PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

23rd Public Meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

March 23–24, 2023

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Meeting Proceedings

Welcome, Overview, and Roll Call

Martin Blaser, M.D., Council Chair; Michael D. Apley, D.V.M., Ph.D., DACVCP, Vice Chair; and Jomana F. Musmar, M.S., Ph.D., Designated Federal Officer, Advisory Council Committee Manager, Office of the Assistant Secretary for Health (OASH), U.S. Department of Health and Human Services (HHS)

Dr. Blaser opened the meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) at 9:30 a.m. ET and welcomed the participants. Dr. Musmar described the Council's establishment and charter and summarized the rules governing the Council under the Federal Advisory Committee Act and conflict-of-interest guidelines. She then called the roll. (See the appendix for the list of Council members and staff. This hybrid meeting offered the option to participate virtually or attend in person.)

Patient Story

Bradley Burnam, CEO, Turn Therapeutics

Mr. Burnam described his own painful experience with a recurrent antimicrobial-resistant infection that required multiple surgeries, which spurred him to build a laboratory in his garage with secondhand equipment and find a cure. With no formal funding or assistance, he secured approval by the U.S. Food and Drug Administration (FDA) and put the product on the market. The product proved to be exceptionally good at closing stubborn, colonized wounds and clearing up toenail fungus—but only the latter was of interest to investors. Because antimicrobial development does not yield a worthwhile return on investment, the pipeline is dry amidst an ever-worsening resistance crisis, said Mr. Burnam.

The Orphan Drug Act of 1983 stimulated investment in treating rare diseases by offering tax breaks and other incentives and could be a model for investing in antimicrobial research and development (R&D). Mr. Burnam expressed frustration that companies have a huge economic incentive to study rare diseases that are not present in the United States but not an infection like the one he suffered. The current approach to antimicrobial resistance (AMR) is rudderless. Subscription models such as the proposed Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act are an encouraging start, but incentives are needed to approach the problem from all angles. The public has little awareness of the consequences of AMR, and conversations about AMR are too focused on economics. Cutting-edge treatments for cancer and other diseases will be useless if they are compromised by AMR.

Mr. Burnam urged policymakers to pass the PASTEUR Act, fund incentives, and leverage every possible mechanism to incentivize startups, laboratories, and others to find new ways to treat infections. New tools should be explored. Mr. Burnam said his product is based on a broad-spectrum antimicrobial used in Europe for decades but unknown in the United States. AMR is a global problem, and government and industry must step up efforts to address it. The One Health approach encourages interpersonal collaboration and teaches the value of individual contributions. Current inaction is causing active harm, said Mr. Burnam. Rather than continue to

reward development of drugs for cosmetic purposes, it is time to incentivize development that really matters, he concluded.

Panel: Emerging Issues in AMR: A Global Perspective

Bracing for Superbugs: Strengthening Environmental Action in the One Health Response to AMR

Amy Pruden, Ph.D., Virginia Tech, and Fatou Ndoye, United Nations Environment Programme (UNEP)

Dr. Pruden summarized the UNEP report, which emphasizes that AMR can be framed as an environmental contaminant, but unlike other pollutants, the resistance can be transferred and amplified in the environment. The environment itself, particularly soil, plays a key role in development, transmission, and spread of AMR. Pollutants added to the environment exert pressure that triggers resistance. AMR is integral to all the factors in the triple planetary crisis of climate change, loss of biodiversity, and pollution and waste. There are benefits to addressing these crises together. For example, improving access to safe drinking water, sanitation, and hygiene (WASH) will decrease the need for antibiotics and reduce the spread of AMR.

A systems approach to AMR in the environment is paramount. The UNEP report identified three fundamental value chains in which to focus efforts to mitigate the development and spread of AMR: pharmaceutical and other manufacturing (including pesticides), agriculture and food production, and health care systems. Across all three, prevention is key. The report recommends, for example, that pharmaceutical manufacturing pay more attention to waste management, share production and use data, and better monitor its environmental impact. Agriculture and food production can reduce antimicrobial use by promoting animal and plant health and seek to mitigate environmental pollution following antimicrobial use. Health care systems should focus on proper disposal of unused medication, specialized treatment of sewage, and procurement of products from pharmaceutical makers that follow best practices.

More research is needed from coordinated surveillance efforts, and such efforts would have more impact if there were consensus on targets and measures. Expanding the National Antimicrobial Resistance Monitoring System (NARMS) to include environmental sources is a good example. The United Nations' (U.N.'s) Quadripartite (the World Health Organization [WHO], Food and Agriculture Organization of the United Nations, UNEP, and the World Organisation for Animal Health), is convening a group to discuss how to look at AMR in the environment from a global lens. Access to technology in low- and middle-income countries (LMICs) must be addressed. Dr. Pruden emphasized that there is enough evidence to act now. A robust environmental perspective within the One Health context is urgently needed to combat the spread of AMR at all scales.

Ms. Ndoye added that UNEP supports U.N. members in addressing the root causes of the triple planetary crisis. The report highlights global priorities, such as improving structures for environmental planning and regulation and integrating AMR into other action plans, such as those addressing food safety and pollution management. The U.N. is prioritizing financing, innovation, and capacity development to support environmental action, and the UNEP report makes the case for public–private collaboration. Ms. Ndoye asked the PACCARB to consider how the United States can support the U.N. Quadripartite's Strategic Framework for Collaboration on AMR.

Environmental AMR and Policy Considerations

Keiji Fukuda, M.D., M.P.H., University of Hong Kong

Dr. Fukuda summarized the progression from increased awareness of AMR in science and medicine to the U.N.'s efforts to encourage all nations to create AMR national action plans that incorporate a One Health approach. Trends in AMR and antibiotic use demonstrate that significantly more work is needed. Combating AMR must be institutionalized as a priority at the local and community levels. Many plans lack clear guidance for implementation, and nations face competing priorities at every level. More public support for addressing AMR is needed, and individuals need to know what they can do to help.

Although there are many scientific issues to address, Dr. Fukuda said two are foundational to advance policy. First, determining the proportion of AMR affecting people that is attributable to the environment is critical to allocating resources to address it. Second, more understanding is needed of the pathways that lead to AMR—across multiple sectors—so that the most effective and cost-effective strategies can be identified. For policymakers, the most important issues are whether environmental AMR represents a real concern and how to address it with limited resources. The UNEP report makes the case that the threat is real and that nations need to address AMR simultaneously with the triple planetary threats.

Dr. Fukuda emphasized that AMR is a global phenomenon, but patterns of resistance are local. Solutions must be tailored locally to accommodate local resources and capacity, including lack of political will to act and institutional cultures that do not support formal policies. Practicality and sustainability are vital for any solution. Dr. Fukuda called for immediate policies and actions to reduce contamination of the environment with antimicrobials, linked to policy agendas that are tackling climate change, pollution, land use, and WASH, among others. The UNEP report offers many options, and decision makers should select some to emphasize in new policies, he concluded.

AMR and the Environment: Implementing AMR-Programs in LMICs

Robert Skov, M.D., International Centre for Antimicrobial Resistance Solutions (ICARS)

Dr. Skov echoed the importance of raising awareness of the threat of AMR. Many interventions have been proposed, but few have been implemented and even fewer adapted for widespread use, owing to insufficient political commitments, lack of local ownership, and limited resources, among other reasons. Research that combines intervention with a sustainable implementation approach is effective. Individual countries must identify the problems, and solutions should be tailored to the context, with buy-in from all stakeholders, down to the community level. Dr. Skov pointed out that solutions should incorporate effective methods for behavioral change. Solutions must be cost-effective, especially for LMICs, and span the One Health spectrum, supporting engagement across sectors.

ICARS was founded in Denmark in 2018 to partner with governments in LMICs to develop and implement context-specific solutions for AMR. The organization works with high-level policymakers to gain political commitment and with local universities and researchers to identify and implement projects on the ground. Solutions go beyond biomedical intervention and incorporate attention to implementation, behavior change, economic impact, and cost-

effectiveness. In one project in Tanzania, where farmers use poultry manure for fertilizer in food and crop production, ICARS is partnering to break the cycle of AMR and resistant gene transmission that spreads across the food chain. Dr. Skov gave other examples of partnerships and invited other government organizations, foundations, and others to join ICARS.

