

White Paper

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Antibiotic Stewardship: From Metrics to Management

Information synthesized from Nov. 3-5, 2015, symposium in Atlanta, Ga.: “Antibiotic Stewardship: From Metrics to Management”

*DISCLAIMER: The information provided in this White Paper is strictly the perspectives and opinions of individual speakers and results of discussions at the 2015 “Antibiotic Stewardship: From Metrics to Management” symposium and does not represent the position of the National Institute of Animal Agriculture.*

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## BACKGROUND

The symposium *Antibiotic Stewardship: From Metrics to Management* was developed by the National Institute for Animal Agriculture (NIAA) and was conducted Nov. 3-5, 2015, in Atlanta, Ga. The symposium was a continuation of discussions and sharing of information that commenced with the Oct. 26-27, 2011, *Antibiotic Use in Food Animals: A Dialogue for a Common Purpose* symposium conducted in Chicago, Ill.; the Nov. 13-15, 2012, *A One Health Approach to Antimicrobial Use & Resistance: A Dialogue for a Common Purpose* symposium conducted in Columbus, Ohio; the Nov. 12-14, 2013, *Bridging the Gap Between Animal Health and Human Health* symposium conducted in Kansas City, Mo.; and the Nov. 12-14, 2014, *Antibiotics Use and Resistance: Moving Forward Through Shared Stewardship* symposium conducted in Atlanta, Ga.

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

The 2015 symposium was funded in part by the Beef Checkoff®, U.S. Department of Agriculture Animal and Plant Health Inspection Service – Veterinary Services, Zoetis™, Merial – A Sanofi Company, United Soybean Board, *Drovers CattleNetwork*, *Dairy Herd Management*, *Bovine Veterinarian*, *PorkNetwork*, Pork Checkoff®, Merck Animal Health, Elanco™, American Veterinary Medical Association™, Norbrook® and Auburn University – Food Systems Institute.

**PURPOSE AND DESIGN OF THE SYMPOSIUM**

The symposium provided a platform where academia, government researchers, the scientific community and stakeholders within animal agriculture, human and veterinary medicine and environment stewardship interacted and shared the most current science-based information as well as their professional insights in order to seek greater clarity about the issues of antimicrobial use and resistance. An integral part of the annual NIAA antibiotics symposium is discussion within small breakout groups and large group sessions where individuals learn from each other, engage in productive dialogue and create successful strategies to preserve antibiotic efficacy.

The goals of the 2015 symposium were consistent with those of the previous symposia:

- To lead and engage participants in an open conversation and exchange of ideas
- To build relationships within and among stakeholders in animal, human and environmental health, and gain a better understanding of other participants' perspectives
- To identify common ground and formulate a path forward for cooperative action
- To focus on continuous improvement and commitment to long-term health of people and animals

**Symposium Planning Committee Co-Chairmen**

Dr. Brian Lubbers, Kansas State University

Dr. Eric Moore, Norbrook, Inc.

**Symposium Planning Committee Members**

Dr. Kelley Garner, Arkansas Department of Health

Dr. Annette Jones, California Department of Food and Agriculture

Dr. Barbara Mahon, Centers for Disease Control and Prevention (CDC)

Mr. Jeff Morelli, CDC

Dr. Gatz Riddell, American Association of Bovine Practitioners

Dr. Tom Shryock, Antimicrobial Consultants, LLC

Dr. Steve Solomon, Global Public Health Consulting, LLC

Dr. Nate Smith, Arkansas Department of Health

Dr. Susan Weinstein, Arkansas Department of Health

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

Symposium Moderator: Dr. Steve Solomon, Consultant, Global Public Health Consulting

“Welcome and Opening Comments,” Dr. Chris Braden, Director, Division of Foodborne, Waterborne and Environmental Diseases, National Center for Emerging and Zoonotic Infectious Diseases Centers for Disease Control and Prevention, Centers for Disease Control and Prevention (CDC)

“Historical Perspective,” Dr. Thomas Shryock, Chief Scientific Officer, Antimicrobial Consultants, LLC

“Antibiotic Stewardship and Animal Agriculture,” Dr. Mike Apley, Professor, Production Medicine/Clinical Pharmacology, Kansas State University

“Human Health Viewpoint and Setting the Tone for the Symposium,” Dr. Robert Tauxe, Deputy Director, Division of Foodborne, Waterborne and Environmental Diseases, CDC

“Measure that Makes a Difference: Why Measure and What to Measure,” Thomas J. Chapel, Chief Evaluation Officer, CDC

“Stewardship for Poultry,” Dr. Chuck Hofacre, Center for Food Safety, Department of Avian Medicine, University of Georgia College of Veterinary Medicine

“Stewardship and the Environment: Waste Water Treatment and Antibiotics,” Dr. Tim Lapara, Professor, Department of Civil, Environmental and Geo-Engineering, University of Minnesota

“Stewardship for Swine,” Dr. Jennifer Koeman, Director, Producer and Public Health, National Pork Board

“Stewardship for Beef,” Dr. David Sjeklocha, Director of Animal Health and Welfare, Cattle Empire

“Producer Survey Results,” Dr. Tiffany Lee, Beef Cattle Institute, Kansas State University

“CDCs Overall Effort on Antibiotics, FY 2015 Requested Funding and Combating Antibiotic Resistant Bacteria (CARB) Program,” Dr. Beth Bell, Director of the National Center for Emerging and Zoonotic Infectious Diseases

“Out-Patient Antimicrobial Resistance (AMR) Issues,” Dr. Lauri Hicks, Commander, U.S. Public Health Service, Medical Epidemiologist, Respiratory Diseases Branch, Medical Director, Get Smart: Know When Antibiotics Work Program

“In-Patient AMR Issues,” Dr. Arjun Srinivasan, Associate Director for Healthcare-Associated Infection Prevention Programs, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, CDC

“Antimicrobial Stewardship: The State Health Department Perspective,” Dr. Marion A. Kainer, Director, Healthcare Associated Infections and Antimicrobial Resistance Program, Tennessee Department of Health

“Building Consumer Trust,” Donnie Smith, Tyson Foods, President and Chief Executive Officer

“Building Consumer Trust,” Christine Summers, Costco Wholesale, Director of Food Safety and Quality Assurance

“Build Consumer Trust,” Mike Morris, Yum! Brands, Global Quality Assurance

“USDA Antimicrobial Resistance Strategy – Farm Foundation Results,” Dr. Larry Granger, Leads the Antimicrobial Resistance Program for the U.S. Department of Agriculture’s (USDA) Animal and Plant Health Inspection Service (APHIS), Veterinary Services

“Food and Drug Administration (FDA) Antibiotic Strategy,” Dr. Craig Lewis, Veterinary Medical Office, FDA Center for Veterinary Medicine

“Antimicrobial Resistance in Humans and the Global Health Security Agenda,” Dr. Benjamin Park, Senior Advisor for International Healthcare Quality, Division of Healthcare Quality Promotion, CDC

“Actions and Recommendations from the Association of Public and Land-grant Universities (APLU) and Association of American Veterinary Medical Colleges (AAVMC),” Dr. Chase Crawford, Director, Antimicrobial Resistance Initiative, APLU and AAVMC

## EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) is an extraordinarily complex problem that is global and results from the actions of a broad and very diverse set of individuals and groups in the United States, including human and animal health professionals, hospitals and healthcare organizations, farmers and companies engaged in animal and field crop agriculture, Federal, state and local governments in the United States and especially consumers of healthcare and food products. Similar and comparable groups in other countries also can have a direct impact of the AMR problem in the United States. Through its series of annual antibiotic resistance symposia beginning in 2011, the National Institute of Animal Agriculture has sought to provide a platform where multiple stakeholders can come together and establish productive relationships and find common ground, with the goal of producing a consensus of opinion on how to move forward to address this problem of growing international concern. Each symposium has built upon the lessons and outputs of those that came before.

The theme of the 2015 symposium, *Antibiotic Stewardship: From Metrics to Management*, addressed the issue of how to determine whether the many efforts underway and planned to improve antibiotic use in animal and human health and in animal agriculture were succeeding. To this end, participants from previous symposia who had forged relationships across subject matter expertise and boundaries of professional discipline came together with an array of attendees attending NIAA antibiotic symposia for the first time. As at the preceding symposia, the 2015 conference combined information delivered during plenary sessions with facilitated discussions in breakout groups, each of which had defined tasks for developing output. The content and results of these efforts is summarized below.

Attendees heard presentations from scientists, animal and human health professionals, governmental public health officials, and representatives of companies involved in the animal protein supply chain. These presentations pointed out particularly the dramatic changes which have taken place since the first NIAA antibiotic symposium in 2011:

- Animal and human health professionals and medical practitioners are much more aware of the concept of antimicrobial stewardship
- Consumers have begun to drive change with their increasing interest in having “antibiotic-free” options at the retail groceries and restaurants
- Federal and state governments have instituted a variety of new guidelines and regulations covering both animal and human health pertaining to the labeling and use of antibiotics
- The Federal government has issued a new National Strategy and formed an independent advisory panel to address AMR and provide guidance to government agencies
- Virtually all stakeholders who use or prescribe antibiotics as well as consumers of healthcare and food products are changing their practices in an ongoing way and adopting new approaches that are highly variable as they seek to conform both to external expectations as well as their own evolving understanding of the AMR problem
- Despite the many reports, action plans, meeting and conferences which have taken place and the numerous initiatives announced by both public and private sectors organizations, there is a dearth of established, well-accepted metrics to assess the success of the efforts which are underway and planned.

The 2015 NIAA antibiotic symposium was designed to provide leadership by asking the diverse set of conference participants to take a first step in discussing, debating and creating quantifiable metrics for evaluating activities to improve antibiotic use and reduce the risk of resistant infections in people and animals were progressing optimally.

Tom Chapel, MA, MBA, who serves as the Chief Evaluation Officer at Centers for Disease Control and Prevention, in consultation with the 2015 NIAA Symposium program committee, developed a strawman roadmap and framework to guide the breakout groups in their discussions and creation of proposed metrics. A cadre of trained facilitators led the breakout groups which first revised the roadmap (Figure), and in subsequent sessions, developed four specific measures as a first step in leading the way to consensus metrics for progress in antimicrobial stewardship (Table). Symposium attendees were able to listen to plenary presentations on current stewardship efforts in animal and human health and drivers of change in antibiotic usage with an awareness of the revised roadmap and used the information presented in developing the measures.

These measures are:

1. The percentage of states with ongoing, working committees overseeing collection and dissemination of data on antimicrobial resistance from human, animal and environmental sources
2. The number of useful and practical new diagnostic tests for the rapid identification and characterization of infection and AR (developed within a specific time frame)
3. Proportion of production units that have a documented Veterinarian-Client-Patient Relationship (VCPR) with at least one veterinarian.
4. The degree to which new and alternative interventions are being used in practice by veterinarians

For each measure, the breakout groups identified potential obstacles to creating the metric, including possible barriers to obtaining needed data, as well as challenges in implementing the metric. In addition, these metrics were developed to incorporate both human and animal health concerns (numbers 1 and 2) or in parallel to metrics in development for human health (number 3, paralleling requirements for antimicrobial stewardship programs to be in place in all hospitals and nursing homes; number 4 assessing improvements in infections control among inpatients and reducing unnecessary antibiotic prescribing among outpatient physicians).

