

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

**18th Public Virtual Meeting of the
Presidential Advisory Council on
Combating Antibiotic-Resistant Bacteria
November 30–December 1, 2021**

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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 meeting.

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 Fellow, OASH, HHS

Dr. Musmar called the meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (Council) 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.)

Opening Remarks from the Secretary

Xavier Becerra, Secretary, HHS

Sec. Becerra praised the Council for being an indispensable member of the team fighting to tackle COVID-19 through its support and promotion of infection prevention, surveillance, novel drug and diagnostics development, and pandemic preparedness. He noted that COVID-19 exacerbates antimicrobial-resistant infections. The President and Vice President are committed to a comprehensive approach to detecting emerging threats, infection prevention, antibiotic stewardship, and promoting innovation in new product development, including vaccines and diagnostics.

The agenda for this meeting includes updates on global efforts to address antimicrobial resistance (AMR). Sec. Becerra said he is proud of the strides made against AMR globally but much more work remains. He appreciated that the Council shares the administration's goals of combating climate change, which are evident in the Council's One Health approach to all of its work, and advancing equity, which the Council addressed in its recent report, *Bridging the Gap: Improving Antimicrobial Access and Use Across One Health*.

Sec. Becerra noted that pandemic preparedness remains a high priority for the administration, which recognizes the need for large-scale initiatives. For example, the American Rescue Plan empowers the Centers for Disease Control and Prevention (CDC) to invest \$2.1 billion in improving infection prevention and control in public health and health care. Sec. Becerra was encouraged by the Council's recommendations to delink product payment from sales revenue as a method for incentivizing new AMR product development. HHS included this idea in its report, *Comprehensive Plan for Addressing High Drug Prices*, which responds to President Biden's

Executive Order aimed at promoting competition in the U.S. economy. Sec. Becerra concluded that he anticipates a strong continuing partnership between HHS and the Council.

Global Leaders Group: Perspectives on Global AMR Efforts

Dame Sally Davies, One Health Global Leaders Group on AMR

Dame Sally emphasized the need to learn about the importance of preparedness from the COVID-19 pandemic. The COVID-19 vaccines were developed rapidly because of the years of active investment in research (in the case of mRNA, work originally aimed at cancer treatment). The pipeline for new AMR interventions, therapeutics, and diagnostics must be filled now. Dame Sally called for a bold vision and tangible action toward global access to new interventions, stewardship, surveillance, and rapid capacity development to combat AMR with the same level of intensity applied to the COVID-19 pandemic over the past 22 months.

Furthermore, the threat of AMR is integral to and should be aligned with efforts to address pandemic preparedness, climate change, and health equity. All multinational initiatives should incorporate AMR. Dame Sally said the Global Leaders Group is working to accelerate political leadership and action around AMR, with the aim of raising awareness around AMR as a political and societal priority. Policies promoting immunization, infection prevention, and effective methods for ensuring clean water, sanitation, and hygiene (WASH) must be incorporated into national and international initiatives with support from the International Monetary Fund. AMR must be embedded in national response and recovery plans and long-term global treaties.

The Global Leaders Group recognizes the need to maximize and leverage existing investments and to break down siloes to advocate for action. Working together, partners should urge the establishment of an independent panel on evidence for action against AMR. The Council is among the entities with the influence to push for a global process like the United Nation's Climate Change Conference of the Parties. The Council can also call on the U.S. Agency for International Development (USAID) to include AMR in its investments in public health, WASH, and infection control in developing countries.

Addressing these priorities requires sustainable financing for AMR surveillance. AMR surveillance should be integrated into the agenda outlined by the Group of Seven (G7) in its Carbis Bay G7 Summit Communique on global action to build back better from the pandemic. For the first time, G7 finance ministers recognized the need to pursue economic actions to prevent AMR. Every country has a stake in being part of the pipeline for access to new antimicrobials and stewardship. Passage of the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act in the United States would be a global game-changer, said Dame Sally, and the United States would join the United Kingdom (U.K.) as the first countries to use novel approaches to incentivize product development. Dame Sally hoped the Council would strongly support the proposed PASTEUR Act, which could have real economic impact on patients and families.

Dame Sally pointed to progress on recognizing AMR as an environmental issue globally in AMR and to bringing forth innovative solutions. She also noted the United Kingdom's Investor Initiative, which calls for sustainable private investment that aligns with global best practices on AMR. To increase understanding about the AMR threat in general, the U.K. supported

development of a musical theater production, which has been performed to sold-out U.K. theaters and will travel to the United States thanks to partnerships to scale up the project. Dame Sally concluded that there is a short window in which to capitalize on the awareness and attention to public health that resulted from the COVID-19 pandemic.

Discussion

Dr. Blaser observed that AMR is a slow-burning pandemic. COVID-19 demonstrated the close connections between countries. Dr. Blaser stressed the need to understand the economic incentives for using antibiotics and find alternatives for those whose livelihoods depend on the sale of antibiotics. Dame Sally responded that some steps have already been taken to find alternatives to antibiotic use in food production and, in human medicine, to stop tying profits to sales volume. As with climate change, she noted, it is necessary to address the problem at the grassroots level by changing the behavior of clinicians and consumers.

Dame Sally applauded the U.S. contribution of knowledge, experience, research, and funding to international and multinational efforts. Funding should be tied to metrics of progress to encourage effective partnerships. More collaboration is needed to ensure that international partners across the One Health spectrum are aware of and contribute to discussions and initiatives around AMR so that policies are aligned. Passage of the PASTEUR Act would be a model for G7 countries of the use of economic incentives to address AMR.

Collaborative work at the ground level—for example, education for pediatricians and pharmacists on the judicious use of antibiotics—feeds into the World Health Organization’s (WHO’s) guidelines, which are invaluable to small countries. Dame Sally encouraged USAID to fund more scholarships to bring experts to low- and middle-income countries (LMICs) to work with clinicians to improve antimicrobial stewardship, infection control, surveillance, and data collection. The rise of videoconferencing has expanded opportunities to educate students in the health sciences, she added.

Dame Sally said her friendships with journalists led to increased media attention to AMR. Major progress toward sustained awareness is possible when (1) clinicians start talking with patients about the risk of inappropriate antibiotic use and (2) the role of antibiotics in death is recorded on death certificates. The public must understand that AMR reduces the number of available effective treatments and that people are already dying as a result. Information campaigns should emphasize what individuals can do, such as getting vaccinated, washing their hands, and using antibiotics only when necessary.

Perspectives on AMR Priorities

Eric Lander, Ph.D., Science Advisor to the President and Director of the Office of Science and Technology Policy

Dr. Lander reminded the participants that the President’s Council of Advisors on Science and Technology (PCAST) called for establishing the Council in 2014, under the Obama Administration. President Biden recognizes the role of AMR in public health and preparedness. His directive to the Office of Science and Technology Policy links pandemic preparedness, AMR, and emerging pathogens. Dr. Lander encouraged the Council and others to frame AMR as a slow pandemic that could eliminate 100 years of medical innovation and lifesaving therapies.

Although he praised the progress made toward many of the items identified in the 2014 PCAST report, Combating Antibiotic Resistance, Dr. Lander raised concerns about the lack of metrics and surveillance to determine progress toward its intended goals. Since the report was released, the number of hospitals with antimicrobial stewardship plans increased from 40 percent to 90 percent. At the same time, nursing homes and long-term care facilities continue to struggle with AMR, which can pose a serious threat to the entire health care system. Similarly, there has been success in eliminating the use of antibiotics as growth promoters in livestock, but questions persist about whether such use continues under the guise of prophylactic applications.

Great strides have been made toward development of new classes of antibiotics, but more work remains, said Dr. Lander. Financial incentives to bring new products to market remain critical. Dr. Lander said equity was overlooked in the 2014 report, but COVID-19 highlighted health inequities, as the pandemic most severely affected the least well-served communities in the United States. Those inequities came to light because data were collected early on to better understand the effects of the pandemic, and changes were made in response to the findings. Similarly, more data are needed to demonstrate where AMR is occurring and how to tackle it.

