PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

Sixth Public Meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

May 3–4, 2017

Department of Health and Human Services
Great Hall, Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

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Day One

Welcome and Overview

Martin Blaser, M.D., Chair

Dr. Blaser called the meeting to order at 9:00 a.m. and welcomed the participants.

Call to Order, Roll Call, and Rules of Engagement

Jomana F. Musmar, M.S., Ph.D.c, Designated Federal Official

Ms. Musmar explained the rules governing the PACCARB under the Federal Advisory Committee Act and conflict-of-interest guidelines. She then called the roll. (See Appendix A for the list of participants.)

Opening Remarks

Don Wright, M.D., M.P.H., Acting Assistant Secretary for Health, Department of Health and Human Services (HHS)

Dr. Wright said HHS Secretary Tom Price, M.D., has a special interest in antimicrobial resistance (AMR), which poses a global health threat. He said the World Health Organization's (WHO's) target list of high-priority antibiotic-resistant pathogens will help prioritize research on new treatments. Dr. Wright appreciated the Council's attention to both human and animal health and the connections between them. Antibiotics must be used responsibly among both populations, because both contribute to the development of persistent and resistant bacteria.

Dr. Wright announced that the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) and the Biomedical Advanced Research and Development Authority (BARDA) just selected 10 semifinalists for its jointly funded Antibiotic Resistance Diagnostic Challenge, a federal prize that will provide up to $20 million for innovative tests. Also, BARDA recently gave 11 awards to companies under the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), a novel approach to boost the pipeline of development of new antibiotics. The PACCARB recommendations on incentives to address antibiotic resistance will complement these efforts, and the Department looks forward to receiving them. Dr. Wright thanked the Council members for their experience, expertise, knowledge, and commitment.

Infection Prevention in Animal Health

Introductory Remarks

Lonnie King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair

Dr. King pointed out that antibiotic resistance is a complex problem that must be addressed with a holistic, integrated strategy that includes animal health. He said veterinary medicine typically focuses on herd or population health. The rise of antibiotic resistance has created a new urgency around infection prevention and a renewed interest in managing disease and preventing resistance.

Bacterial Disease Challenges: Perspectives from Food Animal Representatives

Moderator: Michael D. Apley, D.V.M., Ph.D., DACVCP, PACCARB Member

BACTERIAL DISEASE CHALLENGES: PERSPECTIVE FROM SWINE VETERINARIANS

Locke Karriker, D.V.M., M.S., DACVPM, Professor and Director, Swine Medicine Education Center, Iowa State University College of Veterinary Medicine

Dr. Karriker defined some terms in the context of swine health and described the most commonly seen pathogens affecting herds. These scenarios pose the greatest concerns:

- A disease outbreak occurs close to marketing (or harvest) date. Such an outbreak is expensive, and antibiotic therapy options are limited because of the time it takes for the drug to clear the animal's system. Preventive measures have limited effectiveness at the end of animal's life, especially killed vaccines. Late outbreaks are most likely to raise food safety issues.
- Research about individual animal pathology does not adequately inform about population disease dynamics. The larger the animal population, the wider the range of infection timelines across the herd, which in turn necessitates longer treatment times. Drug studies in swine usually assess a few identical pigs, while a herd has much more variation.
- Limited use of antibiotics reduces welfare. Producers recognize that tools are available but cannot use them.
- Animals are infected with immune-compromising viruses that can exacerbate stressors, making them more susceptible to disease. Influenza A virus of swine is present on 22 to 55 percent of farms depending on the season and phase of production. Porcine reproductive and respiratory syndrome virus is common; in 2009, it was present on 71 percent of farms. Porcine circovirus type 2 is ubiquitous.

Veterinary oversight provides veterinarians with more opportunities to engage owners and influence treatment choices. Population structure (static vs. dynamic), size, and housing (indoor vs. outdoor) influence the clinical severity of disease and need for drugs. Flexibility on dose and treatment duration helps reduce potential for resistance. Reducing access to antimicrobials reduces animal welfare. If bacteria are recognized, said Dr. Karriker, there are opportunities to prevent disease and conserve antibiotics.

Alternatives to antibiotics include increased biosecurity—that is, infection prevention and control practices—although biosecurity methods are less effective when the disease is not well understood. Vaccination is the preferred prevention method, but it is a poor alternative when the disease targets the immune system. Elimination of disease is accomplished by manipulating animal immunity, exposure, and herd dynamics, supplemented by antibiotics and vaccines. However, elimination is not effective in settings that lack barriers to prevent reinfection. In some cases, combinations of these alternatives are effective, but for the diseases of most concern, issues will persist until all three approaches can be used together to prevent disease.

MANAGEMENT OF BACTERIAL DISEASES ON DAIRY FARMS

Pamela Ruegg, D.V.M., M.P.V.M., Professor, Department of Dairy Science, University of Wisconsin, Madison

Dr. Ruegg explained that dairy farmers have strong economic incentives to avoid using antibiotics in dairy cows, because milk and meat from treated cows must be discarded. Young cows are at highest risk of disease in the first 60 days of life and again around weaning. Adult female cows are at high risk for infection immediately postpartum, while lactating, and in the dry period between pregnancies. After about two-and-a-half rounds of lactation, cows are less profitable than younger cows for milk but are still healthy enough to be sold for meat.

Antibiotics are most commonly used in calves for diarrhea and pneumonia. The most effective preventive intervention is ensuring calves develop immunity by consuming adequate colostrum while nursing. Good housing, nutrition, and husbandry practices, plus vaccination, are key to disease control. The Food and Drug Administration's (FDA's) Veterinary Feed Directive (VFD) has affected calf management by, for example, eliminating over-the-counter (OTC) medicated milk replacers.

Antibiotics are most commonly used to treat mastitis in adult dairy cows (far more than any other bacterial infection). Treatment involves infusion of one of seven FDA-approved antibiotics through the udder for 3–5 days. Milk is discarded during and immediately after treatment. Every day, about 1–2 percent of milk is discarded because of antibiotic treatment. Antibiotics are commonly used in dry cows to treat subclinical disease and prevent the spread of disease. In adult cows, OTC antibiotics have been given by hoof-trimmers to treat lameness. Under the VFD, such practices are no longer allowed, so it is likely fewer antibiotics will be used for this indication.

Dr. Ruegg concluded that dairy farms focus on preventing the well-known risks of disease and reducing the use of antibiotics not just for purposes of good stewardship but to protect their economic investment. She called for more mechanisms to determine which cows will benefit from antibiotic treatment.

PREVENTING AND CONTROLLING INFECTION IN BEEF CATTLE

Tom Portillo, D.V.M., Friona Industries(by phone)

Dr. Portillo said antibiotics used in beef cattle most commonly target bovine respiratory disease syndrome, which affects cows at all stages of the production process. Prevention falls into three categories: immunization, maturation, and acclimation. Immunization requires an effective vaccine given at the appropriate time and in the appropriate environment. Early vaccination is ideal, but some vaccines are given too early to achieve immunity. Maturation of the immune system is also important. Acclimation involves good animal management and husbandry so that the stressors of the environment do not contribute to disease.

Preventing the spread of disease involves treating individual animals with the aim of achieving disease control across the herd. Producers who recognize subtle signs of disease can remove affected animals from the herd. When symptoms are overt, antibiotic use is warranted for the individual animal. Group treatment may be needed when producers cannot keep up with the outbreak or there is likelihood of extensive morbidity and mortality among the herd.

Dr. Portillo noted that the industry uses mortality as a crude measure of the effectiveness of disease prevention efforts. Focusing on prevention through immunization, maturation, and acclimation can reduce morbidity and subsequent mortality. Dr. Portillo concluded that the industry needs better case definition to improve disease control, and he appreciated the Council's focus on diagnostics for animal health. Improving case definition will contribute to more judicious use of antibiotics.

DISCUSSION

Dr. Portillo clarified that the beef industry needs better point-of-care testing. Such tests do not need to be "cheap" if they are effective and yield an adequate return on investment (ROI) for producers. Some behavioral tools are in place to identify animals with subtle signs of potential disease, but they have not been used on a large scale.

In response to Aileen M. Marty, M.D., FACP, Dr. Karriker listed several examples of mechanisms to prevent the compounding factors that contribute to disease. Many involve biosecurity measures, such as separating animals and providing filtered air. He added that swine producers have a growing disincentive to use antibiotics for metaphylaxis (treatment for suspected exposure), as they pose a direct cost and may inhibit the utility of antibiotics to treat disease. However, for cases in which disease exposure is suspected, producers might employ metaphylaxis by administering antibiotics in food or water. Dr. Karriker added that in carefully controlled situations, a producer might opt to allow a virus to spread to foster group immunity.

Dr. Portillo said there are concerns about antibiotics resistant to the diseases seen in animals but also about the effect on the food chain, so there are efforts to reduce antibiotic use. Data from the National Animal Health Monitoring System (NAHMS) show that increased monitoring and testing have led to decreases in resistant isolates. Dr. Portillo noted that one injectable antibiotic comes with a tool for risk analysis that helps producers determine when to use it.

Although antibiotics are not used subtherapeutically, according to the presenters, the use of antibiotics has not decreased, said Ramanan Laxminarayan, Ph.D., M.P.H. Dr. Karriker believed the data are lagging behind, and the impact of new rules will be seen in a few years.

