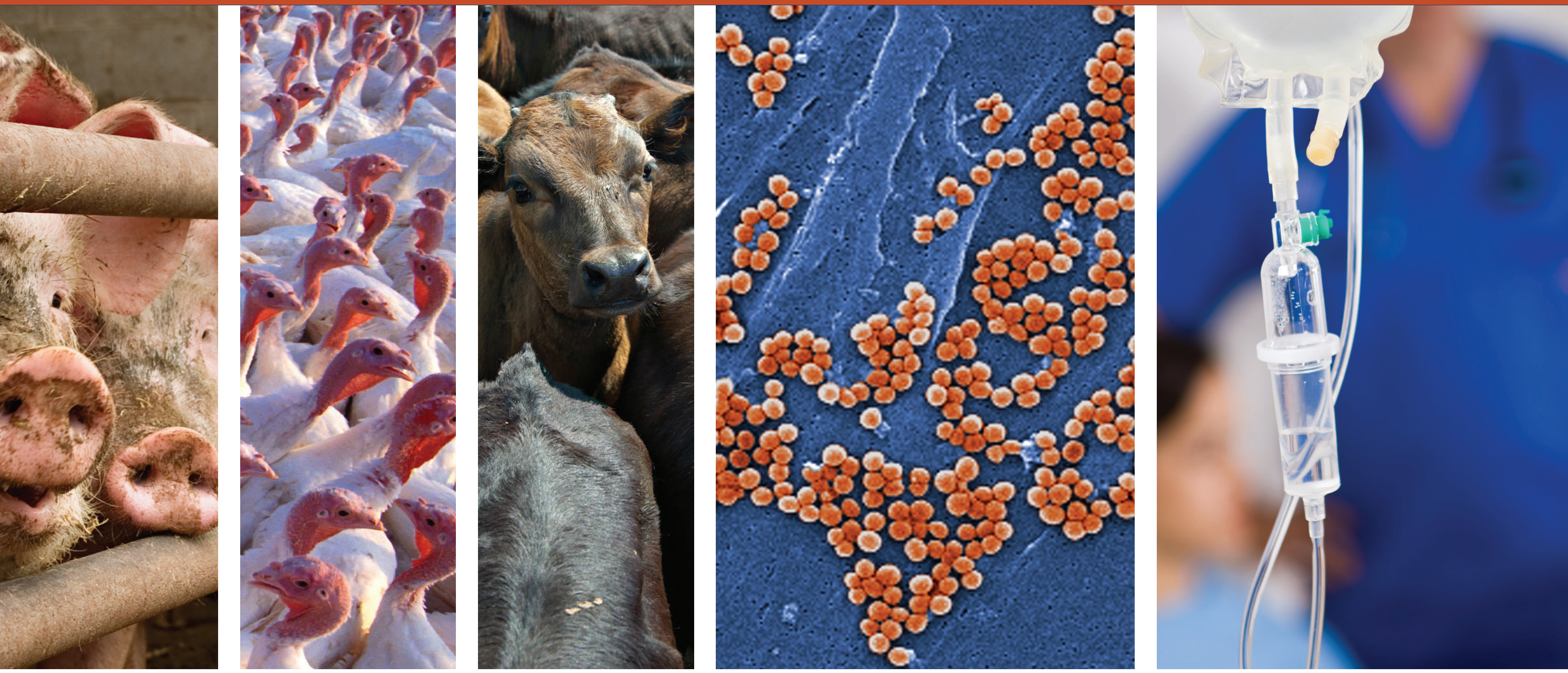
ANTIBIOTIC RESISTANCE 101

How Antibiotic Misuse on Factory Farms Can Make You Sick



food&waterwatch

About Food & Water Watch

Food & Water Watch works to ensure the food, water and fish we consume is safe, accessible and sustainable. So we can all enjoy and trust in what we eat and drink, we help people take charge of where their food comes from, keep clean, affordable, public tap water flowing freely to our homes, protect the environmental quality of oceans, force government to do its job protecting citizens, and educate about the importance of keeping shared resources under public control.

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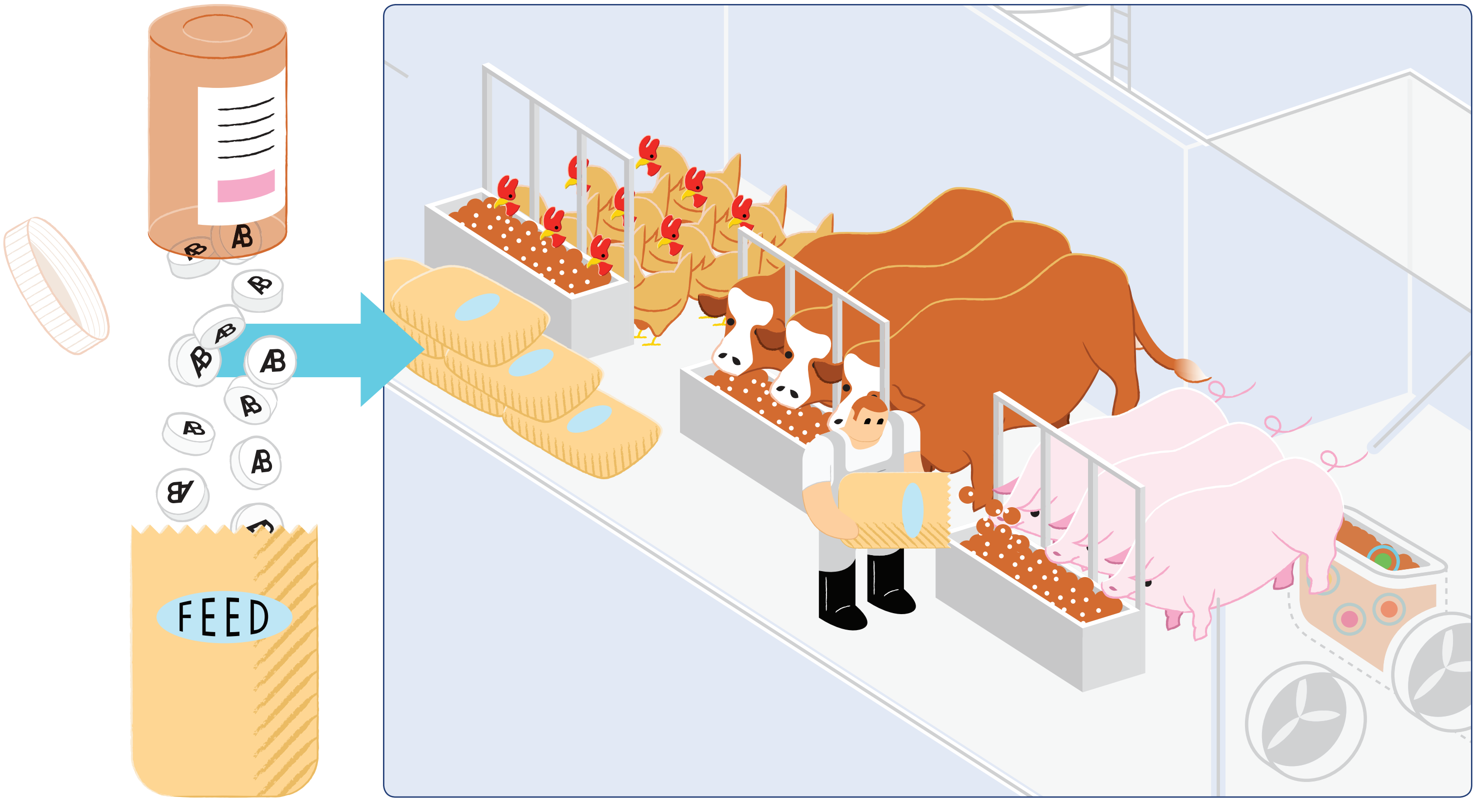


Executive Summary

Antibiotics are critical tools in human medicine. Medical authorities are warning that these life-saving drugs are losing their effectiveness, and there are few replacement drugs in the pipeline.[1] Bacteria evolve in response to the use of antibiotics both in humans and in animals. Those bacteria that are resistant to antibiotics prosper as antibiotics kill the non-resistant bacteria. Once they emerge, antibiotic-resistant (AR) bacteria can transfer AR traits to other bacteria in animals and the environment. The development of antibiotic resistance is hastened by the use of low doses of antibiotics at industrial farms. The drugs are used routinely, not to treat sick animals, but for growth promotion and disease prevention, a practice known as subtherapeutic use.[2]

Both in the United States and worldwide, agriculture uses vastly more antibiotics than human medicine,[3] and agriculture uses drugs from every major class of antibiotics used in human medicine.[4] The Food and Drug Administration (FDA) reported in 2011 that 80 percent of antibiotics in the United States are sold for agricultural purposes.[5]

AR bacteria can spread from farm animals to humans via food, via animal-to-human transfer on farms and in rural areas, and through contaminated waste entering the environment (see infographic on pages 10 and 11). The most commonly affected are those with under-developed or compromised immune systems — pregnant women, children, the elderly and people with certain health conditions — but increasingly, AR bacteria have the potential to affect anyone.

