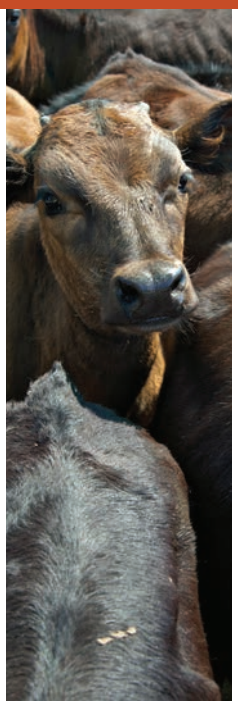
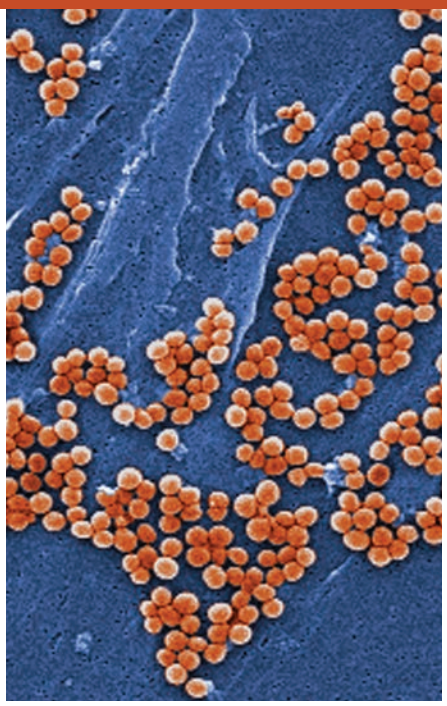
ANTIBIOTIC RESISTANCE 101

How Antibiotic Misuse on Factory Farms Can Make You Sick

food&water watch

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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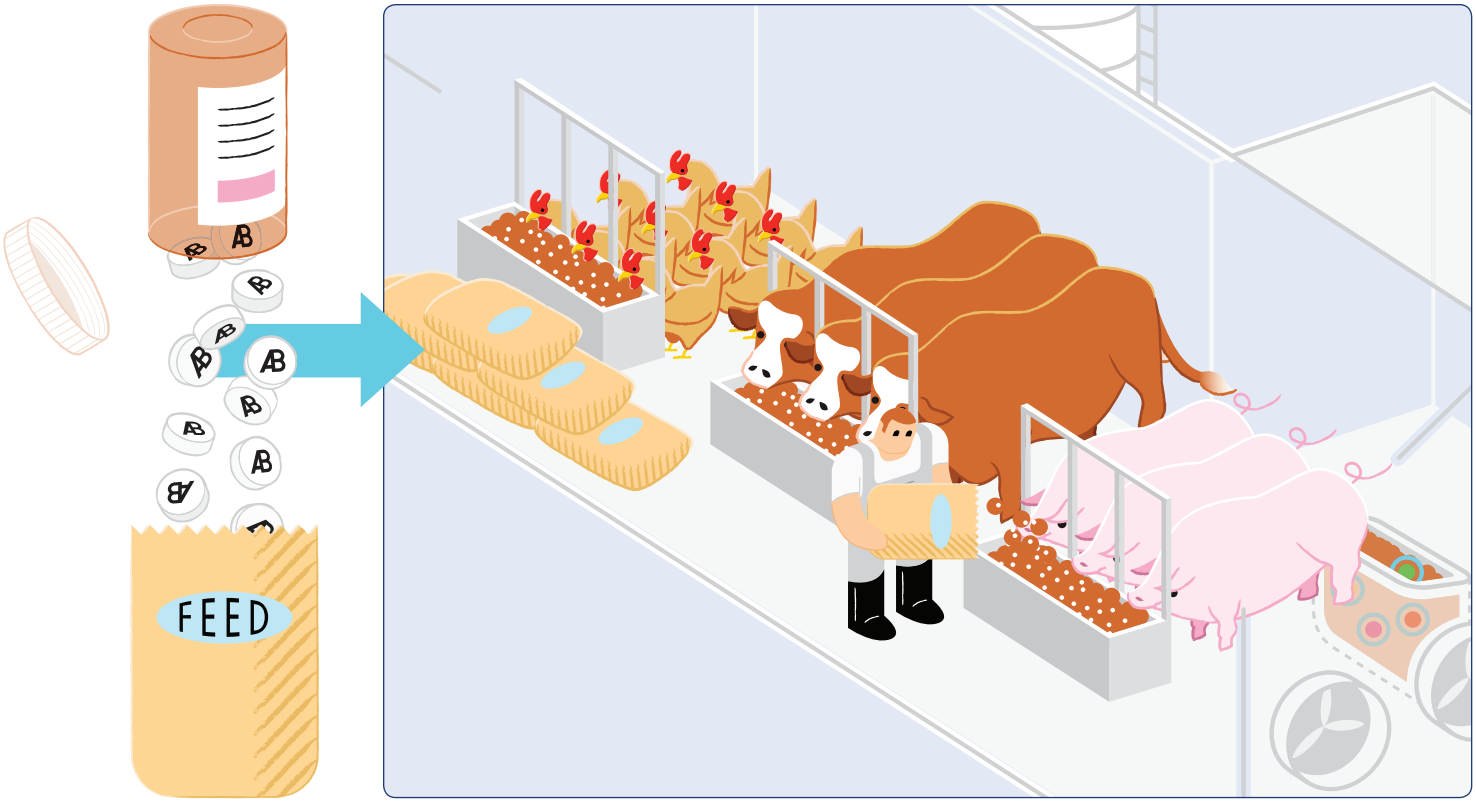


