White Paper

Antibiotic Stewardship:
Collaborative Strategy for Animal Agriculture and Human Health

Information synthesized from the National Institute for Animal Agriculture's Symposium, "Antibiotic Stewardship: Collaborative Strategy for Animal Agriculture and Human Health" conducted October 31 – November 2, 2017 in Herndon, VA. Full presentations are available online at www.animalagriculture.org.

DISCLAIMER: The information provided in this White Paper is strictly the perspectives and opinions of individual speakers and discussions at the 2017 Antimicrobial stewardship Symposium

Table of Contents

Background

The symposium, "Antimicrobial stewardship: Collaborative Strategy for Animal Agriculture & Human Health", conducted October 31 – November 2, 2017, in Herndon, VA, was the seventh antimicrobial stewardship symposium hosted by the National Institute of Animal Agriculture (NIAA). The forum brought together producers, retail food industry representatives, veterinarians, representatives of pharmaceutical companies, university researchers, and regulatory animal and human health officials. The goal was to review the successes in the path to antimicrobial stewardship, review current research recommendations and response capabilities, and obtain stakeholder input regarding the advancement and direction of antimicrobial stewardship moving forward.

Over the last decade, antibiotic resistance has increasingly been in the public eye. Multi-drug resistant bacteria are becoming more common. Representatives protecting both animal and human health have been working for years to discover common ground and mutually beneficial solutions, and have been experiencing modest success. This symposium began 7 years ago as animal agriculture talking to animal agriculture, and in the past seven years has grown and expanded to include human physicians, regulatory officials, pharmaceutical companies, retail food providers, and others in the discussion. This group has discovered that more is learned from the sometimes contentious discussions between those with disparate views than from internal discussion, and symposium participants have gone back to their professions every successive year and made steady progress in the fight against antibiotic resistance through multi-agency discussion and collaboration. This symposium provided an opportunity for stakeholders to review our past successes, explore ongoing antibiotic resistance challenges, evaluate current research in antibiotic resistance and stewardship, and discuss how to continue moving forward to more comprehensive antimicrobial stewardship.

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

The NIAA 2017 Symposium on Antibiotic Stewardship was funded in part by the Auburn University Food Systems Institute, the Beef Checkoff, Elanco, FFAR, GlobalVetLINK, Merck Animal Health, Norbrook Inc., PharmGate Animal Health, the United Soybean Board, and Zoetis.

Purpose and Design of the Forum

The purpose of the forum was to bring leaders from all parts of the animal agriculture industry to join with veterinarians, researchers and experts in human and public health, and regulatory officials to present new information and talk about their experiences in adapting to a rapidly changing business environment and marketplace. The objective was to recognize the progress in antimicrobial stewardship that has been made across the business and regulatory spectrum, identify and reinforce common values among diverse stakeholders, discuss communication strategies to deliver an accurate and unified message to consumers, and acknowledge the continued challenges faced going forward.

Symposium Planning Committee

Co-Chairs:

Dr. Eric Moore, *Director of Technical Services – North America, Norbrook Inc.*

Dr. Steve Solomon, *Global Public Health Consulting, LLC*

Symposium Planning Committee Members:

Dr. Christopher Braden, *Deputy Director, National Center for Emerging and Zoonotic Infectious Diseases, CDC*

Mr. Chase DeCoite, *Associate Director of Beef Quality Assurance Programs, National Cattleman's Beef Association*

Dr. Susan Duran, *Professor, Department of Clinical Sciences, Auburn University*

Dr. William T. Flynn, *Deputy Director, Science Policy, FDA Center for Veterinary Medicine*

Dr. Karin Hoetzler, *Senior Officer, Health Programs, the Pew Charitable Trusts*

Dr. Kerry Keffaber, *Chief Veterinarian, Scientific Affairs and Policy, Elanco Animal Health*

Mr. Jeff Morelli, *Associate Director for Policy, Division of Foodborne, Waterborne & Environmental Diseases, CDC*

Ms. Amanda Raziano, *Policy Analyst, CDC*

Dr. Roger Saltman, *Group Director, Cattle and Equine Technical Services, Zoetis*

Dr. Dawn Sievert, *Associate Director for Antimicrobial Resistance, Division of Foodborne, Waterborne, & Environmental Diseases, CDC*

Dr. Bob Smith, *Veterinary Research and Consulting Services, LLC*

Symposium Topics and Speakers

(in order given at the symposium)

Welcome and Opening Comments

Eric Moore, DVM, *Technical Director, Norbrook Inc., and* Steve Solomon, MD*, Global Public Health Consulting, LLC*

One Health Antimicrobial Stewardship: A Collaborative Approach

Ruth Lynfield, MD, *State Epidemiologist and Medical Director, Minnesota Department of Health*

Panel One: Update Progress

Moderator Roger Saltman, DVM, MBA, *Group Director, Cattle and Equine Technical Services, Zoetis*

Panelists:

Shannon Wharton, *Research Manager, Hy-Plains Feedyard*
Joe Swedburg, *Chairman of the Board, Farm Foundation, Hormel Foods Corporation (retired)*
William T. Flynn, DVM, *Deputy Director, Science Policy, FDA Center for Veterinary Medicine*
Amy Batal, PhD, *Corporate Nutritionist, Sanderson Farms*

Panel Two: Update Progress

Moderator Eric Moore, DVM, *Technical Director, Norbrook Inc.*

Panelists:

Andrew T. Maccabe, DVM, MPH, JD, *Chief Executive Officer, AAVMC*
Michael Costin, DVM, *Assistant Director, Division of Animal & Public Health, AVMA*
Deepanker Tawari, BVSc, PhD, *Director, Pennsylvania Department of Agriculture Veterinary Laboratory*

Panel: Goal Setting and Buy-In

Moderator Rear Admiral David P. Goldman, *Assistant Surgeon General & Chief Medical Officer, United States Public Health Service, Food Safety & Inspection Service*

Panelists:

Rosie Busch, DVM, *Veterinarian and Director*, *Animal Health and Food Safety Services, California Department of Agriculture*
Angie Siemens, PhD, *Vice President, Food Safety, Quality & Regulatory, Cargill*
Ron Phillips, *Vice President for Government and Public Affairs, Animal Health Institute*

Panel: Human Health Examples,

Moderator Dawn Sievert, PhD, MS, *Associate Director for Antimicrobial Resistance, Division of Foodborne, Waterborne, and Environmental Diseases, CDC*

Panelists:

Edward J. Septimus, MD, *Vice President, Research & Infectious Diseases, Hospital Corporation of America (HCA)*

Lauri Hicks, DO, *Director, Office of Antibiotic Stewardship, CDC*

Panel: Science and Practice – How does the Science of Antibiotic Resistance and Use Get Applied in Veterinary and Farming Practices?

Moderator Eric Moore, DVM, *Technical Director, Norbrook Inc.*

Panelists:

H. Morgan Scott, DVM, PhD, *Professor of Epidemiology, Texas A&M University*

Donna Carver, DVM, PhD, *Extension Specialist, Poultry Veterinarian, North Carolina State University*

Joel Nerem, DVM, *Pipestone Veterinary Services*

Panel: State of Science – What Do We Know? What Don't We Know?

Moderator Rick Sibbel, DVM, *Technical Service, Food Animal Business Team, Merck Animal Health*

Panelists:

Larry M. Granger, DVM, *Senior Leader of Antibiotic resistance, USDA-APHIS*

Shelley Rankin, PhD, *Associate Professor, Microbiology, University of Pennsylvania School of Veterinary Medicine*

Mark G. Papich, DVM, MS, *Professor, Clinical Pharmacology, North Carolina State University*

Patrick McDermott, MS, PhD, *Director, National Antibiotic resistance Monitoring System (NARMS), FDA Center for Veterinary Medicine*

Panel: Science and Practice – What are the Major Gaps in Knowledge or Translation? How Do WE Find the Answers to What We Don't Know?

Moderator Kerry Keffaber, DVM, MSC, *Chief Veterinarian, Scientific Affairs & Policy, Elanco Animal Health*

Panelists:

Jeff Bender, DVM, MS, *Professor, Environmental Sciences, University of Minnesota*

Nora Schrag, DVM, *Clinical Assistant Professor, Agricultural Practices, Kansas State University*

Joe Swedburg, *Chairman of the Board, Farm Foundation, Hormel Foods Corporation (retired)*

David G. White, PhD, *Associate Dean for Research, University of Tennessee Institute for Agriculture*

Panel: Data Needs – What Information Would be Most Helpful to: Producers, Veterinarians, Retailers, Government/Public Health Officials?

Moderator Steve Solomon, MD, *Global Public Health Consulting, LLC*

Panelists:

Shannon Wharton, *Research Manager, Hy-Plains Feedyard*
Bob Smith, DVM, *Veterinary Research & Consulting Services, LLC*
Peter Davies, BVSc, PhD, *Professor, University of Minnesota*
Lori J. Marco, *Senior Vice President, External Affairs & General Counsel, Hormel Foods Corporation*
Mike Brown, *Director, the Dairy Supply Chain, the Kroger Corporation*
Dawn Sievert, PhD, MS, *Associate Director for Antimicrobial Resistance, Division of Foodborne, Waterborne, & Environmental Diseases, CDC*

Who Do You Trust? Breaking Through to the Consumer in a Post-truth World

Leah Beyer, *Director, Global Digital and Social Media Communications, Elanco Animal Health*, and Colleen Parr Dekker, *Global Corporate Communications Lead, Elanco Animal Health*

One Health and the Politics of Antimicrobial resistance

Laura H. Kahn, MD, MPH, MPP *Research Scholar, Princeton University*

We Are the World, Collaboration is not Optional

Elizabeth D. Hermsen, PharmD, MBA, BCPS-AQ(ID), FIDP, *Head of Global Antimicrobial Stewardship, Merck & Co., Inc.*

Panel: What are the Communication and Research Needs to Take the Next Steps?

Moderator Nevil Speer, PhD, *Vice President, United States Operations, AgriClear*

Panelists:

Eric Moore, DVM, *Technical Director, Norbrook Inc.*
William T. Flynn, DVM, *Deputy Director, Science Policy, FDA Center for Veterinary Medicine*
Karin Hoelzer, DVM, PhD, *Senior Officer, Health Programs, the Pew Charitable Trusts*
Larry M. Granger, DVM, *Senior Leader of Antibiotic resistance, USDA-APHIS*
Nora Schrag, *Clinical Assistant Professor, Agricultural Practices, Kansas State University*
Lori J. Marco, *Senior Vice President, External Affairs & General Counsel, Hormel Foods Corporation*
Bob Smith, DVM, *Veterinary Research & Consulting Services, LLC*

What MUST Be Done Next: Prioritizing Immediate Actions

Lonnie King, DVM, MS, MPA, *Professor and Dean Emeritus, College of Veterinary Medicine, the Ohio State University*

Executive Summary

Antimicrobial Stewardship has been defined many ways by many different entities, but all generally describe improvement of antimicrobial use by coordinated action. The goal of antimicrobial stewardship is not to withhold or even reduce the use of antibiotics, but rather, to optimize the judicious use of those antibiotics. There are five 'D's' of judicious antibiotic usage common to all users: diagnosis, drug, dose, duration, and de-escalation. Get the diagnosis right, choose the correct drug, choose the right amount, choose the minimum effective duration, and if the antibiotic is not resolving the medical problem, switch drug or route to better target treatment.

Supporting antimicrobial stewardship requires the engagement of multiple diverse stakeholders. A collaborative approach, involving partnership of both public and private entities, fostering an ongoing dialogue, is essential to successful strategy, policy, implementation, and control.

The NIAA Antimicrobial stewardship symposium is in its 7th year, and in that time, much progress has been made. Many organizations have developed strategic plans; developed messages to communicate about antimicrobial stewardship; partnered with diverse organizations to discuss concerns, find common ground, and implement practical actions to address antimicrobial stewardship; organized task forces; and developed curriculum to train veterinarians, students, and physicians. The American Association of Veterinary Laboratory Diagnosticians (AAVLD) has been working to harmonize laboratory methodologies to ensure that results of antimicrobial susceptibility testing are consistent, providing accurate data for providers making antimicrobial use decisions.

While those pursuing antimicrobial stewardship have experienced significant progress toward the goal, there is still much to do, and the goal is not attained yet. Stakeholders continue to struggle with finding a good metric to measure improvements in antibiotic resistance. Policies are being developed and put into place, but continual monitoring of those policies for undesirable unintended consequences is important. Ongoing research contributes significantly to our knowledge base, but brings to light new details which must be accounted for as antimicrobial stewardship policy evolves.

There is much unknown about antibiotic resistance, and much that research has recently revealed. The microbial world is a complex, adaptive system. Bacteria appear to use resistance genes to communicate with each other. Resistance genes move freely horizontally and vertically, between the environment, animals, and people. Beneficial bacterial populate the gut of both humans and animals, and interact with pathogenic bacteria and antibiotics as well. Bacteria become resistant in drug concentrations that are so low that these concentrations have been historically disregarded. Antibiotic resistance must be addressed in light of these new and future findings. Public-private partnerships and coordinated plans across disciplines and across countries are essential for progress to continue toward the goal of antimicrobial stewardship.

Action Plans move knowledge toward implementation. These action plans represent science and policymakers' response to antibiotic resistance. The National Action Plan for the United States comprises 5 goals: slowing the emergence and spread of resistant bacteria; strengthening One Health

surveillance; advancing development of rapid diagnostic tests; accelerating development of new antimicrobials; and improving international collaboration. As antibiotic resistance is a global challenge, 85% of the countries around the world have developed their own national action plans. These plans vary in comprehensiveness, but are an important step toward the global goal of antimicrobial stewardship.