Antibiotic resistance has become a global problem.[6] People get sicker from these infections, as it takes multiple rounds of increasingly stronger antibiotics to stop the infection, allowing the infection to progress further than it might otherwise. Fewer drug options can make it harder for doctors to treat patients with allergies and make it more likely for patients to require stronger drugs given intravenously.[7]

The medical and social costs of AR infections in just one Chicago hospital for one year have been estimated to be between $13 million and $18 million.[8] Extrapolating from that study puts national cost estimates of AR infections in the billions.[9] Antibiotic resistance has become such a serious problem that there are few or no treatment options in some cases, and pharmaceutical companies are not producing new treatments fast enough to keep up with the need.[10]

The livestock industry still asserts that there is not enough scientific evidence to ban subtherapeutic uses of antibiotics,[11] but the evidence is clear. Several DNA analyses of AR bacteria point to livestock as the source. The American Public Health Association,[12] American Medical Association,[13] American Academy of Pediatrics,[14] Infectious Disease Society of America[15] and World Health Organization[16] have all issued statements calling for restrictions on subtherapeutic uses of antibiotics in livestock.

The federal government's National Antimicrobial Resistance Monitoring System (NARMS) collects samples of bacteria from chicken breasts, ground turkey, ground beef and pork chops and measures the presence of several drug-susceptible and AR foodborne pathogens.[17] Food & Water Watch has analyzed the 2010 NARMS data to estimate how widespread AR bacteria were as a whole in the retail meat samples collected. Some level of AR bacteria was common in all four meats. AR *Salmonella* was present in 8 percent of chicken breast samples and 11 percent of ground turkey samples. The presence of AR *E. coli* in the samples collected varied widely: 66 percent in ground turkey, 52 percent in chicken breasts, 20 percent in pork chops and 14 percent in ground beef.[18]

Despite the urgency of this growing public health threat, neither Congress nor the FDA have taken sufficient steps to restrict the subtherapeutic use of antibiotics in livestock. On the one hand, the FDA has limited subtherapeutic uses of a class of antibiotics called cephalosporins and banned all uses of another class called fluoroquinolones, but it has taken a lawsuit to make the FDA address a proposal to ban these same uses in two other major antibiotic classes, tetracyclines and penicillins. The FDA currently insists that voluntary guidance to industry will solve the problem, citing lack of resources as an impediment to withdrawing current drug approvals for subtherapeutic uses.[19]

Food & Water Watch recommends that:

- Congress should pass the Preservation of Antibiotics for Medical Treatment Act (PAMTA) and ban subtherapeutic uses of antibiotics in livestock, thereby avoiding the cumbersome drug-by-drug process currently required of the FDA to achieve the same goal.
- The FDA should assess the impact of its voluntary strategy and start the regulatory process now to withdraw drug approvals for injudicious uses within three years. The FDA should also strongly enforce the existing bans on certain uses of antibiotics.
- The FDA should address the Government Accountability Office's recommendations to improve data collection on the use of antibiotics and the development of antibiotic resistance.[20] NARMS must be broadened to allow the FDA to identify and respond rapidly to emerging resistance.
- Government agencies should collaborate to increase research on antibiotic resistance, including the mechanisms of resistance emergence, spread and remediation as well as alternative means of preventing illness in livestock.
- The U.S. Department of Agriculture (USDA) should provide training and technical assistance to livestock producers that are transitioning away from subtherapeutic antibiotic use. The USDA should address contract stipulations that require livestock producers to use feed with antibiotics already added.

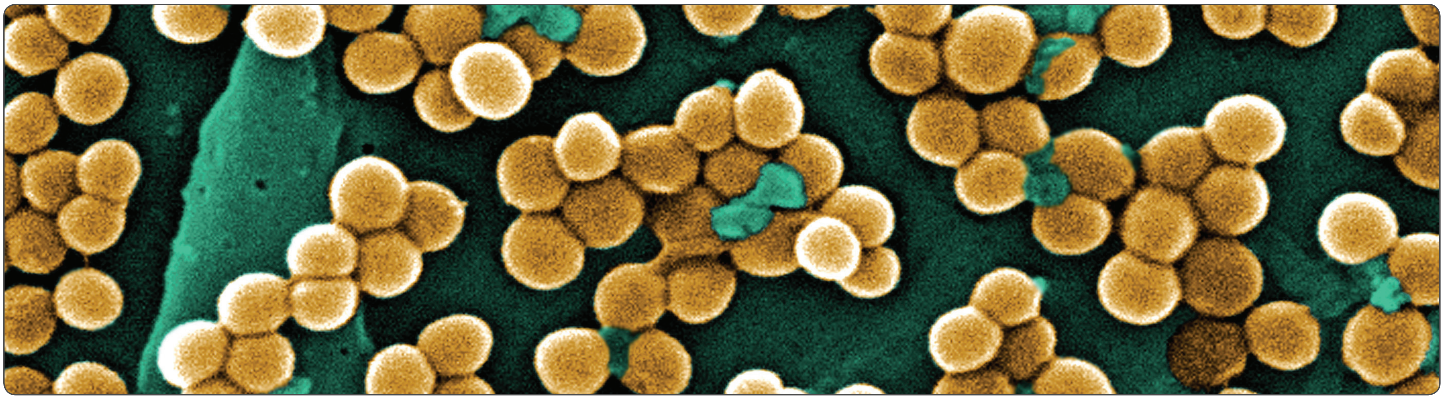


IMAGE COURTESY OF JANICE HANEY / U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

Introduction

Antibiotics are critical tools in human medicine. Medical authorities are warning that these life-saving drugs are losing their effectiveness, and there are few replacement drugs in the pipeline.[21] Over time, bacteria have developed and continue to develop resistance to antibiotics. Far more antibiotics are given to livestock than to people,[22] and the livestock taking them are usually not sick. This practice, designed to prevent infection and promote faster growth, accelerates the development of antibiotic-resistant (AR) bacteria, threatening human health.[23]

All species evolve in response to their environment, including bacteria. Bacteria reproduce rapidly, encouraging faster adaptation. Antibiotics kill bacteria, but if a few bacteria withstand the treatment, these bacteria will not only survive, but reproduce and pass on the traits that allow them to resist antibiotics. This process is more commonly known as "survival of the fittest." In the case of bacteria and antibiotics, the "fittest" are those that survive exposure to antibiotics. Thus, any use of antibiotics to some degree leads to resistance.[24]

Given this inevitable trend, it is important to maintain the effectiveness of antibiotics for as long as possible. Antibiotics are a resource that should be used wisely. When your doctor prescribes antibiotics, you are told to take the whole prescription, even if you start to feel better before you are done. The point is to ensure full treatment and not leave bacteria behind that develop resistance to that particular drug, which would require even stronger antibiotics to fight.[25]

Similarly, public health campaigns work to educate people about not using antibiotics to treat problems caused by viruses, like a cold or the flu. Because antibiotics don't kill viruses, doctors don't want antibiotics to be used when they have no chance of working and will only increase the threat of resistance in bacteria in the body that happen to be exposed.[26] The livestock industry, however, uses antibiotics much differently than human medicine, in a way that contributes to the emergence of AR bacteria.