Executive Summary

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. The development of antibiotic resistance is hastened by the use of low doses of antibiotics at industrial farms. For decades, the drugs have been used routinely not to treat sick animals, but for disease prevention and growth promotion, a practice known as nontherapeutic 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]

Antibiotic-resistant (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. The most commonly affected populations 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 to some antibiotics and make it more likely for patients to require stronger drugs given intravenously.[7]

The Centers for Disease Control and Prevention (CDC) estimates that at least 2 million Americans each year experience AR infections, leading to at least 23,000 deaths.[8] Approximately 22 percent of those infections originate from foodborne pathogens.[9] Multiple studies have found AR bacteria in retail meat and fish products, including the federal government's National Antimicrobial Resistance Monitoring System (NARMS),[10] and AR bacteria have caused notable foodborne illness outbreaks.[11]

The livestock industry still minimizes its role in antibiotic resistance,[12] but the evidence is clear. Several DNA analyses of AR bacteria point to livestock as the source. The CDC, American Public Health Association, American Medical Association, American Academy of Pediatrics, Infectious Disease Society of America and World Health Organization all agree that nontherapeutic uses of antibiotics in livestock pose a threat to human health.[13]

Despite the urgency of this growing public health threat, neither Congress nor the FDA has taken sufficient steps to restrict the nontherapeutic use of antibiotics in livestock. 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 nontherapeutic uses, despite having restricted certain uses of particular antibiotics.[14]

Food & Water Watch recommends that:

- Congress should pass the Preservation of Antibiotics for Medical Treatment Act (PAMTA)/Prevention of Antibiotic Resistance Act (PARA), which would ban nontherapeutic uses of antibiotics in livestock, thereby avoiding the cumbersome drug-by-drug process currently required of the FDA to achieve the same goal. City councils across the country have passed resolutions urging Congress to pass PAMTA, and more are joining their ranks.
- Congress also should pass legislation to greatly improve available public data on antibiotic use in livestock.
- The FDA should assess the impact of its voluntary strategy and start the regulatory process now to withdraw drug approvals for injudicious uses. The FDA also should strongly enforce the existing bans on certain uses of antibiotics.
- The FDA should address the Government Accountability Office (GAO)'s recommendations to improve data collection on the use of antibiotics and the development of antibiotic resistance.[15] 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 nontherapeutic antibiotic use. The USDA should address contract stipulations that require livestock producers to use feed with antibiotics already added.

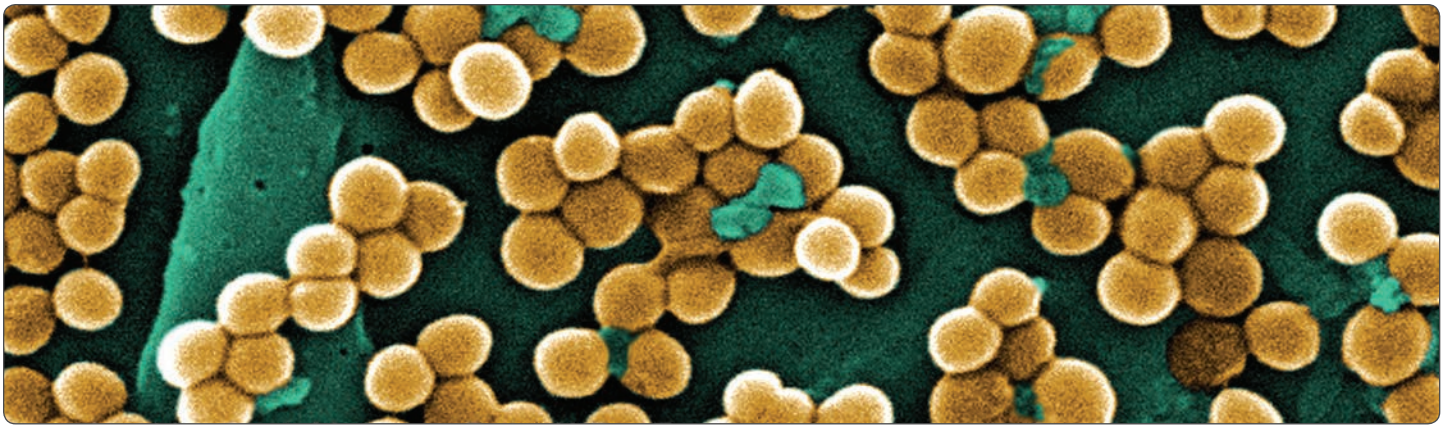


IMAGE COURTESY OF JANICE HANEY / U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

