PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

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

September 26, 2018

Sheraton Columbus Hotel at Capitol Square
75 East State Street
Columbus, OH 43215
Governors Ballroom A & B

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Meeting Proceedings

Welcome

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

Dr. Blaser called the meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) to order at 9 a.m. and welcomed the participants.

Overview, Rules of Engagement, and Roll Call

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

Dr. Musmar described PACCARB's charter and gave an overview of the agenda. She explained the rules governing the Council under the Federal Advisory Committee Act (FACA) and conflict-of-interest guidelines and called the roll. (See Appendix A for the list of participants.)

Opening Remarks

David Daniels, Director, Ohio Department of Agriculture

Mr. Daniels welcomed the participants and pointed out that agriculture accounts for $124 billion worth of Ohio's economy and provides one out of every eight jobs located in the state. The Ohio Department of Agriculture seeks to protect the industry and consumers and uphold laws and rules on food safety, consumer protection, and plant and animal health. To combat antibiotic resistance, agriculture and other areas need to become less siloed and communicate more. The first step is building relationships within and across agencies locally, nationally, and internationally. Antibiotic resistance is not a human versus animal health issue but a One Health issue, so continued cooperation with all, including HHS, the U.S. Department of Agriculture (USDA), the Food and Drug Administration (FDA), among others, is necessary.

As the population grows and animal production agriculture increases, the greater the issue becomes. Soil health and other components of the ecosystem are also vital concerns. More and more viruses and vector-borne diseases are changing and adapting every day, surviving harsh temperatures, morphing into deadly animal diseases, and becoming resistant to antibiotics. Individual efforts cannot succeed on their own; collaborative efforts are needed. Mr. Daniels named some of Ohio's top scientists and doctors who are on the forefront of antibiotic resistance. The department also works every day with USDA, FDA, the Environmental Protection Agency (EPA), and the Ohio Department of Health to protect animal, human, and environmental health in Ohio.

Patient Story

Rick Bright, Ph.D., Director, Biomedical Advanced Research and Development Authority (BARDA), HHS

Dr. Bright said his recent personal experience with a multidrug-resistant organism (MDRO) was "shocking" and demonstrated how much more work is needed to address antimicrobial resistance

(AMR). He contracted the MDRO from a small scratch while gardening. He began suffering symptoms and visited three urgent care clinics before he found one that would treat his wound, and that provider only agreed to culture the wound because he insisted. Dr. Bright described a stressful, frustrating, and frightening ordeal during which surgery and possibly even amputation of his thumb were considered. Finally, an ID specialist examined the wound and prescribed two new antibiotics— which were effective and prevented surgery but were also very costly and not fully covered by the insurance provider. Dr. Bright doggedly tracked down the results of the culture he had insisted be taken and was diagnosed with methicillin-resistant *Staphylococcus aureus* (MRSA). Even more concerning, Dr. Bright noted, was that he had been housed on an orthopedic ward in the hospital for 3 days while awaiting surgery, where he may have exposed others to the organism.

The experience demonstrates the need for new standard procedures, such as immediate culturing and point-of-care diagnostics in the emergency department, so providers can prescribe the right treatment. In Dr. Bright's case, this approach would have resulted in immediate, effective treatment; dramatically lower costs; much less risk of exposing others in the hospital to infection; and preservation of hospital resources. BARDA can work with PACCARB and other partners to ensure public health and security by finding solutions to AMR, Dr. Bright concluded.

Infection Prevention and Stewardship Working Group (WG) Activity

Peter Robert Davies, B.V.Sc., Ph.D., and Sara E. Cosgrove, M.D., M.S., Infection Prevention and Stewardship Working Group

Dr. Cosgrove, WG Co-Chair, and Dr. Davies, speaking on behalf of WG Co-Chair Michael D. Apley, D.V.M., Ph.D., DACVCP, presented the recommendations from the report *Key Strategies to Enhance Infection Prevention and Antibiotic Stewardship*. Dr. Cosgrove said some can be acted on immediately, while others will involve a lot of work and collaboration. The recommendations overlap and interconnect around some common themes. The report offers seven broad recommendations, with sub-recommendations for animal and human health, although there were many parallels across the two domains, Dr. Cosgrove noted. The body of the report provides a brief explanation for each recommendation. Dr. Cosgrove and Dr. Davies read aloud the recommendations and sub-recommendations.

DISCUSSION

For recommendation II-5 on developing new federal guidelines and standards, in sub-recommendation four, Thomas R. Shryock, Ph.D., suggested adding the proper name of FDA's 5-year blueprint to promote stewardship in companion animal practice and to add food animals to the description of what that document addresses. Alicia Cole suggested that in recommendation I-7 to improve training for the health care workforce, in sub-recommendation two, appropriate use of gloves should be included as well as hand hygiene, because many health care workers are not properly trained or lack knowledge about how and when to use gloves.

Dr. Cosgrove said recommendation I-4 describes rapid diagnostics for antibiotic stewardship; it should also address how they would benefit infection prevention. Aileen M. Marty, M.D., FACP, asked whether PACCARB could explore when it would be appropriate to mandate insurance coverage for a diagnostic test, and Dr. Blaser responded that the question may be considered by

PACCARB in the context of the new task from the Secretary to evaluate the National Action Plan on Combating Antibiotic-Resistant Bacteria (CARB).

Kathryn L. Talkington, pointed out that the recommendations are not prioritized. Dr. Blaser asked each PACCARB member to choose one key recommendation for the purpose of getting a sense of what stakeholder experts value (recommendation numbers are given in parentheses):

- Dr. King: Building resource capacity (6) and workforce training (7)
- Dr. Davies: Understanding prescribing behavior in veterinary medicine (II-1.2)
- Dr. Cosgrove: Eliminating siloes by developing infection prevention and stewardship approaches that involve many settings (6)
- Ms. Talkington: Developing federal policies on stewardship (5) for humans and animals
- Alice L. Johnson, D.V.M.: Promoting innovation (2, 4)
- Tiffany Lee, D.V.M., Ph.D., M.S.: Promoting diagnostic testing (4)
- Denise M. Toney, Ph.D.: Developing and using rapid diagnostic testing (4)
- Elaine Larson, Ph.D., RN: Changing the provider culture through education about stewardship (7)
- Paige Waterman, M.D., FACP, FIDSA: Requiring medical education linking it to accreditation (7)
- Brian Tse, Ph.D.: Promoting rapid diagnostics (4)
- Dennis M. Dixon, Ph.D.: Understanding etiologic diagnosis and treatment (1) and improving hand hygiene (7)
- Kent E. Kester, M.D., FACP, FIDSA, FASTMH: Developing strategies for influencing provider behavior (I-1.2)
- Dr. Shryock: Promoting innovation for animal and human health (2), as in PACCARB's report, *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic Resistance*, which urged the establishment of a National Policy and Innovation Institute for animal health.
- Dr. Marty: Promoting diagnostic testing (4)
- Helen W. Boucher, M.D., FIDSA, FACP: Building the ID workforce (I-6.4 and I-6.5)
- Randall Singer, D.V.M., M.P.V.M., Ph.D.: Developing tools to evaluate efficacy and assess return on investment (ROI) of infection prevention and stewardship programs in animal health (II-2.3)
- Dr. Blaser: Promoting rapid diagnostics (4) and expanding education (7)
- Dr. Apley: Developing programs for peer comparison to understand variability in animal health settings (II-3.3)
- Ms. Cole: Improving basic understanding of infection prevention, disease pathology, and urgency of rapid diagnostics and surveillance (7), with appropriate funding support
- Robert A. Weinstein, M.D.: Improving detection (I-2.3) and staffing requirements (I-6.3) in long-term care settings
- Neena Anandaraman: Supporting research (II-1), promoting innovation (II-2), and developing the future workforce (II-6)
- Ramanan Laxminarayan, Ph.D., M.P.H.: Developing federal policies on stewardship (5) for humans and animals

