrug resistance. Expression of a variety of different pumps can be regulated by various stress factors including low-level antibiotic exposure.[17]

The second major mechanism of acquired drug resistance, modification of the antibiotic target, leads to some of the most important examples of antibacterial resistance in *Streptococcus pneumoniae* and *Staphylococcus aureus*. The *mecA* gene, for example, encodes for a penicillin-binding protein (PBP-2a) that has dramatically reduced binding to most β-lactam antibiotics and leads to methicillin resistance in staphylococci.[16] A variant of *mecA* known as *mecC* was recently identified; *mecC* produces a broad-spectrum β-lactam resistance phenotype as well as a diagnostic challenge because *mecC* is not detected by *mecA* PCR or *mecA* PBP-2a latex agglutination assays.[18] This resistance element was first described in milk samples from cattle with mastitis in England. Subsequently, over half of methicillin-resistant *S. aureus* (MRSA) isolates from human sources in Denmark, Scotland, and England that did not harbor *mecA* were found to carry *mecC*.[19]

The third major mechanism of acquired resistance is the protection of the target site from the antibiotic. As with the mechanisms discussed earlier, many of these clinically relevant examples have been known to be transferred across species. Resistance to macrolides, lincosamides (including clindamycin), and streptogramins can be produced through acquisition of the erythromycin ribosome methylase (*erm*). This mechanism alters the bacterial ribosome, preventing binding of these three drug classes. Fluoroquinolone resistance can be produced by *qnr* resistance genes. This mechanism produces pentapeptide repeat proteins on topoisomerase IV that promotes the release of the bound fluoroquinolone.[16]

Lastly, direct modification of antibiotics has been demonstrated in several different antibiotic classes. Perhaps the most important example of antibiotic modification is the hydrolysis of β-lactam antibiotics by β-lactamase enzymes. Numerous classes of β-lactamases have described a variety of affinities for medically important β-lactams. The last decade has seen a proliferation of β-lactamases that encode for resistance to third-generation cephalosporins, β lactam-β lactamase inhibitors, and carbapenems through numerous genetically diverse enzymes. These agents have traditionally been the last line of defense against gram-negative bacteria. Many of these resistant genes are now encoded on plasmids and able to transfer between species.[16]

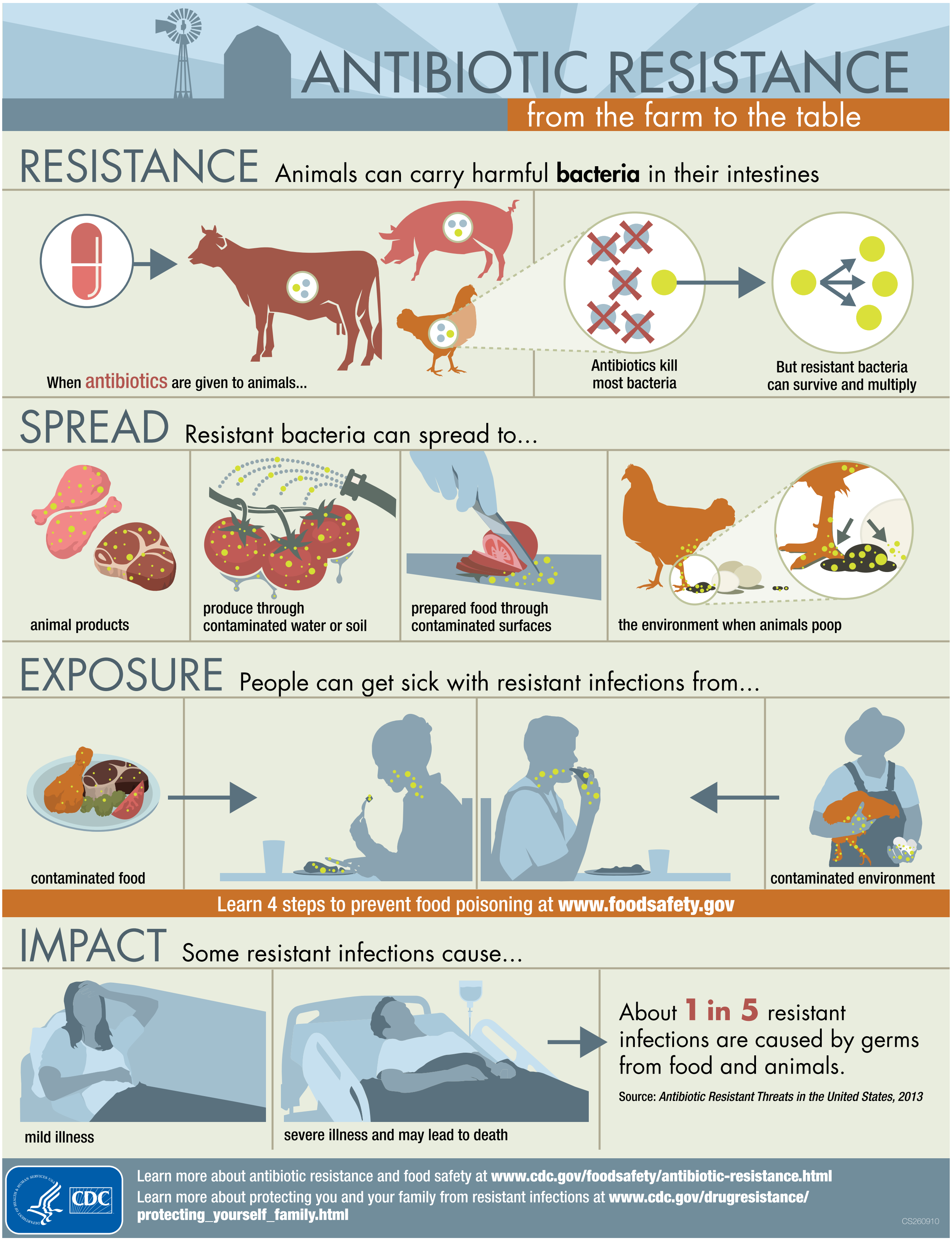
Bacteria have developed resistance mechanisms over thousands of millennia as they have competed against naturally produced antibiotics from other species or microorganisms to control their own ecological niches.[20] Importantly, many of these mechanisms may confer resistance to synthetic antibiotic classes such as the fluoroquinolones or oxazolidinones, without prior exposure.[21] The genes that encode for these resistance mechanisms may then transfer via plasmids and spread among many species of bacteria.[22] This transferable pool of resistance is called the antibiotic resistome and has important implications for human health.[23] Given the nonspecific mechanism of a number of resistance mechanisms such as efflux pumps and reduced cell entry, resistance to one antibiotic class may lead to resistance to another, unrelated class. In addition, because the resistance genes are already dispersed, it is unlikely that eradication will occur.