Asked to comment on alternatives to antibiotics, Dr. Ruegg said some dairy farms use probiotics, and new immune modulators are promising, but more data are needed on both. On dairy farms, the biggest concern is treating mastitis, and about half of cases may not require antibiotic treatment. Some diagnostic tests are available to determine which cows should be treated, but only big farms use them. Better diagnostic tests and more investment in clinical trials are needed. Dr. Karriker agreed that more data are needed. None of the alternatives for treating swine have yet proven to be as effective as current treatment nor are likely to pass regulatory hurdles. Dr. Portillo called for a focus on better vaccine technology and better tools for case definition (e.g., to determine which cows would benefit from treatment).

Kent E. Kester, M.D., FACP, FIDSA, FASTMH, asked why the animal health industry lacks capacity to update its influenza vaccines periodically to reflect prevailing strains. Dr. Karriker pointed to the depth and breadth of strain differences among swine. He also noted that killed vaccines do not provide good cross-protection. In addition, some data indicate that using the wrong strain in a vaccine could cause harm later on. However, Dr. Karriker continued, there has been impressive collaboration between the livestock and human health fields to arrive at a common nomenclature, build a database, and begin monitoring strains across groups. He observed that swine producers can control pigs' activity to prevent or mitigate exposure, then use vaccines when exposure occurs.

Brian McCluskey, D.V.M., Ph.D., added that the Department of Agriculture (USDA) has been gathering surveillance data on swine influenza for at least the past 6 years. Dr. Karriker said that farmers need better data at the local and county level for decision-making.

Asked what tools are needed to improve infection prevention, Dr. Karriker responded that regulatory constraints limit access to technology used in human health. For example, modified live influenza vaccines are not plausible for livestock. Technological advances must be paired with regulatory approval to be useful. More basic and applied research is needed, said Dr. Karriker.

Elizabeth Jungman, J.D., M.P.H., asked the presenters' opinions on how to reduce antibiotic use while continuing to ensure animal welfare. Dr. Karriker hoped that any changes aimed at improving judicious use of antibiotics would be based on good evidence. He also saw many opportunities to improve animal welfare, such as through alternatives to antibiotics. Dr. Ruegg said the hygiene and management practices used to maintain udder health were developed in the 1960s. She anticipated that antibiotic use could be halved with updated data and practices and new tools to identify which animals will benefit from treatment. Dr. Portillo said the beef industry has economic incentives to avoid antibiotics (cost per animal and potential for creating resistance within the herd). The ability to better identify which animals should be treated goes back to risk analysis and better case definition.

Dr. Blaser observed that new data shed light on the unintended consequences of antibiotics; for example, treatment in animals increases their susceptibility to new pathogens. Dr. Karriker reiterated the importance of pairing evidence-based, judicious use policies with considerations for animal welfare. His wish list consists of (i) guidelines for antibiotic use that provide enough flexibility for decision-making at the local level, (ii) efficacy research on alternatives to antibiotics gathered from in vivo research on farms, and (iii) access to the same range of technology solutions for animals as in humans.

In response to Dr. Blaser, presenters gave brief assessments of daily use of antibiotics in cattle. Dr. Blaser requested data on the defined daily dose for future discussions.

Bacterial Disease Challenges: Perspectives from Food Animal and Companion Animal Representatives

Moderator: Randall Singer, D.V.M., M.P.V.M., Ph.D., PACCARB Member

ANTIMICROBIAL DRUG USE IN COMPANION ANIMALS

Paul Morley, D.V.M., Ph.D., DACVIM, Professor, Colorado School of Public Health, Colorado State University, Director of Infection Control, James L. Voss Veterinary Teaching Hospital

Dr. Morley pointed out that companion animals do not fall under the same regulatory guidance as food animals. Veterinary practice for companion animals is similar in many ways to human medicine and must take into account the strong emotional connection between people and their pets. Also, humans have much more direct physical contact with their pets than with food animals, which poses challenges to resistance. Little research exists on antibiotic use for companion animals. Dr. Morley offered observations from two surveys of veterinarians treating companion animals (primarily dogs, cats, and horses).

About 90 percent of antibiotic prescriptions by companion animal veterinarians are for the top two most common conditions for each species. Few good alternatives to antibiotics exist, although some novel therapies are in development. Large- and small-animal veterinarians mostly use antibiotics for treatment, though some use them for metaphylaxis and, rarely, for prophylaxis. Concerns about AMR affect drug selection.

Dr. Morley said that statements from professional organizations advising prudent use of antibiotics are important but are too general to be helpful for veterinarians. He said recent guidelines that describe the best use of antibiotics and give more specific recommendations are an advance for companion animal medicine, and he would like to see such recommendations for more species.

Finally, Dr. Morley said the survey data suggest that veterinarians believe human use of antibiotics is responsible for 80–90 percent of resistance. They also believe most of the animal contribution to resistance comes from food animals. Finally, they believe their own individual practices around antibiotics rarely or never contribute to resistance.

COMMERCIAL BROILER PRODUCTION

David French, D.V.M., M.A.M., Dipl. ACPV, Sanderson Farms, Inc.

Dr. French pointed out the economy of scale involved in poultry production. With huge flocks, producers must treat the "house" (typically about 12,000 birds of parent stock or 25,000 broilers), not individual birds. A typical female parent will lay approximately 160 eggs and produce 135 chicks, so losing just one has a significant economic impact. Medication, if needed, is given via food or water to the house. Some birds from breeders are delivered to the commercial production plant with eggs that have been treated with gentamicin at 18 days (unless the plant stipulates no antibiotics may be used).

The poultry industry has had judicious use guidelines in place for some time. New regulations and guidance prohibiting OTC antibiotics have heightened awareness and increased the number of farms with in-house veterinarians. Dr. French said the trend to forego or limit the use of antibiotics in poultry production was driven entirely by consumer preferences with no supporting scientific evidence. In poultry plants that do not use antibiotics, veterinarians face a quandary when a flock becomes sick. Questions arise about animal welfare, when to treat, and how quickly. Because the risk of losing birds is

higher in plants that do not use antibiotics, they may build more houses, creating concerns about sustainability across the industry. Moreover, food safety may be in jeopardy if antibiotics are never used, raising concerns about the potential of passing disease on to humans.

Dr. French said the poultry industry has not used antibiotics routinely in feed for more than 50 years, yet most Americans think it does. Among parent stock, *Escherichia coli* contamination of eggs is the primary reason for using antibiotics. Gentamicin is labeled for use starting on day 1, but the indications were approved before breeders developed the capacity to inject chicks in the egg, so such off-label use requires a prescription. Dr. French described other common infections and the drugs used to treat them, noting that penicillin is approved for treating *Staphylococcus* infections in turkeys but not chickens and, is therefore, used off-label. Alternatives to antibiotics mostly include interventions that address hygiene and stress.

Broiler chickens face similar disease risks as parent stock. Dr. French indicated that one drug frequently used for respiratory disease (RofenAid®) is no longer manufactured. Alternatives again include sanitation and hygiene measures but also, in some cases, vaccination.

Dr. French concluded that industry has done a lot to comply with judicious use guidelines. The no-antibiotics-ever approach on some farms has created problems for veterinarians who seek to protect animal health, prevent suffering, and ensure public health.

COMBATING ANTIBIOTIC-RESISTANT BACTERIA IN AQUATIC LIVESTOCK PRODUCTION

David Starling, D.V.M., Aqueterinary Services

Dr. Starling set the stage by reminding the participants that 70 percent of the earth is covered with water. He described the appropriate first responses to marine animal health in an ideal world where antibiotics are never (or rarely) used. These include biosecurity for primary pathogens, environmental control or modification, and vaccines for expected and economically important diseases. The latter are exempt from regulation and can be created privately to respond to an infectious disease outbreak. Clinically useful diagnostics are an area of interest but are not currently on the horizon for fish. Another tactic is passive immunity for contrary infections, which mammals produce better than fish. Lastly, discussion is needed about resistance caused by disinfectants; discontinuing or alternating use of disinfectants is another approach to reducing the spread of resistance.

About 1 billion people worldwide use fish as their main source of animal protein, and 20 billion get at least 20 percent of their animal protein from fish. In the United States, three antibiotics are approved for use in food fish. These antibiotics are not approved for use in ornamental fish, but such use is a low priority for regulators; as a result, ornamental fish are a significant source of antibiotic resistance, said Dr. Starling. Japan and Chile use a lot of antibiotics in fish production. Other countries sometimes use antibiotics that are banned in the United States or production strategies that include using animal and human feces to enrich the water. Numerous species of fish are imported to the United States from about 40 countries. Imports are evaluated by the FDA.

Dr. Starling described a successful operation in Norway to address antibiotic resistance that emerged in the late 1970s among farmed salmon. The Norwegian Veterinary Institute created effective vaccines; as a result, minimal medication is needed to treat diseased fish.

Among the barriers to combating antibiotic resistance in fish is the fact that aquaculture is regulated by three federal agencies. Disease reporting across different settings is inadequate. Few states have regulations to support effective biosecurity measures. In addition, aquatic livestock facilities vary considerably across the United States, and each faces difficulty with biosecurity.

DISCUSSION

Thomas R. Shryock, Ph.D., asked what role clinical diagnostic laboratories play in guiding veterinarians' use of antibiotics in companion animals. Dr. Morley responded that the usefulness of laboratories varies; a few advanced laboratories provide expertise, but most veterinarians treat empirically. He believed veterinarians would benefit from better training and more specific guidance on drug selection. Veterinarians do not have enough training or laboratory support to engage in critical thinking about interpreting test results.

