NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Progress Report: Year 4

September 2019

Prepared by the United States Taskforce for Combating Antibiotic Resistant Bacteria

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Background

Antibiotic resistance (AR) continues to be one of the most significant threats to public health in the United States and globally. Effective antibiotics are a crucial part of human and veterinary medicine, saving lives and facilitating medical advancements. However, pathogens continually adapt to survive exposure to antibiotics, which increasingly results in infections that are very difficult or impossible to treat. In 2013, the U.S. Centers for Disease Control and Prevention (CDC) released conservative estimates of national antibiotic resistance threat, which catalyzed U.S. efforts to prevent infections, stop the spread of resistance, and improve antibiotic use in humans, animals, and the environment. CDC has now updated those estimates, and new data show that the burden of deaths and infections from antibiotic-resistance threats in the United States was actually greater than initially thought. Today we know that more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result.

In 2015, the U.S. Government implemented the National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB), which provides a five-year road map to guide the Nation toward five overarching goals:

1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections.
2. Strengthen national one-health surveillance efforts to combat resistance.
3. Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.
4. Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.
5. Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control and antibiotic research and development.

Each goal of the Plan is supported by objectives, sub-objectives, and milestones for Years 1, 3, and 5. The Plan is implemented by the CARB Task Force, which is chaired by the Secretaries of the U.S. Departments of Health and Human Services, Agriculture, and Defense.

In the four years since the CARB National Action Plan was launched, activities conducted by the U.S. Government have contributed to substantial progress, which has been particularly successful thanks to enhanced coordination of efforts. However, the evolutionary nature of antibiotic resistance creates a constantly moving target, and continued forward momentum is needed. For example, the past year has seen a rise of infections from *Candida auris* (*C. auris*), a multi-drug resistant fungus only discovered in 2009. This recent development highlights the complicated nature of detection and treatment of resistant infections.

The original CARB National Action Plan was launched in 2015 and will be completed in 2020. Given the continued need to pursue the goals of the Plan, the CARB Task Force is working throughout 2019 to develop the next iteration of the Plan. The 2020–2025 CARB National Action Plan will maintain the five original goals of antibiotic stewardship and infection prevention, surveillance, diagnostic development, treatment development, and international coordination. The CARB Task Force will also consider recommendations from public stakeholders, in addition to feedback from the Presidential Advisory Council on Combating

Antibiotic-Resistant Bacteria (PACCARB). The PACCARB is a Federal Advisory Committee that provides advice, information, and recommendations to the Secretary of Health and Human Services (HHS) regarding policies to support and implement the National Strategy for Combating Antibiotic-Resistant Bacteria and the National Action Plan for Combating Antibiotic-Resistant Bacteria, as directed in Executive Order 13676. The CARB Task Force continues to assess the progress of work under the current Plan, and aims to ensure that the next iteration of the plan supports future progress toward the original plan's five goals through innovative objectives. The CARB Task Force anticipates that the new Plan will be launched in March of 2020 upon the conclusion of the original Plan.

Highlights of Progress in Year Four of the CARB National Action Plan

The CARB Task Force has developed this report to highlight select achievements toward the five goals that occurred during the fourth year of the National Action Plan's implementation. The National Action Plan includes milestones for Years 1, 3, and 5, and as such, this report includes highlights from each department and agency to share progress toward the Year 5 milestones, from the period between spring 2018 and spring 2019. Progress during the first three years of implementation was reported in a combined summary report from Years 1 and 2 and a report on milestones for Year 3. A comprehensive summary report will be developed at the conclusion of Year 5. The CARB Task Force is currently assessing barriers to implementation of National Action Plan activities, and the Year 5 Summary Report will discuss these barriers.

United States Department of Agriculture (USDA)
Animal and Plant Health Inspection Service (APHIS)

In 2015, APHIS-Veterinary Services (VS) engaged the American Association of Veterinary Laboratory Diagnosticians (AAVLD) to participate in a joint working group comprised of representatives from veterinary diagnostic laboratories belonging to AAVLD, the Clinical Laboratory Standards Institute (CLSI), Food and Drug Administration Center for Veterinary Medicine's Veterinary Laboratory Investigation and Response Network (Vet-LIRN), USDA APHIS' VS Centers for Epidemiology and Animal Health (CEAH) and USDA APHIS' National Veterinary Services Laboratories (NVSL) and National Animal Health Laboratory Network (NAHLN). This working group developed recommendations for an implementation plan to monitor antimicrobial resistance in bacteria from sick animals, which included standardized antimicrobial testing and data collection, and identifying concerns or gaps that could impede the implementation of this plan. This working group also provided input on a survey that was administered to U.S. veterinary diagnostic laboratories in 2015. This survey assessed current practices for antimicrobial susceptibility testing and data sharing, and the survey results were published in 2017.