The common antimicrobial stewardship goal of all stakeholders is to optimize animal and human health, while reducing the pressure for antibiotic resistance. While in pursuit of this goal, many organizations have come to the conclusion that antimicrobial use cannot be addressed without taking into account animal welfare, animal well-being, food safety, and food security. The industries of animal agriculture must work together to develop clear, concise communications beneficial to both producers and consumers. That communication must begin within each specific industry, presenting a unified front instead of dividing the industry with negative marketing claims. The consumer is asking for more transparency and clarity about what they eat. They are tired of negative campaigns, tired of being told what to do, and have begun to question all food marketing. This is an opportunity for agriculture to step in and explain. Agriculture can explain the difference between 'No Antibiotics Ever' and antimicrobial stewardship. Agriculture can explain what preventative medicine means, and how antibiotics are used as a part of prevention programs. Agriculture must acknowledge consumer concerns and accept responsibility for the antibiotics that are used, and then explain why in a way the consumer can understand. Words and approach matter – success is more likely if the approach shifts away from educating toward engaging.

Antibiotic resistance is a political issue because food security is a political issue. Food security is the foundation of civilization, and intimately linked to international security and global health. In 1995, Denmark voluntarily banned the antibiotic avoparcin, because it is chemically related to the human antibiotic vancomycin, and vancomycin resistant bacteria were starting to appear in livestock. The ban led to a 90% drop in VRE on farms. However, at the same time, cases of VRE in hospitals were on the rise. Years later, VRE was analyzed using whole genome sequencing, upon which it was discovered that a VRE clone was responsible for much of the global hospital cases. The clone did indeed come from animals, just not necessarily from farm animals. The VRE clone appeared to come from dogs. These findings do not necessarily apply to other bacteria such as *Salmonella*, *Campylobacter*, or *E.coli*. Nevertheless, many assumptions are made based on limited scientific findings such as the surveillance of resistance genes. Whole genome sequencing surveillance is essential if we are to fully understand the etiology and epidemiology of antibiotic-resistant bacteria.

Antimicrobial stewardship is part of the solution, but not the whole solution. Policies and strategies must be implemented for reducing demand, preventing infection, and improving diagnosis and surveillance. Multi-sector collaboration is absolutely necessary. Development of frameworks with voices from animal, human, and environmental health fosters ongoing communication. Finally, while progress has been made in the battle against antibiotic resistance, the fight is not even close to over. The sense of urgency about this slow-burning crisis must be maintained. Stewardship is key, and cost effective. The United States needs a national leader who can boost awareness and make this a major social issue. A national institute for innovation, policy, and research should be created – the will is

there, and the creation should be able to occur quickly. Finally, the business model needs to change, providing incentives for the development of new, effective, accessible antimicrobials.

Presentation Highlights

One Health Antibiotic Stewardship: A Collaborative Approach

Dr. Ruth Lynfield*, Minnesota Department of Health*

The ability to successfully treat disease with antibiotics has affected almost every area of medicine, particularly surgery, intensive care, transplant medicine and oncology. The introduction of antibiotics decreased death rates significantly across the board, ranging from 10% reduction in mortality from skin infections to an astonishing 75% reduction from heart infections. In contrast, as Dr. Brad Spellberg, an infectious disease expert at UCLA has pointed out, the clot-busting drugs currently used to treat heart attacks, considered by many as a significant advance in medicine, reduce the heart attack mortality rate by just 3%[1,2,3,4,5,6,7]

However, with widespread use of antibiotics, comes increased antibiotic resistance. Every time an antibiotic is administered it impacts the entire bacterial population it reaches in the host, including target pathogenic bacteria as well as the non-target, non-pathogenic bacteria that make up the normal flora of the organism. Selective pressure from antibiotics enables resistant bacteria to surviveand subsequently experience reduced competition as susceptible bacteria are killed. Recently, pan-resistant infections have been identified in many parts of the world. These infections are frequent in places like India, where antibiotics can be purchased without a prescription, and sanitation, hygiene and infection control measures are often lacking. In the United States, two million people become infected, and 23,000 people die each year, as a direct result of antibiotic resistant infections. The total cost of resistant infections in the U.S. approaches $35 billion per year[8]. If we are to retain these life-saving tools, we have no choice but to become proficient stewards of its use. Antimicrobial stewardship, at its most broad definition, is the improvement of antibiotic use by using coordinated actions. The goal is not to withhold antibiotics, but rather to optimize their use.

Antibiotic resistance is not only a problem in the living organism, but also within the environment. Antibiotic residues have been found in ground and surface water, representing a possible method of resistance spread with the potential to reach far beyond the treated animal or human. One Health, as defined by the AVMA, is the integrative effort of multiple disciplines working locally, national, and globally to attain optimal health for people, animals and the environment.[9] The Minnesota Department of Health believes that a One Health approach is imperative to antbiotic stewardship, as it allows us to fully understand the picture of antibiotic resistance and craft a coordinated, comprehensive response. Minnesota's five year strategic plan addresses this approach and response by promoting understanding of One Health antibiotic stewardship, improving both human and animal antibiotic stewardship, and maintaining an awareness that urban and agricultural pathways each lead to antibiotic contamination of the environment, and both hospitals and farms have environmental impact.

When bringing the antimicrobial stewardship discussion to medical and veterinary care providers, it is important to approach the discussion in a positive and constructive way. Most important is not to point fingers – everyone has a role to play both in propagation and in stewardship. Talking points include recognition of the importance of antibiotics but also that any use of antibiotics leads to development of resistance; acknowledgement that human, animal and environmental use are inseparable; and discussion of the process of improving antibiotic use with the understanding that lack of proof of harm isn't an excuse, and greater abuse in other disciplines 'doesn't excuse yours.' The 'Five D's' of judicious antibiotic usage are common to all fields. These are Diagnosis, Drug, Dose, Duration, and De-escalation. A specific diagnosis with antibiotic susceptibility testing allows the provider to choose the correct antibiotic for the disease at hand. Ongoing research into dose and duration is continually improving the ability of the provider to choose the minimal effective dose and duration of drug to treat the diagnosed infection. Finally, de-escalation means being open to changing the drug or route of administration to better target treatment.

The key to an effective One Health antimicrobial stewardship plan is to recruit people that are both invested in the issue and empowered to recruit other forward thinkers to the discussion, and then to listen constructively to the concerns of all interested parties s with the humility that allows the group to recognize issues outside their own discipline. In this manner, the discussion and the group can identify a comprehensive path forward.

Panel One – Progress Update: Agribusiness

Dr. Roger Saltman*, Zoetis,* moderator

Panel: Ms. Shannon Wharton, *Hy-Plains Feedyard*, Mr. Joe Swedburg, *Farm Foundation, Hormel Foods Corporation (retired),* Dr. William T. Flynn, *FDA Center for Veterinary Medicine,* Dr. Amy Batal, *Sanderson Farms*

There is recognition across agribusiness that antibiotics must be used judiciously, with a medical professional overseeing their use. However, that recognition comes with the conviction that agribusiness must also ensure the continuing availability of antibiotics in the industry, with an appropriate place in resource management.

Hy-Plains Feedyard

Ms. Shannon Wharton, *Hy-Plains Feedyard*

Hy-Plains Feedyard is a 50,000 head commercial feedyard, with 85% of cattle customer-owned. Hy-Plains operates an Education and Research Center, designed to facilitate research benefiting food animal production, including genetics and improved feed efficiency, responsible antibiotic use and reduction, nutrition and animal welfare.

The beef industry is a segmented industry, and the various parts of the industry are not known for their cross-communication skills. Partly as a result of this lack of communication, cattle experience significant weight loss associated with transportation and processing, termed 'shrink', as they move through the system. However, this shrink can be eliminated, through better communication and coordination throughout the system.

At the beginning, every beef calf has performance potential, but it is up to the growers and producers to convert that potential to a high quality end product. Treatment of sick animals is important, but investment in genetics, attention to nutrition starting prior to conception, preventative health measures such as vaccination, and low stress handling techniques throughout the life of the animal have a huge impact on health. Employing these measures reduces illness and failure to thrive, leading to less need of treatment. Genetics plus the environment lead to the end product. Data on all animals in the system are needed prior to the feedyard, reaching beyond vaccination to data which give the finisher a picture of the complete management of the animal and leads to the highest quality, most economically viable product.

Stewardship of Antimicrobial Drug Use in Food Producing Animals

Mr. Joe Swedburg, *Farm Foundation, Hormel Foods Corporation (retired)*

The Farm Foundation is a nonprofit agriculture policy institute which cultivates dynamic, non-partisan collaboration to provide objective policy analysis on the entire food chain, from agricultural to consumer issues.[10]

Antibiotics have been used in agriculture since the 1950s, when their ability to promote growth was recognized. Over the past half century their use evolved, and in 2015 the Veterinary Feed Directive (VFD) final rule was published, ultimately placing all antibiotics of use to human medicine under veterinary oversight and control.

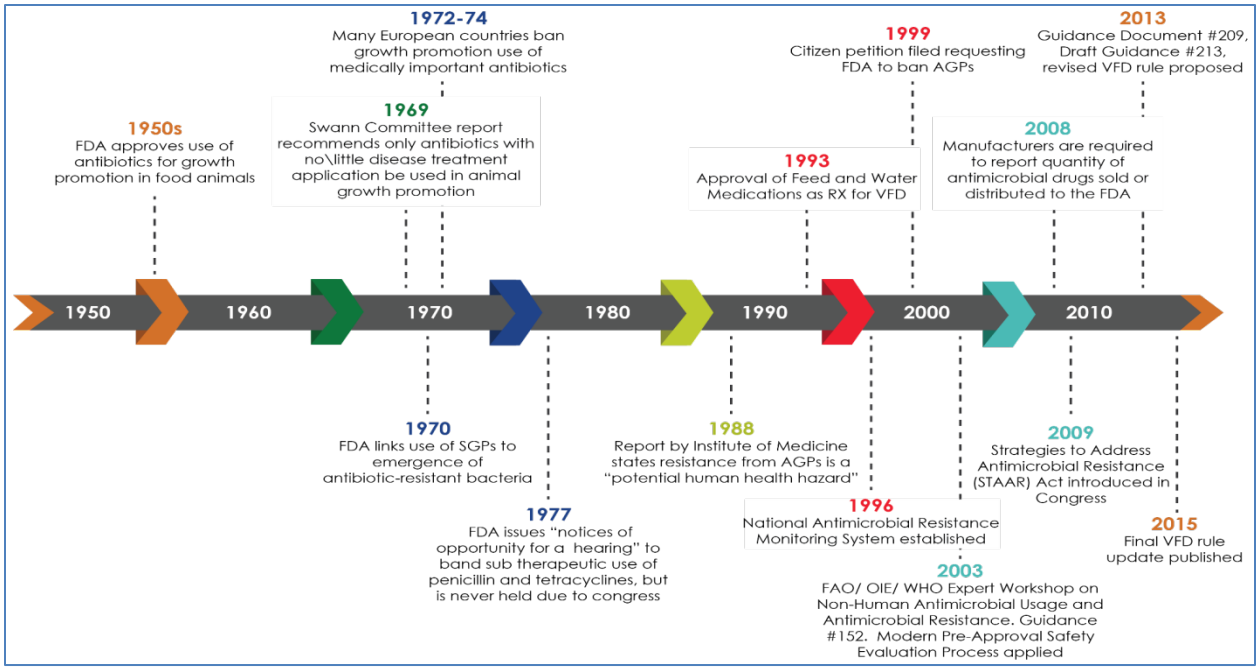

Figure 1. History of Antibiotics in Livestock Production (Sources: Center for Disease Dynamics, Economics & Policy, Natural Resource Defense Council)

The Farm Foundation approach to voluntary compliance with the VFD outlines how to help stakeholders – veterinarians, producers, and feed suppliers – implement the rule. This approach began with the institution of a public-private partnership between the Farm Foundation, FDA, and USDA. Once this partnership was established, they developed a regional workshop model, bringing the discussion to the veterinarians, producers, and feed suppliers where they lived and worked, around the United States. A key factor in the success of these workshops was the presence of FDA and USDA leadership at every meeting.

Thirty-six major questions came out of these working groups. Three major themes were distilled from these questions: a need for education and outreach to those affected by the VFD; the need for continued dialogue between industry and regulators; and a lack of access to veterinary services for food animal producers. Moving forward, the Farm Foundation has partnered with the Pew Charitable Trusts, companies and livestock groups to form the Antimicrobial Stewardship Working Group. This working group represents a voluntary effort to address these questions, and to move forward with animal health stewardship and responsible use of antibiotics.

FDA Center for Veterinary Medicine

Dr. William T. Flynn, *FDA Center for Veterinary Medicine*

The FDA Center for Veterinary Medicine (CVM) regulates animal drugs, animal feed, and veterinary devices. The CVM's mission includes ensuring animal drugs, feed, and feed additives are safe and effective. The goal of the CVM regarding antimicrobial stewardship is to optimize the use of antibiotics in animals, as well as minimize the need for that use. To address this goal the FDA CVM focused on three areas: drugs regulated by the FDA, particularly medically important antimicrobials; support of

efforts to facilitate 'good use' practices at the farm level; and enhancement of data collection to facilitate monitoring of progress in antimicrobial stewardship.

The FDA's first focus area is embodied by FDA's Guidance for Industry #213. This Guidance experienced an unprecedented level of engagement and collaboration by pharmaceutical companies, leading to a fundamental change to how antimicrobials are distributed and used in animal agriculture. 292 animal drug applications were affected, resulting in 208 drugs brought from OTC to veterinary oversight, with an 84 additional drugs completely withdrawn from the market. All feed and water uses of medically important antimicrobials are now under veterinary oversight. Next steps will be to consider further product updates to ensure appropriate use; reviewing medically important antibiotics that are still available OTC such as intramammary dosage forms; and looking at companion animal uses of medically important antibiotics.

One of the conference attendees raised the question of unintended consequences and financial impact of the VFD. Dr. Flynn noted that there have been some access issues due to changes in distribution channels, lack of access to veterinary services or lack of approved feed formulations has hampered product access. The honeybee sector has also had access problems, as prior to VFD implementation honeybee producers had very limited interaction with veterinarians. The FDA is aware of these problematic areas and is working to assure access to products and services. The FDA is also committed to addressing any new unintended problems associated with the VFD as they arise.

