White Paper

Bridging the Gap between Animal Health and Human Health

Information synthesized from Nov. 12-14, 2013, symposium in Kansas City, Mo.: “Bridging the Gap between Animal Health and Human Health”

DISCLAIMER: The information provided in this White Paper is strictly the perspectives and opinions of individual speakers and results of discussions at the 2013 “Bridging the Gap between Animal Health and Human Health” symposium.

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BACKGROUND

The symposium *Bridging the Gap between Animal Health and Human Health* was developed by the National Institute for Animal Agriculture (NIAA) and conducted November 12-14, 2013, in Kansas City, Mo. The symposium was a continuation of discussions and sharing of information that commenced with the October 26-27, 2011, *Antibiotic Use in Food Animals: A Dialogue for a Common Purpose* symposium conducted in Chicago, Ill., and *A One Health Approach to Antimicrobial Use & Resistance: A Dialogue for a Common Purpose* symposium conducted November 13-15, 2012, in Columbus, Ohio.

NIAA is a non-profit, membership-driven organization that unites and advances animal agriculture: the aquatic, beef, dairy, equine, goat, poultry, sheep and swine industries. NIAA is dedicated to furthering programs working toward the eradication of diseases that pose risk to the health of animals, wildlife and humans; promote the efficient production of a safe and wholesome food supply for our nation and abroad; and promote best practices in environmental stewardship, animal health and well-being.

The 2013 symposium was funded in part by the Beef Checkoff, Our Soy Checkoff, Missouri Farmers Care, *DairyBusiness*, *Bovine Veterinarian*, *Dairy Herd Management*, *Drovers*/*CattleNetwork*, *PorkNetwork,* Merck Animal Health, Pork Checkoff, U.S. Department of Agriculture - Veterinary Services, Bayer, Missouri Farm Bureau, Elanco, Dairy Farmers of America, *BEEF* magazine, *BEEFVet*, Midwest Dairy Association and Shook, Hardy & Bacon.

PURPOSE AND DESIGN OF THE SYMPOSIUM

The symposium provided a platform where animal health and human health scientists and other experts interacted , shared the most current science-based information as well as their professional insights and created an environment to learn from each other. Adding further dimension to the symposium were presentations by a consumer advocacy organization, grocery retailers, staff members and selected media representing agriculture and consumer advocates.

The goals of the 2013 symposium were the same as the 2012 symposium[1]:

- To lead and engage participants in an open conversation.
- To build relationship within animal, human, and environmental health and gain a better understanding of other perspectives.
- To find common ground and formulate a path forward.
- To focus on continuous improvement and commitment to long-term health.

Symposium Planning Committee Co-Chairs

Nevil Speer, PhD, Western Kentucky University

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Planning Committee Members

Dr. Richard Raymond, MD, Private Consultant and former USDA Undersecretary for Food Safety

Dr. Jennifer Koeman, DVM, MSc, MPH, DACVPM, Director, Producer and Public Health, National Pork Board

Ms. Kathy Talkington, MPAff, Senior Director, Immunization & Infectious Disease Association of State and Health Officials

Mr. Abraham Kulungara, Director, Environmental Health Association of State and Health Officials

SYMPOSIUM TOPICS AND SPEAKERS (in order given at the symposium)

Moderator—Dr. Richard Raymond, MD, Consultant and former USDA Undersecretary for Food Safety

"Recap of Antibiotic Symposia in Chicago, Ill., 2011, and Columbus, Ohio, 2012"—Dr. Leah Dorman, DVM, Senior Director of Animal & Food Policy, Ohio Farm Bureau Federation, NIAA Board of Directors

"Public Health Concerns about Resistant Foodborne Infections"—Dr. Robert Tauxe, MD, Deputy Director, Division of Foodborne, Waterborne and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention

"Public Health Impact of Antibiotic Resistance"—Dr. Steven L. Solomon, MD, Director of the Office of Antimicrobial Resistance, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Office of Infectious Diseases, Centers for Disease Control and Prevention

"Antibiotic Resistance: What Can We Do?"—Dr. Terry L. Dwelle, MD, State Health Officer, North Dakota Department of Health

"Evidence-Based Policy Development in Public Health"—Dr. Paul Halverson, PhD, Indiana University Richard M. Fairbanks School of Public Health

"Livestock-associated *Staphylococcus aureus*: Recent Trends"—Dr. Paul Fey, Professor and Medical Director of Clinical Microbiology Laboratory, University of Nebraska Medical Center

"Where Are We With Resistance in Vet Medicine? Are We Having An Effect on Human Medicine?"—Dr. Mike Apley, DVM, Kansas State University College of Veterinary Medicine, Department of Production Medicine/Clinical Pharmacology

"Antibiotic Residue Testing in Meat and Poultry, Bridging the Gap to Protect Human Health"—Captain David P. Goldman, MD, MPH, Chief Medical Officer, USPHS Office of Public Health Science, Food Safety and Inspection Service

"FDA Center for Veterinary Medicine Activities Regarding Antimicrobial Resistance and Food-Producing Animals"—Dr. Craig A. Lewis, DVM, Veterinary Medical Officer, U.S. Food and Drug Administration Center for Veterinary Medicine

"USDA Initiatives and Data on Antimicrobial Drug Use and Resistance on Livestock Facilities"—Dr. David A. Dargatz, DVM, PhD, Epidemiologist, USDA: APHIS Center for Epidemiology and Animal Health

"Did This Come from That? Antibiotic Resistance and the Science behind 'Knowing the Unknowable'"—Panel moderated by Dr. Mike Apley. Panel members: Dr. H. Morgan Scott, DVM, PhD, Professor, Epidemiology, College of Veterinary Medicine, Kansas State University, and Dr. Guy Loneragan, BVSc, MS, PhD, Professor of Food Safety and Public Health, Texas Tech University