In response to Elizabeth Jungman, Dr. French said that a no-antibiotics-ever policy for poultry could pose food safety risks. He believes the goal should be judicious use of antibiotics, giving veterinarians the possibility for using them as needed in sick birds. Dr. French emphasized that both traditional and no-antibiotics-ever poultry plants aim to do the right thing for animals and protect food safety. Asked to suggest opportunities for reducing antibiotic use in traditional poultry plants, Dr. French said that better environmental controls and vaccines for *Clostridium* infections would eliminate a significant source of antibiotic use.

Dr. Marty asked about the impact of fish farm antibiotic use on wild-caught fish. Dr. Starling explained that in most cases, an antibiotic ends up in the environment. Fish caught in waters near such farms are likely exposed; in deep water, the antibiotic is probably highly diluted. Freshwater fish are also exposed through human runoff from wastewater treatment.

Asked about the prevalence and impact of pharmacies compounding antibiotics for companion animals, Dr. Morley said the issue becomes a concern when unlicensed pharmacies compound drugs. A professional association is cracking down, but veterinarians still do it, often without training, he added. In the past, the problem arose when no effective medication was available (e.g., for long-term treatment) or the medication was very expensive and use was not regulated in companion animals.

Dr. King wondered what could be done to raise awareness among individual veterinarians about their contributions to AMR. Dr. Morley said the survey he cited was 16 years old, and the issue has received a lot of attention since then. The Association of American Veterinary Medical Colleges (AAVMC) produced a set of learning objectives around AMR that spell out what should be addressed across groups, from the lay public

to the veteran prescriber. Dr. Morley said work is underway to incorporate the learning objectives into education.

Angela Caliendo, M.D., Ph.D., FIDSA asked if better diagnostics were available for companion animals, would veterinarians use them. Dr. Morley said financial issues are important in both food and companion animal medicine but they differ. The lack of insurance reimbursement drives a lot of empirical use, because diagnostic tests are expensive.

Dr. Blaser asked about the scope of AMR in companion animal health and the role of pet food in transmitting AMR. Dr. Morley responded that pets frequently experience chronic conditions that require long-term treatment, develop resistance, and require higher-tier drugs. Resistance develops for certain organisms, such as *Staphylococcus*, as in humans. In some cases, people and their pets transmit infections back and forth, such as *S. aureus*, because of the constant close contact in households. People who frequently have contact with infected food animals—such as swine veterinarians—also face problems with antibiotic resistance. Dr. Morley said the fats and oils added to dry pet foods can be a source of antibiotic residue. Also, raw diets carry the same risks related to raw meat and dairy.

Dr. Apley observed that genetic research is underway in swine and inquired about similar work in aquaculture and poultry. Dr. Starling said such research is just beginning in aquaculture, with one large program in the Philippines to select for disease resistance in tilapia. Dr. French said genetic research in poultry has focused on noninfectious disorders.

Combating AMR: Perspectives from Animal Health Associations and Organizations

Moderator: Lonnie King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair

Ensuring Antibiotics Remain Available and Effective Tools for All

Thomas Meyer, D.V.M., American Veterinary Medical Association (AVMA)

Dr. Meyer emphasized that the AVMA is committed to ensuring that medically important antibiotics remain effective. Veterinarians play an important role in advancing health care management, improving food safety, and developing alternatives to antibiotics.

The AVMA provided expertise and input to the FDA during the development of the VFD. It has conducted an extensive education campaign about the VFD for members and other partners online and in person. The AVMA has long had policies for the field on judicious use of antibiotics, as well as guidance on a broad range of related topics for numerous veterinary medicine populations.

The AVMA recently established a committee on antimicrobials that brings together representatives across the field to oversee AMR issues in a centralized, coordinated manner. The committee is charged with developing an overarching strategy for creating and implementing an AMR policy. The committee will collaborate with other stakeholders, including the human medicine community, on a One Health approach to

AMR. In its first few months, the committee has reviewed 21 AVMA policies on antimicrobials. It is hoped that the committee's proposed strategy will serve as a trusted source of reliable information, promote antibiotic stewardship, and facilitate collaboration across the field to ensure that antibiotics remain available, effective tools for all. The committee is just one mechanism that allows the AVMA to work with partners and stakeholders around developing professional guidelines to prevent antibiotic resistance.

The Role of Academic Veterinary Medicine in Combating Antimicrobial Resistance

Andrew Maccabe, D.V.M., M.P.H., J.D., AAVMC

The AAVMC and the Association for Public and Land-Grant Universities (APLU) created a joint task force on AMR in production agriculture, which included representatives from other professional organizations (including the AVMA), federal government, and industry. The task force's final report, *Addressing Antibiotic Resistance*, includes recommendations for academic institutions on education, research, and stewardship.

As mentioned by Dr. Morley, the task force developed AMR learning outcomes for students at various levels—vocational (e.g., youth in 4-H programs), undergraduate, graduate, and professional. The task force is currently evaluating where the learning outcomes fit in to existing curricula. Outreach and messaging are critical components of education. The AAVMC is reaching out to representatives on Capitol Hill to discuss the research needs and policy implications of AMR.

The task force report describes research needs from basic to advanced science. It calls for models and metrics that can be used to predict risk to human health. The task force members had differing opinions about the right metrics, but there was consensus that tonnage (that is, the amount of antibiotics sold) is not useful in understanding what is being used or how. The report also addresses incentives and motivations for change. The AAVMC hired a program manager who will build partnerships and coalitions to advance the proposed recommendations.

Combating AMR: Perspectives from the American Association of Bovine Practitioners (AABP)

Fred Gingrich II, D.V.M., AABP

Dr. Gingrich outlined the mission of the AABP- to educate the field about judicious use of antimicrobials in bovine practice to mitigate the risk of AMR. Among its continuing education opportunities, the annual conference includes numerous topics on antibiotic use, including a "myth-busting" session. Dr. Gingrich explained that there are about 650,000 beef producers in the United States, most from farms with fewer than 50 beef cows. Cows intermingle at feed lots, where they can get sick and spread infection as they are transported to finishing facilities. A lot of education focuses on managing high-risk situations.

The AABP has developed publicly available guidelines for bovine practice throughout the field. One addresses the veterinarian-client-patient relationship. In the cattle industry, the "patient" is not one animal but a herd, Dr. Gingrich explained. This guideline

emphasizes the critical role of veterinarian oversight in reducing antibiotic resistance. Another guideline covers judicious use for beef and dairy farms, stressing the importance of preventive medicine to decrease the need for antibiotics. It also describes methods to prevent residue. The AABP hopes to have its new guideline on antibiotic stewardship approved in 2017. It is modeled after the Centers for Disease Control and Prevention's (CDC's) antimicrobial stewardship policy for human health and applies the key elements identified by the CDC to bovine practice.

Combating AMR: Perspectives from the American Association of Swine Veterinarians (AASV)

Locke Karriker, D.V.M., M.S., DACVPM, AASV

Dr. Karriker summarized a number of ways the AASV educates the field about judicious use of antibiotics, with an emphasis on disease prevention, such as the following:

- The AASV website, a central site for judicious use resources
- Guidelines, updated in 2014, that emphasize a comprehensive animal health plan and alternatives to antibiotics
- A standing committee on pharmaceutical issues, which recently developed outreach materials on antimicrobials for disease prevention
- Annual meeting workshops and sessions on topics such as implementing the VFD and antibiotic-free pig production
- Member outreach about the VFD, key components of the Animal Medicinal Drug Use Clarification Act, and extra-label drug use of fluoroquinolones and enrofloxacin
- Cooperation with the USDA and FDA on meaningful metrics of antibiotic use
- Interaction with other professional organizations to ensure a consistent, unified approach to antibiotic use in veterinary medicine
- Financial support for swine pharmacology courses for veterinary students, including a webcast on FDA guidance
- The *Journal of Swine Health and Production*, which focuses heavily on topics related to disease prevention and antibiotic use

One Health

Jeffrey Simmons, Elanco Animal Health

Mr. Simmons said that Elanco and its parent, Eli Lilly & Company, were part of a slew of leaders representing human and animal health at a White House meeting on antibiotic stewardship. That meeting resulted in a multi-stakeholder commitment to combat antibiotic resistance. Mr. Simmons described progress on labeling and advances in analytics made to support that commitment. He said that Elanco brought two new animal-only antibiotics to the poultry and pork industries and launched four antibiotic alternatives, including vaccines enzymes and a first-of-its-kind protein that supports a cow's immune system, reducing the incidence of mastitis.

As a result of an international One Health summit to promote antibiotic stewardship, nearly 40 meat and dairy industry leaders from around the world signed a commitment to address priority areas that align with the goals of the National Action Plan on Combating Antibiotic-Resistant Bacteria.

Mr. Simmons said the greatest impact on AMR is likely to come from a combination of the right metrics, the right regulatory pathways, and the right labels. Better metrics are needed to evaluate progress toward appropriate use of antibiotics in all settings. The main measure being tracked now is volume of use, which does not take into account numerous factors affecting animal health. Current metrics do not capture data on the presence, frequency, or distribution of antibiotic-resistant bacteria.

Mr. Simmons suggested the field focus on eliminating inappropriate prescribing. However, even complete elimination of antibiotics in animal agriculture would not have a meaningful impact on resistance that affects humans. The pathogens of most concern in are not related to antibiotic use in food animals, said Mr. Simmons. He cited a recent study from the United Kingdom that concluded that curtailing antibiotic use in animals alone would not affect antibiotic resistance in humans but instead increase the health risk to humans by exposing them to untreated, sick animals.

