PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

13th Public Meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria July 10–11, 2019

Hilton McLean
Tysons Corner, VA

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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. The main goal of this meeting was to finalize the Council's recommendations on updating the National Action Plan for Combating Antibiotic-Resistant Bacteria (NAP for CARB). Dr. King noted that the Council is now operating under new authority thanks to the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 (PAHPAIA). He appreciated that the administration recognizes the urgency of antimicrobial resistance (AMR).

Overview, Rules of Engagement, and Roll Call

Jomana F. Musmar, M.S., Ph.D., Designated Federal Officer, Advisory Council Committee Manager, Office of the Assistant Secretary for Health (OASH), Department of Health and Human Services (HHS)

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

Opening Remarks

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

In a prerecorded video message, Dr. Giroir thanked the Council for its work and staff for their support. Inclusion of PACCARB in PAHPAIA codifies and broadens the scope of the Council's work. The legislation is a testament to the U.S. Government's accomplishments so far and dedication to resolving AMR. Dr. Giroir said he is committed to supporting PACCARB and maintains a personal interest in the issue, based on his work as a pediatric critical care physician. Safe antibiotics are needed to save the lives of ill children; even 10 years ago, health care providers had to alter their work because of growing antibiotic resistance.

On behalf of HHS Secretary Alex M. Azar II, Dr. Giroir thanked the PACCARB working group that crafted the recommendations for the NAP. He said the Council has done tremendous work and that he, the Deputy Secretary, and the Secretary are confident it will continue to provide valuable insights.

In April, as a result of OASH reorganization, the National Vaccine Program Office—which housed PACCARB—merged with the Office of HIV/AIDS and Infectious Disease Policy to establish the Office of Infectious Disease and HIV/AIDS Policy (OIDP). Dr. Giroir assured the Council that it will remain an OASH priority.

Patient Story: Surviving a Multidrug-Resistant Infection: My Experience

Thomas Patterson, Ph.D., Professor of Psychiatry, University of California, San Diego School of Medicine

Dr. Patterson described how a sudden illness during a vacation in Egypt led to him contracting *Acinetobacter baumannii*, a devastating bacteria that is resistant to most antibiotics and only partially sensitive to a few. His wife, Steffanie Strathdee, Ph.D., an infectious disease epidemiologist, uncovered a research paper on using phages to attack bacteria. Dr. Patterson's bacteria had become resistant to all treatment, and his condition was considered fatal.

Dr. Strathdee found two researchers experimenting with phage therapy and received approval from the U.S. Food and Drug Administration (FDA) for researchers to treat Dr. Patterson (who was in a coma at this point) under a compassionate-use designation. People from around the world helped locate the right phages for this bacteria. The initial response was promising, but bacteria can develop resistance even to phage therapy. One of the researchers developed a phage cocktail, demonstrating how quickly phage therapy can be adapted when resistance occurs. Dr. Patterson emerged from his coma and recovered.

To date, six more patients have been treated with phage therapy for various bacteria at the University of California, San Diego (UCSD), medical center where Dr. Patterson was treated, and researchers are experimenting with clinical use of phages around the world. The UCSD School of Medicine established the Innovative Phage Applications in Therapy center, co-directed by Dr. Strathdee.

Dr. Patterson shared some observations from his long episode of hospitalization and care. He said that despite being in a coma, he could hear what was going on around him, and he experienced hallucinations colored by the conversations. He cautioned those in a patient's room to be mindful of what they say. Dr. Patterson said he could feel human touch while in the coma, and he urged health care providers, family, and friends to visit, talk to, and touch comatose patients. He added that the stigma around infectious diseases can be devastating for patients.

Dr. Patterson hoped PACCARB and others would consider the potential of phage therapy not only to kill bacteria but, in some cases, to re-sensitize bacteria to some medications that are no longer used. His experience is captured in a book he co-authored with his wife, *The Perfect Predator: A Scientist's Race to Save her Husband from a Deadly Superbug*.

Discussion

Dr. Blaser asked how such an approach to AMR could be scaled up. Dr. Patterson responded that a first step would be to create libraries of bacteria around the world so that researchers can find matches and grow phages quickly when needed. He noted that a Navy scientist created the phage cocktail that cured him, and the Navy collects bacteria from around the world by taking samples from ships' bilge water, among other techniques.

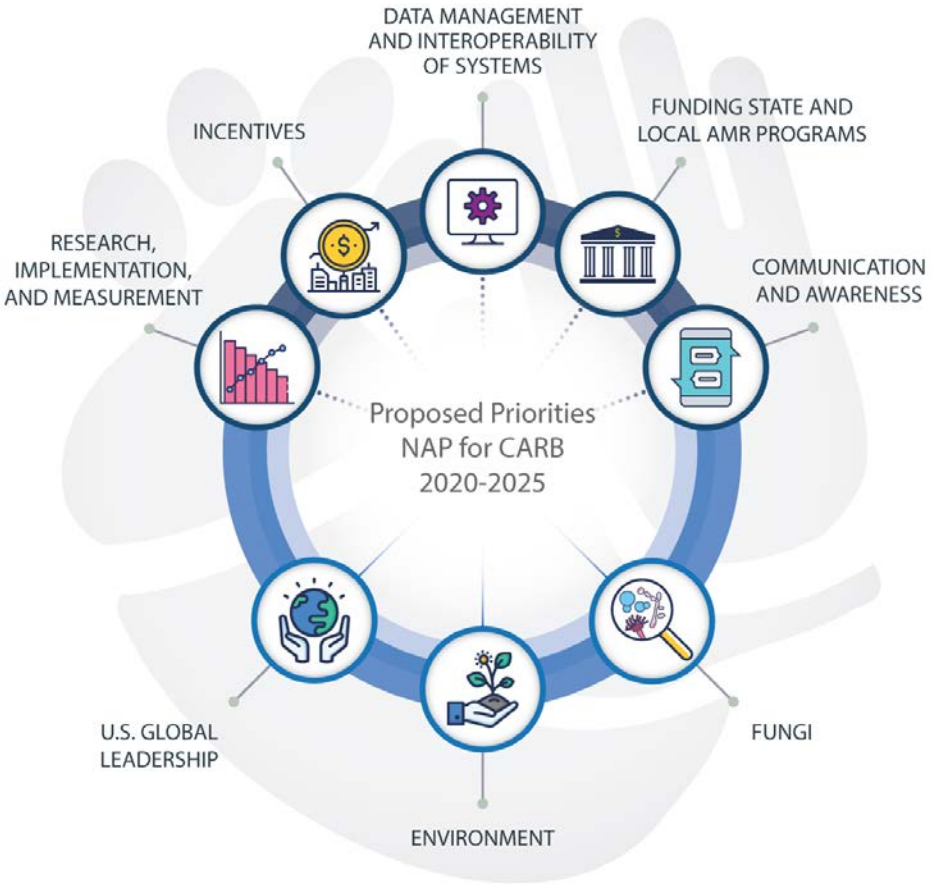
Kent E. Kester, M.D., FACP, FIDSA, FASTMH, said phages were used in medicine before antibiotics were developed. Phage therapy is complicated by the need for FDA regulation and approval. Dr. Patterson said FDA representatives were very helpful and told his wife that it would not be necessary to license each phage in a cocktail. Dr. Patterson acknowledged that the regulatory issues will likely be complicated as developers seek to create FDA-approved phage treatments. Dennis M. Dixon, Ph.D., added that phage therapy suffers from stigma because of

past failures, but there is renewed interest in the field. The National Institutes of Health (NIH) is exploring phage therapy and has had good cooperation with FDA, he added.

Alicia R. Cole asked for advice on how to encourage health care providers to listen to patients and their families when they bring in new information, especially about experimental therapies. Dr. Patterson said families need training on how to participate in care, because they are vital advocates for the patient. UCSD's medical center now offers family members the opportunity to participate in rounds with health care providers. Medical students should be educated about the importance of accepting family members as part of the health care team, said Dr. Patterson.

Report Out: National Action Plan for CARB 2020 – 2025: Priorities Recommended Martin J. Blaser, M.D.; Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM; Michael D. Apley, D.V.M., Ph.D., DACVCP; and Kathryn L. Talkington; Working Group Co-Leads

Dr. King explained that the HHS Secretary tasked PACCARB with identifying emerging areas of concern within the five broad goals of the existing NAP. A working group drafted recommendations and sought public input, ultimately identifying five major priorities and three broad priorities that cross all five goals, as described by the figure:



Dr. Apley and Ms. Talkington described the priorities identified for each existing NAP goal:

- Goal 1: Slow the emergence of resistant bacteria and prevent the spread of resistant infections.
    - Priority 1: Advance implementation of infection prevention (IP) and antibiotic stewardship (AS) programs through measurable, outcomes-based research.
    - Priority 2: Widely implement IP and AS strategies that have been proven effective throughout healthcare settings and animal agriculture.
    - Priority 3: Promote AS in companion animal health settings.
    - Priority 4: Facilitate and support the adoption of new technologies and management practices that can reduce the need for antibiotic use in animal agriculture.
    - Priority 5: Increase the use and interoperability of data systems to support AS.
- Goal 2: Strengthen national One Health surveillance efforts to combat resistance.
    - Priority 1: Enhance antibiotic use and resistance reporting systems for human and animal health.
    - Priority 2: Expand AMR reporting through the National Antimicrobial Resistance Monitoring System (NARMS) and fund supporting research.
    - Priority 3: Understand the role of antibiotics and resistance in the environment.
- Goal 3: Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.
    - Priority 1: Support studies that use clinical outcomes to evaluate the use of diagnostics and advance their integration into care.
    - Priority 2: Develop incentives and reimbursement strategies to support uptake of diagnostics.
    - Priority 3: Promote and support the development of new diagnostics and their integration into stewardship and AMR prevention programs in both human and animal health settings.
- Goal 4: Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.
    - Priority 1: Adopt effective pull incentives for development of new antibiotics, vaccines, and alternatives.
    - Priority 2: Continue to create push incentives for development of new antibiotics, vaccines, and alternatives.
    - Priority 3: Advance research on optimal dose and duration of existing antibiotic therapies.
    - Priority 4: Address shortages of existing antibiotics.
- Goal 5: Improve international collaboration and capacities for antimicrobial prevention, surveillance, control, and antimicrobial research and development.
    - Priority 1: Enhance U.S. leadership in the global fight against AMR.
    - Priority 2: Promote and support AMR activities in low- and middle-income countries.
- Additional Recommendations: 5 Years and Beyond
    - Integrate antibiotic resistance surveillance systems for One Health surveillance.
    - Develop an integrated federal One Health research strategy.
    - Develop a national, interagency effort to address antibiotic resistance issues around the globe.

