

# PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

## **Meeting Summary**

**Eleventh Public Meeting of the  
Presidential Advisory Council on  
Combating Antibiotic-Resistant Bacteria  
January 30–31, 2019**

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

## Table of Contents

Day 1 .....	1
Welcome .....	1
Overview, Rules of Engagement, and Roll Call .....	1
Opening Remarks and Member Appreciation .....	1
Overview of Day 1: Innovations In CARB.....	2
<b>Panel 1: One Health Surveillance and Big Data .....</b>	<b>3</b>
Global Infrastructure and Surveillance: The U.S. Role Abroad .....	3
Using Clinical Data to Create a Regional One Health AMR Surveillance Database.....	3
Big Data Analysis of Integrative Conjugative Exchange (ICE) and AMR Evolution .....	4
Discussion.....	4
<b>Panel 2: Infection Control and Prevention.....</b>	<b>5</b>
Rush to Brush Health Initiative: Reducing the Incidence of Hospital-Acquired Pneumonia with Oral Hygiene.....	5
Prophylactic Use of Vaccines (Passive/Active Immunity) to Prevent AMR Infections .....	6
Internal Biosecurity Project and Geofencing for Infection Control in Swine Farms .....	6
Biosecurity in Africa.....	6
Discussion.....	7
<b>Panel 3: Antibiotics, Therapeutics, and Alternatives .....</b>	<b>7</b>
Discovery of Veterinary-Spectrum-Specific Antibacterial Agents: The Need for Innovation in Animal Health.....	7
Phages as Antibiotic Alternatives and Their Use in Humans, Agriculture, and Aquaculture	8
Antibiotic Manufacturers’ Commitments: Supporting Measures to Reduce Concentrations of Antibiotics in Manufacturing Waste Discharges.....	8
Realities and Challenges of Pharmaceutical Development .....	9
Discussion.....	9
<b>Panel 4: Vaccines and Diagnostics.....</b>	<b>10</b>
Earlier Targeted Effective Antibiotic Therapy Through Culture-Independent Diagnostics	10
Prioritization of Vaccines to Reduce Antibiotic Use in Animals .....	10
Discussion.....	10
Public Comment.....	11
Final Comments and Adjournment for the Day.....	16
Day 2.....	16
Roll Call.....	16
Debrief of Day 1: Innovation.....	16
Overview of Day 2: Use of Antibiotics .....	16
<b>Panel 5: Grass Roots Engagement and Advocacy .....</b>	<b>17</b>
U.S. Federal Policy and Agricultural Antibiotic Use .....	17

One Water and Public Health: Research to Action Through Outreach and Education .....	17
The Importance of WASH in Preventing AMR and Improving Health Outcomes .....	18
Engaging the Public With AMR and Hand Hygiene .....	18
Discussion .....	18
<b>Panel 6: Consumer Impact on Antibiotic Use .....</b>	<b>19</b>
Antibiotic Use in Small-Scale Livestock Producers in Ecuador .....	19
Addressing AMR as a Global Restaurant Company.....	20
Outpatient Antibiotic Stewardship: Interventions That Work .....	20
Sustainability of Antibiotics .....	20
Discussion .....	21
<b>Panel 7: One Health Surveillance.....</b>	<b>21</b>
AMR in South Africa.....	21
Small Animal Surveillance and One Health .....	22
One Health Data Reporting, Sharing, and Collaborating .....	22
Using Medicaid Data to Map Avoidable Prescribing Practices.....	22
Discussion .....	23
<b>Panel 8: Prescriber Behavior Change.....</b>	<b>24</b>
Big Data to Improve Antibiotic Prescribing .....	24
Reducing Antimicrobial Use in Animals and Promoting a Mindset Change .....	24
Minnesota One Health Antibiotic Stewardship Collaborative.....	24
Accelerating International Progress on AMR.....	25
Discussion .....	25
Public Comment.....	26
Final Comments and Adjournment.....	30
Appendix A: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Members .....	31
Glossary of Abbreviations .....	33

# Meeting Proceedings

## Day 1

### 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 goal of this meeting was to respond to the charge of the Secretary of the Department of Health and Human Services (HHS) to PACCARB to gather broad public input on combating antimicrobial resistance (AMR).

### Overview, Rules of Engagement, and Roll Call

*Jomana F. Musmar, M.S., Ph.D., Designated Federal Officer (Acting), National Vaccine Program Office, 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 (FACA) and conflict-of-interest guidelines and called the roll. (See Appendix A for the list of participants.)

### Opening Remarks and Member Appreciation

*Assistant Secretary for Health Brett P. Giroir, M.D., ADM, U.S. Public Health Service, HHS; and Deputy Secretary for Health Eric D. Hargan, HHS*

Dr. Giroir thanked the Council for its work. He said AMR is a national and global priority that must be addressed. In his work as a pediatric critical care physician, he dealt with the effects of AMR every day, and he realizes how important combating AMR is to parents, children, and anyone in contact with the healthcare system. Dr. Giroir said the Department's efforts to take a One Health approach to AMR are bolstered by the appointment of Tammy R. Beckham, D.V.M., Ph.D., a veterinarian and bioscientist, as Acting Director of the National Vaccine Program Office. Dr. Giroir emphasized that the Council has his full support and attention.

Mr. Hargan welcomed the Council members and other attendees and thanked them and all the stakeholders who play a role in the effort to combat AMR. The National Action Plan (NAP) for Combating Antibiotic-Resistant Bacteria (CARB), published in 2015, has enhanced the work of the CARB Task Force, which represents nine HHS divisions and seven other Departments, including the Task Force co-chairs, the Department of Defense (DoD) and the Department of Agriculture (USDA). The Task Force coordinates efforts to ensure alignment across federal agencies that is vital to addressing AMR challenges. Mr. Hargan said HHS makes AMR a priority in its global and domestic work. He emphasized that AMR is a real and looming threat to the promise of modern medicine. The United States has made significant investments in research and development (R&D) but needs partners, such as the stakeholders taking part in this meeting, to take efforts further. Collaboration with nongovernmental organizations and the private sector is crucial to moving forward.

Secretary Alex M. Azar II launched the AMR Challenge, a year-long global call to action to accelerate the fight against AMR, at the United Nations General Assembly in fall 2018, and Mr. Hargan reiterated the importance of AMR at the Global Health Security meeting later that year.

The AMR Challenge invites stakeholders across the public and private sectors and around the world to identify ways that they can contribute to the fight. Mr. Hargan said HHS is grateful for the Council's leadership across this initiative and hoped it would encourage others to join in this important endeavor to protect people, animals, and the environment around the world from this terrible threat.

Despite existing initiatives to support early-stage product development and incentives provided through legislation, HHS remains concerned about the pipeline of new antibacterial drugs. Along with several partners, HHS is working to understand what is needed to foster innovation in antibiotic development in the short and the long term to ensure effective antibiotics for generations to come. Early and aggressive action can keep pathogens with new or unusual resistance from spreading. Under the NAP, the Centers for Disease Control and Prevention's (CDC's) domestic investments and partnerships have increased laboratory, epidemiological, and outbreak response capacity to effectively respond to emerging threats, such as the potentially fatal multidrug resistant fungus *Candida auris*.

Some positive signs of progress are emerging, said Mr. Hargan. According to the U.S. Food and Drug Administration (FDA), U.S. sales and distribution of antimicrobials approved for use in food-producing animals dropped by 33 percent from 2016 to 2017, suggesting progress in efforts to reduce unnecessary use and improve stewardship. Still, other challenges remain. Globally, gaps in knowledge and capacity prevent progress and undermine efforts to prevent the global spread of AMR pathogens. The threat of AMR is evolving, domestically and internationally, so it is time to update the NAP. The Council will play a key role in ensuring that the country keeps moving forward. Gathering public input on the NAP is crucial to the work ahead.

On behalf of Secretary Azar, Mr. Hargan thanked the retiring Council members:

- Peter Robert Davies, B.V.Sc., Ph.D.
- John H. Rex, M.D.
- Thomas R. Shryock, Ph.D.
- Randall Singer, D.V.M., M.P.V.M., Ph.D.

He also welcomed the new members who are beginning their terms at this meeting:

- Paula J. Fedorka-Cray, Ph.D.
- Christine Ginocchio, Ph.D., MT
- Locke Karriker, D.V.M., M.S.
- David White, M.S., Ph.D.

## **Overview of Day 1: Innovations in CARB**

*Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, and Kathryn L. Talkington, Innovation and R&D Subgroup Leads*

Dr. King explained that the NAP is being updated to reflect changes in the landscape around AMR. The document will maintain the five goals and its One Health perspective. Ms. Talkington

added that the initial NAP galvanized energy and progress on this critical issue. She stressed the need to ensure that the next iteration is equally meaningful.

## **Panel 1: One Health Surveillance and Big Data**

### **GLOBAL INFRASTRUCTURE AND SURVEILLANCE: THE U.S. ROLE ABROAD**

*Marc Sprenger, M.D., Ph.D., Director, AMR Secretariat, World Health Organization (WHO)*

Dr. Sprenger emphasized that information is key to action. The number of sites reporting to WHO's Global Antimicrobial Resistance Surveillance System (GLASS) tripled from 2017 to 2018 but still only accounts for about 30 percent of countries. Many countries have data that they do not provide. Gathering reliable information on human clinical use requires, at minimum, a laboratory that follows procedures for providing high-quality data, which is a struggle for even middle-income countries. With a better understanding of antimicrobial use, the WHO and others can educate countries about changing practice patterns and using the right drugs for treatment.

In low- and middle-income countries, 40 percent of healthcare facilities have no source of water; furthermore, 61 percent of the world's population does not have access to safe sanitation. Without investment in the basics of infection prevention and control (IPC), new antimicrobials will not fix the growing problem of AMR. Dr. Sprenger called on the United States for support of the following to strengthen health security and the health system:

- Surveillance infrastructure and monitoring of antimicrobial use in low- and middle-income countries
- Appropriate use of antibiotics (stewardship programs)
- Water, sanitation, and hygiene (WASH) and IPC expertise and capacity
- Good animal husbandry and veterinary and environmental surveillance systems (One Health)

### **USING CLINICAL DATA TO CREATE A REGIONAL ONE HEALTH AMR SURVEILLANCE DATABASE**

*Peter Rabinowitz, M.D., M.P.H., University of Washington Center for One Health Research*

Dr. Rabinowitz described a statewide effort to integrate human, animal, and environmental data to understand emerging AMR in the region, develop interventions, and foster a shared stewardship model. Data are gathered from the National Antimicrobial Resistance Monitoring System (NARMS), area hospitals, outpatient laboratories, and diagnostic laboratories for animals. Challenges include the variations in antibiotic use between human and animal medicine, differences in susceptibility, confidentiality and ethics concerns, and data integration. However, combining regional data allows stakeholders to look at patterns of resistance, in animals and humans, that affect specific areas. The approach offers the potential for tracking resistant strains even without whole genome sequencing capacity. The ability to feed data back is key to progress.