FDA CVM's experience demonstrates that supporting stewardship requires engagement of multiple stakeholders, utilizing a collaborative approach. Through this approach significant progress can be made toward the goal of optimizing antibiotic use.

Sanderson Farms

Dr. Amy Batal, *Sanderson Farms*

Sanderson Farms is the third largest poultry producer in the United States, and has publicly confirmed and defended the judicious use of antibiotics in their chickens. The defense grows out of a strong sense of responsibility to customers and consumers, to provide the safest product possible while maintaining the highest standards of animal welfare. Animal welfare, food safety, and sustainability all rely on the judicious use of antibiotics. The welfare of animals with access to antibiotics is improved as they can escape the suffering caused by prolonged disease. Additionally, the judicious use of antibiotics provides a means to reduce overall animal pathogen load. Finally, animals raised with the benefit of antibiotics require less time to reach the market, resulting in a reduced burden in terms of feed, land, fuel, water, and fecal matter. Healthy chickens make safe, affordable food, and the judicious use of antibiotics supports both health and economics.

There is an inherent risk to the industry in 'raised without antibiotics' marketing. Like 'raised without hormones,' this marketing implies that anything without the label is unsafe. The marketing department, not the veterinarian, is deciding what products can and can't be used, and joining the veterinarian in making treatment decisions. This decision process is dangerous for both the industry and for the

consumer. In the interest of food safety, animal welfare, and sustainability, Sanderson Farms refuses to take this approach.

For Sanderson Farms, there is one significant positive outcome of the Veterinary Feed Directive. Consumers now believe that the poultry industry is taking better care of their chickens, and employing veterinary oversight in treatment decisions. This veterinary oversight was already the case throughout most of the industry, but the consumer's awareness boosts confidence and validation for their products.

One conference attendee pointed out that while VFD is a great step in the right direction, both in antimicrobial stewardship and in the message to the consumer, there remains real difficulty in educating the consumer. She echoed Dr. Batal in her concern that veterinarians and producers are failing at educating the consumer about the safety of our food supply. In that gap, marketers and others are able to step in and propagate their messages, sometimes accurate but beside the point, and sometimes wholly inaccurate. In the end the consumer becomes confused, suspicious, and frustrated. Not only do we need to ensure veterinary oversight, protection of animal welfare, and the judicious use of antibiotics, we also need to communicate these assurances to the consumer.

Panel Two – Progress Update: Research & Academia

Dr. Eric Moore, *Norbrook Inc.*, moderator

Panel: Dr. Andrew T. Maccabe, *AAVMC*, Dr. Michael Costin, *AVMA*, Dr. Deepanker Tawari, *Pennsylvania Department of Agriculture Veterinary Laboratory*

One Health Approach

Dr. Andrew T. Maccabe, *AAVMC*

Antibiotic resistance is a global issue, and global organizations have tackled the stewardship challenge. Their approach, like that of the AVMA and the Minnesota Department of Health, is through the interconnected lens of One Health. The Global Health Security Agenda, WHO Global Action Plan, and US National Action Plan all offer a One Health approach to antimicrobial stewardship.

Until recently, academia had not developed a plan of their own to address stewardship. To remedy this gap, the Association of Agricultural and Veterinary Medical Colleges (AAVMC) and the Association of Public and Land-Grand Universities (APLU) joined forces to form a task force representing their members, government, and industry. The charge to the task force was two-fold: to propose antimicrobial stewardship recommendations with a focus on research and outreach, for academic institutions related to production agriculture; and to advise government agencies and the government task force on Combating Antimicrobial Resistant Bacteria (CARB).

The AAVMC-APLU Task Force developed a model curriculum for veterinary and animal science students, addressing competencies across six domains ranging from antimicrobial stewardship to roles and relationships. The Task Force also partnered with the Association for Prevention Teaching and Research (APTR) to develop One Health case studies. These are 15 case studies designed to be 'pulled off the

shelf' and used in a professional curriculum, and approximately one third address antibiotic resistance. Additionally, the Task Force has partnered with Dr. Jeff Bender at the University of Minnesota to help develop an antibiotic resistance learning website, containing open source teaching models for veterinarians, veterinary students, animal scientists and others.[11] Finally, through a series of meeting on Capitol Hill, the Task Force has developed key messages and communication strategy designed to reach veterinarians, producers, agricultural youth groups, and the general public.

Moving forward, more research is needed from a range of disciplines including behavioral and social scientists. We need to learn how to incentivize and change behavior. Dr. Lucas Pantaleone suggested that the only way to change behavior may be to publish outcomes to show how providers are performing. Dr. Maccabe agreed, but also noted that economics is a significant driver, and we need incorporate that into behavioral change as well. The Task Force envisions an AMR Research Institute, formed to provide global leadership to sustain and preserve the use of antimicrobials using a One Health approach.

Ensuring Antibiotics Remain Available & Effective Tools for All

Dr. Michael Costin, *AVMA*

AVMA antimicrobial policies address a wide variety, depth, and breadth of issues, and are reviewed at minimum every five years by a volunteer committee with a broad representation of background, expertise and specialty. Upon review, the AVMA concluded that the process followed by previous review committees was slow and not necessarily representative of the entire profession. Therefore the most recently convened committee has taken a different approach, focusing on AVMA membership and unification of the diverse aspects of the veterinary profession, with a goal of working toward better antimicrobial stewardship.

The AVMA's antimicrobial stewardship strategy addresses efficacy, advocacy, and improving AVMA value through consensus building, working collaboratively with stakeholders, and the development of a unifying stewardship definition that reaches across disciplines and practice modalities. The AVMA is committed to ensuring that antibiotics remain available and effective tools for all.

Antimicrobial Susceptibility Testing in State Veterinary Diagnostic Laboratories in the United States

Dr. Deepanker Tawari, *Pennsylvania Department of Agriculture Veterinary Laboratory*

State Veterinary Diagnostic Laboratories comprise American Association of Veterinary Laboratory Diagnosticians (AAVLD) labs, National Animal Health Laboratory Network (NAHLN) labs, and Laboratory Investigation and Response Network (LIRN), university, research, and clinic labs. AAVLD designation recognizes a certain level of achievement in quality control; NAHLN is a USDA-sponsored network for addressing diseases of 'high consequence'; and LIRN, university, research, and clinic labs address small animals.

The AAVLD has formed a working group with NAHLN to harmonize laboratory methodologies so that antimicrobial testing results are consistent across all laboratories. Objectives of the working group include developing a tracking process; deployment of standardized methodology across all laboratories; identification to veterinary diagnostic laboratories of important trends in antibiotic resistance; and the facilitation of antimicrobial stewardship.

Dr. Thomas Shryock brought up the National Antibiotic resistance Monitoring System (NARMS) program recommendation of advocating for pre-treatment sampling of healthy animals. Susceptibility data on healthy animals would give a more complete and accurate clinical picture of antibiotic susceptibility than that of exclusively sick animals. Dr. Tewari agreed that almost all samples currently tested are from animals that are either very ill or going to die soon, and data from healthy animals are important in making resistance determinations. However, data from healthy animals are difficult to obtain.

Dr. Michael Costin pointed out that the AVMA has looked into investigating when and why treatment failures occur. They recognize that is could be a useful tool, but there is no consensus on how to move forward. While there is a will and a need to determine the antimicrobial susceptibility of the general animal population, following up on these recommendations is complicated by the challenge of the clinical setting, and there is no consensus on how to move forward.

At the conclusion of Panel Two, moderator Eric Moore reiterated an earlier message: collaboration is essential across all stakeholders. The antibiotic resistance issue is complex, and each stakeholder has a different view. Diverse representation among collaborators is key in arriving at a comprehensive and successful path forward.

Panel: Goal-Setting and Buy-in

RADM David P. Goldman, *United States Public Health Service,* moderator

Panel: Dr. Rosie Busch, *California Department of Agriculture*, Dr. Angie Siemens, *Cargill*, Mr. Ron Phillips, *Animal Health Institute*

California Senate Bill 27

Dr. Rosie Busch, *California Department of Agriculture*

The goal of the California Department of Agriculture (CDFA) is to serve California's animal population, public health, veterinarians, and consumers. This goal is currently being served in many ways, among them the recently enacted California Senate Bill 27. Two requirements of California Senate Bill 27 are that the CDFA develop antimicrobial stewardship guidelines and best management practices, and also that they gather data on medically important antimicrobial drug usage, antimicrobial resistant bacteria, and livestock management practices.[12] This senate bill came about through discussions among the CDFA, State Senator Jerry Hill, and a variety of stakeholders. Through these meetings, a common goal was identified: that of optimizing animal and human health while reducing the pressure for antibiotic resistance. That common goal led to the ultimate enactment of the Senate Bill.

CDFA developed a strategic plan to enable achievement of the goal and mandates of the senate bill – a work plan providing checks and balances that allowed CDFA to maintain focus toward goal achievement. A vital key to the success of this strategic plan, and a theme that has resonated throughout presentations today, is cooperation among diverse stakeholders.

Maintaining relationships and discussion is important in all aspects of making antimicrobial stewardship work. The second requirement of the senate bill is that CDFA collect data on antimicrobial usage, antibiotic resistance, and livestock management. However, producers' provision of this data is voluntary. CDFA must gain the producers' cooperation and support to demonstrate to the senate, stakeholders, and the public that a voluntary, producer-driven system will work.

Goal Setting and Buy-in at Cargill

Dr. Angie Siemens, *Cargill Protein Group*

Cargill Protein Group includes all of Cargill's North American beef, turkey, food service and food distribution businesses. Customers include food service operators, retailers, food manufacturers and others. Cargill defines food safety as protecting people and animals at every step of the supply chain from illness or injury through a science- and risk-based approach to policy, operation and supply.

In response to antibiotic resistance pressure and the subsequent need to develop judicious use policies to protect the antibiotic supply, Cargill Protein Group has set concrete, measurable goals throughout its supply chain. Goals include: reducing antibiotic use in turkeys through elimination of antibiotics for growth promotion (accomplished in 2014); reducing overall antibiotic use in turkeys and offering choice to consumers through elimination of antibiotics in their Honest Turkey® brand; reduction of shared class antibiotics in beef cattle feedlots by 30%; increased implementation of beef antimicrobial stewardship programs through BQA; and development of a list of animal agriculture antimicrobial stewardship principles to be used in all species management systems. These goals are driven by two guiding principles: serving the customer and protection of the health, welfare, and safety of their animals in all production lines.

Antimicrobial stewardship must be addressed in a comprehensive program encompassing animal welfare, animal well-being, and food safety. Progress is slow, but progress is occurring, and animal agriculture needs to tell the story of success. We must let the consumer know about our efforts and achievements in addressing antibiotic resistance. We continue to struggle to find a metric for antibiotic resistance. A metric of that nature would provide the data to measure changes in resistance, and data indicating a decrease would help demonstrate success to the consumer.

Policy and Progress

Mr. Ron Phillips, *Animal Health Institute*

In the past 3 to 4 years, government, industry and many stakeholders have moved away from accusations and finger-pointing to arrive at a productive atmosphere of collaboration and cooperation. The White House was instrumental in this change, soliciting opinions, input, and buy-in from a large

group of stakeholders. This ultimately led to the creation of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), a council in which people of disparate backgrounds have come together to share antibiotic resistance information with each other and change the tone and tenor of the public policy arena.

Data from the National Antimicrobial Resistance Monitoring System (NARMS) shows agriculture is making significant progress in the antibiotic resistance fight. Fewer pathogens are being recovered from retail meat samples. Resistance in salmonella in humans has continued to decrease. Resistance rates in foodborne pathogens in the U.S. compare very favorably with the rest of the world. The unusual approach by the FDA of gaining voluntary compliance by drug manufacturers is credited with accomplishing the goals of judicious use..

Voluntary data collection supported through producer group inputs offers an example of public-private collaboration toward accomplishing stewardship goals. The voluntary, cooperative stakeholder driven approach is working, and works better and faster than a regulatory driven approach. This voluntary approach, combined with setting consensus goals such as pursuing optimal use of antibiotics, mitigating unintended consequences, and thoughtfully approaching data collection are key to continued progress and success in antimicrobial stewardship.

One conference attendee asked how we can balance both regulators and producers regarding data collection, as often neither side trusts the other. Mr. Phillips suggested that asking the private sector to collect data and feeding it into a publicly funded program can work because no one is trying to hide anything, and that transparency provides a level of credibility.

Panel: Human Health Examples

Dr. Dawn Sievert, *Division of Foodborne, Waterborne, and Environmental Diseases, CDC,* moderator

Panel: Dr. Lauri Hicks, *Division of Healthcare Quality Promotion, CDC,* Dr. Edward Septimus, *Hospital Corporation of America*

Antimicrobial Stewardship in Human Health – Progress and Opportunities

Dr. Lauri Hicks, *Division of Healthcare Quality Promotion, CDC*

The mission of the Division of Healthcare Quality Promotion at the CDC is 'to protect patients; protect healthcare personnel; and promote safety, quality, and value in both national and international healthcare delivery systems.'[13] This focus leads to a working definition of antimicrobial stewardship that focuses on improving antibiotic treatment to improve patient safety, and includes measuring antibiotic prescribing; improving prescription practices; minimizing misdiagnoses and underdiagnoses; and ensuring correct drug, dose, and duration every time. Data collected between 2011 and 2014 show that the number of outpatient antibiotic prescriptions decreased 14%. This progress is due almost entirely to a decrease in pediatric prescriptions – no significant change has occurred in the numbers of adult prescriptions. In spite of the progress, data show that at least 30% of outpatient antibiotic prescriptions

are unnecessary, representing an unnecessary risk both to the individual patient and to the general environment of antibiotic resistance.