Discussion

Council members had no comments, which Dr. Blaser attributed to the fact that the recommendations had been discussed and vetted for many months.

> **Vote:** Council members unanimously approved the report as written for submission to the HHS Secretary.

Panel 1: Emerging Resistant Fungi: *Candida auris*

Moderator: Angela Caliendo, M.D., Ph.D., FIDSA, PACCARB Voting Member

Centers for Disease Control and Prevention (CDC) Activities on *C. auris*

Tom Chiller, M.D., MPHTM, Chief, Mycotic Diseases Branch, CDC

Dr. Chiller observed that *C. auris* is more drug-resistant than other fungi in human medicine. People with *C. auris* can be colonized for long periods and develop invasive infections. The fungus spreads readily in health care settings. It has been reported in more than 30 countries, where it is increasingly causing candidemia. Four distinct clades simultaneously emerged on three continents. The United States has all four, circulating at different rates.

C. auris affects the sickest patients—such as those on ventilators or who have had tracheostomies. The mortality rate is 50 percent, some of which may be attributable to the poor condition of patients most likely to be infected. Dr. Chiller emphasized that *C. auris* is not a significant concern for healthy people or the general public. Most cases in the United States were introduced locally following international travel. Skilled nursing facilities that provide ventilator care (vSNFs) have higher rates of *C. auris* than those that do not provide ventilator care. Mapping the spread of *C. auris* over time in a vSNF raises concerns that vSNFs are reservoirs of the fungus, which is also associated with other multidrug-resistant organisms. Common disinfectants do not kill *C. auris* but rather spread it around.

All of the major laboratories in CDC's Antibiotic Resistance Laboratory Network can now identify *C. auris*. *C. auris* is mostly resistant to azoles, and 33 percent of cases are resistant to two or more drugs. Two pan-resistant isolates were found in 2019 in New York and a few others have been identified elsewhere in the world. Some of the techniques and principles used to control the spread of similar germs can be applied to *C. auris* (e.g., hand hygiene, personal protective equipment and precautions, and environmental disinfection), but Dr. Chiller remains concerned that *C. auris* will leapfrog ahead of other Candida infections.

National Institute of Allergy and Infectious Diseases (NIAID) Activities for *C. auris*

Dennis Dixon, Ph.D., Chief of Bacteriology and Mycology Branch, NIAID, NIH

About one third of the basic extramural research portfolio for the Mycology Branch centers around Candida species, with most efforts relevant to *C. auris*. Dr. Dixon was impressed by the speed at which researchers are ramping up to address Candida. On the translational side, about 60 percent of the extramural therapeutic research on antifungals involves Candida species. NIAID is reviewing the first batch of applications for special awards for fungal diagnosis.

NIAID offers a host of preclinical services to support translational research toward product development, such as resources for in vitro screening, animal models, toxicology testing, and manufacturing. Many researchers have taken advantage of these services to test products against *C. auris*. Most antifungal candidates currently in clinical trials have had some NIH funding or assistance, said Dr. Dixon. NIAID offers access to its Vaccine and Treatment Evaluation Units and its Clinical Trial Units for Therapeutics. NIH is currently supporting two phase-I clinical trials for products against *C. auris*, one of which is a first-in-humans trial.

Intramurally, NIH's Clinical Center has been part of a study of the first U.S. cases of *C. auris*. NIH has developed a mouse model of cutaneous *C. auris*. NIAID was fundamental in the research leading to a vaccine candidate, NDV-3, to protect against candidiasis and *Staphylococcus aureus* infection. Early trials indicate the vaccine is 80-percent effective.

Oxford Hospital Outbreak of *C. auris*: United Kingdom Experience

Derrick Crook, M.D., Professor of Microbiology, Nuffield Department of Medicine and Infectious Disease, University of Oxford; Physician, Oxford University Hospitals National Health Service Trust

Dr. Crook described an outbreak of *C. auris* in England beginning in 2015, primarily in neurologic surgery intensive care units, that resulted in five cases of candidemia. Hospitals employed standard outbreak management techniques (detection and isolation of cases, decontamination of affected areas and devices, general environmental controls, and so on). Once the fungus was identified, patients undergoing device-related surgical procedures were given prophylactic micafungin. The outbreak abated, and no further *C. auris* infections have occurred since October 2017. Dr. Crook theorized that the primary driver of infection was skin surface temperature probes—which are used routinely in patients on ventilator support.

Dr. Crook found some reassurance in the finding that only about one quarter to one fifth of patients exposed to *C. auris* acquire it. Analysis of deaths found no evidence that *C. auris* acquisition increased mortality. The findings from the outbreak were translated into guidance for hospitals and community-based care facilities.

Overview of Azole Use in Agriculture

Wayne Jurick II, Ph.D., Lead Scientist and Research Plant Pathologist, Food Quality Laboratory, Agricultural Research Service, U.S. Department of Agriculture

Dr. Jurick explained that azoles, or sterol biosynthesis inhibitors, are the only fungicide used in both agricultural and human medicine settings. The Fungicide Resistance Action Committee classifies azoles as group 3, or medium risk for developing resistance. Azoles are commonly used in the United States and Europe to protect crops from fungal diseases. Azoles work by targeting the CYP51 gene in plants. Resistance develops as a result of CYP51 mutations or overexpression, efflux, or detoxification.

Triazole and Multifungicide Resistance in Agricultural Pathogens

Kerik Cox, Ph.D., Tree Fruit and Berry Research, Cornell Cooperative Extension; New York State Agricultural Experiment Station; and School of Integrative Plant Science, Cornell University

Dr. Cox noted that Cornell's AgriTech programs work to translate basic research into practice for growers. Perennial fruit crops are a good model for monitoring pathogens and resistance over time. Population size is a key factor in resistance, said Dr. Cox: the dirtiest orchards with the most trees are more likely than cleaner, smaller orchards to see mutations and resistance develop. Resistance response is dictated by a combination of the environment, the host, and the type of fungicide used.

Dr. Cox distinguished cross-resistance (which can develop within fungicide classes) from multiple resistance (which results in resistance across classes). While commercial orchards attempt to prevent resistance by rotating the type of fungicide used, whenever a fungicide was used for which there is some resistance (more than 50 percent), the risk of introducing multiple resistance increases. Dr. Cox evaluated isolates from managed populations and identified super isolates with multiple resistance.

Discussion

C. auris in Humans

Dr. Dixon said research is underway to understand the relationship of *C. auris* to the skin microbiome and the potential effects of a vaccine. Dr. Chiller said it is not clear why or how the resistant strains of *C. auris* developed. Dr. Dixon pointed out that mortality from *C. auris* is lower than that from *C. albicans*, and *C. auris* is not catastrophic for the average patient. However, Dr. Chiller noted, the mortality rates are higher in other countries, such as South Africa, and not just among the sickest patients but in patients in intensive care units. *C. auris* develops resistance quickly and is killing people around the world, he added. Dr. Crook pointed out that the natural habitat for *C. auris* has not been identified, so it is difficult to understand the emergence of the new clades.

Dr. Chiller said hospitals have improved their infection control practices, but the spread of *C. auris* in community care settings suggests that vSNFs and similar facilities should educate staff on infection control and implement more stringent IP mechanisms. He noted that CDC, the Centers for Medicare and Medicaid Services (CMS), and others are working to improve IP in long-term care and other settings.

In terms of better understanding the epidemiology, Dr. Chiller said the first step has been to educate hospitals and health departments in identifying *C. auris*. When it appears, health systems have enacted aggressive containment strategies. Dr. Chiller remains concerned that long-term acute care facilities are not thoroughly prepared to enact the stringent IP controls needed. In addition, health care providers are used to seeing Candida among patients; they will need to be more vigilant about recognizing and reacting to *C. auris*. Globally, *C. auris* is entrenched in some countries. In those areas, Dr. Chiller said, the focus should be on preventing resistance, particularly development of pan-resistant isolates, through antifungal stewardship.

Neither Dr. Chiller nor Dr. Crook could provide figures to describe how often *C. auris* colonization results in candidemia. Dr. Crook pointed out that if much of the exposure is related to environmental factors, such as contaminated devices, then low- and middle-income countries that reuse supplies (rather than use disposable supplies) face higher risks of transmission. Dr.

Chiller added that effective means for disinfecting hospitals and care facilities when *C. auris* is present is not well known.

Dr. Crook noted that investigators evaluated hospital drain systems but did not find evidence of *C. auris* colonizing there; sophisticated air sampling found *C. auris* only once. Dr. Chiller added that other studies took samples from health care workers' hands and did not find them to be a source of transmission. A recent paper demonstrated that among people heavily colonized with *C. auris*, skin shedding correlates with the presence of *C. auris* on bedrails, which suggests that skin shedding may explain how *C. auris* gets on to surfaces, Dr. Chiller noted.

Dr. Crook described the testing for *C. auris* in the hospital that eventually led to confirmation that the outbreak had been eliminated. He suspects that there is a limit to the duration of carriage of the fungus. However, there might be something unique about long-term care facilities in the United States, where *C. auris* persists, and the same might be said of facilities in other countries where, as Dr. Chiller noted, infection and mortality rates are high. Dr. Chiller added that he has seen U.S. patients remain colonized for over a year. He said recent research suggests that, when disinfectant is used on the skin, the fungus may travel to an area of the patient's body that the disinfectant does not reach, such as the nares.

C. AURIS IN AGRICULTURE

Aileen M. Marty, M.D., FACP, asked whether there is evidence of horizontal transfer of resistance genes among fungi and, if so, whether it poses a risk for humans. Dr. Cox said he did not see much horizontal transfer, although there is some vertical transfer among fungi that reproduce sexually; he said the problem of resistance transference tends to occur in densely populated environments, such as orchards or hospitals, but not in the wild. Moving infected plants into other areas can cause damage, especially if moved into young orchards, for example.

Dr. Cox said some growers have used gene modification and minimal fungicide application to develop disease-resistant apples, but the apples have not been popular with consumers. However, he believed such an approach could eventually be successful.

David White, M.S., Ph.D., noted that a new agricultural antifungal is expected to reach the market soon; he questioned whether PACCARB should look more closely at how the U.S. Environmental Protection Agency (EPA) evaluates and approves such products. None of the panelists had insights into the EPA regulatory process.