The APHIS-VS NAHLN Antimicrobial Resistance (AMR) Pilot Project was launched in September 2017, to monitor antimicrobial resistance in bacteria from sick animals. Concurrently, an electronic messaging process using the HL7 messaging format was developed and is being used to successfully upload data from laboratory reporting spreadsheets into an APHIS database. Approximately 10% of the isolates from Year 1 were also identified for sequencing, being

performed by USDA APHIS National Veterinary Services Laboratories NVSL. A report describing AMR results from the initial year of this pilot is available through the USDA APHIS NAHLN website.

Year 1 of USDA's AMR pilot project covered January 1, 2018, through December 19, 2018. Nineteen laboratories (18 with membership in the NAHLN and one laboratory outside the NAHLN, associated with a U.S. college of veterinary medicine) contributed antimicrobial susceptibility testing data from 3,213 veterinary bacterial isolates. Four major livestock species (cattle, swine, poultry, and horses) and two companion animal species (dogs and cats) were covered. Bacterial isolates surveyed were *Escherichia coli* (*E. coli*) (1700 isolates across all animal species), *Salmonella enterica* spp. (584 isolates across all species), *Mannheimia haemolytica* (380 isolates from cattle), and *Staphylococcus intermedius* group (548 isolates from dogs and cats). Data evaluated included diagnostic source of the isolates, antibiotic resistance, multi-drug resistance, and epidemiological cutoff values. Evaluation of antibiotic resistance was confounded by the fact that veterinary clinical breakpoints have not been established for the majority of antibiotic/bacterial combinations in most animal species. Notable exceptions were for dogs/*E. coli*, dogs/*Staphylococcus* spp. and cattle/*M. haemolytica*.

Multi-drug resistance (MDR), defined as acquired non-susceptibility to at least one agent in three or more antimicrobial classes, was evaluated in all animal species where sufficient clinical breakpoints were available. Epidemiological cutoff values (ECVs) were also evaluated in the Year 1 report. ECVs distinguish between organisms with and without phenotypically expressed resistance mechanisms for a bacterial species and a corresponding antibiotic. Generally, these two groups are termed "non-wild type" and "wild type," respectively. ECVs are not designed to be used to guide therapy, but instead serve as a standardized method for comparison of antibiotic resistance internationally, as each country may set clinical breakpoints differently.

Publications:
2019 National Animal Health Monitoring System Antimicrobial Drug Use Surveys: Beef Feedlots and Swine Operations

United States Department of Agriculture (USDA)
Agricultural Research Service (ARS)

USDA ARS continues to implement Alternatives to Antibiotics (ATA) research and development projects, including development of products that could reduce the need for medically important antibiotics through vaccines, bacterial-derived products, immune-related products, phytochemicals, and other chemicals and enzymes. In Fiscal Year (FY) 2018, USDA ARS published 85 peer reviewed journal articles relating to characterizing AMR in food producing animals and their environments and/or alternatives to antibiotics in food producing animals. In addition to the 25 intramural research projects that perform AMR and antibiotic alternatives research, 13 one-year mini-proposals were funded through an internal funding call to address emergent questions within AMR and ATA research. In FY2018, seven patent applications were filed and four patents were awarded for technologies to combat antimicrobial resistance.

United States Department of Agriculture (USDA)
Food Safety and Inspection Service (FSIS)

USDA FSIS strengthened collaborations in AMR activities. For example, to enhance understanding of AMR activities and partnerships in Latin America, FSIS in collaboration with the Food and Drug Administration (FDA) engaged with the Interamerican Network of Food Analysis Laboratories (INFAL), the Pan American Health Organization (PAHO), PulseNet Latin America and the Inter-American Institute for Cooperation on Agriculture (IICA). FSIS conducted training on food safety, antimicrobial susceptibility testing, and surveillance for international partners including representatives from Latin America. Additional international collaborations included work with regional partners to identify a common vehicle to survey regional capability and capacity for AMR monitoring, establish international proficiency programs, and standardize antimicrobial susceptibility methods, with collaborators including the Asia-Pacific Economic Cooperation and INFAL.