Farm to Table: Tracing Antibiotic Resistance from Agricultural Use to Human Disease

The animal-to-human transfer of antibiotic-resistant bacteria to humans through the consumption of contaminated food products or by direct contact with animals or animal waste harboring antibiotic resistance is a significant threat to human health. As such, human omnivores and vegetarians are both susceptible to acquiring agriculture-developed antibiotic resistance. The following summarizes major antibiotic-resistance transmission mechanisms and is graphically presented in Figure 2.[24]

Direct Transmission

In the most straightforward cases, antibiotic resistance may be directly transmitted from farm animals to farmers and other animal handlers. The transmission of drug-resistant enterococci—including vancomycin-resistant enterococci—from broiler (i.e., domesticated chickens for meat production) hens to broiler farmers was clearly documented in the Netherlands.[25] Similar studies have documented the transmission of fluoroquinolone-resistant *Escherichia coli* to poultry farmers[26] and MRSA to pig farmers and their close contacts.[27] Analogous to the spread of antibiotic resistance from human to human, antibiotic-resistant bacteria may spread clonally



ANTIBIOTIC RESISTANCE
from the farm to the table

RESISTANCE Animals can carry harmful **bacteria** in their intestines

When antibiotics are given to animals...

Antibiotics kill most bacteria

But resistant bacteria can survive and multiply

SPREAD Resistant bacteria can spread to...

animal products

produce through contaminated water or soil

prepared food through contaminated surfaces

the environment when animals poop

EXPOSURE People can get sick with resistant infections from...

contaminated food

contaminated environment

Learn 4 steps to prevent food poisoning at **www.foodsafety.gov**

IMPACT Some resistant infections cause...

mild illness

severe illness and may lead to death

About **1 in 5** resistant infections are caused by germs from food and animals.

Source: *Antibiotic Resistant Threats in the United States, 2013*

Learn more about antibiotic resistance and food safety at **www.cdc.gov/foodsafety/antibiotic-resistance.html**
Learn more about protecting you and your family from resistant infections at **www.cdc.gov/drugresistance/protecting_yourself_family.html**

Figure 2. Resistant organism transfer from animals to humans. Depiction of varying methods of transfer of resistant organisms to humans from food-producing animals. (Used with permission from www.cdc.gov).

from animal to handler or resistance genes may be horizontally transferred by mobile genetic elements. In addition, several studies have demonstrated that generally uncommon bacterial strains or antibiotic-resistance patterns, such as tetracycline-resistant *S. aureus*, may be highly prevalent in farm animals and farmworkers but not the community at large.[14, 28] These findings suggest a strong epidemiologic link between antibiotic resistance in farm animals and transmission to humans with subsequent colonization.