Participants noted that these early efforts will require discussion and input from an even broader array of interested and concerned parties and that these four metrics can only be a start in identifying an agreed-upon set of process and outcome measures. However, as several plenary speakers had noted, and as the breakout group participants reiterated, difficulties in reaching consensus and implementing metrics must be overcome as ongoing evaluation and continuous improvement in antibiotic stewardship practices is an urgent imperative in which all stakeholders have a direct interest.



oversight and make recommendations as to the progress of the five goals of the plan. The idea is that the Presidential Advisory Council will be taking charge of evaluating the programs that have been proposed by various agencies and reviewing their progress going forward. The committee's purpose is to make sure the proposed plans can be carried forward and the goals can be achieved.<sup>17</sup>

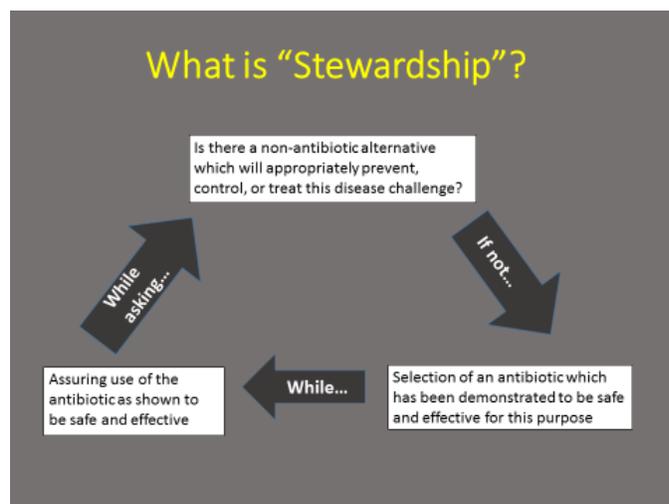
Recommendations from the 2015 meeting of the CARB Advisory Council are to establish:

- Outcome measures (i.e. clinical) and process measures
- Metrics of success in an effort to minimize the development of antibiotic resistance, including:
  - Assessing the effectiveness of antibiotic stewardship programs
  - Increasing veterinarian oversight in animal agriculture
  - More careful monitoring of antibiotic usage and resistance in human and animal health
  - Ongoing evaluation of individual and aggregate case outcomes
  - Population health indicators
  - Measuring the economic impact of resistance on health costs and society

### ANTIBIOTIC STEWARDSHIP AND ANIMAL AGRICULTURE

Stewardship starts with prevention of infectious diseases and administering antibiotics correctly. Veterinarians must ask themselves if every step possible has been taken to eliminate the need for an antibiotic and/or if an antibiotic is necessary. For example, will this disease respond to an antibiotic or is it viral. Veterinary clinical pharmacology asks if the administration of the drug can do good, can do harm, can get in the animal(s) and at what cost. Direct harm to animals with antibiotics can happen; just as direct harm to people with antibiotics can happen.<sup>18</sup>

Stewardship also includes judicious use via treatment protocols, case definitions, regimen, success/failure definitions and post-mortems. Monitoring of animal daily doses and animal regimens provide a look into drug exposure as well as number of animals receiving the regimen. There may be



different regimens for the same drug within a species. This assumes there are CLSI approved breakpoints which apply to the pathogen/disease/animal regimen in question. There is an opportunity to move forward in both expanding the repertoire of breakpoints and advancing the understanding of how these are properly applied in the veterinary profession.<sup>19</sup>

Where metrics are concerned, the amount used, reasons for use and the population it is being applied to are challenges. Sales data do not drive accurate estimates of indications for use or actual use. Antimicrobial use monitoring should be actual use, tied to a reason for use.<sup>20</sup> The only way to move forward with metrics is to understand the value and limitations of various metric approaches. Different kinds of metrics provide different views of the issue.

Actual use tied to a reason for use drives antimicrobial stewardship in food animals.

Actual use tied to reason for use will propagate antimicrobial stewardship in food animals.

In both human and veterinary medicine there are things that can be improved with research and data collection. A government audit of the sampling strategy and data handling is needed. Voluntary compliance is dependent on anonymity and the sampling structure, balancing a view of the industry with utility for individual participants so they can see how they are doing for use and reason for use compared to the rest of the industry and at distribution to the rest of the industry.

Part of data collection is label use. Label use doesn't necessarily mean judicious use, that it is compatible with stewardship or that it is the regimen most likely to minimize selection for resistant organisms. Still, having a labeled product to apply in a situation is valuable. There is a difference in what went into the label for something approved 45 years ago than what goes into something approved today. Label use has nothing to do with magnitude of selection for resistance, just like ranking drugs in medical importance to human medicine has nothing to do with the potential for use in food animals to select for resistant organisms.<sup>21</sup>

A component of label use is withdrawal time. Withdrawal time in food animals is very important to meet residue tolerance requirements so animals can be marketed. Antibiotics labeled for food animal production are approved with a tolerance, and withdrawal time is based on them being below tolerance. An approved antibiotic in food animals has a tolerance at which the FDA says is safe; therefore, there can, by law, be a legally acceptable amount of antibiotic in the meat when the animal has met the withdrawal time.<sup>22</sup> Veterinarians have a commitment to animal welfare and are using antibacterial drugs that are safe and effective for the treatment of disease, control of disease and prevention of disease.

Don't confuse a policy decision to reduce total kilograms (kg) of drug with proof that this exposure is the worst exposure to select for resistant organisms.

- The pharmacokinetics/pharmacodynamic parameters for efficacy don't necessarily match with optimal exposure for minimizing the selection for resistant organisms
- Studies focusing on dose comparisons for the same duration in veterinary and human medicine were unable to show a benefit for the longer duration, concluding that single, high dose exposure can be effective
- It is hard to differentiate between a narrow spectrum and a broad spectrum antibiotic – does a definition based on therapeutic effect apply to avoiding selection for resistant organisms? It may or it may not, but only thinking about that ignores the fact that there may be multiple-drug resistant (MDR – an organism resistant to at least three agent classes tested) bacteria out there, and understanding the complexity of the microbiota and the diversity within the pathogen population is expanding at a rapid rate<sup>23</sup>

Education is an important component, but without looking at the inherent drivers, the positive feedbacks and the availability for change in that system, it is incomplete. Movement forward is going to have to take place without a clearly defined plan. It becomes complicated when the choices are to 1) prove it does cause a problem or 2) prove it doesn't cause a problem.

Prohibition of growth promotion uses of medically important antimicrobials (the FDA has classified medically important drugs as anything that is used in human medicine) has become policy through Guidance for Industry (GFI) 209, Judicious Use Strategy, which 1) limits medically important antimicrobials to therapeutic purposes (those uses considered necessary for ensuring animal health) and 2) requires veterinary oversight or consultation for such therapeutic uses in food animals. As a follow up to GFI 209, GFI 213 establishes a more detailed guidance on implementing key principals in GFI 209, sets

a 3-year timeline and defines medically important. By Jan. 1, 2017, the use of medically important antibiotics in food and water will be limited to therapeutic purposes only, and production (growth promotion) uses of these products will no longer be legal. Use of medically important antibiotics will require the authorization of a licensed veterinarian; products used in water will change from over-the-counter to prescription and products used in or on feed will change from over-the-counter to veterinary feed directive (VFD). Data collection is necessary because without an intentional effort to assess actions taken, it will be difficult to know over time whether those actions are making a difference, need to be adjusted or additional actions are needed.<sup>24</sup>

About 98 percent of antimicrobials sold (by kg) in 2013 with a food animal label will be coming under veterinary control as a VFD for in-feed use or prescription for water use. Participating partners are being encouraged to provide electronic formats as well as establish veterinary client-patient relationships (VCPR's) to fulfill those VFD's, and find out where people will and will not be able to obtain those drugs. Veterinarians are very cognizant of that responsibility and they are well-trained in pharmacology – it is a transition to increased responsibility for additional classes of antibiotics.

The veterinary profession is not only going to be responsible for all medically important antimicrobial uses in food animals, but will also be held more accountable.

- The days of verbal treatment protocols are gone
- The days of unacceptable treatment records are gone – the future of stewardship as it relates to animal agriculture includes emphasis on treatment records
- The days of nontransparent use of antimicrobials in food animals are coming to an end
- Neither veterinarians or producers can be passive in these efforts

Veterinary medicine has components similar to the community practice in human medicine that are widespread, smaller groups or individual practitioners who have a different relationship with a set of guidelines and feedback capabilities than someone working in a large veterinary practice, which may be more similar to a hospital. However, hospital settings have the ability to have a committee that sets rules, whereas veterinarians have a different set of challenges. There are multiple animal agriculture organizations that have developed guidelines and recommendations regarding stewardship practices. There are also standards in animal agriculture organizations, for example quality assurance programs aimed at producers.

## **DEFINITION/SUMMARY OF ANIMAL STEWARDSHIP PROGRAMS BY SECTOR**

### ***Stewardship for Poultry***

A steward is someone who is directing the affairs of antibiotic usage, and is primarily the veterinarian. Drivers for stewardship in poultry include:

- 1) Use of antibiotics can be a significant cost of production; because of the large volume of broilers a company produces, small changes in cost can have a significant impact on the bottom line
- 2) Customers (not consumers) move toward antibiotic free (ABF); the customers of the poultry industry are large retailers
- 3) Governmental regulations established by the FDA, and guidelines and recommendations from the CDC
- 4) Export markets: 18 to 20 percent of the 8.5 billion broilers produced in the U.S. are exported

There are two groups of people that are involved in the production of poultry: primary breeding companies and integrated poultry companies. There are probably less than 100 veterinarians

responsible for the entire poultry industry. The integrated poultry industry has fairly tight controls over what is administered in feed and water. The producer that owns the farm and is caring for the birds can't use or do anything without approval from the company whom they are growing birds for. Virtually all of the companies either have a veterinarian on staff or have a consulting veterinarian. The trend in poultry production field condemnations has significantly dropped, which means bird health has significantly improved and it is not because of antimicrobial usage – it is because of disease prevention based on improved environment and animal husbandry. Prevention of disease is a significant portion of the stewardship program that the poultry industry utilizes.

A poultry veterinarian's job is to prevent disease. Poultry veterinarians teach their students that if a flock of chickens or turkeys has to be treated for a bacterial disease with an antibiotic, then they failed.<sup>25</sup> The poultry industry has worked very hard to reduce disease incidence. Liveability is the number of birds that make it to market, and today that is about 98 percent of broilers on 8.5 billion birds.

In the U.S. poultry industry, the debate is over growth promoter antibiotics; reasons for use is known, but the labels are where the argument begins. Those most criticized, but never used as growth promotants – even though there is a label for that – are the tetracyclines and penicillin because those are the primary therapeutic drugs for respiratory disease and enteric diseases. The top five health issues in broilers are coccidiosis, necrotic enteritis, infectious bronchitis, infectious process and infectious bursal disease. In the past, the growth promotant antibiotics have been used for sub-therapeutic prevention. The poultry industry no longer uses ceftiofur because it can no longer be used extra-label.<sup>26</sup>

All broilers are injected in the egg for a virus that causes tumors call Merck's Disease; an antibiotic was added with that vaccine and ceftiofur at one time was one of those, but it is not any longer because it was only labeled for one-day-old injection. There is reduced use of gentamicin; it is sometimes injected in ova to help a baby chick's immune system because it doesn't become fully competent until the chick is about two to three weeks of age, so it is there as an aid during that period of time.

How antimicrobial resistance transfers is not fully understood and picking up on the fluoroquinolone is the most difficult because that is not by transferable plasmid resistance, that is by direct mutation.<sup>27</sup> *Campylobacter* – especially *C. coli* – is inherently more resistance to the fluoroquinolones. Resistance in bacteria that could infect a human and transfer resistance genes are monitored; in poultry those bacteria are primarily *Campylobacter* and *Salmonella*, so antibiotics that are medically important for humans are looked to.<sup>28</sup>

The poultry industry has agreed voluntarily to on-farm sample collection as part of the National Antimicrobial Resistance Monitoring System (NARMS). USDA has had NARMS looking at *Salmonella* and *Campylobacter* in poultry at the processing plants. Several years ago they noticed the incidence of *Salmonella* and *Campylobacter* dropping coming out of processing plants, so they started a pilot program where they took samples on farms and looked at antimicrobial resistance. The industry agreed to voluntarily provide those samples. The money comes from FDA, passes through USDA and is handled with a Cooperative Research and Development Agreement (CRADA). The industry agreed to provide samples as long as the study was blinded, and CRADA prevents anyone from asking for information about where the samples came from. The samples are coded and run through the university diagnostic lab. The goal was to get at least 60 percent of the industry to participate and that goal was met. Another goal was to establish antibiotic usage on the farms the samples were coming from. It took 1,448 samples from 362 farms (46 complexes) to be representative of the U.S., and that was accomplished by sampling eight farms a week, four boot socks per farm, one week prior to processing. A survey was also sent out,

which was completed by the production people that took the samples on those farms. Currently, the results are being presented to the poultry industry. This data is only valuable as a trend. The results for 258 broiler farms and 39 turkey farms showed a *Salmonella* prevalence of 57 percent for broilers, 32.1 percent for turkeys and a *Campylobacter* prevalence of 22.5 percent for broilers, 11.4 percent for turkeys. For the study, broilers lived to 48 days on average, turkeys up to 88 days on average.<sup>29</sup>

The data is there, the industry is cooperating and the industry wants to understand what amount of antimicrobial resistance in foodborne pathogens could potentially transmit to humans. There is some use of ionophores (a class of coccidiostat) as anti-coccidials, there is growth promoter use in broilers and there is some therapeutic usage on the farms that were tested. There is also a class of coccidiostats that have just been termed the chemicals, which are non-fermentation produced coccidiostats.<sup>30</sup> Amprolium is a chemical coccidiostat, so a company that is on an antibiotic-free label can legally use a chemical anti-coccidial. They can't use ionophores because they are, by definition, antibiotics.

The poultry industry is being good stewards of antimicrobials because they want to understand what the risk is, and what the effect of usage is on those two potential major sources of antimicrobial resistance transfer with *Salmonella* and *Campylobacter* to humans. Compliance by the broiler and turkey industries has been very good, and they're continuing to willingly participate.

The second step is to utilize a survey published looking at swine to try and understand antimicrobial use by estimating volume of usage because that is the next major question. The U.S. Poultry Association has agreed to fund a survey of the entire poultry industry to better understand antimicrobial use metrics to learn how much is used as growth promotants, how much is used as therapeutic, how much is ionophores, how much goes in the water and how much goes in the feed. It is predicted that having veterinarians involved with GFI 209 and 213 will result in decreased usage of antibiotics, including therapeutic use.

