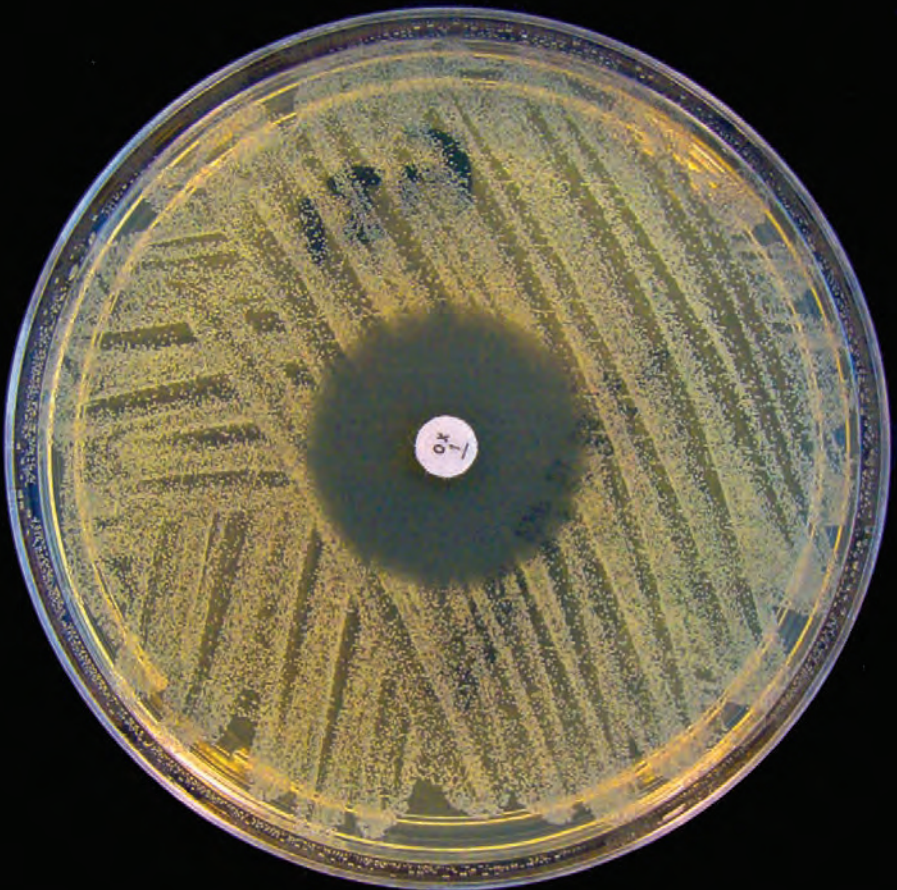


ANTIBIOTIC RESISTANCE

Seeking solutions in a
time of growing concern



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There are two facets of the antibiotics conundrum: The increasing and occasionally inappropriate prescription of antibiotics has led to significant bacterial resistance in humans, and the use of antibiotics in animal agriculture allows these drugs to enter the environment in numerous ways.

Felicia Wu
Director of the MSU Center for
Health Impacts of Agriculture



Antibiotic resistance is not only a human health issue, it is a matter of national security. Michigan State University (MSU) is home to leading agriculture, animal health and veterinary medicine experts diligently working to address the biologically complex issue. These Spartans are answering a global call to action that will prevent the loss of the great strides in controlling infectious diseases over the past few decades.

The facts:

- Antibiotics are the most commonly prescribed drugs in human medicine.
- Antibiotics are commonly used in food animals to prevent, control and treat disease.
- About one-third to one-half of antibiotic use is unnecessary or inappropriate.
- Antibiotic resistance develops naturally over time and cannot be prevented.
- About 2 million U.S. residents per year acquire serious bacterial infections that are resistant to one or more antibiotics.
- Antibiotic use is the single most important factor leading to resistance around the world.
- No new class of antibiotics for animal agriculture has been brought to market in more than 30 years.

For more in-depth articles on antibiotic resistance, read MSU AgBioResearch's *Futures* magazine at agbioresearch.msu.edu/resistance.

Drug resistance

For generations, society has relied on antibiotics to cure a number of illnesses and diseases, some of which are life-threatening. Today, however, there is concern that we are moving toward a time when the current supply of antibiotics is no longer useful. Becoming ill with an infection untreatable by modern medicine is terrifying. But that is likely preventable if society becomes more judicious about the use of these drugs and new antibiotics are brought to the marketplace.

We're leading efforts to combat this serious problem, educate the public, work with industry and discover new solutions to attain optimal health for humans, animals and the environment.

Antimicrobial resistance, or drug resistance, is one of the most urgent health threats facing society. And while there has been progress, much work lies ahead.

