Listening Sessions Hosted by the U.S. Department of Health and Human Services: Combating Antimicrobial Resistance

February 26–27, 2020

Great Hall, Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

Meeting Summary

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Welcome

Martin Blaser, M.D., Rutgers University, and Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, The Ohio State University

Dr. Blaser welcomed the participants to the listening session on combating antibiotic resistance. The Department of Health and Human Services (HHS) organized this gathering to hear from experts about innovations to fight antimicrobial resistance (AMR), such as new antibiotics, vaccines, alternative therapies, and diagnostics, as well as animal health management products and practices. Dr. Blaser noted that the rapid spread of COVID-19 (or coronavirus) demonstrates how vulnerable the public is to emerging infectious diseases. Building the infrastructure for combating (AMR) will help address COVID-19 and other such threats.

Overview, Rules of Engagement, and Roll Call

Jomana F. Musmar, M.S., Ph.D., Public Health Advisor, Office of Infectious Diseases and HIV/AIDS Policy, Office of the Assistant Secretary for Health, HHS

Dr. Musmar explained that the listening session was intended to gather information and exchange ideas about One Health issues and AMR. The listening session was open to the public and streamed live online. (See the appendix for the list of invited participants.)

Opening Remarks

RADM Erica G. Schwartz, M.D., J.D., M.P.H., Deputy Surgeon General, HHS

RADM Schwartz recognized the public health threat posed by AMR, which is a top priority for HHS and the entire U.S. Government (USG). She emphasized the importance of appropriate use of existing antimicrobials and the need for new antibiotics, diagnostics, alternative therapeutics, and preventive technologies to address resistant disease. The Surgeon General and his staff provide the best available scientific information to the public, and participants in this listening session all have a role in evaluating and sharing that information. RADM Schwartz thanked the participants for coming together to engage in active problem solving in a public forum.

RADM Schwartz recognized four individuals who made outstanding contributions in the field of AMR and who recently retired from the Presidential Advisory Council on Combatting Antibiotic Resistant Bacteria, which advises the HHS Secretary: Angela Caliendo, M.D., Ph.D., FIDSA; Alicia R. Cole; Aileen M. Marty, M.D., FACP; Robert A. Weinstein, M.D.

Keynote Speaker

Charles Keckler, J.D., M.A., Associate Deputy Secretary, HHS

Mr. Keckler said the spread of COVID-19 is a vitally important reminder of the need to constantly monitor and prepare for new and challenging infectious disease threats. Addressing AMR, like responding to COVID-19, will require coordination among many stakeholders. Later this year, HHS will release an updated National Action Plan for Combating Antibiotic-Resistant Bacteria, which describes the USG's AMR efforts over the next 5 years. Many of the goals and

objectives of the first National Action Plan were achieved. The new iteration builds on those successes and identifies new priorities and objectives. Meetings like this listening session are an excellent way to share information and bring in outside viewpoints to ensure that deliberations reflect the current state of the field.

An HHS call to action resulted in nearly 350 commitments to fight AMR from government entities, nongovernmental organizations, pharmaceutical and biotech companies, and others, such as continued efforts to reduce antibiotic use in animals. In addition, innovative public–private partnerships have increased progress toward development of new antibiotics and diagnostic tests. Mr. Keckler said the challenges ahead are daunting, but there are plenty of reasons for hope. AMR will continue to remain a priority for HHS and across the USG.

Patient and Stakeholder Stories

Antibiotic-Free Food Animal Production

Marshall Bartlett, Home Place Pastures

Mr. Bartlett said his hog farm in Northern Mississippi avoids relying on antibiotics by using traditional practices (e.g., providing a lot of space for animals to spread out and maintaining animals in discrete populations) and biosecurity techniques (e.g., sterilization of equipment and machinery and staff hygiene practices). Notably, the farm has its own U.S. Department of Agriculture (USDA)-inspected slaughtering house on site. Mr. Bartlett said he has built a successful business in a rural area with few jobs and scaled up to meet growing demand. However, the business sells to a niche market of restaurants. USDA Farm Service Agency microloans and resources from land-grant universities enabled Mr. Bartlett to design a unique production system that does not rely on antibiotics. He called for continued funding support for USDA initiatives and federal research that will enable the next generation of farmers to succeed by producing meat that does not contribute to AMR.

Clostridium difficile Survivor

Christina Fuhrman, Patient Advocate

Ms. Fuhrman said she was accustomed to taking antibiotics to avoid the inconvenience of a cold or influenza, and her health care providers prescribed them without question. In hindsight, she said, the more antibiotics she took, the sicker she became. Ms. Fuhrman was hospitalized with *C. difficile* at age 31 and was unable to work or care for herself. She received a fecal transplant and eventually recovered. She went on to have two children, avoiding antibiotics throughout both pregnancies. However, her first child was hospitalized with *C. difficile* at age 22 months. Although her child also recovered, Ms. Fuhrman said the painful ordeal underscored the challenges of AMR: the impact of inappropriate and excessive antibiotic use, the lack of incentives to develop new antibiotics, the waning potency of existing antibiotics, and the myth that superbugs only affect people who are immunocompromised. Ms. Fuhrman concluded that a catastrophic and unstoppable crisis is on the horizon.

Health-Care-Associated Infection (HAI) Survivor

Mary Millard, Patient Advocate

Ms. Millard emphasized that she had been very healthy and had never had a prescription until 2014, when she was diagnosed with atrial fibrillation and learned that she had a large aneurism and a partially collapsed valve. Subsequently, Ms. Millard suffered heart failure and required weeks of intensive care before she was strong enough to endure open heart surgery. Following surgery, she became infected with *Pseudomonas*. She must now take antibiotics for the rest of her life, rotating between three that are effective, all of which have significant side effects. Ms. Millard expressed concern about the waning effectiveness of the antibiotics. She urged federal investment in developing new antibiotics, not just repurposing existing products. Since her initial event, she has had numerous rehospitalizations, surgeries, and dozens of emergency department visits. Ms. Millard said the problem of HAIs is worsening and must be addressed. She has dedicated her life to advocacy to spread the message that many are dying from infections, and many like her are living with infections every day.

Father of a Victim of an Antibiotic-Resistant Infection

Chris Romm, Patient Advocate

Mr. Romm explained that his son was discharged from the Army because of an injury that required amputation of a finger. Eventually, it became clear that his initial wound was infected with *Staphylococcus aureus*. He was hospitalized several times and discharged with antibiotics, but his condition worsened whenever he was not taking them. Mr. Romm explained how terrifying it was for him and his family to see his son deteriorate to critical condition, improve, and then deteriorate again, over and over. At one point, Mr. Romm had to administer cardiopulmonary resuscitation to his son shortly after his son had undergone open heart surgery. He revived his son, but his son died in the hospital soon after. Mr. Romm asked that the federal government direct more funding to the critical area of AMR, because he hoped that no one else would have to endure the pain that he and his wife did when they lost their child.

Discussion

Dr. King appreciated the powerful, sobering stories, which remind all of the participants of the importance of their work to fight AMR. Alicia Cole said the common thread among all the stories was the need for prevention. She added that while experts discuss the data and the science, they must be mindful that those numbers stand for real people. Ms. Cole stressed the urgency of the situation and the need to put patients and the public first.

When asked about the challenges to scaling up a farming approach that does not rely on antibiotics, Mr. Marshall stressed that federal funding enabled him to invest in the facilities needed, which in turn allowed him to take more control of the operation, create jobs, and grow the business. However, his approach means the product costs more. Mr. Marshall called for more support for good stewardship and more research on farming practices that do not require antibiotics. He also urged the USG to ensure that low-interest loans and grants are available to support entrepreneurial farmers who can revitalize and sustain rural economies. Centralizing the food system results in inexpensive proteins, but it also extracts resources from the rural economy, said Mr. Marshall, and he hoped to reverse that.

Dr. Blaser asked Ms. Fuhrman for her perspective on the overuse of antibiotics. Ms. Fuhrman said she shares her story frequently to raise awareness about overuse, and people are always shocked to learn about the adverse effects. Health care providers, especially pediatricians, feel pressure from patients and parents to prescribe antibiotics. Ms. Fuhrman emphasized the need to educate the general public so that they can be their own advocates.

Panel 1: Innovation in an Era of Stewardship

The Role of Stewardship in Optimizing the Use of New Agents

Sara E. Cosgrove, M.D., M.S., Johns Hopkins University

Dr. Cosgrove explained that uptake of novel drugs for infectious diseases, even when they appear to be more effective at first glance, might be slow for various reasons, such as limited understanding of the effects on patients with drug-resistant organisms. To increase uptake, much more research beyond the initial studies required for approval by the Food and Drug Administration (FDA) is needed. New drugs are often more expensive than existing drugs and might lack corresponding susceptibility tests.

Antibiotic stewardship programs (ASPs) play a key role in determining which drugs are used and how, and they are unlikely to support empiric use of new drugs. Already, there is evidence of baseline and emerging resistance to the new beta-lactams. These drugs are a last resort, used to help very sick patients become healthy enough for procedures such as organ transplantation. Insurers are reluctant to pay for such high-cost drugs in the outpatient setting, especially if prescribed off-label, and nursing homes often lack access to the drugs. Recent Centers for Medicare and Medicaid Services' (CMS') payment changes for inpatient and long-term care do not address the cost challenges.

A number of new, expensive antibiotics have been approved, but they are not indicated for drug-resistant organisms. Dr. Cosgrove hoped the new antibiotics would remain available, despite current cost, limited utility, and manufacturing concerns, because they might prove useful for other conditions. Dr. Cosgrove called for more education of infectious disease specialists, and updated guidelines, more efforts to predict which patients might benefit from empiric use of new drugs, more corresponding susceptibility tests for new drugs, and updated breakpoints.

2020 Antimicrobial Resistance Benchmark: Report from the World Economic Forum

Fatema Rafiqi, Ph.D., Access to Medicine Foundation

The Access to Medicine Foundation presented its 2020 Antimicrobial Resistance Benchmark report at the January 2020 World Economic Forum. The report identifies what 30 pharmaceutical developers and manufacturers are doing in the area of antimicrobial drug development, using an analysis framework that addresses research and development (R&D), responsible manufacturing, and appropriate access and stewardship. The report looks at all stages of R&D, from investments and products in the pipeline to sharing intellectual capital and planning for access and stewardship. It compares companies' strategies for limiting the impact of manufacturing on resistance through environmental risk management. The report also evaluates companies'

strategies to improve access and stewardship of approved drugs. It includes detailed report cards on each company.

The 2020 report reveals signs of improvement since the 2018 report in the way companies address AMR, but progress has been slow. More pharmaceutical companies have plans for access and stewardship for key candidate antibiotics. Some companies are tackling overselling of antimicrobials; for example, 10 companies are either decoupling bonuses from sales volumes or refraining from deploying sales agents for antimicrobials. Publicly sharing AMR surveillance results is common, yet only one company shares raw data.

At the World Economic Forum, there was discussion of economic incentives for the pharmaceutical industry to do more in light of the urgent need for better access to antibiotics, especially for children in low- and middle-income countries (LMICs). At that meeting, procurers such as the Global Fund showed interest in using the Benchmark report to inform decisions about product selection. The Foundation is also partnering with governments and private organizations around an Investor Year of Action on AMR.

Overview of CMS Rule Changes to Promote Antimicrobial Stewardship Programs, and Medicare Inpatient Prospective Payment System (IPPS) & New Technology Add-on Payment Provision

Scott Cooper, M.M.Sc., PA-C, and Michael Treitel, CMS

Mr. Cooper outlined CMS policies requiring facilities to develop ASPs and improve infection prevention and control. CMS works closely with the Centers for Disease Control and Prevention (CDC) to create guidance for its policies. To decrease the regulatory burden, CMS allows hospital systems to use a unified, integrated approach to quality assessment and performance improvement as well as a centralized ASP and infection prevention and control program.