Discussion

Dr. Blaser emphasized that new antibiotics—and particularly broad-spectrum antibiotics—will quickly be rendered obsolete by fast-evolving microbes. More attention to stewardship and development of narrow-spectrum, targeted antibiotics is needed, and both require better diagnostic tools. Dr. Lander responded that the PCAST report spotlighted the need for narrow-spectrum antibiotics but also for economic incentives to develop and use them. He encouraged the Council to offer more recommendations on improving stewardship and overcoming the paradox of urging clinicians to withhold treatment.

Ramanan Laxminarayan, Ph.D., M.P.H., pointed out that the pandemic offers an opportunity to create a global treaty on pandemics, which could also be an opportunity to address AMR and antimicrobial stewardship. Dr. Lander said that the concept has pros and cons, but he urged the Council to consider how to leverage the energy around pandemic preparedness and apply it to AMR, keeping in mind the distinctive features of AMR. The moment is right for an AMR plan for the next decade, Dr. Lander noted. He called for a clear articulation of actions that can be taken now to address AMR.

Elaine Larson, Ph.D., RN, reminded the group that preventing transmission is key to mitigating AMR, and more information is needed on how to encourage lasting behavior change around infection prevention in health care and in communities. Dr. Lander said that, in health care settings, reimbursement mechanisms can change behavior, as can the use of new monitoring techniques to identify the source and spread of infections. Outcomes research also plays a role in behavior modification.

Sara E. Cosgrove, M.D., M.S., stressed the need for more resources to improve the quality of stewardship and infection control programs that are optimized to ensure patient safety, not designed only to meet the criteria for reimbursement. Encouraging good stewardship and infection prevention requires financial and human resources, and COVID-19 highlighted the gaps in those resources. Dr. Cosgrove expressed concerns about the lack of qualified people to

fill the increasing number of positions in stewardship, infection prevention, and public health. Dr. Lander agreed, stressing that now is the moment to explore how to ramp up efforts to address AMR. For example, health care settings could be required to provide data demonstrating that their stewardship programs have had a positive impact on disease transmission and patient outcomes. Dr. Lander encouraged the Council to reach out to Julie Segre, Ph.D., of the National Human Genome Research Institute at the National Institutes of Health (NIH), who has focused on AMR for more than 10 years.

Combating AMR and Protecting the Miracle of Modern Medicine

Gillian J. Buckley, Senior Advisor, National Academies of Science, Engineering, and Medicine (NASEM), and Andy Stergachis, Ph.D., Associate Dean, School of Pharmacy, University of Washington

In 2019, Congress directed NASEM to conduct a consensus study on progress toward the goals of the 2014 National Strategy for Combating Antibiotic Resistant Bacteria (which guides both iterations of the National Action Plan on Combating Antibiotic-Resistant Bacteria [NAP CARB]). Ms. Buckley summarized the findings and recommendations that appear in the resulting report, *Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine*.

Regarding surveillance, the report notes that WHO aims to build capacity for surveillance in LMICs and that considerable information has already been collected by industry, academic researchers, and various disease-specific programs. It recommends that the NIH's National Library of Medicine establish an open-source, unified AMR database that integrates national and international, raw phenotypic data. The report notes that environmental monitoring of resistance is limited, and wastewater treatment plants are an important bridge between human contamination and the natural environment. Therefore, the Environmental Protection Agency (EPA) should provide guidance and funding to states for testing discharge at wastewater treatment plants for AMR traits and integrating these data with other surveillance networks.

Although great progress has been made in antimicrobial stewardship in human medicine, more is needed, especially in settings that serve particularly vulnerable patients. Therefore, the report recommends that the Centers for Medicare and Medicaid Services (CMS) require nursing homes, long-term acute care hospitals, and dialysis centers to have antimicrobial stewardship programs. For animal health, the report recommends that the Food and Drug Administration (FDA) establish a process and clear metrics to facilitate better tracking of antimicrobial consumption in animals. It should also convene an advisory committee to coordinate development of antimicrobial susceptibility test breakpoints in animals and identification of priority animal, drug, and pathogen combinations.

Appropriate use of diagnostic testing could reduce improper antimicrobial prescribing. To this end, key HHS agencies and the Patient-Centered Outcomes Research Institute (PCORI) support outcomes research to drive guideline development and reimbursement for diagnostic testing. Recognizing the role of vaccines in mitigating the use of antibiotics, the report calls on NIH and CDC to provide supplemental research funding to track antimicrobial use and AMR in immunization trials and large cohort studies to measure the indirect benefits vaccines provide.

The NASEM report points out the government should ensure it is incentivizing truly novel and useful product development. Therefore, an HHS interagency committee should establish well-targeted, objective criteria to identify novel antimicrobials with high potential for satisfying a critical, unmet need. HHS should support trials to establish the optimal use of these drugs and demonstrate any additional clinical benefits.

To ensure that new antimicrobials reach those in need, FDA should reduce regulatory hurdles by coordinating the review of new antimicrobials with the review of their automated susceptibility tests. FDA should work with the Clinical Laboratory Standards Institute to issue and update breakpoints for microbe–drug combinations. Other recommendations call on Congress and CDC to help facilitate development and application of automated susceptibility tests.

Response to the COVID-19 pandemic demonstrated the value of broad, coordinated partnerships. To support a One Health approach to antimicrobial product development, HHS should establish a public–private partnership for AMR similar to the Accelerating COVID-19 Therapeutic Interventions and Vaccines initiative.

The Government Accountability Office should evaluate progress toward the NAP CARB 2020–2025 goals biennially and consider mechanisms for making mid-course corrections. To support the U.S. role in coordinated global action against AMR, the NASEM report recommends creation of an entity to strengthen surveillance, tackle infection prevention, and promote antimicrobial stewardship under the leadership of a global coordinator for AMR, modeled after the President’s Emergency Plan for AIDS Relief (PEPFAR).

Discussion

Dr. Stergachis, a member of the consensus committee whose deliberations informed the NASEM report, noted that a growing number of studies of antibiotic consumption recognize the phenomenon of unrestricted antibiotic sales on the open market. However, because of wide variations in consumption and numerous underlying factors, the research cannot demonstrate the direct effects of access to unprescribed antibiotics. Dr. Stergachis added that empiric use of antimicrobials also contributes to the problem, as does underuse of antimicrobials in some cases.

WHO Update on AMR

Hanan Balkhy, M.D., Assistant Director-General, Antimicrobial Resistance, WHO

WHO established the AMR division to bring attention to the AMR agenda and to incorporate AMR response into the United Nations’ (U.N.’s) sustainable development goals. Dr. Balkhy described progress toward each of the division’s four strategic priorities:

- **Stepping up leadership for AMR response:** The Tripartite (WHO, U.N. Food and Agricultural Organization, and the World Organisation for Animal Health) and the U.N. Environmental Programme will launch a strategic framework for AMR in early 2022. WHO facilitated the U.N. Call to Action on Antimicrobial Resistance in 2021, signed by numerous U.N. member states. It created advocacy tools for the Global Leadership Group and established the Partnership Platform for AMR to enhance communication and collaboration.

- **Driving public health impact in every country:** Although numerous countries have national action plans (NAPs), only 20 percent of countries fund and monitor implementation of those plans. WHO will publish the NAP Implementation Handbook in 2022 to offer practical steps for these countries.
- **Research and development (R&D) for better access to quality AMR prevention:** WHO is updating materials that guide priority setting and coordination as well as fostering R&D through the Global Antibiotic Research and Development Partnership and the AMR Action Fund. It is collaborating with WHO, the Global Antibiotic Research and Development Partnership, the United Nations International Children’s Emergency Fund (UNICEF), the Clinton Health Access Initiative, and SECURE, which aims to expand sustainable access to antibiotics.
- **Monitoring the AMR burden and global AMR response:** The Tripartite AMR Country Self-Assessment Survey enables countries to monitor progress annually, but the best clinical indicator is the emergence of AMR. Implementation of the WHO access, watch, and reserve (AWaRe) classification system, environmental research, and antimicrobial consumption tracking are among the many steps needed to evaluate progress earlier. WHO supports national AMR surveys, improved routine surveillance, and guidance on data use.

