PRIORITIES FOR THE NATIONAL ACTION PLAN ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA: 2020–2025

A REPORT WITH RECOMMENDATIONS

JULY 2019

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

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EXECUTIVE SUMMARY

The rise of antibiotic-resistant bacteria poses a serious threat to public health and the economy. Antibiotic use in both human and veterinary settings selects for antibiotic resistance which has a negative effect on both human and animal health. The Centers for Disease Control and Prevention (CDC) estimated in 2013 that more than two million people in the United States acquire antibiotic-resistant infections every year, and at least 23,000 people die as a result; more recent estimates suggest the toll may be much higher.[1,2] To address this threat, the U.S. Government (USG) developed a National Strategy and accompanying National Action Plan (NAP) for Combating Antibiotic-Resistant Bacteria (CARB), which provides a roadmap for the federal government to work domestically and internationally to detect, prevent, and control illness and death related to antibiotic-resistant infections over five years (2015–2020). In September 2018, the Secretary of Health and Human Services tasked the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) with providing recommendations on key priority areas for the next iteration of the NAP, which will outline new objectives and milestones for continuing and expanding USG efforts to combat antibiotic resistance from 2020 to 2025.

Since 2015, the nation has made significant progress toward current NAP goals through the coordinated efforts of entities within the U.S. Department of Health and Human Services (HHS), the U.S. Department of Agriculture (USDA), the Department of Defense (DoD), and other departments and agencies, working in collaboration with international stakeholders and partners. In this report, the PACCARB assesses how the landscape has changed since the release of the NAP and identifies priorities that will facilitate USG progress towards advancing the objectives and milestones in the next iteration of the NAP. Some of the major developments achieved thus far are described below. For an extensive accounting of accomplishments, see the NAP progress reports for years 1 & 2 and year 3.

Infection Prevention (IP) and Antibiotic Stewardship (AS) in Health Care Settings

Promoting the appropriate use of antibiotics and limiting the need for antibiotics by supporting IP practices together have been a central focus of USG activities. Through the Antibiotic Resistance Solutions Initiative, CDC is coordinating hundreds of millions of dollars in investments at the federal, state, and local levels to combat antibiotic resistance. As a result of CDC's efforts, the number of hospitals with antibiotic stewardship programs (ASPs) that meet all of CDC's Core Elements of Hospital Antibiotic Stewardship Programs rose from 41 percent in 2014—the year the Core Elements were released—to 76 percent in 2017.[3] CDC also developed Core Elements for Outpatient Antibiotic Stewardship in 2016. To further incentivize adoption of ASPs, the Centers for Medicare & Medicaid Services (CMS) established a new Condition of Participation in 2016 for long-term care (LTC) facilities to develop and implement an ASP and have proposed a similar rule for hospitals.

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[1] Centers for Disease Control and Prevention. (2013). *Antibiotic resistance threats in the United States, 2013*. Retrieved from https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

[2] Burnham, J.P., Olsen, M.A., & Kollef, M.H. (2019). Re-estimating annual deaths due to multidrug-resistant organism infections. *Infection Control & Hospital Epidemiology, 40*(1), 112–113.

[3] Centers for Disease Control and Prevention. (n.d.). *Patient Safety Atlas*. Retrieved from https://gis.cdc.gov/grasp/PSA/STMapView.html

The USG has also increased its support for healthcare providers and local health departments through programs such as CMS' Hospital Improvement Innovation Networks and Quality Innovation Network-Quality Improvement Organizations and promotion of IP and AS implementation strategies in diverse healthcare settings through the Comprehensive Unit-Based Safety Program of the Agency for Healthcare Research and Quality (AHRQ). A significant part of AHRQ's recent work has focused on improving antibiotic prescribing in LTC facilities; such settings are increasingly recognized as key regional epicenters for the emergence and spread of antibiotic-resistant pathogens to acute care hospitals and into the community and will be critical to the CARB effort going forward.

Antibiotic Stewardship in Veterinary Settings

The Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM) has undertaken several key initiatives to optimize the use of medically important antimicrobials in animals. In 2012—even before the NAP was released—FDA published Guidance for Industry No. 209, which laid out principles for judicious use of medically important antibiotics in animal feed or water; by early 2017, all affected sponsors (i.e., developers and manufacturers) of animal drug products had worked voluntarily with FDA to align their products with the recommendations in the guidance documents.[4] In September 2018, CVM released a five-year plan, Supporting Antimicrobial Stewardship in Veterinary Settings. The plan includes specific objectives and actions to support the goals of aligning antimicrobial product use in animals with the principles of AS, fostering AS in veterinary settings, and enhancing monitoring of antimicrobial use and antimicrobial resistance (AMR) in animals.

Coordination and Enhancement of Reporting and Surveillance

Much of the progress in the CARB effort can be seen through enhanced coordination of federal agencies—working across the human and animal health domains—in tracking antibiotic use and antibiotic-resistant infections. Both DoD and the Department of Veterans Affairs are now participating in CDC's National Healthcare Safety Network (NHSN) antibiotic use and resistance reporting capabilities. Meanwhile, CDC, USDA, and FDA continue to expand the use and functionality of the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS), including development of interactive data visualization and analysis tools such as NARMS Now. Further supporting interagency coordination on CARB is the CDC and FDA Antibiotic Resistance Isolate Bank, which provides access to collected strains of antibiotic-resistant bacteria for further analysis, including whole genome sequencing. The National Institutes of Health (NIH) is partnering with CDC and FDA to sequence strains from the Antibiotic Resistance Isolate Bank and adding the sequence data to its National Database of Antibiotic Resistant Organisms. In 2016, CDC created the Antibiotic Resistance Laboratory Network to support laboratory capacity in all 50 states to detect and respond to antibiotic resistance.

[4] U.S. Food and Drug Administration. (2017, January 3; updated 2017, February 17). *FDA announces implementation of GFI #213, outlines continuing efforts to address antimicrobial resistance* [FDA News Release]. Retrieved from https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm535154.htm

Incentivizing the Development of New Products

New diagnostics, antibiotics, other therapeutics, and vaccines are needed to prevent, diagnose, and treat antimicrobial-resistant infections in humans and animals. Since 2015, new policies and programs have been established to incentivize development of new products to combat antibiotic resistance, and strategic investments have expanded the product pipeline significantly. The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is a five-year, $550-million, global public-private partnership dedicated to accelerating research and advancing antibacterial products into clinical development.[5] Funded by the Biomedical Advanced Research and Development Authority (BARDA), NIH/National Institute of Allergy and Infectious Diseases (NIAID), the Wellcome Trust, the Bill & Melinda Gates Foundation, and the governments of the United Kingdom and Germany, CARB-X has invested more than $110 million in 42 projects conducted by companies in six different countries since its launch in 2016. Outside of CARB-X, since 2010, BARDA has supported advanced clinical research and development (R&D) of a portfolio of 14 novel antibacterial candidates. In the past two years alone, BARDA has successfully shepherded three products—plazomicin, meropenem/vaborbactam, and eravacycline—through the FDA's regulatory approval process. NIH and BARDA also launched the Antimicrobial Resistance Diagnostic Challenge in September 2016, which incentivizes the development of rapid, point-of-need, in vitro diagnostics that can be used to improve AS. BARDA's investment in diagnostics continues, for example a new point-of-care *C. difficile* diagnostic assay received FDA clearance in 2017.

Additionally, the 21st Century Cures Act established the Limited Population Pathway for Antibacterial and Antifungal Drugs, which provides the FDA a novel mechanism to review and approve drugs intended to treat serious or life-threatening infections in a limited population of patients with unmet medical needs. In September 2018, amikacin liposome inhalation suspension became the first drug approved under the new pathway; it is indicated for treatment of lung disease caused by *Mycobacterium avium* complex in patients who do not respond to conventional treatment.[6]

Improving International Collaboration and Capacities

The USG has promoted immediate and lasting action globally to combat AMR through diplomacy, scientific engagement, and capacity-building activities that seek to garner political support for combating AMR and enable country and community ownership of AMR initiatives. World leaders at the 71st United Nations General Assembly High-Level Meeting on AMR affirmed AMR as a grave threat to human health and adopted a U.N. Resolution calling for specific global multisectoral actions to combat AMR. In April 2019, the U.N. Interagency Coordination Group on AMR, which includes U.S. representatives, published its final AMR guidelines describing practical approaches to support sustained, global action to address AMR.

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[5] Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator. (n.d.). *About CARB-X*. Retrieved from https://carb-x.org/about/overview/

[6] U.S. Food and Drug Administration. (2018, September 28.) *FDA approves a new antibacterial drug to treat a serious lung disease using a novel pathway to spur innovation* [FDA News Release]. Retrieved from https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm622048.htm

Through the Transatlantic Task Force on Antimicrobial Resistance, the United States has worked with the European Union, Canada, and Norway to coordinate R&D of new AMR products—including aligning NIH and EU clinical trial networks to facilitate access to patients and working toward alignment of regulatory requirements and processes for new product approval—and to harmonize AMR surveillance practices. For animal health, in 2015, the World Organisation for Animal Health (OIE) convened a group of experts to prioritize investments in animal vaccine development for diseases and syndromes that are the primary drivers of antibiotic consumption in animal agriculture. The group also developed recommendations for securing sustained and sufficient funding for R&D on these important animal vaccines.[7] Concurrently, United States and partners began implementing the Global Health Security Agenda AMR action package in 2015 to assist the 17 Phase I countries identified in the agenda in developing national action plans and surveillance capacity. Work on this action package will continue in 2019 and beyond.

Remaining Challenges and Identified Priority Areas

Despite these advances, significant obstacles to combating AMR remain, and more work is needed to reduce the health and economic burden of AMR infections in the United States and globally. The USG has made substantial investments in spurring the development of new antibiotics, diagnostics, and other products for combating AMR; however, this area of R&D continues to be unattractive to the private sector, so novel models are needed to incentivize new R&D. Challenges also remain in achieving AMR surveillance through a One Health lens, particularly the environmental surveillance needed to discover reservoirs of AMR bacteria and to characterize their role in AMR transmission dynamics for human and animal health. Over the past several years, hospitals have observed a sharp rise in fungal infections caused by resistant pathogens such as *Candida auris*, raising significant concerns about IP and appropriate treatment. These examples provide a snapshot of the continued challenges facing the USG in combating AMR. Therefore, sustained financial and long-term organizational support of ongoing CARB initiatives and the development of novel initiatives to address outstanding gaps are critical to building on the significant investments and gains described above.

Overall, the PACCARB has concluded that most of the priorities already included in the NAP should continue and be updated on a regular basis. The following priorities apply to human, animal, and environmental health and are further explained in the body of the report. Any action items are for consideration by the USG and respective agencies involved in the CARB effort.

1. **Research, Implementation, and Measurement**

    - Continue to research, develop, and implement best practice interventions for AS and IP within and across all human and animal healthcare settings through evidence-based approaches.

[7] Hoelzer, K., Bielke, L., Blake, D. P., Cox, E., Cutting, S. M., Devriendt, B., … Van Immerseel, F. (2018). Vaccines as alternatives to antibiotics for food producing animals. Part 1: challenges and needs. *Veterinary Research*, *49*, 64. Retrieved from https://veterinaryresearch.biomedcentral.com/articles/10.1186/s13567-018-0560-8

- Develop metrics to measure and track the effectiveness and outcomes of the interventions.