Environmental Contamination

In addition to direct transmission from farm animals to their handlers, antibiotic-resistant bacteria may spread beyond the farm animals and into the surrounding environment with a significant impact on human health. Environmental sampling from a large industrial farm for growing chickens in Germany showed that extended-spectrum β-lactamase (ESBL) or AmpC-producing *E. coli* could be found in 86% of waste slurry samples and 7.5% of samples taken of ambient air.[29] Antibiotic-resistant bacteria also appear to be more prevalent downwind, rather than upwind, of cattle feed yards.[30] Furthermore, ~2–3% of flies sampled at poultry farms in the Netherlands are carriers of ESBL *E. coli*, indicating the potential risk for vector-based dissemination of antibiotic-resistant bacteria.[31] Although most of the evidence regarding the harms to the surrounding community of agricultural antibiotic use is largely theoretical, a population-based study conducted in central Pennsylvania linked proximity to high-intensity pig farming to an increased risk of community-acquired MRSA infections.[32]

In addition, the antibiotics used on farms may enter the surrounding environment through contaminated wastewater and persist indefinitely, leading to natural selection pressure for antibiotic resistance.[33] A comprehensive literature review found that of the 61 most commonly recovered pharmaceutical products recovered from freshwater ecosystems worldwide, 24 (39%) were antibiotics.[9] The highest median concentration of any drug examined in this review belonged to ciprofloxacin; the median ciprofloxacin concentration was 0.164 mg/L and the highest recorded ciprofloxacin concentration was 6.5 mg/L, within the range expected of patients receiving therapeutic ciprofloxacin.[10] Among all antibiotics studied, the overall median concentration was 0.008 mg/L. Although there are other more important sources of antibiotic residues in the environment, including hospital wastewater and sewage, farm runoff remains a contributing factor to antibiotics in the environment.[34]

The spillover of antibiotic resistance into the surrounding environment may also have unexpected effects. Although antibiotic-resistant pathogens can be identified in agricultural soil samples from diverse sources, multidrug resistance and high-level antibiotic resistance are found almost exclusively in soil samples that have been exposed to manure originating from animals that have received antibiotics.[35] In turn, certain antibiotic-resistance elements may be found more frequently in vegetables grown in the presence of manure.[36] Although antibiotic resistance in manure has been linked to animals exposed to antibiotics, resistance has also been shown to bloom in manure derived from animals that were never exposed to antibiotics, highlighting the complex interplay between natural resistance presence in the environment and selection by antibiotic pressure.[37]

The Commercial Food Supply

Antibiotic resistance among classic foodborne illnesses, such as those caused by *Salmonella* and *Campylobacter* species, is a significant threat to human health.[38] Data from the United States and Europe strongly link the use of fluoroquinolones in animals with fluoroquinolone resistance in *Campylobacter* sp isolates obtained from animal and human sources.[39, 40] In contrast, Australia has a long-standing policy banning the agricultural use of fluoroquinolones with correspondingly low fluoroquinolone resistance rates.[41] One period-prevalence study surveyed the susceptibility of *Campylobacter jejuni* isolates from 585 patients in five Australian states and found that only 2% of isolates were resistant to ciprofloxacin.[42] A second surveillance study identified fluoroquinolone resistance in only 12 of 370 Australian human *Campylobacter* isolates, with 10 of these isolates having a proven travel association.[41]

The use of antibiotics in agriculture has also been linked to the development of resistance in *Salmonella enterica*. In New England, the prevalence of multidrug resistance among human-origin *S. enterica* serotype Newport isolates rose from 0–53% between 1998 and 2001, coinciding with the emergence of the same multidrug-resistant strains in livestock in the same area.[43] Similar rises among *S. enterica* serotype typhimurium were noted among humans and livestock in both the United States and the United Kingdom.[44]

Antibiotic resistance in pathogens not considered to be strictly foodborne has also been identified. Resistance to quinupristin-dalfopristin, a drug in the same class as the widely used feed additive virginiamycin, occurred in 18–54% of enterococci identified in retail meat.[45] *Clostridium difficile* has also been identified in retail meat, and molecular analysis found that isolates identified in patients and retail meat samples were of similar ribotypes.[43] A more in-depth analysis demonstrated that farm animals and farmers shared identical strains.[46, 47]