### **Stewardship for Swine**

The pork industry has a long history of antibiotic use guidance, and it started with the We Care Ethical Principals by which pork producers undertake production best practices:

- Produce safe food: U.S. pork producers closely monitor the health of their herd and, when necessary, may use antibiotics to protect the health and welfare of their animals to produce safe food
- Ensure practices to protect public health: Use management practices consistent with producing safe food and manage the use of animal health products to protect public health

Antibiotics are used in the pork industry for individual treatments (injection or oral administration) and for group uses through feed and water. Producers work closely with veterinarians when using antibiotics as part of Pork Quality Assurance (PQA) Plus Certification.<sup>®</sup> PQA was introduced in 1989 to provide producers education to assure delivery of a safe product to the marketplace. It started as an animal welfare and food safety program, and over time it has incorporated several different pieces, including antibiotic use guidance. A PQA re-write this year involves public health, influenza, worker health and safety, and the environment.

In 1999, the Judicious Use of Therapeutic Antibiotics Guidelines for pork producers was developed. These guidelines addressed the use of antibiotics for disease prevention, control and treatment.

The National Pork Board Position Statement's focus has always been on protecting public health, food safety, animal health and wellbeing, the environment, and making sure antibiotics used are effective and available for use as needed.

The Take Care Program – Use Antibiotics Responsibly was introduced in 2006. The program was designed to build awareness among producers and provide guidelines about the responsible use of antibiotics.

In 2007, PQA Plus was introduced. All major U.S. pork harvest facilities require PQA Plus Certification as a condition of sale.<sup>31</sup> Within PQA are Good Production Practices, and No. 3 is use antibiotics responsibly. A set of principles provides guidelines designed for producers to think about issues not only related to residues, but how antibiotics are used on the farm and how that impacts public and animal health.

#### Principles and Guidelines for Responsible Antibiotic Use

The National Pork Board has developed the following five principles to help producers use antibiotics responsibly:

**Principle I.** Take appropriate steps to decrease the need for the application of antibiotics.

**Principle II.** Assess the advantages and disadvantages of all uses of antibiotics.

**Principle III.** Use antibiotics only when they provide measurable benefits.

**Principle IV.** Fully implement the management practices described for responsible use of animal health products into daily operations.

**Principle V.** Have a working veterinarian/client/patient relationship (VCPR) and follow the responsible antibiotic use guidelines.

The National Pork Board Policy on Antibiotic Use in Pork Production includes using antibiotics responsibly; preventing disease, rather than treating disease; protecting the efficacy of antibiotics; and reducing the need to use medically important antibiotics.

The pork industry took a proactive approach because there are several regulatory activities occurring that producers need to be aware of and need to comply with, including having their VCPR in place. There is also pressure from retailers; the National Pork Board has a group that works specifically with retailers and the public through the retailers to talk through

some of the pressures that are occurring, and educate about how and why antibiotics are used and the importance of having them available to animal health.

The National Pork Board's Three-Point Antibiotic Stewardship Plan includes education, research and communication through producer venues, earned media and paid media. Producer messaging is focused on a "be ready" theme and emphasizes to-do's, like understanding new regulations, strengthening the VCPR, communicating with feed mills, ensuring record keeping compliance, continuing focus on swine health and welfare, and reviewing guidelines at [www.pork.org/antibiotics](http://www.pork.org/antibiotics). The National Pork Board also reaches out to producers one-on-one in person.

Priority research areas for 2016 are:

- 1) Analysis and assessment of preventive uses of antibiotics at therapeutic doses in pork production to optimize swine health and public health
- 2) Analysis and assessment of specific animal population antibiotic treatment versus individual animal treatment in pork production to optimize swine health and public health
- 3) Evaluation of on-farm challenges to antibiotic record keeping and identification of strategies to improve antibiotic record keeping practice for continuous improvement of responsible antibiotic use on the farm
- 4) Characterization and assessment of the environmental fate of antibiotics, antibiotic metabolites, antibiotic resistant bacteria and antibiotic resistant genes on swine farms
- 5) Exploration of strategies to protect herd health and minimize the need for antibiotics

Pork producers support the responsible use of antibiotics, whether in human or veterinary medicine; professional veterinary input for guidance on antibiotic use; sound science for antibiotic research through their contribution to the Pork Checkoff; and the use of science-based principles to develop producer guidelines about antibiotic use.

Pork producers have received the message that by the end of 2016 it will be illegal to use medically important antibiotics for growth promotion if the label no longer exists. The pork industry is confident veterinarians will use labels appropriately. In a study with the American Association of Swine Veterinarians on the in-feed estimates, growth promotion in general was a much smaller percentage of the use of antibiotics. If animal illness results because of label use limitations, then therapeutic uses and treatment uses may rise – there is a concern with potential loss of preventative use as well. Moving forward, research will need to be conducted to monitor antibiotic use to better understand how it is used.

Continuous improvement is needed for record keeping. Numerous management practices have already changed/improved how antibiotics are used, like improving ventilation and moving livestock indoors, that may have reduced the need to use antibiotics. Looking at livestock husbandry improvements as a whole and communicating those improvements more widely so people recognize them is helpful as well.

Producers want to use antibiotics responsibly. It has always been important to have antibiotics available for animal health; also, since producers are running a business, they want to use antibiotics efficiently. Different pressures from consumers, retailers and the market place play into what is driving antibiotic use. Input on our priorities are established through subject matter experts, external stakeholders and a variety of additional audiences.

Antibiotics approved for use in the swine industry to treat illnesses are those that are medically important to human health, so movements or pressures to go antibiotic-free (ABF) could potentially have a huge impact on animal welfare/swine health. Most antibiotic-free systems have the option to treat sick animals and send them through a different market that is not part of the antibiotic-free flow. Should that option go away, then sick animals can't be treated.

### ***Stewardship for Beef***

Cattle Empire is a beef feedlot in southwest Kansas with a one-time capacity of 229,000 head. Management at Cattle Empire was very concerned about animal welfare and antimicrobial use. They felt the use of an antibiotic was an indication that management practices had failed, and if cattle were managed better, antibiotic use would decrease.

In 2004, Cattle Empire decided to manage cattle that are free of Bovine Viral Diarrhea Virus (BVDV) Persistently Infected (PI). A fetus becomes infected with BVD virus between 40 and 120 days gestation. The fetus accepts the BVD virus as a part of itself and never gets rid of the virus, resulting in PI. As the animal grows, it sheds huge amounts of the virus every day of its life, resulting in pen mates/herd mates who are constantly under immune challenge. Today, all cattle are tested for BVD PI virus upon arrival at Cattle Empire, and positive animals are quarantined.

Cattle Empire also initiated post-treatment intervals because re-treatment was taking place 24 to 48 hours after initial treatment with long-acting antibiotics, which was not giving the long-acting antibiotics a chance to work.

According to data collected in May 2013, average U.S. and Central Plains feed conversion was approximately 6.5 pounds of feed to 1 pound of gain; Cattle Empire's feed conversion was 6.08 pounds of feed to 1 pound of gain; dollars spent per head on medicine were approximately \$20 and \$12.31, respectively, while death loss was more than 2 percent and 1.71 percent, respectively. Cattle Empire has seen this trend since they started taking out BVD PI cattle and started implementing post treatment intervals. In the last few years, other feedlots have started to narrow the gap; Cattle Empire's number have not gone up, other's numbers have gone down, indicating they are moving in the same direction.

Another implementation at Cattle Empire is Southfork, a high frequency ear tag with an antenna that tracks how often a calf visits the bunk and how long he stays there (it doesn't detect if the calf eats or how much he eats). Bunk visit data is entered into an algorithm and a daily pull list is made. Cattle Empire tested this technology and compared conventional disease detection methods (feedlot cowboys) with Southfork. Cattle were randomized by 5 head (5 head from a load went into a conventional pen, 5 head went into a Southfork pen) until each pen was full. At initial processing, tulathromycin was used for metaphylaxis with a 10-day post-metaphalactic interval (PMI) on a 60-day starter period. (Metaphalaxis is the treatment of an entire group of calves with an antibiotic upon arrival to avoid a severe break out of respiratory disease.<sup>32</sup> There are several antibiotics labeled for metaphalactic use.) Once PMI was met, cowboys pulled as normal from the conventional pen, but only pulled cattle from a generated list from the Southfork pens.

The expectations were that the Southfork pens would have a longer list of cattle than the conventional pens, however, it did not turn out that way. On first pulls, nearly twice as many head were pulled by the conventional method compared to Southfork; 44 percent of conventional pulls needed a second treatment, 23 percent of Southfork pulls needed a second treatment; 54 percent of conventional second pulls needed treated a third time, 36 percent of the Southfork second pulls needed treatment a third time. Bovine Respiratory Disease mortality was 5.1 percent conventionally, 3.9 percent Southfork. By virtue of this, antibiotic use and mortality decreased. As an industry, beef is finding opportunities to use antimicrobials in a more judicious way and in a good stewardship manner.

Still, the veterinary community needs to be more aggressive working with their clients, especially in the cow-calf sector concerning disease prevention. Ninety-three percent of cow herds in the U.S. have less than 100 head. Communication is key; getting the word to people and perhaps creating a new cow-calf business model so herd operators can work together to select for better genetics and market cattle in larger groups is one way to generate more pre-conditioning in the cow-calf sector.

The ABF market may pose a problem in the beef industry.<sup>33</sup> If there is an ABF premium, there is motivation to wait and see how cattle get along untreated. There are some natural programs that have the "never ever" label for beef, and they do seem to enjoy a premium, but it can be a struggle to maintain supply. From a veterinarian's perspective, especially in the beef industry, it is difficult to manage an ABF beef operation, especially on any kind of large scale.

### ***Producer Survey Results***

A survey was conducted asking beef producers what they thought about antibiotic use and resistance in their industry. Producers have first-hand knowledge about how and why antibiotics are used. The

majority of producers reported using injectable antibiotics less than once a month; the majority of oral antibiotics were reported as being used less than once a month or never. The majority of producers get their antibiotics from a veterinarian. Most of the time, label directions are followed; if label directions aren't followed, most producers consult with their veterinarians. 248 of 249 respondents reported following withdrawal times. One-hundred percent respondents indicated they think adherence to withdrawal times is important. Eighty-five percent of producers utilize the services of a veterinarian regularly, but most use veterinarians as needed. Seventy-seven percent of respondents reported not having a VCPR, however, that is something that may come in the future. Most respondents found Beef Quality Assurance to be a useful industry program for antibiotic use guidance. 200 of 248 respondents were aware of the VFD. Producer opinion of risk factors for antibiotic resistance in the beef industry include over-use, misuse and lack of education.<sup>34</sup>

### **USDA ANTIMICROBIAL RESISTANCE STRATEGY – FARM FOUNDATION RESULTS**

Many stakeholders have raised the need for metrics to evaluate the impacts of GFI 209 and 213. FDA and Veterinary Services will collaborate in developing a more robust picture of the way antibiotics are used in animal production systems.

USDA surveillance, data collection and analysis aim to help define good stewardship and judicious use because having good public policy depends on having access to complete and correct information verified by accepted scientific methodology.

Giving information back to the production sector that is useful is vital so they can make management decisions to lower the need for antibiotics. It is very resource intensive to collect representative data and characterize antibiotic use throughout the industry.<sup>35</sup> The rate of adoption of FDA's changes and what the impact of those changes is going to be needs to be accessible so it can be gauged whether the adoption of the new rule in the production sector has resulted in a different way of managing animals.

The FDA collects information about the amounts of antibiotics sold from most of the pharmaceutical companies and makes that information available to the public, but there is limited information on species it is used for and indications for use, and no information on exact amounts used or dosage.<sup>36</sup>

It has been proposed to take the National Animal Health Monitoring System (NAHMS) approach and continue to conduct national studies, but do them more frequently, monitor use on volunteer farms and do it progressively over time – a period of months or annually. National studies are designed to be representative in the sense that they seek to target 70 percent of the operations where 70 percent of production capacity in the country is held. Because of funding, studies have been limited in recent years to being conducted every 5 to 7 years. They only look at what is happening on the farm at the time the survey is administered, and there are usually a couple of questionnaires that go with taking biological samples. Information is provided back to the voluntary operation. However, NAHMS studies only provide information in terms of percent of animals receiving or percent of operations using a specific antibiotic and purpose for use. It does not provide total kilograms used or animal daily doses.[footnote could be placed here: "As of January 2016, funding to conduct annual antimicrobial use surveys and longer term studies has not been identified, and these studies are on hold".]

Analysis of data from past NAHMS studies are needed to utilize existing data to meet current information needs. National estimates are needed to assess the effects of FDA policy changes. An annual survey is needed to provide national estimates of antibiotic use in feed or water for feedlot cattle, broilers, swine and, potentially, turkeys. Information collected is brought into a data lab for

epidemiology where it is held in confidence. Because these are statistically based and because they are representative of the population, an inference about the population at large can be made, and that is the strength of national studies.<sup>37</sup> A sufficient number of operations could be sampled and tested for the presence of zoonotic pathogens (e.g., *Salmonella*, *Campylobacter*) and commensals (e.g., *Enterococcus*, *E. coli*) to provide national, population-based estimates about prevalence and antimicrobial resistance in these organisms. The goal is to be able to look at specific bacteria pathogens of interest, commensals of interest, and look for patterns in the emergence of resistance that might be associated with the use of antibiotics on a particular premises.

