

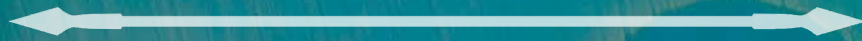
futures

Michigan State University • AgBioResearch

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ANTIBIOTIC RESISTANCE

SEEKING SOLUTIONS
in a time of
GROWING CONCERN



TACKLING A TOUGH, UNDENIABLY IMPORTANT TOPIC

I recall standing at the kitchen counter trying to muster the courage to drink the dose of smelly syrup staring me in the eye. My mother intently watching over me, “Just plug your nose and drink it. It will make you better.” As usual, she was right. After a couple days of choking down the medicine, my health usually improved. Fast forward 30 years and I was the mom making the same plea to my young sons with a bit of added commentary: “At least yours is bubble gum-flavored.”

For generations, society has become reliant on antibiotics to cure a number of illnesses and diseases, some even life-threatening. Today, however, there is concern that we could be moving toward a “post-antibiotic era,” a time when our current supply of antibiotics is no longer useful. Unquestionably the thought of becoming ill with an infection that is not treatable by modern medicine is daunting. This is likely preventable, however, as long as society is more judicious about the use of these drugs and pharmaceutical companies bring new antibiotics to the marketplace.

In this issue of *Futures*, we explore some of the research taking place at Michigan State University to help combat this serious problem. To be clear, our intent is not to place blame or point fingers. Enough of that has already taken place. Instead we have interviewed some of our leading researchers examining the issue from various perspectives — human medicine, animal health and environmental impacts. At the same time, we realize this is a very complex topic and that we have only begun to scratch the surface.

At the very minimum, we hope that the articles in this magazine serve as a dialogue starter because finding solutions to attain optimal health for humans, animals and the environment has never been more important. By now, nearly everyone has heard of antimicrobial resistance, or drug resistance. Labeled by the Centers for Center for Disease Control and Prevention as one of the most urgent health threats facing society today, it is a topic of news stories around the globe. There has been progress, but there is still a long way to go.

My personal outlook on antibiotic use has certainly changed in recent years. I’ll stick out a running nose and congestion longer than I would have before and all the while, my mother insisting a doctor’s prescription is the only remedy. Overcoming the generational beliefs and sometimes misbeliefs (e.g. antibiotics will get rid of a cold — NOT SO!) is perhaps the toughest feat of all.

But let’s face it, that nasty-tasting medicine (no wonder it kills bacteria!) — when properly prescribed — does pack a powerful punch against many serious illnesses and diseases. I sure hope it continues to be around to save lives and, less importantly, of course, to serve as a childhood rite of passage. 🍬

Holly M. Whetstone
Editor

(Photo courtesy of the
Centers for Disease Control
and Prevention.)



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ON THE COVER: A positive test for antibiotic resistance as evidence by the circles around the white tabs of antibiotics.



CDC report brings renewed attention to seriousness of antibiotic resistance

BY HOLLY WHETSTONE
Editor

“When I woke up just after dawn on Sept. 28, 1928, I certainly didn’t plan to revolutionize all medicine by discovering the world’s first antibiotic, or bacteria killer. But I suppose that was exactly what I did.”

— Scottish biologist **Sir Alexander Fleming** on his discovery of penicillin

In an untidy hospital lab in London, Alexander Fleming accidentally discovered an infection-fighting agent that would change the course of history. Amidst a stack of forgotten bacteria-filled petri dishes, Fleming found one sample with a fungus that had killed the surrounding germs. He was able to extract the mold and grow it, and he found that it could ward off many other types of bacteria as well. By the 1940s, that mold — eventually called penicillin — had become the first commercially available antibiotic.

Early in his studies, however, Fleming found that bacteria developed resistance whenever too little penicillin was used or if the drug wasn’t taken for an adequate amount of time. As he traveled the world making speeches about his discovery, Fleming alerted listeners about the need for proper use and dosage of the antibiotic.

That cautionary tale of drug resistance continues to be told with greater intensity and perhaps more emotion than ever before. Much of the recent attention was initiated last year, when the Centers for Disease Control and Prevention (CDC) released a 114-page report titled “Antibiotic resistance threats in the United States, 2013” (<http://www.cdc.gov/drugresistance/threat-report-2013/>), which some say has set off much-needed alarms.

Steven Solomon, director of the Office of Antimicrobial Resistance for the CDC, said the report is intended to educate the public in simple terms about the severity of antibiotic resistance, which has escalated in the past 10 to 15 years, largely because of a marked decline in new drug discoveries (see related story on page 22). With cases emerging of untreatable hospital-acquired infections, multidrug-resistant and extensively drug-resistant tuberculosis, and drug-resistant gonorrhea, Solomon said there is little doubt that society is on the verge of what is being called the “post-antibiotic era.”

“There is a real risk that we’re going to get to the point where we are more commonly encountering resistant bacteria that cannot be treated with existing antibiotics,” he said. “We’re facing the prospect of returning to the world of 80 years ago and the nightmarish possibility of not being able to treat seriously ill people with infections.

“We’re already getting reports from clinicians that they have seen patients who, often after extended hospitalizations and who have had multiple infections and multiple courses of antibiotics, are now infected with bacteria that cannot be treated.”

Because there was a constant flow of new antibiotics developed between 1950 and 1980, many healthcare providers — including Solomon, who was in medical

practice during part of that time — became complacent about antibiotic use, he said.

“I think there was a sense that we didn’t need to worry all that much about resistance because there was always a new antibiotic coming along that would take care of that resistant bacteria. For the first 30 or 40 years, that was largely true,” Solomon said. “Since the 1990s, however, there has been a significant decrease in the number of new antibiotics coming onto the market. The new drug pipeline is drying up.”

Antibiotics are the most commonly prescribed drugs in human medicine, but studies estimate that about a third to a half of their use is unnecessary or inappropriate. Antibiotic resistance develops naturally over time and cannot be prevented.

About 2 million people in the United States each year acquire serious bacterial infections that are resistant to one or more antibiotics.

According to the CDC, the use of antibiotics is the single most important factor leading to antibiotic resistance around the world. In addition to use in human medicine, antibiotics are also commonly used in food-producing animals to prevent, control and treat disease, and to promote growth (see related story on page 8), and, in very small amounts (less than 0.5 percent of total usage), to treat plant crops against bacterial infections (see related story on page 19).

Because of the many factors contributing to its development, antibiotic resistance is a polarizing topic that has caused friction between industries and individuals. Experts warn, however, that there is no time to point fingers or place blame. Instead, they say the focus should be on raising awareness and, ultimately, finding solutions.

James Averill, state veterinarian in the Michigan Department of Agriculture and Rural Development (MDARD) Animal Industry Division, said antibiotic resistance poses a major communication hurdle because of its scientific complexity.

“If you think you understand antimicrobial resistance and its impact, you haven’t begun to scratch the surface,” Averill said. “This is an extremely complex issue. It’s the whole relationship of us — as a world — that plays into this. It’s part of the reason why

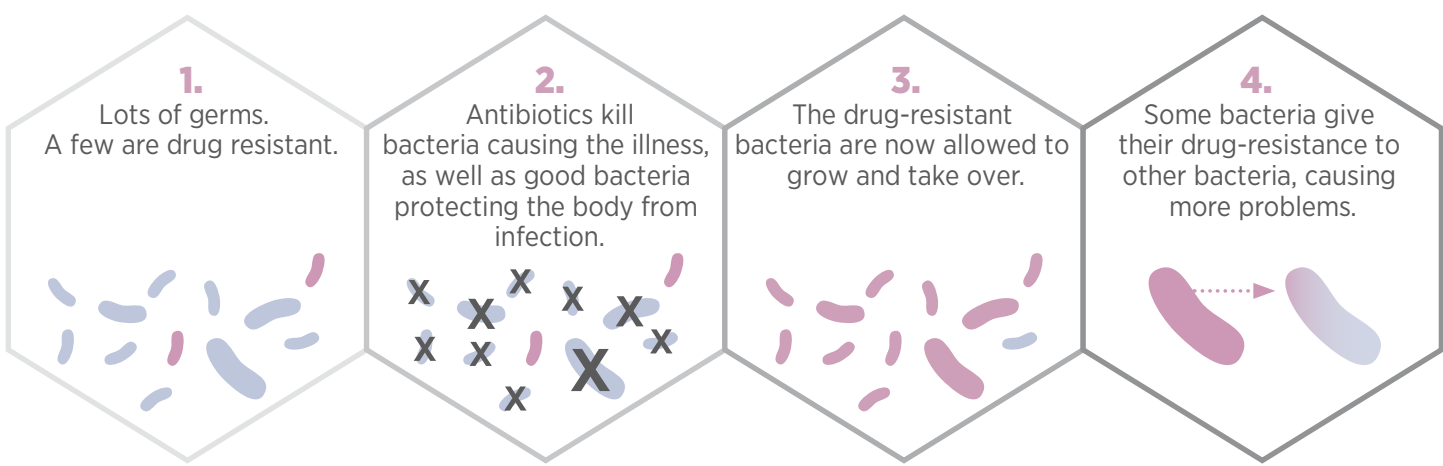
“If you think you understand antimicrobial resistance and its impact, you haven’t begun to scratch the surface. This is an extremely complex issue. It’s the whole relationship of us — as a world — that plays into this. It’s part of the reason why MDARD is involved in the One Health initiative.”

— James Averill



ABOVE: James Averill, state veterinarian in the Michigan Department of Agriculture and Rural Development, led a workshop in 2013 with industry representatives who gathered to learn more about new antibiotic use guidelines from the U.S. Food and Drug Administration.

How Antibiotic Resistance Happens



Source: Centers for Disease Control and Prevention.

MDARD is involved in the One Health initiative.”

The foundation of One Health is that worldwide the health of humans is connected to the health of animals and the environment. It is often referred to when discussing antibiotic resistance because of its simplistic, unified message that all life is connected. It has also been the topic of National Institute of Animal Agriculture symposiums, which Solomon and Averill have both attended.

“I’ve become a big fan of the One Health approach,” Solomon said. “Antibiotics are being overused everywhere, so we all need to be more circumspect, and we need to be better stewards of antibiotics everywhere. It’s not about affixing blame, and it’s not saying this area is a problem versus this area. 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.”

Despite mounting resistance concerns, experts agree that antibiotics should not be banned. The drugs have life-saving capabilities for both humans and animals, and they also help to keep the food supply safe. Engaging in dialogue has consequently become a top priority for many of the

groups affected by antibiotic resistance. For example, Averill led an MDARD-sponsored workshop in early 2013 with industry representatives who gathered to discuss the issue and learn more about new guidelines set by the U.S. Food and Drug Administration, the regulatory agency overseeing antibiotic use in livestock.

“It’s not about affixing blame, and it’s not saying this area is a problem versus this area. 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

“During the workshop, what it really boiled down to was ‘What can we do to help assure that there is a good, valid producer-veterinarian relationship?’” he said. “And, that producers understand the importance of utilizing antibiotics prudently or judiciously because there really has been no

new class of antibiotics brought onto the market for animal agriculture in 30-plus years.”

The Food Animal Committee from the Michigan Veterinarian Medical Association will continue to drive conversations and hold meetings on the topic with stakeholders. In the meantime, Averill said he is confident that the agriculture industry will rise to the occasion.

“I really see these recent changes and initiatives as an opportunity for agriculture to step up to the plate and demonstrate that we are using our antibiotics prudently and in a way to maintain animal health and well-being while making sure we have a safe, wholesome product for consumers,” Averill said.

Because a significant amount of meat consumed in the United States is imported, many have voiced concern that similar measures as those employed by the FDA need to be taken to keep the food supply safe here and in other countries as well.

Solomon is optimistic that strides are under way in the United States to help improve the antibiotic resistance situation.

“When bacteria are exposed to antibiotics, they inevitably take an evolutionary step toward developing resistance,” he said. “We can’t risk compromising the effectiveness

of the antibiotics we have right now through overuse and inappropriate use. Any step that makes us more judicious in our use of antibiotics — whether it’s in human medicine, veterinary medicine or agriculture — is a step in the right direction, and we need to be moving toward better antibiotic use in all of those areas. At the same time, it shouldn’t have to be one sector against the other.”

For the past decade or so, antibiotic resistance has outpaced new drug development, a trend that experts agree

must be reversed. The twofold solution, according to Solomon, is to work on the development of new antibiotics while at the same time taking steps to slow down the development of new resistance.

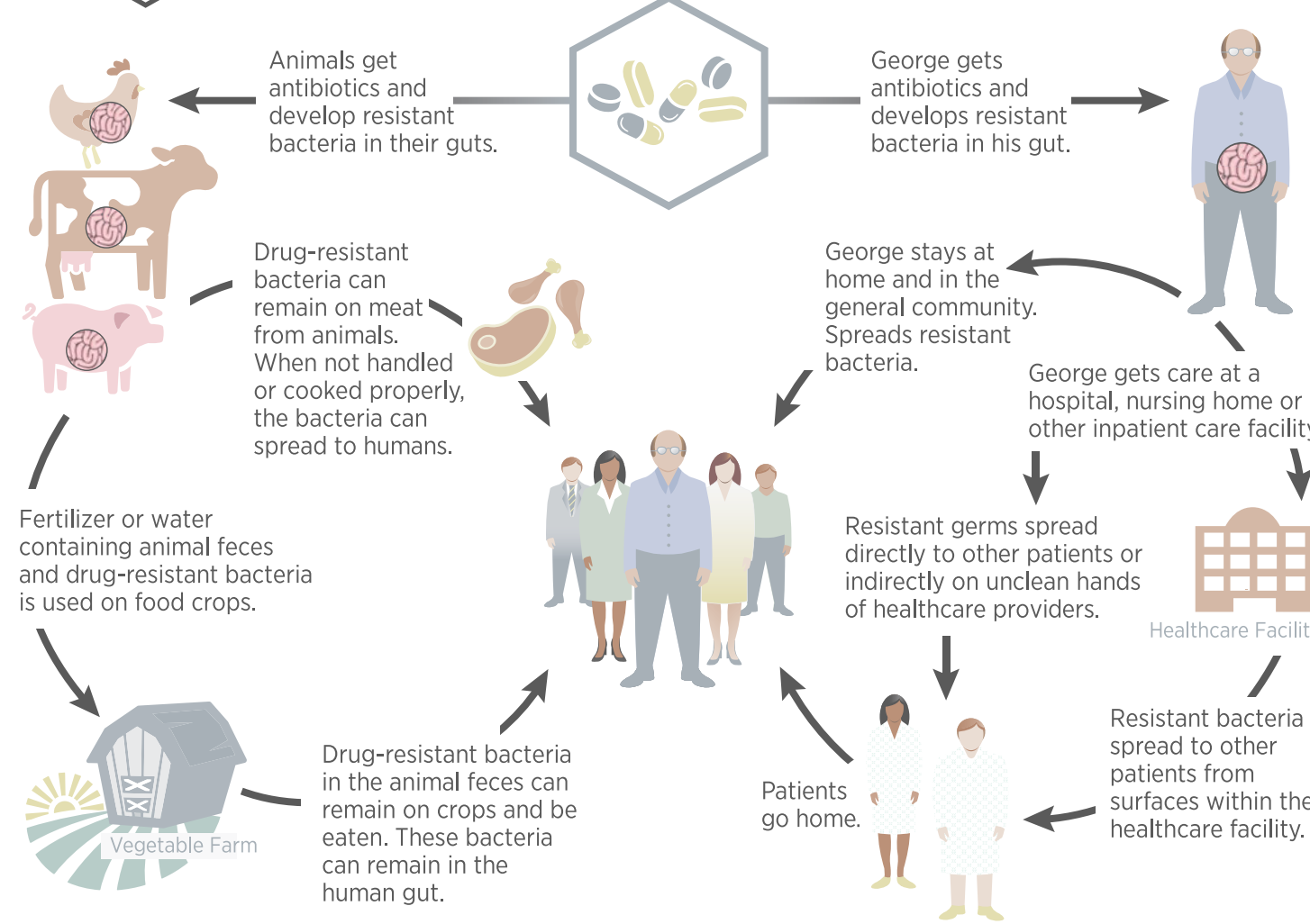
“We’re never going to stop resistance, but by slowing it down significantly we can give ourselves more time for development of new antibiotics,” Solomon added. “And that will be our solution.”

