Building a Healthy Herd without Antibiotics

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Livestock producers seek strategies to control infection while limiting antibiotics.

Antibiotics are excellent assassins—they go after their targets swiftly and powerfully. Until recently, most U.S. commercial livestock producers regularly administered them at low doses, both to protect the animals from microbial invaders and to boost growth.

But antibiotics’ ability to kill can fade quickly as their targets acquire defenses in the form of antimicrobial-resistance genes—an increasingly frequent and worrying occurrence that threatens to render us humans and the animals we raise for food defenseless against infection.

Propelled by alarm over growing microbial resistance to antibiotics crucial for human health, consumer and societal demand for antibiotic-free meats and dairy has surged, and regulators have begun to address the problem. In 2017, the U.S. Food and Drug Administration forbade commercial farmers from administering antibiotics chronically at low doses and began requiring that most antibiotics also used by humans be prescribed by veterinarians for use in livestock. The agency is now considering regulations that would make all such antibiotics available for livestock by prescription only.

That leaves the U.S. agriculture community with a hole to fill. “Antibiotics are obviously a very important tool for veterinarians, and when you lose a tool, you have to replace it with something,” says Noelle Noyes, a veterinary epidemiologist at the University of Minnesota who studies antimicrobial resistance in livestock production. But finding alternatives that are as efficacious “is a tall ask,” she says.

Filling this hole means finding new ways to prevent infection and keep animals healthy and growing quickly. Other approaches could include boosting healthy microbes to build strong immunity in animals and nipping infections in the bud by detecting them early. Supplements or probiotic cocktails of living microbes, better animal management, and artificial intelligence to detect the first signs of illness are all approaches that scientists are investigating.

“There’s no silver bullet that’s going to solve all of our problems,” says Paul Plummer, a veterinary microbiologist at Iowa State University and executive director of the National Institute of Antimicrobial Resistance Research and Education. Some combination of countermeasures will be needed, he says.

One stumbling block in developing alternatives to antibiotics is that any given product is unlikely to be as effective as an antibiotic, but the cost of developing it could be similar. Evaluating their efficacy is also tricky. “If right off the bat it’s not performing as well as the gold standard—that is, an antibiotic—then it’s not clear what is the acceptable level of performance,” Plummer says.

Producers are hungry for solutions, however. “We’re excited to implement new science that can benefit these animals, whether it’s on health or production,” says Heather Fowler, Director of Producer and Public Health at the National Pork Board, a U.S. Department of Agriculture-funded organization that supports pork producers.

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Seeking good microbes
In killing pathogens, a specific antibiotic also kills a subset of bacteria in an animal’s microbiome, thereby altering its composition. Probiotics and prebiotics might sidestep pathogens by making it hard for them to grow in animals’ guts. Probiotics are living microbes designed to benefit the microbial ecosystem of an animal’s gut, and prebiotics are compounds designed to feed and enhance the growth of beneficial microbes. So researchers are exploring whether probiotics or prebiotics can replace some of the bang that antibiotics delivered. So far, results have been spotty. Although multiple probiotics for use in farm animals are on the market, “the evidence base for them is not very robust,” Noyes says. “The problem is, we just haven’t identified even which bacteria need to be in those formulations, or the dosage, timing, or route of administration.”

Noyes’s lab is characterizing microbial communities on cows’ teats to determine whether a particular bacterial makeup could protect dairy animals from developing a common and costly infection of the udders called mastitis. Other labs are exploring microbial composition elsewhere, such as in pigs’ nasal passages, to address respiratory or other infections. Researchers could then use that knowledge to develop ways to ratchet up numbers of good bugs at these sites—but that’s still a long way off, Noyes says.

Agricultural scientists are coming up with grips with the fact that farm animals’ microbiomes vary enormously, by species and even by farm. Probiotics on the market are designed as mixtures of microbes that might broadly boost gut health in particular animals; they aren’t tailored to specific health outcomes or environmental conditions. But there are hints that such targeting could help. For instance, one recent study found that probiotics customized to mimic the gut microbes of especially healthy and robust turkeys work as well as low-dose antibiotics to promote growth and keep the birds healthy.