There is also an initiative to do targeted studies, where if it were determined that resistant organisms show a pattern of detection or emergence from particular samples collected at slaughter, one would be able to go back to the farm, conduct targeted studies, see why antimicrobial resistance is persistent on that particular farm, why it emerged in the first place, what sort of usage pattern resulted in that emergence, if there is a possibility of altering the management structure or practices on that farm, and if so, and those changes are implemented, whether resistance regresses.

Partnering with industry in a variety of ways would help bring data that is collected in an integrated production system unit to the data labs so it can be analyzed and compared to national studies. Several national associations have suggested they may be able to collect data in a useful way that could assist with the study design, collect data, bringing it to the data lab, holding it in confidence, analyzing it and providing the information back to volunteers as well as to the rest of the industry in a way that would be useful.

An important part of this is having the diagnostic capacity to detect these organisms and look for resistance patterns and that involves the National Veterinary Services Laboratories, the National Animal Health Laboratory Network, laboratories at the Agricultural Research Service, the Veterinary Laboratory Investigation and Response Network at FDA, any variety of numbers of labs that are doing tests from slaughter samples with FSIS, and be able to have these labs look at opportunistic samples from clinically ill animals that come into the diagnostic lab to seek a diagnosis to target those studies in a way that would follow up with a visit to the farm to collect information about antibiotic usage.<sup>38</sup> It is also a goal to contribute data in a way that is consistent internationally with MedNet and PulseNET, and with all of the information gathering databases around the globe that are going to be used to determine what management practices are effective at controlling resistance in the agriculture sector. Work with the National Animal Health Laboratory Network has been conducted to put together standardized methodologies and look at targeted pathogens that are of interest to the agricultural sector.

Stewardship is hard to measure because it is an ethic that guides behavior toward the responsible planning and management of resources. Stewardship is informed by an understanding of ecology of antimicrobial resistance (Gaia, endosymbiotic theory, self-regulating, complex systems, autopoiesis).<sup>39</sup>

Judicious use includes a consideration by the veterinarian of relevant factors for determining risk – not just the risk of whether the disease will abate with or without antibiotic use, but whether the use of medically important antimicrobials is appropriate in a particular situation.

Before now, producers were generally able to buy directly the antibiotics they needed; now there is going to be an intermediary party – the veterinarian – who is responsible for determining if that use is appropriate. Appropriate use is going to be targeted to animals at risk and there may be no reasonable alternatives to antibiotic use; that decision will be made by the veterinarian that writes the VFD. Where

alternative treatments are concerned, stewardship has a place because even if a new drug or product is created, it still has to be used in the proper way at the right time.

Veterinarian responsibilities under existing VFD regulation requires a VCPR as defined by regulation for extra-label use of drugs and requires a “veterinarian may only issue a VFD for use in animals under his or her supervision or oversight in the course of his or her professional practice, and in accordance with all applicable veterinary licensing and practice requirements.”

Practical implications of a VCPR include an integral understanding of the management system:

- Assume responsibility for animal care
- Focus appropriately on animal welfare, health and well being
- Timely site visits – always examine the patient(s)
- Appropriate diagnosis/risk assessment/prescriptions
- Knowledge of animal feeding and nutrition
- Knowledge of approved drug combinations/interactions
- Licensed in state where VFD is written and will be applied

The need for greater veterinary oversight of feed use antimicrobials has raised concerns about VFD requirements, including:

- Limited experience with process
- Administrative burden concerns
- Veterinary workforce limitations
- Increased costs to producers
- Impacts on feed industry
- Impacts on animal health
- A myriad of logistical challenges

The National Veterinary Accreditation Program is part of the veterinary education curriculum and is an education and outreach program that concentrates on judicious use and VFD training. Another reason why this is important is because some veterinarians who have never had farm animal practice as part of their clinical practice will be called upon to write VFDs, and that is because of the lack of veterinarians in some areas, particularly for exotic species and minor species producers.

Veterinarians and producers have differing opinions on the types of services that are provided by veterinarians. It is almost an even split between those that have and have not had conversations around the GFIs. 68 percent of producers view the impact of VFD on the negative side, while 63 percent of vets think it will have a positive impact. As a result of having greater documentation and transparency, there will be a big impact on increased paperwork.

Integrated production systems (swine/poultry), milking dairies, beef feeders and feed manufacturers report that they understand the policies, but cow-calf producers may have challenges. This will impact minor species, and heightened awareness of extra-label use could be a major issue. Veterinarians are concerned about compliance and liability, and how to serve their clients/patients. Measurement of success is an issue. The most important thing is gathering information because there will need to be answers to these questions before policies are put into place that aren't particularly appropriate.<sup>40</sup>

## FDA ANTIBIOTIC STRATEGY

Antibiotic resistance is a global problem affecting both humans and animals. Given the complexities of antibiotic resistance, no single action can be taken to “fix” the problem. Rather, it requires a long-term commitment to multiple actions, on multiple fronts, to monitor and address the problem.<sup>41</sup> Tracking progress is a critical element. Data is needed to assess the rate of adoption of changes outlined in GFI 209 and 213, help gauge the success of antibiotic stewardship efforts, guide their continued evolution and optimization, and assess associations between antibiotic use practices and resistance.

Questions can be considered at several different levels that may require different types of data varying in terms of difficulty to collect and assess. That is, success can be assessed by determining if actions are:

- 1) Actually being adopted as intended
- 2) Having the desired effect in terms of antibiotic use behaviors/practices (stewardship)
- 3) Having the desired effect in terms of managing antibiotic resistance

The data needed is:

- 1) Quantity of antibiotics sold/distributed: summary reports have been published since 2009 and rulemaking is underway to obtain additional detail about animal species; while this information is an indicator of quantity of antibiotics entering distribution channels, it is not actual use and doesn’t specify species or indication of use
- 2) On-farm antimicrobial use and resistance: limited data is available; while this information would provide more specificity about actual conditions of use and may help link use to resistance, it is resource intensive to collect
- 3) Resistance data for pathogenic foodborne bacteria and commensal bacteria: NARMS data is available since 1996; while a robust resistance database is available, resistance data is not linked to information about antimicrobial use in animals
- 4) Animal demographics/animal health: Some data available that provides context for assessing antibiotic use information, but animal health data is currently limited
- 5) FDA inspectional activities: there is a FDA program currently in place for inspecting licensed feed manufacturers that provides a mechanism for inspecting VFD records and provides an indicator of appropriate veterinary oversight of VFD feeds, but resources are limited and there are a large number of feed manufacturers

It is proposed to create a new U.S. Government Summary Report to provide a summary of antibiotic drug use and resistance in animal agriculture that integrates data about animal health, demographics, drug sales, resistance and additional on-farm data. The purpose of the new report would be to enhance transparency regarding antibiotic use practices in food-producing animals and summarize data important for assessing the adoption of changes outlined GFI 209 and 213, gauging the success of stewardship efforts and guiding their continued evolution and optimization.

Drug use indicators would summarize data about extent and purpose of antibiotic use in various animal agriculture settings and could include such information from sales/distribution data and survey data about antibiotic use. Antibiotic resistance indicators would summarize available data about antibiotic resistance among foodborne bacterial pathogens and commensal bacteria, and potential inclusion of animal pathogen data.

A discussion section would provide observations regarding antibiotic use practices in various animal agriculture settings, discuss resistance in relation to antimicrobial use, and identify areas of

improvement and areas where further efforts are needed. Further, the discussion section would assess the adoption of changes outlined in GFI 209 and 213, and gauge the success of stewardship efforts and guide their continued evolution and optimization.

One of the strengths of laying out the needed data is that many of the required items are already established. It is possible to either continue independently reporting the different streams that exist or put them together in something similar to the structure described. Collection of on-farm data is scheduled for 2016, with a goal of publishing the first integrated report in 2018.

### **ACTIONS AND RECOMMENDATIONS FROM THE ASSOCIATION OF PUBLIC AND LAND-GRANT UNIVERSITIES (APLU) AND ASSOCIATION OF AMERICAN VETERINARY MEDICAL COLLEGES (AAVMC)**

The task force between APLU and AAVMC believes that to be equal partners with human health in this initiative, a One Health perspective must be utilized. During antibiotic resistance initiatives, the agriculture side needs to think about how to maintain animal health and ensure enhanced production to feed the growing global population.<sup>42</sup>

Recommendations are for:

- 1) Education: building a common body of knowledge through curriculum, reaching practitioners through continuing education and utilizing existing avenues, such as the National Veterinary Accreditation Program
- 2) Outreach: producers, farmers, cooperative extension, next generation (4-H; FFA; and Science, Technology, Engineering and Math), public education, partnerships between human and animal health, objective third-party verification
- 3) Research: need for trans- and inter-disciplinary teams, incorporate private sector as collaborators, embrace the concept of One Health, perform both basic and applied research

Increased understanding of antibiotic resistant bacteria is dependent upon learning how resistance is transferred, impacts of co-selective pressures on emergence and dissemination, interaction between host immune competence and resistance, and generation and analysis of metagenomic data.<sup>43</sup>

Both the animal agriculture and human health sectors need to find alternatives to current antibiotics through new products, potential alternatives and developing the pipeline. Applied research would help to develop methods and tools to carry out metagenomics analyses, model antibiotic use and resistance, risk assessment and improve diagnostic capabilities.<sup>44</sup>

Assessing resistance in production agriculture includes incentives and motivations for antibiotic use across sectors; comparing, contrasting and assessing best practices; evaluating the success of stewardship programs for both farm and companion animal populations; assessing the impacts of GFI 209 and 213; and evaluating economics, animal welfare and health, and reduction of antibiotic resistance. Also, the development of models and longitudinal studies to measure changes in antibiotic resistance patterns and predict true risk to human health.<sup>45</sup>

Next steps include engaging stakeholders, holding educational workshops and leadership forums, congressional outreach, university-based pilot projects and university research organization.

### **STEWARDSHIP AND THE ENVIRONMENT: WASTE WATER TREATMENT AND ANTIBIOTICS**

Antimicrobial resistance is a complex problem driven by many interconnected factors. It is detected/quantified through either a medical approach (isolate pathogen from a patient, then

determine which antibiotics are effective) or a model organism approach (isolate a model organism, then determine which antibiotics are effective). Microbiologically, there is a problem with this because there are times in which organisms can't be cultured.<sup>46</sup>

There is a new methodology that targets genes quantified by real-time polymerase chain reaction. The method is to track the genes that encode for resistance by quantitative polymerase chain reaction and it allows for an estimate of resistance of a specific kind for a specific antibiotic. But, there are large numbers of antibiotics and large numbers of resistance genes for each antibiotic.<sup>47</sup>

There are a lot of nutrients in waste water; in the right conditions, microbes want to eat those nutrients and grow.

About half of residual wastewater solids – i.e. sludge – goes to landfills and about half of it goes to farmland. Treated wastewater nutrient levels are on par with most surface waters. Antibiotic resistance levels tend to have about the same amount of bacterial biomass, and treated wastewater is rich in resistance.<sup>48</sup>

Antibiotic resistant genes in a study in Minnesota determined that in almost every case, resistance levels measured were less than predicted, concluding that 1) there is a lot of decay in the river and 2) the river is really big – there is a huge dilution effect. Further, a lot of decay was seen in the southern part of the state, which is where all the agricultural activity is, so where there is agricultural activity is where the lowest levels of resistance in general in the state is.<sup>49</sup>

Treatment of wastewater solids determines that:

- The majority of bacteria (antibiotic resistant or otherwise) in sewage ends up in sludge
- Treatment technologies vary substantially depending on the end goal – anaerobic digestion at 37°C is most common (decay the nutrients and get some methane out of it); air drying also slowly reduces antibiotic resistance genes levels
- Higher temperatures are better at eliminating antibiotic resistance genes during anaerobic digestion<sup>50</sup>

Treated wastewater solids are often applied to agricultural soils, much like animal manure is applied. Half-life's for the genes in these different systems has been computed. Applied to the soil, the half-life is one to two months. Aerobic digestion is one to two weeks, and thermophilic anaerobic digestion is a few hours. The removal of antibiotic resistance can be engineered by choosing different technologies. The best technology is incineration.<sup>51</sup>

The wastewater industry doesn't treat for resistance and treatment isn't intentionally designed to get rid of antibiotic resistance, but the existing infrastructure (sewers and wastewater treatment plants) could be upgraded relatively inexpensively.