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There are many academic institutions developing antibiotics, and if we can keep up the federal funding for research, we can continue to develop them and get them in the pipeline.

– Christopher Waters
Microbiologist and molecular geneticist





The first warning

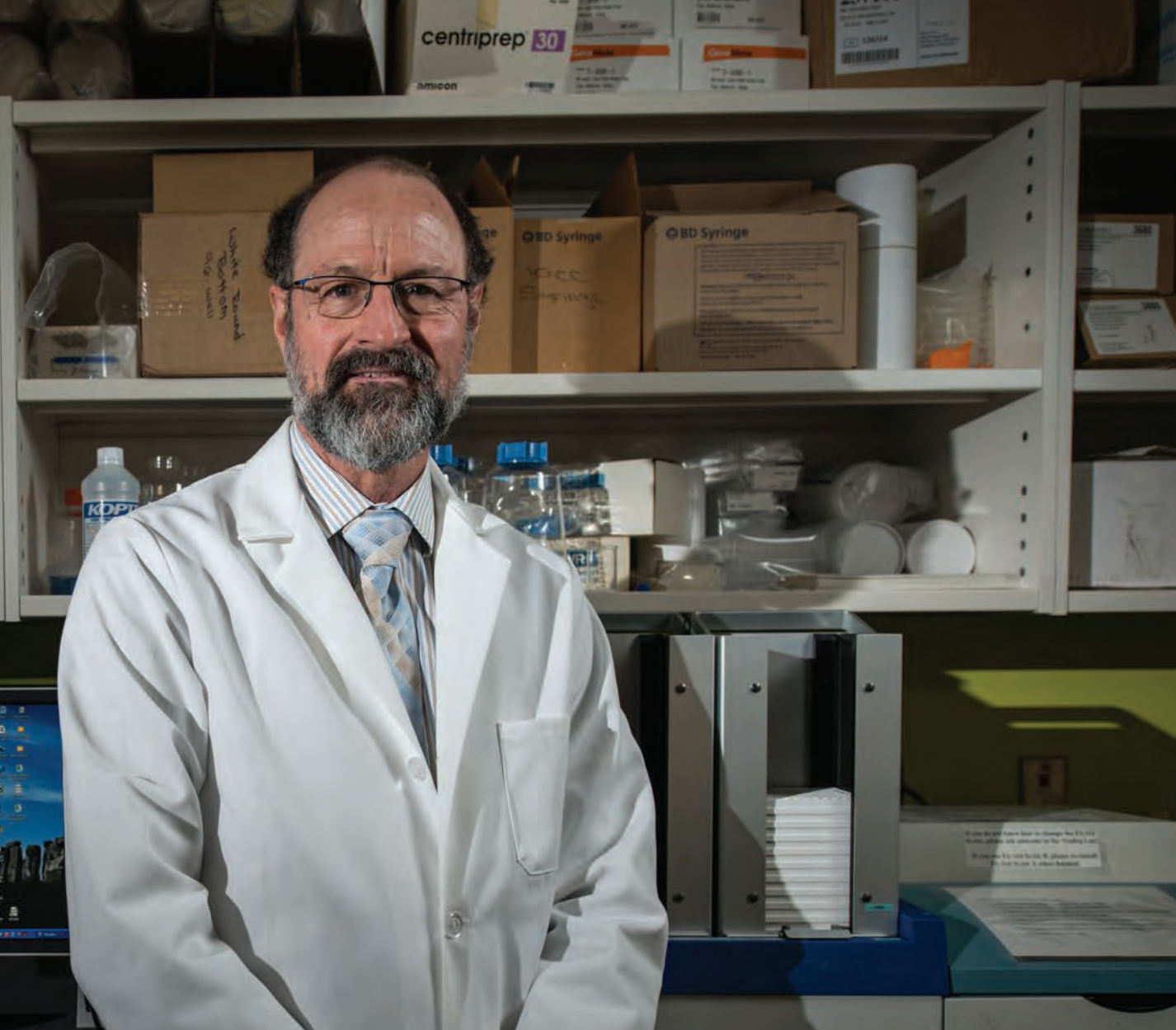
When Scottish biologist Alexander Fleming awoke on Sept. 28, 1928, he had no idea that he would revolutionize medicine by discovering the world's first antibiotic. But that's what happened in his untidy hospital laboratory in London. Amidst a stack of forgotten bacteria-filled petri dishes, Fleming found one with a fungus that had killed the surrounding germs. He extracted the mold, grew it and found that it could ward off many other types of bacteria as well. By the 1940s, Fleming's mold became the first commercially available antibiotic – penicillin.