"Antibiotics Used in Animals Raised for Food"—Dr. Richard Raymond, MD, Consultant and former USDA Undersecretary for Food Safety

"Consumer Perceptions—Superbugs in Our Food Supply"—Susan Vaughn Grooters, MPH, Food Safety Research & Policy, Center for Science in the Public Interest

"What do People Really Think about Their Food"?—Dr. Joe Cardador, PhD, Chief Research Officer for Service Management Group

“Consumer and Food: Perceptions, Realities and Steps towards Instilling Confidence”—Mrs. Leann Saunders, Director of Where Food Comes From and President of IMI Global Inc. and Mr. Tom Heinen, Heinen’s Fine Foods

“Consumers and Antibiotics”—Kathleen O'Donnell, Chief Food Scientist, Wegmans Food Markets

“Seeking Credibility with Consumers in a Confusing Marketplace”—Dr. John Stika, PhD, President, Certified Angus Beef LLC

“Managing Conflict: Engaging Media on Controversial Topics”—Mr. Andy Vance, Staff Editor, *Feedstuffs* magazine, and Ms. Katy Keiffer, producer and host of "What Doesn't Kill You: Food Insights," HeritageRadioNetwork.org

EXECUTIVE SUMMARY

The 20 presentations delivered by antibiotic use and resistance experts representing animal health, human health and public health; a consumer advocacy organization; grocery retailers; staff members; and selected media representing agriculture and consumer advocates resulted in a robust dialogue and exchange of information.

The following points were among those brought forth during the Symposium by the speakers and participants:

1. The science behind the emergence, amplification, persistence and transfer of antibiotic resistance is highly complex and open to interpretation—and sometimes misinterpretation—from a wide variety of perspectives and misuse. If you think you understand antimicrobial resistance, it hasn't been explained properly to you.[2]
2. The extremely complex relationship between animal health, human health and environmental health is driven by two premises: 1) Antimicrobial resistance is a naturally occurring phenomenon that is present with or without the use of antimicrobials; and 2) Anytime an antibiotic enters the ecosystem, it has the potential to contribute to the development of antibiotic resistance.[3]
3. Antibiotic resistance is not just transferred from animals to humans; resistance is also transferred from humans to animals.[4]
4. Antimicrobial resistance occurs not only in food-production animals and in humans but in companion animals as well.[5]
5. Antibiotic resistance is not just a U.S. challenge; it's an international issue that requires a strategic global One Health approach.[6]
6. Evaluating antimicrobial resistance involves balancing risks vs. needs while constantly recognizing the importance of maintaining an efficacious arsenal of human antibiotics.
7. New tools that address food animal infectious diseases must be developed, whether they are in the field of prevention or new molecules for therapeutics.[7]
8. Although food-borne illnesses are down 29 percent in the last decade, media hits on food-borne illness have increased 150 percent during the same time frame.[8]
9. No antibiotic is guaranteed to kill 100 percent of the pathogens causing an illness.[9]
10. The great majority of antibiotic classes used in human and animal health have very little or no overlap. The two classes with a higher level of overlap are the sulfas and macrolides.[10]
11. Research studies and findings are often viewed through different lenses. Individuals can look at the same study and interpret the study very differently from each other based on their understanding of the science as well as their values and beliefs.[11]

12. Decisions and policy should be grounded in science, and policy should be based on science. The question, however, is who decides what should be considered when making those decisions and policies. For effective interventions to complex problems, the solutions should be developed by a broad representation of relevant stakeholders and their sometimes-competing perspectives and values.[12]
13. Significant efforts are being led by the public health community to reduce inappropriate antibiotic prescribing in human health and reduce hospital-acquired infections. Agriculture needs to be open to change as well.
14. Change will happen. Open dialogue must continue, with animal agriculture at the table or change will be drastic and by statute and will not be a deliberative policy change.[13]
15. Food animal production should enforce current regulations and address any antibiotic misuse or be prepared for an unfavorable outcome.[14]
16. Solving antibiotic resistance requires collaboration and raises the question, "How does human health, environmental health and animal health work together to address antibiotic use and resistance?".

PRESENTATION HIGHLIGHTS

Antibiotics

By strictest definition, only 75 percent of antimicrobials used against microorganisms are antibiotics. The rest are synthetic compounds.[15]

No antibiotic is guaranteed to kill 100 percent of pathogens causing illness. Over time, in the presence of antibiotics, bacteria are capable of developing resistance. The full mechanism of how resistance develops and is subsequently transferred is not totally understood.[16]

Consumer Concerns and Perceptions

Today's consumers want to know where their food comes from and how that food was raised.[17] In their search for information, consumers are hearing and reading about overuse of antibiotics in food animal production and are concerned.[18] The antibiotics issue is further complicated by the fact that today's average consumer is disconnected from agriculture and is at least three generations removed from the farm or ranch.[19]

While consumers can obtain certain information from product labels, a majority of consumers outside of agriculture rely on the media and the Internet for their product information, and misinformation or incomplete information is quite common within media stories and online.[20] One example of erroneous and polarizing information that the media frequently quotes stems from Congresswoman Louise Slaughter (D-NY)[21] who claims that "over 80 percent of all antibiotics sold in the United States are given to perfectly healthy animals raised for food."[22] Rep. Slaughter misinterpreted information and completely ignored that a large percentage of the antibiotics used to treat and prevent illness in animals are ionophores, compounds not used in human medicine.[23]

A 2013 consumer perception study independently conducted by Service Management Group (SMG) to better understand consumer perceptions around important issues in food production involved close to 2,000 consumers of all ages and income levels from all 50 states shopping at all grocery retailers. In this study, 54 percent of consumers indicated that knowing whether animals received antibiotics was important or very important to them when purchasing meat and 52 percent responded that it was important or very important to know if the animals that produced their dairy or egg products were given antibiotics. Nearly two-thirds of the shoppers surveyed were much more concerned or more concerned about the safety and impact of antibiotics now than in the past.[24]

When consumers participating in a survey conducted by Wegman's Foods were asked about most important food attributes, 65 percent indicated "For meat—Contains no antibiotics, no hormones and no animal by-products in. . ."[25]

Antibiotics are a type of antimicrobial, but not all antimicrobials are antibiotics. This paper uses the word "antibiotics" when information was presented specifically about antibiotics and uses the word "antimicrobial" when information presented referred specifically to antimicrobials.