## **BIG DATA ANALYSIS OF INTEGRATIVE CONJUGATIVE EXCHANGE (ICE) AND AMR EVOLUTION**

*James Kaufman, Ph.D., Distinguished Research Staff Member, IBM Almaden Research Center*

Dr. Kaufman described the use of cloud computing to assemble and annotate all the bacterial genomes in the National Center for Biotechnology Information's (NCBI's) Sequence Read Archive, which resulted in a database and technique for exploring questions. He and his colleagues used the database to identify ICE genes and related cargo genes. They found that the cargo genes are associated with resistance to the newest antibiotics; older, more common AMR genes are never cargo genes.

Dr. Kaufman emphasized that resistance genes transmit in response to the stress of antibiotics. Combating antibiotic resistance requires big data (e.g., from publicly available resources like the NCBI's databases), machine learning and artificial intelligence tools to link genotype and phenotype, and controlled experiments to understand resistance and transmission of resistance.

## **DISCUSSION**

### *Challenges to Tracking and Addressing AMR Globally*

Asked why so many parts of the world fail to report AMR data, Dr. Sprenger said that AMR surveillance requires a huge investment in infrastructure, a tailored approach, and a strong political effort. CDC and public health authorities in the United Kingdom are actively trying to coordinate efforts around the world, but in some countries, other immediate concerns take attention away from the need to monitor and address AMR. Dr. Sprenger added that the first step is political awareness of the problem. In addition, ministers of health and agriculture must talk to each other and truly collaborate to achieve the goals set out in their countries' national action plans, which often does not happen without political pressure. Dr. Sprenger said the countries involved in GLASS have committed to providing data.

Dr. Sprenger observed that WHO provides a lot of support for information technology (hardware and software) and for national coordination centers to collect and report data. However, countries need financial support for access to the right antimicrobials when the results of antimicrobial susceptibility tests are available.

Dr. Blaser pointed to overuse of over-the-counter antibiotics in many developing countries. Dr. Sprenger added that counterfeit or tainted antimicrobials are another problem that arises when antibiotics are available on the open market. However, he said, it is not clear whether to restrict the use of antibiotics in areas that do not have any healthcare providers. Health security is intertwined with the need for universal health coverage, which WHO considers its highest priority, and he hoped the United States would see the bigger picture and support developing countries in their efforts.

### *Domestic Approaches to Tracking AMR*

Dr. Rabinowitz said Washington State is building up capacity to report antibiotic use through CDC's National Healthcare Safety Network (NHSN) at the hospital level, but, in general, clinical laboratories and pharmacy systems are not connected around inpatient and outpatient data.

Ramanan Laxminarayan, Ph.D., M.P.H., pointed out that the value of data depends on what one can do with the information, particularly whether data can drive changes in practice or policy. Dr. Rabinowitz said there is growing interest in Washington State, but its program is just rolling out now. Asked whether human medicine clinicians and veterinarians use data differently, Dr. Rabinowitz said that, because of costs, veterinarians have not had local data. Having the data has changed the nature of the discussion from finger-pointing to seeking solutions.

In response to Dr. Fedorka-Cray and Dr. White, Dr. Rabinowitz said he would like to gather much more data, and more granular data, that would help assess the relationship of AMR to the environment. At present, the system cannot produce data at the household or even ZIP code level. Data sharing is hampered by the concerns of hospitals and clinics that fear being identified as hotspots of AMR. To better understand the environmental component of AMR, funding and cost-effective techniques are needed to support, for example, sampling wastewater and analyzing the findings in the context of human clinical and agricultural data. Dr. Sprenger noted that the WHO and the Food and Agriculture Organization of the United Nations (FAO) are collaborating on a tricycle AMR surveillance project that gathers samples from animals, humans, and the environment to assess resistance.

#### *New Mechanisms for Understanding Resistance*

Regarding the timeliness of the NCBI data source, Dr. Kaufman said efforts are underway to detect genomes, analyze them, and add them to the database quickly to pinpoint areas of resistance, but the mechanism can only detect genes already known to be resistant. The tools developed by IBM are being used by others to develop tests and treatments—for example, to identify protein sequences as drug targets or to determine whether an individual’s infection involves an ICE gene, signaling potential resistance. Dr. Kaufman believes the ICE data could lead to individualized treatment regimens.

Regarding the tension between reporting healthcare-acquired infections and maintaining privacy, Dr. Kaufman said that bacteria do not have a right to privacy, and every state requires reporting of certain diseases. The ability to offer assistance to hospitals could be an incentive to improve reporting, as could regulations.

## **Panel 2: Infection Control and Prevention**

### **RUSH TO BRUSH HEALTH INITIATIVE: REDUCING THE INCIDENCE OF HOSPITAL-ACQUIRED PNEUMONIA WITH ORAL HYGIENE**

*Mary Lee Conicella, D.M.D., Chief Dental Officer, Aetna*

Tooth brushing can prevent acquisition of pneumonia in hospitals, according to research conducted by Dian Baker, Ph.D., M.S.N.; one hospital reduced the incidence by more than 70 percent over 2 years. Aetna has partnered with manufacturers to create an oral healthcare kit with supplies and education that it will mail to members who are planning inpatient, elective procedures in the coming months. Dr. Conicella suggested hospitals and inpatient facilities should prioritize oral health to reduce the risk of nosocomial infections. She also called for better access to comprehensive dental benefits in government-funded programs, pointing out that people who achieve good oral health through regular dental care have fewer oral bacterial when they begin a hospital stay. Dr. Conicella was encouraged by recent federal attention to improving dental health.

## **PROPHYLACTIC USE OF VACCINES (PASSIVE/ACTIVE IMMUNITY) TO PREVENT AMR INFECTIONS**

*Timothy Cooke, Ph.D., Chief Executive Officer (CEO), Novadigm Therapeutics, Inc.*

Vaccines can prevent infections, thus decreasing antibiotic use and potential resistance. Dr. Cooke compared the product profile of vaccines with that of monoclonal antibodies, which appear to have strong potential for treating infectious diseases. He compared the development pipeline of both, noting some successes and failures. Innovation in both products is strong, but more products are needed at the earliest stages of the pipeline. Dr. Cooke said products can get stuck in phase-II development if investors do not provide funding; he called for investment by the Biomedical Advanced Research and Development Authority (BARDA) or a similar mechanism to help products move through the pipeline. Funding for biotechnology companies working on infectious disease is not favorable, he concluded.

## **INTERNAL BIOSECURITY PROJECT AND GEOFENCING FOR INFECTION CONTROL IN SWINE FARMS**

*Andreia Arruda, D.V.M., M.S., Ph.D., Assistant Professor, The Ohio State University*

Dr. Arruda described a technology solution that tracks workers' movement in real time throughout a farm. Preliminary data from pilot programs indicate the information can identify patterns related to risk (e.g., of swine mortality before weaning). Dr. Arruda and colleagues are also looking at movement among farms by evaluating when a device (e.g., cell phone) crosses into or out of a specified area. This approach gathers real-time movement data that can help with investigating outbreaks. Farmers and veterinarians can use the data to identify potential problem areas and evaluate the effectiveness of interventions. Dr. Arruda said both projects overcame the technological challenges of ensuring sufficient internet access in remote areas and encouraging workers to wear the monitoring devices. She added that the preliminary data are not disease-dependent and so may be useful for broad understanding of pathogens in livestock production.

## **BIOSECURITY IN AFRICA**

*Juan Lubroth, D.V.M., Ph.D., ACVPM, Chief Veterinary Officer, Chief, Animal Health Service, FAO*

Food biosecurity in Africa is limited by the reality on the ground. Most farmers lack education and do not have access to extension services. Many livestock and food transactions occur through informal systems, such as street sales. Animals and humans often live closely together, increasing the likelihood of transmitting pathogens. Access to vaccines and drugs for prevention or treatment is very limited.

Africa needs new approaches in financing and incentives to invest in, for example, extension services, rapid diagnostics, and waste management. It needs accessible, inexpensive, high-quality technological solutions. Dr. Lubroth urged the United States and other governments to increase attention to the barriers to good practices in food and agriculture and to invest in development.

## DISCUSSION

### *Using Vaccines to Prevent AMR*

Referencing PACCARB's report, *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic Resistance*, Dr. Cooke said it is possible to assess the value of vaccines that reduce AMR, but vaccine pricing never reflects the full value. In fact, vaccines are expected to be cost-neutral to the healthcare system. Dr. Laxminarayan said that vaccines targeted for specific uses have more favorable economic profiles and could be distinguished from the broad category of childhood preventive vaccines. Dr. Cooke agreed that vaccines for well-defined, high-risk groups should merit higher payment, but when such vaccines reach the market, bundling them with procedures and supplies for payment (as Medicare frequently does) leads to underpayment. On the upside, he noted, vaccines can be used prophylactically without causing resistance. Dennis M. Dixon, Ph.D., stressed the need to help small companies gather the right data to demonstrate the effectiveness of their products. He called for a more open approach to the drug approval process.

Asked whether manufacturers look at the unintended consequences of vaccines, such as their effects on the environment, Dr. Cooke said they do consider the long-term ramifications of vaccine use but there are not enough data on which to base conclusions.

### *Novel Techniques Targeting AMR*

Dr. Arruda acknowledged that once data confirm that real-time tracking is effective, the technology could be rolled out more broadly to enhance prevention. Her group seeks to further analyze the data collected from geofencing and demonstrate to stakeholders that sharing data can have positive results.

Dr. Conicella said research demonstrates that dental care can lower healthcare costs and morbidity, potentially saving the healthcare system billions of dollars. One barrier to making the case for dental coverage is that medical and dental providers do not share electronic health records (EHRs), even in big universities that have both medical and dental schools. Dr. Conicella said the Rush to Brush initiative exemplifies a simple, inexpensive solution; if larger studies underway confirm its effectiveness, it can be expanded.

### *The United States' International Role*

Dr. Lubroth echoed Dr. Sprenger's observation that political will is key to helping countries implement their action plans. He said the lack of private-sector voices at the table and the lack of accountability within countries represent failures. All the national action plans claim to have a One Health underpinning, but it is not realized. FAO hopes to offer guidance, assistance, and advocacy.