To learn more about One Health visit onehealthinitiative.com

Antibiotics are the most commonly prescribed drugs in human medicine, but studies estimate that about a third to a half of their use is unnecessary or inappropriate. Antibiotic resistance develops naturally over time and cannot be prevented.

Source: Centers for Disease Control and Prevention.

Examples of How Antibiotic Resistance Spreads



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

RIGHT: Paul Thompson, MSU professor of philosophy and Kellogg chair of agricultural, food and community ethics, walks through a cattle barn on campus. Thompson has found that most agriculture producers are willing to give up antibiotics as a growth promotant as long as they retain use to treat animal diseases.

BELOW: FDA Guidance Document 213 seeks to require producers to consult with a veterinarian prior to administering antibiotics through livestock feed.

BY JAMES DAU
Communications Coordinator

LINE DRAWN on the farm

FDA calls for end of antibiotic use for animal growth promotion

Antibiotics, formidable assets for human health care, have similar applications in animal agriculture, where they are used to combat a range of serious infections caused by bacteria, such as bovine mastitis, enteritis and respiratory disease. Antibiotics have proven so effective in livestock that, for the past half century, they have been applied in low doses to animal feed and water even in the absence of disease for small gains in growth and productivity. That practice, however, is likely to end following a guideline issued by the U.S. Food and Drug Administration (FDA) in December 2013.

Resistance to antibiotics was noted in animal agriculture as far back as 1951, when researchers found a streptomycin-resistant strain of coliform bacteria in turkeys. More cases, covering an ever-widening

array of pathogens, have been reported since. Responding to growing consumer concern about antibiotic resistance, the FDA released Guidance Document 213 in an effort to eliminate the use of feed- and water-based antibiotics for livestock production enhancement.

The FDA has two major goals in combating antimicrobial resistance:

- Reduce the usage of medically important antimicrobials, those used in both human and animal medicine, in food-producing animals as growth and productivity promotants.
- Ultimately have all antimicrobial use for food-producing animals take place under the guidance of veterinarians.

Michigan State University (MSU) professor of large animal clinical sciences

Daniel Grooms, who is also president of the American Association of Bovine Practitioners, is helping veterinarians and livestock producers gear up for the changes that the guidance document presents to the industry.

“Essentially what [the FDA] wants to do over time is eliminate the over-the-counter markets for antimicrobials,” the MSU AgBioResearch veterinarian explained. “Rather than producers getting them from a local feed store or ordering them from an online catalog, the FDA wants them all to be used under the supervision of veterinarians, who can prescribe them only for prevention or therapeutic reasons.”

In the document, the FDA requests that pharmaceutical companies remove growth or production claims from the

product labels. The intent is to help reduce the amount of antimicrobials in the environment and thus slow the formation of antimicrobial-resistant pathogens. The guideline, however, will not limit the availability of these drugs for therapeutic use on animals.

“Many of these drugs have more than one label,” Grooms explained. “One might say ‘mix in feed at a rate of 0.1 milligram per pound to increase livestock weight gain and improve feed efficiency’ — that’s a performance claim. It might also have disease control claims. Under the new guidance, the only one that the pharmaceutical company will remove is the one for growth promotion — the performance claim.”

The new guidance document will also

eliminate the availability of feed- and water-based antimicrobials from over-the-counter sources. Producers will have to go through a veterinarian to get a veterinary feed directive (VFD) to obtain feed-grade antibiotics for their animals.

“This is essentially the same as a prescription in human medicine. A veterinarian will have oversight over the use of antibiotics in food-producing animals,” Grooms explained. “He or she will have to write this VFD and can write one only for the prevention or treatment of disease.”

FDA officials have given the companies three months to declare whether they will follow the document and then an additional three years to incorporate the new product labels. According to Grooms,



ABOVE: Livestock feed is mixed at the dairy farm facility on the campus of Michigan State University.



nearly all of the large pharmaceutical companies have already stated intentions to comply with the FDA recommendations.

Livestock producers examine options

Livestock producers will have to adapt to the new antimicrobial use landscape as well.

“The producers that use antimicrobials for growth are going to have to turn toward other management strategies,” Grooms said. “It could be improved nutritional or environmental management or using other types of growth promotants, such as ionophores. The point is, there are management tools already available that producers can implement to make up for this void.”

Dale Rozeboom, MSU professor of animal science and Extension specialist for swine nutrition and production management, said he views the changes in antimicrobial policy as an opportunity for positive growth within the animal agriculture industry.

“It will help farmers discuss the use of antimicrobials,” Rozeboom said. “I think that, together, the veterinarian and the farmer will be able to determine the judicious use of antimicrobials in order to protect the efficacy of the medically important ones and diminish the opportunity for resistance to them to develop.”

The more antimicrobials are used, the greater the chance that genes for resistance

will be passed on to future generations of pathogens. This process increases the hardiness of their genes and reduces the effectiveness of drugs employed against them. According to Rozeboom, limiting the use of antimicrobials has opened the doors to exploring a range of new techniques — some that may be better suited to specific farm conditions — to be used on the farm to improve animal productivity.

► *“I think [livestock producers] see it as a challenge; it doesn’t cause any fear or trepidation. They see it as a new approach in that the antimicrobial products aren’t lost. They’re still available in those serious [animal health] situations, which is what we all want because they’re very good for therapeutic and preventive purposes.”*

— Dale Rozeboom

“From a farm perspective, we’re thinking that there may be cases where farmers will be able to simply discontinue the use of antimicrobials,” he said. “There’s a whole range of management strategies and non-pharmacological additives that are available for farmers.”

Of the alternatives available, farmers will be able to select those that best fit the



specific situations of their farms. According to Rozeboom, tactics such as adding zinc or copper microminerals, enzymes, probiotics, organic acids or herbal oils to animal feed have all shown promise in helping improve the productivity of livestock and could become more viable in the future.

Water is another possible means to deliver additives to the animals. Rozeboom and his colleagues recently completed a research trial in which dried egg yolk that contained antibodies for specific *E. coli* strains was added to the drinking water of young pigs to optimize their health. The egg yolk antibodies were produced by a private lab that inoculated hens with the pathogens. The hens then developed an immune response to the pathogens, causing antibodies for those pathogens to develop in their eggs. Results are being analyzed to assess the health benefits of this technique.

“There’s evidence showing that, in certain farm-specific situations, these techniques are effective to varying degrees,” Rozeboom said. “Not all environments are conducive to the same microbial populations, which is why it’s important to explore a range of possibilities. As an animal nutritionist, my job will be 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.”

Additives are just one way that farmers can improve animal productivity without antibiotics. Sanitation, climate control, weaning age and farm traffic are all important dimensions of the livestock



industry that researchers are studying to improve animal health.

“We’re going to talk to farmers about sanitation protocols — specifically, what we call all-in/all-out sanitation,” Rozeboom said. “It’s a technique designed to break disease cycles on the farm by ensuring that rooms that have been cleaned are not immediately re-exposed to pathogens.”

Rather than emptying and cleaning only half a room of animals, the producer cleans and dries an entire room before new animals are introduced. This slows the spread of disease by preventing pathogens from jumping from the still-occupied side of the room and contaminating the newly disinfected one, Rozeboom said.

Improvements in ventilation and heating also stand to benefit livestock. In a project conducted last year, Rozeboom’s MSU Extension colleagues noted that reducing housing temperatures at night may actually improve animal health.

“We’re learning from the animals that cooling things off a bit at night not only conserves energy but may, in fact, be improving their growth and energy,” Rozeboom said. “Managing their environment is something to scrutinize as we go forward without antimicrobials.”

Another means of making up for the lack of antimicrobials for production purposes could come in adjusting the age at which animals are weaned. Currently, pigs are weaned between 19 and 21 days, but new research suggests delaying that to 24 or 25 days may help the animals be less

susceptible to disease, Rozeboom said.

Improving biosecurity is an additional means of protecting farm animals. Preventing unnecessary traffic to and from the farm, keeping the feed trucks clean and knowing where they come from is one of the best ways to limit the spread of pathogens, Rozeboom said.

“These new regulations have opened up opportunities to explore other techniques and practices and take a more integrative approach to animal health and nutrition,” he said. “It’s not to say that antimicrobials have been misused; we’ve used them to the best of our knowledge. Now the FDA is challenging us to use them even more judiciously. I think farmers are up for that challenge.”

Industry concern focuses on an “even playing field”

With the passage and adoption of Guidance Document 213, producers will strive to maintain production levels without the use of antimicrobials to bolster animal growth. Both researchers and producers are confident in meeting this goal.

“I was at the Michigan Pork Producers meeting in late February, and the producers responded [to Guidance Document 213] very favorably,” Rozeboom said. “I think they see it as a challenge; it doesn’t cause any fear or trepidation. They see it as a new approach in that the antimicrobial products aren’t lost. They’re still available in those serious [animal health] situations, which is what we all want because they’re

FAR LEFT: Dale Rozeboom, MSU professor of animal science and Extension specialist for swine nutrition production management, examines content labels for feed on the MSU swine farm. He said research is leading to a variety of techniques to promote growth and improved health in livestock without the use of antibiotics.

CENTER: Most antibiotic livestock labels include claims for improving growth. A new FDA recommendation, however, requests that such claims be removed by 2016 in an effort to reduce exposure and slow the development of antibiotic resistance.

LEFT: Daniel Grooms, MSU professor of large animal clinical sciences, believes that the new FDA recommendations to limit the use of antibiotics in livestock feed helps to reinforce the supply of safe and secure food in the United States.

very good for therapeutic and preventive purposes.”

Retaining antimicrobials to combat disease is a key concern of industry producers. It was the central theme in early research by **Paul B. Thompson**, MSU professor of philosophy and Kellogg chair of agricultural, food and community ethics.

“The information we collected showed that livestock producers were quite concerned about losing antibiotics as a treatment against infections,” said the MSU AgBioResearch philosopher, referencing a survey of Texas and Colorado beef producers that he and his colleagues conducted 10 years ago. “One of the problems at that time was that the campaigns against antibiotic use were very broad-blanket approaches that wanted to ban all antibiotics. They were getting a lot of pushback from the livestock producer community, which wanted to be able to use antibiotics to treat sick animals.”

Rather than adopting such an all-encompassing approach to antimicrobial regulation, the FDA has recognized the importance of antibiotics for animal health. By eliminating over-the-counter markets and production-related label claims but continuing to allow access to the drugs for the treatment of disease, the agency has created a situation that industry, government and researchers can all accept.

“We found that producers would be willing to stop using antibiotics as a growth promotant if they could be assured that other people were going to stop using them,

too,” Thompson said. “They saw this not so much as something really essential to their production, but that they’d be put at a disadvantage if some producers were able to use them and others weren’t. They wanted an even playing field.”

In the years since Thompson’s survey, the industry and the FDA have worked to ensure this equality. **Scott Ferry**, a Litchfield, Mich., dairy farmer and president of the MSU Extension and AgBioResearch State Council, said livestock producers have been taking the use of antibiotics very seriously.

Grooms and his colleagues are now working to help producers take advantage of alternatives for improving animal productivity in an effort to minimize the impact of Guidance Document 213.

“As an industry, we have significantly reduced our need for antibiotics,” Ferry said. “The appropriate use of antibiotics to help animals survive, to nurture and care for them, is something that’s important to all of us, so making sure our drugs remain effective for animal health is what matters most. The utmost care is being taken to ensure our food supply is always protected.”

Sam Hines, executive vice president of the Michigan Pork Producers Association, echoed Ferry’s thoughts.

“We will adapt reasonably well [to the new guidance document],” Hines said. “There aren’t a lot of antibiotics used in the pork industry that are also used in human medicine to begin with. The bottom line is that we’ve focused on this issue for a long time and we’ve eliminated most antibiotic residue already.”

The Pork Quality Assurance program, developed by the National Pork Producers Council in 1989, was the first industrywide effort to reduce antibiotic residues in pork products. The program, distributed by the Michigan Pork Producers Association and its counterparts in other states, has

expanded to include farm assessments for animal welfare and has certified 59,000 pork producers and 16,000 farms. To become certified, producers must have an established relationship with a veterinarian, have a health management system for their farm, provide proper care and housing for their animals, and demonstrate responsibility in the storage and administration of animal health products, including antibiotics.

Jury still out on the impact

Antibiotic resistance has been a serious issue in both agriculture and human medicine for decades. Researchers, government officials and industry representatives are hopeful that the new FDA guidance document will help alleviate it.

“The evidence for antibiotic resistance is just overwhelming,” Thompson said. “I had an antibiotic-resistant infection last fall, and it was pretty frustrating. I had to go through four different antibiotics to find one that worked for this relatively commonplace illness, and while mine wasn’t serious, a lot of people are experiencing infections that are life-threatening.”

In the face of this problem, voluntarily sacrificing antibiotics for production is a small price to pay for the possibility of safeguarding against a greater threat.

“The most recent estimate I saw is that, of all the medically important antibiotics used in feed and water for livestock, only about 10 percent have been used for performance,” Grooms said. “So really, only about 10 percent of antibiotics will be reduced by this document.”

Grooms and his colleagues are now working to help producers take advantage of alternatives for improving animal productivity in an effort to minimize the impact of Guidance Document 213. They are providing educational sessions such as the annual Great Lakes Professional Cattle Feeding and Marketing course and helping veterinarians prepare for the increased demand that producers will have for their services.

The terms of the guidance document do

pose some new problems for producers, particularly in areas with limited access to veterinarians.

“We’re in decent shape here in Michigan, but there are portions of the Midwest and the Corn Belt where swine veterinarians are not very plentiful, and producers in those regions might have trouble getting the veterinary feed directives they need for antibiotics,” Hines added. “It’s a potential problem that we’re going to have to find a good solution to.”

The primary challenge to the document is whether the changes will be effective at improving the antibiotic resistance situation.

“A good case in point is what has happened in Denmark in the past 15 years,” Hines said. “When they stopped all subtherapeutic use of antibiotics, their use of antibiotics for therapeutic purposes went up. You can make the argument that this presents an animal welfare issue, and we in the industry would like to see more conclusive scientific evidence that this will help.”

