

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

**16th Public Virtual Meeting of the
Presidential Advisory Council on
Combating Antibiotic-Resistant Bacteria
June 29–30, 2021**

Table of Contents

Day 1	1
Welcome and Overview	1
Roll Call	1
Patient Story	1
Opening Remarks.....	1
Advancing Interprofessional Education (IPE) and Practice to Combat AMR: IPE Working Group (WG) Report and Recommendations.....	2
Discussion.....	3
Bridging the Gap: Improving Antimicrobial Access and Use Across One Health: Antibiotic Access and Use WG Report and Recommendations	4
Discussion.....	4
Antibacterial R&D: Past, Present, and Future	5
Discussion.....	6
Provocative Questions in AMR	7
Public Comments: Innovation Spotlight.....	8
Final Comments and Recess for the Day	9
Day 2.....	10
Welcome and Overview.....	10
Roll Call	10
Operationalizing One Health	10
Challenges in HICs and a Nordic Example	10
Discussion.....	10
One Health Trust Demographic One Health Surveillance Site	11
Discussion.....	12
Expanding Epidemic Intelligence in One Health.....	12
Discussion.....	13
The Tricycle Project: World Health Organization (WHO) Integrated Global Surveillance on Extended-Spectrum Beta-Lactamase-Producing <i>E. coli</i> Using One Health Approach.....	13
Discussion.....	13
The Federal One Health Response to COVID-19.....	14
The One Health Systems Mapping and Analysis Resource Toolkit (OH-SMART™)	14
Discussion.....	15

Introduction to Environmental Dimensions of AMR	15
Triazole Resistance in <i>Aspergillus fumigatus</i> : CDC Update	16
Discussion	16
Informing Policy and Practice for Combating AMR Through Surveillance of Water and Wastewater Environments	17
Discussion	18
The Collective Global Responsibility to Do No Harm: Ethics and Drug Resistance.....	18
Discussion	19
Dynamics of the Soil Resistome: Contribution of Horizontal Gene Transfer	19
Discussion	20
Public Comment.....	20
Final Comments and Adjournment	22
Appendix: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Members	23
PACCARB Voting Members Present.....	23
Organizational Liaisons Present	23
Regular Government Employees Present	24
Designated Federal Official	24
Advisory Council Staff	24
Glossary of Abbreviations	25

Meeting Proceedings

Day 1

Welcome and Overview

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

Drs. Blaser and King opened the meeting at 10 a.m. ET and welcomed the participants. Dr. Blaser gave an overview of the agenda for the day.

Roll Call

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

Dr. Musmar called the meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) to order. She described the Council's establishment and charter. Dr. Musmar summarized the rules governing the Council under the Federal Advisory Committee Act and conflict-of-interest guidelines. Ms. Simmons called the roll. (See the appendix for the list of participants.)

Patient Story

Jillian Thibault, Sepsis Alliance

Ms. Thibault was hospitalized and unable to present her story. Dr. Blaser presented Ms. Thibault's written comments, which explained that she had been a healthy individual all her life and a college athlete until August 2011, when she had her gall bladder removed. She developed gastroparesis three months after the surgery and eventually required a feeding tube to survive. In 2016, she was no longer able to tolerate tube feeding, so central lines, total parenteral nutrition, and sepsis took over her life. Total parenteral nutrition over the past five years has made it incredibly hard to avoid sepsis. Each time a central line is removed because of sepsis, that access site is no longer available. Ms. Thibault wrote that she is down to her last access site, at which point total parenteral nutrition will not be an option. Infectious organisms continue to develop resistance to antibiotics—including the antibiotics that Ms. Thibault relies on to save her life.

Dr. Blaser thanked Ms. Thibault for sharing her story, which demonstrates how antibiotic resistance is ruining lives.

Opening Remarks

Rachel L. Levine, M.D., Assistant Secretary for Health (ASH), HHS

Dr. Levine stated that COVID-19 is the biggest public health crisis the world has faced in more than 100 years. She offered sincere condolences to all those who suffered and lost loved ones, as well as gratitude and respect for the efforts of all the front-line and public health workers, including many who serve on this Council.

Dr. Levine said that under the current administration, there is light at the end of the tunnel, but COVID-19 has not yet been defeated, and the world cannot afford to be complacent. Safe and effective vaccines are key to overcoming the pandemic, especially in the face of the Delta variant. The situation offers an example of how antimicrobial resistance (AMR) develops; as the virus spreads around the world, mutations and variants can emerge that are potentially resistant to antimicrobial treatment with monoclonal antibodies or vaccines. Therefore, vaccinating more people now is key to containing the national and global health threat. The Delta variant is more contagious than previous variants and may be more virulent, so it is more important than ever to get vaccinated. Dr. Levine appreciated help getting that word out.

Combating AMR requires coordination across government agencies, with state and local public health departments, and with other industries and sectors, such as agriculture. It also involves dealing with deep inequities in the health care system. COVID-19, AMR, and other threats impact some communities more than others. Health equity is a priority for this administration, for the Secretary, and for the ASH. Dr. Levine called for a comprehensive approach to advancing health equity for all, and she was very encouraged that PACCARB is taking on the issue.

Another top priority for HHS is addressing the impact of the environment on public health, including climate change, and the need for environmental justice. It is becoming increasingly critical to address climate systemically in efforts to make communities healthier. HHS is forming the Office of Climate Change and Health Equity within OASH to deal with the impact of climate change, such as the excessive heat, wildfires, and drought in the West and rising sea levels on the coasts. HHS supports PACCARB in promoting a One Health perspective and commits to engaging with PACCARB and other stakeholders around environmental health policies.

Dr. Levine appreciated PACCARB's work and acknowledged the expertise of members and presenters. PACCARB presentations play an important role in sharing critical information and insights, as well as facilitating ongoing discussion. Furthermore, open meetings with content experts are important for addressing issues in the public sphere, and HHS will maintain transparency as it acts assertively on the issues. Dr. Levine invited the Council to keep challenging her and her colleagues with recommendations and considerations, especially those related to health inequities and disparities and the role of the environment in public health. AMR is a complex, persistent, challenging topic that involves many sectors and represents a critical intersection of the public health system. Dr. Levine encouraged PACCARB to ask the hard questions around this complicated issue and looked forward to its recommendations.

Advancing Interprofessional Education (IPE) and Practice to Combat AMR: IPE Working Group (WG) Report and Recommendations

Elaine Larson, Ph.D., RN, and Paul Plummer, D.V.M., Ph.D., DACVIM, DECSRHM, WG Co-Chairs

The ASH, on behalf of the Secretary, tasked the WG with investigating how IPE can be used to improve antibiotic stewardship and infection prevention curricula. The WG determined that One Health and IPE are both interdisciplinary approaches but are not interchangeable. For example, IPE tends to refer to human medicine, while One Health encompasses humans, animals, plants, and the environment. Both share similar competencies, goals, and outcomes, although IPE emphasizes individual outcomes while One Health focuses on population outcomes. The WG

report uses the umbrella terms “collaborative education” and “collaborative practice” in reference to both One Health and IPE paradigms.

The WG developed 10 recommendations, which fall into the following three categories:

- Sharing a vision: Promote interprofessional collaboration and One Health in health sciences pedagogy to reduce AMR and improve health outcomes.
- Implementation: Promote integration of AMR topics and collaborative education into curricula and extracurricular learning and incentivize AMR collaborative education and practice through accreditation and funding.
- Monitoring outcomes: Assess the effectiveness of collaborative education and practice programs.