The transmission of antibiotic resistance in *E. coli* deserves special consideration. A molecular-epidemiologic comparison in Barcelona, Spain, analyzed 117 *E. coli* isolates of human or chicken origin with varying ciprofloxacin resistance profiles. The resistant isolates of human origin were epidemiologically distinct from susceptible human isolates but indistinguishable from the resistant isolates from chicken, indicating that ciprofloxacin-resistant *E. coli* may be transmitted to humans via the food supply.[48] Studies conducted in the United States have shown that contamination of meat in retail settings with antibiotic-resistant *E. coli* is frequent, with as many as 94% of *E. coli* samples displaying resistance to clinically important antibiotics including resistance to third-generation cephalosporins in up to 26%.[49, 50] Although relatively few studies have linked the onset of human infections to antibiotic resistance in the food supply, a recent review of the published literature indicates that a substantial proportion of infections due to ESBL *E. coli* may originate from food production animals, particularly from poultry.[51] Furthermore, the prevalence of fluoroquinolone resistance in Australian human-origin *E. coli* isolates is low and stable, providing additional supporting evidence of the link between low agricultural use of fluoroquinolones and corresponding low levels of human resistance.[52]

The emergence of the *mcr-1* polymyxin resistance gene provides an example of the speed at which novel resistance mechanisms can emerge in farm animals, enter the commercial food supply, and disseminate globally to cause human disease.[53] Originally identified in a pig-origin *E. coli* isolate, *mcr*-1 was subsequently identified in 15% of Chinese pork and chicken retail samples, 21% of pigs at slaughter, and 1% of inpatients with infections caused by *Enterobacteriaceae*. Of significant concern, the annual prevalence of *mcr-1* increased between 2011 and 2014, indicating that the emergence of *mcr-1* is an ongoing process. Subsequent reports have confirmed that *mcr*-1 has spread globally and can now be found in Europe and North America.[54, 55]

Antibiotic Residues in Meat, Milk, and Egg Products for Human Consumption

In addition to antibiotic-resistant bacteria, antibiotics themselves can appear in the commercial food supply as a result of agricultural antibiotic use. There is a paucity of literature on how these antibiotic residues may affect human health, although there have been rare reports of allergic reactions following consumption of meat contaminated with antibiotics.[56, 57] In addition, antibiotic residues may have other less obvious consequences, such as disruption of the human microbiota and its own antibiotic resistome. It has been hypothesized that subtherapeutic antibiotic exposure, including exposure through our food supply, may lead to deleterious metabolic effects including obesity.[58, 59]

As a result of these and other concerns, the United States has enacted regulations to limit these exposures.[60] The U.S. National Residue Program for Meat, Poultry, and Egg Products, administered by the USDA Food Safety and Inspection Service (FSIS), sets acceptable daily intake (ADI) and maximum residue limits (MRL) based on antibiotic-specific pharmacokinetics, pharmacodynamics, and toxicodynamics. These ADI and MRL are then reviewed to inform the selection of a *withdrawal time* (defined as the period of time for which an animal can receive no antibiotic[s] prior to its meat or milk being delivered for human consumption). The FSIS tests meat, milk, and eggs destined for human consumption; however, these inspections happen only sporadically. Currently in the United States, testing for antibiotic residues is performed on random samples from each major class of production animal as well as eggs.[61] Targeted sampling by FSIS may also be performed when there is suspicion of disease or antibiotic use within an animal population. FSIS currently tests for the following antibiotics: aminoglycosides, β-lactams, fluoroquinolones, macrolides, tetracyclines, and sulfonamides. In 2011 FSIS tested 5006 samples for antibiotic residues of which 47 samples (0.94%) had detectable levels of antibiotic residues; 8 (0.16%) samples had antibiotic residue levels above the maximum allowable level.[61]

Few nongovernmental studies have evaluated the presence of antibiotic residues in meat, milk, or eggs destined for human consumption, and there is significant heterogeneity between studies with respect to antibiotics studied, analytical methodology, and geographic location. In addition, most studies were published more than 15 years ago when regulations were less strict and analytical technologies were less robust. Recently, tetracyclines have been recovered from milk and pork destined for human consumption, despite having passed the mandated 4-day withdrawal time.[62, 63]