Even more specific strategies are emerging, says Jeffrey Watts, a scientist working on antibiotic alternatives at the animal health company Zoetis. For example, researchers collaborating with Zoetis are developing a brew of microbes that produces a substance capable of interfering with cross talk between bacteria, including the signals that pathogens send to one another to mount an infectious attack. Scrambling this signal prevents pathogenic bugs from taking hold in a microbial community.

Scientists are coming up with more savvy strategies for manipulating farm animals’ microbiomes—by delivering immune-modulating chemicals, administering microbe-stimulating supplements, or using other approaches besides live microbes. For example, in 2015 Bayer received U.S. FDA approval for a nonantibiotic immunostimulant called Zelnate that protects cattle against bovine respiratory disease, which causes lung infections. “I think we’re just starting to skim the surface of how these technologies could be used,” says Keith Belk, an animal sciences and meat safety researcher at Colorado State University.

Belk is also exploring a completely different strategy: using CRISPR gene editing—an extremely precise gene-editing tool developed over the past decade—to assassinate bacteria that carry antimicrobial-resistance genes. The idea, he says, is to design CRISPR constructs that home in on especially common resistance genes and package those constructs in bacteria-targeting viruses called phages. These search-and-destroy packages would chew up the problematic gene and then, instead of fixing the DNA, just let the cell die. In lab tests, the approach kills pathogens while also wiping out resistance genes, Belk says.

Managing for health
These are early days for effective probiotics, and approaches like Belk’s are further still from commercial use. Producers are also re-examining animal management practices to make sure feed, water, and air are as clean as possible and that animals’ stress levels are kept low. That might involve going back to basics—improving ventilation systems or regrouping animals at different points in the production cycle, for example—but it may also involve some new tricks. For example, Melissa Reynolds, a chemist at Colorado State University, is developing metal–organic frameworks (MOFs) with antibiotic properties that latch onto the surface of textiles or polymers. The most effective of these MOFs, in which Cu²⁺ is immobilized within the material, prevents 85% of bacterial cells from attaching to it and seems to remain effective indefinitely. In comparison, standard antimicrobial materials lose efficacy quickly.
because they leach silver or other microbe-killing substances. Reynolds and her colleagues are also developing other materials that release Cu²⁺ or nitric oxide, which also kills bacteria. These materials could coat bandages or bedding, for example, to tamp down the risk of infection from injuries or daily interactions among animals in the herd.

On the management side, agricultural researchers are upping their game in using the vast numbers of data collected on farms. They’re devising machine-learning algorithms that could help farmers better monitor animals’ health and diagnose animals early, before an infectious disease has had time to spread. Robotic milking systems, for example, can meticulously record milk weight from each animal, and monitoring systems flag animals that produce less than the norm to be checked for illness. Audio monitors in pig facilities record vocalizations like coughs and trigger alerts when the frequency and pitch of coughs change. New systems are being developed to detect increased levels of volatile organic compounds that animals exhale when they have a respiratory infection and to track behavior—aggression, lameness, or even increased respiration rates—using a video camera. “Precision technologies have been around since the mid-to-late ’90s, but they’re really picking up now,” says Brett Ramirez, an agricultural engineer at Iowa State University.

The aim of all these efforts and the new regulations is to reduce resistance to antibiotics. So as livestock producers replace antibiotic use with a combination of these approaches, researchers should take the opportunity to track changes in antimicrobial resistance among animals, Noyes says. Although national data for resistance exist, measuring resistance is expensive, so neither farmers nor veterinarians nor researchers do much of it locally or regionally. “We are really missing an opportunity here to understand the real connection between antibiotics and resistance,” she says.

She and other experts also note that it’s unlikely that antibiotics can ever be fully eliminated from use in livestock agriculture. The industry produces large numbers of animals, and some of them will invariably get sick. “I think we have to invest in these new approaches while we are still making good decisions with the antibiotics that we do use,” Plummer says.

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