Drs. Plummer and Larson summarized the key takeaways of the WG report and recommendations as follows:

- Bridge the differences between IPE and One Health by having both paradigms learn from each other and by expanding the roles traditionally included.
- Develop a core AMR curriculum that can be used across all health science disciplines.
- Incentivize the incorporation of AMR concepts through harmonization of accreditation standards across all health science disciplines.
- Define measurable outcomes that can then be used to monitor collaborative education and practice programs for positive impacts on AMR.

Discussion

Dr. Larson emphasized several barriers: the lack of a common language around IPE and One Health; siloed educational approaches and schedules that prevent team learning among medical, pharmacy, and nursing students; and lack of data to assess outcomes. Dr. Plummer said the report defines health science broadly, including all disciplines that have some influence on the use of antimicrobials. Dr. Larson noted the report acknowledges that AMR goes beyond acute care settings and is a community-wide problem. Dr. Plummer pointed out that moving IPE into real-world practice is key, and Dr. Larson added that even exemplar programs have difficulty finding settings where students can take part in IPE in the field.

Dr. King observed that a core competency that spans across One Health and IPE is respect for the ideas and abilities of colleagues. Dr. Plummer said there is a movement in health science toward competency-based outcomes, and veterinary educators, for example, have devised a competency framework that includes communication, collaboration across professions, and professionalism. There is an opportunity to integrate IPE and One Health education into the context of outcome-based competencies. Dr. Larson noted the need for harmonization of competencies that still allows sectors and professions to define the content. There was little enthusiasm for requiring uniform competencies around AMR, but it is likely that AMR will be integrated into other courses. Dr. Plummer said that even in exemplar programs, most did not include AMR and antibiotic stewardship as central components, driving the need for IPE.

Vote: PACCARB members voted unanimously to approve the report, *Advancing Interprofessional Education and Practice to Combat Antimicrobial Resistance*.

Bridging the Gap: Improving Antimicrobial Access and Use Across One Health: Antibiotic Access and Use WG Report and Recommendations

Stephanie Black, M.D., M.Sc., and Locke Karriker, D.V.M., M.S., DACVPM, WG Co-Chairs

The Antibiotic Access and Use WG was tasked by the ASH, on behalf of the Secretary, to identify persistent research gaps in antimicrobial access and use and to address antimicrobial stewardship within a virtual care landscape. The COVID-19 pandemic revealed the disparities in access to care and exacerbated the growing threat of AMR. Although stewardship is needed in all settings, the WG's report focused on virtual care, including telehealth services connected to outpatient settings and direct-to-consumer (DTC) encounters that might not involve personal interaction with a physician. The report offers seven recommendations, each with sub-recommendations that speak to implementation:

- Increase funding of research investigating the impact of virtual health care delivery on new and existing health disparities related to antimicrobial use.
- Increase understanding among human and animal health professionals about the use of antimicrobials within crops and other agricultural domains and their impact on clinical AMR.
- Increase funding to support research and development (R&D) of new innovations to promote antimicrobial stewardship efforts in several agricultural and plant domains.
- Support and encourage a standardized nationwide system for the collection of data on antimicrobial use and resistance in food and companion animals.
- Collate, review, and evaluate current federal policies, regulations, and requirements for antimicrobial stewardship and develop new incentives to better standardize stewardship practices across different modalities of care delivery, with a focus on telehealth.
- Increase access to data about individual prescribers and create actionable feedback to improve antimicrobial stewardship.
- Adapt and apply existing antimicrobial stewardship resources and tools to virtual care settings, specifically DTC telemedicine.

Drs. Black and Karriker summarized some of the key takeaways of the recommendations:

- Fully integrate crop and environmental health experts in all AMR discussions and research opportunities.
- Support state and local commodity groups to continue to build a stronger relationship of trust between veterinary practitioners and federal partners.
- Adapt existing outpatient stewardship interventions to the DTC telemedicine context and work with companies to align corporate incentives with the goals of antimicrobial stewardship.

Discussion

Dr. Karriker acknowledged that all stakeholders want more money for research; the WG suggested that the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Agency for Healthcare Research and Quality (AHRQ) increase research funding, but it also recognized the need for resources from a broader range of supporters. Dr. Black hoped that increased funding in response to COVID-19 to address health disparities at the

community level would carry over to support research on disparities around antimicrobial access and use.

Dr. Blaser highlighted the need for regulation and standardization in telehealth to avoid overprescribing of antibiotics. Dr. Black agreed that telehealth providers must be engaged in antimicrobial stewardship. Dr. Karriker said understanding the many ways in which antimicrobials are obtained and used is a first step; in some cases, existing regulations can serve as roadblocks if they are inadequately enforced.

Dr. Larson proposed using the term “telehealth” throughout rather than “telemedicine,” because it is broader and aligns with the IPE WG’s report. Dr. Black said the report defines both terms and primarily uses telehealth, but telemedicine is used occasionally for specificity—for example, when referring to DTC virtual care. Discussion revealed differing understandings of the use of the terms in different fields, but there was general agreement that both terms should be clearly defined, and inclusive terminology used when possible.

Action Item: PACCARB staff will compare the definitions in the report of “telehealth” and “telemedicine” with those in the literature and edit the report and recommendations to ensure the terms are used accurately.

Vote: PACCARB members voted unanimously to approve the report, *Bridging the Gap: Improving Antimicrobial Access and Use Across One Health*, amended as described.

Antibacterial R&D: Past, Present, and Future

Kevin Outterson, J.D., Boston University and Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)

Mr. Outterson explained that the R&D pipeline for antibiotics is leaking. Beginning in the 2000s, clinical antibiotic development has become steadily slower, riskier, and in the hands of smaller companies. CARB-X supports the preclinical pipeline. Its portfolio is diverse and attacks the problem through a number of novel classes, novel targets, and nontraditional approaches. Sales revenue from antibiotics is low, which limits commercial interest in development, and many antibiotics makers are in economic distress. Most of the available antibiotics are accessible in a few high-income countries (HICs). Even approval by the European Medicines Agency does not guarantee that a product will be launched in an HIC if the prospect for sales is poor. Access for low- and middle-income countries (LMICs) is very challenging. CARB-X helps advance projects to the point of phase I clinical trials and seeks to foster good stewardship, access, and innovation.

Mr. Outterson emphasized the need for more, and better, pull incentives to get products through development now so that they will be available when needed. It is difficult for systems to reimburse makers for products that yield population-level benefits when the market is geared toward patient-level benefits. Subscription approaches launched in England and Sweden are underfunded, so they support access to approved drugs but not R&D. The proposed Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act would fund a 10-year subscription to novel antibiotics at a rate sufficient to reward R&D investment and ensure access.

Among the pitfalls of proposals to create pull incentives are rewarding market entry without ensuring access, assuming push incentives will increase, and calculating potential sales using the most successful antibiotic to date. Mr. Outtersen summarized a transparent and reproducible model of net present value that employs publicly available data to determine what size pull incentives are needed; it determined that a global subscription approach should provide up to \$3.1 billion per drug for 10 years. The PASTEUR Act would resolve some commercial issues blocking R&D, and the amount of money proposed is consistent with Group of Seven (G7) and Group of 20 (G20) estimates of fair share.

Discussion

Mr. Outtersen said the PASTEUR Act was recently reintroduced in Congress, and there is a proposal to include it in an update of the 21st Century Cures Act. He added that PACCARB's support would improve the chances of passage. He noted that antifungals are included in the PASTEUR Act, but the data on market issues around antifungals are less robust.

