

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

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

May 16, 2018

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

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Meeting Proceedings

Welcome and Overview

Martin Blaser, M.D., Chair

Dr. Blaser called the meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) to order at 9:00 a.m. and welcomed the participants. He noted that Carl Flatley, who had been slated to provide a patient's perspective, was unable to attend due to the weather. Dr. Blaser thanked the liaison members retiring from the Council: Jay C. Butler, M.D., of the Association of State and Territorial Health Officials; Sherrie Dornberger, R.N., of the National Association of Directors of Nursing Administration in Long-Term Care; Elizabeth Jungman, J.D., M.P.H., of the Pew Charitable Trusts; Richard Carnevale, V.M.D., of the Animal Health Institute; and Elizabeth Allen Wagstrom, D.V.M., M.S., of the National Pork Producers Council. He welcomed the following new liaison members:

- Alice L. Johnson, D.V.M., National Turkey Federation
- Elaine Larson, Ph.D., R.N., American Nurses Association
- Tiffany Lee, D.V.M., Ph.D., M.S., North American Meat Institute
- Kathryn L. Talkington, Pew Charitable Trusts
- Denise M. Toney, Ph.D., Association for Public Health Laboratories

Call to Order, Roll Call, and Rules of Engagement

Jomana F. Musmar, M.S., Ph.D., Designated Federal Officer (Acting), National Vaccine Program Office, Department of Health and Human Services (HHS)

Dr. Musmar explained the rules governing the Council 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

Brett P. Giroir, M.D., ADM, U.S. Public Health Service, Assistant Secretary for Health, HHS

Dr. Giroir said he dealt with antibiotic resistance daily as a pediatric critical care physician in the early 1990s, and he worried particularly about the effects of antibiotic resistance on chronically hospitalized children. Later, resistant infections became common even among naïve patients, leading to enormous problems in the hospital and critical care unit. With increasing resistance, antibiotics are becoming less effective and more expensive. As a result, patients suffer, and the health care system suffers. Dr. Giroir appreciated PACCARB's commitment to offering a patient's perspective at each meeting to put a human face on the statistics.

Dr. Giroir reaffirmed the importance of the Council and gave his personal commitment that its work would be taken seriously, evaluated at the highest level, and implemented, as appropriate, as soon as possible. He was pleased about the One Health focus of the Council, recognizing the importance of the intersection between human and animal health in solving the problem.

On behalf of HHS Secretary Alex Azar, Dr. Giroir recognized the retiring liaison members with certificates of appreciation for their dedicated service.

Agency Updates: Research, Infection Prevention, and Stewardship Activities Centers for Disease Control and Prevention (CDC)

Rima Khabbaz, M.D., National Center for Emerging and Zoonotic Infectious Diseases

CDC recently cosponsored a meeting on the environmental aspects of antimicrobial resistance (AMR) that focused on contamination from human and animal sewage, antimicrobial manufacturing, and antimicrobials used as pesticides. The meeting summary should be finalized over the summer. Earlier this spring, CDC solicited applications for innovative and foundational work on AMR. Through this mechanism, CDC will partner with educational institutions, nonprofit organizations, state and local governments, and private industry to advance applied research and development to fill gaps in the current AMR, prevention, and control pipeline. Awards will be announced later this year.

The April issue of *Vital Signs* presented data from CDC's Antibiotic Resistance Laboratory Network, which identified over 200 unusual resistance occurrences across the country between January and September of 2017. It also described the containment strategy, which is an aggressive approach that involves health care facilities, health departments, and laboratories working together to identify unusual threats and respond quickly. Modeling demonstrates that even when infections are not fully contained, quite a few infections can be prevented.

National Institutes of Health (NIH)

Jane Knisely, Ph.D., National Institute of Allergy and Infectious Diseases (NIAID)

NIH is hosting a workshop on infectious diseases in the central nervous system and therapeutic strategies to cross the blood-brain barrier in August and another, with the Food and Drug Administration (FDA), in September on science and regulation of live microbe-based products used as drugs. NIH is funding two programs to generate new insights and mechanistic understanding of antibiotic resistance development, with awards in three topic areas:

- Discovery-based clinical research, focused on the microbiome of human cohorts at high risk for acquiring drug-resistant infections
- Novel approaches to studying human-associated microbial communities and the mechanisms that generate colonization resistance or promote the emergency of drug-resistant bacteria
- Identification and characterization of combinations of existing antimicrobials to improve therapy for infections caused by multidrug-resistant gram-negative bacteria by leveraging model systems or existing cohorts

In February, NIH funded four partnership projects to develop tools to advance therapeutic discovery for select antimicrobial-resistant, gram-negative bacteria. This initiative aims to support the development of novel predictive assays, models, and research tools and grew out of a workshop focused on the problem of gram-negative therapeutic discovery.

Awards are expected for two more funding opportunities later this fiscal year for partnerships for developing, vaccines, immunoprophylactics, and clinically useful diagnostics for antimicrobial-resistant bacteria. In addition, NIH continues to provide preclinical services in support of the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), which

currently has 27 therapeutic and 6 diagnostic candidates in its portfolio. Most of these therapeutic candidates are focused on the top gram-negative threats identified by CDC and the World Health Organization. NIAID also provided support for many of these candidates prior to their entry into CARB-X. CARB-X will have another call for antibacterial candidates in early June.

Finally, in 2017, the Biomedical Advanced Research and Development Authority's diagnostics prize competition identified 10 semifinalists who each received \$50,000 to develop concepts into prototypes. Submissions for the next phase are due in September of this year.

Food and Drug Administration (FDA)

William Flynn, D.V.M., M.S.