Antibiotic Use in Aquaculture

The use of antibiotics in aquaculture, or the farming of aquatic organisms, is pervasive and less regulated than the use of antibiotics in milk and meat-producing animals. In addition, ~90% of global aquaculture comes from Asia where the use of antibiotics in aquaculture is not tightly regulated.[64] The presence of antibiotic residuals in aquatic products of South Asian source and destined for South Asian markets is correspondingly high.[65] Although strict regulations in the United States and European Union theoretically limit the presence of antibiotic residuals in imported fish products, this is not always the case. A recent study of seafood purchased in the southwestern United States but originating from 11 different countries found that five antibiotics were routinely detectable in various sources including so-called antibiotic-free salmon.[66] Of note, none of the antibiotics exceeded the federally determined MRL. A number of different classes of antibiotics were detected, although tetracyclines were found at the highest concentrations in all samples in line with aquaculture usage patterns. Not unexpectedly, tetracycline resistance in *E. coli* originating from commercial seafood exceeds 30%.[67]

Furthermore, regulations limiting antibiotic use in aquaculture are not universally followed. A recent global survey of aquaculture professionals found that use of fluoroquinolones in aquaculture was reported by 70% of respondents from the United States, a rate similar to other countries worldwide.[68] These results are remarkable given that the FDA has banned fluoroquinolone use in aquaculture destined for human consumption, unless a sponsor obtains an approval for such use; extra-label use of fluoroquinolones in food-producing animals is prohibited by the FDA.[69]

Antimicrobial Use in Horticulture

The agricultural use of antibiotics extends beyond meat and fish production and into crop management. In the United States, ~36 metric tons of antibiotics were used in crop production in 2011. This is in contrast to the 13,542 metric tons sold as animal feed additive, indicating that crop production accounted for 0.26% of all agricultural use.[70] Although the percentage of overall antibiotic use is small, any antibiotic use in crop production is nevertheless concerning. Streptomycin accounts for the vast majority of tonnage used and is generally used as a topical spray to prevent the spread of the bacteria *Erwinia amylovora* (the causative agent of fire blight) in apple and pear orchards. Several studies have noted that the use of streptomycin does not alter the environmental prevalence of antibiotic-resistant bacteria or resistance genes, but studies on the impact of this practice on farmworkers or the community at large are lacking, and no systematic surveillance mechanisms are in place.[71, 72]

Of additional concern is the widespread use of azole and sterol demethylation inhibitor (DMI) fungicides in horticulture to limit the development of fungal plant infections. In the Netherlands, a country with a relatively high use of DMI fungicides, 6–13% of *Aspergillus fumigatus* isolates from patients with invasive aspergillosis are resistant to azole antifungals.[73] In the United States, DMI fungicide use is lower than in Europe or Asia. A recent surveillance study of clinical *Aspergillus* isolates conducted by the CDC found that 5% were above the epidemiologic cutoff value for resistance to itraconazole and that mutations in the *cyp51a* gene, which are associated with reduced susceptibility to azole antifungals, were more common in these isolates than those with lower MICs.[74] During this time, 381,018 kg of DMI fungicides were used by states providing the clinical isolates.[74] A firm link between environmental DMI fungicide use and azole resistance in clinical *Aspergillus* isolates has not been established, but no mandatory surveillance mechanisms are in place to ensure the necessary study of this important question. Furthermore, the use of these fungicides falls outside the purview of the FDA.

Conclusions

Despite substantial efforts in antibiotic development, infection control, and human antibiotic stewardship, antibiotic resistance continues to propagate. Given that the vast majority of antibiotics used worldwide are for nontherapeutic agricultural purposes and that the transfer of antibiotic resistance to humans is a well-documented consequence, an increased effort to curb antibiotic use in agriculture is critical to a national and global strategy of combating antibiotic resistance. Antibiotic stewardship efforts to date have focused on increasing appropriate antibiotic use in humans; however, these efforts fail to address more than 80% of inappropriate antibiotic use nationwide. Health care providers, policymakers, and consumers must understand the clear link between antibiotic use in agriculture and antibiotic-resistant bacteria in humans to inform discussion, policies, and other actions aimed at combating the antibiotic-resistance epidemic.