Ramanan Laxminarayan, Ph.D., M.P.H., pointed out that companies that have already invested in advanced R&D would reap a windfall under the PASTEUR Act. Mr. Outtersen said the legislation would also ensure that those companies can sustain their efforts, which would draw private investors back into the fold.

Mr. Outtersen hoped that the PASTEUR Act would establish rigorous criteria for the products it supports (i.e., target product profiles) and that support would not be limited to the first product in a class but open to products that demonstrate substantial improvements. A thorough process of public rulemaking with significant input is key to establishing useful target product profiles.

Mr. Outtersen acknowledged that the difficulty of treating antimicrobials as pieces of the global infrastructure is that the rate of decay is not known. If the rate of decay is slow, governments might only need to invest in a few new products per decade. Mr. Outtersen added that HICs have a responsibility to ensure global access to products that can prevent infections from spreading around the world. The subscription models underway and the many international reports on incentives can offer insights into how much money should be invested in pull incentives.

The United States underwrites 84 percent of the antibacterial innovation for the world, Mr. Outtersen stated. The PASTEUR Act would encourage other countries to employ subscription approaches so that they carry their fair share. Mr. Outtersen suggested that the G7 lead the way and then encourage other HICs to join the effort.

Dr. Blaser said that how an antibiotic is used and by whom strongly influences the duration of its utility. For example, a new antibiotic to treat ear infections in young children would be very heavily used, and that consideration should be part of the target product profile. Mr. Outtersen observed that amplifying CDC's excellent work to promote antibiotic stewardship and infection prevention and control would offer some breathing room, allowing some antimicrobials to remain useful for a longer time. However, he noted, evolution ensures that resistance will always develop, so there should always be a plan to support development of new antimicrobial products.

Provocative Questions in AMR

Dr. Musmar described this session as an opportunity for Council members to offer their opinions on issues of concern around human, animal, crop, and environmental health. The Council did not seek to reach consensus or make recommendations as a result of this session.

Julie Segre, Ph.D., of the White House Office of Science and Technology Policy (OSTP) said President Biden asked OSTP to consider how the United States can improve its ability to address threats like AMR and emerging pandemics rapidly, with an eye toward strengthening U.S. and global pandemic readiness. Dr. Segre posed several questions around integrating pandemic readiness with combating AMR, raising issues such as the need to expand the targets for vaccination, and the use of diagnostics to improve patient outcomes and antibiotic stewardship, all of which should be addressed through the lens of equity and diversity.

Dr. Blaser proposed that PACCARB could serve as the body that determines the criteria for products supported by the PASTEUR Act, should it become law, if the Council added more patient advocates to the membership.

Dr. King suggested more focus should be on the global challenges posed by AMR, with particular attention to adequate funding and monitoring in LMICs that have national action plans but lack leadership and local capacity to progress toward the stated goals.

Kent E. Kester, M.D., FACP, FIDSA, FASTMH, asked whether the new administration plans to revise the country's AMR strategy or expand on existing work.

Christine Ginocchio, Ph.D., MT, pointed out that COVID-19 highlights the need for rapid, accurate diagnostics in a way that the public can appreciate, which offers an opportunity to promote diagnostics as a preventive measure to reduce unnecessary antibiotic use.

Dr. Plummer called for fostering innovation around alternatives to antimicrobials for animal and agricultural uses—such as new and improved vaccines, improved tools for biosecurity, better diagnostics for early intervention, and new immunotherapeutic approaches—and ensuring a clear pathway for regulatory approval of such products.

Greg Frank, Ph.D., suggested identifying the gaps in understanding around equity and AMR, revising the National Action Plan on Combating Antibiotic-Resistant Bacteria (NAP CARB) to articulate the policies needed to support development of countermeasures, and working to address global equity and access to prevent or mitigate AMR.

Elizabeth Dodds Ashley, Pharm.D., M.H.S., FCCP, BCPS, emphasized the importance of better training personnel to prevent and combat AMR and to respond to pandemics.

Dr. Karriker similarly raised the need to recruit and train veterinarians for the food animal field who can implement practices to fight AMR.

Helen W. Boucher, M.D., FIDSA, FACP, also pointed to the need for workers who are competent in the areas of surveillance, public health, and infectious disease; she called for a national champion for AMR and consistent investment in the workforce.

Michael D. Apley, D.V.M., Ph.D., DACVCP, expressed the need for more relevant, interoperable data; continued emphasis on prescribing behavior; development of diagnostic tests that give practitioners the confidence not to prescribe unnecessary drugs; increased focus on basic infection prevention and control and stewardship practices; and more research on the optimal use of existing antimicrobials.

Paula J. Fedorka Cray, Ph.D., suggested establishing global surveillance to identify emerging microbial populations, particularly in areas undergoing significant environmental or population changes, that may harbor new or different resistance mechanisms or serve as vectors for transferring resistance.

Carla L. Huston, D.V.M., Ph.D., Dipl. ACVPM, said basic knowledge gaps hinder development of guidelines for the judicious use of antimicrobials in veterinary medicine at the client, patient, and farm levels, which speaks to the need for continued research and education about disease prevention, control, and treatment.

Dr. Blaser said society overvalues the benefits of antibiotics while underestimating their biological costs to individual patient health (as well as the costs to society at large of AMR); he called for exploration of the critical link between antibiotic overuse and individual health risks, noting that AMR is just one manifestation of human microecological change, which increases susceptibility to pandemics.

Via email, Dr. Black said that the COVID-19 pandemic provides an opportunity to raise awareness about AMR by (1) taking advantage of plans to create “equity zones” that facilitate access to care in neighborhoods with high burden; (2) educating all health care workers about AMR, antimicrobial stewardship, and infection prevention and control; and (3) sustaining collaboration among public and private health laboratories to support AMR surveillance.

Public Comments: Innovation Spotlight

Dr. Musmar explained that the Innovation Spotlight is an opportunity for public comment open to all those with relevant new and emerging technologies they wish to present to the Council. The Council does not endorse or sponsor any of the companies or products described.

Gary Cohen and Marc Oshima of AeroFarms summarized the benefits of indoor vertical farming in relation to AMR: crops do not need pesticides, herbicides, or fungicides (including antibiotics used as pesticides in agriculture); the method leaves no impact on soil; and crops do not need to be washed or treated before eating. Plants grown in indoor vertical farms are safer for consumption and require less water and land than traditionally grown plants. Food safety is built-in to the indoor vertical farming process. AeroFarms has collaborated with the U.S. Department of Agriculture (USDA), the Food and Drug Administration (FDA), CDC and others since it started in 2004.

Andrew Satz of EVQLV said his organization combines computer and synthetic biology to lower the cost of biologics for therapeutics and diagnostics. It applies artificial intelligence to learn patterns of antibody formation in DNA reference sequences. With this information, EVQLV can generate millions of antibodies specific to a target, creating a digital version of laboratory assays but at a much larger scale. EVQLV uses this process to screen for drug targets

that can then be tested in a laboratory. The approach can speed the process of antibody and monoclonal antibodies discovery, which speaks to the NAP CARB goals of accelerating research and advancing the development of rapid diagnostics. EVQLV applied its technique to COVID-19 antibodies and predicted many of the mutations later identified in the field.

Thomas Heymann of Sepsis Alliance said his organization’s global public awareness survey found that, across five countries, 52 percent of adults have heard of AMR. People over 55 years of age, those with lower incomes, and Black people were less likely than those who are younger, have higher incomes, or are white to have heard of AMR. Few respondents had any knowledge about AMR. Surveyors then defined AMR and asked respondents whether they felt AMR is a major problem—and 68 percent globally said it is. Sepsis Alliance launched a public education campaign to increase the sense of urgency around combating AMR. Responses have been strongly positive. More information and targeted versions of the campaign can be found at EndSuperBugs.org.