This challenge remains unanswered.

“The jury is still out a little bit on how much of an impact these changes are going to make,” Grooms said. “If you look at the data from Denmark, it suggests that there really hasn’t been a change in antibiotic resistance in the public sector. Maybe it will be 10 years from now, but there hasn’t been a significant change yet.”

Substantial improvement or not, the changes are being instituted by the FDA. It is an attempt to tackle an issue with serious human and animal health repercussions, and with implications on the American food system.

“The big thing to understand, from the public’s point of view, is that our food supply is still one of the safest, if not the safest, in the world with regard to animal foods,” Grooms said. “We understand consumer concern and are always looking to improve our production practices, and this is one step we can take to improve on an already pretty safe system. At MSU we’re always looking for ways to help producers adapt without antibiotics and make that transition while still maintaining productivity and economic viability.”

EVOLUTION IN ACTION — Long-term project stimulates research in many areas

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

Originally, Lenski wanted to keep the experiment going for at least a year, which would have spanned about 2,000 bacterial generations. Now, 26 years later, the project — known as the Long-Term Evolution Experiment (LTEE) — has reached 60,000 generations. It is currently supported by a National Science Foundation grant for long-term research in environmental biology.

BELOW: Richard Lenski, Hannah distinguished professor of microbial ecology, started the Long-Term Evolution Experiment 26 years ago. The research results continue to provide useful information on the tempo and mode of evolution and serve as a framework for practical applications in biotechnology.



BY JANE L. DEPRIEST
Writer

Though Charles Darwin’s theory of natural selection has been confirmed by many lines of scientific evidence, the evolutionary process has never been directly observed for so many generations and in such detail as in Lenski’s experiment. The work is set apart by the many questions that can be answered by the long-running study. 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.

In addition to taking advantage of the speed with which bacteria reproduce and evolve, Lenski and his research team periodically freeze samples of the bacteria for future study in what he calls a “frozen fossil record.” Over the years, powerful new technologies were invented to analyze the DNA that is found in every living cell, culminating in the ability to sequence entire genomes.

“I had no idea then that new technologies would help us find all of the changes in the DNA,” Lenski said. “But since we saved bacterial samples throughout the experiment in a deep freezer, it’s like time travel because we can now directly compare their genomes across tens of thousands of generations.”

LTEE is not the only project in Lenski’s lab. In another recent experiment, Lenski’s team showed for the first time that a virus called “Lambda” could evolve to find a new way to enter host cells,

an innovation that took four mutations to accomplish. Fortunately, Lambda is not dangerous to humans — instead, it infects *E. coli* bacteria. However, the research provides a quintessential model for understanding how viruses evolve complex and potentially deadly new traits.

Lenski’s work on evolution also has crossed into the digital world. He has teamed up with computer scientists to use computer programs that self-replicate, mutate and evolve new abilities.

“My colleagues developed this biology-inspired software that we can use to explore evolutionary processes,” he said. “At the same time, they are using these evolutionary processes to help develop new technologies in the areas of networks, communication systems and robotics.”

While Lenski continues to pursue basic research with the bacteria, the LTEE project has led others to work toward various applications — from strain improvement and microbial forensics on the biology side, to new strategies for harnessing evolutionary mechanisms on the computational side.

“I think the major benefit of these experiments is that they give us a better understanding of evolution because it is experimentally tested, not an interpretation,” said **James Tiedje**, University Distinguished Professor of plant, soil and microbial sciences and director of the Center for Microbial Ecology. “Rich sees evolution in real time, and because he has replicates, he can see the differences as well as similarities of evolutionary outcomes. This is directly relevant to development of antibiotic resistances, and his basic work can help with finding solutions to the appearance and spread of resistances of all types.”



Bo Norby, MSU associate professor of large animal clinical sciences, is examining different types of substances such as honey and oregano in an effort to find effective antibiotic alternatives that will treat livestock and help reduce antibiotic resistance.

DAIRY FARMS DELIVER

Antibiotic use on the decline while new alternatives remain on the uptick

BY JAMES DAU
Communications Coordinator

Keeping livestock free from infectious disease 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, another novel set of tactics is needed to ensure food security and safety. Michigan State University (MSU) AgBioResearch scientists from the College of Veterinary Medicine are working to develop new techniques aside

from conventional antibiotics to fight and prevent diseases on the farm.

MSU associate professor of large animal clinical sciences **Bo Norby** has been studying antibiotic resistance on and off since graduate school. He began as a Ph.D. student at MSU measuring the impact of antibiotic elimination of resistance levels of bacteria in pigs raised on organic farms versus those raised on conventional farms.

“I think we were hoping it would be more of a slam dunk, with respect to lowering resistance, than it was,” he said. “It certainly has an impact, but on the other hand, it’s taken decades to reach the levels of resistance we currently see. It was probably naïve of me to think it would just go away so quickly.”

John Kaneene, director of the MSU Center for Comparative Epidemiology,

studies the epidemiology and mechanisms of antibiotic resistance in both livestock and humans. One focus is on identifying the factors that cause resistance to form.

“By understanding the mechanisms and dynamics of antibiotic resistance, we can get a sense of the magnitude of the problem,” said the MSU professor of epidemiology.

“I think we were hoping it would be more of a slam dunk, with respect to lowering resistance, than it was. It certainly has an impact, but on the other hand, it’s taken decades to reach the levels of resistance we currently see.”

— Bo Norby

Kaneene has conducted research that found that regularly using antibiotic-medicated milk replacers on calves plays a role in resistance levels. Milk replacers are commercial substitutes for whole milk that are commonly used to feed calves on farms because they are typically less expensive and have less risk of contamination than whole milk. Taking a sample of Michigan dairy farms, all of whom initially fed calves with antibiotic-medicated milk replacers, Kaneene divided them into two groups. One group continued to use the medicated replacers, and the other switched to replacers without antibiotics. Kaneene and his team took samples from the animals and environments of each farm over the course of one year and found that, in the group without antibiotics, resistance had decreased.

Though the initial results looked promising, Kaneene said that soon changed. Those farms eventually began to experience a resurgence of resistance. Like Norby, Kaneene found that simply eliminating the use of antibiotics was not enough — new techniques would be needed. Currently, he is in the beginning stages of research to investigate new treatments for gastrointestinal disease in cattle that do not

involve antibiotics.

“In some cases, you can minimize antibiotic use, which helps us to reduce the formation of resistance on the farm,” Kaneene said. “That’s just a starting point, however.”

Norby, who returned to MSU in 2011 this time to work, renewed the efforts he began while a doctoral student to examine antibiotic-resistant *Escherichia coli* in dairy cattle. By subjecting samples of *E. coli* to a battery of 14 to 16 antibiotics, Norby was able to quantify the level of resistance it had to various antibiotics.

“We had to understand the quantity of resistance in the bacteria before we could assess the impact of different interventions in the animals,” Norby explained. “I was bothered. When we began researching resistance, we found that cutting out antibiotics was not the quick-fix solution. When I came back to MSU, we started looking for alternatives to stopping cold turkey.”

Norby began testing a variety of substances to create products that can be injected into the udder of a cow like an antibiotic. He is particularly optimistic about the potential of honey derived from the nectar of the manuka tree, which has natural antibacterial and tissue-repairing properties, as well as oregano.

“The hope is to find something that will give dairy producers a non-antibiotic option for treating their animals,” Norby said.

The first step in determining a substance’s viability is to test it against isolated strains of bacteria in the lab. Norby exposes a sample of bacteria to increasing amounts of a candidate until he finds the point at which it prevents bacteria from growing, known as the minimum inhibitory concentration.

The candidate must also be tested for safety. Norby’s team will first shave the fur from the portion of the cow’s udder and apply the candidate to the bare skin to test for inflammation. Next, it will be injected into the udder to ensure it does not make the animal sick or cause more inflammation, thereby exacerbating the illness it was designed to treat. Only

>>> Success story:

In 2003, Green Meadows Farms in Elsie, Michigan, worked with MSU veterinarians to set up a system to take on-farm bacterial cultures. This allowed the farm to assess whether a cow was infected with mastitis and determine if treatment with antibiotics was the best course. **Louis Neuder**, MSU associate professor of large animal clinical sciences, said the farm has since decreased its antibiotic use by more than 70 percent.

“We were concerned about the misuse of antibiotics,” Neuder said. “We theorized that, instead of just treating the cows with whatever the current antibiotic on the market was, if we had the herd manager take a culture of every cow that had mastitis and got a good identification of which specific bacteria were present, we could treat the animals a lot more effectively and use fewer antibiotics to do so.”

Neuder said that the results of the bacterial cultures, which take about a day to develop, generally fell into three categories:

- Grand positives, such as *Streptococcus* and *Staphylococcus*, that could be treated effectively with antibiotics.
- Environmental coliforms, such as *E. coli*, about which there is disagreement over the effectiveness of antibiotic treatment, with the best course of action being to treat the affected animal on the basis of its symptoms.
- No bacteria present because the cow’s immune system had already limited the spread of infection.

“By taking a targeted approach, treating only curable cases and finding the most effective drugs to treat them with, our system reduced antibiotic use and, therefore, antibiotic resistance, and improved all of the farm’s milk quality indicators,” Neuder said.

Other farms across Michigan and the nation have begun to emulate the system started at the farm in Elsie. This approach is especially appealing because it allows individual producers to tailor treatment of mastitis and other bacterial infections to their specific needs, which vary from farm to farm. 🌱





FAR LEFT: John Kaneene, MSU University Distinguished Professor of Epidemiology, has found that eliminating antibiotics from livestock feed has resulted in decreased antibiotic resistance.



LEFT: Bob Cooley, milk processor at the MSU dairy farm, takes a milk sample at the MSU milk parlor. All dairy farm milk is rigorously tested for antibiotic residues before shipment in an effort to ensure a secure dairy supply.

after these rounds of testing can it move to the clinical trial stage, where multiple candidates are tested both against one another and against an already medically approved antibiotic to determine which of the alternatives is most effective.

Finding alternatives to traditional antibiotics represents an important middle ground in reducing antibiotic resistance, Norby said.

“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,” he said. “By having alternatives, we take some of that selective pressure away and slow the propagation of resistance.”

New practices for a healthier farm

While Norby and Kaneene study alternative medical treatments to antibiotics, other MSU researchers are approaching the issue from a different angle. They are examining livestock practices that promote better animal health and maximize the efficacy of the immune system to reduce the incidence of disease and, therefore, the reliance on antibiotic therapy.

MSU AgBioResearch veterinarian **Ronald Erskine’s** research focuses on mastitis, a bacteria-caused inflammation of the cow’s udder and the most common disease to afflict dairy cattle in the United States. According to the U.S. Department of

Agriculture, mastitis affects 15 to 20 percent of Michigan dairy cows annually. For an average-size dairy farm of 187 cows, the disease can result in the annual loss of about 25,000 pounds of milk and an annual cost of up to \$10,000 in medical treatment. Severe cases can result in even greater losses along with long-term impacts on the health, welfare and fertility of the affected animals.

“Mastitis is caused by white blood cells moving into the udder to fight an infection,” Erskine explained. “It’s not much different from when you have a head cold — that’s when your immune system responds to an invading bacterium or virus. So when we’re talking about mastitis, we’re talking about the classic signs of immune response: inflammation, redness, soreness.”

As the most common disease in dairy cows, mastitis is likewise the most common reason for antibiotic use on dairy farms. Erskine has dedicated much of his career to finding new ways to combat the illness.

“Mastitis is a problem dairy producers have to tackle every day,” Erskine said. “They have to make a choice to treat a cow with antibiotics or not. From the standpoint of both productivity and cow well-being, the goal is to reduce mastitis, and we’re trying to find the most effective ways of doing that.”

Part of Erskine’s research is determining when antibiotic therapy is an appropriate tactic. Mastitis is caused by a wide range of bacterial pathogens, not all of which are susceptible to antibiotics. The most

common agents of mastitis, *streptococci* and *staphylococci*, respond very well to antibiotics if caught in time. Other causes, however, do not.

“Much like the debate that goes on with pediatricians or doctors when you have a cold, the question is do you want to jump in and start with antibiotics?” Erskine said. “We try to help dairy producers and their veterinarians make informed decisions on when it’s appropriate to use antibiotics and when to wait and see if the cow’s own immune system can fight it off. It’s all about prudent, judicious use of antibiotics, using them only when they’re necessary.”

To determine whether the case is treatable with antibiotics, Erskine conducts bacterial cultures of milk from the infected cows to determine the type of bacteria causing the disease.

“It’s no different than what happens at a hospital,” Erskine said. “If you have strep throat, somebody collects a swab and identifies the organism before they give you antibiotics.”

The other key aspect in determining whether to use antibiotics is to understand the medical history of both the entire herd and the individual cows within the herd. Some bacterial infections can cause a chronic change in the cow udder, producing scar tissue and becoming more difficult to treat.

“You try to treat these infections as soon as you can, but sometimes they become chronic,” Erskine said. “We try to help farmers make the right choices based on

records of the cow’s health. For instance, maybe we’ve treated a cow before and it didn’t work. The question then becomes: do we really want to keep using antibiotics on this cow, or do we recognize her as a poor candidate for this kind of therapy?”

“We try to help dairy producers and their veterinarians make informed decisions on when it’s appropriate to use antibiotics and when to wait and see if the cow’s own immune system can fight it off.”

— Ronald Erskine

Erskine believes that training practices on the farm are an effective means of improving animal health while reducing reliance on antibiotics. As farms have dramatically increased productivity levels in the past two decades, he said producers have become increasingly reliant on employees to manage the expanded herds.

“The classic story you’ll hear is that when Dad took over the farm from his father in the ’80s, they had 100 cows,” Erskine said. “Now, in 2014, he has 300 or 400 cows, six full-time and three part-time employees.”

In addition to increased production, this expansion of farm personnel has introduced new challenges to the industry.

“We have a very progressive dairy industry in Michigan, when you look at our

ranking in terms of milk production and quality,” Erskine said. “We have a group of producers that are very good at what they do — this goes beyond mastitis to how cows are housed, fed, bred, everything — but I think there are challenges in managing labor. All of a sudden they’ve gone from dealing with farm issues among immediate family to having to manage 10 or 15 people. The more people you have, the more variance there is from protocol, and that increases the risk of diseases appearing.”

Establishing and following protocols for the daily operations of a dairy farm, from milking procedures to administering antibiotics to preparing feedstocks, is paramount to a healthy herd. To help producers and their employees implement and follow farm protocols, Erskine leads a multi-institutional research team developing training programs that engage employees with farm owners, managers and veterinarians.

A survey of dairy farm employees revealed a strong desire to be trained on how, as well as why, to perform farm operations.

“We have a belief that, if employees are engaged like this, protocol drift will be reduced and incidences of things like mastitis are going to come down,” Erskine said.

On the basis of a survey of the concerns and practices of more than 600 producers in Michigan, Florida and Pennsylvania, Erskine’s team crafted an evaluation system to develop protocols and educational

materials to help veterinarians educate farm employees.

“We’re going to help people set goals, communicate and find ways to educate employees to generate long-term change,” Erskine said. “We’re all learning here. This is a new environment for dairy farmers and we’re all just trying to find the right dance partners, so to speak.”