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References

1. **Spellberg B.** The future of antibiotics. Crit Care 2014;3:228.
2. **U.S. Centers for Disease Control and Prevention.** Antibiotic resistance threats in the United States, 2013. 2014.
3. **Ogle M.** In meat we trust: an unexpected history of Carnivore America. New York, NY: Houghton Mifflin; 2013: 111.
4. Anonymous. Infectious drug resistance. N Engl J Med 1966;5:277.
5. **Soulsby L.** Antimicrobials and animal health: a fascinating nexus. J Antimicrob Chemother 2007;60 Suppl 1:i77–8.
6. **Antibiotic resistance and the use of antibiotics in animal agriculture.** Subcommittee on Health of the Committee on Energy and Commerce 2010.
7. **Hollis A, Ahmed Z.** Preserving antibiotics, rationally. N Engl J Med 2013;26:2474–6.
8. **U.S. Food and Drug Administration.** Summary report on antimicrobials sold or distributed for use in food-producing animals. 2013. Available from http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm440585.htm. Accessed March 20, 2016.
9. **Hall JO.** Ionophore use and toxicosis in cattle. Vet Clin North Am Food Anim Pract 2000;3:497–509, vii.
10. **Graham JP, Boland JJ, Silbergeld E.** Growth promoting antibiotics in food animal production: an economic analysis. Public Health Rep 2007;1:79–87.
11. **Miller GY, McNamara PE, Singer RS.** Stakeholder position paper: economist's perspectives on antibiotic use in animals. Prev Vet Med 2006;2–3:163–8.
12. **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.
13. **Cordova C, Kar A.** Playing chicken with antibiotics: previously undisclosed FDA documents show antibiotic feed additives don't meet the agency's own safety standards. NRDC Issue brief. New York, NY: Natural Resources Defense Council, 2014. Available from http://www.nrdc.org/food/saving-antibiotics/files/antibiotic-feed-fda-documents-IB.pdf. Accessed March 20, 2016.
14. **Stobberingh E, van den Bogaard A, London N, Driessen C, Top J, Willems R.** Enterococci with glycopeptide resistance in turkeys, turkey farmers, turkey slaughterers, and (sub)urban residents in the south of The Netherlands: evidence for transmission of vancomycin resistance from animals to humans? Antimicrob Agents Chemother 1999;9:2215–21.
15. **Li XZ, Nikaido H.** Efflux-mediated drug resistance in bacteria: an update. Drugs 2009;12:1555–623.
16. **Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ.** Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol 2015;1:42–51.
17. **Li XZ, Plesiat P, Nikaido H.** The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. Clin Microbiol Rev 2015;2:337–418.
18. **Paterson GK, Harrison EM, Holmes MA.** The emergence of mecC methicillin-resistant *Staphylococcus aureus*. Trends Microbiol 2014;1:42–7.
19. **Garcia-Alvarez L, Holden MT, Lindsay H, et al.** Methicillin-resistant *Staphylococcus aureus* with a novel mecA homologue in human and bovine populations in the UK and Denmark: a descriptive study. Lancet Infect Dis 2011;8:595–603.
20. **D'Costa VM, King CE, Kalan L, et al.** Antibiotic resistance is ancient. Nature 2011;7365:457–61.
21. **Schwarz S, Werckenthin C, Kehrenberg C.** Identification of a plasmid-borne chloramphenicol-florfenicol resistance gene in *Staphylococcus sciuri*. Antimicrob Agents Chemother 2000;9:2530–3.
22. **Allen HK, Donato J, Wang HH, Cloud-Hansen KA, Davies J, Handelsman J.** Call of the wild: antibiotic resistance genes in natural environments. Nat Rev Microbiol 2010;4:251–9.
23. **Andersson DI, Hughes D.** Persistence of antibiotic resistance in bacterial populations. FEMS Microbiol Rev 2011;5:901–11.
24. **U.S. Centers for Disease Control and Prevention.** Antibiotic use in food-producing animals: tracking and reducing the public health impact. Available from http://www.cdc.gov/narms/animals.html. Accessed September 16, 2015.
25. **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;3:497–505.
26. **van den Bogaard AE, London N, Driessen C, Stobberingh EE.** Antibiotic resistance of faecal Escherichia coli in poultry, poultry farmers and poultry slaughterers. J Antimicrob Chemother 2001;6:763–71.
27. **Voss A, Loeffen F, Bakker J, Klaassen C, Wulf M.** Methicillin-resistant *Staphylococcus aureus* in pig farming. Emerg Infect Dis 2005;12:1965–6.
28. **Oppliger A, Moreillon P, Charriere N, Giddey M, Morisset D, Sakwinska O.** Antimicrobial resistance of *Staphylococcus aureus* strains acquired by pig farmers from pigs. Appl Environ Microbiol 2012;22:8010–4.
29. **Laube H, Friese A, von Salviati C, Guerra B, Rosler U.** Transmission of ESBL/AmpC-producing *Escherichia coli* from broiler chicken farms to surrounding areas. Vet Microbiol 2014;3–4:519–27.
30. **McEachran AD, Blackwell BR, Hanson JD, et al.** Antibiotics, bacteria, and antibiotic resistance genes: aerial transport from cattle feed yards via particulate matter. Environ Health Perspect 2015;4:337–43.
31. **Blaak H, Hamidjaja RA, van Hoek AH, de Heer L, de Roda Husman AM, Schets FM.** Detection of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* on flies at poultry farms. Appl Environ Microbiol 2014;1:239–46.