How Industrial Agriculture Makes Antibiotic Resistance Worse[a]

Although livestock producers do use antibiotics to treat sick animals, the far more common usage is for "subtherapeutic" purposes including disease prevention and growth promotion. In the 1950s, researchers discovered that a small, constant dose of antibiotics helped animals grow faster. Livestock producers began using feed with antibiotics mixed in, both to promote faster growth and as an attempt to prevent infections in densely packed and unsanitary confined animal feeding operations (CAFOs).[27] These subtherapeutic doses are just a fraction of the amounts typically used to treat infections.

Imagine taking a fraction of a regular dose of antibiotics every day, even when you are healthy. Does that make sense given the advice we hear from doctors to take the full course of antibiotics and to take antibiotics only when needed to treat bacterial infections? Could you imagine including a low dose of antibiotics in your food, taken without even consulting a doctor? That's essentially what happens in modern livestock production. And it creates conditions that promote the development of AR bacteria.

Treatment of sick animals requires just a few animals to receive medicine for a short time and is less likely to contribute to resistance. Subtherapeutic uses mean an entire herd or flock of animals receives small doses for an extended period. This practice kills bacteria that are susceptible to the drug, leaving the AR bacteria to survive and reproduce. The use of even one antibiotic in this manner can select for resistance to multiple classes of

a See infographic on pages 10-11, which illustrates the processes described on pages 4-11.

antibiotics because the genetic trait that allows bacteria to survive exposure to one antibiotic is often linked to traits allowing it to survive others.[28]

Both in the United States and worldwide, agriculture uses vastly more antibiotics than human medicine, and agriculture also uses drugs from every major class of antibiotics used in human medicine.[29] Estimates differ on precisely how many antibiotics are used in agriculture in general and for subtherapeutic purposes in particular. There is no centralized system for collecting such data, as the pharmaceutical industry is not eager to share business information it wants to keep confidential,[30] and even some livestock producers may not know just how much antibiotics is in the pre-mixed feed their contracts with meat companies require them to use.[31]

> *"Our findings underscore the potential public health risks of widespread antibiotic use in food animal production.* Staph *thrives in crowded and unsanitary conditions. Add antibiotics to that environment and you're going to create a public health problem."*[183]
>
> — DR. LANCE PRICE, DIRECTOR OF THE TRANSLATIONAL GENETICS RESEARCH INSTITUTE'S CENTER FOR FOOD MICROBIOLOGY AND ENVIRONMENTAL HEALTH

The best estimates of antibiotic use come from the U.S. Food and Drug Administration (FDA). The FDA reported in 2011 that 80 percent of antibiotics in the United States are sold for agricultural purposes.[32] The FDA also reports that 74 percent of antibiotics used in livestock are sold for use in feed, 16 percent for use in water and only 3 percent for use as injection.[33] Although the FDA cautions that the method of delivery does not correlate exactly with the purpose of use,[34] scientific evidence makes clear that putting medicine in feed makes dosing imprecise and not as effective for disease treatment.[35] In other words, the antibiotics used in feed and water are most likely used for subtherapeutic purposes.

The mechanisms of AR and its spread are complicated. Many drugs used for subtherapeutic purposes are also used for disease treatment, both in veterinary and human medicine, and many AR genes are already widespread.[36]

Evidence tying subtherapeutic antibiotic use in livestock and AR comes in different forms. A study comparing strains of *Staphyloccocus* in poultry from the 1970s and 2006 found much higher levels of resistance to eight antibiotics in the more recent strains.[37] In the United States, Spain and the Netherlands, researchers found eight- to sixteen-fold increases in AR *Campylobacter* within just three years of the introduction of the antibiotic class fluoroquinolone in poultry.[38]

Although evidence tying subtherapeutic antibiotic use in livestock and AR has been largely circumstantial, a 2011 experiment offered direct evidence. This highly controlled trial took piglets from the same litter and raised them in two groups under the same conditions, except that one group was given low doses of antibiotics in the feed.[39] After only two weeks, the treated piglets developed significantly higher levels of AR *Escherichia coli*. The AR *E. coli* in the treated piglets carried a higher variety of AR genes, including some that conferred resistance to drugs not used in the study.[40]

Beyond Survival of the Fittest

Subtherapeutic antibiotic use selects for AR bacteria, but the story doesn't end there. AR bacteria reproduce, becoming more numerous, but they also share genes with other bacteria in the environment and in people.

Most AR genes in bacteria are located on mobile pieces of DNA known as plasmids. Bacteria can share plasmids, even across species. So, not only do AR bacteria become more common in response to selective pressure by reproducing more copies of themselves, but they can also share the resistance genes with neighboring bacteria.[41] These DNA swaps, known as "horizontal gene transfer," allow both faster spread of AR genes and easier acquisition of resistance to multiple drugs by multiple types of bacteria.[42]

The gene sharing can occur among the bacteria in animal digestive tracts and then continue as bacteria from the animal spread via waste into the environment.[43] The resistance gene, in a way, takes on a life of its own, no longer tied to a specific species of bacteria, but persisting in the larger microbial environment. The collective effect is known as "reservoirs of resistance," in which resistance genes are widespread in the environment and can be acquired by bacteria through horizontal gene transfer.[44]

Once AR genes have developed and spread, they are exceedingly hard to control. Researchers have gone so far as to call some bacteria "highly promiscuous" because of how easily they spread AR traits.[45] Eliminating subtherapeutic uses of antibiotics removes the selective pressure that allows AR bacteria to thrive in livestock operations, but may not stop the spread of already existent AR bacteria.[46]

Let's be clear: Subtherapeutic antibiotics select for resistance genes in bacteria that would not become so prevalent otherwise, and these AR bacteria make their way into the human population. It is not just that AR bacteria make people sick, although they do, but that through horizontal gene transfer, the resistance genes perpetuate themselves in good bacteria in humans as well. These good bacteria form reservoirs of resistance genes that are available to bacterial pathogens.

Even occasional transmission to humans can have a significant negative impact because of how resistance genes spread.[47] It is basically impossible to trace AR bacteria directly from a livestock operation to a sick person,[48] but scientific understanding of bacterial evolution demonstrates that practices driving resistance in livestock have far-reaching effects by increasing the overall reservoir of resistance.

Studies of AR bacterial DNA over time indicate that livestock treated with subtherapeutic doses of antibiotics are the likely origin for some AR bacteria in humans. *E. coli* that is resistant to ciprofloxacin, from the drug class fluoroquinolones once used subtherapeutically in poultry, is very similar in humans and chickens and more commonly found in chicken than in other meats in which the drug is not used. This evidence points to poultry as the source of the AR bacteria, not medical use of the drugs in humans.[49]

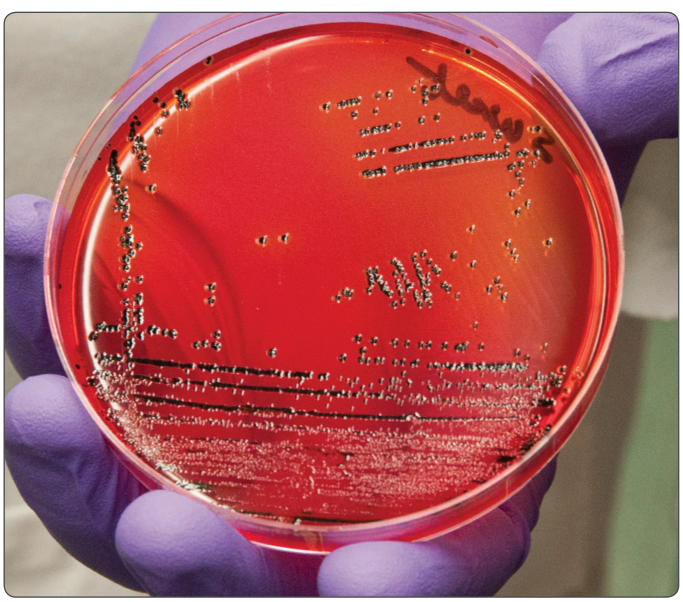


PHOTO COURTESY OF THE U.S. FOOD AND DRUG ADMINISTRATION

Testing of *E. coli* from urinary tract infections in people across multiple states reveals it to be very similar to AR *E. coli* in livestock, suggesting that the source was common in food.[50]