Fighting disease by promoting health

Animals, including livestock, were fighting bacterial infections long before the dawn of antibiotics. Under the right conditions, the immune system serves as a formidable defense against disease. MSU professor of large animal clinical sciences and bovine immunology specialist **Lorraine Sordillo** is developing ways to bolster the immune system through a cow’s environment and diet to reduce mastitis and other infections on dairy farms.

“It’s not that antibiotics are a bad thing, but we don’t want to use them arbitrarily,” Sordillo said. “The best way of reducing the need for them is to prevent the disease from occurring in the first place.”

When cows are stressed, the capabilities of their immune systems become diminished and the incidence of illnesses rises. Sordillo’s research aims at reducing that stress.

“The focus of our research is to understand the mechanisms that compromise the animal’s immune system and try to come up with intervention strategies that

bolster the immune system during times of increased exposure to mastitis-causing pathogens,” Sordillo said.

The many ways to strengthen the immune system range from vaccines to dietary adjustments. Because of the sheer variety of bacteria that cause infections such as mastitis in dairy cows, the effectiveness of vaccination is limited because it targets individual strains of bacteria.

Instead of vaccination, Sordillo looks at changing nutritional and metabolic conditions to reinforce the bovine immune system.

Among the most stressful periods is the birthing of a calf and the initiation of milk production. Some changes in the ways cows use available nutrients during this time can suppress immune function, leaving them susceptible to disease. Through improved nutrition, Sordillo has found ways to mitigate the negative effects of this altered nutrient metabolism.

“We want to make sure the cow’s dietary intake is optimized because that reduces stress on the body and the need to metabolize fat stores,” Sordillo said. “A lot of energy is expended in the calving process and at the onset of lactation. For a cow to be able to meet those energy demands, she has to consume enough feed. If not, then she’s going to start mobilizing her tissue stores to release fats for energy.”

The mobilization of fats introduces free

fatty acids into the bloodstream, which represses the immune system. Ensuring that cows have enough energy from their feed reduces this mobilization, and the immune system remains intact.

The energy consumed during lactation also results in the production of metabolic waste called reactive oxygen species. These molecules, natural byproducts of energy consumption in the body, are highly toxic in the high quantities present during milk production, and coping with this accumulation of toxins strains the cow’s antioxidant defenses. This can be exacerbated during periods of infection, when the immune system produces further quantities of reactive oxygen species in order to kill bacteria.

Sordillo’s research indicates that increasing the dietary concentration of antioxidant nutrients such as selenium and vitamin E during early lactation may mitigate the harm caused by these molecules.

“The production of reactive oxygen species is a natural part of metabolism and a normal response of the immune system, but, like anything, the problem comes when there’s too much,” Sordillo said. “In order to get back to normal levels, you have to increase the antioxidants the cow is receiving. When you don’t, the toxins can not only damage tissues but have a profound effect on the immune system, and that’s a major factor in disease susceptibility.”

Better health through better treatment

Eight millennia after the first livestock were domesticated, Plato wrote that necessity is the mother of invention. Though the venerable philosopher was referring to the politics of ancient Greece, his words ring true for the work of MSU AgBioResearch scientists examining livestock health. With the development of resistance, unilateral antibiotic therapy is no longer a viable option for disease treatment.

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

The development of alternative treatment strategies has already led to techniques not only to treat diseases but to help prevent them. There will always be cases that require antibiotic therapy, but these new practices reduce the need.

“When you look at the overall trend here in Michigan, and even nationally, antibiotic use has been steadily declining in dairy,” Erskine said. “Our producers have been working hard at that, and with the new techniques and technologies we’re developing, they’re going to be able to do even better.” 🍀

LEFT: Ronald Erskine, MSU professor of large animal clinical sciences, inspects a milk pail on the MSU dairy farm. His research has found that by improving animal health through more effective farm employee training, the need for antibiotics, and therefore the development of resistance, is reduced.



AGBIO PLANTS

THE PRESSURE IS ON

BY HOLLY WHETSTONE
Editor

New ruling will end antibiotic use in organic fruit production; growers need alternatives

ABOVE: George Sundin, MSU plant pathologist and Extension specialist, has been guiding the fruit industry on fireblight treatment options for more than a decade. He says the pressure has never been higher to find viable solutions.

BELOW: Fireblight is a costly and destructive plant disease caused by a bacterial pathogen. The brown, curled leaves in the shape of shepherd’s crook on this fruit tree are one sign of the disease.

For generations, apple and pear growers in the United States have been dependent on a small number of antibiotics applied during bloom time to protect trees from infection by a destructive and costly bacterial disease known as fire blight. Despite effectiveness in the field, however, antibiotic use in plant agriculture has become part of the discussion of increasing human drug resistance concerns.

In fact, a new regulation will eliminate the use of antibiotics in organic apple and pear production beginning this fall. The controversial decision was made by the National Organic Standards Board (NOSB) after urgings from consumer and environmental advocates, who cited mounting evidence that antibiotic resistance is a serious health threat. The ruling also marks the end of antibiotic use in all organic food production, including livestock.

David Epstein, a former Michigan State University (MSU) entomologist who has worked closely with the fruit industry and is now with the U.S. Department of Agriculture (USDA), said the recent NOSB decision may dampen fruit grower interest in organic production.

“I’ve already heard from a number of organic growers in Michigan who told me

that they will stop producing organically if they can’t protect their trees [from fire blight] because of a lack of effective organic treatment options,” Epstein said. “Antibiotic use in tree fruit orchards is relatively minor, occurring early in the season and only when necessary, not prophylactically. Many growers believe that antibiotic use in apple and pear production is generally misunderstood.”

The new regulation has unquestionably added pressure to find workable fire blight control alternatives, not just for the organic industry but for conventional fruit growers as well.

The problem at hand: fire blight

Fire blight is caused by the bacterial pathogen *Erwinia amylovora* (*E. amylovora*), which infects the flowers of blooming apple and pear trees. It can quickly spread into the branches and ultimately kill the tree and sometimes entire orchard blocks. Signs of infection include cankers, which ooze sticky amber-colored droplets, each containing millions of bacterial cells onto the shoots and leaves, and branches of dry, brown, curled leaves in the shape of a shepherd’s crook. It is a serious problem

(Continued on page 36.)





Lorraine Sordillo, PhD

BEST VACATION: Crete. We had a great tour guide so we were able to really look around and see the ruins.

Lorraine Sordillo

TITLE: MSU professor and Meadowbrook Chair in the College of Veterinary Medicine

EDUCATION: Master's degree in dairy science from the University of Massachusetts; Ph.D. from Louisiana State University in bovine immunology, vascular biology and mastitis (an inflammatory disease of the mammary gland primarily caused by bacteria)

JOINED MSU IN: 2004

HOMETOWN: Malden, Mass.

MUSE: My mentor at Penn State (where I started my academic career as an assistant professor and stayed for 13 years) Channa Reddy [a retired faculty member and former Veterinary Science chair]. He was a ball of fire. I was one of the only women in the vet science department at the time, and he scooped me under his wing and really challenged me. As professors, it's really our obligation to make sure the next generation of scientists is going to be better than we ever were.

FAVORITE FOOD: I'm Italian so I love authentic Italian food, which you can't really get here. It can only be found in a grandmother's or great-grandmother's kitchen.

BEST SONG/GROUP: The Mamas and the Papas. My daughter even has one of their songs as the ringtone for when I call her.

BOOK I'D RECOMMEND: Sir Arthur Conan Doyle's *The Adventures of Sherlock Holmes*. It's just amazing how his mind must have worked to come up with not only this crazy character but the intricate plots.

COOLEST GADGET: The iPhone with Siri. I recently discovered that it even tells jokes! Plus, I'm totally directionally impaired — I'd get lost without it.

BEST INVENTION: It has to be the computer. When I did my master's, that was the era of data cards. We didn't have PCs, just typewriters. And now, I can't imagine writing a thesis the old-fashioned way.

WORST INVENTION: Social networking sites. I can half-understand Facebook, because it's good for connecting with old friends and such, but Twitter? It seems like a time sink to me.

ON MY BUCKET LIST: I'm an avid fly-fisher — I even used to teach a women's fly-fishing class — but what I've never done is saltwater fly-fish. It's a challenge I'd like to try. Also, my husband and I would like to travel across the country in our RV.

PERSON I'D MOST LIKE TO MEET (living or dead): That's easy, Thomas Edison. What an inventor! He had no formal graduate education, yet he was able to accomplish things using his ingenuity, determination and elbow grease.

BEST TRIP/VACATION: I travel so much that I get weary just thinking about it, but the best trip I went on would be Crete. We had a great tour guide, so we were able to really look around and see the ruins.

SATURDAY AFTERNOON, YOU'LL LIKELY FIND ME: Gardening. I listen to audiobooks and garden. I also like fly-fishing and golfing.

MAJOR RESEARCH BREAKTHROUGH OF THE NEXT DECADE: Gene therapy for cancer. There have been major breakthroughs in how to take immune cells from the patient and manipulate them genetically — much like what I do with cows' immune cells with mastitis — to specifically identify cancer cells and kill them. You have the patient's own immune cells combating the cancer, which is what fails with a cancer like leukemia. I seriously anticipate this in the next decade. All the investment in genomics is going to pay off! 🍀

MSU mastitis expert follows her passion far from home

Lorraine Sordillo's origins are surprisingly far-removed from agriculture. While growing up in the suburbs of Boston, she never spent any time on a farm nor did she plan to.

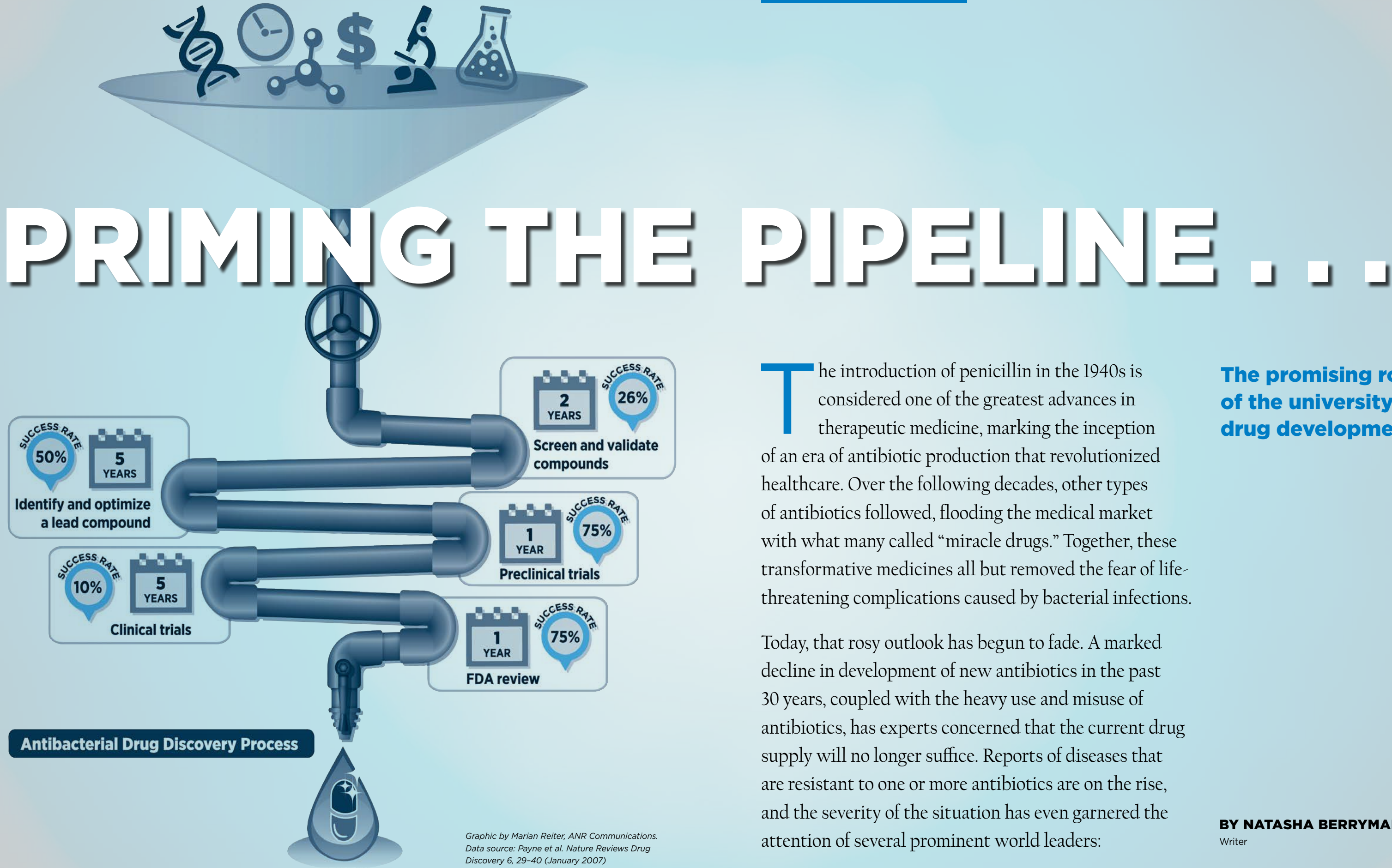
Initially, while attending the University of Massachusetts, she wanted to become a small animal veterinarian. That changed after experiences at two dairy cattle research labs, where she worked to help bolster her vet school credentials. Suddenly, her career path seemed to click.

Much of her research today is focused on mastitis, a bovine disease that costs the U.S. dairy industry more than \$2 billion annually. She is investigating non-antibiotic approaches such as preventive hygiene to bolster the immunity of the cows and to help control the infection that occurs in the mammary glands.

And her work has broad implications.

"Inflammation is the underlying cause of a number of pathologies in humans as well as farm animals," she said. "The fundamental research that we do is really applicable to human health and dairy cattle health, as well as other species. Some of our work is very basic, and some is very applied specifically to the cow."