Education of physicians is important, but it is not enough. Improving prescribing practices requires changing behavior, both in inpatient settings (hospitals) and outpatient settings. Examples of evidence-based strategies to improve antibiotic use include restriction policies and antibiotic time-outs in inpatient settings, and communications training, watchful waiting or delayed prescribing, and commitment posters in outpatient settings. CDC can make recommendations regarding antimicrobial stewardship, but CDC isn't a regulatory body. Partners such as healthcare insurers, Centers for Medicare and Medicaid Services (CMS), the Joint Commission, and even state legislators have the influence, support, and enforcement capability needed to mandate antimicrobial stewardship. Examples include the Joint Commission accreditation standard requiring hospitals to have stewardship programs and a CMS regulation that all nursing homes must have stewardship programs. Modest improvements have been made, but there is still much work to be done. CDC is reaching out to providers beyond traditional hospital and outpatient providers to expand the uptake of antimicrobial stewardship practices. Hospitalists, physician assistants, nurse practitioners, and dentists represent the next frontier of antimicrobial stewardship, and their support will continue the momentum and further increase uptake. Changing behavior is difficult, and it takes time, creativity, and patience. CDC is committed to continuing to expand and innovate new approaches in its pursuit of improving patient care and antibiotic use.

Two of the veterinarians attending the conference expressed concern about the CDC's data associating success with decreased prescription numbers. Historically, when setting a benchmark for reduction of antibiotics usage has been tried in veterinary medicine, it has had a negative impact on animal health. When CDC began measuring the number of antibiotic prescriptions, many people involved in human medicine had similar concerns human health. Dr. Hicks acknowledged that monitoring antimicrobial stewardship benchmarks for unintended consequences and responding to mitigate these outcomes is important. CDC approached the measurement of antibiotic prescriptions in a very conservative way, focusing on conditions that don't need antibiotics, such as the 50% of respiratory infections that don't require antibiotics. Additionally, CDC acknowledges that the information supplied by volume-based reporting does not represent a balanced clinical picture. Volume-based reporting has provided useful information, such as geographical variations in antibiotic prescribing, and the dental prescribing of 10% of all antibiotics. However, volume-based reporting doesn't give any information about the equally important aspect of appropriateness of use.

Changing Prescribing Behavior

Dr. Edward Septimus, *Hospital Corporation of America*

The world is facing a crisis in infectious diseases, with widespread antimicrobial drug resistance occurring as increasing numbers of patients are immunosuppressed, new pathogens are emerging, and new drug development is decreasing. Misconceptions and barriers among physicians only add to the problem. For small clinics and physician groups, the problem seems to be real, but not of practical concern at their clinic level.

Passive intervention doesn't work, restrictive policies can be circumvented, and audits can be 'gamed'. When developing an intervention to change antibiotic prescribing practices, the attitudes, motivation and intentions among the immediate clinic culture must be understood. Antimicrobial stewardship is a team sport. Engagement of senior physician leadership and designation of an effective senior physician champion are imperative to developing a high performing clinical team and enactment of long term stewardship solutions. High-performing teams have a high degree of interaction, communication, and respect, with energy directed toward team vision and goals. Team members take great personal satisfaction from belonging to such a team, and all of this leads to an ability to hard wire a new culture and bring about lasting change.

Dr. Thomas Shryock asked if HCA and others have considered instituting changes in preventative medicine in addition to changes in antibiotic prescribing behavior? Both Dr. Septimus and Dr. Hicks responded that infection prevention through practices such as vaccination is critical, and a great strategy to prevent antibiotic use. Evidenced-based practices to prevent healthcare associated infections are another important part of prevention, which reduces antimicrobial use. Dr. Septimus also pointed out that, similar to successes in antibiotic prescription practices, human medicine in general has been successful in promoting vaccination among children, but has not had similar success with the adult population.

Panel: Science and Practice – How does the Science of Antibiotic Resistance and Use Get Applied in Veterinary and Farming Practices?

Dr. Eric Moore, *Norbrook, Inc.,* moderator

Panel: Dr. H. Morgan Scott, *Texas A&M University,* Dr. Donna Carver, *North Carolina State University*, Dr. Joel Nerem, *Pipestone Veterinary Services*

How does the Science of Antibiotic Resistance and Use Get Applied in Veterinary and Farming Practices?

Dr. H. Morgan Scott, *Texas A&M University*

In response to the crisis of antibiotic resistance, the World Health Organization developed a Global Action Plan in 2015, with objectives of strengthening the knowledge base, reducing infection incidence, and optimizing antimicrobial usage in both human and animal medicine.[14] Nations around the world have responded by developing their own national antimicrobial action plans (NAPs). China, Australia, and the United States report excellent progress, and many other countries are addressing the issue.

Antibiotic resistance can be approached through the DPSIR framework (Fig 2), which was originally developed by the European Environmental Agency (EEA) to describe response to pollutants. Resistant antimicrobials can be conceptualized as a type of pollutant. This framework identifies (D) driving forces, (P) pressures, (S) state, (I) impact, and (R) responses. The bacterial infection rate is the driving force for the use of antibiotics. The pressures leading to antibiotic resistance are the use of antibiotics. The state

for which we are concerned is antibiotic resistance itself. The impact of antibiotic resistance is treatment failure, leading to increased morbidity and mortality and increased costs of healthcare, and the responses of society and policymakers worldwide are the national action plans.

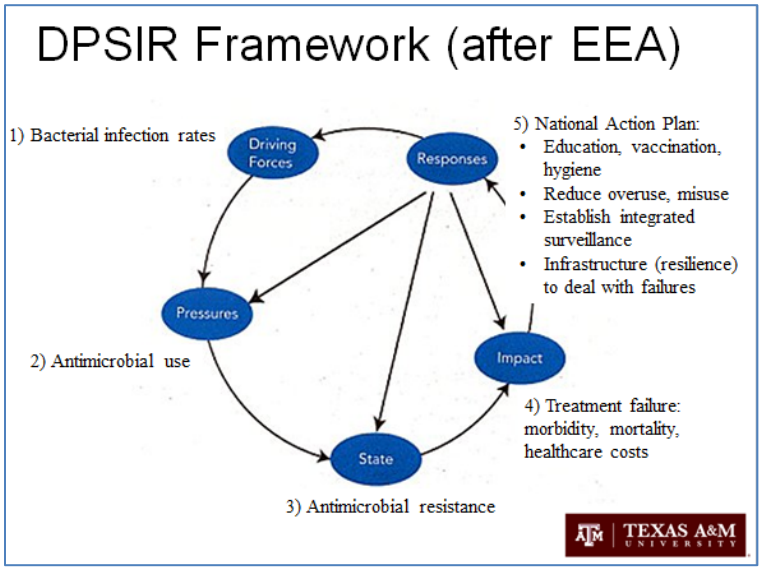

Fig 2. DPSIR Framework (Driving forces, Pressures, States, Impacts, Responses) for Antibiotic resistance

The U.S. National Action Plan includes five goals that reflect those of WHO, as well as specifically addressing national challenges:

1) Slow emergence and spread of resistant bacteria
2) Strengthen One Health surveillance efforts
3) Advance development of rapid diagnostic tests for resistant bacteria
4) Accelerate research and development for new antibiotics, other therapeutics, and vaccines
5) Improve international collaboration

These goals are necessarily vague, allowing for pursuit of broad steps and creative solutions.

One key to antimicrobial stewardship in production agriculture, like that in human medicine, is to target specific pathogens at work in livestock. However, antimicrobials don't attack only target pathogenic bacteria; they also attack non-target pathogens and commensals such as those of the gut microbiome. Similar to the difficulty of treating human patients in the ICU, treating animals in production agriculture involves trade-offs between killing target bacteria and non-target bacteria. The veterinarian may be successful in eliminating the infection treated, but at a cost of increased resistance among ancillary bacteria. Complicating the stewardship picture for production veterinarians are the questions of the number of animals treated (one or the entire cohort), where to address resistance (on- or off-farm), concerns for fostering increased resistance, and whether to slaughter a resistant animal. The antibiogram changes, sometimes dramatically, with each of these decisions.

Antibiotic Use in Poultry Production

Dr. Donna Carver, *North Carolina State University*

Caretakers of production animal health face challenges from often competing fronts: protecting antibiotics used in human health; protecting the welfare of the animals; protecting the market; and improving public perception of livestock production practices. There is significant conflict between meeting the consumer's desire for antibiotic free (ABF) chicken and the welfare of those chickens in the face of a disease outbreak . Antibiotic free birds meet market demand and reduce the exposure of the overall food animal population to antibiotics, but the science does not clearly indicate whether this reduced exposure leads to reduced antibiotic resistance. On the other hand, antibiotic free birds incur increased production costs, experience increased morbidity and mortality, and can have an increased incidence of salmonella. Veterinarians overseeing the health of ABF birds must balance market versus welfare needs, treating the birds when their welfare is threatened by illness, but understanding that treating with antibiotics results in losing the ABF status and disposition of the flock. This significantly raises the cost of production.

Attitudes are changing; groups important to the conversation are starting to consider commonalities. Research efforts are beginning to address the gut microbiome, and explore the use of pre- and pro-biotics to exclude pathogenic organisms. Because there are very few remaining antibiotics available to treat poultry, prevention, vaccination, botanicals and other alternatives are developing into the new front line in poultry medicine. Poultry production is moving toward a future where antibiotics are used only as a last resort.

Antibiotic Use in Pork Production

Dr. Joel Nerem, *Pipestone Veterinary Services*

Pipestone Veterinary Services is a large mixed-animal veterinary practice servicing mostly pigs. The practice believes strongly in the promotion of responsible use of antibiotics, and to that end, has developed a novel antimicrobial stewardship tool: the Pipestone Antibiotic Resistance Tracker (PART). This tool addresses the antimicrobial stewardship tenant of 'optimal use', tracking resistance over time of 175 independent producers with approximately 6.5 million pigs. Participants in the system are provided with tangible data on their antibiotic usage and resistance trends. Participation in the PART program is high, indicating that pig farmers, in addition to veterinarians and consumers, care about the issue of antibiotic resistance.

Initial data from a PART resistance study of 5 major swine pathogens yielded little change in resistance over 16 years. A pilot study comparing resistance differences between groups of pigs with high and low antibiotic use revealed little difference between the two groups. This initial data does not demonstrate that use of antibiotics in production swine affect antibiotic resistance in a significant way. However, the datasets are limited and preliminary. The PART system does demonstrate how practitioners are addressing resistance in the field, provides data on trends over time both for individual drugs and categories of drugs, and provides an antibiotic use benchmark for future comparisons.

Panel: State of the Science – What Do We Know? What Don't We Know?

Dr. Rick Sibbel, *Merck Animal Health*, moderator

Panel: Dr. Larry M. Granger, *USDA-APHIS*, Dr. Shelley Rankin, *University of Pennsylvania School of Veterinary Medicine*, Dr. Dr. Mark G. Papich, *North Carolina State University*, Dr. Heather Tate, *FDA Center for Veterinary Medicine.*

State of the Science

Dr. Larry Granger, *USDA-APHIS*

Research and education regarding antibiotic resistance is proceeding through multiple avenues. In 2015, the USDA developed an antimicrobial resistance (AMR) Action Plan which included the objective of instituting longitudinal studies to collect data regarding livestock antimicrobial use, AMR patterns, and livestock management practices. In 2017, the USDA received a $7 million appropriation to conduct on-farm surveillance sampling and testing to understand farm usage of antimicrobials and impact on antibiotic resistance levels and to inform policy decisions. As the AMR Action Plan objective and funding appropriation intersected, the USDA was able to undertake the studies needed to meet the objective. Data collection took place from May to September 2017, and a final report is expected in mid-2018.

At the laboratory level, the National Animal Health Laboratory Network (NAHLN) Pilot Project has been developed to implement AMR monitoring in veterinary diagnostic laboratories, and will be initiated in January 2018. This pilot project includes antimicrobial susceptibility testing of animal pathogens, with a target of 3000 samples. The objective of the NAHLN is to standardize methodologies in these labs, allowing data to be compared. Results from this pilot project are designed to offer partial fulfillment of a huge industry need for metadata, with reports generated to inform veterinary practitioners and enable them to make optimal treatment choices.

Finally, in the area of education, the National Veterinary Accreditation Program has developed two modules addressing antimicrobial use in animals, 'Antibiotics in Animals' and 'the Veterinary Feed Directive' to satisfy veterinary license renewal requirements. A third module on beekeeping, which includes information about the use of antimicrobials in bees, is slated to be released in 2018.[15] All modules are available at no cost and are approved by the Registry of Approved Continuing Education (RACE). In 2017, the module regarding the Veterinary Feed Directive was the most popular course offered by the National Veterinary Accreditation Program.

The state of the science is changing. Regulators, veterinarians, producers, and the livestock industry in general need to take note. In the past, we have treated pathogenic bacteria as isolates and viewed the bacteria world as a black and white constellation of good bugs and bad bugs. We have matched up specific drugs to specific bugs, and not really considered a drug's effect on non-target bacteria. However, bacteria in nature don't exist as isolates. Dysbiosis describes the effect that the community of bacteria has on expression of pathogenicity. Bacteria are constantly evolving, and exist in a dynamic network of interactions. The system is unpredictable and non-linear. Bacteria are even capable of self-organization, with emergence of complex character traits as a result of that organization. The microbial world is a complex, adaptive system, and antimicrobial use is a perturbation to that system. We need to

place more research emphasis on observational inquiry to help us understand the effect of antibiotic use on the microbiota and treatment of dysbiosis in the individual patient, as well as in large populations of animals in a specific phase of production and their environment. Predictive models based on this understanding will be most useful in decision making.

Antimicrobial Selection to Combat Resistance

Dr. Shelley Rankin, *University of Pennsylvania School of Veterinary Medicine*

For a long time, researchers have held the belief that mutant, resistant bacteria are only selected when antimicrobial drug concentrations fall within the window between the upper boundary of the mutant prevention concentration (MPC) and the lower boundary of the minimum inhibitory concentration (MIC). However, recent research advances have shown the development of resistance at antimicrobial concentrations well below the MIC. Reactive resistance is the theory that bacteria exposed to low concentrations of bactericidal antibiotics can become multi-drug resistance (MDR) through an increase in the mutation rate driven by the generation of reactive oxygen species. Under this theory, bacteria can become resistant when exposed to drug concentrations that are so low that they cannot be considered to be useful for treatment purposes.