Canada's AMR Task Force: An Introduction to Canada's AMR Advisory Group

Joel Denis and Donald Sheppard, M.D., Public Health Agency of Canada

Mr. Denis explained that Canada's federal AMR plan prioritizes strengthening access and stimulating innovation; preserving effectiveness through surveillance, stewardship, and infection prevention and control; focusing on key populations at risk (e.g., long-term care residents and indigenous people); and demonstrating leadership domestically and internationally. The Pan-Canadian Action Plan is a broader 5-year plan that engages provincial and territorial ministers, using a One Health approach, and promotes collaboration with industry, health professionals, and others, with a focus on the most practical and meaningful actions where partnerships can be advanced now.

Dr. Sheppard said the AMR Task Force, created in 2021, advocated for including environmental issues throughout the Pan-Canadian Action Plan. The Task Force provides specific advice on achieving the goals of the plan, such as how to develop a multisectoral, collaborative research vision that complements the global agenda; which economic incentives should be considered; and how to create a risk assessment framework for comparing different products for different contexts. The Task Force will assess options for surveillance, with more focus on the environment and attention to measuring the most meaningful pathogens.

The Task Force will also advise on how Canada can complement international efforts and contribute on a global scale. For example, it will determine which of the UNEP report's recommendations can be implemented in Canada with a reasonable probability of success. Dr. Sheppard said Canada has no antibiotic manufacturing plants but does have many fill-and-finish plants, which dump antimicrobial residues in wastewater. Canada's concentrated health care system offers an opportunity to study waste management and contamination. A genomics research initiative underway would identify important pathways for AMR transmission across One Health domains.

Mr. Denis hoped the AMR Task Force could engage with the PACCARB around key drivers of AMR transmission; high-priority gaps in research; identifying and prioritizing effective economic incentives; models for evaluation, product distribution, and procurement; and potential regional planning and cooperation.

Discussion

Dr. Blaser asked for input on how to jumpstart understanding of AMR in the environment, based on lessons learned from human and animal health. Dr. Pruden emphasized the importance of seeing the big picture and identifying critical areas of overlap. She also advocated for coordinated action that supports context-specific solutions and links AMR with other important issues, such as climate change. Dr. Fukuda said there is a clear argument to be made for immediately reducing contamination of environment with antibiotics. Dr. Skov agreed that there is plenty of information now to begin implementing much-needed intervention, although more

information is needed to understand the relative risk from different sources. Mr. Denis pointed out that, as with other broad-reaching problems, spurring people to action requires articulating the risk and consequences. Dr. Sheppard called for more research in context to better quantify the risk, such as determining what compounds are in wastewater and what impact they have.

Ramanan Laxminarayan, Ph.D., M.P.H., pointed out that the cost of AMR in environment cannot be calculated until it affects humans or animals. He asked panelists whether efforts should focus on identifying the risks in terms of how they transfer to humans and animals. He also agreed with the need to link AMR with other priorities, such as children's health, which was not achieved at the 2016 U.N. high-level meeting on AMR. Dr. Pruden said the UNEP report gives a lot of options for how to focus efforts, but they are context-specific. The next step is helping nations and states implement interventions in their settings and tie them to related issues, such as WASH. Surveillance is needed to understand what works to reduce the risk of transmission. Dr. Fukuda observed that linking priority issues eliminates the need to dwell so much on whether to take a precautionary approach or focus on cost-effectiveness. He added that while waiting for more detailed evidence, there are prudent actions that can be taken now, such as focusing on wastewater.

Paul Plummer, D.V.M., Ph.D., DACVIM, DECSRHM, asked whether One Health surveillance would be improved by investing in expanding capacity for genomics or cultures or both. Dr. Sheppard anticipated that the different approaches would converge over time, but laboratories in all domains are moving toward genomics, especially for surveillance.

Michael Craig, M.P.P., invited discussion on how to prioritize environmental interventions to achieve the highest potential impact. Dr. Pruden said there is no "silver bullet," but a good example of effective surveillance comes from metagenomic sequencing of sewage. It has shown that highly resistant genes are most common where AMR policies are lax and least common where policies are strict. Dr. Pruden added that the COVID-19 pandemic led to increased infrastructure to support sewage surveillance.

Dr. Blaser asked how the costs of addressing AMR should be shared globally. Dr. Skov pointed out that the COVID-19 pandemic showed how quickly a pathogen can spread around the whole world, so all nations have some responsibility. The most resistant genes are generated in LMICs but spread to high-income countries; therefore, a global solution is needed. Dr. Fukuda said the critical questions around AMR cannot be treated as a cost issue. He proposed focusing on the issues of concern to LMICs, such as lack of health care access.

Panel: Environmental Impacts on AMR

Climate Change Impacts on Crop Pests: AMR Implications

Jim Stack, Ph.D., Kansas State University

Dr. Stack described various ways in which climate change affects plants—for example, climate-related migration is separating plants from their pollinators—and summarized the development and evolution of new pathogens and resistance. He emphasized the need for a systems-based approach that takes into account the consequences of crop failure and chronic hunger. Evidence demonstrates that food-borne pathogens (e.g., *Salmonella*, *Shigella*, and *Escherichia coli*) are not just surface contaminants but rather are colonizing plants. Dr. Stack said the data suggest some

exchange of genetic information between plants and the antibiotics used for plant disease management. Researchers are testing whether plant pathogens can evolve into human pathogens.

Fungicide resistance is an increasing problem, notably in wheat, a very important staple food crop. In 2022, WHO noted that fungi cause more deaths globally than malaria. Fungicide resistance is of concern because the fungicides used in agriculture have the same mechanism of action as those used in human medicine. A new antifungal, olorofim, has promise for treating human infections, but manufacturers are seeking approval for agricultural use.

Dr. Stack called for coordinated policies on strategic deployment of antibiotic and antifungal chemicals across public health, agriculture, and other sectors, developed through collaborative processes internationally. Failure to manage these products rationally could limit the ability to feed and treat the diseases of the world's rapidly growing population.

Centers for Disease Control and Prevention (CDC): The Changing Environment and Antifungal Resistance in Human Infections

Nancy Chow, Ph.D., M.Sc., CDC

Few fungi survive at human body temperature, but climate change is raising the question of whether fungi will adapt rapidly enough to cause disease in humans. Dr. Chow cited the example of Valley fever, which is caused by *Coccidioides immitis*, a fungus that grows in soil as mold and can convert into a form that causes pulmonary infection in humans. Most patients with Valley fever are misdiagnosed and receive multiple courses of antibiotics, which, in itself, promotes AMR. To assist with diagnosis, CDC mapped the spread of *C. immitis*, which was mostly limited to the Southwest in the 1950s but has since emerged as far north as Washington State and is projected to move further north and east as more states experience wet winters and arid summers. The increase in extreme climate events will increase the risk for Valley fever.

Agricultural fungicides that have the same makeup and mechanism of action as human medications are posing problems—notably, driving *Aspergillus fumigatus* infections and azole resistance. Dr. Chow said CDC was not surprised that more resistant *A. fumigatus* infections have been reported in people who received constant treatment with azoles, but such infections are now occurring in people with no azole exposure. The genotypes of these azole-resistant *A. fumigatus* infections are specifically linked to fungicide use. Notably, olorofim is effective against azole-resistant aspergillosis but shares a mechanism of action with the new agricultural fungicide, ipflufenoquin, which could ultimately generate resistance. Dr. Chow said CDC, the Environmental Protection Agency (EPA), the U.S. Department of Agriculture (USDA), and others created an interagency work group to consider the threat of antifungal resistance across One Health domains globally.

Recent news highlighted the rapid spread of *Candida auris*, which emerged 15 years ago as a highly transmissible, highly resistant infection that has since become increasingly resistant to all available drugs. It is theorized that rising temperatures allowed for selection of species that can grow at human body temperatures and persist in saline environments. If the theory is correct and climate change plays a role in the evolution of resistant pathogens in the environment, more should be anticipated, Dr. Chow noted.