Four in 10 consumers have lost trust in food.[26] A certain subset of consumers believe that animal agriculture puts profits before people and that animal agriculture is compromising human health by using antibiotics for other than treating sick animals.[27]

The Center for Science in the Public Interest (CSPI), a consumer advocacy organization, is a proponent of strong U.S. food safety laws and actively petitions the government for action, comments on federal food regulations and conducts collaborative work. CSPI has taken the position that antibiotics are overused in livestock production and that antibiotics are losing their effectiveness due in part to overuse in food-animal production. The group believes that, to preserve effective human antibiotics, subtherapeutic use of antibiotics in food animal production must be banned. The group encourages animal agriculture to voluntarily lessen antibiotic use or contend that a law will be passed to curtail such activity.[28]

CSPI has concerns regarding the April 11, 2013, FDA issued guidelines intended to curb non-therapeutic use of antibiotics in food animal production. Key concerns are that the guidances do not outline how FDA will monitor the effectiveness of the guidelines and do not clearly outline what uses are considered sub-therapeutic.[29]

While ranchers and farmers may be well intentioned when it comes to using antibiotics, not every rancher and farmer is 100 percent compliant. To that end, an increasing number of retailers are seeking third-party verification of product to ensure suppliers are doing what is expected.[30] If food-animal producers do not do what's best for the customer, then consumers will quit buying protein. They will turn to alternatives such as fish, seafood, pasta and other non-meat sources.[31] The last time the beef industry made the consumer sit in the back seat, a two-decade decline in beef market share occurred.[32]

A growing number of consumers are seeking full disclosure on antibiotic use: quantity used, type of antibiotic used, what species receives what antibiotic, how the antibiotic is administered, etc. Consumer activist and advocacy groups do not want food-animal production to whitewash the antibiotic issue by using "disease prevention" in exchange for "growth promotion." The bottom line is that there must be transparency at all levels.[33]

Animal well-being is a top priority for most people. While consumers agree that failing to treat sick animals would be inhumane, consumer activists and advocates are concerned about antibiotic use terminology, including the term "judicious use," and are confused regarding how antibiotic resistant microbes are passed through the food chain. Activist and advocacy groups would like food-animal production to act aggressively to find and use alternatives so reliance on antibiotics can be reduced. Suggested alternative practices include use of vaccines, probiotics, improved housing and sanitation.[34]

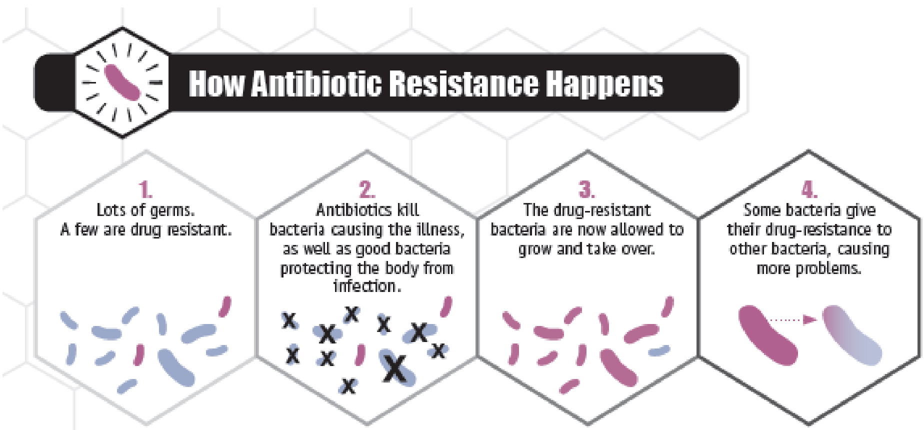
Because food purchases are often emotional purchases[35] and science lacks the emotional connection with consumers, communicating and earning the trust of the consumers involves more than presenting consumers with science-based facts. Those in food-animal production must be transparent and real. They must think about the words they use, the audience/person they are talking to, the knowledge level of their audience and know that consumers are people like themselves. Imagery is important to food production discussion.[36]

Non-rural consumers and those involved in food-animal production have more in common than what might appear at first blush. The solution to bridging the credibility gap and building trust starts with transparency,[37] being real, choosing words carefully, changing the way issues are viewed and moving away from the mindset of "You think you're right, and I know that I'm right."[38]

Antibiotic Resistance

Antimicrobial treatments have been critical in human and veterinary medicine for more than 60 years, and antimicrobial resistance has been a challenge for almost as long.[39] Antibiotic resistance is a naturally occurring process in bacterial populations and is the single most complex problem in public health.[40] The introduction of every new class of antimicrobial drug has been followed by emergence of resistance to that class of antibiotics.[41]

Selection for resistance occurs as antibiotics kill off all susceptible bacteria, with the surviving bacteria being resistant. Bacteria have had more than three billion years to develop the mechanism that leads to resistance.[42]