FDA continues to focus on enhancing data collection to assess progress on AMR in the veterinary sector. The National Antimicrobial Resistance Monitoring System, a collaboration between FDA, the U.S. Department of Agriculture (USDA) and CDC, published its 2015 integrated report. FDA also launched its Resistome Tracker, an interactive research tool for visualizing whole genomic sequencing data. FDA published its annual antimicrobial sales and distribution data for 2016, which for the first time includes estimates of sales by major food animal species. Notably, 2016 was the first reporting year that showed a decline in sales, which had been gradually increasing annually. In 2016, there was a 10-percent decline in overall sales and a 14-percent decline in sales of medically important antimicrobials. These sales data precede the January 2017 regulations restricting antibiotic use in animals. FDA is analyzing responses to its call for public comments on a methodology for developing a biomass denominator as a way to give more context for these sales data.

Recognizing the limitations of sales and distribution data, FDA continues to collaborate with USDA to develop additional approaches for collecting actual use information on antimicrobials in veterinary sectors. As part of that effort, FDA funded two cooperative agreements to fund pilot studies on strategies to collect direct use data. One pilot is looking at both beef and dairy cattle; the other is looking at swine and poultry; results are expected this fall.

The transition to complying with the January 2017 regulations bringing the feed and water uses of medically important antibiotics under veterinary oversight (i.e., the Veterinary Feed Directive [VFD]) and eliminating growth promotion uses, has gone fairly well. FDA is seeking public input to inform potential refinements to labeling available medically important antibiotics that currently do not have specifically defined durations. FDA is working on an overarching plan outlining the key issues of focus for the next 5 years, including medically important antibiotics that are still available over the counter.

Steven Gitterman, M.D., Ph.D., Center for Devices and Radiological Health

There has been tremendous progress in diagnostics on multiple fronts. A genotypic test panel to diagnose respiratory tracheal aspirate specimens, including 19 bacteria and 8 resistance markers, is now commercially available. A phenotypic and a genotypic test are available for rapid testing for carbapenem-resistant Enterobacteriaceae or carbapenemase-producing organisms. More panels are becoming available for different targeted uses for clinical practice. Other new rapid phenotypic devices include one that identifies pathogens from isolates within 90 minutes and

completes antimicrobial susceptibility testing (AST) within 7 hours. A lot of work is underway around biomarkers using different specimen types, such as rectal swabs (as opposed to stool specimens), which may contribute to antibiotic stewardship and hospital surveillance.

FDA has determined that sponsors who have validated mechanisms in place to add information to large databases can extend the use of their devices in response to the new data without approaching FDA. More drug manufacturers are working with device manufacturers to ensure corresponding AST devices are available when new drugs are approved. The CDC/FDA Antibiotic Resistance Isolate Bank is growing. The combined efforts of FDA, the Office of the National Coordinator on Health Information Technology, CDC, NIH, and the Centers for Medicare and Medicaid Services (CMS) to standardize reporting of laboratory results will substantially aid efforts to combat antibiotic resistance.

Substantial challenges remain. For example, recent recalls demonstrate that genotypic contamination can occur with the very sensitive DNA technology. New diagnostic tools provide more information than clinicians can interpret. More data must be incorporated into databases to enable clinical predictions. The need persists for more dissemination of information. As more tests become available, there is a need to capture and push this information out to practitioners—both the infectious disease (ID) specialist and general practitioners.

Agency for Healthcare Research and Quality (AHRQ)

James Cleeman, M.D.

The National Action Plan for Combating Antibiotic-Resistant Bacteria specifically tasked AHRQ with sponsoring research on antibiotic stewardship in various care settings. AHRQ has awarded more than \$37 million in grants for investigator-initiated research and has new funding opportunity announcements for research in stewardship and prevention. AHRQ conducted a webinar in March to inform members of the Society for Health Care Epidemiology of America (SHEA) about AHRQ grant opportunities. The agency is funding research on lower respiratory tract infections in primary care and use of clinical decision support tools for using diagnostics in pediatric intensive care units. To prevent *Clostridium difficile* infection, various modalities are being tested, such as prophylactic vancomycin and fecal microbiota transplant to prevent recurrent *C. difficile* infections in patients on antibiotics.

AHRQ is applying its Comprehensive Unit-Based Safety Program (CUSP) to three current nationwide projects for infection prevention and stewardship. One addresses persistently elevated rates of central line-associated bloodstream infection and catheter-associated urinary tract infection. Another aims at reducing surgical-site infections and venous thromboembolism after surgery. A major national CUSP seeks to promote implementation of antibiotic stewardship in all acute care, long-term care, and ambulatory care settings. In December 2017, AHRQ launched a 1-year cohort of over 400 acute care hospitals trying to improve their implementation of antibiotic stewardship, and Dr. Cleeman said he would bring results of that effort to the Council when they are available.

Centers for Medicare and Medicaid Services (CMS)

Shari Ling, M.D., Deputy Chief Medical Officer

CMS finalized the conditions of participation (CoPs) for over 15,000 Medicare/Medicaid participating long-term care facilities in 2016. Subsequently, the Quality and Oversight Group (formerly the Survey and Certification Group) implemented a phased-in approach for surveyors to assess compliance, which includes establishing infection control antibiotic stewardship programs. Interpretive guidance was developed with significant stakeholder input and implemented with technical assistance provided by quality improvement contractors. Long-term care facilities will be required to have an infection preventionist oversee their infection control and stewardship programs by November 2019. CMS is in the rulemaking process for measures that would require infection prevention and antibiotic stewardship programs in more than 4,900 acute care hospitals and 1,300 critical access hospitals.