## **Panel 3: Antibiotics, Therapeutics, and Alternatives**

### **DISCOVERY OF VETERINARY-SPECTRUM-SPECIFIC ANTIBACTERIAL AGENTS: THE NEED FOR INNOVATION IN ANIMAL HEALTH**

*Jeffrey Watts, Ph.D., RM(NRCM), M(ASCP), Research Director, Zoetis*

Laying out the need for novel, non-shared agents to treat zoonotic disease, Dr. Watts described the barriers to and potential benefits of research on traditional small molecules and small

molecule antibiotic replacements (SMARs) that can take the place of traditional antibacterials. He compared the pros and cons of pursuing individual assets (i.e., potential products) with focusing on substrate-specific assets from an R&D perspective. Dr. Watts offered a number of recommendations to add to the NAP's Goal 4:

- Section 4.3: Identify R&D for new therapeutics.
  - Add a requirement for need for novel animal health agents to address multidrug-resistant animal pathogens.
  - Require all human health programs to include veterinary pathogens in screening programs for identification of agents that may have animal-pathogen-specific activity.
- Section 4.4: Develop nontraditional therapeutics.
  - Provide clear research guidance by defining alternatives to antibiotics, separating SMARs from other agents (e.g., vaccines, disinfectants).
- Sections 4.6 and 4.7: Enhance public-private partnerships.
  - Include animal health components.
  - Support veterinary startups with additional funding and expertise.

#### **PHAGES AS ANTIBIOTIC ALTERNATIVES AND THEIR USE IN HUMANS, AGRICULTURE, AND AQUACULTURE**

*Nancy Tawil, Ph.D., Vice President, Research, Phagelux Inc.*

Dr. Tawil described her company's success using bacteriophages as an adjunct or alternative to antibiotics, particularly targeting antibiotic-resistant bacteria. She gave an overview of the use of products to treat or prevent infections in humans, food crops, livestock, and aquaculture. Dr. Tawil emphasized that phages are naturally occurring products that are safe and effective. They can re-sensitize resistant bacteria to antibiotics, and there is therapeutic synergy between phages and antibiotics.

#### **ANTIBIOTIC MANUFACTURERS' COMMITMENTS: SUPPORTING MEASURES TO REDUCE CONCENTRATIONS OF ANTIBIOTICS IN MANUFACTURING WASTE DISCHARGES**

*Steve Brooks, Vice President, Global Environment, Health, and Safety, Pfizer; and Manufacturing Group Leader, AMR Industry Alliance*

The AMR Industry Alliance is concerned about the effects of pollution by drug manufacturing plants on the environment. While manufacturing is not the main source of antibiotic residue in the environment, it is a concern, particularly for livestock producers located around manufacturing plants. In 2016, Alliance members agreed to reduce the environmental impact of production with a series of commitments. So far, the Alliance has published the Common Antibiotic Manufacturing Framework, which codifies good practices, such as the need to understand the supply chain. It also created discharge targets. Mr. Brooks pointed out that meeting the targets will require time and increase costs. In 2020, the Alliance will report industry progress toward the commitments.

Mr. Brooks recommended that the NAP include the need for more research to better understand the nature and extent of the link between environmental sources of antibiotics and clinical antibiotic resistance and to illuminate the contributions of various sources (agricultural production, hospitals, manufacturing effluent, and human waste, among others). Domestically,

the U.S. Government (USG) should fund more research on wastewater treatment technology and offer incentives for municipalities to upgrade such technology. Internationally, the USG should work with other governments on improved sanitation to prevent the spread of AMR.

## **REALITIES AND CHALLENGES OF PHARMACEUTICAL DEVELOPMENT**

*Elaine Hamm, Ph.D., CEO, Ascend BioVentures*

Among the pitfalls facing startup biotechnology companies are the lack of sufficient funding or, in some cases, long delays in receiving promised funding; inexperienced management; lack of industry guidance; and entrenched age discrimination in funding. One company under her purview was a finalist for CARB-X funding, but it failed because the product was not yet ready for a startup effort, and potential partners offered conflicting feedback on the next steps. Another company developed a product with strong potential for treating a limited population, but no partners would fund the expensive research needed because the likely return on investment was low—a situation that frequently affects product development in the infectious disease realm. Startup companies would benefit from earlier help from pharmaceutical companies, new business and partnership models, more experienced personnel, and support for younger entrepreneurs (and minorities and women) and for early-stage innovation.

## **DISCUSSION**

### *Barriers to New Product Development*

Asked about the benefits of CARB-X, Dr. Hamm said she appreciated the program's willingness to take risks and also the attention to helping applicants work through the process. Still, small startup companies are struggling in this arena. Mr. Brooks said the AMR Industry Alliance includes biotechnology companies and seeks to share knowledge and expertise with them. Dr. Watts said early research findings often come from academics who lack experience in product development and marketing. The long development cycle for pharmaceuticals (15–20 years) poses a substantial barrier. The CARB-X model provides expertise and troubleshooting, but development is expensive, Dr. Watts noted.

Dr. Tawil said FDA has provided helpful guidance to her company and others in the development of phage therapy. Scaling up products for human use is difficult. For phase I, Phagelux partnered with the Canadian government for production. For phase II, it may be necessary to build a new production facility or partner with some entity that can offer high-quality facilities. Scaling up products for agricultural use is easier. Dr. Tawil said the ability to swap out the phages in the treatment cocktail is helpful for preventing resistance, and the company has not seen any resistance to the product in the field.

Dr. Watts predicted that more products are coming from startup companies, through public-private partnerships. FDA is beginning to offer some flexibility for the development of novel products, and Dr. Watts anticipated that manufacturers will interact with regulators earlier in the process to determine the regulatory pathways to market.

Incentivizing the development of antibiotics is challenging, said Dr. Hamm, and investors do not always base their decisions on past successes or failures. To increase antibiotic R&D, drug pricing must be addressed, and venture capitalists must be convinced of the benefits of investing despite the likelihood of lower returns than possible for other drugs.

### *Environmental Impact*

Mr. Brooks pointed out that generic drug makers largely outsource production to manufacturers in emerging markets, which do not have the same infrastructure for sanitation and waste management as the United States and Europe. Even if all the members of the AMR Industry Alliance met their commitments, the effect would be limited; many more groups must focus on reducing the environmental impact of antibiotics.

### **Panel 4: Vaccines and Diagnostics**

#### **EARLIER TARGETED EFFECTIVE ANTIBIOTIC THERAPY THROUGH CULTURE-INDEPENDENT DIAGNOSTICS**

*Thomas Lowery, Ph.D., Chief Scientific Officer, T2 Biosystems*

When bloodstream infection is suspected, clinicians prescribe antibiotics while awaiting the results of blood culture tests, which can take days. Nearly half of patients receive the wrong antibiotic therapy during that period, and the delay in starting effective therapy increases the risk of morbidity and mortality. T2's diagnostic instrument uses magnetic resonance technology to evaluate blood directly in a standard clinical laboratory setting and provides results in 3–5 hours. Once the species is detected, about 90 percent of patients get the right antibiotic treatment. T2 has produced several diagnostic panels for use with its direct-from-blood, culture-independent instrument, two of which were supported by CARB-X investment. Hospitals using the new diagnostic tool demonstrate improved length-of-stay and mortality rates for affected patients and cost-savings for the institutions. Dr. Lowery concluded that the technology has the potential to boost antibiotic stewardship and aid early decision making; the challenge is to promote uptake.

#### **PRIORITIZATION OF VACCINES TO REDUCE ANTIBIOTIC USE IN ANIMALS**

*Elisabeth Erlacher-Vindel, Doctor's Degree, Head, Antimicrobial Resistance and Veterinary Products Department, World Organisation for Animal Health (OIE)*

In its effort to identify alternative approaches to disease treatment in animals that would reduce or mitigate AMR, the OIE found few accurate data on which to base recommendations. It created criteria to help prioritize vaccine research needs for the most important diseases in certain food animal groups. The criteria assess the availability of vaccine for treatment and constraints on their use, among other parameters. The OIE then developed specific priority pathogen lists for poultry, swine, and fish and a fourth list for cattle, sheep, and goats collectively. It identified several research gaps to address and acknowledged that, lacking sufficient data, its recommendations rely heavily on expert opinions. The OIE also acknowledged that the lists reflect global priorities, not regional or individual country priorities.

### **DISCUSSION**

#### *Promise of New Diagnostics*

Council members were interested in the novel diagnostic approach put forth by Dr. Lowery and discussed how it could translate to broad use. Dr. Lowery stressed that the tool requires a different way of thinking about the data to inform decisions. He noted that the current system for diagnosing infections is fraught with misaligned pressures and incentives—for example, those overseeing stewardship may see the benefits of testing but lack the budget to implement it.

Dr. Lowery said that when T2's technology is introduced to a hospital, the company analyzes the patient population and determines the potential economic and clinical benefits. Eventually, the company will have enough data to make the case for broader implementation, and it is already working with the Centers for Medicare and Medicaid Services (CMS). Dr. Lowery said a carve-out (i.e., not bundling the test with other related procedures and supplies for payment purposes) would benefit the company, but hospitals need to continue gathering data to determine effectiveness. An appropriate pull incentive would be tied to effectiveness of the test in the populations where its use has the biggest impact. Dr. Dixon added that education and outreach must go beyond the laboratory to the clinicians who would order the tests and use the results for making decisions about treatment.

Asked about the utility of the test in low- and middle-income countries, Dr. Lowery said the testing requires laboratories that have sufficient power supply and quality controls; the company already has a presence in the Middle East. Michael D. Apley, D.V.M., Ph.D., DACVCP, suggested that healthcare providers and decision makers apply the same level of attention to ensuring the proper application and interpretation of existing antibiotics and tests as they do to new diagnostic tests.

#### *Barriers to Data Gathering in Agriculture*

Dr. Erlacher-Vindel said the difficulty of getting current data on the costs of vaccines for animals makes it hard to calculate the potential economic advantages. She hoped to inspire a more professional approach to farm management that takes into account biosecurity and the use of vaccines and other approaches to decrease the use of antibiotics. In some countries, antibiotics are cheap and widely available, but vaccines are not. Dr. Erlacher-Vindel said it is a struggle to draw the attention of agencies such as OIE to diseases that affect animals but not humans. Vaccines have the potential to increase economic value, especially in developing countries. Dr. Erlacher-Vindel encouraged authorities to work toward streamlining all the different aspects of research to demonstrate the global benefits.