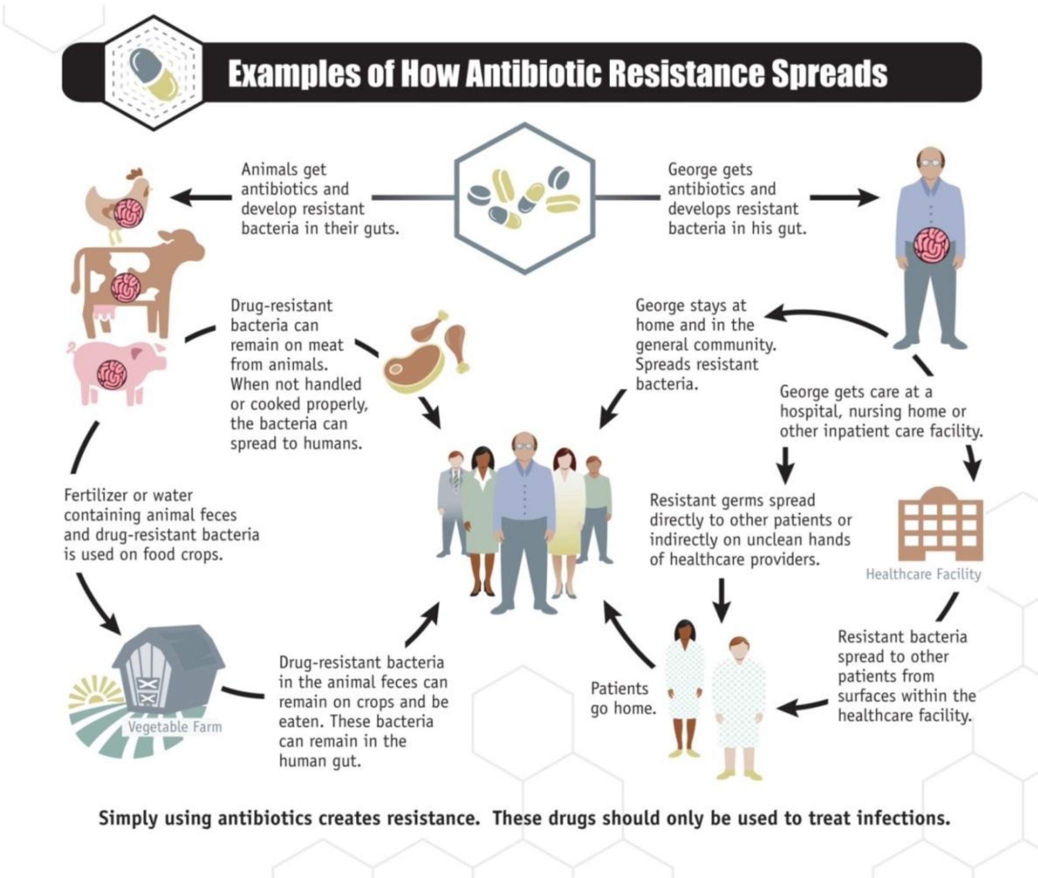


[43]

The use of antibiotics in animal production can develop populations of resistant pathogens that can cause adverse health effects to humans.[44] The logic of what might connect antibiotic use in animals with human health involves several steps: 1) Use of antibiotics in food-producing animals selects for antibiotic-resistant bacteria—including ones pathogenic to humans; 2) Resistant bacteria can be transmitted to humans from food-producing animals through the food supply; 3) Resistant bacterial pathogens can cause illness in humans; and 4) Infections caused by resistant bacteria can result in adverse health consequences for humans.[45]

Resistant strains are of particular concern for several reasons: 1) Treatment choices may be limited; 2) Resistant infections cause increased morbidity and mortality; 3) When resistance is located on a mobile genetic element, it may be transferred to other bacteria horizontally;[46] 4) Resistant strains have a selective advantage in individuals who are taking an antimicrobial for other reasons; 5) If the individual takes an antibiotic, colonization with a resistant pathogen can result and lead to a clinical antibiotic-resistant infection and disease.[47]

The following diagram, while greatly oversimplistic,[48] represents a schematic view of the pathways of resistance transfer[49]:



Some of the organisms that have caused concern due to the development of resistance over the past few decades include *Streptococccus neumoniae*, *Moraxella atarrhalis*, *Hemophilus influenza* Type B, *Stretococucs pryogenes*, *Escherichia coli*, *Neiseria meningitidis*, *Campylobacter*, *Salmonella*, *Shigella*, *Staphylococcus aureus*, *Enterococcus*, *Mycobacterium tuberculosis* and *Pertussis*.[50] Reasons cited for decreased susceptibility to certain drugs include inappropriate antimicrobial prescribing within the human health community and food-animal applications.[51]

Resistance can also be picked up while individuals are living and/or traveling in other countries. A case in point is decreased susceptibility to ciprofloxacin to treat non-typhoidal Salmonella, where most resistant infections have been found to be travel related. Not only is there a difference globally in the presence of antibiotic resistant bacteria but some countries have more widespread use of antibiotics.[52]

Staphylococcus aureus is a pathogen known to create a wide range of infections. The mortality rate for *S. aureus* infections in the early 1900s was approximately 80 percent, with certain strains being 100 percent fatal. By the 1950s, penicillin-resistant *S. aureus* were a major threat in hospitals and nurseries. By the 1970s, methicillin-resistant *S. aureus* (MRSA) had emerged and spread—a phenomenon that encouraged widespread use of vancoymycin. In the 1990s, vancomycin-resistant *enterococci* emerged and rapidly spread, with most of these organisms resistant to other traditional first-line antimicrobial drugs. By the end of the century, the first *S. aureus* strains with reduced susceptibility to vanomycin were documented, prompting concerns that *S. aureus* fully resistant to vancomycin may be on the horizon. In June 2002, the first case of vancomycin-resistant *S. aureus* was detected.[53]