As part of the CMS Meaningful Measures Effort, CMS identified duplicative reporting requirements and so removed a set of measures from the hospital value-based purchasing program that are retained elsewhere. CMS also retained the Merit-Based Incentive Payment System, specifically targeting physicians, in the implementation of antibiotic stewardship as a clinical practice improvement activity. Dr. Ling said CMS is focusing on using payment as a lever to reducing health-care-associated infections (HAIs).

CMS is providing technical assistance on how to use data to drive behavior change toward a culture of safety and improvement. Its quality improvement networks-quality improvement organizations (QIN-QIOs) are working with over 2,300 nursing homes to track *C. difficile* and implement stewardship programs. CMS has helped implement CDC's Core Elements of outpatient antibiotic stewardship and reduction of HAIs in 7,500 outpatient facilities, in more than 4,000 hospitals, and among 140,000 clinicians. Its programs use data to help practitioners understand their own practice behaviors, with an eye toward transformation to value-focused care, as opposed to volume-focused care.

Department of Defense (DoD)

Adrian Kress, M.D.

One of DoD's largest facilities is engaged in a pilot program to identify patients who have been erroneously labeled with a penicillin allergy. Of 362 patients evaluated so far, 358 have been cleared to use penicillin if needed. This policy will be implemented across the military health system broadly in the coming year, substantially increasing the available armamentarium for a large portion of the population. DoD recently finalized a cooperative research and development agreement to allow several of its facilities to participate in the AHRQ safety program for improving antibiotic use. More than 60 percent of all DoD inpatient facilities are enrolled in the National Healthcare Safety Network's Antibiotic Use and Resistance module, and DoD hopes to have all of them enrolled by the end of this year. DoD approved a policy for combating antibiotic-resistance bacteria last October and is finalizing its implementation guidelines.

U.S. Department of Agriculture (USDA)

David Goldman, M.D., Food Safety and Inspection Service (FSIS)

FSIS operates under the principles of hazard analysis and critical control point (HACCP). In HACCP, the industry must design the system to minimize hazards in food products by identifying and monitoring critical control points in production. FSIS conducts inspection and sampling activities and is concerned about all bacterial contamination. However, most foodborne illness is caused by a drug-sensitive pathogen. Dr. Goldman provided examples of FSIS regulations around *Salmonella*, Shiga toxin-producing *Escherichia coli*, *Listeria*, and *Campylobacter* that decreased contamination in food production facilities. Its focus on decreasing pathogen contamination in foods results in decreased exposure to these pathogens and lower illness rates, Dr. Goldman concluded.

Larry Granger, D.V.M., Animal and Plant Health Inspection Service (APHIS) (by phone)

The Center for Veterinary Biologics works with FDA on areas of overlapping licensure authority, such as animal vaccines. In December of 2017, the Center for Veterinary Biologics published guidelines that enable manufacturers of prescription platform product biologics to modify their vaccines and get them to market more quickly if they have been continuously monitored. Autogenous vaccines can be built on an isolate from a particular herd or flock and can be approved quickly if they have a reasonable expectation of efficacy. There is also a provision for addressing quickly mutating agents, like influenza, so vaccine manufacturers can get a product to market rapidly.

APHIS began work on data collection to characterize the use of antibiotics in animal agriculture in late 2017. Much of APHIS' work to combat antibiotic-resistant bacteria involves surveillance and monitoring under the National Animal Health Monitoring System, which conducts surveys to characterize antibiotic use and resistance in animal agriculture. Data from the first survey in cattle and swine are expected to be released this fall.

APHIS has partnered with academia to access proprietary data from the industry and with FDA to fund data collection on farms. Issues persist around what to measure and how to ensure confidentiality of the data. APHIS is working with stakeholders to modify its questionnaires to better reflect regulatory changes made in January 2017. APHIS has also been working with industry on a longitudinal study design that would provide information of value back to producers and veterinarians, who have shouldered the legal and ethical responsibility for antibiotic stewardship.

A pilot project was launched through the National Animal Health Laboratory Network and the National Veterinary Services Laboratories, in conjunction with FDA, to gather opportunistic samples, test them for antibiotic resistance, and enter that data into a database. The National Veterinary Accreditation Program has educational modules available in every veterinary school and online, including modules on using antibiotics in animals and the VFD.

Jeff Silverstein, Ph.D., Agricultural Research Service (ARS)

One exciting area of progress around infection prevention and stewardship is the development of an automated monitoring system of large pens of pigs to detect illness earlier by recording and analyzing behavior. The system identifies feeding and drinking behavior changes—often an

indication of illness—long before clinical signs are observed. Producers can then detect illness earlier and quarantine and treat the sick animals without it spreading to the rest of the herd.

A research project that has been going on for 10 years at the National Animal Disease Center in Ames, Iowa, has developed a *Salmonella* vaccine that works in both swine and turkeys and is cross-protective against several *Salmonella* strains. ARS is supporting a lot of work around the microbiome in swine, ruminants, and poultry. Researchers are examining intervention strategies to modulate the microbiota of the eggshell to provide chicks with beneficial bacteria. Others recently discovered a way to minimize the toxicity of tunicamycin and pair it with penicillin to enhance penicillin activity by 30- to 60-fold. These scientists have also discovered an easier chemical way to produce the drugs, which will be important for large-scale production.

Discussion

Dr. Granger offered some more details on the proposed longitudinal study design. He noted the coordination between USDA and FDA to harmonize data, as in the pilot project to gather laboratory data on antibiotic resistance. Dr. Granger explained some of the shortcomings of APHIS' 2017 survey, including a delay in funding, which may limit the utility of the findings. The surveys recently initiated for cattle and swine do not involve biological samples, but the proposed longitudinal study would.