Guidance for new policies affecting hospitals and critical access hospitals incorporates CDC's seven core elements for antibiotic stewardship in hospitals. The guidance is designed for training and educating surveyors, and it will likely refer to antibiotic stewardship measures from CDC, the Agency for Healthcare Research and Quality, and other nationally recognized organizations. Following stakeholder input and internal clearance, the guidance should be ready by early 2021. In the future, CMS plans to propose expanding antibiotic stewardship requirements to home health agencies, ambulatory surgical centers, dialysis facilities, and other providers and suppliers that participate in the Medicare program, said Mr. Cooper.

Mr. Treitel explained that Medicare's Inpatient Prospective Payment System includes an add-on payment for new, high-cost products that provide substantial clinical improvement and are inadequately paid under the current system. By statute, CMS uses claims data to recalibrate its payment system annually, and the data lag behind by 2 years, so new technologies are not reflected in the current payment rates.

To address the serious impact of AMR, as of October 1, 2019, CMS pays for qualified infectious disease products using the new technology add-on payment. These products will not have to

demonstrate substantial clinical improvement over existing products. CMS will pay 75 percent of the costs of the products (compared with 65 percent for other new technology add-on payments). In addition, CMS will adopt updated diagnostic codes for AMR, which is likely to result in conditions involving AMR being assigned to higher-severity diagnostic codes that are paid at a higher rate because of the increased resources associated with treatment.

Urgent Need for Novel Incentives in a Broken System

Emily Wheeler, Antimicrobials Working Group

USG-funded efforts to spur development of new antimicrobials have helped exceed the goal set by the Infectious Diseases Society of America of bringing 10 new antimicrobials to market by 2020. However, revenue from those products is low, and about one fourth of them came from companies that have since gone bankrupt. The market for antimicrobials is unique, as products are intended for limited use in narrow populations yet must be affordable and accessible.

Reimbursement is a major barrier in the marketplace, said Ms. Wheeler. In the inpatient setting, Medicare bundles antimicrobials with other products and services for payment by condition, which prioritizes cost containment and creates a disincentive for providers to use newer, higher-cost antimicrobials. Stakeholders are encouraged by CMS' changes, but more action is needed.

Incentives to push development are essential, but the market also needs incentives that pull products forward, after approval. Among the incentives under consideration are federal legislation to pay for antimicrobials separately from Medicare's current system and new funding and authority for the Biomedical Advanced Research and Development Authority (BARDA) and others to support antimicrobials after FDA approval. Ms. Wheeler's organization believes that reimbursement is critical in the near term to stabilize the ecosystem, along with initiatives that look at the big picture, such as BARDA's Project BioShield awards to accelerate R&D, purchase, and make new antimicrobials available. Novel pull incentives that separate revenue from sales are being explored by stakeholders. A host of incentives are needed. Ms. Wheeler said that efforts should reflect the urgency of AMR, as small companies in particular, which make up most of the development sector, will not be able to sustain their efforts over time.

Merck's Approach to Antibiotic Stewardship

Elizabeth Hermsen, Pharm.D., M.B.A., BCPS-AQ(ID), FIDP, Merck & Co., Inc.

Merck recognizes that slowing the development of AMR helps prolong the lifespan of currently available antimicrobials, and good antimicrobial stewardship protects the long-term viability of products used in various therapeutic areas (e.g., oncology, surgery, and diabetes). Antimicrobial stewardship efforts allow Merck to collaborate with stakeholders around a key public health priority that benefits global health and results in shared value. Merck's involvement in antimicrobial stewardship contributes to its credibility in the field.

Dr. Hermsen said antimicrobial stewardship is built into every aspect of Merck's engagement on AMR. The company advocates for policies that facilitate access to novel therapies and diagnostics. Its Antimicrobial Stewardship Council holds the company accountable to its public commitments, ensures internal alignment, and maintains momentum. The company also educates

employees about the importance of AMR and antimicrobial stewardship. In the course of product development and marketing, Merck:

- pursues indications in areas of unmet need;
- identifies study populations most likely to benefit from products;
- employs responsible manufacturing practices to limit active antibiotic discharges into the environment;
- incorporates antimicrobial stewardship principles into promotional materials and practices, drug positioning, and strategy;
- supports postmarket data generation to further inform appropriate antimicrobial use;
- conducts ongoing surveillance studies; and
- works with external stakeholders to support responsible antibiotic use.

Discussion

Dr. Cosgrove pointed out that it is up to ASP leaders to emphasize that the new requirements for ASPs and infection control and prevention are intended to help patients. Large hospitals and systems have come to see the benefits of stewardship, even if it does not save costs, but across the health care system, acceptance of that tradeoff varies. Dr. Hermsen added that it is difficult to find concrete and easy-to-use measures of good stewardship. ASPs are often run by pharmacists who are used to thinking in terms of cost savings.

Regarding off-label use of new drugs, Dr. Cosgrove said ASP leaders should seek out information and develop recommendations for their own facilities (with input from infectious disease specialists and others). However, broader dissemination of such recommendations is needed, because the manufacturers are restricted from marketing drugs for off-label use.

Kent E. Kester, M.D., FACP, FIDSA, FASTMH, pointed out the shortage of infectious disease physicians to lead ASPs. Mr. Cooper said that CMS' requirements for well-qualified leadership of ASPs recognize the need for input from medical, nursing, and pharmaceutical staff. In response to Elaine Larson, Ph.D., RN, Mr. Cooper said he would seek out data on the impact of CMS' stewardship requirements on the facilities that have implemented them so far.

Ms. Wheeler said her organization supports delinkage models that would separate payment from the volume of product sold, but near-term policies to fix reimbursement are also needed.

Dr. Hermsen described mechanisms Merck uses to support development of diagnostic and susceptibility tests, including working with susceptibility test manufacturers while products are in development so that the tests are available soon after the product reaches the market. She called on CDC and others to support more research on implementation science, so that interventions can be implemented effectively.

Denise Cardo, M.D., asked what could be done to better integrate stewardship into every aspect of patient care, at every patient encounter, particularly when the concept of "stewardship" is still seen as a method for cutting costs. Dr. Cosgrove described progress toward an infrastructure that

supports stewardship in acute care settings. She said better training surveyors to understand true stewardship will help organizations implement better programs. In addition, leadership must educate and empower providers to change their behavior around antimicrobial prescribing. Dr. Cosgrove added that incentives and resources for stewardship are needed (and not just disincentives), because it is unreasonable to ask facilities to undertake all of this work without additional payment.

Panel 2: Innovations in Prevention and Diagnostics

Current Trends in the Research Pipeline for AMR-Related Vaccines and Diagnostics

Kent E. Kester, M.D., FACP, FIDSA, FASTMH, Sanofi Pasteur

Vaccines in development hold promise for stemming the use of antibiotics by protecting against resistant bacteria and viral pathogens that may be mistaken for bacterial infection. Rapid diagnostics can help providers better tailor treatment. Susceptibility testing is vital to successful application of new antibiotics. Many vaccine candidates are in development, thanks in part to support from the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) and the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), but the total cost from concept to market can be up to $1 billion, and the process can take 15–20 years. New technologies, such as mRNA, new adjuvants, new expression systems, systems biology, reverse vaccinology, structural vaccinology, and bioconjugates, are being explored, but the regulatory pathways to approval are not always clear. Mr. Kester emphasized that the long-term challenges of marketing, deployment, and utilization of new vaccines must be addressed.

Most of the vaccines in the pipeline are being developed by academic laboratories and biotech companies that may not be capable of making the leap to large-scale production and marketing. Work is underway toward a broad or universal influenza vaccine, which would stem antibiotic use by minimizing influenza morbidity and bacterial infection associated with influenza. Some investigators are looking at passive and active immunization techniques for respiratory syncytial virus, particularly for the elderly and infants.

On the diagnostics side, researchers are evaluating new technologies, such as molecular amplification, sequencing, imaging technology, and detection of volatile organic compounds. However, the costs of implementing new diagnostic technology are considerable for health care facilities, which rely on insurance reimbursement to cover such costs. NIAID and CARB-X initiatives are also supporting diagnostics research. Dr. Kester concluded that vaccines and diagnostics can play an important role in tackling AMR, but both face significant barriers.

Vaccine Pipeline for Prophylactic Antimicrobial Resistance Prevention

Jan Poolman, Ph.D., Janssen, a Johnson & Johnson Company

Large U.S. and European studies demonstrate that *Escherichia coli* (particularly extraintestinal pathogenic *E. coli*, or ExPEC) and *S. aureus* are the leading causes of HAIs among all of the ESKAPEE pathogens (*Enterococcus, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas,*

Enterobacter, and *E. coli*). Dr. Poolman noted that *E. coli* should be added to CDC's Active Bacterial Core surveillance list of pathogens.

Failed efforts to develop a vaccine for *S. aureus* reveal that new animal models are needed, focus should shift from surface antigens to virulence factors and immune escape mechanisms, and a TH1 adjuvant should be explored. Janssen has applied bioconjugation technology for an ExPEC vaccine that has shown promise in a Phase I–II dosing study.

Dr. Poolman said that universal immunization—rather than focusing on those at high-risk—works for pediatric populations, and Janssen believes it will work for senior populations as well. Vaccines alone will not be sufficient to address AMR, he noted; diagnostics and new antibiotics are also needed.

Vaccines and Innovations in Facility Infection Control to Prevent Neonatal Sepsis

Padmini Srikantiah, M.D., M.P.H., Bill & Melinda Gates Foundation

The Gates Foundation's AMR strategy primarily focuses on prevention of infections, including drug-resistant infections and their associated mortality, particularly in LMICs, where populations are at greatest risk of mortality. The strategy is implemented in two broad categories: 1) supporting surveillance platforms to better generate evidence about the etiologies, resistance patterns, outcomes, and burdens of neonatal sepsis; and 2) using these data to guide investment in product development.

K. pneumonia is the leading etiology behind neonatal sepsis in most LMICs and contributes substantially to neonatal deaths. From 5 percent to 20 percent of *K. pneumonia* isolates are carbapenem-resistant. Most of the *Klebsiella* isolates related to sepsis come from a relatively small number of serogroups, and those serogroups could be the target of a maternal vaccine. To pursue such an effort, better characterization of the *Klebsiella* serogroups in neonatal sepsis found in additional locations is needed, as is stronger evidence that a maternal vaccine would protect neonates against *Klebsiella* sepsis. A number of vaccine candidates are in development for adults at risk of *Klebsiella* infection, particularly for HAIs. The Foundation recognizes that it is not possible to develop vaccines for every pathogen that causes neonatal sepsis but believes that *Klebsiella* in particular should be pursued.

The Foundation is also interested in exploring innovations that would facilitate better infection prevention and control practices in LMICs to mitigate neonatal sepsis, such as technologies that address contamination of surfaces in health care environments. Novel approaches can be categorized as either disinfecting surfaces differently (e.g., using ultraviolet light), altering the surfaces (e.g., through ordered micropatterns that prevent bacterial adhesion), and microbial management involving probiotic infection control. The latter uses nonpathogenic probiotic bacteria to colonize hard surfaces and counteract proliferation of pathogenic species, and further research is needed to confirm its utility.

Host-Based Solution to Addressing Antibiotic Misuse: One Prototype Solution

Richard Rothman, M.D., Ph.D., Johns Hopkins University, School of Medicine

The limitations of current diagnostics prevent their widespread usefulness in helping providers decide when to prescribe antibiotics. Various studies have explored the use of protein signatures to illuminate host response to infection as a way to distinguish bacterial from viral infection. Approaches using combinations of biomarkers have performed well, but the speed of testing and their clinical utility have been limited. A 2015 study using machine learning narrowed down the proteins of interest. The accuracy of the results was comparable to that of a panel of experts who made diagnoses based on a combination of history and physical examination findings, laboratory results, imaging, and DNA testing.