Genetic analysis of methicillin-resistant *Staphylococcus aureus* (MRSA) indicates that the strain that is associated with livestock originated in humans, transferred to pigs where it acquired resistance to tetracycline and methicillin, and then jumped back to humans.[51] This research required the participation of 20 institutes studying 89 genomes from humans and animals over 19 countries, a complicated and painstaking effort.[52]

Otherwise-healthy people can carry AR bacteria for years without realizing it, and that same AR bacteria can pose grave danger as an infection.[53] Whether it is a persistent foodborne illness, urinary tract infection or infection in a hospital, AR bacteria make themselves known in patients whose illnesses just do not clear up, leading to round after round of escalating treatments. Antibiotic resistance has become such a serious problem that there are few or no treatment options in some cases,[54] and pharmaceutical companies are not producing new treatments fast enough to keep up with the need.[55] In the face of such a complex problem, much more effort must be directed at trying to slow the development of resistance at its source.

How Antibiotic-Resistant Bacteria Spread

Reservoirs of AR bacteria persist in livestock and in the environment around farms. Illness-causing bacteria are relatively common in meat. Consumers encounter these bacteria while handling raw meat and eating it undercooked. It's why the government reminds consumers to cook meat to certain temperatures and educates about cross-contamination.[56] Tests of retail meat samples have found antibiotic resistance among the bacteria responsible for foodborne illnesses. DNA tests of AR bacteria from sick people and livestock reveal the likelihood of an agricultural source. AR bacteria can spread from livestock not just to humans but to rodents and flies as well. The bacteria fester in waste lagoons, and that waste is then often used as fertilizer, potentially contaminating soil, waterways and crops.

From Meat to Consumers

Multiple studies have found AR bacteria in many types of retail meat and fish products.[57] In other words, when you buy meat at the grocery store, there's a decent chance that it has AR bacteria on it. Whether the bacteria are AR

Figure 1. AR *Salmonella* in NARMS Retail Meat Samples

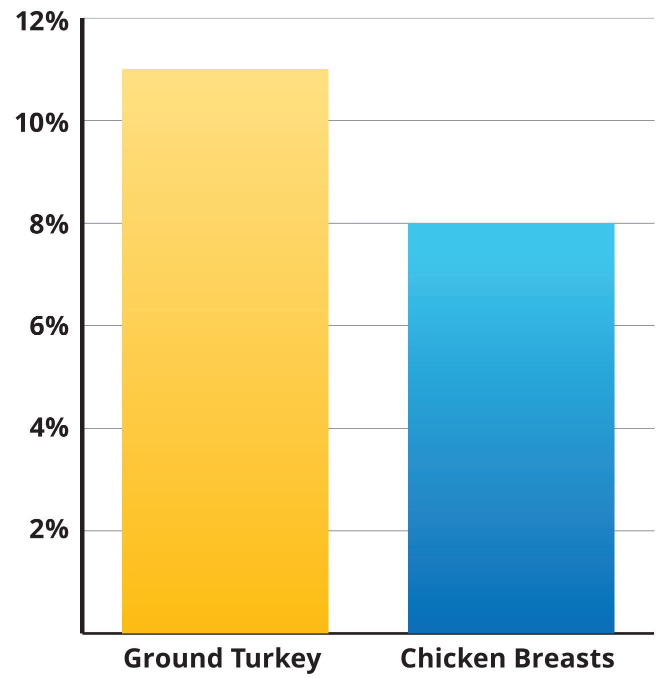
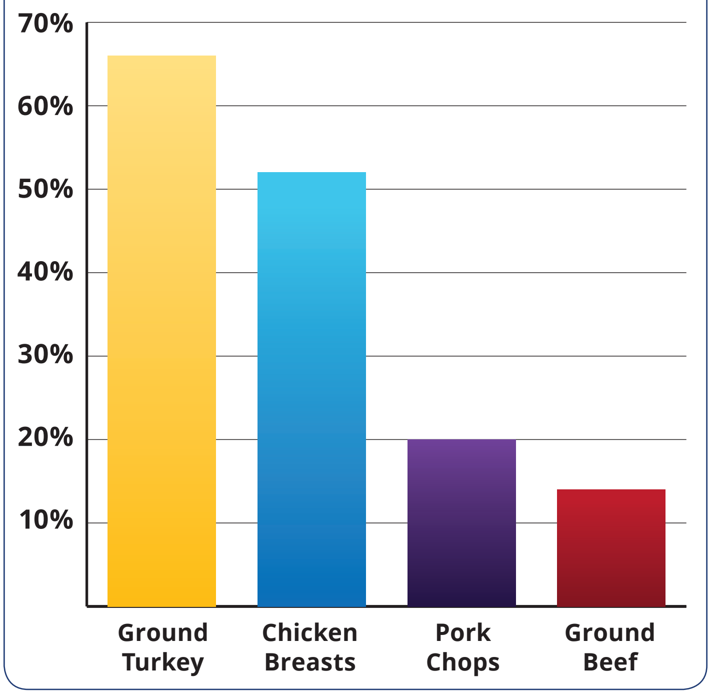


Figure 2. AR *E. Coli* in NARMS Retail Meat Samples



SOURCE FIG. 1 and 2: Food & Water Watch analysis of FDA NARMS. "2010 Retail Meat Report." 2012.

or not, handling raw meat and undercooking can lead to foodborne illness.[58] The FDA stated in 2012, "In regard to antimicrobial drug use in animals, the Agency considers the most significant risk to the public health associated with antimicrobial resistance to be human exposure to food containing antimicrobial-resistant bacteria resulting from the exposure of food-producing animals to antimicrobials."[59]

In 1996, the FDA, Centers for Disease Control and Prevention (CDC), and U.S. Department of Agriculture (USDA) partnered to create the National Antimicrobial Resistance Monitoring System (NARMS).[60] Among other functions, NARMS collects samples of bacteria from chicken breasts, ground turkey, ground beef and pork chops and measures the presence of the drug-susceptible and AR foodborne pathogens *Campylobacter*, *Salmonella*, *Enterococcus* and *E. coli*.[61] Because of the variety of antibiotic classes and species of bacteria, it can be hard to gather an overall picture of the AR problem from the sampling data.

Food & Water Watch has analyzed the 2010 NARMS data to estimate how widespread AR bacteria were in the retail meat samples collected. AR *Salmonella* was present in 8 percent of chicken breast samples and 11 percent of ground turkey samples. The presence of AR *E. coli* in the samples collected varied widely: 66 percent in ground turkey, 52 percent in chicken breasts, 20 percent in pork chops and 14 percent in ground beef.[62]

The vast majority of *Enterococcus* found in each type of meat contained at least one AR trait. *Enterococcus* was also highly prevalent in all types of meat tested, leading to a high overall risk of encountering AR *Enterococcus*. Of the *Campylobacter jejuni* samples tested, 49 percent of those from chicken breasts and 80 percent of those from ground turkey contained at least one AR trait. The prevalence of AR traits among *Salmonella* samples ranged from 42 percent in ground beef to approximately two-thirds in ground turkey, chicken breasts and pork chops. The presence of AR traits in *E. coli* samples also varied widely: 83 percent in ground turkey, 67 percent in chicken breasts, 49 percent in pork chops and 23 percent in ground beef.[63]