New regulatory pathways are needed to enable the animal health industry to bring novel therapeutics with unique modes of action to the market in a timely manner. Mr. Simmons stressed that the field is not requesting adjustments in safety evaluation but rather new approaches to demonstrating efficacy, as have been developed for products from human biopharmaceutical companies.

Consumers need more accurate information on which to make informed decisions, so labeling must be addressed. Most consumers believe that buying meat and poultry raised without antibiotics helps farmers use fewer antibiotics. However, studies have found that chickens raised without antibiotics are more likely to develop infections that require treatment with medically important antibiotics. In closing, Mr. Simmons called for cooperation among stakeholders to take on the challenge of AMR.

Animal Health Industry Perspective on AMR in Food-Producing Animals

Richard Carnevale, V.M.D., Animal Health Institute (AHI)

Dr. Carnevale gave a detailed history of AMR regulation in animal agriculture, beginning in the 1970s, when the FDA required testing of antibiotics used in feed, specifically for resistance to *E. coli* and salmonella. In the 1980s, concerns were raised about the unregulated use of OTC antibiotics, which were considered necessary because of the lack of availability of veterinarians at the time. Eventually, the FDA began requiring prescriptions for new antibiotics but not for medications found in feed. By the late 1990s, the first VFD was enacted, and the National Antimicrobial Resistance Monitoring System (NARMS) was established. The 2000s brought requirements to assess potential selection for resistance in food animals and report antimicrobial sales data.

In 2012, the FDA issued Guidance for Industry (GFI) #209 on judicious use to eliminate growth promotion indications and limit use of medically important antibiotics to prescription use or VFD. Dr. Carnevale pointed out that compliance is viewed as voluntary, but in fact, extra-label use of feed medications is not permitted, so the requirements are mandatory. He also noted that the intent of GFIs #209 and #213 was not to reduce sales of antibiotics but to promote judicious use.

Dr. Carnevale said it is encouraging that the FDA continues to support the use of medically important antibiotics for prevention of disease in animals. Vaccines and other products are important alternatives but are not yet sufficient to eliminate the use of antimicrobials.

Dr. Carnevale pointed out the unintended consequences of raising food animals without antibiotics. In farms that do not use antibiotics, sick animals are either left to die or are converted to conventional production processes and treated with antibiotics. Therefore, the antibiotic-free label is misleading to consumers, as it does not improve food safety.

Also, as Dr. Simmons noted, reducing use of antimicrobials in food animals does not necessarily correlate with decreased resistance. Dr. Carnevale said this contention is borne out of NARMS data and the 2017 U.K. study mentioned by Dr. Simmons. While he agreed that it may be necessary to reduce the use of certain medically important antimicrobials when there is evidence of an effect on specific pathogens, simply reducing use overall will not achieve the desired effect.

New restrictions on antimicrobial use should be based on scientific data, not perceptions or market pressures, Dr. Carnevale stressed. New vaccines and alternatives to antibiotics are needed. Dr. Carnevale echoed other presenters in stating that antibiotic sales data are not an adequate substitute for use data. He said the AHI supports funding for the USDA and FDA to collect data of on-farm use of antibiotics.

Discussion

Dr. Marty asked presenters to comment on the potential of immune modulators. Mr. Simmons said companies recognize the need to advance animal health and have invested substantially in new research and product development. He said there has been more activity in the past 5 years in this space than in the previous 30 years, which drives innovation. Dr. Karriker added that the field is racing to generate new ideas and new technology, demonstrate effectiveness in animal health, and translate findings into practice.

Dr. Laxminarayan asked Mr. Simmons to explain how the data he presented on the risk of infection in one flock of birds not treated with antibiotics can be extrapolated to the entire industry. He also asked why sales data is not a reasonable measure of use. Mr. Simmons said the risk of infection can vary substantially, but the cited study supports the conclusion that there are unintended consequences of raising poultry without antibiotics. He pointed out that employing good preventive health measures and using animal-only antibiotics are appropriate ways to stem AMR rather than bowing to market pressures never to use antibiotics. Dr. Carnevale said sales data is a crude metric that does not explain what is being used, in which animals, or for what purposes.

Dr. Laxminarayan observed that antibiotic use in food production has been decreasing as other practices—disease prevention, nutrition, and genetic manipulation—are implemented. He asked Dr. Meyer where these trends might lead over the next 20 years. Dr. Meyer responded that recent regulations will force producers, especially those on small farms, to limit their use of antibiotics. Education of producers and consumers is an

important component. There is a growing awareness that society in general has a responsibility for the use and abuse of antibiotics. Scientific advances will play into the ongoing need for antimicrobials to fight pathogens, said Dr. Meyer. He added that the role of the AVMA is to educate, which is supported by bringing together experts in the field to develop policies.

Dr. Blaser asked what principles can be embedded in education to help the next generation of veterinary students learn about the biological costs and benefits of using antibiotics. Dr. Maccabe agreed that training today's students is key to long-term change. Instead of creating a curriculum, the AAVMC and APLU joint task force defined learning outcomes and competencies. These are transformed into rubrics and then curriculum maps, before being translated into curricular materials. Taking this approach can change the learning and teaching processes and result in better outcomes, said Dr. Maccabe. He added that the AAVMC and others are working with veterinary schools in the developing world to institute the same learning outcomes, beginning with a pilot project in concert with Elanco and the World Organization for Animal Health (OIE) in Ethiopia.

Dr. Karriker added that initiatives around curriculum are incredibly important. The fastest way to update students' problem-solving skills is to expose them to updated clinical problems through interactions with industry and by producers sharing information about real-world scenarios. Such opportunities are challenging, because they may require carving time out of the curriculum for students to engage on farms and in plants, but they can speed up the learning process.

Dr. King asked Dr. Maccabe to discuss how learning can be expanded to others in agriculture, such as the hundreds of thousands of young people involved in 4H and similar programs who are future agriculture industry leaders. Dr. Maccabe reiterated that the learning outcomes are tailored for different categories of learners. The novice category includes young people. He recognized the opportunity to address the entire spectrum of those likely to be involved in the field.

Given the challenges of educating the public about the appropriate use of antibiotics in human medicine, Dr. Caliendo asked Mr. Simmons how to begin educating consumers that antibiotic-free meat may not be safer or healthier. He noted that food choices are extremely personal. In light of growing animal protein consumption, education is important. Manufacturers and producers need to better understand consumers and then work together across the protein industry to educate consumers.

Dr. Shryock asked whether the presenters have considered forming an alliance similar to that of the European Platform for the Responsible Use of Medicines in Animals to avoid duplicating efforts or getting in one another's way. Dr. Maccabe said the AACVM is part of several collaborations among educators. Dr. Meyer said the AVMA also seeks broad representation across the field to develop policies collaboratively.

In response to a question about antibiotic stewardship in manure management, Dr. Karriker said the topic is just beginning to be introduced in veterinary education. It fits with the idea of a comprehensive approach that includes the impact of animals on the

environment. Dr. Meyer said the One Health concept requires all sectors to work together and innovate rather than point fingers.

Dr. Jungman found it dispiriting that debate continues about the science linking antibiotic use with resistance, and she hoped the PACCARB would discuss the issue in more depth. She asked the presenters for suggestions on effective metrics, particularly which metrics could be useful for training veterinarians on selecting antibiotics. Mr. Simmons said efforts should be made to look at behaviors—specifically, the need to make the right diagnosis, prescribe the right product, and give the right treatment for the condition. The voluntary approach to updating labeling that has been going on for the past 5 years can have an impact globally, he said. The goal for the next 5 years is to understand on-farm behavior and educate food producers.

Dr. Gingrich pointed out that looking at sales data only ignores the important distinctions of where, when, and in what animals antibiotics are used. It does not capture regional differences in how antibiotics are used, nor does it reflect the impact of other factors, such as weather patterns. Good metrics would come from use data and follow-up data that confirms pathogen correlation. Some of the large beef and dairy producers can collect such data quickly. Dr. Carnevale said AHI supports use data, and he pointed out that the USDA and FDA are trying to collect such data through NAHMS but need additional funding to do so.

John H. Rex, M.D., said the commitment cited by Mr. Simmons does not appear to be readily available to the public, but it may be useful to the PACCARB in making recommendations. Such forward-thinking approaches have been helpful on the human side, and Dr. Rex suggested all the industry groups collaborate around such a joint effort.

Peter Robert Davies, B.V.Sc., Ph.D., pointed out that the role of veterinarians has changed over time. In response, education should emphasize the importance of professional communication with those in complementary fields to exchange clinical and technical information. Dr. Maccabe said the learning outcomes seek to link veterinary medical education with animal science and environmental science to help bridge gaps. Dr. Gingrich said that veterinarians treating herds or flocks often work as part of a consulting team that includes nutritionists, health managers, and others. Lots of veterinarians now mine farm data to look at outcomes, he added.

Asked about the use of the term “antibiotic-free” in packaging, Dr. Carnevale said such claims are misleading, because they suggest the product is safer. He pointed to the FDA’s requirement that products that are labeled as free from bovine somatotropin (bST, a growth hormone) include a disclaimer that the products are not safer than those with bST. Mr. Simmons suggested more discussion about production practices linked to marketing as it relates to resistance. Dr. Meyer said the AVMA can educate its members about the complexities around package labeling.