MeMed's BV diagnostic assay incorporates the machine learning approach to assess host-response signatures. It outperformed routine parameters and biomarkers in distinguishing viral from bacterial infections. Subsequent studies have shown high sensitivity and specificity of the assay in a large cohort. MeMed is focusing on making the testing easy to use in clinical settings at the point of care by developing single-use cartridges and a reader that can provide results within 15 minutes. The assay adapts well to identify evolving and difficult-to-detect pathogens. The company is designing a clinical study to support its application for FDA approval.

Other manufacturers are developing assays using similar approaches. For example, Inflammatix created a test that uses mRNA signatures to distinguish viral from bacterial infection, and it has performed well in initial tests. Dr. Rothman stressed that as these new tests move through the FDA approval process, makers should be working with hospitals to determine how well the tests perform in real-world settings and how they affect clinical decision making.

AI Diagnostics for Combating Antibiotic Resistance

Kwangmin Son, PhAST Corp.

PhAST is developing a rapid, all-in-one, fully automated, direct-from-sample diagnostic that provides results in minutes. The company gathers patient samples from a local hospital and employs machine learning to distinguish those positive for infection. Positive tests go through subsequent pathogen identification and antibiotic susceptibility testing. Identifying pathogens involves assessing cell features in detail, such as motility and morphology. Antibiotic susceptibility testing evaluates the cell features in response to antibiotics, such as speed of movement, size, and growth.

PhAST is still training its artificial intelligence model and building its database of samples. Preliminary assessment of the all-in-one diagnostic demonstrated good performance and rapid time to results. The system uses simple, affordable, off-the-shelf hardware. The company is working with manufacturers to build a compact diagnostic instrument that would cost about $10,000, with cartridges that would cost about $10 per test, all relying on cloud-based technology.

Mr. Son envisions PhAST technology being used to enhance the efficacy of clinical drug trials by helping researchers target patient recruitment. As a diagnostic platform, the product could

help clinicians make rapid decisions about prescriptions, improve health care outcomes, and lower health care costs. The company also is interested in exploring the utility of its technology for animal health, biodefense, and global health, particularly in LMICs.

Discussion

Participants expressed interest in the novel technologies for reducing pathogens on surfaces. Dr. Srikantiah said one product is commercially available in Europe, but regulations must be developed for its use in health care settings. She and Michael Craig, M.P.P., agreed that a combination of products will be needed to address surface contamination, which is especially important for settings in LMICs with limited access to running water.

It was suggested that the Gates Foundation invest in development of a vaccine for group B streptococcus as part of its neonatal health initiative. Dr. Srikantiah said the Foundation has funded development of two vaccine candidates that are currently in preclinical and clinical trials.

Dennis M. Dixon, Ph.D., noted that NIAID has solicited applications from the field to take on the ESKAPEE pathogens, and there has been some interest in *S. aureus* but not a robust response overall. The applications received were not well reviewed because there are few successes for researchers to build on. Investigators also find it difficult to test vaccine candidates in targeted populations in the United States.

Concerns were raised about the lack of diagnostics for animal health. Dr. Kester noted that human health care is supported by a system of payers and a clinical infrastructure for diagnosis and care. It is possible that the principles of artificial intelligence could be applied to animal health diagnostics, but funding and incentives would be needed.

Mr. Craig asked participants how CDC could do more to support vaccine development, particularly in terms of data platforms. Dr. Poolman said more data from surveillance after vaccines reach the market would be useful. He added that the United Kingdom requires reporting of all *E. coli* cases, and a similar mandate in the United States would be helpful. Dr. Srikantiah said her organization would like more surveillance data on neonates in LMICs as well as in various regions and populations to help identify which strains are causing disease in which areas and, ultimately, how well approved products work.

Mr. Son said PhAST is researching ways to identify polymicrobial infections in samples and the effects of multiple antibiotics. He said the more samples the company had to work with, the better and faster it could train its systems.

Panel 3: Disease Prevention and Management in Animals

Challenges in Animal Agriculture Antimicrobial Stewardship Programs

Locke Karriker, D.V.M., M.S., DACVPM, Iowa State University

Dr. Karriker said veterinarians share a vision of a world where veterinary antibiotics are used responsibly in animals and where they maintain their value as therapeutic tools. He outlined five themes that underscore the challenges and gaps around stewardship in animal health.

1. **Generalization.** Current One Health recommendations and strategies are not granular enough to understand antibiotic use or assess alternatives that would inform training around behavior change to reduce antibiotic use and resistance. Each species is physiologically different, limiting the utility of alternatives to antibiotics in some species and settings. Data collection is complicated by differences in how animals are managed, whether individually or in groups. Knowledge about species varies; few veterinary schools offer training on swine medicine, for example.
2. **Culture.** Veterinarians and farmers have adapted practices to move away from antibiotic use, but the veterinary curriculum has evolved more slowly, as most students do not pursue agricultural veterinary careers. Ingrained beliefs and cultures are slow to change. Enhancing stewardship will require more attention to alternatives and dissemination of effective management practices.
3. **Advocacy.** Advocates for stewardship must earn trust over time to reach positions of influence where they can offer locally relevant solutions to minimize antimicrobial use. Veterinarians have the knowledge base and skills but must also earn their seat in policy and decision-making bodies, where they can advocate as members of the team, not adversaries. Outside advocacy—resulting from regulations or consumer preferences, for example—raises attention to issues but does little to change behavior. Internal advocates can provide evidence and shed light on the costs of stewardship, who bears those costs, and who benefits from the effort. They can also offer insights into realistic benchmarks and continuous quality improvement approaches.
4. **Alternatives.** As in human medicine, there are few alternatives to antimicrobials in the pipeline. The costs and challenges of R&D are magnified in animal agriculture, where potential profit is lower, the regulatory challenges may be more complicated, and implementation is hard to achieve. The field also faces a workforce shortage that inhibits research. With few alternatives to antibiotics, veterinarians are not highly motivated to order diagnostic tests because of the expense.
5. **Communication.** Real change in animal welfare was not achieved until large producer groups agreed not to use distinctions in their welfare programs as grounds for marketing and rather agreed to work together to implement and establish basic standards, which eventually became the baseline for participation in the marketplace. The field needs more conversations about AMR that include industry representatives, researchers, and practitioners who can connect clinical outcomes to antimicrobial use and compare the production circumstances—which requires a trustworthy forum for sharing information. The existing research should be aggregated and disseminated.

Precision Technology Opportunities to Enhance Animal Health

Justin Sexten, Ph.D., Performance Livestock Analytics

Performance Livestock Analytics looks at opportunities to address AMR through statistical process engineering. The biggest challenge on the farm is identifying "normal" so that providers can determine when animals need treatment. As the size and scope of animal agriculture

operations grow, the number of large animal veterinarians in rural areas continues to decline, so boosting the workforce is one opportunity to improve animal health, Dr. Sexten observed. Good technologies (e.g., sensors and trackers) exist to monitor animal health, behavior, and nutrition, but it is difficult for producers to aggregate the data from them into information that can drive decision making. Dr. Sexten pointed out that investment in rural wireless connectivity is needed to support the growing potential of such technology.

Dr. Sexton said standardizing and improving existing technology, such as ultra-high-frequency ear tags, will increase adoption. Because solutions must be easy to incorporate into the normal workflow, simple technologies like ear tags are ideal. Performance Livestock Analytics uses ear tags and a camera to determine, for example, how often animals visit the water tank, at what time of day, and for how long, to gain a sense of normal, baseline behavior.

Analysis of tracking data for normal feed behavior can reveal signs of respiratory disease in animals 4 days before it is diagnosed by trained staff, with 90 percent accuracy. The data can be evaluated on the farm, allowing producers to focus attention on animals that need it and to transmit data to a veterinarian for earlier treatment, if needed. The ability to identify sick animals early could decrease preventive use of antimicrobials.

Applications of Next Generation Sequencing to Inform Disease Management Decisions for Livestock

Maria Clavijo, D.V.M., Ph.D., Iowa State University Veterinary Diagnostic Laboratory; Genus PIC

A multidisciplinary collaboration among Iowa State University, industry, and the veterinary community gathered samples from 32 swine producers in the highest-producing states to populate a swine bacterial database. The whole-genome-sequencing information from the samples can be used to improve ongoing surveillance programs for the bacteria identified. The database can capture a baseline of current strains on a floor or a farm, which helps identify the emergence of new pathotypes and changes in prevalence. The information generated can also aid epidemiologic investigations by identifying sources of introduction, risk factors for disease occurrence, and novel transmission routes. In one sample involving *Glaesserella parasuis*, researchers used the whole genome sequencing data to pinpoint the source of introduction of a novel strain. Ultimately, the knowledge gained helped to further refine biosecurity and reduced the spread of disease associated with the novel strain.

To address concerns about whether the database is getting the correct isolate from these cases, educational materials were created to help veterinarians optimize sample collection and handling. The collaborative is developing an online platform for visualizing and sharing data that can be used by producers and diagnostic laboratories to improve control and prevention for endemic pathogens.

Dr. Clavijo also described work by Genus PIC to produce disease-resistant breeding stock through genetic improvement. With gene editing technology, Genus created a pig that is resistant to porcine reproductive and respiratory syndrome, a viral infection that often results in the use of

antibiotics to treat secondary infections. The virus has a significant impact across the food chain. Genus is now evaluating the safety of the technology and working with the FDA and its counterparts in four countries on regulatory issues. It is also engaging stakeholders to clarify the technology and address stakeholder concerns.

Innovations in Animal Feed (Additives)

Leon Marchal, Ph.D., DuPont & Wageningen University

Decreasing the amount of antibiotics used in food animal production requires a holistic approach that takes into account environmental hygiene, nutrition, gut and immune function, and the microbiome. Dr. Marchal described how improvements to feed structure for swine and poultry decreased infections and stabilized the animals' microbiome.

Avoiding overfeeding protein, especially in young animals, is important because the undigested protein in the small intestine is potentially fermented by pathogens in the large intestine, where pathogens can thrive. Hydrolytic enzymes improve protein digestibility and can reduce potential fermentable protein as well as reduce nitrogen emission. Use of probiotics can lead to less use of antibiotics. The mechanism of action of probiotics is not fully understood, but they are believed to support healthy gut development, help with recovery from infection, and produce beneficial metabolites.

Dr. Marchal said that the total amount of antibiotics can be reduced drastically in the United States and the European Union with the right incentives, which will increase prices. Further reducing antibiotic use will require more consistent feed additive solutions. A lot of data from trials are not published but could be used to help with decision making. Increasing the robustness of animals is key, because healthy animals fend off disease better. Finally, the efficacy of antibiotics must be preserved for treating sick animals.

Discussion

It was noted that there must be truthful, transparent communication and stakeholder engagement around the use of antibiotics and gene editing in animals.

Dr. Sexten noted that by providing a platform for data collection and sharing, the ideal solutions will evolve organically from users. Such a platform could track animals across a supply chain for the purpose of tracking disease transmission. Dr. Sexten confirmed that once baseline data are collected, the platform can detect signals of disease about 4 days sooner than farm workers do, and Dr. Karriker said the findings have been confirmed in several species. Dr. Sexten reiterated the need for more large-animal veterinarians, which could be aided by government financial assistance.

Mr. Craig noted that a different bioinformatic pipeline would be needed to look at how organisms excreted from animals survive in the environment, but such an approach would be useful in seeing how pathogens persist in a facility and the role they play in disease.