Dr. Kress elaborated on the DoD's finding that 99 percent of those thought to be allergic to penicillin can take the drug with no problems. The result will have tremendous benefits for the whole health care system by opening a previously closed door to treatment.

Dr. Khabbaz specified that the unusual threats detected by the CDC system were primarily localized. While the system could detect a multistate threat, it is designed to identify local threats early so they can be stamped out.

Dr. Knisely clarified that NIH supports research into infection prevention as well as treatment. Traditional approaches, such as vaccines and immunoprophylactics, and nontraditional efforts, such as bacteriophages, are being studied. In addition, NIH has a large research portfolio around vaccines for upper respiratory viruses, and NIAID has made a concerted push toward a universal influenza vaccine.

Dr. Ling said CMS recognizes the shortage of clinicians with ID training. Dr. Ling said the mandate that long-term care facilities have ID preventionists by the end of 2019 is an opportunity to think broadly and flexibly about how those services can be provided in the field. She planned to follow up with the Health Resources and Services Administration, which has long been a partner in addressing workforce issues.

Dr. Khabbaz explained CDC's approach to disseminating key findings like those published in *Vital Signs*. Alicia Cole added that CDC collaborates with patient safety advocates and relies on them to help spread information at the community, local, and state levels.

Thomas R. Shryock, Ph.D., asked panelists to expand on their use of partnerships to implement regulatory policy. Dr. Flynn described a long-term voluntary process to decrease the use of

medically important antibiotics in the food animal industry, which smoothed the transition to regulations. Dr. Ling also emphasized that working with clinicians, facilities, and patients at the beginning of the regulatory process leads to regulations that are more meaningful and easier to implement. Dr. Gitterman added that working with industry partners to gather data facilitates creation of large public databases that can provide valuable information to many.

Dr. Ling said CMS will collect and review a lot of information from long-term care facilities about compliance with CoPs around infection prevention and stewardship. Stratifying the facilities by types of services provided may be one approach to assessment. Dr. Ling said CMS is gathering information about hospitals that have implemented CDC's Core Elements and have established infection control and antibiotic stewardship programs through the QIN-QIOs and Hospital Improvement Innovation Networks, which can also push best practices out to facilities.

Stewardship for Animal Health

Introduction

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

Dr. Apley said a number of veterinary organizations have developed guidelines, best practices, and other materials around infection prevention and antimicrobial stewardships, most recently the American Veterinary Medical Association (AVMA). The Council invited panel members to share their experience and expertise in the field.

Intersection of Human and Animal Antibiotic Stewardship Programs

Brian Lubbers, D.V.M., Ph.D., Kansas State University

Dr. Lubbers compared Infectious Diseases Society of America (IDSA)/SHEA and CDC guidelines on antibiotic stewardship for humans with those recently developed by AVMA for animals, noting similarities in their emphases on judicious use, evaluation of stewardship efforts, improving patient outcomes, and minimizing harm to the patient and the community. Dr. Lubbers pointed out that didactic education as part of school curricula is not sufficient. Veterinary students have no context for applying stewardship guidelines and find them difficult to effect in real-world settings. Some recommendations are not applicable to food animal health settings, such as converting from intravenous to oral dosing and doing pharmacokinetic monitoring. Diagnostic tools are in the pipeline that could help veterinarians better select antibiotics.

More research is needed to support decision-making on using the shortest effective duration of antibiotics in food animals. More clinically relevant metrics are needed to drive uptake. The role of microbiology laboratories in stewardship bears more attention in the food animal health realm. Similar to human health settings, animal health providers are busy, have little time for decision-making, and are concerned about client satisfaction and expectations.

Veterinarians treat a large variety of patients of different species and sizes, so antibiotic stewardship programs must have sufficient flexibility to allow appropriate treatment across a broad patient spectrum. Veterinary practices are challenged to capture and analyze data. More research is needed on optimizing dosing regimens.

Kate KuKanich, D.V.M., Ph.D., Kansas State University

In companion animal medicine, most practices and facilities lack infection prevention teams, said Dr. KuKanich. Veterinarians want to support stewardship but need help with implementation. In many settings, veterinarians find it challenging to confirm bacterial infection. Students are trained in using diagnostics, and most veterinarians will provide free consultations to practices that do not have specialists, but a number of barriers remain to antibiotic stewardship, such as the following:

- Expense of diagnostics, which clients pay out of pocket in most cases
- Limited diagnostic tests and expertise to interpret them, especially in rural areas
- Client expectations for immediate treatment
- Convenience of in-house pharmacies, which can provide bottles of antibiotics on the spot
- Lack of pharmacokinetic studies to determine optimal dosages
- Lack of funding for research in companion animals (even less than for food animals)
- Lack of electronic health records systems, which could promote guidelines and facilitate monitoring

Dr. KuKanich said veterinarians excel in educating clients about patient conditions and treatment options, which suggests one promising avenue for stewardship efforts. More research is needed for optimal dosing for the most common infectious diseases, as is more use of antibiograms following laboratory testing. The impact of antibiotics on normal flora and how shedding affects human contacts in the home merit more study. The influence on stewardship of approved versus compounded antibiotics must be evaluated.

Referral Institution Prescriber Behavior

Mark Papich, D.V.M., M.S., North Carolina State University

Dr. Papich said referral veterinary hospitals see more complicated and challenging cases than general practices, and many of those cases have already involved a course of antibiotics, so resistance may already be developing. Of the very few studies of antibiotic use in veterinary referral hospitals, one found that veterinarians are concerned about AMR and use more diagnostic testing than their counterparts in general practice. However, the referral veterinarians do not see themselves as part of the problem and do not want limits imposed on their own prescribing.