EPA Initiatives to Monitor Environmental AMR and Analyze Risk

Jay Garland, Ph.D., EPA

Dr. Garland highlighted interagency work to inform policymaking, such as expansion of NARMS, which represents cooperation across EPA, CDC, FDA, and USDA. Spurred by the NARMS Strategic Plan, a collaborative, interagency pilot project, the Surface Water AMR Monitoring (SWAM) study, is underway to conduct a national-scale, quantitative assessment. It will create a library of samples using standardized measures that can be used in models of AMR risk for water use. SWAM project will also quantify drivers of AMR occurrence and selection pressure and identify critical control points for mitigation. The study uses a phased design that combines the benefits of small, rapid research projects and large, broad initiatives. It incorporates cultures, targeted gene analysis, and metagenomics.

SWAM will also draw on results from the National Aquatics Resource Surveys, a cooperative effort across EPA, states, and tribes to assess the quality of the nation's waters. Using survey findings, EPA assessed the geospatial distribution of certain antibiotic-resistant genes in water and found variations across ecoregions. With additional research, it will increase the number of analytes assessed. EPA has already determined that urbanization and poor watershed integrity are significantly associated with certain antibiotic-resistant genes. It is not clear whether waterways with few antibiotic-resistant genes have not been contaminated or rather have some mechanism for preventing the evolution of antibiotic-resistant genes.

In response to a 2021 National Academy of Sciences report, EPA is funding an upcoming request for proposals to evaluate the fate and transport of AMR through municipal wastewater treatment and its relative impact on the environment. EPA is also developing quantitative microbial risk assessment models for relevant exposures. Current work focuses on waterborne exposure, and future efforts will develop models of use of antimicrobials in crops.

Climate, Environment, and Health: Belmont Forum International Funding Opportunity

Maria Uhle, Ph.D., National Science Foundation

The Belmont Forum is an international collaboration that mobilizes domestic resources to address global environmental challenges through multinational, transdisciplinary teams with representatives from at least three countries. Researchers are supported by funding agencies in their own countries. The Forum is currently calling for proposals that address the intersection of climate, environment, and health, with goals that include providing knowledge and evidence to support policies and decision making, developing systems-level approaches, and fostering a collaborative community of practice.

All of the proposals must incorporate decision science that addresses behavior and implementation. For example, research teams can expand the knowledge base about barriers to adopting the interventions proposed in national or global action plans, such as the lack of local data to support implementation. A second research theme revolves around food, environment, and biological security, with the ultimate goal of understanding systems-level strategies for mitigating and adapting to environmental changes. A third theme is climate risks to ecosystems and populations.

Dr. Uhle said the Belmont Forum offers training, workshops, and networking opportunities to help researchers and others across the One Health domains put together their teams and develop their proposals. It created a tool for comparing funding opportunities and eligibility that can help reveal opportunities for collaboration. To date, 18 federal and international organizations (including the National Science Foundation) have pledged funding to the Belmont Forum, and some organizations are focused on ensuring inclusion of LMICs. The Forum aims to leverage research investments through international cooperation.

Discussion

Dr. Apley asked whether the risk assessments around environmental transmission and resistance are distinct enough across different contexts that they can be considered independently. Dr. Garland said EPA is looking mostly at existing disease rather than emergence of new disease pathogens, although some work is focused on whether resistance is developing or increasing. Current risk models for AMR are adapted from other frameworks. Dr. Garland said it is not yet fully clear how to quantify the emergence of resistance.

Dr. Blaser asked whether reasonable substitutes exist to prevent the use of medically important drugs in non-humans. Dr. Chow said the federal interagency work group she mentioned seeks to incorporate concerns about human medical use in the evaluation process for agricultural fungicides. Dr. Apley added that there are few alternatives to antifungals for agricultural use, in part because there has been little investment in alternative products for agricultural and animal use.

Christine Ginocchio, Ph.D., MT, noted that there is a strong profit motive to use an antifungal that is effective in the agricultural setting. She asked what economic incentives could help preserve drugs for medical use, at least for a limited period. Dr. Stack responded that early antifungals attacked broad targets, but regulation drove manufactures to create products with more specific modes of action, which increases the likelihood of resistance. Only a few companies are making agricultural fungicides, and the profit margins are small. He said some sort of regulatory structure will likely be needed to limit how and where products are used. Dr. Uhle added that the Belmont Forum seeks to promote collaborative research that addresses the tradeoffs and financial incentives needed to balance human and environmental health. She pointed out that Dr. Ginocchio's question highlights the need for a systems approach across domains, because decisions in one sector can jeopardize results in another sector.

Mr. Craig said the approval of olorofim illustrates the challenges of a market with different regulatory entities that have different approaches and timeframes. Once research is published, any entity can pursue any indication. A pesticide can gain EPA approval much faster than a human drug can achieve FDA approval. Mr. Craig said investments in new drugs for humans could be undermined by the approval of a pesticide with a similar mechanism of action. These challenges are among those that the federal interagency work group must discuss.

Asked by Mr. Craig to discuss CDC's work on *A. fumigatus*, Dr. Chow said the Antimicrobial Resistance Laboratory Network (ARLN) is collecting clinical isolates and screening them for azole resistance, which represents a first step toward a One Health surveillance approach.

However, metagenomics is different for fungi than bacteria, and it is much more difficult to detect a fungus in a sample using metagenomics.

Jason Newland, M.D., M.Ed., stressed the challenge of getting the public to care about emerging infectious disease threats. Dr. Chow said there is heightened awareness of the threat of mold infection for people who are immunocompromised or taking certain drugs. With the population living longer and experiencing more exposure to health care systems, concerns are beginning to take hold. Mr. Craig added that CDC and others have called for connecting AMR with other issues to better illustrate the threat. Dr. Garland added that people want to know whether their water is safe to drink or use for recreation; EPA is trying to incorporate AMR into the risk assessments that states consider when they enact federal guidance. Dr. Uhle pointed out that earlier efforts to communicate about AMR failed to engage affected communities. Consistent, strong messaging must be informed by and tailored to the community. Gathering input from all sources, from the federal level down to local community groups, is key to creating messages that resonate and help people make informed decisions.

Elizabeth Dodds Ashley, Pharm.D., M.H.S., FCCP, BCPS, noted that raising awareness about AMR in the context of other important issues is key, and the PACCARB recognizes the need for more and better communication. She asked whether panelists can point to best practices for interventions. Mr. Craig said news media outlets report on outbreaks, which leads them to focus on a narrow threat; more must be done to call attention to the larger issue of AMR that links outbreaks together. He added that other CDC representatives have described some effective techniques, such as personalizing the issue and helping people see what they can do to protect themselves or their families.

Dr. Garland expressed that it is difficult to communicate the value of things taken for granted, such as clean water—in contrast to the obvious value of agriculture or health care systems, as highlighted by the UNEP report. He agreed with the call to link AMR with other initiatives. Currently, EPA is focusing on reducing per- and polyfluoroalkyl substances (PFAS) in water, which should reduce the risk of AMR in biosolids—demonstrating how issues and solutions overlap. Dr. Uhle added that messaging should incorporate real-world experiences, and people should be able to see what they can do in response. She called for embracing communication science to inform the messaging. Julia E. Szymczak, Ph.D., advocated for aligning AMR with social movements to address universal human concerns, such as the health of children, the elderly, and other vulnerable populations.

Drs. Apley and Stack highlighted the costs of antifungals per acre of use in agriculture and antimicrobial use in animal food production, which can quickly eat into profits. Dr. Stack added that resistance is not the only challenge posed by chemicals used in agriculture; chronic exposure is a major health issue, especially in developing countries, as is indiscriminate use of chemicals in all countries.

Public Comment

David Hyun, M.D., of the Pew Charitable Trusts urged the Council to consider creative policy solutions like the PASTEUR Act to incentivize the development of urgently needed new antibiotics. The clinical pipeline for antibiotics is stagnant, and very few drugs target the most

critical and urgent threats, in part due to a broken market for antibiotics that creates a disincentive for R&D. Most major pharmaceutical companies have shifted their focus away from antibiotic development. Today, small companies and nonprofit organizations account for nearly 90 percent of the antibiotic candidates in the current clinical pipeline. The PASTEUR Act, introduced during the previous Congress, would provide a lifeline for new and promising antibiotics approved by FDA by providing a funding commitment based on the drug's value for public health, de-linking payment from the volume of use. More importantly, the PASTEUR Act would award these contracts only to those drugs proven to address an unmet need in AMR with notable clinical impact. Dr. Hyun said this innovative approach will strongly incentivize companies and investors to recommit to R&D of new antibiotics. The legislation also provides new grant funding for antibiotic stewardship programs, which are critical to preparedness and response to public health emergencies and deserve and need sustained research support. The legislation is strongly bipartisan, supported by HHS and the White House, and endorsed by a diverse group of stakeholders. Earlier this month, the Pew Charitable Trusts joined 230 other organizations calling on Congress to pass the PASTEUR Act as part of the renewal of the Pandemic and All-Hazards Preparedness Reauthorization Act.