For four decades, MRSA was only acquired in hospital settings. Beginning around 2000, MRSA became recognized as being community acquired. From 2005 to 2008, hospital-acquired MRSA declined 28 percent, and community-acquired MRSA dropped 17 percent during the same time period.[54] *(Post Symposium update: A report appearing in JAMA Internal Medicine, November 25, 2013, Volume 173, No. 21 compared 2005 to 2011 and noted that the United States has experienced a 54 percent drop in hospital-acquired MRSA,a 27.75 percent drop in health care-associated, community-onset-acquired MRSA and a 5 percent drop in community-acquired MRSA. In 2011, there were 80,461 cases of invasive MRSA in the United States. Of these, 48,353 were health care-associated, community-onset cases; 14,156 hospital-acquired cases; and 16,560 community-acquired cases with no links to healthcare establishments.*)

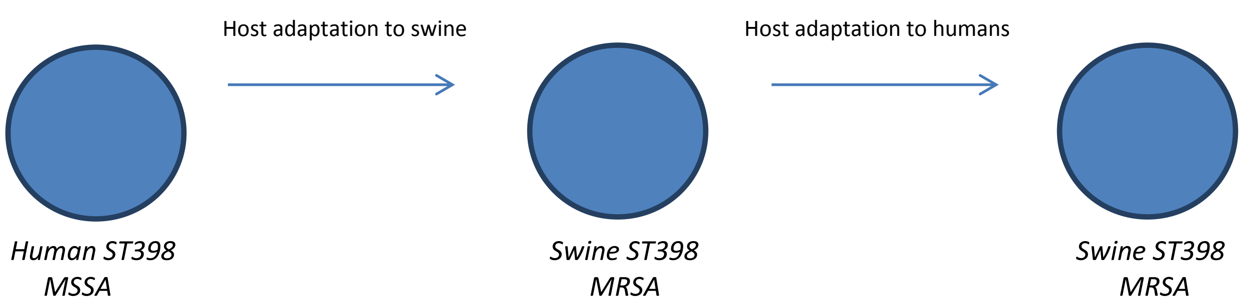
In addition to being resistant to methicillin, methicillin-resistant *S. aureus* is resistant to all β-lactam antibiotics such as cephalosporins, penicillin and carbapenems. β-lactam products bind to the enzymes in the cell wall and an antibiotic does not allow the cell wall to grow.[55]

The most prominent *S. aureus* lineage isolated in the United States is USA 300 CA-MRSA. This pathogen is not restricted to community as it has been isolated from hospital environments and from companion animals.[56]

Termed the "superbug" by the media, livestock-associated MRSA is associated with sheep, goats, poultry, rabbits, cows and swine. Population biology suggests that *S. aureus* evolved with humans and were transferred to food animals. [57] No one in the United States, however, has ever been known to become ill with livestock-acquired MRSA.[58]

Due to the rapid exchange of mobile genetic information, strains can evolve rapidly to colonize new hosts including humans. One example of a MRSA is ST398—which is widespread in the Netherlands, Europe and Asia—which colonized from humans to animals to humans. After passing from humans to swine, ST398 developed a methicillin resistance. Once transferred back to humans, the strain is developing new virulence factors.[59]

STS398 Population Biology[60]



One of the newest “superbugs” is Vancomycin Resistant *Staphylococcal aureus* (VRSA). The FDA has determined that this new “superbug” is not due to the overuse or misuse in animal or human health as some suggest. The “why” VRSA has developed is baffling as Vancomycin is only used for life-threatening infections and is always administered under the direct guidance of a health care professional.[61]

An FDA report indicates that multidrug resistant *Salmonella* (MDS) is increasing, and some individuals have voiced concern. The February 2013 NARM’S report shows that, for retail chicken and ground turkey, the four most common antibiotics that *Salmonella* showed resistance to were tetracycline, streptomycin, sulfisoxazole and penicillin. None of these four drugs would be used to treat *Salmonella* infection as macrolides, trimethoprim-sulfisoxazole and quinolones are the first-line antibiotics for food-borne illnesses and are still effective treatments.[62]

A 2013 Centers for Disease Control and Prevention (CDC) report estimates the minimum number of illnesses and deaths caused annually by antibiotic resistance at 2,049,442 illnesses and 23,000 deaths.[63]

The CDC’s “Antibiotic Resistance Threats in the United States, 2013” report focused on 18 pathogens of which four are often transmitted by food. Two of the four often-transmitted-by-food pathogens are animal reservoirs—*Campylobacter* and non-typhoidal *Salmonella*—and two are human reservoirs—*Salmonella* serotype Typhi and *Shigella*.[64] *Campylobacter* is showing resistance to ciprofloxacin and azithromycin. Non-typhoidal *Salmonella* is showing resistance to ceftriaxone and ciprofloxacin as well as multiple classes of drugs. *Salmonella* serotype Typhi is showing resistance to ceftriaxone, azithromycin and ciprofloxacin with resistance to ciprofloxacin rising from 20 percent in 1999 to more than 70 percent in 2011. *Shigella* is resistant to ciprofloxacin and is showing resistance to ciprofloxacin and azithromycin.[65]

The accompanying chart shows the percent of resistance to principal agents used for treatment of the pathogens *Campylobacter* and non-typhoidal *Salmonella*—and two are human reservoirs—*Salmonella* serotype Typhi and *Shigella:*

Pathogen	**Percent Resistant**	**No. of Illnesses/Year**	**No. of Deaths/Year**
Campylobacter	24%	310,000	28
Non-typhoidal *Salmonella*	8%	100,000	38
Salmonella serotype Typhi	67%	3,800	<5
Shigella	6%	27,000	<5

A 2008 study of the microbiological characterization of non-typhoidal *Salmonella* strains from food animals, retail meat and people shows the bacteria strains had decreased susceptibility to the antibiotic ceftriaxone-ceftiofur as well as substantial overlap in the strains across sources, the presence of same CMY gene in all three sources and the same CMY gene in several serotypes. The CMY2 gene for ceftiofur-ceftriaxone (Cft/Cx) resistance was first described on a plasmid that easily transferred between *Salmonella* and *E. coli*.[66] The CMY2 gene confers its resistance to third-generation cephalosporins.[67]