Dr. King asked for presenters’ opinions on the implementation of GFI #213. Dr. Gingrich said the cattle industry is managing the transition well. The biggest challenge for the near future is working with producers who do not want to pay for access to veterinarians to prescribe medications. (Dr. Gingrich added that he believes there is an adequate supply of

veterinarians but a distribution problem.) Dr. Karriker said larger producers were well prepared for the transition; his organization is now working with those in other settings who are just now adjusting to the fact that OTC antibiotics are not available. The AASV is also working with veterinarians to get answers to questions about applying the new rules. It also provides a forum for producers to ask questions anonymously and get answers that can be shared broadly.

Public Comment

Steven Roach of the Food Animal Concerns Trust and Keep Antibiotics Working said that the use of antibiotics for disease prevention is counterproductive for combating resistance, particularly when it becomes routine. In accordance with the OIE, prophylactic use should be restricted for drugs that are critically important in human and animal medicine. Even for drugs approved for disease control, there should be better distinction between "prevention" and "control." Use of drugs for control should be limited to cases in which an outbreak has occurred and many animals are showing clinical signs of disease.

Mr. Roach proposed using on-farm management techniques for prevention—for example, increasing sanitation in hatcheries instead of injecting all eggs with gentamicin or giving cows an appropriate diet to promote health and avoid use of certain drugs. He stressed that critically important drugs for animal and human health should not be used on farms routinely for disease prevention. Mr. Roach took exception to presenters citing the U.K. study that concluded that addressing antimicrobial use on farm will not impact human health. He pointed out that the paper also concluded that addressing antimicrobial use only in human health without addressing animal use will also have a limited impact—a One Health approach is needed.

Stephanie Fox-Rawlings of the National Center for Health Research said her organization supports efforts by federal agencies to reduce unnecessary exposures to antibiotics, which can reduce antibiotic resistance and thus preserve the use of these antibiotics for animal and human health. The organization agrees with the legal limits on antibiotic use in animals, but the limits are voluntary and contain loopholes that allow for continued widespread use for disease prevention. "Disease prevention" can be broadly interpreted.

Food manufacturers are recognizing the commercial benefit of selling animal products raised without antibiotics or with only limited exposure to antibiotics. Thus, alongside concerns about antibiotic resistance, business concerns encourage drastically reduced use of antibiotics when other alternatives are available. National incentives and regulations are needed to reduce unnecessary exposure to antibiotics. Such regulations must be enforceable and enforced. The responsible use of antibiotics is important for the proper care of livestock and for public health for all.

The Council also received written comments from Matthew Wellington of the U.S. Public Interest Research Group Education Fund and the Natural Resources Defense Council.

Final Comments and Adjournment

Martin Blaser, M.D., Chair
Dr. Blaser adjourned the meeting for the day at 4:32 p.m.

Day Two

Welcome and Overview

Martin Blaser, M.D., Chair

Dr. Blaser called the meeting to order at 9:00 a.m. and welcomed the participants.

Roll Call and Rules of Engagement

Jomana F. Musmar, M.S., Ph.D.c, Designated Federal Official

Ms. Musmar reiterated the rules governing the PACCARB under the Federal Advisory Committee Act and conflict-of-interest guidelines. She then called the roll.

Patient Story

Mary Millard (by phone)

In keeping with the PACCARB tradition of including patients' stories as a way to put a human face to the problem of AMR, Ms. Millard described several events that likely contributed to the chronic infection (*Pseudomonas aeruginosa*) that changed her life. She had led an active, healthy life and had never been hospitalized until she visited the emergency department in 2014 with a large aneurysm and a collapsed aortic valve. She went into cardiac arrest before surgery could start and then received extracorporeal membrane oxygenation, a very invasive intervention, for 5 days. She recovered sufficiently for open heart surgery 2 weeks later, following which she suffered from septic shock and spent more than 2 months in the hospital.

Since leaving the hospital, Ms. Millard has taken a high dose of ciprofloxacin daily for 2 1/2 years and has been hospitalized five times. The medication has "nasty" side effects, said Ms. Millard, and it is not covered by her insurance for long-term use, so she pays for it out of pocket. Moreover, the infection is fatal, and eventually it will no longer respond to the medication. As a result of the life change, Ms. Millard had to stop working. She is prohibited from driving, which leaves her isolated in the rural area where she lives. Her husband, who works full-time, serves as her caretaker.

Ms. Millard said that conservative estimates from the CDC indicate that hospitals lose $20 billion each year as a result of health-care-acquired infections (HAIs), and those costs are passed on to consumers and insurance companies. If the infection is deemed to be the fault of the hospital, the Centers for Medicare and Medicaid Services (CMS) no longer reimburses hospitals for the care provided. Data indicate that 1.8 million Americans get an HAI every year, and 99,000 die each year from them. Ms. Millard said she had never even heard of such infections until she was diagnosed. She hoped to raise awareness about the devastation they cause.

Dr. Blaser thanked Ms. Millard for sharing her story and expressed sympathy on behalf of the Council for the difficulties she has suffered.

Overview of PACCARB Working Group (WG) Activity

Martin Blaser, M.D., Chair, and Lonnie King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair

Dr. Blaser explained that the PACCARB WGs on incentives are still identifying the issues and crafting recommendations to address them. However, this meeting offers an opportunity to share with the public their initial thoughts and preliminary suggestions. Dr. Blaser reminded the participants that the PACCARB was charged with making recommendations about the best way to incentivize development of therapeutics (including alternatives to antibiotics), rapid diagnostics, and vaccines for humans and animals while maximizing ROI and encouraging access and appropriate stewardship. The Council formed three WGs, one for each type of product. Each WG drafted issue statements and recommendations for humans and animals and categorized them accordingly:

- Economic: Issues that influence the ROI to companies regarding product development or use
- Research and Development (R&D): Issues related to discovery research and the development process
- Regulatory: Issues related to federal regulatory processes that influence the development or modification of a product, ranging from basic research through studies that meet approval criteria
- Behavioral: Issues related to the behavior of consumers, providers, or companies relative to product use or development

The draft report is available online; it offers background information and describes the rationales that support the WGs' recommendations. The issue statements and draft recommendations are in Appendix B. The final report and recommendations will be presented to the full Council at its September 2017 meeting for approval.

PACCARB Working Groups—Human

John H. Rex, M.D., PACCARB Member

Underlying all the issues identified, said Dr. Rex, is the common problem of reimbursement. Each situation represents a market failure that can only be addressed through government intervention. Dr. Rex gave the analogy of firefighting, saying diagnostics are both the smoke detectors that identify a fire and the fire chiefs who decide how to address problems. Vaccines are the fire prevention steps. Antibiotics are the fire trucks and firefighters, which must be in place before a fire occurs. Moreover, every individual benefits from the presence of a fire department, even those who have never had to call for help, because the protection extends to the whole community. For that reason, the community pays for the service as a whole, not per fire.

From a market perspective, antibiotics enable an individual to undergo surgery with the reassurance that an antibiotic will be available to fight infection if it occurs. Having a range of antibiotics and preventive measures reduces the antibiotic resistance selection pressure on other drugs. The existence of effective diagnostics and antibiotics acts like insurance for every individual, making a lot of everyday medical practice possible. Dr. Rex said antibiotics, diagnostics, and preventives must be thought of in much the same way as the fire department when it comes to financing. Some major financial incentive initiatives are already underway in this country and others.

Leaders of each WG presented the issue statements and draft recommendations for vaccines, diagnostics, and therapeutics for humans. See Appendix B for the issue statements and draft recommendations.

Discussion

Moderator: Martin Blaser, M.D., Chair

Dr. Blaser said AMR appears to be a symptom of a wider problem. A better health infrastructure could mitigate the problem. Better influenza vaccines would reduce the need for antibiotics for respiratory conditions, and better support for clinical laboratories would lead to more effective use of diagnostic tests. It was noted that antibiotics are used as a substitute for good health infrastructure that supports prevention. Dr. Blaser said building the infrastructure to combat AMR could have a broad impact on the health system.

Council members offered the following suggestions for revising the report:

- Better frame the national security threat posed by AMR and the importance of supporting approaches internationally to prevent AMR and the spread of infection.
- Highlight the need for better diagnostics and global surveillance, as well as truly novel therapeutics to circumvent resistance.
- Address preventive mechanisms other than vaccines, such as infection control and biosecurity.
- Clarify the need for investment in basic science to propel vaccine development.
- Consider the need to balance investments in prevention and treatment, recognizing that investing in prevention often provides significant "bang for the buck."
- Stress the importance of solid data to inform research and funding priorities, so that investments are not based on opinions about what pathogens are important.
- Clarify why the recommendations vary depending on the product, better explaining the logic behind them.
- Acknowledge the value of in-house clinical laboratories.
- Note (in the introduction or conclusion) that other factors affect AMR (e.g., stewardship, infection control), and the PACCARB plans to address them. Explain that this report only addresses some parts of the WHO's Global Action Plan.
- Highlight the power of vaccines to mitigate resistance, using the example of *Streptococcus pneumoniae*.
- Acknowledge the need for more research and investment in alternatives to antibiotics for humans, such as bacteriophages and immune-modulators. Incentives to spur development of traditional antibiotics should also be applied to nontraditional products.
- Emphasize the need for behavioral science R&D to understand and address stakeholders' barriers to combating AMR. (Antibiotic stewardship and infection control are strongly affected by behavior.)