Public Comment

Kevin Kavanaugh of Health Watch wondered, in light of the intense infection control efforts regarding the coronavirus, why more emphasis on screening and isolation strategies have not been advocated for other contagions. The overdependence on handwashing alone and almost completely ignoring patients' biomes have set the country on a dangerous path. Mr. Kavanaugh called for comprehensive guidelines. CDC recently recommended enhanced precautions for nursing homes, but its guidelines allow resident carriers to roam freely within a facility, and the guidelines limit use of precautions to patient encounters that have a high risk of transmission. Similar precautions have been recommended for two of the CDCs most urgent threats, carbapenem-resistant Enterobacteriaceae (CRE) and methicillin-resistant *S. aureus* (MRSA). Low-risk encounters, such as passing out medications, occur frequently in nursing homes, and hand hygiene and wearing gloves may only prevent two thirds of the MRSA carrier transmission.

With the high rate of carriage of these pathogens in nursing homes, Health Watch calculated that even following enhanced precautions, health care workers whose jobs involve passing out medications will contaminate their clothes with MRSA 11 times a week. A strategy must be implemented in nursing homes based on the existing microbiome at the facility and the capability of the resident's microbiome. If the resident carries dangerous contagions, then detailed colonization should be attempted. Some organisms, such as CRE, may have a very long duration of colonization, and how to decolonize them is not known. In such cases, admission to a compatible facility or zone isolation should be implemented. Those who argue that these strategies do not preserve the dignity of nursing home residents need to realize that residents also would not wish to contaminate their children with dangerous pathogens.

Tamara Johnson of Magnolia Medical Technologies observed that every year in America over one million patients are impacted by a contaminated blood culture, which leads to a misdiagnosis of bacteremia or sepsis, and a majority of those patients have an extended length of stay. They receive multiple unnecessary and inappropriate broad-spectrum antibiotics that only increase their morbidity and mortality. This chain of events significantly contributes to the antimicrobial crisis. The United States spends over $4 billion in health care dollars every year treating these patients unnecessarily. Sepsis is the leading cause of death for hospitalized patients, and blood cultures remain the gold standard for diagnosis. Therefore, accurate blood cultures are critically needed. Current training, education, and other measures have not met this need. A recent article by Robert Weinstein, M.D., found that 35–50 percent of positive blood cultures are wrong. It also noted that patients with contaminated blood cultures are just as likely to receive antimicrobial therapy as patients with true bacteremia. Patients who are misdiagnosed because of a contaminated blood culture have a 450-percent increase in their vancomycin dosing compared with patients who are correctly diagnosed.

Ms. Johnson questioned whether such diagnostic inaccuracy would be tolerated for a cancer test or whether it would be acceptable to give chemotherapy erroneously 50 percent of the time. Even if the hospital has polymerase chain reaction (PCR) testing that identifies the common contaminant coagulase-negative *Staphylococcus* infection, this organism is responsible for true bacteremia anywhere from 15 percent to 38 percent of the time. The treating physician has a

diagnostic conundrum; historically, providers choose to treat about 65 percent of the time, and the inappropriate use of antibiotics leads to HAIs, such as *C. difficile*. False-positive diagnoses caused by contaminated cultures result in antibiotic therapy of highest-risk patients. Ms. Johnson requested new benchmarks that would decrease the tolerance for blood culture contamination from the current 3 percent to 1 percent or lower.

Jonathan Lawrence of Kaleido Biosciences noted that drug-resistant pathogens pose a significant health risk. While new antibiotics are being discovered, they will eventually fail. A growing body of evidence indicates that the gut microbiome can be a reservoir for resistant bacteria, include CRE and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. These pathogens exist due to selection pressure caused by the use and overuse of antibiotics. Nonantibiotic treatments intended to support the normal bacteria in the gut microbiome and thereby minimize colonization by pathogens has great potential and should be pursued.

While efforts to use the microbiome to treat infection should be applauded, more can be done. Compelling data demonstrate that the microbiome can be harnessed to prevent infections. Success in reducing pathogens in the gut would allow for more effective antibiotic stewardship, as antibiotics could be used more sparingly, thus slowing the development of resistance. The challenges of incentivizing sponsors to develop and market antibiotics are well known and account, in part, for the paucity of companies making antibiotics. Strategies to prevent infections using nonantibiotic approaches are attractive for patients, clinicians, and drug developers alike. Mr. Lawrence expressed the need for reasonable pathways for the development of microbiome-directed, nonantibiotic preventive therapies with reasonable clinical requirements, costs, and market opportunity.

Robert DeVol of Tetraphase Pharmaceuticals said his company is developing synthetic tetracycline compounds along a compressed timeline so that it can remain viable in the face of management and financial challenges. Mr. DeVol cited a 1999 article that identified AMR as a complex, multifactorial, intractable problem for which incremental changes will not be sufficient. That article offered three solutions. First, develop national performance measures that health systems could use to guide their performance and improve their activities. Second, improve management of information, pool data, and organize data on a population level through the use of electronic health records. Third, use the data to develop clinical decision support tools that health care providers can use in real time at the bedside.

Mr. DeVol pointed out that advances have been made in all three areas, such as CMS' incentive payment programs and CDC's National Healthcare Safety Network, which set national performance improvement targets. Enhancements in electronic health records and decision support tools have helped support stewardship, but the changes are incremental. Mr. DeVol called for thinking more transformationally because evolution is going to stay ahead of technology. He asked whether there is a way to share risk in the CMS incentive-based program that involves not just the payer and the provider but also the manufacturer, so, that everybody with a financial stake is motivated to improve the metrics. Mr. DeVol concluded that the best

way to change things quickly is through incentive payments that get all the key players aligned and working together.

Jennifer Katz of the Global Antibiotic Research and Development Partnership pointed out that the United States has played an important role in early R&D through BARDA, NIH, CARB-X, and CDC. Her organization focuses on late-stage clinical R&D of treatments to combat drug-resistant infections. It seeks to address the areas of greatest public health need, focusing on CDC and World Health Organization (WHO) priority pathogens and the needs of priority populations. Notably, the Partnership is working on treatment for sexually transmitted infections and for serious bacterial infections in hospitalized adults, children, and infants.

Last year, the Partnership launched a Phase III trial in the United States on treatment for gonorrhea. It is also starting the first global, neonatal AMR study of its kind to collect data from 3,000 infants with sepsis to better inform the prevention and treatment of neonatal sepsis. The Partnership is an important player that can provide a clear delivery path for innovations being developed by the U.S. public and private sector, said Ms. Katz. She hoped for the continued collaboration with and leadership of the USG.

Phi Vu of AdvaMedDx, a division of the Advanced Medical Technology Association, appreciated that CMS finalized conditions of participation requiring the adoption of ASPs in hospitals. He said that diagnostics are critical to the success of antibiotic stewardship efforts. These innovative tests are used to identify, monitor, and track resistance and, perhaps even more importantly, to inform antibiotic prescribing of the right drug, for the right patient, at the right time, for the right microbe.

Diagnostic stewardship is the use of diagnostic testing and laboratory expertise to guide patient management and treatment decisions. AdvaMedDx has developed practical diagnostic stewardship recommendations intended to bolster hospital inpatient ASPs. The recommendations focus on understanding key timeframes from when the test is ordered to when the results are returned and acted upon by the treating clinician, harnessing the power of electronic health records to ensure that clinicians understand how to interpret and apply test results. AdvaMedDx is eager to work with public and private sector partners to encourage increased focus on diagnostic stewardship to support the successful implementation of ASPs across the country.

Kevin McDermott said **Summit Therapeutics** seeks to bring novel antibiotics to the market, focusing on significant unmet medical needs. The company has two Phase III clinical trials underway for a novel *C. difficile* treatment, thanks to support from BARDA and a few courageous U.S. investors. Mr. McDermott said the role of patients in preventing the spread of resistant infection is being overlooked. Patients being treated for urgent threats (as defined by CDC) are not treated exclusively in the hospital setting. For *C. difficile* especially, the community is a major site of care. The ability of a Medicare or Medicaid patient to pay for an antibiotic prescription to treat an urgent threat should never stand between a desired outcome and the risk of spreading infection, recurrence, or contribution to resistance.

Mr. McDermott asked that CMS, CDC, and FDA collaborate to designate qualified infectious disease products with an approved indication for urgent threat infections to be considered mission-critical agents and waive all patient out-of-pocket expense to help enable stewardship as originally intended. The goal of treatment is to get the most appropriate and effective treatments to patients to support patient-friendly outcomes, not economic ones. Mr. McDermott asked that the request be considered for fiscal year 2020. Summit's data indicate that some Medicare and Medicaid patients are not starting therapy or deciding to end therapy prematurely because they either cannot afford it or failed to secure external support in a timely manner. Mr. McDermott said the cost would be easily offset by reduced medical utilization and improved quality of life.

Eric Petrosinelli said that in 2008, his mother passed away from septic shock brought on by an intestinal infection. He said he was aware of such infections, but his mother did not have any of the predisposing risk factors other than age. She was experiencing diarrhea for a few days, and both assumed it was a virus. After 3 days, Mr. Petrosinelli offered to take his mother to the emergency department, but she asked to wait one more day. The next morning, his mother asked him to call 911 because she could not urinate, and she was feeling very weak and unsteady. At the hospital, she was immediately diagnosed with sepsis. The clinicians assumed she had *C. difficile* and treated her accordingly. She was originally given broad-spectrum antibiotics, as well as vasopressin to increase her blood pressure. After a few days in the intensive care unit, she appeared to improve, but then things changed dramatically, and by the fifth day she was gone. Mr. Petrosinelli hoped to raise awareness about *C. difficile* on his mother's behalf but also to encourage funding for the development of new antibiotics. Bacterial infections like *C. difficile* are becoming increasingly resistant to current antibiotics. Mr. Petrosinelli said he would have liked to have new medications available to give his mother more of a fighting chance.

Barry Fox, M.D., professor at the University of Wisconsin in Madison, said he has been working in the field of antimicrobial stewardship for over 20 years. He is a hospital epidemiologist and the epidemiologist and stewardship liaison for a long-term care facility. Dr. Fox planned to visit members of Congress along with a delegation of professionals and patient advocates to provide education on the threats of AMR and support the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act, which would enable CMS to pay separately for new, expensive antibiotics. The DISARM Act is imperfect but would represent a first step toward helping the development of new anti-infectants, said Dr. Fox. He also noted that the President's FY 2020 budget includes cuts to CDC's funds, which would affect AMR issues. He expressed opposition to such cuts.

Melinda Pettigrew, Ph.D., an infectious diseases epidemiologist at the Yale University School of Public Health, asked for increased funding for molecular epidemiologic studies to assess AMR in the community. There is an increase in antibiotic resistance in the community, such as *C. difficile*. In Connecticut, for example, 30 percent of new *C. difficile* infections occur in the community, but community risk factors are not understood, nor are the reservoirs of transmission. It is critically important to understand the risk factors and how antimicrobial-resistant bacteria are transmitted. Traditional epidemiologic trials are needed to better understand the problem and where the reservoirs lie.

A. J. Tarpoff, an extension veterinarian at Kansas State University, asked for support of further research in livestock on antibiotic resistance as well as support for surveillance and outreach. Stewardship begins with education—particularly on the producer side and among practicing veterinarians. Mr. Tarpoff called for attention on how to improve education and protect the usefulness of available products for the future. He said cooperative extension services, based in land-grant institutions, can play a significant role. The main goal of extension service providers is to turn usable information that comes from research sponsored by federal and state governments into practical strategies for the farm.

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 observed that control of AMR is a model for other contagious diseases. Clearly, he said, investments in the public health infrastructure for controlling AMR will be helpful for controlling COVID-19 and other infectious diseases. Dr. Blaser adjourned the meeting for the day at 4:20 p.m.

Day 2

Welcome

Jomana F. Musmar, M.S., Ph.D., Public Health Advisor, Office of Infectious Diseases and HIV/AIDS Policy, Office of the Assistant Secretary for Health, HHS

Dr. Musmar welcomed the participants and called the roll.