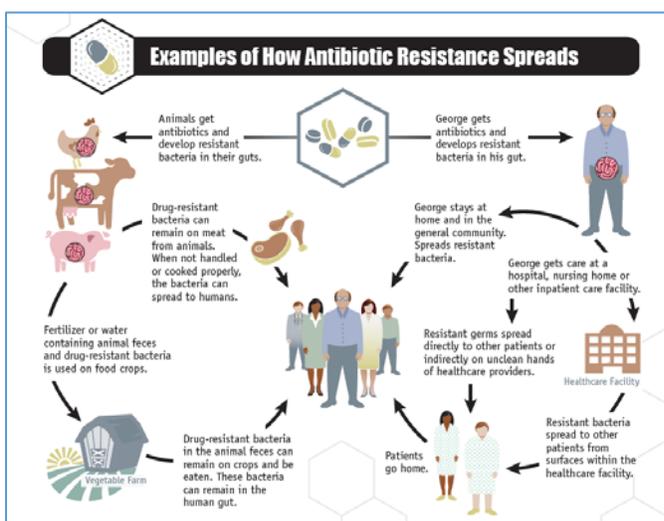
Antibiotics by one definition are natural compounds – they're produced by bacteria to kill other bacteria, and they've existed for a long time. In most microbial systems, unless something is there to destroy them, those genes are in living creatures, are viable and can be transferred – they could be in pathogens or benign organisms. In some of the systems where organisms are intentionally killed, those could be free-floating pieces of genetic material that haven't cycled back.<sup>52</sup> An example of this is pasteurized sewage sludge; in theory, it is all dead. It can still be measured, and when it is applied to soil

it disappears quickly (within a week). Then, at that point, it is all cycled into the regular soil microbiology.

The municipal waste treatment industry is largely a government entity that is regulated by different government entities and at this point the regulations don't consider antibiotic resistance at all; they do consider pathogens, but the regulations for pathogens are weak.

### HUMAN HEALTH VIEWPOINT

There are applicable commonalities between all sectors in which antimicrobials are used, and opportunities to learn from the experience of one another when talking about human health, animal health, antibiotic use strategies, and principals of how antibiotic stewardship works.<sup>53</sup>



The development of the emphasis on antibiotic stewardship has been going on for some time and is a fascinating and ever-changing dialogue among the components of the human health system—the clinical sector and the public health community. Human healthcare settings, the clinical sector, include out-patient clinics, in-patient acute care hospitals, tens of thousands of physician practices, and the communities in which they work, and antibiotic resistance can come from any of these settings. Stewardship in human health must be applied in all these diverse settings across the country and globally. On the public health side, working collaboratively

are the local health departments, state health departments, U.S. Public Health Service, and the Department of Health and Human Services, including both CDC and FDA in a tiered approach. These two sectors within human healthcare continue to work on integrating their efforts to be most effective in improving health across a range of health problems. However, antibiotic resistance is an issue that has brought them together with a sense of urgency.

Within the federal government, there are several agencies that are involved. CDC conducts national disease surveillance; detects and investigates outbreaks to determine vehicle and source; tracks burden, trends and attribution; and works to improve public health methods and practices. CDC also works to provide information to guide action both within the healthcare sector and within other sectors involved in food safety.

The FDA and FSIS, USDA, are regulatory agencies and are primarily involved in food safety policy; management of problems that are identified; inspecting, monitoring and enforcing; and are the ones who investigate issues on the farm/production facilities with state partners.

Antibiotic treatments have been critical in both human and veterinary medicine since the 1940s, and resistance has been a challenge for almost as long. Antibiotic resistance always emerges in settings

Pathogen	Percent Resistant	# illnesses/year	# deaths/Year
<i>Campylobacter</i>	24%	310,000	28
Non-typhoidal <i>Salmonella</i>	8%	100,000	38
<i>Salmonella</i> Typhi	67%	3,800	<5
<i>Shigella</i>	6%	27,000	<5
Total		441,000	66-70

where antimicrobials are used. For example, in Japan after World War II, there were

enormous problems with *Shigellosis* (bacillary dysentery). The early introduction of antibiotics to treat *Shigella* in Japan lead rapidly to the early recognition of transmissible resistance.

*Annual burden of human illnesses and death caused by resistant infections often spread through food; resistant to important drugs used for treatment.*

Resistance appears in a variety of bacteria, viruses, fungi and parasites, and can sometimes spread from one strain to

another. Stewardship is central to better managing infections and preserving effectiveness of antibiotics.

A report CDC released Sept. 17, 2013, identified 18 different pathogens, including several that are either hospital-associated, foodborne or community-associated. The total burden of antibiotic resistance is more than 2 million illnesses and 23,000 deaths. Four of the 18 pathogens are often transmitted through food – two with animal reservoirs (*Campylobacter* and Non-typhoidal *Salmonella*), two with human reservoirs (*Salmonella* Typhi and *Shigella* spp) – and are increasingly resistant to important drugs used for treatment.<sup>54</sup>

Reservoirs for bacterial foodborne pathogens include:

- *Salmonella* Typhi: humans
- *Shigella* spp: humans
- *Campylobacter* spp.: poultry, other birds, cattle
- *E. coli* O157:H7: cattle and other ruminants (swine?)
- *Salmonella*: poultry, cattle, swine, reptiles and others
  - Enteritidis: poultry
  - Heidelberg: poultry
  - MDR Newport: cattle
  - MDR Dublin: cattle
- *Vibrio*: shellfish
- *Yersinia enterocolitica*: swine

Bacteria with animal reservoirs are often not associated with animal illness, and it is a challenge dealing with something that is largely a commensal in a host species that is rather well adapted to it, but when food products from the host species are eaten, people are exposed to those bacteria and may become ill.<sup>55</sup>

Resistant strains are of particular concern because when treatment is needed, treatment choices are limited and early empiric treatment may fail. In a number of occasions and epidemiological settings, increased morbidity and mortality associated with resistant infections, longer illnesses, more invasive infections, higher probability of hospitalization and increased number of deaths have been observed as a result of infection with resistant strains.<sup>56</sup>

When multiple resistance genes are grouped, use of any one antibiotic can co-select for all the resistance genes. For example, antibiotic treatment for another infectious condition with an agent to which *Salmonella* is resistant can convert silent carriage into overt disease by killing off normal human gut bacteria and allowing the *Salmonella* to produce clinical symptoms. Resistance on a mobile genetic element may be transferred to other bacteria horizontally.<sup>57</sup>

CDC addresses these challenges in alliance with other agencies by tracking resistance through NARMS:

- CDC tests isolates from ill people (1 in 20 *Salmonella* isolates are tested)

- FDA tests isolates from meat and poultry
- FSIS tests isolates from animals at harvest

CDC also makes real-time resistance data part of outbreak investigations; refines the understanding of sources and spread of resistant bacterial strains and resistance genes and plasmids; estimates the health impact of resistance; and works with partners to prevent foodborne infections. The availability of NARMS data has recently been greatly improved and is now available much more quickly than in the past at the CDC NARMS Now website.

Trends in antimicrobial resistance in non-typhoidal *Salmonella* in the U.S. show MDR *Salmonella* are in a long-term and slow decline. From 1996 to 2013, MDR in isolates from humans declined from 16 percent to 10 percent. Of that 10 percent, 70 percent is found in the four most resistant serotypes: Dublin (92 percent resistant), 1:4, 5, 12:i:- (51 percent resistant), Heidelberg (33 percent resistant) and Typhimurium (17 percent resistant).<sup>58</sup>

Ceftriaxone is an important drug for invasive infections in human medicine; only 3 percent of all non-typhoidal *Salmonella* are ceftriaxone resistant. However, Dublin is 92 percent resistant and Heidelberg is 15 percent resistant, so certain serotypes are contributing to the problem of resistance more than others. Further, 3 percent of all non-typhoidal *Salmonella* are quinolone resistant, but the serotype Enteritidis account for 6 percent, and plasmid-mediated quinolone resistance has been identified.<sup>59</sup>

Trends in antimicrobial resistance in *Salmonella* Dublin in the U.S. shows that all are MDR, and in 2013, almost all were ampicillin, chloramphenicol, streptomycin, sulfisoxazole, tetracycline, amoxicillin-clavulanic acid, ceftriaxone (ACSSuTAuCx) resistant. Nine human strains since 2007 had lower susceptibility to fluoroquinolones, and 6 of those 9 were also ceftriaxone resistant.<sup>60</sup>

*Salmonella* Dublin has been a problem in calves. It is an invasive organism, and when it comes up in a human it is usually in their bloodstream, so it is a serious human health problem, although not a particularly common one. There is a commercial bovine vaccine for Dublin.<sup>61</sup>

MDR *Salmonella* 1:4,5,12:i:- is a serotype that evolved from Typhimurium, and was the fifth most common among human strains in 2012 and is still rising. It is also becoming more resistant as it was 51 percent MDR resistant in 2013. It is present in swine and beef cecal (large intestine) samples as well as on pork chops.<sup>62</sup>

Ciprofloxacin-resistant *Shigella* spreads from human to human via food, water and direct contact, typically in settings with poor hygiene. It can become resistant rapidly, and in 2013 showed 54 percent resistance to ampicillin and trimethoprim/sulfamethoxazole. Ciprofloxacin is the first choice of treatment for adults, but resistance is increasing. Resistance problems were observed mostly in travelers.<sup>63</sup>

Antibiotic stewardship is critical to prolong usefulness of antibiotics. Antibiotics are among the most commonly prescribed drugs used in human medicine. As much as 50 percent of antibiotics prescribed for people are not needed or are not prescribed in the optimal way.

Core elements of antibiotic stewardship in hospital settings include defining the program with leaders and accountability, implementing interventions to improve use, requiring prior authorization for certain agents, revisiting empiric treatment decisions routinely after 48 hours, conducting care audits with

feedback, optimizing dose and duration practices, tracking patterns of antibiotic use and resistance, reporting regularly on use and resistance, and educating practitioners and staff.

Expertise in animal health and management is vital to address resistant foodborne zoonotic infections by reducing introduction of resistant strains or genes via breeding stock, hatcheries, animal feed sources, water, environment, employees, etc.; reducing spread and selection of resistant genes or strains through policies that reduce selective pressure and practices that prevent spread of infection among animals; and implementing antibiotic stewardship and prevention measures through judicious antimicrobial use policies, tracking antibiotic use, alternating treatment and prevention measures, and implementing measures that reduce contamination of food.<sup>64</sup> A major part of stewardship is reducing the risk of transmission of the pathogens themselves as well as reducing the transmission of resistance among bacteria.

There has been some important progress, but it is hard to know exactly what contributed to that progress. The collective problem of MDR has diminished a lot. Disease control efforts on farms were likely part of that reduction as well as attention to which animals were harvested where. Still, there are newly resistant serotype combinations that are rapidly emerging as a problem; they need to be identified and those specific resistant issues need to be focused upon because, with attention, they can be controlled.<sup>65</sup>

## **DEFINITION/SUMMARY OF HUMAN STEWARDSHIP PROGRAMS**

### ***CDCs Overall Effort on Antibiotics, FY 2015 Requested Funding and CARB Program***

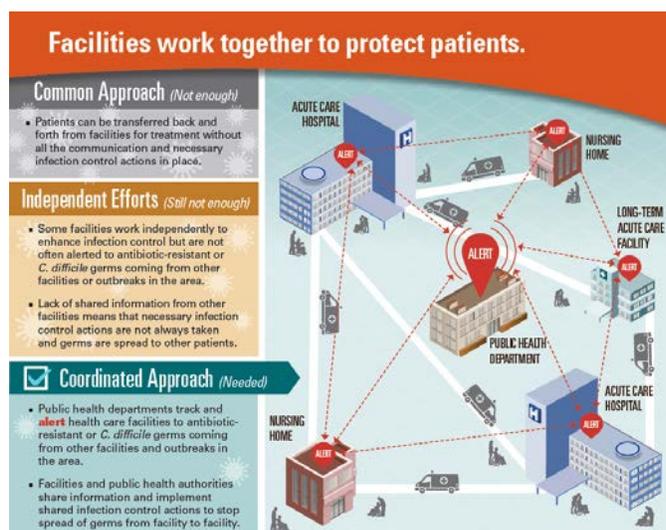
Since the publication of the 2013 threat report, there has been a growing national momentum about antibiotic resistance, which was galvanized by the development of CARB, and a report of the President's Council of Advisors on Science and Technology that came out in 2014, followed by the CDC's proposed Fiscal Year (FY) 2016 Antibiotic Resistance Solutions Initiative. Then the government developed a national action plan for CARB and an accompanying presidential directive; this was followed by the White House Antibiotic Stewardship Forum in June 2015, and then the formation of the Presidential Advisory Council on CARB, which held its first meeting in Washington, D.C., in October 2015.

There are three activities across the different antibiotic resistance threats that characterize CDCs work:

- Prevention
  - Develop evidence-based guidelines
  - Assist in outbreak response
  - Implement prevention strategies with states and partners
  - Conduct applied research to inform prevention
- Stewardship
  - Track antibiotic use, especially in healthcare settings
  - Provide research tools and guidance about improving antibiotic use
  - Improve consumer and provider education
- Surveillance
  - Implement real-time data systems for tracking and quality improvement
  - Define risk populations
  - Provide national and international laboratory expertise, testing and diagnostic capacity

The FY 2016 Antibiotic Resistance Solutions Initiative, which is included in the President's FY 2016 budget at \$264 million, is divided into three general areas: detect and respond, protect, and innovate.