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.[16] Over time, bacteria have developed and continue to develop resistance to antibiotics. Far more antibiotics are given to livestock than to people,[17] 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.[18]

> *"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."*[28]
>
> — DR. LANCE PRICE, DIRECTOR OF THE TRANSLATIONAL GENETICS RESEARCH INSTITUTE'S CENTER FOR FOOD MICROBIOLOGY AND ENVIRONMENTAL HEALTH

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.[19]

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.[20]

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.[21] 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

Although livestock producers do use antibiotics to treat sick animals, the far more common usage is for "nontherapeutic" 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

* The FDA recently published voluntary Guidance for Industry 213, intended to end the growth-promotion uses of medically important antibiotics. This transition is in progress and will leave non-medically important antibiotics available for growth-promotion use.

antibiotics mixed in, both to promote faster growth and as an attempt to prevent infections in densely packed and unsanitary concentrated animal feeding operations (CAFOs).[23] These nontherapeutic 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. Nontherapeutic uses mean that 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 antibiotics, because the genetic trait that allows bacteria to survive exposure to one antibiotic is often linked to traits that allow it to survive others.[24]

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.[25] Estimates differ on precisely how many antibiotics are used in agriculture in general, and for nontherapeutic purposes in particular. There is no centralized system for collecting such data, as the pharmaceutical industry is not eager to share business information that it wants to keep confidential,[26] and even some livestock producers may not know just how much antibiotics is in the pre-mixed feed that their contracts with meat companies require them to use.[27]

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

The best estimates of antibiotic use come from the Food and Drug Administration (FDA). The FDA reported in 2011 that 80 percent of antibiotics in the United States are sold for agricultural purposes.[28] The FDA also reports that 70 percent of antibiotics used in livestock are sold for use in feed, 24 percent for use in water and only 4 percent for use as injection.[29] Scientific evidence makes clear that putting medicine in feed makes dosing imprecise and not as effective for disease treatment.[30] In other words, the antibiotics used in feed and water are most likely used for nontherapeutic purposes.

The mechanisms of AR and its spread are complicated. Many drugs used for nontherapeutic purposes are also used for disease treatment, both in veterinary and human medicine, and many AR genes are already widespread.[31] Evidence tying nontherapeutic 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.[32] 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.[33]

Although evidence tying nontherapeutic 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.[34] 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.[35]

Beyond Survival of the Fittest

Nontherapeutic 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 also can share the resistance genes with neighboring bacteria.[36] 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.[37]

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.[38] 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.[39]

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.[40] Eliminating nontherapeutic 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.[41]

Let's be clear: nontherapeutic 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.[42] It is basically impossible to trace AR bacteria directly from a livestock operation to a sick person,[43] but scientific understanding of bacterial evolution demonstrates that practices driving resistance in livestock have far-reaching effects by increasing the overall reservoir of resistance. Recent evidence suggests that antibiotic use in agriculture may affect resistance patterns in bacteria that live naturally in the human digestive tract.[44]

Studies of AR bacterial DNA over time indicate that livestock treated with nontherapeutic doses of antibiotics are the likely origin for some AR bacteria in humans. *E. coli* that is resistant to ciprofloxacin, a drug from the class fluoroquinolones once used nontherapeutically in poultry, is very similar in humans and chickens and is 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.[45] 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.[46]

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.[47] This research required the participation of 20 institutes studying 89 genomes from humans and animals over 19 countries, a complicated and painstaking effort.[48]

How Do I Find Meat Raised Without Antibiotics?

1. **Buy organic.** Organic livestock in the United States must be raised without antibiotics.[52]
2. **Look for a label stating that the meat has been raised without antibiotics.** The USDA allows companies to use this label if the companies provide documentation of their practices.[53] Labels that also say "USDA Process Verified" or that list a certification from another independent body offer another level of assurance. A "natural" label claim does not necessarily mean that antibiotics were not used.[54]
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 nontherapeutic antibiotics.