CDC Antibiotic Resistance Threat Report, 2019

Michael Craig, M.P.P., National Center for Emerging and Zoonotic Infectious Diseases, CDC

Mr. Craig said CDC's latest report determined that antibiotic resistance caused 2,600,000 illnesses and 44,000 deaths annually since 2013, higher than the conservative estimate in its 2013 report or 2 million illnesses and 23,000 deaths annually. On the positive side, overall deaths from antibiotic resistance are down 18 percent since 2013, and deaths in hospitals are down 28 percent. However, community-acquired drug-resistant infections are increasing, a number of which are urinary tract infections (UTIs), which disproportionately affect women. Such infections previously would have been treated with a prescription on an outpatient basis, but now require hospitalization.

CDC categorizes threats as urgent, serious, or concerning. Among the notable updates to the list is the inclusion of *Candida auris*, highlighting how rapidly threats can emerge. CDC determined that carbapenem-resistant *Acinetobacter* raised as many alarms as CRE, so it was added to the urgent threat category. The new report has a watch list of pathogens that are either poorly understood or not yet seen in the United States. It includes azole-resistant *Aspergillus fumigatus*, which is seen in humans in Europe in relation to the use of azoles in crop management. Also on the watch list are *Mycoplasma genitalium*, a sexually transmitted infection, and *Bordetella pertussis*, which can be prevented by vaccination.

The new report emphasizes a One Health message, more so than previous CDC work, and reflects a collective call to action. The infographics in particular illustrate the interconnectedness of the antibiotic resistance threat. Mr. Craig said the report is a starting point for discussion of what else needs to be done. Improvements have been made in the United States in infrastructure, programs, and policy, and there is a good understanding of the issues in this country and Europe. However, understanding the global picture requires better data and more recognition of the interconnectedness of the problem. Much more can be done to improve prevention and treatment, Mr. Craig concluded.

Discussion

Mr. Craig observed that the burden of UTIs in the United States and around the globe has not been studied in depth, but it should be, and CDC would like to better understand it. The agency is also interested in how to measure disruption of the microbiome, which could potentially lead to identification of endpoints that might be helpful for the development of a drug, therapeutic, or decolonizing agent as an alternative to antibiotic treatment. Helen W. Boucher, M.D., FIDSA, FACP, added that CARB-X has some nondrug alternatives in its portfolio. She added that infection prevention measures have decreased unnecessary treatment of asymptomatic bacteria, which contributed to the decrease in HAIs.

Panel 4: New Insights on the Changing AMR Landscape

The Collective Antibiotic Resistance Landscape through a One Health Lens

Paula J. Fedorka Cray, Ph.D., North Carolina State University

Dr. Cray reiterated the interconnectedness of systems that the One Health approach embodies. She and her colleagues have developed a customized search engine, AMR Genie, that draws from animal health AMR online data sources, publications, and news from around the world. It is hoped that AMR Genie will allow users to find useful information and education that they can tailor to their needs.

In addition, Dr. Cray and colleagues are applying the same artificial intelligence concepts to create a large database that incorporates national online AMR databases, such as the National Antimicrobial Resistance Monitoring System (NARMS) and its international counterparts, as well as other national and global data sets about weather, infectious disease, genetic sequencing, and animal migration, among others. Users will be able to evaluate and compare data across any of the parameters captured by the database. For example, Dr. Cray said, one could evaluate migratory bird patterns along with bacterial disease patterns. She anticipated that the database would bring together complementary and supportive data, facilitating rapid diagnostic development and generating new knowledge.

Finally, Dr. Cray explained that natural disasters offer unique opportunities to study AMR and the environment, because they cause the environment affected to reset the microbiota of the soil or water or both. Following Hurricane Florence, investigators sampled sites along a 30-mile stretch of the Neuse River in North Carolina. They expected to find AMR salmonella but instead found many more isolates of ESBL *E. coli* that demonstrated AMR. The findings are still being analyzed.

Microbiome Research in the Pre-Antibiotic Age

Anna Dhody, Mütter Research Institute

The Mütter Museum houses thousands of historical medical specimens. In 2007, it established the Ancient DNA Center with McMaster University, which resulted in the extraction of ancient pathogen DNA from the preserved specimen of an individual who died of cholera in Philadelphia. The DNA was used to reconstruct the entire genome of a pandemic cholera strain. Subsequently, the Mütter Research Institute was created to collaborate with scientists and institutions on health research within a cultural and historical context.

In 2017, a construction site in Philadelphia, located where an 18th century cemetery had been, found that the remains of people buried there had not been relocated, as previously thought. Ms. Dhody and colleagues helped remove and identify 491 sets of human remains, gathering permission to study, sample, and analyze the remains before they are reburied in 2023. The Mütter laboratory collected dental calculus from the remains, and McMaster University analyzed the DNA from the samples. The analysis confirmed that the sampling procedure can recover the oral microbiomes from the samples and identify genomic profiles that are distinct from other soft tissue and free from external contamination.

Ms. Dhody said that as the research continues, the findings will provide knowledge about circulating pathogens among people who lived from 1707 to 1850, long before antibiotics came into widespread use. Philadelphia experienced an epidemic of cholera and yellow fever in 1700; some of the people represented in the samples would likely have survived that epidemic, and their DNA may offer important insights. Ms. Dhody said there is significant potential for analysis of the sample population.

Delabeling Penicillin Allergy: An Integral part of Antimicrobial Stewardship

David Khan, M.D., FAAAAI, American Academy of Allergy, Asthma and Immunology (AAAAI)

Penicillin allergy is reported by as many as 25 percent of patients in some populations, but only about 2–5 percent of patients have a true penicillin allergy, as determined by skin testing. Many people who are labeled as allergic to penicillin were designated as such during childhood. These people go on to receive other antibiotics, often broad-spectrum antibiotics, and drugs that may be more toxic or less effective than penicillin for their condition. The use of alternatives to penicillin contributes to antibiotic resistance, which in turn increases rates of hospitalization and *C. difficile* infection, among other conditions. Two large studies showed that patients labeled with penicillin allergy are at higher risk for MRSA, *C. difficile*, and CRE and that they have higher mortality rates than those not labeled as allergic to penicillin.

Evaluating patients for penicillin allergy to identify those who are not allergic—known as de-labeling—reduces health care utilization by these patients, translating to a cost savings of about $1,800 per patient according to one study. Dr. Khan's hospital developed a system to train pharmacists in penicillin allergy testing in the hospital, which has been shown to decrease the use of broad-spectrum antibiotics and increase use of penicillin. CDC and AAAAI have advocated for evaluating patients with self-reported penicillin allergy, which lays the foundation for allergy clinicians to test for penicillin allergy as part of routine care, rather than waiting until a need for

penicillin arises. Proactive testing will de-label patients who are not, in fact, allergic and can therefore avoid delays in appropriate therapy, especially for hospitalized patients.

Dr. Khan called for raising awareness among public health professionals and the general public about de-labeling. In particular, people with cancer or diabetes, those who have undergone transplants, and pregnant women would benefit from de-labeling. A commercial test is available but does not have all the reagents needed to confirm the absence of penicillin allergy. Dr. Khan asked the FDA to support products that include the complete penicillin skin test reagent. Increased reimbursement would also encourage providers to test and de-label as appropriate. Dr. Khan recommended that ASPs incorporate penicillin allergy testing.

Antimicrobial Resistance and Environmental Hotspots

Randy Singer, D.V.M., M.P.V.M., Ph.D., University of Minnesota

Dr. Singer illustrated how antibiotic use in humans, animals, and crops affects the environment, noting that other sources, such as pharmaceutical manufacturing, may also release antibiotics into the environment and contribute to AMR. Applying the principles of landscape ecology to AMR illuminates the correlations between various factors. For example, livestock are given antibiotics, which they excrete into the soil, where a copper deposit may assist in selecting for AMR. Geospatial analysis could account for other distribution by pinpointing, for example, hospitals or wastewater treatment plants that disseminate antimicrobials into the soil and water.

Other studies have refined this method, taking a stepwise approach and using geospatial tools:

1. Release assessment, e.g., how much product is released from treated animals
2. Exposure assessment, e.g., how much of the released product will get into the soil and how long it will persist, based on chemical properties
3. Consequence assessment, e.g., how the affected soil will be used
4. Risk assessment, e.g., how vulnerable the soil is

The Minnesota One Health Antimicrobial Stewardship Collaborative is supporting the Antibiotic Footprint Group, which seeks to build a geospatial model for the state to predict where AMR might arise in the natural environment as a tool to guide intervention. The model uses estimates of antimicrobial use in humans and animals; incorporates hospitals, wastewater treatment plants, and agricultural facilities; and layers on geospatial attributes such as land cover and surface water. The results of the analysis are combined with findings from environmental sampling to validate and update the model.

Dr. Singer said that ultimately, the Antibiotic Footprint Group hopes to communicate that AMR is the result not just of consumption but of metabolism, excretion, and environmental persistence. Importantly, one model cannot account for all the tremendous variation in drugs, genes, and how they interact with the environment. The most difficult barrier is the lack of understanding about how to predict the health impacts of environmental AMR.

Discussion

Dr. Kahn confirmed that health care providers could ask some simple screening questions that would result in de-labeling some patients who report a penicillin allergy. However, even after allergy testing, some continue to be mislabeled, possibly because they continue to report an allergy or because medical records are inconsistent. Dr. Kahn said there are not enough board-certified allergists to test all those who report penicillin allergy, so screening would be a good first step.

Dr. Boucher advocated for providing incentives to health care providers to test for penicillin allergy, because de-labeling might benefit people at high risk for drug-resistant infection. Stephanie Black, M.D., M.Sc., recommended developing a registry to ensure that people who are de-labeled are not then re-labeled in records as allergic. Dr. Khan offered a low-tech solution of a laminated card that patients could carry that identifies their drug allergies and clearly confirms the absence of penicillin allergy.

Dr. Khan acknowledged that penicillin is among those drugs associated with a high rate of fatal anaphylaxis, but the frequency is very low (e.g., about one in 100 million doses of oral amoxicillin). Some data suggest that the rates are higher with parenteral and oral administration. Dr. Khan agreed that some providers may avoid penicillin because of fears of a lawsuit, but the literature on such suits is thin, and many related cases are settled out of court. There is a constant need to find a balance between patient risks and benefits. While skin testing for allergies is effective, the needed reagents are not commercially available, so some advocate for direct challenge, which has proven safe with careful selection of those at low risk.

Since 2014, Dr. Khan's hospital has de-labeled about 900 patients. It has been difficult to show the cost savings, but other institutions have identified some savings.

Dr. Singer noted that most efforts to assess interventions around environmental AMR have focused on wastewater treatment. Some such interventions have proven successful in decreasing the concentration of genes in the effluent that might enter the waterways, but none seem to address how to reduce the amount of antimicrobial metabolites. Dr. Singer pointed out that there are huge data gaps in interventions for environmental AMR that does not involve wastewater, but on the other hand, wastewater is among the most significant sources of import into the natural environment. He emphasized that geospatial modeling can be applied even in LMICs, but sampling to validate the model is key.

Panel 5: The Gut Microbiome and Antimicrobial Resistance

Microbiome and Health

Martin J. Blaser, M.D., Rutgers University

Dr. Blaser highlighted the large amount of antibiotics used domestically and globally, which alter the microbiome, with developmental, metabolic, and neoplastic consequences. As they are expelled from the womb, neonates are exposed to maternal microbes, which contribute to the neonate's microbiome. The use of antibiotics, antiseptic practices, cesarean delivery, and bottle-feeding are just a few examples of how human practices have altered the microbiome, resulting

in a loss of microbial diversity. As these practices have become more common, diseases such as juvenile diabetes and obesity are increasing.