Discussion

Dr. King expressed surprise at the number of countries that have plans but do not actively monitor implementation. Dr. Balkhy said that some high- and middle-income countries have not prioritized AMR, lack good communication across sectors, and do not know how to finance implementation of NAPs targeted at AMR. They may legislate good practices but lack the human resources to monitor them. Some countries lack sufficient laboratory data to identify a starting point for their AMR efforts. WHO seeks to provide technical assistance to help countries implement NAPs. However, Dr. Balkhy said, it is time to take a different approach by helping countries identify their own priorities and agenda, then assisting them with funding, personnel, and support on the ground to achieve those priorities.

Dr. Balkhy pointed out that WHO can help countries identify specific problems and plan how to move forward. Addressing a lack of access to clean water, for example, requires a different approach than controlling the spread of multidrug-resistant organisms (MDROs) in tertiary care hospitals. To fund AMR work, Dr. Balkhy said, it is necessary for the International Monetary Fund and other world banks to incorporate AMR into the financial framework. Dr. Balkhy said WHO needs more money to achieve its goals, and countries need funding from domestic and international sources.

Ms. Buckley said that in the United States, Congress and government agencies must determine how to prioritize the NASEM recommendations. Dr. Stergachis added that advocacy for evidence-based recommendations is crucial, and he appreciated the opportunity to publicize them at this meeting. Ms. Buckley said that there is consensus about the importance of AMR, and NASEM’s recommendations offer concrete steps to address specific elements of AMR, which can help leaders prioritize actions. However, progress comes down to raising awareness about

AMR and generating the political will to address it. Dr. Stergachis pointed out the need to take advantage of timely opportunities to advance the AMR agenda, such as Congress considering legislation about AMR and funding for related topics. There is an opportunity to apply lessons learned from the COVID-19 pandemic and PEPFAR's experience engaging on the international front.

To address the problem of access to antibiotics without a prescription, WHO has policy guidance on antimicrobial stewardship and materials addressing the misuse of antibiotics. Dr. Balkhy said many countries hesitate to establish antimicrobial stewardship and regulatory policies because they are concerned about the consequences of implementation, or they lack the resources to monitor and enforce their policies. In many areas, the solution lies in improved access to health care. WHO can create a framework to help guide these countries that links AMR with health care access.

Codex Alimentarius Report and AMR

Donald Prater, D.V.M., Chair, Codex ad hoc Intergovernmental Task Force on AMR; Office of Food Policy and Response, FDA

The Codex Alimentarius is a collection of internationally adopted, voluntary food standards and related guidance aimed at protecting consumer health and ensuring fair trade practices. Dr. Prater explained that the Task Force recently updated its 2005 Code of Practice to Minimize and Contain AMR to address the whole food chain beyond animal production and offer new strategies. The updated Code of Practice incorporates risk management tools throughout, includes new and updated definitions, and broadens the scope of the content.

The updated Code of Practice follows a set of general principles, such as taking a One Health approach and considering existing lists of antimicrobials of critical importance to human or veterinary medicine. In addition to risk management, the principles address infection prevention and responsible use of antimicrobials; put forth boundaries for appropriate use of medically important antimicrobials; and promote the use of diagnostics, monitoring, and surveillance.

The largest section of the document provides risk management guidance for various participants along the food chain, including food animal and plant/crop producers, veterinarians and other professionals, distributors, manufacturers, and regulatory authorities. The Code of Practice emphasizes risk management—for example, the need to recognize counterfeit and illegal substances—and offers guidance on processing, storage, and transport as well as communication with consumers. The current draft was approved by the Codex Alimentarius Commission, and the final report is pending.

Discussion

Dr. Prater emphasized that outreach is important for raising awareness about the Codex Alimentarius guidelines. The Tripartite Secretariat can encourage countries to implement the guidance and share their successful implementation approaches with others. Measuring and evaluating implementation on the ground would be helpful. Dr. Prater acknowledged that U.S. food producers have stopped using antimicrobials for growth promotion, but more progress is needed globally toward that goal. The updated Code of Practice focuses on how to eliminate

such use. The Code of Practice contains a wealth of information and reveals gaps in knowledge, particularly around AMR in plants and crops.

NAP CARB: Progress and Next Steps

Casey Sullivan, Ph.D., Office of the Assistant Secretary for Planning and Evaluation, HHS

Dr. Sullivan described the makeup and role of the Federal Combating Antibiotic-Resistant Bacteria Task Force, which works closely with the Council. Through its annual progress assessments, the Task Force determined that many milestones in the 2015–2020 NAP CARB have been reached. Among the most effective strategies have been the implementation of hospital antimicrobial stewardship programs, the new national Antibiotic Resistance Laboratory Network, the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), and global engagement around AMR. These steps have led to fewer deaths related to antibiotic resistance, but there are still too many resistant infections and too many deaths, said Dr. Sullivan. Furthermore, challenges persist in the development of new antibiotic products.

The Task Force reiterated and refined the five goals of the initial NAP CARB in their 2020–2025 version, which incorporates many recommendations from the Council. The revised plan includes an updated measurement strategy to better understand progress and challenges. For example, the new milestones set quantitative targets, when possible, taking advantage of the infrastructure put in place with the initial NAP CARB. Specific quantitative targets are embedded in goals and objectives and can be updated annually in response to the changing landscape around AMR.

A new format will be established to increase the efficiency and transparency of annual reporting. It will enable agencies to better clarify progress toward targets, update targets (with accompanying rationale), and describe challenges and solutions. It also offers an opportunity to describe progress in a narrative format.

Discussion

Dr. Blaser pointed out that it is cheaper and faster to prescribe antibiotics than it is to conduct diagnostic tests and wait for the results, even though the results could eliminate the need for antibiotics or direct antibiotic selection. Dr. Sullivan responded that increased coordination among antimicrobial stewardship programs in various settings could support appropriate use of diagnostics; CMS and CDC may be in a good position to address the issue.

Dr. Sullivan emphasized that the members of the Task Force communicate frequently with each other and with external partners, such as NASEM, about recommendations. The existing relationships and collaborations are influential as each agency prioritizes how it will implement recommended steps. The Task Force went to great lengths to ensure that the goals and objectives of the 2020–2025 NAP CARB were harmonized across agencies and departments. Each member has its own distinct mission, but all recognize the need for collaboration to get the work done.

Dr. Sullivan pointed out that as a result of significant efforts of all the relevant federal agencies and meticulous planning, there is financial support for implementation of the NAP CARB, and the plan helped agencies make the case for that funding. She recognized that other countries may face challenges implementing their NAPs.

The Intersection of Antibiotic Resistance, Antibiotic Use, and COVID-19

Arjun Srinivasan, M.D., CDC; Captain, U.S. Public Health Service

Dr. Srinivasan pointed out that the \$2.1 billion directed to help CDC strengthen public health infrastructure includes a specific focus on nursing homes, which were particularly hard hit by COVID-19. The pandemic triggered an increase in healthcare-associated infections (HAIs) and AMR due to longer hospital stays, higher acuity patients, and increased use of invasive medical devices. Early in the pandemic, antibiotic use in hospitals and nursing homes increased sharply while outpatient use fell dramatically; in all settings, use has since rebounded to pre-pandemic levels. Across health care facilities in every state, HAI rates remain elevated compared to 2019, except for *Clostridioides difficile* infections.

Use of azithromycin and ceftriaxone in hospitals has been higher in 2020 and 2021 than in 2019. Use of both increased when the COVID-19 Delta variant hit, although the increase in ceftriaxone use was not as large as with previous COVID-19 waves. Use of broad-spectrum antibiotics for resistant pathogens has remained slightly below pre-pandemic levels. Together, these findings suggest that antimicrobial stewardship programs and messaging might be impacting prescribing habits. Analysis of outpatient prescribing also suggests that providers might be more comfortable diagnosing and managing respiratory illness without resorting to antibiotics.