- Support collaboration between human and animal health scientists on basic research of pathogens that commonly affect both humans and animals (e.g., influenza, *S. aureus*).
- Frame the report in terms of the reduced cost to the health care system, based on outcome studies, of improving tools to combat AMR. More conversation is needed about the cost-benefit of developing new products, and more data are needed to understand the costs.

Robert A. Weinstein, M.D., noted that the WGs must come up with a structural approach to cutting down the recommendations to a manageable number. Some suggestions were made:

- Group recommendations thematically. Potential themes include (i) assessment and demonstration of the value of products, (ii) the need to bundle certain products (e.g., development of complementary diagnostic and therapeutic products), (iii) specific product or administration recommendations (e.g., value of a universal influenza vaccine), and (iv) novel technologies for treatment.
- Categorize recommendations by inpatient and outpatient challenges.
- Categorize products as either tools of disarmament (vaccines and therapeutics) or detection (diagnostics).

PACCARB Working Groups—Animal

Thomas R. Shryock, Ph.D., PACCARB Member

Dr. Shryock reminded the group that veterinary medicine deals with multiple species living in different environments that face different disease concerns. The economic structures around animal health also vary from those of humans. The issues and recommendations of the WGs for animal health focused on food animals, rather than companion animals, because the greatest need to address AMR occurs in food animal production. Dr. Shryock also explained that food animal medicine takes a population health approach rather than focusing on individual animals.

The WG on Incentives for Therapeutics recognized that new antibiotics are still needed for animal health (and some are in the pipeline) but chose to target its recommendations to alternatives to antibiotics. Dr. Shryock reminded participants that the use of antibiotics in food production is trending downward.

Many of the recommendations for animal health center around a proposed Innovation Institute, housed at the USDA and charged with facilitating R&D, and the creation of a national policy on antibiotics in food animals. The proposed Innovation Institute would support entrepreneurship by providing a one-stop-shop for federal resources and connecting animal health organizations, funders, private companies, and others. The Innovation Institute is not intended to replace any agencies but rather to improve access to existing resources by linking them together through a centralized mechanism.

Leaders of each WG presented the issue statements and draft recommendations for vaccines, diagnostics, and alternatives to antibiotics for animals. See Appendix B for the issue statements and draft recommendations.

Discussion

Moderator: Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, PACCARB Vice Chair

Dr. Kester supported the concept of the proposed Innovation Institute, which could address some of the challenges identified. Dr. Shryock emphasized that the goal of such an organization is to share knowledge across domains. Dr. Carnevale said it may be more useful for the USDA to partner with existing incubators to foster innovation rather than create a new entity. However, he said, an Innovation Institute could address questions about which agency has oversight over a given product in development. Dr. Carnevale noted that the FDA has a conditional approval process, which is ideal for spurring development. Expedited product review would also be helpful.

Dr. King pointed out that the AAVMC/APLU task force recommended a university research organization to coordinate public and private efforts, similar to the proposed Innovation Institute, and some models already exist in universities. Dr. Rex suggested that the recommendation for establishing an Innovation Institute include the role that combating AMR plays in ensuring food security, which, in turn, contributes to global security.

Dr. Blaser said the animal health field is poised for an infusion of funding to move forward. He cited several factors that favor a focus on vaccine development. Dr. King agreed that the convergence of a number of conditions—increased consumption of animal protein worldwide, availability of private capital to fund new agricultural products and processes, consumer interest in healthy, and sustainable farm practices—could pave the way for a new model to address AMR.

Dr. McCluskey reminded the participants that food animal production is driven by profits. Most of the projected future production will be driven by traditional practices, and profitability will remain a key concern.

Dr. Singer pointed out that the recommendations focus on reducing antibiotic use, which does not always translate into reductions in AMR. Also, while the report section on alternatives to antibiotics describes the need to demonstrate efficacy and equivalency compared with antibiotics, it does not mention the importance of ensuring that alternatives do not make AMR worse. Dr. Davies agreed that such concerns should be mentioned in the report; he cited an example from Europe of the unintended consequence of an alternative product used in swine.

Elizabeth Allen Wagstrom, D.V.M., M.S., said the report should recognize other means for improving animal health and preventing infection, such as production methods, nutrition, and genetic mechanisms, as alternatives to antibiotics.

Public Comment

Hua Wang, Ph.D., a professor of microbiology from the Ohio State University, said the biggest problem of antibiotic resistance is not necessarily due to the use of the drug itself but rather how it has been used in the past decades—specifically, the dissemination of mainstream oral antibiotics in both human medicine and food animal production. This

practice has not only led to the rapid rise of antibiotic resistance but also disruption of the healthy microbiota in all those who receive oral treatments. Understanding the source of the problem can lead to potential practical strategies to address it. However, Dr. Wang and colleagues have run into significant difficulties in getting funding to support the work that is necessary for a paradigm change and dissemination of the message broadly. She asked the Council and government agencies for help carrying out such work and disseminating the message. Secondly, Dr. Wang said, it is now known that oral intake of bacteria that carry antibiotic resistance genes, not necessarily pathogens, can cause problems by enriching the antibiotic resistant bacteria in the gut microbiota. The resistant bacteria are initially acquired from food, and therefore this a food safety issue. The shedding out the antibiotic-resistant genes and bacteria through the feces to the environment is increasing the abundance of AMR in the global ecosystem. Much of the antibiotic-resistant bacteria in the microbiota is independent of direct exposure to antibiotics. Therefore, it is important to interrupt and control this pathway in both humans and animals to achieve effective mitigation. Dr. Wang hoped the Council would discuss specific strategies to achieve that goal.

Amanda Jezek of the Infectious Disease Society of America (IDSA) said that despite encouraging progress, AMR remains a persistent problem for many patients and jeopardizes decades of medical progress in areas such as organ and bone marrow transplants, chemotherapy, and complex surgeries. She emphasized that AMR is not a looming threat but rather a real problem affecting many people right now. Ms. Jezek expressed hope, saying that the enactment of the limited population antibacterial drug (LPAD) mechanism as part of 21st Century Cures Act last year and ongoing FDA discussions about new approaches to developing antibiotics that address unmet needs might establish a more feasible regulatory environment for antibiotic R&D. Such steps are essential, but they are not enough. Parallel efforts are needed to improve the regulatory climate for diagnostics as well, and IDSA is very encouraged that the PACCARB has devoted so much work to incentives for antibiotics, diagnostics, and vaccine R&D.

Without economic incentives, the lifesaving new products that patients need will not be developed. The IDSA continues to urge Congress to advance incentives, advocating for the Reinvigorating Antibiotic and Diagnostic Innovation (READI) Act, which is modeled after the orphan drug tax and would provide a 50-percent tax credit for new antibiotics that address an unmet need and new rapid diagnostics. Ms. Jezek noted that Secretary Price referred to the orphan drug act as a potential model for antibiotic incentives when he was questioned about this topic during his Senate confirmation hearing. The IDSA hopes that the Council will look closely at the proposed legislation.

Tharini Sathiamoorthy of AdvaMed DX said diagnostics can and must be a critical component of any approach to reduce the threat of antibiotic resistance. AdvaMed DX appreciates the recommendations proposed. Examining ways to improve the uptake and utilization of diagnostic tests for antibiotic resistance is critical to public health. A number of diagnostic tests are currently available that are simply not being used by health care providers. One way to improve uptake is through the development and adoption of public and private coverage payment policies that incentivize appropriate use of diagnostic tests. Another key way is through the development and adherence to clinical

practice guidelines for appropriate use of diagnostic tests to inform infection prevention diagnosis and treatment, said Ms. Sathiamoorthy.

Dele Ogunseitan, professor of public health at the University of California, Irvine, said that is important to continue the work of public engagement and increase understanding of AMR to minimize litigation and protect the workforce in public health. Also, environmental stewardship of antibiotics is an important topic for the One Health approach. Very little is known about the state of antibiotics in the environment, said Mr. Ogunseitan, and a focus on agricultural use makes the point very clearly. He encouraged the Council to think more about how to stimulate research in this direction, which is one of the missing links in understanding how to intervene outside of hospitals and pharmaceutical systems.

Final Comments and Adjournment

Martin J. Blaser, M.D., Chair

Dr. Blaser expressed appreciation for the excellent presentations. He thanked the PACCARB staff for their hard work pulling together the report on incentives. The next public meeting of the Council is scheduled for September 13–14, 2017. At that time, the current liaison members will reach the ends of their terms, although they can be nominated to continue for another term. The Council's website has information on the application process for new liaison members. Dr. Blaser adjourned the meeting at 12:27 p.m.

Appendix A: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Members

May 3–4, 2017

PACCARB Voting Members Present

Martin J. Blaser, M.D., Chair
Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair
Michael D. Apley, D.V.M., Ph.D., DACVCP
Helen W. Boucher, M.D., FIDSA, FACP (by phone)
Angela Caliendo, M.D., Ph.D., FIDSA
Sara E. Cosgrove, M.D., M.S.
Peter Robert Davies, B.V.Sc., Ph.D.
Kent E. Kester, M.D., FACP, FIDSA, FASTMH
Ramanan Laxminarayan, Ph.D., M.P.H. (day one)
Aileen M. Marty, M.D., FACP
John H. Rex, M.D.
Thomas R. Shryock, Ph.D.
Randall Singer, D.V.M., M.P.V.M., Ph.D.
Robert A. Weinstein, M.D.