United States Department of Agriculture (USDA)
National Institute of Food and Agriculture (NIFA)

USDA NIFA has funded studies to slow the emergence of resistant bacteria in agriculture. For example, a team of dairy scientists are working to mitigate the transmission of AMR on farms by reducing behavioral pathways of exposure to resistant bacteria. They plan to identify farm worker behaviors associated with increased risk of carriage of selected pathogens and antimicrobial resistance genes (ARGs) on farms having cows with varying exposure to antimicrobials, and subsequently develop interventions to change worker behaviors that are associated with exposure to pathogens and ARGs. Ultimately, the scientists will transfer the knowledge gained to end-users through extension networks and innovative multimedia interactive materials, in order to lower the risk of AMR transmission from dairy cattle to humans. In another study, researchers have shown that targeting behavioral patterns of farm workers is more effective than attempting to influence animal producers.

Department of Defense (DoD)

In Year 4 of the CARB National Action Plan, the Department of Defense (DoD) highlights include publishing its Antimicrobial Stewardship Program Implementation Guidance, Defense Health Agency Procedural Instruction (DHA-PI) 6025.09, aligned with the prior year's Antimicrobial Stewardship Program Policy, DoD-I 6025.26. These two documents meet the requirements stated in Goal 1 of the CARB National Action Plan.

Implementation of this policy is coordinated by the Antimicrobial Resistant Monitoring and Research Program (ARMoR), which is comprised of the Multi-drug resistant Repository and

Surveillance Network (MRSN) at the Walter Reed Army Institute of Research (WRAIR), the Navy and Marine Corps Epi-Data Center (EDC), and the Army Pharmacovigilance Center (PVC). These groups each contribute large portions of their efforts to the chartered Antimicrobial Stewardship Program Working Group (ASPWG). Individually, the MRSN collects, characterizes, and stores over 700 new clinical isolates per month and has contributed more than 150 reports on its findings since January 2017, many of which detail unique outbreaks within the Military Healthcare System (MHS). Following its success as the first to identify the mcr-1 gene within the U.S., the MRSN has worked with the Defense Health Agency (DHA) to standardize identification methods of the newest worrisome pathogen, *Candida auris*, for all of its medical facilities. The MRSN also assisted with a hospital's efforts to evaluate its *Clostridium difficile* isolates and found no relatedness among the strains thus providing no evidence for nosocomial transmission (CARB Goal 2). Diversity panels have been created from its over 65,000 isolate repository for further use in developing therapeutics and diagnostics (CARB Goals 3 & 4). The EDC and PVC continue to serve as the centralized source for MHS compliance with National Healthcare Safety Network (NHSN) submissions for antibiotic resistance and use, respectively, doing so for more than 90% of eligible MHS facilities (CARB Goal 1).

Global surveillance and international collaboration (CARB Goals 2 and 5) spanning 28 countries also continue through work done at the Armed Forces Health Surveillance Branch Global Emerging Infections Surveillance and Response System (AFHSB-GEIS) and the MRSN, as well as in Africa and Southeast Asia via the Austere Environments Consortium for Enhanced Sepsis Outcomes.

The WRAIR Experimental Therapeutics (ET) branch continues on its path to identify a lead candidate for a traditional antibiotic (CARB Goal 4). ET scientists awarded funding for a joint small molecule lead optimization campaign for development of broad spectrum, dual-acting antibiotics for the treatment of Gram negative AMR bacterial pathogens. The lead portfolio candidate will serve as a "sprint to the finish" project to meet its CARB NAP Goal. WRAIR ET, with the DHA and across DoD, also fielded an Integrated Product Team (IPT) to guide additional preclinical candidate identification and clinical advanced development transition, and prioritization of the intra/extramural discovery pipeline and hit-to-lead funded projects behind the lead series. The IPT will also serve as a DoD-wide integrator of antibiotic development stakeholders. Finally, WRAIR ET has validated automated (robotized) preclinical assays within its efficacy tiered test systems utilizing bacteria from the MRSN. These resources are available as collaborative tools across the U.S. Government (USG), public, and private sectors to enable antibacterial therapeutic efforts.

Department of Health and Human Services (HHS)
The Agency for Healthcare Research and Quality (AHRQ)

AHRQ has made notable achievements in Antibiotic Stewardship (AS) and Infection Prevention (IP) through its robust program of research and implementation.

AHRQ has significantly increased its support for research to develop improved methods for combating antibiotic-resistant infections and promoting antibiotic stewardship. AHRQ-supported

research has made major contributions to CARB efforts; a prime example is a series of studies that have generated evidence providing guidance to the field on effective strategies for decolonization of patients who harbor resistant bacteria. The decolonization strategies have reduced resistant infections, and these research results will thus improve patient outcomes.