Dr. Cox explained that in a very wet year, resistant fungi thrive and spread, but the spread can be reversed in dry years with intervention. He added that in some cases, growers can "rescue" an antifungal that was abandoned because resistance had developed, because the selective pressure that led to resistance has abated.

Dr. Jurick hoped to investigate packing and storage environments to assess the microbes that live there and whether interventions can be used to promote good bacteria and fungi and inhibit rot. Such an approach might involve genetic sequencing. Dr. Jurick proposed that cocktails using grass substances or other natural products with low probability of developing resistance might be developed in the future to protect crops. He also said RNA interference technology might be

used to inhibit fungal pathogens on fruit. Dr. Jurick pointed out that a genetically modified apple is commercially available; it does not brown when cut. Dr. Cox pointed out that growers are rotating fungicides in a responsible way, as well as using sanitation practices, so resistance is not as big a problem as it had been in the past.

Dr. Cox said it is likely that resistant fungi can travel from one plant to another, but such cases are limited and, at present, manageable. In many cases, sanitation—that is, cleaning up fruit on the ground—is effective in preventing the spread of resistance.

Panel 2: Emerging Resistant Fungi: *Aspergillus fumigatus*

Moderator: Aileen M. Marty, M.D., FACP, PACCARB Voting Member

Resistance in *A. Fumigatus*—Human Health Implications

Tom Chiller, M.D., MPHTM, *Chief, Mycotic Diseases Branch, CDC*

A. fumigatus is largely an environmental infection that affects humans; it is the most common species of Aspergillus that causes aspergillosis. *A. fumigatus* can be deadly, particularly for immunocompromised patients, which includes people undergoing transplants, chemotherapy, or steroid therapy. There are few U.S. surveillance mechanisms for fungi in general and none for *A. fumigatus*, so the prevalence is not well understood.

The primary treatment for aspergillosis is a voriconazole, a triazole. When it was introduced in the 1990s, mortality rates dropped from as high as 80 percent down to around 30 percent. With emerging resistance, mortality rates are increasing—even in patients treated with non-azole drugs. The resistant *A. fumigatus* is more virulent than susceptible *A. fumigatus* Resistance develops along two pathways. In the first, the individual inhales *A. fumigatus* from the environment, develops a chronic lung nodule with aspergillosis, and receives long-term treatment with azoles, eventually developing azole-resistant Aspergillus. In the second pathway, an individual inhales resistant *A. fumigatus*—that is, the *A. fumigatus* began as a susceptible organism and then came into contact with triazole pesticides that caused resistance—and develops a condition that requires treatment, entering the hospital with resistant *A. fumigatus*. Notably, two thirds of the genotypes in the azole-resistant pesticide *A. fumigatus* acquired resistance de novo, without exposure to azoles.

In Europe, the pesticide-induced resistant *A. fumigatus* is increasing, and health-care-induced resistance is declining. Dr. Chiller said it is possible that resistant isolates only exist in certain parts of the world, but it is also possible that the lack of detection reflects the lack of surveillance. He also noted that azole use in U.S. agriculture has increased dramatically in the past 10 years, especially in the South and Midwest. An informal request for *A. fumigatus* samples from laboratories revealed numerous resistant isolates, some with the mutation linked to pesticides. Dr. Chiller said more surveillance is needed to better understand the resistance. In terms of patient treatment, he said providers should be thinking about the possibility that resistance might explain why a patient is not responding to treatment.

The Environment and Azole Resistance in Aspergillus

Sally Miller, Ph.D., Professor of Plant Pathology, State Extension Specialist for Vegetable Pathology, The Ohio State University

After a brief explanation of fungi taxonomy, Dr. Miller described the biology of Aspergillus. Many Aspergillus species are critical to decomposition of vegetation. *A. flavus* can produce toxins that cause liver cancer and other conditions. Aspergillus produces copious amounts of conidia, or spores, that are resistant to heat, cold, stress, hypoxia, ionizing radiation, and ultraviolet lights. *A. fumigatus* can grow in a broad range of pH settings. Aspergillus reproduces sexually, which leads to genetic recombinations. The areas where the sexual spores are produced are even more resistant than conidia to environmental stressors.

Aspergillus is the predominant fungi in decomposing vegetation but also lives in soil, plants, compost, water, aerosols, animal systems, and indoor environments. It has an extremely flexible way of using nutrients, so it can live in various environments and also cause disease in humans and animals. Dr. Miller explained that because Aspergillus conidia are very small and can withstand so many environmental stressors, they can be spread through air and water. A lot of conidia have been found in surface water, groundwater, and in hospitals in biofilms.

The use of triazoles as fungicides began to increase in 2006, and by 2009, manufacturers were marketing fungicides to increase crop yield, not just to kill disease. Dr. Miller posited that some other environmental factors might also affect Aspergillus. For example, less frequent soil tilling (to promote conservation in agriculture) means that crop residue remains on the soil surface; Dr. Miller wondered whether this situation could result in more exposure of decomposers (Aspergillus) to fungicides. Climate change might also play a role—in particular, fungi favor wet environments, so more heavy rains might promote Aspergillus. Some mitigating factors might be the use of canopies that prevent triazole from reaching the soil when applied to corn and soybeans; reduced use of triazole when corn and soybean prices are low; and use of combinations of products to prevent resistance. Dr. Miller concluded that the agricultural practices described by Dr. Cox can reduce the risk of environmental azole resistance.

Emergence of Azole-Resistant *A. fumigatus* and One Health

Jacques Meis, M.D., Ph.D., Deputy Director, Center of Expertise in Mycology Radboudumc/CWZ; Consultant, Department of Medical Microbiology and Infectious Diseases, Canisius Wilhemina Hospital, The Netherlands (by phone)

The Netherlands has conducted surveillance for azole resistance since 2013, publishing the results every year. The data demonstrate a steady increase in resistant isolates for *A. fumigatus*. The highest percentage of resistance appears in a heavily agricultural area of the country that primarily grows tulips. The heavy use of fungicides in tulips leads to resistance in Aspergillus. Fungicides are also used to protect human environments, such as hotels.

About 10 years ago, hospitals in the Netherlands began seeing patients developing resistance to voriconazole. Investigators found resistant fungi in patients' homes and yards and throughout hospitals. Dr. Meis pointed out that there is less resistance in the east side of the country and more in the west, where most agricultural production occurs. Analysis demonstrates that resistant isolates for *A. fumigatus* emerged in the late 1990s and that *A. fumigatus* continuously adapts to the fungicides. Recent research determined that compost heaps were a significant hotspot for

development of resistance when the compost had remnants of material exposed to azoles but not when the compost did not have fungicide-exposed remnants. Eliminating such hotspots could reduce resistance.

The burden of azole resistance correlates with the market share of fungicides, Dr. Meis observed, which further suggests a strong connection between agricultural use of azoles and the emergence of azole-resistant clinical Aspergillus infections. The European Center for Disease Prevention and Control (ECDC) identified the potential threat to human health 6 years ago. It recommended that hospitals increase surveillance and resistance detection. Antifungal stewardship has increased, but the role of environmental exposure is underrepresented, Dr. Meis said.

Discussion

Dr. Marty asked whether use of fungicides to increase yield in healthy plants should be banned. Dr. Miller said most academics do not favor such use, but it is not known whether triazoles reach the soil surface in some applications, so she did not have an opinion.

Dr. Marty asked whether the fungicides associated with azole resistance should be banned. Dr. Meis said hundreds of fungicides are available for treating plants, but very few azoles are effective in humans; he hoped more growers would consider using other fungicides, but he understood their desire to use the best fungicide available. He acknowledged that tulip growers in particular are fighting against proposals to ban certain fungicides. However, they sponsored the research on hotspots, which revealed that getting rid of compost piles could mitigate the spread of resistance. It is much easier to ban the use of products for growth promotion than for treating disease, Dr. Meis said, and there is little support for research on antifungal resistance. Notably, in the Netherlands, patients are not dying from antibiotic-resistant infections but rather from resistant fungal infections.

Dr. Miller noted in her presentation that climate change is likely related to resistance development. She further said that increased precipitation and increased intensity of storms encourage fungi growth, which leads to increased use of fungicides to protect crops. Also, like humans, plants that have infections are more susceptible to other diseases.

Asked whether genetic sequencing for resistance would be an effective approach, Dr. Meis said Europe has commercial tests for diagnosing invasive aspergillosis, and it identifies about 80 percent of the resistant forms of *A. fumigatus*. Dr. Chiller said an assay is being used in some U.S. laboratories to identify resistance, and CDC is thinking about how to make such testing more widely available, beginning with regional laboratories. Christine Ginocchio, Ph.D., MT, said clinicians would likely be willing to screen for resistance if a convenient, FDA-approved tool were available.

Dr. White pointed out that risk analysis was used to inform FDA guidance on use of medically important antibiotics in food animals. He wondered whether antifungals could be assessed and ranked in relation to the likelihood of developing resistance to human drugs. Dr. Meis agreed with the approach and noted that U.S. farmers have access to diagnostic tests for fungal infections that can provide next-day results and guide intervention. Dr. Chiller agreed on the importance of judicious use, but he noted that banning use of certain fungicides might not have

an impact on resistance to drugs in humans, and some of the mutations causing resistance will definitely not go away.

Panel Session 3: Innovations in Combating AMR

Moderator: Robert A. Weinstein, M.D., PACCARB Voting Member

Utilizing Big Data to Track Outbreaks of Antimicrobial-Resistant Pathogens

Jeffrey Shaman, Ph.D., Professor, Department of Environmental Health Sciences, and Director, Climate and Health Program, Mailman School of Public Health, Columbia University

Dr. Shaman described a data model he created to predict methicillin-resistant *S. aureus* (MRSA) colonization and infection. A total of 10 years of hospital data from a single Swedish county revealed almost 1,000 cases of MRSA, and nearly 300 of those were attributed to a single strain (UK E15). Dr. Shaman built a network model of hospital patients and identified them as susceptible, colonized, or infected; the model tracked their movements throughout the hospital and transmission of MRSA. The model sought to estimate the rates of (1) transmission, (2) importation of infection, and (3) importation of colonization. Using first synthetic data then real data, Dr. Shaman confirmed that the model can infer the three parameters from data.