Among the report's other key findings, nearly half of the *Salmonella* samples from chicken breasts and a third of those from ground turkey were resistant to three or more classes of antibiotics. *Salmonella* resistance to third-generation cephalosporins increased in retail poultry. Between 2002 and 2010, this type of resistance more than tripled from 10 to 34.5 percent in samples from chicken breasts and doubled from 8 to 16 percent in ground turkey.[64] This increase led the FDA to ban certain subtherapeutic uses of cephalosporins. Among the *Enterococcus* samples, there was no resistance to vancomycin and linezolid, two drugs used in human medicine but not agriculture, but the vast majority of *Enterococcus* samples were resistant to other drugs.[65]

The NARMS surveillance system does not include any forms of *Staphylococcus*, although it has been found in the food supply. MRSA was once considered only endemic to hospitals, but one strain of MRSA, ST398, has been found in food production animals, in people who work with those animals and in retail meat.[66] A study of retail meats in five U.S. cities found *S. aureus* in just under half of the samples. Nearly all the *S. aureus* found was resistant to one antibiotic; half of the *S. aureus* found was multi-drug resistant.[67] The researchers recommended that "multidrug-resistant *S. aureus* should be added to the list of antimicrobial-resistant pathogens that routinely contaminate our food supply."[68]

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Several studies have linked AR bacteria in retail meats to livestock sources. In a study of AR *E. coli* from different types of meat across a wide geographic range, the antibiotic-susceptible and AR *E. coli* from each type of meat resembled other samples from the same species and varied greatly with samples from other species.[69] This finding indicates that livestock is the likely source of the bacteria, with the AR bacteria developing from drug-susceptible *E. coli* under selection pressure within each species of livestock.[70]

A study of ground meats in three grocery stores from three different chains in the Washington, D.C., area found that 20 percent of the samples contained *Salmonella*. Eighty-four percent of the bacteria were resistant to one antibiotic, and just over half were resistant to three or more antibiotics.[71] The findings included a particularly virulent strain that has been the culprit of previous outbreaks of foodborne illness.[72] The commonality of AR bacteria in all the types of ground meats indicates the presence of a reservoir that can affect people.[73]

Not all livestock are raised using subtherapeutic antibiotics. U.S. organic standards require that livestock not be treated with antibiotics,[74] and some companies market meat "raised without antibiotics."[75] Because AR bacteria are so widespread in the environment, it is possible for livestock raised without antibiotics to carry AR bacteria. Studies have found that *Enterococcus faecium* and *Campylobacter* were less likely to be antibiotic resistant in organic chicken and chicken raised without antibiotics compared to conventional chicken.[76]

Studies of MRSA have found mixed results, with some studies finding a difference between MRSA levels in conventional meat and meat "raised without antibiotics" and one study finding no difference. That study, however, cited the possibility that processing equipment or workers carrying MRSA contaminated the meat "raised without antibiotics."[77] It is clear, however, that raising livestock without antibiotics does not add to the reservoir of resistance.

Antibiotic-Resistant Foodborne Illness

The CDC estimates that approximately one in six Americans gets a foodborne illness each year, resulting in 128,000 hospitalizations and 3,000 deaths.[78] Foodborne illnesses from AR bacteria have been tracked back as far as the 1970s and 1980s. There were 38 known outbreaks of AR foodborne illnesses between 1973 and 2011, resulting in more than 20,000 illnesses, over 3,000 hospitalizations and nearly 30 deaths. The estimate is undoubtedly low,

How Do I Find Meat Raised Without Antibiotics?

1. **Buy organic.** Organic livestock in the United States must be raised without antibiotics.[180]
2. **Look for a label stating that the meat has been raised without antibiotics.** The USDA allows companies to use the label if they provide documentation of their practices.[181] Labels that also say "USDA Process Verified" or list a certification from another independent body offer another level of assurance. A "natural" label claim does not necessarily mean antibiotics were not used.[182]
3. **Buy directly from the farmer**, which allows you to ask the farmer directly about his or her practices.

Buying meat raised without antibiotics is no guarantee that the meat will be free of AR bacteria, and consumers should still follow good food safety practices when preparing any meat product. But making the effort to buy products produced without antibiotics helps prevent the further emergence of AR bacteria by supporting producers who do not use subtherapeutic antibiotics.

however, as health officials do not always test for AR, and the CDC does not track all outbreaks of AR pathogens.[79] In 2011, the United States experienced two major food recalls due to illness outbreaks from AR bacteria.

In the face of an illness outbreak caused by AR *Salmonella*, Cargill voluntarily recalled 36 million pounds of ground turkey in August 2011, and an additional 185,000 pounds the next month.[80] This recall, the third largest meat recall in the USDA's records, represented several months' worth of production from one plant in Arkansas. It took several months for the cluster of illnesses to be traced back to the plant.[81] In total, 136 people across 34 states were infected, yielding 37 hospitalizations and one death.[82] A disproportionate number of people infected were hospitalized due to the bacteria's antibiotic resistance.[83] While *Salmonella* can run its course without treatment, it can also cause severe complications, especially in the very young, elderly and immune-compromised. It is those vulnerable to more complicated infections that particularly need effective treatment options.[84]

The second illness outbreak involved another AR *Salmonella* strain, this time tied to ground beef from the Hannaford grocery store chain in New England. This outbreak was smaller, with 20 infections and eight hospitalizations reported.[85] The strain causing the outbreak was resistant to multiple classes of drugs, including cephalosporins, the drugs of choice to treat *Salmonella* infections in children.[86]

The nature of our concentrated food system is such that meat is aggregated from many sources through a tight processing stream before distribution to retailers and consumers across the country, offering more points for potential cross-contamination.[87] In the Hannaford outbreak, limited records kept by the retailer prevented the USDA from tracing the contamination back to the supplier, although Hannaford officials claim they followed industry standards.[88] Clearly, strong food safety practices are particularly important to prevent AR bacteria outbreaks, which cause more serious illnesses. But it is also critical to prevent the emergence and spread of AR bacteria among livestock to minimize AR bacteria's entry into the food supply.

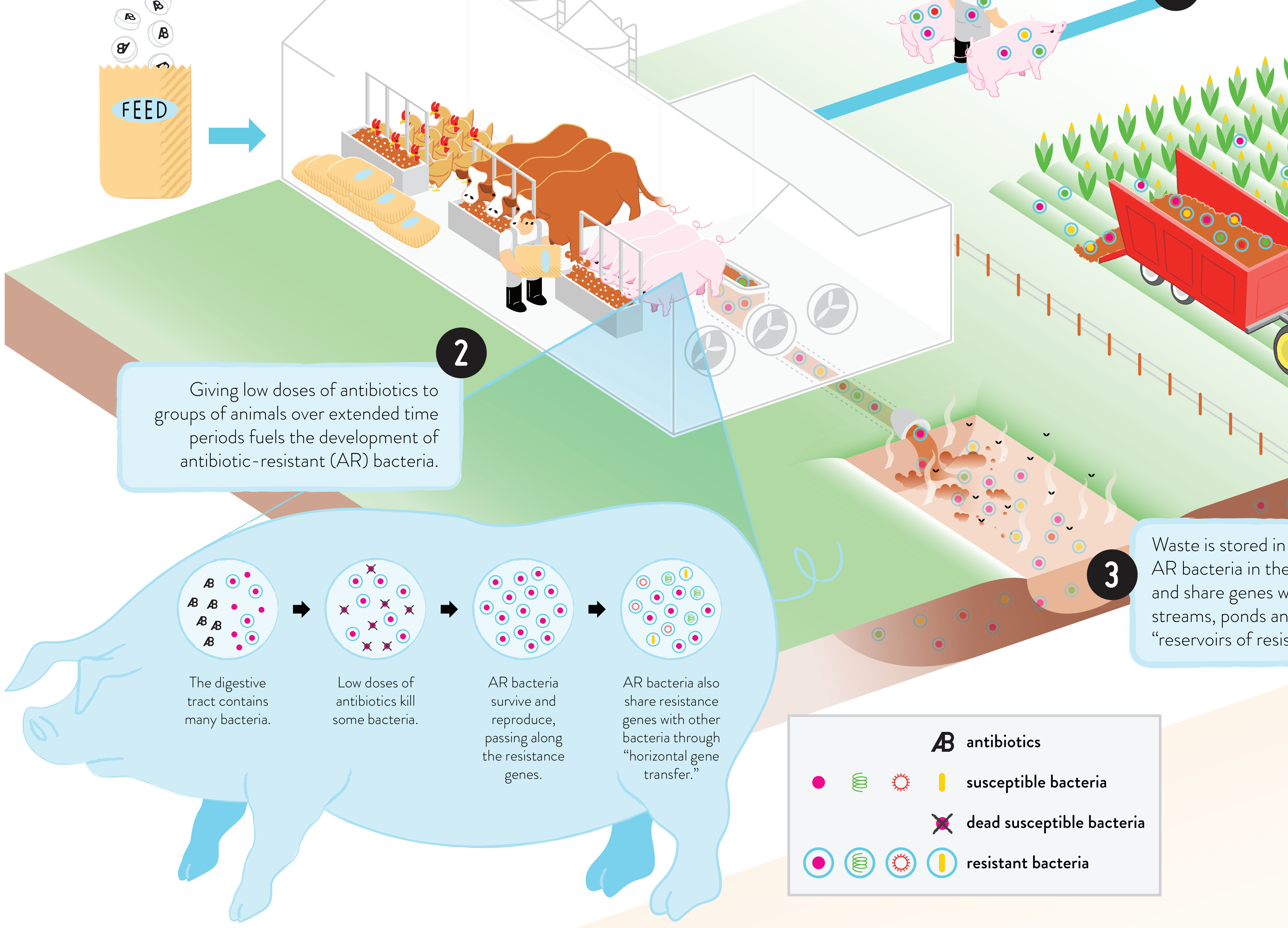
From Livestock to Farmers and the Environment