Dr. Laxminarayan added that a next step may be setting some targets, establishing milestones, and estimating the costs of implementing the recommendations.

Vote

PACCARB members voted unanimously to approve the report with the revisions suggested to recommendations 4, II-5.4, and I-7.2.*

New Task from the HHS Secretary

Alex Azar, II, Secretary, HHS

Via a prerecorded video, Sec. Azar said HHS is working to address antibiotic resistance at the highest levels of the federal government in concert with the private sector and with foreign governments. The dedicated efforts of many across the U.S. government and in the private sector have resulted in a framework for addressing this challenge, but there is more work to do. Part of that framework is the National Action Plan on CARB, which was developed by the Interagency CARB Task Force for 2015 through 2020. Everyone involved in this fight deserves credit for the fact that the United States is on target to meet most of the milestones set.

Now, it is time to look over the horizon to a National Action Plan for 2020 through 2025. Sec. Azar formally charged PACCARB with developing a report about areas of concern around antibiotic resistance that have emerged since the first National Action Plan. More details about the nature of this report and the scope of this task will be provided by the Interagency CARB Task Force. Sec. Azar said antibiotic resistance is an ever-evolving threat, and PACCARB's expertise is vital to helping HHS and the entire federal government understand it.

Sec. Azar looked forward to reviewing PACCARB's report, Key Strategies to Enhance Infection Prevention and Antibiotic Stewardship. He thanked PACCARB for its diligent and dedicated work, adding that he values PACCARB's expertise and insight in helping to keep the health care system, fellow citizens, and the entire world safe from antibiotic resistance.

Discussion

Dr. King noted that the Secretary's letter to PACCARB describing the charge stressed that PACCARB should hold a stakeholder meeting to bring multiple voices in to the conversation. Dr. Blaser explained that the National Action Plan is organized into five pillars, and PACCARB was asked to provide three to five recommendations within each of the pillars. The Council will establish a new WG to address the charge and develop the report to the Secretary, which is due August 1, 2019. Dr. Marty pointed out a new area of concern to address: the recognition of a whole new set of mechanisms for AMR. In addition, Dr. Marty said that as a medical educator in medical schools, she was appalled at the lack of attention to antibiotic resistance and stewardship in medical school curricula, which is important for the future of this issue.

The Environment and One Health

Ramanan Laxminarayan, Ph.D., M.P.H., and Randall Singer, D.V.M., M.P.V.M., Ph.D.

* Angela Caliendo, M.D., Ph.D., FIDSA, and John H. Rex, M.D., voted to approve the report by proxy via Dr. Musmar.

Dr. Singer said the environment plays a critical role in the presence, persistence, and dissemination of AMR and antimicrobial residues. It is a key link between human and animal health and it is one of the three components of One Health. The environment and its impact on health remain poorly understood and understudied. Dr. Singer hoped the following questions would be addressed by today's presentations:

- What are the health risks associated with AMR and residues in the natural environment?
- How do we assess those potential health risks?
- How should we be measuring AMR in the natural environment—especially in an age of metagenomics?
- How do we assess the environmental sustainability of strategies that are intended to minimize antibiotic use and to mitigate AMR?
- What are the economic effects of AMR in the natural environment?

Panel Session 1: Environmental Residue and Human Exposure

OVERVIEW OF ANTIBIOTIC RESISTANCE IN THE ENVIRONMENT

Jo Handelsman, Ph.D., University of Wisconsin-Madison (by phone)

Using new analytic techniques Dr. Handelsman and colleagues found the same resistant genes in soil in West Madison, WI (a new clade of acetyltransferases) and Alaska—despite any clear connection or common relevant features between the two areas. They also found bifunctional proteins that confer antibiotic resistance; these proteins have two active domains and seem to influence each other's activities. Both of these findings suggest that the environment harbors genes that have not been and might never be seen in the clinic. Another resistant gene was first identified in samples from Puerto Rico but then seen throughout the metagenomic database; it was linked to genes found only in archaea, not bacteria.

From these studies, Dr. Handelsman summarized some key findings:

- Related genes can appear across vast geographic distance that might or might not be influenced by humans.
- Bifunctional resistance proteins might represent a fusion of resistant genes.
- Resistant genes may emerge as a result of interdomain gene transfer.

Dr. Handelsman outlined key findings from others' research:

- Selection for multidrug-resistant bacteria from soil and polymerase chain reaction (PCR) amplification yielded resistance genes with high sequence identity to genes found in clinical settings.
- In 30,000-year-old permafrost, researchers found ß-lactamases with medium to very high identity to previously known genes.
- A cave-dwelling bacterium was discovered in a cave very deep in the earth and was thought to be isolated there for about 4 million years. The isolate demonstrated multidrug resistance and five new resistance determinants that do not have modern homologues.

Dr. Handelsman concluded that the environment contains new motifs for antibiotic resistance that should be considered as a potential source for antibiotic resistance not yet seen in the clinic. It is unclear where or how all of the resistance determinants seen in the clinic actually evolved to their current conditions.

Geospatial Distribution of AR Genes in U.S. Rivers and Streams
Jay Garland, Ph.D., EPA

Dr. Garland described EPA's mission and organization and its research, which includes annual National Aquatics Resource Surveys (NARS). Analysts collect millions of water samples from thousands of U.S. sites to identify antibiotic-resistant genes (ARGs). Because the agency has limited resources, it focuses on seven genes of concern. Hotspot analysis shows high rates of two genes, *intl1* and *sul1,* from the Northeast to the Midwest, with some occurrences the Southern coastal regions and very little in the West. In contrast, the gene *tetW* is most common in Ohio and the upper Midwest. EPA's studies allow it to see when ARGs appear in concentrations higher than background rates are found in the natural environment and to quantify the increase.