Using the model, Dr. Shaman observed that infection is more likely to be imported from the community than transmitted among hospital patients. It might be useful for screening. With real-time data, the model could identify clusters of people more likely than others to be colonized. Dr. Shaman theorized that using the model to identify and treat the 1 percent of patients at highest risk for MRSA would avert 38 percent of infections and reduce colonization by 9 percent. He concluded that the model might be applicable for *C. auris* if data were available.

Whole Genome Sequencing and Machine Learning to Modernize AMR Diagnostics

Jong Lee, Chief Executive Officer and Co-Founder, Day Zero Diagnostics

At present, clinicians must choose between comprehensive antimicrobial identification and rapid susceptibility testing. Mr. Lee said Day Zero is working on a solution that uses a clinical sample, such as blood, to generate comprehensive results in about 6 hours—fast enough to switch treatment regimens before the second cycle of drugs is administered.

One challenge is to translate clinical samples into samples that can be sequenced. Day Zero has succeeded in manipulating samples so that bacterial DNA remains for five common bacteria and human DNA is eliminated. With such samples, whole genome sequencing can be conducted using commercially available technology. Sequencing provides complete genomic data, which should enable the clinician to target treatment more precisely.

Day Zero is also developing an algorithm that will use machine learning to identify resistance and susceptibility from genomic data. Machine learning requires a very large data set for training; the more data, the better the accuracy of predictions. To build its data set, Day Zero has agreements with microbiology laboratories to collect clinically relevant samples. It sequences these samples to populate the database and train the algorithm. If Day Zero's device ultimately succeeds, Mr. Lee predicted clinicians would use it daily in hospitals around the country,

generating data that Day Zero would incorporate into its database. In that case, he said, the device could pinpoint the source of infection and use that data for infection control.

Using Educational Programming, Games, and Comics for Impact

Russell Shilling, Ph.D., Chief Scientific Officer, American Psychological Association

Dr. Shilling said that many government education efforts fail because they focus on providing information but do not tell a story, which is central to how people communicate. Crafting the right narrative around antibiotic resistance is particularly challenging, because the message is complex. For children, it is important to explain that antibiotics save lives and they should not be scared of using them.

Communicating a complicated message requires professional messengers, child psychologists, and experts in learning who take into account potential consequences and unintended messages. Targeting young people is an excellent idea, said Dr. Shilling, and comics are ideal for reaching young children, teens, and even non-English speakers. They are relatively inexpensive to produce and easy to distribute; there is already an established field of developers. Dr. Shilling suggested hiring professional storytellers to create the narratives.

Online games are more expensive to produce but can be very engaging. A number of online games address antibiotic resistance but mostly in the form of simulations. Such games would not be appropriate for young children but could be effective for teaching teens. Most of the existing games lack a story that helps communicate when antibiotics are good and when they are not.

Dr. Shilling felt that videos are the best way to get a story out but also the most expensive technique to do well. Videos can be streamed online to reach a broad audience; they can be subtitled for use in multiple languages. With emotionally charged issues, messaging is critical, Dr. Shilling emphasized. He presented a short video produced by Sesame Street from a series for children of military families about sensitive issues, such as losing a parent. He said a team of experts worked for 2 years to get the messaging right before airing the series.

Discussion

To communicate about antibiotics, Dr. Shilling recommended keeping the message simple for the youngest children, then using narrative games and comics as children get older to teach, for example, the difference between viral and bacterial infections. Having health care providers on board with the messaging is key. Dr. Shilling acknowledged that parents might be the ones pushing for antibiotics, but he said children can be very effective in educating their parents, as demonstrated with antismoking campaigns. He reiterated that parents would benefit from stories that illustrate the negative impact of antibiotic resistance.

Dr. Shilling pointed out that the National Academies of Sciences, Engineering, and Medicine has an Entertainment Science Exchange in Los Angeles to consult on the science portrayed in television and film. He recommended that government agencies hire consultants to test messages before they are disseminated. He also noted that music is an effective teaching tool but usually in the context of a visual medium.

Mr. Lee said that while it would be very useful to have patients' clinical data along with laboratory samples, the privacy issues are difficult to surmount. The current approach aims to keep the process simple for the laboratories. Day Zero would like to collaborate on clinical research to assess the effects of its diagnostic platform on treatment.

Dr. Shaman said the model he described is similar to approaches used for forecasting infectious disease patterns. Creating such a model involves some assumptions, but it can be challenged with real, retrospective data to determine whether it is accurate. The next step with the MRSA model will be testing its utility for predicting disease.

Elaine Larson, Ph.D., RN, said it has taken her team 2 years to build a data set of 1.2 million patient discharges from four New York City hospitals. With all the challenges to data collection and exchange, she wondered how the field could gather real-time data for prediction. Dr. Shaman added that even ILINet (Influenza-Like Illness Network) is always using data that are 4–6 weeks old. However, he said, such systems can produce credible forecasts with demonstrable accuracy. Dr. Shaman described how retrospective data could be used to develop models for prediction. Mr. Lee stressed the need to gather data with a specific purpose in mind. Algorithms can take advantage of machines' capacity to evaluate data much more quickly than humans, so solutions could be scaled up and linked to real-time data.

Dr. Apley asked which is more important in a diagnostic device—sensitivity or specificity. Mr. Lee said Day Zero is more concerned with sensitivity. He added that clinicians will still have to use judgment in interpreting the results in the context of the individual clinical situation. Once the diagnostic device is deemed to be accurate, Mr. Lee said, algorithms can be adjusted to prioritize sensitivity or specificity as desired.

Dr. Apley said other presenters have contended that providing too much susceptibility information leads clinicians to treat when it might not be necessary. Mr. Lee said Day Zero's sample preparation aims to narrow down the bacteria that are potentially causing infection. Again, he said, clinicians must use their judgement and knowledge of the clinical situation.

Dr. King asked whether Dr. Shaman's model could be applied in food animal production for early detection of disease. Dr. Shaman distinguished forecasting from risk mapping; he said with investment, models could be developed that incorporate variables and used to anticipate potential outbreaks shortly before they occur.

Mr. Lee observed that the FDA will play a significant role in determining how artificial intelligence (AI) is used in medical devices. At present, Day Zero's device, like any other diagnostic, must demonstrate that it can provide validated results of sufficient accuracy compared with some standard. However, that approach does not make use of the ability of AI to evolve. Mr. Lee said FDA is considering new regulatory frameworks for AI-driven devices.

Public Comment

Sherrie Smart, medical director for Thermo Fisher, described what her company is doing to support appropriate decision making for antibiotics. The Coalition for Improving Sepsis and Antibiotic Stewardship includes Thermo Fisher and other companies; it commends PACCARB

for continuing to include diagnostics in the five key goals of the NAP for CARB. Ms. Smart encouraged a continued focus not only on new diagnostics but also on currently available, FDA-approved diagnostics to support the judicious use of antibiotics.

The Coalition has focused on working to encourage CMS to finalize the Conditions of Participation requiring AS programs. Ms. Smart appreciated PACCARB's public meeting in April on this topic and its ensuing letter to Sec. Azar, which was timely and succeeded in creating a pause so that the proposed Condition of Participation rule would not disappear. This pause is a great opportunity to look at how to finalize that rule. The Coalition encourages approving and implementing the rule sooner rather than later, because AS programs are critically important to creating a foundation of standardized quality for patient outcomes in this area. Ms. Smart cited a recent Global Health Agency and the United Nations report that found that although 70–80 percent of all hospitals had some sort of antimicrobial stewardship program, the operation and quality standards are not uniform, and too many institutions lack such programs altogether, so that not all patients are getting the benefit of best practices and the standardization of care.

Ms. Smart said, in light of the afternoon's presentations, that a program is only as good as the behavior that responds to that program. She highly appreciated the emphasis on behavior and education for antimicrobial stewardship. She emphasized that diagnostics are crucial and increasingly important tools that can guide wise and appropriate antibiotic use. Ms. Smart reiterated the call to encourage use of existing diagnostics as well as development of new ones and to define what will become diagnostic stewardship.

Kevin Kavanaugh of Health Watch said CDC estimates that 20 percent of resistant bacterial infections in humans comes from food and animals, with the vast majority of the rest associated with the health care industry. In the 1980s, entire wards were closed for a single MRSA infection. In the early 2000s the public was reassured that MRSA outbreaks were under control and legislative mandates were not needed. That assertion was bolstered with poorly designed research which shut down on the effectiveness of surveillance and isolation.

Next, the industry advocated treating all patients the same and using universal daily bathing with chlorhexidine. However, a recent study in the *Lancet* found this approach to have limited effectiveness on general hospital wards. An accompanying editorial recommended that chlorhexidine use should be limited to situations with a clear patient benefit. Now that MRSA is epidemic, some hospitals view these infections as no big deal and nothing for the public to worry about. Some facilities are not even isolating MRSA patients, arguing that healthy individuals have little reason to be concerned. Advocates have similar narratives regarding *C. auris* and carbapenem-resistant Enterobacteriaceae. However, pathogens are most efficient when they only affect the sick and frail, and this equates to a shortening of our lifespan, because we almost all age and develop chronic illnesses, with a drop in our defenses, said Mr. Kavanagh.

Mr. Kavanagh stressed the importance of a healthy patient's microbiome, initially focusing on the identification and elimination of dangerous pathogens. Of utmost importance, he said, there is a need to protect health care workers, who may well be acting as reservoirs to spread these pathogens to both patients and their families. An economic safety net should be established.

Medical screening needs to be established. Until these reforms are enacted, Mr. Kavanagh said, he has grave reservations that this epidemic will be brought under control.

Final Comments and Adjournment for the Day

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

Dr. Blaser reminded the participants that everyone has a role to play in the fight against antibiotic resistance. There is still time to join the AMR Challenge. For details, visit CDC's AMR Challenge web page. Dr. Blaser adjourned the meeting for the day at 5 p.m.

Day 2

Welcome and Overview

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

Dr. Blaser and Dr. King welcomed the participants. Dr. King said the day's panels would center on behavioral change.

Roll Call

Jomana F. Musmar, M.S., Ph.D., Designated Federal Officer, Advisory Council Committee Manager, OASH, HHS

Dr. Musmar welcomed the participants and called the roll.