Another study found that those who completed veterinary education after 1999 were less concerned about AMR than those who graduated earlier, which suggests a need for more emphasis on AMR in veterinary education. A third study evaluated a targeted stewardship program in Ontario, Canada, and found the intervention reduced overall antibiotic use. Dr. Papich pointed to the lack of research in many key areas of practice, particularly the management of complicated infections and the risks to humans when pets develop resistant infections.

International guidelines focus on prudent use and more reliance on diagnostic tests (although they are expensive), discouragement of polypharmacy approaches and long courses of antibiotics, and better surveillance (which is nonexistent in companion animal medicine). Dr. Papich stressed that there are no regulations restricting the drugs that veterinarians can prescribe,

and some in the field believe regulations or voluntary restrictions may be appropriate. He noted that for commonly used drugs for uncomplicated infections, sponsors are beginning to come forward with guidance for diagnostic testing. However, for those drugs approved for human use that should be used in animals when the most common drugs fail, sponsors are less likely to step up, and the field is seeking to develop its own susceptibility tests.

Discussion

Dr. Lubbers pointed to the challenges of modifying labelling for approved dosages and suggested creating new models for determining optimal dosages that incorporate resistance as a factor. Human medical research all points to the efficacy of shorter durations of antibiotics, he added, which suggests that shorter courses can be used in animals. Better metrics are needed to assess use of antibiotics, but it is unlikely that a single metric will be meaningful for both regulators and food producers, said Dr. Lubbers.

Dr. KuKanich was not aware of any studies of potential antibiotic residue in pet foods; however, there is concern about animals consuming raw food diets, their increased risk of antibiotic-resistant infections, and the likelihood of shedding antibiotic-resistant bacteria that can affect humans in the household and the community. Certain pet treats, such as rawhides and pig ears, are notoriously contaminated with bacteria, she added.

Drs. Papich and KuKanich both agreed that the influence of senior clinicians on students entering practice is substantial. Dr. KuKanich felt that strong evidence-based guidelines are needed to counter less-than-optimal practices that students learn from established veterinarians.

Drs. KuKanich and Papich both pointed to evidence that pets and humans share bacteria in the household, including antibiotic-resistant bacteria. There is not a lot of evidence of direct transmission, said Dr. KuKanich, but the issue demands more attention.

Dr. Papich said California has mandated continuing education on antibiotic stewardship as part of veterinary licensure, which is one way to reach clinicians. Dr. KuKanich said another way would be to include antibiotic stewardship in One Health sessions at veterinary conferences. She added that many are not aware of existing guidelines or how to implement stewardship in their practices. Dr. Papich noted that recent graduates entering food animal medicine are aware of antibiotic prescribing restrictions and so may be more aware of AMR issues, but no surveys have measured that.

None of the panelists could pinpoint a specific motivation for veterinarians to implement antibiotic stewardship in companion animal medicine beyond individuals' personal commitment to address AMR or concerns for public health. Data, technology, and tools are needed to help veterinarians implement such programs, said Dr. KuKanich.

There are no data with which to determine how much companion animal medicine contributes to the overall use of antibiotics, but Dr. Papich estimated that the figure is less than 10 percent. He said generic drugs approved for human use are often prescribed, so figures from a veterinary drug company would not be accurate. Dr. Papich acknowledged that many antibiotics are

available online with no prescription, and the range of drugs available in pet stores for fish is alarming.

Veterinary Antibiotic Prescribing Behavior and Plant Disease and Control Surveys of Veterinary Prescriber Behavior among Private Practitioners in the United States

Paul Morley, D.V.M., Ph.D., Colorado State University

Dr. Morley said the concerns around AMR are similar for humans and animals, but the funding for research in animals is much lower, which poses a significant problem for the field. He noted that many of the psychosocial factors affecting prescribing behavior for human patients, described in a 2017 PACCARB report, can be applied to animal patients (e.g., client expectations and relationships among prescribers).

Data from a 2001 national survey demonstrate the differences in antibiotic use for different species and the differences in the most prevalent diseases treated. As in human health settings, diagnostic testing is underused in animal health, especially among general practitioners treating small animals. Notably, Dr. Morley said, veterinarians are influenced by their peers and by complicated etiologies of disease in different species. In some cases, use of antibiotics for viral conditions is warranted, which complicates determinations of best practices.

The survey showed different patterns of antibiotic use across species for the same disease, likely related to convenience and ease of use. Cost is also a critical factor. Manufacturers take all these factors into account to determine what products are marketable in what forms.

Veterinarians believe that prescribing practices, patient compliance, and client expectations are drivers of AMR. They believe that use of antibiotics in farm animals is a more critical driver of AMR than use in companion animals, although Dr. Morley stressed that no data are available to confirm that. Many believe that their own prescribing patterns do not contribute to AMR. Dr. Morley said surveys using practice scenarios as the basis for questions appears to be an effective way to understand actual practice and attitudes among veterinarians.

Heather Fowler, V.M.D., Ph.D., M.P.H., National Pork Board

A Washington State survey of veterinarians found that about three quarters use some diagnostics, but few use them routinely. Analysis indicated that lack of healing is a factor in the decision to order culture and sensitivity testing, cost is a barrier, and best practices are a facilitator. The survey determined that veterinarians are concerned about AMR but need help leveraging facilitators to improve judicious use of antibiotics.

Looking at studies of antibiotic prescribing around the world for food animals and companion animals, Dr. Fowler said the human factors affecting antibiotic prescribing can be categorized as clinical (e.g., the disease and its response to medication, the veterinarian's comfort and experience using the drug) and nonclinical (e.g., pressure from the client, costs, regulations, and public perceptions). A very small study from the Netherlands underscored the impact of client expectations on prescribing patterns.