2. **Incentives**
    - Develop and implement incentives to advance uptake of AS and IP programs.
    - Expand push incentives and adopt pull incentives to spur drug and diagnostics discovery and licensing.[8]
3. **Data Management and Interoperability of Systems**
    - Use all available data sources across One Health domains to improve surveillance and stewardship.
    - Determine a priori the specific goals and objectives for collecting data to better refine the analysis and decrease the burden of reporting.
4. **Funding State and Local AMR Programs**
    - Dedicate funds to enhance collaboration among federal, state, and local AMR programs.
    - Incentivize such collaborations to include more interdisciplinary One Health efforts among animal, agriculture, and environmental domains.
5. **Communication and Awareness**
    - Provide resources to study and support effective programs that promote awareness of the complex issue of AMR among the public and strengthen the understanding of AS, IP, and other AMR issues among professionals.
    - Prioritize research that identifies behavioral obstacles among all audiences and focuses on strategies that address these obstacles.

The PACCARB also recommends the following three areas be incorporated across all goals in the NAP to embody a One Health approach to combating resistance:

1. **U.S. Global Leadership**
    - Provide technical, political, and societal leadership to champion AMR issues as a global priority and provide support to low- and middle-income countries for implementation of national AMR plans.
    - Dedicate funds to support USG efforts to lead global AMR programs so as not to overburden domestic CARB efforts.

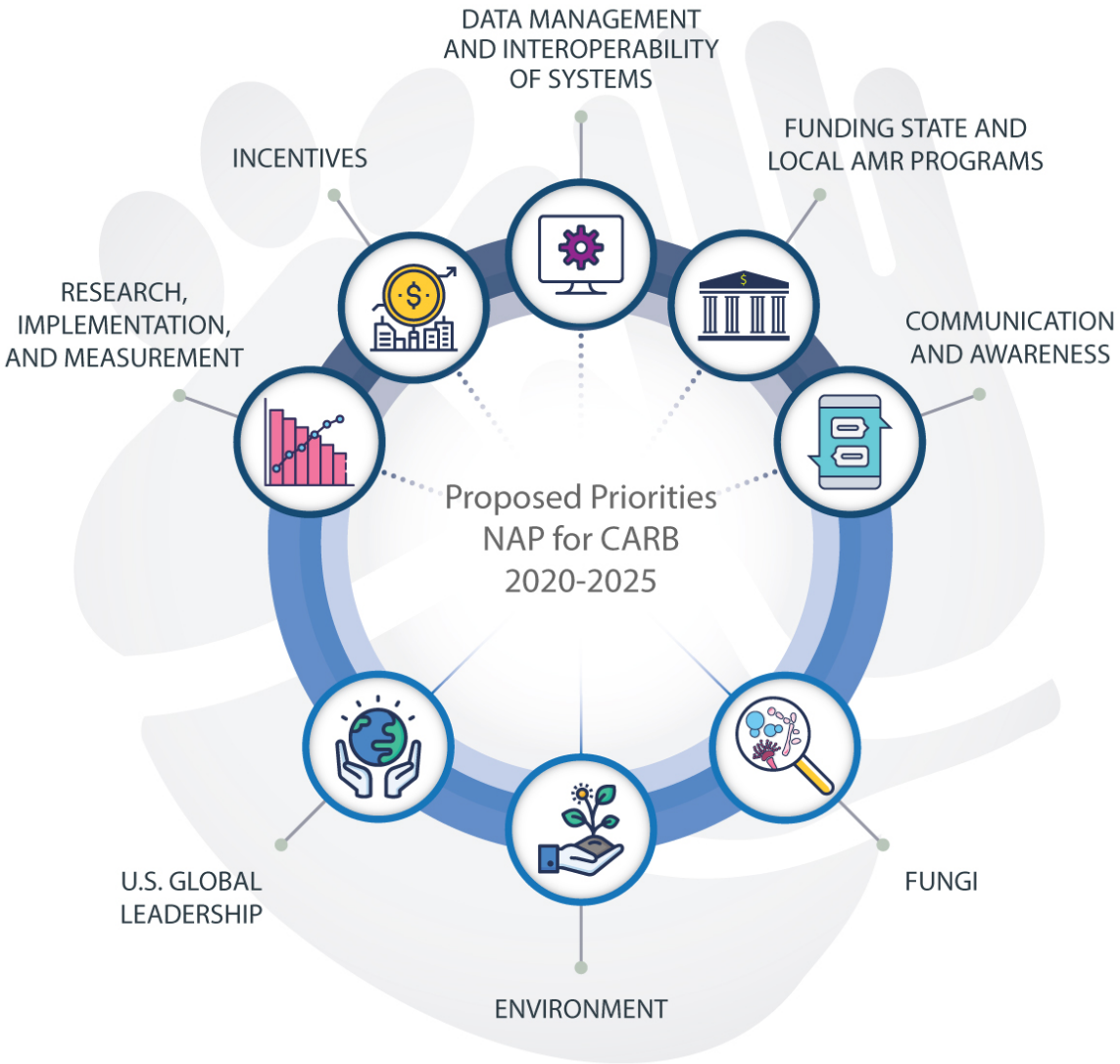
[8] Push incentives provide support for research and development of products, while pull incentives help ensure adequate commercial markets for products once developed.

2. **Environment**

    - Conduct interdisciplinary research to better understand the role of the environment as a reservoir for clinically significant AMR in humans and animals and include environmental data points in surveillance based on that research.

3. **Fungi**

    - Include milestones and objectives for prevention and control of pathogenic fungi resistant to antimicrobial agents and periodically include other nonviral pathogens of clinical and epidemiological importance.



The diagram depicts the five priorities (top) within the context of the three additional areas (bottom) that are recommended to be further emphasized in the NAP for CARB, 2020–2025, through a One Health perspective (background image).

INTRODUCTION

In September 2018, the Secretary of Health and Human Services, the Honorable Alex M. Azar II, tasked PACCARB to provide recommendations on key priority areas for the federal interagency CARB Task Force to consider when developing the next iteration of the NAP for CARB (see Annex I). The recommendations in this report reflect what PACCARB recommends that the USG prioritize as key areas under each of the five existing NAP goals to continue and expand national progress on combating AMR.

Summary of the NAP

The NAP for CARB was released in March 2015 and outlines specific objectives and milestones for implementing the National Strategy for CARB. The objectives and milestones are organized under five major goals:

Goal 1: Slow the emergence of resistant bacteria and prevent the spread of resistant infections.

Goal 2: Strengthen national One Health surveillance efforts to combat resistance.

Goal 3: Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.

Goal 4: Accelerate basic and applied R&D for new antibiotics, other therapeutics, and vaccines.

Goal 5: Improve international collaboration and capacities for antibiotic resistance prevention, surveillance, control, and antibiotic R&D.

The current NAP outlines activities for the years 2015 to 2020. The CARB Task Force is in the process of writing the next iteration of the NAP, which will provide new objectives and milestones for 2020 to 2025.

Role of the Task Force and the PACCARB

Established in 2015, the federal interagency Task Force on CARB is made up of government agencies that have a stake in combating antibiotic resistance. Its membership includes HHS agencies, DoD, USDA, the Environmental Protection Agency, the State Department, and other federal agencies. As designated through the founding executive order, the Task Force's goal is to promote collaboration and awareness of AMR-related activities across all government sectors. As such, the Task Force was the initial creator and holder of the current NAP, and it continues to oversee the NAP's progress. This progress is reflected in annual progress reports and year 1, 3, and 5 milestone reports.

The PACCARB was established along with the Task Force as part of a coordinated effort by the USG to respond to the threat of AMR. The role of the PACCARB is to use subject matter expertise outside of the USG, with input from the public, to provide recommendations to the Secretary on key policy directions or needs as the USG continues to fight AMR. This report describes the PACCARB's recommendations on priority areas to be considered by the Task Force for inclusion in the next iteration of the NAP.

Process

To accomplish its task, the PACCARB created the NAP for CARB 2019 Working Group (WG), with members from PACCARB and the federal interagency Task Force. The purpose of the WG was to foster collaboration and information-sharing between government and external subject matter experts in the development of recommendations. The federal agencies represented on the WG served as resources to the PACCARB members on the WG. Ultimately, the WG ensured that recommendations made by the PACCARB would not only advance efforts to combat AMR but also that the identified priority areas include feasible, attainable actions for consideration by federal partners.

To gain extensive feedback from involved stakeholders, the PACCARB put out a request for information asking for public input on priority areas for consideration in the next iteration of the NAP. A total of 180 comments from 67 respondents were consolidated and presented to the PACCARB and members of the WG. In addition to the request for information, the PACCARB received input from stakeholders and the public during its 11th public meeting, January 30–31, 2019. This meeting included two days of panel presentations with a range of stakeholders from animal health, human health, and the environment, with both domestic and international perspectives. Thirty-one panelists over eight panels made presentations. These presentations were carefully curated to ensure input from a diverse range of stakeholders as a way to prioritize PACCARB's commitment to a One Health perspective on all recommendations found in this report. As requested by the Secretary, this report includes the summary from the 11th public meeting (see Annex II). A draft of this report with recommendations was presented to the full PACCARB at the July 10, 2019 public meeting for further evaluation and discussion. At that meeting, the final version was approved unanimously for transmittal to the Secretary.

Organization of the Report

The recommendations put forth in this report represent the perspectives of the PACCARB as informed by public comment through the request for information, expert advice from the 31 panelist presentations at the 11th public meeting, analysis and synthesis work completed by the WG, and accumulated input from previous PACCARB meetings and working groups. The recommendations reflect close collaboration and deliberation between WG members and USG agency partners, resulting in a thorough set of priorities. Even though this report represents the consolidated opinions of the PACCARB members, the public meeting and discussions constitute a much broader depiction of the public's perspective. (Members of the PACCARB are listed in Annex III. The PACCARB Charter and Authorizing Legislation appear in Annex IV.)

The top priorities for the next NAP, as identified by the PACCARB, are presented in the context of the existing five goals of the NAP. Each priority is stated as an overarching objective and is followed by additional, specific actions that would advance progress toward the objective. Consistent with a One Health approach, priorities may encompass any combination of human, animal, and environmental health concerns. Some of the recommendations also represent reiterations of previous reports developed by the PACCARB; therefore, cross-reference to previous recommendations is indicated in the text. Given the current NAP's focus, the priorities in this report address antibiotic-resistant bacteria only.

In addition to the priorities within the five goals of the NAP, the PACCARB presents three additional recommendations for large-scale, interdisciplinary programs to help coordinate and advance national and international CARB efforts, within five years or beyond.

GOAL 1

SLOW THE EMERGENCE OF RESISTANT BACTERIA AND PREVENT THE SPREAD OF RESISTANT INFECTIONS

The current NAP offers objectives and strategies for reducing unnecessary antibiotic use in healthcare and veterinary settings and for identifying factors that lead to successful AS and IP. The next NAP should advance the progress that has been made over the past five years by focusing on research and implementation of programs and approaches that are demonstrated to be effective for IP and promoting judicious use of antibiotics. These efforts should be paired with measurement of implementation success (in terms of uptake and impact on use and resistance) for continued quality improvement and long-term sustainability. To further advance progress in this area, the NAP should encourage utilization of new technologies and cross-sector data streams to enable identification and implementation of successful intervention strategies.[9]

Priority 1: Advance implementation of IP and AS programs through measurable, outcomes-based research.