The CDC's "Antibiotic Resistance Threats in the United States, 2013" report identifies three threat levels regarding human disease risks: 1) Urgent; 2) Serious; and 3) Concerning.[68]

Research shows that antibiotics create a selection pressure that favors less susceptible—and sometimes resistant—bacteria. Stronger selection pressure also comes from higher concentrations and times.[69]

A look at several scientific papers published in the past three years regarding various bacteria and antibiotic resistance illustrates that science can be viewed through different lenses. Cause and effect can be argued by the authors and others from different perspectives. While some scientists and advocates may claim that a study is not valid—perhaps because it doesn't have a control group, those on the other end of the spectrum may insist that the study is valid. One person can look at a study and interpret results and what the study infers in one light while a second person interprets the data differently. Provocative titles, even in professional journals, gain attention but may be overstating research findings. Discussions show that individuals can examine the same scientific paper and come to different conclusions, with individuals making a value decision rather than a scientific-based decision. In addition, while some assumptions made from scientific papers are reasonable, they are still just assumptions.[70]

A one-size-fits-all model for antimicrobial resistance doesn't encompass the complexity of the issue, and simple models fail to capture the entirety of the issue. Emergence, amplification, persistence and the transfer of antibiotic resistance is highly complex. If a person thinks he or she understands antimicrobial resistance, it hasn't been explained properly.[71]

The debate over the amounts of antibiotics sold or used is diversionary and should not be the main issue in the public health debate about antibiotic resistance.[72] The real issues are the judicious use of antimicrobials and is there a significant impact on human health.[73]

Gaps in the understanding of antibiotic resistance will continue to exist as science continues to evolve.[74] At this point in time, science does not show that the cause of antibiotic resistance lies solely with food-animal production or with the human health or environmental health communities. Antibiotic resistance is a systems issue and requires an all-encompassing approach.[75]

Human Health

"The use of antibiotics is the single most important factor leading to antibiotic resistance around the world. Antibiotics are among the most commonly prescribed drugs used in human medicine. However, up to half of the antibiotic use in humans . . . is unnecessary or inappropriate."[76] Additional research also indicates up to 20 percent of antibiotics in pediatric hospitals and clinics are not adequately prescribed.[77] A 2003 study found that 46 percent of patients with the common cold or non-specific upper respiratory infections received antibiotics, and these are viral diseases for which antibiotics do not work.[78] Despite when a narrower spectrum antibiotic could have been used, patients received broad spectrum antibiotics 54 percent, general; 51 percent, colds; 53 percent sinusitis; 62 percent, acute bronchitis; and 65 percent, otitis media.[79]

Patient pressure impacts the prescription of antibiotics. A study in the Journal of Emerging Infectious Diseases showed that 12 percent of patients had recently taken antibiotics; 27 percent believed taking antibiotics during a cold made them better, 32 percent believed taking antibiotics during a cold prevented more serious illness; 48 percent expected antibiotics when seeking medical care with a cold; and 58 percent were not aware of the health risks of antibiotics.[80]

The frequency at which physicians prescribe antibiotics varies greatly from state to state, and the CDC is investigating the reasons for this variation. The object is to determine areas in the United States where improvements in antibiotics prescribing would have the most impact on the greatest number of people.[81]

The CDC is focused on educating physicians regarding why antibiotics should be prescribed more carefully and the importance of talking to their patients about antibiotics and their use and helping parents understand why giving an antibiotic to their child is not always the answer.[82]

Six simple and smart facts being emphasized to physicians include antibiotics are life-saving drugs; antibiotics only treat bacterial infections; some ear infections do not require an antibiotic; most sore throats do not require an antibiotic; green-colored mucus is not a sign that an antibiotic is needed; and there are potential risks when taking any prescription drug.[83]

Animal Health

Antibiotics are used in food-animal production, and their use has been the subject of scientific and policy debate for decades.[84]

The last new class of antibiotics developed and introduced in 1978. The likelihood of veterinarians and producers having new antibiotic tools that are not a derivative of an early form of antibiotic is extremely slim.[85]

According to an FDA report on all antibiotics sold or distributed in 2011 for food-producing animals, 28.3 percent are ionophores—which are not used in human medicine; 41.5 percent are tetracyclines—which have very limited use in human medicine when many better choices are available; 12 percent NIR (not independently reported category)—most of which are not used in human medicine; 0.2 percent are cephalosporins—which are of critical importance to human medicine and are limited to therapeutic treatment only in animals; and 0.1 percent are flouroquinolones—which are of critical importance to human medicine and are limited to therapeutic treatment only in animals.[86] For swine, 64 percent of the medically important antibiotics are tetracylines, with antibiotics used for growth promotion comprising about 15 percent of the total antibiotics used.[87]

The terms “non-therapeutic” or “sub-therapeutic” are sometimes inappropriately used by groups to describe the use of antimicrobials in animals to promote growth, prevent disease, control disease and to improve feed efficiency. The FDA and the American Veterinary Medical Association do not use these terms as they are incorrect describers of an FDA-approved use and approved dosage for intended results. The question arises whether the inappropriate use of “subtherapeutic” is intended to deceive and paint a negative picture of food-animal production practices.[88]

Because antimicrobial use in food animals can change bacterial population susceptibility profiles that can lead to resistant pathogens and other microbiota that may then be transferred through the food chain or directly transferred to people, the benefits of their use versus their risks must be considered.[89] The use of antimicrobials in food-animal production also requires judicious use, meaning no effective alternative to the antimicrobial is available for the treatment or prevention of disease. In addition, the use of an antimicrobial for therapy or control should not be the permanent solution for an infectious disease challenge and evidence shows that the antimicrobial is safe and effective for its particular use.[90]