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

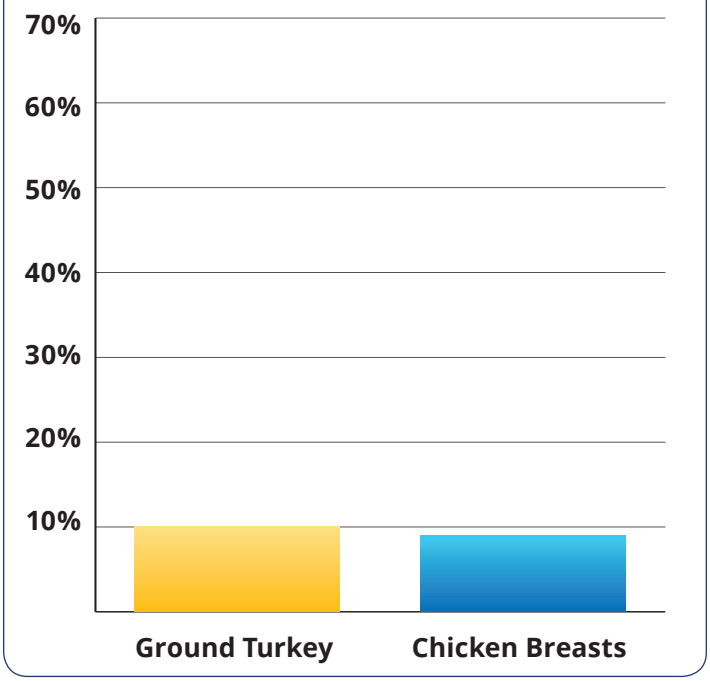
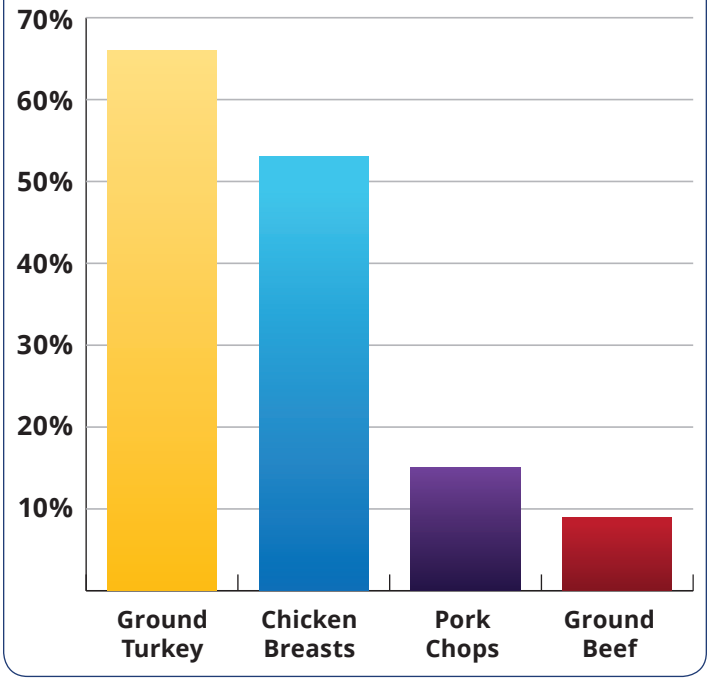


Figure 2. AR *E. Coli* in NARMS Retail Meat Samples



SOURCE FIG. 1 and 2: Food & Water Watch analysis of FDA NARMS. "2011 Retail Meat Report." 2013.

Otherwise-healthy people can carry AR bacteria for years without realizing it, and those same AR bacteria can pose grave danger as an infection.[49] Whether it is through 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,[50] and pharmaceutical companies are not producing new treatments fast enough to keep up with the need.[51] 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. That's why the U.S. Department of Agriculture (USDA) reminds consumers to cook meat to certain temperatures and educates about cross-contamination.[55]

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 retail meat and fish products.[56] 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 or not, handling raw meat and undercooking can lead to foodborne illness.[57] 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."[58]

In 1996, the FDA, Centers for Disease Control and Prevention (CDC) and USDA partnered to create the National Antimicrobial Resistance Monitoring System (NARMS).[59]

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*.[60] 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 2011 NARMS data to estimate how widespread AR bacteria were in the retail meat samples collected. AR *Salmonella* was present in 9 percent of chicken breast samples and 10 percent of ground turkey samples. The presence of AR *E. coli* in the samples collected varied widely: 66 percent in ground turkey, 53 percent in chicken breasts, 15 percent in pork chops and 9 percent in ground beef.[61]

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*.[62] The prevalence of AR traits among *Salmonella* samples ranged from 44 percent in ground beef to approximately 75 percent in ground turkey, chicken breasts and pork chops. The presence of AR traits in *E. coli* samples varied widely: 87 percent in ground turkey, 75 percent in chicken breasts, 48 percent in pork chops and 21 percent in ground beef.[63]

Among the report's other key findings, nearly half of the *Salmonella* samples from chicken breasts and half of those from ground turkey were resistant to three or more classes of antibiotics. *Salmonella* resistance to third-generation cephalosporins has shown a decade-long increase in retail poultry. Between 2002 and 2011, this type of resistance more than tripled from 10 percent to 33.5 percent in samples from chicken breasts and nearly tripled from 8.1 percent to 22.4 percent in ground turkey.[64] This increase led the FDA to ban certain nontherapeutic uses of cephalosporins. Among the *Enterococcus* samples, there was no resistance to vancomycin and linezolid, two drugs used in human medicine but not agriculture,[65] but the vast majority of *Enterococcus* samples were resistant to other antimicrobial drugs.[66]