In implementation for AS, the AHRQ Safety Program for Improving Antibiotic Use has adapted its existing Comprehensive Unit-Based Safety Program (CUSP) to promote AS programs in acute care hospitals, long-term care, and ambulatory care across the country. The project has created the "Four Moments of Antibiotic Decision Making," a significant advance in antibiotic stewardship that provides step-by-step guidance empowering clinicians to serve as stewards of their own antibiotic prescribing, which was published in the Journal of the American Medical Association (JAMA) in January 2019 to expand the impact of this innovative approach. The project has completed a one-year cohort in 400 hospitals, and preliminary data suggest that antibiotic use has been reduced in this cohort. The project has also recruited over 450 nursing homes for a one-year cohort that will be completed in November 2019, and an ambulatory care cohort will be launched in December 2019. Through these cohorts, the Safety Program is spreading the implementation of AS in diverse healthcare settings.

AHRQ has also developed a Guide for AS in Nursing Homes, which is based on the results of four previous AHRQ-supported studies of AS in long-term care. The Guide provides four sets of toolkits to help nursing home staff address the challenges of how to create an antibiotic stewardship program, how to determine whether to treat with antibiotics, how to choose the right antibiotic, and how to engage residents and families in decisions regarding antibiotic use. The Guide is available on the AHRQ website, is being offered to nursing homes by Centers for Medicare and Medicaid Services (CMS) State surveyors, and is available on the CMS Quality Assurance and Performance Improvement (QAPI) website. In these ways, the Guide is supporting the development and sustainability of AS programs in nursing homes.

In implementation for IP, the AHRQ Safety Program for Long-Term Care adapted AHRQ's CUSP Program to this setting and achieved a 54 percent reduction in the rate of catheter-associated urinary tract infections (CAUTI) in over 400 nursing homes nationwide, as well as a reduction in the rate of urine cultures. Both of these achievements are contributing to the attainment of CARB goals. Reduction of CAUTI means a decrease in the need for and use of antibiotics, and reduction of urine cultures likely means fewer cases of asymptomatic bacteriuria being treated unnecessarily. The toolkit developed by this project is currently available on the AHRQ website to enable long-term care facilities to implement the effective practices for reducing CAUTI that were used successfully in the project.

Department of Health and Human Services (HHS)
Assistant Secretary for Preparedness & Response (ASPR)
Biomedical Advanced Research and Development Authority (BARDA)

A key objective of the 2018 National Biodefense Strategy is to reduce the emergence and spread of antibiotic-resistant pathogens domestically and internationally by accelerating research and development of new antibiotics. BARDA and the Public Health Emergency

Medical Countermeasures Enterprise (PHEMCE) recognize the critical need to prepare for an outbreak of natural or engineered drug resistant bacterial biothreat pathogens. Supporting the development and stockpiling of medical countermeasures that treat antibiotic resistant bacteria including biothreats will augment the USG response to any biothreat agent or public health emergency.

In August 2018, the FDA approved XERAVA™ (Eravacycline), which was developed by Tetraphase Pharmaceuticals and supported by BARDA since 2012. XERAVA was approved to treat complicated intra-abdominal infections due to drug-resistant bacteria. XERAVA is the third BARDA-supported antimicrobial product to achieve FDA approval.

In 2019, BARDA released a Request for Proposal (RFP) and intends to make one to two awards in FY2019 to support the late-stage development and potential procurement and delivery to the Strategic National Stockpile (SNS) of up to two different antibiotics that can be used to treat a biothreat infection under Emergency Use Authorization (EUA) or have received FDA marketing authorization for a biothreat indication. Importantly, these antibiotics must have the ability to overcome known mechanisms of antibiotic resistance, and therefore augment those currently held in the SNS. These acquisitions will allow BARDA to invest in the late stage development, marketing authorization, procurement, and stockpile of antibiotic products which are developed and have received FDA marketing authorization for commercial use and also have utility in treating biothreat pathogens. The acquired products will directly address PHEMCE requirements established in the Product-Specific Requirement (PSR) for Medical Countermeasures to combat antibiotic-resistant bacterial infections, the National Strategy and Action Plan to Combat Antibiotic Resistant Bacteria, and the National Biodefense Strategy.

Department of Health and Human Services (HHS)
Centers for Disease Control and Prevention (CDC)