To combat AMR and infectious disease, CDC recently announced new investments in the Global Antibiotic Resistance Laboratory and Response Network, which will facilitate rapid detection and response to AMR, particularly emerging threats, and activities to combat them. CDC also announced the Global Action in Healthcare Network to detect and respond to emerging infectious disease threats like AMR, HAI, and COVID-19. In addition, CDC is launching its first global AMR research projects to identify public health solutions to combat AMR around the world.

Increasing AMR and the COVID-19 pandemic demonstrate that infection prevention in communities and health care settings is crucial to limit the spread of disease and resistance. Investment in drug discovery and development must be balanced by equal investment in infection control and prevention. The \$2.1 billion investment in infrastructure is long overdue, said Dr. Srinivasan; existing systems for pathogen detection and control were not sufficient to combat the challenge posed by the COVID-19 pandemic. However, areas that had built infrastructure, such as state-level CDC programs on antibiotic resistance, were able to help nursing homes around the country respond to the pandemic. Sustainability of funding remains a concern.

The pandemic revealed how public health and health care providers work together to save lives, and those collaborations must be strengthened. The mechanisms needed to prevent AMR—the ability to detect new pathogens, recognize their potential impact on health care delivery, respond, and prevent their spread—are all fundamental components of pandemic preparedness. A better response to AMR and HAIs translates to better preparedness for pandemics, Dr. Srinivasan concluded.

Discussion

Dr. Srinivasan clarified the variations between inpatient and outpatient changes in antibiotic use but said more evaluation is needed to better understand variations in use by age. CMS requires nursing homes to report COVID-19 infections to CDC's National Healthcare Safety Network (NHSN) weekly. CDC and CMS are discussing how to take advantage of new reporting infrastructure in nursing homes to sustain and expand reporting. Dr. Srinivasan recognized the burden of reporting in facilities facing shortages of staff and resources and said CDC is exploring ways to reduce the burden. CDC and CMS are also discussing requiring hospitals to report antibiotic use and resistance data. Dr. Larson pointed out that data are only useful to the facilities (particularly nursing homes) if they also get feedback they can use to improve care.

Dr. Srinivasan acknowledged that the CDC funding for infrastructure could be hampered by the lack of public health workers. He proposed partnering with educational institutions to highlight rewarding careers in public health. Dr. Srinivasan also recognized the need to address equity so that funding for effective infection prevention and control reaches poorly resourced communities and facilities. A lot of AMR data reveal the same kinds of health disparities as other care; minority populations, those with limited access to care, and those with low socioeconomic status are all at higher risk for resistant infections.

Armando Nahum raised the concept of public reporting. Dr. Srinivasan responded that HHS' Vaccine Adverse Event Reporting System and CDC's V-safe after vaccination health checker application have set a precedent, so public reporting of AMR and HAIs is worth discussing.

Dr. Srinivasan anticipated that more data will soon emerge on patient outcomes in relation to antibiotic prescribing patterns since the pandemic began, which will shed light on the link between AMR patterns and health outcomes. He added that resistant infections are usually more lethal than nonresistant infections.

Public Comment

Madeleine Kleven of the Food Animal Concerns Trust, a founding member of the **Keep Antibiotics Working Coalition**, called for increased national response to emerging threats and antibiotic resistance. The United States must optimize pandemic preparedness and efforts to combat AMR by monitoring use of antimicrobials on feedlots and farms. The White House's recent National Biodefense and Pandemic Preparedness Plan omits actions related to tracking and controlling animal pathogens that have the potential to cause illness in humans, even though three fourths of all animal pathogens have such potential. The Keep Antibiotics Working Coalition recommends that federal agencies address zoonotic disease surveillance as part of pandemic preparedness. To facilitate comprehensive assessment, a surveillance system is needed that describes how medically important antibiotics are used in feedlots. FDA requires feedlots to track the amount and use of antibiotics and make that information available to the agency. FDA should build a system to collect data from firms that manufacture and distribute antibiotics for farm or feedlot use, and the data should be publicly reported.

Jonathan Romanowsky of Inflammatrix reiterated concerns about the market failure around the use of diagnostic tests, which are significantly more expensive than antibiotics. Government and

stakeholders should address that failure. Excellent progress on the subscription-based payment model for hospital antibiotics, which is part of the PASTEUR Act, can inform further discussion.

Mr. Romanowsky explained that CMS' Medicare Coverage for Innovation Technology rule allowed for reimbursement of FDA-designated breakthrough devices, including diagnostics, but it has been rescinded. He hoped CMS would implement a new, similar measure or that comparable legislation, as described in the proposed Cures 2.0 Act, would be adopted. Removing uncertainty and delays around reimbursement for diagnostic tests will encourage adoption by health care providers and investor support in new diagnostic development. Furthermore, extending such reimbursement to other government-funded health care systems, such as TRICARE and Medicaid, would increase patient access to diagnostic tests and have a significant impact in communities where health equity concerns have been raised.

Tabitha Reefer, ambassador for AMR Insights in the Netherlands, requested better coordination of AMR awareness programs around the world that reach out to children and their caregivers. As a result of mitigation efforts during the first year of the pandemic, antibiotic use decreased, but it is not expected to hold steady as the world enters a new phase of the pandemic. Some schools are fully open and do not require masking or social distancing. Before the pandemic, about one fourth of children were prescribed antibiotics inappropriately; without interventions, such prescribing will soon rebound. Ms. Reefer stressed that children are highly susceptible to the side effects of antibiotics, such as fungal infection and diarrhea, and incorrect use of antibiotics contributes to AMR and increases health care costs. Health care providers can take a leadership role by educating parents on ways to reduce antibiotic use, such as watchful waiting, and by working with childcare centers to improve policies around excluding sick children. U.S. experts can increase assistance for stewardship, education, and policies in the United States and globally by engaging providers and caregivers.

Ms. Reefer said that AMR Insights established an Ambassador Network that is free to join. AMR Insights' new working group for health care providers, AMR Engaged, will focus on AMR education, and outreach and provide a forum for experts to learn from each other, participate in outreach, and lead education efforts. The new working group will organize a competition for children, modeled after a Pennsylvania Department of Health art competition. AMR Insights will offer technical and marketing assistance to help ambassadors implement competitions in their country or local regions. The competition seeks to promote conversations among children, their caregivers, and health care providers about hand hygiene, vaccination, and infection prevention. AMR Insights welcomes expert participants from all fields, including pharmacists, microbiologists, pediatricians, and community health experts, to join its ambassador network. It hopes to foster global engagement and education around reducing unnecessary prescribing, increasing awareness among caregivers, and decreasing resistant bacteria.

Final Comments and Recess for the Day

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

Dr. Blaser thanked the participants and staff. Dr. King added that the day's deliberations elicited a challenge to PACCARB to position combating AMR as key to pandemic preparedness and to

learn from the COVID-19 experience how to operationalize new plans to address AMR. Dr. Blaser recessed the meeting for the day at 2:53 p.m.

Day 2

Welcome and Overview

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

Dr. Blaser opened the meeting at 10 a.m., welcomed the participants, and outlined the agenda for the day. Dr. King said he was encouraged by the support and acknowledgment of the Council's work by Sec. Becerra and Dr. Lander.

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 Fellow, OASH, HHS

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

Re-Energizing Patient Safety

Armando Nahum, PACCARB Member and Founding Member, Patients for Patient Safety US

Mr. Nahum described how his father, wife, and son were all affected by HAIs within a 10-month period in the mid-2000s at hospitals in different states. His father received appropriate antibiotic treatment following a minor procedure; his wife contracted a postsurgical staphylococcus infection that compromised her immune system and requires ongoing management. Tragically, Mr. Nahum's son died at age 27—not from the injuries he sustained after a skydiving accident but from the HAI he contracted during his hospital stay and the poor-quality care he received.

With encouragement from CDC, Mr. Nahum and his wife initiated the Safe Patient Care Campaign, an effort to prevent HAIs in the United States, Canada, and South America. CMS subsequently created the Partnership with Patients to improve safety, quality, and affordability, which was implemented under the Patient Protection and Affordable Care Act with great success. In 2016, under a new administration, programs for patient and family engagement lost funding, and patient safety took a back seat, said Mr. Nahum. Between 220,000 and 444,000 lives are lost each year as a result of medical errors, he noted, and the United States has failed to meet the goals set out more than 20 years ago in the landmark Institute of Medicine report, *To Err Is Human*.