## **Public Comment**

**Tsung-Hsi Wang, a public health official of Taiwan's Ministry of Health and Welfare,** emphasized the importance of international cooperation to share the responsibility of combating antibiotic-resistant bacteria. To that end, systemic surveillance is extremely important. As an example, Taiwan has had a nationwide surveillance system for antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and drug-resistant tuberculosis for more than 20 years, and it accumulates a lot of data. In addition, Taiwan's national health insurance covers more than 99 percent of its population. That allows the country not only to intensely monitor the clinical usage of antibiotics but also accumulate more big data.

The next step is using big data from clinical settings and laboratories to capture the trends and emerging bacteria. Although that is crucial, there are still many challenges, such as data integration, analysis, and data sharing nationally and internationally. The common energy of humankind—every country in the world—should work together with innovations and actions to achieve the ultimate success of the field. In 2018, Taiwan hosted the Asia-Pacific Economic Cooperation conference, “Strategies Against the Evolving Threat From Antimicrobial Resistance: From Awareness to Concrete Action.” In April, an international workshop will

address drug-resistant tuberculosis, which is an extremely important public issue and needs tremendous efforts to conquer. If we lose the war to bacteria, no one can survive from it, said Ms. Wang. She called for attention to international cooperation on combating antibiotic-resistant bacteria as a part of the action plan to safeguard global health security.

**Kevin Kavanagh of Health Watch USA** said prevention of the spread of multidrug-resistant organisms (MDROs) has been dealt with only superficially, and mostly in the context of detection and control of poorly defined outbreaks. Some drug-resistant bacteria, such as MRSA, have become endemic in the general population. MRSA has also become more virulent. Knowing rates and identifying carriage is of utmost importance in stopping this epidemic. Containment will be expensive. Mr. Kavanagh feared that the safety of patients is being relegated to the facilities' bottom line. The strategy of destroying microbiomes with chlorhexidine makes little sense. Chlorhexidine is classified as an antiseptic as opposed to an antibiotic because it has such a wide spectrum. It is a contradictory policy to advocate for antibiotic stewardship in the use of narrow-spectrum antibiotics but at the same time advocate for daily use of total body bathing with chlorhexidine.

Handwashing should be viewed as a very important component of an IPC bundle, but in the context of MDROs, it is a backup measure, because these organisms should not be on a healthcare worker's hands in the first place, and if they are, there is a problem with containment, control, and identification of carriers. There are over 18 million healthcare workers in the United States. Multiple studies have reported the MRSA carriage rate among healthcare workers is approximately 5 percent.

A recent study by Chen et al. confirms previous research regarding rapid environmental spread of MDROs. The lack of firm standards and policies is placing healthcare workers, their patients, and families at risk for acquisition of these dangerous pathogens. At a minimum, said Mr. Kavanagh, routine testing is needed to identify carriers, along with a standardized national reporting system for healthcare worker acquisitions and an economic safety net for workers who acquire these dangerous pathogens.

Some actionable steps this Council could take would be (i) further consideration of the importance of identification and decolonization of MDRO carriers in stopping this epidemic; (ii) consideration of having a session at a future meeting devoted to healthcare worker safety, with presentations from a wide variety of stakeholders; (iii) deliberation on the possibility of having CDC adding a field to their Emerging Infections Program surveillance network to designate healthcare worker acquisitions and infections from MDROs; and (iv) recommendation of the removal of over-the-counter analogs of colistin from household medicine cabinets.

These organisms do not respect standards, academic degrees, or notoriety. They are evolving, getting stronger, and are out to win. The epidemic of drug-resistant organisms represents an important turning point in medical history similar to the discovery of cell theory and invention of antibiotics, and it is a disastrous threat to the ability to treat patients. Two hundred years from now, the Council's decisions will be studied and dissected by others, and the Council's legacy will then be cemented for eternity. Mr. Kavanagh encouraged the Council to make bold and specific recommendations to stop this epidemic.

**Kerry LaPlante of the Society of Infectious Diseases Pharmacists (SIDP)** said pharmacists are scrambling to concoct mixtures of antibiotics using in vitro data, hoping to override resistance, hoping to identify some synergy for dying patients. Many of these patients have already endured and overcome months of chemotherapy and other diseases, only to find themselves beaten down and fighting for their lives again. The SIDP has a vision of safe and effective antimicrobial use for now and the future, and its focus is advocating for patients. Ms. LaPlante asked that the Council look at improving the antimicrobial pipeline, uses, and access. The SIDP applauds the goals of the Task Force and has submitted formal recommendations for each of these goals. The SIDP asked that the Council prioritize NAP Goal 4, to accelerate basic and applied R&D for new antimicrobials—specifically, to promote the development of new antimicrobials. Pharmacists must ensure access to anti-infective agents through increased regulation, coordination with insurance providers, and public–private, academic–manufacturing partnerships. There is an overall need for both push and pull incentives that promote investment for discovery and development.

The SIDP asks for the creation of new and innovative funding mechanisms and partnerships for antibiotic research from CDC, the National Institutes of Health (NIH), the Agency for Healthcare Research and Quality (AHRQ), and FDA. It advises recommendations that reform CMS policy toward inpatient reimbursement of antibiotics outside of the current diagnosis-related group (DRG) payment system, and it asks to develop a system that incorporates local epidemiology and patient risk factors, moving away from a one-size-fits-all approach. Emphasis should be placed on reimbursement for appropriate use rather than amount of use.

Also, the SIDP asks for efforts to protect the supply of existing drugs. Each day, pharmacists struggle with national anti-infective drug shortages, which are associated with patient harm and increased risk of *Clostridioides difficile* and undertreatment of serious infections due to inappropriate options for antimicrobials. The SIDP suggests a new priority that will further develop strategies to change the impact of anti-infective shortages and decrease risk of shortages through enhanced communication and early response from manufacturers.

Lastly, the SIDP applauds the hard work and dedication of the physicians, veterinarians, and researchers on the Council, but the lack of a pharmacist’s expertise should be noted. Antimicrobial resistance is a drug safety issue. Pharmacists are medication safety and efficacy experts. Like infectious disease physicians, infectious disease-trained pharmacists have over 10 years of formal education, including residency and often fellowship training in antimicrobial pharmacology, antimicrobial stewardship, and medication safety and efficacy. Pharmacists lead antimicrobial stewardship efforts at institutions, coordinate medication access, ensure appropriate use, and are critical in safeguarding all medication.

**Karen Hoffmann of the Association for Professionals in Infection Control and Epidemiology (APIC)** said that, as infection preventionists, APIC members have a primary role in implementing Goal 1 of the NAP, to slow the emergence of resistant bacteria and prevent the spread of resistant infections. The NAP adenovirus activities are essential to achieving this goal, including implementation of healthcare policies and antibiotic stewardship programs that improve patient outcomes and efforts to minimize the development of resistance by ensuring that

each patient receives the right antibiotic, at the right time, at the right dose, for the right duration. Without oversight of antibiotic use, we are at risk of making antibiotics both more ineffective and harmful, said Ms. Hoffmann.

In 2015, CMS proposed revisions to the Medicare requirements for long-term care facilities and revisions to the Medicare conditions of participation for hospitals and critical access hospitals in 2016, both of which included requirements for healthcare facilities to implement antibiotic stewardship programs within their IPC programs. Although the long-term care facility revisions were finalized and implemented, the proposed revisions for hospitals and critical access hospitals have not been. Therefore, not only are acute and critical access hospitals burdened by requirements that are outdated and inefficient, patients suffer because of inconsistent care requirements across the healthcare continuum. Stewardship in all care settings is the most important first step to begin reducing the worldwide threat of antibiotic resistance.

Acute care hospitals typically lead the way; other care settings such as long-term care are important infection prevention priorities. However, ironically, the failure to finalize revisions to the conditions of participation for acute care hospitals may erode their efforts to address antibiotic stewardship. APIC appreciates this Council's efforts to advance the fight against antibiotic resistance but believes we cannot move forward until we have implemented already-identified initial steps in the fight. Therefore, APIC urges the Council to encourage the HHS Secretary to call on CMS to finalize the 2016 draft revisions to the hospital and critical access hospital conditions of participation, especially the provisions requiring establishment of antibiotic stewardship programs within the oversight of the IPC programs.

**Chandra Daniel of the World Alliance Against Antibiotic Resistance** said recent data on drug-resistant infections are distressing and indicate that even in developed countries like the United States, where healthcare systems work very well and the quality is great, AMR infections still occur, and transmission is happening from patient to patient, from patient to healthcare workers, and from healthcare workers to patients. Intensive care units are much talked about, but drug-resistant infections exist in all sectors of hospital care.

While emphasis has been put on mechanisms to spur economic models, R&D, and industrial manufacturing for new antibiotics, the rest of the medical technology sector has not been taken into account as they very much could be. In addition, IPC and health systems are neglected worldwide. In areas with high-level health services, such as the European Union (EU) and the United States, we cannot continue with IPC as usual in the AMR era, said Ms. Daniel. Instead, we need to pay a lot more attention to resources, such as staff composition and training and research into outbreaks and modes of transmission and health structures, as well as examining how the nonpharmaceutical medical technology sector could be brought into the picture.

The World Alliance recommends more focus on the need to stop transmission, because AMR is very costly—in terms of human lives, disability, and hospital and state budgets. There will always be patients with AMR infections, but attention must be given to the whole transmission chain so as to break it. Early diagnosis; well-ventilated waiting rooms; attention to biofilms; and use of advanced technology, well-trained cleaning personnel, and proper architecture are all needed to control AMR. The strongest IPC systems are needed for biosecurity here and

worldwide, as referenced in the new biodefense document as of September 2018. Ms. Daniel referred to the presentation by FAO, which focused on behavior and practices, and recommended attention to those factors.

**David Wallinga of the Natural Resources Defense Council (NRDC)** recommended that the PACCARB focus on Goal 1 of the NAP, preventing the spread of resistant infections. The 2015 NAP had an explicit outcome: that inappropriate antibiotic use in human outpatient settings be reduced by 50 percent and, in hospitals, by 20 percent, but no equivalent target or outcome was set for antibiotic overuse in food animal settings. The next NAP should reiterate that antibiotic use and overuse is driving worsening resistance. The NRDC recommends that the NAP set the target that, by 2021, sales of medically important antibiotics for food animal use be reduced by at least 45 percent relative to 2009 levels, perhaps with a further extension of that goal to a 55-percent reduction by the year 2025.