CDC's nationwide infrastructure investments in capacity for detection, prevention, and containment are enabling tailored, rapid, and aggressive action to combat resistant threats in the U.S. The U.S. has made great progress in preventing infections domestically, though much more work remains to be done in the U.S. and overseas. During the past few years, the U.S. has seen declines in multiple infection types (e.g., Central Line-Associated Blood Stream Infection [CLABSI], CAUTI, surgical site infection (SSI) as well as pathogen reductions (e.g., Methicillin-Resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* Infection (CDI) in healthcare. In addition, CDC is supporting further aggressive action to identify and respond to new and emerging threats to protect Americans from new kinds of resistance. The containment strategy complements foundational CDC efforts, including improving antibiotic use and preventing new infections, and builds on existing detection and response infrastructure. CDC's AR Lab Network labs in all 50 states, five cities, and Puerto Rico—including seven regional labs—identify new resistance, track emerging resistance more effectively, and generate stronger data for public health action. When a germ with unusual resistance is detected by the AR Lab Network, experts from state and local health departments work with healthcare facilities to quickly isolate patients and begin aggressive infection control and screening actions to discover, reduce, and stop transmission. This testing and containment response has been directed at

emerging threats, like "nightmare bacteria" carbapenem-resistant Enterobacteriaceae (CRE), *C. auris,* and Verona Integron-encoded Metallo-β-lactamase-producing (VIM) *Pseudomonas aeruginosa*. In 2018, CDC supported 158 antibiotic resistance containment responses.

CDC is partnering with stakeholders around the world to improve antibiotic use. Improving the way healthcare providers prescribe antibiotics—and the way patients use antibiotics—helps keep patients healthy now, helps fight antibiotic resistance, and ensures that these life-saving drugs will work when they are needed most. In order to improve antibiotic use, CDC is working with partners throughout the United States to ensure antibiotics work to protect patients from life-threating infections or sepsis. These investments have led to 76% of hospitals implementing stewardship programs that meet CDC's *Core Elements of Hospital Antibiotic Stewardship* and improved outpatient prescribing practices. Specifically, antibiotic prescribing in the outpatient setting declined by 5% from 2011-2016. This decrease was driven by a 13% decrease in prescribing to children. CDC leveraged the successes and lessons learned from its effective, domestic antibiotic resistance stewardship framework to work with international partners to identify and implement practical strategies that use the Core Elements for Antibiotic Stewardship concepts in international resource-limited settings. In its *Core Elements of Human Antibiotic Stewardship Programs in Resource-Limited Settings: National and Hospital Levels*, CDC provides guidance for national policies that can improve use across the spectrum of care and facility-level activities that can improve use in acute care facilities. These strategies reflect the dual need for countries to ensure access to antibiotics when needed and to reduce inappropriate use of antibiotics in low- and middle-income countries and international public health programs, such as the global sepsis initiative.

Department of Health and Human Services (HHS)
Centers for Medicare and Medicaid Services (CMS)

This year, CMS finalized policies to remove barriers for new antimicrobial therapies, which treat drug-resistant infections and are currently in short supply. In April, CMS released the Notice of Proposed Rulemaking (NPRM) for the Fiscal Year (FY) 2020 Hospital Inpatient Prospective Payment System (IPPS) final rule. As part of the final rule, CMS modernized the evidence requirement and increased the payment level to hospitals for new antimicrobial drugs designated by the Food and Drug Administration (FDA) as Qualified Infectious Disease Products (QIDP). These antibiotics are specifically designed to address resistant infections.

Additionally within the IPPS, CMS finalized a change in payments to hospitals for treating patients with antimicrobial drug resistant infections. This change recognizes the added clinical complexity and cost of treating patients with drug resistant infections. CMS intends to seek further feedback about additional changes to the payment system, such as additional payment adjustments for antimicrobial resistance based on the relative hospital resources used in these cases.

In October 2016, CMS published a final rule, "Medicare and Medicaid Programs: Reform of Requirements for Long-Term Care Facilities" (81 FR 68688). Training webinars for CMS surveyors were created and are available on the requirements for infection prevention and control

and antibiotic stewardship. CMS and the CDC have collaborated on the development of a free on-line training for staff titled the "Nursing Home Infection Preventionist Training Course". The course includes information about the core activities of an infection prevention and control program, with a detailed explanation of recommended practices to prevent pathogen transmission and reduce healthcare-associated infections and antibiotic resistance in nursing homes.

While CMS has made significant progress this year in addressing Medicare payment to hospitals and providing training on antibiotic stewardship requirements for nursing homes, CMS has not completed the CARB Plan milestone requiring product developers to provide data to CMS for use in developing Interpretive Guidelines that facilitate the use of tests for patient treatment, hospital infection control, and reporting of disease during outbreaks. CMS routinely receives information from all stakeholders, including product developers, regarding Medicare payment and conditions of participation. In addition, CMS and the FDA have established the Parallel Review Program, which is a collaborative effort that is intended to reduce the time between FDA marketing approval or FDA's granting of a de novo request and Medicare coverage decisions, in order to ensure prompt and efficient patient access to safe and effective and appropriate medical devices for the Medicare population.