It has been suggested that exposure of bacteria to concentrations of antibiotics below the MIC may be the fast track to MDR, and also that any bactericidal drug in a treatment cocktail may be able to generate MDR. We need to determine not why we should stop using antimicrobials, but rather, how we can use them such that this reactive resistance does not prevail.

CLSI: Clinical Laboratory Standards Institute

Dr. Mark Papich, *North Carolina State University*

One way to use antimicrobial drugs 'smarter' is to have standards for testing. The Clinical Laboratory and Standards Institute (CLSI) has set standards for defining antibiotic resistance.

We know that resistant strains in the intestine of animals have potential to be transmitted to people. However, this is where the controversy comes in – what is that potential? As demonstrated by this DC infographic (Fig 3), much of the current concerns about transfer of antibiotic resistance lie with the effects in the gut.

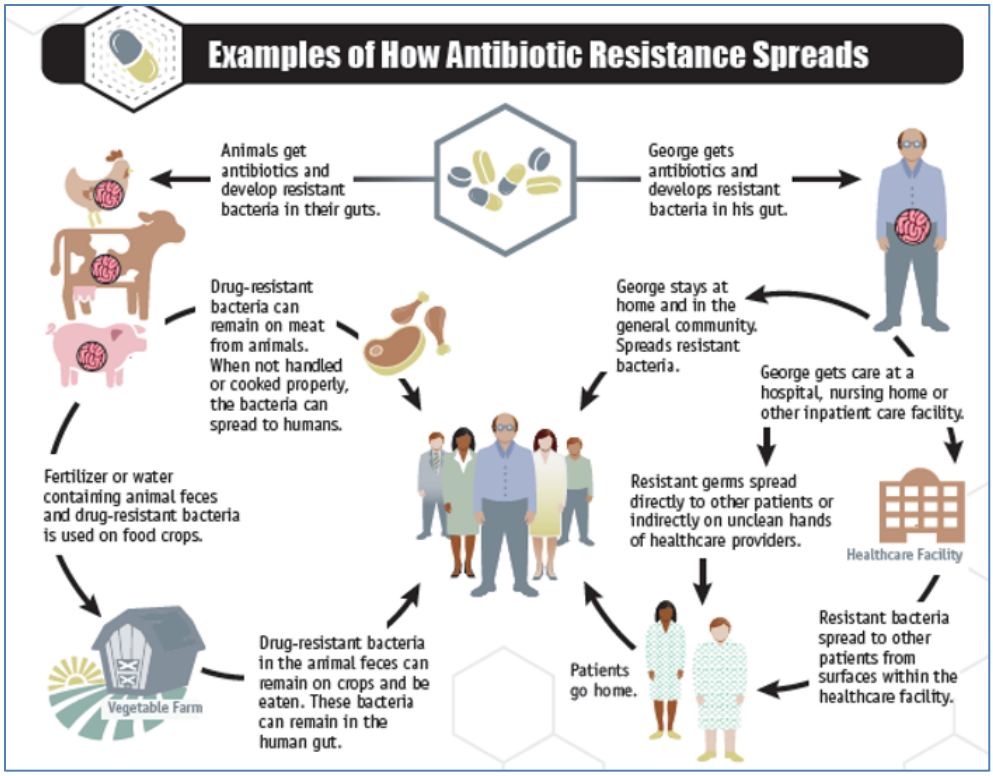

Fig. 3. CDC infographic describing how antibiotic resistance spreads via the gut.[16]

The most recent FDA 2015 Summary Report of Antimicrobial Use in Food Animals[17] indicates that most livestock antimicrobials are distributed in feed and water. What, if any, of these antimicrobial drugs ends up in the animal's gut? Antibiotic distribution studies in cattle focusing on two medically important drugs, enrofloxacin and ceftiofur, address the question of how much drug gets into the intestine, how it gets there, and if it is active or degraded in the gut.[18] Results of these studies indicate that much more drug ends up in the intestine than the plasma (Fig 4.) These studies also indicate that fecal *E.coli* concentrations, indicative of gut microflora, are initially suppressed after antibiotic treatment but rebound with time (Fig. 5). Populations of susceptible bacteria are responsible for this rebound. Finally, antibiotic resistance studies demonstrate an "inverted U" relationship where resistant bacteria rise initially and then decline with increasing antimicrobial exposure, until reaching a threshold at which resistance is suppressed (Fig 6).[19]

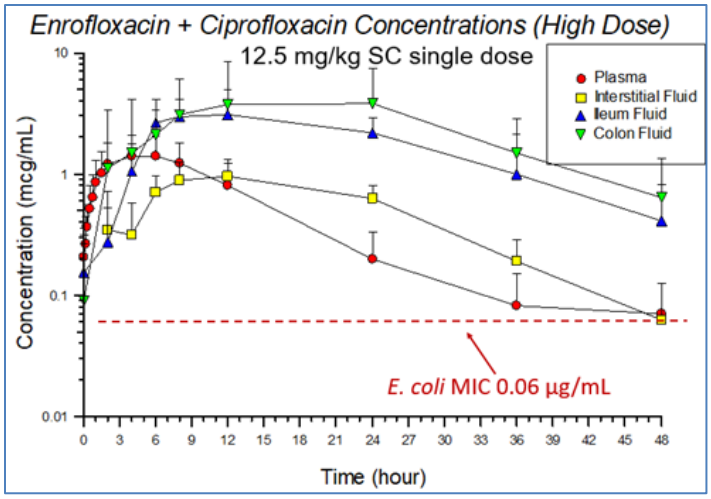

Fig 4. Concentration of enrofloxacin and ciprofloxacin in plasma, intestinal fluid, ileum fluid, and colon fluid over time.[17]

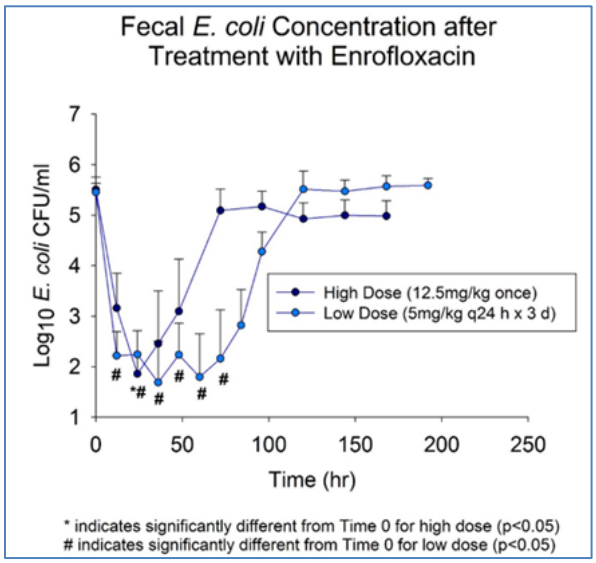

Fig 5. Fecal *E.coli* concentration after treatment with enrofloxacin, from 0 to 200 hours.[17]

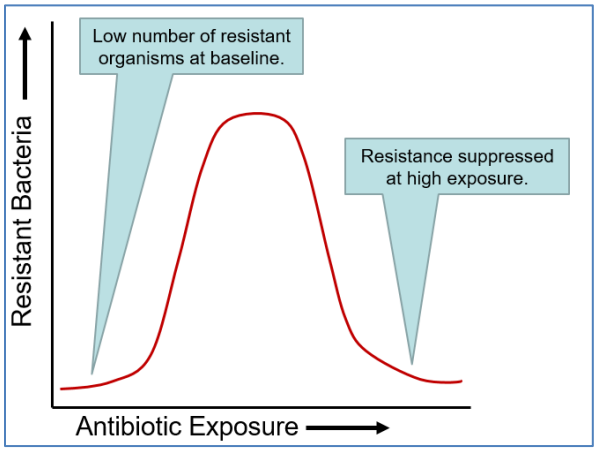

Fig 6. The 'inverted U' relationship between resistant bacteria and antibiotic exposure.[18]

We need to look at how we give antimicrobial drugs, and which drugs we give. Short course, high concentration treatment regiments have the potential to minimize development of resistance. However, that is only one piece of the puzzle. We should look more in depth into what happens in the intestine. We have the mechanisms to look, as demonstrated by these preliminary antimicrobial studies. Moving forward in the future, efforts should focus on developing agents either with low distribution to the intestine or that are inactivated in the intestine.

Twenty Years of Antibiotic Resistance Monitoring System (NARMS)

Dr. Heather Tate, *FDA Center for Veterinary Medicine*

NARMS is a collaborative program of state and local public health departments and universities, the FDA, the CDC, and the USDA. This national public health surveillance system tracks changes in the antimicrobial susceptibility of enteric bacteria found in ill people, retail meats, and food animals in the United States.[20] In 2012, the NARMS released a 5 year strategic plan with a number of different objectives directed toward completing four goals: to develop a more representative sampling strategy; to optimize data acquisition; to strengthen collaborative research projects; and to collaborate with international institutions. All of these goals have been successfully met via creative responses that are moving the antimicrobial stewardship conversation into the future.

To develop a more representative sampling strategy, the FDA has encouraged states to join the retail meat testing program, which has just 11 states in 2012. By 2018 participation in the program will have more than doubled, increasing to 21 states. Additionally, the number of samples collected has increased dramatically. In 2018 the number of samples collected will have almost tripled the amount collected in 2016. At the same time that the number of samples collected has increased dramatically, the contamination measures in retail meat samples has decreased, providing evidence for a significant decrease in contamination of retail meat overall. The FDA has also worked in conjunction with the USDA-FSIS to create a fecal sampling program closer to the slaughter plant's 'front door' and more representative of production classes than previous animal slaughter sampling schemes.

To optimize data acquisition, NARMS developed and launched the 'NARMS Now' database tool in 2015.[21] With this tool, resistance trends can be visualized and compared, whole genome sequencing data describing salmonella are available, and multidrug resistance can be compared among antimicrobial agents.

Through collaborative research projects, the FDA has been able to evaluate and apply existing research tools and develop new ones. Much of this development relies on using whole genome sequencing as a routine part of antimicrobial surveillance. NARMS has shown that WGS can accurately predict antimicrobial resistance in a number of organisms, setting the stage for development of a resistome tracker tool. This tool fits on top of the National Center for Biotechnology Information (NCBI) platform, allowing easy visualization of resistance trends. Among other research foci is the field of metagenomics which is being used to survey resistance genes in animal ceca and retail meat samples.

Looking forward, NARMS is moving toward an integrated to a One Health Surveillance program to better address the complex issues surrounding antimicrobial stewardship. The FDA is partnering with at least twenty organizations, representing a variety of stakeholders.

Panel: Science and Practice – Moving on to Solutions and Positive Outcomes Based on Science

Dr. Kerry Keffaber, *Elanco Animal Health*, moderator

Panel: Dr. Jeff Bender, *University of Minnesota*, Dr. Nora Schrag, *Kansas State University*, Joe Swedburg, *Farm Foundation, Hormel Foods Corporation (retired)*, Dr. David G. White, *University of Tennessee Institute for Agriculture*

How Do We Find the Answers to What We Don't Know?

Dr. Jeff Bender, *University of Minnesota*

In the assessment of the antimicrobial stewardship knowledge base from the perspective of a hospital epidemiologist and public health veterinarian, five topics emerge as foci for efforts at finding answers. These are infection control and prevention, antimicrobial use, stewardship programs, educational outreach, and global policy.

There are many guidelines and clinical trials supporting infection control and prevention on the human side of medicine. However, on the veterinary side there is very little information. In the specific area of antimicrobial use, human medicine has penned a number of antibiotic use and clinical practice guidelines, while veterinary medicine has very limited guidance documentation. Data from Banfield Pet Hospital indicate that when there are guidelines, the alignment of veterinary antibiotic usage with recommendations ranges widely, from 22% to 80%.[22] Many veterinarians are not aware of even these limited guidelines for antimicrobial usage. Additional tools and supporting materials that would improve veterinary antimicrobial stewardship include the development of rapid diagnostic tests, and development and distribution of regional antibiograms and biosecurity in infection control best practices.

The core elements of any animal stewardship program, regardless of species, include a practice commitment to stewardship, an identified champion of antimicrobial stewardship within the practice, a list of specific actions to be implemented, measurable stewardship outcomes, and provision of resources and education for both staff veterinarians and clients. One example of educational outreach to veterinarians is a series of species-specific, case-based web training modules developed at the University of Minnesota.[23]

Dr. Jeff Watts of Zoetis Corporation asked about the role of the Responsible Use of Medicines in Agriculture (RUMA) Alliance and other similar organizations in developing and delivering antimicrobial stewardship infrastructure. Dr. Bender pointed out that organizations like RUMA have potential for

bringing together people to facilitate education, engagement and action. Dr. Sue Duran, a pharmacist from Auburn Veterinary College, noted that many pet owners are unaware of antibiotic resistance dangers related to pets under treatment with antibiotics. Companion animals often interact with their owners in intimate setting, such as co-sleeping, and when under treatment, there is potential for transfer of antibiotic resistance through this interaction. It is imperative that companion animal owners' knowledge gaps be addressed, in addition to those of veterinarians and livestock producers.

Antibiotic resistance and responsible use are global issues, and as such, require global policy. Eighty-five percent of countries have in place antimicrobial resistance (AMR) Action Plans, which is a good start. However, only 52% of low to middle income countries – those countries that are the most vulnerable to increased deaths from AMR – have national level plans, and of those, just 7% have systems in place for animals.

In summary, antibiotic resistance is a global challenge. To address the challenge, both human and veterinary medicine must apply practical interventions, evaluate and improve stewardship programs, identify and institute best practices, and develop key communication messages for practitioners, patients, and the public.