CDC is working to build state health department capacity to address the spread of infectious disease across healthcare settings and in the community. The goals of state core capacity are to provide regional awareness of antibiotic resistance threats; assess and improve infection control; assess and improve prescribing across healthcare settings; and protect patients from antibiotic resistance and other infectious threats.



Antimicrobial resistance is a community problem and state health departments are pivotal in addressing the problem. Facilities in cities, counties and states need to work together to protect patients. The public health department is a central node in tracking patients as they are transferred among different types of facilities, so they can be the pivotal point to help keep track of where patients are so prevention strategies can be implemented appropriately.<sup>66</sup>

Modeling methods were used to try to quantitate what the potential impact of using a coordinated approach might be. Starting with a common approach, which would be each individual facility implementing infection control and other interventions in their own facility, and continuing across the spectrum to

*The public health department is a central node in tracking patients as they are transferred among different types of facilities.*

independent efforts in small groups of facilities, down to a fully coordinated approach with a health department as a central nodal point, it was estimated that up to 70 percent fewer patients would get carbapenem-resistant Enterobacteriaceae (as an example) over 5 years with a fully coordinated approach. This is a foundational focus of CDC's FY 2016 Antibiotics Solutions Initiative. Antibiotic resistance is a community problem and it will take a community approach to address it.<sup>67</sup>

One element of that approach is tracking and improving prescribing by:

- Providing real-time data about antibiotic use to better understand prescribing
- Setting national standards of antibiotic use to improve use and reduce resistance
- Ensuring all hospitals have effective stewardship programs
- Understanding and acting upon state-by-state differences in antibiotic prescribing rates
- Evaluating and testing intervention strategies to improve antibiotic prescribing
- Creating state programs to improve antibiotic prescribing in hospitals and the community

Part of the Antibiotics Resistance Solutions Initiative includes utilizing regional labs to:

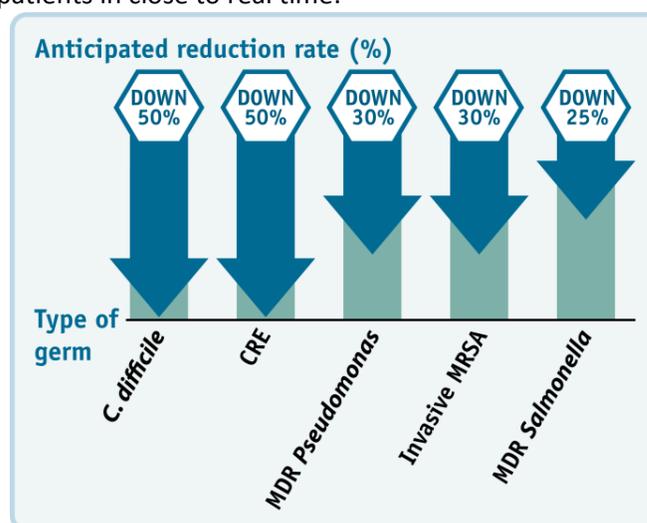
- Detect resistance and connections among strains
- Accumulate real-time, actionable information
- Support hospital labs with confirmation and characterization
- Improve health outcomes by testing all resistant *Salmonella* and other resistant foodborne pathogens through NARMS

- Integrate with the antibiotic resistance Isolate Bank (launched in 2015 and contains more than 220 isolates) and National Sequence Database

NARMS for Enteric Bacteria is a collaborative system operated by CDC, FDA and USDA with the cooperation of state and local public health departments, in which antibiotic resistance in foodborne pathogens are tracked in people (CDC), retail establishments (FDA) and on the farm (USDA). CDC now reports NARMS results routinely with all *Salmonella* outbreak reports. Other improvements include NARMS Now – a new interactive tool that provides public access to NARMS antimicrobial susceptibility data for *Salmonella*, *Campylobacter*, *E. coli* 0157 and *Shigella* isolates from people; and interactive maps, graphs and tables.

Currently, NARMS tests 1 in 20 *Salmonella*, and 3 strains from each outbreak, usually weeks after illness. The CARB Action Plan calls to test all *Salmonella* from patients in close to real time:

- Benefits of enhancement in outbreaks, know resistance as soon as outbreak is detected; resistant outbreaks can be prioritized for investigation
- Closer tracking of resistance trends in different parts of the country, different demographic groups, different *Salmonella* serotypes
- Better tracking of sources of resistant infections (e.g., domestic vs international, outbreak sources, etc.)



CARB could achieve reductions in many infections.

### Out-Patient AMR Issues

Nov. 16-22, 2015, was International Get Smart Week around the world to raise awareness of antibiotic resistance and the importance of appropriate antibiotic prescribing and use. The CDC Get Smart program historically focused on acute respiratory tract infections because that is where the most inappropriate antibiotic use occurs in the community.<sup>68</sup> The program aims to reduce the spread of antibiotic resistance by promoting provider adherence to appropriate prescribing guidelines, decreasing demand for antibiotics among healthy adults and parents of young children, and increasing adherence to prescribed antibiotics.

Get Smart provider tools include treatment guidelines and academic detailing sheets, continuing education resources, medical school curriculum, symptomatic prescribing pads and a guide to outpatient antibiotic stewardship interventions on the website.

The goal of Get Smart about Antibiotics week is to increase the number of actively engaged program partners in the promotion of Get Smart messages to target audiences (general public, providers, hospital administrators, global interest groups and policy makers). Partners include government agencies, professional societies, non-profit organizations, businesses and media outlets.

Measuring human antibiotic use in the community takes a multi-faceted approach:

- CDC surveys help assess volume of antibiotic use and appropriateness through:
  - The National Ambulatory Medical Care Survey (NAMCS)
  - The National Hospital Ambulatory Medical Care Survey (NHAMCS)



- A strong national measurement system
- A national emphasis on solving the problem, including national goals
- New policies to spur action
- Research

Turning this into a national program for antibiotic stewardship will require:

- Education and training about interventions and implementation
- Measurement, including total antibiotic use and appropriate use, and prevalence of stewardship programs
- National goals
- National policies
- Research to expand implementation and develop new interventions

One of the big things that hospitals have historically struggled with and that was identified as a big gap for effective stewardship was guidance for hospitals that would lay out for them how they might implement effective antibiotic stewardship programs across the varied spectrum of hospitals that exist in this country. CDC has now produced specific guidance for setting up these programs in hospitals and nursing homes; these guidelines are available at CDC's website.

Antibiotic measurement challenges in hospitals include:

- 1) Data not available from any single source
- 2) Amount purchased is what is available from large suppliers, but that doesn't correlate well with what is used and when
- 3) Need to know what is given, why it is given and if it was given correctly
- 4) Hospitals want to benchmark use to drive improvement because benchmarking has proven to be a powerful improvement tool for healthcare associated infections – benchmarking requires common definitions, acceptable risk adjustment and collection of a large volume of data

The CDC approach to measuring in-patient antibiotic use is broad assessments of aggregate use, facility-specific assessments of administration data and detailed assessments of appropriate use.

The National Healthcare Safety Network (NHSN) antibiotic use module is fully electronic and allows hospitals to track antibiotic use. The CDC is working with enrolled hospitals to determine factors that contribute to variations in antibiotic use and how to best benchmark antibiotic use to develop national measures. There is 300 percent variation in the use of broad spectrum antibiotics on medical wards in hospitals.<sup>72</sup> Now that that variation has been found, it needs to be determined why it is occurring. The Standardized Antibiotic Administration Ratio (SAAR) is CDC's first attempt at developing a quality improvement measure for antibiotic use. SAAR expresses observed antibiotic use compared to predicted use. The expected use is defined by the average use of facilities reporting data (expected is still not optimal). Each SAAR is risk adjusted based on facility characteristics, but not patient characteristics. The ultimate goal of stewardship is to improve appropriate use of antibiotics. CARB has a 2020 goal to reduce inappropriate in-patient human antibiotic use for monitored agents and conditions by 20 percent from 2014 levels. CDC came up with some tools to assess appropriate antibiotic use to try and drive things around criteria that are relatively objective.

Appropriateness can be difficult to judge. It is often a judgment call whether a human or an animal needs an antibiotic; there are instances, though, where there are relatively objective criteria based on what is recommended in national guidelines for best practices for prescribing.<sup>73</sup>

CDC is working to combine overall assessment of use through the standardized antibiotic administration ratio with assessments of appropriate use to help hospitals determine if high use is also inappropriate use, and CDC is exploring ways to do this electronically.

Many experts, including advisors to the president, have called for the government to require hospitals and nursing homes to have antibiotic stewardship programs. The Center for Medicare and Medicaid Services (CMS) has the power to make this a requirement through the Conditions of Participation, which establish criteria hospitals must meet to get funds from CMS. Private groups that accredit hospitals can also do this. The stewardship program would be part of the facility's infection prevention and control program. CDC has developed core elements for Antibiotic Stewardship Programs in Hospitals and in Long Term Care to help with implementation.

This will require a multi-faceted approach; education alone or regulation alone won't get the job done. Measurement is very important, but data has to be actionable. The challenges are too complex for any group to address alone; collaboration is essential.<sup>74</sup>

#### ***Antimicrobial Stewardship – the State Health Department Perspective***

Prevention of infection is a critical component of stewardship. Every infection, including healthcare associated infections (HAI's), represents one less episode of antibiotic use and, thus, one less opportunity for the development of resistance, and one less exposure to a potentially resistant infection.<sup>75</sup>

For HAI's, a metric used is a Standardized Infection Ratio (SIR), which is a risk adjusted summary measure. It is the observed number of HAI's divided by the predicted number of HAI's. A SIR of 1.5 means infections are 50 percent higher than predicted; a SIR of 0.4 percent means infections are 60 percent lower than predicted. The HHS 5-year goal is a SIR of 0.5 percent. In 2008, many Tennessee hospitals started to participate in an effort to decrease Central Line Associated Blood Stream Infections (CLABSI). Despite this effort, the state-wide SIR remained above 1.0 percent because several large facilities hadn't made progress, while many smaller facilities had. It was only after the first report was sent to hospitals – showing hospital-specific names – that a dramatic reduction in SIR has been seen. Now, Tennessee hospitals are below the HHS goal of 0.5 percent.

Another metric that has been found to be helpful for targeting prevention efforts in HAI is part of CDC's Targeted Assessment for Prevention Strategy – the Cumulative Attributable Difference (CAD). CAD is the number of observed infections minus the number of predicted infections, with a multiplier that affects the goal (observed infections – (predicted infections x HHS goal SIR)).

Tennessee is one of 10 Emerging Infections Program (EIP) sites funded by CDC. In 2011 they participated in a point-prevalence survey of HAI's and antimicrobial use. The overall prevalence of in-patient antimicrobial use was nearly 50 percent; at 56.3 percent Tennessee was the highest. The point-prevalence survey showed which hospitals had the highest antimicrobial use; lower respiratory infections and urinary tract infections accounted for 57 percent of therapeutic use, and an understanding of the five most common antibiotics prescribed was gained, of which vancomycin topped the list.

In Tennessee-specific data, the highest antimicrobial use occurred in small hospitals. The proportion of oral antimicrobial use was much higher in large hospitals, and likely reflects that larger hospitals have already done some work on intravenous vs. oral conversion as part of antimicrobial stewardship. 46 percent of patients received antibiotics for treatment of active infection. Surgical prophylaxis was an indication in just under 10 percent.

An assessment of antimicrobial use appropriateness was then piloted among in-patients and found that a high proportion had inadequate microbiology testing or inappropriate tailored antimicrobial therapy.

### 7 Core Elements of Antimicrobial Stewardship

- **Leadership commitment:** Dedicate necessary human, financial, and IT resources
- **Accountability:** Appoint a single leader responsible for program outcomes.
- **Drug expertise:** Appoint a single pharmacist leader to support improved prescribing
- **Act:** Take at least one prescribing improvement action, such as requiring reassessment after 48 hours to check drug choice, dose, and duration
- **Track:** Monitor prescribing and antibiotic resistance patterns
- **Report:** Regularly report to staff prescribing and resistance patterns, and steps to improve
- **Educate:** Offer education about antibiotic resistance and improving prescribing practices

Tennessee  
Department of  
Health

70 percent of U.S. hospitals have implemented at least five of the seven Core Elements of Antimicrobial Stewardship. Tennessee is behind at 58 percent and only about 29 percent of Tennessee hospitals have all seven core elements implemented. Statewide, only 23 percent of facilities have salaried support for antibiotic stewardship activities. 45 percent have a written statement of support for antimicrobial stewardship from leadership. Preliminary analysis shows that both of these metrics are pretty good predictors of a robust antimicrobial stewardship program.