The NARMS surveillance system does not include any forms of *Staphylococcus*, although this bacterium has been found in the food supply. MRSA was once considered endemic only 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.[67] 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, and half of the *S. aureus* found was multi-drug resistant.[68] The researchers recommended that "multidrug-resistant *S. aureus* should be added to the list of antimicrobial-resistant pathogens that routinely contaminate our food supply."[69]

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.[70] This finding indicates that livestock are the likely source of the bacteria, with the AR bacteria developing from drug-susceptible *E. coli* under selection pressure within each species of livestock.[71]

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*. 84 percent of the bacteria were resistant to one antibiotic, and just over half were resistant to three or more antibiotics.[72] The findings included a particularly virulent strain that has been the culprit of previous outbreaks of foodborne illness.[73] The commonality of AR bacteria in all the types of ground meats indicates the presence of a reservoir that can affect people.[74]

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.*

Not all livestock are raised using nontherapeutic antibiotics. U.S. organic standards require that livestock not be treated with antibiotics,[75] and some companies market meat "raised without antibiotics."[76] 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.[77]

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."[78] 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 at least 2 million Americans each year experience AR infections, leading to at least 23,000 deaths.[79] Approximately 22 percent of those AR infections originate from foodborne pathogens.[80] Since 2011, the United States has experienced three major foodborne illness outbreaks from AR bacteria.

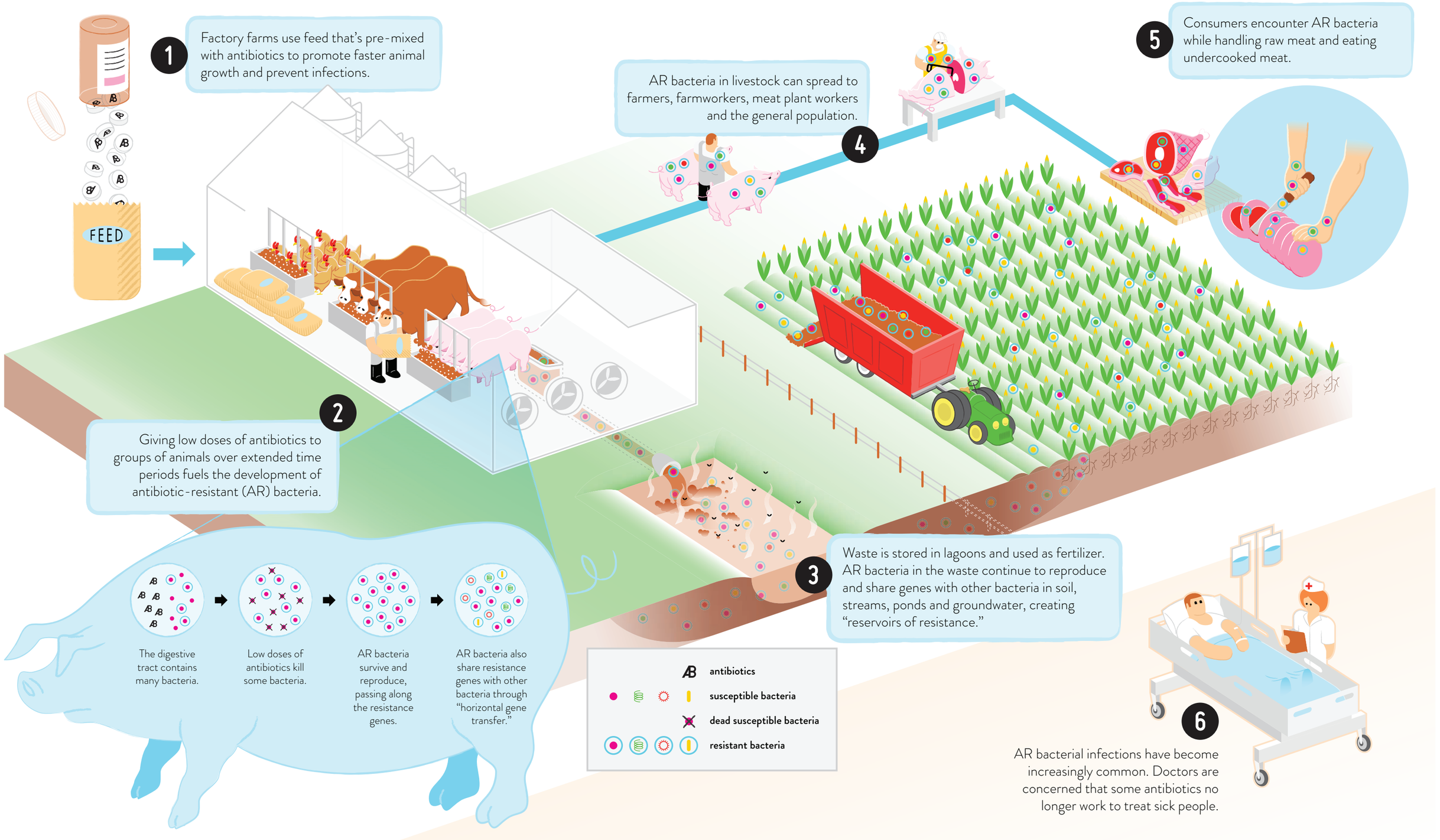
- **Foster Farms Chicken:** A major outbreak of AR *Salmonella* Heidelberg from a company called Foster Farms sickened 574 people over the course of over a year, mainly in California.[81] The USDA issued a public health alert about products from three Foster Farms plants in October 2013 after 278 people in 18 states had fallen ill with *Salmonella* Heidelberg. Yet the plants remained open, and no recall was issued.[82] Foster Farms finally issued a recall of 170 different products in July 2014,[83] despite the initial outbreak having occurred several months before. Detailed violation reports from the two plants connected to the outbreak reveal that the plants were receiving a violation every other day between October 2013 and March 2014. One plant was closed briefly in January for "egregious insanitary conditions," including the presence of cockroaches.[84]