Dr. Garland said EPA also looks at the drivers of the patterns of occurrence, bringing in other data from water quality testing, evaluations of fish and algae, etc., and combining them with other information, such as human activity and agricultural population density. Dr. Garland hoped to have results from compiled data soon. Dr. Garland noted that hotspot analysis for fecal contamination shows a distinctly different pattern than AMR, and he hoped to conduct more analyses to provide comparative information. As next steps, his office will analyze samples from the 2015 Coastal Condition Assessment and the 2018–2019 NARS and continue to develop predictive models of drivers.

In addition, EPA is conducting research on human exposure, particularly the risks from recreational exposure, using predictive modeling, which will inform regulatory decisions. In addition to its national-level assessment of watersheds, EPA also analyzes wastewater in the same manner and focusing on potentially high-strength streams of waste (e.g., hospitals).

Antibiotic Use in Organic vs. Conventional Disease Management
Sally Miller, Ph.D., The Ohio State University

Dr. Miller said copper is used more commonly than antibiotics in agricultural crops. Its use raises concerns about potential co-selection of resistance to metals and antibiotics. Copper is frequently used by organic farms and has a long history of agricultural use. Multiple formulations have been developed, some of which are intended to reduce the amount of copper in the environment. Copper is widely used in plant protection—although not for large acreage crops such as corn, soy beans, and grains—because there are so few ways to control bacteria.

For disease management, conventional agriculture can use preventive and rescue treatments, such as raising disease-resistant varieties (e.g., genetically modified organisms [GMOs]); employ farm practices such as crop rotation and soil improvement to prevent pathogen buildup; and use biopesticides and other products. Organic farms face restrictions on sulfur- and copper-based pesticide use and outright prohibitions on synthetic fungicides, pesticides, and GMOs. In 2014, the global market for fungicides was $11 billion; for copper-based fungicides alone, it was $970 million. Resistance to fungicides and bactericides, including copper, is common.

Copper has many limitations. It is phytotoxic at a low pH. It has no systemic activity and works only on contact, so it is not effective for infected plants. Because copper washes off with rain or watering, crops require frequent reapplications; the run-off can cause toxic buildup in the soil. Conventional growers have some better, safer fungicidal options to choose from, but organic growers do not. On the other hand, copper is the best available bactericide for most crops (and antibiotic use is highly restricted) and is relatively inexpensive.

The European Union (EU) has drastically reduced copper use. In the United States, the National Organic Standards Board acknowledged copper's harm to the environment but determined that its continued use is necessary to protect many crops. Some mechanisms for reducing copper use include breeding for disease resistance (possibly using gene editing), improving tactics for bacterial disease management, seeking more effective natural competitors (perhaps through microbiome research), and more use of protected culture (e.g., covers and greenhouses).

BEES AND RESISTANCE

Kasie Raymann, Ph.D., University of North Carolina

Dr. Raymann said honeybees pollinate $15 billion worth of U.S. crops each year, but the number of honeybees and hives have declined significantly since 2006. Multiple factors are thought to be involved in the decline, and Dr. Raymann believes that antibiotics may play a role. Antibiotics have been used in beekeeping since the 1950s; they were not regulated until 2017. Dr. Raymann's research details how tetracycline kills bees' beneficial gut bacteria, and the microbiome disruption did not resolve after the drug was discontinued. When these bees returned to the hive, they had much lower survival rates than untreated controls. The findings held true in a laboratory setting and among laboratory-raised, untreated, germ-free bees, which led Dr. Raymann to conclude that the disruption of the microbiome, not the antibiotic, was the cause of death. In another study, she found that tetracycline increases bees' susceptibility to pathogens.

The United States uses more antibiotics than other countries, resulting in a higher prevalence of antibiotic resistance in bees. The two most common pathogens, American foulbrood and European foulbrood, have developed resistance to antibiotics, which has led to the introduction of new antibiotics in beekeeping. In 2006, the agricultural industry began using tylosin in bees—which is coincidentally when the major population declines began.

Dr. Raymann noted that antibiotic resistance can be spread by bees to the environment and vice versa, and the antibiotic residue in bee products can cause resistance to spread to humans. She offered some suggestions to combat the spread:

- Use antibiotics only as a last resort in beekeeping.
- Educate veterinarians, beekeepers, and the public about proper use and impacts of antibiotics in beekeeping.
- Push for regulations on antibiotic residues in U.S.-derived and imported bee products.
- Support and incentivize research on alternatives to antibiotics for bee diseases.

CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE (CPE) FROM WASTEWATER DISSEMINATED IN THE ENVIRONMENT

Tom Wittum, Ph.D., The Ohio State University

Dr. Wittum said CPE are most frequently found in hospitalized patients, then discharged with hospital waste, where municipal wastewater treatment systems reduce but do not eliminate them. Thus, the bacteria make their way into nearby waterways; are transported by vectors such as fish, wildlife, or irrigation systems; and wind up in animal agriculture settings, where they pose a risk to animals and humans.

To assess the presence of CPEs, Dr. Wittum and colleagues gathered fully treated effluent and upstream and downstream samples of discharge into surface waters from 50 wastewater treatment plants, about half metropolitan and half rural, then cultured the samples for carbapenem-resistant Enterobacteriaceae (CRE). They detected CRE in 15 samples (30 percent); of those, 13 samples came from metropolitan plants and two came from rural plants. Dr. Wittum hypothesized that the concentration of health care facilities in metropolitan areas contributes to the increased CRE detected in samples. Dr. Wittum expected to see more CRE-positive samples from the East Coast, where the most common genotype (KPC) emerged, but they mostly appeared in the center of the country, with a few in the West.

The findings laid the foundation for an ongoing intensive study of a local wastewater treatment plant that serves Columbus, OH, and discharges into the Scioto River. The team collected samples at several points upstream and downstream, including treated effluent. Their analysis from the first year of the project found nearly 250 isolates, about 200 of which were *Enterobacter* or *Klebsiella* species—the most common CRE bacteria and genotypes seen in diagnostic laboratories and human health care environments around the country. Dr. Wittum noted that a large number of isolates had *Escherichia coli* genotypes, even though a diagnostic isolate with that genotype has never been reported in Ohio. One hypothesis is that they came from the biofilms in the wastewater system.

While CPE were most common in untreated influent and least common upstream, they could be detected in samples at any point. Most were of the KPC genotype. Dr. Wittum's team has been recovering isolates from fish in the Scioto River. The top three sites for recovering CRE isolates were within 25 km upstream or downstream of the treatment plant—again with genotypes commonly found in hospitals. Downstream, 50–135 km from the plant, no CRE was detected in fish. Dr. Wittum believes that there is a risk that these organisms in the water will be introduced into animal agricultural populations, but he did not yet have that evidence.

DISCUSSION

In response to Dr. Blaser, Dr. Garland said a next step in EPA's analysis is to compare the patterns of ARGs to agricultural practices to see whether there are links that relate to human activities. By looking nationally, he said, analysts can see the impact of changes in practice.

Also in response to Dr. Blaser, Dr. Miller said copper washes off easily, so it is unlikely that humans get much copper residue when eating produce, and any residue is generally below federally accepted levels. Dr. Raymann said there are likely antibiotic residues in bee products; she said monitoring is needed and may be informed by EU practices.