Frustrated with the lack of progress, Mr. Nahum and others formed a U.S. chapter of WHO's Patients for Patient Safety to implement WHO's Global Patient Safety Action Plan in this country. It is made up of people affected by medical errors and partners representing government, civil society, and health care. The group's work is guided by a WHO matrix that outlines the need for clear policies, leadership, data, skilled health care providers, and effective patient involvement in care. Mr. Nahum said the U.S. chapter has established four goals:

- **Achieving patient safety in the United States**, with a vision of zero harm to patients, aided by a national coordinator on patient safety, incident reporting (including patient and family reporting), and transparency and full disclosure when harm occurs.
- **Creating skilled communities** of patient and family advocates who can forge strategic partnerships with health care leaders and promote successful patient and family engagement.
- **Engaging the community** through national workshops and other forums to share the experiences and expectations of patients and implement the WHO Global Action Plan.
- **Disseminating and communicating information** about successes, lessons learned, and examples of the pivotal role of patients and families in patient safety efforts.

Mr. Nahum invited all individuals and organizations within and outside the United States to become part of an international alliance for patient safety.

Discussion

Several PACCARB members expressed condolences to Mr. Nahum on the loss of his son, noting that stories like his put a human face on the consequences of AMR. Dr. Laxminarayan asked how PCORI's work is perceived among patient safety advocates. Mr. Nahum said PCORI has been instrumental, particularly because its research involves patient advocates, but more than one such organization is needed. He added that new technology with the promise of predicting and preventing HAIs will play a role in improving patient safety.

Jason Newland, M.D., M.Ed., raised concerns that staff shortages and burnout could cause hospitals to postpone their patient safety efforts. Mr. Nahum said that when the pandemic hit, hospitals' patient/family advisory councils looked for ways to assist, and many have focused on helping health care workers (HCWs) cope with the crisis. These councils' members have also reached out to COVID-19 patients after discharge to learn about their health care needs and link them to services. Mr. Nahum said patient safety has returned to the forefront.

Mr. Nahum called for a uniform approach to patient safety that focuses on prevention on a daily basis, rather than in response to a surge of infections. In other industries, such as air travel, safety is embedded in every component of work. By recognizing that patients are the experts on their own bodies and including them as partners to achieve better health outcomes, the goal of zero harm—and especially zero preventable harm—is achievable.

The Role of Emerging AMR in Pandemic Preparedness

Mark Kazmierczak, Ph.D., Gryphon Scientific

Despite significant progress against AMR, threats remain, said Dr. Kazmierczak. COVID-19 has given a new materiality to pandemic preparedness and an alternative lens through which to view the threat of AMR. The new focus on preparedness offers an opportunity to raise awareness about the need to prepare for AMR, particularly by investing in surveillance to detect and track AMR. Rather than propose a different strategy or approach, Dr. Kazmierczak called for a renewed appreciation of the urgency of tackling AMR, expanding the community of stakeholders involved, and seeking new opportunities to implement or increase pandemic preparedness. The

panel sessions for the day offer a platform for stakeholders to address how to embed AMR into preparedness strategies.

The needs and challenges remain the same: new therapeutics; strong stewardship programs; robust surveillance and data sharing; resilient agricultural, environmental, and public health systems that can respond to large-scale events; greater understanding of the interconnectedness of agriculture, health care, and the environment in AMR spread; and stronger biosecurity and prevention across domains. Approaching these challenges with a One Health framework is essential. Just as COVID-19 and influenza jumped from animal reservoirs to become human concerns, AMR in animals pose a threat to animal and human health. Therefore, surveillance in animals, humans, and the environments is essential. More understanding is needed about how the changing climate and environment may affect AMR. As practices change, it is important to ensure they are sustainable and not driving resistance further. In preparation for future pandemics, potential threats from viral, bacterial, and fungal diseases all should be recognized.

Panel 1: Strengthening Public and Agriculture Health Systems and Building Core Capabilities

Healthcare Infection Control Practices Advisory Committee (HICPAC) Activities

Lisa Maragakis, M.D., M.P.H., Senior Director of Infection Prevention, Johns Hopkins Health System, and Co-Chair, HICPAC

Dr. Maragakis explained that HICPAC provides advice to HHS agencies, including CDC. Its guidelines and policy statements promote evidence-based practices around infection control ranging from general practices, such as hand hygiene and disinfection, to procedures related to a specific condition, such as surgical site infections and *C. difficile*. HICPAC also conducts surveys and partners with colleagues in antimicrobial stewardship to prevent AMR.

The COVID-19 pandemic led to increases in HAIs and MDROs, demonstrating the challenges posed by staff shortages, burnout, and competing priorities. Systems were not as robust or resilient as hoped or needed. Dr. Maragakis called for reinvigorating efforts against HAIs and MDROs and examining how to strengthen systems so they would be more resistant to disruptions like the pandemic.

To that end, a HICPAC working group on occupational health is addressing routine infection control practices and prevention of transmission between health care providers and patients. It is developing guidelines to control transmission of *Staphylococcus aureus* infections, including methicillin-resistant *S. aureus* (MRSA), among HCWs. A working group published guidance on *S. aureus* and central-line-associated bloodstream infections in neonatal intensive care units; it is also developing guidance on transmission of respiratory illnesses among neonates. Another working group provides feedback to CDC about the NHSN, including its Antibiotic Use and Resistance module. HICPAC is convening a working group to craft new guidance on isolation and infection prevention in health care settings.

Defend the Flock Outreach Campaign

Julie Gauthier, D.V.M., Assistant Director for Poultry Health and Veterinary Medical Officer, Animal and Plant Health Inspection Service, U.S. Department of Agriculture (USDA)

In response to the highly pathogenic avian influenza outbreak in 2014–2015 (the largest avian emergency in the United States to date), FDA launched Defend the Flock to prevent the spread of disease in flocks of all sizes and to promote good biosecurity practices. Dr. Gauthier stressed that biosecurity is improving nationally but requires constant attention. Defend the Flock employs a resource center, social media, paid advertising, and stakeholder outreach, in English and Spanish, to communicate its message. Its Flock Defender youth program aims to reach young people, especially those participating in 4-H and the National Future Farmers of America Organization.

Dr. Gauthier shared examples of Defend the Flock materials available in various formats and the use of social media to advance the campaign. The resources reflect the knowledge and insight of experts from USDA, veterinarians, growers, and scientists. The website offers practical tips on numerous topics in multiple languages. Campaign partners include state agriculture departments, universities, commercial organizations, industry, and trade groups that share campaign resources through their own communication channels. Dr. Gauthier said the campaign produces new material frequently to maintain interest.

Impact of Bacterial Infections on Hospitalized COVID-19 Patients

Mark Albrecht, Ph.D., Antibacterials Branch Chief, Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response, HHS

The 2009 influenza pandemic exposed a direct relationship between secondary bacterial infection and death among those with influenza; recent findings suggest a similar connection between COVID-19 deaths and bacterial infection. Dr. Albrecht said BARDA explored the concept by surveying providers through the Emerging Infections Network (funded by CDC and managed by the Infectious Diseases Society of America).

Responses to an initial survey suggested that secondary bacterial infections among COVID-19 patients were relatively infrequent. A second survey found that the major pathogens involved were those identified by CDC as priority pathogens and that non-pulmonary infections were more likely to be gram-positive than gram-negative.

A third survey requested details on cases of both COVID-19 and secondary infection. Of the 108 cases reviewed, 67 percent of patients had sepsis, but the timing of the diagnosis suggested viral rather than bacterial infection. The most common bacterial pathogens were *S. aureus* and MRSA, *Pseudomonas*, and *Klebsiella* species. Unresolved bacterial infection was a significant predictor of death. Among all the patients, 74 percent had one or more preexisting conditions; hypertension and coronary artery disease were significant predictors of death.