One of the core elements is action, and within it there are five components: policies present, treatment recommendations, review of treatments, antibiotic approval by a physician and antibiotic review by a physician. Statewide, 21 percent of facilities have a policy requiring prescribers to document an indication for all antibiotics. If indication isn't documented, it is hard to gain an understanding of the reasons why antibiotics are prescribed, and whether or not they were prescribed appropriately.<sup>76</sup>

In human health, it is strongly recommended to take a "time out" at 48 to 72 hours to review the appropriateness of antibiotics. At that time, it can be seen whether there has been a clinical response, the results of cultures should be in and it is a good time to see if de-escalation is possible. The "6 D's" in human medicine are right diagnosis, right drug, right dose, right duration, de-escalation and drainage/debridement.<sup>77</sup>

Overall in Tennessee, 22 percent of hospitals had a formal procedure for all clinicians to review the appropriateness of antibiotics.

NHSN is a surveillance system used by:

- 17,000 healthcare facilities to track HAIs, antimicrobial use and resistance, and adherence to prevention guidelines; guide prevention efforts; submit data for public reporting and quality measurement purposes
- Health departments for surveillance, prevention and public reporting
- CMS for quality measurement and reporting, reimbursement and prevention
- HHS to measure national progress

The NHSN Antimicrobial Use and Resistance (AUR) Module uses data extracted from parts of the electronic health record. Two Tennessee hospitals are reporting using the NHSN AUR Module, and opportunities are being set up for those two facilities to share lessons learned. An inventory of different electronic health records components used in Tennessee facilities is being compiled so partnership with other facilities can be established to help troubleshoot data extraction.

Because there is a time lag until more facilities report to the NHSN AUR module, as an interim measure, serial point prevalence surveys to measure antimicrobial use are being performed and educational training opportunities are being promoted for pharmacists.

The Council of State and Territory Epidemiologists (CSTE) last year passed a position statement about strengthening antimicrobial stewardship, including the role of state and local health departments:

- 1) CSTE recommends all state health departments evaluate and incorporate stewardship activities across healthcare settings into their HAI programs
- 2) CSTE recommends CDC identify a standardized metric for measuring in-patient antimicrobial use to facilitate risk-adjusted benchmarking
- 3) CSTE recommends CDC evaluate existing measures for monitoring out-patient antibiotic prescribing practices

CSTE partnered with the National Association of State and Public Health Veterinarians and passed a position statement recommending CDC engage state HAI programs and public health veterinarians to collaborate with other agencies about state and national initiatives to build relationships and facilitate sharing of antimicrobial stewardship strategies between human and veterinary medicine and animal agriculture. It also recommends FDA and other stakeholders develop appropriate metrics for tackling antimicrobial use in animal agriculture and companion animal practice, and that increased funding be provided for strengthening the monitoring of antimicrobial resistance, including state AMR surveillance activities as well as surveillance of resistant bacteria in food, and that there should be a publically accessible library where stewardship models, projects and educational tools can easily be shared across jurisdictions.

### ***Antimicrobial Resistance in Humans and the Global Health Security Agenda***

The challenges faced internationally are similar themes, but the reality is different; resources are limited and the capacity to respond isn't as great as it is in the U.S.

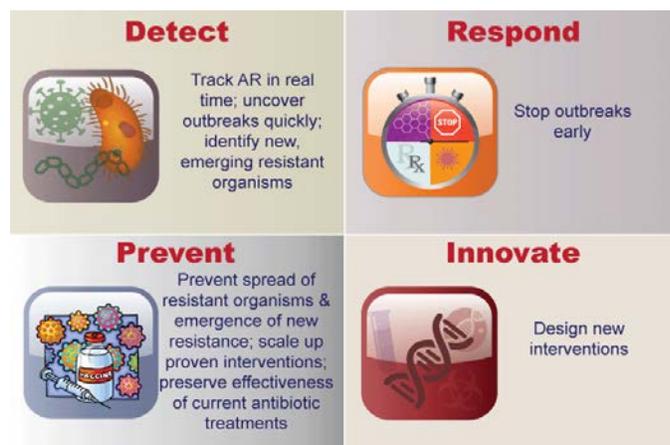
A health threat anywhere is a health threat everywhere. As early as the 14<sup>th</sup> Century, people used quarantine to keep diseases like the plague from spreading across borders. What affects one country can affect other parts of the world. This is especially true today.

Severe antibiotic resistance – when bacteria change and cause antibiotics to fail – is happening right now, across the world. AMR has reached alarming levels in many parts of the world, and resistance is seen in all 6 World Health Organization regions (Africa, Americas, Southeast Asia, Europe, Eastern Mediterranean and Western Pacific). Treatment options are limited, and there are gaps in surveillance standards, data sharing and coordination. For many areas of the world, there is limited capacity to detect AMR in laboratories and there is even less capacity to coordinate and report data.

AMR is likely a worse problem in the developing world. The full impact is unknown because there is no reliable system in place to track antibiotic resistance globally.

Antibiotic resistance is a natural phenomenon, but it is exacerbated by over and under prescribing, poor regulation of access to medicines, lack of infection control programs, inadequate equipment, weak laboratory capacity and inadequate surveillance.

Development of AMR is due to unnecessary antibiotic exposure, and transmission of AMR primarily occurs in healthcare settings due to poor hygiene and lack of transmission precautions.<sup>78</sup> To reduce the burden of AMR in human medicine, infection control in healthcare settings must be a focus. The importance of infection control for emerging diseases can't be underestimated.



*CDC Strategy to fight antimicrobial resistance.*

One of the main goals of CARB is to improve international collaboration and capacity for prevention and surveillance control as well as research and development.

The Global Health Security Agenda focuses on a few countries through a twinning framework where the U.S. works in partnership with another country to help them come up with their own solutions to prevent avoidable catastrophes, detect threats early, and respond rapidly and effectively. The 5-year target is an integrated and global package of activities to combat AMR. The desired impact is enhanced

infection prevention and control; prevention of the emergence and spread of AMR, especially among drug-resistant bacteria; and strengthened surveillance and laboratory capacity.<sup>79</sup>

### ***Building Consumer Trust***

At his symposium, representatives of the retail grocery sector, the producer sector and the restaurant sector presented their perspectives to symposium attendees. This was a well-received panel and one which filled a gap that attendees felt was present in previous meetings. Among the key points highlighted by the panelists were:

- Consumer interest is driving the marketplace to offer “antibiotic-free” alternatives
- However, consumers have a very limited, if any, understanding of where animal protein comes from, how it is grown and produced and how it reaches the market
- Consumers also have a very limited understanding of the terms organic, natural, free-range, antibiotic-free and other marketing and labelling terms on grocery products and restaurant offerings
- Similarly, consumers often seem to be confused about the role of antibiotics in food production and the assurance that antibiotic residues even in conventionally raised meat legally falls below very restrictive tolerances
- Producers are reducing and eliminating their dependence on antibiotics as growth promotants and many are offering products from animals which are raised without any antibiotics at all.
- Similarly, many companies are ensuring their compliance with the FDA VFD guidance, although small producers may need assistance in meeting the new requirements, due at least in part to a shortage of large-animal veterinarians
- Producers are actively looking at ways to reduce the need for antibiotic use either by changing husbandry practices or using new avenues to minimize enteric animal health issues.
- Because we will always need to treat sick animals, and it would be inhumane not to do so, antibiotics will also be used in animal agriculture, but alternatives will be found for some current disease prevention uses.
- Retailers are requesting greater transparency from producers who are responding by making the best and most efficient possible use of the multiple inputs and complicated interplay of resources necessary for successful meat production, including land, water, animals, fuel, labor and technology and maximizing their ability to manage disease and prevent disease.

## MEASURES THAT MAKES A DIFFERENCE: WHY MEASURE AND WHAT TO MEASURE

Thinking strategically about antibiotic resistant efforts and what to measure is more important than how to measure.<sup>84</sup>

Six things need to be understood:

1. The “need” being contributed to
2. “What” vs. the “so what” of the program
3. Sequence of short-term outcomes → middle-term outcomes → long-term outcomes
4. “Accountable” outcome – the outcome that equals success
5. “Moderators” – contextual factors that get in the way
6. “Outputs” – activities strong enough to get to the outcomes

If a goal isn’t accomplished, it is usually for one of two reasons, and these effect what gets measured: 1) the nature of the problem was guessed right, but the activities were implemented poorly or 2) despite best efforts, there are too many things out of control.<sup>85</sup>

The payoff for strategy is:

- 1) The key outcomes that are “owned”
- 2) How to implement activities in way that most assures outcomes
- 3) How to mitigate/own outside factors that may deter outcomes

The payoff for measurement is:

- 1) Accountable outcome is key one to measure
- 2) What short-term/middle-term activities drive it
- 3) Outputs are process measures for activities
- 4) Moderators are the ability to explain (lack of) progress

A roadmap helps define what is the big downstream need in the “what” vs. the “so what.”

The “What” of antibiotic resistance

- Monitor sales, use and management practices
- Mobilize, advocate and engage across sectors
- Strengthen infrastructure for surveillance and reporting
- Establish regional public health lab networks with standard platform for resistance testing
- Provide research and development funding and support
- Form public-private research partnerships
- Deliver education programs

The “So What’s”

- Less drug resistance
- Preserve the usefulness of antibiotics and effective treatment of infection
- More effective prevention, control and treatment of infection/disease in humans and animals
- Prevention of infection and disease
- Reduced spread of antibiotic resistant pathogens
- Fewer resistant infections; less disease in humans and animals

Some “So What’s” that drive them

- Improved use of antibiotics in healthcare settings
- Improved use of antibiotics in food production
- Increased trust and reduced blame
- Rapid recognition of resistance in humans, animals and environment
- Rapid identification and characterization of infection
- New diagnostic tests
- New antibiotic therapeutics/non-antibiotic prevention methods and therapies
- New and innovative animal management and food production innovations

What is being done is complex and there are multiple pathways, so it can be called a networked intervention.<sup>86</sup>

Choosing an accountable outcome:

- 1) Relevant: sufficiently “downstream” to matter to stakeholders
- 2) Responsive: sufficiently “upstream” that program’s efforts can be expected to make a difference

What is/are the accountable outcome(s) for the antibiotic resistance effort?

- Think about the whole effort – all pathways working jointly
- Look to balance relevance with responsiveness

What other things should be measured? They should be measured for two reasons: 1) they’re the major drivers of getting to that big outcome or 2) they’re the things most likely to fail.

The committee made some judicious choices of measures to make changes to the road map. They tried to purposely choose measures that crossed some of the pathways.

The purpose was to create a simple roadmap to decide what outcomes to be most responsible for. The purpose of measurement is to track where progress is being made and where it is not. Issues that lent themselves to measurement and that were actionable were prioritized.

## SUMMARY OF BREAKOUT GROUPS

An important part of the annual Antibiotic Symposium is the discussion that takes place and the output that results from the breakout group discussions. This year's breakout groups were designed and led by Dr. Tom Chapel from and his team of facilitators and scribes.

Breakout group work began on the first day of the symposium with a presentation, "Thinking Strategically About Antibiotic Resistance Efforts" which reviewed the key elements in developing and designing metrics and measures. These key elements include a critical understanding of the program being monitored, the types of outcomes that are the aim of the program, and concepts of accountability, ownership, drivers, pathways and moderators. A straw-man roadmap was described and presented. The first day's work for the breakout groups was to review and revise the roadmap based on the expertise and experience of symposium attendees.

Participants were briefed about how to engage their own accountability in the task of revising the roadmap to assure the relevance (importance to stakeholders) and responsiveness (likelihood of program efforts impacting outcomes) of its content, as well as the need to incorporate contextual factors which may be political, economic, social and/or technological.

The revised roadmap which resulted from the work in these breakout sessions is presented in the attached figure.

The second set of breakout groups, conducted on the final day of the meeting, continued the work begun in the first session. In the second session, each of four groups was assigned a different critical short-term or medium-term outcome or related set of outcomes. These were selected from the roadmap as being most likely to lend themselves to measurement and be actionable. Each group was then asked to design and develop a metric for that outcome, including supporting measures, data sources for those measures, and possible issues, concerns and barriers related to that metric. Those critical outcomes assigned to the groups were:

1. Strong antibiotic stewardship in food production and animal husbandry
2. One health surveillance; integrated surveillance
3. Rapid ID and characterization of infection; new diagnostic tests
4. New antibiotic therapies; new non-antibiotic alternatives; new & innovative animal management innovations

The results of those discussions and the output of the breakout groups is presented in the following table.

## TABLE: PROPOSED MEASURES AND METRICS DEVELOPED BY BREAKOUT GROUPS

**METRIC 1:** Percentage of states with ongoing, working One Health committees overseeing collection and dissemination of data on antimicrobial resistance from human, animal and environmental sources

Outcome to which the measure/metric is applied:

- Need for integrated one health surveillance with accessible, useful data for decision-making and assessment

Supporting measures:

- Include but not limited to:
  - Resistance rates for targeted bugs from humans, animals, food sources, environment
  - Antimicrobial use in a variety of human (hospital, outpatient, etc.), animal (farm, companion animal practice, etc.), and environmental sources

Issues/concerns with the metric:

- Would need to create a functional, integrated repository for human, animal and environmental AMR data
- Would need to incorporate some existing data which is publicly available (but in different places and systems), some data which exists but is not easily accessible or available, and some data which would need to be generated
- Would need to include the “right” data in the “right” form—too much data (“data dumps”) is of limited value
- Criteria include:
  - Accessible data
  - Downloadable data
  - Real-time data
  - Consistent case definitions (we all need to agree on what we’re measuring)
- Each state would need to establish a governing body with necessary funding and knowledgeable and trained staff. Other criteria might include (but not be limited to):
  - A charter defining goals, explicitly establishing public sector/private sector cooperation, and purposes and intents of how the data will be used for policy decisions
  - Agreements for data-sharing (e.g., memoranda of understanding [MOUs])
  - Appropriate protections for individual privacy and confidential and proprietary business information
- How would data from other states/other countries be handled (travelers, visitors, imported food/products)?