- **Cargill Ground Turkey**: 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.[85] 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.[86] In total, 136 people across 34 states were infected, yielding 37 hospitalizations and one death.[87] A disproportionate number of people infected were hospitalized due to the bacteria's antibiotic resistance.[88]

- **Hannaford Ground Beef:** Another illness outbreak involved an 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 8 hospitalizations reported.[89] The strain causing the outbreak was resistant to multiple classes of drugs, including cephalosporins, the drugs of choice to treat *Salmonella* infections in children.[90]

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.[91] 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 that they followed industry standards.[92] 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.

HOW ANTIBIOTIC MISUSE ON FACTORY FARMS CAN MAKE YOU SICK



From Livestock to Farmers and the Environment

AR bacteria in livestock do not just remain there, but spread to farmers, farmworkers and rural residents.[93] As early as 1976, researchers found that AR bacteria spread rapidly in the intestines of chickens raised using nontherapeutic antibiotics. Farmers on the same poultry operations developed higher levels of AR bacteria in their intestinal tracts as well, compared to their neighbors.[94] Multiple studies have identified the similar strains of AR bacteria in farmers and their livestock.[95] 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 people that raise them.[96] One strain of MRSA has been found in both pigs and the people that raise them, but not in neighbors who do not raise pigs.[97] 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.[98] Two studies have found farmworkers and pigs carrying the same strains of MRSA on conventional livestock farms, but not on farms that do not use antibiotics in raising livestock.[99]

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.[100] Researchers have even found an increased likelihood of rural residents experiencing MRSA skin infections if they live near fields treated with swine manure.[101]

In large livestock operations, manure is collected in lagoons.[102] 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.[103] 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.[104] Several studies have found DNA matches between AR bacteria in the soil and water and in manure lagoons.[105]

Manure storage itself does not constitute a form of treatment, and treatment is necessary to reduce bacteria. Unlike chemical pollutants, bacteria reproduce. Thus, treatment 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.[106] Poultry litter has also been found to harbor multiple-drug-resistant *E. coli* and antibiotic residues.[107]

Most livestock waste stored in lagoons is applied to nearby fields as fertilizer, introducing AR bacteria into the local environment.[108] 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.[109] Thus, AR bacteria from livestock contribute to a reservoir of antibiotic resistance in rural environments.

Other opportunities for AR bacteria to spread include wind, the transport of 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 nontherapeutic antibiotics.[110] Even vehicles carrying livestock leave bacteria — AR and otherwise — in the air behind them.[111] Flies attracted to livestock waste also pick up and may disperse AR bacteria.[112]

Tackling Antibiotic Resistance

Alternatives to Nontherapeutic Uses 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.[113] 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.[114] Eliminating nontherapeutic uses of antibiotics, however, can make a difference in reducing the prevalence of AR bacteria.[115]

Animals can be raised successfully without nontherapeutic antibiotic use. The European Union (EU) has banned nontherapeutic use of antibiotics for growth promotion.[116] Some antibiotics no longer work as growth promoters or yield a result so slight that the additional profit does not even cover the cost of the antibiotics, yielding a net loss.[117] U.S. organic standards require that livestock not be administered antibiotics.[118] Companies such as Chipotle, Niman Ranch and Applegate Farms have made meat raised without antibiotics much more visible in grocery stores and restaurants.[119]

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.

Raising livestock without nontherapeutic antibiotic use requires changes in herd management, including lowering animal density and changing nutritional programs.[120] 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 nontherapeutic use of antibiotics. Other alternatives to nontherapeutic antibiotic use include vaccines and probiotics, the use of less-harmful bacteria to compete with AR bacteria in the digestive tract.[121]

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

The European Union's Experience Ending Nontherapeutic Use of Antibiotics

The EU has taken a different path than the United States on antibiotics used for growth promotion in livestock. 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.[122]

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.[123] Following these decisions, prevalence of AR bacteria has declined in livestock, meat and people in the EU.[124] Even as few as two years of changed practices can result in improvements in the level of resistance in bacteria in livestock and meat.[125]