Kevin Outterson, J.D., LL.M., of Boston University estimated the cost to develop six innovative new antibiotics, including investments in federal research projects and acceleration programs, arriving at a total of about $12 billion per decade in global costs. Mr. Outterson further estimated that projects starting now through Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) are, on average, more than 12 years, away from FDA approval. Data going back to 1999 on global revenue from antibiotics show that over the past 20 years, generic antibiotics sales have overtaken branded products, which represents remarkably positive public health news in terms of global access. However, it has also systematically undermined the R&D engine behind the next generation of antibiotics. Revenue from branded antibiotics peaked in 2001, and the subsequent decline represents $150 billion in lost revenue from the past two decades. If spending on branded antibiotics had continued at the same level as 2001, companies would have seen an additional $150 billion of revenue, and the pipeline for antibiotics would not be dry today. Currently, about $1.2 billion is spent per year on antibiotics, and the cost of enacting the PASTEUR Act could be about $1 billion per year (although cost estimates have varied). Therefore, Mr. Outterson reasoned, $2.2 billion in revenue per year would restore the spending to 2016 levels and revive the innovation pipeline. He emphasized that companies should not be over subsidized, but going back to 2016 or 2015 revenue levels for branded antibiotics would deliver six innovative antibiotics per decade.

Steve Roach of Food Animal Concerns Trust (FACT) reiterated the urgency of the problem, noting that since this meeting started, at least 22 people have died from resistant infections in the United States. Despite committees and panels and meetings, the problem grows worse by the day. A clear example is EPA's approval of the antifungal ipflufenoquin for use on fruit trees while azole-resistant aspergillosis is killing growing numbers of patients. Mr. Roach asked whether there was any communication between EPA, FDA, and CDC during the approval process of this new antifungal. He characterized FDA's response to the antibiotic resistance crisis as sluggish and nonresponsive, with decades of delays. The Intergovernmental Task Force on AMR identified the need for data on antibiotic use in agriculture as a priority over 20 years ago, yet no system is in place to collect these data. In 2018, FDA released a plan to promote

antimicrobial stewardship in veterinary settings, but over the life of the plan, which ends this year, use climbed by 8 percent, and resistance in food system isolates has increased. The FDA plan itself was not very ambitious, yet several of the target actions were not completed on time. Most disturbing among these was a failure to issue a final guidance requiring duration limits on the 30 percent of drugs approved for use in feed that do not have them. The plan laid out many actions that FDA would take but included no indicators to measure the efficacy of the effort. One clear indicator would be that antibiotic use, as measured in sales, would go down. Mr. Roach said there should also be indicators related to antibiotic resistance in food system isolates.

FACT would like to see a new 5-year plan from FDA that includes actual expected outcomes in terms of antibiotic use and antibiotic resistance. A huge gap in the original 5-year plan was the failure to set a goal to create a system to collect data on antibiotic use. The agency has used its own failure to put a use-data collection system in place as a reason it cannot set use-reduction targets, as has been done in other sectors. FACT hopes that efforts to increase monitoring and surveillance as part of pandemic preparedness would at least include on-farm surveillance of antibiotic resistance and antibiotic use.

Louis Sokolow of the Public Interest Research Group (PIRG) reminded the group that antibiotic resistance is, first and foremost, a crisis that impacts individuals. PIRG's Coalition to Preserve Antibiotics is composed of 80 farmers and health professionals dedicated to addressing this issue. In a webinar, one of the Coalition's farmer members explained that when she sought antibiotics from her veterinarian for a lamb's broken leg, she was told to use twice the dosage she expected. This story provides more evidence that these miracle drugs no longer always perform miracles. Thanks to the Council, significant progress has been made to improve antibiotic stewardship on the human health care side by reducing inappropriate prescribing and educating Americans about when antibiotics are effective. However, more attention is needed to antibiotic use in meat production, where almost two thirds of the medically important drugs go. Mr. Sokolow proposed that the Council recommend the following to Congress: First, set a target for reducing antibiotic use in meat production, an approach that worked in the European Union, which cut antibiotic use in meat production almost in half from 2011 to 2021. Second, gather existing farm-level data, like veterinary feed directives from feed mills, to track progress towards the target and hold government agencies accountable for achieving it. In closing, Mr. Sokolow urged that more attention be paid to antibiotic use in meat production to keep these drugs effective going forward.

Minmin Yen, Ph.D., of PhagePro said the current linear product development model for antimicrobials is not working. It requires high investment in R&D and clinical trials; products are only modestly priced after approval; and their effectiveness ultimately is decreased by resistance. The current model disincentivizes investment and innovation and subsequently decreases access and international collaboration, especially in LMICs. Dr. Yen proposed an iterative product development model in which the product is updated on the basis of evidence on resistance from surveillance data, as has been done for influenza and COVID vaccines. This approach can be achieved by strengthening capacity for environmental surveillance not only in the United States but also supporting and coordinating efforts across the world to identify resistance patterns. Ultimately, accelerated regulatory approvals of modified products are needed so that the solutions can reach patients quickly, perhaps even proactively. This effort should not

be centralized in one country, but the United States could lead a global, coordinated effort to harmonize international regulation requirements, because the problem affects everyone. AMR is a nuanced and complex crisis that will not be solved by one actor or one solution. Changing the model for developing and updating new antimicrobials will accelerate their development and sustained effectiveness. It is a critical strategy that will help prioritize access, Dr. Yen concluded.

Ari Frenkel, M.D., of Arkstone Medical Solutions said that addressing the gap in antimicrobial stewardship is paramount. He reported seeing firsthand the overutilization of antimicrobials in rural America. Statistics are alarming; for example, most U.S. counties do not have access to infectious disease specialists, and only a fraction of health care providers are infectious disease specialists. Therefore, the use of technology to bring evidence-based medicine into practice is ever more important. During his time as a solo infectious disease physician in private practice, Dr. Frenkel was the only infectious disease doctor in two large counties, serving approximately 150,000 people spread across three hospitals. Throughout the United States, access to essential expertise is lacking, and community needs far outweigh the ability to deliver care. Just as society has embraced technology for communication, transportation, and information, technology can be used fight AMR. However, there is considerable pushback to technology by health care providers and systems. Dr. Frenkel said he is committed to improving the lives of others and reducing suffering. He encouraged everyone to think of technology as a tool to enhance the ability to treat infections and embrace it as a mechanism of extending care and expertise with boundless possibilities.

Jester Jersey noted that he had worked with Kiwanis and UNICEF on the Eliminate Project, a joint global campaign from 2010 to 2020 to vaccinate women of childbearing age against *Clostridium tetani*, the bacteria that causes tetanus. He highlighted the low vaccine rates for influenza and COVID-19, as well as a lag in routine vaccine rates in general, pointing to the recent resurgence of polio and measles. Even if a vaccine for respiratory syncytial virus became available, current vaccine trends suggest it may not be enough to prevent the spread of disease or save lives. Whether a pathogen has viral or bacterial origins, more investment is needed in trusted messaging to increase vaccine rates. As the COVID public health emergency ends in May, continued funding for immunization programs through the Public Health Service Act, Section 317, is also essential to address future health concerns. To get vaccines to people who need them the most, the federal government should work with local community-based service organizations, Mr. Jersey said. In 2021, U.S. Surgeon General Vivek Murthy said trusted messengers are the key to boosting COVID vaccine rates. In January of this year, Jagan Chapagain, secretary general of the International Federation of Red Cross and Red Crescent Societies, mentioned the important role community-based organizations have in pandemic response and preparedness. Mr. Jersey recommended that the PACCARB, CDC, other HHS health advisory committees, and the Biden administration reach out to community-based service organizations to collaborate on future vaccine campaign efforts. Together, Mr. Jersey said, we can encourage those who have missed routine vaccines to catch up, increase vaccination rates, and protect Americans of all ages.