Remarks from the Office of Infectious Disease and HIV/AIDS Policy (OIDP) Director

Tammy Beckham, D.V.M., Ph.D., Director, OIDP, HHS

Dr. Beckham said the new OIDP brings together several HHS efforts with clear commonalities. The merging of offices provides opportunities to enhance communication, synergize efforts, and strengthen the work of HHS across the spectrum of disease. Dr. Beckham said that, as a veterinarian, PACCARB is especially important to her, and she appreciates the true One Health perspective it applies. Codifying PACCARB in legislation will provide more sustainability. Dr. Beckham reiterated that the Council has the full support of OIDP, OASH, and HHS. She thanked the Council for its work guiding the national, federal, and global efforts against AMR.

Discussion

Dr. Blaser noted that "One Health" initially referred to humans and animals, but the field is now expanding to include the impact of the environment, plants, and agriculture on human health. He asked whether PACCARB should change its name to reflect the broader scope of AMR. Dr. Beckham agreed that PACCARB should widen the scope of its work as it moves forward. She suggested that PACCARB make a recommendation to the Secretary about changing its name.

Panel 4: Day-to-Day Provider Challenges to Client/Patient Behavior Change

Moderator: Angela Caliendo, M.D., Ph.D., FIDSA, PACCARB Voting Member

Striking a Balance between Oral Health and Antibiotic Use

Glen Miller, D.D.S., Dentist and Dental Entrepreneur, Dental Whale Practice Group

Dr. Miller said that dentists write about 24.5 million prescriptions for antibiotics each year; dentists and dental specialists are the third-highest prescribers of antibiotics. Commonly, they prescribe prophylactic antibiotics before procedures such as extractions, implant placement, and cleanings, often for patients with endocarditis. A recent study found 81 percent of prophylactic antibiotics in dentistry were unnecessary. Dr. Miller outlined a slew of situations that lead to overprescribing, including the following:

- Undiagnosed or untreated periodontal disease
- Oral health conditions that are not diagnosed or treated before invasive surgery
- Failure to follow guidelines for prophylactic antibiotic therapy
- Patient demand for antibiotics
- Lack of access to oral health care

The risk of adverse reactions to prophylactic antibiotics, especially penicillin, in healthy patients is high, said Dr. Miller. Dentists are the top prescribers of clindamycin, which is prescribed for those allergic to penicillin and is strongly associated with *Clostridium difficile* infection.

Dr. Miller offered a number of recommendations aimed at preventing infection with proper periodontal treatment. Dentists should better understand periodontal disease, identify it early, and treat it. Dental schools should increase education about periodontal disease, systemic medicine, and use of antibiotics. Dentists and their professional societies should raise public awareness of and educate patients about periodontal disease. The field should promote thorough evaluation for periodontal disease (rather than spot probing) and the use of oral rinses such as chlorhexidine rather than systemic antibiotics.

In the broader medical field, physicians should consult with dentists before invasive surgery to address issues that could lead to postoperative infections or a lifetime of prophylactic antibiotics. Physicians, not dentists, should write prescriptions for prophylactic antibiotics for their patients when needed. Physicians and dentists should come together in joint meetings. Oral medicine should be better incorporated into medical education. The insurance industry should recognize and support early diagnosis and treatment of periodontal disease.

Challenges to Implementing an AS Program in a Community Pharmacy Setting

Nathan Wiehl, Pharm.D., BC-ADM, Director of Clinical Services, AuBurn Pharmacies; Pharmacist-in-Charge, Anderson County Hospital Pharmacy, Garnett, KS

Dr. Wiehl explained that in hospitals, patients are monitored closely, and health care providers have access to infectious diseases consultants and laboratory test results to guide decision making—all of which support AS programs. For the pharmacist serving individuals in an outpatient setting, none of that information is available, and the patient might not even be the person the pharmacist sees. Hospitals have policies, incentives, and data resources to support AS programs, while outpatient settings that are not affiliated with large provider practices or health systems typically have none of those.

Dr. Wiehl said pharmacies make very little profit on prescription drugs, and the situation is worsened by pharmacy benefit management companies that require direct and indirect remuneration (DIR) fees. The fees "cripple" profit margins, Dr. Wiehl said, so pharmacies lack the resources to implement mechanisms that could improve antibiotic selection. In addition, insurance restrictions and administrative requirements pose a barrier to ensuring that patients get the right drug at the right time. Public understanding of appropriate antibiotic use is also poor. Dr. Wiehl noted that community pharmacies are well positioned to educate people but lack sufficient time and resources to do so.

Pediatric Challenges to AS Programs in the Urgent Care Setting

John Santos, M.D., M.B.A., Director of Urgent Care, Children's Hospital Colorado; Assistant Professor of Pediatrics, University of Colorado

Dr. Santos pointed out that antibiotic prescriptions have been slowly rising despite years of decline. A recent study in the *Journal of the American Medical Association* (*JAMA*) found that at least 30 percent of outpatient antibiotics are for inappropriate indications, including upper respiratory infections and influenza.

The number of urgent care sites is growing rapidly; especially in heavily populated states. In 2017, urgent care sites accounted for 10 percent of all outpatient visits. In 2018, *JAMA* reported that inappropriate antibiotic use was linked to nearly 40 percent of urgent care visits. Of those, 45 percent were for respiratory diagnoses. Dr. Santos pointed out that retail clinics had a similar antibiotic prescription rate but the lowest rate of inappropriate antibiotic use.

Notably, while health care providers who treat children often prescribe antibiotics inappropriately, pediatric specialists have made great strides in improving stewardship. To further those gains, the Society for Pediatric Urgent Care and the Antibiotic Resistance Action Center began a quality improvement initiative in 2019 that seeks to build capacity for quality improvement in pediatric urgent care, understand antibiotic prescribing patterns in specialized pediatric urgent care, and test interventions to reduce inappropriate antibiotic use. Preliminary data from a study in progress under this initiative found that providers are prescribing narrow-spectrum antibiotics when needed.

Effective interventions to promote antibiotic stewardship include posting a signed letter in patient care rooms indicating the provider's commitment to appropriate antibiotic use; educating providers on how to talk with parents about pediatric respiratory illnesses; and offering patient education on strep throat and strep throat testing. Children's Hospital Colorado has adopted these interventions, along with giving parents options for supportive care as a way to delay or prevent the prescription of antibiotics. Dr. Santos gave examples of effective communication with parents to address common scenarios in which antibiotics are often inappropriately prescribed. He noted, for example, that true penicillin allergy is quite low, but presumed allergy drives a lot of prescriptions for broad-spectrum antibiotics.

Antibiotics for Small Animals: Barriers to Change

Mark E. Hitt, D.V.M., M.S., D-ACVIM, Internal Medicine Specialist, Atlantic Veterinary Internal Medicine & Oncology, Maryland

Dr. Hitt noted that university-based, tertiary care veterinary hospitals are more likely to have infection control and stewardship programs than general and specialty veterinary practices. He outlined the primary barriers to appropriate antibiotic use in private veterinary practices:

- Lack of awareness and education among veterinarian practices about pharmacokinetics and pharmacodynamics and use of cultures and sensitivity tests
- Rising costs to consumers (e.g., the high cost of testing compared with inexpensive courses of antibiotics)
- Lack of consumer compliance with treatment regimens
- Need for more alternatives to antibiotics (current options include ultraviolet light for sanitation and hyperbaric oxygen therapy for certain infections)
- Need for guidelines on selecting an antibiotic without waiting for culture and sensitivity test results
- Need for more products approved for veterinary medicine
- Overuse of antibiotics that should be used in limited cases (i.e., reserved drugs)
- Lack of metrics and data in small practices to guide use (and the lack of data from laboratories)

Dr. Hitt pointed out that most antibiotics used in human medicine are also available for animal use. Veterinarians are aware of the importance of judicious use but also are very resistant to give up any of their antibiotic options. Dr. Hitt said a lot of veterinarians who completed training more than 10 years ago are not likely to assess whether their antibiotic selections are concentration-dependent or time-dependent. He called for more education on the basics of infectious disease, including host status, organisms, and infective doses, and the need for appropriate treatment selection, correct dosing, and consumer compliance with treatment. Life-threatening adverse drug reactions to antibiotics are unusual in veterinary medicine but do occur. Frequently, less prominent side effects are interpreted as adverse drug reactions. Dr. Hitt emphasized that overall antibiotic use in small animal veterinary practices is miniscule compared with, for example, aquaculture.

Veterinary practices face antibiotic resistance, just as in human medicine. Veterinarians also deal with zoonosis and reverse zoonosis. *Helicobacter pylori*, for example, an organism common in dogs and causes a minor infection of no real significance. It is overtreated by veterinarians because it also affects humans, said Dr. Hitt. Nosocomial infections are a rising threat, especially at referral hospitals, where patients have often been subject to various antibiotics, leading to resistance. Dr. Hitt anticipated more regulation of antibiotic use in the near future.

Discussion

Dr. Miller clarified that dentists tend to monitor periodontal disease until it gets out of control, which opens the door to infection that requires antibiotics. Patients who have periodontal disease are more likely to get prophylactic antibiotics. Therefore, much of the overprescribing in dental care comes from the lack of definitive care to treat periodontal disease early. In addition, said Dr.

Miller, many dentists follow long-outdated protocols of freely prescribing antibiotics for everything and are not up to date on current literature and guidelines.

Dr. Wiehl observed that more detailed patient information from health care providers would help pharmacists assist with better drug selection. Access to electronic health records would be very helpful too. Dr. Wiehl said he believed pharmacists could save the health care system money by intervening with better information and communication from providers. He added that eliminating the retroactive DIR fees would help pharmacies better control their budgets and assess how they can provide more services.

Dr. Hitt said that the veterinary field is just now seeing consolidation of practices, and with that comes access to new data collection systems and recordkeeping to assess spending and revenue. Many different software systems are available, and the pet insurance industry is not yet driving the field towards uniform data collection methods. About 2 percent of U.S. pet owners have insurance compared with as much as 80 percent in some European countries. In human medicine, insurance companies drive data collection through reporting requirements. Dr. Hitt added that requirements are increasing for reporting on the use of controlled substances in veterinary medicine, which currently takes 20 hours a month of employee time in his practice, and veterinary practices are struggling with those requirements. Paula J. Fedorka Cray, Ph.D., and Dr. Hitt agreed that more research is needed on transmission of infectious pathogens between humans and companion animals, particularly transmission of resistant organisms.

Sara E. Cosgrove, M.D., M.S., raised concerns that large pharmacy chains allow automatic refills for antibiotics, which is an open invitation for unnecessary use. Dr. Wiehl was unaware of such events but suspected that automated phone systems for refills might facilitate them. He added that independent and community pharmacies tend to be more involved with patients than large chains. Walgreens and CVS are promoting health initiatives but cutting support staff, putting more burden on pharmacists, said Dr. Wiehl.