Sasan Amini of Clear Labs described his company’s fully automated, next-generation sequencing-based platform, which provides descriptive diagnostics of pathogens. The technology extracts a range of clinically relevant information, such as identifying the pathogen and the antibiotic to which it will respond. Clear Labs seeks to offer an advanced diagnostic platform that is easy to use, cost-effective, reliable, and accessible; integrates seamlessly with other data sources; and provides fast, reproducible results. Since January, the technology has been deployed in more than half of U.S. public health laboratories for COVID-19 surveillance. It has helped states rapidly sequence samples and identified the first Alpha and Delta variants of COVID-19. Clear Labs’ solution can identify variants sooner than other technologies.

Brett Baker of Microbion Corporation outlined his company’s development of a new class of anti-infective drug, pravibismane, which has been assessed in clinical studies for three indications. It incorporates revolutionary technology that works against planktonic pathogens and can eradicate microbial biofilms, the most prevalent form of bacteria on earth. Pravibismane works against highly resistant pathogens, including carbapenem-resistant bacteria. Its targeted delivery limits the impact on the microbiome by sending the drug directly to the source of infection. It is safe and well tolerated and has been found to be effective for treating diabetic foot ulcers and infections related to the use of orthopedic devices. If approved, an inhaled pravibismane formulation could be used to treat patients during a respiratory illness pandemic like COVID-19.

Final Comments and Recess for the Day

Martin Blaser, M.D., Chair

Dr. Blaser thanked the participants and recessed the meeting for the day at 1:43 p.m.

Day 2

Welcome and Overview

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

The meeting began at 10 a.m. Dr. King welcomed the participants and outlined the agenda for the day.

Roll Call

Jomana F. Musmar, M.S., Ph.D., Designated Federal Official, Advisory Council Committee Manager, OASH, HHS, and Taylor Simmons, M.P.H., ORISE

Dr. Musmar reiterated the rules of engagement. Ms. Simmons called the roll.

Operationalizing One Health

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

At its June 2021 meeting, the G7 recognized the growing pandemic of AMR and the need for clear leadership and bold, science-based actions under a One Health approach. Dr. King said that given this readiness at the highest levels of governance, critical resources must be invested in One Health policies and programs to ensure that One Health is executed across domains.

Challenges in HICs and a Nordic Example

Carlos das Neves, D.V.M., Ph.D., Norwegian Veterinary Institute

Dr. das Neves pointed out that interest in the One Health approach was steadily increasing before the pandemic and has spiked since. He believed that too much time has been spent trying to identify who is to blame (for COVID-19 and AMR), defining the terms of One Health, and mapping the concept so that every sector is represented. Dr. das Neves called for more focus on solutions. These solutions must look beyond the sectors of animal, human, and environmental health and integrate political leadership, science, and social awareness.

Several countries in Africa, for example, have One Health policies embedded in strategic plans, but the United States does not have a One Health strategic plan. Norway has a One Health strategy and Sweden is experimenting with an approach that involves no political integration, but other Nordic states do not seem to have a sense of urgency on the matter. Dr. das Neves emphasized that One Health goes beyond AMR. The message that a One Health strategy is needed to combat human disease and the food supply has resonated in Norway. Norway has instituted a participatory model that brings together policy, private sector investment, society, and strong research. Dr. das Neves concluded that many opportunities have been lost but now, all the pieces might be in place to act.

Discussion

Dr. King asked how to communicate the goals of One Health to a public that distrusts science. Dr. das Neves recommended breaking down the components into smaller pieces and communicating them to targeted groups. Norway has focused on doctors and veterinarians, but it might be helpful to educate K–12 students by focusing on the importance of protecting nature.

The pandemic illustrated the interconnectivity and complexity of global health and raised awareness about the local impact of a global threat. Dr. das Neves noted that neither the public nor the private sector will be fully engaged if national policies do not align with the science. More funding is needed to put words into action, he added.

Dr. White echoed the concern that although people support One Health, bringing people together and deciding what to address has been difficult. Dr. das Neves said Norway is moving toward a One Health platform that would bring together politicians, scientists, industry, and the private sector and encourage them to create and implement targeted solutions. The virtual platform intends to promote more open discussion about how to enact plans rather than protracted talk about the problem.

To better communicate the urgency of the threat of AMR, Dr. das Neves advised efforts should highlight how it can affect individuals directly, such as the impact on food sources. Despite excellent biosecurity measures, the pandemic revealed the fragility of the food supply system. The public might need to take more responsibility for AMR, and much more funding is needed to address it.

One Health Trust Demographic One Health Surveillance Site

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

Dr. Laxminarayan described CDDEP's approach to One Health surveillance:

- Stage 1: Tracking resistance and the presumed drivers of resistance, which are often not quantified. Resistance has increased nearly threefold among food animals since 2000, and consumption is a major driver of resistance in human health, but the connection is largely ignored.
- Stage 2: Correlate resistance across different domains. For example, there is a high correlation between resistance rates of *Escherichia coli* found in urine samples of hospitalized patients and in the sewage from those hospitals.
- Stage 3: Build evidence about the drivers of resistance between domains. Studies demonstrate that the relationship between higher temperatures and antibiotic resistance is increasing, and climate change may be driving adaption of fungal pathogens to higher temperatures.
- Stage 4: Design and test One Health interventions using the platforms created for surveillance. Better surveillance can determine where spillover (between domains) occurs and allow measurement of progress when interventions are implemented.

Dr. Laxminarayan described the spread of several pathogens that could have been predicted and possibly mitigated with better surveillance. For example, the gene that confers carbapenem resistance is 20 times higher in the Ganges River in India during pilgrimage season than any other time of the year. It was detected in 2008 in India and then spread around the world. Educating people about the risks and preventive steps could limit the spread of the gene. CDDEP is currently setting up a One Health surveillance site in Bangalore that will provide longitudinal data on animal, environmental, and human health to identify spillovers. Dr. Laxminarayan called

for a more consistent approach to surveillance that better integrates animal and environmental components with human health.

Discussion

Dr. Blaser asked whether the emergence of drug-resistant *Candida auris* is the result of selection (driven by climate change) or the broad use of antifungals in agriculture. Dr. Laxminarayan said there is evidence that *C. auris* is adapting to higher temperatures and that human basal temperatures are increasing. Both of these findings suggest that fungal pathogens are emerging that are of concern for humans. Better data are needed to establish causality.

Dr. Laxminarayan said the Netherlands tracks AMR on farms, but no country has systemic data that are sufficient to demonstrate clearly that farm practices affect the emergence of resistance. Some research studies address the issue in limited settings, but broad surveillance systems are needed to look for the emergence of resistance and spillover events.

Dr. Laxminarayan said that the various depictions of a One Health framework are intended to act as organizing principles for policymaking and research, but the public does not really care which terms are used. There is a general understanding of the concept of interconnectedness, such as the recognition that cholera is transmitted as a result of poor water sanitation. Dr. Laxminarayan noted that although there are many human health surveillance programs, no large, systemic platform captures One Health data consistently and longitudinally across all domains.