Public Comment: Innovation Spotlight

The Innovation Spotlight is an opportunity for public comment open to all individuals 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.

Nancy Tawil, Ph.D., of Phagelux explained that the company's product portfolio includes bacteriophages and lysins. It has two human health therapeutics currently being assessed by FDA and a clinical trial underway, developed with the input of the Antibacterial Resistance Leadership Group. Bacteriophages are an abundant, natural predator of bacteria, but they lack environmental stability. Phagelux encapsulates bacteriophages in a biodegradable matrix that makes them amenable for adjunct therapy and provides other benefits, such as prolonged release at the site of action and faster wound healing. The company's bacteriophage capsule, Bactelide, treats pressure ulcers, a hospital-acquired infection that affects millions of people in the United States and is on the rise. The cost of treating these chronic wounds is high and has been exacerbated by the COVID pandemic, and it is not completely covered by Medicare. Phase I and II clinical trials will soon recruit patients to evaluate the safety and potential efficacy of Bactelide. To ensure that Bactelide can be used in LMICs, Phagelux kept the cost of goods for the product very low. Dr. Tawil anticipated that by treating pressure injuries with Bactelide, hospitals will save about $10,000 per patient. Phagelux is also harnessing the power of bioinformatics for high-throughput screening of target organisms and engineering Gram-negative and Gram-positive endolysins. The most advanced endolysins developed to date target Acinetobacter baumannii and Staphylococcus aureus. Dr. Tamil noted that large pharmaceutical companies are pulling out or winding down their anti-infective programs, so biotechnology companies like Phagelux are turning to governments for financing, infrastructure, and regulatory support to bring new antimicrobials to the market.

Ava Alkon of Doctors Without Borders (or Médecins Sans Frontières [MSF]) said many of the primary drivers of AMR are especially present in low-resource settings. MSF teams have directly witnessed alarming rates of drug-resistant infections affecting war-wounded patients in conflict zones, newborns, and malnourished children, to name just a few examples. As a result, MSF has made addressing drug resistance a priority. Its interdisciplinary approach includes infection prevention and control, antibiotic stewardship, increasing access to microbiology and diagnosis, and building capacity among health care staff. MSF has steadily increased its own diagnostic capacity in recent years and has developed some innovative strategies and tools with potential to advance diagnosis in resource-constrained settings. One such innovation is the free, not-for-profit Antibiogo smartphone application. Access to accurate diagnosis is key for tackling AMR. Interpretation of test results usually requires clinical microbiologists, who are frequently not available in LMICs. Antibiogo works offline and supports laboratory technicians interpret antimicrobial susceptibility tests, which help determine which antibiotics will be effective for treating a given patient—even in the absence of microbiologists. Today, the app is certified by the European Union as a medical device and is used routinely in five MSF laboratories. MSF is collaborating with regional partners on a phased scale-up of access, with a 2024 goal of making it available for any LMIC for use as a diagnostic testing surveillance and training tool.
MSF believes that global collaboration to address drug resistance is crucial to safeguard both global and U.S. domestic health. Ms. Alkon expressed the hope that MSF can contribute its experience to inform U.S. global policy and assist U.S. stakeholders interested in addressing AMR around the world.

Ari Frenkel, M.D., of Arkstone Medical Solutions pointed out that antimicrobial stewardship programs are limited to academic centers and well-resourced facilities, but according to CDC, 90 percent of antibiotic prescriptions occur in the outpatient setting, where antimicrobial stewardship is lacking. Skilled nursing facilities are required to have stewardship programs, but they account for less than half a percent of the total population, making little impact on antibiotic usage. Arkstone's decision-making software employs technology (OneChoice) that uses electronically transmitted laboratory results, artificial intelligence, and an extensive database of AMR data to formulate a patient-specific plan for infection treatment that provides targeted recommendations, factoring in the patient's age, allergies, pregnancy status, diagnosis, and the sample source, as well as resistance and the organism detected. In practice, limited knowledge or experience can lead clinicians to choose the wrong drug, the wrong dose, or the wrong duration or even to treat microbes that are colonizers or possible contaminants. With Arkstone, physicians order the laboratory results, as usual, and Arkstone generates the OneChoice report automatically, so the physician receives the recommendation with the laboratory result instantaneously, with a clear treatment regimen that includes the optimal drug, dosage, and duration to treat the infection with the least chance of adverse reaction.

Dr. Frenkel said that OneChoice recognizes commonly pathogenic microbes based on the sample source and often recommends no treatment at all when microbes are likely colonizers, contaminants, or self-limiting viruses. The proprietary ArkScore scoring system breaks down hard-to-understand concepts around resistance, allowing doctors to easily compare patients or understand the differences between antimicrobials. Physicians can add additional factors, such as a patient's drug allergies, or check for drug interactions. The physician can even access the references and data that support the recommendation. All of this information allows physicians to make well-informed decisions that benefit their patients and reduce the overuse of antibiotics. Arkstone software is currently being used to reduce antibiotic use in the United States. At present, nearly a third of OneChoice reports recommend no treatment; thus, despite patient demand, doctors have receive clear, evidence-based guidance that they can share with their patients to help avoid prescribing unnecessary antibiotics. Arkstone software also acts as a powerful surveillance tool. By integrating with dozens of laboratories across the country, it can detect upticks in infection and resistance trends. This information is already being used to help individual laboratories track trends within their patient base. With further development and the right partners, these data can be used to benefit the entire population. Arkstone has proven that outpatient antimicrobial stewardship is possible. Dr. Frenkel called for more collaboration to change the face of outpatient prescribing together.

Minmin Yen, Ph.D., of PhagePro said that without a global, coordinated effort to combat AMR, organisms have more chances to evolve and become stronger. The current system must strengthen and leverage on-the-ground collaborations to build a resilient, coordinated, and cohesive ecosystem that can address AMR proactively. One main challenge is the negative return on investment: on average, it takes at least 9 years and about a billion dollars to develop an antimicrobial, and companies then face bankruptcy because sales are not enough to sustain them. PhagePro advocates for prioritizing access and finding ways to accelerate development, thereby decreasing upfront costs. The company develops phages or viruses that specifically target and kill bacteria, particularly in resource-limited settings. To prioritize access, it is formulating

phages in a solid dose that does not require refrigeration, is stable in hot and humid environments, and is easily administered and distributed. Despite all of the innovation and technology, resistance pops up quickly, and a systems-level approach is needed for any antimicrobial to be sustainable. Surveillance must be conducted, and developers must be ready to respond rapidly to surveillance data. Phages evolve with the bacteria. That evolution can be harnessed to accelerate development timelines when resistance occurs. Accelerating development can decrease overall costs to fight resistance and keep the product sustainable and effective for patients.

Stakeholder and partner engagement is needed across the spectrum, said Dr. Yen, and surveillance goes well beyond traditional health departments. As an example, PhagePro's first product disrupts transmission of cholera, an acute diarrheal disease that is currently surging around the world. Cholera is antibiotic resistant and lives in the environment with many other critical AMR pathogens. PhagePro partnered with the International Center for Diarrheal Disease in Dhaka, Bangladesh, to conduct surveillance on resistance so that it could update its phage cocktail. The partnership is building capacity, adding resources and knowledge, and consolidating efforts across borders to keep up with these microbes. PhagePro believes that iterative product development is critical for all antimicrobials and should be informed by on-the-ground partnerships with stakeholders and patient communities to ensure uptake of the innovation. Dr. Yen said developers need help from the government to get products to the people. Regulatory review should be accelerated in a way that maintains safety but reduces timelines so that developers can respond to resistance in a timely way. If manufacturers can rapidly update influenza and COVID vaccines, there must be sustainable ways to do the same for the many diseases affected by AMR. Doing so will give LMICs easier access to innovative products. The United States must lead on the global level to prioritize AMR on all of the different government agendas and coordinate strategies across borders.

Council Perspectives

Dr. Blaser invited Council members to offer observations and takeaways from the day's discussion and to suggest topics for the PACCARB to pursue. Several participants appreciated the inclusion of a wide range of perspectives in presentations and Council deliberations. The feedback is summarized here according to broad categories of interest.