Early on, Fleming found that bacteria developed resistance whenever too little penicillin was used or if the drug wasn't taken for an adequate length of time. As he traveled the world making speeches about his discovery, Fleming warned listeners about the need for proper use and dosage of the antibiotic. That cautionary tale of drug resistance is now being told with greater vigor than ever before.

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When we use antibiotics, even only when we're clinically supposed to, we affect the levels of resistance in the animals and environments in which we use them. By having alternatives, we take some of that selective pressure away and slow the propagation of resistance.

– Bo Norby, large animal veterinarian serving on U.S. Committee addressing antibiotic resistance



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By exploring off-beat drug targets, academics are reducing the risk for commercial ventures that explore a completely new approach. Faculty may be able to find new targets that work and push them forward in a way that pharmaceutical groups hesitate to.

– Richard R. Neubig
Chair of the Department of Pharmacology and Toxicology



A “post-antibiotic” era

From the 1950s through the 1980s, healthcare providers became complacent about antibiotic use, in large part due to a steady supply of new drugs. Since then, however, that pipeline has slowed, and development of new drugs was eventually outpaced by development of drug resistance. As cases of untreatable hospital-acquired infections, multidrug-resistant tuberculosis and drug-resistant gonorrhea emerge, experts believe a “post-antibiotic era” is nearing.

In 2013, the Centers for Disease Control and Prevention released a 100-plus page report listing all types of antibiotic resistance threats in the United States. Since then, numerous national and global plans have gotten underway to address the issue, including the formation of the Task Force on Antibiotic Resistance in Production Agriculture created by the Association of Public and Land Grant Universities and the Association of American Veterinary Medical Colleges. There is no time to point fingers or place blame. MSU is working with healthcare, agriculture and environmental industries to seek solutions.



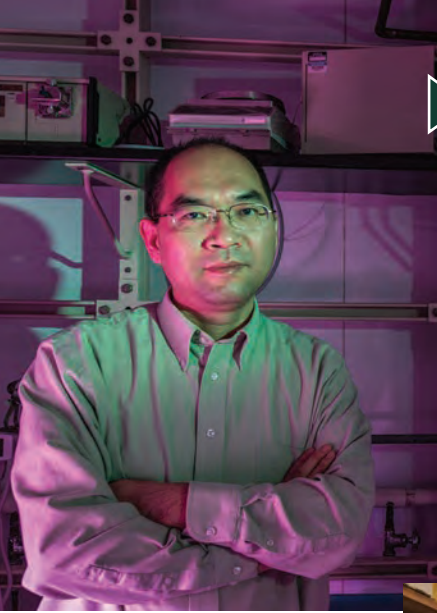
To assist the National Institutes of Health with insights about all of the microorganisms on and in the human body, Linda Mansfield, MSU AgBioResearch microbiologist and veterinarian, is exploring the role of antibiotics in making humans more susceptible to infections caused by *Campylobacter jejuni*, a serious bacterial threat. She believes there is a link between antibiotic use, microbiota modification and the onset of an autoimmune disease triggered by the bacterium.



Embracing “One Health”

“One Health” is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of healthcare for humans, animals and the environment. These efforts are accelerating biomedical research discoveries, enhancing public health, expanding scientific knowledge, and improving medical education and clinical care.

These types of collaborations are happening at MSU every day. Multi-disciplinary projects are highly encouraged and supported across campus. Having the diverse and revered programs that the pioneer land-grant university offers is an asset in addressing issues from agriculture to human medicine and environmental preservation. These are our core strengths.



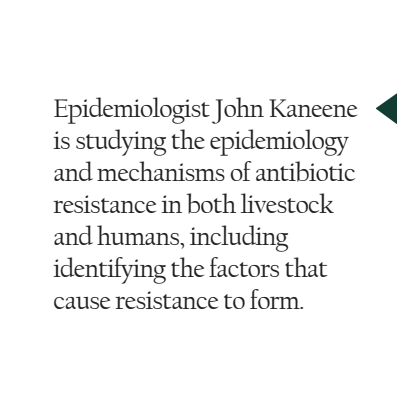
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We need more advanced treatments in the animal waste facilities to deal with antibiotics and their resistance genes, but that is difficult to do right now. If we knew more about fundamental processes in the environment and how they affect microbial communities, perhaps we could figure out better ways to mitigate the antibiotic resistance effect.