Dr. Laxminarayan asked for more detail about the potential risk to animal health in agricultural settings from resistant genes in water. Dr. Wittum said that extended-spectrum cephalosporins are widely used, so the presence of cephalosporin-resistant pathogens would pose an animal health issue. The United States does not use carbapenems in agriculture, and CRE genes are not present in U.S. animal agriculture. But, if carbapenem-resistant organisms from human health care were introduced into agriculture, they would be resistant to all ß-lactams, including cephalosporins, posing animal health, economic, and food safety risks.

In response to Dr. Laxminarayan, Dr. Raymann said the amount of tetracycline used in bees is difficult to gauge. Tetracycline is widely available online. Beekeepers mix the tetracycline powder with sugar, powdered or in syrup form, and spread it on the hive, so it is difficult to determine how much the bees ingest. Before FDA's 2017 regulations, Dr. Raymann estimated, some beekeepers used the antibiotic cautiously and others frequently. She hoped new regulations would limit how much antibiotic could be used and how often.

Dr. Lee asked whether there are recommended withdrawal times following antibiotic use in bees that would impact the likelihood of residues in bee products. Dr. Raymann said that because the tetracycline is spread all over the hive, the antibiotic cannot be removed. There are some regulations about the use of pesticides, but the antibiotic regulations are still new.

Dr. Marty asked whether the use of antibiotics in bees affects the honey produced, particularly, the immune-regulating and antibiotic properties of honey. Dr. Raymann said such effects are possible, but the question has not yet been studied.

Dr. Kester asked why, if tetracycline and other antibiotics have been in use for more than 50 years, hives only began showing resistance in the past 10–15 years. Dr. Raymann responded that some foul brood strains are resistant and some are not, so the development of antibiotic-resistance is not well understood. She pointed out that the bee's microbiome has a lot of resistance to tetracycline now, and it appears that the introduction of new antibiotics is very detrimental to the microbiome because of the lack of resistance in the bee gut. Dr. Blaser cited a study of tylosin in mice that demonstrated co-selection for resistance beyond the drug's spectrum of activity. Dr. Raymann added that when American foul brood is found in a hive, it is not treated with antibiotics. Rather, that hive and all the hives near it are burned. The bee may develop resistance through exposure to bee gut bacteria over time, rather than direct exposure to the antibiotic.

Dr. Singer wondered why EPA's data showed such low levels of resistant genes in the West. Dr. Garland said population density may be a driver.

Dr. Cosgrove asked whether some of the resistant genes found in water could originate from the general population (outside of hospitals), such as people with the NDM-1 gene who travel a lot. Dr. Wittum responded that the resistance genotypes he found were far more diverse than expected, which supports Dr. Cosgrove's hypothesis that they are not all coming from hospitals.

Dr. Cosgrove asked what proportion of isolates demonstrate genes of resistance. Dr. Wittum said he did not yet have good data yet on the specific concentrations.

Dr. Shryock asked the presenters what PACCARB should spend more time evaluating. Dr. Garland said national surveys are helpful to understand the current state and anticipate the future. He called for more robust analyses of environmental reservoirs and hotspots of production, particularly related to wastewater, at a national scale. Dr. Miller said antibacterial resistance is less important in crop-based agriculture, but antifungals are critical, particularly the ASO fungicides, because those are used in humans and animals and widely in crop production. Europe is sounding the alarm about these fungicides, but it has not been discussed much in the United States. Michael Craig said the Centers for Disease Control and Prevention (CDC) is monitoring resistance to fungicides.

Dr. Raymann suggested more stringent regulations on antimicrobial residues in bee products, particularly imported products. She also recommended more education for veterinarians about antibiotic use in beekeeping. Dr. Wittum agreed with Dr. Garland on the need for more surveillance data. He also suggested seeking a better understanding of the drivers of antibiotic use in veterinarian medicine and agriculture. Dr. Handelsman said more assessment of antibiotic residues in food is needed. She also expressed concern about the impact of antibiotics on the microbiome, which may affect susceptibility to disease, pointing to recent data about the effect of glyphosate on the microbiome.

In response to Dr. Marty, Dr. Miller elaborated that copper is mediocre as a fungicide, and newer, better, safer products are available for conventional agriculture but not organic farms. Newer products must meet very strict standards that demonstrate low risk to humans, animals, and the environment. A lot of fungal disease could be treated effectively with the newer formulations, rather than using frequent copper application. Copper does not degrade in soil, which likely increases the danger of co-selection for resistance, said Dr. Miller.

Panel Session 2: Detection and Control of Antibiotics and Antibiotic Resistance in the Environment

Resistance Genes Measurement

Noelle Noyes, D.V.M., Ph.D., University of Minnesota

Dr. Noyes explains that metagenomics allows investigators to identify resistant genes without prior knowledge about which bacteria or genes might be present or any need to select for specific organisms, unlike culture- and PCR-based methods of detecting resistance. Metagenomic enrichment increases the sensitivity of the approach by capturing all of the resistance genes or other sequences that may be present within a given sample, enriching them, then sequencing them. The process yields a comprehensive view of the resistome. This method could help establish a baseline assessment of genetic resistance that occurs in natural environments. The sequenced samples are compared with known resistance gene DNA sequences to determine their relative proportions within the sample, and the result is the resistome.

Sampling cows on the day they were introduced into a feedlot—some that were given antibiotics on the day arrived and some that were not—and again 11 days later, Dr. Noyes and colleagues found no differences in the resistome between the treated and untreated cows. However, they did see dramatic changes in the resistome of all the cows between day 1 and day 11, which could be attributed to the stress experienced by the cows, change in diet, and exposure to other cows. Dr. Noyes said antimicrobial usage is just one aspect of animal and environmental health; numerous factors affect the animals and the environment and can put pressure on the bacteria.

Dr. Noyes' team went on to collect samples from the same cows all the way through the production process, including carcasses and beef products. During the feeding period, diversity of the resistome decreased. Resistance to tetracycline and glycosides persisted, which may suggest that drug use is negatively affecting diversity, but that hypothesis is incomplete, as genes resistant to another drug not used in livestock reduction also persisted. In the samples from slaughtered cows, the team found no resistance genes, which means the burden of resistance is reduced in the finished product. Dr. Noyes said these findings illustrate different implications for public health and the need for more practical understanding of the resistome. She concluded that measuring environmental AMR is relatively easy, but interpreting the findings in the context of animal, environmental, and human health requires cooperation and partnerships.

DETECTION OF ANTIBIOTIC METABOLITES

William Arnold, Ph.D., University of Minnesota

Dr. Arnold described the complexities of detecting antibiotic chemicals in the environment and his methods for extracting antibiotics from water and sediment samples. Sediment samples allow researchers to look at the layers of sediment deposits over years and detect the presence of antibiotics over time. Some samples from Minnesota lakes go as far back as 1865. Dr. Arnold presented findings from three waterways in Minnesota, each with different inputs.