Denmark, the next country to implement such a ban on growth-promotion uses, reduced antibiotic use while increasing hog production. Hog farms experienced a brief spike in therapeutic antibiotic use in swine after the ban.[126] Yet, 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.[127] One production change is that farmers now leave piglets with their mothers longer, as newborn piglets are very susceptible to infection. Extensive government tracking both of antibiotic use in animals and humans and of resistance in AR bacteria has been key to Denmark's success.[128]

The Netherlands offers another example in which government tracking of antibiotic use facilitated significant decreases in use. Besides banning nontherapeutic uses, the Dutch government tracks all antibiotic use on farms by veterinarians and even enforces fines for overuse.[129] In the Netherlands, sales of antibiotics for veterinary purposes have decreased by 58 percent since 2009, surpassing the government goal of a 50 percent reduction, and antibiotic resistance trends in animals have improved.[130] Note that, in the same time period, sales of antibiotics for agriculture *increased* by 16 percent in the United States,[131] a very poor record of antibiotic stewardship.

In the case of the drug vancomycin, the United States and the EU took different approaches that affect rates of antibiotic resistance in human illnesses. EU doctors found increasing rates of vancomycin-resistant infections in hospital patients during the 1990s. Researchers found the same resistance patterns in AR bacteria in meat and manure.[132] The EU responded by restricting vancomycin use in agriculture, and rates of vancomycin-resistance in people fell. The United States never approved vancomycin for nontherapeutic uses in livestock, and, while resistance to the drugs does exist in *Enterococcus* infections in U.S. hospitals, the problem has never been as great as the point reached in the EU.[133]

The EU's experience managing antibiotic use in livestock and poultry demonstrates the importance of setting strong policies and collecting sufficient data to track progress in both antibiotic use and the prevalence of resistance. The policies of the United States leave much to be desired.

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. As far back as 1970, an FDA Task Force recommended limiting the use of medically important antibiotics in animal feed.[134] In 2004, the Government Accountability Office (GAO), the investigative oversight agency that works for Congress, criticized the FDA for collecting insufficient details about antibiotic use in livestock, such that the FDA doesn't even have enough information to measure the effectiveness of policy changes.[135]

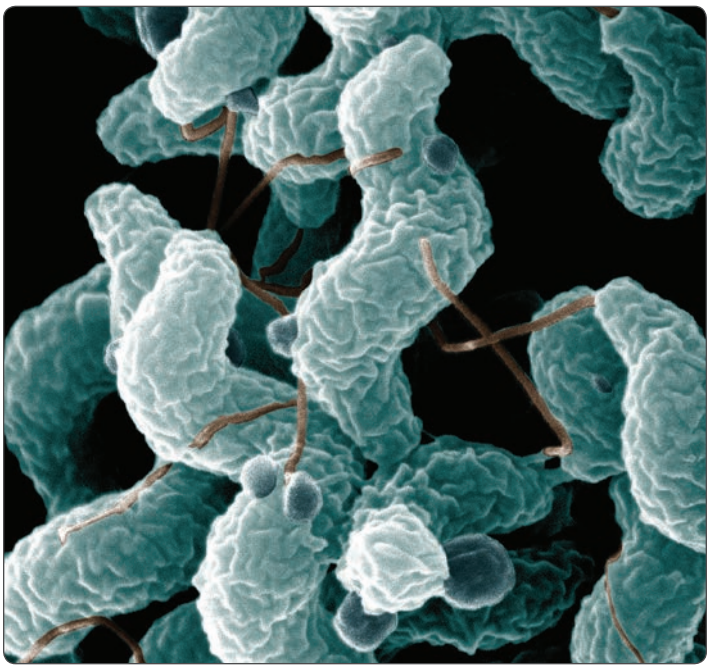
The FDA insists that industry voluntary efforts will solve the problem, citing the agency's lack of resources as an impediment to creating new regulations.[136] Yet the FDA has successfully regulated specific uses of certain classes of antibiotics in the past, despite industry pressure.

Voluntary Guidance

The FDA's Center for Veterinary Medicine (CVM) publishes non-binding Guidance to Industry in place of regulation on topics of interest.[137] In Guidance to Industry 209, released in 2012, the FDA recommended "limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health," a rather broad definition that did little to change antibiotic use.[138]

The centerpiece of the FDA's current antibiotic policy, Guidance for Industry 213 (Guidance 213), relies on pharmaceutical companies changing drug labels to remove growth-promotion uses for medically important antibiotics and to require that medically important antibiotics used in feed and water be used only under the oversight of a veterinarian.[139]

Most antibiotics in feed were approved originally for multiple purposes, including over-the-counter sales for growth promotion.[140] Using medically important antibiotics for growth promotion is perhaps the most injudicious use of antibiotics in livestock, as is using antibiotics without veterinary oversight.