Could such a measure/metric be developed?

- Yes, and recent improvements in NARMS are a good example of an appreciated effort in this direction. However, there is a great deal more data already available, and as described in the CARB National Action Plan, several Federal agencies have committed to developing additional data sources. However, these data are not well-integrated and optimally interpretable now; additional data may only compound that problem.
- Suggest we need a special meeting with broad public/private participation to talk about AMR data: needs, sources and gaps, availability, accessibility, privacy and confidentiality protections, and who

will be responsible for what. Participants would need to come prepared to work on developing solutions for integrating one-health data, not just presenting organization-specific plans.

Challenges in defining/creating the data source and implementing the metric:

- Ensuring that information of value regarding antimicrobial resistance and antimicrobial use is available to human and animal health practitioners, interested organizations and the public appropriately available in a timely manner.
- Really need to ensure greater participation from folks in environmental fields and science. This is often overlooked by the human and animal health people.
- There are very significant challenges to accomplishing this metric, but we cannot effectively address the AMR problem without really understanding all the complicated aspects of it and we need the data to do that. Among the barriers to overcome are:
  - Lack of funding; government will need to be the main supporter in terms of funds
  - Lack of coordination at Federal and state levels. The CARB Advisory Panel may be able to help but they would need to prioritize this issue. The CARB National Action Plan is encouraging but the coordination plans for how the agencies will work together are not clear.
  - Public and private sectors need to coordinate better as well. There is already a great deal of data out there that is not being used effectively.
  - Some states don't have a functioning One Health component within their health departments
  - The increasing use of culture independent diagnostic testing (CIDT) is a threat to collecting good AMR data. Lots of groups are discussing this but addressing it with a specific plan it needs to be priority for ensuring the availability of required AMR data.

**METRIC 2:** The number of useful and practical new diagnostic tests for the rapid identification and characterization of infection and AMR (developed within a specific time frame)

Outcomes to which the measure/metric is applied:

- Need for rapid identification and characterization of infection and new diagnostic tests. (More rapid identification and testing for antimicrobial resistance will allow animal [and human] health practitioners to provide the best care and also be good stewards of antibiotics.)

Supporting measures:

- Number of new tests becoming available at the farm level, for field use, that enable veterinarians to make diagnostic decisions more quickly and more accurately
- Number of new tests becoming available for ensuring food safety at production and processing level (before going to market)
- Improvement in how rapidly diagnostic information is available (current three to five days wait for results is too long)

Issues/concerns with the metric:

- Tests need to be accurate, rapid, affordable, cost-effective, and specific
- Tests need to be targeted first at the most common problems that veterinarians face

Could such a measure/metric be developed?

- Yes, both FDA and USDA would have role in approving and assessing implementation and effectiveness of such tests, but would need to fully engage state health and agriculture departments, producers and veterinarians, especially to ensure that helpful tests are utilized as widely as necessary and appropriate

Challenges in defining/creating the data source and implementing the metric:

- Someone has to produce the test. Manufacturers may need help in furthering the basic science required (can NIH help?)
- Would need to establish training and perhaps accreditation standards for dissemination and use of tests once they are developed; perhaps this could be part of continuing education

**METRIC 3:** Proportion of production units that have a documented Veterinarian-Client-Patient Relationship (VCPR) with at least one veterinarian.

Outcome to which the measure/metric is applied:

- Need for strong antibiotic stewardship/veterinary oversight in food production and animal husbandry.

Supporting measure:

- Does a specific production unit have a VCPR with a veterinarian in place (yes/no)?

Issues/concerns with the metric:

- Can we be certain that all veterinarians with VCPRs have the appropriate training/accreditation to write FDA compliant veterinary feed directives?

Does an existing data source exist for this metric?

- No.

Could such a measure/metric be developed?

- Possibly, but it would require a great deal of cooperation from USDA, FDA, producers and the veterinary profession (e.g., AVMA)

Challenges in defining/creating the data source and implementing the metric:

- Definitions and criteria would need to be established, e.g., what constitutes proper documentation of VCPRs
- Producers would need a guarantee of anonymity to cooperate, especially if data were shared with a regulatory agency, and would need support to correct identified gaps and meet requirements

**METRIC 4:** The degree to which new and alternative interventions are being used in practice by veterinarians

Outcome to which the measure/metric is applied: Need for new antibiotic therapeutics, new non-antibiotic prevention methods and therapies, and new innovations in animal management and husbandry to reduce infection risk

Supporting measure(s):

- The number of new therapies approved by FDA/USDA/EPA
- The number of non-antibiotic alternatives for prevention and treatment tested and proven effective
- The number of applications for patents for new technology likely to reduce antimicrobial use on the farm
- The number of applications for small business innovation research (SBIR)<sup>1</sup> funding for new technology and products likely to reduce antimicrobial use on the farm
- The number of grants from relevant Federal agencies (e.g., NIH, CDC) for new technology and products likely to reduce antimicrobial use on the farm

Issues/concerns with the metric:

- We need to establish definitions:
  - what is an intervention likely to reduce antibiotic use;
  - what classifies as a new therapy—does it need to be a new class of antibiotic; does it need to be a non-antibiotic treatment
- Even if new interventions are developed, would they be cost-effective. People won't use new techniques just because they spare antibiotics; they need to be economically beneficial

Could such a measure/metric be developed?

- Although this is hard to measure, it is very important.
- Need further discussion to figure out how to measure progress in this area

Challenges in defining/creating the data source and implementing the metric:

- Definitions
- Who will do the measurement and what will they count
- How to measure what is actually useful in practice and then, if useful, whether it's being used

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<sup>1</sup> Each year, Federal agencies with extramural research and development (R&D) budgets that exceed \$100 million are required to allocate 2.8 percent of their R&D budget to these programs. Currently, eleven Federal agencies participate in the SBIR program, including USDA and DHHS

## CONCLUSION AND NEXT STEPS

Antibiotic resistance is an extremely complex and multifaceted problem; no single solution is possible and no one scientific or professional discipline or sector of society can hope to address it alone. We will succeed in addressing this emerging crisis from a systems-based approach that strives to close gaps of misunderstanding and avoid implementing meaningful and effective interventions. While action is urgently necessary, these actions must be based on a solid foundation of science, be economically and socially viable, grow out of transparent and open dialogue among all concerned parties and be evaluated carefully at each phase of implementation to ensure successful and sustainable outcomes.

The commitment to antibiotic stewardship from stakeholders throughout animal agriculture and the animal protein supply chain is clear and definitive, matching the seriousness and commitment we heard from representatives of human medicine and public health. High priority areas from the roadmap were chosen for metrics development because: 1) AMR and antibiotic use need to be carefully monitored and much better understood, 2) research on developing and implementing new, rapid and accurate diagnostic tests for antibiotic resistance that can be used in the field and at the bedside needs to be vigorously supported, 3) similarly, research to find alternatives to antibiotic use, including preventative treatments and improved production management practices requires both Federal and private sector support, and 4) the application of new regulations and guidelines will need to be thoughtfully and carefully assessed and assistance will need to be deployed to help practitioners and producers fully understand the changing requirements and put them into practice.

While the symposium succeeded in bringing together experts from diverse backgrounds to discuss the subject theme--*Antibiotics Stewardship: From Metrics to Management*—and resulted in the development of four potential metrics to monitor progress, participants and organizers understood that these efforts are a very early step forward and must lead to further dialogue and cooperative efforts to achieve the goals shared by the many stakeholders. NIAA will continue to provide leadership within animal agriculture and establish a platform to facilitate collaborations for identifying and helping to implement solutions to improve antibiotic use through stewardship and reduce the spread of antibiotic resistant bacteria. These collaborations will proceed from a One Health perspective, promoting a better understanding of the science and working to overcome political, social and cultural divides between the worlds of veterinary and human medicine, and between agriculture and food production industries and consumers.

**FIGURE:** Revised roadmap based on small group Tuesday discussion—**principal changes from initial roadmap in bold**

1 Activities	2 ST Outcomes	3 MT Outcomes	4 MT Outcomes	5 LT Outcomes
<p><b>[WHICH PLAYER(S)] ID and educates on best stewardship practices</b></p> <p>[WHICH PLAYER(S)] Monitors sales, use, and management practices</p> <p>[WHICH PLAYER(S)] Mobilizes, advocates, engages across sectors</p> <p>[WHICH PLAYER(S)] strengthens infrastructure for surveillance and reporting</p> <p>[WHICH PLAYER(S)] establishes regional PH lab network with standard platform for resistance testing</p> <p>[WHICH PLAYER(S)] provides R&amp;D funding and support</p> <p>[WHICH PLAYER(S)] forms public-private research partnerships</p> <p>[WHICH PLAYER(S)] delivers education programs</p>	<p>Strong antibiotic stewardship in humans/healthcare</p> <p>(1) Strong antibiotic stewardship/vet oversight in food production <b>and animal husbandry</b></p> <p>More regional cross-sectoral cooperation</p> <p>Consensus on strong and supportive policy</p> <p>Stronger lab capacity</p> <p>(2) One health surveillance; Integrated surveillance</p> <p>Development of new tests and technologies</p> <p><b>Development of mgmt. and production innovations</b></p> <p>Increased private sector interest and investment</p>	<p>Improved use of antibiotics in healthcare settings; Optimal treatment decisions</p> <p>Improved use of antibiotics in food production <b>and animal husbandry</b></p> <p>Real-time info sharing on resistance and infections</p> <p>Increased trust and reduced blame</p> <p>Rapid recognition of resistance in humans, animals, and environment</p> <p>(3) Rapid ID and characterization of infection</p> <p>(3) New diagnostic tests</p> <p>(4) New antibiotic therapeutics; New non-antibiotic prevention methods and therapies</p> <p><b>(5) New and innovative animal management and food production innovations</b></p>	<p>Less drug resistance</p> <p>Preserve the usefulness of antibiotics and effective treatment of infection</p> <p>More effective prevention, control, and treatment of infection/disease in humans and animals</p> <p>Prevention of infection and disease</p>	<p>Reduced spread of antibiotic resistant pathogens</p> <p>Fewer resistant infections; Less disease in humans and animals</p>

*STRAWMAN Roadmap – Antibiotic Resistance – Based on National Action Plan and 2014 White Paper*

## FOOTNOTES

<sup>1</sup>Apley, Mike. “Antibiotic Stewardship and Animal Agriculture,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 3 November 2015.

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<sup>3</sup>Lewis, Craig. “FDA Antibiotic Strategy,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 5 November 2015.

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<sup>5</sup>Hofacre, Chuck.

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<sup>7</sup>Koeman, Jennifer. “Stewardship for Swine,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 4 November 2015.

<sup>8</sup>Granger, Larry. “USDA Antimicrobial Resistance Strategy – Farm Foundation Results,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 5 November 2015.

<sup>9</sup>Lapara, Tim. “Stewardship and the Environment: Waste Water Treatment and Antibiotics,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 4 November 2015.

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<sup>11</sup>Tauxe, Robert.

<sup>12</sup>Hicks, Lauri. “Out-Patient AMR Issues,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 4 November 2015.

<sup>13</sup>Srinivasan, Arjun. “In-Patient AMR Issues,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 3 November 2015.

<sup>14</sup>Park, Benjamin. “Antimicrobial Resistance in Humans and the Global Health Security Agenda,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 5 November 2015.

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<sup>17</sup>Shryock, Tom. “Historical Perspective,” National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 3 November 2015.

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<sup>32</sup>Sjeklocha, David. "Stewardship for Beef," National Institute for Animal Agriculture Antibiotics Symposium, Antibiotic Stewardship: From Metrics to Management, Atlanta, Ga., 4 November 2015.

<sup>33</sup>Sjeklocha, David.

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<sup>46</sup>Lapara, Tim.

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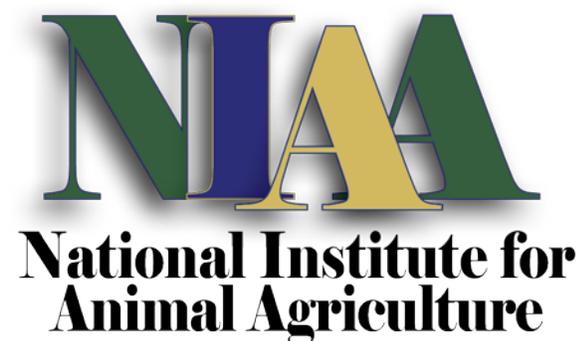
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**THE SYMPOSIUM WAS FUNDED IN PART BY:**

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