Measuring Antimicrobial Use

Dr. Nora Schrag, *Kansas State University*

As antibiotic resistance and antimicrobial stewardship has emerged as challenging global issue over the past two decades, many antimicrobial use measures that have been employed to try to characterize the problem and response. An obvious starting point is the measurement of drug use – but such a measurement is not straightforward, and does not yield straightforward data. Some drug measurement choices include the total drug amount used, the number of days of drug therapy, the number of days of drug exposure, or the number of animals treated. However, depending on what is measured, the data collected differ dramatically. In this, there is a cautionary tale: if we start setting policy based upon total amount of drug used we will miss the drastically different, and many would argue far more important, granular individual-level data.

Instead of driving to simply reduce the total amount of antimicrobial drugs used, a more useful goal is to optimize antimicrobial use. Field efficacy studies can determine what works, in terms of drug, dose, route, and regiment. With those data, any use that does not work could be eliminated, allowing for targeted optimization of antimicrobial drug use – a much more refined and efficacious approach to antimicrobial stewardship than simply reducing gross amounts.

Partnership: Farm Foundation and Pew Charitable Trusts

Mr. Joe Swedburg, *Farm Foundation, Hormel Food Corporation (retired)*

The Farm Foundation is a nonprofit agriculture policy institute dedicated to cultivating non-partisan collaboration to provide objective food-chain policy analysis on the entire food chain.[9] The Pew Charitable Trusts is a non-profit non-governmental organization (NGO) public policy think tank. [24] The

Farm Foundation has recently entered into a collaboration with the Pew Charitable Trusts, forming the Farm Foundation Pew Working Group. This working group consists of processors and producers, livestock groups, pharmaceutical companies, retailers and food service operators, all of whom are willing to 'think outside the box' and work with partners often considered adversaries. By the second meeting of the group, the various participants had started sharing each other's philosophies, and the initial conversations coalesced into shared values and beliefs. From this point, the group was able to focus on commonalities instead of differences. We have a lot more in common that we do differences, and the Farm Foundation Pew Working Group is proving that collaboration can work.

One of the things that has often been lacking across all levels of the antimicrobial stewardship conversation is communication. A lot of excellent work that has happened in the past and is continuing to occur, but has failed to be communicated. Research indicates that 50% to 70% of people haven't made up their minds about antimicrobial stewardship, and this group can be reached with targeted messaging. If we can identify a receptive audience and produce effective education messaging, we can move the antimicrobial stewardship conversation forward through understanding of the work that has been done, the work that is currently being done, and the work that needs to get done in the future.

Ernie Birchmeier from the Michigan Farm Bureau asked how agriculture can partner with a group like Pew Charitable Trusts that has, in the past, presented a negative opinion of the entire livestock industry? Mr. Swedburg pointed out that Pew has a voice and large audience, and Pew approached the Farm Foundation Working Group with an interest in collaboration. Pew's position and visibility gives leverage and range to the antimicrobial stewardship message. It has been a very positive collaboration so far, and the Farm Foundation Pew Working Group has found that they can get a lot more done working together across the aisle than moving in opposite directions.

Can We Build the Perfect One Health AMR Intersection?

Dr. David White, *University of Tennessee Institute for Agriculture*

The resistome is defined as all AMR genes and their precursors in pathogenic and non-pathogenic bacteria. Genes move laterally through the resistome, without regard for boundaries, travelling back and forth between the normal flora of humans and animals, pathogens, and soil organisms. The mobilome is the term describing the elements of the resistome that move freely throughout the system. As a result of this mobility, the available gene pool is quite large, and the environment, animals, and humans all share the same resistome (Fig 7).[24]

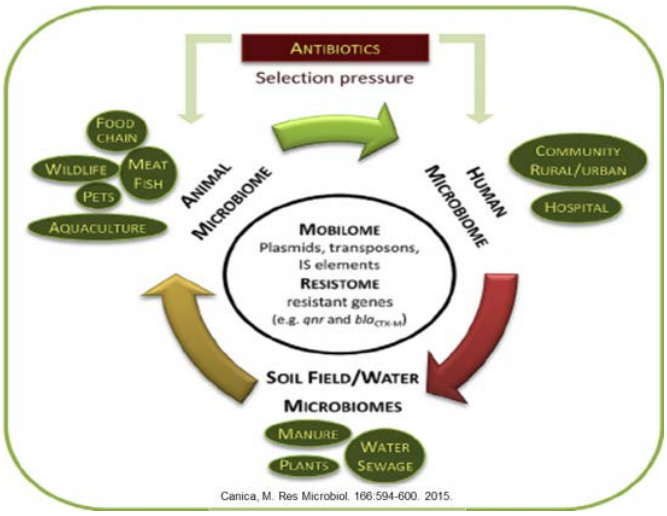

Fig 7. Genes move laterally through the resistome.[25]

From a research perspective, this mobile resistome generates a number of questions. How do resistance mechanisms evolve over time? How is resistance transferred, and how often? What is the contribution of the normal microbiome to resistance? What is the environmental dimension of antibiotic resistance? These and other questions are the focus of ongoing antibiotic resistance research.

How do we find the answers? Researchers start with the usual methods of answering research questions: strengthening the knowledge base; publishing research findings; collaboration with other researchers; and use of the data to inform future research efforts. However, because of the mobility of the resistome and the shared burden of antibiotic resistance between animals, humans, and the environment, obtaining answers to research questions requires a creative, expansive approach. We must be willing must bridge different disciplines and reach out to non-traditional research partners not only to address the questions, but also to determine what the issues really are. We must create strategic public-private partnerships among diverse stakeholders, and build a coordinated multidisciplinary road map to the answers and solutions – a road map that includes funding support, global consortiums, and action plans that move knowledge to implementation.

Panel: Data Needs – What Information Would be Most Helpful to Producers, Veterinarians, Retailers, and Government & Public Health Officials?

Dr. Steve Solomon, *Global Health Consulting LLC*, moderator

Panel: Ms. Shannon Wharton, *Hy-Plains Feedyard*, Dr. Bob Smith, *Veterinary Research and Consulting Services*, Dr. Peter Davies, *University of Minnesota*, Ms. Lori J. Marco, *Hormel Foods Corporation*, Mr. Mike Brown, *The Kroger Company*, Dr. Dawn Sievert, *Division of Foodborne, Waterborne & Environmental Diseases, CDC*

Antibiotic resistance is a One Health Issue

Dr. Dawn Sievert, *Division of Foodborne, Waterborne & Environmental Diseases, CDC*

Because antibiotic resistance is an issue across the One Health spectrum, a focus on preventing and controlling disease and death caused by foodborne, waterborne, and environmentally transmitted infections must be considered in the conversation. The CDC's efforts with regards to foodborne outbreaks and the issue of resistance are often focused on response. The future goal is to become more proactive, getting ahead of the outbreaks and their sources via improved data, earlier indicators, new relationships, and stronger collaborations.

How to Collect and Disseminate Information Accurately and Without Fear

Mr. Mike Brown, *the Kroger Company*

Government regulatory agencies produce rules that are relied upon to protect and meet consumer needs. However, the message generated by regulation often gets muddled as parts are received out of context, leading to fear and mistrust by the consumer. We need to communicate a message that is clear, complete and to the point, and ensure that the message supports the agriculture that provides the food.

Dr. Solomon asked about Kroger's efforts with dairy producers. Kroger's Dairy Checkoff Program is a tool Kroger uses to audit their producers' management practices. The program started with animal welfare, and is now moving toward sustainability. Participating producers are helping to act on more judicious use of antibiotics. The dairy industry is making positive progress, and formal programs such as Kroger's Dairy Checkoff Program demonstrate to the public exactly what producers are doing to address pressing issues such as antibiotic resistance.

Dr. Lucas Pantaleon of Virox Animal Health suggested that agriculture overall needs to find a unifying message despite any differences that we may have. Dr. Davies agreed, emphasizing that individual industries need to do the best job they can to unify within their own industry. Ms. Wharton pointed out that industry working together, instead of competing among themselves, presents a positive message to the consumer. Ms. Marco agreed, and went one step further. Once each industry has worked out their particular unifying message, the entirety of the agriculture industry may be able to aggregate a message that conveys understanding of antibiotic resistance issues while demonstrating a united front as the industry works together to move forward as better stewards of antibiotics. This is an extremely positive message for the consumer.

Helping the Consumer and Producer Understand Antimicrobial Stewardship

Ms. Lori Marco, *Hormel Foods Corporation*

Consumers report an interest in reducing consumption of protein raised with antibiotics. However, as discussed throughout this forum, completely eliminating antibiotic use in animal agriculture is not a feasible or even a desirable solution. We need to work with consumers, in addition to producers, veterinarians, the agriculture industry and government officials, to understand and disseminate the message of what antimicrobial stewardship means. The solutions are not simple, but both sides deserve to understand the realities of antibiotic resistance and their role in its prevention.

Dr. Smith postulated that the acceptance of animal protein will have to be done at the local level. Bringing people onto farms to visit and see for themselves how animals are raised and how antibiotics are used within the greater scope of the production system can be tremendously helpful.

Understanding How Activities in the Farm and Production Environment Translate to Human Health Risk

Dr. Peter Davies, *University of Minnesota*

From a livestock industry perspective, the most important aspect of discussion to give direction to data collection is the definition of 'herd'. A focus on simply reducing total amount of drugs used fails to take into account the numbers and size of animals in production. If we want to achieve a long-term goal of judicious use of antibiotics, we need to understand what exactly constitutes judicious and proper use. In addition to judicious use, we need to understand how farm and production environment activities translate to human health risk. Only once we have an understanding of the drugs we should be using, and how that use might affect human health, can we effectively realize stewardship goals.

Successes and Challenges in the Beef Industry

Dr. Bob Smith, *Veterinary Research and Consulting Services, LLC*

There are 92 to 93 million cattle in the United States. As Dr. Davies mentioned, this population uses thousands of tons of antibiotics simply due to sheer numbers. This amount of use alone does not indicate suboptimal use of antimicrobials – it simply means that there are a lot of animals to treat.

The beef industry has had several successes since the 1990s. Intervention strategies have been put in place to protect the food supply from *E.coli* contamination. Injection site lesions, a huge issue in the 1990s, have been reduced in incidence significantly through industry-wide adoption of a simple, but effective, mitigation. Animal welfare standards have been instituted, and low stress handling is now the norm throughout the industry.

Dr. Davies noted other agriculture industry success: violative residues in hogs, and FDA's findings of resistance isolates. In 1978, 14% of hog slaughter samples in the Unites States had violative residues at slaughter. As of 2017, only 0.2% have violative residues.

The beef industry has a proven track record in addressing and finding solutions to tough problems. As a representative of that industry, he is happy to be at the table, discussing antimicrobial stewardship solution with representative from a range of backgrounds and perspectives. It is this sort of non-traditional collaboration that will enable us to find and implement solutions.

Collecting Useful Data

Ms. Shannon Wharton, *Hy-Plains Feedyard*

Labor and economics are what drive the producer. Data collection and analysis are the keys to successful solutions. We can solve the antibiotic resistance problem – it is just a question of collecting the data.

Dr. Bender raised the question of how the agriculture industry can collect data in a robust fashion while maintaining the integrity and confidentiality of the data. Dr. Davies' response emphasized the importance of aggregate metadata in decision-making. Dr. Sievert noted that the accurate and meaningful aggregation of non-standardized data would be extremely challenging or impossible. She pointed out that data can be collected and used successfully for benchmarking, while protecting confidentiality, and cited hospital reporting into the CDC National Healthcare Safety Network as an example.

What Can Be Done to Get the Data We Need?

Panelists

At the conclusion of the panel, Dr. Solomon noted that much of the discussion has involved data needs. He asked the opinions of the panelists on one or two barriers that can be overcome to help obtain the data needed to address antibiotic resistance.

Many panelists voiced a concern and need for data security and trust in those who are collecting and holding that data. Producers and others must overcome the need to protect their data if it is to be shared, and in order for them to set aside that instinct, they must trust that their data will be held and used confidentially, and protected from theft.

A corollary to the collection of data is comparison of disparate data and the ease of collection of that data. Electronic data transfer systems are not currently in place for antibiotic resistance data. Development of a standard platform for collected data, so that it can be meaningfully compared, is imperative to such a system. An electronic data transfer system would allow for timely collection and accurate comparison of collected data, maximizing its use and efficacy and honoring the trust placed by those providing that data.

Dr. Smith voiced a need for policy based on science, and better public messaging and communication across the spectrum to describe the issue, the needs, and steps to solutions.

Finally, Dr. Dawn Sievert emphasized the need for reliable laboratory diagnostics and reporting of standardized information to provide accurate, comparable, useful data with which to make judicious antimicrobial use decisions.

Who do you trust? Breaking through to the Consumer in a Post-Truth World

Ms. Leah Beyer & Ms. Colleen Parr Dekker, *Elanco Animal Health*

There is a changing consumer mindset regarding the food they eat and feed their families. The consumer is asking for more transparency and more clarity. Even as this shift is occurring, negative

claims have accelerated, with marketing announcing not what's in the food, but rather what is not in the food. The unintended consequences of these campaigns are compromised animal welfare, increased mortality, and increased cost of production among animals that are 'antibiotic free'. Environmental resources are overused as animals take longer to reach market weight. The consumer is asking for clarity, but only getting more confusion. Label fatigue has set in as the consumer loses confidence that they know which foods are good and which foods are bad. Consumers have begun to question all food marketing, including organic and 'free from' labels. They have become skeptical of all sides of the conversation. This skepticism has opened a window of opportunity to share accurate agriculture information. If this information can be shared without an agenda, the consumer is open to it.

There is a disconnect between food and agriculture on social media. Although the agriculture industry perceives that the conversation is mostly about food production issues, in reality only a very few people are having this conversation. Most people are talking about taste and cost – a huge percentage of the social media is actually recipe sharing (Fig 9).