- Support implementation of AS and IP programs by focusing on activities that have been demonstrated to be effective in reducing antibiotic use and incidence of antibiotic resistance in both human and animal health. The next iteration of the NAP should include a focus on how to move from research to implementation as it applies to IP and AS through a combination of the following:
    - Supporting research to develop improved methods and approaches for IP and AS
    - Supporting research to develop effective implementation strategies for IP and AS
    - Prioritizing evidence-based methods and approaches that warrant implementation in the near term
    - Conducting wide-scale projects to promote the implementation of these methods and approaches by clinicians and veterinarians and to sustain their impact (see Priority 2)
    - Incorporating measurement and evaluation of program outcomes, through devised metrics that will help track uptake and success of interventions, to determine how well programs work to achieve their intended goals and to understand whether they need to be modified
- In addition to continuing work in the acute care setting, support research on and implementation of other high-priority improvement initiatives, such as the following:

[9] Several of the items in this section were previously recommended in the PACCARB report on IP and AS (see Sections I-1, I-5, I-6, II-1, II-5, and II-7): Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (2018, September). *Key strategies to enhance infection prevention and antibiotic stewardship. Report with recommendations for human and animal health*. Retrieved from https://www.hhs.gov/sites/default/files/final-ips-report-10-03-2018.pdf

- Develop and evaluate programs for IP and AS at LTC facilities, particularly those that care for ventilator-dependent patients (e.g., long-term acute care hospitals [LTACHs] and ventilator skilled nursing facilities [vSNFs]) to assess how these high-risk facilities can control the spread of AMR within and outside of the facility, improve AS, and produce the safest environments for residents. These facilities are key regional epicenters for emerging AMR.
- Determine and evaluate what approaches to implementation of best practices are successful for improving antibiotic stewardship in the outpatient setting. Conduct further studies to identify additional AS practices to implement in these settings.
- Determine and evaluate approaches to improve communication among facilities and providers at the time of transitions of care (e.g., LTACH to acute care hospital or acute care hospital to outpatient provider) regarding patient-specific data on colonization or infection with resistant organisms and antibiotic regimens.
- Evaluate national variability in antibiotic prescribing practices to understand the basis for these differences and to develop interventions to improve prescribing in areas that have the highest per capita rates of antibiotic use.
- Evaluate IP and AS strategies for animal agriculture to determine what practices are being used and how well they work to reduce antibiotic use or incidence of resistance. For example, evaluate the impact of better biosecurity on disease risk or impact of stewardship practices on antibiotic consumption.
- Support research efforts within the USG (e.g., USDA Agricultural Research Service [ARS]) and universities to identify mitigation strategies and critical control points.

- Address specific gaps in research funding that are needed to promote implementation of AS and IP programs as outlined in the points above.
  - Fund research on approaches for behavior change as it relates to IP and AS interventions undertaken by healthcare workers and veterinarians. A better understanding of evidence-informed behavior change strategies, overall, will improve implementation and uptake of IP and AS best practices for both human and animal health.
  - Fund academic efforts to develop and study transdisciplinary educational strategies and curricula to facilitate knowledge of best practices in IP and AS. Education is a critical component of implementation of IP and AS, but optimal strategies for effectively delivering it to healthcare workers and veterinarians are lacking.
  - Increase funding for career development awards to support new investigators in IP and AS research and implementation science. While agencies such as NIH/NIAID and AHRQ provide some support for career development (through K grants), the lack of prioritization of funding for career development awards in IP and AS limits the entry of clinician-scientists in these areas.

Priority 2: Widely implement IP and AS strategies that have been proven effective throughout healthcare settings and animal agriculture.

- Increase federal funding for state and local health departments and regional healthcare quality improvement support networks, including CMS' quality improvement and innovation networks such as the HIINs and QIN-QIOs, which provide technical assistance to help implement successful IP and AS programs across multiple settings of care, including acute, long-term, and outpatient care. These organizations are encouraged to employ existing, tested, publicly available toolkits for implementation of IP and AS activities, such as those developed by AHRQ and CDC.
- Finalize the CMS Conditions of Participation requiring AS programs in hospitals, including critical access hospitals. As indicated in the April 2019 one-page report, the PACCARB believes that doing so represents a critical step in ensuring widespread adoption of AS principles.
- Ensure that CMS creates accompanying interpretive guidance for anticipated Conditions of Participation in hospitals and uses its quality, safety, and oversight mechanisms to facilitate and enforce IP and AS across healthcare settings, for example through surveys that identify specific actions to improve IP and AS.
- Support and create where necessary a set of regulatory and financial incentives for LTC facilities and outpatient providers to improve IP and antibiotic prescribing. Include incentives for outpatient providers and LTC facilities—especially LTACHs and vSNFs—to improve IP and antibiotic prescribing through the use of existing CMS levers, such as quality reporting programs. The goal of such incentives is to encourage providers to incorporate appropriate antibiotic use and stewardship principles into their facilities' operational structure and use data to improve performance.
- Implement specific IP and AS requirements and allocate IP and AS resource reimbursement for higher-risk services that could benefit the most from such interventions (e.g., LTACHs and vSNFs, which treat large numbers of patients on ventilators or who have tracheostomies). Investigate ways for agencies to create positive financial incentives for IP and AS in all areas of healthcare. Positive incentives can help to ensure adequate staffing levels for IP and AS work and to avoid the spiral of institutions being penalized for inadequate IP and AS, resulting in a further decrease in resources for this work.
- Support and encourage agricultural cooperative extension services to include stewardship in their educational programs at the state and local levels.
- Encourage the adoption of IP and AS programs along the food supply chain and ensure education incentives are incorporated into such programs. For example, financial incentives and cost-sharing for producers could promote uptake of proven mitigation strategies.

Priority 3: Promote AS in companion animal health settings.

- Enact full and timely implementation of FDA's Supporting Antimicrobial Stewardship in Veterinary Settings plan (the CVM five-year plan) to promote stewardship in companion animal settings with special emphasis on animal hospitals and companion animal clinics. This plan calls for robust stakeholder engagement in the development of a comprehensive companion animal AS strategy.
- Establish an FDA Companion Animal Task Force that engages with professional organizations, including those representing animal hospitals and companion animal clinics, to create and encourage adoption of an effective antibiotic and diagnostic stewardship program that includes reporting and sharing of antibiotic usage data. Initially, this task force should emphasize the availability, quality, and understanding of antibiotic use data and practices in multiple animal species and settings. In the longer term, focus should include understanding the unique veterinarian-client-patient relationship in various animal practice areas and how behavior influences prescribing practices and antibiotic resistance selection.
- Support implementation of existing best practice consensus guidelines for companion animal medicine (e.g., urinary tract infections, dermatology) and develop additional guidelines. The implementation of these guidelines also requires a strong emphasis on diagnostic stewardship. As in human medicine, the cost, availability, and interpretation of diagnostic tests greatly influences the ability to implement AS in daily practice. (See Goal 3 for detailed recommendations on diagnostic stewardship.)

Priority 4: Facilitate and support the adoption of new technologies and management practices that can reduce the need for antibiotic use in animal agriculture.

- Identify the specific areas where new technologies are needed most and will have the greatest impact. There is a need for an organized focus on management and technological interventions such as rapid animal-side tests (i.e., those that can be administered in an exam room or pen-side instead of requiring a laboratory), precision agriculture, epidemiological data management, and nonantimicrobial disease interventions. The USG, through agencies such as the Animal and Plant Health Inspection Service (APHIS) and ARS, can help direct private development of solutions by providing a roadmap that (1) assesses gaps, (2) prioritizes needs, and (3) develops strategies and initiatives to address the needs. The roadmap should align with existing agency and sector plans (e.g., the CVM five-year plan) and advance beyond them as needed.
- Streamline regulatory management of novel technologies. Additional funding for the appropriate entities in USDA and FDA will not only increase the speed of evaluation but also the speed at which the approval pathways are developed. Streamlining evaluation and approval will also address regulatory uncertainty, which can pose barriers to innovation and adaptation of new technologies.

- Explore and leverage data technologies (such as artificial intelligence) to enable new advances in combating AMR. Collect retrospective, publicly available, AMR-related data from disparate sources into one database and use these data to develop and validate new analytical tools. These data technologies can be used in a variety of ways, including performing risk assessments, developing mitigation strategies, informing future research, and early detection of emerging organisms and resistance (e.g., the mediated colistin resistance gene *mcr*-1).

Priority 5: Increase the use and interoperability of data systems to support AS.

- Develop incentives to encourage the use of standardized and interoperable electronic health records (EHRs) for both animal and human health. While much progress has been made in adopting the use of EHR in healthcare settings, the industry is plagued with a lack of standardization and interoperability across disparate systems. Meanwhile, EHR use across veterinary medicine remains inconsistent.
    - Work with the major EHR developers to ensure that AS, AMR, and IP data needed for local and regional stewardship and infection control activities can be generated routinely. Using existing regulatory levers, the USG should make the ability to produce such electronic reports a requirement for all healthcare EHRs by 2025.
    - Encourage the development and adoption of interoperable EHR systems for animal health. Learning from the experience of implementing EHRs in human health, provide USG guidance and recommendations on standardization to ensure interoperability from the outset.
- Encourage diagnostic laboratories to collaborate and share data across the One Health domains.
    - Support continued development and coordination of FDA's Veterinary Laboratory Information Network and USDA's National Animal Health Laboratory Network. Fund required infrastructure for cooperating laboratories, which is as critical for the success of the programs as internal support for FDA and USDA. Prioritize support for expanding AMR monitoring for animal pathogens.
    - Address the inability to get retrospective data from commercial laboratories. Commercial laboratories often do not dedicate resources to accumulate the data they generate in an accessible and usable format. Investigate incentives and guidance that would encourage data to be collected in a way that facilitates AS-related research.
    - Ensure that all laboratories—commercial, private, institution-based, and regional—have the capacity to produce isolate-level AMR electronic line list reports containing data elements necessary for meaningful regional AMR surveillance routinely and as needed. Through reimbursement policy and other regulations, require that all laboratory information systems be able to produce such electronic reports by 2023.

GOAL 2

STRENGTHEN NATIONAL ONE HEALTH SURVEILLANCE EFFORTS TO COMBAT RESISTANCE

Systems such as the NHSN, the National Animal Health Monitoring System (NAHMS), and NARMS are excellent resources for tracking antibiotic use and resistance in humans and animals. The PACCARB acknowledges the tremendous amount of data already being gathered by these systems and the extensive surveillance work they enable. To reach the next generation of One Health surveillance, these systems should be expanded and better leveraged through incentives aimed to increase reporting and expand animal and especially environmental reporting systems integration, across One Health domains.

Priority 1: Enhance antibiotic use and resistance reporting systems for human and animal health.