Dr. Albrecht said BARDA seeks to understand whether AMR will increase as a result of extensive use of antibiotics early in the pandemic. Each surge in COVID-19 infections has resulted in a deviation from hospitals' normal infection control practices, which could also lead to increased AMR. Dr. Albrecht cited evidence that breakdowns in infection control contributed to a rise in MDROs in some hospitals.

Antifungal Resistance and Climate Change

Arturo Casadevall, M.D., Ph.D., Johns Hopkins University School of Public Health

Dr. Casadevall explained that mammals have been remarkably resistant to fungal infection, which can be devastating to reptiles and other species. Heat, whether body temperature or environmental temperature, tends to offer protection against fungal infection. Human fungal diseases, such as those that cause athlete's foot, diaper rash, and dandruff, are more common in cooler areas. Humans are generally protected from fungal disease by body temperature and adaptive immunity.

However, as the earth is getting warmer, fungi are adapting to higher temperatures. Dr. Casadevall suggested that the simultaneous emergence of three unrelated isolates of *Candida auris* in 2007 could be a leading indicator that fungi are evolving to survive warmer temperatures. *C. auris* appears to be the first fungus to overcome the mammalian thermal barrier to become pathogenic in humans.

Dr. Casadevall presented evidence that human body temperature has decreased over the past 100 years, even as the earth is warming. He predicted that *C. auris* is the first of many fungal diseases to come that will affect mammals.

Environmental Azole Resistance in Target and Non-Target Fungal Pathogens in Crop Production

James E. Adaskaveg, Ph.D., University of California, Riverside

Demethylation-inhibitor (DMI) fungicides are very effective in crop management and represent the foundation of fungal disease control programs, said Dr. Adaskaveg. When DMI fungicides are used correctly, resistance is very slow to develop. When it does occur, resistance can be overcome by using higher doses of fungicide or by pausing use for some time, after which the target fungus returns to a state of susceptibility.

Management guidelines exist to preserve the effectiveness of fungicides. However, the availability of low-cost generic formulations encourages some growers to use more fungicide rather than other modes of protection, and the lack of alternatives results in overuse of DMI fungicides. Using DMI fungicides in concert with other fungicides or other methods can prevent resistance. DMI fungicides should be limited to preventive rather than curative use. The management guidelines are promoted by the Fungal Resistance Action Committee, which includes industry and academic partners, and informed by crop resistance monitoring conducted by multiple organizations.

Aspergillus fumigatus isolates resistant to medical triazole have been recovered from humans and environmental samples, which suggests that there may be an environmental route of selection. *A. fumigatus* can grow at high temperatures, such as those of self-heating compost piles. Dr. Adaskaveg opined that *A. fumigatus* spores are commonly inhaled, but they only cause problems in people with compromised immune systems. Data from 2014 suggest that agricultural use of DMI fungicides poses a low risk of *A. fumigatus* resistance, although environmental origin cannot be ruled out. Dr. Adaskaveg said selection seems to require high populations, warm temperatures, and specific environments—such as compost piles, suggesting that *A. fumigatus* resistance to DMI fungicide stems from sources other than agricultural use.

DISCUSSION

Dr. Maragakis said it is not well understood why some forms of AMR increased while others decreased during the pandemic. Disruptions to operations, particularly in intensive care units and medical units, combined with increased patient acuity and shifting personnel into new settings to meet staff needs, among other variables, may have contributed.

Dr. Casadevall said he saw no association between increasing resistance to azoles and the rise of *C. auris* infections. He believes that *C. auris* is naturally resistant to azoles. The lack of surveillance mechanisms to detect the impact of fungal infections in other species poses a serious barrier to understanding the threat. Dr. Casadevall did not know whether the current spate of extinction of numerous species could be creating selective pressure that makes humans and other mammals more susceptible to fungal infection.

Dr. Maragakis noted that HICPAC strives to provide guidance rapidly in line with the latest evidence. It updates guidelines in segments as needed and posts new guidance on specific questions online when possible to speed up translation into practice. A recent document urged professional societies to include antimicrobial stewardship in their treatment guidelines to ensure new efforts to prevent infection do not inadvertently increase the use of broad-spectrum antibiotics. Dr. Maragakis said she would raise the idea of specific guidelines on AMR to HICPAC.

Dr. Gauthier indicated that there are no plans to expand the Defend the Flock campaign approach to other infections in other species, although there are concerns about African swine fever reaching the United States. USDA works with producers to enhance compliance with biosecurity. Defend the Flock does not include evaluation measures, but USDA's Center for Epidemiology and Animal Health looks at risk factors around outbreaks and reveal where to target outreach efforts.

Dr. Albrecht observed that empiric use of antibiotics for COVID-19 patients with bacterial infections was unusually low according to the BARDA survey results. It appears that CDC and FDA recommendations for treatment were implemented quickly.

Dr. Maragakis pointed out that effective infection prevention interventions must be reinforced continuously with every patient interaction. For example, HICPAC focuses on consistent and appropriate implementation of cleaning, isolation, hand hygiene, and personal protective equipment. Effective workflows are needed to ensure these practices work as intended. It may be necessary to retool isolation protocols and tailor them to the type of pathogen, level of risk, and setting. The pandemic demonstrated that it may also be necessary to consider the mode of transmission and the type of personal protective equipment available to support effective isolation approaches.

Panel 2: Ensuring Situational Awareness

National Antimicrobial Resistance Monitoring System (NARMS) and the Evolution of One Health Surveillance

Patrick McDermott, MS, Ph.D., D(AAM), Director, NARMS, Center for Veterinary Medicine, FDA

Dr. McDermott outlined the goals and objectives of the NARMS Strategic Plan, 2021–2025, which expands the scope of NARMS to a broader One Health approach. NARMS' enhanced sampling for foodborne pathogens will include animal feed and pet food, seafood, and other potential sources of AMR pathogens. To broaden inclusion of environmental sources, FDA will incorporate more EPA data into NARMS, including a national survey of rivers and streams slated for 2023. It will also partner with the Veterinary Laboratory Investigation and Response Network and the National Animal Health Laboratory Network to capture more microbial data from companion animals. Ultimately, FDA seeks to link NARMS with NIH's whole genome sequencing repository.

FDA also aims to use advanced technology to better understand the spread of resistance in foodborne pathogens, such as artificial intelligence and machine learning, improved susceptibility testing, metagenomic approaches to characterize resistance, and other efforts to fully characterize samples and understand adaptive microbial features. NARMS has enabled researchers to identify genotype-phenotype correlations, and this demonstrates that whole genome sequencing can predict antimicrobial resistance. Currently, NARMS enables transparent, real-time data reporting, which offers a tremendous advantage in understanding resistance.

Dr. McDermott summarized some pilot projects underway to explore surface waters as points of confluence of AMR runoff from built human and agricultural environments. He noted that the scope of NARMS surveillance is being evaluated with pilot surveys of other food animals raised with antibiotics. He concluded that NARMS is taking full advantage of DNA sequencing technologies to get detailed information on resistance and associated biological features and sharing these data as soon as possible.

Action on Data and the Agricultural Research Service (ARS) Systems Approach

Kim Cook, Ph.D., National Program Leader, ARS, USDA

ARS has in-house expertise to conduct targeted, multidisciplinary research across systems that will position it to be a leader in innovative, equitable, sustainable solutions for AMR in agriculture. Dr. Cook pointed out that agricultural environments are extremely complex and require multifaceted, tailored responses. For example, when data showed an increase in cases of salmonella in humans, ARS collaborated with the poultry industry to create a genetic map of *Salmonella infantis* in plasmid sequences from animals and humans and an assay for characterization. ARS also established a working group to disseminate these findings and tools to stakeholders and foster collaboration.

Similarly, a multidisciplinary research effort involving ARS revealed the genetic changes involved in a salmonella outbreak among turkeys in 2017, which quickly led to the development of a vaccine. Dr. Cook said the work exemplified the importance of taking a holistic approach

that combines surveillance to identify threats, research to understand them, and targeted solutions to address them.