AR bacteria in livestock do not just remain there, but spread to farmers, farmworkers and rural residents.[89] As early as 1976, researchers found that AR bacteria spread rapidly in the intestines of chickens raised using subtherapeutic antibiotics. Farmers on the same poultry operations developed higher levels of AR bacteria in their intestinal tracts as well, compared to their neighbors.[90] Multiple studies have identified the similar strains of AR bacteria in farmers and their livestock.[91] This trend has continued as new strains of AR bacteria threaten the human population.

Strains of MRSA, for instance, have now been found not only in pigs but also in the farmers that raise them.[92] One strain of MRSA has been found in pigs and the people that raise them, but not in neighbors who do not raise pigs.[93] Researchers have found strong evidence that this strain of MRSA originated in humans, migrated to pigs where it acquired antibiotic resistance, and now is infecting humans again.[94] A study of poultry workers found the presence of a strain of *E. coli* resistant to gentamicin, an antibiotic commonly used in chickens, to be 32 times higher in the workers compared to other members of the community. Half of the poultry workers carried the AR strain, compared to 3 percent of the neighboring population.[95] AR bacteria have sickened farm family members too.[96]

In large livestock operations, manure is collected in lagoons.[97] The fecal bacteria also collect in these lagoons and then spread into the environment when the waste is applied to land as fertilizer. Fecal bacteria can survive for weeks or even months outside the animal.[98] With that amount of time to live and reproduce, it is not surprising that AR bacteria spread into the environment. Most of the antibiotics fed to livestock are also excreted in waste, adding an additional low-level exposure to bacteria in the lagoon and in the environment, perpetuating the further development of AR bacteria.[99] Several studies have found DNA matches between AR bacteria in the soil and water and in manure lagoons.[100]

Manure storage itself does not constitute a form of treatment, and treatment is necessary to reduce bacteria. Unlike chemical pollutants, bacteria reproduce. Thus, treat-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2
Giving low doses of antibiotics to groups of animals over extended time periods fuels the development of antibiotic-resistant (AR) bacteria.
The digestive tract contains many bacteria.
Low doses of antibiotics kill some bacteria.
AR bacteria survive and reproduce, passing along the resistance genes.
AR bacteria also share resistance genes with other bacteria through “horizontal gene transfer.”
3
Waste is stored in
AR bacteria in the
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resistant bacteria

ment that only partially eliminates bacterial contamination can be rendered ineffective when the bacteria simply grow back. Neither lagoon storage nor anaerobic digestion, a process used to convert livestock waste into energy, significantly decreases the presence of AR genes.[101] Poultry litter has also been found to harbor multiple-drug-resistant *E. coli* and antibiotic residues.[102]

Most livestock waste stored in lagoons is applied to nearby fields as fertilizer, introducing AR bacteria into the local environment.[103] The AR bacteria not only spread, but share genes with naturally occurring bacteria in local fields, streams, ponds and even groundwater. These bacteria are adapted to their environment, just as the fecal bacteria are adapted to living in the digestive tracts of livestock, and may carry on reproducing with these new traits.[104] Thus, AR bacteria from livestock contribute to a reservoir of antibiotic resistance in rural environments.

Other opportunities for AR bacteria to spread include wind, transporting livestock, and even flies and other animals. Researchers have found higher concentrations of AR bacteria downwind of hog facilities a few weeks after hogs received a dose of subtherapeutic antibiotics.[105] Even vehicles carrying livestock leave bacteria, AR and otherwise, in the air behind them.[106] Flies attracted to livestock waste also pick up and may disperse AR bacteria.[107]

Tackling Antibiotic Resistance

Animals can be raised successfully without subtherapeutic antibiotic use. The European Union (EU) has banned subtherapeutic use of antibiotics for growth promotion.[108] U.S. organic standards require that livestock not be administered antibiotics.[109] Companies such as Chipotle, Niman Ranch and Applegate Farms have made meat raised without antibiotics much more visible in grocery stores and restaurants.[110]

Some antibiotics no longer work as growth promoters or yield a result so slight that the additional profit does not cover the cost of the antibiotics, yielding a net loss.[111] Alternatives to subtherapeutic antibiotic use include vaccinations, when available. Research continues on new vaccines and probiotics, the use of less harmful bacteria to compete with AR bacteria in the digestive tract.[112]

Raising livestock without antibiotics requires changes in herd management. Animals crowded into CAFOs may face increased stress and poor hygiene, which facilitates the spread of pathogens and slows animal growth. In other words, minimizing livestock stress and maximizing hygiene can provide growth-promotion and infection-prevention benefits without the subtherapeutic use of antibiotics.[113]

Ending Subtherapeutic Use of Antibiotics

By far the best way to prevent the spread of AR bacteria is to prevent their development in the first place. It is also more effective to take action when AR bacteria first emerge, rather than wait until the trait becomes widespread and threatens animal or human health.[114] Once AR traits spread via horizontal gene transfer throughout the ecosystem, the AR trait may be virtually impossible to eradicate and may persist for many years.[115] Eliminating subtherapeutic uses of antibiotics, however, can make a difference in reducing the prevalence of AR bacteria.[116]

By far the best way to prevent the spread of AR bacteria is to prevent their development in the first place. It is also more effective to take action when AR bacteria first emerge, rather than wait until the trait becomes widespread and threatens animal or human health.

The EU has taken a different path than the United States on antibiotics used for growth promotion in livestock. The EU banned the use of medically important antibiotics for growth promotion and established an EU-wide AR monitoring system in 1999, followed by a phase-out of all antibiotics used for growth promotion by 2006.[117] Following these decisions, prevalence of AR bacteria has declined in livestock, meat and people in the EU.[118]

In 1986, Sweden became the first EU country to ban the use of antibiotics as growth promoters. Sweden's livestock producers faced increases in livestock disease immediately after the ban, but the government also devoted money to research and extension services for farmers, and its data showed no decrease in production due to the ban.[119]

Denmark, the next country to implement such a ban, experienced a brief spike in therapeutic antibiotic use in swine.[120] Between 1992 and 2008, pig farmers in Denmark increased production by nearly 40 percent, while their use of antibiotics per pig dropped by 50 percent.[121]

In the 1990s, vancomycin-resistant infections were increasingly found in hospital patients in the EU. The finding of the same AR bacteria in meat and manure from farms using growth promoters led to the broader restrictions across the EU, instead of just individual countries.[122] The prevalence of bacteria resistant to vancomycin in people fell once the EU eliminated its use as a livestock growth promoter. The U.S. never approved this class of drugs for subtherapeutic uses in livestock, and, while resistance to these drugs does exist in *Enterococcus* infections in U.S. hospitals, the problem has never been as great as the point reached in the EU.[123] But the EU's experience with this drug offers important lessons about the consequences of the subtherapeutic use of antibiotics in livestock and outcomes when such use ends.