The Council or others can come up with its own targets, said Mr. Wallinga, but the numbers proposed by the NRDC are both modest and justified. According to the European Medicines Agency's latest report, France, the Netherlands, and Germany report having dropped their milligram-per-kilogram livestock use of antibiotics by between 47 percent and 68 percent from 2010 to 2016. Mr. Wallinga anticipated that when the next report comes out in the fall reflecting 2017 data, usage will have dropped even further. He explained how he applied the European milligram-per-kilogram calculations to the relevant data from USDA and FDA and estimated U.S. antibiotic use as roughly three times that of the Netherlands and two times that of Germany. This comparison suggests strongly that there is more than ample room for the U.S. meat industries to collectively reduce overall milligram-per-kilogram usage of antibiotics even further, perhaps much further than the 28 percent from 2009 to 2017.

In conclusion, Mr. Wallinga urged the Council to recommend a new priority in the next NAP that sets a target of reducing use by 45 percent over 2009 levels by 2021, which should not be a big lift over the reductions already achieved and would still mean that U.S. usage remains substantially higher than that of many of Europe's largest meat producers.

**Jean Halloran of Consumer Reports** said her organization is concerned both about overuse of antibiotics in medicine and medical settings and in animals. The Chain Reaction scorecard, created by Consumer Reports along with five other organizations, including the NRDC, rated fast-food companies on their policies for antibiotic use in the food that they sold. The top 25 fast-food chains were rated not on FDA policy (which prohibits use for growth promotion but allows use for disease prevention), but rather on the WHO guidelines, which call for no routine use of antibiotics for disease prevention. The project has been ongoing for 4 years. In the first year, only five of the top 25 had any policies limiting antibiotic use beyond FDA guidelines. Last fall, 18 of the top 25 had a policy limiting antibiotic use beyond FDA guidelines, limiting use for prevention.

Most of these limitations were in chicken, and use in chicken has dropped dramatically. Now, some attention is being paid to trying to accomplish reductions in beef, as McDonald's will describe to the Council tomorrow. But the progress so far underlines what Mr. Wallinga just said: more can be done if use for disease prevention is restricted. It is both possible to do so and

necessary to move forward to preserve antibiotics for human health. Ms. Halloran hoped the Council would make recommendations in this area.

The USG could also help make progress at the global level. Currently, negotiation is going on at Codex Alimentarius, the United Nations' food standards agency, for a code of practice on antibiotic use in agriculture. One issue in dispute is whether it should recommend a global ban on use of antibiotics for growth promotion. Ms. Halloran believes that is "a no-brainer." It should be the very first step. It is already U.S. policy and EU policy, but it should be global policy because antibiotic resistance that develops in Asia or Africa will soon be something the United States has to deal with. Ms. Halloran hoped that the Council would recommend that the USG, as forcefully as it can, support a global ban on antibiotic use for growth promotion and seek further restrictions on use for disease prevention.

## **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 thanked the presenters, public commenters, and the audience for their participation. He adjourned the meeting for the day at 3:55 p.m.

## **Day 2**

### **Roll Call**

*Jomana F. Musmar, M.S., Ph.D., Designated Federal Officer (Acting), National Vaccine Program Office, HHS*

Dr. Musmar welcomed the participants and called the roll.

### **Debrief of Day 1: Innovation**

*Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, and Kathryn L. Talkington, Innovation and R&D Subgroup Leads*

Dr. King summarized the presentations from day 1 of the meeting. Ms. Talkington said that as the Council considers recommendations for the next 5-year NAP, it should think about incentives (e.g., carve-outs and pull incentives) to foster continued innovation and mechanisms for prioritizing interventions and research efforts. Day-1 presentations also raised questions about how to ensure that effective interventions are implemented in practice, which may be easier to address in human medicine than animal care. Dr. Talkington observed that the United States has some effective interventions for antibiotic stewardship and other methods for reducing AMR that it could help other countries tailor to their capacities.

### **Overview of Day 2: Use of Antibiotics**

*Martin Blaser, M.D., and Michael D. Apley, D.V.M., Ph.D., DACVCP, Surveillance and Stewardship Subgroup Leads*

Dr. Blaser said the day's presentations would focus on the use of antibiotics and surveillance mechanisms now and in the future.

## **Panel 5: Grass Roots Engagement and Advocacy**

### **U.S. FEDERAL POLICY AND AGRICULTURAL ANTIBIOTIC USE**

*Steve Roach, M.A., Food Safety Program Direct, Food Animal Concerns Trust; and Senior Analyst, Keep Antibiotics Working*

Limited data are available to understand the use of antibiotics in food animal production and agriculture. The most recent NARMS data come from 2015, and the industry saw a substantial decrease in antibiotic use in 2017. Keep Antibiotics Working's analysis found proportionally intensive antibiotic use in turkeys and an apparent increase in multidrug-resistant salmonella in turkeys. Domestic and international guidelines and proposals for reducing use of medically important antibiotics in animals consistently recommend some key steps:

- **Establishing targets for reductions in use:** Keep Antibiotics Working suggests setting feasible, sector-specific targets, with input from industry and insights drawn from other countries.
- **Stopping routine use:** Keep Antibiotics Working suggests encouraging alternatives to antibiotics for prevention of disease and reserving antibiotics for injured and sick animals.
- **Addressing priority drugs:** Keep Antibiotics Working suggests certain classes of antibiotics should be reserved for disease treatment.
- **Improving surveillance of use and resistance:** Keep Antibiotics Working calls for annual data collection through NARMS and updating of CDC reporting on resistant infections.

In addition, farms can take simple steps to reduce the need for antibiotics, such as keeping animals on farms longer before sending them to processing facilities where they are more likely to get sick.

### **ONE WATER AND PUBLIC HEALTH: RESEARCH TO ACTION THROUGH OUTREACH AND EDUCATION**

*Amy Sapkota, Ph.D., M.P.H., Director, University Global STEWARDS, University of Maryland School of Public Health; and Director, Coordinating Nontraditional Sustainable Water Use in Variable Climates (CONSERVE)*

Water is a diverse source of antibiotic resistance genes that can transmit resistant bacteria to humans. Dr. Sapkota oversees research that identifies concentrations of antibiotics in different water sources, which can be transmitted to humans through direct or indirect exposure (e.g., water used for irrigation of crops). The University of Maryland and CONSERVE seek to expand education about water to the agricultural community and the general public and promote systems thinking about water in science. The next NAP should support the following:

- Research on understanding the role of water in transferring resistant bacteria and the subsequent effect on the human microbiome and health outcomes
- Adding questions about water-related exposure to existing CDC surveys
- Incorporating a One Water perspective
- Protecting source water (especially waste water)—for example, by strengthening FDA's ban on triclosan and other antimicrobials in over-the-counter products, providing

programs for consumers to return unused antibiotics for safe disposal, and educating consumers and others about protecting water

## **THE IMPORTANCE OF WASH IN PREVENTING AMR AND IMPROVING HEALTH OUTCOMES**

*Danielle Zielinski, Health and WASH Officer, WaterAid America*

The WASH concept is so basic it is often left out of conversation, but it remains critical to preventing infections, which prevents AMR. In low- and middle-income countries, antibiotics are often a substitute for good WASH practices. Breaking the chain of transmission of infectious disease is critical. Much more attention is needed to managing waste.

Numerous public health authorities and government bodies have proposed efforts and action plans to address AMR, but at the country level, leaders are confused about which framework to follow and how to find the resources to support the efforts needed. The USG and others could work to align recommendations and help countries figure out how to tackle the problem. Action on AMR is more likely to be sustained if it is part of mainstream health improvement approaches and included in the national budget. More coordination at the ministry level is needed to ensure that human health issues and water concerns are addressed together. The World Health Assembly will deliberate soon on resolutions to prioritize WASH in AMR plans, and the United States should support those resolutions. Access to clean water and sanitation is critical, and investment in fecal sludge management is equally important.

## **ENGAGING THE PUBLIC WITH AMR AND HAND HYGIENE**

*Lesley Price, Ph.D., Glasgow Caledonian University*

The public engagement activities of the Safeguarding Health Through Infection Prevention program include novel approaches to educating children and adults in schools and community settings. Public engagement disseminates information and builds trust in science, while providing researchers with insights for improving research. Dr. Price described a number of highly interactive educational efforts in the community. A review of interventions to enhance public understanding about AMR, mostly targeting children, parents, and the general public, found that most were effective in improving knowledge, attitudes, and beliefs—with the exception of mass media. Dr. Price said targeted messages and direct education are more effective than mass media communication campaigns. She recommended engagement interventions that are multimodal, targeted and delivered simultaneously to multiple audiences, fun, interactive, clear in message, based in theory, and evaluated afterward.

## **DISCUSSION**

### *Water Quality and Data*

Dr. Sapkota said data are not comprehensive enough to tease out various factors contributing to water contamination—e.g., human or animal excretion, manufacturing—but such information is important to gather. To better quantify the impact that antibiotic residue in water has on human and animal health, more monitoring and surveillance data are needed. Dr. Sapkota suggested incorporating more water data into NARMS. CONSERVE is working with FDA on a genome tracker to learn more about strains, resistance patterns, and effects on human and animal health.

Aileen M. Marty, M.D., FACP, asked about data on antibiotic residue in saltwater, given that some countries are considering desalination to increase the supply of drinking water. Dr. Sapkota

did not have such data; she said the desalination process would likely remove organisms but could have other ramifications, so it is important to take a holistic view of the problems and the solutions. Some data are available on levels of exposure to contaminated water. Ms. Zielinski added that some data are available from the WHO and UNICEF on water access and quality.

#### *Consumers Outreach and Messaging*

Helen W. Boucher, M.D., FIDSA, FACP, appreciated the suggestion to have more mechanisms for consumers to return unused antibiotics for safe disposal. Dr. Sapkota said her organization is just beginning to address the issue, but states would take responsibility for such action.

Dr. Price said she and her colleagues work to raise awareness in community settings but do not have a specific plan for broad outreach. Her research and experience confirm that people need different, targeted messages. For example, physicians often appreciate evidence, while nurses and the general public respond to messages that address the impact on patients. There is some evidence that a campaign that simultaneously targets multiple messages to different audiences can be effective, said Dr. Price. However, a follow-up study of first-year nursing students found they did not remember the hand-hygiene protocol they had learned. Healthcare providers tend to follow the model they see in the field rather than their academic learning. Dr. Price also acknowledged that messages can be complex, such as distinguishing between “good” and “bad” bugs.

#### *Advancing ARM Policies and Practice*

After responding to questions about the methodology his organization used to draw its conclusions, Mr. Roach observed that is difficult to compare humans and animals and to make comparisons across animal species. He emphasized that the industry should weigh in on setting reasonable targets for reducing antibiotic use in food animal production and should consider what other countries have done.