NHSN and NAHMS provide important tools and data to support antibiotic use and resistance surveillance. These programs should be enhanced by providing incentives for use and financial resources to enable collection of more granular data.[10]

- Support, enhance, and refine reporting through NHSN.
    - Develop incentives to promote more widespread uptake and usage of the NHSN Antimicrobial Use and Resistance (AUR) module, which provides acute care facilities with an effective tool to strengthen their antibiotic surveillance through reporting and analysis of antimicrobial use and resistance. For example, the CMS Hospital Inpatient Quality Reporting Program could require the reporting of antibiotic use or resistance data to NHSN. Additionally, the proposed Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act of 2019 (S. 1712), which would provide an economic incentive for new antibiotic development by removing certain antibiotics from the Medicare Diagnosis-Related Group, would require hospitals that participate in the alternative payment mechanism to also report into AUR module.
    - Expand the NHSN AUR module to facilitate collection of antibiotic use and resistance data from settings other than acute care settings and develop incentives and mechanisms to assist such sites with collection of data.
    - Provide funding to CDC to expand NHSN such that increased collection and analysis of data on antibiotic use, antibiotic resistance, and healthcare-associated infections is feasible.

[10] Similar recommendations were made by PACCARB in its 2017 report on incentives (see Sections I-1.2 and II-1.2) and its 2018 report on IP and AS (see Section I-3). Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (2017, September). Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance. Retrieved from https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf; and Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (2018, September). *Key strategies to enhance infection prevention and antibiotic stewardship. Report with recommendations for human and animal health*. Retrieved from https://www.hhs.gov/sites/default/files/final-ips-report-10-03-2018.pdf

- Enhance the DoD Antimicrobial Resistance Monitoring and Research program, which provides centralized support to all DoD medical treatment facilities through reporting to NHSN. The program should apply clinically relevant outcomes analyses to the information obtained.

- Enhance participation in and use of NAHMS antibiotic use surveys.
  - Provide incentives for food animal producers to encourage participation in and use of the NAHMS antibiotic use and stewardship surveys. These surveys provide key insights into swine, catfish, dairy, beef cow-calf, sheep and goats, and beef feedlot production practices. Previous incentives that have shown promise include opportunities for benchmarking and free, confidential, on-farm testing.
  - To optimize incentives for using NAHMS, give additional funding to USDA/APHIS to conduct research for determining which incentives would be most valuable to participants. Support APHIS' proposed Antimicrobial Resistance Action Plan, which calls for longitudinal studies, national cross-sectional studies, and targeted studies to address knowledge gaps in AMR.[11] These efforts are essential in enhancing antibiotic use and resistance reporting.
  - To further enhance their usefulness, NAHMS surveys should strive to collect more granular, detailed, and comprehensive data. Surveys should eventually collect detailed antibiotic use data, including dosage, duration, and indication. To contextualize these data, the survey should also capture information on the incidence of key diseases that drive antibiotic use and on AS practices, such as the use of vaccines or management practices that can prevent the need for antibiotics to address certain animal health issues. In addition, expand the collection through NAHMS of other data important to stewardship—such as the use of animal health plans, role of the veterinarian in herd health management, or use of antibiograms to guide treatment decisions.
  - Implement legally binding protection of producer confidentiality and establish databases that can be used to capture data without compromising producer interests.
  - Incorporate research and outreach opportunities to provide producers with information that will help inform mitigations and interventions, including education regarding resistance and critical control points.

Priority 2: Expand AMR reporting through NARMS and fund supporting research.

NARMS tracks changes in the antimicrobial susceptibility of foodborne bacteria isolated from humans, retail meats, and cecal samples from food animals. While the current program provides useful

[11] U.S. Department of Agriculture, Animal and Plant Health Inspection Service. (2015, April). *Proposed initiatives from the USDA Antimicrobial Resistance Action Plan* [Info Sheet]. Retrieved from https://www.aphis.usda.gov/animal_health/nahms/amr/downloads/ProposedInitiatives.pdf

information, funding should be increased and incentives offered to allow for additional data collection and increased reporting. Likewise, efforts should be taken to promote a One Health approach while expanding the program through additional sampling and collaborations.

- Increase NARMS funding to grow its capacity and facilitate the collection of needed data.[12]
    - Expand antibiotic susceptibility test (AST) use to include more enteric bacteria. Currently NARMS only uses ASTs against *Salmonella* species, *Escherichia coli*, *Campylobacter* species, and *Enterococcus* species.
    - To serve One Health surveillance needs, expand NARMS surveillance to include environmental sampling. Furthermore, expand the NARMS trend analysis, which currently focuses on human health outcomes, to include AMR patterns within food animal pathogens.
    - Implement an on-farm component in coordination with APHIS' NAHMS program that includes maintaining premise confidentiality and rotation of sampling among different livestock and poultry sectors.
    - Broaden the collaboration of NARMS to include programs across other agencies and universities. Increased collaboration, particularly with the use of whole genome sequencing, will allow for easier and more meaningful analyses.
    - Implement incentives to increase reporting of needed data, for example free resistance testing and data for benchmarking across operations (which has been employed successfully by NAHMS).
    - Provide funding to support the expanded NARMS capabilities described above, including funding to conduct necessary research to identify methodologies, statistical validity, scope, and scale of sampling needed for environmental and on-farm sampling.
- Enhance NARMS data collection and use to include attribution studies, risk assessments, and identification of emerging resistant bacteria.
    - Fund research to identify the most appropriate laboratory indicators for resistance tracking in animal agriculture (e.g., target bacteria, antibiotics, and appropriate interpretive criteria), and ensure those data are captured in NARMS. Using historical data, develop recommendations for future surveillance that provide an accurate assessment of resistance trends (e.g., on-farm versus slaughter versus retail sampling).
    - Fund research to enhance the usefulness of NARMS data, to characterize emerging resistance on farms and in the environment, to identify risk associated with resistance,

[12] U.S. Food and Drug Administration. (2017, June). *Science Board review of the National Antimicrobial Resistance Monitoring System.* Retrieved from https://www.fda.gov/media/105455/download

and to define outcomes and mitigation opportunities associated with known and emerging resistances.

  - To enhance the usefulness of NARMS data, ensure data and reports, including emerging trend reporting, are produced and made available in a timely fashion. Data should be available in near real-time, and reports should be produced annually. Additionally, increase the transparency of data collected by providing timely public access to the data.

- Promote collaboration and data-sharing between NARMS and veterinary diagnostic laboratories.
  - Expand One Health surveillance efforts to include information on changing resistance patterns within food animal pathogens. Support expansion of NARMS to incorporate existing veterinary expertise at universities and data from veterinary diagnostic laboratories.
  - Encourage sharing of isolates within and outside NARMS to enhance information not captured in NARMS.
  - Establish a collaboration between NARMS and an existing isolate bank or create an isolate bank that includes both human and animal pathogens in an effort to implement the One Health approach in AMR surveillance. Several repositories for AMR isolates currently exist. The CDC and FDA maintain an AMR isolate bank that provides information on resistance of samples gathered from healthcare specimens, food, and the community to support diagnostic and drug development. The DoD's Multidrug-Resistant Organism Repository and Surveillance Network maintains a collection of resistant isolates originating from participating military hospitals.

Priority 3: Understand the role of antibiotics and resistance in the environment.

A One Health perspective requires an understanding of the flow of resistance within the environment caused by the release of antibiotics, resistance genes, and pathogens from production facilities and human and agricultural waste. The USG should formally include environmental objectives in the NAP to be met within the next five years.

- Study the introduction of antibiotics in the environment, including where they are found, where they come from, how they get there, how long they last, and whether they maintain antibiotic activity. Quantify the persistence of environmental antibiotics and associated resistance stemming from hospital, healthcare, and agricultural sources (especially those that produce wastewater).
- Perform research to better understand how antibiotics in the environment contribute to AMR. Develop new risk assessment models to study the fate and transport of antibiotics and resistance genes in the environment.

- Adopt an integrated water management, or One Water, approach to control the flow of resistance from wastewaters back to drinking water supplies. Fund research studies to fill the gaps in understanding of resistance dynamics across the One Water cycle and better define the magnitude of the risks.
- Connect environmental microbiology with existing animal and human health networks such as NARMS to help develop and implement mitigation strategies.

GOAL 3

ADVANCE DEVELOPMENT AND USE OF RAPID AND INNOVATIVE DIAGNOSTIC TESTS FOR IDENTIFICATION AND CHARACTERIZATION OF RESISTANT BACTERIA

The objectives within Goal 3 of the current NAP remain priorities for the next five years, and the next NAP should continue to focus on them, including development of new diagnostics and better integration of diagnostics into care. In addition, the next NAP should support more effective use of available diagnostics and emphasize enhancing their use in animal health (two areas that are lacking in the current NAP).[13]

Priority 1: Support studies that use clinical outcomes to evaluate the use of diagnostics and advance their integration into care.

- Fund outcomes research studies to monitor and evaluate the effectiveness of existing diagnostic use strategies and to identify new ways to integrate diagnostics into veterinary and human healthcare decisions.
    - Provide additional support to ensure optimal use of diagnostic tests across health care settings. Make new investments, such as through NIH, CDC, and AHRQ, to support outcomes studies to demonstrate to clinicians the impact specific diagnostic tests could have on patient outcomes and how to best incorporate them into clinical care and stewardship activities (in inpatient and outpatient settings). Use the data gathered from these studies to develop incentives to promote the use of appropriate diagnostic testing and the development of new diagnostic tests.
    - Study the relationship between early intervention and later treatment efficacy and how diagnostic tests could support using this relationship to influence decision making in production animal populations.
    - In companion animals, perform studies that demonstrate the value of integrating a diagnostic test over empiric use of broad-spectrum therapeutic regimens (which often overlap with human use).
- Perform research to understand the factors influencing uptake of diagnostics, especially in animal health settings.
    - Perform research to identify the cost-based factors that influence which tests are offered to practitioners by diagnostic laboratories and which tests are chosen by practitioners for a particular client or case. These factors may be different for companion animal

[13] Similar recommendations were made by PACCARB in its 2017 report on incentives (see Sections I-2 and II-2) and its 2018 report on IP and AS (see Sections I-4 and II-4). Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (2017, September). *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance*. Retrieved from https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf; and Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (2018, September). *Key strategies to enhance infection prevention and antibiotic stewardship. Report with recommendations for human and animal health*. Retrieved from https://www.hhs.gov/sites/default/files/final-ips-report-10-03-2018.pdf

diagnostics, which are generally relevant for individual patients, and production animal diagnostic results, which may be leveraged by a large population.

- Conduct research to understand the perceptions of practitioners and patients or clients on the value of diagnostic tests for limiting AMR and evaluate how, or even whether, factors such as the global spread of resistance change the behavior of practitioners, patients, or clients when choosing diagnostics.

- Support the optimal use of diagnostics and promote physician and patient education on appropriate use of diagnostics—that is, diagnostic stewardship.
  - Identify diseases for which effective treatment or prevention options exist and for which an existing diagnostic test might influence the choice of treatment or prevention, recognizing the significant economic and regulatory restrictions on treatment options. Link the value of a diagnostic test to its connection to treatment options rather than only factors such as sensitivity and specificity.
  - Support education that includes the benefits and limitations of diagnostics and focuses on behavioral aspects of implementing appropriate use of diagnostics, testing the correct patient, choosing the correct test, understanding performance characteristics, and interpreting the result within the clinical context. Expand education beyond the technical mechanics and epidemiological properties of the test to better illustrate how sample selection and collection procedures can influence test outcomes and interpretations. Promote an openness to innovative ways to assist clinicians in clinical decision making in addition to diagnostics (e.g., computerized algorithms).

Priority 2: Develop incentives and reimbursement strategies to support uptake of diagnostics.