Integration of AMR Into Other Global Agendas

- AMR overlaps with a wide range of concerns, including access to clean water, food security, and access to preventive health measures such as vaccines. Relating AMR to other global issues is an important concept for messaging and policymaking.
- AMR should be institutionalized as a priority in care systems and linked with other agendas.
- The link between AMR and other issues of concern should be clarified through communication and messaging that raises public awareness.
- The public needs more and better education on complex issues, such as what constitutes "safe drinking water" and the risks that even "clean" water can pose to certain populations at high risk.

Improving Communication About AMR

- The PACCARB must highlight the delicate balance required to keep antibiotics safe and effective, emphasizing the real cost of overuse.
- To overcome barriers to change, often attributed to a lack of political will or lack of ownership, the Council should consider how to frame AMR and potential solutions in a way that acknowledges complex and competing priorities. At the same time, research strategies and public engagement efforts must acknowledge that AMR patterns are local.
- Behavior change remains a persistent concern, but across domains, the drivers of decision making are more similar than different.
- Communication should reach out to all stakeholders, including, for example, veterinarians and farmers.
- Social media toolkits should be created to spread the word about AMR.
- The environmental component of One Health often gets overlooked. The PACCARB and its partners can better educate the public and other stakeholders about environmental programs and concerns around AMR. The PACCARB and others should keep pushing to break down silos so that information and solutions are shared.
- Communication is needed to build trust, which is the only way for guidance to be effective.

Putting Policies Into Action

- The PACCARB should articulate a preventive strategy to control AMR.
- The PACCARB should determine how to clarify the options for implementing its recommendations without oversimplifying the problem.
- Messaging should emphasize the impact of AMR on treating infectious diseases and how that affects people differently in various circumstances. Recommendations should not overgeneralize, because that leads to massive gaps in implementation.
- The PACCARB should consider the question of how much more evidence is needed before it is appropriate to act.
- More exploration is needed on alternatives to antimicrobials for use in agriculture, aquaculture, and animal health, which can help maintain food security and protect human health.
- All Council members and stakeholders should commit to taking concrete steps to educate the public about AMR, such as writing an opinion piece, responding to a media request, or developing a toolkit for patients.
- Implementation strategies should be developed to accompany existing guidelines.
- Clinicians should be armed and motivated to educate patients and others about prudent use of antimicrobials.
- Veterinary medicine representatives should continue to be included in AMR discussions.
- Efforts should be made to support drug development across domains by sharing information, which could lead to novel approaches and lower costs of development.
- The PACCARB's proposed report on pandemic preparedness, if approved, should be disseminated with a social media toolkit so that stakeholders can share the recommendations with a broad audience.
- Patient and community stories bring important perspectives to the Council's work; the Council can help amplify those perspectives and broaden the constituency around AMR.
- Initiatives should capitalize on the momentum generated by disasters and emergencies.

- Better risk assessment and other tools are needed to identify priorities.
- Although many solutions to AMR have been proposed, few have been implemented. The PACCARB can do more, in part by encouraging risk assessment and prioritization led from the local level.
- The PACCARB's recommendations should help veterinarians and health care practitioners make better decisions on when to use antimicrobials that take into account the potential harms to patients, animals, and the environment.
- Unified, standardized approaches to surveillance can help bring more data together.
- Antibiotic stewardship and infection prevention and control should be key components in any approach to AMR. Beyond judicious use of products, an effective system to prevent common diseases can help avoid use of antimicrobials.

Future Topics for the PACCARB

- The PACCARB has tackled the hard science around AMR and the big issues involving communication. Next, it must address workforce development and support, with urgent attention to building the workforce pipeline. The workforce must be expanded; front line workers are needed in every field.
- The PACCARB should reach out to stakeholders to determine future directions.
- The PACCARB has been focused on domestic concerns; more information is needed about what other countries are doing.
- More conversation is needed on alternatives to antimicrobials, such as vaccination, decolonization, and alternative products.
- The PACCARB should look more closely at the use of antifungals and make recommendations about preventing resistance. There are some straightforward ways to address antifungal resistance in health care settings.
- For the future, the PACCARB should look at the capacity to integrate data into a multilayered system to inform about the disease burden from different angles (e.g., combining wastewater surveillance with whole genome sequencing and other water surveillance).
- Equity must be at the forefront of all issues. The Vaccines for Children program is effective, but there is no counterpart for adults.
- The fragile pipeline of new antimicrobials is a burning issue that requires investment and incentives, or all progress will be undermined.
- The PACCARB should look closely at mechanisms to prevent the simultaneous use of drugs in human, veterinary, and agricultural settings.
- The PACCARB and its partners should look for small steps that can have an outsized impact, such as President Obama's directive requiring all federal cafeterias to include an antibiotic-free meat option, which led many meat processors to stop using antibiotics.
- The PACCARB should keep current on local applications of research and policy (by veterinarians, physicians, farmers, etc.)

Other Important Points

- The distinction between action plans and implementation guidance is worth noting, as is the need to measure progress.

- Presentations highlighted the importance of considering the environment in any discussion about AMR, but they also revealed the complexity, which can be an excuse for inaction.
- More discussion is needed about implementation science to ensure that recommendations and policies that work are implemented.
- The PACCARB should take a systems approach to tackling AMR, because there are consequences to every action across domains.
- AMR is part of the bigger picture of climate change, and changes in microecology, including the human, animal, and plant microbiomes.

Recess for the Day

The meeting recessed at 4:43 p.m.

Day 2

Welcome and Roll Call

Martin Blaser, M.D., Council Chair; Michael D. Apley, D.V.M., Ph.D., DACVCP, Vice Chair; and Jomana F. Musmar, M.S., Ph. D., Designated Federal Official, Advisory Council Committee Manager, OASH, HHS

Drs. Blaser and Apley welcomed the participants at 9 a.m. Dr. Musmar reiterated the rules governing the Council under the Federal Advisory Committee Act and conflict-of-interest guidelines. She then called the roll.

Community Story: Tracing AMR in Eye Drops

Maroya Spalding Walters, Ph.D., Sc.M., CDR, U.S. Public Health Service (USPHS)

Dr. Walters said that carbapenemase-producing *Pseudomonas aeruginosa* is extremely rare in the United States but more common in other parts of the world. It is associated with high mortality. Detecting the pathogen is challenging and few hospitals have capacity to test for it in their laboratories. Since 2016, CDC's ARLN has expanded testing for these organisms in public health laboratories, and in 2021, thanks to funding from the American Rescue Plan Act, the network dramatically increased the number of public health laboratories' that could screen for colonization and conduct whole genome sequencing.

In the summer of 2022, clusters of carbapenemase-producing *P. aeruginosa* cases were identified in three states—one in an ophthalmology clinic and two in long-term-care acute hospitals—as well as some isolated infections. The strains were unique and susceptible only to cefiderocol, a recently approved antibiotic. Whole genome sequencing suggested a common source, leading CDC to suspect a contaminated product. Its investigation employed prospective and retrospective case evaluation, outreach to ophthalmology professional societies, a call for submission of samples to the ARLN for whole genome sequencing, and chart reviews and patient interviews conducted by local health departments. Potential products responsible were identified and cultured. Public health response programs also screened for exposure and implemented infection control protocols at high-risk facilities to prevent secondary transmission.

As of mid-March, 2023, CDC had identified 68 patients in 16 states with the outbreak strain, from a variety of settings and across all age ranges. More than one third of specimens came from sources other than the eye, including urine, sputum, blood, and tissue. Most patients had at least one serious underlying condition, and most of those with eye infections had an underlying eye disease. Of those with a clinical culture demonstrating infection, about 60 percent had a new hospitalization. Three patients died, eight suffered vision loss, and four had an eyeball removed.

Through a case–control study at a long-term care facility, investigators determined that those infected were more likely than controls to have been exposed to artificial tears—most likely EzriCare artificial tears. CDC found the specific bacteria in open bottles of EzriCare from five lots in two states; FDA is currently testing unopened bottles to distinguish intrinsic from extrinsic contamination. The link between the contaminated product and infections was confirmed with whole genome sequencing. CDC put out its findings to the public and clinicians. Shortly thereafter, EzriCare artificial tears were no longer available through Amazon; the maker, Global Pharma, issued a voluntary recall; and FDA posted an alert.