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How Antibiotics Are Regulated

The Food and Drug Administration

Federal government recognition of antibiotic resistance goes back decades, but action to address the problem has been intermittent and slow. A 1970 FDA Task Force on the use of antibiotics in animal feed recommended limiting those uses for medically important antibiotics. In 1977, the FDA proposed withdrawing approval for subtherapeutic uses of penicillins and multiple tetracyclines, as both of those drugs play an important role in human medicine. Congress ordered studies before the withdrawal could be considered, and the National Academies of Science concluded that the evidence of the need for drug withdrawal was very limited.[124] Further reports from government agencies and the World Health Organization drew attention to evidence linking subtherapeutic antibiotic use in livestock and antibiotic resistance. These reports often called for further data collection and consideration of human health risks when approving veterinary uses of livestock.[125]

In 2004, the Government Accountability Office (GAO), the investigative oversight agency that works for Congress, found much amiss in the FDA's and USDA's handling of antibiotic resistance. The FDA tracks antibiotic use data for livestock, but the GAO criticized the system for lacking details including the species receiving the drugs and the purpose for which the drugs were given. Without such specificity, the FDA not only cannot say how much antibiotics are used for growth promotion, disease prevention, or treatment, but cannot measure the effectiveness of its policies designed to curb antibiotic resistance.[126] The GAO also found that the sampling of retail meat to examine the prevalence of AR bacteria is "not representative of antibiotic resistance in food animals and retail meat throughout the United States."[127] The deficiencies prevent examination of trends in antibiotic resistance relative to antibiotic use.[128]

The FDA acknowledges that there's a problem, but what has it done to rein it in? On the one hand, the FDA has limited subtherapeutic uses of cephalosporins and banned all uses of fluoroquinolones, but it took a lawsuit by public interest groups to make the FDA address a proposal to ban these same uses in two other major classes, tetracyclines and penicillins. The FDA for years has insisted that industry voluntary efforts will solve the problem, citing lack of resources as an impediment to creating regulations.[129]

Tetracyclines and Penicillins

In 1977, the FDA proposed withdrawing approval for subtherapeutic uses of penicillins and tetracyclines, as both of those drugs play an important role in human medicine.[130] For 34 years, the FDA kept the proposal open; all the while these drugs, which are commonly used to treat human infections, were added to livestock feed and water, often without prescriptions.[131]

In 1999, five advocacy organizations[132] filed a citizen petition requesting that the FDA follow through on its proposal. In 2005, an overlapping set of organizations[133] made a similar request, asking for the withdrawal of herdwide and flockwide uses of several more classes of antibiotics.[134] Having received no response to either petition, the coalition[135] filed suit against the FDA in May 2011 to force the FDA to respond to the 1999 and 2005 citizen petitions.[136]

The FDA's eventual response left much to be desired. Despite acknowledging shared concern, the FDA denied the petitions, citing the difficulty of the formal process of withdrawing a drug approval.[137] In December 2011, the FDA withdrew the 1977 proposal to withdraw approval of subtherapeutic uses of penicillins and tetracyclines altogether. Among the reasons for its decision, the FDA cited other ongoing regulatory options and the focus on voluntary initiatives.

The FDA stated that the withdrawal "should not be interpreted as a sign that FDA no longer has safety concerns or that FDA will not consider re-proposing withdrawal proceedings in the future, if necessary."[138] Meanwhile, the most recent NARMS report, covering data from 2010, indicated that resistance to tetracyclines and penicillins is quite common across different types of bacteria in retail meats.[139] The plaintiff organizations, however, disagreed with that assessment, as did a federal court.[140]

In the spring of 2012, federal district court Judge Theodore Katz issued two rulings indicating that the FDA's voluntary approach to regulating subtherapeutic antibiotic use is insufficient. The first ruling compels the FDA to revisit the withdrawal process begun in 1977 for penicillins and tetracyclines. According to Judge Katz, "The scientific evidence of the risks to human health from the widespread use of antibiotics in livestock has grown, and there is no evidence that the FDA has changed its position that such uses are not shown to be safe."[141]

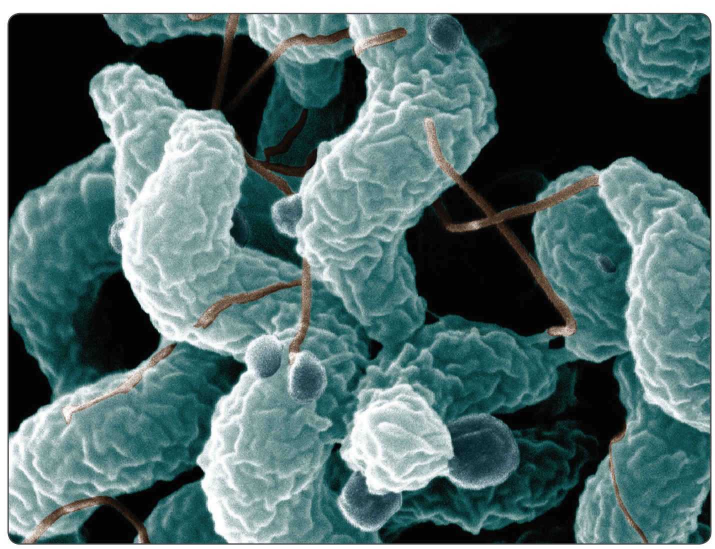
The judge's ruling indicates that the FDA should have triggered the withdrawal proceedings to move ahead as soon as the FDA ruled that the practices were no longer shown to be safe.[142] The drug manufacturers may request a hearing to demonstrate that the drugs are safe to use subtherapeutically in livestock. The companies bear the burden of proof at the hearing, and if they cannot prove that the uses are safe, the FDA must formally withdraw its approval of those uses.[143] The FDA appealed this ruling.[144]

Judge Katz's second ruling prescribes a broader re-evaluation of subtherapeutic uses of antibiotics, calling the FDA's decision to deny the 1999 and 2005 citizen petitions on the basis that they were "too time and resource-intensive" to be "arbitrary and capricious."[145]

Fluoroquinolones

The FDA licensed a new class of antibiotics, fluoroquinolones, for subtherapeutic uses in the mid-1990s. Prior to the approval, NARMS found no resistance to these drugs in *Campylobacter*, a common type of bacteria in poultry. By 1999, however, nearly 20 percent of *Campylobacter* were resistant to these drugs. Scientific modeling estimated that more than 150,000 people were infected with fluoroquinolone-resistant *Campylobacter* from poultry consumption in 1999 alone and that 1.2 billion pounds of boneless chicken were contaminated with this variety of AR bacteria. In the face of such rapid development of resistance, the FDA proposed withdrawal of the approval of all uses of fluoroquinolones in chicken in 2000. The pharmaceutical industry responded with legal action, dragging the final action out until 2005 while resistance continued to increase.[146]

The struggle to implement this withdrawal led the FDA to change its approach to new applications to use antibiotics important in human medicine in livestock.[147] In 2003, the FDA released guidance to pharmaceutical companies on how to assess the risk of a new drug causing resistance problems. Depending on the findings, the FDA may require that the new drug may, for instance, be used for treatment only under a veterinarian's care, or it may simply not approve the drug. This risk assessment is not required, however, but is just one of a few options that companies can use to evaluate the drug's safety.[148] But what about the many drugs approved before 2003? The FDA, citing cost concerns, has not conducted post-approval evaluations and has instead focused on voluntary approaches to change antibiotic use.[149]