Dr. Fowler concluded that AMR is a One Health issue, yet antibiotics remain an important tool. The efficacy of antibiotics must be retained for future use. The animal health field needs to use more diagnostic tests to avoid unnecessary prescribing and must overcome existing barriers (and leverage the facilitators) to reduce antibiotic use. Any recommendations could address multiple populations but should not be too specific.

Defining Stewardship and Maximizing Voluntary Compliance

H. Morgan Scott, D.V.M., Ph.D., Texas A&M University (by phone)

Dr. Scott outlined the ethical imperative to preserve antibiotics for future use and the competing values that make it difficult to reach consensus on how to do so. He pointed out that veterinarians in private practice do not answer to any oversight bodies for infection control and so set their own practice boundaries. In addition, veterinarians have obligations to their clients, their patients, and the public health of the community, and those three can sometimes conflict.

Where there are competing sets of values, one starting point for consensus is to identify shared values, such as the following:

- Antimicrobials enhance the health and well-being of both humans and animals.
- There is room for improvement in terms of overuse and misuse in both human and animal settings.
- There is a moral imperative to protect the efficacy of antimicrobials for future generations.

A risk-based framework for stewardship can help categorize threats—for example, according to the risk of release and exposure and the potential consequences. One component of stewardship in the agricultural setting, for example, may be a commitment not to increase the risk of releasing antibiotic-resistant bacteria through the food supply. Dr. Scott and colleagues are conducting a research project to conceptualize stewardship by engaging with stakeholders from agriculture, consumer, and public health groups around an approach to voluntary compliance in the beef and dairy industry focused on reducing risk in the public health sector. A number of researchers in human health are investigating factors influencing prescribing behavior; additional concerns among veterinarians (particularly around the concept of withholding antibiotics) are competition for business, economic considerations of the clients, and the moral duty to treat sick animals.

Education about antibiotic stewardship should be grounded in understanding the factors that affect decision-making, Dr. Scott explained. In the absence of randomized, controlled trials, evidence will have to come from observation and modeling, and clinicians will continue to try to figure out how to dodge the bullet of AMR. A framework from the European Environmental Agency focuses on the interactions between driving forces, pressures, state actions, impact, and responses.

Education and Outreach

Emily Yeiser Stepp, M.S., National Milk Producers Federation

The Farmers Assuring Responsible Management (FARM) program began in 2009 as an effort to convey to the public that dairy farmers treat animals humanely and ethically. The focus on

animal care expanded to antibiotic stewardship and more recently to environmental stewardship. FARM uses a continuous improvement model, with policies identified by a committee representing various stakeholders and supported by science. The program covers 98 percent of all dairy supply in 49 states—a testament to the industry’s commitment to a unified program that various stakeholders can support, said Ms. Stepp.

The program includes best management practices that inform the criteria for evaluation. Evaluators undergo annual training and review of credentials. Third-party verification is conducted on a random sampling of a statistically significant number of producers to ensure the integrity of the program and its evaluators.

When the program debuted, participation was not as robust as hoped. The second version of the program involved mandatory participation with voluntary action plans, as the industry’s cooperatives and processors felt pressure to communicate to consumers that they care about their animals’ well-being. The third version, which began in 2017, increased accountability, mandated corrective action plans, and included disciplinary actions for violations. The Federation communicates with producers through its website and in collaboration with the Beef Quality Assurance program. It develops resources in English and Spanish on ways to comply with the FARM program and uses various outreach mechanisms to disseminate them.

Plant Disease and Control

George W. Sundin, Ph.D., Michigan State University

Antibiotics have long been used in apple and pear orchards to treat fire blight, a bacteria that can spread quickly and kill thousands of trees in a season, resulting in huge economic losses, said Dr. Sundin. The most popular apple varieties at present (e.g., gala) are highly susceptible to fire blight and have little resistance against disease. Copper bactericides are effective, but prolonged use pollutes the soil. Biological controls are promising but have limited effectiveness so far, especially in damp climates.

Streptomycin and oxytetracycline have been used in apple and pear orchards since the 1940s. Kasugamycin was introduced in 2015 and has no uses outside of plant agriculture; it is effective and has a limited range, so it puts less pressure on the environment than other antibiotics. Plant agriculture accounts for less than 0.5 percent of antibiotic use in the United States but increasing use of streptomycin and oxytetracycline in citrus plants may increase that contribution.

Over the past decade, outbreaks of Huanglongbing (HLB), or citrus greening, disease have devastated citrus crops in Florida, driving a search for new treatment approaches. Efforts are underway to engineer resistant plants using clustered, regularly interspaced, short palindromic repeats (CRISPR) technology, but even if successful, it will take years before those plants can be harvested. The Environmental Protection Agency (EPA) used its emergency authority to allow citrus growers in Florida to use streptomycin and oxytetracycline. Oxytetracycline degrades quickly in sunlight, so accurately timing the application to prevent disease spread is crucial. Dr. Sundin said there were no examples of antibiotic resistance that have affected animals or humans. Some studies have found no measurable impact on soil of streptomycin use over many seasons. Dr. Sundin and colleagues are seeking funding to conduct genetic sequencing to study the antibiotic resistome.

Discussion

Dr. Sundin said it is too early in the evolutionary cycle to detect natural selection for resistant trees. In addition, fire blight is a unique pathogen that is difficult to identify. Some European studies have found that streptomycin affects bees, but Dr. Sundin said the study conditions did not seem consistent with real-world conditions. In 50 years of using streptomycin in apple trees, U.S. researchers have not seen a significant impact on bees.