Dr. Walters noted that there is always a lag between the first infections and confirmation, because it takes time to collect and sequence specimens. Since the alerts and the manufacturer's recall, some additional cases have been reported. This is the first time in the United States that an outbreak of carbapenemase-producing organisms has been linked to a contaminated product. Identification of this novel source can be directly attributed to the national, coordinated effort between public health laboratories and ARM response programs.

Dr. Walters concluded that controlling pathogens traditionally associated with health care is going to be further challenged by exposures and reservoirs outside of health care. This outbreak showcased how whole genome sequencing of resistant pathogens can be a critical tool for addressing AMR threats. To build on the lessons learned from this outbreak, efforts should focus on improving surveillance for these uncommon carbapenemase producers and decreasing timelines for whole genome sequencing. To use laboratory information effectively to prevent transmission, pandemic investments in public health infrastructure control must be sustained.

Discussion

Dr. Walters noted that not everyone with carbapenemase-producing *P. aeruginosa* used the eyedrops; some did not use the eyedrops but were clearly linked to someone who did. The situation highlights the many potential routes to infection that can be overlooked. Helen W. Boucher, M.D., FIDSA, FACP, observed that having only one drug to treat the infection illustrates the potential calamity of a weak pipeline. Dr. Newland pointed out that small hospitals probably do not have cefiderocol on hand.

Mr. Craig noted that CDC is ideally suited to track down the origins of diseases. The people who identified carbapenemase-producing *P. aeruginosa* were the same ones who identified COVID-19 in long-term-care facilities and other settings, thanks to supplemental resources provided via the American Rescue Plan Act. This situation clearly demonstrates the need to sustain financial and human resources to protect public health. Mr. Craig warned that the increased capacity to conduct whole genome sequencing will disappear without sustained funding. Before this outbreak, carbapenemase-producing *P. aeruginosa* was very rare in the United States—but it got

packaged, shipped globally, and distributed widely—and more cases are out there, Mr. Craig said. Moreover, secondary transmission will continue for years by people who were colonized but not acutely infected, posing a major concern. The strain could even become endemic in the United States. Mr. Craig added that this incident illustrates how decolonizing agents would be a game-changer for stopping secondary transmission.

Dr. Walters said CDC has not seen reports of cases outside the United States, and it appears that the contaminated product was only sold in the United States. She said there are a lot of carbapenemase-producing organisms in the environment in India, where the product was made, so CDC hypothesized that the initial outbreak is probably related to an environmental source in the manufacturing plant. How the product became contaminated is not yet known.

Dr. Walters pointed out that the pathogen stood out because it is so rare. To look more broadly at transmission that is not isolated to a single site, in addition to building capacity for genomic sequencing, systems need more capacity to better identify outbreaks on a regular basis. With so many reports of resistance emerging every day, the picture can seem bleak. However, more steps can be taken to address potential pathogens before an outbreak occurs. CDC has used some of its supplemental funding to promote prevention strategies, such as infection control and screening at facilities with a lot of high-risk patients.

AMR and Pandemic Preparedness Working Group Report

Ramanan Laxminarayan, Ph.D., M.P.H., and Joni Scheftel, D.V.M., M.P.H., DACVPM, Co-Chairs, PACCARB AMR and Pandemic Preparedness Working Group

Dr. Scheftel explained that HHS Secretary Xavier Becerra tasked the PACCARB with providing recommendations on how to strengthen defense against antimicrobial-resistant pathogens by revising current pandemic preparedness and response plans and policies using a One Health approach. In response, in May 2022, the Council created the AMR and Pandemic Preparedness Working Group, which met frequently to hear from key subject matter experts.

The working group created a mock pandemic scenario to serve as the basis for a public meeting in September 2022 that highlighted potential gaps in the current pandemic preparedness policies and response. Among the major themes that emerged was the critical need to invest in steady-state operations to ensure antimicrobial stewardship systems remain functional during an emergency. The meeting also highlighted the need to build in flexibility, particularly in regulations to allow for rapid deployment of resources, and to ensure a One Health approach that balances the health concerns of people, animals, and the environment. In addition, the meeting emphasized the importance of health communication, especially during a crisis, and the impact of health inequity during a public health emergency.

In January 2023, the PACCARB devoted its public meeting to further exploring communication, health equity, and disparities in relation to a public health emergency. It brought forth several issues of concern that persist even outside the context of an emergency—specifically, the lack of trust in public health, exacerbated by lack of access to care, and poor transparency in communication. The meeting also highlighted the insufficient attention to the needs of vulnerable and marginalized communities in pandemic preparedness planning. The findings from both public meetings substantially informed the working group's recommendations.

Dr. Laxminarayan pointed out that the working group considered a number of hypothetical scenarios in which bacterial infection occurred secondary to a viral pandemic, but it also recognized the potential for a bacterial pandemic as well as secondary fungal infections. In response to the Secretary's task, the working group made recommendations to incorporate AMR into two existing policies, the American Pandemic Preparedness Plan and the National Biodefense Strategy.

Most of the recommendations fall into four categories: infection prevention and control and antimicrobial stewardship, workforce expansion, data sharing and security, and product innovation. Within each category, recommendations are divided according to whether action and investments are needed to promote steady-state operations or would be mobilized during a public health emergency. Equity, trust, and communication sit at the heart of all the recommendations. Even when not explicitly stated, all future pandemic preparedness must include the input of marginalized and vulnerable populations. Dr. Laxminarayan emphasized that these populations were disproportionately affected by the COVID-19 pandemic, which is unacceptable. Addressing health disparities starts with inclusion, and every recommendation reiterates that concept. Building equity, trust, and communication across all populations must begin right away, rather than waiting for the next pandemic.

Dr. Laxminarayan summarized the 14 recommendations put forth in the working group's report. The first two recommendations emphasize health equity and inclusion of marginalized and vulnerable populations in all efforts. The recommendations on infection prevention and control and antimicrobial stewardship address the need for guidance during steady-state and emergency operations. The workforce expansion recommendations recognize the lack of human and financial resources to face another pandemic, so innovative and flexible incentives are needed to build the workforce. Bolstering surveillance and data systems is a crucial part of detecting the next emerging public health threat and tracking its spread, so that resources can be better targeted during an emergency. Existing systems must be improved to handle a surge while continuing to support steady-state efforts to address AMR. The product development recommendations reiterate the call for incentives to develop new therapeutics, vaccines, and diagnostics.

Discussion

Dr. Musmar thanked the co-chairs of the working group for their leadership. She acknowledged the outstanding work of the writers of the report, Sarah McClelland, M.P.H., OASH public health advisor, Mark Kazmierczak, Ph.D., of Gryphon Scientific, as well as the staff who make up the PACCARB team.

Dr. Blaser appreciated the focus on trust and communication, which are central to pandemic preparedness and response, as demonstrated by the COVID-19 pandemic. Timothy Jinks, Ph.D., applauded the working group for centering equity and trust in its recommendations. However, he said the actions proposed could have been more concrete and that the report should have asked for more accountability from the U.S. government for ensuring that all interventions are equitable and trustworthy. He suggested looking for ways to link recommendations to ongoing efforts to eliminate poverty and racism.

Dr. Jinks also suggested rewording recommendation 12 to state clearly that AMR should be identified as a material threat, a determination that triggers specific U.S. government actions. The suggestion had already been incorporated into the draft recommendations before this meeting and was accepted. Dr. Musmar said the point would also be highlighted in the executive summary of the report.

Dr. Boucher pointed out that the field of infectious disease is facing a severe workforce crisis, and fewer people are entering the field. She suggested that the workforce recommendations be strengthened by specifying the types of professionals most needed. Following brief discussion, the Council agreed to revise recommendation 5 to read, "Bolster the workforce by expanding recruitment and support of public health professionals, infection preventionists, and infectious diseases specialists and engaging a broader set of providers in human and animal health care."

> **Vote:** The PACCARB members in attendance voted unanimously to approve the working group's report and recommendations, *Preparing for the Next Pandemic in the Era of Antimicrobial Resistance*.