- Address current deficiencies in diagnostic testing reimbursement that create barriers to use of diagnostics.
  - Ensure adequate reimbursement to support and incentivize the use of diagnostics as a way to limit empiric antibiotic use and encourage innovation in test development.[14]
  - Develop a strategy for diagnostics reimbursement that combines clinical and financial factors. Establish USG subspecialty WGs to create guidelines for clinically appropriate testing and collaborate with government and private payers to establish reasonable financial reimbursement strategies based on applicable technologies. Additionally, provide federal support for studies to establish the clinical and financial impact of

[14] For example, CMS, through the Protecting Access to Medicare Act has reduced reimbursement for most diagnostic tests by 10 percent in 2018 and an additional 10 percent in 2019, with another 10 percent cut anticipated in 2020. Alternate avenues are necessary to compensate for these continuing annual shortfalls. Otherwise, such cuts to diagnostics reimbursement threaten patient access to testing, which can drive increased empiric antibiotic use. In addition, inadequate reimbursement can discourage innovation of urgently needed new tests.

diagnostics and inform reimbursement strategies, including using data gathered from outcomes studies.

- Identify diagnostic tests that demonstrate a high medical value in combating AMR and prioritize their development and use.
    - Fund studies to determine which specific diagnostics are needed to combat AMR and that take into consideration any potential barriers to uptake of these priority tests, using data from outcome studies to demonstrate their effectiveness and value.
    - Once priority diagnostics are identified, establish a consortium in which manufacturers, professional organizations, and regulatory agencies can (1) cooperatively determine safe and effective reductions in regulatory requirements for medical and veterinary diagnostics with high medical value and (2) work to establish financial incentives that allow diagnostics manufacturers to develop priority tests and support the clinical trials required for FDA approval of diagnostics with high medical impact.
- Coordinate pull incentives for new antibiotics and new diagnostics. As policymakers develop and advance proposals to provide market entry rewards for new antibiotics that address unmet medical needs, include in these proposals components to appropriately incentivize diagnostic development and uptake. For example, require antibiotic developers who receive an entry reward to work with AST developers by providing active pharmaceutical ingredients or other necessary information and material for the development of ASTs. Set aside a portion of the award for diagnostic development.
- Leverage outcomes studies to incentivize appropriate use of diagnostics. Studies that show utility of diagnostics could drive financial return for companies and in turn drive diagnostic use. The results of such studies could then be used to devise clinically appropriate reimbursement strategies. For example, highly multiplexed tests for respiratory pathogens should be covered in the outpatient setting for specific, high-risk populations, such as immunocompromised patients, where their value is highest.

Priority 3: Promote and support the development of new diagnostics and their integration into stewardship and AMR prevention programs in both human and animal health settings.

- Align incentives for development of new diagnostic tests, especially those that provide real-time support for antibiotic prescribing, with the diseases for which antibiotics are most commonly prescribed (e.g., outpatient respiratory infections). Doing so will allow private and public entities to ensure resources are allocated to developing tests that will be adopted in both veterinary and human medical settings. Incentivize and promote cooperative relationships between industry and professional societies to prioritize test development in key areas.
- Support the development of new diagnostics for use in veterinary settings (for both food and companion animals), especially animal-side diagnostics that allow precise selection of

antibiotics. Foster development of rapid and economical test applications for individual animal diagnostics to offset the barriers to veterinary applications (e.g., in situations where the client must choose between a diagnostic test and a less-expensive trial course of antibiotics). Additionally, support creation of rapid and economical test applications for population surveillance.

- Foster continued development of animal-specific AST breakpoints for key diseases and antibiotics. Support the activities of the Clinical and Laboratory Standards Institute Veterinary Antimicrobial Susceptibility Testing Subcommittee to promote understanding of AST interpretation and its application in clinical settings.
- Through CDC, NIH/NIAID, and AHRQ, continue to fund studies on diagnostic stewardship to increase understanding of best practices to promote appropriate diagnostic uptake across care settings. When sufficient data are available, update CDC's Core Elements for Antibiotic Stewardship to include more detailed information about diagnostic use.

GOAL 4

ACCELERATE BASIC AND APPLIED RESEARCH AND DEVELOPMENT FOR NEW ANTIBIOTICS, OTHER THERAPEUTICS, AND VACCINES

The landscape for development of new antibiotics, alternative therapeutics, and vaccines has changed dramatically since the NAP was released in 2015, but much work remains. Although efforts to incentivize research of new products exist (e.g., CARB-X), the lack of long-term market incentives has prevented companies from making the investment to remain in the industry, placing our nation in a vulnerable position. We must continue to emphasize development of new products to combat bacterial infections, including but not limited to new antibiotics, vaccines, microbiome-based products, and immunomodulatory therapies.[15]

Priority 1: Adopt effective pull incentives for development of new antibiotics, vaccines, and alternatives.

- Adopt a package of novel pull incentives for antibiotics, vaccines, and alternatives, including short-term reimbursement relief and long-term market entry reward, as proposed by many associations and organizations.
    - Create some form of a delinkage model to provide a market entry reward for new antibiotics rather than a traditional market.[16]
    - Promptly decide on a set of USG incentives that would halt the current exodus of developers and stakeholders in this field, including small biotech firms, large pharmaceutical companies, and venture capitalists.[17]
    - Subsidize and adopt a USG strategy that values novel antibiotics, given the significantly low return on investment from these new products.
    - Support commercialization of vaccines for bacterial pathogens that have high rates of AMR, which face particular market barriers because of the limited target population despite the potential to significantly reduce antibiotic use.

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[15] Similar recommendations were made by PACCARB in its 2017 report on incentives (see Sections I-3 and II-3). Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (2017, September). *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance*. Retrieved from https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf

[16] Similar recommendations were made by PACCARB in its 2017 report on incentives (see Section I-3.1). Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (2017, September). *Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance*. Retrieved from https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf

[17] Achaogen, Antimicrobial Innovation Alliance, Antimicrobials Working Group, Biotechnology Innovation Organization, GlaxoSmithKline, Infectious Diseases Society of America … Trust for America's Health. (2019, February 5). *Joint letter to Senate Committees on Health, Education, Labor & Pensions and Finance*. Retrieved from https://www.idsociety.org/globalassets/idsa/policy--advocacy/current_topics_and_issues/antimicrobial_resistance/10x20/legislative-efforts/020519-joint-letter-to-senate-help-and-finance-re-economic-incentives-for-antibiotics.pdf

- Establish a USG Antibiotic Incentive Fund to provide advance market commitments and milestone payments as incentives for bringing a new antibiotic to market, as recommended by the President's Council of Advisors on Science and Technology.[18]

Priority 2: Continue to create push incentives for development of new antibiotics, vaccines, and alternatives.

- Create an advanced development and manufacturing (ADM) program for AMR countermeasures, including new antibiotics and antibiotic alternatives, similar to the DoD's ADM program and BARDA's Centers for Innovation in Advanced Development & Manufacturing. These products face similar market barriers as the countermeasures for bioterrorism, pandemic, and emerging infectious disease supported by these programs.
- Expand on existing USG activities and provide additional funding for R&D of new antibiotics, vaccines, and other therapeutics, including activities through NIAID; BARDA; DoD; CDC; CARB-X; and other departments, agencies, and programs. Increase funding for these CARB activities so that their reach can be expanded (for example, the CDC and FDA's Antibiotic Resistance Isolate Bank, which provides panels of isolates to support R&D of new drugs and diagnostics).
    - Through federal R&D efforts, support development of all treatment and prevention technologies, including nonantibiotic treatments (e.g., phage therapy, microbiome products, lysins, and peptides) and vaccines. Focus such efforts, in part, on developing and evaluating models with improved predictive value for assessing new therapeutics and vaccines against AMR infections.
- Support the development of nonantibiotic products for animal health.
    - Accelerate development of alternatives to antibiotics. Prioritize and accelerate activities such as ARS R&D on alternatives to antibiotics (including antimicrobial peptides, prebiotics, bacteriophage endolysins, monoclonal antibodies, and antivirals)[19] and USDA-funded extramural research on alternatives and other AMR-related issues through the National Institute of Food and Agriculture.
    - Provide basic research funding to support development of antibiotic alternatives. For example, expand the USDA's Minor Use Animal Drug Program[20] to include development of alternatives for major food animal species. Prioritize research needs through public-private partnerships (e.g., the Global Strategic Alliances for the

[18] President's Council of Advisors on Science and Technology. (2014, September.) *Report to the president on combating antibiotic resistance.* Retrieved from https://www.cdc.gov/drugresistance/pdf/report-to-the-president-on-combating-antibiotic-resistance.pdf
[19] U.S. Department of Agriculture, Agricultural Research Service. (n.d.). *The Agricultural Research Service list of available technologies.* Retrieved from https://www.ars.usda.gov/alternativestoantibiotics/Symposium2012/technologies-ARS.html
[20] Formerly National Research Support Project 7.

Coordination of Research on the Major Infectious Diseases of Animals and Zoonoses [STAR-IDAZ] International Research Consortium on Animal Health).

- Encourage new vaccine formulation and delivery for diseases for which effective vaccines would prevent the need for antibiotics in animal agriculture. Perform USG research to understand the effectiveness of common vaccines and other interventions at precluding the need for antibiotic use.

- To further spur R&D on new antibiotics, vaccines, and alternatives, support the training pipeline for new researchers and new entrants in the field, who will be crucial to solving the long-term problem of AMR.
    - Provide funding for new researchers through mechanisms such as career development awards (e.g., K grants) to develop new antibiotics, alternative therapies, and vaccines. Support young entrepreneurs, minorities, and women to help unlock the potential of these important groups.
    - Provide technical support for startups and small businesses that lack extensive experience in drug development. Efforts such as CARB-X's global accelerator network and bootcamps (intensive technical assistance workshops) for drug developers serve as excellent models for engagement with emerging players in drug discovery.

Priority 3: Advance research on optimal dose and duration of existing antibiotic therapies.

Antibiotic therapy often involves long courses of antibiotics, despite the fact that most regimens have not been clinically tested and shorter durations may be equally effective. Much remains to be learned about how antibiotic dose and duration impacts development of resistance, and the USG should prioritize research to further understand this relationship.

- Study dose and duration of antibiotic therapies to determine optimal regimens that minimize the likelihood of resistance while maintaining efficacy.[21]
- Prioritize dose and duration trials for the infectious syndromes that lead to the largest amount of antibiotic use in animals. This is important to animal health where doses and durations have not been well defined because of outdated or incomplete labels. The CVM five-year plan identified a need to include duration of use information on all medically important antibiotics used in food-producing animals.

[21] Similar recommendations were made by PACCARB in its 2018 report on IP and AS (see Section I-1.3). Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. (2018, September). *Key strategies to enhance infection prevention and antibiotic stewardship. Report with recommendations for human and animal health.* Retrieved from https://www.hhs.gov/sites/default/files/final-ips-report-10-03-2018.pdf

- Conduct in vitro studies and clinical trials of combinations of existing antibiotics to assess their activity against resistant pathogens, especially Gram-negative bacteria.

Priority 4: Address shortages of existing antibiotics.

- To prevent shortages of antibiotics, develop strategies and incentives to ensure that consistent and safe manufacturing of existing antibiotics is not impacted by loss of financial viability by the manufacturing companies.
- Provide CDC and FDA guidance, through collaboration with professional societies and other healthcare associations, on what healthcare facilities should do to mitigate antibiotic shortages.