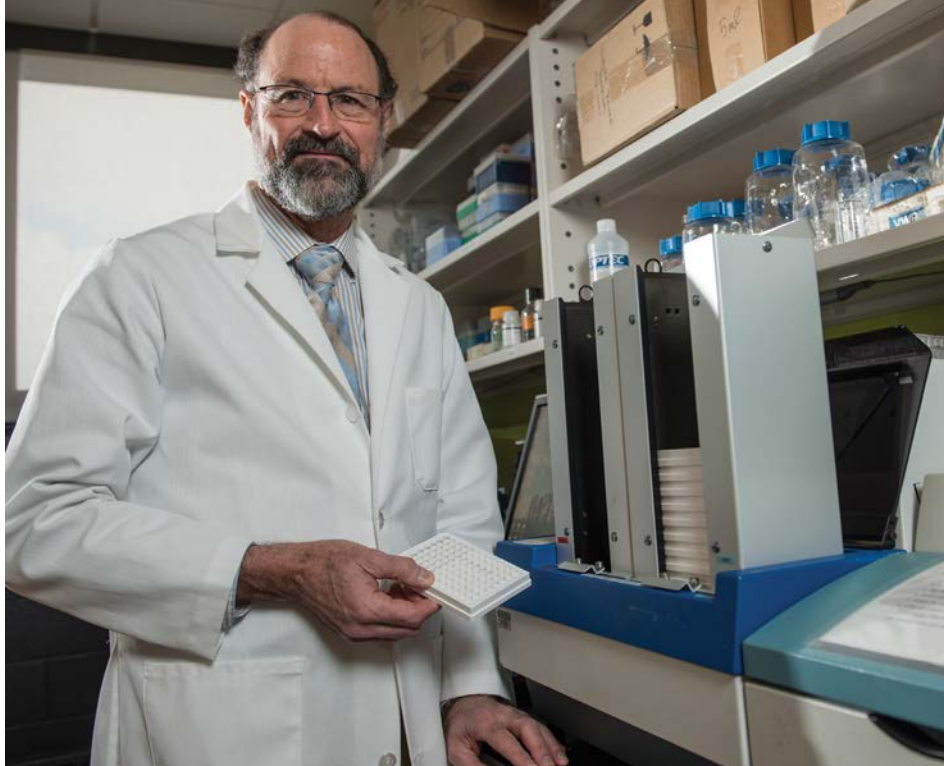


The introduction of penicillin in the 1940s is considered one of the greatest advances in therapeutic medicine, marking the inception of an era of antibiotic production that revolutionized healthcare. Over the following decades, other types of antibiotics followed, flooding the medical market with what many called “miracle drugs.” Together, these transformative medicines all but removed the fear of life-threatening complications caused by bacterial infections.

Today, that rosy outlook has begun to fade. A marked decline in development of new antibiotics in the past 30 years, coupled with the heavy use and misuse of antibiotics, has experts concerned that the current drug supply will no longer suffice. Reports of diseases that are resistant to one or more antibiotics are on the rise, and the severity of the situation has even garnered the attention of several prominent world leaders:

The promising role of the university in drug development

BY NATASHA BERRYMAN
Writer



“Faculty may be able to find new targets that work and push them forward in a way that pharmaceutical groups hesitate to.”

— Richard Neubig

LEFT: Richard R. Neubig, MSU professor and chairperson of the Department of Pharmacology and Toxicology, is establishing a new drug-discovery lab MSU researchers can use to explore viable drug candidates — a process he believes MSU scientists are well positioned to achieve because of a strong foundation in basic science.

- President Barack Obama acknowledged the need to address drug-resistant bacteria in his 2014 State of the Union address.
- The Centers for Disease Control and Prevention (CDC) issued a detailed report describing the extent of bacterial drug resistance in the United States in 2013.
- Margaret Chan, World Health Organization (WHO) director, warned, “In the absence of urgent corrective and protective actions, the world is heading towards [an] era in which many common infections will ... once again, kill unabated” on World Health Day in 2011.

The CDC explained that, during the past 70 years, bacteria have shown the ability to develop resistance to every known antibiotic. Not only are drug-resistant bacteria capable of rendering many routine therapies ineffective, but they also increase the risk of complications for patients undergoing life-saving procedures.

Several Michigan State University (MSU) researchers are responding to this urgent call for new antibiotics and other novel drug therapies.

Constructing a niche

The process of developing and introducing a new antibiotic from concept to market can

take as many as 14 years and costs upwards of a billion dollars — not including the investments in the fundamental science required to understand disease mechanisms. Couple the high costs with low success rates (see page 22) and most pharmaceutical companies avoid such endeavors altogether. University researchers, however, aren’t as timid.

Richard R. Neubig, MSU professor and chairperson of the Department of Pharmacology and Toxicology, is well aware of the risk but recognizes the important role that research universities such as MSU can play in this under-occupied niche. Neubig left his position with the University of Michigan in the spring of 2013 and came to work at MSU, bringing more than 15 years of drug discovery expertise.

“We’re trying to open the door for MSU academics to use powerful drug discovery tools to attack long-term problems that don’t necessarily fall into the immediate plans of the pharmaceutical industry,” he said.

Neubig, president of the American Society for Pharmacology and Experimental Therapeutics, explained that pharmaceutical companies often focus on developing drugs for persisting diseases (such as heart disease) or working to improve already-existing drugs. In

contrast, university researchers often nudge away at unconventional approaches that pharmaceutical companies might typically ignore.

“By having academics explore off-beat drug targets, they reduce the risk of commercial ventures that explore a completely new approach,” he said. “Faculty may be able to find new targets that work and push them forward in a way that pharmaceutical groups hesitate to.”

Neubig is establishing a high-throughput screening lab at MSU that will enable researchers to quickly screen thousands of compounds and identify those that could be developed into new drug candidates.

“The faculty already has expertise in the biology — either the proteins they’re working on or the biological mechanisms — so we can help them convert that understanding into an assay [an analysis used to measure the activity of a protein molecule or biological response in a cell] they can use in high-throughput screens,” he explained.

Researchers will use the new lab to screen compounds for applications in many types of drug therapies, not just antibiotics. Neubig noted, however, that antibiotic drug discovery presents an interesting challenge.

“There are a number of known cell

mechanisms: penicillin affects the cell wall of the bacteria; others affect the way DNA is handled inside the cell,” he said. “However, many other processes are important for pathogenesis of bacteria that allow them to cause damage or survive in the host — mechanisms that are risky for commercial groups to explore but that fit in well with the academic’s creative pursuit of answers to basic biological questions.”

Embracing risk

Tuberculosis (TB) — caused by *Mycobacterium tuberculosis* (MTB) — is among the most common infectious diseases and frequently causes death worldwide, according to the CDC. It is estimated that one-third of the global population (2.3 billion people) is infected with latent TB, a form of the disease that has no symptoms but allows the bacteria to live in the body for decades.

In the past 40 years, only one new drug has been successfully developed to treat TB. **Robert Abramovitch**, MSU AgBioResearch microbiologist, is in the second stage of screening compounds that he hopes will lead to a new, fast-acting, affordable antibiotic treatment for TB.

“When MTB infects humans, our immune system walls off the infection by building a granuloma — a tumor — around the

bacteria, which is why you seem healthy if you have latent TB,” explained the MSU assistant professor of microbiology and molecular genetics.

The granuloma does not kill the bacteria; instead, the bacteria sense environmental cues and substantially slow their growth, changing the way they use and make energy to survive inside the tumor. Abramovitch believes that oxygen may play a pivotal role in this process.

“MTB needs oxygen to grow,” he said. “We believe the bacteria have the ability to sense when oxygen levels around them decrease — a state known as ‘hypoxia.’ When they sense that the environment has become hypoxic, that’s their cue to hunker down.”

TB bacteria in this dormant, slow-growing state are difficult to kill with antibiotics. Additionally, current therapies require patients to take antibiotics daily for six months. Missing several doses causes patients to remain ill longer and inadvertently breeds drug resistance.

To target MTB’s hypoxia-sensing ability, Abramovitch genetically engineered an MTB strain that glows green when it transitions to a dormant state. Abramovitch was recently awarded the 2014 MSU Innovation of the Year award for creating this inventive assay, which he uses to screen for compounds that turn off the glow. Obstructing this signal indicates that

a compound has successfully prevented the bacteria from sensing its hypoxic environment and entering a dormant state.

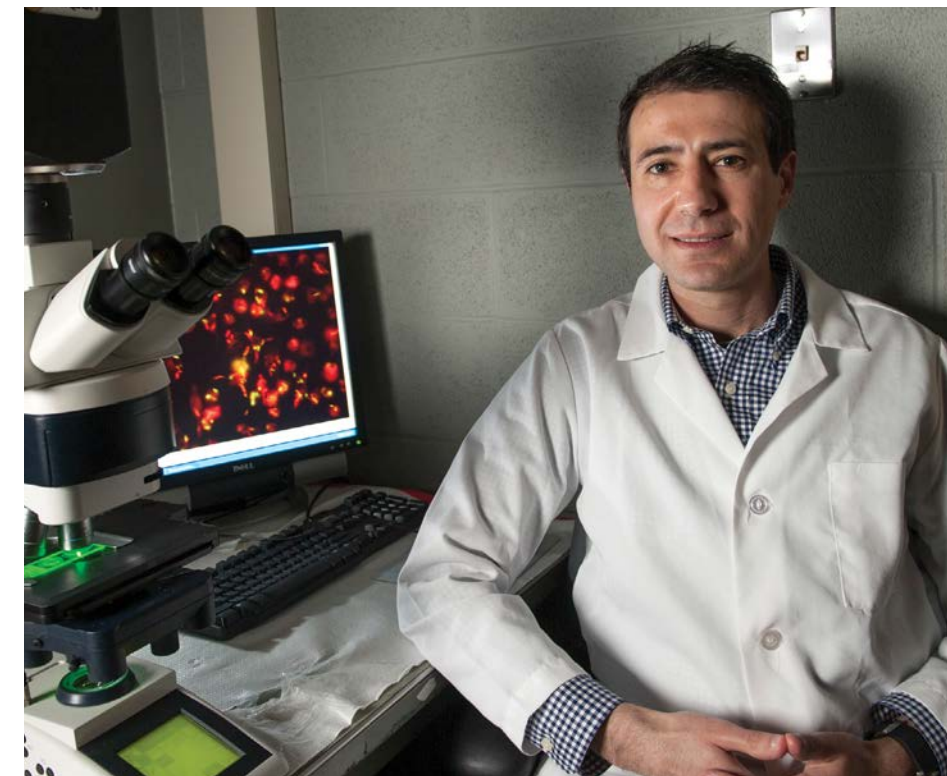
“Inhibiting the ability of the bacteria to establish dormancy may shorten the course of antibiotic treatment, thus eliminating the disease more quickly and reducing the emergence of drug-resistant TB,” he explained.

Abramovitch used the assay to screen 273,000 compounds and, after running many validation tests, has identified several compounds that turn off the green signal, are non-toxic to humans and work inside the cells in which TB grows. He and his lab then investigated how each compound targeted a specific pathway in the bacteria.

“That part is really exciting from the scientist’s perspective because it leads you back to basic science,” he explained. “By figuring out how the compounds work, we learn something about the biology of the bacterium we never knew before. It’s a virtuous circle, and the hope is that basic biology will lead to some new ideas for other treatments.”

Abramovitch is now focusing on identifying a lead compound to navigate through the rest of the development process. Because drug discovery is prone to failure, Abramovitch said it is not uncommon to choose one lead compound and prepare one or two other alternatives.

Because drug discovery is prone to failure, Abramovitch said it is not uncommon to choose one lead compound and prepare one or two other alternatives.



LEFT: Robert Abramovitch, MSU assistant professor of microbiology and molecular genetics, is working to develop new antibiotics to treat tuberculosis, which has only seen one drug treatment option in the last 40 years. Abramovitch stresses the important role basic biological discoveries play in the process of developing new antibiotics.

“Any sort of drug discovery operation is high-risk, high-reward,” he concluded. “There has been one new drug approved for TB in the past 40 years — it’s a field littered with failed projects, but you still have to try. Our goal is to have something come out of the lab, but the joy of the lab is in making basic biological discoveries — that’s the importance of it. You have to be able to find purpose in that process.”

Exploiting weakness

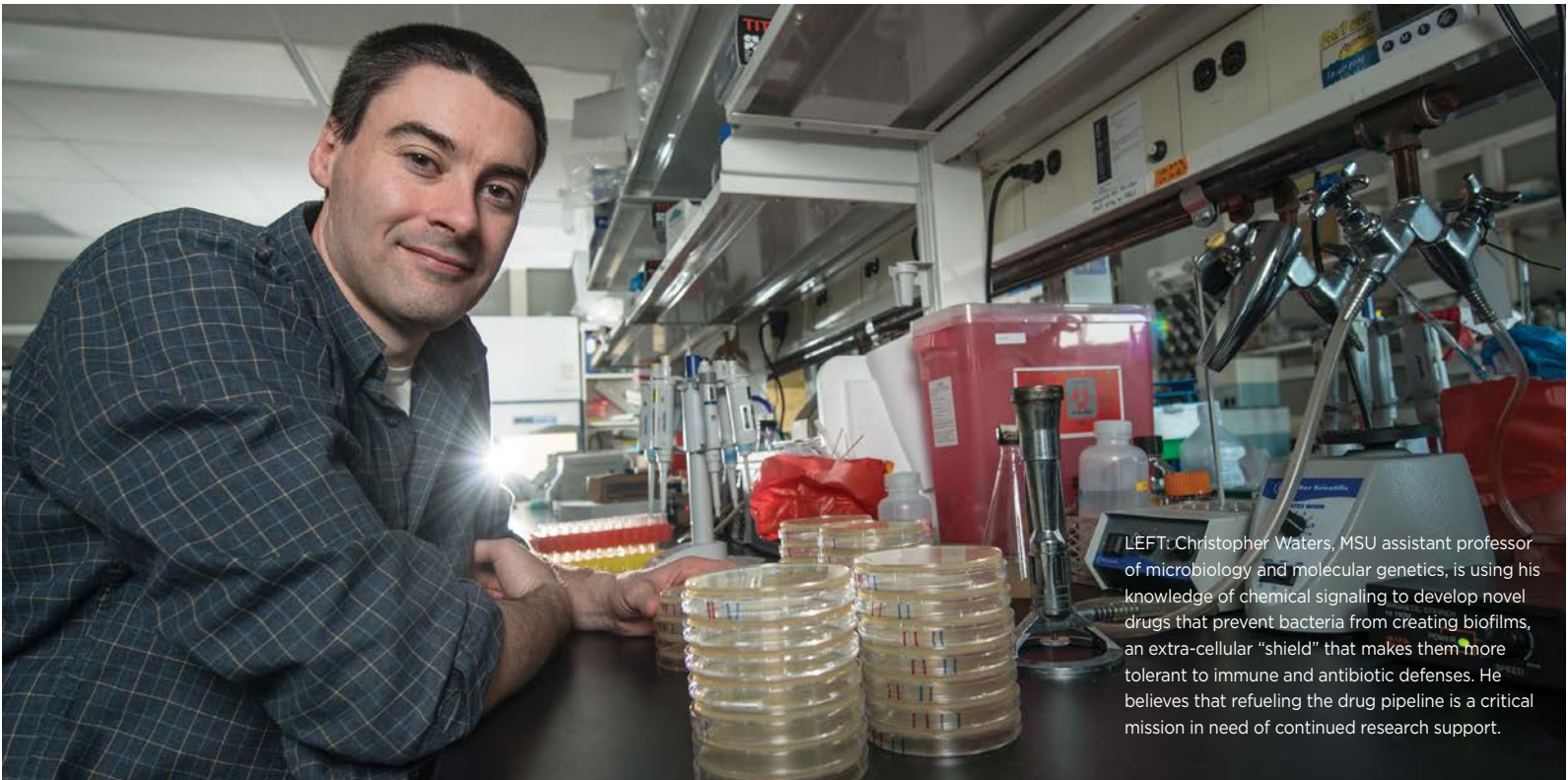
On an 1831 expedition to South America and the South Seas, Charles Darwin formed the basis of his theory of evolution. He hypothesized that natural selection is the mechanism by which evolution occurs: in the competition to survive, individuals within a species adjust to their environment and perpetuate genetic qualities that enable them (and future generations) to survive. Bacteria also experience this pressure to select genetic qualities for survival.