Until 2014, Dr. Sundin noted, organic farms could use antibiotics that were produced naturally by streptomycin bacteria. Currently, they may use copper to control fire blight, but it can damage both the tree and the fruit. In drier climates, like Washington State, growers can take advantage of biologics such as yeast that may control disease. Some organic farms focus on disease-resistant varieties.

Dr. Sundin said there have been no studies of the microbiomes of orchard workers to assess the effects of pesticides, but those applying the pesticides use many forms of protection, and those picking the fruit do so months after application, when there should be no residue on the plants. Those applying pesticides must be certified and licensed by the state and maintain their certification through continuing education; however, Dr. Sundin said, growers can purchase the materials online and could overspray. Growers must keep records of their antibiotic use, and states track usage, but no further monitoring occurs. When kasugamycin was first available, farms had to be certified by a state-recognized expert to use it; once EPA granted registration for kasugamycin, the certification requirement was lifted, said Dr. Sundin.

Asked about potential gaming of the system, Dr. Scott said that since the FDA enacted the VFD and other restrictions on antibiotic use in food animals in 2017, the costs of antibiotics have gone up, and most producers do not want to use them unless necessary. Dr. Fowler added that the Pork Board, like others in the field, conducted outreach to raise awareness of the regulations before they took effect and promoted responsible antibiotic use. Dr. Johnson pointed out that all producers began cutting back on antibiotic use before the new regulations took effect.

Ms. Stepp said her organization is considering offering a product label or some other mechanism to identify for consumers those milk producers that comply fully with the FARM program. Ms. Cole said PACCARB should keep in mind the common thread from the presentations that industries need a combination of carrots and sticks to enact policies. She said it takes a long time to translate evidence-based recommendations into practice on the human side (17 years) and asked how the National Milk Producers Federation put change management practices in place. Ms. Stepp said that the more the Federation works with producers, the better it understands what drives change and what others in the food animal industry would support. Some mandates were implemented with consequences for not complying. Ms. Stepp said there is much focus on “the moveable middle”—that is, those who just need help to do the right thing.

Dr. Scott expressed concerns that producers who take a “no antibiotics ever” approach are backed into a corner when an animal needs antibiotic treatment. The consumer’s desire to avoid antibiotics may come at the expense of treatment in the animal’s best interest, he said. If “no antibiotics ever” becomes a significant part of the food production landscape, studies should analyze and compare the effects with conventional approaches. Ms. Stepp added that organic

farmers participating in the FARM program see it as an opportunity to ensure the well-being of their animals. Antibiotic stewardship and usage evaluation criteria may apply differently to them, but the program measures outcomes, which accommodates all types of farms.

Public Comment

Kevin Kavanagh of Health Watch USA said his home state is still having difficulty controlling even common resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). Two of its major hospitals have the sixth and seventh highest number of MRSA bloodstream infections in the nation. Many of the institutions feel hand hygiene is the key to control and are focusing their efforts on this intervention. However, despite being an essential part of infection control, in the context of multidrug-resistant organisms, hand hygiene should be a backup measure; these dangerous pathogens should not be on health care workers' hands in the first place.

Formulation of optimal interventions has been clouded by both research and editorial integrity problems. For example, PACCARB heard testimony that unit-wide daily chlorohexidine bathing combined with intranasal mupirocin resulted in major reductions of blood stream infections of all causes. But in the reference studies, the main reduction was seen in commensal bacteria and yeast. In another presentation, it was asserted that this intervention could reduce uropathogens, but in the study a significant effect was not observed in high-level candiduria in women and was not effective in high-level bacteriuria in either sex.

Student nurses in the state have questioned why hospitals are approaching the MRSA epidemic differently. The excuse has been that one size does not fit all, but no one has explained why there are different sizes and how these are determined. Mr. Kavanagh strongly recommended that this Council refocus its efforts on containment and control at the facility level and emphasize surveillance and isolation/decolonization protocols similar to those adopted by the United Kingdom's National Health Service and the Department of Veterans Affairs (VA) health care system.

Steven Roach of the Food Animals Concern Trust noted the focus of speakers at today's panel and the Council's discussion quickly drilled down to prescriber practice. Mr. Roach said his organization believes more attention is needed around what is done before animals get sick. He agreed with the set of values described by Dr. Scott that contends that restrictions on antibiotic use may be inappropriate when animals need treatment. Mr. Roach encouraged PACCARB and others to think about what farms can do or what the agricultural system can do that prevents animals from getting sick in the first place. An easy example is the diets of beef cattle; when given a high-starch diet, cattle get liver abscesses that are then controlled with macrolides. Mr. Roach believes there are other options, and he asked that the Council advise the federal government to look at the broader picture and to encourage or incentivize changes.

Regarding FDA comments at this Council meeting and its concern about the duration limits of antibiotic use, Mr. Roach said it would be helpful if this Council could support FDA and encourage the agency to speed up, because it tends to move very slowly. Finally, Mr. Roach pointed out that the amount of antimicrobials authorized for emergency use for citrus greening disease is huge compared to the amounts being used in apple orchards. He proposed asking the

VA, EPA, or the Florida Department of Agriculture how much of those antibiotics were actually used in Florida, whether there is evidence of effectiveness, and whether there are signs of resistance.

Closing Remarks

Eric D. Hargan, J.D., Deputy Secretary, HHS

Mr. Hargan said Secretary Azar was unable to attend. He thanked the Council for its advice, noting that the Council's work plays a critical role in ensuring the continued availability of effective antibiotics, which are critical to the health and well-being of all Americans. He also thanked the myriad stakeholders, inside and outside of government, who are working to combat this growing public threat.