Expanding Epidemic Intelligence in One Health

Mark S. Smolinski, M.D., M.P.H., Ending Pandemics

Dr. Smolinski explained early approaches to digital disease detection to improve surveillance, such as tracking Google searches about influenza symptoms as a way to identify influenza outbreaks sooner than traditional monitoring approaches. Participatory surveillance engages the public directly in monitoring. For example, Flu Near You enables people to report their symptoms or identify as symptom-free, providing both a numerator of influenza cases and a denominator of respondents. The system provides a useful signal and can be implemented broadly.

Ending Pandemics pioneered the Participatory One Health Disease Detection (PODD) system in Thailand, winning the 2021 Trinity Challenge's grand prize. Individual farmers use their mobile devices to send data and images about symptoms among their animals, and a veterinarian visits within 24 hours. The system rapidly detects outbreaks, allowing for treatment and containment. For example, PODD identified the first case of foot-and-mouth disease in the district where it was piloted; swift treatment allowed farmers in the village to continue exporting milk, preventing the loss of \$4 million in sales.

Another participatory surveillance mechanism—a free national hotline in Cambodia—enables any citizen to report health issues. About 95 percent of the country's COVID-19 cases were identified through the hotline, which also served as a primary source of public information. The Connecting Organizations for Regional Disease Surveillance initiative is analyzing current models around AMR in hotspots to identify gaps and create common surveillance protocols. It will contribute to a better global picture of AMR.

Discussion

Dr. Smolinski said the Flu Near You application led to a COVID Near You application, and both were incorporated into a broader tool, Outbreaks Near Me, that Ending Pandemics hopes to expand. It also hopes to add at-home testing results and potentially genomic testing to the tool. Dr. Smolinski pointed out that PODD identifies threats in LMICs that are endemic, as AMR is.

Dr. Laxminarayan noted that PODD focuses on animal surveillance. He asked whether a human health surveillance component could be added and whether there would be privacy concerns in doing so. Dr. Smolinski said PODD is linked to a companion tool, created by the same team, that allows villagers to report human illness. Together, the systems capture issues around food safety, water quality, and environmental concerns, among others. The PODD users see it as a tool for community engagement, and the access to rapid veterinary services acts as an incentive. Banks in the region now require use of PODD as a condition for farm loans because it detects disease outbreaks early, demonstrating how locally relevant incentives can sometimes emerge organically.

The Tricycle Project: World Health Organization (WHO) Integrated Global Surveillance on Extended-Spectrum Beta-Lactamase-Producing *E. coli* Using One Health Approach

Shivaramu Keelara, D.V.M., North Carolina State University

Dr. Keelara summarized the Tricycle Project's implementation of global surveillance systems for *E. coli* in nine countries. The project incorporates human, environment, and food chain surveillance, as well as molecular characterization of samples and links to other surveillance systems. Dr. Keelara's institution played a major role in optimizing a protocol for isolating *E. coli* from animals using a medium that is readily available, familiar, and reasonably priced so that it can be employed in LMICs.

Following training of local experts from each One Health domain on identifying *E. coli* and ensuring quality control, sites were established in nine countries across four WHO regions. Progress was slowed by the pandemic, but more countries are expected to join. Among the results so far, there is evidence of a link between *E. coli* in poultry and in pregnant women. Environmental samples show a similar percentage of *E. coli* in drinking water in rural areas and in wastewater.

The Tricycle Project will enable the global community to establish a baseline surveillance system for AMR at the country level using a One Health approach. The data from this harmonized project can be compared at the global level and support creation of global mitigation strategies to combat AMR. Dr. Keelara concluded that a similar approach could be extended to monitor other emerging infectious diseases and pathogens.

Discussion

Dr. Jinks pointed out that implementation of national action plans is weak in LMICs, and he asked how Tricycle Project results could bolster implementation. Dr. Keelara noted that Malaysia, for example, is using the results of the *E. coli* surveillance in implementing its national action plan. The ultimate goal is for countries to use the results to develop action plans on AMR.

Dr. King asked where interventions should be targeted to prevent transmission of resistance. Dr. Keelara observed that all three sectors (animal, human, and environment) are equally involved in transmission of pathogens. Educating veterinarians and medical professionals as well as those who have an impact on the environment helps reduce AMR, he noted. The samples collected will be sequenced and categorized, and WHO will publish the results soon.

The Federal One Health Response to COVID-19

Casey Barton Behravesh, M.S., D.V.M., Dr.P.H., DACVPM, CDC

In 2017, CDC partnered with USDA and the Department of the Interior to strengthen One Health collaboration at the federal level, culminating in a joint workshop, Prioritizing Zoonotic Diseases for Multisectoral, One Health Collaboration in the United States, that identified eight priority zoonotic endemic and emerging diseases (including coronavirus). The workshop report proposed creating a national action plan for U.S. health security, a formal One Health coordinating mechanism, and a national One Health framework.

With the emergence of COVID-19, CDC established the One Health Federal Interagency COVID-19 Coordination Group (OH-FICC), bringing together 150 federal partners from 22 agencies. Among the materials created so far are a toolkit for managing companion animals with COVID-19, a case definition for animals, and answers to frequently asked questions about bats, wild animals, and game meat.

The OH-FICC coordinated efforts among public health, animal health, and wildlife protection partners at the state, tribal, and local levels. It created a telephone hotline for One Health emergencies and deployed teams to help with local investigations. Through a monthly webinar, it provides regular updates at which participants from all facets of One Health can pose questions directly to federal agency representatives. In-depth epidemiologic investigations brought forth information that allowed experts to compare the public health risks of transmission and clinical course of COVID-19 between humans and animals. Federal agencies were able to react in real time and adapt guidelines with new information.

The SARS-CoV-2 Interagency Group's One Health Genomics Working Group aims to understand the emergence of variants, transmission dynamics involving animals and humans, and the research needed to evaluate the impact of COVID-19. Dr. Behravesh said it is important to coordinate federal guidance and to house it in one place that is easily accessible for the public and professionals.

The One Health Systems Mapping and Analysis Resource Toolkit (OH-SMART™)

Tracey Dutcher, D.V.M., M.S., DACVPM, Animal and Plant Health Inspection Service, USDA

OH-SMART supports interdisciplinary groups of stakeholders in defining a specific One Health challenge and coming up with a results-oriented process for tackling it that ultimately strengthens the whole system. Systems analysis and mapping are key, as they help people move away from blame and toward solutions. Mapping processes enables users to develop a shared understanding of partners' different perspectives and to appreciate the integration of partners' capacities.

Minnesota used OH-SMART to address the avian influenza outbreak of 2014. A collaborative group mapped the resources and response capacity of stakeholders. Using OH-SMART, Minnesota addressed key gaps in communication, identified new policies and procedures for communication, revised its list of emergency responders to identify which roles could be filled by others, improved coordination among agencies, and created a portal for sharing information.

The University of Minnesota partnered with the WHO and the Food and Agriculture Organization of the United Nations to use OH-SMART to inform AMR national action planning in Lower Mekong countries. The process identified themes and gaps, and multisectoral stakeholders reached agreement on resolutions and specific actions to achieve them. For example, they agreed to instate communication channels, review laws and regulations across agencies, hold multisectoral meetings, and strengthen the infrastructure and capacity for sharing information across departments and ministries. Dr. Dutcher emphasized that OH-SMART provides a platform for creativity and innovation and helps move One Health from theory to application.

Discussion

Dr. Behravesh said that, unrelated to COVID-19, another platform, the One Health Federal Interagency Network, promotes information exchange and highlights opportunities for collaboration. It will evaluate the capacity of existing partnerships to determine whether more perspectives are needed as conversations about One Health evolve. Dr. Dutcher said USDA is doing a lot to ensure effective communication across its many agencies and with its federal partners. She added that USDA looks forward to continued collaboration beyond COVID-19.