Christopher Waters, MSU assistant professor of microbiology and molecular genetics, has been studying a genetic quality that nearly all bacteria select for: biofilm formation. It is a process in which communities of bacteria attach to a surface and secrete extracellular matrix material. The substance acts as a shield, empowering the bacteria to tolerate a range of environmental stresses including human immune defenses and antibiotic drugs.

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

— Christopher Waters

“Biofilms are a big problem during infection,” he explained. “To bacteria, there’s no distinction between humans and any other environment they’re adapting to. In this particular case, our environment is trying to get rid of them, so if causing



LEFT: Christopher Waters, MSU assistant professor of microbiology and molecular genetics, is using his knowledge of chemical signaling to develop novel drugs that prevent bacteria from creating biofilms, an extra-cellular “shield” that makes them more tolerant to immune and antibiotic defenses. He believes that refueling the drug pipeline is a critical mission in need of continued research support.

disease allows them to stay and spread, then it will be selected for.”

These bacterial communities appear in a variety of chronic inflammatory and infectious diseases, including diabetic foot ulcers, cystitis, endocarditis and infections caused by medical implants. They are also responsible for the pulmonary infections that cystic fibrosis patients endure that ultimately end in lung transplants.

Waters has devoted much of his career to understand the chemical signals bacteria employ as they adapt to changing environments. In the hunt to unravel the role of chemical signaling in infection, he has stumbled upon the Achilles’ heel of biofilms — and he plans to take advantage of it.

He explained that chemical signaling is imperative to synchronizing the activities of large groups of cells. Bacteria rely on a process called “quorum sensing,” which enables them to monitor their environment for other bacteria through self-generated messenger molecules. When enough bacteria are present and concentrations of these messenger molecules reach a certain level, the bacteria begin to behave

collectively rather than as individual cells.

“In many species of bacteria, biofilms are controlled by quorum-sensing,” Waters said. “As a postdoctoral scholar, I started studying how quorum sensing impacts biofilm formation and found that one way it works is through a messenger molecule called ‘cyclic di-GMP.’ This appears to be a key in bacteria switching between the biofilm state and a planktonic (or motile) state.”

When bacteria are in an unattached, roving state, they are more likely to be susceptible to natural immune defenses and antibiotics.

“If we can tip the balance away from the biofilm to the planktonic state, we have a way to treat infection,” he explained.

In 2009, Waters screened 66,000 compounds and identified seven that inhibited cyclic di-GMP synthesis.

“This was the first time that cyclic di-GMP inhibitors had been described,” he said. “Now, we’re working to optimize the compounds so they more effectively inhibit cyclic di-GMP production. We’re also trying to determine if they have any efficacy in animal disease models — that’s

the big hurdle to getting [pharmaceutical] companies excited about your compounds.”

Waters is also searching for compounds that increase the effectiveness of antibiotics against biofilms.

“If you treat a biofilm infection with antibiotics, you might kill 95 percent of the cells — so it works, but it doesn’t kill everything because some of the cells in the biofilm are in a dormant state,” he explained. “These cells are not targeted well by antibiotics, so we’re also trying to find compounds that work with antibiotics to kill any remaining cells.”

Waters has developed an assay and screened 6,000 compounds in an initial screen to identify this second class of compounds. He plans to follow up on the promising hits from the screen.

When asked about the possibility of reverting to a pre-antibiotic era, Waters said he thinks of a time when amputation was often the only way to survive an infection.

“That isn’t too far off [from where we are today] if we lose the ability to treat infections with antibiotics,” he concluded.



Pharmaceutical compounds ready for inclusion in a second-round, high-throughput screen. Researchers routinely employ high-throughput screens to sift through thousands of drug-like compounds in large batches, enabling them to quickly identify those with promising biological or biochemical activity. These screens play a foundational role in the drug-discovery process.

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

Leveraging favorable traits

Staving off the loss of antibiotic effectiveness will require a systems-based effort from medicinal, agricultural, governmental and public health leaders — the pressures of evolution are far too great for a solution to come from a single source. The pharmaceutical industry and research universities will play equally important roles in this endeavor. The antibiotic drug pipeline is drying up at an alarming rate because of the high costs and large investment of time involved in developing new drugs, and extremely high failure rates.

Despite these obstacles, some large pharmaceutical companies have remained committed to the process. Others are slowly making their way back to it, and

small private and non-profit groups are actively pursuing prospective treatments. Still, many wonder if more can’t be done.

With a strong tradition of embracing risk and the ability to garner extramural funding, researchers such as those at MSU are ideal candidates to jumpstart the flow of this drying drug pipeline.

“Academics don’t necessarily start with the idea that they’re going to cure disease,” Neubig concluded. “They come from a place of innate curiosity: they want to understand a process or biological function. They may not be able to predict the therapeutic indications of their results, but they are well positioned to take their findings and move forward. The practical application of basic discoveries often only becomes obvious in time.”

For more information:

On Neubig’s efforts,
visit phmtx.msu.edu.

On Abramovitch’s progress,
visit mmg.msu.edu/abramovitch.

On Waters’ research,
visit msu.edu/~watersc3.

THE GOOD AND THE BAD:

Reconceptualizing bacteria and their roles in human health and disease

BY NATASHA BERRYMAN
Writer

Much of the Western world appears on a mission to keep bacteria at bay. The increased use of antibacterial soaps and cleaning solutions has resulted in a billion-dollar industry that encourages consumers to destroy the microscopic foes inhabiting homes and workspaces to prevent the spread of illness and disease. What often goes unmentioned is the fact that the human body is home to roughly 100 trillion microbes living on the skin and in the mouth, nose and intestines — and not all of them are bad.

For decades, scientists have been well aware of these microbial communities, which assist in many vital physiological processes ranging from digestion to synthesizing vitamins. Collectively termed the “microbiota,” these communities include all of the microorganisms — bacteria, fungi and viruses — that reside in or on the human body.

Over the past 10 years, several labs have discovered evidence that suggests that long-term changes in the microbiota can increase susceptibility to infections and chronic disease. Some believe antibiotics are a key source of this change because they do not discriminate between beneficial bacteria and the disease-causing bacteria they’re meant to target. Scientists across the United States are exploring the microbiota and the millions of genes associated with them (referred to as the “microbiome”). Some are specifically focused on understanding the consequences of disrupting or depleting these microbial communities.

To assist the National Institutes of Health (NIH) with insights about the microbiome, **Linda Mansfield**, Michigan State University (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.

A double-edged sword

During the 20th century, antibiotics completely changed how infectious diseases were treated and helped raise life expectancy in the industrialized world by more than 55 percent. When used properly, they are generally safe and effective, and can be lifesaving. The Centers for Disease Control and Prevention (CDC) reports, however, that frequently these drugs are prescribed incorrectly — and to the detriment of people around the globe.

According to the CDC, studies show that up to 50 percent of all the antibiotics prescribed for people are unnecessary or are not optimally effective as prescribed. They report that 30 percent of antibiotics received by hospitalized adult patients are unnecessary, and 58 percent of all antibiotics prescribed in 2007 were for children with acute viral respiratory infections — illnesses antibiotics cannot cure.

Mansfield said that these practices and the

misuse of antibiotics in other industries, such as to promote the growth of food animals (see related story on page 8), have resulted in the evolution of infectious bacteria that demonstrate resistance to every antibiotic currently on the market. Additionally, each time an individual takes an antibiotic, he or she is exposed to the drug side effects. The most common are allergic reactions, adverse drug reactions and potentially deadly bouts of diarrhea caused by the bacterium *Clostridium difficile* (*C. difficile*).

“Antibiotic treatments can predispose people to being susceptible to certain pathogens; *C. difficile* is one of them,” Mansfield explained. “There are functions of the microbiota that help ward off pathogens and prevent infections. Certain antibiotics can deplete microbial communities and, we hypothesize, remove some of the healthy, defensive bacteria.”

When antibiotics kill beneficial bacteria, disease-causing bacteria such as *C. difficile* can go unchecked. It colonizes the gastrointestinal tract and releases toxins that cause inflammation in the large intestine, resulting in diarrhea, fever, abdominal cramps and, in some cases, death.

C. difficile is the most common cause of antibiotic-associated diarrhea; it is also the most common cause of hospital-acquired infections. Once infected, a number of patients experience recurring *C. difficile* infections, enduring as many as 25 bouts in a year. The most effective therapy for breaking the cycle of these recurring infections is a fecal transplant, which involves transferring stool from a healthy, usually related, donor into the infected individual’s gastrointestinal tract.

“You are basically resistant to *C. difficile* until you receive antibiotics,” she said. “My colleague, **Robert Britton**, has been researching this pathogen as part of our work with the MSU Enterics Research Investigational Network [ERIN] and is working to [develop a platform for the delivery of biotherapeutics].”

Mansfield, a professor in the MSU College of Veterinary Medicine with a joint appointment in the Department of Microbiology and Molecular Genetics,

is the principal investigator in ERIN. She collaborates with two co-principal investigators: Britton, MSU AgBioResearch microbiologist, and **Shannon Manning**, MSU AgBioResearch molecular epidemiologist. Together, the three study the gastrointestinal microbiome and how food-borne pathogens affect it. NIH funds this multidisciplinary research in support of its Human Microbiome Project.

Just as evidence points to a relationship between antibiotic exposure and *C. difficile* susceptibility, there is a link between antibiotic exposure and the development of Guillain-Barré Syndrome (GBS), an autoimmune disease that attacks nerve cells.

“We’re working on another pathogen that has the same kind of presentation as *C. difficile*: *Campylobacter jejuni*,” she said. “This is a very common pathogen that is usually derived from chicken meat. We have evidence that susceptibility is influenced by antibiotic treatment.”

Past antibiotic drug treatments are not the only trigger of the disease, but they have become the most common.

Campylobacter jejuni (*C. jejuni*) is part of a family of drug-resistant bacteria characterized by the CDC as a serious threat to global health. There are approximately 1.3 million *Campylobacter*



ABOVE: Linda Mansfield, MSU professor in the college of Veterinary Medicine and the department of Microbiology and Molecular Genetics, is exploring several facets of the bacterium *Campylobacter jejuni*’s disease-causing abilities. One project focuses on better understanding the role antibiotics play in increasing human susceptibility to the pathogen.

OPPOSITE PAGE: An electron microscopy of *Campylobacter*, courtesy of the Centers for Disease Control and Prevention (CDC).



Exercising Antibiotic Safety

Complete the full course of the drug.

Unless otherwise noted by a medical professional, it's important to take all of the medication in the intervals prescribed.



Prevent infections.

Employ hand hygiene and food safety practices, and get the recommended vaccines.



Safely discard any leftover antibiotics once the prescribed course is completed.



You might think that you can save an antibiotic for the next time you get sick, but an antibiotic is meant for your particular infection at the time.

Only take antibiotics prescribed for you.

Do not share antibiotics with others or take antibiotics that were not prescribed to you.

Talk with your healthcare professional.

Antibiotics have side effects and are not always warranted. Engage in dialogue with your healthcare provider to determine the best course of treatment for you.

Graphic by Marian Reiter, ANR Communications.

infections in the United States each year, resulting in 13,000 hospitalizations and 120 deaths. Understanding the disease mechanisms and their relation to the human microbiome has become increasingly important as the number of infections has risen and the link to GBS has become clear.

Mansfield is determined to further that understanding.

A matter of life and limb

As part of their work with ERIN, Mansfield and Manning set out to identify the root of the high incidence of diarrheal infections in Michigan. Manning hypothesized that the food-borne pathogen *Enterohaemorrhagic Escherichia coli* (EHEC) was to blame, but together they found that *C. jejuni* was the primary culprit.

C. jejuni infections are the most common cause of bacterial gastroenteritis in Michigan and are most often acquired when people consume raw or

undercooked poultry, unpasteurized milk or contaminated water. Like *C. difficile*, *C. jejuni* colonizes the gastrointestinal tract and causes intestinal inflammation resulting in vomiting and diarrhea, and, for some, the long-term complications associated with GBS.

"People start out with a *C. jejuni* infection and recover from the gastrointestinal disease; some then begin to feel a progressive tingling in their hands and feet — this is the GBS," she said. "It tends to ascend, starting in the nerves in the legs and then moving upward toward the chest, eventually leading to paralysis in some."

She explained that a percentage of patients experience paralysis only in their limbs; in others, the paralysis advances until they can no longer breathe on their own, forcing reliance on an iron lung or respirator for support.

"It's a very frightening disease for people because they never know if they're going to get better," she explained. "The good

news is that many people do get better, but others are left with permanent disabilities."

C. jejuni initiates the disease because some components of its surface coat look like human nerves. When this happens, the immune system is tricked into producing antibodies that attack and damage the peripheral nervous system.

Mansfield and her research team were the first to use a mouse model to show that *C. jejuni* employs this molecular mimicry. Their goal was to learn more about the factors that facilitate the intestinal inflammation and destructive autoimmune response caused by the bacterium.

"In our mouse models, we found that significant changes occurred in the genes that were controlling *C. jejuni*'s surface coat during infection," she said. "When genes are replicated, they can slip a little bit, so the matching isn't always perfect. When this occurs, it changes the reading frame of the gene, affecting which genes are expressed and which ones aren't. We think that's one

of the mechanisms involved in altering *C. jejuni*'s surface coat so that it can make the molecular mimicry [that leads to] GBS."

She also uncovered a second important insight about *C. jejuni*: the bacterium can evolve inside its host in real time.

It's widely understood that pathogens adapt to their environment by changing the genes they express through the evolutionary processes of mutation and selection, which preserve favorable genetic changes that help organisms survive. However, very little is known about how bacteria adapt during infection.

She and her lab made progress in exploring this area of microbiology by demonstrating that *C. jejuni* rapidly changes from one heritable genetic state to another in its host.

"The results of the study tell us that it will be difficult to develop a vaccine to protect against a bug like *Campylobacter jejuni*, so traditional vaccine strategies are probably not useful," she explained. "This could explain why so many vaccines that have been developed for this bacterium in humans and animals have not worked."

Additionally, this finding warns researchers and healthcare professionals that each time someone is infected, *C. jejuni* changes, increasing the odds that it might change in such a way as to stimulate an autoimmune response.

"We want to prevent people from becoming infected because there will always be some who will have adverse immune reactions," she concluded. "Currently, the only form of treatment is plasmapheresis, which involves 'cleaning' the blood — but it works for only a small number of patients. Because there's no other cure, in aggressive cases of GBS, treatment becomes a matter of giving patients the breathing support they need until they recover or pass away. There is a desperate need for a cure."

A part to play

Scientists believe that humans are born essentially bacteria-free and spend the first three years of life acquiring the vast communities of microbes that will be their constant companions, changing and

growing along with their host. Research suggests that these commensal communities have evolved with humans over thousands of years and are essential to survival.

In light of this understanding and all of the new findings produced through research efforts across the nation, people are urged to be mindful of their tiny allies. Despite the persuasive messaging heard in the media, some bacteria are good for humans, and taking small precautions such as employing basic hand hygiene and good food safety practices, and exercising antibiotic safety (see opposite page) will go a long way toward protection.