From the perspective of food-animal production, antibiotic resistance in the United States has three threat levels: 1) Threats of concern to animal agriculture; 2) Threats that can be attributed to animal agriculture; and 3) What can be done regarding these threats.[91]

At this time, the statement by the U.S. Farmers and Ranchers Alliance that “All antibiotics administered to animals raised for food are given under the direct supervision and direction of a Doctor of Veterinary Medicine”[92] is not accurate.[93] One goal of the veterinary medical community, however, is to turn the current situation around and make the statement true by having veterinarians control all uses of antimicrobials in animals.[94]

A challenge within food-animal production is that information is lacking for many antimicrobial classes regarding optimal duration of therapy and optimal pharmacodynamics for the suppression of resistance development. Another challenge is the availability of additional, more in-depth training and information for veterinarians across all food-animal practices. While veterinary school is a good starting point, post-graduate training is imperative.[95]

Other steps to address judicious use of antibiotics in food-animal production include a close working veterinary-producer partnership, the constant search for alternative management practices to alleviate the need for an antimicrobial and an intolerance of inappropriate activities by veterinary, livestock and poultry producer organizations.[96]

The ability to address infectious disease in food animals is extremely important. As such, policy should not be developed in the name of human health that results in harm to food-animal health—particularly policy that has either no benefit to human health or has a possible detrimental result to human health.[97]

Additional items of importance to food-animal production and veterinary medicine include continual emphasis on the prevention—rather than the treatment—of infectious disease, enforcement of current regulations regarding antibiotic use and the inclusion of data and correct analysis in the decision process.[987]

Regulation of Antibiotic Use in Food-Animal Production

The Federal government has been monitoring bacteria in meat and poultry since the early 1970s. Its National Residue Program (NRP), which partners USDA's Food Safety & Inspection Service (FSIS) with the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) to monitor food-animal products, is the cornerstone program of the USDA and provides a structured process for identifying and evaluating chemical compounds—including approved and unapproved veterinary drugs—of concern in food animals. In addition to inspector programs at slaughter plants, FSIS conducts random sampling to ensure food-animal products are safe, testing for 58 drug residues. Its new multi-residue testing method screens a single sample for multiple compounds.[99]

The NRP uses a three-tiered model. Tier 1 involves scheduled random sampling. Should a violative residue be identified in a sample, additional targeted sampling is conducted (Tier 2). Tier 2 also includes inspector-generated testing of suspect animals. At this point, Tier 3 has not been implemented but would involve targeted flock or herd sampling, testing for violative residues.[100]

In an attempt to increase program transparency for all stakeholders, the FSIS recently published its first quarterly report that provides chemical residue testing results. FSIS will continue to publish its Red Book—annual report of residue results—as well since the Red Book contains information beyond what is in the quarterly reports.[101]

A pilot survey conducted by FSIS in the summer of 2013 of in-plant testing at slaughter facilities shows that 35 percent of establishments have a residue-control program, 20 percent have a residue-testing plan and 10 percent conduct screening tests for residues. Of the plants surveyed, 8 percent experience fewer violative residues due to their residue-testing plan, 6 percent of residue-testing plants implement testing at the livestock unit and 10 percent do not address residues.[102]

The FDA has had a formally established framework in place since 2003 to evaluate the safety of new animal antimicrobials with regard to their microbiological effects on bacteria of human health concerns. Concerns remain regarding products that pre-date the current assessment process. While the FDA does not write the laws regarding food-animal drugs, it does enforce the law through the drugs that it approves.[103]

The FDA's Draft Guidance 209, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals," was published as a draft in June 2010 and finalized April 2012. Two key principles outlined in Guidance 209 are to limit the use of medically important antimicrobial drugs to those uses considered necessary for assuring animal health and to increase veterinary involvement and consultation. Per the guidance, antimicrobials must be available to treat, control and prevent disease in food animals, with growth promotion removed from the equation.[104]

The FDA's Guidance 213 was published as a draft in April 2012 and provides more detailed guidance on implementation of key principles of Guidance 209. The comment period for draft Guidance 213 closed July 12, 2012 and comments have been analyzed. Final Guidance 213—published on December 12, 2013—addresses what is considered medically important, the process for updating product labels, data required to obtain approval of new therapeutic uses for drugs, etc. In addition to the removal of production indications, Guidance 213 recommends changes in the status of certain drugs from over-the-counter to veterinary feed directive (VFD) which requires a written statement that authorizes the farmer to use an FDA-approved drug in livestock feed under their oversight. Guidance 213 provides a three-year timeline for implementing these recommended changes.[105]

At this point in time, during the pre-approval evaluation of human food safety, the FDA's risk versus benefit analysis for target animal safety encompasses risk to the animal versus benefit to the animal, with food animal products having an additional evaluation—human food safety—for which there is only a consideration of risk .[106]

The USDA's National Animal Health Monitoring System (NAHMS) has conducted, and continues to conduct, studies focused on animal health, production, public health and the environment. Certain studies include the collection of antimicrobial use and resistance data from U.S. food-animal production systems. Studies to date reveal that antimicrobials are widely used in livestock and poultry, with product use, level of use and purpose of use varying widely by species. While some data are available to characterize use and resistance, data has limitations. In addition to providing study results to decision-makers, NAHMS leaders have conducted stakeholder workshops to identify gaps. Identified gaps include measures of antimicrobial drug use and resistance, producer management practices and their impacts on antimicrobial resistance, producer knowledge of alternative medical interventions and education, training and outreach. The USDA is crafting a plan that addresses antibiotic resistance, and is prioritizing actions based on stakeholder input. All agencies and stakeholders must be open and transparent with all parties involved, including consumers, and policies must be developed based on science and not on blind emotion.[107]