Ms. Zielinski said her organization seeks to meet districts where they are, piloting projects that respond to the capacities of the area, no matter how simple and narrowly focused. She recognized that prioritization is important but noted that it is difficult to know where to start. Her organization seeks to help countries find their own path to improved sanitation. In response to Dr. Fedorka-Cray, Ms. Zielinski said WASH works primarily outside of the United States and so has not partnered with U.S. toilet manufacturers. However, many toilet systems are available that do not require water, and a major investment in those products could help solve the problem.

### **Panel 6: Consumer Impact on Antibiotic Use**

#### **ANTIBIOTIC USE IN SMALL-SCALE LIVESTOCK PRODUCERS IN ECUADOR**

*Jay Graham, Ph.D., M.P.H., University of California, Berkeley, School of Public Health*

Outside the United States, small households are responsible for a lot of food animal production, antibiotics are sold over the counter for veterinary and human use, and families and their livestock share resistance genes. Veterinary expertise is lacking in small communities, and people raising animals rely on personal experience or a salesperson’s recommendation to select antibiotics for treatment. Decision making about treatment is based on personal economic concerns, not the effects of resistance on the community. Dr. Graham called for better understanding of community-acquired antibiotic resistance. In low- and middle-income

countries, research is needed to unpack which interventions might be effective in which settings. In some cases, strict regulations are needed (e.g., barring the sales of certain antibiotics); in others, a combination of outreach, education, and incentives can change practices.

#### **ADDRESSING AMR AS A GLOBAL RESTAURANT COMPANY**

*Bruce Feinberg, Senior Director, Global Protein/Dairy Quality Systems, McDonald's Corp.*

McDonald's provides guidance on antibiotic stewardship for all the producers in its supply chain. It partners with producers, veterinarians, industry leaders, and suppliers to set criteria for using antibiotics appropriately and judiciously. The guidance also seeks to replace antibiotics with preventive measures to ensure the health and welfare of animals throughout their lives. The policies draw on recommendations from the WHO and other expert advisors and take into account different stakeholder perspectives. McDonald's recently announced new policies for antibiotic use in beef production, which is more complex than chicken production. Mr. Feinberg said no other restaurant has tackled this issue on a global scale. The beef policy will be phased in, first in the top 10 beef sourcing markets. By 2020, McDonald's will have data on which to base market-specific reduction targets. By 2022, it will start reporting on progress toward antibiotic reduction in the top beef sourcing markets.

#### **OUTPATIENT ANTIBIOTIC STEWARDSHIP: INTERVENTIONS THAT WORK**

*Jeffrey Gerber, M.D., Ph.D., Children's Hospital of Philadelphia and American Academy of Pediatrics*

Ongoing audits of prescribing practices paired with feedback to healthcare providers about their practices, requiring prescription justification in EHRs, and giving providers comparative data about their peers' prescribing are all interventions shown to reduce unnecessary prescription of antibiotics. Working with a medical anthropologist, Dr. Gerber and colleagues found that pediatricians misperceived pressure from parents to prescribe antibiotics; in fact, most parents want to understand what is wrong with their child and want a contingency plan if the child's condition does not improve. They also found that doctors prescribe more judiciously when a medical student is present in the room and at certain times of day; the patient's race and practice location also play a role. Dr. Gerber said the NAP should give more attention to outpatient prescribing, which plays the biggest role in direct human exposure. Also, the Council membership should include a pediatrician. Messaging should highlight the potential for direct patient harm from overprescribing of antibiotics. Sociobehavioral interventions, such as communication training and accountability, can improve prescribing practices.

#### **SUSTAINABILITY OF ANTIBIOTICS**

*Harshika Sarbajna, Global Head of Anti-Infectives, Sandoz*

One significant contributor to AMR is the lack of access to the right antibiotic for a given infection. Shortages of antibiotic availability remain a persistent problem around the world. Shortages are driven primarily by economic factors. Antibiotics are cheap, and the market is not attractive. The supply chain is fragile. The industry is consolidating and contracting, making it difficult to maintain production of some antibiotics. To improve the situation, Ms. Sarbajna suggested holding manufacturers accountable for quality and reliability but not necessarily for providing the lowest-price product possible. The real market value of antibiotics should be considered. More collaboration is needed across stakeholders to address the problem of AMR.

## **DISCUSSION**

### *Decreasing Antibiotic Use in Food Animals*

Mr. Feinberg said the goal of the McDonald's program is to ensure responsible practices. In food animal production, less use of antibiotics is better, but zero use is probably not an option, he said, and it is important to preserve the effectiveness of antibiotics for future generations. Rather than focus on enforcement, McDonald's works with stakeholders to set meaningful reduction targets. It will develop ways to monitor antibiotic use with its supply partners. McDonald's has close control over the raw material supplied to franchises, even in other countries, Mr. Feinberg noted.

Mr. Feinberg said McDonald's is engaged with competitors in discussion about improving animal health and welfare, particularly regarding antibiotic use. Regarding consumer input, he said parents express concerns about antibiotics in the food their children eat.

### *Overuse and Overprescribing of Antibiotics*

Elaine Larson, Ph.D., RN, said that in some communities in America, antibiotics are widely available over the counter, so the global approach may be applicable domestically.

Dr. Gerber said data show that retail-based healthcare clinics adhere to appropriate antibiotic prescribing guidelines as well or better than internists and pediatricians, probably because the setting demands strict adherence. It is difficult to get data from urgent care clinics, and there is a perception that these clinics are more likely to prescribe antibiotics. Dr. Gerber said his organization offers toolkits to be used with EHRs to pull data and feed it back to healthcare providers, along with clinical decision support tools. Not all settings have the technology and personnel capable of gathering and analyzing the data.

### *Manufacturers' Challenges*

Ms. Sarbajna said the most pressing problem in manufacturing generic drugs is maintaining the integrity of the supply chain, which is very fragmented. In addition, the number of suppliers of raw materials decreases every year, and it is difficult to find new suppliers with high-quality products who are reliable.

## **Panel 7: One Health Surveillance**

### **AMR IN SOUTH AFRICA (PHONE)**

*Olga Perovic, M.D., Principal Pathologist, National Institute for Communicable Diseases*

South Africa began evaluating AMR in 2011, eventually developing a national action plan at the same time as the United States, with enhanced surveillance as one of the key strategic objectives. South Africa's efforts are informed by laboratory-based and electronic surveillance mechanisms. The country aims to support a One Health approach to reporting and surveillance. Despite advances in raising awareness, expanding education, promoting stewardship, and limiting the use of antibiotics for growth promotion in animal feed, South Africa faces challenges implementing a One Health surveillance approach, establishing hospital IPC programs, and standing up a WHO Collaborative Center for the region. The country is particularly interested in identifying and addressing regionally specific AMR.

## **SMALL ANIMAL SURVEILLANCE AND ONE HEALTH**

*Jennifer Granick, D.V.M., Ph.D., D-ACVIM, Chair, Animal Health Working Group, Minnesota One Health Antibiotic Stewardship Collaborative*

Antibiotic overprescribing in veterinary practices is significant, but no national or regional agency oversees companion animal health, so there are few surveillance data on which to base recommendations for practice. Minnesota gathered data using a low-tech, point prevalence survey in a veterinary medicine teaching hospital; the results informed best practices and stewardship targets. Dr. Granick and colleagues are collaborating with U.K. researchers to implement an electronic surveillance system already in use in the U.K. that can identify targets for intervention. These data can be used to create local antibiograms, compare provider prescribing practices, and set benchmarks. They can also guide preventive care. The veterinary field needs more ways to gather data and provide practice guidelines, while keeping the cost to veterinary providers minimal.

## **ONE HEALTH DATA REPORTING, SHARING, AND COLLABORATING**

*Laura Goodman, Ph.D., Cornell University College of Veterinary Medicine*

Bringing animal and public health laboratories and stakeholders together in 2018 to discuss data-sharing strategies was an important step forward for the field. The gathering revealed the need for confidentiality to ensure that individual pet owners and producers are not identified. The results of whole genome sequencing are relatively standardized across laboratories and easy to communicate. These data can feed into databases in real time. Some extreme cases of AMR demonstrate the importance of including companion animals in NARMS, and Dr. Goodman hoped the next NAP would address such reporting. She also suggested the NAP:

- include data-sharing initiatives through CDC's Integrated Food Safety Centers of Excellence;
- expand veterinary diagnostic capacity-building through FDA and USDA mechanisms;
- add corporate veterinary laboratories to federal surveillance networks;
- support the NCBI pathogen detection team in adding veterinary pathogens to its pipeline;
- establish an environmental monitoring network using advanced molecular biology practices; and
- implement active monitoring of imported dogs for infectious diseases.

## **USING MEDICAID DATA TO MAP AVOIDABLE PRESCRIBING PRACTICES**

*Emily Lutterloh, M.D., M.P.H., Director, Bureau of Healthcare Associated Infections, New York State Department of Health*

To better understand regional variations in antibiotic prescribing practices, Dr. Lutterloh's team used state Medicaid data to map Medicaid prescriber patterns by county, focusing on potentially avoidable antibiotic prescriptions for upper respiratory infections. The Department of Health then sent letters to providers in high-prescribing counties, followed by educational materials and sample interventions. The Department will continue to evaluate the same data over years, and the research project will add other conditions and information from other insurers. Dr. Lutterloh said the project's goal was to identify target areas for intervention, and multiple interventions are underway. She hoped to look at prescribing rates in different settings, including urgent care clinics, but they are hard to distinguish from private practices in the state.

## DISCUSSION

### *Data Management in Companion Animals*

Dr. White asked whether Dr. Granick contacted the Banfield Pet Hospital system for data. She responded that Banfield has made some data publicly available but generally keeps its data private. She hoped more organizations would see the value of sharing data. The lack of standardization of data collection in veterinary practices and laboratories remains a barrier to sharing data. Dr. Goodman pointed to some large, coordinated data collection efforts that are pushing standardization forward. She added that large veterinary diagnostic laboratories have expressed interest in participating in research.

Dr. Granick said that if companion animal practices were required to report diseases, they would need a lot of support and resources. At present, it may be more feasible to share lessons learned from practices that are already reporting, she said. Despite available guidelines for treating infectious disease in companion animals, veterinarians are not aware of them. More such guidance is needed, as is better dissemination.

Asked how to jumpstart the use of EHRs in veterinary practices, Dr. Granick said the animal health system is very different from the human health system. Advancing research does not necessarily require EHRs, and researchers can pull data from medical records despite the lack of a uniform coding system.

One relatively simple step to reduce unnecessary use of antibiotics in companion animals is for laboratories to provide diagnostic results and recommendations in a tiered format, as they do for human health. That change could encourage veterinarians to prescribe more judiciously. Dr. Goodman added that raw food pet diets are a perfect matrix for gene transfer and should be reconsidered.