Dr. Hitt emphasized that consumer education and good provider communication are as important in veterinary practice as in pediatric practices to reduce patient demand for unnecessary antibiotics. He acknowledged that prescribing antibiotics might have been a source of revenue for veterinary practices as little as 10 years ago, but the market has changed dramatically, and consumers have access to many other options for filling pet prescriptions now, so that incentive is gone.

Asked about diagnostics, Dr. Santos said practitioners at Children's Hospital Colorado use the rapid diagnostic test for strep throat frequently to dictate treatment. He did not think the rapid influenza diagnostic test would be very useful, because the only available antivirals for influenza in children are not generally indicated for otherwise healthy pediatric patients, so confirming the infection with a test would not aid in treatment decisions.

Dr. King wondered whether very large, national veterinary practices (e.g., as proposed by Walmart) would be likely to institute stewardship programs or whether they would be driven by profit motive to prescribe antibiotics that can be purchased on site. Dr. Hitt said such practices would face the same pressures that retail-based outpatient clinics do in human medicine, which is

the client's demand for a quick answer to the problem. Clinics profit by the volume of patients seen, which Dr. Hitt said translates to pressure to dispense antibiotics. Also, as in human medicine, general practices will not be able to rely on providing routine care and treating minor conditions to offset the cost of more intensive care, which will further affect practices.

Panel 5: Solutions to Facilitate Behavior Change

Moderator: Robert A. Weinstein, M.D., PACCARB Voting Member

Tracking Antibiotic Resistance and Demonstrating Responsible Antibiotic Use

Joel Nerem, D.V.M., Swine Veterinary Team and Applied Research Group Lead, Pipestone Veterinary Services

Dr. Nerem described the Pipestone Antibiotic Resistance Tracker (PART), an interactive, web-based tool for surveillance at the farm level (primarily pig farms) that also provides a platform for independent producers to communicate about antibiotic resistance. More than 150 producers subscribe, accounting for 300 sites and about 8 million pigs. Subscribers participate in quarterly reviews of antibiotic use and also receive complementary veterinary visits.

Dr. Nerem explained that Pipestone looked retrospectively at the susceptibility and resistance patterns of the isolates from clinical cases submitted to area veterinary diagnostic laboratories over the past 18 years to develop a resistance index across five of the main swine pathogens. It showed no significant changes in susceptibility among the five pathogens over the time assessed. A pilot project is comparing samples from farms with those from other types of sites to assess resistance patterns in isolates. A prospective study is evaluating antibiotic use protocols in relation to resistance in infected pigs.

The PART tool enables subscribers to benchmark and track antibiotic use, which will help improve AS. The tool captures antibiotics delivered by water, injection, or feed as grams-per-pig (to simplify interpretation); users can also look at antibiotic use by class, relative importance to human medicine, and cost. To encourage responsible antibiotic use, subscribers see where their overall antibiotic use falls in terms of a group—least, intermediate, or most antibiotic use—so they can focus on moving toward lesser use. Dr. Nerem noted that Pipestone collaborates with the Minnesota One Health program, the University of Minnesota, and the International Consortium on Antibiotic Stewardship in Agricultural Research.

Antimicrobial Stewardship Messaging in Canada

Denise Gilby, M.Sc., Acting Manager for AMR Program Policy, Center for Communicable and Infectious Disease Control, Public Health Agency of Canada

Ms. Gilby emphasized that (1) effective messaging involves understanding knowledge, attitudes, and behaviors of patients, prescribers, and the general public and (2) messaging must be tailored to the target population and recognize relevant social and cultural factors. The Public Health Agency of Canada's June 2019 report "Handle With Care: Preserving Antibiotics Now and Into the Future" examines some of the social and cultural reasons behind unnecessary antibiotic use. It assumes that individuals are more likely to change their behavior in response to a coordinated approach that considers individual life experiences and the interplay between barriers and

opportunities. To address the root causes of unnecessary antimicrobial use, interventions must be tailored to address obstacles and capitalize on opportunities for sustained behavior change.

The Public Health Agency and partners created the Using Antibiotics Wisely campaign, which applies principles of implementation science to address barriers to behavior change. It provides stewardship tools for providers as well as education for patients (available in multiple languages). The Public Health Agency developed accredited professional continuing education modules on antimicrobial stewardship in public health as well as a community education program, Do Bugs Need Drugs?, for the public and community-based health care professionals. It also created a school curriculum on understanding antibiotic resistance that has been internationally recognized as a best practice; it provides training so that interested Canadian provinces and territories can customize the program to local needs.

To increase public awareness, the Public Health Agency ran a five-week social marketing campaign using print and digital media, including social media. It targeted adults over the age of 60 because data from the 2018 Canadian Antimicrobial Resistance Surveillance System report showed that prescribing rates are increasing in that population. The Public Health Agency is conducting public opinion research on knowledge, attitudes, and behaviors related to AMR and antibiotic use. It is also analyzing data from a 2018 survey on antimicrobial use, adherence to prescriber directions, and disposal of unused medications.

Guidelines for Implementing AS in the Dental Industry

Alonso Carrasco-Labra, D.D.S., M.Sc., Ph.D.(c), Senior Director of Evidence Synthesis and Translation Research, American Dental Association (ADA)

Dr. Carrasco-Labra referenced the *JAMA* article finding that 81 percent of antibiotic prophylaxis in dentistry was unnecessary. He said general dentists and specialists have few tools to effectively implement many of the core elements of AS. In 2019, the World Dental Federation highlighted the need for guidance on AS in dentistry, calling for updated evidence-based guidance on infection management and education on communication (to address patients' and clinicians' ingrained perceptions). It also framed three messages that could reduce antibiotic use:

- Antibiotics do not cure toothache.
- Pain should be treated with analgesics.
- Prevention of oral disease reduces the likelihood of infections.

In 2015, ADA published a guideline on antibiotic prophylaxis before dental procedures in patients with prosthetic joints, which is by far the most popular guideline it has ever published. Later this year, it will publish two evidence-based clinical practice guidelines on antibiotics in emergency management settings, where dentists are not readily available. A multidisciplinary panel of experts created the guidelines to include the perspective of emergency medicine practitioners so that they reach the broader medical community. The guidelines include algorithms to facilitate implementation and materials for patient education.

Dr. Carrasco-Labra said ADA aims to disseminate the key messages articulated by the World Dental Federation to professionals and the public. ADA is gathering data to quantitate the harm of overprescribing antibiotics in dentistry to better inform practice. It is developing tools to

facilitate shared decision making with patients (which is not common in dentistry) to achieve better outcomes. Dr. Carrasco-Labra noted that ADA's initial efforts to encourage coordination with other health care providers and inclusion of dentists in the multidisciplinary health care team have been very well received.

Discussion

Asked whether Canada sees regional differences in antibiotic use, Ms. Gilby said analysis pinpointed high prescribing rates in eastern Canada, and her office is targeting efforts there. Data found that high prescribers of antibiotics also tend to be high prescribers of opioids and other medications. Ms. Gilby noted the Do Bugs Need Drugs? program has been rigorously evaluated and shown to be effective in reducing antibiotic prescribing among physicians (but results in an increase in prescribing among dentists).

Dr. Nerem observed that variations in antibiotic use on farms depends highly on location, among other factors. On farms in areas with high animal density, animals are more often exposed to viral disease and secondary bacterial infections than animals on farms in less dense areas. Council members looked forward to seeing more data from the PART tool.

Ms. Gilby said uptake of Choosing Wisely Canada has been high, particularly among family practice physicians, thanks to the strong support of the College of Family Physicians of Canada. Because it is driven by prescribers, the program is tackling the barriers to implementing guidelines for appropriate antibiotic use in practice.

Asked how to overcome entrenched beliefs about the utility of antibiotics, Dr. Carrasco-Labra said the first step is to conduct research specific to dentistry that can support the message that antibiotics do not cure toothaches. The challenge is to make the distinction between bacterial infections that require antibiotics and other infections that do not.

Helen W. Boucher, M.D., FIDSA, FACP, noted that the American Academy of Orthopedic Surgery's 2016 guidelines recommend dental prophylaxis for patients who have had joint replacement; she asked whether ADA has support from that group for its 2015 guidelines. Dr. Carrasco-Labra said the situation is complicated, because only a very small proportion of the population has prosthetic joints and infections are infrequent in this group—but they can be devastating. The ADA guidelines recommend against antibiotic prescription in general for patients with joint replacements; Dr. Carrasco-Labra hoped that future recommendations would clarify the strength of the evidence behind the recommendations and discuss any related discrepancies between the dental and medical communities.

Dr. Nerem said that in the future, it might be possible to use the PART tool to compare producers' antibiotic prescribing practices against resistance changes. He added that Pipestone plans to expand resistance surveillance to all subscribers and to build a large data set of antibiotic resistance in swine pathogens. Dr. Cray emphasized the need to distinguish pig pathogens from ancillary pathogens.

Dr. Musmar pointed out that in many dental practices, hygienists and technicians spend much more time with patients than dentists and so might be effective collaborators for communicating

key messages. Dr. Carrasco-Labra said hygienists are included in the expert panels that create guidelines and have been very effective in strengthening ADA's messages within the community. He said ADA strives to produce materials that can be used easily by the whole dental team but acknowledged that it is challenging. Dr. Carrasco-Labra noted that once ADA gathers more quantitative data on antibiotic use in dentistry, it will address antibiotic use in oral surgery.

Dr. King wondered whether the long-established quality assurance programs in the pork industry led to pork producers being interested in and subscribing to the PART tool. Dr. Nerem agreed, noting that those programs have been in place for decades. In addition, he believed that many pork producers are attuned to consumer concerns and anticipate that the PART tool will help them demonstrate appropriate antibiotic use in their products.

Panel 6: Solutions to Facilitate Behavior Change: Education at the Foundation

Moderator: Aileen M. Marty, M.D., FACP, PACCARB Voting Member

CDC Antibiotic Resistance Education Efforts for the Public

Nicole Coffin, Senior Advisor, Strategic Policy, Communications, and Partnerships, CDC

Ms. Coffin explained that the Be Antibiotics Aware campaign expands on the Get Smart campaign to improve appropriate antibiotic use. She described the process involved in creating the award-winning public service announcement video for the new campaign, which emphasizes using the right tool for the job. CDC is currently targeting a number of specific groups, including, for example, Spanish-speaking women and healthy adults who visit urgent care centers. In-depth formative research revealed that many people believe antibiotic resistance is serious, but few understand how it occurs. Most consumers say they would be satisfied if a health care provider did not prescribe antibiotics as long as they received something to address their symptoms. Many like the idea of delayed prescribing, but not all would wait before filling the prescription. CDC conducts several rounds of testing to get the messages right and drills down into research to identify specific audiences and how to reach them.