Remarks From the Deputy Secretary

Andrea Palm, Deputy Secretary, HHS

Ms. Palm thanked the PACCARB for being a critical advisory body to HHS since the Council was created in 2015. She cited the millions of deaths attributable to drug-resistant bacteria in the United States and globally, noting that the COVID-19 pandemic added another layer of complexity to the issues around combating AMR. The department is immensely grateful for the PACCARB's work, particularly for being so responsive to the Secretary's request to make recommendations in the context of current pandemic preparedness policies.

Ms. Palm said the report just approved by the Council provides thoughtful and actionable recommendations that HHS will consider as it moves forward. It also highlights equity, a priority of the current administration that HHS seeks to embed in all of its work. In addition, the report emphasizes the One Health approach and recognizes that climate change has consequences for AMR, creating new public health challenges while it exacerbates existing ones. Ms. Palm appreciated the importance of addressing these interconnected issues. Although much of the response to climate change falls to other departments, HHS has a critical role to play by bringing expertise to bear on AMR and other issues exacerbated by climate change.

On behalf of President Biden, Secretary Becerra, and the rest of the administration, Ms. Palm thanked the retiring members of the Council for their contributions, which will influence the work going forward. She added that all of the PACCARB's recommendations have been very helpful in anticipating and meeting the public health challenges ahead.

PACCARB Member Retirements and Closing Remarks From HHS Leadership

Rachel L. Levine, M.D., ADM, USPHS, Assistant Secretary for Health, HHS, and Dawn O'Connell, J.D., Assistant Secretary for Strategic Response and Preparedness, Administration for Strategic Response and Preparedness (ASPR), HHS

ADM Levine recognized the continued commitment to stopping the spread of AMR, acknowledging the valuable work of the Council over the past 7 years. With the public health emergency declaration for the COVID-19 pandemic ending in May, there is an opportunity to evaluate past efforts and reflect on lessons learned. The pandemic highlighted many pre-existing societal issues, such as health inequity and disparities. The Biden administration and HHS are focused on achieving health equity in this country, and it is heartening to hear those goals upheld in the Council's work, said ADM Levine.

Underserved groups continue to experience unique challenges and complications when combating AMR. ADM Levine said it is critical to maintain transparency during the often difficult conversations needed to make progress on this complex health threat, and she encouraged the Council to keep pushing the envelope on the issues of equity, trust, and communication.

ADM Levine thanked the Council members for their diligent and dedicated work to make the nation more prepared for the next pandemic, expressing the utmost gratitude and commendation on behalf of Secretary Becerra and herself. She particularly noted the leadership of the chair, Dr. Blaser, and vice chair, Dr. Apley, in driving the Council to explore and champion innovative ways to combat AMR. ADM Levine welcomed Dr. Plummer as the next Council chair. She hoped the department's continued support would empower the PACCARB to continue asking hard questions and pushing boundaries to tackle the complicated problem of AMR.

Ms. O'Connell reminded the group that she helped launch the PACCARB during the Obama administration alongside Dr. Musmar and others. Since the enactment of the Pandemic and All-Hazards Preparedness Act in 2006, ASPR has led the nation's medical and public health preparedness for, response to, and recovery from disasters and other public health emergencies. Recent reorganization within HHS has strengthened ASPR's capabilities to mobilize in the event of emergencies like the COVID-19 pandemic. ASPR is dedicated to bolstering preparedness for a number of deadly threats, including AMR.

ASPR recognizes that the speed of the so-called silent pandemic of AMR creates unique challenges and magnifies existing gaps in the U.S. health care system. Through the Biomedical Advanced Research and Development Authority (BARDA), ASPR encourages public–private partnerships to maximize the R&D of antimicrobial products through programs such as CARB-X and Project BioShield. Antibiotics are a vital component of the nation's response capabilities, making this Council's insights more relevant than ever. Ms. O'Connell looked forward to reviewing the report just approved, adding that she is grateful and proud to have been part of this effort from the start. She acknowledged each of the 16 retiring Council members by name, and added special acknowledgement to Dr. Blaser, who has chaired the Council since it was established. The entire HHS community is overwhelmingly appreciative of the PACCARB's commitment and engagement, and its guidance and esteemed knowledge have transformed how this nation approaches AMR-related issues. Ms. O'Connell congratulated Dr. Plummer and looked forward to his leadership.

Final Comments and Adjournment

Martin Blaser, M.D., Council Chair, and Michael D. Apley, D.V.M., Ph.D., DACVCP, Vice Chair

Dr. Apley pointed out that he and other retiring members will continue to promote the Council's work and inform the Council of advances and challenges in their respective fields. He added that his participation on the Council over the past 7 years changed his perception of the challenges of AMR and deepened his resolve to address antimicrobial stewardship in veterinary medicine.

Dr. Blaser appreciated the Council's many accomplishments. He noted that all of the PACCARB reports have been approved unanimously, attesting to the ability to achieve consensus despite differences. Dr. Blaser thanked the Council members, staff, and HHS for their contributions. He adjourned the meeting at 10:54 a.m.

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

March 23–24, 2023

PACCARB Voting Members Present
Martin J. Blaser, M.D., Chair
Michael D. Apley, D.V.M., Ph.D., DACVCP
Stephanie Black, M.D., M.Sc.
Helen W. Boucher, M.D., FIDSA, FACP
Virginia R. Fajt, D.V.M., Ph.D., DACVCP
Paula J. Fedorka Cray, Ph.D. (*day 2 only*)
Christine Ginocchio, Ph.D., MT
Locke Karriker, D.V.M., M.S., DACVPM
Elaine Larson, Ph.D., RN
Ramanan Laxminarayan, Ph.D., M.P.H.
Payal K. Patel, M.D., M.P.H.
Paul Plummer, D.V.M., Ph.D., DACVIM, DECSRHM
Julia E. Szymczak, Ph.D.
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
Emily Wheeler

Minor Crop Farmers Alliance
James Adaskaveg, Ph.D. (*day 1 only*)

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

Michael Craig, M.P.P., Antibiotic Resistance Coordination and Strategy Unit, Centers for Disease Control and Prevention
Dennis M. Dixon, Ph.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health (*day 1 only*)
Jose Fernandez, Ph.D., Office of Pandemics and Emerging Threats, Office of Global Affairs (*day 2 only*)
William Flynn, D.V.M., Center for Veterinary Medicine, Food and Drug Administration (*day 1 only*)
Christopher Houchens, Ph.D., Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response
Melissa Miller, M.D., M.S., FCCM, Agency for Healthcare Research and Quality
Kyung Moon, Ph.D., (for Dennis M. Dixon, Ph.D.), National Institute of Allergy and Infectious Diseases, National Institutes of Health (*day 2 only*)
Ribhi Shawar, Ph.D. (for William Flynn, D.V.M.), Center for Veterinary Medicine, Food and Drug Administration (*day 2 only*)

U.S. Department of Agriculture
Roxann Motroni, D.V.M., Ph.D. (for Jeffrey Silverstein, Ph.D.), Agricultural Research Service *(day 2 only)*
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 1 only*)
Kis Robertson-Hale, D.V.M., M.P.H. RADM, Food Safety and Inspection Service *(day 1 only)*

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

U.S. Environmental Protection Agency, U.S. Department of the Interior
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
Chloe Loving, M.P.H., CHES, CPH, ORISE Fellow, HHS
Sarah McClelland, M.P.H., Public Health Advisor, OASH, HHS
Jennifer Adona, Rose Li Associates

Glossary of Abbreviations

AMR	antimicrobial resistance
ARLN	Antibiotic Resistance Laboratory Network (CDC)
ASPR	Administration for Strategic Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
EPA	Environmental Protection Agency
FACT	Food Animal Concerns Trust
FDA	U.S. Food and Drug Administration
HHS	U.S. Department of Health and Human Services
ICARS	International Centre for Antimicrobial Resistance Solutions
LMICs	low- and middle-income countries
MSF	Médecins Sans Frontières (Doctors Without Borders)
NARMS	National Antimicrobial Resistance Monitoring System
OASH	Office of the Assistant Secretary for Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PASTEUR	Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (Act)
PIRG	Public Interest Research Group
R&D	research and development
U.N.	United Nations
UNEP	United Nations Environment Programme
USDA	U.S. Department of Agriculture
USPHS	U.S. Public Health Service
WASH	water, sanitation, and hygiene
WHO	World Health Organization