The samples show increasing concentrations of ofloxacin, which was introduced in 1980, in two of the lakes sampled, with higher levels in the lake that gets the most direct wastewater inflow. Sulfapyridine, an old antibiotic that is used exclusively in humans, shows up in water beginning around 1940, when it was introduced. The concentrations are lower than ofloxacin, possibly because sulfapyridine is used less often than ofloxacin or because it degrades in the environment differently. Although it was taken off the market in 1980, sulfapyridine shows up in sediment samples through 2015. Dr. Arnold said the sulfapyridine may be coming from the anti-arthritis drug sulfasalazine, which has a sulfapyridine metabolite.

Looking more closely at one lake that has significant wastewater inflow and agriculture activities within the watershed, Dr. Arnold's team found antibiotics for human use in sediment samples, and often the synthetic and semisynthetic compounds were much more prevalent than naturally produced compounds. Agricultural-use antibiotics were detected in much lower concentrations, although, Dr. Arnold noted, it may take longer for those antibiotics to migrate into waterways from the soil on farms than human-use antibiotics that are deposited directly through wastewater. Further assessment showed that the presence of antibiotics correlates with the presence of resistance genes for those antibiotics. Dr. Arnold believes wastewater is likely the predominant source of the antibiotics and the resistance genes, so more attention should be paid to wastewater and AMR. This research is continuing on a broader scale and may yield information for designing and engineering interventions as well as policymaking, he concluded.

ENVIRONMENTAL ASSESSMENT AND ANALYSIS
Amy Pruden, Ph.D., Virginia Polytechnic Institute and State University

Dr. Pruden illustrated the correlating patterns of antibiotics and ARGs in waterways as human use and agricultural use come into play. That finding led her to think of ARGs as contaminants, which makes sense because bacteria have the unique ability to share genes. Targeting ARGs directly and thinking of them as contaminants offer some advantages in how the environment is assessed and treated. Dr. Pruden noted that the United Nations has designated antibiotic resistance as a top priority, and water is the common thread for inputs and exposures that contribute to resistance.

Building on the metagenomics techniques described earlier, Dr. Pruden's laboratory created a platform that applies a deep learning algorithm to identify ARGs, which is one of many novel methods to assess resistance. A global metagenomic survey found the highest rates of ARGs in Hong Kong and India and the lowest in Sweden (which has been proactive in addressing AMR). Another assessment indicated that advanced wastewater treatment approaches appear to minimize pathogens and antibiotic resistance.

A study of ARGs at critical control points in agricultural and animal food production (so-called farm to fork) found that total numbers of ARGs in manure of cows treated with antibiotics, for example, decreased over time (120 days) to levels similar to untreated cows, but those measurements do not give good insight into risk of resistance genes in the environment. Dr. Pruden's team collected metagenomic data and ranked the resistome risk from different sources. Hospital sewage carried the highest risk and treated wastewater effluent the lowest. Applying these findings to the farm-to-fork study, Dr. Pruden said, suggests that the manure from treated cows would still pose an elevated resistome risk 120 days later.

Dr. Pruden echoed the calls for more environmental monitoring, using appropriate sampling and experimental designs, to understand the baseline or background levels of resistance. A number of targets could be monitored, but the selected targets should be meaningful and inform risk assessment. Finally, more discussion is needed between scientists and policymakers to determine what, where, and when to monitor.

ROLE OF INDUSTRY TO MITIGATE ENVIRONMENTAL AMR
Gabrielle Breugelmans, Ph.D., Access to Medicine Foundation

Dr. Breugelmans said her organization seeks to incentivize the pharmaceutical industry to do more to provide access to essential medicines and other products to people living in low- and middle-income countries. It recently published its first Antimicrobial Resistance Benchmark, an independent comparison of pharmaceutical companies' efforts to address AMR. The Foundation is independent and funded by the governments of the United Kingdom and the Netherlands. The Benchmark encourages competition among companies to implement best practices and holds them accountable to their commitments to tackle AMR. It tracks three types of companies: large, research-based pharmaceutical companies, generic drug manufacturers, and biotech companies working on pharmaceuticals.

In 2016, more than 100 companies signed a commitment to reduce environmental pollution from antibiotics and support the One Health approach to prudent and responsible antibiotic use; later that year, a subset of those companies created an industry roadmap for combatting AMR. The Benchmark's metrics for manufacturing and production align well with the goals outlined in the industry roadmap. The large pharmaceutical companies tend to perform better on these metrics than the generic manufacturers. For example, the large pharmaceutical companies not only have environmental AMR risk-management strategies at their own plants but also extend those strategies to third-party sites and, in some cases, to external waste treatment plants. Most of the companies that have such risk-management strategies disclose them publicly, but no company discloses its limits or levels of antibiotic discharge.

At about the same time the Benchmark was published, the AMR Industry Alliance published a new antibiotic manufacturing framework and discharge targets that recognize the pharmaceutical industry's role and the need for appropriate management. However, their audit reports will remain confidential. The Access to Medicine Foundation believes the industry should adopt these targets and apply them across the supply chain but that companies should disclose more information about antibiotic discharge. Governments should explicitly include environmental standards in their assessments of Good Manufacturing Practice and include "green" criteria in antibiotic procurement. Academia should collaborate with government to refine the evidence base and work with companies and governments to improve environmental surveillance.

DISCUSSION

Mr. Craig described the CDC's AMR Challenge—a year-long effort to encourage stakeholders, including companies, governments, foundations, and nongovernmental organizations, to make formal commitments to address AMR. The launch event in New York City was sponsored by several high-profile philanthropic organizations and garnered more than 100 commitments from diverse sectors. CDC is working with stakeholders to ensure that their voluntary efforts are measurable, time-limited, and accountable.

Mr. Craig noted that a meeting on environmental AMR issues in Vancouver in April 2018 included a focus on pharmaceutical runoff. Since then, CDC has been talking with the AMR Industry Alliance about setting discharge limits, which the Alliance announced at the AMR Challenge launch event. Mr. Craig said one of the world's leading experts on this topic indicated he is encouraged by the Alliance's targets. Many questions have yet to be resolved, but CDC sees the announcement as a strong commitment and appreciates the Alliance's transparency.

Dr. Marty asked Dr. Pruden whether Sweden has adopted measures for addressing AMR in water that the United States should consider. Dr. Pruden said she did not know, but a Danish researcher is leading a broad sewage resistome survey to determine which policies are having a measurable impact. She added that it can take years to see the impact of policies. Mr. Craig pointed out that Sweden uses about one third the amount of antibiotics as the United States, which likely affects the amount seen in the environment.

Dr. Marty asked what tools are available to pharmaceutical companies to help them improve access to and stewardship of their new antimicrobial products. She also wondered what incentives and regulations are used by federal governments to encourage access to and stewardship of new antimicrobials. Dr. Breugelmans said her Foundation asks pharmaceutical companies to consider access early in the product development stage. It also addresses equitable pricing and the company's use of salesforce incentives that encourage overselling.