GOAL 5

IMPROVE INTERNATIONAL COLLABORATION AND CAPACITIES FOR ANTIMICROBIAL PREVENTION, SURVEILLANCE, CONTROL, AND ANTIMICROBIAL RESEARCH AND DEVELOPMENT

Antimicrobial resistance is a growing, global public health crisis that is pervasive across all nations and sectors, threatening the prevention and treatment of infections across international borders. As resistance continues to increase worldwide, disparities have become even more apparent, as many nations lack the resources to conduct adequate surveillance or implement successful prevention strategies. Increased media attention to the issue highlights the global interaction of disease and its immediate spread far and wide. Domestic and global efforts continue to emphasize the need for additional attention to AMR, such as the following:

- The World Health Organization (WHO) designated AMR as one of the 10 global health threats of 2019.
- CDC's updated AMR threat report (expected in late 2019) will include updated data showing AMR as a continued major threat.
- The OIE and the U.N. Food and Agriculture Organization have demonstrated enhanced interest in and visibility of AMR.

The future success of U.S. efforts and our ability to make significant progress over the long term to reduce and eliminate AMR nationally will be based, in part, on the success of other countries. Thus, it is imperative that the United States, as a global leader, take a more visible role to demonstrate its commitment and support to control AMR globally.

Priority 1: Enhance U.S. leadership in the global fight against AMR.

- Provide stronger and more focused leadership, encouragement, and support to global organizations working on AMR programs, including community engagement and nongovernmental organizations, using a One Health approach. To best support these efforts, identify a federal champion to advance global AMR issues and cultivate leaders in other countries who can similarly be national champions, skilled in CARB.
- Provide additional support for organizations (both public and private) that have initiated programs to help support country-specific CARB strategies, as well as global CARB efforts. Also support demonstration projects that meet predetermined endpoints to show progress in AMR control efforts.
- Partner with G20 countries to provide guidance in supporting more appropriate use of antibiotics globally. Consider all options for promoting stewardship and education programs, combating substandard and falsified medicines, and encouraging responsible manufacturing that, in turn, would serve to better protect our national priorities from importation of resistant organisms.
- Serve as a global leader in the prevention and control of fungal diseases exhibiting aggressive resistance by dedicating additional support to mycotic disease research and by promoting

collaborative global partnerships to address this growing issue in public and environmental health.

Priority 2: Promote and support AMR activities in low- and middle-income countries.

- Continue to work closely with partner organizations and systems to promote and support AMR activities in low- and middle-income countries, which have a high burden of AMR and low levels of resources. Emphasize education and training, hygiene, stewardship, IP, animal husbandry, and veterinary and environmental surveillance. Provide dedicated funding to support these activities through federal aid, nongovernmental organizations, and public-private partnerships. Prioritize programs that emphasize a One Health approach and include strategies to encourage appropriate use of antibiotics.
- Continue to support, encourage, and work with national organizations to help them move from creating national action plans for combating AMR to active, measurable, and cost-effective implementation of these plans. Provide technical support that includes train-the-trainer programs to facilitate skills development, guidance on use of cost-effective diagnostic technology, and education on ASPs. Focus on measurement and evaluation to track progress in implementation of national action plans and their impact on AMR. Implement outcome studies to determine the success of these plans in combating AMR, as well as their global impact on reducing the spread of AMR.

ADDITIONAL RECOMMENDATIONS: FIVE YEARS AND BEYOND

The priorities presented above provide specific recommendations to accomplish within the next five years to further the goals of the NAP. In addition, the PACCARB offers additional considerations for wide-reaching, interdisciplinary efforts and programs to help coordinate and advance national and international CARB efforts. While these aspirational recommendations may require more than five years to fully implement, they will, in the long-run, facilitate USG implementation of the NAP goals and objectives.

Integrate antibiotic resistance surveillance systems for One Health surveillance.

- As described in Goal 2, several robust national surveillance systems are currently used to track antibiotic use and resistance and are very accomplished in supporting their respective surveillance goals. Building off these successes, the USG should further integrate surveillance data across One Health domains. The NHSN AUR module captures information in healthcare settings, and NAHMS focuses on animal agriculture; NARMS enables surveillance among human, animal, and food samples, although it focuses on enteric, foodborne pathogens. An integrated, multisectoral antibiotic use and resistance surveillance system for humans, livestock, companion animals, and the environment would further advance the country's capabilities in the fight against AMR and should be developed. Several programs exist that can serve as exemplars for working toward a full, integrated AMR surveillance system:
    - Washington Integrated Surveillance for Antimicrobial Resistance is collaborating with the Washington State Department of Health and several hospitals and medical centers to create a database of AMR, which will include AMR profiles from human and animal subjects.
    - The Minnesota One Health Antibiotic Stewardship Collaborative promotes understanding of One Health AS and provides information, tools, and guidance to improve AS and surveillance. One such tool is the Small Animal Veterinary Surveillance Network, which harnesses electronic health and environmental data in the United Kingdom for rapid and actionable research and surveillance in small animals, including AMR.
    - The WHO Global Antimicrobial Resistance Surveillance System supports a standardized approach to the collection, analysis, and sharing of AMR data at a global level. This program fosters, encourages, and facilitates the establishment of national AMR surveillance systems that are capable of monitoring AMR trends and producing reliable and comparable data.
    - The Codex Committee on Residues of Veterinary Drugs in Foods determines priorities for the consideration of veterinary drug residues in foods including methods of sampling, analysis, and recommendations for maximum residue limits.

Develop an integrated federal One Health research strategy.

- The NAP has served to focus USG regulatory, scientific, and political activities to address a common goal of reducing antibiotic resistance and has identified several important areas of research to be expanded. To achieve these goals and maximize the return on investment of limited federal research dollars, a roadmap on one health research should be developed. The roadmap would coordinate research across One Health domains (human, animal, and environment) and support all of the major activities described in the goals of the NAP (IP, AS, surveillance, and development and integration of new drugs and diagnostics).
- The roadmap would serve as a strategy to avoid duplication, provide a focus on answering the key questions needed to improve outcomes, and ensure that limited funds are being used most effectively. The roadmap should place a special emphasis on the use of new technologies and scientific discovery, should empower regional and LTC facility control measures, and should be forward-looking rather than examining and evaluating existing programs.

Develop a national, interagency effort to address antibiotic resistance issues around the globe.

- The USG should consider a new global **Presidential Antimicrobial Resistance Initiative** to coordinate national and international efforts and define priorities that meet the best interests of health, safety, and welfare of the United States and the global community. The initiative would define goals and objectives for international CARB efforts and provide dedicated resources to accomplish them.
- The core of the initiative would be led by the U.S. president and include a global collaborative team of experts from U.S. and international agencies who would develop a plan that incorporates AS and IP best practices demonstrated to be effective in the United States and other countries. The plan should include an identification and analysis of high-risk populations, high-threat microbes, and highly vulnerable antimicrobials from a One Health perspective.

ANNEX I – TASK LETTER FROM SECRETARY

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

AUG 27 2018

Martin J. Blaser, MD
Chair
Presidential Advisory Council on
Combating Antibiotic-Resistant Bacteria
U.S. Department of Health and Human Services
Washington, DC 20201

Dear Dr. Blaser:

Thank you for your leadership of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (Advisory Council). As you know, the emergence and growth of antibiotic resistance is a major public health challenge. The launch of the National Action Plan (NAP) for Combating Antibiotic-Resistant Bacteria (CARB) in 2015 led to enhanced coordination among Federal agencies in pursuit of five broad goals encompassing infection prevention and stewardship, surveillance, diagnostic and treatment innovation, research, and international efforts. The U.S. Government, led by the CARB Task Force, has made meaningful progress toward these goals, increasing implementation of antibiotic stewardship programs, ending the use of medically important antibiotics for food animal growth promotion, and supporting a broad foundation of basic and applied research as well as targeted drug product development.

The evolution of antibiotic resistance can be slowed, but it cannot be stopped. While most of the NAP milestones are on target for completion by 2020, opportunities exist to continue this progress. The CARB Task Force will therefore be considering continued and new efforts to address antibiotic resistance beyond 2020. The Task Force plans to renew the NAP for the period 2020-2025, retaining the five major goals while updating the key activities to maximize their achievement. To inform these next steps, the Task Force would benefit from understanding the Advisory Council's views of the current landscape in combating antibiotic resistance. I, therefore, request that the Advisory Council, based on the collective expertise across the sectors you represent, identify significant areas that have emerged since the original NAP was launched in 2015. Please identify between three and five areas within each of the existing five NAP goals and include an appropriate evidence base to support why each area should be considered by the CARB Task Force when developing the next iteration of the NAP. This request does not include a retrospective examination of the existing NAP. Please work with the CARB Task Force to inform the process throughout your assessment.

As the primary external body to inform the Federal government's efforts in this area, your proposed areas should be drawn from a broad range of perspectives, including human, animal, and environmental health sectors. I, therefore, request that you convene a public, in-person stakeholder meeting, as part of a planned Advisory Council meeting, including both invited and open public comments.

By August 1, 2019, the Advisory Council should provide me with a report that concisely summarizes the proceedings and key themes from comments at the public meeting, describes the proposed challenges, and articulates how consideration of these challenges would support further progress toward the NAP's five goals. I look forward to reviewing the report and considering your proposals to inform our work moving forward.

A copy of this letter is being sent to Vice Chair Dr. Lonnie King.

Sincerely,

Alex M. Azar II

ANNEX II – JANUARY 2019 PUBLIC MEETING SUMMARY

PACCARB

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Meeting Summary

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

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

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Meeting Proceedings
Day 1

Welcome

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

Dr. Blaser called the meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) to order at 9 a.m. and welcomed the participants. The goal of this meeting was to respond to the charge of the Secretary of the Department of Health and Human Services (HHS) to PACCARB to gather broad public input on combating antimicrobial resistance (AMR).

Overview, Rules of Engagement, and Roll Call

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

Dr. Musmar described the Council's charter and gave an overview of the agenda. She explained the rules governing the Council under the Federal Advisory Committee Act (FACA) and conflict-of-interest guidelines and called the roll. (See Appendix A for the list of participants.)

Opening Remarks and Member Appreciation

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

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

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

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

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

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

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

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

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

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

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

Overview of Day 1: Innovations in CARB

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

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

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

Panel 1: One Health Surveillance and Big Data

Global Infrastructure and Surveillance: The U.S. Role Abroad

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

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

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

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

Using Clinical Data to Create a Regional One Health AMR Surveillance Database

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

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

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

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

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

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

DISCUSSION

Challenges to Tracking and Addressing AMR Globally

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

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

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

Domestic Approaches to Tracking AMR

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

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

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

New Mechanisms for Understanding Resistance

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

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

Panel 2: Infection Control and Prevention

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

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

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

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

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

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

INTERNAL BIOSECURITY PROJECT AND GEOFENCING FOR INFECTION CONTROL IN SWINE FARMS

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

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

BIOSECURITY IN AFRICA

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

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

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

DISCUSSION

Using Vaccines to Prevent AMR

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

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

Novel Techniques Targeting AMR

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

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

The United States' International Role

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

Panel 3: Antibiotics, Therapeutics, and Alternatives

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

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

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

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

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

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

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

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

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

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

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

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

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

REALITIES AND CHALLENGES OF PHARMACEUTICAL DEVELOPMENT

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

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

DISCUSSION

Barriers to New Product Development

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

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

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

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

Environmental Impact

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

Panel 4: Vaccines and Diagnostics

Earlier Targeted Effective Antibiotic Therapy Through Culture-Independent Diagnostics

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

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

Prioritization of Vaccines to Reduce Antibiotic Use in Animals

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

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

Discussion

Promise of New Diagnostics

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

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

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

Barriers to Data Gathering in Agriculture

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

Public Comment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Final Comments and Adjournment for the Day

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

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

Day 2

Roll Call

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

Dr. Musmar welcomed the participants and called the roll.