Mansfield points out that, though there is still much to be done in the agricultural and medical industries, consumers have more control over their exposure to potentially harmful bacteria — and ultimately the direction of their long-term health — than they might realize. Many health-threatening diarrheal infections are the result of food-borne pathogens. As a veterinarian, Mansfield is as equally invested in reducing the risk of food-sourced pathogen exposure as she is in understanding their pathological mechanisms.

"It's so important to know where your food comes from and to take simple steps — such as keeping meat separate from greens, cooking food thoroughly and washing produce before it's eaten — that provide another level of important protection fully within our control," she concluded. "It's enlightening to know how much risk you can eliminate by performing these simple practices."

There is much to be learned about the microbial communities residing in and on the human body, but one thing is clear: in the face of the daunting issue of antibiotic resistance and all of the complications surrounding it, even the small steps — and life forms — have a significant impact. 🌱

For more information on Linda Mansfield's research, visit mmg.msu.edu/mansfield.

For more information about the MSU Enterics Research Investigational Network, visit mmg.msu.edu/erin.



ANTIBIOTICS: facts and stats >>

> Adverse drug reactions to antibiotics account for almost 1 out of 5 emergency department visits.

Source: Centers for Disease Control and Prevention and Prevention

> Antibiotics are the most common cause of emergency department visits for adverse drug events in children under 18 years of age.

Source: Centers for Disease Control and Prevention and Prevention

> In 2011, 7.7 million pounds of antibiotics were sold to treat ill people in the United States

Source: IMS Health Inc.

> The human body contains trillions of microorganisms, outnumbering human cells 10 to 1.

Source: National Institutes of Health

> The human microbiome contributes an estimated 8 million unique protein-coding genes responsible for human survival.

Source: National Institutes of Health, Human Microbiome Project

> *Campylobacter* causes approximately 1.3 million infections, 13,000 hospitalizations and 120 deaths each year in the United States.

Source: Centers for Disease Control and Prevention and Prevention

> About 1 in 6 (or 48 million) people get sick each year from contaminated food.

Source: Centers for Disease Control and Prevention and Prevention



THE DRIVING FORCE

Stephen Boyd, University Distinguished Professor of plant, soil and microbial sciences, works with a clay mineral sample in an instrument called an x-ray diffractometer, which measures very small distances between layers of clay. The instrument provides molecular scale information on the structure of crystalline materials and helps to determine the extent of soil contamination. It was purchased with funding from MSU AgBioResearch.

Technological innovations accelerate environmental antibiotic resistance research

BY JANE L. DEPRIEST
Writer

The evolution of antibiotic resistance and its impact on the environment is highly complex, and understanding it requires extensive time and energy. But thanks to modern-day advances in technology, some parts of the process move at what comparatively seems like lightning speed. High-capacity tools for sequencing whole genomes, including those in nature, along with analytical methods for the enormous amount of data produced have significantly accelerated the rate of the research.

James Tiedje is the director of the MSU Center for Microbial Ecology, which was founded 25 years ago as one of the first National Science Foundation Science and Technology Centers in the United States. Work at the center focuses on the

competitiveness, diversity and function of microorganisms in their natural and managed habitats. Tiedje said the benefits acquired through technology have helped to improve scientists' understanding of microbes and how they affect their surroundings.

"The information gained through these technologies is allowing insight into the microbial world around us — in soil, water and even air — that was previously unimaginable," said Tiedje, an MSU AgBioResearch scientist.

One of the latest breakthroughs is the ability to detect hundreds of genes at a time, rather than just one or two as in the past. This technology has been particularly helpful for Tiedje and other researchers

who are working to determine the extent to which antibiotic use in agriculture may be contributing to the growing antibiotic resistance problem in pathogens.

Though technological advances have helped to expedite research on antibiotic resistance, researchers say that working collaboratively is critical as well.

"Collaborations allow researchers to do things that, alone, none of us could have done," said MSU AgBioResearch environmental and soil scientist **Stephen A. Boyd**. "The results can be obtained and examined from several viewpoints — experimental, spectroscopic, computational and analytical — instead of relying on a single method or area of expertise. In the end, the results from all these sources must all be consistent, which makes the conclusions far more convincing."

Databases and advanced screening technologies target ARGs

Today, much of the research at the MSU Center for Microbial Ecology is focused on the microbiome — communities of microbes that are nearly everywhere, including those living with larger organisms such as plants and humans.

"These studies have led to a new field of ecological genomics with two components: the high-capacity technologies and devices that provide the data about biological systems, and the gene databases and computational analysis tools to make sense of the huge amounts of data generated," explained Tiedje, a University Distinguished Professor in the Department of Plant, Soil and Microbial Sciences.

As an example of this work, Tiedje and a multidisciplinary MSU and Chinese research team used a new high-capacity DNA technology and a sophisticated database to determine the levels of antibiotic-resistant genes — ARGs — on commercial pig farms in China. ARGs reduce the ability of antibiotics to fend off diseases in humans and animals and can reach the general population through food crops, drinking water and interactions with

farm workers (see diagram on page 7).

The database for the foundation of the work was developed by **Robert Stedtfeld** and **Syed Hashsham**, both from the MSU Department of Civil and Environmental Engineering, in collaboration with Benli Chai and James Cole, bioinformatics specialists in the Center for Microbial Ecology.

"In some cases, these antibiotic-resistant genes can be highly mobile, meaning they can be transferred to other bacteria, some of which could cause illnesses in humans."

— James Tiedje

"By going through DNA databases in public references and looking at other research done on antibiotic resistance, we developed an extensive database for ARGs," Stedtfeld explained. "Then we designed primers, which are pieces of DNA sequence specific to each targeted gene. These primers aid in the detection of specific genes present in the sample being tested."

The database with the primers is one of the most comprehensive for detecting ARGs.

Manure, compost and soil samples from the Chinese pig farms were screened by a high-throughput tool used for sensitive detection of hundreds of genetic signatures in multiple samples simultaneously. These capabilities are available commercially in technologies from WaferGen (SmartChip) and Life Technologies (OpenArray), both life science companies offering genomic solutions.

"The capabilities of tools offered by WaferGen and Life Technologies are advanced techniques for performing thousands of screening reactions in parallel, revealing gene presence and abundance," Stedtfeld said.

Testing by Tiedje and his research groups has been with laboratory instruments, but researchers are working to put the most

important genes from the database on a hand-held analyzer that can be used in the field.

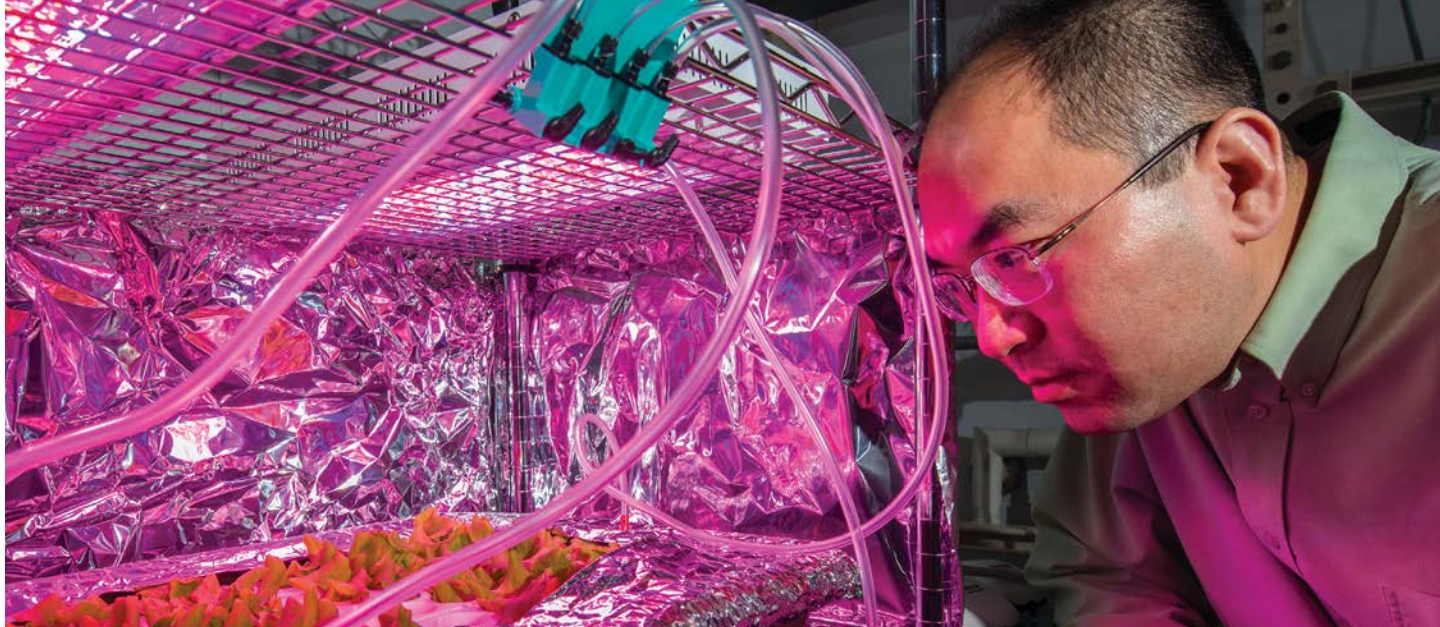
"The continuing developments of these kinds of technologies can help us to better track genes of interest in the environment," Tiedje said. "They also can help us learn more about the critical points for intervention to minimize the growing problem of multiple-drug-resistant pathogens."

Tiedje also worked on a controlled study with collaborators at the National Animal Disease Laboratory in Ames, Iowa. The findings showed that antibiotics used as growth promoters in feed increased the number of ARGs in the gastrointestinal tract of pigs compared with those found in littermates not fed antibiotics.

"Daily exposure to antibiotics allows microbes carrying ARGs to thrive," Tiedje explained. "In some cases, these antibiotic-resistant genes can be highly mobile, meaning they can be transferred to other bacteria, some of which could cause illnesses in humans. That's a growing concern because the infections those bacteria cause can no longer be treated with antibiotics."

Laboratory instruments and techniques fuel research on contaminants in soils

Soil and surface waters are other important areas of ARG investigation. MSU AgBioResearch soil chemist **Hui Li** in collaboration with Boyd and **Brian Teppen**, an MSU AgBioResearch scientist, researches soil contaminants, including antibiotics. A key instrument in this work is a liquid chromatograph with tandem mass spectrometers (LC-MS/MS), which gives specific analytical information and has a higher throughput analysis than gas chromatography, another laboratory technique for the separation of mixtures. The LC-MS/MS, purchased with funds from MSU AgBioResearch and other sources for Li's lab, helps to identify antibiotics and many other pharmaceuticals in the environment and measure their quantities in water and soil.



“With the LC-MS/MS we are able to get the big picture,” said Li, an associate professor of plant, soil and microbial sciences. “We can bring samples back to the lab and do extractions to measure the antibiotics in soil and water.”

Li has focused on emerging organic contaminants in soil and water, especially identifying and measuring antibiotics in the environment. Tetracyclines, broad-spectrum antibiotics used in the treatment of numerous infections and also in animal feeding operations, are the focus of much of his research.

“If tetracyclines get into the soil or water, they can exert selective pressure on native bacterial populations, which can cause the development of antibiotic resistance in bacteria,” Li said. “However, our research has shown that if there is more calcium or magnesium in the water, the antibiotic response is much lower than in water without these minerals. This could reduce the bioavailability and hence selective pressure of tetracyclines.”

Bioavailability describes the degree and rate at which a substance from an environmental matrix is absorbed into a living system and is a key factor linking environmental exposure with the development of ARGs.

Other factors affecting bioavailability are environmental conditions, such as wet, dry or moist soils.

“Tetracyclines become more bioavailable to bacteria particularly in moist conditions,” Li said. “In soil that is moist but not watery,

tetracyclines become highly bioavailable. If tetracyclines are bound to soil particles suspended in water, however, they will not become bioavailable.”

Those that are more available to bacteria would be expected to exert more selective pressure, he added.

Li notes that antibiotic resistance has always existed in the environment and that bacteria will pick up resistant genes, if needed.

“If you have selective pressure from chemicals or other antibiotics, exposed bacteria will self-protect. They will grab resistant genes into their bodies, and they can transfer these genes to other bacteria. All of that adds to the environmental sources of antibiotic resistance.”

Li agrees with Boyd that, in addition to innovative tools and equipment, collaborations are an important part of the work.

“For me as a soil chemist, I don’t know much about microbiology, for example,” Li said. “By working with researchers in other fields, such as James Tiedje, we can obtain more information that can spur our own research.”

Using geosorbents to sequester contaminants in soils

New molecular tools that allow researchers to measure the proliferation of ARGs in soil have helped to advance the work of Boyd, an MSU University Distinguished Professor of Plant, Soil and Microbial Sciences. His research focuses specifically on the environmental fate and effects of organic

contaminants and pesticides in soil.

“We can use engineered bacteria as very sensitive detectors of pharmaceuticals such as tetracyclines, and we don’t have to work in really clean systems, as once was the case. That has been a big step forward,” Boyd explained. “On the analytical side, the LC-MS/MS has enabled us to work with more complex mixtures and detect them at lower concentrations, which is important in dealing with pharmaceuticals.”

His research, which began in the 1980s, has recently expanded to include pharmaceuticals in the soil.

“Pharmaceuticals — everything from codeine to tetracyclines to antidepressants — are showing up in the environment, especially when you look at surface water,” Boyd said.

Pharmaceuticals in soil and water are considered emerging contaminants because they are not highly regulated.

“For example, there are no drinking water standards or tolerances for them in soils,” Boyd explained, “but industrial organic compounds and pesticides are regulated to limit their occurrence in soils and groundwater.”

In collaboration with Li and Teppen, 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.

“The basic idea is what we call sorbent amendments,” Boyd explained. “We want

to see if contaminant molecules that are sequestered by geosorbents in soils and sediments display reduced bioavailability to a target organism, whether a bacterium or a human being. Does a molecule have to escape from the geosorbent before it can enter the cells of bacteria, plants or humans? Those are the kinds of basic questions we are trying to answer because they have big practical implications.”

The geosorbents that Boyd and his collaborators are most interested in are chars — in essence, burnt pieces of plant material. Some char occurs naturally in soils from fires, but it can be produced as a byproduct in biofuels production. They also are attractive as geosorbents because they are an effective way of sequestering carbon. In addition, chars can be beneficial to soil productivity in terms of crop growth.

“The bottom line is to use chars or some other sorbent amendment to reduce the bioavailability of chemicals that occur as contaminants in soils and sediments,” Boyd said. “This reduces risks associated with these contaminants and may let us safely relax cleanup criteria. This might allow, for example, more contaminated sites to be remediated using the limited funds available.”

Modeling the chemical speciation of antibiotics

Any given antibiotic in the environment can take many chemical forms at the same time. For example, some are attached to dissolved compounds in the water, and

some are attached to soil particles. Teppen tries to understand this complexity.

“We call it chemical speciation,” said Teppen, a professor of plant, soil and microbial sciences. “We use computational tools to try to model the complex distribution of antibiotics among all their forms.”

First, experimental data is collected under a variety of controlled conditions.

“Then we use chemical models to help extract all the information we can from the data. One goal is to understand exactly which chemical forms of a given antibiotic induce resistance in the bacteria,” Teppen explained. “Perhaps then we would be able to suggest management schemes that would minimize the antibiotic-resistance selection pressure in fields where manures are applied.”