Staff working with the Be Antibiotics Aware campaign meet regularly with staff from the Getting Ahead of Sepsis campaign to share research and tactics and to make sure the two campaigns do not contradict each other but rather amplify each other. Ms. Coffin stressed that people should understand that antibiotics are lifesaving, especially to address early signs of sepsis. Professional organizations, patient advocates, and consumer representatives have been crucial to disseminating campaign materials broadly. Since the campaigns launched, 2.6 million people have visited CDC's antibiotic use website.

Ms. Coffin said CDC spreads the message about antibiotic resistance on a regular basis through many channels, including Facebook and Instagram. It is also updating its 2013 antibiotic resistance threat report, applying many principles for effective communication, such as plain language and high-impact visuals.

Outcomes of European and World Antibiotic Awareness Campaigns

Herman Goossens, Ph.D., Professor of Microbiology, University of Antwerp; Director, Department of Clinical Pathology of the University Hospital, Antwerp (via phone)

In 2008, ECDC launched the European Antibiotic Awareness Day (EAAD), which is supported extensively by the European Commission, the European Parliament, European Union (E.U.) member states, and nongovernmental stakeholders. Dr. Goossens said EAAD focuses on both changing behavior and raising awareness around antibiotic resistance and prudent use among the public, primary care providers, and health care providers in hospital and other settings. It also aims to contribute to E.U. and global discussions about emerging antibiotic resistance.

Dr. Goossens described the timeline and planning activities around the annual EAAD, which takes place annually on November 18. Much effort revolves around translating materials into different languages and encouraging countries to specify target audiences. The materials are similar to those developed by CDC. The main "customers" for these materials are the national health authorities, which organize and fund EAAD and promote it in their countries. However, materials are available for free online for anyone to use for noncommercial purposes only (which has been an issue in some countries).

As a result of EAAD, knowledge among the general public about antibiotic use and resistance has increased slowly. Participation has risen steadily in EAAD and in World Antibiotic Awareness Week (WAAW, launched by the World Health Organization in 2015) to include most European countries, with significantly more traffic to the EAAD and WAAW websites during the week of November 18. Media coverage has been positive or neutral throughout and has gone up in most years; it spiked in 2018 thanks to related news on AMR in the E.U. and survey results from European hospitals on antimicrobial use. Dr. Goossens said EAAD uses social media but learned in 2016 to be careful about diffusing attention by using too many hashtags. During WAAW in 2018, messaging focused on a different objective of the WHO's Global Action Plan each day of the week.

Dr. Goossens summarized lessons learned so far from the EAAD and WAAW:

- Develop clear objectives and clear, evidence-based messages and slogans.
- Understand local populations and conditions (e.g., some countries focus on self-medication).
- Allow for adaptive design.
- Engage behavioral scientists.
- Invest in social media.
- Provide compelling real-world cases.
- Plan ahead for evaluation of impact.

Dr. Goossens said the evaluation data can show how countries saved a lot of money on health care costs as a result of the campaigns.

Animal Health Programs for 4-H Youth

Christopher Anderson, 4-H Youth Development Specialist, Animal Science, University of Maryland Extension, Maryland 4-H Center

Mr. Anderson explained that the 4-H program is administered by the National Institute of Food and Agriculture of the U.S. Department of Agriculture, coordinated within each state by cooperative extension programs of land-grant universities, and delivered locally at the county and parish levels. He described the many activities and programs serving youth ages 5–18 years. In Maryland, for example, more than half of the 10,000 youth in community 4-H programs are involved in animal science projects, which emphasize responsible management practices to ensure animal well-being, safety, and quality assurance. Education includes understanding the Veterinary Feed Directive and the need for good recordkeeping as an essential element of compliance. The importance of biosecurity to prevent the spread of pathogens is also covered.

The 4-H Youth Development Program seeks to provide consistent messages across a variety of contexts, said Mr. Anderson. In addition to club activities, 4-H hosts various animal science educational meetings, workshops, demonstrations, and field days at the county and state level, and youth participate in fairs and exhibitions. Youth demonstrate animal science knowledge and skills through judging programs (i.e., learning to select animals based on desirable characteristics), academic competitions (e.g., quiz bowls), arts and communications contests, and animal science camps.

The topic of AMR comes up in various 4-H programs. For example, recent workshops have addressed management practices to slow the development of resistant worms in certain animal species. When regulatory requirements change, 4-H uses the opportunity to provide education around compliance. Grant funding also plays a role; the Maryland 4-H program received CDC funds to partner with the state to develop materials and strategies to teach youth about identifying and preventing zoonotic diseases. Mr. Anderson said 4-H sees youth as important public representatives of animal agriculture as well as the future leaders in agriculture.

Tiny Earth: Crowdsourcing Antibiotic Discovery

Jo Handelsman, Ph.D., Director, Wisconsin Institute for Discovery; Vilas Research Professor, University of Wisconsin—Madison; Professor, Howard Hughes Medical Institute

Tiny Earth was an effort to increase the number of science-literate college graduates, address the serious soil crisis, and address increasing antibiotic resistance paired with a decreasing number of new antibiotics. The course trains students to discover antibiotic-producing bacteria from soil. Instructor training is offered twice a year and is open to teachers at all postsecondary institutions and some high schools. The training links instructors to a network of peers who interact regularly to share ideas and troubleshoot problems. At the end of the course, students send their isolates to the chemistry hub in Madison, WI, for characterization. Dr. Handelsman noted that a new approach using mass spectrometry speeds up the process of profiling crude mixtures before determining whether they are worth the effort of purification. The chemists partnering with Tiny Earth have also created powerful programs to identify new signatures for compounds and to characterize compounds by family.

The information gathered by students goes into an online database. Dr. Handelsman said another course is being developed that will guide students through applying machine learning to the

database to better understand existing antibiotics and perhaps discover new ones. Despite skepticism in the pharmaceutical industry, Dr. Handelsman believes it is possible to discover new antibiotics. Crowdsourcing the effort by using students opens the door for innovation, as students are not bound by dogma. For example, students in the first Tiny Earth class discovered that using potato dextrose agar media doubles the frequency of antibiotic producers over any of the standard media used in industry. Sequencing of antimicrobial-producing isolates discovered by Tiny Earth students identified 824 biosynthetic gene clusters that revealed new information, including some as-yet unknown clusters.

Tiny Earth is expanding to train more instructors in new countries. A recent pilot program funded Tiny Earth students from 20 colleges to conduct outreach education about antibiotics and resistance in their communities. Evaluation of the impact is underway. Because children have a large impact on parents' behavior, Dr. Handelsman believes that targeting outreach to high school students could be effective in changing knowledge and behavior. Tiny Earth students take part in a competition to develop public service announcements, which will be expanded to include high school students this year. Evaluation of the Tiny Earth program overall depends on funding.

Discussion

Dr. Goossens said that to enhance media attention to EAAD, the Technical Advisory Committee engages health communication specialists from the member states, each of whom has a network of journalists with whom they have developed relationships. The Committee also invites journalists to spend a day at the ECDC to talk about antibiotic resistance and use. Journalists can also meet senior health and science government officials during EAAD and WAAW events.

Dr. Goossens said ECDC supports development of materials that are then used by the member states. He said it is disappointing that only about one quarter of member states are willing to make substantial investments in campaigns for their countries. Insufficient funding of the campaigns is a consistent complaint. Some data from Belgium and France demonstrated savings as a result of campaigns, said Dr. Goossens, but it is difficult to convince governments to invest.

The European Surveillance on Antimicrobial Consumption project was created to evaluate the impact of public health campaigns in European communities and hospitals; its metrics are imperfect but offer some basic data. Dr. Goossens said measuring antibiotic use at the hospital level and assessing the impact of public campaigns on hospital antibiotic use is extremely difficult. Additional information comes from the Eurobarometer, a periodic survey of citizens to gauge public knowledge and opinion on various topics that includes questions about antibiotics. Dr. Goossens said there is a direct correlation between media coverage and public knowledge. Evaluating the impact of the campaigns on health care costs is complicated by the fact that antibiotic costs are decreasing. In addition, antibiotic resistance is not a reliable measure of success, because the link between decreasing antibiotic use and decreasing resistance is confusing. The impact on prescribing is easier to measure and also more immediate, which appeals to policymakers.

Ms. Coffin said CDC uses similar surveillance methods. It plans a more robust evaluation of Be Antibiotics Aware in 2020 that includes baseline testing before messages are rolled out. Such

mechanisms can reveal whether messages reach the target audience. However, said Ms. Coffin, creating behavior change is hard to do, and measuring behavior change is equally difficult. It can take years before the impact of new knowledge is visible. Change requires a constant drumbeat of exposure to messages combined with socioeconomic and policy factors that support it.

Dr. Handelsman said Tiny Earth students who engaged in outreach had leeway to pursue advocacy if they chose, and some have contacted legislators. Mr. Anderson urged Council members not to underestimate the passion and ability of a teenager with a cause. 4-H aims to arm youth with reliable information that they carry with them into their communities and homes.

Ms. Coffin said the Be Antibiotic Aware campaign has a paid media budget of about $200,000, compared with the $30 million per year allotted for CDC's antitobacco campaign. With such a low budget, Ramanan Laxminarayan, Ph.D., M.P.H., noted, it is difficult to deliver a message that will affect behavior change. Mr. Craig said CDC's overall budget for addressing antibiotic resistance is $160 million. However, CDC supports all 50 states and the U.S. territories as well as countries around the globe. Dr. Laxminarayan hoped PACCARB would address the insufficient funding in future recommendations. Mr. Craig added that CDC has already developed excellent materials that can be distributed more broadly if more resources were available, as demonstrated by the award-winning video for Be Antibiotics Aware. Ms. Cole pointed out that CDC has an excellent presence on social media.

Dr. Handelsman noted that the chemistry hub at Madison has only just hired a chemist who can do the kind of testing needed to identify novel compounds. If new antibiotics are discovered, efforts will be made to commercialize them using a public model of development. Some big pharmaceutical firms have expressed interest in the program. A small group of entrepreneurs has provided some support. The Wisconsin Alumni Research Foundation has managed the patenting and licensing processes for some of the most frequently used drugs in the country, Dr. Handelsman added.