Relevant Links:
Revised Interpretive Guidance (tag F880-F883, pages 673-714)

Current surveyor tool for infection prevention and control (Form CMS-20054)

Surveyor training on the revised requirements for participation (Infection Control)

Department of Health and Human Services (HHS)
Food and Drug Administration (FDA)

To continue addressing the complex challenges associated with AMR, on September 14, 2018, FDA released an agency-wide strategic approach for combating antibiotic resistance, published a five-year plan for Supporting Antimicrobial Stewardship in Veterinary Settings, and launched a new web page on FDA.gov. These efforts provide a consolidated overview of the widely diverse FDA activities that address antimicrobial resistance in humans and animals, including:

- facilitating efficient development of new antibiotics, vaccines for humans, nontraditional antimicrobial products, and diagnostic devices;
- promoting appropriate and responsible use of antimicrobials and disseminating information to promote interventions that help slow development of resistance;
- supporting the development and enhancement of tools for conducting surveillance of antimicrobial use and resistance; and
- advancing regulatory science to develop tools, standards, and approaches to facilitate the translation of breakthrough discoveries in science and technology into innovative, safe, and effective medical products.

Addressing the rising threat of antimicrobial resistance requires a collaborative, multisectoral,

and interdisciplinary One Health approach that recognizes that human and animal health are inextricably linked. Consistent with this approach, the consolidated FDA web page provides consumers, scientists, medical product developers, veterinarians, and other stakeholders a single landing spot to find up-to-date information on FDA's multifarious activities to combat antimicrobial resistance in humans and animals.

At the top of the web page is a "What's new" box, which is updated at least once per month with relevant information including new product approvals, new public meetings and workshops, and new funding opportunities. In addition, the web page expands on each strategic area, providing more in-depth information on each topic. "Product development" has links to relevant programs describing regulatory pathways, incentives, and other activities facilitating development of novel diagnostics, antibiotics, and novel and nontraditional antimicrobial products; "Antimicrobial stewardship" includes more information on both veterinary and human healthcare stewardship; "Surveillance and monitoring" provides details on the National Antimicrobial Resistance Monitoring System; and "Regulatory science" provides links to a variety of tools for scientists, including the CDC-FDA Antimicrobial Resistance Isolate Bank and the Database for Reference Grade Microbial Sequences. In addition to providing links to relevant FDA publications, there is also a special section with "Information for consumers."

Relevant Links:
Antimicrobial Resistance Information from FDA

Department of Health and Human Services (HHS)
National Institutes of Health (NIH)

NIH continues to make significant progress in stimulating research to drive the discovery, development, and evaluation of diagnostics, preventives, and therapeutics for drug-resistant infections, as well as gathering crucial data to guide use of existing therapeutics. NIH's National Institute of Allergy and Infectious Diseases (NIAID) supports and conducts research on a broad range of AMR threats, including *Neisseria gonorrhoeae,* the bacterium that causes gonorrhea. Additional information about NIH/NIAID's robust AMR research portfolio is available on the NIH/NIAID website.

In 2017, more than 550,000 cases of gonorrhea were reported in the U.S., according to the CDC. If left untreated, gonorrhea infections can cause serious health problems including pelvic inflammatory disease, ectopic pregnancy, infertility, and an increased risk of acquiring HIV. Pregnant women can pass gonorrhea to their babies, who can become blind or develop life-threatening infections.

While gonorrhea is one of the most commonly reported sexually transmitted infections in the U.S., treatment options are limited. *N. gonorrhoeae* has become resistant to nearly all therapeutic options. Currently, the CDC recommends only one treatment regimen, which relies on an injection of ceftriaxone and orally administered azithromycin. Ceftriaxone-resistant *N. gonorrhoeae* has been discovered abroad, and azithromycin-resistant *N. gonorrhoeae* has been discovered in the U.S. As resistance grows, few treatment options for gonorrhea remain.

NIH/NIAID has advanced the clinical evaluation of zoliflodacin, a first-in-class antibiotic developed by Entasis Therapeutics for the treatment of gonorrhea. Zoliflodacin has the potential to add another line of defense in the fight against the increasing occurrence of antimicrobial-resistant gonorrhea. Zoliflodacin differs from approved antibiotics as it uses an alternative mechanism to inhibit bacterial DNA synthesis, which prevents *N. gonorrhoeae* from replicating. Zoliflodacin is taken orally and does not require an injection like the current CDC-recommended first-line treatment regimen. The drug was awarded Fast Track Status and designated as a Qualified Infectious Disease Product by the FDA.