Dr. Boucher pointed out that three of the high-performing large pharmaceutical companies in the Benchmark have stopped producing anti-infectives, which raises concerns about the capacity of smaller companies to lead efforts to reduce AMR. Dr. Breugelmans said governments should consider incentives to encourage the large companies to continue producing antimicrobials.

Dr. Blaser asked Dr. Pruden to elaborate on the significance of the findings of the Global Metagenomic ARG Survey. She said the survey highlights the need for ways to better understand the risk that ARGs pose, because so many exist and may pose no problems. One approach may be to mine the data for rare genes.

Ms. Talkington asked the presenters what policy options should be considered to mitigate the impact of antibiotics on the environment. Dr. Pruden suggested first looking at immediate fixes, such as integrating current wastewater treatment technologies as plants are upgraded or as water recycling projects are initiated. Dr. Arnold added that, as water reuse becomes more common, antibiotics and resistance should be addressed through new policies and regulations around reuse. Technologies exist, but they require money and will to implement. Dr. Laxminarayan said Dr. Arnold's finding that an anti-arthritis medication is the potential source of antibiotic in water raises the question of whether unexpected sources that may be affecting the microbiome are being overlooked.

Dr. Laxminarayan asked the presenters to advise on where policymakers should focus their efforts to curb antibiotic residue in wastewater. Dr. Noyes cautioned against making changes before the problem is fully understood; she advocated for putting more resources into surveillance. Dr. Arnold agreed that more information and more granular data are needed. He also suggested investing in infrastructure in anticipation of the need for more clean water. Dr. Pruden said the potential for background resistance to become clinically relevant is concerning, so more monitoring is needed to better understand the circumstances that lead to that change and also to target some antibiotic levels. She said there has been a lot of monitoring of pharmaceuticals in water but little monitoring of resistant bacteria and resistance genes. Mr. Craig said all the presenters indicated that resistance can be measured in many ways and is seen throughout the environment. He hoped policymakers would focus on what has a relevant impact on human and animal health.

Dr. Singer wondered whether researchers can assess mutations as part of understanding the resistome. Dr. Noyes said such analysis could be undertaken with the current data, but software applications are needed. Dr. Pruden added that the costs and resources required are a concern. Dr. King asked whether presenters had innovative recommendations for research or policy. Dr. Noyes proposed creation of a method for tagging and tracking individual genes as they move across systems so that researchers could follow them through physical space and time. She said sequencing data might contain that information. Dr. Arnold said he would like to talk with drug designers about what happens to drugs as they break down into the water and environment. Dr. Pruden suggested focusing on improving the use of antibiotics so that they reach the people who need them. Understanding critical control points and where the antibiotics and ARGs end up could help with preventing evolution and spread of resistance, she added. Dr. Breugelmans said more transparency from industry would contribute to better understanding.

Panel Session 3: Public Health Risk, Impact, and Global Implications

HUMAN HEALTH RISK ASSESSMENT

Nicholas Ashbolt, Ph.D., University of Alberta

Dr. Ashbolt described how quantitative microbial risk assessment (QMRA) can help address questions about AMR, such as how to determine acceptable discharge limits. The process gathers input from scientific evidence and feeds it into a model with a target. Dr. Ashbolt pointed out that focusing only on wastewater and drinking water treatment is not sufficient, because pathogens can grow and ARGs can amplify in the environment after treatment.

In applying QMRA to AMR, the first step is to determine the reference list of pathogens, ARGs, resistomes, or some combination, perhaps relying on defined sources, such as the World Health Organization's (WHO's) priority list of pathogens. The analysis must select either environmental pathways of exposure or focus on hotspots, and local, national, and international aspects must be considered. Pinpointing dose-response is particularly problematic for AMR, because the genes might come with virulence factors, so the organisms might have a higher probability of infection and illness. Quantitative evidence can come from measures of the increased human health burden. Finally, a benchmark level must be determined to get a sense of the goal, and infections might be a good starting point.

Some data come from published literature and groups of experts, but understanding the nature of pathways and scale of the problem requires input from stakeholders. Dr. Ashbolt explained that conceptual models and Bayesian networks are used to collect missing information. Bayesian networks are less subject to bias than other approaches. They can be used to work backward to determine, for example, the likely cause of an AMR infection. They can incorporate qualitative and quantitative data and apply artificial intelligence to mine the data, which can reveal hidden variables. Dr. Ashbolt presented a theoretical, high-level model that indicates what variables could be targeted for intervention to reach goals set for human exposure and risk, such as pharmaceutical and hospital effluent or wastewater treatment. He concluded that the Bayesian network approach provides a formal mechanism for gathering evidence-based data in a less biased way to make better decisions on what levels might be important to target at various control points throughout the whole system.

ENVIRONMENTAL SUSTAINABILITY IMPLICATIONS TO FOOD ANIMALS RAISED WITHOUT ANTIBIOTICS

Matthew Salois, Ph.D., American Veterinary Medical Association

Using broiler chickens as an example, Dr. Salois described the unintended consequences of raising food animals without antibiotics. He emphasized that "sustainability" involves not just environmental health but also economic viability (e.g., food affordability) and social responsibility (e.g., animal health and welfare). Good policy should seek to balance these three pillars. Some important factors to consider around sustainability are population growth and increasing demands for animal products; loss of animals to disease; and limited natural resources—and they will be addressed by gains in efficiency in production, Dr. Salois noted.

In terms of animal health and welfare (part of the social responsibility pillar), Dr. Salois said that, starting around 2013, mortality among broiler chickens began increasing for the first time in 90 years, which correlates with significant increases in the number of chickens raised without antibiotics. Drilling down to compare different types of approaches to antibiotic use, data show that those raised without antibiotics have higher morbidity and mortality rates than those raised with conventional approaches. Regarding the environmental pillar, Dr. Salois pointed to the inefficiencies (e.g., increased use of resources) involved in raising chickens without antibiotics, and he estimated that these farms would have to raise hundreds of millions more birds to meet current meat demands. The additional birds would require more feed and water and produce more manure, and the process would eat into finite natural resources.

Economic considerations are affected by the premium that consumers have been willing to pay for chicken raised without antibiotics, although the premium is decreasing. Dr. Salois said that more than half of the supply of chickens is raised without antibiotics, but conventional growers have the lion's share of retail sales (90 percent). That glut of chickens raised without antibiotics is contributing to the declining premiums. Despite the fact that 60 percent of consumers claim to understand how chickens are produced, they hold a lot of misconceptions about the use of antibiotics, hormones, and steroids, and there is also a lot of confusion about what poultry labels on packaging really mean.