– Hui Li
Associate Professor of
Environmental and Soil Chemistry



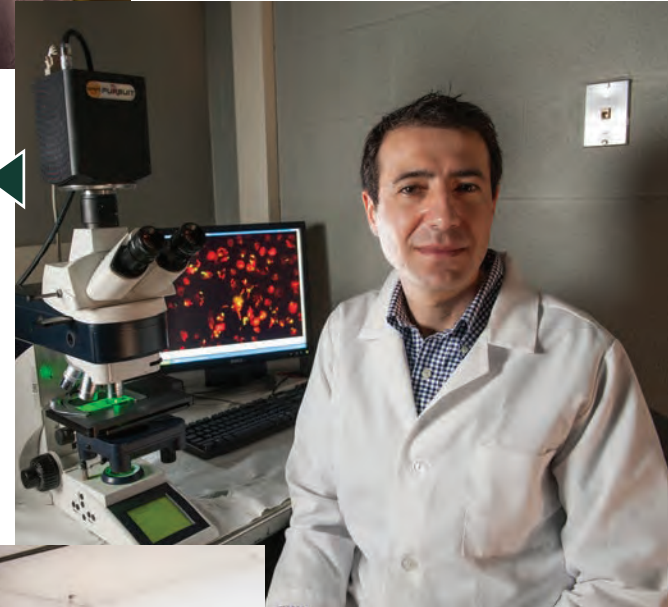
Veterinarian Ronald Erskine is examining ways to treat mastitis, a bacteria-caused inflammation of the cow’s udder and the most common disease of dairy cattle in the United States. Severe cases can result in great economic farm loss and produce a long-term impact on the health, welfare and fertility of the animal. “It’s all about prudent, judicious use of antibiotics, using them only when they’re necessary.”



Epidemiologist John Kaneene is studying the epidemiology and mechanisms of antibiotic resistance in both livestock and humans, including identifying the factors that cause resistance to form.



Microbiologist Robert Abramovitch is screening compounds that could lead to a new, fast-acting, affordable antibiotic treatment for tuberculosis. Only one anti-TB drug has been developed in the past 40 years.



Soil scientist Stephen Boyd is working on ways to make the soil sequester contaminants, whether industrial or pharmaceutical organic molecules, and use bioavailability as a way of managing the risks posed by contamination in soils and sediments.



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As an animal nutritionist, my job is to collaborate with the veterinarians, who understand the farm health situation, and farmers, who want the best of both worlds in health and nutrition for their animals.

– Dale Rozeboom
Animal scientist and
extension specialist



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We have a problem in the United States and globally with using more antibiotics than we need to. We have not been protecting what is – as we now know and realize – a fairly precious and exhaustible resource.”

– Steven Solomon
 Director of the Office of Antimicrobial Resistance
 Centers for Disease Control and Prevention



Evolution in action

Worldwide, researchers seeking solutions to antibiotic resistance and working on other projects are unquestionably inspired by Richard Lenski, an MSU evolutionary biologist and Hannah distinguished professor of microbial ecology. His long-running experiment with *Escherichia coli* began in 1988, when he placed 12 populations of bacteria – all from the same ancestral strain – into 12 flasks with the same medium to see how similarly or differently they would evolve.



Originally, the goal was to keep the experiment running for a year, which would have spanned about 2,000 bacterial generations. Now, nearly 30 years later, the project – known as the Long-Term Evolution Experiment (LTEE) – has surpassed more than 60,000 generations. It has led to new insights about the speed of adaptation and the origin of new capabilities. It also revealed an evolutionary tension between short-term success and long-term persistence – more adaptable bacterial types sometimes prevail over lineages that hold a short-term competitive advantage.



Significant healing power

Antibiotics not only save human and animal lives - they also help keep our food supply safe. Preventing infectious disease in livestock has been a concern since the first sheep and goats were domesticated in Mesopotamia almost 10,000 years ago. Sick animals produce less food, pose a risk to humans that consume their meat and milk, and threaten the health of the entire herd by spreading the contagion. After struggling to fight infection by quarantine and natural remedies, livestock producers began using antibiotics in the last century to combat disease with unprecedented efficiency.

However, with antibiotic resistance threatening to undermine the past 70 years of progress, other tactics are needed to ensure food security and safety. MSU scientists are developing new techniques aside from conventional antibiotics to fight and prevent diseases on the farm. They are working with federal and state agencies to conduct workshops and learn more about new guidelines from the U.S. Food and Drug Administration (FDA), the agency overseeing animal antibiotic use.

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The development of new antibiotics in no way keeps up with the potential development of antibiotic-resistant bacteria. The bacteria are far faster at adapting than we are at developing new antibiotics.