Solutions to Antibiotic Use and Resistance

Antibiotic resistance can be reversed.[108] A study in Iceland showed that resistance to Penicillin-Resistant *Streptococcus pneumoniae* (PRSP) declined from 20 percent in 1993 to 15 percent in 1995 after an information campaign directed toward physicians was conducted and a regulatory change required that patients pay for prescription drugs.[109] Another resistance reversal study in Finland addressed concerns involving macrolide use tripling in the 1980s followed by erythromycin resistance for Gp A strep rising 17 percent in the early 1990s. After national campaigns for physicians, resistance declined to 9 percent between 1992 and 1996.[110]

The rate of resistance to avoparcin, virginiamycin and avilamycin in *Enterococcus faecium* sampled from Danish broiler chickens fell dramatically in the late 1990s after growth-promotion uses of these drugs were phased out. Drug-resistance rates that had ranged from 60 to 80 percent fell to 5 to 35 percent within a few years.[111] Following the banning of Avoparcin in Europe, vancomycin resistance in humans decreased.[112]

Antimicrobial resistance in food-borne infections is a substantial challenge to human and animal health, and the CDC is addressing the challenge of resistant food-borne infections by promoting prevention, tracking resistance through the National Antimicrobial Resistance Monitoring System, making information available more quickly, refining estimates of the health impact of resistance, making real-time resistance data part of outbreak investigations and refining the understanding of sources and mechanisms of resistance genes and resistant bacterial strains.[113]

Since the emergence of antibiotic resistance cannot ultimately be prevented, the CDC's goal is to slow down the emergence of the spread of resistance to allow for more progress in the development of new antimicrobial drugs. CDC recommends four "core actions" that can greatly reduce the spread of antibiotic resistance: 1) infection prevention and control, including practices ranging from greater attention to washing hands to more widespread use of vaccines to careful food preparation in the home; 2) public health surveillance—the tracking of antibiotic resistance identified by laboratory reports ; 3) improving antibiotic prescribing and use—stewardship; and 4) developing new drugs and diagnostic tests for resistant bacteria.[114] A first step in antibiotic stewardship is promoting antibiotics best practices—ensuring all orders have dose, duration and indications; cultures are obtained before antibiotics are started; and taking an "antibiotic timeout" to reassess the antibiotic choice after 48 to 72 hours.[115] A University of Maryland study showed that an antibiotic stewardship program in one hospital saved a total of $17 million over eight years. In addition, antibiotic stewardship helps improve patient care, lead to better patient outcomes and can shorten hospital stays, thus benefitting patients as well as hospitals.[116]

Additional steps that can be taken to reduce the threat of developing antibiotic resistance include[117]:

- Use antibiotics only when indicated.
- Use the least wide-spectrum antibiotic possible.
- Use antibiotics for the least amount of time possible.
- Use adequate doses.
- When treating livestock, use non-human categories when possible.
- Use cultures to determine resistance patterns.

Policy development has also been shown to influence appropriate use of antibiotics. One study shows that, in the 1980s, appropriate use of advanced spectrum antibiotics was 65 percent. When all advanced spectrum antibiotic orders received a form that required completion within 24 hours and included justification of usage, appropriate use of antibiotics increased to more than 95 percent. The consequence of an adequate response not being received resulted in a consult with the physician or a loss of privileges.[118]

Policy is made quite often to protect public health. For a policy to become implemented, the legislature must pass a law which will become the basis for regulatory change. Once the draft regulation has been presented for consideration, the public comment period begins. It then moves on to the board for final approval, and must be approved by a state's governor.[119]

While policy development may appear to be one answer to addressing antibiotic resistance, no policy development is devoid of politics. Public health by its nature is political, and the political dynamics of the time has the potential to negate some solutions.[120]

Policy development calls for rigorous examination to ensure the science is present. While the development of policy should be science based, science doesn't necessarily speak to consumers. What consumers perceive as accurate can be different than what goes along with good public health. Despite rock-solid science showing one thing, vocal consumers can ask for something different and lead the way to laws being passed that end up harming others. A case in point is the sale of raw milk approved in Arkansas where science showed one thing and vocal advocates of raw milk demanded its sale despite the science.[121]

The development of public policy often requires a trade-off between personal freedom and desired results.[122]

Private policy is typically quicker to develop and implement than public health policy and does not require a change in law but a change in desire. Going the private policy route regarding the use of antibiotics has not been viewed as important to date but it should not be underestimated.[123]

Establishing a collaborative task force comprised of veterinarians, physicians and public health officers is another tactic that could prove highly beneficial to addressing antibiotic resistance.[124]

NEXT STEPS

While the symposium was key in bringing together experts from human medicine and veterinary medicine to discuss the complications of antibiotic resistance from a One Health perspective, the seriousness of antibiotic resistance calls for further dialogue and cooperative efforts to be sustained going forward. Resistance needs to be carefully monitored and better understood, and better incentives are needed to hasten the development of new antibiotics.

Animal agriculture takes its role in this matter seriously, and NIAA will continue to provide leadership within animal agriculture and establish a platform to develop further collaboration whereby antibiotic resistance solutions can be developed from the perspective of science and not simply a political divide between animals and people.

Antibiotic resistance is a comprehensive issue and doesn't derive from any single source. As such, it is best addressed from a systems-based approach that strives to close gaps of misunderstanding and avoid implementing impetuous remedies that may produce meaningless solutions.[125]

CONTACT INFORMATION

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The symposium was funded in part by:

Bayer
Beef Checkoff
BEEF magazine
BEEFVet
Bovine Veterinarian
DairyBusiness
Dairy Farmers of America
Dairy Herd Management
Drovers/CattleNetwork
Elanco
Merck Animal Health
Midwest Dairy Association
Missouri Farm Bureau
Missouri Farmers Care
Our Soy Checkoff
Pork Checkoff
PorkNetwork
U.S. Department of Agriculture, Veterinary Services
Shook, Hardy & Bacon

FOOTNOTES

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