Farmers have long known that antibiotics promote growth, and studies show they lead to increased body fat in animals. Dr. Blaser conducted fecal transplants in mice, determining that the fat-promoting effects of antibiotics on the microbiome transferred to the transplant recipients who had never been directly exposed to antibiotics, confirming that the microbiome carries a metabolic signal for obesity. Other studies revealed the link between antibiotic use and cancer risk, type II diabetes, and kidney stone disease. Dr. Blaser summarized that antibiotics have long-term effects on metabolism and immunity that result from perturbing the microbiome. Other factors of modern life also contribute. The effects may be transmitted to the next generation.

In the face of declining diversity of the microbiome, Dr. Blaser said, restorative steps will be needed. He predicted that in the future, pediatricians will examine the content of babies' diapers to assess whether they have all the microbes they should and, if not, administer specific probiotics to try to optimize babies' health. He noted that a group of scientists established a microbiome vault to serve as a repository to save disappearing microbes for future generations.

Novel Small Molecule Antibiotic Targeting *C. difficile*

Urs Ochsner, Ph.D., Crestone, Inc.

Antibiotic overuse is leading to resistance and collateral damage in the form of *C. difficile*. Even new antibiotics are facing emerging resistance within a few years of launch. Dr. Ochsner outlined the projected public health and financial consequences of antibiotic resistance. Addressing AMR will require preserving utility of existing drugs, reducing demand, increasing supply, and ensuring accountability. New approaches to combating AMR include developing new antibiotics with novel mechanisms of action, among others.

C. difficile infection often follows treatment with a broad-spectrum antibiotic that disrupts the healthy gut microbiota. Metronidazole is no longer recommended for *C. difficile*. Some new agents—all broad spectrum—have failed. Among new narrow-spectrum agents, one has been approved by FDA, one is in Phase III trials, and Crestone's candidate, CRS3123, is in Phase II studies. CRS3123 inhibits protein synthesis, blocks toxin production, and inhibits spore formation. Because the drug targets a narrow spectrum, it was expected that gut microbiota would recover sooner than with other drugs, and animal trials confirmed this hypothesis. Early clinical trials showed a dose-dependent alteration of the gut microbiota in humans, with restoration to baseline after treatment.

Dr. Ochsner concluded that narrow-spectrum agents improve patient outcomes because they provide faster relief of symptoms and reduce the recurrence rate. These agents decrease economic burden through shorter hospital stays, fewer follow-up visits, and fewer health care costs. Overall, narrow-spectrum agents for *C. difficile* hold great promise for public health.

Nonantibiotic Strategies to Modify the Microbial Population of Dairy Cattle: Impacts on Milk Production, Animal Health, and Food Safety

Todd Callaway, Ph.D., University of Georgia

The food animal industry has sought to develop alternatives to antibiotics, implementing a lot of products that enhance production, but the mechanisms are not fully understood. Bacteriophages, for example, target specific microbes, but overdoses can backfire. One antibiotic alternative, an additive, sodium chloride, is particularly effective in reducing *E. coli* and salmonella in animals. Another antibiotic alternative, ionophores improve energy efficiency by inhibiting methane production in cattle, resulting in increased weight gain and milk production. Ionophores have been used for years in the cattle industry with little increase in resistance and no cross-resistance. A new product in development in Europe, 3-nitroxypropanol, further prevents methane production, which results in better weight gain and milk production in cattle.

Direct-feed microbials include probiotics, a category that encompasses traditional formulas, or eubiotics, as well as nutraceuticals and postbiotics. Some affect gene expression, decreasing inflammatory response or signaling growth hormones, for example. The use of probiotics is very promising, said Dr. Callaway. A lot of feed contains phytochemicals, such as essential oils and different organic acids that can alter the microbial population. Stress also affects the microbiome, and animals experience a lot of stress when transported or mixing with other herds.

Dr. Callaway said it is not known what constitutes a "good" or "bad" microbiome. Understanding the impact may require an individualized approach. Dr. Callaway noted that a multipronged approach is needed to address AMR in animals.

Microbiome Live Biotherapeutics as a Novel Approach to Treat Infectious and Inflammatory Diseases

Matthew Henn, Ph.D., Seres Therapeutics

Thanks to funding from CARB-X and other sources, Seres has combined commensal bacteria with specific pharmacologic properties into live microbiome biotherapeutics. They capture the breadth of phylogenetic and functional diversity in the gut, are designed to target multiple inflammatory and immunological disease pathways simultaneously, engraft in the human gut (which then also leads to restructuring the microbiome more broadly), and are formulated for oral delivery. The products seek to inhibit the growth of specific pathogens, such as *C. difficile*, vancomycin-resistant *Enterococcus*, and CRE.

Dr. Henn described clinical studies that support the potential of Seres' live microbiome biotherapeutics to modulate host inflammation and immunity and to target infection. For example, a product for *C. difficile* was shown to engraft in the gut and promote development of secondary bile acids, which prevented the growth and recurrence of *C. difficile*. Similarly, a product for ulcerative colitis increased rates of remission by changing the profile of important microbial mediated metabolites in the gastrointestinal tract.

Antibiotic-resistant infections can derive from reservoirs of antibiotic-resistant organisms living in the gastrointestinal tract. Inflammation and compromised integrity of the gastrointestinal tract

facilitate this dynamic, which can then lead to translocation of multidrug resistant bacteria into the bloodstream with specific clinical consequences. Seres' studies suggest that microbiome-based therapeutics can restructure the microbiome and have a meaningful impact on metabolic pathways that have disease relevance.

Discussion

Dr. Blaser noted that there is increasing evidence that the gut microbiome signals the brain via neurotransmitters produced by the microbiota and also by enteric hormonal cells. The relationship of the microbiome to brain development is a very active area of research. Dr. Callaway said there are efforts underway to study how the microbiome affects behavior in cattle, but there is little funding to support such work.

Dr. Blaser said that the vast majority of microbiota in the human intestine are anaerobic. Organisms such as Enterobacteriaceae make up a very small proportion of the microbiome. Research seeks to reveal which microbiota are important, which are protective, and which are pathogenic.

Armando Nahum suggested increasing education about the negative effects of antibiotics. Dr. Blaser said there is enormous variation in antibiotic use, reflecting regional differences in culture and practice. He said a first step would be to reduce variation in a way that leads to less antibiotic use. CDC conservatively estimates that one third of all antibiotic use is unnecessary, and Dr. Blaser believes the actual figure is higher. Practitioners are prescribing antibiotics with the philosophy that they may not help but they will not hurt. Mounting evidence demonstrates that antibiotics can harm patients, and health care providers must reevaluate the costs, risks, and benefits of using antibiotics, particularly for infections that are not serious, said Dr. Blaser.

Dr. Blaser pointed out that the duration of disruption to the microbiome following antibiotic use in children varies depending on the antibiotic. Dr. Henn added that the extent of the insult to the microbiome and the frequency of insults also have an impact. Some patients with *C. difficile* experience multiple recurrences, and their microbiome never fully recovers. Dr. Callaway pointed to some studies suggesting that the microbiome might be restored to baseline in cattle within 19 days, and a study of young adults is underway that addresses the issue.

Dr. Blaser observed that the recommendations for the duration of antibiotic therapy were developed when antibiotics were thought to be harmless. Further assessment of the optimal duration of therapy, given the potential for collateral damage to the microbiome, would likely result in much shorter antibiotic regimens.

Participants expressed interest in the mechanisms of action of the various products in development as well as the findings from early studies.

Panel 6: Future Demands on Food Production

Population Growth and Demands on Food

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

The demand for animal protein around the world has been rising steadily since the 1960s. With the global population expected to reach 10 billion by the end of this century, the demand for meat—and the corresponding use of antibiotics in food production—will grow. Humans and the food they consume constitute the bulk of the mammal biomass on the planet.

The current protein demand for Earth's 7.3 billion inhabitants is about 202 million tons globally. Since 2000, meat production has plateaued in high-income countries, but it has been growing in the rest of the world. Demand for poultry in India and China is set to increase between two-fold and seven-fold from 2000 to 2030. Per capita consumption in China is already high and is likely to double before 2030. India started with a much lower baseline, primarily because many people there have not been able to afford meat, but demand is rising substantially.

Per capita pork consumption has risen dramatically in China since the 1970s, and China dominates the pork industry. China also consumes half of the world's antibiotics. Among all mammals in the world, Chinese pigs consume the most antibiotics. In contrast, aquaculture accounts for a small proportion of antibiotic use. Dr. Laxminarayan pointed out that regardless of where antibiotics are used, their residue shows up everywhere. In 2013, the global consumption of all antimicrobials in food animals was estimated at 131,109 tons, and it is projected to reach 200,235 tons by 2030.

Antibiotic Consumption in Animals: A Reporter's Perspective

Jason Gale, Bloomberg News

Bloomberg News sought to evaluate claims by two of India's largest poultry producers that no antibiotics were used in production. Farm visits revealed clear evidence of routine antibiotic use in poultry from birth and continuing until a few days before slaughter, including gentamicin, three fluoroquinolones, colistin, neomycin, doxycycline, and tylosin. Mr. Gale and colleagues then turned their attention to China, where they were particularly interested in the circulation of biologically active antibiotic residues from humans and animals in the environment and food systems along with the associated antibiotic resistance genes. It was estimated that Chinese pigs excrete about 2,460 tons of antibiotics each year into the environment, including the waterways. Traces of antibiotics have been found in the public water supplies of major Chinese cities and in the urine of 80 percent of children who live in those cities.

For thousands of years, Asian farmers have recycled animal and sometimes human waste through fish ponds, which has been a very successful and sustainable use of nutrients with negative infectious consequences. One farm might raise ducks, pigs, and tilapia, all exchanging pathogens and paving the way for emerging zoonotic infections. Mr. Gale found that pig farmers use a wide range of antibiotics, switching every month because of resistance. The antibiotics end up in a pond used to raise fish for local and export markets, and that pond drains into the river that runs through some of China's largest cities.

China accounts for about 60 percent of aquaculture in the world, the fastest growing segment of the global food economy. Shrimp are a lucrative part of that market, and they are harvested from rivers that receive the farm runoff. When the FDA intensified monitoring of imported Chinese farm-raised seafood in 2006, it found a quarter of samples tested contained unapproved drug residues and unsafe food additives, some of them cancer-causing. Although authorities detained shipments for scrutiny, Chinese exporters found a way around the regulations by fraudulently identifying their shrimp as being raised in Malaysia. FDA now scrutinizes Malaysian aquaculture products as well. Mr. Gale concluded that the media can be a useful ally in exploring AMR threats by identifying gaps and weaknesses.

Sustainability of Seafood Systems

Michael Tlusty, Ph.D., University of Massachusetts, Boston

Dr. Tlusty pointed out that 20 percent of the world's population depends on aquatic proteins as their main protein source. The United States does not consume or produce a lot of seafood compared with other countries. Over 2,500 species are consumed as seafood, and the aquaculture approach varies by species. Most of the production involves harvesting wild animals in oceans and fresh water. In some settings, the animals are not fed but rather live off the phytoplankton in the water, filtering out some of the nitrogen that is dumped into waterways. In other cases, animals are bred in a hatchery and fed.

The United States has the largest economic exclusion zone of any country in the world—it extends to 200 miles from the coast. Dr. Tlusty predicted that offshore aquaculture will play an important role in future food production. Technology used by offshore aquaculture is highly automated. Some aquaculture is housed in facilities built on land, but that involves high greenhouse gas emissions and constant pumping of water.