32. **Casey JA, Curriero FC, Cosgrove SE, Nachman KE, Schwartz BS.** High-density livestock operations, crop field application of manure, and risk of community-associated methicillin-resistant *Staphylococcus aureus* infection in Pennsylvania. JAMA Intern Med 2013;21:1980–90.
33. **Martinez JL.** Environmental pollution by antibiotics and by antibiotic resistance determinants. Environ Pollut 2009;11:2893–902.
34. **Brown KD, Kulis J, Thomson B, Chapman TH, Mawhinney DB.** Occurrence of antibiotics in hospital, residential, and dairy effluent, municipal wastewater, and the Rio Grande in New Mexico. Sci Total Environ 2006;2–3:772–83.
35. **Popowska M, Rzeczycka M, Miernik A, Krawczyk-Balska A, Walsh F, Duffy B.** Influence of soil use on prevalence of tetracycline, streptomycin, and erythromycin resistance and associated resistance genes. Antimicrob Agents Chemother 2012;3:1434–43.
36. **Marti R, Tien YC, Murray R, Scott A, Sabourin L, Topp E.** Safely coupling livestock and crop production systems: how rapidly do antibiotic resistance genes dissipate in soil following a commercial application of swine or dairy manure? Appl Environ Microbiol 2014;10:3258–65.
37. **Udikovic-Kolic N, Wichmann F, Broderick NA, Handelsman J.** Bloom of resident antibiotic-resistant bacteria in soil following manure fertilization. Proc Natl Acad Sci USA 2014;42:15202–7.
38. **White DG, Zhao S, Simjee S, Wagner DD, McDermott PF.** Antimicrobial resistance of foodborne pathogens. Microbes Infect 2002;4:405–12.
39. **Wegener HC.** The consequences for food safety of the use of fluoroquinolones in food animals. N Engl J Med 1999;20:1581–2.
40. **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. Emerg Infect Dis 2001;1:24–34.
41. **Unicomb L, Ferguson J, Riley TV, Collignon P.** Fluoroquinolone resistance in Campylobacter absent from isolates, Australia. Emerg Infect Dis 2003;11:1482–3.
42. **Unicomb LE, Ferguson J, Stafford RJ, et al.** Low-level fluoroquinolone resistance among *Campylobacter jejuni* isolates in Australia. Clin Infect Dis 2006;10:1368–74.
43. **Gupta A, Fontana J, Crowe C, et al.** Emergence of multidrug-resistant *Salmonella enterica* serotype Newport infections resistant to expanded-spectrum cephalosporins in the United States. J Infect Dis 2003;11:1707–16.
44. **Glynn MK, Bopp C, Dewitt W, Dabney P, Mokhtar M, Angulo FJ.** Emergence of multidrug-resistant *Salmonella enterica* serotype typhimurium DT104 infections in the United States. N Engl J Med 1998;19:1333–8.
45. **Hayes JR, English LL, Carter PJ, et al.** Prevalence and antimicrobial resistance of enterococcus species isolated from retail meats. Appl Environ Microbiol 2003;12:7153–60.
46. **Rodriguez C, Taminiau B, Avesani V, Van BJ, Delmee M, Daube G.** Multilocus sequence typing analysis and antibiotic resistance of Clostridium difficile strains isolated from retail meat and humans in Belgium. Food Microbiol 2014;42:166–71.
47. **Knetsch CW, Connor TR, Mutreja A, et al.** Whole genome sequencing reveals potential spread of *Clostridium difficile* between humans and farm animals in the Netherlands, 2002 to 2011. Euro Surveill 2014;45:20954.
48. **Johnson JR, Kuskowski MA, Menard M, Gajewski A, Xercavins M, Garau J.** Similarity between human and chicken *Escherichia coli* isolates in relation to ciprofloxacin resistance status. J Infect Dis 2006;1:71–8.
49. **Johnson JR, Kuskowski MA, Smith K, O'Bryan TT, Tatini S.** Antimicrobial-resistant and extraintestinal pathogenic *Escherichia coli* in retail foods. J Infect Dis 2005;7:1040–9.
50. **Schroeder CM, White DG, Ge B, et al.** Isolation of antimicrobial-resistant *Escherichia coli* from retail meats purchased in Greater Washington, DC, USA. Int J Food Microbiol 2003;1–2:197–202.