Dr. Ginocchio asked how outcomes of the federal initiatives would be measured. Dr. Behravesh said the OH-FICC recognizes the importance of monitoring and evaluation but is not yet ready to implement such steps. Dr. Dutcher said OH-SMART is valuable for measuring progress. She noted that during the Minnesota avian influenza response, USDA held workshops in four states about protecting emergency responders. The concepts were implemented in state plans, and tabletop exercises were used to test emergency response plans.

Dr. Black asked what lessons have been learned about emerging threats, particularly from animal investigations, and how to expand state and local laboratory capacity and engagement. Dr. Behravesh said the OH-FICC will capture lessons learned formally when its efforts wrap up. She noted that check-ins have been valuable for getting feedback, identifying gaps, and addressing issues. For example, a subgroup on animal testing worked with laboratories that identified challenges in detecting and responding to emerging animal threats. As a result, CDC helped fund USDA's National Animal Health Laboratory Network to assist with animal testing early in the pandemic. Through weekly calls with state and federal partners, Dr. Behravesh continued, it emerged that one in five U.S. jurisdictions do not have a public health veterinarian to address public health problems like rabies.

Introduction to Environmental Dimensions of AMR

Timothy Jinks, Ph.D., Wellcome Trust

Despite mounting evidence that the environment plays a key role in AMR, global and national action plans do not adequately address environmental factors. Human contamination of water

and soil contributes to AMR. Drug resistance can emerge from the environment, driven by lower concentrations of antimicrobials than previously thought. However, the evidence is brushed off, and research funding remains low.

Dr. Jinks said that progress is limited because key actors in the public and private sectors do not prioritize environmental factors around AMR or recognize the need to implement readily available solutions, such as wastewater detection. Systemic risk analysis will quantify the risk posed by AMR in the environment and the risk of inaction, making the case for prioritization. Even in areas where the level of concern has risen (mostly in HICs), the focus has been on research and data generation rather than policymaking. Promising approaches are not limited to addressing AMR. In LMICs, solutions aimed at the environmental dimensions of AMR can reinforce progress toward sustainability goals. Dr. Jinks said PACCARB should identify practical interventions and recommend them to policymakers.

Triazole Resistance in *Aspergillus fumigatus*: CDC Update

Tom Chiller, M.D., M.P.H.T.M., CDC

Triazole antifungals are critical for treating *Aspergillus* infection in humans, which causes at least 15,000 hospitalizations and 800 deaths per year. *Aspergillus* is the most common missed diagnosis in intensive care units. It is increasingly diagnosed in people who are not immunocompromised, including people with influenza and COVID-19 infections. Emerging resistance to triazoles is contributing to rising numbers of deaths in people with *A. fumigatus*, reaching rates similar to those before triazoles were available for treatment.

Within a decade of the introduction of azoles for medical treatment in the 1990s, new genotypes emerged. It was determined that patients inhaled *A. fumigatus* that had developed triazole resistance in the environment. Although azoles have been used in agriculture since the 1970s, the newer formulations share molecular structures with azoles used in clinical medicine. So far, triazole-resistant aspergillosis remains rare in the United States, and CDC is increasing public health surveillance. In some European hospitals, more than 20 percent of cases are resistant. Notably, azole-resistant strains of *Aspergillus* identified in humans are also resistant to other classes of fungicides, such as strobilurins.

Triazole use dramatically increased starting in 2006 as farms started using azoles for wheat, corn, and soybean crops. Although manufacturers claim that triazole fungicides quickly degrade and do not spread beyond the area of application, Dr. Chiller said they are detected across the country and in specimens far distant from their use. However, environmental surveillance is limited.

Stewardship is critical for all antimicrobials, including antifungals. Inpatient and outpatient use of azoles has declined. However, agricultural use of triazoles is evolving to focus on effects beyond plant disease prevention and treatment. A One Health approach is important to prevent the spread of resistance and pathogens.

Discussion

Dr. Chiller said CDC is trying to understand the environmental influences that drove up azole use in wheat, corn, and soybeans. It is seeking information from the farming and agriculture community on how azoles are marketed and used.

Dr. Blaser opined that people with resistant organisms might have been exposed to *Aspergillus* through food consumption. Dr. Chiller said *Aspergillus* might travel through food but noted that *Aspergillus* spores are airborne and easily inhaled. Spores from tulip farms in the Netherlands (which has seen aspergillosis outbreaks) may travel to nearby urban areas relatively easily. Dr. Chiller said the increased use of fungicides in the environment might also play a role.

Dr. Chiller said that CDC hopes to engage plant pathologists to determine the best approaches to antifungal stewardship for agricultural and human health. It is funding some partnerships, such as a contract with the University of Georgia to collect samples and analyze isolates. CDC hopes to set up formal surveillance for human infection eventually, but for now it is expanding its Antibiotic Resistance Laboratory Network to test for *Aspergillus* and resistance isolates. CDC is also reaching out to USDA and the Environmental Protection Agency (EPA) and hopes to engage academia.

Dennis M. Dixon, Ph.D., pointed out that in the 1980s, the USDA determined that *Aspergillus* spores incubated in a compost heap and spread to the surrounding community. Dr. Chiller added that tulip farms in the Netherlands have huge compost heaps that contribute to the spread of *Aspergillus* in adjacent urban areas. In Europe, most cases of aspergillosis are seen in urban areas, but it is not clear whether there is more infection in urban areas or whether rural patients are treated in urban hospitals.

Informing Policy and Practice for Combating AMR Through Surveillance of Water and Wastewater Environments

Amy Pruden, Ph.D., Virginia Tech

Any wastewater stream can be analyzed to inform AMR solutions. Dr. Pruden summarized findings from several water research projects underway that use genomics, real-time polymerase chain reaction (qPCR), metagenomics, or antibiotic monitoring, depending on the goals of measurement. One study tracked the fate of antibiotic-resistant bacteria and antibiotic resistance genes in two water reuse systems, one for farm irrigation and one for potable water. It illustrated the importance of optimizing wastewater monitoring systems to identify and target pathogens of concern, such as *Klebsiella pneumoniae*, which can rebound in water distributions systems if not captured during wastewater treatment.

Another study looked at the same two water systems and used metagenomics to examine how antibiotic resistance genes co-occur with mobile genetic elements and human pathogens in wastewater. The findings offered encouraging indications that the risk of pathogens decreases with each stage of treatment but there is some regrowth during distribution.

Dr. Pruden said that monitoring hospital waste systems could identify what is circulating among patient populations, which could inform prescription and hygiene practices but also help determine the benefit of on-site hospital wastewater treatment. A longitudinal study found that predicted pathogen antibiotic resistance gene combinations found in the treated effluent corresponded to the local clinical patterns of AMR in raw sewage, suggesting that the effluent is a valuable monitoring point with clinical relevance. Yet another analysis determined that pathogens do not necessarily acquire resistance during wastewater treatment, as is often suggested.

The Water Research Foundation drafted a decision tree to help AMR monitoring programs determine which method of analysis to use depending on the goals of the program. Ideally, national and international bodies will establish integrated environmental surveillance of AMR, which includes standardizing methods and reporting to enhance data sharing. Some systems are in place, such as USDA's National Antimicrobial Resistance Monitoring System (NARMS). The United States joining WHO's Joint Programming Initiative on AMR would be a significant step for international coordination of environmental surveillance. Work is underway to develop cyberinfrastructure to support wastewater monitoring. Dr. Pruden noted that COVID-19 sparked the implementation of sewage surveillance efforts all around the world.