Because the nature of AMR threats varies widely across agricultural settings and systems, ARS needs continued support of integrated, multidisciplinary research. ARS recognizes that interventions have a ripple effect across the food system. Dr. Cook said that preventing the emergence of resistant pathogens requires expertise from many sectors who can help create innovative strategies to predict, prevent, and address resistance with real-world solutions.

Health Care Surveillance for Emerging and Enduring Threats: CDC's NHSN

Shari Ling, M.D., CMS, and Arjun Srinivasan, M.D., CDC; Captain, U.S. Public Health Service

Dr. Ling underscored the critical collaboration across federal agencies, and between CDC and CMS in particular, to coordinate authorities in support of maximizing public health protection and improving outcomes. Dr. Srinivasan explained that CDC's data modernization initiative relies on systems like the NHSN, which has input from almost every type of health care facility. Since 2012, the NHSN has captured AMR data, but it required manual entry. NHSN now extracts data from various electronic sources, eliminating the need for manual data entry.

CDC created the standardized antimicrobial administration ratio to support quality improvement in hospital antimicrobial stewardship programs. CDC continues to refine the measure so that programs can apply it for risk adjustment and other needs. Dr. Srinivasan said CDC is also partnering with CMS to expand reporting by including the NHSN Antimicrobial Use and Resistance module as part of CMS' Promoting Interoperability program and as a mechanism for hospitals to meet requirements for public health and clinical data exchange elements. CDC is also engaged with external partners, such as The Joint Commission, to increase reporting.

The COVID-19 pandemic demonstrated how quickly CDC can update the NHSN to meet emerging needs. Within weeks, thousands of health care facilities had the ability to report cases. CMS required 15,000 long-term care facilities and 5,000 dialysis units to provide COVID-19 data, which helped public health authorities monitor the impact of the pandemic on facilities and direct critical supplies to the areas most affected. NHSN data informed guidance on vaccine effectiveness and booster recommendations, as well as vaccine mandates for HCWs. Dr. Srinivasan said the NHSN realizes the promise of electronic health data for public health surveillance; CDC envisions it as the central data system for health care preparedness.

DISCUSSION

Dr. McDermott noted that there is no established, routine approach to comparing animal AMR data across global systems. Cooperative approaches wax and wane, although targeted efforts do occur. There is consensus that NARMS should capture actual antimicrobial use on farms rather than infer use based on sales data, and that is a long-term goal. William Flynn, D.V.M., of FDA's Center for Veterinary Medicine added that much work remains to achieve that goal.

Marjory Cannon, M.D., of CMS explained that her agency uses a combination of regulatory authority, interagency partnerships, and quality improvement programs to reach out to nursing homes with deficiencies in infection prevention and control. Dr. Larson noted that, in some

cases, deficiencies persist. She urged CMS and CDC to focus on using the data collected to change practice on the ground.

Dr. Srinivasan said that CDC captures granular data on antibiotic use in outpatient settings through a separate information source that can be linked to NHSN data through geocoding. CDC hopes to eventually combine the findings of multiple national data collection systems, such as the Department of Veterans Affairs health system, to identify geographic variations in resistance patterns and correlation with antimicrobial use.

Dr. Srinivasan acknowledged that new drugs approved under an FDA emergency use authorization (EUA) sometimes require patient-level data collection; the NHSN is not equipped for such collection currently, but it could be considered for the future. Dr. Srinivasan looked forward to a time when NHSN data could assess antimicrobial use and resistance patterns, which could allow CDC to encourage uptake of effective new drugs in areas that would benefit from them.

Dr. Cook said ARS works closely with stakeholders and collaborators across agencies to identify its research priorities. ARS pursues research in areas where it is likely to have the most impact and for which it has the personnel and funding to support high-quality work. Dr. Cook added that ARS' work aims to promote equitable and sustainable solutions that work for humans, animals, and the environment. The effect of climate change on AMR is addressed through ARS working groups and is recognized as a focus area.

Panel 3: Transforming Medical Defenses

An Introduction to Project Firstline

Elizabeth McClune, M.S.W., M.P.A., CDC

Project Firstline reframes infection prevention and control in health care settings by spotlighting the actions that everyone in that setting should take and the systems that support those actions in a culture of shared responsibility. Without sufficient education and training, gaps remain, and that culture cannot develop, Ms. McClune observed. Project Firstline's training includes tailored materials that responds to individual HCWs' reading level, preferred language, role, and setting. It seeks to highlight the vital role of every HCW and create a culture of expertise across the field.

The project began by months of listening sessions with HCWs to understand their needs and challenges. This step revealed that HCWs sometimes perceive infection prevention and control guidelines as arbitrary rules and the related training as irrelevant to their daily work. Project Firstline developed more responsive materials and short, on-demand educational content that always convey clearly why infection control is relevant. It brings its tools and messages to HCWs through social media platforms they are already using. When new guidance emerges, Project Firstline offers platforms for HCWs to get answers to specific questions. Notably, Project Firstline relies on partnerships and collaborations to reach HCWs through people and channels they trust with consistent messages tailored to target audiences.

Project Firstline seeks sustainable funding to expand its reach to all segments of the health care workforce, empowering more HCWs to implement and advocate for better infection control. It aims to collaborate with more health care facilities to better integrate infection control in

practice. Project Firstline also seeks to build the capacity of public health systems to communicate about the threats of AMR and HAIs. Ultimately, it hopes to integrate AMR prevention into formal health care professional educational curricula.

Agency for Healthcare Research and Quality (AHRQ) Safety Program for Improving Antibiotic Use: Development and Implementation of Three National Antibiotic Stewardship Interventions and Toolkits

Sara E. Cosgrove, M.D., M.S., PACCARB Member and Professor, Johns Hopkins University School of Medicine

Dr. Cosgrove described the implementation of the AHRQ Safety Program for Improving Antibiotic Use, which combines fundamental tenets of patient safety, teamwork, communication, and evidence-based practice. Three interventions—lasting one year each in acute, long-term, and ambulatory care settings over three consecutive years—revolved around four key steps, or moments, in decision making about antibiotic use, which varied slightly depending on the setting. The four moments prompted HCWs to (1) consider whether the patient needs an antibiotic, (2) take steps to determine which antibiotic is needed, (3) consider the appropriate duration of treatment, and (4) determine when and how to reassess the treatment. The interventions and toolkits addressed three domains:

- **Activities required for successful stewardship:** Defined leadership structure, interventions to improve antibiotic use, and metrics to track progress and guide activities
- **Behavioral issues in antibiotic prescribing:** Addressing behavioral drivers of decision making among clinicians, patients, and families and improving teamwork and communication
- **Best practices for common infectious diseases:** Offer training by syndrome, not by antibiotic, and organize materials around the four moments of decision making

Participating sites took part in webinars, at least monthly, throughout the year and monthly checkups with an expert who was always available for questions. Sites reported data and received quarterly feedback so they could compare their performance with other participating sites. Participation in all three intervention programs was excellent and, overall, each setting type demonstrated significant measurable success around antibiotic use. Dr. Cosgrove said the results suggest that behavioral issues around antibiotic use should receive as much attention as knowledge gaps. There remains a critical need for approaches to ensure that robust antibiotic stewardship activities are implemented and maintained across health care settings. Toolkits available on the AHRQ website offer detailed guidance for sites to implement the intervention on their own.

Catalyzing Antibiotic Development

Mark Albrecht, Ph.D., Antibacterials Branch Chief, BARDA, Office of the Assistant Secretary for Preparedness and Response, HHS

Development of new antibiotics, and addressing MDROs in particular, is an ongoing priority for BARDA, whose mission encompasses biological, chemical, radiological, and nuclear threats. BARDA works with other federal agencies and international partners to support a robust pipeline for antibiotic development and to overcome the economic disincentives that discourage businesses from pursuing new antibiotics. The initial NAP CARB called for the creation of

CARB-X, which concludes this year. BARDA's next-generation biopharmaceutical accelerator, NEXT-X, is a 10-year project that will offer a more flexible structure for funding projects and a strategy for sustainability over the long term.