Debrief of Day 1: Innovation

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

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

Overview of Day 2: Use of Antibiotics

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

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

Panel 5: Grass Roots Engagement and Advocacy

U.S. Federal Policy and Agricultural Antibiotic Use

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

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

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

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

One Water and Public Health: Research to Action Through Outreach and Education

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

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

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

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

THE IMPORTANCE OF WASH IN PREVENTING AMR AND IMPROVING HEALTH OUTCOMES

Danielle Zielinski, Health and WASH Officer, WaterAid America

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

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

ENGAGING THE PUBLIC WITH AMR AND HAND HYGIENE

Lesley Price, Ph.D., Glasgow Caledonian University

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

DISCUSSION

Water Quality and Data

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

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

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

Consumers Outreach and Messaging

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

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

Advancing ARM Policies and Practice

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

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

Panel 6: Consumer Impact on Antibiotic Use

ANTIBIOTIC USE IN SMALL-SCALE LIVESTOCK PRODUCERS IN ECUADOR

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

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

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

ADDRESSING AMR AS A GLOBAL RESTAURANT COMPANY

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

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

OUTPATIENT ANTIBIOTIC STEWARDSHIP: INTERVENTIONS THAT WORK

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

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

SUSTAINABILITY OF ANTIBIOTICS

Harshika Sarbajna, Global Head of Anti-Infectives, Sandoz

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

DISCUSSION

Decreasing Antibiotic Use in Food Animals

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

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

Overuse and Overprescribing of Antibiotics

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

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

Manufacturers' Challenges

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

Panel 7: One Health Surveillance

AMR IN SOUTH AFRICA (PHONE)

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

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

SMALL ANIMAL SURVEILLANCE AND ONE HEALTH

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

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

ONE HEALTH DATA REPORTING, SHARING, AND COLLABORATING

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

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

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

USING MEDICAID DATA TO MAP AVOIDABLE PRESCRIBING PRACTICES

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

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

DISCUSSION

Data Management in Companion Animals

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

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

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

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

Integrating Surveillance Efforts Nationally

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

Leveraging State Medicaid Data

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

Panel 8: Prescriber Behavior Change

BIG DATA TO IMPROVE ANTIBIOTIC PRESCRIBING

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

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

REDUCING ANTIMICROBIAL USE IN ANIMALS AND PROMOTING A MINDSET CHANGE

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

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

MINNESOTA ONE HEALTH ANTIBIOTIC STEWARDSHIP COLLABORATIVE

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

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

ACCELERATING INTERNATIONAL PROGRESS ON AMR

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

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

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

DISCUSSION

Effecting Global Change

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

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

Economic Impact of Reducing Farm Use of Antibiotics

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

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

Behavior Change

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

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

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

Public Comment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Final Comments and Adjournment

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

Dr. Blaser thanked all the presenters and commenters for their contributions. He adjourned the meeting at 4:51 p.m.

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

January 30–31, 2019

PACCARB Voting Members Present
Martin J. Blaser, M.D., Chair
Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair
Michael D. Apley, D.V.M., Ph.D., DACVCP
Helen W. Boucher, M.D., FIDSA, FACP
Angela Caliendo, M.D., Ph.D., FIDSA
Sara E. Cosgrove, M.D., M.S.
Paula J. Fedorka-Cray, Ph.D.
Christine Ginocchio, Ph.D., MT
Locke Karriker, D.V.M., M.S.
Kent E. Kester, M.D., FACP, FIDSA, FASTMH
Ramanan Laxminarayan, Ph.D., M.P.H.
Aileen M. Marty, M.D., FACP
Robert A. Weinstein, M.D.
David White, M.S., Ph.D.

Organizational Liaisons Present
American Nurses Association
Elaine Larson, Ph.D., RN

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

National Turkey Federation
Alice L. Johnson, D.V.M.

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

Pew Charitable Trusts
Kathryn L. Talkington

Ex Officio Members Present
U.S. Department of Health and Human Services
Dennis M. Dixon, Ph.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health (day 1)
Lynn Filpi, Ph.D. (for Lawrence Kerr, Ph.D.), Office of Pandemics and Emerging Threats, Office of Global Affairs
Rima Khabbaz, M.D., National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention
Jane Knisely, Ph.D. (for Dennis M. Dixon, Ph.D., on day 2), National Institute of Allergy and Infectious Diseases, National Institutes of Health

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

U. S. Department of Agriculture
Neena Anandaraman (for Sarah Tomlinson, D.V.M.), Animal and Plant Health Inspection Service
Emilio Esteban, D.V.M., M.BA., M.P.V.M., Ph.D., Food Safety and Inspection Service
Roxanne Motroni, D.V.M., Ph.D. (for Jeffrey Silverstein, Ph.D.), Agricultural Research Service

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

Advisory Council Staff
Ayah O. Wali, M.P.H., Committee Management Officer, Office of the Assistant Secretary for Health, Department of Health and Human Services
Mark Kazmierczak, Ph.D., Gryphon Scientific
Sarah McClelland, M.P.H., ORISE Fellow

Glossary of Abbreviations

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

ANNEX III – PACCARB MEMBERSHIP

SPECIAL GOVERNMENT EMPLOYEES – VOTING MEMBERS

CHAIR, Martin J. Blaser, M.D.
Henry Rutgers Chair of the Human Microbiome
Professor of Medicine and Microbiology, Robert Wood Johnson Medical School
Director, Center for Advanced Biotechnology and Medicine
Rutgers University
Piscataway, NJ 08854

VICE CHAIR, Lonnie J. King, D.V.M., M.S., M.P.A., DACVPM
Professor and Dean Emeritus
College of Veterinary Medicine
The Ohio State University
Columbus, OH

Michael D. Apley, D.V.M., Ph.D., DACVCP
Professor, Department of Clinical Sciences
College of Veterinary Medicine
Kansas State University
Manhattan, KS

Helen W. Boucher, M.D., FIDSA, FACP
Director, Infectious Diseases Fellowship Program
Director, Heart Transplant and Ventricular Assist Device Infectious Diseases Program
Professor of Medicine
Tufts University School of Medicine
Division of Geographic Medicine and Infectious Diseases
Tufts Medical Center
Boston, MA

Angela Caliendo, M.D., Ph.D., FIDSA
Professor and Executive Vice Chair of Medicine
Director, Division of General Internal Medicine
Alpert Medical School
Brown University
Providence, RI

Alicia R. Cole
Founder, Alliance for Safety Awareness for Patients
Sherman Oaks, CA

Sara E. Cosgrove, M.D., M.S.
Professor of Medicine and Epidemiology
Division of Infectious Diseases
Johns Hopkins University School of Medicine
Johns Hopkins Bloomberg School of Public Health
Director, Johns Hopkins Hospital Department of Antimicrobial Stewardship
Baltimore, MD

Paula J. Fedorka Cray, Ph.D.
Department Head, Population Health and Pathobiology
College of Veterinary Medicine
North Carolina State University
Raleigh, NC

Christine Ginocchio, Ph.D., MT
Vice President, Global Microbiology
Medical and Scientific Affairs
bioMerieux
New York, NY

Locke Karriker, D.V.M., M.S.
Professor and Interim Chair, Veterinary Diagnostic and Production Animal Medicine
Director, Swine Medicine Education Center
Iowa State University
Ames, IA

Kent E. Kester, M.D., FACP, FIDSA, FASTMH
Vice President and Head, Translational Science and Biomarkers
Sanofi Pasteur
Swiftwater, PA

Ramanan Laxminarayan, Ph.D., M.P.H.
Director and Senior Fellow
Center for Disease Dynamics, Economics and Policy
Washington, DC

Aileen M. Marty, M.D., FACP
Professor, Infectious Diseases
Department of Medicine, Family Medicine, and Community Health
Director, Health Travel Medicine Program and Vaccine Clinic
Florida International University
Miami, FL

Robert A. Weinstein, M.D.
Former Chair, Department of Medicine
Cook County Health and Hospitals System
Chief Academic Officer and C. Anderson Hedberg, M.D., Professor of Internal Medicine
Rush Medical College
Chicago, IL

David White, Ph.D., M.S.
Associate Dean for Research
Professor of Food Science
Department of Agriculture Research
University of Tennessee
Knoxville, TN

REPRESENTATIVE MEMBERS

American Nurses Association
Designated Representative:
Elaine Larson, Ph.D., RN
Silver Spring, MD

Association for Public Health Laboratories
Designated Representative:
Denise M. Toney, Ph.D.
Washington, DC

National Turkey Federation
Designated Representative:
Alice L. Johnson, D.V.M.
Washington, DC

North American Meat Institute
Designated Representative:
Tiffany Lee, D.V.M., Ph.D., M.S.
Washington, DC

The Pew Charitable Trusts
Designated Representative:
Kathryn L. Talkington
Washington, DC

REGULAR GOVERNMENT EMPLOYEES

U.S. Department of Agriculture

Agricultural Research Service
Jeffrey Silverstein, Ph.D.
Deputy Administrator
Animal Production and Protection
Office of National Programs
Washington, DC

Animal and Plant Health Inspection Service
Sarah M. Tomlinson, D.V.M.
Executive Director, Strategy and Policy
Veterinary Services
Fort Collins, CO

Food Safety Inspection Service
Emilio Esteban, D.V.M., M.B.A., M.P.V.M., Ph.D.
Chief Scientist
Office of Public Health Science
Washington, D.C.

U.S. Department of Defense

Walter Reed Army Institute of Research
Paige Waterman, M.D., FACP, FIDSA COL, MC
Director, Translational Medicine
Bethesda, MD

U.S. Department of Health and Human Services

Centers for Disease Control and Prevention
Rima Khabbaz, M.D.
Director, National Center for Emerging and Zoonotic Infectious Diseases
Acting Director, Office of Infectious Diseases
Acting CDC Deputy Director, Infectious Diseases
Atlanta, GA

Centers for Medicare & Medicaid Services
Shari Ling, M.D.
Deputy Chief Medical Officer
Center for Clinical Standards and Quality
Baltimore, MD

National Institutes of Health
Dennis M. Dixon, Ph.D.
Chief, Bacteriology and Mycology Branch
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
Rockville, MD

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

Office of the Assistant Secretary for Preparedness and Response
Christopher Houchens, Ph.D.
Director (Acting), Division of Chemical, Biological, Radiological, and Nuclear Medical Countermeasures
Biomedical Advanced Research and Development Authority
Washington, DC

U.S. Food and Drug Administration
Daniel W. Sigelman, J.D.
Senior Advisor
Office of Public Health Strategy and Analysis
Office of the Commissioner
Silver Spring, MD

DESIGNATED FEDERAL OFFICER

Jomana F. Musmar, M.S., Ph.D.
Advisory Council Manager
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
Washington, DC

ADVISORY COUNCIL STAFF

Ayah O. Wali, M.P.H.
Committee Management Officer
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
Washington, DC

Mark Kazmierczak, Ph.D.
Consultant
Gryphon Scientific
Takoma Park, MD

Sarah McClelland, M.P.H.
ORISE Fellow
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
Washington, DC

ANNEX IV – PACCARB CHARTER AND AUTHORIZING LEGISLATION

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

CHARTER

PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Authority

Executive Order 13676, dated September 18, 2014, requires establishment of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (Advisory Council). The Advisory Group is currently operating under the authority given in Executive Order 13811, dated September 29, 2017. Activities of the Advisory Council are governed by the provisions of Public Law 92-463, as amended (5 U.S.C. App.), which sets forth standards for the formation and use of federal advisory committees.