### *Integrating Surveillance Efforts Nationally*

South Africa mandates some reporting, but most surveillance is not mandatory yet, said Dr. Perovic. The country has human health surveillance in place; animal and environmental surveillance are future aims of its initiative. Dr. Perovic acknowledged that only a few countries, such as Sweden and Denmark, have taken meaningful steps toward integrating reporting. More research is needed on how to standardize indications across sectors. Regarding a collaborative approach, Dr. Perovic said the professional societies remain active, but federal departments have not made strong commitments to proceed with the steps outlined in the initiative.

### *Leveraging State Medicaid Data*

Sara E. Cosgrove, M.D., M.S., asked whether Medicaid data are generalizable to the broader population and whether it would be feasible for other states to model New York's mapping project. Dr. Lutterloh said an all-payer database is in development that would provide more information on the general population. Her project required funding and data expertise, and it also leveraged the relationship between the state's Medicaid administrators and epidemiology staff. In addition, the research proposal was required to demonstrate some benefit to the Medicaid program. Dr. Lutterloh said her research cannot yet be used to determine the potential cost savings of reduced antibiotic prescribing.

## **Panel 8: Prescriber Behavior Change**

### **BIG DATA TO IMPROVE ANTIBIOTIC PRESCRIBING**

*Dan Knecht, M.D., M.B.A., Vice President, Clinical Strategy and Policy, Aetna*

As other presenters have noted, drawing attention to individual prescribing habits and prescribing guidelines can nudge providers toward better behavior. Aetna used its substantial claims data and data analytics tools to identify and notify providers who inappropriately prescribed antibiotics. Preliminary analysis found a 16-percent reduction in antibiotic overprescribing. Aetna also congratulated antibiotic stewardship “champions” who demonstrated judicious prescribing patterns, although of the 175 champions identified in year 1, only 20 performed as well in year 2. Dr. Knecht encouraged collaboration across stakeholders to share data, raising public and provider awareness about AMR, and considering value-based reimbursement for appropriate antibiotic prescribing.

### **REDUCING ANTIMICROBIAL USE IN ANIMALS AND PROMOTING A MINDSET CHANGE**

*David Speksnijder, D.V.M., Ph.D., University of Utrecht*

Over the past 10 years in the Netherlands, a combination of voluntary and mandatory practices implemented by the government and the private sector have led to decreased use of antibiotics in farm animals. The practices correlate to validated approaches to behavior change in human medicine. They include increased public pressure to reduce antibiotic use, mandatory reduction targets, guidelines and updated formularies for veterinarians, and publicly transparent benchmarks. Some classes of antibiotics were banned. Farmers and veterinarians received education on why and how to reduce antibiotic use. The country saw a 60-percent decline in antibiotic use from 2007 to 2017. Current efforts are targeting persistent variations in antibiotic use. Dr. Speksnijder’s research identified some of the common characteristics of high and low users. Notably, preliminary data suggest that high users do not perceive a problem with their antibiotic use. A new initiative aims to apply to veterinarians the behavioral approaches used in human medicine to increase adherence to guidelines.

### **MINNESOTA ONE HEALTH ANTIBIOTIC STEWARDSHIP COLLABORATIVE**

*Amanda Beaudoin, D.V.M., Ph.D., DACVPM, Director, One Health Antibiotic Stewardship, Minnesota Department of Health*

The One Health Minnesota Antibiotic Stewardship Collaborative created a 5-year strategic plan for improving stewardship and developing tools to raise awareness of AMR. More than 100 members representing most aspects of human, animal, and environmental health are working together to leverage the state’s commitment to improving stewardship by networking, exchanging ideas, implementing evidence-based practices, and disseminating information to the public in varied settings. The Collaborative publicly recognizes good performance toward stewardship goals, provides tools for measuring antibiotic use, and provides evidence-based materials to encourage stewardship. Dr. Beaudoin suggested the NAP encourage states to establish One Health collaboratives with cross-disciplinary leadership that understand stakeholder needs, with dedicated funding to support them. Minnesota has a strong history of collaboration across the health, agriculture, and environmental sectors, but the threat of AMR can spur other states without such a history to create such connections.

## **ACCELERATING INTERNATIONAL PROGRESS ON AMR**

*Keiji Fukuda, M.D., M.P.H., Director and Clinical Professor, University of Hong Kong School of Public Health*

Successfully tackling complex societal issues requires countries to demonstrate political will by devoting high-level political leadership to the problem, engage in advocacy and diplomacy, take part in global agreements and frameworks, enact national legislation and regulations, empower agencies and programs to address issues, and provide funding to incentivize innovation and address problems. The AMR Global Action Plan and the United Nations' high-level AMR meeting succeeded in mobilizing action by focusing on a global problem of deep concern, bringing together champions from different sectors, and instilling a sense of the need for cooperation. Still, public awareness about AMR is inadequate, and many countries lack sufficient funding to act.

The United States could play a pivotal role by engaging and energizing other decision makers. Its participation in international forums is critical to driving consensus. Strong, effective U.S. agencies such as BARDA, CDC, the Environmental Protection Agency (EPA), NIH, and FDA have great influence on their global counterparts. The NAP should recognize that success in addressing AMR domestically depends on the United States providing strong international engagement and support. AMR must be a visible, explicit priority of U.S. policy and leadership. Economic issues and One Health considerations must be better addressed. Dr. Fukuda called for scaling up investment in technology and support for combating AMR. He pointed to the President's Emergency Plan for AIDS Relief (PEPFAR) as a model for revolutionizing the approach to AMR.

## **DISCUSSION**

### *Effecting Global Change*

Asked what the United States could do to accelerate international progress on AMR, Dr. Fukuda said it can send a strong signal that AMR is a global problem and engage in discussions about possible solutions. A significant investment initiative, similar to PEPFAR, could galvanize efforts to combat AMR. Asked why AMR does not seem to spark a sense of urgency, Dr. Fukuda said that AMR is difficult for people to understand. At some point, people will begin hearing about it from various different sources, which will raise the profile.

One barrier to sharing data, said Dr. Fukuda, is concern about whether the data will be used for financial gain. Advances in technology are making it easier to use big data from various sources, but tough issues about managing and sharing data must be addressed.

### *Economic Impact of Reducing Farm Use of Antibiotics*

Dr. Speksnijder said there are no cost analyses of the Dutch effort because analysis was not built into the planning. The government set targets, and most of the implementation costs fell to the private sector. Some research from the Netherlands, Belgium, and Denmark indicates that reducing antibiotic use at the farm level might be expensive at the start but can be cost-effective within 5 years. The Dutch initiative did not require fiscal measures, but the government held out the potential to remove providers' ability to prescribe and sell antibiotics if they did not meet the targets.

Dr. Speksnijder said the initiative faced a lot of pushback from farmers and veterinarians at the outset, but the combination of animal disease outbreaks and evidence of increasing AMR in the Netherlands convinced the private sector to agree to government targets. Data has since demonstrated that the veterinarians are not losing money, because they have increased sales of vaccines and alternatives to antibiotics, while the farmers are seeing lower production costs because of less antibiotic use.

### *Behavior Change*

Dr. Knecht said physicians are data-driven and competitive, so Aetna's intervention appeals to those traits. When physicians demand to see the data demonstrating their poor performance, Dr. Knecht walks them through it, and they usually see how they can improve their practices.

Dr. Beaudoin said many efforts are underway at the national level to improve antibiotic use in food animals. She noted that Minnesota is among the states working to improve IPC in human and companion animal practices. At the national level, veterinary guidelines for IPC exist but should be updated to address AMR more in depth. Dr. Beaudoin said the Collaborative's effort emphasized improving antibiotic use while effectively treating infections. In some cases, protocols are not available, and the Collaborative sought to address those grey areas.

Asked whether interventions for physicians and veterinarians could be combined to spark collaboration across disciplines, Dr. Beaudoin said antibiotic stewardship must be honed within one's own discipline. However, a One Health approach to stewardship is important; exchanging best practices can be enlightening, and collaboration can identify new solutions, she said. Dr. Fukuda added that relationships among the WHO, FAO, and OIE improved when the three came together around areas of interest. Dr. Speksnijder noted that medical doctors were initially very defensive and blamed veterinarians for overprescribing; through collaboration, they learned how to communicate and learn from each other.

## **Public Comment**

**Elizabeth Lovinger of the Treatment and Action Group** said the weight of tuberculosis as an AMR threat must not go unaddressed. Drug-resistant tuberculosis is the leading cause of death from AMR and was declared to be a significant threat to global public health by the United States and WHO in 2015. To reduce the impact of deadly drug-resistant bacterial infections such as tuberculosis, HHS research agencies, such as BARDA and CDC, DoD, and the State Department's U.S. Agency for International Development (USAID) must prioritize a robust research agenda into innovative diagnostics, better treatments, and effective prevention options, including a vaccine for tuberculosis. The USG's longstanding leading role in global tuberculosis R&D is noteworthy and laudable, said Ms. Lovinger. However, tuberculosis research spending constituted only 0.007 percent of the overall gross domestic expenditure on R&D (GERD) by the USG. More could be done in terms of increasing investment with relatively little funding.

In addition, U.S. research agencies that currently do not prioritize tuberculosis can be doing more and should be given the opportunity to drive innovation in this area. To build on its success, the USG should increase HHS, DoD, and State Department spending for tuberculosis R&D research to 0.1 percent of GERD, a fair-share funding target that has been recognized by member states of the United Nations. Reaching this level means investing an additional \$131 million on top of the

current \$313.5 million investment to boost total investment to \$444.5 million across U.S. agencies, including those with the ability to shift and catalyze new diagnostics, treatments, and vaccines. For example, BARDA can do more to catalyze the tools needed to upend this threat. Increasing investment will allow U.S. agencies to contribute their innovative approach to product development to the benefit of ending tuberculosis here and everywhere. This small increase in investment would support the necessary research to eliminate drug-resistant tuberculosis as an AMR threat by 2030.

Lastly, the U.S. fight against AMR must include efforts against tuberculosis, and increasing USG funding for tuberculosis research would fulfill key recommendations to advance needed public health tools across diagnostics, treatment, prevention, and vaccines through a well-resourced and science-based strategy, led by the best and brightest from esteemed U.S. research institutions.

**Hua Wang from The Ohio State University** said she and her colleagues discovered 15 years ago the massive antibiotic resistance gene pool present in many ready-to-eat foods, including almost all cheese and yogurt products on the market, and horizontal gene transfer by foodborne commensal microbiota. She felt sad to hear that 15 years later, the topic is just becoming openly recognized. Meanwhile, the National Notifiable Diseases Surveillance System is still mainly focused on disaster reporting, which means that when antibiotic resistance is detected in pathogens, there is no way to push it back. Ms. Wang said proposals to collaborate with HHS have been ignored for over a decade.