Among BARDA's top priorities is a mechanism to address both multidrug-resistant infections and biothreats. It remains focused on innovative products, such as first-in-class compounds with novel mechanisms of action and nontraditional compounds, as well as improved formulations, delivery approaches, and other advances that offer significant improvements over existing products. BARDA is committed to supporting R&D that tackles the most challenging indications and reaches underserved patient populations (especially pediatric populations, who represent 25 percent of the U.S. population but for whom the fewest antibiotics are approved).

Dr. Albrecht described various BARDA efforts to expand health security through Project BioShield, including its goal of developing four new antibiotics by 2030 through public-private partnerships and updating the U.S. stockpile of antibiotics to prepare for new and emerging drug-resistant pathogens. Project BioShield supported development of omadacycline, which was approved by FDA in 2018 for community-acquired bacterial pneumonia.

National Institute of Allergy and Infectious Diseases' (NIAID's) Ongoing Role in AMR Initiatives

Dennis M. Dixon, Ph.D., Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, NIAID, NIH

NIAID's 2019 document, [Antibiotic Resistance Research Framework: Current Status and Future Directions](#), remains the most current outline of its approach to AMR. Dr. Dixon pointed out that NIAID's work to support development of medical countermeasures is often overlooked but includes free preclinical services to investigators to support product development and targeted initiatives aimed at areas of public health need. These efforts help investigators advance their work to the point where BARDA can propel the work toward commercial development. Several of NIAID's targeted solicitations call for research on diagnostics, recognizing that good antimicrobial stewardship relies on better, faster diagnostic tools.

NIAID funds many AMR research efforts involving, for example, gram-negative pathogens, vaccines, immunoprophylactics, and bacteriophage therapy. Dr. Dixon described a clinical trial using automatic prompts from the electronic health record to decrease unnecessary prescribing of antibiotics, which successfully reduced use of broad-spectrum antibiotics for hospitalized patients with pneumonia or urinary tract infections. The trial is continuing and is currently developing algorithms to inform the provider about the likely risk of a given syndrome in a particular hospital, based on hospital and patient data.

DISCUSSION

Dr. Cosgrove pointed out that the AHRQ intervention in ambulatory settings kicked off in December 2019 and thus coincided with the start of the COVID-19 pandemic, making it difficult to distinguish the effects of the intervention from those of the pandemic. However, rates of antibiotic use in the participating ambulatory sites continue to decline, which is not the case in other facilities. Dr. Cosgrove noted that the use of home tests for COVID-19 before seeking in-

person care is an approach that could translate to other conditions for which diagnostic tests are available.

Participating sites committed about 10 hours a month of time, without funding support, to engage in the program. Dr. Cosgrove and her colleagues provided advice and aided site staff in making decisions about the use of antibiotics. She acknowledged that some of the success of the interventions may have resulted from selection bias, as sites volunteered to take part, but she pointed out that many were small facilities, such as community and rural hospitals, that needed the external expertise provided. The toolkits are not a perfect substitute for access to experts, Dr. Cosgrove noted, but they do offer useful information on managing infectious diseases.

Dr. Cosgrove observed that during the intervention, webinars and other materials covered the need to individualize the duration of antibiotic treatment, which may counter the current dogma of completing the entire course of antibiotics. Dr. Dixon noted that large, expensive trials have yielded only moderately useful answers to questions about the ideal duration of antibiotic therapy. He added that the Antibiotic Resistant Leadership Group seeks to disseminate results around limiting antibiotic treatment duration and using diagnostics when available, among other ways to improve antibiotic use.

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.

Brad Chartrand of Prevent Plus pointed to research calling for development of novel polymeric systems to treat resistant microbial infections. Preventogen is a liquid polymer that kills viruses, fungi, and bacteria on contact by lysing the cell. It leaves a durable film on the skin that keeps out debris and promotes wound healing. Data indicate Preventogen is effective against multiple pathogens, including MRSA and *Enterobacter cloacae*.

John Sperzel of T2 Biosystems described his company's products, which identify sepsis-causing pathogens from blood tests within hours. FDA has approved T2 rapid detection tests for bacteria and *Candida* infection and has given EUA for a system that detects the virus that causes COVID-19. T2 Biosystems has four rapid diagnostic products in development with support from BARDA. Two are slated to begin clinical trials in 2022—one that detects antibiotic resistance genes and one that identifies pathogens designated as biological threats. It is also working on a comprehensive sepsis detection panel and an automated instrument to detect a wide range of pathogens and resistance genes.

Matt Sweede of Locus Biosciences said his company developed bacteriophage therapy. With support from BARDA, its phage therapy for urinary tract infections caused by *Escherichia coli* has advanced to clinical trials. Thanks to a CARB-X award, a product targeting UTIs caused by *Klebsiella pneumoniae* is advancing. Other efforts are focused on *Pseudomonas aeruginosa* and *S. aureus*. Mr. Sweede called for support of the PASTEUR Act and the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act.

Matthew Henn, Ph.D., of Seres Therapeutics explained that his company is developing mechanisms to restore the microbiome and prevent colonization and overgrowth of pathogenic bacteria. SER-109 delivers spore-forming Firmicutes bacteria orally to reduce the risk of recurrent *C. difficile* infection. It has been shown to be effective in a phase III trial. SER-155 is a combination of bacteria designed to prevent multiple diseases by targeting bacterial pathogens in the gastrointestinal system and reducing their abundance. Studies have provided strong proof of concept in humans that SER-155 can address novel AMR infections, and the compound is currently in clinical safety trials.

Oliver Liesenfeld, M.D., of Inflammatrix described two diagnostic tests in clinical trials; both use mRNA to identify viral or bacterial infection with high sensitivity and specificity. These host response tests will provide information that allows clinicians to rule in or rule out infection at the point of care, with confidence, and in less than 30 minutes. The findings will help guide initial antibiotic prescribing and assessment of the need for additional antibiotic therapy.

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 felt the meeting highlighted a lot of challenges but also offered more reasons for optimism than past convenings. The strong support from new leadership bodes well for the Council's future work, he noted. Dr. Blaser adjourned the meeting at 3:12 p.m.

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

November 30–December 1, 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
Emily Wheeler

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

Marjory Cannon, M.D. (for Shari Ling, M.D.), Centers for Medicare & Medicaid Services (*day two*)

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

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

Shari Ling, M.D., Centers for Medicare & Medicaid Services

Melissa Miller, M.D., M.S., FCCM, Agency for Healthcare Research and Quality

U.S. Department of Agriculture

Neena Anandaraman (for Jeffrey Silverstein, Ph.D.), Agricultural Research Service (*day two*)

Emilio Esteban, D.V.M., M.B.A., M.P.V.M., Ph.D., Food Safety and Inspection Service

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

Chloe Loving, M.P.H., CHES, CPH, ORISE Fellow, 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
ARS	Agricultural Research Service
AWaRe	access, watch, and reserve (WHO classifications)
BARDA	Biomedical Advanced Research and Development Authority
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
COVID-19	coronavirus disease 2019
DMI	demethylation inhibitor
EPA	U.S. Environmental Protection Agency
EUA	emergency use authorization
FDA	U.S. Food and Drug Administration
G7	Group of 7
HAI	healthcare-associated infection
HCW	health care worker
HHS	U.S. Department of Health and Human Services
HICPAC	Healthcare Infection Control Practices Advisory Committee
LMICs	low- and middle-income countries
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NAP	national action plan
NAP CARB	National Action Plan on Combating Antibiotic-Resistant Bacteria
NARMS	National Antimicrobial Resistance Monitoring System
NASEM	National Academies of Science, Engineering, and Medicine
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
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)
PCAST	President's Council of Advisors on Science and Technology
PCORI	Patient-Centered Outcomes Research Institute
PEPFAR	President's Emergency Plan for AIDS Relief
R&D	research and development
U.K.	United Kingdom
U.N.	United Nations
UNICEF	United Nations International Children's Emergency Fund
USAID	U.S. Agency for International Development
USDA	U.S. Department of Agriculture
WASH	water, sanitation, and hygiene
WHO	World Health Organization