Regarding the challenge of behavior change, Dr. Handelsman noted that changing diet or quitting smoking requires an individual to give up something that provides immediate gratification and releases dopamine in the brain. Antibiotics do not offer such gratification, so it should be easier to convince people not to use them. Highlighting, for example, the link between antibiotics and obesity might be sufficient, Dr. Handelsman suggested. Dr. Blaser added that antibiotics involve two people—the prescriber and the patient—so campaigns must address both. Ms. Coffin agreed but noted that the challenge is to communicate the adverse effects of unnecessary antibiotic use while ensuring people still feel comfortable using antibiotics when needed, which is the goal of CDC's campaign on sepsis.

Ms. Cole pointed out that new messaging seems to counteract the message of patient empowerment. A constant stream of drug advertising urges patients to talk with their providers about specific drugs, and 70 years of thinking about antibiotics has led patients to believe that antibiotics are a safe cure-all. Those concepts should be considered in messaging, said Ms. Cole. She also proposed talking with FDA and advertising agencies about the language used in pharmaceutical advertising. Ms. Coffin replied that some of CDC's materials for providers seek to help them respond to pressure to provide antibiotics. Urgent care centers in particular are very

sensitive to customer satisfaction as a measure of performance. CDC is working with professional organizations to understand what kind of support providers need to avoid unnecessary prescribing.

Ms. Coffin said CDC is working to make more data publicly available about antibiotic use and to communicate the data in more user-friendly ways. Mr. Craig added that the online Patient Safety Atlas is updated annually and is an excellent resource. The National Healthcare Safety Network is getting better data at the hospital level. Mr. Craig believed that CDC will soon be able to provide hospital-level data by state to identify some trends over time. Ms. Coffin said CDC recently purchased data that will allow it to drill down into information by class of antibiotic. Mr. Craig noted that a new release of the Patient Safety Atlas gives users more ways to sort the data.

Mr. Anderson indicated that the One Health perspective is growing throughout 4-H programs. Dr. Handelsman said there is discussion about offering Tiny Earth as an online course. She is currently developing an online bioinformatics course that will focus on biosynthetic clusters for small molecules and will be broadly available.

Public Comment

Kevin Kavanagh of Health Watch encouraged the Council to evaluate the issue of risk adjustment of reported infection rates. For MRSA, risk adjustment cut the infection rate of a facility in half. It can also double rates in facilities with few infections. Interfacility variability is decreased, and performance comparisons become more difficult to make. An additional concern is that risk adjustment is based on old data from facilities that may not have implemented optimal current strategies, thus baking underperformance into the reporting system. It also can discourage innovation.

Recently the opioid epidemic is being used as an excuse for some to call for increased risk adjustment. But, Mr. Kavanagh asked, instead of mathematically decreasing elevated infection rates associated with opioid injection abuse, wouldn't it be better to allocate additional resources and perform admission screening and decolonization to lower actual infections? The actual number of patient infections is important to report. It is possible that similar to (unintelligible), low infection rates may be obtainable by almost all facilities, making the end so low that reliable interfacility comparisons may not be possible, which would also negate the need for risk adjustment.

In recent years the number of infections in the United States may have also been mitigated by the doubling of the number of bacteria needed to report a urinary tract infection, by increasing the time for occurrence of a hospital-acquired MRSA infection from 2 to 3 days postadmission. Almost no one is reporting on health care worker acquisition and infections from dangerous pathogens, said Mr. Kavanagh. A national reporting system for health care workers is desperately needed. Yesterday's presentations repeatedly referenced a lack of data on the incidence of these infections. It is necessary to start reporting and accurately tracking all dangerous pathogens, not just a few.

Data for action was one of the four pillars of health-care-associated infection elimination in the 2010 HHS' white paper, published in the *American Journal of Infection Control*. Almost a decade later, the task is still not accomplished.

Hua Wang of The Ohio State University said antibiotic resistance is a major public health challenge worldwide. It is important that key risk factors directly impacting the life and health of all human beings be spelled out clearly by the Council. At the meeting on May 4, 2017, Mary Millard shared her heartbreaking story of a hospital-acquired infection during a surgical procedure. Weeks later, she came down with sepsis. Despite a temporary rescue by antibiotics, the problem recurred once the treatment stopped. She has since been taking the highest dosage of antibiotics to suppress the deadly bacteria in her body, while suffering from various side effects, and knowing this maintenance would fail one day. She sadly said that she is pretty much sentenced to death.

While most, including the patient, believe that her problems were due to irresponsible uses of antibiotics, the real causes were different. Dr. Wang reinterpreted the case afterwards to the patient and the microbiologists in this country. Her problems were likely due to the lack of preventive antibiotic application, giving the chance for *Pseudomonas aeruginosa* to form as biofilm, which is naturally resistant to any drug treatment, including antibiotics. Meanwhile, the oral antibiotic she was given massively destroyed her gut microbiota, which further led to many of the side effects she suffered.

During the same meeting, Dr. Wang gave her first public comment, and again in September 2018 and January 2019, sharing her findings, published in a news release in 2013 by the American Society for Microbiology. Dr. Wang discovered that the uses of antibiotics would not necessarily lead to massive antibiotic resistance and gut microbiota dysbiosis. Instead, the real and the direct causes are giving drugs orally and using drugs excreted through the liver and the gut, which unnecessarily exposes trillions of gut bacteria to high-dosage antibiotics, causing massive resistance as well as disturbing gut microbiota, which are now known to cause additional serious health consequences from side effects like Ms. Millard suffered to the deadly C. difficile flare, as well as many noncommunicable modern diseases.

This conclusion was further supported by clinical and animal data from more research teams showing that an injection of antibiotics primarily excreted through the kidney or urine, like vancomycin, causes almost no damage to the gut microbiota. These discoveries separated antibiotic applications from the mentioned side effects, which may prompt the prevention and treatment with minimized side effects—an achievable goal. They further presented the pressing need for innovative research for targeted mitigation of the mentioned key risk factors, and to change the mainstream practice in both medicine and food animal production. However, this knowledge remains unknown to most health professionals, legislators, and the general public. Meanwhile, the massive, unnecessary losses in public health and the social economy still continue. Dr. Wang said the information has been shared a number of a number of times. She expected the Council to justify the reason why it is not being discussed or mentioned in the NAP or recommendations.

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 and participants. He highlighted some questions that PACCARB might want to explore:

- Who is really allergic to penicillin?
- Can diagnostics be assessed for their ability to distinguish viral from bacterial infection?
- What tools have the widest application to change public and provider behavior?
- Are there alternatives to antibiotics not yet considered by the Council?
- What is the role of large pharmacies in AMR?

In closing, Dr. Blaser reminded participants that vaccines can help prevent the infections that require antibiotics. Developing and improving access to vaccines can help improve antibiotic use, enhance patient treatment, and bolster the fight against antibiotic resistance. More information is available at vaccines.gov. Dr. Blaser adjourned the meeting at 3:17 p.m.

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

July 10–11, 2019

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 R. Cole
Sara E. Cosgrove, M.D., M.S.
Paula J. Fedorka Cray, Ph.D.
Christine Ginocchio, Ph.D., MT
Kent E. Kester, M.D., FACP, FIDSA, FASTMH
Ramanan Laxminarayan, Ph.D., M.P.H.
Aileen M. Marty, M.D., FACP
Robert A. Weinstein, M.D.
David White, M.S., Ph.D.

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. (by phone, day 1)

Pew Charitable Trusts
Kathryn L. Talkington

Regular Government Employees Present
U.S. Department of Health and Human Services
Michael Craig, M.P.P. (for Rima Khabbaz, M.D.), National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (day 2)
Dennis M. Dixon, Ph.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health (day 1)
Lynn Filpi, Ph.D. (for Lawrence Kerr, Ph.D.), Office of Pandemics and Emerging Threats, Office of Global Affairs

William Flynn, D.V.M., M.S. (for Daniel W. Sigelman, J.D.), Center for Veterinary Medicine, Food and Drug Administration (day 2)
Christopher Houchens, Ph.D., Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response
Rima Khabbaz, M.D., National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (day 1)
Jane Knisely, Ph.D. (for Dennis M. Dixon, Ph.D., on day 2), National Institute of Allergy and Infectious Diseases, National Institutes of Health
Daniel W. Sigelman, J.D., Office of Public Health Strategy and Analysis, Office of the Commissioner, Food and Drug Administration (day 1)

U.S. Department of Agriculture
Neena Anandaraman, D.V.M. (for Emilio Esteban, D.V.M., M.BA., M.P.V.M., Ph.D.), Food Safety and Inspection Service
Roxanne Motroni, D.V.M., Ph.D. (for Jeffrey Silverstein, Ph.D.), Agricultural Research Service (day 1)
Chelsey Shivley, D.V.M., Ph.D., DACAW (for Sarah Tomlinson, D.V.M.), Animal and Plant Health Inspection Service
Jeffrey Silverstein, Ph.D., Agricultural Research Service (day 2)

U.S. Department of Defense
Twee Sim (for Paige Waterman, M.D., FACP, FIDSA) (day 2)
Paige Waterman, M.D., FACP, FIDSA, Walter Reed Army Institute of Research (day 1)

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

Advisory Council Staff
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

ADA	American Dental Association
AI	artificial intelligence
AMR	antimicrobial resistance
AS	antibiotic stewardship
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
DIR	direct and indirect remuneration
EAAD	European Antibiotic Awareness Day
ECDC	European Center for Disease Prevention and Control
EPA	U.S. Environmental Protection Agency
E.U.	European Union
FDA	U.S. Food and Drug Administration
HHS	U.S. Department of Health and Human Services
IP	infection prevention
JAMA	*Journal of the American Medical Association*
MRSA	methicillin-resistant *Staphylococcus aureus*
NAP CARB	National Action Plan for Combating Antibiotic-Resistant Bacteria
NARMS	National Antimicrobial Resistance Monitoring System
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OASH	Office of the Assistant Secretary for Health
OIDP	Office of Infectious Disease and HIV/AIDS Policy
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PAHPAI	Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019
PART	Pipestone Antibiotic Resistance Tracker
UCSD	University of California, San Diego
vSNFs	Skilled nursing facilities that provide ventilator care
WAAW	World Antibiotic Awareness Week