Discussion

Dr. Pruden observed that collaboration across funding agencies could support the kind of environmental research needed, such as environmental phenotyping. Involving federal laboratories in such research would contribute to standardization. For example, NARMS is looking at environmental targets that have clinical relevance.

Dr. Pruden explained that nontarget analysis techniques are useful for examining wastewater without looking for specific antimicrobials. It is also important to look broadly at wastewater to identify, for example, heavy metals. Notably, the amount of antibiotics measured in sewage does not necessarily correspond with reported use, so wastewater can provide a more accurate picture of use (after accounting for differences in antibiotic degradation rates).

The Collective Global Responsibility to Do No Harm: Ethics and Drug Resistance

D. G. Joakim Larsson, University of Gothenburg, Sweden

Antibiotic-resistant bacteria are extremely common in industrial pollution sites, especially where drug manufacturers are located. India produces a lot of the world's drugs and also provides an extensive environment for the emergence of antibiotic resistance, including many previously unknown types of resistance genes. Emissions from large manufacturers everywhere—China, Europe, Asia, and the United States, among others—contribute to the problem. Furthermore, because antibiotic resistance spreads, the problem must be managed globally, not just where drugs are produced. Professor Larsson said that those who can address the issue are morally obligated to do something.

Various stakeholders have a role to play in reducing antibiotic emissions, and each has incentives and counterincentives to act. Scientists and research institutions are obligated to provide good data, and the media has an important role in informing the public and policymakers. Countries also have responsibilities; India proposed limits on antibiotic pollution in water, but the legislation has stalled.

Clearly, the drug manufacturing industry should take action, but there are obvious counterincentives. The AMR Industry Alliance addressed manufacturer emissions, but drug manufacturers are unwilling to reveal where or by whom active ingredients are made or the size of the emissions, so they avoid accountability. Other stakeholders must push for action.

Prof. Larsson offered four steps that countries can take to incentivize a reduction in industrial pollution by drug makers:

- Demand transparency into the production chain so that the sellers of products can be held responsible. New Zealand published where active ingredients are made for various substances, and the United States can do so as well.
- Specify pollution control as a criterion of drug procurement (a tactic used by hospital organizations in Sweden and Norway).
- Weigh pollution control into the subsidies that governments (or, in the United States, insurance providers) give to drug companies for their products.
- Include pollution control as a component of Good Manufacturing Practice, which would influence practices by drug makers around the world that want to export their products to Europe, the United States, or both.

Discussion

Dr. Blaser pointed out that China has more than 1,000 factories that make antibiotics, and there is no authority monitoring their practices. Prof. Larsson said that some of the proposed measures for tackling pollution are most effective for drugs that are exported globally. Controlling domestic markets entails local regulation, and China is becoming concerned about AMR. Prof. Larsson noted that China can move fast once it decides to address the issue.

Dr. Jinks asked how far measures should go in terms of transparency. Prof. Larsson proposed looking at ingredients at the stage at which they have known pharmacologic activity. He acknowledged that restrictive criteria can potentially threaten access to medications, but measures could also reward compliance, a concept Dr. Jinks endorsed.

Dr. King asked how to get better insight into the incentives and disincentives that influence decision-making by various stakeholders. Prof. Larsson replied that social science and humanities perspectives can help. Some incentives are obvious, such as the profit motive, which is a valid incentive. However, there remains a strong need to develop incentives other than profit to encourage companies to make new antibiotics, for example.

Dynamics of the Soil Resistome: Contribution of Horizontal Gene Transfer

Barth F. Smets, Ph.D., Technical University of Denmark

Soil is extremely heterogenous. It includes inorganic compounds mixed with organic substances. Its composition varies depending on whether it is wet or dry. It supports high microbial density with abundant genetic diversity. The bacteria in soil change with the seasons but always revert to a springtime state, making the soil microbiome seasonal yet stable.

Antibiotic resistance genes are endemic to soil, and there is evidence that they increase when manure is applied to soil. Antibiotic resistance genes from soil can be found in the internal microbiome of plants grown in that soil (i.e., the endosphere). It does not appear that the original host survives to allow the genes to enter the plant microbiome or that the selective pressure for antibiotic resistance genes is strong enough to support entry. Rather, Dr. Smets believes, the genes are located on mobile genetic elements that allow them to enter the endosphere, a process known as horizontal gene transfer.

Of significant concern is that when antibiotic resistance genes are added to soil and then transferred to the plant's microbiome, many of these genes contain genera that are not distant

from human pathogens. This transfer can pose a major problem for crops that are eaten raw, such as leafy vegetables. Therefore, caution must be exercised when materials containing antibiotic resistance genes are added to soil used for agricultural production.

Discussion

Dr. Smets noted that there is no pristine soil against which to compare the influences of a given compound. Researchers often use samples from soil adjacent to the testing area. The greater the capacity to look at the molecular construction of the soil, the more information can be gathered to identify elevated concentrations of antibiotic resistance genes. Dr. Smets was not aware of research that evaluated soil before and after significant events, such as wildfire or flooding. On the basis of anecdotal evidence, Dr. Smets said, plant endospheres are most vulnerable to antibiotic resistance gene transfer early in life.

Public Comment

Brett Baker from Microbion Corporation spoke in favor of support for the PASTEUR Act at the highest level. He added that there is a disconnect around the best formulations for antibiotics with respect to the microbiome. Easy-to-administer formulations are highly desirable. Oral formulations are frequently favored in that respect, but they can harm the microbiome and potentially lead to dysbiosis. Dysbiosis may currently be an underappreciated element of many different disease processes. Careful thought should be given to whether an oral antibiotic should always be favored. More limited, targeted forms of administration should also be an important part of the conversation.

Madeleine Kleven of the Food Animal Concerns Trust said her organization joined others to create the Keep Antibiotics Working Coalition to eliminate a major cause of antibiotic resistance: the inappropriate use of antibiotics in food animals. COVID-19 illustrated that the world is unprepared to handle pandemics and their associated health and economic ramifications. Antibiotic resistance is a slower but just-as-deadly pandemic that is rendering critical drugs ineffective and is already putting an immense health and economic burden on the United States and the globe. Unfortunately, the U.S. federal response to antibiotic resistance has not been nearly urgent or comprehensive enough. FDA, as the regulator of antibiotics used in animals, must play an important role in addressing antibiotic resistance and must speed up implementation of actions targeting this urgent threat.

Ms. Kleven said one such action is setting duration limits for the use of medically important drugs in food animals. Under FDA's planned schedule, 14 years will have elapsed from the year that FDA identified duration limits as a priority in 2016 to the year when its modest rules may go into effect in 2030, which is unacceptable. The Keep Antibiotics Working Coalition urges PACCARB to hold the FDA accountable to an expedited timeline for implementation of duration limits and that the Council demand that FDA prioritize protecting public health rather than the regulated industry when setting durations. The Coalition also asks that PACCARB set ambitious national targets for reducing antibiotic use in agriculture and human settings and urge the FDA to establish a national surveillance system that describes what, when, where, and how antibiotics are actually used on U.S. farms and feedlots.