Preclinical studies of zoliflodacin have found that the drug demonstrated *in vitro* activity against bacterial strains that often are resistant to ceftriaxone or azithromycin. Building on these preclinical findings, NIH/NIAID has funded three clinical trials to advance zoliflodacin's development. The NIH/NIAID-supported Sexually Transmitted Infections Clinical Trials Group conducted a Phase II clinical trial which showed in 2018 that zoliflodacin was effective and well-tolerated. In 2018, NIH/NIAID also completed a pharmacokinetic study to bridge the Phase II clinical trial formulation to the final formulation for testing in Phase III clinical trials. In 2019, NIH/NIAID completed enrollment for an additional pharmacokinetic study to evaluate the drug's potential to cause cardiac arrhythmia, a standard safety test often used for new drugs. Results are expected by early 2020.

The NIH/NIAID-funded clinical trials have been critical to advancing zoliflodacin through the product development pathway. Building on these accomplishments, the Global Antibiotic Research and Development Partnership (GARDP) is sponsoring an international Phase II trial of zoliflodacin, expected to begin in 2019. The clinical trial will be conducted in the Netherlands, South Africa, Thailand, and the United States. NIH/NIAID scientists continue to participate in the partnership with GARDP and Entasis Therapeutics, providing guidance and critical data to advance zoliflodacin's clinical evaluation and development towards licensure.

Department of Health and Human Services (HHS)
Office of Global Affairs (OGA)

In Year 4 of the CARB National Action Plan, the United States continued to promote action to combat AMR at the highest political levels including at the United Nations (UN), World Health Organization (WHO), and through the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR). The United States sponsored a resolution on AMR that was adopted at this year's World Health Assembly. The resolution lays out Member State requests for WHO to take action on combating AMR, asks WHO to strengthen the Tripartite (comprised of WHO, Food and Agriculture Organization [FAO], and World Organisation for Animal Health [OIE]), and provides for continued Member State input on the implementation of WHO programs and activities. During the 73rd Session of the United Nations (UN) General Assembly High Level week, Secretary Azar launched The AMR Challenge, a year-long initiative to build momentum in the fight against AMR. The AMR Challenge gathers public and private stakeholders around the globe to make commitments in the following areas: tracking and data, infection prevention and control, sanitation and the environment, antibiotic use, and vaccines, diagnostics and therapeutics. The Challenge embraces a One Health approach, recognizing the

interconnectedness of human health, animal health, and the environment. In the six months since the launch, The AMR Challenge had over 200 commitments from regional partners, national ministries, local governments, non-governmental organizations, academia, and industry. Also in this year, the United States, led by the CDC, hosted the biannual in-person TATFAR meeting with our partners from Canada, Norway, and the European Union. TATFAR continues to improve cooperation in the therapeutic use of antimicrobial drugs in medical and veterinary communities.

Department of State

In Year 4 of the CARB National Action Plan, the U.S. Department of State focused on activities that empower on-the-ground action. Starting in July 2018, the Department of State deployed Dr. Michael Osterholm of the University of Minnesota as a Science Envoy for Global Health Security. During this one-year appointment, Dr. Osterholm engaged foreign governments, spoke at major conferences, and used public diplomacy activities to encourage governmental transparency and citizen involvement in global health security issues, including antibiotic resistance. Under the program, Dr. Osterholm visited Australia, Ghana, Indonesia, Malaysia, New Zealand, and Vietnam, earning significant media attention and meeting with an array of policymakers in each country. In Accra, Dr. Osterholm gave plenary remarks at the "Call to Action" Conference co-hosted by the Wellcome Trust, the United Nations Foundation, and the governments of Ghana and Thailand to help drive pioneering action to stop the rise and spread of drug-resistant disease. In December 2018, the Department of State, along with CDC, the United States Geological Survey (USGS), the World Bank, the Massachusetts Institute of Technology (MIT), and the Governments of Singapore and Australia, convened a workshop on implementing AMR national action plans in Southeast Asia under the U.S.-Singapore Third Country Training Program. The program brought together more than 20 mid-career AMR experts from across the Association of Southeast Asian Nations (ASEAN) region to discuss public awareness raising, benchmark-setting, financing, and the One Health approach. The course strengthened ties between regional partners and has served as the basis for ongoing regional collaboration on AMR issues.

Department of Veterans Affairs (VA)

In January 2019, the VA published an updated Directive 1031 Antimicrobial Stewardship Program, expanding on the stewardship requirements itemized in the version previously published in 2014. The revised Directive mandates NHSN Antimicrobial Use (AU) Option reporting for all Veterans Health Administration (VHA) acute care facilities with 30 or more acute care beds and includes recommended staffing guidelines for antimicrobial stewardship programs. By January 2020, all VHA acute care facilities with 30 or more acute care beds are required to be enrolled in the NHSN AU Option.