– Lorraine Sordillo
MSU bovine immunology specialist

Judicious use

It is clear that society must be more judicious in its use of antibiotics, whether it's in human medicine, veterinary medicine and/or agriculture. MSU researchers and Extension specialists in the College of Agriculture and Natural Resources, the College of Veterinary Medicine, MSU AgBioResearch and MSU Extension are addressing this cause. They are committed to:

- Designing and implementing a model curriculum to improve awareness, understanding and help in the implementation of effective actions to combat antibiotic resistance.
- Creating and delivering courses and plans on antibiotic stewardship through a variety of educational and continuing education programs.
- Developing and incorporating new training modules and initiatives on combating antibiotic resistance in collaboration with U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Services and Veterinary Services
- Implementing stewardship programs for veterinarians as part of the USDA's National Veterinary Accreditation Program.
- Developing key messages and pertinent information to inform and educate producers and farmers of the changing landscape for antibiotic use and accessibility in animal agriculture – including recent FDA guidelines, changes to the veterinary feed directive, on-farm disease prevention strategies and emerging stewardship programs.
- Developing and delivering a series of public education and communication plans, strategies and messages.
- Developing and implementing educational and informational strategies, tools and programs that focus on various groups across our education spectrum.



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Bacteria will eventually develop resistance to any new drug. It's inevitable – but that just means we need to develop lots of new compounds and use them judiciously.

– James Tiedje
Director of the MSU Center for Microbial Ecology



Leading change

The use of antibiotics is the single most important factor leading to antibiotic resistance around the world. In addition to human medicine, antibiotics are also commonly used in food animals to prevent, control and treat disease, and to promote growth.

MSU is working alongside veterinarians and livestock producers in order to transition toward a new guidance document issued by the FDA. The document aims to eliminate over-the-counter sales of antimicrobials by making livestock producers work with veterinarians in order to receive antibiotics for their animals. Pharmaceutical companies must also remove any growth enhancement or production enhancement claims from antibiotic product labels.

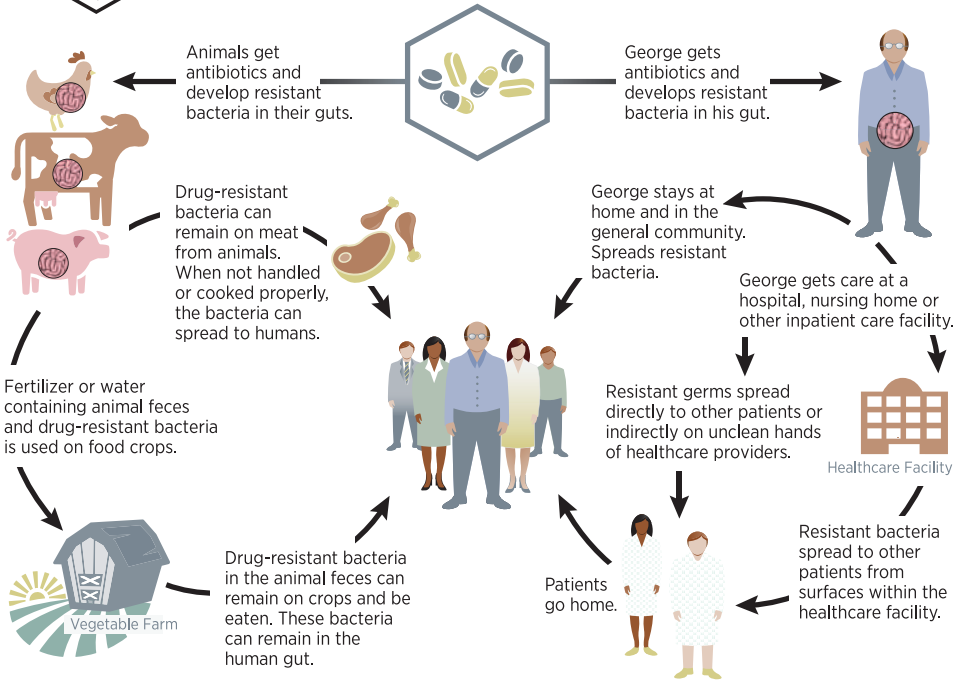
Producers will need to acquire a veterinary feed directive from a veterinarian in order to obtain feed-grade antibiotics for their animals. Ultimately, the FDA wants all antibiotic use under the supervision of veterinarians, who can prescribe them for prevention or therapeutic reasons only.

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The veterinary feed directive (VFD) is essentially the same as a prescription in human medicine. A veterinarian will have oversight over the use of antibiotics in food-producing animals. He or she will have to write this VFD and can write one only for the prevention or treatment of disease.

– Daniel Grooms
MSU professor of large animal clinical sciences
President of the American Association of Bovine Practitioners

Examples of How Antibiotic Resistance Spreads



Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

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