Ms. Wang challenged the suggestion to invest more in political leadership instead of science and innovation. Antibiotic resistance is a scientific issue that needs scientific solutions, not political manipulation, especially against science. As an example, without any political manipulation, the food safety problem of commensal microbiota, including beneficial bacteria, contaminating almost all cheese and yogurt products on the market before 2007 was quickly solved in just 4 years, effectively protecting both public health and the multibillion-dollar food industry, in contrast to the intense industry relationship and messy situation in food animal production. Other antibiotic resistance challenges in the food chain need to be addressed scientifically and responsibly. In addition, proper disease prevention and treatment are essential; usually, quicker treatment can prevent serious consequences with minimal side effects.

Another knowledge breakthrough revealed that the mainstream practices of taking drugs orally and using drugs with the wrong pharmacological property instead of antibiotics are both direct drivers for massive antibiotic resistance and microbiota dysbiosis in hosts. Ms. Wang said that, from her experience organizing national and international conferences on antibiotic resistance, she knows that scientific and outreach efforts have run into significant difficulties in the past couple years. Despite the availability of practical solutions to minimize side effects of both antibiotic-resistant and gut microbiota dysbiosis, the key risk of oral antibiotic administration remains a secret to the general public as well as to healthcare professionals and policymakers. Injectable antibiotic options are still not available for outpatients almost 8 years after initial discovery and 6 years since the official publication of results and multiple news releases by the American Society for Microbiology.

The antibiotic residuals in USDA-certified meat and poultry products are much lower than the minimum inhibitory concentrations of bacteria, while high doses of therapeutic drugs—especially by oral administration—have real side effects on gut microbiota in hosts. It is important to recognize that proper cooking effectively kills bacteria in foods, including antibiotic-resistant bacteria. The industry and consumers need to know the real risk of resistant bacteria from ready-to-eat foods as well as from animal feces and waste. While better food animal production practices are critical and need to be encouraged, the potential health benefits of the corresponding foods further need to be discovered. The scientific facts on antibiotic resistance should not be messed up.

In addition to her previous comments to the Council on the need for food science expertise, Ms. Wang agreed on the need for the Council to have expertise in pharmacology. Outreach and global collaboration are also needed, but political campaigns without the fundamental scientific truth have proven to be detrimental.

While the damage of oral antibiotics remains a hidden secret in the United States, China released a policy in 2016 to eliminate intravenous injection of antibiotics in clinics in favor of promoting oral drugs, completely opposite to the science and against the clinical evidence. In fact, in China, the prevalence of vancomycin-resistant *Enterococcus* so far is less than 5 percent, while in the United States it is already more than 50 percent. This is likely attributed to the unavailability of oral vancomycin as an option in China. Clinical evidence in the United States further confirm that oral administration of vancomycin is the true cause of the side effects mentioned. The history of penicillin resistance is another illustration. The recent changes in policy in China are detrimental not only to people there but also worldwide, as antibiotic-resistant bacteria do not recognize country boundaries.

To this point, no single mainstream public media dares to cover these facts and air the story. Furthermore, the online documentation regarding the findings, including information on a conference and news releases, are now mysteriously unavailable. It is unfortunate that the innovators are so far suppressed and stressed, and new innovative science and solutions in this area are hindered. Antibiotic resistance should have never simply been an avenue to get funding. Innovators and sponsors should be encouraged to communicate the scientific truth, instead of threatened, penalized, and losing funding and even jobs. In summary, 250–350 million antibiotic prescriptions are given annually in this country, mostly oral antibiotics, impacting almost every family and child in this country, contributing to not only antibiotic resistance but the epidemic of modern disease due to gut microbiota dysbiosis.

Antibiotics used in animals are still primarily given by mouth, whether for food animal production or companion animals, by mixing with water and feed. It is unacceptable that the current situation should be allowed to continue. Paradigm changes are necessary. Cutting-edge science and scientists need to be recognized and empowered to find more solutions. What we really need is scientific leaders with a successful record to sit down with agency leaders to figure out the top priorities for investment, key messages to disseminate, and support from the political leaders and industry for implementation, said Ms. Wang. We do not need political dealership to further mess up and even mislead public knowledge, consumer opinions, and, therefore, policies and practices, causing massive losses.

**David Wallinga of the NRDC** hoped the next NAP prioritizes reporting on antibiotic use in food animals on a milligram-per-kilogram basis. He offered some clarifying observations to address the questions raised about Mr. Roach's presentation. First, the denominator in a milligram-per-kilogram metric does not reflect an actual measurement. In other words, meat producers and farmers do not need to weigh individual animals to calculate the denominator. The kilograms in the denominator reflect a very deliberate construct that is supposed to represent the mass of the entire population of animals that might receive antibiotics.

Some basic assumptions have to be made in calculating that denominator. Talking about antibiotics used in pig production, for example, the denominator using the European approach would be calculated by looking at the number of finisher pigs slaughtered over the course of the year multiplied by 65 kilograms—the assumed average weight at the time of slaughter—plus the total inventory of breeding sows multiplied by 240 kilograms, their assumed average weight, according to EU data. The same kind of assumptions would be made for populations of cattle, chickens, turkeys, and other animals receiving antibiotics. So, for example, the assumed average weight for chickens is 1 kilogram; for turkeys, 6.5 kilograms; for adult cattle, 425 kilograms—all at the likely time of treatment. Even though the average weights can vary from country to country, Europe specifically assumes that the average weights are the same across the EU to allow for comparison on a milligram-per-kilogram basis of usage from one country to the next.

Mr. Wallinga used U.S. data and the European Medicines Agency published methodology for his calculations. With the data now available in the United States, the milligram-per-kilogram method is better and more defensible than what has been done to date in the United States, so the NAP should make it a clear priority. Last year, Public Health Canada for the first time applied milligram-per-kilogram calculations in its reporting in two different ways. First, it made Canada-specific assumptions about animal weights (hypothesizing that they differ from European animal populations) and then using the same average weights as the EU. The results were presented side by side; while there were some minor differences, they were not significant. The same general conclusions were drawn regarding antibiotic use in Canadian food animals. More importantly, the approach allowed Canada to make more direct comparisons about antibiotic use by similar industries in European countries.

**Kevin Kavanagh from Health Watch USA** called for a paradigm shift regarding the prevention of infections of MDROs—one that is designed around the prevention and promotion of an optimal protective microbiome. Antibiotic stewardship—although very important—probably will not succeed as a sole intervention. Even a 50-percent reduction would mean billions of bacteria are exposed to antibiotics. Resistance will still develop, but hopefully at a slower rate.

The importance of the microbiome along with antibiotic stewardship is demonstrated by an up to 32-percent reduction observed in *C. difficile* infections with proper prescription practices. This reduction is primarily due to the avoidance of the destruction of the gastrointestinal tract's beneficial bacteria, which help prevent the acquisition and growth of *C. difficile* along with the development of resistance. The most effective treatment for severe *C. difficile* infections is not antibiotics but microbiome reconstruction with fecal transplantation. Identification of carriers is also important. Currently, the WHO recommends preoperative testing for *S. aureus* for all

patients undergoing major surgery. For countries with adequate resources, such as the United States, the WHO recommends testing all surgical patients. In the United States, there is not even a system-wide standard to preoperatively identify MRSA carriers, which could then allow for their decolonization.

Mr. Kavanagh envisioned that in the future, hand hygiene will evolve and take on a different form. Instead of destroying hands' microbiome over 200 times a day, risking exposure to the facility's microbiome at the same time, there will be a more selective approach, destroying microbiome when exposed to dangerous pathogens but in other cases cleaning that maintains beneficial and protective bacteria. It is of utmost importance that the healthcare system prepare for testing of the patient's microbiome. In the future, Mr. Kavanagh said, this will be part of a standard physical examination. Knowledge of the microbiome's characteristics will be an important part of addressing many different types of diseases, not just infectious disease, so the system must build this capability. Until then, efforts should be made at least to identify the carriers of dangerous pathogens in an attempt to eliminate this carriage and to modify their microbiome.

### **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 commenters for their contributions. He adjourned the meeting at 4:51 p.m.

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

**January 30–31, 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  
Sara E. Cosgrove, M.D., M.S.  
Paula J. Fedorka-Cray, Ph.D.  
Christine Ginocchio, Ph.D., MT  
Locke Karriker, D.V.M., M.S.  
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.

*Pew Charitable Trusts*

Kathryn L. Talkington

### **Ex Officio Members Present**

*U.S. Department of Health and Human Services*

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

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

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., Senior Advisor, Office of Public Health Strategy and Analysis, Office of the Commissioner, Food and Drug Administration

*U. S. Department of Agriculture*

Neena Anandaraman (for Sarah Tomlinson, D.V.M.), Animal and Plant Health Inspection Service

Emilio Esteban, D.V.M., M.B.A., 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

**Designated Federal Officer (Acting)**

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

**Advisory Council Staff**

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, M.P.H., ORISE Fellow

## Glossary of Abbreviations

AMR	antimicrobial resistance
APIC	Association for Professionals in Infection Control and Epidemiology
BARDA	Biomedical Advanced Research and Development Authority
CARB	Combating Antibiotic-Resistant Bacteria
CDC	Centers for Disease Control and Prevention
CEO	chief executive officer
CMS	Centers for Medicare and Medicaid Services
CONSERVE	Coordinating Nontraditional Sustainable Water Use in Variable Climates
DoD	Department of Defense
EHR	electronic health record
EU	European Union
FAO	Food and Agriculture Organization (of the United Nations)
FDA	U.S. Food and Drug Administration
GLASS	Global Antimicrobial Resistance Surveillance System
HHS	U.S. Department of Health and Human Services
ICE	integrative conjugative exchange
IPC	infection prevention and control
MDROs	multidrug-resistant organisms
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NAP	National Action Plan
NARMS	National Antimicrobial Resistance Monitoring System
NCBI	National Center for Biotechnology Information
NIH	National Institutes of Health
NRDC	Natural Resources Defense Council
OIE	World Organisation for Animal Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PEPFAR	President's Emergency Plan for AIDS Relief
R&D	research and development
SIDP	Society of Infectious Diseases Pharmacists
SMARs	small molecule antibiotic replacements
U.K.	United Kingdom
USDA	United States Department of Agriculture
USG	United States Government
WASH	Water, sanitation, and hygiene
WHO	World Health Organization