NARMS tracks two types of Campylobacter *in retail chicken breasts. Resistance to ciprofloxacin, a fluoroquinolone commonly used in human medicine, in* C. coli *in retail chicken breasts rose from 10 percent in 2002 to nearly 30 percent in 2005. Since the ban, resistance to ciprofloxacin dropped to 13.5 percent in 2010, a substantial improvement.*

NARMS tracks two types of *Campylobacter* in retail chicken breasts. Resistance to ciprofloxacin, a fluoroquinolone commonly used in human medicine, in *C. coli* in retail chicken breasts rose from 10 percent in 2002 to nearly 30 percent in 2005. Since the ban, resistance to ciprofloxacin dropped to 13.5 percent in 2010, a substantial improvement.[150] Resistance to cipro in *C. jejuni* has been more varied, with an increase from 15 percent in 2005 to 23 percent in 2010.[151] Meanwhile, a 2012 study found fluoroquinolones in feather meal, a byproduct of chicken processing made from feathers, suggesting that producers and feed companies may not all be following the ban.[152]

Cephalosporins

In April 2012, the FDA finalized a ban on specific subtherapeutic uses of cephalosporins.[153] Cephalosporins play an important role in treating foodborne illnesses in humans, especially children, as well as pneumonia and skin and soft tissue infections.[154] The 2011 Hannaford ground beef recall involved cephalosporin-resistant bacteria.[155] The FDA had issued a similar order in 2008, but revoked it after receiving a negative reaction, including threats of legal action, from the livestock and pharmaceutical industries.[156] The 2012 ban covers a narrower range of uses, leaving exceptions for older cephalosporins and those used with veterinary prescriptions.[157] The ban prohibits most "extralabel" uses in major food animals, meaning that the drugs cannot be used at an unapproved dose, frequency or duration and cannot be used for disease prevention.[158]

In its decision, the FDA reported increased antibiotic resistance to ceftiofur, one common cephalosporin. Government monitoring in 2009 found ceftiofur-resistant *Salmonella* in 14.5 percent of samples from cattle, 4.2 percent from swine, 12.7 percent from chickens and 12.4 percent from turkeys. In 1997, neither cattle nor swine had been found to carry this strain of AR bacteria, and it was present in only 0.5 percent of chicken samples and 3.7 percent of turkey samples.[159]

Examining specific strains of *Salmonella* over the same time period, ceftiofur resistance in *Salmonella* Typhimurium increased from 0 to 33 percent in chickens and from 3 to 28 percent in cattle, and ceftiofur resistance in *Salmonella* Heidelberg rose from 0 to 18 percent in chicken and from 0 to 33 percent in turkey.[160] Other researchers have noted that broad-spectrum cephalosporin use in livestock promotes the development of MRSA.[161]

Voluntary Guidance for "Judicious Use"

The FDA released formal guidance on antibiotic use in 2012 entitled, "Guidance 209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals."[162] The FDA defines judicious use as "using an antimicrobial drug appropriately and only when necessary."[163] The guidance specifically recommends "limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health" and "limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation."[164] Unfortunately, the FDA states clearly that the former includes prevention purposes, including giving antibiotics to otherwise healthy animals, so long as a veterinarian is involved.[165]

These limitations would occur if pharmaceutical companies voluntarily changed the labels listing how the drugs can be used. Most antibiotics in feed have been approved for multiple purposes including over-the-counter sales for growth promotion.[166] The FDA focused the recommendations on antibiotics approved prior to 2003, growth promoters, antibiotics in feed sold over-the-counter and antibiotics used continuously in feed and water.[167]

Along with Guidance 209, the FDA released two other documents. The first, Draft Guidance 213, advises pharmaceutical companies on how to apply Guidance 209 to new drug approval applications for antibiotics used in feed or water.[168] The second, draft regulatory changes to the Veterinary Feed Directive (VFD), instructs veterinarians on the type of oversight required for antibiotics no longer labeled for over-the-counter uses.[169]

All of these documents pre-suppose that pharmaceutical and feed companies and livestock producers will follow the voluntary guidance. Neither Guidance 209 nor Guidance 213 are mandatory, although should the industry choose to follow through, the changes would be binding.[170] The new rules for the VFD only apply when pharmaceutical companies change the allowed uses of their products on the label.[171]

The FDA has declared that it will re-evaluate the situation three years after the date finalizing Guidance 213 and then determine if the voluntary response has been sufficient. At that point, it will determine whether to take further regulatory action.[172] The FDA has previously argued that voluntary initiatives would be "more timely and resource-efficient," citing positive responses from industry regarding the initial judicious-use guidance released in 2010.[173] Certainly, it would be easier for the FDA if the pharmaceutical and feed industries voluntarily changed their practices. But will they?

Industry reactions have been mixed so far, ranging from lukewarm to critical. A few indicate that fear of future regulation is driving compliance with the voluntary initiative.[174] Meanwhile, the bans on subtherapeutic uses of fluoroquinolones and cephalosporins indicate that the FDA can put forth mandatory regulations on this issue. The FDA should use every tool in its regulatory toolbox to reduce subtherapeutic uses of antibiotics in livestock and not rely on voluntary industry measures.

Congress

Congress could also act to reduce subtherapeutic uses of antibiotics in livestock. Since 2003, several members of Congress have introduced legislation to limit the use of medically important antibiotics in healthy livestock: the Preservation of Antibiotics for Medical Treatment Act (PAMTA). As a microbiologist, sponsor Representative Louise Slaughter (D-NY) has relevant expertise on this issue. She has stated, "If an animal is sick, then by all means we should make them well, but the routine use of antibiotics on healthy animals in order to promote growth is dangerous. It would be like a mother giving their son or daughter antibiotics every morning in their Cheerios. We're wasting our precious antibiotics."[175]

As of spring 2012, PAMTA had not received a committee hearing or vote and had 85 co-sponsors between the House and Senate.[176] More than 300 organizations have expressed support for the bill.[177] Over 30 organizations have lobbied on PAMTA over the years with organizations representing the meat, livestock and pharmaceutical industries all voicing opposition.[178]

Who Supports PAMTA?[184]

More than 300 agricultural, consumer, health and environmental organizations, including:

American Academy of Pediatrics
American Medical Association
American Nurses Association
American Public Health Association
Infectious Disease Society of America
Keep Antibiotics Working Coalition
National Catholic Rural Life Conference
National Organic Coalition
National Sustainable Agriculture Coalition
Union of Concerned Scientists

Who Opposes PAMTA?[185]

American Farm Bureau Federation
American Feed Industry Association
American Meat Institute
American Veterinary Medical Association
National Cattlemen's Beef Association
National Chicken Council
National Milk Producers Federation
National Pork Producers Council
National Turkey Federation
United Egg Producers

Recommendations

The development and spread of AR bacteria are complicated processes, and efforts to reverse these processes are equally difficult. But one thing is abundantly clear: the best way to address the issue of antibiotic resistance is to prevent the development of AR bacteria in the first place, which means ending the subtherapeutic use of antibiotics in livestock.

The FDA continues to pursue voluntary initiatives with an industry that has resisted attempts to regulate subtherapeutic antibiotic use for decades. Relying on industry efforts is simply not enough to address this problem.

Food & Water Watch recommends that:

- Congress should pass PAMTA and ban subtherapeutic uses of antibiotics in livestock, thereby avoiding the cumbersome drug-by-drug process currently required of FDA to achieve the same goal.
- The FDA should closely monitor the impact of its voluntary strategy and start the regulatory process

now to withdraw drug approvals for injudicious uses within three years. The FDA should also strongly enforce the existing bans on certain uses of antibiotics.

- The FDA should address the GAO's recommendations to improve data collection on the use of antibiotics and the development of antibiotic resistance.[179] NARMS must be broadened to allow the FDA to identify and respond rapidly to emerging resistance.
- Government agencies should collaborate to increase research on antibiotic resistance, including the mechanisms of resistance emergence, spread and remediation as well as alternative means of preventing illness in livestock.
- The USDA should provide training and technical assistance to livestock producers that are transitioning away from subtherapeutic antibiotic use. The USDA should address contract stipulations that require livestock producers to use feed with antibiotics already added.

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