In the United States, large-scale aquaculture came into practice in the 1980s, and the industry is still learning about the challenges and how to address them. The U.S. population eats a lot of shrimp and salmon, while the rest of the world consumes mostly carp and oysters. Different species face different disease threats, and some seafood species are invertebrates whose immune systems not well understood. Any antibiotics used in production are immediately disseminated into the environment. Contaminants can come in from external sources. One animal can produce millions of eggs, which is good for breeding, but the eggs are tiny and highly susceptible to bacteria. Sanitation in hatcheries likely involves a lot of antibiotics, which is rarely discussed. Small farms in developing countries may be using antibiotics as growth promoters, with no attention to issues of resistance.

Dr. Tlusty said that, ideally, sustainability is achieved by balancing environmental integrity with socioeconomic benefits and farming animals in a way that does not pose health challenges. In reality, health challenges are a given in animal production, so efforts must focus on managing for sustainability. The goals of stewardship can be compromised by the need to make a profit. However, Dr. Tlusty concluded, there is a concerted effort in the United States around sustainable seafood.

Discussion

Dr. Blaser observed that China uses 162,000 tons of antibiotics but exports another 80,000 tons. India's estimates of its antibiotic production undercount the amount. Dr. Laxminarayan agreed that it is difficult to get accurate estimates, and the world probably uses as much as 300,000 tons per year.

Asked about infection prevention in aquaculture, Dr. Tlusty said salmon production is highly consolidated among a small number of companies, which use vaccines to prevent disease. Norway has decreased antibiotic use in salmon to nearly zero. In Chile, however, antibiotic use in salmon is increasing—even though many of the plants are owned by Norwegian companies. A lot of seafood certification programs are working toward zone or area management, which takes into account the total impact of antibiotic use among all farms within a specific area. In such cases, coordinated disease treatment is key.

Dr. Tlusty noted that in some cases, distrust of imported seafood led to certification requirements, but the Aquaculture Stewardship Council, for example, has no policies on antibiotics. Because there is no central monitoring system, there is little awareness of the spread of pathogens such as *Vibrio parahaemolyticus*, which dramatically affected the Thai shrimp industry in 2013. In addition, said Dr. Tlusty, aquaculture farmers often do not see their animals until they harvest them, so disease can go unrecognized.

Dr. Tlusty said a lot is known about currents and particle flow among cages, and much of that knowledge comes through modeling. The models could be applied to understand how antibiotics flow through cages in aquaculture settings.

Panel 7: The Increased Demand for Aquaculture Protein

Aquaculture Overview

David White, M.S., Ph.D., University of Tennessee

Dr. White underscored the growing role of aquaculture in food production globally and domestically with more details on rates of consumption and the economic impact of the industry. He described production methods, noting that an integrated system in which several species sustain each other is the ideal. As in land farming, disease and health management pose challenges. About 40 percent of losses in aquaculture stem from disease.

Numerous bacterial pathogens affect aquatic production, and most of them are not well understood. The World Organisation for Animal Health has international principles for use of antimicrobials in aquaculture as well as a list of infectious diseases in seafood that must be reported. In the United States, four aquaculture antimicrobials are approved (in the form of medicated feed), of which only three are on the market. Dr. White noted that few scientists around the world are investigating aquaculture pathogens, and research questions are complicated by the effects of different water temperatures, which influence pathogen growth and AMR mechanisms.

A lot of seafood consumed in this country is imported or exported to other countries for processing and then returned. Some importing countries, such as Chile, do not have regulatory standards as rigorous as those of the United States, and it is not known what antimicrobials they are using. As aquaculture expands, so does the risk of significant disease outbreaks.

Dr. White said there is a pressing need for investment in aquatic health and greater access to disease management tools, including more data on pathogens and host species data and more surveillance data. More vaccines will help prevent the use of antimicrobials, but they are challenging to develop, as shrimp, for example, do not have an innate immune system. Aquaculture ASPs exist, but compliance and enforcement vary by country. Rapid diagnostics are needed to quickly detect pathogens and dictate response. Dr. White also pointed to the need for biosecurity measures and guidelines on sustainable development.

Certification Standards for Antibiotic-Free Seafood

Sebastian Belle, Maine Aquaculture Association

Reiterating that aquaculture is a young industry in the United States, Mr. Belle said producers are learning as they go how to apply new methods in new places. Mr. Belle pointed out that antibiotics are not effective growth promoters for aquatic animals, and prophylactic antibiotic use generally does not occur in this country, although it does occur in other countries with less infrastructure for diagnosing and managing pathogens. In the United States, antimicrobial treatment options are limited, and application even when warranted is complicated by the nature of the aquatic environment. There are few health professionals in the field of aquaculture.

Considering all the barriers to chemical management in aquaculture, producers in Maine shifted to a nonchemical approach, going back to the early 1990s, when the industry lobbied for strict comprehensive health surveillance regulations in the world. Over time, Maine fish farmers have collectively implemented increasingly stringent biosecurity, such as third-party biosecurity audits. Area management programs included site rotation and fallowing, which resulted in a dramatic decrease in aquaculture antibiotic use in Maine. Expanded surveillance and cooperative communication plans among farms spurred group action in response to suspected diseases or pathogen, even if not confirmed.

In 2016, more Maine fish farmers began taking part in large international certification programs. Many of these programs are driven by large buyers seeking assurance of minimal or no antibiotic use. However, the certifications programs cover less than 3 percent of the world production. About 52 percent of the world seafood supply is certified under programs that include antibiotic use and stewardship criteria that does not prohibit use of antibiotics. Mr. Belle stressed that balancing animal health and welfare with human health and welfare is not always easy.

NARMS Seafood Pilot Program

Patrick McDermott, M.S., Ph.D., D(AAM), Center for Veterinary Medicine, FDA

A collaboration of FDA, CDC, and USDA, the National Antimicrobial Resistance Monitoring System (NARMS) is transforming into a One Health model of surveillance by incorporating an expanded range of data, for example, environmental water test findings from the U.S.

Environmental Protection Agency, among other data. The expansion of NARMS offers an opportunity to evaluate antibiotic use in seafood production and aquaculture and its effect on resistance. A study was designed to assess resistance in salmon, shrimp, and tilapia, which, other than canned tuna, are the most consumed seafood in the United States and which are all raised in aquaculture systems. Traditional culturing methods are complicated in part by the fact that the fact that the animals live in cold water. After 24 hours in laboratory incubation, the phylogenetic profile of the samples changes substantially. Therefore, investigators decided to combine the traditional methods with meta-genomic assessment to better understand the microbial status during their surveys.

The study targets specific organisms and, starting in 2019, began gathering samples from eight states. Preliminary analysis of findings revealed resistance profiles that Dr. McDermott characterized as "fairly tame," possibly reflecting the relatively small amount of antibiotics going into aquaculture under current practices. The goal of the project is to see what genes are underlying resistance through meta-genomic sequencing, and the findings so far show it is possible to track resistance genes from the meta-genome that correspond to the phenotypes seen, but with the added advantage that the approach does not have the limitations of culture. Investigators hope to capture a comprehensive resistome, which can then be further categorized according to specific allele type and resistance by source.

Dr. McDermott emphasized the need to envision the study as a resistome monitoring project that looks at the resistance gene itself as the point of focus, rather than a number of sentinel organisms that have different capacities to carry resistance. The study will continue using the two-pronged approach to identify the meta-genomics of resistance.

Discussion

Mr. Belle noted that nearly every aquaculture farm complies with the criteria of several different international certification programs to meet the requirements of its various customers, and from that perspective, a single federal standard would simplify matters for the farmer. However, the U.S. regulations around antibiotic use are already quite strict, he said, yet farmers do whatever it takes to meet the demands of individual buyers. Antibiotic use must comply with regulations under the Clean Water Act, and data indicate that Maine has succeeded in minimizing environmental antibiotic spread. The challenge of embedding good stewardship practices into law is that the technology for surveillance and administration are evolving rapidly, and codification could inhibit innovation.

Mr. Belle said aquaculture diagnostic tools are evaluated by USDA's national laboratory. Depending on the pathogen, the sensitivity of the tools range from sophisticated to primitive. The United States is challenged by the lack of a national plan for aquatic animal health, so some standards are set at the state level. A national plan would lead to standardized diagnostic methods across state lines and among species, which would be very helpful, Mr. Belle stated, particularly for interstate commerce. He noted that current diagnostic tests yield a lot of false-positive results, so farmers use multiple methods to confirm the presence of pathogens.

Public Comment

Kevin Kavanagh of Health Watch said the government of China has received worldwide criticism over its almost 1-month delay in notifying the public about the coronavirus. He asked whether the United States is any better at notifying the public regarding dangerous outbreaks of resistant bacteria in health care facilities. He cited examples of MRSA and CRE outbreaks in U.S. hospitals that were underreported or for which reports were long delayed. In comparison, the CDC rapidly and urgently reported publicly about a resistant *Pseudomonas* outbreak in a Mexican hospital, which suggests politics and not science is shaping infectious disease policy.

Of the four urgent threats identified by CDC for 2019 that are emerging HAIs, only one, *C. difficile*, is publicly reported on a national basis. Those reports are delayed more than 9 months, which limits their public usefulness, said Mr. Kavanagh. All too often, the excuse is given that transparency will cause the public to panic or that these organisms only affect the frail and the elderly and thus should not be cause for heightened concern. There is little evidence of the formal notification of pathogen outbreaks in the food sector. Before criticizing other countries, the United States should get its own house in order, said Mr. Kavanagh. He called for more comprehensive data for action, complete public transparency, and citizen notification of dangerous outbreaks.

Tamara Johnson of Magnolia Medical Technologies said the current benchmark for contaminated blood cultures is 3 percent. While this sounds like a low number, it allows for an almost 50-percent positive blood culture error rate, which impacts over 1.2 million patients every year in the United States. As a nurse-leader deeply concerned about the number of patient deaths each year from multidrug-resistant organisms, Ms. Johnson asked that a new blood culture contamination threshold be set at less than or equal to 1 percent, a level that has proven to be sustainable in many hospitals, according to the results of multiple controlled clinical studies published in renowned, peer-reviewed medical journals. Sustaining contamination rates as low as zero over 11,200 cultures and 0.2 percent over 1,800 cultures is achieved using evidence-based practices and an evidence-based, disruptive technology known as an initial specimen diversion device. It is proven to reduce days of therapy in which vancomycin is used hospital-wide by 36 percent. The new benchmark proposed is in line with the recently published Clinical Microbiology Reviews consensus article by thought leaders in this field. With the initial specimen diversion device, it is now known that zero and near-zero are possible and sustainable. The health of patients and the viability of antibiotic therapy depends on delivering quality health care with diagnostic stewardship that first prevents harm, Ms. Johnson concluded.

Hua Wang, Ph.D., of The Ohio State University said that it is essential to spell out the direct cause of antibiotic resistance, which is the mainstream oral antibiotic administration in human medicine and food animal production. The problems started in industrialized countries in the 1960s that switched from injection to oral derivatives. Dr. Wang published the original study on the impact of oral versus injected ampicillin and tetracycline, which appeared in a news release by the American Society for Microbiology in 2013 and was later supported by further studies on vancomycin by other teams in the United States. It is important to recognize that antibiotic applications and medical procedures are essential and inevitable. While microbiota

transplantation may help recover some losses by antibiotic treatment, it has never been able to recover all, and the practice further introduces risk to the host, such as the death reported by FDA last year due to the patient acquiring ESBL *E. coli* from the donor.

Dr. Wang appreciated that the topic of penicillin allergy testing was on the agenda, but penicillin still can cause severe allergic reactions, including death. Furthermore, the prevalence of ESBL bacteria potentially negates the function of penicillin, so penicillin is no longer the same magic bullet it had been. But there are many antibiotics that have been used in hospitals via injection worldwide, many with very mild or no obvious allergic reactions.