ECONOMIC EFFECT OF ENVIRONMENTAL EXPOSURE TO AMR

Ramanan Laxminarayan, Ph.D., M.P.H., Center for Disease Dynamics, Economics, & Policy

Dr. Laxminarayan explained the complexity of determining where to invest resources so that they will have the most impact on preventing the effects of AMR. To address some of the many questions, Dr. Laxminarayan and colleagues combined multiple data sources and found that consumption was a poor predictor of resistance. Stronger governance and better infrastructure were correlated with less resistance, while higher health expenditures and higher education levels correlated with more resistance. Thus, consumption remains an important factor but is just one of many things that drives resistance.

A CDC study of water coming in to health care facilities in India (where microbial contamination of such water remains a concern) looked at the costs of interventions in different clinical scenarios. It concluded that interventions for water can cost $47,000 to $127,000 to avert a single death; by comparison, the cost of using malarial drugs to avert one death ranges from $2,000 to $5,000. From an economic standpoint, improving water and sanitation is an expensive and inefficient way to address AMR and disease. Such approaches are important for overall hygiene and other public health priorities. Water interventions are needed to facilitate infection prevention and control, but they are not sufficient in themselves. Sanitation interventions had only a marginal positive impact on health-care-associated infections. Water-based interventions are more cost-effective than non-water-based interventions.

Another study looked at the timing and exposure to antibiotics and the likelihood of having resistant bacteria in the gut, then correlated those events to childhood obesity. It found that 69 percent of children were exposed to antibiotics in their first year of life, and that was associated with increased rates of obesity, with broad-spectrum antibiotics playing a significant role in the association. One in five school-aged children in the United States is obese, and the average lifetime cost of obesity is $17,000. Even a 5 percent increase in childhood obesity in this country could add more than $9 billion to overall lifetime costs. Dr. Laxminarayan said these findings underscore the need to look at impacts of AMR more broadly. He concluded that there are a lot of avenues to pursue, and the economics of them are unclear.

DISCUSSION

Dr. Blaser wondered whether there is a middle ground between conventional chicken production and raising chickens without antibiotics that could better balance the costs and benefits. Dr. Salois said the regulatory environment could dictate a middle ground. For example, ionophores are not used in humans and could have preventive health benefits for chicken producers. They are classified as antibiotics in the United States but not in Europe.

Dr. Blaser asked what can be done to improve chicken mortality rates, such as breeding for disease resistance. Dr. Salois said growers are adopting management approaches to decrease mortality rates, and many options are available for keeping chickens raised without antibiotics healthy, but there are a limited number of alternative treatment options. Breeding for disease resistance takes longer, and Dr. Salois was not aware of any recent innovations in that area.

Dr. Shryock asked how to gather the evidence and answer the questions needed to begin to apply QMRA. Dr. Ashbolt said the first step is to construct a Bayesian network model, with help from stakeholders, to determine what the variables are and their impacts on the target. He emphasized the importance of bringing experts from different fields together to map out the sensitivities and the potential ramifications of various interventions.

Mr. Craig noted that the study finding that consumption is a poor predictor of risk highlights that even if prescribing practices were perfect, AMR would still be a problem. Moreover, it highlights that focusing on any one area will not be enough.

In response to Ms. Talkington, Dr. Salois said the premium price for chickens raised without antibiotics has decreased probably because of the increased supply. Prices remain fairly high for breast meat in the U.S. market, but thighs, wings, and other parts are exported because of low domestic demand, and that reduces the premium. In addition, Dr. Salois said, the labeling for chickens raised without antibiotics gives consumers the impression that antibiotics are a negative. He said it is not easy to distinguish consumer-driven preferences from the impact of marketing. Ms. Talkington said there may be important lessons from improved management practices that could be applied across food production.

Ms. Talkington asked Dr. Laxminarayan to elaborate on whether to prioritize government interventions and infrastructure improvements as mechanisms to reduce resistance. He said his study emphasizes the need to control transmission where possible.

Dr. Marty asked for suggestions on rebranding good, safe solutions that are affected by negative perceptions or misperceptions. Dr. Salois responded that the solution may begin with rebuilding trust between consumers and producers by increasing transparency. In addition, he called for more education, noting that less than 1 percent of the population now works in agriculture.

Dr. Weinstein asked about levels of per capita consumption of animal protein in America compared with other countries and the potential relationship to the obesity epidemic in the United States. Dr. Salois did not have consumption statistics on hand, but he noted that despite the obesity problem, the United States also faces problems with childhood malnutrition and food insecurity. In countries with emerging economies, the increased consumption of animal proteins has played a role in healthy cognitive development.

Dr. King noted that the World Organisation for Animal Health (OIE) has a lot of data from the assessments it conducts in 180 member countries. With that evidence base, Dr. King asked, what cost-effective interventions could be recommended, particularly for low- and middle-income countries, around animal health to reduce AMR. Extrapolating from a human health perspective, Dr. Laxminarayan said infection prevention, biosafety, and biosecurity at the highest levels are effective but expensive. As lower-income countries grow and erect new facilities around large-scale agricultural production, there is an opportunity to build in effective infrastructure.

Dr. Salois added that biosecurity is a positive way to reduce burden. However, he noted a paradox: U.S. consumer demand for eggs from cage-free chickens is growing, which means more birds are exposed to manure and thus to new pathogens that caged chickens do not face. So biosecurity can be a challenge for growers. Dr. Johnson pointed out that poultry producers increased biosecurity following the avian influenza outbreak in 2015.

Dr. Johnson described how turkey production differs from chicken production. Turkey farmers face similar consumer demands and on-farm challenges but often on a more limited scale. Dr. Johnson said no new drugs have been approved for use in turkeys for 40 years, while many have been restricted or taken off the market.

Dr. Davies asked whether researchers have looked at the effects of contaminated meat carcasses in the context of mechanical harvesting. Dr. Salois said more work is needed to understand the food safety issues that arise from such approaches.

In concluding the discussion, Dr. Singer said the environmental dimension of One Health has been recognized internationally by the United Nations, the WHO, and others. He hoped that future discussion would look at how to tie environmental findings to health outcomes, what kinds of models are needed, how to move from risk assessment to risk management, and how to ensure that policy decisions made on the basis of models are appropriate to a given region or country.

Public Comment

Kevin Kavanagh of Health Watch USA reminded the Council that antibiotic stewardship alone may not result in a needed drop in resistance. Even if antibiotic usage decreases by 50 percent, there would still be billions of bacteria exposed to antibiotics and resistance may still emerge. So far there has been little action on removing polymyxin B from over-the-counter products, even though there are theoretical risks to patient safety and its incorporation into these products has not been shown to increase their effectiveness. In addition, there is no assurance that effective and safe antibiotics that retain their therapeutic efficacy over the long term can be developed. Thus, controlling the spread of MDROs is of utmost importance. On June 18, the CDC reaffirmed contact precautions for MRSA. Hand hygiene is a very important component in an infection control bundle. Within the context of MDROs, it should be viewed as a backup measure, because these organisms should not be on a health care worker's hands in the first place. Mr. Kavanagh said he would have liked the Council to substitute “contact precautions” for “hand hygiene” in their key strategy I-7.2.