HHS is working hard to realize the vision outlined in the National Action Plan for Combatting Antibiotic-Resistant Bacteria, said Mr. Hargan. Antibiotic resistance is a complex and far-reaching issue that needs coordinated and sustained action from a variety of partners in both the public and private sectors.

Antibiotics are vital to fighting off common illnesses, such as strep throat, as well as potentially life-threatening infections. For example, over half a million Americans are brought to the hospital each year because of pneumonia. More than 90 percent of them survive, in part because of the antibiotic regimens currently available. This Council serves as an absolutely crucial part of the larger effort to ensure antibiotics remain effective and contribute to improving health care, national security, and public health.

Mr. Hargan appreciated the One Health approach to addressing the human, animal, and environmental complexities associated with the threat of antibiotic resistance, noting that the presentations today nicely reflect that holistic approach. It is not unusual to have to consider both animal health and human health in the same complex area, and it is necessary to bring a variety of stakeholders together to achieve progress in this area, he said.

HHS is working hard to provide both funding and staff investments to help build and advance a multifaceted solution to antibiotic resistance. In the agency updates, the Council heard about the great work going on throughout the department, including new research and opportunities to promote better infection prevention practices and antibiotic stewardship approaches for health care professionals. Mr. Hargan urged the audience members to read the Council's report on the significant progress in implementing the National Action Plan.

More work is ahead to make the monumental strides needed to ensure a more resilient nation, said Mr. Hargan. HHS looks to the Council for additional guidance and advice to ensure success in this mission. As a lawyer and an administrator, not a clinician, Mr. Hargan acknowledged the work of all the people in the public health arena. He said the doors must remain open to make sure that HHS hears from all stakeholders as it addresses this complex situation.

HHS has a lot of resources: over \$1 trillion dollars, 80,000 employees, and about 120,000 contractors. Yet it still requires expertise and knowledge from outside the department to address an issue this complex. Mr. Hargan thanked the PACCARB for its most recent recommendations

to Secretary Azar and said the Secretary looks forward to receiving the next set of recommendations following the September meeting.

Mr. Hargan emphasized that HHS is extremely grateful for the work of this Council. He thanked the retired, new, and continuing members for their dedication, expertise, insights, and ongoing participation with the department. He looked forward to ongoing cooperation and consultation with the Council.

Final Comments and Adjournment

Dr. Blaser thanked all the presenters for their enlightening comments and praised Dr. Apley for organizing the panels. He thanked the public for taking part and Mr. Hargan for attending. Dr. Blaser adjourned the meeting at 4:05 p.m.

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

May 16, 2018

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
Angela Caliendo, M.D., Ph.D., FIDSA
Alicia Cole
Sara E. Cosgrove, M.D., M.S.
Peter Robert Davies, B.V.Sc., Ph.D.
Ramanan Laxminarayan, Ph.D., M.P.H. (by phone)
Aileen M. Marty, M.D., FACP (by phone)
John H. Rex, M.D. (by phone)
Thomas R. Shryock, Ph.D.
Randall Singer, D.V.M., M.P.V.M., Ph.D. (by phone)
Robert A. Weinstein, M.D.

Organizational Liaisons Present

American Nurses Association

Elaine Larson, Ph.D., R.N.

Association for Public Health Laboratories

Denise M. Toney, Ph.D.

National Turkey Federation

Alice L. Johnson, D.V.M.

North American Meat Institute

Tiffany Lee, D.V.M., Ph.D., M.S.

Pew Charitable Trusts

Kathryn L. Talkington

Ex Officios Present

U.S. Department of Health and Human Services

Lynn Filpi, Ph.D. (for Lawrence Kerr, Ph.D.), Office of Pandemics and Emerging Threats,
Office of Global Affairs

Rima Khabbaz, M.D., National Center for Emerging and Zoonotic Infectious Diseases, Centers
for Disease Control and Prevention (CDC)

Jane Knisely, Ph.D. (for Dennis M. Dixon, Ph.D.), National Institute of Allergy and Infectious
Diseases (NIAID), National Institutes of Health (NIH)

Shari Ling, M.D., Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services
(CMS)

Daniel W. Sigelman, J.D., Senior Advisor, Office of Public Health Strategy and Analysis, Office of the Commissioner, Food and Drug Administration

U.S. Department of Defense

Adrian Kress, M.D. (for 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 (for Brian McCluskey, D.V.M., Ph.D.), Animal and Plant Health Inspection Service

David Goldman, M.D., Chief Medical Officer and Assistant Administrator, Office of Public Health Science, Food Safety and Inspection Service

Jeff Silverstein, Ph.D., Agricultural Research Service

Designated Federal Officer

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

Advisory Council Staff

MacKenzie Roberston, Committee Management Officer, Office of the Assistant Secretary for Health, Department of Health and Human Services

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

Mark Kazmierczak, PhD, Gryphon Scientific

Glossary of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AMR	antimicrobial resistance
APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
AST	antimicrobial susceptibility test
AVMA	American Veterinary Medical Association
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CoPs	Conditions of Participation
CUSP	Comprehensive Unit-Based Safety Program
DoD	U. S. Department of Defense
EPA	Environmental Protection Agency
FARM	Farmers Assuring Responsible Management
FDA	Food and Drug Administration
FSIS	Food Safety and Inspection Service
HAI	health-care-associated infection
HHS	Department of Health and Human Services
ID	infectious disease
IDSA	Infectious Diseases Society of America
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
QIN–QIOs	Quality Improvement Network–Quality Improvement Organizations
SHEA	Society for Health Care Epidemiology of America
USDA	U.S. Department of Agriculture
VA	U.S. Department of Veterans Affairs
VFD	Veterinary Feed Directive