Despite the fact that some antibiotics are partially excreted through the liver, research data have demonstrated that injections reduce the disruption of healthy gut microbiota caused by oral drugs. Understanding the problems caused by oral administration is important for new antibiotics being developed and introduced to minimize resistance problems similar to those of oral penicillin derivatives. Dr. Wang said it is necessary to reintroduce muscle injection as an option for as many antibiotics as possible and to assess the impact of each drug on gut microbiota, providing doctors with solid evidence for therapeutic decision making. Current dosages used for medical injection are quite high, because the goal is to treat severe infections. For prophylactic purposes and to treat mild infections, the dosage by injection can be reduced to minimize side effects. Up to 350 million antibiotic prescriptions are given annually in the United States, most for oral drugs. The U.S. population was only 330 million in 2018. Dr. Wang asked for recognition of the need to mitigate the direct, unnecessary selective and disruptive pressure caused by using oral antibiotics as soon as possible.

Tanya Gottlieb of MeMed Dx suggested that instead of trying to detect the pathogen, practitioners weed out the individual's immune response to infection and, based on a computational algorithm, devise a score of the likelihood of bacterial versus viral infections as the diagnostic test result. Ms. Gottlieb aimed to highlight the potential of the host-based approach to complement direct pathogen tests and help reduce diagnostic uncertainty for clinicians. There has been a lot of discussion about ensuring the appropriate antibiotic use for bacterial infections when determining the bacterial strain and mapping susceptibility. Ms. Gottlieb reminded the gathering that in many instances diagnostic uncertainty leads to administration of antibiotics to patients with viral infections.

MeMed Dx completed an observational clinical study in Germany and Italy of children presenting to the emergency department with respiratory infections and fever without sores. It enrolled 628 children who were assigned a diagnosis by expert adjudication as having viral infection. Of these, 186 children— roughly 30 percent—were prescribed antibiotics. Similarly, another study suggests that antibiotics are prescribed to more than 30 percent of individuals presenting with antibiotic-inappropriate respiratory diagnoses in urgent care centers in the United States. Ms. Gottlieb hoped for consideration that the use of rapid and accurate host-based tests that differentiate between bacterial and viral infections has potential to reduce this unwarranted use of antibiotics driven by diagnostic uncertainty. This approach would also help avoid the unintentional harm caused by antibiotics and reduce AMR.

Lisa Weddig of the National Fisheries Institute appreciated the inclusion of aquaculture on the agenda. While not as large as other U.S. livestock industries, it is important to address antibiotic use in raising of fish, crustaceans, and other sea animals, especially since the demand for farm-raised seafood will continue to grow. Among the challenges that face the industry is the fact that the vast majority of farmed fish consumed in this country is raised in other countries. In addition, the United States is not the full market for the finished product. Many producers and processors overseas are challenged with understanding the regulations and varying lists of approved aquaculture drugs by the importing countries, which often differ from what is allowed in the growing countries. Therefore, Ms. Weddig said, minimizing the use of antibiotics and other drugs in aquaculture is an issue that must be addressed with a collaborative global effort.

Aquaculture species are diverse. Finfish, crustaceans, mollusks, frogs, and sea cucumbers are all farm-raised, but the only trait they share is being raised in water. Treatments and husbandry practices are not one-size-fits-all. In addition, the list of drugs approved for use for aquaculture in the United States is small, about 10, and only three of those are antibiotics. Not all of these drugs are approved for all species. FDA has only one drug approved for use in raising shrimp, which is the most commonly consumed seafood species in the United States. Almost 100 percent of farmed shrimp is not cultivated in the United States, so there is little incentive for drug companies to seek FDA approval for new drugs.

Many aquaculture industries are not vertically integrated. A single processor overseas might source products from hundreds or even thousands of ponds. So, capacity-building is needed to ensure that there is a basic understanding of the practices that promote healthy growth. The Seafood Hazard Analysis and Critical Control Point Alliance, a 25-year partnership of the USG, academia, and industry, is developing training materials to provide processors that farm fish with tools they need to link farm practice to robust controls.

Finally, contrary to popular belief, the U.S. seafood importing community does not actively seek out products that contain residues of unapproved drugs. Importers support any efforts to minimize the use of antibiotics in raising fish, such as through capacity-building efforts, third-party certifications, and industry verification of farm practices.

Shannon Ross, M.D., a pediatrician at the University of Alabama at Birmingham, said she runs the hospital's ASP. A 2019 analysis of hospital data confirms the concerns raised about community-acquired resistance, with rates up to 10 percent for community-acquired sexually transmitted infections. Pediatric providers avoid using some of the antibiotics available for adults (e.g., fluoroquinolones, tetracyclines) because of the potential toxicity. It takes longer for new antibiotics to be approved for use in children. Dr. Ross described a recent case involving a medically complex child with a multidrug-resistant UTI. With no available options for treatment, Dr. Ross opted to use one of the new combination antibiotics for which the only dosing information came from one small Phase I study. She had to explain to the child's mother that the regimen was the only option, even though she did not know the ideal dose or the potential toxicity. Dr. Ross urged all concerned to keep in mind the need for antibiotics in the pipeline to treat children. She noted that her hospital's robust ASP has reduced HAIs, but community-acquired multidrug-resistant infections are very real.

Laura Sage of Red Bird Acres Farm, located in Corvallis, OR, said her organization is a certified, animal-welfare-approved farm that raises pigs and poultry on pasture. It has worked diligently to develop humane animal handling techniques that greatly reduce the need to use antibiotics. The farm works closely with veterinarians to accomplish this goal, and it relies on the work being done by the Oregon State Veterinarian Diagnostic Laboratory and the cooperative extension agents in the region. The farm is directly affected by the USDA's veterinarian feed directive as well as the plan to move all over-the-counter antimicrobials to use under veterinary supervision only. Ms. Sage says her farm fully supports these moves, which will benefit both the health of the animals on the farm as well as the community that it provides healthy food for.

Final Comments and Adjournment

Martin J. Blaser, M.D., Rutgers University, and Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, The Ohio State University

In closing, Dr. King observed the interconnectedness of human, animal, and environmental health, noting that everyone is accountable and responsible. A holistic approach is needed to address AMR. He called for more outcomes research around products being used in food and companion animals. Dr. Blaser said the discussions exposed the global nature of AMR and the need to get the domestic house in order. He also took to heart the idiom of "first, do no harm," which should be applied to veterinary and human medicine. The meeting ended at 3:06 p.m.

Appendix: Listening Session Invited Participants, February 26–27, 2020

Neena Anandaraman, D.V.M., Agricultural Research Service, U.S. Department of Agriculture (USDA)

Michael D. Apley, D.V.M., Ph.D., DACVCP, Kansas State University

Marshall Bartlett, Home Place Pastures

Sebastian Belle, Maine Aquaculture Association

Stephanie Black, M.D., M.Sc., Chicago Department of Public Health

Martin J. Blaser, M.D., Rutgers University

Helen W. Boucher, M.D., FIDSA, FACP, Tufts Medical Center

Angela Caliendo, M.D., Ph.D., FIDSA, Brown University

Todd Callaway, Ph.D., University of Georgia

Denise Cardo, M.D., Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services (HHS)

Maria Clavijo, D.V.M., Ph.D., Iowa State University Veterinary Diagnostic Laboratory; Genus PIC

Alicia R. Cole, Patient Advocate

Scott Cooper, M.M.Sc., PA-C, Centers for Medicare & Medicaid Services, HHS

Sara E. Cosgrove, M.D., M.S., Johns Hopkins University

Michael Craig, M.P.P., National Center for Emerging and Zoonotic Infectious Diseases, CDC, HHS

Paula J. Fedorka Cray, Ph.D., North Carolina State University

Dennis M. Dixon, Ph.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health, HHS

Anna Dhody, Mütter Research Institute

Emilio Esteban, D.V.M., M.BA., M.P.V.M., Ph.D., Food Safety and Inspection Service, USDA

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

William Flynn, D.V.M., M.S., Center for Veterinary Medicine, Food and Drug Administration, HHS

Christina Fuhrman, Patient Advocate

Jason Gale, Bloomberg News

Christine Ginocchio, Ph.D., MT, bioMérieux; BioFire Diagnostics

Matthew Henn, Ph.D., Seres Therapeutics

Elizabeth Hermsen, Pharm.D., M.B.A., BCPS-AQ(ID), FIDP, Merck & Co., Inc.

Christopher Houchens, Ph.D., Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, HHS

Mark Kazmierczak, Ph.D., Gryphon Scientific

Locke Karriker, D.V.M., M.S., DACVPM, Iowa State University

Charles Keckler, J.D., M.A., Associate Deputy Secretary, HHS

Kent E. Kester, M.D., FACP, FIDSA, FASTMH, Sanofi Pasteur

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

David Khan, M.D., FAAAAI, American Academy of Allergy, Asthma and Immunology

Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, The Ohio State University

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

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

Tiffany Lee, D.V.M., Ph.D., M.S., North American Meat Institute

Leon Marchal, Ph.D., DuPont & Wageningen University

Aileen M. Marty, M.D., FACP, Florida International University

Patrick McDermott, M.S., Ph.D., D(AAM), Center for Veterinary Medicine, U.S. Food and Drug Administration, HHS

Mary Millard, Patient Advocate

Roxanne Motroni, D.V.M., Ph.D., Agricultural Research Service, USDA

Jomana F. Musmar, M.S., Ph.D., Office of Infectious Diseases and HIV/AIDS Policy, Office of the Assistant Secretary for Health, HHS

Armando Nahum, Safe Care Campaign

Urs Ochsner, Ph.D., Crestone, Inc.

Paul Plummer, D.V.M., Ph.D., DACVIM, DECSRHM, Iowa State University Research Park

Jan Poolman, Ph.D., Janssen, a Johnson & Johnson Company

Fatema Rafiqi, Ph.D., Access to Medicine Foundation

Chris Romm, Patient Advocate

Richard Rothman, M.D., Ph.D., Johns Hopkins University, School of Medicine

RADM Erica G. Schwartz, M.D., J.D., M.P.H., Deputy Surgeon General of the United States, HHS

Justin Sexten, Ph.D., Performance Livestock Analytics

Chelsey Shivley, D.V.M., Ph.D., DACAW, Animal and Plant Health Inspection Service, USDA

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

Randy Singer, D.V.M., M.P.V.M., Ph.D., University of Minnesota

Kwangmin Son, PhAST Corp.

Padmini Srikantiah, M.D., M.P.H., Bill & Melinda Gates Foundation

Kathryn L. Talkington, Pew Charitable Trusts

Michael Tlusty, Ph.D., University of Massachusetts, Boston

Denise M. Toney, Ph.D., Association for Public Health Laboratories

Michael Treitel, Centers for Medicare & Medicaid Services, HHS

Paige Waterman, M.D., FACP, FIDSA, Walter Reed Army Institute of Research, U.S. Department of Defense

Emily Wheeler, Antimicrobials Working Group

David White, M.S., Ph.D., University of Tennessee

Glossary of Abbreviations

AAAAI	American Academy of Allergy, Asthma and Immunology
AMR	antimicrobial resistance
ASP	antibiotic/antimicrobial stewardship program
BARDA	Biomedical Advanced Research and Development Authority
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CRE	carbapenem-resistant Enterobacteriaceae
DISARM	Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (Act)
ESBL	extended-spectrum beta lactamase
ESKAPEE	*Enterococcus, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas, Enterobacter,* and *E. coli*
ExPEC	extraintestinal pathogenic *Escherichia coli*
FDA	U.S. Food and Drug Administration
HAI	health-care-associated infection
HHS	U.S. Department of Health and Human Services
LMICs	low- and middle-income countries
MRSA	methicillin-resistant *Staphylococcus aureus*
NARMS	National Antimicrobial Resistance Monitoring System
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PCR	polymerase chain reaction
R&D	research and development
USDA	U.S. Department of Agriculture
USG	U.S. Government
UTI	urinary tract infection
WHO	World Health Organization