Appendix A

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

TABLE 1: National Targets to Combat Antibiotic-Resistant Bacteria
By 2020, the United States will:
For CDC Recognized Urgent Threats:
Reduce by 50% the incidence of overall *Clostridium difficile* infection compared to estimates from 2011.
Reduce by 60% carbapenem-resistant Enterobacteriaceae infections acquired during hospitalization compared to estimates.
Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae* below 2% compared to estimates from 2013.
For CDC Recognized Serious Threats:
Reduce by 35% multidrug-resistant *Pseudomonas spp.* infections acquired during hospitalization compared to estimates from 2011.
Reduce by at least 50% overall methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections by 2020 as compared to 2011.*
Reduce by 25% multidrug-resistant non-typhoidal *Salmonella* infections compared to estimates from 2010-2012.
Reduce by 15% the number of multidrug-resistant TB infections.[1]
Reduce by at least 25% the rate of antibiotic-resistant invasive pneumococcal disease among <5 year-olds compared to estimates from 2008.
Reduce by at least 25%the rate of antibiotic-resistant invasive pneumococcal disease among >65 year-olds compared to estimates from 2008.

* This target is consistent with the reduction goal for MRSA bloodstream infections (BSI) in the *National Action Plan to Prevent Healthcare-Associated Infections (HAI): Road Map to Elimination*, which calls for a 75% decline in MRSA BSI from the 2007-2008 baseline by 2020. Additional information is available at http://www.health.gov/hai/prevent_hai.asp#hai_plan.

Appendix B

AAVLD	American Association of Veterinary Laboratory Diagnosticians
AFHSB-GEIS	Armed Forces Health Surveillance Branch Global Emerging Infections Surveillance and Response System
AHRQ	Agency for Healthcare Research and Quality
AMR	antimicrobial resistance
APHIS	Animal and Plant Health Inspection Service
AR	antibiotic resistance
ARGs	antimicrobial resistance genes
ARMOR	Antimicrobial Resistant Monitoring and Research
ARS	Agricultural Research Service
AS	antibiotic stewardship
ASEAN	Association of Southeast Asian Nations
ASPR	Assistant Secretary for Preparedness and Response
ASPWG	Antimicrobial Stewardship Program Working Group
ATA	Alternatives to Antibiotics
AU	antibiotic use
BARDA	Biomedical Advanced Research and Development Authority
C. auris	*Candida auris*
CARB	Combating Antibiotic-Resistant Bacteria
CAUTI	Catheter-Associated Urinary Tract Infection
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium Difficile* Infection
CEAH	Centers for Epidemiology and Animal Health
CLABSI	Central Line-Associated Blood Stream Infection
CLSI	Clinical Laboratory Standards Institute
CMS	Centers for Medicare and Medicaid Services
CRE	carbapenem-resistant Enterobacteriaceae
CUSP	Comprehensive Unit-Based Safety Program
DHA	Defense Health Agency
DHA-PI	Defense Health Agency Procedural Instruction
DoD	Department of Defense
ECVs	epidemiological cutoff values
EDC	Epi-Data Center
E. coli	*Escherichia coli*
ET	Experimental Therapeutics
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FSIS	Food Safety and Inspection Service
GARDP	Global Antibiotic Research and Development Partnership
HHS	Department of Health and Human Services
IICA	Inter-American Institute for Cooperation on Agriculture
INFAL	Interamerican Network of Food Analysis Laboratories
IP	infection prevention
IPT	Integrated Product Team
JAMA	Journal of the American Medical Association

MDR	multi-drug resistant
MHS	Military Healthcare System
MIT	Massachusetts Institute of Technology
MRSA	Methicillin-Resistant *Staphylococcus Aureus*
MRSN	Multidrug-resistant organism Repository and Surveillance Network
NAHLN	National Animal Health Laboratory Network
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIFA	National Institute of Food and Agriculture
NIH	National Institutes of Health
NVSL	National Veterinary Services Laboratories
OIE	World Organization for Animal Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PAHO	Pan American Health Organization
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
POC	point-of-care
PR/HACCP	Pathogen Reduction/Hazard Analysis and Critical Control Point
PSR	Product-Specific Requirement
PVC	Army Pharmacovigilance Center
QAPI	Quality Assurance and Performance Improvement
RFP	Request for Proposals
SNS	Strategic National Stockpile
SSI	Surgical Site Infection
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
UN	United Nations
USDA	United States Department of Agriculture
USG	United States Government
USGS	United States Geological Survey
VA	Department of Veterans Affairs
Vet-LIRN	Veterinary Laboratory Investigation and Response Network
VHA	Veterans Health Administration
VIM	Verona Integron-encoded Metallo-β-lactamase
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research