Organizational Liaisons Present

Animal Health Institute
Richard Carnevale, V.M.D.
Association of State and Territorial Health Officials
Jay C. Butler, M.D.
National Association of Directors of Nursing Administration in Long-Term Care
Sherrie Dornberger, RN, CDONA, GDCN, CDP, CADDCT, FACDONA
National Pork Producers Council
Elizabeth Allen Wagstrom, D.V.M., M.S.
The Pew Charitable Trusts
Elizabeth Jungman, J.D., M.P.H. (day one)

Ex Officios Present

U.S. Department of Health and Human Services
Marjory Cannon, M.D., Medical Officer, Office of Clinical Standards and Quality, Centers for Medicare and Medicaid Services, CMS
Denise Cardo, M.D., Director, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, CDC
Michael Craig, M.P.P., Senior Advisor for Antibiotic Resistance Coordination and Strategy, National Center for Emerging and Zoonotic Infectious Diseases, CDC
William T. Flynn, D.V.M., M.S., Deputy Director for Science Policy, Center for Veterinary Medicine, FDA
Jane Knisely (for Dennis M. Dixon, Ph.D.), Program Officer, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, NIH
Peter Lurie, M.D., Associate Commissioner for Public Health Strategy and Analysis, Office of the Commissioner, FDA (day one)
Dawn Sievert, Ph.D., M.S., Science Lead, National Healthcare Safety Network, CDC

U. S. Department of Defense

Paige Waterman, M.D., FACP, FIDSA, Antimicrobial Resistance Lead, Armed Forces Health Surveillance Center-Global Emerging Infectious Disease Surveillance

U. S. Department of Agriculture

Neena Anandaraman, D.V.M, M.P.H. (for Jeffrey Silverstein on day one, for David Goldman, M.D., on day two), Senior Advisor for Animal Health, Production, and Products, Office of the Chief Scientist, Food Safety and Inspection Service

Cyril Gay, Ph.D. (for Jeffrey Silverstein on day two), Senior National Program Leader, Agricultural Research Services

Brian McCluskey, D.V.M., Ph.D., Chief Veterinary Officer and Deputy Administrator for Veterinary Services, Animal and Plant Health Inspection Service

Designated Federal Officer

Jomana F. Musmar, M.S., Ph.D.c, Advisory Council Committee Manager, Office of the Assistant Secretary for Health, Department of Health and Human Services

Advisory Council Staff

Tiffany Allen Archuleta, M.P.H., M.Ed., Senior Research Coordinator, PACCARB, New York University Langone Medical Center

Laura Gottschalk, Ph.D., The Oak Ridge Institute for Science and Education (ORISE) Fellow

MacKenzie Robertson (Acting Designated Federal Officer), Committee Management Officer, Office of the Assistant Secretary for Health, Department of Health and Human Services

Ayah Wali, M.P.H., Committee Management Officer, Office of the Assistant Secretary for Health, Department of Health and Human Services

Appendix B: Draft Issue Statements and Recommendations of the Incentives Working Groups

COUNCIL ONLY—DO NOT DISTRIBUTE

HUMAN HEALTH – VACCINES

	ECONOMIC
1	**Issue 1:** Federal and nonfederal stakeholders lack a common understanding about the current and potential economic value and societal impact of vaccines directed at AMR pathogens. Recommendation: Analyses on the cost and societal impacts associated with new vaccine development and administration in the AMR arena
2	**Issue 2:** There is limited funding for infectious disease vaccines, in particular for those targeting AMR pathogens. Recommendation: An expanded range of incentives to encourage development of vaccines that could reduce AMR either directly or indirectly
	RESEARCH & DEVELOPMENT
3	**Issue 1:** There are insufficient epidemiological data on antibiotic use due to infections caused by pathogens currently or potentially preventable through vaccination. Recommendation: Expanded surveillance to measure antibiotic use due to infections that could be prevented or reduced by vaccination to assess the impact or potential impact of prevention through immunization, either by existing or to-be-developed vaccines
4	**Issue 2:** The clinical-stage pipeline for vaccines against AMR pathogens is weak. Recommendation: Focused financial and regulatory incentives to encourage the development of vaccines directed at AMR pathogens across the R&D continuum
	REGULATORY
5	**Issue 1:** The potential market for a new vaccine (as opposed to other AMR products) is uncertain, because vaccine uptake is heavily influenced by recommendations of the Advisory Committee on Immunization Practices (ACIP). Recommendation: Early communication between the manufacturer, CDC, and ACIP to present and discuss a target product profile
6	**Issue 2:** The lack of clarity about regulatory pathways for vaccines focused on AMR pathogens reduces the willingness of sponsors to produce vaccines. Recommendation: Early interaction between sponsors and FDA and workshops, hosted by FDA's Center for Biologics Evaluation and Research (CBER), explaining pathways and best practices
	BEHAVIORAL
7	**Issue 1:** Implementation strategies for optimal vaccine acceptance and utilization are inadequate. Recommendations: 1. Programs and interventions based on behavioral insights that aim to increase vaccine uptake in a variety of populations 2. Continued, broadened economic incentives to influence behavior and increase uptake, such as reimbursement to ensure "first-dollar coverage"—that is, insurance coverage of vaccines without copayments or coinsurance costs
8	**Issue 2:** Providers lack knowledge about the role of vaccines in preventing AMR. Recommendation: Focused governmental vaccine-centric educational policies and approaches, with involvement of health care educational institutions (e.g., medical schools, academic health centers)

HUMAN HEALTH – DIAGNOSTICS

	ECONOMIC
9	**Issue 1:** There is a delay in availability of ASTs for newly approved antibiotics. Recommendations: 1. Dedicated use of a portion of funds provided for incentivizing antibiotic development to development and commercialization of an AST device (e.g., Etest or disc) when the new drug is approved 2. Funding for the development of new antibiotics should always include the development of a concomitant AST device
10	**Issue 2:** Because there is no method to determine the value of a diagnostic test, reimbursement is not aligned with the value of the diagnostic test. Recommendation: A "reimbursement-plus" system, established within the next few years, for tests of key public health importance (e.g., CRE colonization testing). Public health agencies such as CDC and CMS should assist with these decisions.
11	**Issue 3:** There is a lack of clinical and economic outcome studies showing that diagnostic tests prevent the emergence of antibiotic-resistant bacteria and are cost effective. Recommendation: Increased funding for diagnostics outcomes studies (AHRQ, CDC, PCORI, NIH, DOD) including those assessing patient outcomes, reduced length of stay, improved antibiotic use, reduced rates for a certain population of patients, and reduced cost of care
12	**Issue 4:** The high cost of development of diagnostics is a disincentive for diagnostic companies. Recommendation: Tax credit for a portion of the qualified clinical testing expense, potentially modeled after the Orphan Drug Tax Credit
	RESEARCH & DEVELOPMENT
13	**Issue 1:** Rapid point-of-care tests are needed to distinguish between bacterial and viral infections in the outpatient setting.
14	**Issue 2:** There is a need for better biomarker tests to aid clinicians in making decisions regarding when to initiate and discontinue antibiotics in the inpatient setting.
15	**Issue 3**: Tests are needed that rapidly identify or quantify pathogens directly from the clinical specimen and provide rapid susceptibility results. Recommendations: 1. Sustained investment in funding mechanisms (e.g., grants) for developing new, cost-effective diagnostic tests and updating existing diagnostic tests (Small Business Innovation Research (SBIR), Small Business Technology Transfer (STTR), and others) 2. Expanded funding to Clinical Trials networks like ARLG, and ensure these networks work through a common IRB
16	**Issue 4**: Collaboration between diagnostic companies and other stakeholders is limited and inconsistent. Recommendation: Federal government agencies (HHS, FDA, CDC, NIH, DOD, USDA) should come together and create a list of the most critically needed diagnostics for combating AMR. The pathogen list could be used to prioritize funding and tax credits.
	REGULATORY
17	**Issue 1**: The regulatory approval clearance process for modifying and improving existing diagnostic tests is complex and expensive. Recommendation: Revision of FDA regulatory process for improvements or updates of existing tests that consider real-world evidence and postmarketing study results
18	**Issue 2:** The current regulatory process for new diagnostics is time-consuming and costly, posing a disincentive for developers. Recommendations: 1. Additional or enhanced clinical trials networks that function with a common IRB to reduce the regulatory burden of test approval 2. Modified requirements for Clinical Laboratory Improvement Amendments (CLIA) waiver 3. Complementary structuring of the FDA-CDC Antimicrobial Resistance Isolate Bank and the ARLG virtual repository to increase diagnostics companies' access to isolates
19	**Issue 3:** There are no requirements for hospitals to update their microbiology laboratories with newer technologies. Recommendation: CLIA requirements to update microbiology laboratories' technology as part of the accreditation process
	BEHAVIORAL
20	**Issue 1:** Clinicians do not always use diagnostic tests, believe the results, and act on them. Recommendations: 1. Evidence-based research 2. Inclusion of experts in clinical use of diagnostics on clinical guidelines committees that address prevention, diagnosis, and treatment of infectious diseases 3. Clinician education on the use and interpretation of diagnostic tests 4. Development of tools and mechanisms that improve clinicians' abilities to make decisions in the ambulatory setting