Objectives and Scope of Activities

Executive Order 13676 directs the Secretary of Health and Human Services (Secretary) to establish the Advisory Council in consultation with the Secretaries of Defense and Agriculture. The Advisory Council will provide advice, information, and recommendations to the Secretary regarding programs and policies intended to support and evaluate the implementation of Executive Order 13676, including the National Strategy for Combating Antibiotic-Resistant Bacteria (Strategy) and the National Action Plan for Combating Antibiotic-Resistant Bacteria (Action Plan). The Advisory Council shall function solely for advisory purposes.

Description of Duties

In carrying out its mission, the Advisory Council will provide advice, information, and recommendations to the Secretary regarding programs and policies intended to:

1. Preserve the effectiveness of antibiotics by optimizing their use;

2. Advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship;

3. Strengthen surveillance of antibiotic-resistant bacterial infections;

4. Prevent the transmission of antibiotic-resistant bacterial infections;

5. Advance the development of rapid point-of-care and agricultural diagnostics;

6. Further research on new treatments for bacterial infections;

7. Develop alternatives to antibiotics for agricultural purposes;

8. Maximize the dissemination of up-to-date information on the appropriate and proper use of antibiotics to the general public and human and animal healthcare providers; and

9. Improve international coordination of efforts to combat antibiotic resistance.

Agency or Official to Whom the Committee Reports

As stipulated in Executive Order 13676, the Advisory Council provides advice, information, and recommendations to the Secretary. The Secretary will provide the President with all written reports created by the Advisory Council.

Support

To the extent permitted by law and subject to the availability of appropriations, the Department of Health and Human Services (HHS) shall provide the Advisory Council with such funds and support as may be necessary for the performance of its functions. Management and support services provided to the Advisory Council will be the responsibility of the Office of the Assistant Secretary for Health (OASH), which is a coordinating and program office within the Office of the Secretary.

To the extent permitted by law, the agencies that comprise the Task Force for Combating Antibiotic-Resistant Bacteria shall provide the Advisory Council with such information as it may require for purposes of carrying out its functions.

Estimated Annual Operating Costs and Staff Years

The estimated annual cost for operating the Advisory Council, including travel expenses for members, but excluding staff support, is $687,262. The estimate for annual person years of staff support required is 3.0, at an estimated annual cost of $437,738.

Designated Federal Officer

The Assistant Secretary for Health (ASH), in consultation with the Secretary, will select the Designated Federal Officer (DFO) from among full-time or permanent part-time staff within OASH or another organizational component within the HHS, who have knowledge of the subject matter and skills and experience necessary to manage the Advisory Council. The ASH may appoint an Alternate DFO, who will carry out the assigned duties in the event that the DFO cannot fulfill the assigned responsibilities for the Advisory Council.

The DFO will schedule and approve all meetings of the Advisory Council and of its respective subcommittees. The DFO will prepare and approve all meeting agendas. The DFO may collaborate with the Advisory Council Chair in this activity, and when deemed appropriate, with chairs of any existing subcommittees that have been established by the Advisory Council. The DFO, Alternate DFO, will attend all meetings of the Advisory Council and all meetings of any subcommittees/working groups that have been assembled to assist the Advisory Council. The DFO has authority to adjourn meetings, when it is determined to be in the public interest, and the DFO can be directed by the Secretary or designee to chair meetings of the Advisory Council.

Estimated Number and Frequency of Meetings

The Advisory Council will meet, at a minimum, two times per fiscal year depending on the availability of funds. Meetings will be open to the public, except as determined otherwise by the Secretary, or other official to whom authority has been delegated, in accordance with guidelines under Government in the Sunshine Act, 5 U.S.C. 552b(c). Notice of all meetings will be provided to the public in accordance with the Federal Advisory Committee Act (FACA), Public Law 92-463, as amended (5 U.S.C. App.). Meetings will be conducted and records of the proceedings will be kept, as required by applicable laws and Departmental policies. A quorum is required for the Advisory Council to meet to conduct business. A quorum will consist of a majority of the Advisory Council's voting members.

When the Secretary or designee determines that a meeting will be closed or partially closed to the public, in accordance with stipulations of Government in the Sunshine Act, 5 U.S.C. 552b(c), then a report will be prepared by the DFO that includes, at a minimum, a list of the members and their business addresses, the Advisory Council's functions, date and place of the meeting, and a summary of the Advisory Council's activities and recommendations made during the fiscal year. A copy of the report will be provided to the Department Committee Management Officer.

Duration

Continuing.

Termination

The Advisory Council was continued by Executive Order 13811, and will terminate on September 30, 2019, unless continued by the President prior to that date.

Membership and Designation

The Advisory Council will consist of not more than 30 members, including the voting and non-voting members and the Chair and Vice Chair. The Secretary will designate the Chair and Vice Chair from among the voting public members of the Advisory Council who have demonstrated ability both to lead the work of similar bodies and to work effectively in partnership with federal agencies and partner organizations.

Voting Members. There will public voting members selected from individuals who are engaged in research on, or implementation of, interventions regarding efforts to preserve the effectiveness of antibiotics by optimizing their use; advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship; strengthen surveillance of antibiotic-resistant bacterial infections; prevent the transmission of antibiotic-resistant bacterial infections; advance the development of rapid point-of-care and agricultural diagnostics; further research on new treatments for bacterial infections; develop alternatives to antibiotics for agricultural purposes; maximize the dissemination of up-to-date information on the appropriate and proper use of antibiotics to the general public and human and animal healthcare providers; and improve international coordination of efforts to combat antibiotic resistance.

The public voting members will represent balanced points of view from human biomedical, public health, and agricultural fields to include surveillance of antibiotic-resistant infections, prevention and/or interruption of the spread of antibiotic-resistant threats, or development of rapid diagnostics and novel treatments. The public voting members may be physicians, veterinarians, epidemiologists, microbiologists, or other health care professionals (e.g., nurses, pharmacists, others); individuals who have expertise and experience as consumer or patient advocates concerned with antibiotic resistance, or in the fields of agriculture and pharmaceuticals; and they also may be from State or local health agencies or public health organizations. The voting public members will be appointed by the Secretary, in consultation with the Secretaries of Defense and Agriculture. All public voting members will be classified as special government employees (SGEs).

Ex-officio Members (non-voting). The Advisory Council will include members selected to represent various federal agencies, including HHS, DoD, and USDA, that are involved in the development, testing, licensing, production, procurement, distribution, and/or use of antibiotics and/or antibiotic research. The federal *ex- officio* members shall possess the knowledge, skills, experience, and expertise necessary to inform the Advisory Council in generating intelligent recommendations with respect to the issues mandated by Executive Order 13676. Federal agencies will be invited to participate as non-voting *ex-officio* members of the Advisory Council, as it is deemed necessary by the Secretary, in consultation with the Secretaries of Defense and Agriculture, to accomplish the mission the Advisory Council.

Liaison Representatives (non-voting). The Advisory Council structure also may include non-voting liaison representatives from organizations and/or interest groups that have involvement in the development, testing, licensing, production, procurement, distribution, and/or use of antibiotics and/or antibiotic research. Non-voting liaison representatives shall possess the knowledge, skills, experience, and expertise necessary to inform the Advisory Council in generating intelligent recommendations with respect to the issues mandated by Executive Order 13676. Individuals from among the following sample sectors may be invited to serve as non-voting liaison representatives:

- Professional organizations or associations representing providers or professionals for human and/or animal health involved in infection control and prevention; this can include physicians, nurses, pharmacists, microbiologists, veterinarians.

- Public health, environmental health, and/or animal health organizations or associations (state/territorial, county, or local) representing laboratories, health officials, epidemiologists, agricultural state departments, or environmental associations.

- Other organizations representing patients and consumer advocates, hospitals, pharmaceutical industry, food producers and retailers, or other commodity groups.

Invitations may be extended to other organizations and/or interest groups to participate as non-voting liaison representatives, as it is deemed necessary by the Secretary or designee to accomplish the established mission of the Advisory Council.

Terms and Compensation. The public voting and non-voting liaison representative members will be appointed to serve for overlapping terms of up to four years. Any member who is appointed to fill the vacancy of an unexpired term will be appointed to serve for the remainder of that term. The Chair and Vice Chair will be appointed to serve for three years, unless otherwise specified. A member may serve after the expiration of their term until their successor has taken office, but no longer than 180 days.

Pursuant to an advance written agreement, the public voting members shall receive no stipend from the federal government for the services they perform during their tenure on the Advisory Council. However, the public voting members are entitled to receive per diem and reimbursement for travel expenses incurred for attending meetings of the Advisory Council, as authorized by 5 U.S.C. Sec. 5703, as amended, for persons who are employed intermittently in the Government service. The non-voting liaison representatives may be allowed to receive per diem and any applicable expenses for travel that is performed to attend meetings of the Advisory Council in accordance with federal travel regulations.

Subcommittees

With approval or recommendation of the Secretary or designee, the Advisory Council may establish standing and *ad hoc* subcommittees to provide assistance for carrying out its function. The subcommittee shall consist of only members of the Advisory Council. The Department Committee Management Officer will be notified upon establishment of each subcommittee, and will be provided information on its name, membership, function, and estimated frequency of meetings. All reports and recommendations of a subcommittee must be reported back to the full Advisory Council for action. No activity of a subcommittee can be given directly to the Secretary without being provided for discussion by the full Advisory Council.

Recordkeeping

Records of the Advisory Council and the respective subcommittees or working groups will be handled in accordance with General Schedule 6.2 or other approved agency records disposition schedule. These records will be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

Filing Date:

JAN 18 2019

Approved:

JAN 16 2019

Date

Alex M. Azar II

ANNEX V – ACRONYMS AND ABBREVIATIONS

ADM	advanced development and manufacturing
AHRQ	Agency for Healthcare Research and Quality
AMR	antimicrobial resistance
APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
AS	antibiotic stewardship
ASP	antibiotic stewardship program
AST	antibiotic susceptibility test
AUR	Antimicrobial Use and Resistance (module)
BARDA	Biomedical Advanced Research and Development Authority
CARB	Combating Antibiotic-Resistant Bacteria
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CVM	Center for Veterinary Medicine
DoD	Department of Defense
EHR	electronic health record
EU	European Union
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
HIIN	Hospital Improvement Innovation Network
IP	infection prevention
LTACH	long-term acute care hospital
LTC	long-term care
NAP	National Action Plan
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System for Enteric Bacteria
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OIE	World Organisation for Animal Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
QIN-QIO	Quality Innovation Network-Quality Improvement Organization
R&D	Research and development
UN	United Nations
USDA	United States Department of Agriculture
USG	United States Government
vSNF	ventilator skilled nursing facility
WG	working group
WHO	World Health Organization