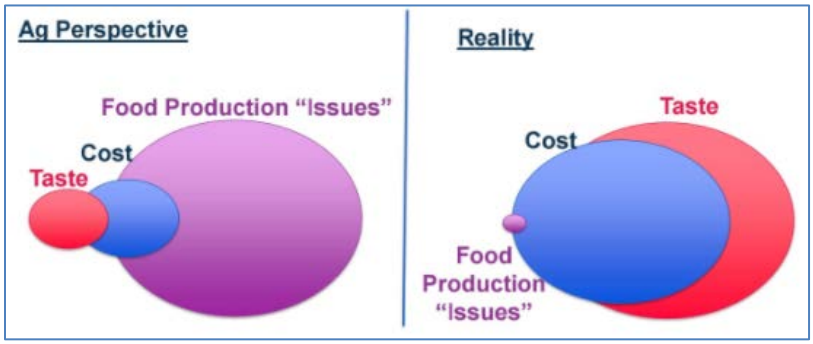

Fig. 9. Social media and the food conversation: the agriculture perspective vs. reality

Of those propagating the discussion of food production via social media, activists don't outnumber agriculture advocates – they are simply doing more online. The average agriculture advocate produces one tweet a week. The average activist produces 300 tweets per week. We need to do more to get our message out. Our shared voice is really small, registering just 0.2% of the total conversation. Most consumers don't know what antimicrobial stewardship even means. We have good stuff coming out, but we do a very poor job of broadcasting our message.

The antibiotic message and conversation is shifting from being driven by the government to being driven by food. This conversation is being led by food companies, with twitter handles such as #promotion and #perduecrew. In fact, Perdue Chicken represents more than 50% of the agriculture advocate conversation, using mechanisms such as the 'Perdue eliminates antibiotics' paid social campaign. Antibiotic alternatives and forum-like discussions lead the agriculture industry discussion.

How do we talk about food production in a way that is meaningful to the consumer? Misconception and fact need to be presented. We need to work with social media influencers: dieticians, food bloggers, and the farmers themselves. Food bloggers have stepped in to fill the gap left when kids stopped taking home economics. People are so insecure about their cooking that if one of these food bloggers tells

them which brands to buy, they will buy the brand. Food bloggers are extremely influential, and agriculture can both use and learn from their success.

We need to rebuild consumer trust in antibiotics as an aid to a humane animal rearing and a healthy food supply. We must acknowledge the legitimate concerns of the consumer - a much better way to begin the conversation than denying concerns exist. We must accept responsibility for being part of the system, thus part of the problem. Messages that suggest the industry isn't to blame utterly fail. As we convey our message, we must discuss the wider range of things that farmers care about and put conversation in context of the larger animal health picture. Talking exclusively about antibiotics comes across as self- interest – discussion of the whole scope of animal health is more credible, and perceived as more trustworthy. Finally, the industry must remember that consumers don't speak jargon or science. The message must be presented in common language that the consumer can understand.

Consumers want to understand more about where their food comes from, and specifics provided by experts build that trust. We must provide those specifics with the understanding that consumers may still choose antibiotic free, non-GMO, or other negative label claims. Regardless, consumers still deserve the choice. Consumers are tired of being told what to do. We must look toward positive label claims to provide explanation. Agriculture must stop fighting with agriculture. We are all on the same team, regardless of production methods, and when we work together, the consumer perceives that as a good thing. Words and approach matter. We have to stop educating, and start engaging.

One Health and the Politics of Antibiotic resistance

Dr. Laura H. Kahn, *Princeton University*

Food security is of paramount importance around the globe. Agriculture and food security are the foundation of civilization. Food security is inextricably linked with global health, global sustainability, and international security. There is no global health without global food security. Many diseases (*e.g.* Ebola, Zika, Chikungunya, SARS, Nipah, etc.) are emerging and spreading because of widespread deforestation, environmental degradation, and bushmeat consumption—and all are linked to food security. Finally, global climate change affects food security, as even small changes in the global temperature affect food supply.

In the 1990s and prior, agriculture in Denmark relied heavily on avoparcin, a close relative of vancomycin, and other growth promoting antibiotics in production livestock. However, in January 1995, VRE (vancomycin resistant *enterococcus faecium*) was identified in healthy Danish pigs and chickens. Danish scientists became concerned about emergence of VRE in their livestock, and concluded they had to change their practices and stop using growth promoting antibiotics. In 1995, Danish producers voluntarily stopped using avoparcin, and in 1999, due to consumer concerns, they stopped using all growth promoting agents.

The ban on avoparcin resulted in a precipitous decrease in VRE measured in farm animals. However, VRE in hospitalized humans continued to increase, well after the effects of the ban were noted in livestock (Fig 10).[26]

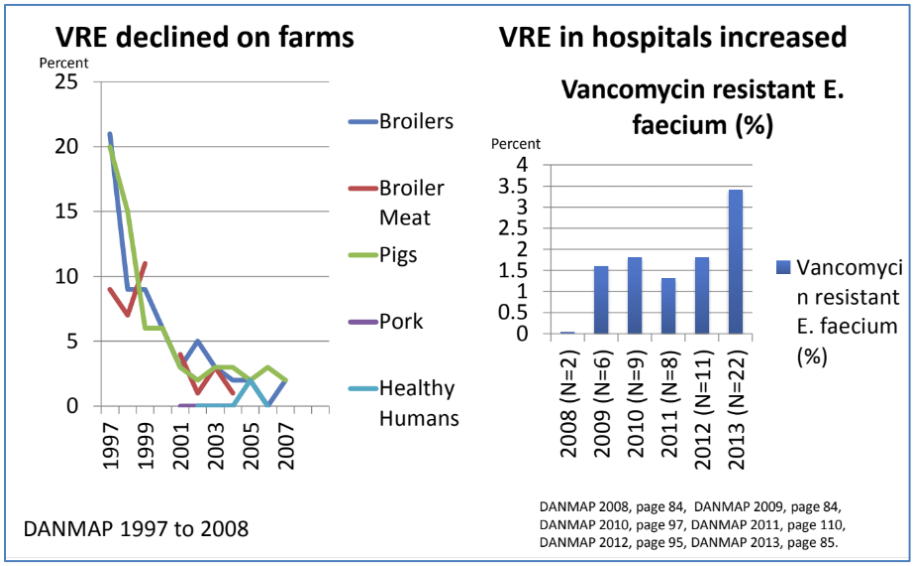

Fig 10. VRE on farms and in hospitals, 1997 to 2013.[25]

In Europe as a whole, antibiotic sales for food animals mostly correspond with the size of livestock production.[27,28] Antibiotic sales for humans vary widely between countries, but not necessarily due to size of the population, suggesting that the human use of antibiotics is cultural. Use may vary by country, but even taking that variation into account, data from the European Antibiotic Resistance Surveillance Network shows no consistent trend in VRE isolates for hospitalized humans (Fig 11.) In Europe, all growth promoting antibiotics, including avoparcin, were banned in January 2006. If avoparcin had been the cause of human VRE, then trend data would have demonstrated a decrease in VRE in every country. Instead, there is no identifiable, collective decrease. The data suggest that the ban on avoparcin had no effect on human VRE.

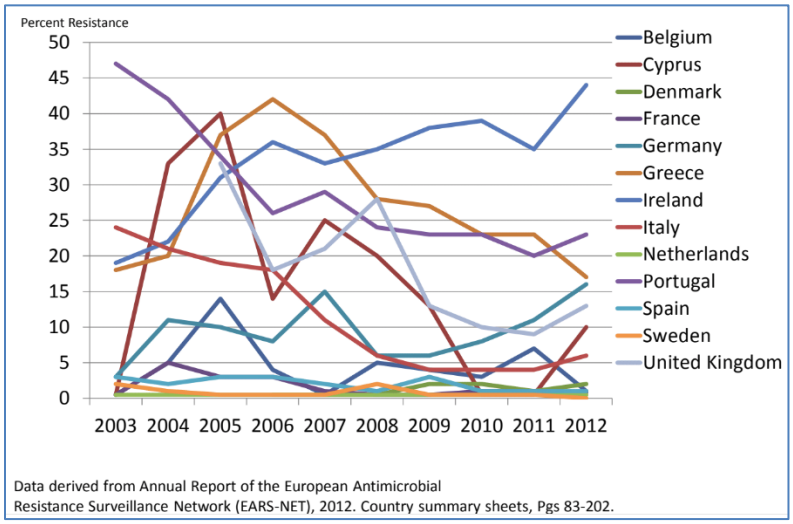

Fig 11. VRE isolates from hospitalized humans in 13 E.U. countries

The United States never approved use of the antibiotic avoparcin, due to concerns for carcinogenicity. However, even without an avoparcin presence, VRE emerged in the 1990s in United States hospitals, preceding the spread in European hospital by approximately a decade. Currently, 77% of healthcare associated infections are due to VRE.[8] Unlike the trend among humans, vancomycin resistance among United States livestock measured zero in all the years tested.[29, 30] There is no evidence that VRE came from food producing animals in the United States.

The United States and the E.U. both have experienced increasing numbers of cases of VRE in hospitalized humans. Cases of VRE appeared among hospitalized humans in the United States 10 years before the E.U. There is no evidence that the VRE experienced by hospitalized humans came from livestock in the United States, and while VRE was found among European livestock, there is no evidence that the avoparcin ban reduced VRE among humans in the E.U. What's going on?[31] Due in part to horizontal gene transmission, the epidemiology of resistant bacteria is confusing. To really tease out the epidemiology, we have to look at the entire genome of the organisms through whole genome sequencing. A clone, VRE CC 17, appears to be responsible for much of the hospital cases around the world. Whole genome sequencing suggests that the VRE CC 17 precursor came from dogs as Ampicillin resistant *Enterococcus faecium* (AREF CC 17). Dogs are treated with ampicillin, not vancomycin. In humans, *Enterococcus faecium* was initially treated with Ampicillin until it developed resistance and subsequently required treatment with Vancomycin. Additionally, from an environmental standpoint, there is plenty of opportunity to share genetic material and microbes between humans and dogs, due to the intimate nature of people's relationships with their pets.

The E.U. ban on growth-promoting antibiotics did not reduce incidence of VRE in humans. Research using whole genome sequencing was required to help explain why. The suggested reservoir, dogs, was a surprise to everyone. Future investigations into the mechanisms of antibiotic resistance must include whole genome sequencing, be conducted with an open mind and without prejudice, and take into account non-traditional avenues of resistance such as infections in pets.

Dr. Peter Davies from the University of Minnesota asked about the generalization of the VRE results? Dr. Kahn indicated that the findings regarding VRE apply to VRE alone, and not other organisms. Because of this fact, long held beliefs regarding the food animal etiology of antibiotic resistance are still the pervasive theory among the medical research community. This belief and the lack of generalized data are some of reasons why whole genome sequencing is so critical in the investigation of antibiotic resistance.

Our bodies are hypersystems of many microbes, and antibiotics indiscriminately kill pathogenic bacteria and beneficial bacteria. There is much we don't know about how the bacterial ecosystem works. Microbes can be both positively and negatively associated with growth. Some studies have found that if starving children are given low dose antibiotics their survival increased markedly above and beyond just giving food, in a similar effect to that seen with farm animal given growth promotants. Antibiotics are

easy to use, and efficient, but they come with significant costs to the environment. AMR genes appear to be ancient, and everywhere. Bacteria seem to use these chemicals as a form of communication – and antibiotic use by humans (on animals and humans), regardless of the effect of the particular antibiotic, disrupts that system, thus is changing the whole microbial ecosystem of the planet.

We Are the World: Collaboration is Not Optional

Dr. Elizabeth Hermsen, *Merck & Co., Inc.*

Three take-away messages from the antimicrobial resistance (AMR) discussion are that AMR is a significant problem; stewardship is part of the solution; and multi-sector stakeholder cooperation is absolutely essential.

Merck uses two analogies to describe two aspects of their approach to antimicrobial stewardship (AMS). The first is the analogy of a house, with a strong foundation of a One Health approach, including human health, animal health, and environmental sciences, supporting walls of infection prevention, diagnosis, and surveillance, and a roof of AMS (Fig 12), emphasizing that all four components are dependent on another. The second is the 'Star of Stewardship.' The center of the star represents the diagnosis, which is required to make optimal treatment decisions, while the points represent Drug, Duration, Dose, De-escalation, and Door. 'Door' refers to setting of care (Fig 13). The goal of the star of stewardship is to optimize outcomes while minimizing unintended consequences.

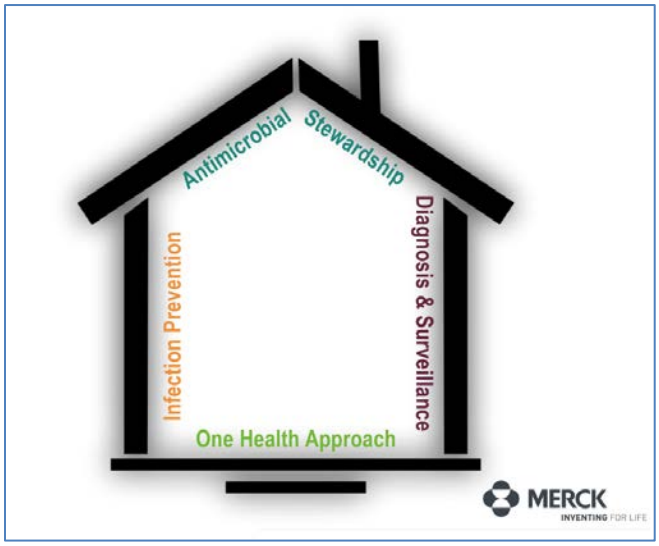

Fig 12. House analogy for antimicrobial stewardship.

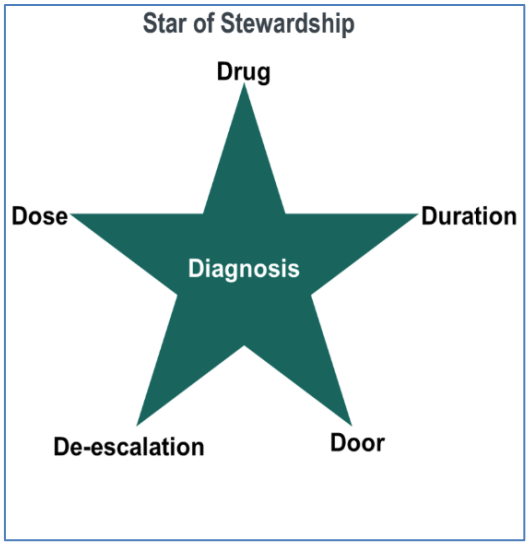

Fig 13. Merck 'Star of Stewardship.'