51. **Lazarus B, Paterson DL, Mollinger JL, Rogers BA.** Do human extraintestinal *Escherichia coli* infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review Clin Infect Dis 2015;3:439–52.
52. **Collignon P, Angulo FJ.** Fluoroquinolone-resistant *Escherichia coli*: food for thought. J Infect Dis 2006;1:8–10.
53. **Liu YY, Wang Y, Walsh TR, et al.** Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 2015;16:161–8.
54. **Webb HE, Granier SA, Marault M, et al.** Dissemination of the mcr-1 colistin resistance gene. Lancet Infect Dis 2016;16:144–5.
55. **Church E.** Canadian scientists find superbug gene in three cases. The Globe and Mail 2016.
56. **Dayan AD.** Allergy to antimicrobial residues in food: assessment of the risk to man. Vet Microbiol 1993;3–4:213–26.
57. **Dewdney JM, Edwards RG.** Penicillin hypersensitivity—is milk a significant hazard? A review. J R Soc Med 1984;10:866–77.
58. **Cox LM, Blaser MJ.** Antibiotics in early life and obesity. Nat Rev Endocrinol 2015;3:182–90.
59. **Riley LW, Raphael E, Faerstein E.** Obesity in the United States—dysbiosis from exposure to low-dose antibiotics? Front Public Health 2013;19:69.
60. **Donoghue DJ.** Antibiotic residues in poultry tissues and eggs: human health concerns? Poult Sci 2003;4:618–21.
61. **Food Safety and Inspection Service, U.S. Department of Agriculture.** 2011 Residue Sample Results. Washington, DC: USDA/FSIS Office of Public Health Science, 2013.
62. **Baron PA, Love DC, Nachman KE.** Pharmaceuticals and personal care products in chicken meat and other food animal products: a market-basket pilot study. Sci Total Environ 2014;490:296–300.
63. **Lindquist D, Wu H, Mason S, et al.** Tetracycline residues in porcine stomach after administration via drinking water on a swine farm. J Food Prot 2014;1:122–6.
64. **Thuy HT, le Nga P, Loan TT.** Antibiotic contaminants in coastal wetlands from Vietnamese shrimp farming. Environ Sci Pollut Res Int 2011;6:835–41.
65. **Pham DK, Chu J, Do NT, et al.** Monitoring antibiotic use and residue in freshwater aquaculture for domestic use in Vietnam. EcoHealth 2015;12:480–90.
66. **Done HY, Halden RU.** Reconnaissance of 47 antibiotics and associated microbial risks in seafood sold in the United States. J Hazard Mater 2015;282:10–7.
67. **Ryu SH, Park SG, Choi SM, et al.** Antimicrobial resistance and resistance genes in *Escherichia coli* strains isolated from commercial fish and seafood. Int J Food Microbiol 2012;1–2:14–8.
68. **Tusevljak N, Dutil L, Rajic A, et al.** Antimicrobial use and resistance in aquaculture: findings of a globally administered survey of aquaculture-allied professionals. Zoonoses Public Health 2013;6:426–36.
69. **Center for Food Safety and Applied Nutrition.** Fish and fishery products—hazards and controls guidance. Rockville, MD: Center for Food Safety and Applied Nutrition, Food and Drug Administration, U.S. Department of Health and Human Services, 2011.
70. **McManus PS.** Does a drop in the bucket make a splash? Assessing the impact of antibiotic use on plants Curr Opin Microbiol 2014;19:76–82.
71. **Duffy B, Holliger E, Walsh F.** Streptomycin use in apple orchards did not increase abundance of mobile resistance genes. FEMS Microbiol Lett 2014;2:180–9.
72. **Walsh F, Smith DP, Owens SM, Duffy B, Frey JE.** Restricted streptomycin use in apple orchards did not adversely alter the soil bacteria communities. Front Microbiol 2013;4:383.
73. **Verweij PE, Snelders E, Kema GH, Mellado E, Melchers WJ.** Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use? Lancet Infect Dis 2009;12:789–95.
74. **Pham CD, Reiss E, Hagen F, Meis JF, Lockhart SR.** Passive surveillance for azole-resistant *Aspergillus fumigatus*, United States, 2011–2013. Emerg Infect Dis 2014;9:1498–503.