There are no easy answers

Even with ongoing advances in technology and equipment that aid ARG research, solutions are not easy. Li and other researchers working on antibiotic resistance issues believe that antibiotics in animal feeding operations have to be better managed and controlled.

“But, at the same time, we need to develop effective treatment procedures to reduce the effect of antibiotics in the environment,” Li explained. “For example, we need more advanced treatments in the animal waste facilities to deal with antibiotics and their resistance genes (ARGs), 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.”

For Tiedje, the ultimate goal is to minimize the rate of development of multidrug-resistant pathogens. Research using new technologies can identify points of intervention where new or altered practices reduce this risk.

“It is extremely difficult to find new antimicrobial drugs, so we must protect the effectiveness of the ones we have for as long as we can,” Tiedje said. “One principle has been not to use antibiotics important in human use on animals.”

The idea is that, if resistance developed in microbes for these animal drugs, it would not affect the effectiveness of the human drugs.

“Our research, however, consistently shows that that principle is not sound because of co-selection,” Tiedje explained. “In other words, the development of antibiotic resistance to one drug also results in resistance to other drugs, including ones important for human use. This is because the resistance genes have become linked on the same piece of DNA and are transferred together to new microbes. When that recipient of the transfer is a human pathogen, a multidrug-resistant pathogen is born.” 📌



OPPOSITE PAGE: Hui Lee, associate professor of plant, soil and microbial sciences, checks on an experiment involving how lettuce takes up antibiotics from water as part of his research on emerging organic contaminants in soil and water, especially identifying and measuring antibiotics.

LEFT: James Tiedje, University Distinguished Professor of plant, soil and microbial sciences, examines manure compost on an MSU farm. Compost is a means to recycle nutrients and, if managed properly, can also reduce the amount of antibiotic resistant genes returned to the field and hence to human food and water.

worldwide, particularly in wet, humid climates such as Michigan, where a fire blight epidemic in 2000 killed 400,000 apple trees and caused \$42 million in damages.

MSU AgBioResearch plant pathologist and Extension specialist **George Sundin**, who has been studying fire blight for 12 years, has guided the Michigan fruit industry on treatment options. He said well-timed sprays of antibiotics are the most effective and economical means of preventing the bacterial disease. Their use in plant agriculture is regulated by the U.S. Environmental Protection Agency (EPA), which requires growers to keep detailed spray records. Despite governmental regulation, the issue is controversial and complex, and consequently ripe for public speculation and misinformation.

“There is no question that some people are potentially not happy about the use of antibiotics in plant agriculture,” Sundin said. “But that’s in large part because they really don’t know much about it. For example, growers apply antibiotics only when disease models indicate a high likelihood of infection. Otherwise, they don’t spray because it would be economically unwise.”

In general, the industry contends that the use of antibiotics in plant agriculture — which amounts to 0.5 percent of all antibiotic use — is extremely low and, therefore, not a significant factor in the antibiotic resistance equation. The bulk of agricultural antibiotic use is in livestock production. Sundin, who spoke last fall at the National Institute of Animal Agriculture symposium “Bridging the Gap between Animal Health and Human Medicine,” explained that the use of antibiotics in plants is markedly different from their use in humans or in animals.

“First, there are a lot of similar bacteria that colonize animals and people,” Sundin explained. “There are even pathogens that occur in animals that can be passed on to people. Also, some animals are given similar antibiotics that people are prescribed, which I believe increases the potential for the transfer of medically important antibiotic resistance genes that

can find their way into the human bacterial population.”

The fact that bacteria found in plants are typically different from those in humans and animals decreases the potential impact on resistance in human pathogens.

“Overall in the plant system, the amount and kinds of resistance genes are much lower than in animals or people,” Sundin explained. “And critical human antibiotics are not used in the plant systems. So, first, I think that helps us because we don’t have these resistance genes to begin with. Second, the bacteria are quite different for the most part. You do find *E. coli* associated with plants and *Salmonella* with incidents of food poisoning, but their levels of association are relatively low. Those bacteria can contaminate plants, but they generally don’t grow on them well.”

The most effective treatment options

It wasn’t long after antibiotics began curing victims of fatal diseases that plant pathologists recognized the potential for treatment of plant diseases. During the 1950s, some 40 antibiotics of bacterial or fungal origin were screened for plant disease control. Low toxicity to the plant and effectiveness in small doses made them appealing to farmers, who had been primarily reliant on metal-based bactericides.

Today, apple and pear growers in the United States primarily utilize three antibiotics — two of which are used in human medicine — for fire blight control:

▮ **Streptomycin** – Discovered in 1944, it was primarily used in human medicine for the treatment of tuberculosis. Because of severe side effects, however, its current use in humans is minimal. It has been used for crop protection in the United States since 1955 and today is the most used antibiotic in plant agriculture.

▮ **Oxytetracycline** – Discovered in 1950, it is a broad-spectrum antibiotic used in human medicine to treat some bacterial infections of the eye, genitals and chest,

to name a few. It is also used to treat some diseases and infection in cattle, poultry and fish (aquaculture). Its use in plant agriculture started in the 1970s after reports of streptomycin-resistant *E. amylovora* in the western United States.

▮ **Kasugamycin** – Discovered in 1965 in the soil of Japan and found to inhibit growth of a fungus causing rice blast disease, this naturally occurring antibiotic used only in agriculture requires a special use permit in the United States from the EPA. It has been used in Michigan for the past five years. It is registered for agricultural use in Canada. It has no human or animal medical use.

Plant-grade antibiotics are typically formulated as powders consisting of 17 to 20 percent active ingredient. The powders are dissolved or suspended in water and applied as a fine mist to the tree canopies. Because they are relatively expensive, the antibiotics are primarily used on high-value fruit.

Both streptomycin and oxytetracycline have been assigned the lowest toxicity rating by the EPA, and neither has shown carcinogenic or mutagenic activities. Those who handle the antibiotics must wear long sleeves, long pants and waterproof gloves. A mask is required for streptomycin application and protective eyewear for oxytetracycline application.

Resistance of plant pathogens to oxytetracycline is rare, but the emergence of streptomycin-resistant strains has impeded the control of several important plant diseases. A fraction of streptomycin resistance genes in plant-associated bacteria are similar to those isolated from humans, animals and soil. The most common vehicles of streptomycin resistance genes in human and plant pathogens are genetically distinct, however.

“The antibiotics streptomycin and oxytetracycline are older, so the resistance genes for those were spread around the world long ago, probably in the 1950s or 1960s, when they were used in humans,” Sundin said. “Plant pathogens have picked up resistance to streptomycin and have picked up resistance genes just because they’re everywhere now. And in oxytetracycline, there’s really not much

evidence for resistance in plant pathogens.”

Two recent studies from the University of Wisconsin examined the use of streptomycin in apple orchards and the corresponding impact on resistance. The research projects, one of which examined the plant leaves while the other looked at the soil, both concluded there were “factors other than streptomycin exposure” that drove the genetic structure of the bacterial community. Studies on Kasugamycin use in Michigan orchards have had similar findings.

“Basically, what we found in our study in Michigan is very similar to what the University of Wisconsin studies show — that the types of resistance and the amount were similar whether Kasugamycin had been sprayed or not,” Sundin said.

The antibiotic application process in crop agriculture is often scrutinized because the treatment is sprayed in the field before infection actually occurs. A protective barrier must be formed on the plant’s surface to prevent infection of the tree.

“Unlike what happens when we take an antibiotic pill and it circulates throughout our blood system, you can’t spray a plant and have that same effect — the drug going throughout its system,” Sundin said. “Instead, you have to spray the antibiotic on the flower surface while the tree is in bloom. This provides a protective barrier so that, when the bacteria land on the flower, they are killed.”

Searching for workable alternatives

A team of Michigan State University (MSU) researchers led by Sundin is examining alternative organic methods for controlling fire blight. The three-year project is funded by a \$464,000 grant from the U.S. Department of Agriculture (USDA). Researchers will begin a renewed investigation into several biological controls, including a yeast product called Blossom Protect and bactericides made from copper solutions.

Blossom Protect, a biological pesticide, works by introducing highly competitive microorganisms onto the fruit blossom,

which block the pathogen from colonizing. It contains live strains of yeast that are mixed with a citric acid buffer. The citric acid lowers the pH in the blossom, inhibiting the growth of the fire blight bacteria when they enter the blossom.

“We’ve had inconsistent results from Blossom Protect in the past, but our goal now is to study it in greater detail,” Sundin said. “We need to better understand the mechanism of how it colonizes the flowers and controls fire blight, how it competes with the pathogen under different temperature and wetness regimes, and when the right time is to apply it.”

Copper bactericides pose trade-offs for growers. Though they’re effective at controlling fire blight, the sprays can cause blemishes that decrease market value of the fruit. Another potential benefit is that researchers have no reason to believe that copper poses a risk of resistance development.

By systematically looking at these options, Sundin said he is hopeful that he will be able to provide growers with the tools they need to protect their crops.

“Understanding how to optimize the use of organically certified materials for fire blight control is really important,” he said. “These materials may seem weaker than streptomycin simply because we’re not using them correctly.”

While the USDA-funded project will likely have results conventional growers can benefit from, the researchers say helping organic growers, especially in Michigan, is of utmost importance. MSU AgBioResearch entomologist **Matt Grieshop** will assist in the farm experiments and outreach objectives.

“Organic growers are in desperate need of antibiotic alternatives if they are to maintain their organic certification,” Grieshop said. “Without effective, organically compliant fire blight management tactics, organic apple production will be greatly reduced.”

Having the right techniques to ensure healthy crops is one of the best ways to prevent the decline of organic production.

“Michigan gets a lot of disease pressure

because of our climate,” Sundin said. “We need good management tools. That’s something we have for conventional apples but not yet for organics. Organic produce is becoming more and more important to Michigan consumers. There’s no reason for them to have to get their apples from Washington if we can grow them here.”

The research project will conclude in summer 2016. Sundin said he plans to upload videos to <http://www.youtube.com/user/treefruitpathology> as progress is made.

In the meantime, Epstein said he has been asked by colleagues at the USDA National Organic Program to help expedite registration of some of these newer materials for organic use in light of the NOSB regulation. He said speeding up the process may bring little comfort to growers faced with losing tried and tested control materials for reasons they believe are unscientifically substantiated.

“For a grower who perceives the elimination of materials as being based on perception rather than reality, it’s certainly a bitter pill to swallow,” he said. 🍏



Antibiotic use on plants >>

w Less than 0.5 percent of the total production of antibiotics*

w Controls plant disease; more than 90 percent is for fire blight in apple, pear and related ornamental plants, and bacterial spot on peach**

w Two classes of compounds approved: streptomycin and oxytetracycline**

Sources:
*National Agriculture Statistics Service
**American Phytopathological Society

MICHIGAN ASPARAGUS FACTS

- w Nationwide, Michigan ranks second along with Washington (the two states are tied!) in asparagus production behind only California.
- w The vegetable is produced primarily on 150 farms in Oceana, Mason and Van Buren counties.
- w The crop has an annual estimated value of \$17 million.
- w In 2013, Michigan produced 18 million pounds of asparagus — 8 million pounds were sold fresh, and 10 million pounds were used for processed products.
- w Asparagus is a nutrient-dense food that is high in folic acid and is a good source of potassium, fiber, and vitamins B-6, A and C, and thiamin. It has no fat or cholesterol and is low in sodium.
- w Asparagus spears grow from a crown that is planted about a foot deep in sandy soil. Each crown will send spears up for six to seven weeks during the spring and early summer.
- w A well-cared for asparagus plant will generally produce for about 15 years without being replanted.

For more information visit the Michigan Asparagus Advisory Board at michiganasparagus.org.

Asparagus Frittata

This omelet cooks in the oven and makes a tasty supper or brunch.



Asparagus Frittata

- 2 tablespoons Italian dressing
- 2/3 cup sliced fresh mushrooms
- 1/3 cup chopped red bell pepper
- ¾ pound fresh Michigan asparagus, trimmed and cut into ½-inch pieces or
- 1 (14.5-ounce) can Michigan asparagus cuts and tips, drained
- 8 eggs
- ¼ cup milk
- ¾ cup shredded provolone or cheddar cheese, divided
- ¼ cup freshly grated Parmesan cheese

Heat dressing in a large ovenproof skillet over medium heat. Add mushrooms and red pepper. Cook and stir 5 minutes. Add asparagus. Beat eggs, milk and ½ cup provolone cheese in a medium bowl. Pour over vegetable mixture in skillet. If handle of skillet is not ovenproof, wrap it in foil.

Bake in a preheated 350-degree oven 20 minutes or until eggs are almost set. Remove from oven and sprinkle with remaining cheeses. Bake 5 minutes or until cheese is melted on top. Cut into wedges to serve.

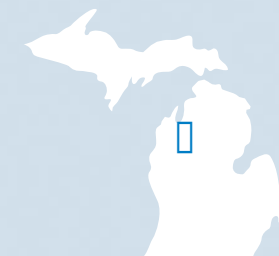
Makes 4 servings.

Recipe and photo courtesy of Michigan Asparagus Advisory Board.



Lake City Research Center

This center, with 810 acres of managed land and 180 beef cows, supports research on forage and beef production systems that are holistic, sustainable and profitable. Cattle and calves are the fifth leading commodity in the state in cash receipts, generating \$480 million in 2012. The center also is a leader in seed potato production research, with more than 60,000 seedlings grown and evaluated each year. Michigan ranks sixth in the nation in potato production value and is the No. 1 producer of potatoes for potato chips in the country. The center is focused on knowledge-based problem solving to bring about — with the assistance of industry partners and the community — practical, commonsense solutions to agricultural sustainability. 🌱



**5401 W. Jennings Rd.
Lake City, MI 49651
Phone: 231-839-4608
Farm manager: Douglas Carmichael**

Established 1928



Watch our new videos: agbioresearch.msu.edu/centers/lakecity_infovideos



Michigan ranks sixth in the nation in potato production value and is the No. 1 producer of potatoes for potato chips in the country.

MSU AgBioResearch supports a network of campus laboratories and 13 off-campus research centers that provide more than 300 scientists the opportunity to focus their research and outreach activities on the agricultural and natural resource needs of particular regions of the state. The off-campus centers range in location from Chatham in the Upper Peninsula to Benton Harbor in southwestern Michigan. Each is dedicated to high-quality science and innovation that benefit the state and its citizens.

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Talking shop with **THE PRESIDENT**

President Barack Obama visited the campus of Michigan State University in February to sign the Farm Bill into law. Before the high-profile event, three MSU AgBioResearch scientists: **C. Robin Buell** (center photo far right), **Bruce Dale** (bottom right) and **Dave**

Douches (center photo far left), had the opportunity to give the President an update on their work in their respective fields of genomics, alternative energy and plant breeding. **Doug Buhler** (upper right), director of AgBioResearch and senior associate dean of research for the College of Agriculture and Natural Resources, also talked with the President during the private tour conducted at MBI. "It was an honor and a privilege to host the President of the United States and to showcase some of the work of our world-class researchers. Opportunities like this are rare so we decided to make the most of it," Buhler said.

Photos courtesy of The White House.



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