AMS is important to the pharmaceutical industry for a variety of reasons, foremost of which is the realization of positive outcomes in both animals and humans. Keeping people and animals healthy is the reason they're in business. In addition, AMS improves molecule longevity, increasing the lifespan of any given antibiotic, prevents collateral damage by keeping patients with other comorbidities (e.g., cancer, diabetes) free of MDR infections, and finally, enhances company credibility and trust with the consumers they serve.

Merck has created an AMS Council whose primary actions are to promote alignment of AMS activities and facilitate championship for AMS across the organization. This Council provides the strong foundation of a One Health approach, encouraging the active participation of representatives of animal health, human health, and environmental health. One output of the AMS Council is the development of a One Merck Global AMR Action Plan. The Action Plan addresses four main areas – infection prevention, innovation, stewardship, and surveillance awareness – underpinned by advocacy for policy solutions to address the global challenges limiting development of and access to new antibiotics, vaccines, and diagnostics.

Merck's pathway to partnership within the company began with a conversation between human health and animal health designees at the White House Forum on AMS, from which grew the AMS Council and the AMS Small Network Model. These groups developed frameworks and committees with voices from animal, human, and environmental representatives, and led to the opportunity for open and continuing communication.

Collaboration is not optional. Stakeholders representing diverse aspects and views must come together in order to fully characterize the issue, and to develop creative, effective stewardship solutions that address all facets of the conversation. Change can only come when we stand together as one.

Dr. Miles Theurer, a veterinarian with Hy-Plains Feedyard, asked if any steps are being taken to share best practices that lead to success? Dr. Hermsen noted that there are steps being taken in the field of human health to move in that direction, however, there is a challenging lack of consensus on which practices constitute the best metrics for success. Certain steps have worked well, such as the development of clinical pathways for prescribers to follow. The application of implementation and behavior sciences is growing – these are two aspects that successful AMS programs must consider.

Panel: What are the Communication Research Needs to Take Next Steps?

Dr. Nevil Speer, *AgriClear*, moderator

Panelists: Dr. Eric Moore, *Norbrook, Inc.*; Dr. William T. Flynn, *FDA Center for Veterinary Medicine*, dr. Karin Hoelzer, *The Pew Charitable Trusts*, Dr. Larry M. Granger, *USDA APHIS*, Dr. Nora Schrag, *Kansas State University*, Ms. Lori J. Marco, *Hormel Food Corporation*, Dr. Bob Smith, *Veterinary Research and Consulting Services LLC*

Communication Must Be Clear & Concise

Dr. Eric Moore, *Norbrook, Inc.*

Communication must be clear, concise and consistent. The message must be consistent across all stakeholders. The consumer must to receive the message in a way they can understand, but in a way that is also fully transparent.

Communication of the Intended Goal

Dr. William T. Flynn, *FDA Center for Veterinary Medicine*

We need to be clear in communicating the intended goal of antimicrobial stewardship. He is concerned about a focus simply on reduction of use. Raising animals without antibiotics isn't the goal – optimal and judicious use of antibiotics is the goal. Creating that message of optimal and judicious use for consumers poses significant challenges for the agriculture industry.

Key Research Needs for Antibiotic Stewardship

Dr. Karin Hoelzer, *The Pew Charitable Trusts*

Three research questions regarding use of antibiotics in livestock are needed to inform antimicrobial stewardship: how are antibiotics currently being used, how should antibiotics be used, and what can be done to reduce the need for antibiotic use?

Research into how antibiotics are currently used provides the baseline to evaluate the impact of stewardship improvements and prioritize research needs. The question of how antibiotics should be used is central to stewardship. Key elements to address include: farmers' and veterinarians' decision-making processes around antibiotic use; how to demonstrate good stewardship; and how to create incentives for continuous improvement and innovation in stewardship. Facilitation of judicious antibiotic use also requires data to answer questions such as how to use antibiotics most effectively and how to prevent unintended consequences. Finally, strategies such as the use of alternative products, the development of disease resistant breeds, and optimizing management practices can be used to reduce the need for antibiotic use. More research is needed in all of these areas.

Cooperation to Obtain Data

Dr. Larry Granger, *USDA-APHIS*

It is important that the agriculture industry and associated stakeholders work together to collect data. The veterinary profession, in particular, needs to embrace the responsibility of the veterinary feed directive, and part of that responsibility is reporting antimicrobial use. In pursuit of any data, we need to remember the big picture – the microbiome. It's not the single bacterium that we need to be concerned with, but rather the bacterial ecosystem.

Unnecessary Use?

Dr. Nora Schrag, *Kansas State University*

We need to be careful how and where we define unnecessary use. For the practitioner, making the decision in the moment is more difficult than in retrospective analysis. The veterinary practitioner is asked to apply population level health information to individual animals – a challenge at best. Adding tools and technology to help the practitioner arrive at the correct diagnosis initially, or be able to delay treatment until there is a diagnosis, could be tremendously helpful in curtailing 'unnecessary' use.

Worthwhile Alternative Treatment

Ms. Lori J. Marco, *Hormel Foods Corporation*

We need alternative treatments that are attractive to producers. These must work to prevent or treat disease, provide ease of use, and be cost effective. Alternative treatments that are attractive will be used.

Preventative Health Tools and Stewardship

Dr. Bob Smith, *Veterinary Research and Consulting Services*

Dr. Smith advocates a focus on non-antibiotic treatment and prevention techniques, such as improvement and support of basic animal husbandry skills, measurement of retreatment risk, and development of technology that improves the producer's and veterinarian's ability to accurately determine which animals in a pen are in need of treatment. Vaccines can be expanded and improved. Immunomodulators show promise in reducing the need for treating animals with antibiotics at all. More tools are needed in the beef industry to prevent disease.

Panel Discussion

Panelists

Moderator Dr. Speer posed a question asking if the VFD is becoming a tool to facilitate conversation and awareness among producers around antimicrobial stewardship? Dr. Smith and Dr. Forshey noted that there has been no concentrated effort in educating producers on AMR and stewardship, and Dr. Forshey indicated that most of the VFD calls he receives are from veterinarians and producers that know nothing about the VFD. Dr. Moore disagreed, feeling that the VFD created a groundswell of discussion, forcing producers with ineffective practices to revisit them anew. We do need to do a better job getting the VFD information out there, but we also need to find the big performance indicators that show the VFD is making measureable stewardship progress.

A broiler veterinarian in the room pointed out the gap in the lack of agreed upon treatment protocols or decision trees for common animal diseases to help use on the '*should* we use an antibiotic?' question. Dr. Karin Hoelzer noted that companion animal researchers tried to come up with protocols, and were able to show that the original guideline of 14 days of treatment is much longer than is probably needed. Dr. Nora Shrag noted that members of her research group have been asked to write protocols, but have resisted due to diversity and complicated nature of production systems across the United States. Dr. Larry Granger postulated that if we were able to gather and share protocol and use information more broadly, behavior would be influenced in the long run. Dr. Rosie Busch from the California Department of Agriculture noted that California has been mandated to develop stewardship guidelines and best management practices. They are in the process of gathering information from California producers, and will be developing species specific production class guidelines. Stay tuned!

One symposium attendee described the economic case study of ivermectin. Merial sales stopped, then many generic labels stepped in to sell drug much cheaper, which caused a tremendous surge in the use

of those products. We need to understand economics as a potential piece of the stewardship puzzle. Economics drives every producer decision, and the FDA policy and pricing by drug companies have a huge impact on antibiotic use.

Everyone is looking for something they can do. If there's not an activity associated with an idea or goal, it tends to fall flat. Dr. Eric Moore pointed out that we in agriculture don't tell our story well. One simple thing every producer can do is to go home and tell their story. Dr. William Flynn agreed, but cautioned that we must make sure that there is a common consensus on talking points, delivering a consistent message across agriculture. Dr. Bob Smith suggested that one aspect of that message could be that keeping animals healthy means they'll eat more, grow faster, and market better. Another aspect of our story is our technology, passion, and goals. Dr. Richard Coulter noted a different activity for the average farmer: biosecurity. Biosecurity is a way to protect your animals from the evils of the human population.

Mr. Joe Swedburg pointed out that a lot of company decisions are driven by investors and shareholders. How do you communicate with investors and other very interested, vocal groups to understand and educate? Ms. Lori Marco encouraged dialogue, and notes that the dialogue between those who don't agree is much richer than the dialogue we have with each other. Dr. Eric Moore encouraged agriculture to consider bringing the discussion to sustainability investors, and consider sustainability messaging.

Ms. Kara Smith, a producer with Double Slash N in Colorado, noted that we in agriculture don't do a very good job at two way communication at the farm level, let alone to consumers. Dr. Bob Smith agreed and pointed out that good resources are not reaching the public – we need to expand the discussion and make use of social media. Dr. Bill Flynn pointed out that it is in the interest of the agriculture industry to make a case for what they're doing to raise animals responsibly. Specifically, there is still a lot of confusion and concern in the area of preventative use of antibiotics, and we need to be more proactive about its role in managing disease.

We need to do a better job at communicating: to producers and veterinarians, to consumers, to our fellow farm and ranch employees, and to the consumer. We must make sure there is a common consensus on talking points, but we must get our story out there. Every person in the agriculture industry can tell their story.

What Must Be Done Next: Prioritizing Immediate Actions

Dr. Lonnie King, *The Ohio State University*

There is a real concern within the antimicrobial discussion that the topic could be overtaken by events with a loss of momentum. Antibiotic resistance is a slow-burning crisis rather than an acute outbreak and thus, it's easy to push to the sidelines. Another related problem is paralysis by analysis. Over than 200,000 scientific articles have been published on AMR and, obviously, we have enough information to make good decisions and to move ahead.

From my perspective, response to antibiotic resistance can be divided into three groups based on cost-effectiveness, time of response and impact. Tier One activities are those that can be done immediately or in the short term. Tier Two activities are those that can be completed in 1 to 3 years, and Tier Three encompasses the long-term planning, with goals at 3 to 5 years.

Tier One actions represent an important focus for this symposium because they include stewardship and infection prevention as key activities which has been our focus over the last few days. Dr. King defined 5 Tier One priority actions which include stewardship, awareness and communication, infection prevention, creation of a national institute, and changing the business model. Stewardship is paramount and cost-effective to implement. Key elements of stewardship cross all species and professionals and use a similar mind set: use antibiotics only when necessary and when used, use the most effective drug, dose, duration and route of administration, in every case. Use of antibiotics in this manner optimizes clinical outcomes and minimizing unintended consequences. A significant barrier to stewardship is the behavior and habits of prescribers. Healthcare professionals working in busy practices often don't have the time to be thoughtful and logical, and will prescribe antibiotics 'just to be safe' or because 'this is the way we have always done it'. However, with the knowledge of significant changes to the intestinal microbiome with antibiotic use and more awareness about AMR and personal accountability, professional behavior is being more scrutinized. We now realize that a cardinal rule of medicine, 'first do no harm," is being violated without the implementation of a stewardship program. Peer pressure is a promising potential driver of behavioral change and the acceptance of stewardship and infection prevention.

In the arena of awareness, education, and communication, national leadership is needed to make antimicrobial stewardship a major social issue. The issue must be relevant to people personally, and voices beyond public and animal health are needed to convey the sense of urgency. It is interesting to note that the UK Five Year Antibiotic Resistance Strategy was co-signed by both the Chief Medical Officer and the Chief Veterinary Officer. We did not start the United States plan this way, but clearly need this type of commitment and mutual partnership and support.

Infection prevention is the basis of veterinary training and education, and is always better than any treatment. Engaging veterinarians, technicians, and producers together to establish and implement infection prevention strategies at the farm level is the key to success. These prevention strategies can enable reduction of environmental contamination, improvement of host immunity, improvement of production practices, and ultimately, reduction of antibiotic costs and optimization of results.

Two national advisory organizations, PACCARB and the AAVMC-APLU Task Force, have recommended the creation of a national institute to support antimicrobial stewardship, innovations, policies and research. There is a natural affinity for creating such institute and it could be started relatively quickly. Creation of a national institute would promote a national focus, establish some national leadership and prioritization, and convey the sense of urgency needed to move an AMR agenda forward.

Finally, changing the business model trickles down and impacts medical professionals. We need to focus on improving incentives, both push incentives such as research, and pull incentives that would reward companies for production of new antibiotics. While the actual changes would take time and significant funding, the decision to change the business model could be accomplished quickly.

Tier Two and Three goals include: research and development; One Health surveillance; field studies to prove success of AMR work; global integration; basic research and developing new antibiotics. These activities are quite important and do not represent a lack of priority but will take longer to rollout and may be too costly. The simultaneous implementation of multiple actions, among tiers, is optimal but likely not realistic due to lack of funding sources.

John Kotter, founder of Kotter International and professor emeritus at the Harvard Business School, has studied many corporations going through major changes and attempting transformations. He has identified seven barriers, which if overcome, greatly increase the possibility of success. These seven barriers are: lack of a sense of urgency; lack of a clear and compelling vision; lack of an effective communication plan of the vision; not removing of obstacles or empowering others; declaring victory too soon; and failure to anchor change in organizational culture. AMR is also a major transformational change and understanding these lessons can be helpful in planning and implementing a successful national AMR program. The agriculture industry and associated stakeholders have the capacity to move forward. We need to find our sense of urgency, overcome our barriers, and adopt and push ahead on Tier One goals and successfully institute the changes demanded; there is too much at stake to do anything less.

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THE FORUM WAS FUNDED IN PART BY:
Auburn University Food Systems Institute
Beef Checkoff
Elanco
Global VetLINK
Merck Animal Health
Norbrook Inc.
PharmGate Animal Health
United Soybean Board
Zoetis