Jennifer Schneider of the Global Antibiotic Research and Development Partnership (GARDP) said her organization is addressing WHO and CDC priority pathogens through the development of therapeutics. One of the challenges in the antibiotic development community is the efficient organization of expertise and resources in both the public and private sectors to deliver for public health. This challenge can be met in part by not-for-profit collaborative R&D organizations like GARDP. Since 2010, public-private partnerships have developed and introduced 66 new health technologies for priority public health needs that have reached more than 2.4 billion people around the world. The not-for-profit model is well suited to addressing the domestic and global challenges of AMR because of its ability to focus on the greatest public health and clinical needs, ensure the best use of public money, create and facilitate strategic partnerships, safeguard the availability and appropriate use of antibiotics through portfolio management, and enhance antibiotic stewardship and access for all populations.

Through this model, GARDP has partnered with two U.S. companies to develop a new drug candidate for serious bacterial infections in hospitalized adults and children, including those for which there are limited treatment options, and to develop a first-in-class treatment for gonorrhea. Both of these companies have also received funding from the U.S. government. GARDP has also completed one of the largest global observational studies on newborns with sepsis, enrolling over 3,000 babies, which will inform an empiric trial to evaluate combination treatments for neonatal sepsis. GARDP is an important player in the antibiotic community and can provide a clear delivery path for innovations being developed by U.S. public- and private-sector actors, bridging an important gap that now exists in the late-stage development of new treatments to address AMR. GARDP commends the leadership of the U.S. government and welcomes strengthened collaboration and support to deliver urgently needed new treatments for the American people and global populations.

Aileen Marty, M.D., of Florida International University praised the two excellent WG reports developed by PACCARB. She strongly endorsed the One Health goal stated in the report, *Advancing Interprofessional Education and Practice to Combat AMR*. She concurred with starting education about combating AMR at the earliest possible levels of learning and integrating these competencies as part of a learning continuum. The collaboration between veterinary and human medical professions is unquestionably one of enormous value and needs prompt attention. There are, however, glaring gaps in the document regarding a fundamental understanding of how, when, and where AMR education can be taught at the graduate level for medical, veterinary, and other students. Medical schools are organized in a way that challenges accomplishment of the goals described. Medical school curriculum real estate is at a premium, and educators are already doing their best to integrate learning.

The report's Figure 2 does not recognize the need to incorporate disciplines within health care that heavily impact combating AMR. Specifically, at a minimum, immunology and molecular biology must be integrated into the study of combating AMR within the curriculum. Interdisciplinary integration must be accomplished in a fashion that captures the One Health aspect of all the interrelated disciplines and reveals the interconnectivity of systems at all levels: molecular, cellular, tissue, organ, organism, community, and world.

Dr. Marty suggested the report specifically add that an individual or a group must be formed to accomplish the report's recommendation to increase funding for collaborative education and

training and that any university that receives such funding should set a time limit for achieving the goal. Dr. Marty said that stovepiping medical care in the United States at a policy level must cease. She praised the report for addressing state-level management of education and the challenges that such a system produces to overall quality to achieve improved health outcomes and reduce the cost of health care services. Dr. Marty called for a national health care system with interoperability of devices, diagnostics, education, and care throughout the United States. She also urged constant surveillance for emerging threats, including training and education for surveillance that is funded at all levels, including universities. The emphasis must be on prevention. Education must focus on the economic and health advantages of prevention.

Final Comments and Adjournment

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

Dr. Blaser thanked the participants and presenters for their contributions and Council staff for their excellent efforts. Dr. King added thanks to the public commenters for providing important information. He observed that COVID-19 offers an opportunity to generate a new sense of urgency around AMR. Dr. Blaser adjourned the meeting at approximately 3 p.m.

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

June 29–30, 2021

PACCARB Voting Members Present

Martin J. Blaser, M.D., Chair
Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair
Michael D. Apley, D.V.M., Ph.D., DACVCP
Stephanie Black, M.D., M.Sc.
Helen W. Boucher, M.D., FIDSA, FACP
Sara E. Cosgrove, M.D., M.S.
Paula J. Fedorka Cray, Ph.D.
Christine Ginocchio, Ph.D., MT
Locke Karriker, D.V.M., M.S., DACVPM
Kent E. Kester, M.D., FACP, FIDSA, FASTMH
Elaine Larson, Ph.D., RN
Ramanan Laxminarayan, Ph.D., M.P.H.
Armando Nahum
Paul Plummer, D.V.M., Ph.D., DACVIM, DECSRHM
David White, M.S., Ph.D.

Organizational Liaisons Present

American Association of Extension Veterinarians

Carla L. Huston, D.V.M., Ph.D., Dipl. ACVPM

American Veterinary Medical Association

Joni Scheftel, D.V.M., M.P.H., Dipl. ACVPM

Biotechnology Innovation Organization

Greg Frank, Ph.D.

Healthcare Infection Control Practices Advisory Committee

Lisa Maragakis, M.D., M.P.H.

Pediatric Infectious Diseases Society

Jason Newland, M.D., M.Ed.

Society of Infectious Disease Pharmacists

Elizabeth Dodds Ashley, Pharm.D., M.H.S., FCCP, BCPS

Wellcome Trust

Timothy Jinks, Ph.D.

Regular Government Employees Present

U.S. Department of Health and Human Services

Marge Cannon, M.D. (for Shari Ling, M.D.), Centers for Medicare and Medicaid Services (*day one*)

James Cleeman, M.D., Agency for Healthcare Research and Quality

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

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

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

Lawrence Kerr, Ph.D., Office of Pandemics and Emerging Threats, Office of Global Affairs

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

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

U.S. Department of Agriculture

Emilio Esteban, D.V.M., M.B.A., M.P.V.M., Ph.D., Food Safety and Inspection Service (*day two*)

Roxann Motroni, D.V.M., Ph.D. (for Jeffrey Silverstein, Ph.D.), Agricultural Research Service (*day two*)

Chelsey Shivley, D.V.M., Ph.D., DACAW (for Sarah Tomlinson, D.V.M.), Animal and Plant Health Inspection Service

Jeffrey Silverstein, Ph.D., Agricultural Research Service (*day one*)

U.S. Department of Defense

Paige Waterman, M.D., FACP, FIDSA, Walter Reed Army Institute of Research

U.S. Environmental Protection Agency

Jay Garland, Ph.D., Center for Environmental Solutions and Emergency Response

Designated Federal Official

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

Advisory Council Staff

Mark Kazmierczak, Ph.D., Gryphon Scientific

Haley Krem, Committee Management Officer, OASH, HHS

Sarah McClelland, M.P.H., Public Health Advisor, OASH, HHS

Taylor Simmons, M.P.H., ORISE Fellow, HHS

Glossary of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AMR	antimicrobial resistance
ASH	Assistant Secretary for Health
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics, and Policy
COVID-19	coronavirus disease 2019
DTC	direct-to-consumer
EPA	Environmental Protection Agency
FDA	U.S. Food and Drug Administration
G7	Group of 7
G20	Group of 20
GARDP	Global Antibiotic Research and Development Partnership
HHS	U.S. Department of Health and Human Services
HIC	high-income country
IPE	interprofessional education
LMICs	low- and middle-income countries
NAP CARB	National Action Plan on Combating Antibiotic-Resistant Bacteria
NARMS	National Antimicrobial Resistance Monitoring System
NIH	National Institutes of Health
OASH	Office of the Assistant Secretary for Health
OH-FICC	One Health Federal Interagency COVID-19 Coordination Group
OH-SMART™	One Health Systems Mapping and Analysis Resource Toolkit
OSTP	Office of Science and Technology Policy
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PASTEUR	Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (Act)
PODD	Participatory One Health Disease Detection (system)
R&D	research and development
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
USDA	U.S. Department of Agriculture
WHO	World Health Organization
WG	Working Group