HUMAN HEALTH – THERAPEUTICS

	ECONOMIC
21	**Issue 1**: The return on investment (ROI) for developing new antibiotics is lower than for most other drugs. Recommendations: 1. A combination of general and targeted incentives to introduce a more predictable and sufficient ROI for antibiotic manufacturers, including push incentives and pull incentives 2. Expansion of targeted push incentives across all phases of discovery and development 3. Adoption of some form of a de-linkage model as a pull incentive 4. For pull incentives, development by CMS and the Treasury Department of value metrics for antibiotics and diagnostics as well as options for plausible business models for antibiotics, including de-linkage
	RESEARCH & DEVELOPMENT
22	**Issue 1:** Finding molecules that kill bacteria without also harming the patient is scientifically challenging. Recommendation: Strengthened funding for existing mechanisms that support innovation and R&D
23	**Issue 2:** Showing the utility of a new antibiotic against resistant bacteria paradoxically requires that resistant infections occur with sufficient frequency to enable clinical study. Recommendations: 1. Continued development of FDA guidance documents, with a particular emphasis on guidance for developing very narrow-spectrum agents 2. By BARDA and NIAID, creation of clinical trials networks (and hence clinical trials capacity) supporting both broad- and narrow-spectrum agents
	REGULATORY
24	**Issue 1:** It is difficult for manufacturers to develop clear and specific data for any new drug on clinical efficacy in infections caused by highly resistant bacteria.
25	**Issue 2:** It is difficult to enroll the number of patients needed to show efficacy of a narrow-spectrum antibiotic because of the low rate of infections caused by specific pathogens. Recommendations: 1. Establishment of clear expectations by FDA through regular stakeholder engagement as guidance is developed 2. Development by CMS, Treasury, and other USG agencies of approaches to assess antibiotic value using limited amounts of data
	BEHAVIORAL
26	**Issue 1:** Stewardship activities appropriately limit the use of current and new antibiotics; therefore, novel antibiotics have a low financial ROI from the perspective of the developer. Recommendation: Continued efforts by CMS and Treasury to ensure that solutions to the problem of incentives incorporate and support stewardship

ANIMAL HEALTH – VACCINES

	ECONOMIC
27	**Issue 1:** The cost of purchasing and administering vaccines can outweigh the cost of purchasing and administering antibiotics. Recommendation: Incentives for use of vaccines that reduce bacterial disease prevalence in farm animals to reduce the need for antibiotics
	RESEARCH & DEVELOPMENT
28	**Issue 1:** There is limited funding for basic research on the immune system in key animal species, which is fundamental to designing the next generation of vaccines, adjuvants, and administration tools. Recommendations: 1. New funding dedicated to supporting basic research of immune systems across species to optimize vaccine development, with shared funds across agencies, as this issue addresses AMR in both human and animals 2. Sufficient funding for the proposed Innovation Institute within USDA to develop new technology accelerator programs
29	**Issue 2:** Vaccine delivery systems for mass vaccination are not optimized for specific animal-pathogen-production scenarios. Recommendations: 1. New funding dedicated to supporting improved vaccine delivery in animal production, with shared funds across agencies, as this issue addresses AMR in both human and animals 2. Sufficient funding for the proposed Innovation Institute
30	**Issue 3:** Epidemiological data are insufficient about the use of antibiotics for infections caused by pathogens that are currently or potentially preventable through vaccination. Recommendation: Increased collaborations with public-private partnerships and specific studies to estimate amount of antibiotic use that can be eliminated with vaccines, including viral disease vaccines
	REGULATORY
31	**Issue 1:** Regulatory processes prevent a flexible approach and rapid approval of vaccine strain updates in vaccine development. Recommendation: Process evaluation by USDA's Center for Veterinary Biologics (CVB) to improve speed of approval of new strains in commercial vaccines
	BEHAVIORAL
32	**Issue 1:** It is challenging for producers and veterinarians to integrate new vaccines and vaccination strategies into overall health management strategies while balancing productivity and welfare with ROI. (32) Recommendation: Education and training in assessing the effectiveness of disease prevention programs that balance productivity and welfare through improvements in veterinary and animal science curricula, continuing education, and funding for training programs that assess herd and flock health programs

ANIMAL HEALTH – DIAGNOSTICS

	ECONOMIC
33	**Issue 1:** Clinical outcome studies are needed to show that the use of diagnostic tests could prevent or quickly detect the emergence of antibiotic-resistant bacteria and is cost-effective. Recommendation: Increase funding of diagnostic outcomes studies, including animal health and welfare outcomes, AMR, and the impact on cost of production
34	**Issue 2:** The use of diagnostic testing can be limited by the expense incurred. Recommendation: Ongoing financial support for veterinary diagnostic laboratories that perform diagnostic testing and AST for animal pathogens
	RESEARCH & DEVELOPMENT
35	**Issue 1:** Few tests rapidly identify pathogens or provide rapid susceptibility results in food animal medicine. Recommendations: 1. Investment in research on diagnostics that rapidly identify pathogens in food animals or provide rapid susceptibility results directly from the clinical specimen in the field setting 2. Investment in translational research to adapt diagnostics platforms developed for humans to animals
36	**Issue 2:** Novel diagnostics are needed to advance process control in the harvest and postharvest sectors of the food supply chain to reduce exposure risk. Recommendation: Support for research to develop culture independent methods for detecting microbial contamination of carcasses and meats to support improved process controls.
37	**Issue 3:** Additional information is needed on AST for key animal pathogens, including validated clinical breakpoints. Recommendation: Research grants for the generation and integration of additional data necessary for the Clinical Laboratory & Standards Institute (CLSI) to establish test methods, quality-control range data, and interpretive categories (i.e., breakpoints) for priority animal pathogens for which there are currently none available or where human breakpoints are used
	REGULATORY
	There is no regulatory issue identified
	BEHAVIORAL
38	**Issue 1:** There is negligible evidence-based data about how veterinarians incorporate diagnostic testing in making decisions to employ antibiotic therapy. Recommendations: 1. Support for research into therapeutic decision-making behavior in veterinary medicine, including the use of AST and the potential for rapid diagnostics 2. Educational programs for veterinarians on the use and interpretation of diagnostic tests and stronger curricula and continuing education programs linked to antibiotic stewardship

ANIMAL HEALTH – ALTERNATIVES

	ECONOMIC
39	**Issue 1:** Funding is lacking to generate a sufficient pool of quality alternative candidates at the early and middle stages of R&D. Recommendation: Sufficient funding for the proposed Innovation Institute within USDA to develop new technology accelerator programs
40	**Issue 2:** Many alternatives on the market do not have efficacy data comparable to that of antibiotic products, yet they are preferred by food animal producers over more expensive antibiotics or alternatives that have proven effectiveness via a regulatory approval process. Recommendation: Enhanced support for small business innovation on alternatives through existing government programs (e.g., SBIR funding) and private-sector investment incentives
	RESEARCH & DEVELOPMENT
41	**Issue 1:** Small companies and independent innovators do not have readily available resources to conduct key studies that de-risk alternatives. Recommendation: Sufficient funding for the proposed Innovation Institute to provide support services and serve as a clearinghouse to connect innovators to the needed resources for R&D and appropriate use of innovative, nonantibiotic alternatives for animal disease intervention
42	**Issue 2:** Due to insufficient comparative data for alternatives and antibiotics, there is an incomplete understanding on how best to use an alternative product(s) in food animal production settings and how a new product can provide an added benefit compared to the existing ones. Recommendation: On-farm demonstration trial research project grants to researchers or food animal production companies to fund and conduct field studies using an alternative product(s)
	REGULATORY
43	**Issue 1:** Early-stage developers of alternatives face the challenge of determining which regulatory agency has jurisdiction over their candidate. Recommendation: Support for the proposed Innovation Institute to act as a single point of contact for basic research scientists and small companies to obtain feedback from the Center for Veterinary Medicine (CVM) and USDA
44	**Issue 2:** There is no standardized regulatory guidance for developers of alternatives because of the diversity of types of alternative products. Recommendation: Ongoing exploration of novel technologies to inform FDA CVM and USDA efforts to find new ways of satisfying evidentiary requirements via innovative regulatory approaches appropriate for the alternative candidates
	BEHAVIORAL
45	**Issue 1:** Researchers lack awareness of the business value and process of patenting novel technology which may result in public disclosure, thereby diminishing value of the technology. Recommendation: Awareness of the need and process for initiating patent protection of new technologies, included as part of the educational resources and outreach efforts of the proposed Innovation Institute
46	**Issue 2:** Stakeholders have not fully accepted alternatives to antibiotics because they lack trust in their effectiveness and safety. Recommendation: Analysis of information gathered in a database repository from alternative product demonstrations to assess how innovative technology may or may not have minimized the identified consequences while maximizing the health outcomes and possibly affected business aspects

Glossary of Abbreviations

AABP	American Association of Bovine Practitioners
AASV	Association of Swine Veterinarians
AAVMC	Association of American Veterinary Medical Colleges
AHI	Animal Health Institute
AMR	antimicrobial resistance
APLU	Association for Public and Land-Grant Universities
AVMA	American Veterinary Medical Association
BARDA	Biomedical Advanced Research and Development Authority
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
FDA	Food and Drug Administration
GFI	Guidance for Industry
HAI	health-care-associated infection
HHS	Department of Health and Human Services
IDSA	Infectious Diseases Society of America
LPAD	limited-population antibacterial drug
OIE	World Organization for Animal Health
OTC	over the counter
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
R&D	research and development
RADI	Reinvigorating Antibiotic and Diagnostic Innovation
ROI	return on investment
USDA	U.S. Department of Agriculture
VFD	Veterinary Feed Directive
WHO	World Health Organization
WG	working group