Thus far, all of the pharmaceutical companies that make drugs that fall under Guidance 213's parameters have agreed to the changes.[141] However, the FDA's initial draft regulation of "veterinary oversight" left open potential loopholes.[142] The FDA has declared that it will re-evaluate the situation in 2016, three years after finalizing Guidance 213, and then determine whether to take further regulatory action.[143]

Even with full compliance, Guidance 213 leaves open a crucial loophole. The FDA still approves of the use of antibiotics for disease-prevention purposes, even though those practices mirror how antibiotics are used for growth promotion.[144]

Food & Water Watch analyzed the FDA's list of drug products affected by Guidance 213 to determine the extent of overlapping uses. Each drug has a list of "label indications," or reasons the drug can be used in certain conditions. The FDA's list includes 217 medically important antibiotics with growth-promotion indications. Of those drugs, 63 percent also have disease-prevention indications, meaning that the drugs can continue to be used nontherapeutically, which will continue to promote the development of antibiotic resistance.

Of the remaining drugs used for growth promotion, 59 can still be used for "disease control" in healthy animals. That leaves only 23 drugs — 11 percent — with no approved nontherapeutic uses under full implementation of Guidance 213. To put it another way, 89 percent of the drugs that are losing growth-promotion uses still can be given to healthy animals for other reasons, leading to the spread of antibiotic resistance.[145]

It seems unlikely that Guidance 213 will be effective in significantly reducing antibiotic resistance levels due to agricultural uses. Two of the largest manufacturers of veterinary pharmaceuticals have predicted that the FDA's decision will have a minimal impact on sales.[146] Advocacy groups have already complained to the FDA that the pharmaceutical companies Novartis and Elanco continue to advertise antibiotic feed additives as being useful in making livestock gain weight faster, although the drugs are no longer supposed to be used for growth promotion.[147]

The FDA has claimed that any action it takes requires industry cooperation and that changing regulations is cumbersome and expensive. Yet, for two specific classes of antibiotics, fluoroquinolones and cephalosporins, the FDA *has* managed to take action, calling into question the claim that regulation is not feasible.

Previous FDA Regulation

In the mid-1990s, the FDA approved a class of antibiotics called fluoroquinolones for nontherapeutic uses in poultry. 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. 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, delaying the FDA's final withdrawal decision until 2005 while resistance continued to increase.[153] 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.[154]

In 2012, the FDA made a similar decision in finalizing a ban on certain specific nontherapeutic uses of cephalosporins.[155] Cephalosporins play an important role in treating foodborne illnesses in humans, especially children, as well

Tetracyclines and Penicillins

In 2014, the FDA backed away from an innovative proposal dating back to 1977 that would have withdrawn approvals for nontherapeutic uses of penicillins and tetracyclines, two classes of medically important antibiotics.[148] 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.[149] After failing to respond to two citizen petitions in 1999 and 2005, a coalition of organizations filed suit against the FDA to force a response in 2011.[150]

In the spring of 2012, federal district court Judge Theodore Katz issued two rulings indicating that the FDA's voluntary approach to regulating nontherapeutic antibiotic use is insufficient. The rulings would have required the FDA not only to revisit the withdrawal process begun in 1977 for penicillins and tetracyclines, but also to undergo a broader re-evaluation of nontherapeutic uses of antibiotics.[151] Unfortunately, rather than follow the rulings, the FDA appealed and won. In his dissent to the appeals court's decision, Judge Robert Katzman argued, "Today's decision allowed the FDA to openly declare that a particular animal drug is unsafe, but then refuse to withdraw approval of that drug."[152]

as in treating pneumonia and skin and soft tissue infections.[156] 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.[157] The 2012 ban covers a narrower range of uses, leaving exceptions for older cephalosporins and those used with veterinary prescriptions.[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, whereas it had been minimally present in poultry in 1997.[159] Other researchers have noted that broad-spectrum use of cephalosporin in livestock promotes the development of MRSA.[160]

Who Supports PAMTA?

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[161]

Who Opposes PAMTA?

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[162]

Congress

Congress, too, could act to reduce nontherapeutic 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."[163]

As of the end of 2014, PAMTA, now also known as the Prevention of Antibiotic Resistance Act (PARA) in the Senate, had not received a committee hearing or vote. More than 300 organizations have expressed support for the bill.[164] Over 30 organizations have lobbied on PAMTA over the years, with organizations representing the meat, livestock and pharmaceutical industries all voicing opposition.[165]

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 nontherapeutic use of antibiotics in livestock.

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

Food & Water Watch recommends that:

- Congress should pass the Preservation of Antibiotics for Medical Treatment Act (PAMTA)/Prevention of Antibiotic Resistance Act (PARA), which would ban nontherapeutic uses of antibiotics in livestock, thereby avoiding the cumbersome drug-by-drug process currently required of the FDA to achieve the same goal. City councils across the country have passed resolutions urging Congress to pass PAMTA, and more are joining their ranks.
- Congress also should pass legislation to greatly improve available public data on antibiotic use in livestock.

- The FDA should assess the impact of its voluntary strategy and start the regulatory process now to withdraw drug approvals for injudicious uses. The FDA also should 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.[166] 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 nontherapeutic antibiotic use. The USDA should address contract stipulations that require livestock producers to use feed with antibiotics already added.

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