Mr. Kavanagh emphasized the importance of acknowledging conflict of interest. A recent article in the journal *Intensive Care Medicine* reviewed over 100 articles and focused on infectious disease research. The authors concluded that the effects of conflicts of interest pervade all aspects of the publication and research process. Finally, Mr. Kavanagh recommended considerations of health care workers from the standpoint of monitoring MDRO acquisitions and the risks of spread to both patients and the environment.

Jennifer Schranz, M.D., of Nabriva Therapeutics, described the extraordinary human and economic impact of AMR. However, large pharmaceutical companies continue to reduce or eliminate investments in anti-infective research and development. The current reimbursement model, where drugs are reimbursed based on each episode of their use, presents incentives that run contrary to effective stewardship over new antibiotics that might be highly effective against very rare and dangerous pathogens. New antibiotics are available but are being used sparingly to delay the development of resistance. While this approach represents responsible stewardship, it also demonstrates the limited market opportunity for new anti-infective agents, resulting in difficulty for companies to recoup their investments. Smaller pharmaceutical companies like Nabriva have interceded to continue to innovate and address this growing public health threat.

Dr. Schranz said her company applauds the progress made thus far with push incentives, such as the Generating Antibiotic Incentives Now Act and others, which have been successful but not sufficient. She agreed with other experts in the field who believe the emphasis now needs to be placed on pull incentives that result in innovative reimbursement strategies that recognize the societal value and benefit of anti-infectives. Strategies to ensure appropriate pharmacy benefit coverage and reimbursement, milestone payments, new technology add-on payments, and subscription-based modeling fees, among others, may serve as a catalyst for continued innovation for new anti-infective drug development.

Vijay Pancholi, Ph.D., from The Ohio State University College of Medicine called attention to the problem of overdiagnosis, particularly for *Clostridium difficile*, which leads to more antibiotic use, which, in turn, increases drug resistance. He recommended epidemiologic reporting on drug-resistant strains to assess causal relationships. In addition, he recommended that when it is not possible to develop new antibiotics, there should be new mechanisms for repurposing existing antibiotics for use in economically challenged countries.

Hua Wang of The Ohio State University recommended redefining “One Health” to better recognize the important roles of food and feed in the whole antibiotic resistance ecosystem. Food and feed are key connections to the microbiota. The microbiota has been a driving force in the past decade to facilitate a paradigm change in antibiotic research scope and the methodology to facilitate innovative mitigation approaches. The new scope enabled the field to achieve effective mitigation of the largest ARG pool in the food chain—which is not associated with retail meat and poultry but rather with ready-to-eat food, particularly cheese, yogurt, and probiotics. Within just 4 years, industry practices changed. Dr. Wang said she would like to see this topic better represented in the Council's deliberations.

Dr. Wang said the microbiota has a key role in antibiotic resistance ecology from ARG and bacteria evolution enrichment, dissemination, and persistence. Since 2011, it was discovered that mainstream oral antibiotic administration partnered with oral exposure to antibiotic-resistant bacteria is a key driver of antibiotic resistance in the microbiota, which further impacted the ARG pool in the ecosystem. Furthermore, oral antibiotic administration is the key driver for the gut microbiota, which is now known to lead to many modern diseases like obesity and diabetes. By separating the application of antibiotics from the main side effects of resistance and microbiota disruption, investigators enabled prompt infection prevention and treatment using antibiotics with minimized side effects for the first time.

These scientific discoveries are of great importance and have prominent impact on the life and health of hundreds of millions Americans, the health care system, and the food production industry. However, the findings from this groundbreaking discovery have been kept secret from most people, including professional physicians, policymakers, and the general public. Furthermore, the innovative team and sponsors had experienced significant hurdles as well as unusual losses in the past few years, which hindered the scientific delivery so essential for the paradigm change. Dr. Wang requested continued, constructive dialogue with the Council about the challenges and how to overcome them at the federal level to best serve the country.

Closing Remarks

Ms. Cole said there was agreement among PACCARB members and others about the need to bring the next generation of scientists and public health authorities into the conversation. She proposed reaching out to nursing and specialty boards about the prospect of offering their members continuing education units for attending PACCARB meetings, because the presentations are so educational. Ms. Cole also recommended partnering with local medical and agricultural schools when feasible, encouraging faculty to offer extra credit to students who attend PACCARB meetings. The proceedings could spark interest in the field.

Mr. Craig said CDC is working with the Wellcome Trust to finalize a report on AMR in the environment, which began in Vancouver in April. The final report will be released soon, and Mr. Craig hoped it would help further efforts around the world.

Final Comments and Adjournment

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

Dr. Blaser thanked all the presenters for their contributions and Dr. Singer and Dr. Laxminarayan for organizing the panels. He thanked the PACCARB members for their insightful questions, and particularly Dr. Apley and Dr. Cosgrove for leading the Infection Prevention and Antibiotic

Stewardship WG. Dr. Blaser expressed gratitude to the public for taking part and to Dr. King for his role in bringing PACCARB to Ohio. He adjourned the meeting at 4:51 p.m.

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

September 26, 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 (by phone)
Helen W. Boucher, M.D., FIDSA, FACP
Alicia Cole (by phone)
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.
Aileen M. Marty, M.D., FACP
Thomas R. Shryock, Ph.D.
Randall Singer, D.V.M., M.P.V.M., Ph.D.
Robert A. Weinstein, M.D. (by phone)

Organizational Liaisons Present

American Nurses Association
Elaine Larson, Ph.D., RN

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

Michael Craig, Senior Advisor for Antibiotic Resistance Coordination and Strategy, Centers for Disease Control and Prevention
Dennis M. Dixon, Ph.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health
Daniel W. Sigelman, J.D., Senior Advisor, Office of Public Health Strategy and Analysis, Office of the Commissioner, Food and Drug Administration (by phone)
Brian Tse, Ph.D., (for Christopher Houchens, Ph.D.), Biomedical Advanced Research and Development Authority

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

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 Robertson, 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, Ph.D., Gryphon Scientific
Sarah McClelland, ORISE Fellow

Glossary of Abbreviations

AMR	antimicrobial resistance
ARG	antibiotic-resistant gene
BARDA	Biomedical Advanced Research and Development Authority
CARB	Combating Antibiotic-Resistant Bacteria
CDC	Centers for Disease Control and Prevention
CPE	carbapenemase-producing Enterobacteriaceae
CRE	carbapenem-resistant Enterobacteriaceae
EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
GMO	genetically modified organism
HHS	Department of Health and Human Services
ID	infectious disease
MDRO	multidrug-resistant organism
MRSA	methicillin-resistant *Staphylococcus aureus*
NARS	National Aquatics Resource Surveys
OIE	World Organisation for Animal Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCR	polymerase chain reaction
QMRA	quantitative microbial risk assessment
USDA	U.S. Department of Agriculture
WG	working group
WHO	World Health Organization